″EFFECTS OF SIX WEEKS INTAKE BERBERIS VULGARIS L, CORNUS MAS, GARLIC AND LEMON IN COMBINATION WITH AEROBIC OR RESISTANCE EXERCISE ON THE FAT METABOLISM AND FATTY LIVER ENZYMES OF RATS FED A HIGH CHOLESTEROL DIET″

DOCTORAL THESIS

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Effects of six weeks intake Berberis Vulgaris L, Cornus Mas, Garlic, and Lemon in combination with aerobic or resistance exercise on the fat metabolism and fatty liver enzymes of rats fed a high cholesterol diet.

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BY COMPENDIUM OF PUBLICATIONS

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The present dissertation, entitled **"Effects of six weeks intake Berberis Vulgaris L, Cornus Mas, Garlic, and Lemon in combination with aerobic or resistance exercise on the fat metabolism and fatty liver enzymes of rats fed a high cholesterol diet"** has been written under their supervision by SaraTorkamaneh. This manuscript corresponds to the Doctoral Program in Sciences of Physical Activity and Sport of the University of Valencia.

In recognition whereof, we sign the present certificate in Valencia, October 2022.

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Preface

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Publications this Doctoral Thesis

Below are the articles, communications and posters published in conferences and scientific journals.

1. List of articles (studies)

1. **Title**: Effects of black Berberis vulgaris L combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes in obese rats.

Name of the Journal: JOURNAL OF HUMAN SPORT & EXERCISE

Authors: SARA TORKAMANEH, JAVIER GENE-MORALES, ALVARO JUESAS, JORGE FLÁNDEZ, RAOUF HAMMAMI, MAHMOUD RAFIEIAN-KOPAEI, JUAN CARLOS COLADO.

2. **Title:** Effects of Cornus mas extract combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes of obese rats.

Name of the Journal: JOURNAL OF HUMAN SPORT & EXERCISE

Authors: SARA TORKAMANEH, ANGEL SAEZ-BERLANGA, FERNANDO MARTIN, PEDRO GARGALLO, JORGE FLANDEZ, JAVIER GENE-MORALES, MAHMOUD RAFIEIAN-KOPAEI, JUAN CARLOS COLADO.

3. **Title:** Preventive effects of garlic and lemon extract combined with aerobic exercise on blood metabolic parameters and liver enzymes.

Name of the Journal: JOURNAL OF HUMAN SPORT & EXERCISE

Authors: SARA TORKAMANEH, JAVIER GENE-MORALES, JORGE FLANDEZ, MAHENDRA YADAV, MOHAMMAD SIDIQ, MAHMOUD RAFIEIAN-KOPAEI, JUAN CARLOS COLADO.

Indexation information of the Journal of Human Sport and Exercise:

- ***Scimago Journal & Country Rank****: Q3 in the area of Physical Therapy, Sports Therapy and Rehabilitation; Q4 in the area of Sports Science.*

-***Journal Citation Reports*** *(Emerging Sources Citation Index): Q4 in the area of Sport Sciences.*

2. Other articles:

1. **Title:** The comparison between effects of *Berberis vulgaris* Extract and aerobic exercise on none-alcoholic fatty liver in male rat.

Name of the Journal: Der Pharma Chemica

Autores: SARA TORKAMANEH, GHOLAMREZA SHARIFI, MAHMOUD RAFIEIAN-KOPAEI.

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Abstract:

Obesity is a worldwide epidemic problem which is among the most important risk factors for cardiovascular disease (CVD) and 30% of mortality. Previous investigations have demonstrated that mortality from CVD is more than three times higher in obese people than in normal-weight people. Due to these facts, it is necessary to continue the efforts to control obesity and overweight.

Medication, health education and diet are the most common ways to manage and control obesity. As well as the implementation of a specific nutritional style along with the practice of physical exercise, are the most traditionally used methods to treat obesity. Physical exercise, represent an effective strategy to prevent and/or treat obesity and cardiovascular disease.

The use of Wistar rats is common for the development of extremely rigorous studies in a laboratory environment. Fundamental implications are transferred to human beings derived from the findings obtained with them. This is why they are usually used for numerous types of studies with different purposes: biomedical, toxicological, nutritional, physical exercise, etc.

The purpose of the present study was to evaluate the effects of some herbal extract such as Berberis vulgaris L, cornus mas, Garlic and Lemon in combination with aerobic and/or resistance exercise on the lipid profile, metabolic parameters, and liver enzymes of obese male rats.

Taking into account this aim, 6 weeks clinical assay based on a sample composed of 169 male Wistar rats and divided into three studies and 22 groups was carried out.

In the first study, the rats received an extract of Berberis vulgaris L in combination with aerobic and resistance exercise, which the animals divided into seven groups:

1) Healthy control (n = 8); 2) hyper-caloric fatty-food-based diet (n = 8); 3) aerobic exercise (AE, n = 8); 4) resistance exercise (RE, n = 8); 5) black berberis vulgaris L extract intake (n = 8); 6) berberis intake combined with aerobic exercise (BAE, n = 8); and 7) berberis intake combined with resistance exercise (BRE, n = 8).

In the second study, the rats received an extract of cornus mas in combination with aerobic and resistance exercise, which the animals divided into seven groups:

1) Healthy control (n = 7); 2) hyper-caloric fatty-food-based diet (n = 7); 3) aerobic exercise (AE, n = 7); 4) resistance exercise (RE, n = 7); 5) cornus mas extract intake (C, n = 7); 6) cornus mas combined with aerobic exercise (CAE, n = 7); and 7) cornus mas combined with resistance exercise (CRE, n = 7).

In the third study, the rats received lemon and garlic in combination with aerobic exercise, which the animals divided into eight groups:

1) control following no treatment (n = 8); 2) hyper-caloric fatty-food-based diet (n = 8); 3) aerobic exercise (AE, n = 8); 4) garlic intake (G, n = 8); 5) aerobic exercise with garlic intake (AEG, n = 8); 6) lemon intake (L, n = 8); 7) garlic and lemon (GL, n = 8); 8) garlic, lemon, and aerobic exercise (GLAE, n = 8).

For the first and second studies, all the rats (except the controls) were induced fatty liver by six weeks of a hyper-caloric diet before the intervention.

After six weeks of intervention, blood samples were taken to obtain cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), glucose of C - reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), creatinine (Cr), urea and uric acid (UA).

First, the assumption of normality and homogeneity of the dependent variables was verified by the Kolmogorov-Smirnov and Levene tests, respectively. After that, a one-way ANOVA or the Kruskal-Wallis tests for the non-normally distributed variables, with post-hoc pair-wise comparisons, were conducted to assess differences between groups. For all the analyses carried out, a confidence level of 95% was accepted (significance of $p \leq 0.05$).

After analyzing the data and comparing the hyper group with all the experimental groups, in the study I:

BAE group obtained the best results in the variables cholesterol (-57.4%), TG (-43.2%), LDL (-67.3%), AST (-77.2%), ALT (-44.5%), CRP (-30.8%). Also, in variables Glucose (-36%), HDL (+45%), Cr (-54.1%) and urea (-38.2%) the best results were obtained in the BRE group.

In the study II:

AEC group obtained the best results in the variables cholesterol (-43.4%), Glucose (-45%), TG (-48.1%), LDL (-64.7%), and the best results for HDL (+34.9%), AST (-60.5%), ALT (-47.5%), CRP (-33.2%) Cr (-60.4%) and urea (-29.8%) were obtained in REC group.

In the study III:

GLAR group obtained the best results in all variables cholesterol (-45%), Glucose (-44.3%), TG (-76.2%), HDL (+24%), AST (-46.3%), ALT (-44.7%), CRP (-29.5%) Cr (-51.3%) and urea (-28.3%) and U.A (-51.3) were obtained in the GLAR group.

In conclusion, the present study shows that the use of natural herbal medicine such as Berberis vulgaris L, cornus mas, garlic, and lemon in combination with aerobic and/or resistance exercise is a suitable alternative may be helpful to influence the lipid profile, liver enzymes, and other blood parameters associated with cardiovascular disease.

Keywords: obesity, herbal medicine, physical activity

Resumen

La obesidad es un problema epidémico mundial que se encuentra entre los factores de riesgo más importantes de enfermedad cardiovascular (ECV) y representa el 30% de la mortalidad. Investigaciones anteriores han demostrado que la mortalidad por ECV es más de tres veces mayor en personas obesas que en personas con peso normal. Debido a estos hechos, es necesario continuar con los esfuerzos para controlar la obesidad y el sobrepeso.

Los medicamentos, la educación para la salud y la dieta son las formas más comunes de manejar y controlar la obesidad. Así como la implementación de un estilo nutricional específico junto con la práctica de ejercicio físico, son los métodos más utilizados tradicionalmente para tratar la obesidad. El ejercicio físico, representa una estrategia eficaz para prevenir y/o tratar la obesidad y las enfermedades cardiovasculares.

El empleo de ratas Wistar es habitual para el desarrollo de estudios sumamente estrictos en un entorno de laboratorio. De los hallazgos obtenidas con ellas se transfieren implicaciones fundamentales a los seres humanos. Es por esto que se emplean usualmente para numerosos tipos de estudios con finalidades diversas: biomédicas, toxicológicas, nutricionales, de ejercicio físico, etc.

El propósito del presente estudio fue evaluar los efectos de algunos extractos herbales como: Berberis vulgaris L, cornus mas, Ajo y Limón en combinación con ejercicio aeróbico y/o de resistencia sobre el perfil lipídico, parámetros metabólicos y enzimas hepáticas de ratas macho obesas.

Tomando en consideración este objetivo, se realizó un ensayo clínico de 6 semanas basado en una muestra compuesta por 169 ratas Wistar macho y dividida en tres estudios y 22 grupos.

El primer estudio, las ratas recibieron extracto de berberis vulgaris L en combinación con ejercicio aeróbico y de resistencia que los animales dividieron en siete grupos:

> 1) control sano (n = 8); 2) dieta basada en alimentos grasos hipercalóricos (n = 8); 3) ejercicio aeróbico (AE, n = 8); 4) ejercicio de fuerza (RE, n = 8); 5) consumo de extracto de Berberis vulgaris L negro (n = 8); 6) ingesta de Berberis combinada con ejercicio aeróbico (BAE, n = 8); y 7) ingesta de Berberis combinada con ejercicio de fuerza (BRE, n = 8).

En el segundo estudio, las ratas recibieron extracto de cornus mas en combinación con ejercicio aeróbico y de resistencia que los animales dividieron en siete grupos:

1) control sano (n = 7); 2) dieta basada en alimentos grasos hipercalóricos (n = 7); 3) ejercicio aeróbico (AE, n = 7); 4) ejercicio de fuerza (RE, n = 7); 5) ingesta de extracto de cornus mas (C, n = 7); 6) cornus mas combinado con ejercicio aeróbico (CAE, n = 7); y 7) cornus mas combinado con ejercicio de fuerza (CRE, n = 7).

El tercer estudio, las ratas recibieron limón y ajo en combinación con ejercicio aeróbico que los animales dividieron en ocho grupos:

1) control después de ningún tratamiento (n = 8); 2) dieta basada en alimentos grasos hipercalóricos (n = 8); 3) ejercicio aeróbico (AE, n = 8); 4) consumo de ajo (G, n = 8); 5) ejercicio aeróbico con ingesta de ajo (AEG, n = 8); 6) ingesta de limón (L, n = 8); 7) ajo y limón (GL, n = 8); 8) ajo, limón y ejercicio aeróbico (GLAE, n = 8).

Para el primer y segundo estudio, a todas las ratas (excepto los controles) se les indujo hígado graso mediante seis semanas de una dieta hipercalórica antes de la intervención.

Después de seis semanas de intervención, se tomaron muestras de sangre para obtener colesterol, triglicéridos, colesterol de lipoproteínas de alta densidad (HDL), colesterol de lipoproteínas de baja densidad (LDL), glucosa de proteína C - reactiva (PCR), alanina aminotransferasa (ALT), aspartato aminotransferasa (AST), fosfatasa alcalina (ALP), creatinina (Cr), urea y ácido úrico (UA).

En primer lugar, se verificó el supuesto de normalidad y homogeneidad de las variables dependientes con las pruebas de Kolmogorov-Smirnov y Levene, respectivamente. Después de eso, se realizó un ANOVA de una vía o las pruebas de Kruskal Wallis para las variables que no se distribuyen normalmente, con comparaciones por pares post-hoc para evaluar las diferencias entre los grupos. Para todos los análisis realizados se aceptó un nivel de confianza del 95% (significación de $p \leq 0{,}05$).

Tras analizar los datos y comparar el grupo hiper con todos los grupos experimentales, en el estudio I:

El grupo BAE obtuvo los mejores resultados en las variables colesterol (-57,4%), TG (-43,2%), LDL (-67,3%), AST (-77,2%), ALT (-44,5%), PCR (-30,8%). Asimismo, en las variables Glucosa (-36%), HDL (+45%), Cr (-54,1%) y urea (-38,2%) los mejores resultados se obtuvieron en el grupo BRE.

En el estudio II:

El grupo AEC obtuvo los mejores resultados en las variables colesterol (-43,4 %), Glucosa (-45 %), TG (-48,1 %), LDL (-64,7 %) y los mejores resultados para HDL (+34,9

%). %), AST (-60,5 %), ALT (-47,5 %), PCR (-33,2 %), Cr (-60,4 %) y urea (-29,8 %) en el grupo REC.

En el estudio III:

El grupo GLAR obtuvo los mejores resultados en todas las variables colesterol (-45%), Glucosa (-44,3%), TG (-76,2%), HDL (+24%), AST (-46,3%), ALT (-44,7 %), PCR (-29,5 %), Cr (-51,3 %) y urea (-28,3 %) y AU (-51,3) en el grupo GLAR.

En conclusión, el presente estudio muestra que el uso de fitoterapia natural como Berberis vulgaris L, cornus mas, ajo y limón en combinación con ejercicio aeróbico y/o de resistencia es una alternativa adecuada que puede ser útil para influir en el perfil lipídico, hepático. enzimas y otros parámetros sanguíneos asociados con la enfermedad cardiovascular.

Palabras clave: obesidad, fitoterapia, actividad física.

Resum

L'obesitat és un problema epidèmic mundial que es troba entre els factors de risc més importants de malalties cardiovasculars (ECV) i el 30% de la mortalitat. Investigacions anteriors han demostrat que la mortalitat per ECV és més de tres vegades més alta en persones obeses que en persones amb pes normal. Per aquests fets, cal continuar els esforços per controlar l'obesitat i el sobrepès.

La medicació, l'educació sanitària i la dieta són les maneres més habituals de gestionar i controlar l'obesitat. Així com la implantació d'un estil nutricional específic juntament amb la pràctica d'exercici físic, són els mètodes més utilitzats tradicionalment per tractar l'obesitat. L'exercici físic, representa una estratègia eficaç per prevenir i/o tractar l'obesitat i les malalties cardiovasculars.

L'ús de rates Wistar és habitual per al desenvolupament d'estudis molt estrictes en un entorn de laboratori. De les troballes obtingudes amb elles es transfereixen implicacions fonamentals als éssers humans. És per això que es fan servir usualment per a nombrosos tipus destudis amb finalitats diverses: biomèdiques, toxicològiques, nutricionals, d´exercici físic, etc.

El propòsit del present estudi va ser avaluar els efectes d'algun extracte d'herbes com: Berberis vulgaris L, cornus mas, All i Llimona en combinació amb exercici aeròbic i/o de resistència sobre el perfil lipídic, els paràmetres metabòlics i els enzims hepàtics dels rates mascles obeses.

Prenent en consideració aquest objectiu, es va realitzar un assaig clínic de 6 setmanes basat en una mostra composta per 169 rates Wistar mascles i dividida en tres estudis i 22 grups.

El primer estudi, les rates van rebre extracte de Berberis Vulgaris L en combinació amb exercici aeròbic i de resistència que els animals van dividir en set grups:

1) Control saludable (n = 8); 2) dieta hipercalòrica basada en aliments grassos (n = 8); 3) exercici aeròbic (AE, n = 8); 4) exercici de resistència (RE, n = 8); 5) ingesta d'extracte negre de Berberis vulgaris L (n = 8); 6) Ingesta de Berberis combinada amb exercici aeròbic (BAE, n = 8); i 7) Ingesta de Berberis combinada amb exercici de resistència (BRE, n = 8).

El segon estudi, les rates van rebre extracte de cornus mas en combinació amb exercici aeròbic i de resistència que els animals van dividir en set grups:

1) Control saludable (n = 7); 2) dieta hipercalòrica basada en aliments grassos (n = 7); 3) exercici aeròbic (AE, n = 7); 4) exercici de resistència (RE, n = 7); 5) Ingesta d'extracte de cornus mas (C, n = 7); 6) cornus mas combinat amb exercici aeròbic (CAE, n = 7); i 7) Cornus mas combinat amb exercici de resistència (CRE, n = 7).

El tercer estudi, les rates van rebre llimona i all en combinació amb exercici aeròbic que els animals van dividir en vuit grups:

1) control després de cap tractament (n = 8); 2) dieta hipercalòrica basada en aliments grassos (n = 8); 3) exercici aeròbic (AE, n = 8); 4) ingesta d'all (G, n = 8); 5) exercici aeròbic amb ingesta d'all (AEG, n = 8); 6) ingesta de llimona (L, n = 8); 7) all i llimona (GL, n = 8); 8) all, llimona i exercici aeròbic (GLAE, n = 8).

Per al primer i segon estudi, a totes les rates (excepte els controls) se'ls va induir fetge gras durant sis setmanes d'una dieta hipercalòrica abans de la intervenció.

Després de sis setmanes d'intervenció, es van prendre mostres de sang per obtenir colesterol, triglicèrids, colesterol de lipoproteïnes d'alta densitat (HDL), colesterol de lipoproteïnes de baixa densitat (LDL), glucosa de proteïna C reactiva (CRP), alanina aminotransferasa (ALT), aspartat aminotransferasa (AST), fosfatasa alcalina (ALP), creatinina (Cr), urea i àcid úric (UA).

En primer lloc, es va verificar l'assumpció de normalitat i homogeneïtat de les variables dependents amb les proves de Kolmogorov-Smirnov i Levene, respectivament. Després d'això, es va realitzar un ANOVA unidireccional o les proves de Kruskal Wallis per a les variables no distribuïdes normalment, amb comparacions post-hoc per parelles per avaluar les diferències entre grups. Per a totes les anàlisis realitzades, es va acceptar un nivell de confiança del 95% (significació de $p \leq 0,05$).

Després d'analitzar les dades i comparar l'hipergrup amb tots els grups experimentals, a l'estudi I:

> El grup BAE va obtenir els millors resultats en les variables colesterol (-57,4%), TG (-43,2%), LDL (-67,3%), AST (-77,2%), ALT (-44,5%), CRP (-30,8%). Així mateix, en les variables Glucosa (-36%), HDL (+45%), Cr (-54,1%) i urea (-38,2%) els millors resultats es van obtenir en el grup BRE.

A l'estudi II:

> El grup AEC va obtenir els millors resultats en les variables colesterol (-43,4%), Glucosa (-45%), TG (-48,1%), LDL (-64,7%), i els millors resultats per a HDL (+34,9%). %), AST (-60,5%), ALT (-47,5%), PCR (-33,2%) Cr (-60,4%) i urea (-29,8%) es van obtenir en el grup REC.

A l'estudi III:

> El grup GLAR va obtenir els millors resultats en totes les variables colesterol (-45%), Glucosa (-44,3%), TG (-76,2%), HDL (+24%), AST (-46,3%), ALT (-44,7%), CRP (-29,5%) Cr (-51,3%) i urea (-28,3%) i UA (-51,3) es van obtenir en el grup GLAR.

En conclusió, el present estudi mostra que l'ús d'herbes medicinals naturals com Berberis vulgaris L, cornus mas, all i llimona en combinació amb exercici aeròbic i/o de resistència és una alternativa adequada que pot ser útil per influir en el perfil lipídic, el fetge. enzims i altres paràmetres sanguinis associats amb malalties cardiovasculars.

Paraules clau: obesitat, fitoterapia, activitat física.

RESUMEN EXTENDIDO

La obesidad es uno de los problemas más graves, no solo a nivel de salud sino también a nivel social en los tiempos modernos (Hernáez et al., 2019; Mazidi & Speakman et al., 2018). En las últimas tres décadas se ha demostrado que el sobrepeso y la obesidad han aumentado casi un 7,5 % en Estados Unidos y más del 200% en España (Soriano-Maldonado et al., 2020; Aslani et al., 2016). Factores ambientales como el sedentarismo y una dieta desequilibrada, así como la interacción de diversos elementos genéticos y conductuales, podrían ser la causa de la obesidad (Payab, M et al., 2019). El exceso de tejido adiposo aumenta la obesidad, el sobrepeso y los factores de riesgo de ECV, así como la enfermedad del hígado graso no alcohólico (EHGNA) (Atkins et al., 2014).

Los métodos más comunes para controlar la obesidad son la medicación, la educación sanitaria y los cambios en la dieta (Jiménez et al., 2020; Li et al., 2018). Además, la actividad física y la implementación de un estilo dietético específico han sido tradicionalmente los métodos más utilizados para tratar la obesidad y las ECV. El ejercicio regular se considera un factor para mejorar la calidad de vida, mejorar la composición corporal y prevenir el aumento de peso, además de prevenir y tratar enfermedades cardiovasculares y trastornos metabólicos como la diabetes y la hipercolesterolemia (Huck CJ et al., 2015).

La actividad física es una parte importante del enfoque general de las enfermedades cardiovasculares y la obesidad, ya que es un componente esencial de un estilo de vida saludable y tiene efectos beneficiosos en personas de todas las edades (Thivel et al., 2018 et al., 2004). La actividad física tiene muchos beneficios para la población, incluido el gasto de energía, la reducción de la hipertensión, la obesidad, el colesterol en sangre, el síndrome metabólico y otras enfermedades crónicas y metabólicas asociadas. (Morelli et al., 2020).

A lo largo de los años, se han utilizado muchas estrategias, como los tratamientos farmacológicos, para perder peso y controlar la obesidad. Sin embargo, varios medicamentos contra la obesidad tienen efectos adversos graves, como ansiedad, depresión y mayor riesgo de ECV. Por lo tanto, algunas hierbas medicinales podrían usarse como una estrategia alternativa para controlar la obesidad con efectos secundarios menos tóxicos que la medicina química (Haselgrübler et al., 2019; Kang & Park, 2012).

En este estudio, se han utilizado algunas hierbas con propiedades antioxidantes, incluyendo berberis vulgaris L; que se cultiva en varias regiones del mundo y tiene una larga historia de uso en la medicina tradicional (Chamorroet al., 2019; Dulić et al., 2019; Fernández-Poyatos et al., 2019; Tabeshpour et al., 2017; Imanshahidi et al., 2008; Kosalec et al., 2009). Algunos de los alcaloides de berberis Vulgaris L cuando se analizan químicamente incluyen berberina, palmatina, oxiacantina y berbamina, que tienen todos los beneficios medicinales, Cornus mas; que pertenece al género Cornaceae. Sus frutos son ricos en antocianinas como cianidina, peonidina, pelargonidina y petunidina, y contienen bioflavonoides, vitamina C y ácido ursólico (Lietava et al., 2019), ajo y limón; la suplementación con ajo tiene un importante efecto positivo sobre el hipercolesterolemia (Banerjee et al., 2002; Ried et al., 2008). El ajo (Allium sativum) y el limón tienen fuertes propiedades antioxidantes y, por lo tanto, pueden reducir el estrés oxidativo debido a su contenido en polifenoles (Aslani et al., 2015).

Por todos estos hechos, surge la pregunta de si la combinación específica de diferentes suplementos naturales solos y en conjunto con el ejercicio aeróbico o de resistencia puede desempeñar un papel en los parámetros asociados con las ECV. Actualmente, no existen estudios que hayan combinado el ejercicio aeróbico y de resistencia con la ingesta de estas hierbas (berberis vulgaris L, curnos mas, ajo y limón) sobre el perfil lipídico y las enzimas del hígado graso. Entonces, esta tesis es la primera en dilucidar esta incógnita.

Por lo tanto, el presente estudio analiza los efectos de la combinación de ejercicio aeróbico y de resistencia en combinación con extractos de tratamiento a base de hierbas (berberis vulgaris L, Curnos mas, ajo y limón) para mejorar los parámetros del perfil lipídico y las enzimas del hígado graso de ratas alimentadas con colesterol alto. dieta.

Según el último informe de la American Heart Association (AHA) y la OMS, las ECV son una de las principales causas de mortalidad en todo el mundo, y representan el 30 %

de las muertes provocadas anualmente (Mazidi& Speakman., 2018; World Health Organization., 2019; Atkins et al., 2014; Aslani et al., 2016 Aslani et al., 2016). Se cree que los lípidos tienen un papel importante en el crecimiento de las ECV, el colesterol, así como el colesterol LDL y HDL y los triglicéridos plasmáticos totales se muestran como predictores de eventos cardiovasculares (Wang et al., 2018; Fernandez et al., 2013). El ejercicio físico es una parte importante del enfoque general para tratar la ECV y la obesidad porque es una parte esencial de un estilo de vida saludable con efectos útiles en personas de todas las edades (Thivel et al., 2018; Afzalpour et al., 2004). La actividad física tiene muchos beneficios para la población, incluidos el gasto de energía, la reducción de la hipertensión, la obesidad, el colesterol en la sangre, el síndrome metabólico y, además, las enfermedades crónicas y metabólicas relacionadas, incluida la ECV (Morelli et al., 2020).

Asimismo, la actividad física reduce los triglicéridos plasmáticos y aumenta la concentración de HDL-c en relación con el gasto energético total. Los triglicéridos del tejido adiposo son una importante fuente de combustible durante la actividad física. Como resultado del ejercicio aeróbico, aumenta la lipólisis y, además de la masa grasa corporal total, reduce la cantidad de triglicéridos y aumenta la cantidad de HDL-c (Thompson et al., 2001). El aumento de la lipólisis y el acceso a los ácidos grasos durante el ejercicio requiere la acción integrada de eventos neurológicos, hormonales y circulatorios que facilitan el transporte de ácidos grasos desde el tejido adiposo hasta las mitocondrias del músculo esquelético para su oxidación (Mogharnasi et al., 2008).

Los ejercicios aeróbicos (AE) suelen ser ejercicios de intensidad moderada que incluyen grupos de músculos más grandes (por ejemplo, brazos o piernas) que se llevan a cabo durante períodos desarrollados para mejorar la función cardiovascular. AE implica caminar, correr, andar en bicicleta y ejercicios en la piscina. Independientemente del tipo de ejercicio que se utilice en el programa de ejercicio aeróbico, es necesario mantener una dosis aeróbica adecuada del 40 % al 60 % de la capacidad aeróbica máxima (frecuencia cardíaca máxima o Vo2max) (Souissi et al., 2020; Farrokhi et al., 2015). La EA se ha sugerido como parte del manejo de pacientes con una variedad de trastornos metabólicos en varias pautas de tratamiento publicadas (Pedisic et al., 2020; Farrokhi et al., 2015; Lakka et al., 2003; Jurca et al., 2004; Farrell et al., 2004; Okura et al., 2007). Para tener beneficios fundamentales para la salud de la actividad física, los adultos deben hacer al menos 150 minutos por semana de actividad aeróbica de intensidad moderada o 75 minutos por semana de actividad de intensidad vigorosa. Las recomendaciones anteriores eran que los adultos también pueden hacer una combinación de actividad de intensidad moderada y vigorosa, utilizando la regla general de que un minuto de actividad de intensidad vigorosa cuenta lo mismo que dos minutos de intensidad moderada (David et al., 2020).

Además, la pérdida de peso está relacionada con la salud y el estado físico (Zhou et al., 2021). La capacidad de ejercicio aeróbico se conoce como un poderoso índice de condición física y un fuerte predictor de mortalidad en todo el mundo (Lee et al., 2010). Como un indicador importante de la actividad física, el ejercicio aeróbico puede ser uno de los mejores reflejados por el consumo máximo de oxígeno por minuto (VO2max) y determinado primero por la eficiencia de los mecanismos que suministran oxígeno del aire a los músculos activos (Zhou et al., 2021). Usando la fórmula de Fick Principal, VO2max = gasto cardíaco (CO) max × diferencia de oxígeno arteriovenoso periférico (C (a-v) VO2) max = frecuencia cardíaca (FC) max × volumen sistólico (SV) max × C (a-v) VO2max = ventilación por minuto (E) max × (fracción de oxígeno de inspiración [FiO2]– fracción de oxígeno de expiración [FeO2]), reconoció que el VO2max está determinado por el sistema respiratorio, la circulación cardiovascular y la extracción/utilización de oxígeno de los músculos (Gregg et al. ., 2016). Es necesario prestar atención a muchos factores que pueden afectar el VO2max, incluido el peso, el tamaño y la composición corporales, el estado de entrenamiento (tipo y duración de la actividad física), la función cardiopulmonar, la concentración de hemoglobina en la sangre, la función mitocondrial, factores genéticos, diferentes métodos de prueba (cinta o bicicleta) y el protocolo utilizado para la elevación (Nuijten et al., 2021; Mohorko et al., 2019).

Por otro lado, uno de los programas de terapia para el control de la obesidad es la inclusión de ejercicios de fuerza que ha sido avalado por la American Heart Association (Pollock et al., 2000), el American College of Sports Medicine (Pescatelo et al., 2006), y la Asociación Americana de Diabetes (Sigal et al., 2006). Hoy en día, el ejercicio de resistencia se está volviendo más popular como modalidad de ejercicio (Hagstrom et al., 2020). El ejercicio de fuerza es un programa de actividad física que se realiza de manera acíclica ejercitando un músculo o un grupo de músculos contra una resistencia externa, que se orienta en primer lugar a la aptitud muscular (Hagstrom et al., 2020; Evans et al., 2019; Schoenfeld et al., 2017; Beqa et al., 2020). El ejercicio de resistencia es efectivo para preservar y mantener la reducción de la presión arterial (Aagaard et al., 2010) y la reducción del riesgo de múltiples enfermedades crónicas como el síndrome metabólico (Hurley et al., 2011).

El órgano principal para la eliminación de triglicéridos y glucosa es el músculo esquelético, que es un determinante particularmente importante de la tasa metabólica en reposo (Barbara et al., 2011). Los fuertes efectos secundarios de la reducción relacionada con la edad en la masa muscular esquelética son varios, y comprenden aumento de la adiposidad abdominal, disminución de la potencia y la fuerza muscular, capacidad para la oxidación de lípidos, tasa metabólica en reposo. La captación de glucosa mediada por insulina en el músculo esquelético en personas mayores aumenta la adiposidad (Niemann et al., 2020; Holten et al., 2004). La investigación previa indica que la preservación de una gran masa muscular podría disminuir los factores de riesgo metabólicos como la diabetes mellitus tipo 2, la dislipidemia y la obesidad que están asociados con las ECV (Williams et al., 2007). Es probable que una mayor masa muscular pueda estar asociada con trastornos metabólicos en personas obesas, lo cual se reporta en algunos estudios (You et al.,2004; Barbara et al.,2011). Uno de los mecanismos probables del entrenamiento de resistencia puede contener el aumento de la concentración de andrógenos libres junto con niveles reducidos de SHBG (globulina transportadora de hormonas sexuales), un efecto ahorrador de proteínas debido al aumento del metabolismo de los lípidos y cambios en la capilarización muscular y la composición de la fibra debido a adiposidad visceral. (Bárbara et al., 2011).

Como se mencionó anteriormente, otra forma sugerida para prevenir y controlar la obesidad es utilizar métodos naturales y plantas medicinales. Vivir en el abrazo de la naturaleza y utilizar materiales naturales y orgánicos y lograr una mayor salud son cada día más bienvenidos que nunca. Si bien muchas medicinas químicas no pueden curar enfermedades, muchas medicinas y métodos naturales, simples y tradicionales funcionan y tienen menos efectos secundarios (Vaezi et al., 2021). Los botánicos recomiendan la medicina herbal para tratar todas las dolencias. Los medicamentos a base de hierbas son más suaves que los medicamentos químicos y tienen una acción más lenta. También tienen efectos secundarios más leves (Rashrash et al., 2017; Rejhan et al., 1998).

El uso de productos naturales y herbales ha sido común durante mucho tiempo en la mayoría de los países. En diversas históricas del ser humano, el uso de productos naturales sufrió varios cambios durante las demandas. Hoy en día, tener un estilo de vida natural y el consumo de productos naturales son cada vez más atractivos y comunes. Los medicamentos naturales se generan en forma de jarabes, ungüentos, pastillas y cápsulas (Vaezi et al., 2021). Además, las plantas juegan un papel importante en la producción de drogas (Ashraf et al., 2015; Luo et al., 1988). Para preparar las medicinas herbales y naturales se utilizan hojas, frutos, raíces y cortezas de tallos de plantas y árboles (Ng et al., 2021; Yang et al., 2015; Sun et al., 2016).

Una de estas hierbas con propiedades antioxidantes es berberis vulgaris L, de la familia Berberidaceae (Soltani et al., 2021; Belwal et al., 2020; Neag et al., 2018; Sabir et al., 1978) un arbusto del género berberis, que se cultiva en la región de South Khorasan en Irán y es una de las pocas plantas cuya raíz, cáscara, tallo, hojas, flores y frutos se utilizan para diversos fines nutritivos y medicinales (Taheri et al., 2012; Andola et al., 2018). La berberina, el compuesto más importante de todos los alcaloides de berberis Vulgaris L, tiene una plétora de beneficios terapéuticos, que incluyen propiedades antioxidantes, antibacterianas, antitumorales y antiinflamatorias, mejora, efecto sobre los trastornos neurales y efecto preventivo en la enfermedad de las arterias coronarias (Soltani et al., 2021; Cao et al., 2020; Imenshahidi et al., 2019; Zarei et al., 2015; Fatehi et al., 2005; Doggrell et al., 2005; Kong et al., 2004; Yin et al., 2002; Ivanovska et al., 1996).

Además, es probable que la berberina pueda mejorar la sensibilidad a la insulina (InsS) al inhibir el almacenamiento de grasa y ajustar el perfil de adipoquinas en los preadipocitos humanos (Yang et al., 2012). Asimismo, su activación aguda de la actividad de transporte del transportador de glucosa 1 (GLUT1) es otro de los efectos hipoglucemiantes de la berberina (Cok et al., 2011; Kulkarni et al., 2010).

Otro efecto de la berberina es la reducción del azúcar en la sangre (Neag et al., 2018). Hay algún mecanismo probable que lo muestra, incluida la disminución del nivel de trifosfato de adenosina a través de la inhibición de la función mitocondrial en el hígado, que puede ser la explicación probable de la inhibición de la gluconeogénesis por la berberina (Xia et al., 2011), - Inhibición de DPP 4 (dipeptidil peptidasa-4), una serina proteasa ubicua responsable de escindir ciertos péptidos, como las incretinas GLP1 (péptido similar al glucagón-1) y GIP (polipéptido inhibidor gástrico); su función es elevar el nivel de insulina en el contexto de la hiperglucemia. La inhibición de DPP4 prolongará la duración de la acción de estos péptidos y, por lo tanto, mejorará la tolerancia general a la glucosa (Al-masri et al., 2009; Seino et al., 2010), la inhibición de la oxidación de la glucosa mitocondrial y la estimulación de la glucólisis y, posteriormente, el aumento de la glucosa. metabolización (Yin et al., 2008). Además, la berberina es eficaz para aumentar la utilización de glucosa y la resistencia a la insulina en los tejidos al disminuir los niveles de lípidos, como los triglicéridos y los ácidos grasos libres en plasma (Chen et al., 2011; Yin et al., 2008).

Otra hierba utilizada, ha sido la Cornelian con nombre científico, cornus mas-land, pertenece al género Cornaceae. Hay 65 del género cornus, y cornus mas L es una de las dos especies del género cornus, que se han utilizado en la etnomedicina tradicional (Przybylska et al., 2020; Darbandi et al., 2016; Czerwińska et al., 2018). Ha sido bien conocido en la medicina popular y tiene un gran valor biológico, que está relacionado principalmente con sus polifenoles e iridoides (Klymenko et al., 2021).

Cornus mas L o (cerezo de cornalina) se conoce desde hace más de 4000 años y desde el Cáucaso y desde allí se extendió por Irán, Turquía, Rumania, Bulgaria y más en el continente europeo (West et al., 2012; Klymenko et al., 2017). Sus frutos son ricos en antocianinas como cianidina, peonidina, pelargonidina y petunidina, y contienen bioflavonoides, vitamina C y ácido ursólico.

Las antocianinas conducen a una mayor secreción de insulina (la pelargonidina aumenta la secreción de insulina hasta 1,4 veces), mejora la resistencia a la insulina y mejora la hiperlipidemia (Dayar et al., 2020). Cornus mas se usa en la medicina tradicional china e iraní para tratar la diabetes y los niveles elevados de lípidos en sangre y sus complicaciones (Abdollahi et al., 2014; Lietava et al., 2019). Recientemente, varios estudios in vitro e in vivo han confirmado la actividad antioxidante, antiinflamatoria, antidiabética, hipolipemiante, antiaterosclerótica, antimicrobiana y anticancerígena de los frutos (Tiptiri-Kourpeti et al., 2019; Kucharska et al., 2009).

Varios estudios han informado que la suplementación con cornus mas puede tener efectos que promueven la salud debido a su amplia gama de actividades biológicas, como hipolipemiantes, antioxidantes, antidiabéticos, antiinflamatorios, antibacterianos, anticancerígenos, anticoagulantes, efectos antiparasitarios y efectos protectores sobre el hígado. y la función renal, así como la influencia en el sistema cardiovascular y los factores sanguíneos (Gąstoł et al., 2013; Sozański et al., 2014; Kazimierski et al., 2019; Hosseinpour et al., 2017; Yamabe et al., 2010; Parque et al., 2011). Es probable que estas actividades biológicas puedan disminuir la ECV, la DM y la obesidad, lo que se ha atribuido a la presencia de niveles elevados de ciertos compuestos polifenólicos (Lietava et al., 2019).

Otros suplementos naturales son el ajo y el limón; la suplementación con ajo tiene un importante efecto positivo sobre el hipercolesterolemia (Banerjee et al., 2002; Ried et al., 2008; Sung et al., 2009). El ajo (Allium sativum) tiene fuertes propiedades antioxidantes y por lo tanto puede reducir el estrés oxidativo por su contenido en polifenoles. El ajo también puede proteger las células y los tejidos metabólicos (por ejemplo, el hígado) del daño químico de las toxinas periféricas debido a su contenido en s alil L cisteína (SAC) y propilcisteína y reducir la peroxidación lipídica a través de los sulfóxidos de cisteína

(Aslani et al., 2016). Los antioxidantes que se encuentran en los alimentos y el cuerpo, incluso en cantidades insignificantes, pueden proteger al cuerpo contra los radicales libres inducidos por el estrés oxidativo (Ashraf et al., 2015).

El ajo, una hierba útil, que juega un papel importante en la dieta y la medicina, a lo largo de la historia. El ajo se usa en diferentes formas, incluido el ajo crudo, las tabletas de ajo en polvo o el aceite extraído (Bayan et al., 2014). Algunas medicinas clásicas, como la medicina china e india, creen que el ajo se puede consumir para ayudar a la digestión y la respiración, y para tratar numerosas enfermedades como la lepra y las enfermedades parasitarias (Sun et al., 2016).

En la actualidad, ha atraído la atención particular de la medicina moderna debido a los efectos generalizados del ajo en el mantenimiento de una buena salud. Se informa que los efectos deseables del ajo se atribuyen principalmente a la reducción del riesgo de cáncer, factores de riesgo de ECV, efecto antimicrobiano y efecto antioxidante (Colín-González et al., 2012; Aviello et al., 2009). Los mecanismos protectores de los efectos beneficiosos del ajo en las enfermedades cardiovasculares pueden obtenerse reprimiendo la oxidación de LDL, aumentando los niveles de HDL, así como disminuyendo los TG y el colesterol total (Iciek et al., 2010).

El ajo tiene muchos efectos cardiovasculares útiles, como la disminución de TG y colesterol total y TG, disminución de la presión arterial y ganancia de actividad fibrinolítica (Lin et al., 2002). Muchos estudios han informado que diferentes extractos de ajo pueden afectar por sí solos el nivel de TG, colesterol total y LDL en humanos y animales (Sun et al., 2018).

El ajo puede reducir el nivel de LDL-C por disminución del colesterol hepático 7α-hidroxilasa, HMG-CoA reductasa, actividades de la ruta de las pentosas-fosfato, aumento de la excreción de ácidos biliares, proteína microsomal de transferencia de triglicéridos, actividad de la proteína de transferencia de ésteres de colesterilo, excreción de ácidos biliares, y prevenir la síntesis de ácidos grasos hepáticos, que fue realizada por la alicina y/u otras partes del ajo (Sun et al., 2018; Qureshi et al., 1983; Gebhardt et al., 1993).

Otro suplemento nutricional que se cree que juega un papel vital en la prevención de enfermedades cardiovasculares y el estrés oxidativo es el limón. El limón cítrico es una de las variedades de frutas más populares en todo el mundo. Estudios previos han demostrado que la ericositrina y la hesperidina presente en el jugo de limón pueden ayudar a reducir el estrés oxidativo debido a sus propiedades antioxidantes (Aslani et al., 2015; van Doorn et al., 2006; Minato et al., 2003).

Por otro lado, las personas con hiperlipidemia tienen una mayor necesidad de antioxidantes, y agregar algunos suplementos de antioxidantes a su dieta o medicación puede reducir su hiperlipidemia. La vitamina C en los compuestos vegetales como antioxidante reduce la peroxidación de grasas y el daño oxidativo de los vasos sanguíneos. La vitamina C y el uso de dietas ricas en estas vitaminas antioxidantes mantienen una buena salud y reducen el riesgo de enfermedades cardíacas (Byers et al., 1992). Hay dos mecanismos principales que causan los cambios en los niveles de HDL y LDL. 1: Al ejercer un efecto antioxidante que reduce la oxidación de las LDL y aumenta su reconocimiento por parte de sus receptores. 2: Al aplicar un efecto competitivo) debido a la similitud estructural (con la glucosa en el proceso de glicación, HDL y LDL aumentan el catabolismo de LDL y disminuyen la excreción de HDL (Khan et al., 2002). Por lo tanto, los jugos de limón se confirman como una protección contra el hipercolesterolemia además puede disminuir el colesterol total, los TG y los niveles de LDL y aumentar el HDL (Oboh et al., 2015; Trovato et al., 1996).

Los medicamentos, la educación para la salud y la dieta son las formas más comunes de manejar y controlar la obesidad. Así como la implementación de un estilo nutricional específico junto con la práctica de ejercicio físico, son los métodos más utilizados tradicionalmente para tratar la obesidad. El ejercicio físico, representa una estrategia eficaz para prevenir y/o tratar la obesidad y las enfermedades cardiovasculares.

El uso de ratas Wistar es común para el desarrollo de estudios extremadamente rigurosos en un ambiente de laboratorio. Se trasladan implicaciones fundamentales a los seres humanos derivadas de los hallazgos obtenidos con ellos. Es por ello que suelen utilizarse para numerosos tipos de estudios con diferentes finalidades: biomédicas, toxicológicas, nutricionales, de ejercicio físico, etc.

El propósito del presente estudio fue evaluar los efectos de algunos extractos herbales como Berberis vulgaris L, cornus mas, Ajo y Limón en combinación con ejercicio aeróbico y/o de fuerza sobre el perfil lipídico, parámetros metabólicos y enzimas hepáticas de obesos. ratas macho.

Teniendo en cuenta este objetivo, se llevó a cabo un ensayo clínico de 6 semanas basado en una muestra compuesta por 169 ratas Wistar macho y dividida en tres estudios y 22 grupos.

En el primer estudio, las ratas recibieron un extracto de Berberis vulgaris L en combinación con ejercicio aeróbico y de resistencia, que los animales dividieron en siete grupos:

1) control sano (n = 8); 2) dieta basada en alimentos grasos hipercalóricos (n = 8); 3) ejercicio aeróbico (AE, n = 8); 4) ejercicio de fuerza (RE, n = 8); 5) ingesta de extracto de black berberis vulgaris L (n = 8); 6) ingesta de berberis combinada con ejercicio aeróbico (BAE, n = 8); y 7) ingesta de berberis combinada con ejercicio de fuerza (BRE, n = 8).

En el segundo estudio, las ratas recibieron un extracto de cornus mas en combinación con ejercicio aeróbico y de resistencia, que los animales dividieron en siete grupos:

1) Control sano (n = 7); 2) dieta basada en alimentos grasos hipercalóricos (n = 7); 3) ejercicio aeróbico (AE, n = 7); 4) ejercicio de fuerza (RE, n = 7); 5) ingesta de extracto de cornus mas (C, n = 7); 6) cornus mas combinado con ejercicio aeróbico (CAE, n = 7); y 7) cornus mas combinado con ejercicio de fuerza (CRE, n = 7).

En el tercer estudio, las ratas recibieron limón y ajo en combinación con ejercicio aeróbico, que los animales dividieron en ocho grupos:

1) control después de ningún tratamiento (n = 8); 2) dieta basada en alimentos grasos hipercalóricos (n = 8); 3) ejercicio aeróbico (AE, n = 8); 4) consumo de ajo (G, n = 8); 5) ejercicio aeróbico con ingesta de ajo (AEG, n = 8); 6) ingesta de limón (L, n = 8); 7) ajo y limón (GL, n = 8); 8) ajo, limón y ejercicio aeróbico (GLAE, n = 8).

Para el primer y segundo estudio, a todas las ratas (excepto los controles) se les indujo hígado graso mediante seis semanas de una dieta hipercalórica antes de la intervención.

Después de seis semanas de intervención, se tomaron muestras de sangre para obtener colesterol, triglicéridos, colesterol de lipoproteínas de alta densidad (HDL), colesterol de lipoproteínas de baja densidad (LDL), glucosa de proteína C - reactiva (PCR), alanina aminotransferasa (ALT), aspartato aminotransferasa (AST), fosfatasa alcalina (ALP), creatinina (Cr), urea y ácido úrico (UA).

En primer lugar, se verificó el supuesto de normalidad y homogeneidad de las variables dependientes mediante las pruebas de Kolmogorov-Smirnov y Levene, respectivamente. Después de eso, se realizó un ANOVA de una vía o las pruebas de Kruskal-Wallis para las variables que no se distribuyen normalmente, con comparaciones por pares post-hoc, para evaluar las diferencias entre los grupos. Para todos los análisis realizados se aceptó un nivel de confianza del 95% (significación de $p \leq 0,05$).

Después de analizar los datos y comparar el grupo hiper con todos los grupos experimentales, en el estudio I:

El grupo BAE obtuvo los mejores resultados en las variables colesterol (-57,4%), TG (-43,2%), LDL (-67,3%), AST (-77,2%), ALT (-44,5%), PCR (-30,8%). Asimismo, en las variables Glucosa (-36%), HDL (+45%), Cr (-54,1%) y urea (-38,2%) los mejores resultados se obtuvieron en el grupo BRE.

En el estudio II:

El grupo AEC obtuvo los mejores resultados en las variables colesterol (-43,4%), Glucosa (-45%), TG (-48,1%), LDL (-64,7%), y los mejores resultados para HDL (+34,9%), AST

(-60,5 %), ALT (-47,5 %), PCR (-33,2 %), Cr (-60,4 %) y urea (-29,8 %) en el grupo REC.

En el estudio III:

El grupo GLAR obtuvo los mejores resultados en todas las variables colesterol (-45%), Glucosa (-44,3%), TG (-76,2%), HDL (+24%), AST (-46,3%), ALT (-44,7%), PCR (-29,5 %), Cr (-51,3 %) y urea (-28,3 %) y U.A (-51,3) se obtuvieron en el grupo GLAR.

El presente estudio revela que el ejercicio regular (aeróbico y/o de resistencia) y el uso de hierbas medicinales (berberis vulgaris L, cornus mas, limón y ajo) podría ser un método alternativo adecuado para disminuir el perfil lipídico y las enzimas hepáticas.

Finalmente, la hipótesis se confirma en todos los parámetros después de seis semanas de entrenamiento aeróbico y/o de resistencia y el uso de hierbas medicinales (berberis vulgaris L, cornus mas, limón y ajo) puede reducir el perfil de lípidos en sangre, los parámetros metabólicos y las enzimas hepáticas en ratas. con obesidad inducida por la dieta.

De manera amplia, se puede señalar que el entrenamiento aeróbico y/o de resistencia en combinación con alguna medicina herbal como berberis Vulgaris L, cornus mas, limón y ajo es, un método eficaz para mejorar el perfil lipídico, el síndrome metabólico y las enzimas hepáticas en ratas con obesidad.

Por otra parte, aunque las variadas formas de intervención por sí solas, son efectivas para mejorar el perfil lipídico, las enzimas hepáticas y los parámetros metabólicos, se concluye que el entrenamiento aeróbico y/o de resistencia en combinación con el uso de fitoterapia (berberis vulgaris L, cornus mas, lemon y ajo) ha proporcionado beneficios superiores en estos parámetros.

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5-HT2C	Approved elective agonist of the serotonin [5- Hydroxytryptamine
ACC	Acetyl-coa carboxylase
AE	Aerobic exercise
AHA	American Heart Association
Allium sativum	Garlic
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMPK	Active protein kinase pathway
ANOVA	Analysis of Variance
ASCVD	Atherosclerotic cardiovascular disease
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
B	Ingestion of black Berberis vulgaris L extract
BAE	Ingestion of Black Berberis in combination with aerobic exercise
BMI	Body mass index
BPD	Bilippancreatic Diversion
BRE	Ingestion of Black Berberis in combination with resistance exercise
BT	Behavioral therapy
BUN	blood urea nitrogen
C	Cornus mas extract intake
CAD	Coronary artery disease

CAE	Cornus mas extract intake in combination with aerobic exercise
CAT	Catalase
CCL4	Carbon tetrachloride
CD36	cluster of differentiation 36
CHD	Coronary heart disease
CO	Cardiac output
Control	Following a normocaloric diet and no treatment
COPD	Chronic obstructive pulmonary disease
Cornelian cherry	Cornus mas
CPT -1	Carnitine palmitoyl transferase 1
Cr	Creatinine
CRD	Cardiorespiratory disease
CRE	Cornus mas extract intake in combination with resistance exercise
CRF	Cardiorespiratory fitness
CRP	C-reactive protein
DM	Diabetes mellitus
DPP 4	Dipeptidyl peptidase 4
EGIR	European Group for the study of Insulin Resistance
ERV	Expiratory reserve volume
FDA	US food and drug administration
FeO2	Fraction of expiration oxygen
FEV1	Forced expiratory volume in 1 second

FFAs	Free fatty acids
FiO2	Fraction of inspiration oxygen
FRC	Functional residual capacity
FVC	Forced vital capacity
G	Garlic extract intake
GAE	Garlic extract intake in combination with aerobic exercise
GDP	Gross domestic product
GGT	Glutamyl transferase
GIP	Gastric inhibitory polypeptide
GL	Intake of garlic and lemon juice
GLAE	Intake of garlic and lemon juice in combination with aerobic exercise
GLP1	Glucagon-like peptide-1
GLUT1	Transport activity of glucose transporter 1
GLUT4	Glucotransportadores de tipo 4
GPx	Glutathione peroxidase
HbA1c	Hemoglobin A1c
HDL	High-density lipoprotein cholesterol
HMG-CoA	β-Hydroxy β-methylglutaryl
HPDs	High protein diets
HR	Heart rate
Hypercaloric	Following a fatty-food-based diet and no treatment
IHD	Ischemic heart disease

IL	Interleukin
IMTGs	Intramyocellular triacylglycerols
IMTGs	Intramyocellular triacylglycerols
InsS	Insulin sensitivity
L	Lemon juice intake
LCHDs	Low carbohydrate diets
LDL	low-density lipoprotein cholesterol
LFP	Lemon fermented products
LMICs	Low- and middle-income countries
LPL	Lipoprotein lipase
Malonyl-CoA	Malonyl-coenzyme A decarboxylation
MCP	Monocyte chemoattractant protein
MET	Metabolic equivalent
MetS	Metabolic syndrome
MI	Myocardial infarction
NADPH	Nicotinamide adenine dinucleotide phosphate
NAFLD	Non-alcoholic fatty liver
NASH	Nonalcoholic steatohepatitis
NHANES	National Health and Nutrition Examination Survey
NPN	Non-protein nitrogenous
OHS	Obesity hypoventilation syndrome
OPC1	Obstructive sleep apnea syndrome

OSA	Oxidized LDL receptor 1
oxLDLs	Cerebrovascular disease, peripheral artery disease
PAD	Peripheral arterial disease
PAD	Paraoxonase-1
PON-1	Peroxisome proliferator-activated receptor
PPAR	Resistance exercise
RE	Reactive oxygen species
ROS	Reduction in remaining volume
RV	S-allyl-L-cysteine
SAC	Stearoyl-Coa desaturase-1
SCD-1	Standard Deviation
SD	Standar Error
SE	Superoxide dismutase
SOD	Stroke volume
SV	Type 2 diabetes mellitus
T2DM	Triglycerides
TG	Ransient ischemic attacks
TIAs	Total lung capacity
TLC	Tumor necrosis factor
TNF	uric acid
UA	Very-low-density lipoprotein
VLDL	Maximum heart rate

Vo2max	Waist circumference
WC	World Health Organization
WHO	obstructive sleep apnea syndrome

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Chapter1.

INTRODUCTION

Obesity is one of the most serious problems, not only at the health level but also at the societal level in modern times (Hernáez et al., 2019; Mazidi& Speakman et al., 2018). In the last three decades, overweight and obesity have been shown to increase by almost 7.5% in the United States and more than 200% in Spain (Soriano-Maldonado et al., 2020; Aslani et al., 2016). Environmental factors such as a sedentary lifestyle and an unbalanced diet, as well as the interaction of various genetic and behavioral elements, could be the cause of obesity (Payab, M et al., 2019). Excessive adipose tissue increases obesity, overweight, and CVD risk factors, as well as nonalcoholic fatty liver disease (NAFLD) (Atkins et al., 2014). In patients with obesity, cardiovascular risk factors are greatly increased in both men and women (Soriano-Maldonado et al., 2016), partially justifying the higher incidence of morbidity, metabolic syndrome, CVD, and mortality. Obesity is one of the most common causes of CVD (Soriano-Maldonado et al., 2020).

The most common methods to control obesity are medication, health education, and dietary changes (Jiménez et al., 2020; Li et al., 2018). In addition, physical activity and implementation of a specific dietary style have traditionally been the most commonly used methods to treat obesity and CVD. Regular exercise is considered a factor in improving quality of life, improving body composition, and preventing weight gain, as well as preventing and treating cardiovascular disease and metabolic disorders such as diabetes and hypercholesterolemia (Huck CJ et al., 2015).

Physical activity is an important part of the overall approach to cardiovascular disease and obesity, as it is an essential component of a healthy lifestyle and has beneficial effects on people of all ages (Thivel et al., 2018 et al., 2004). Physical activity has many population benefits, including energy expenditure, reduction in hypertension, obesity, blood cholesterol, metabolic syndrome, and other associated chronic and metabolic diseases. (Morelli et al., 2020).

After the Industrial Revolution in the 19th century, the invention of labour-saving equipment has caused to a continuous decline in physical activity. In the primitive 1960s most of the jobs in the US needed at least moderate-intensity physical activity whiles now less than 20% request this level of energy expenditure (Church et al., 2011).

However, the lifestyle required by current societies limits the time to practice exercise or access to facilities where it can be done, while developed societies are genetically obese, so the failure rate of nutritional plans is extremely high stop. On the other side, currently, a cleaner, healthier, and more natural life is becoming more attractive to the people of the world day by day (Brook et al., 2017, Newby et al., 2015, Tainio et al., 2021, Johnsen et al., 2013). Living in the embrace of nature and using natural and organic materials and achieving greater health are being welcomed every day more than ever before. While many chemical medicines are not able to cure diseases, many natural, simple, and traditional medicines and methods work and have fewer side effects (Vaezi et al., 2021). Botanists recommend herbal medicine to treat all ailments. Herbal medicines are milder than chemical medicines and have a slower action. They also have milder side effects (Rashrash et al., 2017; Rejhan et al.,1998).

Over the years, many strategies, such as drug treatments, have been used to lose weight and control obesity. Nevertheless, several anti-obesity drugs have serious adverse effects, such as anxiety, depression, and increased CVD risk. Therefore, some medicinal herbs could be used as an alternative strategy to manage obesity with less toxic side effects than chemical medicine (Haselgrübler et al., 2019; Kang& Park, 2012).

In this study, we have utilized some herbs with antioxidant properties, including berberis vulgaris L; a shrub of the genus berberis, which is cultivated in the region of South Khorasan in Iran and is one of the few plants whose root, peel, stem, leaves, flower, and fruits are used for various nutritive and medicinal purposes (Taheri et al., 2012), Cornus mas; which belongs to the genus Cornaceae. Its fruits are rich in anthocyanins such as cyanidin, peonidin, pelargonidin, and petunidin, and contain bioflavonoids, vitamin C, and ursolic acid (Lietava et al., 2019), garlic and lemon; garlic supplementation has an important positive effect on hypercholesterolemia (Banerjee et al., 2002; Ried et al., 2008). Garlic (Allium sativum) and lemon have strong antioxidant properties and can therefore reduce oxidative stress as its content in polyphenols (Aslani et al., 2015)

By cause of all these facts, the question arises whether the specific combination of different natural supplementation alone and altogether with aerobic or resistance exercise may play a role in parameters associated with CVD. Currently, there are no studies that have combined the aerobic and resistance exercise with the intake of these herbs (berberis Vulgaris L, Curnos mas, garlic, and lemon) on lipid profile and fatty liver enzymes. So, this thesis is the first to elucidate this unknown.

Wistar rats are commonly employed for the development of extremely rigorous studies in a laboratory environment (Sengupta et al., 2013). From the findings obtained with them, fundamental implications are transferred to human beings (Szpirer et al., 2020). This is why they are usually used for numerous types of studies with different purposes: biomedical, toxicological, nutritional, physical exercise, etc. (Aitman et al., 2016).

Thus, the present study analyzes the effects of the combination of aerobic and resistance exercise in combination with herbal treatment (berberis Vulgaris L, Curnos mas, garlic, and lemon) extracts to improve lipid profile parameters and fatty liver enzymes of rats fed a high cholesterol diet.

CHAPTER2.

THEORETICAL FRAMEWORK

Next, the theoretical framework will be presented, dealing with all the aspects related to this study, in such a way that it allows knowing the basic concepts necessary for the understanding of the development of this project.

2.1. Lipid profile.

According to the World Health Organization (WHO) CVD are great health problem which provides close to 31% global death in 2017(World Health Organization., 2019). It is thought that lipids have a vital role in growing CVD, cholesterol, as well as low-density lipoprotein (LDL)- and high-density lipoprotein HDL-cholesterol and total plasma triglycerides (TG) are shown as predictors of cardiovascular events (Wang et al., 2018, Fernandez et al., 2013).

Overweight and obesity is accomplice with elevated levels of cholesterol, triglycerides, LDL, and low concentrations of HDL (Jiménez et al., 2020). The idiom 'lipid profile' defines the change of differing levels of lipids in the blood, the most reported one's being TG, LDL and HDL cholesterol (Mann et al., 2014). TG in plasma is obtained from fate eaten in foods or other energy fount. Increase in TG levels has a strong relationship with CVD (Luz et al., 2008). Also, Very-low-density lipoprotein (VLDL) cholesterol has a positive relationship with TG and to be independently connected with cardiovascular risk; even in individuals who shows normal LDL cholesterol levels (Ren et al., 2010). Elevated levels of LDL demonstrate excess blood lipids which are related with increase the risk of cardiovascular complications. HDL carries lipids back to the liver for disposal and recycling; as a result, elevated levels of HDL show of a healthy cardiovascular system (Carroll et al., 2012; Mann et al., 2014).

The lipid profile is specified as the communication between TG, blood concentrations of total cholesterol (TC), HDL and LDL (Escalante et al., 2012). Lipid profile must be measured as one of the most important parts of global risk evaluation, and the frequency checkup is specified by sex, age, and some of the risk factors CVD (Rick et al., 2020; Wang et al., 2018). For its measure, it is recommended to ensure the most precise lipid assessment, specifically triglycerides. Moreover, LDL cholesterol can be calculated directly. Friedewald equation (LDL cholesterol = total cholesterol − HDL cholesterol − triglycerides/5) is the standard method used to derive LDL cholesterol from other components of the lipid panel. This equation should be used with appropriate caution: fasting state samples should be used; it becomes less accurate if triglycerides >200 mg/dL; it becomes invalid with triglycerides >400 mg/dL; LDL cholesterol can be underestimated at levels <70 mg/dL (Rick et al., 2020; Dawson et al., 2015).

LDL is the prevailing cholesterol-transporting lipoprotein and is propounded to be the main atherogenic lipoprotein. On the other hand, other lipoproteins such as HDL-C or very-low-density lipoprotein have shown to play a vital role in atherogenesis. Last studies suggest that isolated low HDL-C in people with normal TG and LDL-C at levels is tantamount to increased LDL-C as a coronary risk factor (Orozco et al., 2017; Cullen et al., 1998). Furthermore, low HDL-C levels and the ratio of TC to HDL-C levels have been presented in the novel CVD risk scores (Hippisley et al., 2007; Orozco et al., 2017).

As well, changes in lipid profile levels have shown directly and a close relationship between TG, TC, HDL, LDL levels and diabetes mellitus (DM) risk factors (Cai et al., 2021). There are some probable mechanisms by which plasma lipids influence DM, such as: People with dyslipidemia are specified by insulin resistance and a chronic inflammation status, which can contribute to insulin resistance (Sears et al., 2015). Moreover, there is a positive association between insulin resistance and peripheral neuropathy (Han et al., 2015; Cai et al., 2021). The other mechanism may be the effect of oxidative stress on DM. Stress oxidative is the most important risk factors of DM.

Neurons express scavenger receptors for oxidized LDLs, such as oxidized LDL receptor 1(Vincent et al., 2011). Increased LDL has elevated susceptibility to oxidation and oxidized LDLs (oxLDLs), and these modified LDLs can interconnect extracellular receptors, triggering signaling cascades that activate oxidative stress (Han et al., 2015). OxLDL-encouraged oxidative stress has been demonstrated to mediate nerve injury in animal studies with dyslipidemia-induced neuropathy. Furthermore, oxLDL is preoccupied in neuron injury through nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activation, which leads to elevated superoxide production (Vincent et al., 2009). Besides, free fatty acids (FFAs) interconnect to excess intramitochondrial pyruvate, leading to the manufacture of reactive oxygen species. FFAs have been demonstrated to close cause damage to Schwann cells in vitro, and they can also cause proinflammatory factors to be liberated from adiposities and macrophages (Cai et al., 2021).

2.1.1. Hyperlipidemia.

Hyperlipidemia is a condition that incorporates diverse genetic and obtained disorders that characterize increased lipid levels within the human body. Hyperlipidemia is extremely common globally (Hill et al., 2021). As another option, a more objective description defines hyperlipidemia as LDL, total cholesterol, triglyceride levels, or lipoprotein levels greater than the 90th percentile in comparison to the general population, or an HDL level less than the 10th percentile when compared to the general population. Lipids typically contain cholesterol levels, lipoproteins, chylomicrons, VLDL, LDL, apolipoproteins, and HDL (Fredrickson et al., 1971; Ballantyne et al., 2000).

It has been consistently reported by several studies that increased levels of LDL cholesterol growth atherosclerotic plaques and subsequent vascular disease (Hill et al., 2021). In stark contrast, HDL levels cooperation’s in controlling cholesterol levels to prevent dis-balances that would elevate the risk of atherosclerotic vascular disease (Elisaf et al., 2011). Each patient’s LDL cholesterol aim is contingent on their overall CV risk, and medical therapy should be independently tailored to the patient (Genest et al., 2009). Managing risk factors, such as hyperlipidemia, to abate the risk for atherosclerotic cardiovascular disease is referred to as “primary prevention”. The ground for decreasing LDL cholesterol derives from widespread epidemiologic data that manifests a positive, continuous connection between LDL cholesterol levels, cardiovascular events, and patient mortality. Hyperlipidemia classifieds into two broad classifications: primary (familial) or secondary (acquired) hyperlipidemia. Primary hyperlipidemia is a genetic disorder which a patient may inherit through birth, but secondary hyperlipidemia typically arises from an alternate underlying etiology, including medications (amiodarone, glucocorticoids), an unhealthy diet, hypothyroidism, uncontrolled diabetes, and/or a poor lifestyle regimen (Soska et al., 2007).

Several factors chip into the advance of atherosclerosis, such as hyperlipidemia, hypertension, inflammatory and immunologic factors, endothelial damage, plaque erosion or rupture and smoking.

Atherosclerosis often rests asymptomatic than plaque stenos is achieves70 to 80% of the vessel’s diameter. Atherosclerosis emanates after underlying endothelial damage happens, which seems to stem from the damage of nitric oxide within the endothelium (Catapano et al., 2016). This process causes to elevated inflammation immediately around the site of dysfunction, authorization the agglomeration of lipids within the innermost layer of the endothelial wall. The lipids are then engulfed by macrophages, leading to the lodgment of “foam cells.” This cholesterol build-up within the “foam cells” leads to subsequent mitochondrial dysfunction, apoptosis, and necrosis of the underlying tissues. Smooth muscle cells encapsulate the pack of “foam cells” or debris, which produces a fibrotic plaque that inhibits the underlying lipids (debris) from being destroyed (Hill et al., 2021).

There are various systemic diseases that stimulate an inflammatory sub-layer with clinical or sub-clinical values, can cause dyslipidemia and atherosclerotic problems including: Psoriasis, Crohn disease, inflammatory bowel disease, Chronic obstructive pulmonary disease, Depression, Chronic pain, Pediatric alopecia areata, chronic kidney disease (Vodnala et al., 2012).

2.1.2. Obesity.

Obesity is a complex, multifactorial, along with overweight, and is an increasing global public health issue which is largely preventable disease (Piché et al., 2020; De Lorenzo et al., 2020; Stevens et al., 2012). Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health. Patients with obesity are at significant risk for expanding a range of comorbid conditions, such as cardiovascular disease, metabolic syndrome, gastrointestinal disorders, type 2 diabetes (T2DM), joint and muscular disorders, respiratory problems, and psychological issues, which may seriously, affect their lives as well as developing mortality risks (De Lorenzo et al., 2020).

While growth trends in overall obesity in most developed countries seem to have lined off, morbid obesity in many of these countries continues to escalade, which includes among children. In addition, obesity outbreak in developing countries continues to trend claiming (González et al., 2017; Blüher et al., 2019). It is thought that if these trends continue, by 2030 an approximated more than 38% of the world’s adult population will be overweight and another 20% will be obese (Kelly et al., 2008; Alberti et al., 2009). Obesity-connected conditions are multiple; but even modest weight depletion can help patients to decrease their risk for CVD, diabetes, and hypertension, among much other comorbidity (Fruh S et al., 2017). It is reported that a small and simple reduction in weight may help patient outcomes and can act as a catalyst for major change (Fruh S et al., 2017; Cefalu et al., 2015).

The World Health Organization (WHO) describes obesity and overweight as unusual or extreme fat accumulation that provides a risk to health (WHO., 2016). Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person’s weight in kilograms divided by the square of his height in meters (kg/m2) (WHO, 2019; Haiyan Meng et al., 2020).

For adults, WHO describes overweight, and obesity as follows: overweight is a BMI upper than or equal to 25; and obesity is a BMI upper than or equal to 30. BMI provides the most useful population-level measure of overweight and obesity, as it is the same for both sexes and for all ages of adults. However, it should be considered a rough guide because it may not correspond to the same degree of fatness in different individuals (Hruby et al., 2015; Alberti et al., 2005).

There is a potent association between abdominal obesity and overall obesity; even so, some patients may be classified as having overall obesity but not abdominal obesity (Piché et al., 2018). The converse may happen also with abdominal obesity in the lack of overall obesity established on the BMI description of obesity (Jensen et al., 2014; Piché et al., 2018). The existence of cardiometabolic disease and CVD in those with “normal-weight obesity” result in misclassification and underdiagnosis of CVD risk in clinical practice, particularly among patients who have surplus fat but not obesity how classified by BMI (Bray et al., 2018). Consequently, great waist circumference (WC) even in individuals with normal weight can show higher CVD risk because WC is an index of abdominal body fat, which is linked to cardiometabolic disease and CVD (Tatsumi et al., 2017). WC as a scale of abdominal obesity supplies a showing of body composition and adds critical information among with BMI (Jensen et al., 2014; Piché et al., 2018; Bray et al., 2018; Tatsumi et al., 2017).

Primary obesity must be considered a social disease, with overcoming of stigma, prejudice, and generalization. The deployment of primary obesity is pandemic, like an infectious disease (Hofmann et al., 2016; Demongeot et al., 2016). The metabolic and cardiovascular sides of obesity are intricately connected. The persistent inflammatory state related to obesity is fixed as a great contributing factor to insulin resistance, which itself is one of the essential pathophysiology of T2DM (Powell et al., 2021; Booth et al., 2015).

The advancement to obesity makes with it a phenotypic change in adipose tissue and the increasement of chronic low-grade inflammation (Martin et al., 2015). This is characterized by raised values of circulating free-fatty acids, soluble pro-inflammatory factors (including interleukin [IL] 1β, IL-6, tumor necrosis factor [TNF] α, and monocyte chemoattractant protein [MCP] 1) and the infiltration and activation of protect cells into sites of inflammation (Franks et al., 2016). Obesity is also usually associated with a characteristic dyslipidemia profile (atherogenic dyslipidemia) that involves small, dense LDL particles and TG levels, and reduced levels of HDL particles, and increased (Franks et al., 2016; Romero et al., 2008). This chronic, low-grade inflammation and dyslipidemia profile causes to vascular dysfunction, which includes impaired fibrinolysis and atherosclerosis formation and rase the risk for CVD, as well as stroke and venous thromboembolism (Jastreboff et al., 2019).

2.1.3. Dyslipidemia.

Cardiovascular disease has some changeable and unchangeable risk factors such as certain disease and disorders including dyslipidemia in most of the population (Enani et al., 2020). Dyslipidemia is the disbalance of lipids like cholesterol, LDL, HDL, and TG. This condition can cause from genetic, diet, tobacco exposure (Pappan et al., 2021; Shattat et al., 2015).

Lipids, such as cholesterol or triglycerides, are attracted from the intestines and are transported throughout the body by lipoproteins for energy, bile acid formation or steroid production; Main participants to these pathways are LDL, HDL, cholesterol, and TG. A disbalance of each factor, either from organic or nonorganic reasons, can cause dyslipidemia (Mozaffarian et al., 2016; Rader et al., 1994).

According to Frederickson phenotype (Fredrickson et al., 1971), there are five different classification of dyslipidemia such as:

Phenotype I is an abnormally of chylomicrons and will outcome in triglycerides upper than ninety-nine percentiles.

Phenotype IIa contains mostly of LDL cholesterol abnormally and will have total cholesterol concentration upper than ninety percentile and possible apolipoprotein B greater than 90 percentiles.

Phenotype IIb contains of abnormally in LDL VLDL. These types will consequence in total TG and/or cholesterol upper than ninety percentile and apolipoprotein upper than ninety percentiles.

Phenotype III is an abnormally in VLDL vestiges and chylomicrons, which cause in increased TG and total cholesterol upper than ninety percentiles.

Phenotype IV is largely when VLDL is unusual and will outcome in total cholesterol upper than ninety percentiles. This type can also be available with TG upper than ninety percentile and low HDL.

And the last one is Phenotype V, whis is when chylomicrons and VLDL are unusual, and TGs are upper than ninety-nine percentiles (Fredrickson et al., 1971; Quispe et al., 2019Rhee et al., 2019; Hegele et al., 2009).

AS mentioned above, several factors chip into the development of dyslipidemia, like sex, increased body mass index (BMI), inactive lifestyle, dietary habits, smoking, genetics, and short duration of sleep (Opoku et al., 2019; Enani et al., 2020; Pappan et al., 2021).

The outbreak of dyslipidemia grows up with age. The initial assessment gadget for dyslipidemia is a fasting lipid panel which embraces of LDL, HDL, TG, and total cholesterol (Hendrani et al., 2016). There are several studies about what age dyslipidemia test must start. It is recommended that all individual age 20 to 78 years get fasting lipid panels every five years if no atherosclerotic disease is present (Pappan et al., 2021; Kopin et al., 2017).

Primary and general handling for dyslipidemia includes lifestyle correction. This approach should involve a healthy diet with an emphasis on the use of fruits, vegetables, and whole grains within a suitable calorie need. As well, it is recommended that adults should have an active lifestyle which participated in moderate to vigorous aerobic physical activity 3 to 4 times a week for at least 40 minutes (Bolli et al., 2014). Besides, there are several studies which recommends or guidelines for the treatment of dyslipidemias focus on LDL cholesterol as the initial goal for lipid control. Secondary goals including HDL and/or non-HDL cholesterol are presented but frequently not contained in the overall evaluation of a patient's lipid profile (Mora et al., 2011; Kontushet al., 2006; Bolli et al., 2014).

2.1.4. Metabolic syndrome and type 2 diabetes.

Other major and escalating clinical challenge and public health worldwide is Metabolic syndrome (MetS) which is specified by a constellation of interconnected biochemical, physiological, clinical, and metabolic factors that straightly excess the risk of CVD and type 2 diabetes mellitus (T2DM). Insulin resistance, increased blood pressure, atherogenic dyslipidemia, endothelial dysfunction, genetic susceptibility, visceral adiposity, hypercoagulable state, and chronic stress are the varied factors which represent the syndrome (Wilson et al., 2005; Kaur et al., 2014; Minich et al., 2008).

MetS began as a concept rather than a diagnosis (Jamka et al., 2020; Shaw et al., 2003; Kaur et al., 2014). MetS has its origins in 1920 when Kylindemonstrated the relationship of high blood glucose (hyperglycemia), high blood pressure (hypertension), and gout (Kylin et al., 1923; Kaur et al., 2014). After that Vague in 1947, defined that the visceral obesity was commonly related with the metabolic abnormalities found in CVD and T2DM (Vague et al., 1947). As well, Banting in 1988 characterized “a cluster of risk factors for diabetes and cardiovascular disease” and named it “Syndrome X”. His essential contribution was a description of the meaning of the insulin resistance. Although, the surprisingly lost obesity or visceral obesity from the determination which was later added as a crucial abnormality. Several investigations groups have tried to expand diagnostic criteria for the diagnosis of the MetS (Haffner et al., 1992; Eckel et al., 2005). One of the first attempts was on 1998 by a WHO diabetes group in to provide an explanation of the MetS (Alberti et al., 1998). On the other side, the European Group for the study of Insulin Resistance (EGIR) countered with a correction of the WHO explanation in 1999 (Haiyan Meng et al., 2020; Balkau et al., 1999).

In 2005, the International Diabetes Federation (IDF) suggested another new definition of the MetS (International Diabetes Federation., 2005).

MetS includes diagnostic specifications that vary according to the definition used. Moreover, there is a constellation of related factors that may be impressed by inactive lifestyle and over nutrition. In most of the western countries co-called dietary patterns prevail are unhealthy (Pérez et al., 2017). In close relationship with the increase obesity epidemic, the outbreak of metabolic syndrome is also raising to epidemic ratio, which needs expensive healthcare costs. MetS grows with exceptionally low levels of physical activities and increase energy intake and diet composition (Rey et al., 2014). Cameron in 2005 has reported that there is a great relevance between (genetic background, diet, levels of physical activity, smoking, family history of diabetes, and education) and MetS (Cameron et al., 2005).

Universal outbreak of MetS depends on several causes such as of the population studied, composition (sex, age, race, and ethnicity, region, urban or rural environment and the definition of the syndrome used (Kolovou et al., 2007; Ford et al., 2005; Pérez et al., 2017; Ter et al., 2020). National Health and Nutrition Examination Survey (NHANES) has reported that the prevalence of MetS was 5% among the people with normal weight, 22% among the overweight, and 60% among the obese patients (Park et al., 2003). MetS also further increases with age (10% in individuals aged 20–29, 20% in individuals aged 40–49, and 45% in individuals aged 60–69), and different from 8% to 43% in men and from 7% to 56% in women around the world (Ford et al., 2002; Ponholzer et al., 2008; Cameron et al., 2004). In several studies it has indicated that a weight develop of ≥2.25 kg over a period of 16 years was related with an up to 45% elevated risk of increasing the MetS, and as well, each 11 cm increase in waist circumference (WC) is related with an adjusted 80% enhancement risk of increasing the syndrome within 5 years (Wang et al., 2020; Ponholzer et al., 2008; Wilson et al., 1999; Reilly et al., 2003; Palaniappan et al., 2004; Andreadis et al., 2007; Mulè et al., 2014).

Also, Metabolic syndrome is a concept of interconnected biochemical, physiological, metabolic, and clinical factors which develops the risk of cardiovascular diseases, fatty liver, T2DM and all-cause mortality. It is added up to by insulin resistance, abdominal fat, hypertension and moreover hyperlipidemia (Krishnamoorthy et al., 2020; Kaur et al., 2014). Nowadays, diet and sedentary lifestyle habits have been demonstrated subscribe to advancement of dyslipidemia and cardiorespiratory disease in the worldwide (Enani et al., 2020). However, the most effective preventive proceeds toward further lifestyle-based interposition purposed at normalizing body weight and achieving and maintaining cardiometabolic control, including lipid levels, blood glucose, and blood pressure (Pérez et al., 2017).

Insulin resistance is associated with several factors of MetS and is currently the most important feature and cause of fatty liver, even in the presence of obesity and the absence of type 2 diabetes (Van Baak et al., 2021; Sreenivasa et al.,2006; Pagano et al., 2002). Aerobic exercise with sufficient intensity and duration has a positive effect on improving insulin resistance, changes in depth levels and skeletal muscle receptors. The main mechanism of insulin resistance is the negative regulation of deep insulin receptors and the decrease of insulin signalling caused by the excessive signalling of free fatty acids in the bloodstream (Sreenivasa et al., 2006; Reid et al., 2006). Increases in insulin-1 receptor substrate and GLUT4 transporter protein are essential for glucose uptake in muscle. Exercise increases GLUT4 and skeletal muscle protein (Short et al., 2003), which in turn leads to better glucose uptake and lower insulin resistance. Therefore, aerobic exercise has a positive effect on the treatment and prevention of fatty liver disease. In addition to positively regulating antioxidant defences, aerobic activity can reduce alanine aminotransferase and aspartate aminotransferase by reducing oxidative stress and inflammation (Schwenke et al., 1998). Aerobic exercise can stimulate lipid oxidation and inhibit lipid synthesis in the liver (Perseghin et al., 2007; Lavoie et al., 2006). This process occurs through activation of the active protein kinase pathway. This enzyme is stimulated and activated by increasing the ratio of AMPK to ATP in tissues, which is a consequence of the physiological stimulus of exercise (Lavoie et al., 2006). The researchers said that the main requirement for the activation of the AMPK pathway during exercise is a reduction in the lack of hepatic Stearoyl-Coa desaturase-1(SCD-1) activity. Recent studies have shown that SCD-1 activity in the liver of mice is significantly reduced after exercise (Lavoie et al., 2006).

AMPK is activated during exercise and its activity is maintained in muscle, liver, and adipose tissue after exercise (Ruderman et al., 2003). In the liver, activation of AMPK inhibits lipid synthesis, as evidenced by inactivation of the enzyme acetyl-coa carboxylase (ACC), activation of the enzyme malonyl-coenzyme A decarboxylation (malonyl-CoA), and inhibition of expression of the lipogenic enzymes ACC. Synthetase, and primarily by reducing the amount of malonyl-CoA, which in turn is an allosteric inhibitor of the enzyme carnitine palmitoyl transferase-1 (CPT -1), which controls the transport of long-chain cytosolic fatty acids into mitochondria. Stimulated in the liver (Ruderman et al., 2003; Lavoie et al., 2006). Therefore, aerobic exercise may have a positive effect on the treatment, control, and prevention of fatty liver disease and Non-alcoholic steatohepatitis (NASH). Waist circumference, which indicates the degree of accumulation of visceral fat (Church et al., 2006), And has a significant correlation with serum aminotransferase levels, especially ALT, fat accumulation in the liver and NAFLD and NASH and is also associated with other pathogeneses of the disease such as insulin resistance, hyperlipidaemia, hyperglycaemia, type 2 diabetes, and metabolic syndrome (Chen et al., 2008). In general, visceral adipose tissue is more resistant to insulin. Therefore, it could further stimulate lipolysis and stimulate more free fatty acids in the bloodstream, which in turn contributes to greater accumulation of triglycerides in the liver (Chen et al., 2008). Regular exercise increases daily energy intake, improves, and increases the oxidation of fats in skeletal muscle and hepatocyte mitochondria, promotes the depletion of visceral fat stores, and reduces visceral obesity and its exacerbation with the redistribution of fat stores in the body. Insulin response in adipose tissue; The result is a decrease in the secretion of free fatty acids into the liver, a decrease in fat deposition in the liver, also an increase in fat oxidation in the liver (Spassiani et al., 2008). Data from other studies show that regular exercise reduces the risk of type 2 diabetes or non-insulin-dependent diabetes and increases serum LDL levels; both are significant risk factors for NASH (Sreenivasa et al., 2006).

2.2. Cardiovascular disease.

Cardiovascular diseases are by far the major reason of death in the world. In 2015, 17.9 million people died from CVDs (Roth et al., 2017). Ischemic heart disease (IHD) and stroke were the highest two major reasons of CVD health lost in each region in the world (WHO., 2016). It is thought that if these trends continue, by 2030 an approximated more than 22.2 million people will die annually from CVDs (WHO., 2016; Kelly et al., 2008; Alberti et al., 2009). The societies in low- and middle-income countries (LMICs) now contribute 75% of the CVD deaths, which leads to 7% depletion of gross domestic product (GDP) in these countries (Stewart et al., 2017). The industrialization of the economy with a consequent change from physically difficult to jobs which is sedentary, with the contemporary consumerism and technology-driven culture that is associated with longer work hours, longer commute, and less leisure time, may describe the considerable and fixed raise in the rates of CVD (Benjamin et al., 2018).

According to the estimation of WHO, over 75% of premature CVD is preventable and risk factor amelioration may help decrease the increasing CVD burden on both individuals and healthcare providers (WHO., 2016). Although age is a well-known risk factor for the increase of CVD, autopsy evidence shows that the process of increasing CVD in the future is not unavoidable, therefore risk depletion is pivotal (Perk et al., 2012).

There are 9 modifiable risks elements accounted for the risk of CVD: dyslipidemia, hypertension, diabetes, abdominal obesity, psychosocial factors, smoking, fruits and vegetables consumption, consumption of regular alcohol, and inactive lifestyle (Stewart et al., 2017).

The cardiovascular system includes of the heart and its blood vessels. A wide array of problems may happen in the cardiovascular system, a few of which involve rheumatic heart disease, endocarditis, and transfer system abnormalities. CVD, also well-known even as heart disease, mentions to the 4 entities including: coronary artery disease (CAD) which is also named to as coronary heart disease (CHD), cerebrovascular disease, peripheral artery disease (PAD), and aortic atherosclerosis (Benjamin et al., 2018).

CAD causes from declined myocardial perfusion which results angina due to ischemia and may outcome in heart failure, and/or myocardial infarction (MI). It includes for one-third to one-half of all reasons of CVD (Powell et al., 2021). Cerebrovascular disease is the being related with strokes, also name cerebrovascular accidents, and transient ischemic attacks (TIAs). Peripheral arterial disease (PAD) is arterial disease including the members that can outcome in claudication. Aortic atherosclerosis is the entity related with abdominal and thoracic aneurysms (Olvera et al., 2021; Benjaminet al., 2018). Atherosclerosis is the pathogenic operation in the arteries and the aorta that can potentially motive disease because of declined or nonexistent blood flow from stenosis of the blood vessels (Olvera et al., 2021).

It includes multiple elements dyslipidemia, immunologic phenomena, inflammation, and endothelial dysfunction. These elements are believed to precipitate the emergence of fatty streak, which is the show in the improvement of the atherosclerotic plaque (Powell et al., 2021; Libby et al., 2011); a continuing process that may arise as early as in the childhood (Libby et al., 2011). This process includes intimal thickening with further accumulation of lipid-laden macrophages (foam cells) and extracellular matrix, afterward association and reproduction of smooth muscle cells constituting the formation of the atheroma plaque (Sata et al., 2002). While these lesions carry on with developed, apoptosis of the profound layers may happen, accelerating further macrophage recruitment that may be calcified and change to atherosclerotic plaques (Sata et al., 2002).

2.3. Liver fat.

Non-alcoholic Fatty Liver Disease (NAFLD) or "Fatty Liver" corresponds to the existence of macro vesicular changes without inflammation (steatosis) and lobular inflammation in the absenteeism of significant alcohol utilization (Brunt et al., 1999; Green et al., 2014). It may be included into two subgroups: NAFLD (Non-Alcoholic Fatty Liver) or simply Steatosis and NASH (Non-Alcoholic Steatohepatitis). NAFL is specified as the existence of hepatic steatosis with no evidence of hepatocellular injury in the figure of ballooning of the hepatocytes (Antunes et al., 2021).

Obesity is a known risk element for the enhancement of NAFLD; although, it has been proposed that dietary fat, both amount and composition, can act a leading role in its progress, autonomous of body fatness (Tomic et al., 2018; Antunes et al., 2021). NAFLD is often related to obesity, Metabolic Syndrome, diabetes, and hyperlipidemia. Almost 80% of patients with Metabolic Syndrome have NAFLD (Antunes et al., 2021; Leoni et al., 2018). Insulin resistance is the main metabolic defect causing to NAFLD. Insulin resistance leads to a raised influence of free fatty acids (FFA) into the liver. This occurs due to the defeat of insulin to repress the hormone-sensitive lipase, leading more FFA to be free from the adipose tissue (Sanyal et al., 2018). Also, high insulin values and insulin resistance promote continual synthesis of TG in the liver. These two origins of triglycerides result in a store of lipids in the hepatocytes leading macro vesicular hepatic steatosis (Cleveland et al., 2018; Sanyal et al., 2018). Lipid store in non-adipose tissue is an essential element for the development of insulin resistance, diabetes mellitus and cardiovascular disease (Cleveland et al., 2018).

The most acceptable theories for NAFLD, is the include oxidative stress, specific cytokines, plus lipopolysaccharides (Fracanzani et al., 2017). Free fatty acids and hyperinsulinemia potentiate lipid peroxidation and the liberation of hydroxy-free radicals, directly hurt the hepatocytes by recruiting neuroinflammatory mediators. Chronic liver harm over time will cause to stellate cells active, making a potential for hepatic fibrosis (Yoo et al., 2019).

It is serious to emphasize that most of the patients with NAFLD will be overweight or obese and asymptomatic. Even as NAFLD may have a benign asymptomatic period and since there is an absence of conclusive evidence about effective interventions, there is currently no compelling cause to screen for the condition in an untargeted fashion (Sattar et al., 2014). NAFLD is normally prime suspected when the outcomes of liver function tests, analyzed as part of normal and routine testing (for instance, health checks), are not normal. The usual showed a biochemical pattern in hepatic steatosis due to NAFLD is of elevated levels of transaminases, with alanine aminotransferase (ALT/GPT) levels exceeding those of aspartate aminotransferase (AST/GOT).

γ glutamyltransferase (GGT) may also be elevated across with the NAFLD pattern for transaminases (Sattar et al., 2014; Marchesini et al., 2008). All ALT, AST and GGT have been shown in cross-sectional studies to be modestly related with the presence of fatty liver on ultrasonography and with liver fat content as measured by magnetic exacerbation imaging spectroscopy.

Another common way in which NAFLD is identified is using ultrasound imaging as a liver biopsy is not possible (Sanyal et al., 2018). Also, imaging studies have an essential role in the diagnosis of NAFLD. The mainstay is ultrasonography; it is least invasive, and low-priced. The sensitivity for an ultrasound to detect NAFLD is in the range of 60% to 90% with a specificity around 90%. Unenhanced abdominal computed tomography and magnetic resonance are alternatives but are more costly and are not significantly superior to ultrasonography (Sanyal et al., 2018). Aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase (GGT) and other markers of liver injury are another useful surrogate measure for diagnosis of NAFLD (Sanyal et al., 2018).Where the liver function test outcomes are moderately increased (transaminases 50-150 U/L (1 to 3 times the upper limit of normal) with AST levels less than those of ALT) and the obtainable information (including family history of type 2 diabetes, glucose, body weight, lipids, HbA1c and alcohol intake) indicates NAFLD, patients must also be demanded to return for repeat liver function tests in 2-3 months, having been advised to reduce any alcohol intake or preferably cut off it and to follow an active lifestyle and decrease weight (Utzschneider et al., 2014). Noticeable increases in transaminases (>150 U/L (>3 times the upper limit of normal) with AST levels less than those of ALT) or the additional increase of alkaline phosphatase (ALP) (Utzschneider et al., 2014; McPherson et al., 2014).

2.4. Cardiorespiratory disease.

Another disease which is associated with obesity and cardiovascular disease is cardiorespiratory disease (CRD). Weight increase and elevating BMI are related to reductions in lung volumes, which are shown by a more restrictive ventilatory pattern on spirometry. Many studies have shown that an increase in BMI reduces forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), functional residual capacity (FRC), and the expiratory reserve volume (ERV). In morbid obesity (BMI > 40 kg/m2), there is also a modest reduction in the remaining volume (RV) and total lung capacity (TLC). At such excessive levels of obesity, FRC approaches RV (Sonpeayung et al., 2019; Dixon et al., 2019; McClean et al., 2008; Nakajima et al., 2008; Jones et al., 2006; Ochs-Balcom et al., 2006).

The relation between FEV1 and BMI is complicated; FEV1 drops at a much lower velocity than FVC or ERV. The association between an enhancement in BMI and a decline in FVC is stronger than with FEV1 (Brandao et al., 2021; Liu et al., 2019). Obesity is more often related to a restrictive lung ventilatory flaw than an obstructive one, with a low FVC and a raised FEV1/FVC ratio (>70) (Brandao et al., 2021; Wang et al., 2021; Nakajima et al., 2008; Wannamethee et al., 2005; Leone et al., 2009).

Low FEV1 levels have also been reported in other chronic medical diseases, including dyslipidemia, cerebrovascular diseases, hypertension, and lung cancer. This relationship with chronic medical conditions is not clear (Brandao et al., 2021; Andersen et al., 2016).

Nevertheless, FEV1 is a good predictor of all-cause morbidity and mortality, with elevated CRP levels correlating with declines in FEV1 (Brandao et al., 2021; Lee et al., 2020).

Low grade inflammatory state is associated with abdominal obesity and poor lung function, and it can chip into metabolic disease and ill-health. Increased values of interleukins (ILs) 6 and 8, tumor necrosis factor α (TNF-α), CRP, leptin, and lower values of adiponectin, which assistances in adjusting insulin sensitivity, have all been discovered. Adipose tissue is now considered as an endocrine organ, with liberation of adipocytokines affecting systemic inflammation triggered by hypoxemia persuaded by obesity and related respiratory disorders like obesity hypoventilation syndrome OHS, obstructive sleep apnea syndrome OSA, or chronic obstructive pulmonary disease COPD (Lee et al., 2020; Zammit et al.,2010; Aquino et al., 2018).

Abdominal obesity is strongly related to worsening respiratory symptoms and lung function (Kawabata et al., 2020; Santana et al., 2001; Wannamethee et al., 2005). Various investigations which studied about the WC observed that increased waist-to-hip ratio and abdominal height had high solidarity with ruined lung function (Salome et al., 2010; Leone et al., 2009). Several medical conditions are also related to an enhanced WC. These contain CVD (atherosclerosis, stroke, ischemic heart disease, hypertension, and hyperlipidemia), Mets, and T2DM (Baffi et al., 2016; Lin et al., 2006).

Relationship between overweight and respiratory disease has been reported (Kawabata et al., 2020; Babb et al., 2008). so that Obese people are much more likely to get respiratory disease than people of normal BMI even without lung disease (Kawabata et al., 2020; Baffi et al.,2016; Choe et al., 2018; Thijs et al., 2014).

Many researchers have demonstrated an enhancement in self-reported dyspnea and wheezing at rest and on exertion in obese compared with lean individuals (Rowe et al., 2017; Park et al., 2011; Choe et al., 2018; Thijs et al., 2014; Salome et al., 2010).

On the other hand, Low levels of muscular strength and cardiorespiratory fitness (CRF) have a strong relationship with a higher risk of CVD (Henriksson et al., 2020). Although one of the most important markers of cardiovascular health is Cardiorespiratory fitness and is the fourth-leading risk factor for CVD (Lee et al., 2010; Ross et al., 2016).

There is much research are revealing that people with high CRF have more beneficial biomarkers for glucose and lipid metabolism in comparison with low CRF. High CRF has positive effects on the heart and the circulation, and the resting heart rate (HR) becomes lower (Reimers et al., 2020; Fernström et al., 2018).

It is known that inactive lifestyle has a strong association with CV mortality (Acevedo et al., 2020). Likewise, low CRF is a powerful prognosticator of mortality in all the population: an enhancement of physical activity and exercise capacity of 1 metabolic equivalent (MET) can reduce CVD risk factors (Acevedo et al., 2020; Kokkinos et al., 2010).

2.5. Treatment and management.

Obesity can be defined as the "New World Syndrome". Its outbreak is on ongoing ascent in all age groups of the world, which is growing public health issue worldwide, with an elevated risk for chronic and aggressive conditions including hypertension, respiratory complications, diabetes mellitus, cardiovascular diseases, and cancer (Salari et al., 2021; Narayanaswami et al., 2017; Kahan et al., 2018).

With the effect of obesity on health, quality of life, and social function, its handling interventions are of excellent value (Kahan et al., 2019). There are Different ways approaches are used to control and treat obesity, which are specified based on the severity of obesity, obesity-related complications, sex, age, puberty status, underlying causes, obesity-related complications, psychosocial factors, and patient and family preferences (Cardel et al., 2020; Forgione et al., 2018).

There are some ways for management of obesity such as behavioral and dietary modifications, exercise, drug therapy (is recommended for those whose lifestyle interventions alone are not responsive, especially if there is no possibility of bariatric surgery in these individuals) (Ren et al., 2021; Hussain et al., 2011; Thompson et al., 2007; Bessesen et al., 2018).

Long-term pharmacotherapy of obesity is structured on decrease of energy intake, facilitation of fullness, lowering sensation of hunger, and caloric absorption, along with lifestyle modification intervention (Wharton et al., 2016). In morbid or intense obesity, shock therapies, intragastric balloon insertion, and bariatric surgery can also be practicable (Ren et al., 2021; Wharton et al., 2016).

2.5.1 Behavioral treatment and Lifestyle interventions.

Behavioral treatment should be the first line of intervention for overweight and obese individuals (Butryn et al., 2011). Lifestyle interventions are geared toward improving dietary habits and physical activity. Given their low cost, great convenience, improvement in the quality of life and the minimal risk of complications, lifestyle interventions are often suggested as the first option for obesity management (Lobelo et al., 2018).

After the Industrial Revolution in the 19th century, the invention of labor-saving equipment has caused to a continuous decline in physical activity. In the primitive 1960s most of the jobs in U.S needed at least moderate-intensity physical activity whiles now less than 20% request this level of energy expenditure (Formanet al., 2020; Michael Daly et al., 2020).

The industrialization of the economy with a consequent change from physically difficult to jobs which is sedentary, with the contemporary consumerism and technology-driven culture that is associated with longer work hours, longer commute, and less leisure time for recreational activities, may describe the considerable and fixed raise in the rates of CVD during the last few decades. Specifically, inactive lifestyle, have a high-calorie diet, saturated fats, and sugars are strongly connected with the enhancement of atherosclerosis and other metabolic disturbances such as T2DM, metabolic syndrome and hypertension that are highly current in people with CVD (Benjamin et al., 2018). The foundation in the management of an obese patient is therapeutic lifestyle intervention, which includes restricting calories and simultaneously enhancement of physical activity. This combination has been known to produce weight loss of up to 10% of the initial weight. To reinforce lifestyle changes, behavioral therapy (BT) has been incorporated into the overall intervention that obesity is a result of maladaptive eating patterns, exercise habits, genetic, metabolic, and hormonal factors (Jacob et al., 2012; Snyder et al., 2003). Self-monitoring, stimulus control, slower eating, goal setting, behavioral contracting, nutritional education, increasing physical activity are the most common behavioral packages for weight control (Jacob et al., 2012).

However, the lifestyle required by current societies limits the time to practice exercise or access to facilities where it can be done, while developed societies are genetically obese, so the failure rate of nutritional plans is extremely high stop (Church et al., 2011).

2.5.1a Weight loose.

Notwithstanding the debatable benefits of obesity paradox, the constellation of findings suggested weight loss, by way of cardiorespiratory fitness and regular exercise, plays a key role in the management and prevention of CVD in obese patients (Failure et al., 2016; Horwich et al., 2018). Most of the studies measure obesity by body mass index, measures of body fat and body composition, including waist circumference, waist-hip ratio, skinfold estimates, and bioelectrical impedance analysis (Horwich et al., 2018).

Obesity-reelevated cardiac remodeling and dysfunction is prevented or even be reversed with weight loss (Salari et al., 2021). For example, in a study by Sankaralingam on 2015 a switch from high fat to low-fat diet in obese mice with heart failure drastically lowered the body weight gain, retarded cardiac remodeling, as well as improved cardiac insulin sensitivity and diastolic function (Sankaralingam et al., 2015), denoting a beneficial effect of weight loss. In addition, another retrospective study reported that weight loss between annual physical examinations showed beneficial effects in general populations (Lee et al., 2018).

2.5.1b Dietary therapy.

Weight loss can be reached by a net deficit of kilocalories (units of energy). The estimated energy expenditure per adult kilogram of body weight is approximately 22 kcal (Farnsworth et al., 2003). Reduction of intake to yield a net energy deficit can be achieved in numerous ways (Ruban et al., 2019).

Management of macronutrient composition is one of the most important parts of the net energy fraction. The three main dietary macronutrients are carbohydrate, fat, and protein, which provide 3.75, 9, and 4 kilocalories per gram, respectively (Montaigne et al., 2018). Fat is the least satiating, most readily absorbed and calorie-dense macronutrient, making it the most appealing target for weight loss intervention. Last meta-analysis of low-fat diets reports significant weight loss when compared to baseline intake (-5.41 kg), but not when compared to other dietary interventions, such as high-fat diets (Tobias et al., 2015). Low-carbohydrate diets (LCHDs) output fast results with better initial weight loss compared to low-fat diets (by up to 3.3 kg at 6 months) (Nordmann et al., 2006). Protein is highly satiating and used in high-protein diets (HPDs) with the purpose of increasing inactive overconsumption of other less satiating and more energy-dense macronutrients (Abete et al., 2010). However, recent meta-analyses have concluded that HPDs have either no effect on body weight, or a small effect of questionable benefit (Schwingshackl et al., 2013).

Calorie restriction is another way to getting a net energy fraction is by strength limiting calorie intake. Low and very low-calorie diets (LCD and VLCD) limit energy intake to 800–1600 kcal/day and <800 kcal/day, respectively (Ruban et al., 2019). VLCDs yield superior short-term weight loss when compared to LCDs (-16.1 kg vs -9.7 kg, respectively) (Tsai et al., 2006). Weight loss from VLCD is achieved primarily through a loss of total body fat (7.8% total body fat reduction at 6 months) (Ruban et al., 2019; sai et al., 2006; Saris et al., 2001).

The other way to achieve a better dietary is meal replacement, either full or partial, includes nutritionally replete but low-calorie substitutes for daily meals, offering an easy and comfortable method for calorie intake restriction. Several studies have showed that there are significant weight loss benefits of meal replacement compared to conventional calorie restriction (Davis et al., 2010; Franz et al., 2007; Heymsfield et al., 2003). It is important that dietary weight loss is accompanied by recovery and even remission of obesity-related complications, such as T2DM, CVD and fatty liver. In a direct study by Lean et al. in 2018, it has reported remission of T2DM in 73% of participants who lost >10 kg of weight after 12 months of low-calorie diet replacement (Lean et al., 2018). The probable mechanisms for this contain decrease hepatic gluconeogenesis, net hepatic glycogenolysis and ameliorated hepatic insulin sensitivity and betterments in blood pressure and triglyceride levels (Perry et al., 2018; Lean et al., 2018).

2.5.1c Physical activity.

According to the latest report from American Heart Association (AHA), and WHO, CVD is one of the leading causes of mortality worldwide, accounting for 30% of deaths caused annually (Mazidi& Speakman., 2018; World Health Organization., 2019; Atkins et al., 2014; Aslani et al., 2016 Aslani et al., 2016). It is thought that lipids have a significant role in growing CVD, cholesterol, as well as LDL- and HDL-cholesterol and total plasma triglycerides are shown as predictors of cardiovascular events (Wang et al., 2018; Fernandez et al., 2013). Physical exercise is an important part of the overall approach to treating CVD and obesity because, is an essential part of a healthy lifestyle with useful effects in people in all ages (Thivel et al., 2018; Afzalpour et al.,2004). Physical activity has many benefits for population include energy expenditure, reduction in hypertension, obesity, blood cholesterol, metabolic syndrome, and moreover related chronic and metabolic disease including CVD (Morelli et al., 2020).

Other factors that can explain the beneficial effects of regular physical activity on prevention of CVD in the absence of insulin, exercise activities convenience the glucose entry into the cell through affecting many signalling pathways. Furthermore, it improves the lipid profile and helps to increase the paraoxonase-1 (PON-1) activity. PON-1 interacts with HDL and, in the attendance of calcium, hydrolyses free radicals, prevents LDL oxidation maintains homocysteine structure in the blood, and inhibits haemoglobin glycation (Fatolahi et al., 2017).

Also, physical activity reduces plasma triglycerides and increases HDL-c concentration in relation to total energy expenditure. Triglycerides from adipose tissue are an important fuel source during physical activity. As a result of aerobic exercise, lipolysis increases and, in addition to total body fat mass, reduces the number of triglycerides and increases the amount of HDL-c (Thompson et al.,2001). The increase in lipolysis and access to fatty acids during exercise requires the integrated action of neurological, hormonal, and circulatory events that facilitate the transport of fatty acids from adipose tissue to skeletal muscle mitochondria for oxidation (Mogharnasi et al.,2008).

On the other hand, increased maximal oxygen consumption results from the adaptation of the cardiovascular, muscular, and metabolic systems to exercise. As a result of exercise, there is usually an improvement in the individual's physical condition and anthropometric indices due to a series of post-exercise adaptations. Increase in maximal oxygen consumption after exercise, due to increased blood volume and plasma and the activity of mitochondrial oxidative enzymes (Barani et al., 2014). The increase in maximal oxygen consumption in novice exercisers is due to improved skeletal muscle oxygenation, which may occur through increased stroke volume, increased capillary and mitochondrial density, and increased oxygen uptake by active muscles. Cardiorespiratory fitness is higher and more desirable in people who are more physically active. Based on their experiments, researchers have found a significant inverse relationship between cardiorespiratory fitness and liver fat in NAFLD patients (Nikroo et al., 2011). Increased cardiorespiratory fitness in NASH patients is due to the improvement of aerobic energy supply system, activation of aerobic muscle enzymes, and increased release and oxidation of fatty acids, which is an effective way to reduce liver fat and improve liver damage indices in fatty liver patients. It counts. Resistance training can improve muscle mass, strength, and power, and is therefore used as a healthy treatment tool in the elderly and obese. Resistance training can increase insulin sensitivity and daily energy expenditure and improve quality of life (Yavari et al.,2011). Resistance training involves skeletal muscle fibers that lead to increased hypertrophy. The increase in body muscle mass provides the capacity for excess glycogen stores or mechanisms that improve insulin sensitivity (Dunstan et al.,2002) And increase resting metabolic rate in patients (Stewart et al., 2004). Visceral fat provides a source of free fatty acids that can be preferentially oxidized to glucose, leading to hyperglycaemia. Reducing visceral fat by decreasing abdominal adiposity may be an important benefit of exercise, that leads to significant improvement in metabolic parameters (Albright et al., 2000).

a) Aerobic exercise

Aerobic exercises (AE) are typically moderate-intensity exercises including larger muscle groups (e.g., arms or legs) that are carried out over developed periods to make better cardiovascular function. AE involves walking, running, cycling, and pool exercises. Regardless of what type of exercise is used in the aerobic exercise program, maintaining an adequate aerobic dose of 40% to 60% of maximal aerobic capacity (maximum heart rate or Vo2max) is necessary (Souissi et al., 2020; Farrokhi et al., 2015). AE has been suggested as part of the handling of patients with a variety of metabolic disorders in several published treatment guidelines (Pedisic et al., 2020; Farrokhi et al., 2015; Lakka et al., 2003; Jurca et al., 2004; Farrell et al., 2004; Okura et al., 2007). To have fundamental health benefits from physical activity, adults should do at least 150 minutes/week of moderate-intensity aerobic activity or 75 minutes/week of vigorous-intensity activity. Previous recommendations were that Adults also can do a combination of both moderate- and vigorous-intensity activity, using the rule of rule that one vigorous-intensity minute of activity counts the same as two moderate-intensity minutes (David et al., 2020).

Regular physical activity is important for physical and also mental health. Exercise training has concepts in epigenetic regulation, aging, an improvement of glycaemic control in patients with T2DM and insulin sensitivity and resistance, prevention of lung diseases, CVD, and multiple sclerosis (Muscella et al., 2020). Consequently, the study of lipid metabolism is particularly important to figure out how physical activity effects on health. Several studies have highlighted that how AE effects on lipid metabolism (Soci et al., 2017; Mendonca et al., 2016; Hansen et al., 2017; Bhati et al., 2018; Powers et al., 2008; Fedewa et al., 2017; Dowman et al., 2017; Palermo et al., 2017).

Fat and carbohydrate provide the most important form of fuel for exercise and sports activities (Markvardsen et al., 2018). During exercise, there are four major internal sources of energy: plasma glucose derived from liver glycogenolysis, free fatty acids (FFAs) released from adipose tissue lipolysis and from the hydrolysis of TG in very-low-density lipoproteins (VLDL-TG), and muscle glycogen and intramyocellular triacylglycerols (IMTGs) available within the skeletal muscle fibres (Muscella et al., 2020). Fats and carbohydrates are oxidized together, but their comparative contribution depends on a diversity of factors, duration, and intensity of the exercise (Chycki et al., 2019).

High-density lipoprotein plays a vital role in plasma lipid transport, preparing to the metabolism of chylomicrons and VLDL and doing as a scavenger of surplus unesterified cholesterol from these lipoproteins (Casella et al., 2011; Slivkoff et al., 2012). The chylomicron particle number remains whit out change during acute and chronic aerobic exercise (Slivkoff et al., 2012). The aerobic and/or resistance exercise decline total cholesterol and LDL-C and growth HDL-C (Slentz et al., 2004; Woudberg et al., 2018; Motiani et al., 2019). HDL concentrations are inversely related with risk for CVD (Motiani et al., 2019), therefor, regular exercise interventions are prescribed to decline the risk of CVD by promoting an enhancement in HDL-C concentration (Argani et al., 2014; Kodama et al., 2007; Kühnast et al., 2015; Ranallo et al., 1998). Furthermore, in adults with CVD, diabetes mellitus, and metabolic syndrome, regular aerobic exercise has helpful effects on different HDL actions, such as endothelial protection, anti-oxidative, and anti-inflammatory properties. However, VLDLs represent the main origin of circulating triglycerides both in fasting and fed states (Peric et al., 2018; Roberts et al., 2006; Sang et al., 2016). VLDLs are converted to lipoproteins with intermediate (IDL) and low (LDL) densities, having low levels of triglycerides (Wang et al., 2017; Brouns et al., 1998; Alves et al., 2017; Nellemann et al., 2014).

On the other hand, weight-loss is related to health and fitness (Zhou et al., 2021). Aerobic exercise capacity is known as a powerful fitness index and a strong predictor of mortality worldwide (Lee et al., 2010). As an important indicator of physical activity, aerobic exercise can be one of the best reflected by maximal oxygen uptake per minute (VO2max) and first determined by the efficiency of mechanisms supplying active muscles with oxygen from the air (Zhou et al., 2021). Using the Fick Principal formula, VO2max= cardiac output (CO) max × peripheral arteriovenous oxygen difference (C (a-v) VO2) max = heart rate (HR) max × stroke volume (SV) max × C (a-v) VO2max = minute ventilation (E) max × (fraction of inspiration oxygen [FiO2]–fraction of expiration oxygen [FeO2]), it recognized that VO2max is determined by the respiratory system, the cardiovascular circulation, and the muscle extraction/utilization of oxygen (Gregg et al., 2016). It is necessary to pay attention to many factors which can affect VO2max, including weight, body size and body composition, training state (type and duration of physical activity), cardiopulmonary function, the haemoglobin concentration in the blood, mitochondrial function, genetic factors, different test methods (treadmill or cycling) and the protocol used for the elevation (Nuijten et al., 2021; Mohorko et al., 2019).

b) Resistance exercise

Nowadays, resistance exercise is getting more popular as an exercise modality (Hagstrom et al., 2020). Resistance exercise is a physical activity program that performed in an acyclic manner by exercising a muscle or a muscle group against external resistance, which is firstly oriented into muscular fitness (Hagstrom et al., 2020; Evans et al., 2019; Schoenfeld et al., 2017; Beqa et al., 2020). Resistance exercise is effective in preservation and maintenance of reduction of blood pressure (Aagaard et al., 2010) and risk reduction for multiple chronic diseases like metabolic syndrome (Hurley et al., 2011).

One of the therapy programs for control obesity is inclusion of resistance exercise which has been endorsed by American Heart Association (Pollock et al., 2000), the American College of Sports Medicine (Pescatello et al., 2006), and the American Diabetes Association (Sigal et al., 2006). The primary organ for triglyceride and glucose disposal is skeletal muscle, which is particularly important determinate of resting metabolic rate (Barbara et al.,2011). The strong after-effects of age-related reduction in skeletal muscle mass are various, comprising increased abdominal adiposity, diminished power and muscle strength, capacity for lipid oxidation, resting metabolic rate. The insulin-mediated glucose uptake in skeletal muscle in older people grows adiposity (Niemann et al., 2020; Holten et al., 2004). The previous research indicates that the preservation of a large muscle mass could decrease metabolic risk factors such as type 2 diabetes mellitus, dyslipidaemia and obesity which are associated with CVD (Williams et al., 2007). It is probable that a higher muscle mass can be associated with metabolic disorders in obese people, which is reported in some studies (You et al.,2004; Barbara et al.,2011). One of the probable mechanisms of resistance training may contain rise concentration of free androgens along of reduced levels of SHBG (sex hormone-binding globulin), a protein-sparing effect due to increased lipid metabolism, and changes in muscle capillarization and fibre composition due to visceral adiposity. (Barbara et al., 2011).

Resistance training promote of muscle growth, muscle strength, endurance, and mass. It is also collaborating in the maintenance of basal metabolic rate (to complement aerobic training for weight control (Williams et al., 2007). Another mechanism of resistance exercise is that this kind of exercises which increase in lean body mass and basal metabolism, assists the body in expending calories (Pollock et al., 2000). Therefore, resistance exercise is recommended for implementation in primary and secondary cardiovascular disease–prevention programs.

2.5.2 Pharmacotherapy.

There are different weight-management options for obesity treatment, including dietary control, exercise, surgery, and medication. Medications are always related with different responses from different people. More safety and efficacy of drugs with fewer side effects are valuable for any clinical condition (Salari et al., 2021).

There are different weight loose medications such as

Phentermine, one of the oldest sympathomimetic medicines that includes diethylpropion. It is the most used medicine in the United States, accounting for 70% of prescriptions. The combination of phentermine and topiramate causes more weight loss than each of them separately (Bessesen et al., 2018). Phentermine and topiramate extended-release (long-acting) capsules are used to help adults who are obese or who are overweight and have weight-related medical problems to lose weight and to keep from gaining back that weight (Bessesen et al., 2018).

Orlistat, (a potent inhibitor of pancreatic lipase that decreases intestinal fat digestion (Salari et al., 2021). Lorcaserin is a US food and drug administration (FDA)-approved elective agonist of the serotonin [5-hydroxytryptamine (5HT)]—2C receptor that is an effective loss weight by reducing appetite and increasing satiety (aunders et al., 2018). This medication is used with behaviour change, a doctor-approved exercise, and a reduced-calorie diet program to help lose weight) (Saunders et al., 2018).

Liraglutide is an anti-diabetic drug used to treat obesity, chronic weight management and type 2 diabetes (Daneschvar et al., 2016).

Pramlintide, which is an injectable medicine that declines the glucose levels in the blood and is used for treating type 1 and type 2diabetes. Pramlintide is a synthetic hormone that resembles human amylin (Daneschvar et al., 2016; Salari et al., 2021; aunders et al., 2018).

It declines appetite by activating a type of serotonin receptor known as the 5-HT2C receptor in a region of the brain called the hypothalamus, which is known to control appetite (Daneschvar et al., 2016).

Some pharmacotherapies, including rimonabant and sibutramine, were used for loose weight, which have been eliminated from the market because of safety concerns. The only available long-term drug therapy for obesity which continues available in united states and Europe is orlistat (Hussain et al., 2011; Snow et al., 2005).

Medications approved in the US/EU are orlistat, naltrexone/bupropion and liraglutide. In the US, lorcaserin and phentermine/topiramate are also available (Bray et al., 2016).

Patients with obesity which have clinically significant atherosclerotic cardiovascular disease (ASCVD) (acute coronary syndromes, history of myocardial infarction, stable or unstable angina, arterial revascularization, and stroke) and are less than 75 years of age must be put on a high intensity.

Over the years, many strategies, such as drug treatments, have been used to lose weight and control obesity. Nevertheless, several anti-obesity drugs have serious adverse effects, such as anxiety, depression, and increased CVD risk. Therefore, some medicinal herbs could be used as an alternative strategy to manage obesity with less toxic side effects than chemical medicine (Haselgrübler et al., 2019; Kang& Park et al., 2012). There are more than 120 drugs have been investigated to obesity treatment over the past 25 years (Hussain et al., 2011).

2.5.3 Natural products.

Obesity is one of the most important epidemics worldwide, which considered many diseases, such as cardiovascular disease (CVD), dyslipidemia, fatty liver, type 2 diabetes, and some cancers (Huaizhu et al., 2020; Payab, M et al., 2019). CVD is one of the most common causes of high mortality (25-45% mortality) in the world (Lumeng et al., 2017; Mobaseri et al., 2003). In this condition, a cleaner, healthier, and more natural life is becoming more attractive to the people of the world day by day (Brook et al., 2017; Newby et al., 2015; Tainio et al., 2021; Johnsen et al., 2013; Hasani-Ranjbar et al., 2013). Living in the embrace of nature and using natural and organic materials and achieving greater health are being welcomed every day more than ever before. While many chemical medicines are not able to cure diseases, many natural, simple, and traditional medicines and methods work and have fewer side effects (Vaezi et al., 2021). Botanists recommend herbal medicine to treat all ailments. Herbal medicines are milder than chemical medicines and have a slower action. They also have milder side effects (Rashrash et al., 2017; Rejhan et al.,1998).

There are several research that reported the potency and lack of side effects of some natural products in the treatment of disease caused by obesity such as CVD, metabolic syndrome, fatty liver, and type 2 diabetes (Soltani et al., 2021; Tian et al., 2019; Sun et al., 2016; Berman et al., 2017; Shi et al., 2012; Xu et al., 2020).

Use of natural and herbal products has long been common in most of the countries. In diverse historical the humans, the usage of natural products undergone several changes during the demands. Nowadays, having a natural lifestyle and consumption of natural products are becoming more attractive and common. Natural medicines are generated as syrups, ointment, pills, and capsules (Vaezi et al., 2021). Also, plants play an important to producing drugs (Ashraf et al., 2015; Luo et al., 1988). To prepare the herbal and natural medicines, Leaves, fruits, roots, and barks of stems of plants and trees are used (Ng et al., 2021; Yang et al., 2015; Sun et al., 2016).

2.5.3a Berberis Vulgaris L.

One of these herbs with antioxidant properties is berberis vulgaris L, from the Berberidaceae family (Soltani et al., 2021; Belwal et al., 2020; Neag et al., 2018; Sabir et al., 1978) a shrub of the genus berberis, which is cultivated in the region of South Khorasan in Iran and is one of the few plants whose root, peel, stem, leaves, flower, and fruits are used for various nutritive and medicinal purposes (Taheri et al., 2012; Andola et al., 2018). This plant is cultivated in various regions of the world and has a long history of use in traditional medicine (Chamorroet al., 2019; Dulić et al., 2019; Fernández-Poyatos et al., 2019; Tabeshpour et al., 2017; Imanshahidi et al., 2008; Kosalec et al., 2009). Some of the alkaloids of berberis Vulgaris L when chemically analysed include berberine, palmatine, oxyacanthine, and berbamine, having each medicinal benefit. Berberine, the most significant compound of all, has a plethora of therapeutic benefits, including antioxidant, antibacterial, anti-tumoral, and anti-inflammatory properties, ameliorative, effect on neural disorders, and preventive effect in coronary artery disease (Soltani et al., 2021; Cao et al., 2020; Imenshahidi et al., 2019; Zarei et al., 2015; Fatehi et al., 2005; Doggrell et al., 2005; Kong et al., 2004; Yin et al., 2002; Ivanovska et al., 1996).

It has been reported that Berberine is a unique natural medicine against insulin resistance in type 2diabetes and metabolic syndrome (Belwalet al., 2020; Kong et al., 2009). Berberine, as a new hypolipidemic medicine, works by a different mechanism of action to that of statin drugs (Kong et al., 2004). It also is a potential weight reducing hypo glycemicagent, hypolipidemic, and it works on multiple molecular targets as a stopper of peroxisome proliferator-activated receptor (PPAR) γ and α and (Huang et al., 2006). Longsome activation of AMP-activated protein kinase (AMPK) by berberine improved cluster of differentiation 36 (CD36) expression in hepatocytes and was elicited in fatty acid uptake via processes related to hepatocellular lipid accumulation (Choi et al., 2017; Andola et al., 2010; Lee et al., 2006).

As well as it is probable that berberine may improve insulin sensitivity (InsS) by inhibiting fat storage and adjusting the adipokine profile in human preadipocytes (Yang et al., 2012). Likewise, its acute activation of the transport activity of glucose transporter 1 (GLUT1) is another hypoglycemiceffects of berberine (Cok et al., 2011; Kulkarni et al., 2010).

Another effect of berberine is lowering blood sugar (Neag et al., 2018). There are some probably mechanism that shows it including decreased adenosine triphosphate level through the inhibition of mitochondrial function in the liver, which may be the probable explanation of gluconeogenesis inhibition by berberine (Xia et al., 2011), - Inhibition of DPP 4 (dipeptidyl peptidase-4), a ubiquitous serine protease responsible for cleaving certain peptides, such as the incretins GLP1 (glucagon-like peptide-1) and GIP (gastric inhibitory polypeptide); their role is to raise the insulin level in the context of hyperglycaemia. The DPP4 inhibition will prolong the duration of action for these peptides, therefore improving overall glucose tolerance (Al-masri et al., 2009; Seino et al., 2010), Inhibition of mitochondrial glucose oxidation and stimulation of glycolysis, and subsequently increased glucose metabolization (Yin et al., 2008). Furthermore, berberine is effective in growing glucose utilization and insulin resistance in tissues by decreasing the lipid such as triglyceride and plasma free fatty acids levels (Chen et al., 2011; Yin et al., 2008).

2.5.3b Cornus mas.

Much research has been focused on food that may be useful in preventing diet-induced body fat agglomeration and diminish the risk of diabetes and heart disease. (Rafieian-Kopaei et al., 2011; Kucharska et al., 2015; Jayaprakasam et al., 2006; Kucharska et al., 2011).

Cornelian cherry with scientific name, cornus mas-land it belongs to the genus Cornaceae. There are 65 of the genus cornus, and cornus mas L is one of the two species from genus cornus, which have been used in traditional ethnomedicine (Przybylska et al., 2020; Darbandi et al., 2016; Czerwińska et al., 2018). It has been well known as in folk medicine and has a great biological value, which is mostly linked with its polyphenols and iridoids contend (Klymenko et al., 2021).

Cornus mas L or (cornelian cherry) has been known for more than 4000 years and from the Caucasus and from there it spread through Iran, Turkey, Romania, Bulgaria, and further on the European continent (West et al., 2012; Klymenko et al., 2017). Its fruits are rich in anthocyanins such as cyanidin, peonidin, pelargonidin, and petunidin, and contain bioflavonoids, vitamin C, and ursolic acid.

The anthocyanins lead to increased insulin secretion (pelargonidin increases insulin secretion up to 1.4 times), amelioration of insulin resistance, and improvement of hyperlipidaemia (Dayar et al., 2020). Cornus mas is used in Chinese and Iranian traditional medicine to treat diabetes and high blood lipids and their complications (Abdollahi et al., 2014; Lietava et al., 2019).

Cornelian cherry bears single-stone fruits of mostly dark-red colour. They have an average length of 1.00–2.22 cm and weight of 0.39–3.78 g and their shape is oval or spherical (Przybylska et al., 2020; West et al., 2012).it Fruits have been proven to be a rich source of health-promoting compounds, such as polyphenols (anthocyanins, flavonols, and phenolic acids), iridoids, terpenoids (ursolic acid), and vitamin C (Efenberger et al., 2020; Dinda et al., 2016; Szczepaniak et al.,2019; Tural et al., 2008; Kucharska et al.,2011; Szumny et al., 2015; Kupczynski et al., 2015). This fact justifies the traditional applications of cornelian cherry (Czerwińska et al., 2018; Sozański et al., 2016; Sozański et al., 2019; Danielewski et al., 2020). Recently, several in vitro and in vivo studies have confirmed antioxidant, anti-inflammatory, antidiabetic, hypolipidemic anti-atherosclerotic, antimicrobial, and anticancer activity of the fruits (Tiptiri-Kourpeti et al., 2019; Kucharska et al., 2009).

The fruits are rich in sugar, oxalic acid, organic acids, anthocyanins, tannins, phenols, flavonoids, and other antioxidants. Fresh Cornelian cherry fruits contain B1, B2, C, and E vitamins, as well as folic acid (Alavian et al., 2014; Vardin et al., 2017; Zarei et al., 2015; Abdollahi et al., 2014).

Fresh fruits contain twice as much ascorbic acid as oranges; compared to other juices obtained from apple, pear and plum, cornelian cherry juice contains elevated levels of calcium, reaching 10 folds higher than other juices; it has high contents of potassium and magnesium but is low in sodium and other essential minerals like Cu, Mn, Fe, and Zn (Dinda et al., 2016). Also, cornus mas levels of toxic elements are also negligible; and the fruits are inordinately wealthy in tannins, organic acids, phenols, anthocyanins, and other antioxidants (Asgary et al., 2014; Gąstołet al., 2013; Krośniak et al.,2010; Abdollahi et al., 2014; Es Haghi et al., 2014).

Several studies have been reported that cornus mas supplementation may have health promoting effects because of its broad range of biological activities, such as lipid-lowering, antioxidant, antidiabetic, anti-inflammatory, antibacterial, anticancer, anticoagulant, antiparasitic effects and protective effect on liver and kidney function as well as the influence on cardiovascular system and blood factors (Gąstoł et al., 2013; Sozański et al., 2014; Kazimierski et al., 2019; Hosseinpour et al., 2017; Yamabe et al., 2010; Park et al., 2011). It is probable that these biological activities may decrease CVD, DM, and obesity, which has been attributed to the presence of elevated levels of certain polyphenolic compounds (Lietava et al., 2019).

Cornelian cherries contain a range of phytochemicals, including anthocyanins, flavonoids, phenolic acids, and tannins (Mohammadi et al., 2021), which may exhibit inhibitory activities on β-Hydroxy β-methylglutaryl- (HMG-CoA) reductase through their ability to bind and inactivate enzymes (Asgari et al., 2014; Sangouni et al., 2021). Though the great content of polyphenolic compounds in cornus mas, the inhibition of HMG-CoA reductase activity seems likely. Lipoprotein lipase (LPL) has a significant role in lipid metabolism, transformed the triglycerides in lipoprotein particles into free fatty acids. The serum level of this enzyme is indicative of LPL production in the adipocytes (Sangouni et al., 2021; Seymour et al., 2008) and is inversely related to TG levels and positively related to HDL-C levels (Sangouni & Hosseinzadeh., 2021; Seymour et al., 2008). Flavonoids elevate the expression of LPL in muscle cells and adipose tissue (Mohammadi et al., 202).

Studies have shown that fruits rich in anthocyanins, flavonoids, and phenolic substances, like cornus mas, have a strong antioxidant activity, which may chip into their ability to decline dyslipidemia by decreasing TC and LDL-C values (Asgary et al., 2014; Hosseinpour et al., 2017). The decreasing effect of cornus mas may be due to their impact on glucose metabolism (Gholamrezayi et al., 2019; Soltani et al., 2015).

2.5.3c Garlic and Lemon.

Other natural supplementations are garlic and lemon; garlic supplementation has an important positive effect on hypercholesterolemia (Banerjee et al., 2002; Ried et al., 2008; Sung et al., 2009). Garlic (Allium sativum) has strong antioxidant properties and can therefore reduce oxidative stress for its content in polyphenols. Garlic may also protect cells and metabolic tissues (e.g., liver) from chemical damage from peripheral toxins due to its contents in s-allyl-L-cysteine (SAC) and propyl-cysteine and reduce lipid peroxidation through cysteine sulfoxides (Aslani et al., 2016). Antioxidants founded on food and the body, even in insignificant amounts, can protect the body against oxidative stress-induced free radicals (Ashraf et al., 2015).

Garlic, a useful herb, which plays an important role in dietary and medicinal, all over the history. Garlic is used in different forms, including raw garlic, powdered garlic tablets, or extracted oil (Bayan et al., 2014). Some classical medicine such as Chinese and Indian medicine, believe that garlic can be consumption to help digestion and respiration, and to treat numerous diseases such as leprosy and parasitic diseases (Sun et al., 2016).

Currently, it has attracted particular attention of modern medicine because of the widespread effects of garlic on maintaining good health. It is reported that the desirable effects of garlic are mainly attributed to the reduction of cancer risk, risk factors for CVDs, antimicrobial effect, and antioxidant effect (Colín-González et al., 2012; Aviello et al., 2009). The protective mechanisms of the beneficial effects of garlic in CVDs may be got by repressing LDL oxidation, gaining the levels of HDL, as well as declining TG and total cholesterol (Iciek et al., 2010).

Garlic has many useful cardiovascular effects such as diminution in TG and total cholesterol and TG, decreasing of blood pressure, and gain of fibrinolytic activity (Lin et al., 2002). Many studies have reported that different extracts of garlic can alone effect on the level of TG, total cholesterol, and LDL in humans and animals (Sun et al., 2018).

Garlic may reduction the level of LDL-C by diminution of hepatic cholesterol 7α-hydroxylase, HMG-CoA reductase, pentose-phosphate pathway activities, gain of bile acid excretion, microsomal triglyceride transfer protein, cholesteryl ester transfer protein activity, bile acid excretion, and preventing hepatic fatty acid synthesis, which was conducted by allicin and/or other parts in garlic (Sun et al., 2018; Qureshi et al., 1983; Gebhardt et al., 1993).

Furthermore, garlic has proven antimicrobial, antithrombotic, anticarcinogenic, antihypertensive, antiarthritic, and lipid and glucose-lowering properties (El-Sabban et al., 2009; Gorinsteina et al., 2006; Mohamed et al., 2011). A further nutritional supplement that is believed to play a vital role in the prevention of cardiovascular diseases and oxidative stress is the lemon. Citrus lemon is one of the most popular fruit varieties worldwide. Previous studies have shown that the erycosytryn and hesperidin present in lemon juice can help in reducing oxidative stress due to their antioxidant properties (Aslani et al., 2015; van Doorn et al., 2006; Minato et al., 2003).

On the other hand, people with hyperlipidaemia have an increased need for antioxidants, and adding some antioxidant supplementation to their diet or medication may reduce their hyperlipidaemia. Vitamin C in plant compounds as an antioxidant reduces fat peroxidation and oxidative damage of blood vessels. Vitamin C and the use of diets rich in these antioxidant vitamins maintain good health and reduce the risk of heart disease (Byers et al.,1992). There are two main mechanisms that cause the changes in HDL and LDL levels. 1: By exerting an antioxidant effect that reduces LDL oxidation and increases its recognition by its receptors. 2: By applying a competitive effect) due to structural similarity (with glucose in the process of glycation, HDL and LDL lead to increased LDL catabolism and decreased HDL excretion (Khan et al., 2002).

Among citrus fruits, lemon (Citrus lemon) production is evaluated to be about 22 million tons every year in the world. It is production of lemon is continuing to acquire each year (Wu et al.,2021; Makni et al., 2018). Lemon Contains copious amounts of nutrients, including vitamin C, flavonoids, phenolic compounds, and citric acid (Diab et al., 2016; Oboh et al., 2014; Ahmadet al., 2013). Lemon contains various beneficial properties, such as anti-oxidation, anti-cancer, immune function regulation, regulation of blood lipids and blood pressure, and the ability to promote wound healing (Wu et al., 2021). Therefore, lemon juices are confirmed as a protection against hypercholesterolemia, and it also can decrease total cholesterol, TG and the levels of LDL and increasing HDL (Oboh et al., 2015; Trovato et al., 1996).

It is reported that fermented lemon juice can prevent hepatic injury by decreasing GOT and GPT levels, hepatic lipid peroxidation, splenomegaly, and liver water (Wu et al., 2021; Chen et al., 2018). There are several studies have indicated that lemon fermented with Lactobacillus OPC1 into lemon fermented products (LFP) exhibited the activity of antioxidant enzymes, including glutathione peroxidase (GPx), superoxide dismutase (SOD), catalase (CAT), and decreased the reactive oxygen species (ROS) content in Clone-9 cells (Hsieh et al., 2020). Moreover, it could keep mitochondrial integrity and decrease oxidative stress damage by acquiring the mitochondrial membrane potential (Wu et al., 2021; Hsieh et al., 2020).

Due to all these facts, the question arises whether the specific combination of different natural supplementation alone and altogether with aerobic or resistance exercise may play a role in parameters associated with CVD.

2.5.4 Surgery.

The other way to treat obesity is through surgical therapy. Bariatric surgery is demonstrated for obese people with a BMI of more than 40, particularly when obesity-worsen health conditions are present. There are 3 basic types of surgical procedures (malabsorptive procedures, restrictive procedures, and mixed procedures), which vary in complexity and efficacy (Hussain et al., 2011; Zhi et al., 1994).

Surgeries for weight loss are named bariatric surgeries. There is no one operation that is effective for all obese patients.

There are different types of bariatric surgeries such as Jejunoileal Bypass, biliopancreatic Diversion (BPD), Gastroplasties, Gastric Banding, Loop Gastric Bypass, Stapled Gastric Bypass, Transected Gastric Bypass, Banded Gastric Bypass, Laparoscopic Surgery (Fobi et al., 2004). Gastric bypass operations are the most common operations currently used (Fobi et al., 2004).

2.6. Bibliographic synthesis and genesis of the research

2.6.1. Physical activities.

There are several studies that highlight the importance of delving into aspects, such as clarifying the effects that regular physical exercise, including aerobic and resistance training, can generate on obesity and cardiovascular disease (Earnest et al., 2013; Calabresi et al., 2010; Miyasita et al., 2010; Ghanbari et al., 2007; Kazeminasab et al., 2013; Kraus et al., 2002; Mazidi& Speakman., 2018; World Health Organization., 2019; Wang et al., 2018; Fernandez et al., 2013; Aslani et al., 2016; Atkins et al., 2014; Thivel et al., 2018; Afzalpour et al., 2004; Morelli et al., 2020; Fatolahi et al., 2017; Thompson et al., 2001; Mogharnasi et al., 2008; Barani et al., 2014; Nikroo et al., 2011; Yavari et al., 2011; Stewart et al., 2004;

Dunstan et al., 2002; Albright et al., 2000; Van Baak et al., 2021; Sreenivasa et al., 2006; Pagano et al., 2002; Reid et al., 2006; Short et al., 2003; Schwenke et al., 1998; Perseghin et al., 2007; Lavoie et al., 2006; Ruderman et al., 2003; Chen et al., 2008; Spassiani et al., 2008; Hagstrom et al., 2020; Evans et al., 2019; Schoenfeld et al., 2017; Beqa et al., 2020; Aagaard et al., 2010; Hurley et al., 2011; Pollock et al., 2000; Sigal et al., 2006; Pescatello et al., 2006; Barbara et al., 2011; Niemann et al., 2020; Holten et al., 2004; Williams et al., 2007; You et al., 2004).

Battista et al. (2021) reported that exercise training is effective in improving cardio metabolic health in adults with overweight or obesity.

Collectively, studies on the effect of have an active lifestyle, whether studied in a cross-sectional cohort or because of a structured exercise intervention, have demonstrated to have an important impact on cardio metabolic risk. Regular exercise can help to reduce blood pressure, lose weight, and improve lipid disorders, including raising HDL and lowering triglycerides (Myers et al., 2019; Pucci et al., 2017; Bull et al., 2017; Sallis et al., 206; Berra et al., 2015; Omura et al., 2018).

It has been reported that regular aerobic exercise improves the lipid profile (Ghanbari et al., 2007; Kazeminasab et al., 2013; Kraus et al., 2002; LeMura et al., 2000). Regular aerobic or resistance training with caloric restriction is a common therapy to control obesity. Although the specific mechanisms of the exercise-induced improvement in the lipid profile remain unclear, previous research suggests that it is due to an increase in lipid consumption (Earnest et al., 2013). One possible mechanism is the increased activity of lipoprotein lipase (LPL), which is responsible for the hydrolysis of fasting triacylglycerol, ultra-low-density lipoproteins (chylomicrons), and very-low-density lipoprotein (Calabresi et al., 2010; Miyasita et al., 2010). Exercise can strongly develop plasma LPL activity, which promotes LPL-mediated triglycerides hydrolysis and therefore enhances the lipid profile (Kobayashi et al., 2007; Miyashita et al., 2010). Another mechanism underlying the beneficial effects of regular exercise is related to fat utilization through increased lipid oxidation during exercise (Morelli et al., 2020).

Physical activity raises the secondary messenger substances in the skeletal muscles, which leads to better glucose consumption and a reduction in insulin resistance (Kim et al., 2017). Studies in humans and rodents indicate that exercise has a positive effect on fatty liver and liver functions, independent of weight reduction. Exercise increases the activity of the liver glucagon, a stimulant for the glucose-producing pathways. The exercise-induced increase in glucagon activity is also responsible for some changes in the expression of those liver genes that are compatible with the increase in fat oxidation (Shamsoddini et al., 2015). All these properties of the exercise help in the control of hyperlipidaemia and hypercholesterolemia, among other benefits. In line with our results in terms of liver enzymes reduction, Shamsoddini et al. (2015) reported exceptional liver enzyme and liver fat decreases with aerobic exercise.

2.6.2. Use of Berberis Vulgaris L.

A literature revision demonstrated that the ethnopharmacological intakes of berberis have been documented from different parts of the world for the treatment of obesity, metabolic syndrome, diabetes, hypertension and other disease (Pirouzpanah et al., 20149; Asemani et al., 2018; Di Pierro et al., 2013; Belwal et al., 2016; Hamayun et al., 2006; Jabeen et al., 2015; Adhikari et al., 2019; (Rahimi Madiseh et al., 2014; Zain-Ul-Abidin et al., 2018; Ahmed et al., 2004; Rana et al., 2019; Phondani et al., 2010; Upwar et al., 2011; Kumar et al., 2019; Chandrasekaran et al., 2018; Uniyal et al., 2006).

Also, in Iranian traditional and modern medicine, berberis vulgaris L is extensively consumed to cure hypertension, diabetes, fatty liver enzymes, and obesity (Torkamaneh et al., 2016; Rahimi-Madiseh et al., 2017; Baharvand-Ahmadi et al., 2016; Rahimi et al., 2017; Durmuskahya and Öztürk., 2013; Alemardan et al., 2013; Bahmani et al., 2016; Bhardwaj and Kaushik, 2012; Feng et al., 2018; Pérez-Rubio et al., 2013; Li et al., 2015; Zhao et al., 2017).

As metabolic syndrome is manifested by the cluster of diseases, the use of an herbal drug candidate might be able to provide therapeutic effects. Traditionally, many medicinal plants and their products (extracts and isolated compounds) have been consumed in the remedy of diabetes and hypertension (Belwal et al., 2017; Oyedemi et al., 2009; Tabassum and Ahmad, 2011; Rizvi and Mishra, 2013; Ezuruike and Prieto, 2014). Several studies demonstrated the protective/ therapeutic effect of plant extracts as an individual and/ or a whole bioactive blend versus metabolic diseases, diabetes, and other disease (Tabatabaei-Malazy et al., 2015; Waltenberger et al., 2016. Hamayun et al., 2006; Uniyal et al., 2006; Rahimi Madiseh et al., 2014; Dong et al., 2012; Lan et al., 2015; Wang et al., 2018; Gulfraz et al., 2008; Meliani et al., 2011; Imenshahidi and Hosseinzadeh, 2016; Mirhadi et al., 2018; Zhang et al., 2010; Pérez-Rubio et al., 2013).

Moreover, berberis vulgaris is recognized within the scientific body of knowledge as one of the functional foods that could be beneficial for the management of hyperlipidaemia and chronic inflammation in humans, having a strong protective effect on the cardiovascular system (Afsharinasabet al., 2020; ChangiziAshtiyani et al., 2013; Emamat et al., 2020; Fatehi et al., 2005). Previous expert literature reported that the intake of berberis vulgaris can reduce lipid profile and liver enzymes in serum (ChangiziAshtiyani et al., 2013; Emamat et al., 2020; Fatehi et al., 2005; Lazavi et al., 2018; IloonKashkooli et al., 2015; Mohammadi et al., 2014; Mohammadi et al., 2011; Shidfar et al., 2012; Taheri et al., 2012; Vrzal et al., 2005). The antioxidant activity of the berberis vulgaris and its content in berberine and polyphenolic compounds can reduce lipid peroxidation, improve lipid profile, liver function, and acid secretion (Firouzi et al., 2018; Lazavi et al., 2018).

2.6.3. Use of Cornus mas.

Jayaprakasam et al., 2006 reported that: the impact of a mixture of pure anthocyanins, cyanidin 3-O-galactoside, pelargonidin 3-Ogalactoside, and delphinidin 3-O-galactoside, and ursolic acid present in C. mas fruits on weight loss, insulin resistance, glucose tolerance, islet function, islet morphology, liver triglycerides, and cholesterol levels in high-fat-fed C57BL/6 mice (Jayaprakasam et al., 2006).

Several studies showed that the effect of cornus mas on different disease such as type 2diabetes, atherosclerosis, high blood lipids, obesity, metabolic syndrome, Alzheimer and other disease and the results are consistent with those of (Dayar et al., 2020; Rafieian-Kopaei et al., 2011; Kucharska et al., 2015; Jayaprakasam et al., 2006; Kucharska et al., 2011;

Przybylska et al., 2020; Darbandi et al., 2016; Czerwińska et al., 2018; Klymenko et al., 2021; Przybylska et al., 2020; West et al., 2012; Abdollahi et al., 2014; Lietava et al., 2019).

The results of this study also are in line with the findings of (Alavian et al., 2014; Vardin et al., 2017; Zarei et al., 2015; Abdollahi et al., 2014; Tiptiri-Kourpeti et al., 2019; Kucharska et al., 2009; Czerwińska et al., 2018; Sozański et al., 2016; Sozański et al., 2019; Danielewski et al., 2020;Efenberger et al., 2020; Dinda et al., 2016; Szczepaniak et al.,2019; Tural et al., 2008; Kucharska et al.,2011; Szumny et al., 2015; Kupczynski et al., 2015; West et al., 2012; Klymenko et al., 2017; Asgary et al., 2014; Gąstołet al., 2013; Krośniak et al.,2010; Abdollahi et al., 2014; Es Haghi et al., 2014).

In the other animal studies, Al-Awwadi et al. (2005) and Asgary et al. (2014) reported that extracts enriched in anthocyanins and procyanidins decrease TG and increase HDL-C levels in high-fructose-fed rats.

2.6.4. Use of Garlic and lemon.

There are some studies that highlight the importance of delving into aspects such as clarifying the effects that lemon and garlic can generate on obesity and cardiovascular disease (Aslani et al., 2016; Batsis & Lopez-Jimenez, 2010; Sohn et al., 2012).

However, few try to elucidate the difference in the effects generated between the use of both methods (Aslani et al., 2016). Their results showed that combination of garlic and lemon juice significantly reduced serum TC, LDL-C, and blood pressure.

In line with these findings, previous research has reported preventive effects of garlic, lemon, and aerobic exercise in fatty liver, atherosclerosis, and metabolic syndrome (Aslani et al., 2016; Batsis & Lopez-Jimenez, 2010; Sohn et al., 2012).

However, there is some evidence that garlic powder does not reduce cholesterol levels (Ali et al., 2000; Koch et al., 1996; Isaacsohn et al., 1998; Turner et al., 2004).

Garlic, such as many other food additives, obtained considerable interest due to its effects on lipid levels (Bhalla et al., 2012; Delaney et al., 1996; Augusti et al., 1996; Simons et al., 1995; Satitvipawee et al., 2003; Saradeth et al., 1994; McMahon et al., 1992; Luley et al., 1986; Kiesewetter et al., 1991; Gebhardt et al., 1993; Yeh et al., 1994; Gupta et al., 2001;

Yeh et al., 2001; Liu et al., 2001; Augusti et al., 2005; Lin et al., 2002; Aouadi et al., 2000; Dhawan & Jain, 2004; Lanzotti et al., 2006; wang et al., 2015; Rivlin et al., 2001; Adler et al., 1997; Sobenin et al., 2009; Ried et al., 2010; Wright et al., 2009; Barrie et al., 1987; De A Santos et al., 1993; Santos et al., 1995; Gardner et al., 2001; Han et al., 2011; Holzgartner et al., 1992; Isaacsohn et al., 1998; Jain et al., 1993; Kandziora et al., 1988). Several animal and human investigations have showed the effects of garlic on BMI, blood pressure, lipid levels, fasting blood sugar, and fibrinogen. Since 1993, 25 clinical trials have been published that have investigated the hypolipidemic effects of garlic. Further, different extracts of garlic alone have been demonstrated to lower serum cholesterol, triglycerides, and LDL in rodents and humans (Mohammadi et al., 2014; Rahman et al., 2003; Budoff et al., 2009; Warshafsky et al., 1993; Matsuura et al., 2001; Gebhardt et al., 1993; Yeh et al., 1994; Gupta et al., 2001; Yeh et al., 2001; Liu et al., 2001; Augusti et al., 2005; Lin et al., 2002; Aouadi et al., 2000). Also, Elmahdi demonstrated that adding 8% raw garlic along with 2% cholesterol to the diet of rats decreased plasma TC and LDL-C (Elmahdi et al., 2008). There are some studies that highlight the importance of delving into aspects, such as clarifying the effects that lemon and garlic can generate on obesity and cardiovascular disease (Aslani et al., 2016; Batsis & Lopez-Jimenez, 2010; Sohn et al., 2012).

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CHAPTER 3

OBJECTIVES AND HYPOTHESIS

Objectives and hypotheses

Based on the bibliographic review carried out and the accumulated professional experience, the following objectives and hypotheses have been proposed that will deal with lipid profile, fatty liver enzymes and metabolic parameters.

3.1. Objectives.

Based on the bibliographic review carried out and the accumulated professional experience, the following objectives and hypotheses have been proposed that will deal with lipid profile and metabolic parameters. The present study aims to answer a series of unknowns that have arisen in relation to the effects of the application of different herbal medicine (berberis vulgaris L, cornus mas, lemon, and garlic) in combination with aerobic or/and resistance exercise, with the purpose of scientifically clarifying the effectiveness of each of them, separately and in comparison. Consequently, the objectives proposed for this doctoral thesis are shown below.

3.1.1 General objective

The general objective was to evaluate the effects of medical herbs such as berberis Vulgaris L, cornus mas, lemon, and garlic in combination with aerobic or/and resistance exercise on lipid profile and metabolic parameters.

3.1.2. Specific objectives

Study I: Analyze and comparison the effects of a six-week

a) Intake of berberis vulgaris L

b) Resistance exercise

c) Aerobic exercise

d) And the combination of Intake of berberis vulgaris L with resistance and/ or aerobic exercise on lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity on the following dependent variables:

- Cholesterol
- Triglycerides (TG)

- High-density lipoprotein cholesterol (HDL)
- Low-density lipoprotein cholesterol (LDL)
- Glucose
- C - reactive protein (CRP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Urea
- Alkaline phosphatase (ALP)
- Uric acid (UA)
- Creatinine

Study II: Analyze and comparison the effects of a six-week

a) Intake of cornus mas
b) Resistance exercise
c) Aerobic exercise
d) And the combination of Intake of cornus mas with resistance and/ or aerobic exercise on lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity on the following dependent variables:

- Cholesterol
- Triglycerides (TG)
- High-density lipoprotein cholesterol (HDL)
- Low-density lipoprotein cholesterol (LDL)
- Glucose
- C - reactive protein (CRP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Urea
- Alkaline phosphatase (ALP)
- Uric acid (UA)
- Creatinine

Study III: Analyze and comparison the effects of a six-week

a) Intake of garlic
b) Intake of lemon
c) Aerobic exercise
d) And the combination of Intake of garlic and lemon with aerobic exercise on lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity on the following dependent variables:
    - Cholesterol
    - Triglycerides (TG)
    - High-density lipoprotein cholesterol (HDL)
    - Low-density lipoprotein cholesterol (LDL)
    - Glucose
    - C – reactive protein (CRP)
    - Alanine aminotransferase (ALT)
    - Aspartate aminotransferase (AST)
    - Urea
    - Alkaline phosphatase (ALP)
    - Uric acid (UA)
    - Creatinine

3.2. Hypothesis

Study I: The six-week of regular exercise (aerobic and/or resistance) in combination with berberis vulgaris L extract intake will improve blood lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity.

Study II: The six-week of regular exercise (aerobic and/or resistance) in combination with cornus mas extract intake will improve blood lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity.

Study III: The six-week of regular aerobic exercise in combination with garlic extract and lemon juice intake will improve blood lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity.

CHAPTER 4.

METHODS

Methodology used in the studies that comprise this paper is explained in detail in the original articles. The main data are described in this section. The following table (Table 1) provides an overview of the methodology used in each article.

Table 1. Design of the methodology used and demographic data (Articles I-III).

Article	Design	Subjects	Studied variables
I	Intervention	56 male obese rats Age: 6 weeks Average weight: 200g	lipid profile: (triglycerides, HDL, LDL, cholesterol) metabolic parameters: (glucose, creatinine, CRP, urea) liver enzymes: (ALT, AST)
II	Intervention	49 male obese rats Age: 6 weeks Average weight: 200g	lipid profile: (triglycerides, HDL, LDL, cholesterol) metabolic parameters: (glucose, creatinine, CRP, urea) liver enzymes: (ALT, AST)
III	Intervention	64 male obese rats Age: 6 weeks Average weight: 200g	lipid profile: (triglycerides, HDL, LDL, cholesterol) metabolic parameters: (glucose, creatinine, CRP, urea, Uric acid) liver enzymes: (ALT, AST, ALP)

CRP: C-reactive protein; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase.

2.1. Environment and sample study.

The intervention process was performed in the Research Center of Medical Plants and Animal Nest of Shahrekord University of Medical Sciences. Iran, with 169 Wistar rats.

2.2. Research variables.

2.2.1. Independent variables.

2.2.1a Aerobic exercise: The six-week (three sessions per week) aerobic training program was performed on a treadmill and was divided into three phases (two weeks of adaptation, two weeks of overload, and two weeks of maintenance/consolidation). A familiarization period was carried out before the aerobic training program (see Table 1) to familiarize the rats with the materials and the procedures. All the phases used no inclination (0°). A 5-minute walk at 10m/min was used as a warm-up and cool-down in every session. The control group walked five minutes once per week at 10m/min and 0º during the six weeks of the intervention (see table 1).

2.2.1b Resistance training: A one-meter ladder with 50 steps separated by 2cm, a width of 50cm, and an inclination of 85º was used for the resistance training. A load pouch attached to the proximal portion of the rats' tail (1-2cm after the hair growth point) was used as resistance. Prior to the six weeks of the resistance training program, a familiarization period without external weight was carried out (see table 2).

2.2.1c Black Barberry Extract: The berberis root was pulverized using a mechanical mill (Moulinex, Osaka, Japan) and the powder was dissolved in 2 liters of 70% alcohol and 30% water. The solution was kept at laboratory temperature for 72 hours. It was then filtered and condensed in a rotary apparatus and kept in an incubator at a temperature of 37°C for three days. A dosage of 400 mg/kg was administered daily to the rats by gavage for six weeks.

2.2.1d Cornus mas extract: The plant was pulverized using a mechanical mill (Moulinex, Osaka, Japan) and dissolved in 2 liters of alcohol (70%) and water (30%). The solution was left to stand for 72h at laboratory temperature. It was then filtered and condensed in a rotary apparatus and kept in an incubator at a temperature of 37°C for three days. A dosage of 400mg of cornus mas per one kilogram of body weight was administered daily to the rats by gavage for 6 weeks.

2.2.1e. Garlic extract: The garlic was mixed with a dilution of 70% water and 30% alcohol and kept in the laboratory for 72 hours. It was then filtered, evaporated, and placed in an incubator at 37ºC for three days. A dose of 200mg/kg was dissolved in one mL of distilled water and given to each rat daily for 6 weeks.

2.2.1f. Lemon juice: To produce the lemon juice, after washing and squeezing the lemons, the extract was diluted with a juicer based on the concentration of 50mg/kg from distilled water for 6 weeks.

2.2.2 Dependent variables.

2.2.2a. Lipid profile. Serum lipid profile is quantified for CVD risk divination and has become almost a routine test. The test contains 4 basic parameters, such as total cholesterol, HDL, LDL and TG (Nigam et al., 2011). It is generally accomplished in fasting blood sample. Fasting refers to 12–14 hours overnight, complete dietary limitation except for medication and water. This may hold real expected to 2 major proofs like: post prandial TG stay high for several hours (Campos et al., 2005), and most mention of levels for serum lipids are established on fasting blood sample. European guidelines also counsel doing lipid profile in fasting blood sample for evaluation of CV risk (De Backer et al., 2003).

Cholesterol. Cholesterol is a lipophilic molecule which is necessary for human life and has several roles that assistance to normally functioning cells. For instance, cholesterol is an important part of the cell membrane and chips into the structural makeup of the membrane as well as modulates its liquidity. Cholesterol actions as a pioneer molecule in the vitamin D's synthesis, steroid hormones (such as aldosterone and adrenal androgens and cortisol), and sex hormones (such as estrogens, and progesterone and testosterone). It is also a constituent of bile salt consumption in digestion to comfort absorption of fat-solvable vitamins A, D, E, and K (Huff et al., 2021).

HDL. It is reported that high-density lipoproteins (HDL) are important biological existences which support against CVD and atherosclerosis (Sacks et al., 2018). As regard as HDL extent is specified often by its cholesterol ester value, extent increase detects cholesterol uptake and esterification, and size contraction demonstrates net transfer of cholesterol to apoB lipoproteins and to liver and bowel wherein it can leave the body or be re-secreted into the circulation (Cuchel et al., 2017). The flux rate of HDL clearance from the circulation is another part of cholesterol expulsion and inverted cholesterol transport. Each of these three inverted cholesterol transport fluxes may be analyzed by apoA1 flux from small to large HDL, large to small HDL, and irretrievable HDL removal (Mendivil et al., 2016).

LDL. Low-density lipoprotein cholesterol, or LDL, is a fat which circulates in the blood, moving cholesterol around the body to where it is required for cell maintenance and dominating it inside of artery walls. Since cholesterol and triglycerides are not soluble in water, they should relate to proteins to current via the hydrophilic blood (Pirahanchi et al., 2021). Cholesterol on Low-Density Lipoproteins (LDL-C) is another major driver of CVD; therefore, its measurement is critical in the management of people at risk (Wolska et al., 2020). LDL may be analyzed directly but is more usually calculated by using the Friedewald formula, which needs TG measurement (Doll et al., 2011).

Triglyceride. A triglyceride molecule contains of a glycerol backbone esterified with three fatty acids. Triglycerides are the major component of animal fats and vegetable in the diet and are the major component of the body's fat reserves. Serum or plasma total TG concentrations can be specified to distinguish metabolic disturbances (Laufs et al., 2020; David et al., 2012). Triglycerides in animals and maybe in plant seeds action as reservoirs of energy. In mammals, they are cumulative in adipose tissue until required, at which time they are broken down into three molecules of fatty acid and a molecule of glycerol. The second incorporate with albumin, a protein in blood plasma, and is transported in the bloodstream to places of usage. Triglycerides also minister as insulation and pincushion for organs in animals (Britannica et al., 2022).

Hypertriglyceridemia is a usual issue in clinical practice. Its outbreak is ∼10% in the adult people with significant interregional change.1–5 The outbreak of mild-to-moderate hypertriglyceridemia parallels that of T2D and obesity (Truthmann et al., 2016). extreme hypertriglyceridemia, specified as plasma TG concentration less than 10 mmol/L (>885 mg/dl) is not so much common, with outbreak ranging from 0.10 to 0.20%, so long as extreme hypertriglyceridemia, specified at TG more than 20 mmol/L (>1770 mg/dl) is infrequent as yet (outbreak 0.014%) (Chyzhyk et al., 2019). A higher level for 'normal' fasting TG of 1.7 mmol/L (150 mg/dl) is sometimes specified; until considering non-fasting TG concentration, However, in normolipidemic people, post-prandial TG levels seldom rise 4.6 mmol/L (400 mg/dL) even post-fat challenge (Dron et al., 2019; Parhofer et al., 2000).

2.2.2b. Glucose. Glucose is central to energy consumption. Lipids, proteins and carbohydrates all finally decompose into glucose, which later works for as the early metabolic combustion of mammals and the universal fuel of the embryo. It works for as the main forerunner for the synthesis of different carbohydrates such as ribose, glycogen, and deoxyribose, glycoproteins, galactose, glycolipids, and proteoglycans. On the opposite, in plants, glucose is synthesized from water and carbon dioxide (photosynthesis) and saved as starch. At the cellular surface, frequently, glucose is the ultimate substrate which arrives the tissue cells and transforms to ATP (adenosine triphosphate) (Nakrani et al., 2021). It is reported that the average fasting blood glucose concentration (no repast food within the recent 3 to 4 hours) is between 80 to 90 mg/dl. The general run, after-meal blood glucose may ascent to 120 to 140 mg/dl, even so the body's feedback mechanism regressions the glucose to normal for 2 hours (Schaefer et al., 2018). Within hunger, the liver prepares glucose to the body via gluconeogenesis: synthesizing glucose from lactate and amino acids (Taneera et al., 2019).

Relevant Testing of glucose: HbA1c. The HbA1C levels show a 2-to-3-month average of a patient's glycemic control. As the HbA1C levels sums up long-range glycemic control, it is most often used to appraise patients with durable hyperglycemia, as observed in patients with diabetes, and to forecast the risk of diabetic difficulties (Schnell et al., 2017).

Fasting Plasma Glucose. Plasma blood glucose values are measured since a term of fasting, usually at least 8 hours. A level larger than 126 mg/dl is related to diabetes (Eun et al., 2016).

C-Peptide. C-peptide is a quantitative quantification of beta-cell action in a single pancreas. Measured by serum samples or urine, a C-peptide level assistance in the assessment and management of diabetes (Leighton et al., 2017).

Oral Glucose Tolerance Test. It is necessary for all pregnant women to obtain gestational diabetes mellitus (GDM) test through an orally used glucose provocation and further plasma blood glucose evaluation (Garrison et al., 2015).

Random Plasma Glucose. A random plasma glucose evaluation is sampled once after postprandial was last ingested. A level of more than 200 mg/dL is extremely indicative of diabetes (Barasch et al., 2013).

2.2.2c. Liver enzymes. Liver enzymes are often used in the measurement of patients with a range of diseases. Classically, they are used to giving information on whether a patient's main disorder is hepatitic or cholestatic in source. However, knowledge of enzyme proportions and design recognition permit much more information to be achieved from these simple tests (Hall et al., 2012). Unusual liver enzyme values may warn liver damage or change in bile flow. Liver enzyme conversion can be either the accompaniment biochemical picture in a people with symptoms suggestive of liver disease or an isolated, unexpected finding in a people who has undergone a wide range of laboratory tests for a nonhepatic disease or for minor, vague complaints (Giannini et al., 2005). There are 3 liver associated enzymes: 1) Alanine Transaminase (ALT), 2) Aspartate Transaminase (AST), and 3) Alkaline Phosphatase (ALP).

Alanine aminotransferase. Alanine aminotransferase: Alanine aminotransferase (ALT, L-alanine:2-oxoglutalate aminotransferase) is a pyridoxal enzyme that catalyzes the eversible interconversion of L-alanine and 2-oxoglutalate to pyruvate and L-glutamate (Sakagishi et al., 1995). ALT is one of the most widely used clinical biomarker of hepatic health (Sakagishi et al., 1995) and formally called serum Goldmark pyruvic transaminase (GPT). Since its name points, ALT is preoccupied with the transamination of alanine, and it is available in the liver at much premier concentrations than in other organs (Simón et al., 2020). It produced in hepatocytes and a particular marker of hepatocellular injury; Its levels are fluctuate during the day, but the normal concentrations in the blood are from 5 to 35 U l-1 (Hall et al., 2012). It is reported that its rise may happen with the utilization of certain drugs or during periods of intense exercise (Moriles et al., 2021).

Aspartate Transaminase. Aspartate aminotransferase is an enzyme found mainly in the liver, but also found in heart and blood cells, muscle tissue and other organs, such as the pancreas and kidneys. AST formerly is called serum glutamic oxaloacetic transaminase (GOT), respectively. AST levels are a valuable aid primarily in the diagnosis of liver disease. Although not specific to liver disease, it can be used in combination with other enzymes to monitor the course of various liver disorders (Huang et al., 2006). The normal concentrations in the blood are from 5 to 40 U l-1 (Hall et al., 2012). However, when body tissue or an organ like the heart or liver is damaged or diseased, extra AST and ALT are liberation into the bloodstream, causing values of the enzyme to rise (Bergmeyer et al., 2012).

Alkaline Phosphatase. The alkaline phosphatases include a heterogeneous group of enzymes which are widely divided in mammalian cells. They mostly are related with cell membranes, but their precise physiologic action is unclear. Alkaline phosphatase activity is an effective serum biochemical index of liver disease (Fernandez et al., 2007). However, raises in the activity of ALP in serum and other body fluids can mirror physiologic or pathologic variations outside those of hepatic origin (Hall et al., 2012).

2.2.2d. C-reactive protein. C-reactive protein (CRP), titled for its capacity to precipitate the somatic C-polysaccharide of Streptococcus pneumonia, was the prime acute-phase protein to be reported and is an exquisitely sensitive systemic marker of inflammation and tissue damage (Pepys et al., 2003). CRP belongs to the pentraxins' family and available in at least two conformationally different forms—including the native pentameric CRP (pCRP) and monomeric CRP (mCRP) (Wu et al., 2015). Studies propose that pCRP contains both pro-inflammatory and anti-inflammatory properties in a context-dependent method (Hu et al., 2017). Conversely, mCRP applies strong pro-inflammatory functions on endothelial cells, endothelial progenitor cells, leukocytes, and platelets and can reinforce the inflammatory reaction (Nathan et al., 2010). Superior CRP concentration for a long time, conversely spikes in CRP, may outcome in CVDs and problems embarking on atherosclerosis (Nadrowski et al., 2016).

2.2.2e. Uric Acid. Uric acid (UA), the terminal production of purine metabolism, is to ward off predominantly via the proximal tubules. Unusual serum values of uric acid are due to changes in production or expulsion (Fathallah et al., 2014). UA actions as an antioxidant and it accounts for 50% of the total antioxidant content of biological fluids in humans (Ndrepepa et al., 2018). When available in cytoplasm of the cells or in acidic/hydrophobic milieu in atherosclerotic plaques, UA transforms into a pro-oxidant factor and promotes oxidative stress and through this mechanism participates in the pathophysiology of human disease such as CVD (Kawai et al., 2012). Evidence present also proposes a relationship between high UA and traditional CV risk factors, metabolic syndrome, insulin resistance, obesity, non-alcoholic fatty liver disease and chronic kidney disease (You et al., 2021). Several clinical and experimental studies have reported sufficient mechanisms via which raised UA values uses disadvantageous results on cardiovascular health such as elevated oxidative stress, diminished accessibility of nitric oxide and endothelial dysfunction, promotion of local and systemic inflammation, vasoconstriction and proliferation of vascular smooth muscle cells, insulin resistance and metabolic dysregulation (Zoppini et al., 2011).

2.2.2f. Urea. Urea, commonly called as blood urea nitrogen (BUN) when analyzed in the blood, is an outcome of protein metabolism. BUN is considered a non-protein nitrogenous (NPN) superfluous crop (Salazar et al., 2014). Amino acids isolated from the separation of protein are deaminated to produce ammonia (Burtis et al., 2014). Ammonia is then transformed into urea by liver enzymes. Therefore, the urea's concentration is conditional on protein intake, the capacity of the body to catabolize protein, and sufficient repulse of urea by the renal system (Salazar et al., 2014).

2.2.2g. Creatinine. Creatinine (Cr) is another non-protein nitrogenous waste product, which is produced by the breaking of creatine and phosphocreatine and may also work as an index of renal function (Milutinovic et al., 1975). Cr is synthesized in the liver, kidneys, and pancreas from the transamination of the amino acids arginine, glycine, and methionine. It then circulates all over the body and is transformed to phosphocreatine by the process of phosphorylation in the brain and skeletal muscle (Salazar et al., 2014).

2.3. Research tools.

2.3.1 Weighing Scale.

2.3.1a. SAIRAN weight scale:
With an accuracy of one gram and up, to measure the weight of animals.

2.3.1b. V-scales.

Accurate one gram up to measure the weights attached to the rats' tails.

2.3.1c. Sartorius weight scales.
With a sensitivity of less than one gram was used to measure the weight of the extract.

2.3.2. Mechanical mil.
A mechanical mill made by Moulinex Company was used to pulverize dried barberry and convert it into an extract.

2.3.3. Rotary.
The IKA-RV10 rotary device made in Germany was used to concentrate the extract.

2.3.4. Incubator.
The concentrated extract was incubated for 3 days in a Memmert incubator at 37 ° C.

2.3.5. Treadmill.
For aerobic exercises, an animal treadmill made by Borj Sanat Company, including 5 lines for rats, was used.

2.3.6. Shocker device.
A stimulator shock device was used to stimulate and force the mice to run

2.3.7. Ladder.
To perform resistance exercises, a 1-meter ladder for animals, including 50 steps with an inclination of 85% and 2 cm distance between the steps and a width of 50 cm, was used.

2.3.8. Weight.
To withstand the increasing load in the subjects, fishing lead weights in weights of 20 to 400 g were used.

2.3.9. Surgical instruments.
Including: syringe, scissors, forceps, physiological serum, formalin, chloralhydrate anesthetic were used for blood sampling and sampling.

2.3.10. Gavage needle.

A gavage needle was used to feed the desired dose of the extract to the animals.

2.3.11. Centrifuge.

A centrifuge (Sigm) made by Rongten Company was used to separate the serum.

2.3.12. Sampler.

Bio hit samplers with a sensitivity of 1 to 10 were used to pour the isolated sera into special falcons.

2.3.13. BT300 device.

BT300 device was used to read serum samples.

2.3.14. Test kits.

To measure the dependent variables (cholesterol, TG, glucose, LDL, HDL, ALT, AST, ALP, CRP, Cr, uric acid, and urea), Pars Azmoun kits were used.

2.4. Execution steps and method of data collection.

The study was divided in to three different studies which is going to explain below:

2.4.1 Article I (Effects of Berberis vulgaris L combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes in obese rats).

2.4.1a. Subjects

56 male Wistar rats (age: six weeks; average weight: 200g) were selected and divided into seven groups:1) control following a normocaloric diet and no treatment(n=8); 2) hypercaloric (n=8) following a fatty-food-based diet and no treatment; 3) aerobic exercise (AE, n=8); 4) resistance exercise (RE, n=8); 5) ingestion of black berberis vulgaris L extract (B, n=8);6) ingestion of Black berberis in combination with aerobic exercise (BAE, n=8); and 7) ingestion of Black berberis in combination with resistance exercise (BRE, n=8). All the groups were homogeneous in terms of number, breed, age, and weight. Six weeks were used to induce hyperlipidemia and hypercholesterolemia in the rats and six weeks to carry out the intervention. The hypercaloric, AE, RE, B, BAE, and BRE groups (n=48) were induced with hyperlipidemia and hypercholesterolemia by diet (see below “Diet formulation” section) and 8control rats remained healthy following a normocaloric diet.

2.4.3.b. Black Berberis vulgaris L extraction and use

Samples of black berberis vulgaris L extract was prepared and used after confirmation from the University's Center for Herbal Medicine Research. The berberis root was pulverized using a mechanical mill (Moulinex, Osaka, Japan) and the powder was dissolved in 2 liters of 70% alcohol and 30% water. The solution was kept at laboratory temperature for 72 hours. It was then filtered and condensed in a rotary apparatus and kept in an incubator at a temperature of 37°C for three days. A dosage of 400 mg/kg was administered daily to the rats by gavage.

2.4.3c. Measures

After six weeks, blood samples were taken in a single session. The rats were anesthetized by intraperitoneal injection of ketamine (70mg/kg) and xylazine (3-5mg/kg). Blood samples were taken from the rats' hearts and placed in a Sigma centrifuge (Rontgen Co., Remscheid, Germany) at 5000 revolutions. The serum was separated using Pars Azmoonkits (Pars Azmoon Co., Tehran, Iran) and transferred to a BT3000 analyzer (Biotecnica Instrument S.p.A., Rome, Italy). Values of the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, CRP, urea), and liver enzymes (ALT, AST) were calculated.

2.4.3d. Data analysis

After a basic data curation, the normality of the distribution and homogeneity of variances of each variable was assessed through the Shapiro-Wilk and Levene tests, respectively. None of the variables complied with normality and homoscedasticity assumption among the seven groups. Therefore, nonparametric tests were performed (Kruskal Wallis testing was conducted). The effect size was reported as the eta squared (h^2) where $0.01<h^2<0.06$ constitutes a small effect, $0.06\leq h^2\leq 0.14$ a medium effect and $h^2>0.14$ constitutes a large effect. After this, paired post-hoc tests with no adjustment evaluated significant differences. A 95% confidence level (significance $p<0.05$) was accepted as statistically significant. Statistical analysis was carried out using commercial software IBM SPSS Statistics for Macintosh (Version 26.0; IBM Corp., Armonk, NY). All data are reported as the means ± the standard deviations and the 95% confidence interval.

2.4.2. Article II (Effects of Cornus mas extract combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes of obese rats).

2.4.2a. Subjects.

49 male Wistar rats(age: six weeks; average weight: 200g) were randomly assigned to seven experimental groups: [1] control (n=7) following a normocaloric diet and no treatment; [2] hypercaloric (n=7) following a high-fat diet and no treatment; [3] aerobic exercise (AE, n=7); [4] resistance exercise (RE, n=7); [5] Cornus mas extract intake (C, n=7) following no exercise program; [6] Cornus mas extract intake in combination with aerobic exercise (CAE, n=7); [7] Cornus mas extract intake in combination with resistance exercise (CRE, n=7). All the groups were homogeneous in terms of number, breed, age, and weight.

2.4.2b. Cornus mas extraction and use.

Samples of cornus mas were procured from reputable suppliers and used after confirmation from the Center for Herbal Medicine Research of the University. The plant was pulverized using a mechanical mill (Moulinex, Osaka, Japan) and dissolved in 2 litres of alcohol (70%) and water (30%). The solution was left to stand for 72h at laboratory temperature. It was then filtered and condensed in a rotary apparatus and kept in an incubator at a temperature of 37°C for three days. A dosage of 400mg of cornus mas per one kilogram of body weight was administered daily to the rats by gavage.

2.4.2c. Measures.

After the six-week intervention, another session was used to extract the blood samples. The rats were anesthetized by an intraperitoneal injection of ketamine (70mg/kg) and xylazine (3-5mg/kg). Blood samples were taken from their hearts and were introduced in a Sigma centrifuge (Rontgen Co., Remscheid, Germany) at 5000 revolutions. At this point, the serum was transferred using Pars Azmoon kits (Pars Azmoon Co., Tehran, Iran) to a BT3000 analyzer (Biotecnica Instrument S.p.A., Rome, Italy). Values of the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, CRP, urea), and liver enzymes (ALT, AST) were calculated.

2.4.2d Data analysis.

After a basic data curation, the normality of the distribution and homogeneity of variances of each variable was assessed through the Shapiro-Wilk and Levene tests, respectively. Only the triglycerides complied with normality and homoscedasticity assumption among the seven groups. Therefore, a one-way analysis of variance (ANOVA) for the triglycerides and Kruskal Wallis testing for the non-normally distributed variables were conducted. The effect size was reported as the eta squared (h^2) where $0.01<h^2<0.06$ constitutes a small effect, $0.06 \leq h^2 \leq 0.14$ a medium effect and $h^2>0.14$ constitutes a large effect. After this, paired post-hoc tests with Tukey adjustments for the parametric analysis and with no adjustment for the non-parametric evaluated significant differences. A 95% confidence level (significance $p<0.05$) was accepted as statistically significant. Statistical analysis was carried out using commercial software IBM SPSS Statistics for Macintosh (Version 26.0; IBM Corp., Armonk, NY). All data are reported as the means ± the standard deviations and the 95% confidence interval.

2.4.3. Article III (Preventive effects of garlic and lemon extract combined with aerobic exercise on blood metabolic parameters and liver enzymes).

2.4.3a. Subjects.

64 male Wistar rats (age: six weeks; average weight: 200g) were randomly assigned to eight experimental groups: [1] control (n=8) following a normocaloric diet and no treatment; [2] hypercaloric (n=8) following a high-fat diet and no treatment; [3] aerobic exercise (AE, n=8) following a high-fat diet; [4] garlic extract intake (G, n=8) following a high-fat diet and no exercise program; [5]garlic extract intake in combination with aerobic exercise (GAE, n=8) and following a high-fat diet;[6] lemon juice intake (L, n=8) following a high-fat diet and no exercise program; [7] intake of garlic and lemon juice (GL, n=8) following a high-fat diet and no exercise program;[8] intake of garlic and lemon juice in combination with aerobic exercise (GLAE, n=8) and following a high-fat diet. All the groups were homogeneous in terms of number, breed, age, and weight.

2.4.3.b. Garlic and lemon extraction and use.

Samples of fresh garlic and lemon from authentic providers were prepared and used after confirmation from the University’s Center for Herbal Medicine Research. To prepare the garlic extract, the fresh garlic was peeled and washed and then cut into smaller pieces with an electric mill (Moulinex, Osaka, Japan). The garlic was mixed with a dilution of 70% water and 30% alcohol and kept in the laboratory for 72 hours. It was then filtered, evaporated, and placed in an incubator at 37ºC for three days. A dose of 200mg/kg was dissolved in one mL of distilled water and given to each rat daily (Ebrahimi et al., 2015). To produce the lemon juice, after washing and squeezing the lemons, the extract was diluted with a juicer based on the concentration of 50mg/kg from distilled water (Nichols et al., 2011).

2.4.3.c. Measures.

After the six-week intervention, another session was used to extract the blood samples. The rats were anesthetized by an intraperitoneal injection of ketamine (70mg/kg) and xylazine (3-5mg/kg). Blood samples were taken from their hearts and were introduced in a Sigma centrifuge (Rontgen Co., Remscheid, Germany) at 5000 revolutions. At this point, the serum was transferred using Pars Azmoon kits (Pars Azmoon Co., Tehran, Iran) to a BT3000 analyzer (Biotecnica Instrument S.p.A., Rome, Italy). Values of the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, CRP, urea, UA), and liver enzymes (ALP, ALT, AST) were calculated.

2.4.3.d. Data analysis.

After a basic data curation, the normality of the distribution and homogeneity of variances of each variable was assessed through the Shapiro-Wilk and Levene tests, respectively. Only the HDL and UA complied with normality and homoscedasticity assumption among the eight groups. Therefore, a one-way analysis of variance (ANOVA) for the normally distributed and Kruskal Wallis testing for the non-normally distributed variables were conducted. The effect size was reported as the eta squared (h^2) where $0.01< h^2<0.06$ constitutes a small effect, $0.06\leq h^2\leq 0.14$ a medium effect and $h^2>0.14$ constitutes a large effect. After this, paired post-hoc tests with Tukey adjustments for the parametric analysis and with no adjustment for the non-parametric evaluated significant differences. A 95% confidence level (significance $p<0.05$) was accepted as statistically significant. Statistical analysis was carried out using commercial software IBM SPSS Statistics for Macintosh (Version 26.0; IBM Corp., Armonk, NY). All data are reported as the means ± the standard deviations and the 95% confidence interval.

2.5. ethical considerations and working protocols.

All ethical considerations and working protocols of this study were approved by Shahrekord's committee for monitoring Laboratory Animal Rights in Medical Sciences University with code 2-1-94.

2.6. Experimental procedures.

The rats were kept for 12 weeks in the Shahrekord University Animal Laboratory Medical Sciences at a temperature between 22 and 27ºC. The room was illuminated in a controlled manner (12 hours off and 12 hours on).

2.7. Diet formulation.

During the six weeks before the intervention, Persintra-M emulsion was included in the diet of the 48 selected rats to induce them with hyperlipidemia. This emulsion was prepared from egg yolk and contained 1g of cholesterol, palm oil of 80% purity, and intralipid liquid per 100g of egg yolk. To produce hypercholesterolemia, 25mg of cholesterol were concentrated on 2ml and daily administered to the rats. In addition, palm oil, sugar, and cow fat were added to the rat’s meal to bring it to 1% cholesterol and 20% sugar.

During the intervention period (six weeks) only the hypercaloric group continued with the above explained hypercaloric diet and the rest of the groups switched to a normocaloricanimal diet. The controls remained all the 12 weeks with a normocaloric diet. Food and water were freely available to all the rats throughout the study.

2.8. Aerobic training program.

The six-week (three sessions per week) aerobic training program was performed on a treadmill and was divided into three phases (two weeks of adaptation, two weeks of overload, and two weeks of maintenance/consolidation). A familiarization period was carried out before the aerobic training program (see Table 1) to familiarize the rats with the materials and the procedures. All the phases used no inclination (0°). A 5-minute walk at 10m/min was used as a warm-up and cool-down in every session. The control group walked five minutes once per week at 10m/min and 0º during the six weeks of the intervention.

To stimulate the rats to walk, an auditory stimulus (tapping on the wall of the treadmill) was used. For this purpose, a low-voltage electrical stimulus was initially used together with an audio stimulus. After the rats were conditioned to two stimuli simultaneously, the single audio stimulus was used in later sessions to comply with the ethics of animal experimentation.

Table 2. Aerobic training plan (articles/studies I-III).

	Adaptation phase		Overload phase		Maintenance phase	
	First week	**Second week**	**Third week**	**Fourth week**	**Fifth week**	**Sixth week**
Speed	8m/min	12m/min	18m/min	20m/min	20m/min	20m/min
Time	10 min	20 min	30 min	40 min	40 min	40 min

2.9. Resistance exercise.

A one-meter ladder with 50 steps separated by 2cm, a width of 50cm, and an inclination of 85º was used for the resistance training. A load pouch attached to the proximal portion of the rats' tail (1-2cm after the hair growth point) was used as resistance. Prior to the six weeks of the resistance training program, a familiarization period without external weight was carried out. The number of repetitions of the training program (see Table 2) in each session ranged from 8 to 12 repetitions, with a two-minute rest in between; each repetition had to be completed in 8 seconds. At the beginning and end of the exercise, 5 repetitions without weight were used as a warm-up and cool-down. The rats were placed at the bottom of the ladder and were motivated to climb the ladder by gently pushing on their backside. No rewards or abnormal stimuli such as electrical stimulation, cold water, or air pressure were used in this study.

Table 3. Resistance training plan (articles/studies I-II).

	Adaptation phase		Overload phase		Maintenance phase	
	First week	**Second week**	**Third week**	**Fourth week**	**Fifth week**	**Sixth week**
Rats' weight average	240g	252g	260g	266g	277g	287g

Ratio overload per bodyweight	50%	75%	85%	95%	110%	120%
Average weight used	120g	189g	221g	253g	305g	344g

CHAPTER5.

RESULTS

Results and plot development

Below is a global summary of the main results found in each of the articles that make up this thesis.

3.1. Article/study I: Effects of Berberis Vulgaris L combined with aerobic or resistance exercise on blood metabolic parameters and liver enzymes in obese rats.

Twelve weeks of fatty food diet were enough to significantly worsen almost all the variables in the hypercaloric group compared to the controls. These changes were not significant only in the Cr variable; however, a 30.7% increase was observed in the hyper group compared to the control. The Kruskal Wallis test indicated that significant differences existed among the groups in all the study variables, with AST: H(6)=36.37, p<0.001, h2=0.62;ALT: H(6)=18.83, p=0.004, h2=0.26; CRP: H(6)=28.07, p<0.001, h2=0.45; creatinine: H(6)=35.51, p<0.001, h2=0.60; urea: H(6)=35.50, p<0.001, h2=0.60; cholesterol: H(6)=38.31, p<0.001, h2=0.66; glucose: H(6)=22.22, p=0.001, h2=0.33; triglycerides: H(6)=20.62, p=0.002, h2=0.30; LDL: H(6)=28.10, p<0.001,h2=0.45; HDL: H(6)=19.15, p=0.004, h2=0.27. Tables 7 and 8 present the outcomes of the intervention in the liver enzymes and metabolic parameters.

Table 4. Levels of liver enzymes (AST and ALT) and metabolic parameters (CRP, creatinine, and urea) in all experimental groups (all n=8).

Group	AST	ALT	CRP	Creatinine	Urea
1 (Control)	93.50±9.94 [(3),4,5,6,7] [85.18-101.81] Median:97.50 IQR:17.25	41.37±7.87 [34.82-47.92] Median:43.00 IQR:10.50	16.55±1.47 [15.31-17.78] Median:17.10 IQR:0.85	0.75±0.07 [3,4,5,6,7] [0.68-0.81] Median:0.70 IQR:0.10	36.00±5.50 [2,3,4] [31.35-40.46] Median:34.50 IQR:8.00
2 (Hyper)	155.62±28.37 [3,4,5,6,7] [131.89-179.35] Median:148.00 IQR:52.00	72.50±17.33* [58.00-86.99] Median:66.50 IQR:19.75	22.93±0.96* [22.12-23.17] Median:23.05 IQR:1.50	0.98±0.14 [3,4,5,6,7] [0.86-1.10] Median:1.00 IQR:0.10	59.50±14.66 [(4),5,6,7] [47.23-71.76] Median:52.50 IQR:19.75

3 (AE)	55.87±24.12 [35.70-76.04] Median:51.50 IQR:36.00	48.62±15.81 [35.39-61.85] Median:44.50 IQR:28.75	17.23±1.30(6) [16.14-18.32] Median:17.25 IQR:2.63	0.46±0.09 [0.38-0.53] Median:0.50 IQR:0.10	47.75±3.65 5,6,7 [44.69-50.80] Median:48.50 IQR:6.25
4 (RE)	38.87±12.63 [28.31-49.43] Median:36.50 IQR:9.50	50.00±8.51(6) [42.87-57.12] Median:49.50 IQR:10.00	17.32±0.93(6) [16.54-18.10] Median:17.15 IQR:1.25	0.48±0.08 [0.41-0.55] Median:0.50 IQR:0.17	45.87±4.29(5),6,7 [42.28-49.46] Median:46.00 IQR:8.50
5 (Berberis)	36.75±8.04 [30.02-43.47] Median:36.00 IQR:14.25	49.50±14.18(6) [37.64-61.35] Median:49.00 IQR:27.75	17.20±1.18(6) [16.20-18.19] Median:17.30 IQR:1.40	0.46±0.05 [0.41-0.50] Median:0.50 IQR:0.10	40.50±5.23 [36.12-44.87] Median: 42.50 IQR:7.75
6 (BAE)	35.75±5.14 [31.44-40.05] Median:38.00 IQR:8.50	40.25±3.95 [36.94-43.55] Median:40.50 IQR:6.25	15.87±0.90 [15.11-16.63] Median:15.57 IQR:1.78	0.48±0.13 [0.37-0.60] Median:0.45 IQR:0.10	37.50±3.89 [34.24-40.75] Median:37.50 IQR:6.25
7 (BRE)	38.50±10.09 [30.05-46.96] Median:37.50 IQR:12.25	44.88±16.39 [31.17-58.59] Median:46 IQR:32.50	16.30±1.03 [15.43-17.16] Median:16.40 IQR:1.75	0.45±0.09 [0.37-0.52] Median: 0.45 IQR:0.10	36.75±6.04 [31.69-41.80] Median:34.50 IQR:8.50

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p<0.05$) with all the rest of the groups;[1,2,3,4,5,6,7]: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5<p<1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; BAE: black Berberis vulgaris extract intake in combination with aerobic exercise; BRE: black Berberis vulgaris extract intake in combination with resistance exercise; AST: aspartate aminotransferase (also known as GOT); ALT: alanine aminotransferase (also known as GPT); CRP: C-reactive protein.

Table 5. Levels of lipid profile in all experimental groups (all n=8).

Group	Cholesterol	Glucose	Triglycerides	LDL	HDL
1 (Control)	49.25±10.11^{2,3,4,5}	126.75±8.29^{2,3,4}	64.25±17.24	10.88±3.48	37.40±4.47$^{2,(3)}$
	[40.79-57.70]	[119.83-133.68]	[49.83-78.66]	[7.96-13.79]	[33.65-41.14]
	Median:49.00	Median:128.00	Median:62.50	Median:10.05	Median:37.45
	IQR:2.75	IQR:9.00	IQR:26.25	IQR:6.79	IQR:8.00
2 (Hyper)	117.62±41.16^{5,6,7}	205.75±41.71$^{(3), (4),5,6,7}$	117.37±26.46*	38.30±5.35*	26.38±5.34$^{(3),4,5,6,7}$
	[83.20-152.04]	[170.87-204.62]	[95.25-139.49]	[33.82-42.77]	[21.91-30.85]
	Median:100.50	Median:206.50	Median: 110.50	Median:36.40	Median:27.55
	IQR:77.00	IQR:58.00	IQR: 16.50	IQR:8.98	IQR:9.88
3 (AE)	85.00±15.95^{6,7}	156.37±25.34$^{(7)}$	70.75±15.74	14.55±2.93	33.15±3.48$^{(5), (7)}$
	[72.16-98.83]	[135.18-177.56]	[57.58-83.91]	[12.10-17.01]	[30.23-36.06]
	Median:81.50	Median:156.00	Median:77.00	Median:14.43	Median:31.75
	IQR:13.50	IQR:35.50	IQR:28.50	IQR:2.72	IQR:6.47
4 (RE)	80.75±14.696, (^{7}	162.87±26.45^{7}	68.87±11.51	15.47±2.94	36.98±5.33
	[68.46-93.03]	[140.75-184.99]	[59.24-78.50]	[13.01-17.93]	[32.52-41.44]
	Median:79.50	Median:171.5	Median:68.00	Median:15.80	Median:36.15
	IQR:24.50	IQR:34.75	IQR:23.75	IQR:5.25	IQR:5.97
5 (Berberis)	70.62±10.30^{6}	147.75±36.51	75.25±19.03	14.46±2.78	37.81±8.29
	[62.00-79.24]	[117.22-178.27]	[59.33-91.16]	[12.13-16.78]	[30.87-44.74]
	Median:72.00	Median:147.50	Median:74.50	Median:14.25	Median:38.80
	IQR:19.75	IQR:61.50	IQR:15.50	IQR:5.15	IQR:14.20
6 (BAE)	50.12±8.25	149.25±17.54	66.62±11.09	12.51±2.68	34.53±2.88
	[43.22-57.02]	[134.57-163.92]	[57.34-75.90]	[10.27-14.76]	[32.12-36.94]
	Median:48.50	Median:154.00	Median:66.50	Median:12.95	Median:35.20
	IQR:9.00	IQR:35.50	IQR:21.75	IQR:5.73	IQR:5.13
7 (BRE)	63.37±12.33	131.75±17.33	70.62±16	12.76±1.32	38.25±6.33
	[53.05-73.69]	[117.25-146.24]	[57.24-84.00]	[11.65-13.86]	[32.95-43.54]
	Median:62.50	Median:130.00	Median:64.00	Median:12.70	Median:36.45

IQR:16.00	IQR:9.50	IQR:32.25	IQR:1.12	IQR:9.85

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p<0.05$) with all the rest of the groups;[1,2,3,4,5,6,7]: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5<p<1.3$);IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; BAE: black Berberis vulgaris extract intake in combination with aerobic exercise; BRE: black Berberis vulgaris extract intake in combination with resistance exercise; AST: aspartate aminotransferase (also known as GOT); ALT: alanine aminotransferase (also known as GPT); CRP: C-reactive protein.

3.2. Article/study II: Effects of Cornus mas extract combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes of obese rats.

Twelve weeks of fatty food diet were enough to significantly worsen almost all the variables in the hypercaloric group compared to the controls. The ANOVA and the Kruskal Wallis test indicated that significant differences existed among the study variables, with AST: $H(6)=29.01$, $p<0.001$, $h2=0.55$; ALT: $H(6)=18.09$, $p=0.006$, $h2=0.29$; CRP: $H(6)=24.20$, $p<0.001$, $h2=0.43$; creatinine: $H(6)=35.29$, $p<0.001$, $h2=0.70$; urea: $H(6)=31.57$, $p<0.001$, $h2=0.61$; cholesterol: $H(6)=34.13$, $p<0.001$, $h2=0.67$; glucose: $H(6)=21.58$, $p=0.001$, $h2=0.37$; triglycerides: $F(6)=14.78$, $p<0.001$, $h2=0.68$; LDL: $H(6)=24.84$, $p<0.001$, $h2=0.45$; and HDL: $H(6)=13.33$, $p=0.038$, $h2=0.18$.Tables 6 and 7 present the outcomes of the intervention in the liver enzymes and metabolic parameters.

Table 6. Levels of liver enzymes (AST/GOT and ALT/GPT) and metabolic parameters (CRP, creatinine, and urea) in all experimental groups (all n=7).

Group	AST	ALT	CRP	Creatinine	Urea
1 (Control)	94.14±9.56[2,4,6,7] [85.29-102.98] Median:97.00 IQR:15.00	39.71±6.77[(3)] [33.44-45.98] Median:41.00 IQR:11.00	16.42±1.54 [14.99-17.85] Median:17.00 IQR:0.80	0.72±0.04[3,4,5,6,7] [0.68-0.77] Median:0.70 IQR:0.10	34.42±3.59* [31.10-37.75] Median:34.00 IQR:7.00
2 (Hyper)	161.00±25.60* [137.46-184.82] Median:150.00 IQR:45.00	74.57±17.62[1,4,5,6,7] [58.27-9087] Median:68.00 IQR:20.00	23.15±0.79* [22.41-23.89] Median:23.20 IQR:0.80	1.01±0.13[3,4,5,6,7] [0.88-1.13] Median:1.00 IQR:0.10	60.85±15.29[4,5,6,7] [46.71-74.99] Median:53.00 IQR:22.00

	83.85±14.39$^{(4)}$	56.71±18.04$^{(4),7}$	17.04±1.27$^{(5)}$	0.44±0.07	48.71±2.62^{5,7}
3	[70.54-97.16]	[40.02-73.40]	[15.85-18.22]	[0.37-0.51]	[46.28-51.14]
(AE)	Median:86.00	Median:60.00	Median:17.20	Median:0.50	Median:49.00
	IQR:24.00	IQR:34.00	IQR:3.00	IQR:0.10	IQR:4.00
	65.85±11.82	42.42±11.02	17.24±0.97^{5}	0.47±0.07	45.28±4.27
4	[54.92-76.79]	[32.22-52.62]	[16.34-18.14]	[0.40-0.54]	[41.33-49.23]
(RE)	Median:66.00	Median:39.00	Median:16.80	Median:0.50	Median:45.00
	IQR:29.00	IQR:8.00	IQR:1.30	IQR:0.10	IQR:9.00
	79.57±19.90	47.51±35.00	15.61±0.93	0.42±0.07	42.85±3.18
5	[61.16-97.98]	[32.61-62.41]	[14.75-16.47]	[0.35-0.49]	[39.91-45.80]
(C)	Median:88.00	Median:45.00	Median:15.80	Median: 0.40	Median:42.00
	IQR:23.00	IQR:35.00	IQR:1.60	IQR:0.00	IQR:4.00
	71.42±14.03	45.00±10.67	16.12±1.73	0.42±0.07	47.14±6.54
6	[58.44-84.40]	[35.12-54.87]	[14.52-17.72]	[0.35-0.49]	[41.09-53.19]
(CAE)	Median:79.00	Median:43.00	Median:16.20	Median:0.40	Median:47.00
	IQR:29.00	IQR:24.00	IQR:3.00	IQR:0.10	IQR:8.00
	63.57±22.04	39.14±10.38	15.47±1.76	0.40±0.00	42.71±3.45
7	[43.18-83.95]	[29.54-48.74]	[13.84-17.10]	[0.40-0.40]	[39.52-45.90]
(CRE)	Median:61.00	Median:39.00	Median:15.50	Median:0.40	Median:45.00
	IQR:48.00	IQR:8.00	IQR:3.40	IQR:00	IQR:7.00

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *:significant difference (p<0.05) with all the rest of the groups;^{1,2,3,4,5,6,7}: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level 0.5<p<1.3); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; C: Cornus mas intake group; CAE: Cornus mas intake in combination with aerobic exercise; CRE: Cornus mas intake in combination with resistance exercise; AST: aspartate aminotransferase (also known as GOT); ALT: alanine aminotransferase (also known as GPT); CRP: C-reactive protein.

Table 7. Levels of lipid profile in all experimental groups (all n=7).

Group	Cholesterol	Glucose	Triglycerides	LDL	HDL
	47.28±9.12^{2,3,4,5,7}	125.00±7.18^{2}	64.00±18.61$^{2,3,4,(5)}$	10.10±2.92*	37.97±6.00^{2,3}
1	[38.84-55.72]	[118.35-131.64]	[46.78-81.21]	[7.39-12.81]	[32.41-43.52]
(Control)	Median:48.00	Median:126.00	Median:59.00	Median: 9.70	Median:37.90
	IQR:18.00	IQR:10.00	IQR:27.00	IQR: 4.90	IQR:12.00
	123.71±40.38$^{(3),4,6,7}$	216.85±29.65*	142.28±24.23*	39.05±5.29*	28.11±6.454, $^{(5),7}$
2	[86.36-161.06]	[189.43-244.27]	[119.78-164.69]	[34.15-43.95]	[22.11-34.08]
(Hyper)	Median:108.00	Median:216	Median:139.00	Median:37.20	Median:30.50
	IQR:71.00	IQR:57.00	IQR:47.00	IQR:9.30	IQR:12.30
	81.85±5.45^{6}	124.42±3.99	97.57±15.45	13.95±2.28	31.84±3.20$^{(4),7}$
3	[76.80-86.90]	[120.73-128.12]	[83.27-11.86]	[11.83-16.06]	[28.87-34.81]
(AE)	Median:80.00	Median:125.00	Median:99.00	Median:14.20	Median:31.40
	IQR:10.00	IQR:7.00	IQR:21.00	IQR:2.80	IQR:3.70
	79.42±2.22	125.00±8.56	93.00±21.97	14.94±2.73	35.81±3.91
4	[77.37-81.48]	[117.08-132.91]	[72.67-113.32]	[12.41-17.47]	[32.19-39.43]
(RE)	Median:79.00	Median:125.00	Median:91.00	Median:15.20	Median:36.30
	IQR:3.00	IQR:11.00	IQR:37.00	IQR:4.50	IQR:2.50
	85.57±8.99^{6}	132.42±12.24$^{(6),(7)}$	89.71±10.45	14.06±4.12	35.05±4.48
5	[77.25-93.89]	[121.10-143.75]	[80.04-99.38]	[10.24-17.88]	[30.90-39.20]
(C)	Median:85.00	Median:131.00	Median:87.00	Median:11.40	Median:36.20
	IQR:9.00	IQR:21.00	IQR:16.00	IQR:7.00	IQR:9.70
	70.00±6.75	119.28±10.30	73.85±10.33	13.76±2.42	34.52±6.84
6	[63.75-76.24]	[109.75-128.81]	[64.29-83.41]	[11.52-16.00]	[28.19-40.85]
(CAE)	Median:70.00	Median:121.00	Median:73.00	Median:14.20	Median:30.80
	IQR:11.00	IQR:19.00	IQR:18.00	IQR:4.70	IQR: 8.90

7 **(CRE)**	78.42±6.80 [72.13-84.72] Median:81.00 IQR:12.00	121.85±5.61 [116.66-127.04] Median:123.00 IQR:7.00	78.85±15.98 [64.07-93.63] Median:81.00 IQR:28.00	13.87±2.14 [11.89-15.86] Median:12.80 IQR:4.30	37.92±4.54 [33.72-42.13] Median:36.50 IQR:6.00

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile ranges (IQR) are also displayed for the non-normal variables. Being *: significant difference (p<0.05) with all the rest of the groups;[1,2,3,4,5,6,7]: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level 0.5<p<1.3); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; C: Cornus mas intake group; CAE: Cornus mas intake in combination with aerobic exercise; CRE: Cornus mas intake in combination with resistance exercise; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

3.3. Article/study III: Prevent effects of garlic and lemon extract combined with aerobic exercise on blood metabolic parameters and liver enzymes.

Six weeks of fatty food diet were enough to significantly worsen almost all the variables in the hypercaloric group compared to the controls. The ANOVA and the Kruskal Wallis test indicated that significant differences existed among the study variables, with ALP: H(7)=49.29, p<0.001, h2=0.76; AST: H(7)=35.92, p<0.001, h2=0.52; ALT: H(7)=35.63, p<0.001, h2=0.51; CRP: H(7)=28.55, p<0.001, h2=0.39; creatinine: H(7)=27.16, p<0.001, h2=0.36; UA: F(7)=34.87, p<0.001, h2=0.71; urea: H(7)=34.79, p<0.001, h2=0.50;cholesterol: H(7)=39.94, p<0.001, h2=0.59; glucose: H(7)=44.65, p<0.001, h2=0.67; triglycerides: H(7)=43.68, p<0.001, h2=0.66; LDL: H(7)=31.84, p<0.001, h2=0.44; HDL: F(7)=21.37, p<0.001, h2=0.60.

Table 8. Levels of liver enzymes (ALP, AST/GOT and ALT/GPT) in all experimental groups (all n=8).

Group	ALP	AST	ALT
1 **(Control)**	281.10±132.40[3,5,8] [170.3-391.8] Median:2.42 IQR:224.00	97.12±7.82[3,4,5,6,7] [90.58-103.66] Median:96.0 IQR: 10.00	29.50±2.61[3,4,5,6,7] [27.31-31.68] Median:30.00 IQR:4.47
2 **(Hyper)**	823.00±146.20* [700.7-945.2]	227.25±62.99* [147.58-279.91]	60.75±7.99* [54.06-67.43]

	Median:768.00	Median:191.50	Median:59.50
	IQR:247.20	IQR: 96.25	IQR:13.00
3	458.80±104.20[4,7]	132.37±18.66	35.37±2.44
(AE)	[371.7-546.03]	[116.76-147.98]	[33.33-37.41]
	Median:448.00	Median:135.50	Median: 35.00
	IQR:150.75	IQR:35.50	IQR:4.75
4	234.50±33.835, ([6),8]	146.62±22.28[(8)]	37.00±2.92[(8)]
(G)	[206.21-262.78]	[127.99-165.25]	[34.55-39.44]
	Median:228.50	Median:146.00	Median:37.50
	IQR:56.50	IQR:39.00	IQR:4.50
5	393.00±48.30[7]	127.62±23.95	34.87±3.27
(GAE)	[352.5-433.2]	[107.59-147.65]	[32.14-37.60]
	Median:410.00	Median:122.50	Median:34.50
	IQR:80.00	IQR:46.00	IQR:2.75
6	339.80±24.21[(7),8]	131.00±29.81	35.00±4.00
(L)	[319.6-360.1]	[106.07-155.92]	[31.65-38.34]
	Median:344.50	Median:116.50	Median:34.50
	IQR:32.00	IQR: 53.00	IQR:5.00
7	235.60±35.02[8]	138.37±31.13	35.62±3.29
(GL)	[206.34-264.90]	[112.34-164.40]	[32.87-38.37]
	Median:223.50	Median:132.50	Median:35.50
	IQR:58.50	IQR: 61.00	IQR:6.25
8	510.80±65.50	122.12±20.96	33.62±3.29
(GLAE)	[456.09-565.65]	[104.59-139.65]	[30.87-36.37]
	Median:523.00	Median:118.50	Median:33.00
	IQR:105.25	IQR: 39.75	IQR:6.00

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile ranges (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p<0.05$) with all the rest of the groups;[1,2,3,4,5,6,7]: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5<p<1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; G: garlic intake group; GAE: garlic intake combined with aerobic exercise group; L: lemon juice intake group; GL: garlic and lemon intake; GLAE: garlic and lemon intake combined with aerobic exercise; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Table 9. Levels of lipid profile in all experimental groups (all n=8).

Group	Cholesterol	Glucose	Triglycerides	LDL	HDL
1 **(Control)**	54.75±3.01[3,4,5,6,7] [52.23-57.26] Median:56.00 IQR: 5.50	105.62±11.103, ([4),5,6,7] [96.3-114.9] Median:103.50 IQR: 21.00	26.62±6.41[2,3, (5),6,7] [21.26-31.98] Median:26.00 IQR: 11.75	19.98±2.25[2,3, (4),5,6,7,8] [17.82-22.09] Median:19.57 IQR: 3.76	44.33±4.20[*] [40.82-47.85] Median:44.80 IQR: 6.82
2 **(Hyper)**	110.75±26.29[*] [88.76-132.73] Median:106.50 IQR: 19.50	218.00±22.27[*] [199.37-236.62] Median:208.50 IQR: 24.25	148.37±26.51[(3),4,5,6,7,8] [126.21-170.53] Median:156.00 IQR: 51.50	30.63±2.26[*] [28.74-32.52] Median:29.60 IQR:4.18	29.17±0.73[(4),5,8] [28.56-29.78] Median:29.00 IQR:1.20
3 **(AE)**	65.5±8.40 [58.47-72.52] Median:66.50 IQR:8.00	146.00±13.25[8] [134.91-157.08] Median:146.50 IQR: 17.25	60.00±16.2 [46.44-73.55] Median:63.50 IQR:29.25	24.93±2.17 [23.11-26.75] Median:24.84 IQR:2.75	31.52±3.27 [28.78-34.26] Median:31.10 IQR:6.57
4 **(G)**	66.125±4.61 [62.26-69.98] Median:65.50 IQR:8.00	129.75±21.86[7] [111.47-148.02] Median:126.50 IQR: 19.75	35.62±12.80 [24.86-46.38] Median:34.00 IQR:18.50	23.46±2.26 [21.56-25.35] Median:23.35 IQR:3.08	33.27±2.40 [31.26-3528] Median:33.70 IQR:3.20
5 **(GAE)**	64.37±9.57[(6), (7)] [56.36-72.38] Median:62.50 IQR:14.25	139.62±17.49[(8)] [125.00-154.24] Median:144.00 IQR: 14. 50	39.75±8.87 [32.32-47.17] Median:36.00 IQR:12.75	24.00±2.08 [22.26-25.73] Median:24.15 IQR:4.02	34.32±2.66 [32.09-36.55] Median:34.95 IQR:5.15
6 **(L)**	75.50±13.50[8] [64.21-86.78] Median:78.00	148.00±23.85[8] [128.05-167.94] Median:139.50	49.87±11.0 [40.66-59.08] Median:53.00	24.53±2.08 [24.86-46.38] Median:22.79	32.61±2.44 [30.56-34.65] Median:32.70 IQR:2.32

	IQR: 23.75	IQR: 38.00	IQR: 18.50	IQR:2.95	
7 (GL)	73.12±6.15[8] [67.98-78.26] Median:72.00 IQR: 8.25	155.25±11.65[8] [145.50-164.99] Median:160.00 IQR: 16.00	45.62±14.70 [38.10-53.14] Median:45.50 IQR: 14.75	25.00±2.70 [23.71-26.28] Median:25.15 IQR:3.27	33.03±2.91 [30.60-35.47] Median:33.10 IQR:3.27
8 (GLAE)	60.87±5.35 [56.39-65.35] Median:62.50 IQR: 8.50	121.50±8.53 [114.36-128.63] Median:122.50 IQR: 15.00	35.25±4.50 [31.65-38.84] Median:34.50 IQR: 7.00	23.93±4.50 [21.64-26.22] Median:23.45 IQR:2.07	36.18±2.28 [34.27-38.09] Median:37.10 IQR:4.73

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile ranges (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p<0.05$) with all the rest of the groups;[1,2,3,4,5,6,7]: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5<p<1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; G: garlic intake group; GAE: garlic intake combined with aerobic exercise group; L: lemon juice intake group; GL: garlic and lemon intake; GLAE: garlic and lemon intake combined with aerobic exercise; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

Table 10. Levels of metabolic parameters (CRP, creatinine, UA, and urea) in all experimental groups (all n=8).

Group	CRP	Creatinine	UA	Urea	CRP
1 (Control)	15.05±1.53[(3), (4), (5),6] [1376-16.33] Median:14.80 IQR:2.95	0.47±0.04[(8)] [.43-0.51] Median:0.50 IQR:0.07	2.95±0.43[3,4,5,6,7] [2.58-3.31] Median:3.00 IQR:0.45	35.12±4.01[2,3,4,5,6,7, (8)] [31.76-38.48] Median:34.00 IQR:4.50	15.05±1.53[(3), (4), (5),6] [1376-16.33] Median:14.80 IQR:2.95
2 (Hyper)	21.70±2.80* [19.35-24.04] Median:31.15 IQR:5.80	0.78±0.12* [0.68-0.89] Median:0.80 IQR:0.25	9.80±1.60* [8.45-11.14] Median:9.50 IQR:1.80	62.25±12.20[3,5,6,7,8] [52.04-72.45] Median:58.00 IQR:11.75	21.70±2.80* [19.35-24.04] Median:31.15 IQR:5.80
3 (AE)	16.48±0.80[(8)] [15.81-17.15] Median:16.5	0.47±0.04[(8)] [0.43-0.51] Median:0.50	4.65±0.72 [5.25-4.67] Median:4.60	47.12±3.94[4] [43.82-50.42] Median:48.00	16.48±0.80[(8)] [15.81-17.15] Median:16.5

	IQR:1.57	IQR:0.07	IQR:0.67	IQR:5.00	IQR:1.57
4	16.70±0.99[8]	0.41±0.09	4.48±0.89	53.50±7.55[8]	16.70±0.99[8]
(G)	[15.86-17.53]	[0.32-0.49]	[3.73-5.23]	[47.18-59.81]	[15.86-17.53]
	Median:16.30	Median:0.40	Median:4.25	Median:54.00	Median:16.30
	IQR:2.05	IQR:0.10	IQR:1.30	IQR:5.50	IQR:2.05
5	16.32±1.54[(8)]	0.45±0.09	4.47±1.04	53.62±7.89[8]	16.32±1.54[(8)]
(GAE)	[15.03-17.61]	[0.37-0.52]	[3.60-5.34]	[47.02-60.22]	[15.03-17.61]
	Median:16.85	Median:0.45	Median:4.25	Median:53.50	Median:16.85
	IQR:2.35	IQR:0.10	IQR:1.40	IQR:9.50	IQR:2.35
6	16.67±0.88[8]	0.47±0.08[(8)]	4.78±0.84	50.25±7.47[(7)]	16.67±0.88[8]
(L)	[15.93-17.41]	[0.41-0.55]	[4.08-5.49]	[43.99-56.50]	[15.93-17.41]
	Median:16.65	Median:0.50	Median:4.80	Median:47.50	Median:16.65
	IQR:1.35	IQR:0.17	IQR:1.45	IQR:11.00	IQR:1.35
7	16.05±1.07	0.47±0.12	4.82±1.03	46.87±8.35	16.05±1.07
(GL)	[16.94-16.05]	[0.36-0.58]	[3.96-5.68]	[39.88-53.86]	[16.94-16.05]
	Median:16.15	Median:0.45	Median:4.80	Median:47.00	Median:16.15
	IQR:1.83	IQR:0.61	IQR:1.85	IQR:16.50	IQR:1.83
8	15.30±1.04	0.38±0.09	4.41±0.68	44.62±3.24	15.30±1.04
(GLAE)	[15.15-16.94]	[0.30-0.47]	[3.83-4.98]	[41.90-47.34]	[15.15-16.94]
	Median:16.15	Median:0.40	Median:4.20	Median:44.50	Median:16.15
	IQR:1.83	IQR:0.15	IQR:1.20	IQR:6.25	IQR:1.83

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile ranges (IQR) are also displayed for the non-normal variables. Being *: significant difference (p<0.05) with all the rest of the groups;[1,2,3,4,5,6,7]: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level 0.5<p<1.3); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; G: garlic intake group; GAE: garlic intake combined with aerobic exercise group; L: lemon juice intake group; GL: garlic and lemon intake; GLAE: garlic and lemon intake combined with aerobic exercise; CRP: C-reactive protein; UA: uric acid.

CHAPTER6.

DISCUSSION

To our knowledge, this is the first study to examine the effects of different herbal medicine such as berberis vulgaris L, and Cornus in combination with two types of physical activities including aerobic and/or resistance on obesity, fatty liver enzymes, lipid profile and metabolic parameters, and the first study which investigated the preventive effects of aerobic exercises in combination with lemon and garlic on lipid profile and fatty liver enzymes. There are no previous studies that compare the effects of exercise training with these herbal medicines.

Preliminarily, it can be highlighted that one of the most relevant findings of this research is that a long-term resistance and/or aerobic training program in combination with some herbal medicine such as berberis vulgaris L, cornus mas, garlic and lemon has a higher effect on lipid profile in comparison with the effects of exercise alone or herbal medicine intake alone.

Next, the main results of this work will be discussed, taking into consideration all those scientific and reference findings that can serve as a reflexive analysis and interpretation of the reality obtained in this doctoral thesis.

The following is a global summary of the main results found in each of the articles/studies that make up this thesis.

6.1. Study I: Effects of Berberis vulgaris L combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes in obese rats.

The purpose of the first article was to analyze the effects of physical exercise (aerobic and/ or resistance training) in combination with black Berberis vulgaris L extract on the blood parameters (lipid profile, liver enzymes, and metabolic parameters) of obese male rats. The most noteworthy findings were that a six-week treatment program was enough to significantly ($p<0.05$) revert the negative values raised by the hyper-caloric diet, showing all the treatments improvements in almost all the assessed variables such as LDL, HDL, TG, glucose, AST, ALT, CRP, and Cr. Although, The combination of the aerobic exercise with the ingestion of the berberis extract (BAE) group, provided significant better results on the levels of cholesterol (-57.4%), TG (-43.2%), LDL (-67.3%), AST (-77.2%), ALT (-44.5%), CRP (-30.8%), also, the better results of HDL (+45%), glucose (-36%), Cr (-54.1%), and urea (-38.2%) levels were obtained in the group of the combination of the resistance exercise with the ingestion of the berberis extract (BRE), in addition, the significant differences between the treatments were observed in BAE and BRE groups in comparison with aerobic and resistance groups alone, which partially supports the study hypothesis.

Concerning the comparison between aerobic and resistance training in improving the assessed parameters, few significant differences were encountered between these two groups. It is worth highlighting that none of both training methodologies alone significantly improved the cholesterol total and glucose levels after six weeks, which is in the same line with study of (Fritzen et al. 2020; Hinkleman et al. 1993; Neiman et al. 1990; Jensen et al. 2020). Due to the different time, intensity, sample (animal or human study), frequency, exercise form and duration of randomized controlled trials, the effects of physical exercise on total cholesterol and glucose levels may be different (Zhao et al., 2021). The probable reason could be the time of training. Some researchers believe that longer time of training, as well as more intensity training, may be more effective on total cholesterol and glucose levels (Wang et al., 2017; Kraus et al., 2002; O'Donovan et al., 2005; Dunn et al., 1997). Kraus et al. (2002) observed that the total energy utilization and exercise intensity was the principal factor which effect on lipid changes (Frampton et al., 2021; Kraus et al., 2002). O'Donovan et al. (2005) also purposed to investigate the effect of exercise intensity on lipid changes and reported that, in the same amount of exercise, the exercise intensity is higher, the more obvious changes in blood lipids.

As mentioned above, aerobic and resistance exercise significantly increased the plasma levels of HDL, but no significant effects on the total cholesterol levels were observed. The reason for this result could be that HDL-C has been shown to be more sensitive to exercise, with an increase even present after only a single exercise session (Kodama et al., 2007; Jensen et al., 2020). These findings are in general agreement with other related research demonstrating stronger relations for physical activity and HDL in comparison with total cholesterol (Pelletier et al., 1987; Skoumas et al., 2003; Eaton et al., 1995; Kokkinos et al., 1995).

In addition, the levels of LDL and TG were decreased after six weeks of both aerobic and resistance training. Several studies, give a demonstration of the positive effects of physical activity on blood cholesterol such as TG, LDL, and HDL levels by adjusting the metabolism of all lipids in the blood. It is widely embraced that regular aerobic or resistance training with caloric restriction is a common therapy to control obesity. Although the specific mechanisms of the exercise-induced improvement in the lipid profile remain unclear, previous research suggests that it is due to an increase in lipid consumption (Earnest et al., 2013). One reason is that regular exercise by decreasing TG, LDL and increasing HDL levels can decrease risk for CVD (Miyasita et al., 2010). Physical exercise may grow LPL, which can conduct to quick elimination of VLDL particles from the circulation, declining LDL (Mazidi& Speakman., 2018). If LDL particles are affluent in TG, apolipoprotein B-100 (apoB 100) receiver binding can be modified, decreasing uptake by LDL receptor (Puglisi et al., 2008). consequently, the decrease in TG for physical exercise may have elevated LDL uptake, reducing LDL (Gill et al., 2003). The fast elimination of TG-affluent lipoproteins may also diminish the potential for cholesteryl ester transfer protein (CETP) to operate on these particles (Puglisi et al., 2008; Lamarche et al., 1999). This reduces the transfer of cholesteryl esters from HDL particles to TG-affluent lipoproteins, such as VLDL and LDL particles, decreasing plasma LDL-C (Puglisi et al., 2008). The desolation in the levels of TG was attended with beginning of physical exercise, by two feasible mechanisms: the first one is an increment in TG elimination with raised LPL, or the second one is, reduction TG production from the liver (Zang et al., 2006). Physical exercise operates AMPK activity to reduce hepatic TG amount and production of TG from the liver (Chen et al., 2003). AMPK interdicts acetyl-CoA carboxylase (ACC), the rate-limiting enzyme in fatty acid synthesis. The decrease in malonyl CoA also reduces deterrence of carnitine palmitoyl transferase-1 (CPT-1), raising fatty acid oxidation (Puglisi et al., 2008).

The levels of liver enzymes such as AST and ALT also were decreased significantly after six weeks of intervention with aerobic and resistance training. Various mechanisms may explain the observed connection between physical exercise with ALT and AST. There is a close relationship between surrogate signs of NAFLD (i.e., ALT, AST), abdominal adiposity (Ruiz et al., 2014). It is reported that physical activity related to the reduction of insulin resistance and effects of adiposity on liver function enzymes (Targher et al., 2010). The enhancement of hepatic lipogenesis and TG-rich lipoprotein secretion persuaded by surplus of central adiposity (Moliner-Urdiales et al., 2009). Last studies also show that physical exercise may act as a key role in hepatic fat content via straight altering hepatic β-oxidation and/or lipogenesis (Ekelund et al., 2012). AST is existing in the liver and other tissues, such as the muscles; thus, it cannot be deprived however that the scene relationship of physical exercise with AST/ALT might be partially explained by increased AST liberation from muscles after physical exercise, especially when the exercise is severe (Ruiz et al., 2014). These findings are agreed with Eidi et al. (2011), regarding the effect of resistance training on the levels of liver indicators as well as, de piano et al. (2012) regarding resistance exercise and its effect on non-alcoholic fatty liver disease is similar. Słomko et al. (2021), regarding the effect of continuous and interval aerobic exercise may be effective at improving ALT. on the other hand, with the research of Davoodi et al. (2012), on the effect of endurance training on liver enzymes and Mir et al. (2012), on the effect of aerobic training on liver enzymes and Marques et al. (2010), on the effects of treadmill exercise on liver indicators and Slentz et al. (2011), about the effects of aerobics and resistance to liver and Zelber-Sagi et al. (2014), regarding the effect of resistance training on ALT and AST enzymes are inconsistent.

Also, the results of the present study showed a significant decrease in the levels of CRP after six weeks of aerobic and resistance training. Previous research has presented that physical activities and exercise training are effective in declining the levels of CRP in patients with obesity, and type 2 diabetes (Alizaei et al., 2021). They also demonstrated that the anti-inflammatory results are strongly related to the types of physical exercise (Alizaei et al., 2021; Annibalini et al., 2017; Balducci et al., 2010; Herder et al., 2009; Davoodi et al., 2012; Haghighi et al., 2010; Taghian et al., 2011). Our outcomes showed that aerobic exercise with (-27.6%) and resistance exercise with (-31.3%) had a significant effect on decreasing CRP levels; these results are consistent with a previous study about decreasing in CRP levels occurs following aerobic and/ or resistance exercises (Fedewa et al., 2017; Alizaei et al., 2021; Balducci et al., 2010; Herder et al., 2009). It is reported that physical activities outcomes in the largest amelioration in CRP levels during the weight loss or a decline in% Fat (Fedewa et al., 2017). Lin and colleagues (2010) have showed that an increment in CRP is forcefully related with percentage of body fat mass, and this association is connected to increment adipose tissue. Adipose tissue secretes many adipokines, which mediate inflammation and promote the hepatic synthesis of CRP and distribution into circulation (Brown et al., 2015; Petersen et al., 2005). CRP is also an easily measured inflammatory biomarker and is liberation via the liver under the incitement of cytokines, such as IL-6, IL-

1, and tumor necrosis factor-alpha. It has been shown hs-CRP is related to endothelial dysfunction and insulin resistance syndrome (Lin et al., 2010; Yudkin et al., 1999), so, it is possible that the physical exercise with its positive effects on liver enzymes and lipid profile may also help to reduce CRP levels. Similar to our results, Campbell et al. (2009), Church et al. (2002) and Muylaert et al. (2003) reported in their studies that physical activity reduced CRP levels. In this sight, some other studies have also showed that weight loss regimens, along with any aerobic or resistance exercises, notably reduced CRP levels and improve other metabolic risk factors like lipid profile, blood pressure and insulin resistance (Torkamaneh et al., 2016; Earnest et al., 2013; Calabresi et al., 2010; Okita et al., 2004).

On the other hand, berberis vulgaris is recognized within the scientific body of knowledge as one of the functional foods that could be beneficial for the management of hyperlipidemia and chronic inflammation in humans, having a strong protective effect on the cardiovascular system (ChangiziAshtiyani et al., 2013; Emamat et al., 2020; Fatehi et al., 2005). In the present study, we have observed significant changes in the levels of TC (-40%), LDL (-62.2%), HDL (+43.3), TG (-35.9%), glucose (-28.2%), ALT (-76.4%), AST (-31.7%), CRP (-25%), Cr (-53.1%), and urea (-31.9%), after 6 weeks of receiving berberis vulgaris L extract. It has been reported that Berberine is a unique natural medicine against insulin resistance in type 2diabetes and metabolic syndrome (Belwalet al., 2020; Kong et al., 2009). In a systematic review and Meta-Analysis of Randomized Clinical Trials study by Ye et al. (2021) reported that berberine can improve obesity and hyperlipidemia by reducing TG, TC, and LDL and increasing HDL; reduce insulin resistance to improve type II diabetes; and prevent diabetic encephalopathy. Berberine, as a new hypolipidemic medicine, works by a different mechanism of action to that of statin drugs (Kong et al., 2004). It also is a potential weight reducing, hypo glycemic agent, hypolipidemic, and it works on multiple molecular targets as a stopper of Peroxisome proliferator-activated receptor (PPAR) γ and α and (Huang et al., 2006). Longsome activation of AMP-activated protein kinase (AMPK) by berberine improved CD36 expression in hepatocytes and was elicited in fatty acid uptake via processes related to hepatocellular lipid accumulation (Choi et al., 2017; Andola et al., 2010; Lee et al., 2006). As well as it is probable, that berberine may improve insulin sensitivity by inhibiting fat storage and adjusting the adipokine profile in human pre-adipocytes (Yang et al., 2012). Likewise, its acute activation of the transport activity of glucose transporter 1 (GLUT1) is another hypoglycaemic effect of berberine (Cok et al., 2011; Kulkarni et al., 2010). There are some human and animal studies which are agreed with our outcomes about the effects of berberis Vulgaris L on the levels of lipid profile such as, TC, TG, glucose, LDL and HDL (Ye et al., 2021; Amini et al., 2020; Emamat et al., 2020; Hemmati et al., 2015; Changizi et al., 2013; Sarraf et al., 2019; Fatehi et al., 2005; Iloon Kashkooli et al., 2015; Lazaviet al., 2018; Mohammadi et al., 2014; Mohammadi et al., 2011; Shidfar et al., 2012; Taheri et al., 2012; Vrzal et al., 2005). Furthermore, in a study of Changizi et al. (2013) reported that the positive effect of alcoholic extract of barberry on lipid profile in a model of a high-fat diet in the rat. Also, in the study of Fatehi et al. (2005) on hypertensive rats, after 5 weeks of intervention with berberis extract, the ambulatory blood pressure monitoring was significantly declined. In another study by Hemmati et al. (2015), regarding the anti-atherogenic effect of hydro-alcoholic and aqueous extract of barberry, saffron, and jujube extracts on diabetic rats, found significantly decreased in serum levels of fasting glucose, TG, VLDL, lipoprotein (a) with an increase in total antioxidant capacity (TAC), and serum adiponectin levels. Moreover, our findings about the positive effects of berberis Vulgaris on liver enzymes are the same line with the findings of Taheri et al. (2012) regarding the hydroalcoholic effect of barberis on liver enzyme activity (ALT and AST) and with the findings of Ashraf et al. (2012) regarding the effect of barberis fruit aqueous extract on liver damage in mice and the findings of Bahari et al. (2014), regarding the effects of liver protection of barberry extract.

Furthermore, observing possible differences between the studied groups. Resistance with consumption of barberry vulgaris L extract (BRE) and aerobic exercise group with consumption of barberry vulgaris L extract (BAE) were the best group treatment and have shown a significant difference in total cholesterol, LDL, HDL, TG, glucose, AST, ALT, CRP, Cr, and urea levels. It is thought that the combination of intake berberis extract and both types of physical activity, including aerobic and/or resistance training, may lead to further improvement in lipid profiles and liver enzymes compared to any of the treatments alone. In the present study, the difference between aerobic training group alone (AE) and resistance training session alone (RE) was observed in comparison with the combination of aerobic training and extract consumption (BAE) and aerobic training and extract consumption (BRE), which is confirmed the hypothesis of our study.

The results of our study reinforced the previous literature such as Schroeder et al. (2019) and Torkamaneh et al. (2016) about the beneficial effect of berberis Vulgaris L and performing aerobic and/or resistance training on weight loss, NAFLD, and CVD. The usefulness of combining this nutritional supplement with physical exercise is, with significant differences (slightly better results for the combination of the extract and both exercise methodologies) or tendencies in the ALT, CRP, urea, cholesterol, glucose, and HDL.

Taken together, all the outcomes of this research suggest that restricting the calories to a norm caloric diet, altogether with the use of berberis vulgaris extract and with aerobic and/or resistance training may be effective in the treatment of CVD and NAFLD. Both treatments (exercise and berberis extract) proved useful in improving the assessed parameters, however, their combination resulted in slightly better values.

6.2. Study II: Effects of Cornus mas extract combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes of obese rats.

The second articles aimed to assess the effectiveness of physical exercise (aerobic and/or resistance) in combination with cornus mas extract intake in improving blood parameters (lipid profile, liver enzymes, and metabolic parameters) of rats with fatty liver and obesity. The results of the present study demonstrated that, all the intervention groups after six weeks of treatment reverted their levels and significantly improved compared to the hyper-caloric group. The most notable findings were that the levels of cholesterol (in all treatment groups), TG levels in (AE, RE) groups, AST levels in (AEC, REC, RE) groups, Cr levels in (AEC, REC, AE, RE) groups and urea levels in (all treatment groups), have reached even better than the healthy group (control) after 6 weeks of intervention. These interesting results provide a solid foundation for the management and treatment of obesity and other associated conditions such as fatty liver, cardiovascular disease, metabolic syndrome, diabetes mellitus, atherosclerosis, and dyslipidemia (Dayar et al., 2020; El Hadi et al., 2019; Huang et al.,2009; Tomeno et al., 2020; Wong et al., 2016).

What is new from this study is the best results were obtained in resistance exercise in combination with cornus extract (REC) group, in HDL (+34.9), LDL (-64.4%), GOT (-60.5%), GPT (-47.5%), CRP (-32.2%), Cr (-60.4%) and urea (-29.8%), And the best results were observed in aerobic exercise in combination with cornus extract (AEC) group in the levels of cholesterol (-43.4%), TG (-48.1%) and glucose (-45%).

Regarding the effects of the physical exercise on the assessed parameters, a six-week program of both exercise methodologies (aerobic and/or resistance training) was enough to improve the values of cholesterol (RE; -35.8%), TG (AE; 31.4%, RE; 34.6%), glucose (AE; 42.6%, RE; 42.4%), LDL (AE; 64.2%, RE; 61.7%), GOT (AE; 47.9%, RE; 59.1%), GPT (RE; 43.1%), CRP (AE; 26.4%, RE; 25.5%), and Cr (AE; 56%, RE; 53.5%), as happened in previous research de Piano et al. (2012), Carbajo-Pescador et al. (2019), Slentzet al. (2011), Shamsoddini et al. (2015). In a systematic review and meta-analysis study by García-Hermoso et al. (2016) reported that concurrent aerobic plus resistance exercise improves body composition, metabolic profiles, and inflammatory state in the obese pediatric population. In the present study, the levels of total cholesterol and HDL were not changed significantly after six weeks of aerobic exercise. One reason for such contradictory findings may be due to differences in the duration, intensity, and level of training of the subjects. The duration of exercise can affect the change of fat profile. These outcomes agree with Bije et al. (2018), Fritzen et al. (2020), Hinkleman et al. (1993), Neiman et al. (1990), and Jensen et al. (2020). In the study by (Bije et al., 2018), they have reported that the levels of TC and HDL were not changed after six months of aerobic exercise (Bije et al., 2018). In another study by Nassef et al. (2020), 7543 healthy people consisting of (3472 men and 4071 women) aged 30–70 years were participated in their study and categorized in three groups, based on exercise status—no exercise (did not exercise at all during the last three months), aerobic exercise (did at most 3 types, which included jogging, strolling, swimming, yoga, taijiquan, biking, and aerobic dance, and badminton (only regular badminton, at least 3 times per week in the last 3 months)). They reported that aerobic exercise and regular badminton were associated with higher levels of HDL-C, with the badminton group being more significant. One of the possible reasons for the difference in Nassef ‘s results with the results of the present study was that the subjects of their study were healthy individuals, and the number of subjects was much higher than our study, which could also be a reason for the difference between the results. In our study, 49 obese male rats with hyperlipidemia (which only 7 were treated with aerobic exercise) were our subjects. As mentioned earlier, the results showed a decrease in cholesterol and an increase in HDL levels, but these changes were not significant.

However, the type of aerobic exercise, the number of participants, and their health status (healthy, obese or with hyperlipidemia) are thought to affect the difference in results. As O'Donovan et al. (2005) Reported, the intensity of exercise is the most important factor in improving fatty disorders affecting the incidence of coronary heart disease, and intense aerobic activity is more effective than moderate and low intensity aerobic activity (O'Donovan et al., 2005).

The results of our study reinforce the results of previous studies on the effect of regular physical exercises on obesity, CVD, and fatty liver (Ruderman et al., 2003; Chen et al., 2008; Spassiani et al., 2008; Sreenivasa et al., 2006; Hagstrom et al., 2020; Evans et al., 2019; Schoenfeld et al., 2017). The specific mechanisms of the exercise-induced improvement in the lipid profile remain unclear, previous research suggests that it is due to an increase in lipid consumption (Earnest et al., 2013). One of the probable mechanisms of resistance training may contain rise concentration of free androgens along of reduced levels of SHBG (sex hormone- binding globulin), a protein-sparing effect due to increased lipid metabolism, and changes in muscle capillarization and fibre composition due to visceral adiposity. (Barbara et al., 2011). Resistance training promote of muscle growth, muscle strength, endurance, and mass. It is also collaborating in the maintenance of basal metabolic rate (to complement aerobic training for weight control (Williams et al., 2007). Another mechanism of resistance exercise is that this kind of exercises which increase in lean body mass and basal metabolism, assists the body in expending calories (Pollock et al., 2000). Therefore, resistance exercise is recommended for implementation in primary and secondary cardiovascular disease–prevention programs. The levels of GOT and GPT were decreased significantly after six weeks of intervention with resistance training. The mechanisms underlying the conversion in liver enzymes after physical exercise are probably to reflect changes in circulatory lipids, energy balance, and insulin sensitivity. Insulin sensitivity plays a key role in liver enzymes homeostasis (Pruchnic et al., 2004). High values of circulatory insulin upregulate SREBP-1c and ChREBP expression in the liver, stimulating de novo lipogenesis and increasing liver enzymes (Ratziu et al., 2010; Dubé et al., 2008). The findings of Hallsworth et al. (2011) suggested that resistance exercise growths whole-body glucose disposal at least partly due to enhancements in skeletal muscle GLUT4, glycogen synthase expression and activity, insulin receptor and glycogen storage. Skeletal muscle in the resistance exercising alone can thus act to separate circulating fatty acids and glucose safely, decreasing the impact of insulin-stimulated de novo lipogenesis in the liver. Resistance exercise has been shown to increase intramyocellular triacylglycerol synthesis, while declining the accumulation of fatty acid metabolites and repressing the proinflammatory state related to insulin resistance (Hallsworth et al., 2011; Dubé et al., 2008). Other similar researches are in the same line with our study about the effect of physical exercise on liver enzymes such as Draz et al. (2021), Abdelbasset et al. (2020), Cuthbertson et al. (2016), Pugh et al. (2014), Sullivan et al. (2012), Hallsworth et al. (2015), Zhang et al. (2016), Shojaee-Moradie et al. (2016), Rezende et al. (2016), Eckard et al. (2013), Houghton et al. (2017), and Bacchi et al. (2013). It is noteworthy that the six-week aerobic training program was not enough to significantly modify the GPT, urea, and HDL levels. The probable reason may be the type of exercise performed. According to the results obtained in the present study, it is thought that resistance training has a greater effect on skeletal muscle and adipose tissue than aerobic exercise. It is reported that, some types of aerobic exercise may cause joint pressure or injury, but resistance exercise is more appropriate and may be more effective on liver enzymes (Xiong et al., 2021). Most studies are about the effects of aerobic exercise on liver enzymes and NAFLD, while the effects of other exercise methods such as resistance training need to be studied further with more randomized trials. Various studies have proven that exercise intervention is effective in patients with NAFLD (Takahashi et al., 2018). AST values in both aerobic (-47.9%) and resistance (-59.1%) training methods showed a significant decrease. The levels of CRP, also decrease after both aerobic (-26.4%) and resistance (-25.5%) training which is in the same line with Alizaei et al. (2021), Annibalini et al. (2017), Balducci et al. (2010), Herder et al. (2009), Davoodi et al. (2012), Haghighi et al. (2010), Taghian et al. (2011), and Torkamaneh et al. (2016), but not the same line with Bije et al. (2018). As mentioned before, it is thought that physical exercises consequences in the largest amelioration in CRP values during the weight loss or a reduction in %Fat (Fedewa et al., 2017). Lin et al. (2010) have reported that an increase in CRP is forcefully relevant with percentage of body fat mass, and it may be connected to increase adipose tissue. Adipose tissue hides many adipokines that mediate inflammation and promote the hepatic synthesis of CRP and distribution into circulation (Brown et al., 2015; Petersen et al., 2005). It is feasible that the physical exercise with its positive effects on liver enzymes and lipid profile may also help to reduce CRP levels (Earnest et al., 2013).

On the other hand, the outcomes presented are in accordance with previously published investigations that found improvements in different hepatic and lipidic parameters (total cholesterol, LDL, HDL, TG, glucose) after intaking cornus mas extract both in rats (Alavian et al., 2014; Asgary et al., 2013, 2014) and humans with type 2 diabetes (Soltani et al., 2015). This beneficial effect of the cornus mas extract may be due to its content in antioxidants, phenolic compounds, and vitamins, which help in the prevention of inflammatory processes and oxidative stress associated with different metabolic and cardiovascular conditions (Abdollahi et al., 2014). Studies have shown that fruits rich in anthocyanins, flavonoids, and phenolic substances, like cornus mas, have a strong antioxidant activity, which may chip into their ability to decline dyslipidemia by decreasing total cholesterol (TC) and LDL-C values (Asgary et al., 2014; Hosseinpour et al., 2017). The decreasing effect of cornus mas may be due to their impact on glucose metabolism (Gholamrezayi et al., 2019; Soltani et al., 2015). However, the results of the present study showed significant changes in the levels of (LDL, HDL, TG, glucose, AST, ALT, CRP, Cr and urea) after 6 weeks of consumption of cornus mas extract and is in line with (Abdollahi et al., 2014; Tiptiri-Kourpeti et al., 2019; Kucharska et al., 2009; Czerwińska et al., 2018; Sozański et al., 2016; Sozański et al., 2019; Danielewski et al., 2020; Efenberger et al., 2020; Dinda et al., 2016; Szczepaniak et al., 2019; Tural et al., 2008; Kucharska et al.,2011; Szumny et al., 2015; Kupczynski et al., 2015; West et al., 2012; Klymenko et al., 2017; Asgary et al., 2014; Gąstołet al., 2013; Krośniak et al.,2010; Abdollahi et al., 2014; Es Haghi et al., 2014).

Taken together, all the outcomes of this research suggest that restricting the calories to a norm caloric diet, altogether with the use of cornus mas extract and with aerobic and/or resistance training may be effective in the treatment of obesity, CVD and NAFLD. Both treatments (exercise and cornus mas extract) proved useful in improving the assessed parameters, however, their combination resulted considerably better values.

6.3. Study III: Preventive effects of garlic and lemon extract combined with aerobic exercise on blood metabolic parameters and liver enzymes.

The main aim of the third article was to analyze the potential preventive effect of garlic and lemon juice supplementation combined with aerobic exercise in the worsening of blood parameters (liver enzymes, metabolic parameters, and lipid profile) resultant from a hyper-caloric diet. It is worth highlighting that all the treatments served to prevent the worsening in almost all the assessed parameters (significant differences to the hyper-caloric group), which affirms the study hypothesis. Furthermore, some values remained at the same levels as in the control healthy group, which followed a normocaloric diet. What is new from this study is that the best results were reached in aerobic exercise in combination with lemon juice and garlic extract (GLAR) group, in all variables such as cholesterol (-45%), glucose (-44.3%), TG (-76.2%), HDL (+24%), LDL (-21.9%), GOT (-46.3%), GPT (-44.7%), CRP (-29.5%), Cr (-51.3%), U. A (-55%), and urea (-28.3%).

After six weeks of aerobic exercise, the levels of lipid profile, including cholesterol (-40.9%), glucose (-33%), and LDL (-18.5%) were decreased significantly. The outcomes of this investigation compared favorably with the finding of other studies. Researches have reported that regular physical exercise decreases or has positive alterations in the lipoprotein profile and the blood lipid (Adeagbo et al., 2020; Tiainen et al., 2016; Blessing et al., 1995; Wilund et al., 2009; Leaf et al., 2003; Stergioulas & Filippou, 2006). One feasible mechanism is the increased activity of lipoprotein lipase (LPL), which is liable for the hydrolysis of fasting triacylglycerol, ultra-low-density lipoproteins (chylomicrons), and very-low-density lipoprotein (Calabresi et al., 2010; Miyasita et al., 2010). Exercise can strongly develop plasma LPL activity, which builds up LPL-mediated triglycerides hydrolysis and therefore helps the lipid profile (Kobayashi et al., 2007; Miyashita et al., 2010). Another mechanism underlying the beneficial effects of regular exercise is related to fat utilization through increased lipid oxidation during exercise (Morelli et al., 2020). Physical activity extends the secondary messenger substances in the skeletal muscles, which contribute to better glucose consumption and a reduction in insulin resistance (Kim et al., 2017). Studies in humans and rodents indicate that exercise has a positive effect on fatty liver and liver functions, independent of weight reduction. Exercise strengthens the activity of the liver glucagon, a stimulant for the glucose-producing pathways. The exercise-induced increase in glucagon activity is also responsible for some changes in the expression of those liver genes that are compatible with the increase in fat oxidation (Shamsoddini et al., 2015). All these properties of the exercise help in the control of hyperlipidaemia and hypercholesterolemia, among other benefits. In line with our results in terms of liver enzymes reduction, Shamsoddini et al. (2015) reported exceptional liver enzyme and liver fat decreases with aerobic exercise. In a study by Blessing et al. (1995) which agrees with our results, they observed a positive alteration in TC, LDL levels after the l6 weeks of aerobic training. Based on the findings of Adeagbo et al. (2020), it was concluded that an aerobic training program may improve changes in total cholesterol and LDL-c levels. In another study by Cho et al. (2019), their findings suggest that exercise with or without ADF enhances cholesterol metabolism as measured by serum sterol signatures, and increased physical activity has a greater effect on cholesterol biosynthesis than weight reduction or calorie restriction. The levels of TG (-59.6%) was demonstrate significant changes after six-week of aerobic training. The probable reason for such contradictory findings may be expected to be differences in the duration, intensity, and level of training of the subjects. As mentioned before, the duration of exercise may be effective in the change of fat profile. The other probable reason may be leading to that the animals were receiving high cholesterol diet during the intervention, which might be affected on TG levels. It is noticed that, in the present study, significant increase in HDL levels only observed in aerobic training and garlic intake (AEG) and aerobic training and lemon and garlic intake (GLAE) groups. None of the groups consuming lemon or garlic alone or doing aerobic exercise session alone, significantly increased HDL levels. The possible reason can be thought that the simultaneous consumption of high-fat diet during the intervention may prevents the effectiveness of the effect of treatment interventions, such as garlic and lemon alone or aerobic exercise alone, on HDL levels changes. However, the combination of two dietary supplements with aerobic exercise showed a significant increase and the best results on HDL values. Therefore, it is thought that the best way to influence the amount of HDL in the blood is to combine physical activity with supplements such as garlic and/or lemon.

The levels of GOT (-41.8%), GPT (-41.8%), ALP (-44.3%) were decline after six-week of intervention with aerobic exercise. Sufficient mechanisms may explain the observed connection between physical exercise with GOT and GPT. There is a close relationship between surrogate signs of NAFLD (i.e., ALT, AST) and abdominal adiposity (Ruiz et al., 2014). As mentioned before, physical activity may relate to the decrease of insulin resistance and, effects of adiposity on liver function enzymes (Targher et al., 2010). The increase of hepatic lipogenesis and TG-rich lipoprotein secretion persuaded by overplus of central adiposity (Moliner-Urdiales et al., 2009). Last studies also report that physical activity can work as a main role in hepatic fat value by direct altering hepatic β-oxidation and/or lipogenesis (Ekelund et al., 2012). GOT is existing in the liver and other tissues such as the muscles; thus, it cannot be deprived, however that the seen relationship of physical exercise with GOT and GOT/GPT might be partially explained by increased GOT liberation from muscles after physical exercise, especially when severe (Ruiz et al., 2014). Our findings about the positive effect of aerobic exercise on liver enzymes are in the same line with several studies such as Charatcharoenwitthaya et al. (2021), Jia et al. (2018), Draz et al. (2021) Abdelbasset et al. (2020), Cuthbertson et al. (2016), Pugh et al. (2014), Houghton et al. (2017), and Bacchi et al. (2013), as well as Słomko et al. (2021), regarding the effect of continuous and interval aerobic exercise may be effective at improving GPT, and Marques et al. (2010), on the effects of treadmill exercise on liver indicators. Also, the results of the present study noted a significant decrease in the levels of CRP (-24.1%), Cr (-39.7%), U. A (-52.6%), and urea (-24.3%) after six weeks of aerobic training. Previous research has shown that physical activities and exercise training can decline the levels of CRP in patients with obesity and type 2 diabetes (Uchiyama et al., 2021; Alizaei et al., 2021). They also established that the anti-inflammatory results are strongly related to the types of physical exercise (Alizaei et al., 2021; Annibalini et al., 2017; Balducci et al., 2010; Herder et al., 2009; Davoodi et al., 2012; Haghighi et al., 2010; Taghian et al., 2011). The probable mechanism of aerobic exercise on CRP levels is that an increment in CRP is forcefully related to the percentage of body fat mass, and this association is related to increment adipose tissue. Adipose tissue secretes many adipokines, which mediate promote the hepatic synthesis and inflammation of CRP and distribution into circulation (Brown et al., 2015; Lin et al.,2010; Petersen et al., 2005). CRP is one of the easiest measured inflammatory biomarker and is liberation by the liver under the incitement of cytokines, such as tumor necrosis factor-alpha, IL-6, and IL-1. It has been shown that CRP is associated with endothelial dysfunction and insulin resistance syndrome (Yudkin et al., 1999), so, it is possible that the aerobic exercise with its positive effects on liver enzymes and lipid profile may also help to reduce CRP levels (Lin et al., 2010).

After 6 weeks of intervention with garlic extract, significant changes were found in the levels of cholesterol (-40.3%), glucose (-40.5%), TG (-76%), LDL (-23.4%), GOT (-35.5%), GPT (-39.1%), ALP (-71.5%), Cr (-47.4%), U. A (-54.3%), and urea (-14.1%). These changes are agree with some other studies about the positive effect of garlic consumption on lipid profile such as Ahmadian et al. (2017), Aslani et al. (2016), Mirunalini et al. (2011), Batsis and Lopez-Jimenez. (2010), Xu et al. (2018), Atkin et al. (2016), van Doorn et al. (2006), Mohammadi et al. (2014), Stabler et al. (2012), Matsuura et al. (2001), Lee et al. (2011), Padiya et al. (2013) Kwak et al. (2014) Alder et al. (2003) Zhang et al. (2001) Williams et al. (2005), Turner et al. (2004), Superko et al. (2000), and Steiner et al. (1996). The fatty acid synthesis such as HDL and reduction in cholesterol absorption may be possible mechanisms of action in garlic (Soleimani et al., 2020). There are some studies which investigated the effect of garlic on lipid profile, such as Ansary et al. (2016), they reported that, different extracts of garlic alone have been described to lower serum cholesterol, triglycerides, and LDL in rodents and humans. In another study, Soleimani et al. (2020) reported that the intake of garlic powder was accompanied by a significant improvement in the hepatic steatosis and comorbidity related to this condition among subjects with NAFLD. Also, Szulińska et al. (2018) in their results suggest that garlic can be effective in the prevention and treatment of cardiovascular diseases in obese postmenopausal women. In a study by Elmahdi et al. (2008) which is in line with the present study, about the effect of fresh crushed garlic bulbs on plasma lipids in hypercholesterolemic rats observed adding 8% raw garlic along with 2% cholesterol to the diet of rats decreased plasma TC and LDL-C. Many food additives, such as garlic, have gained substantial interest due to its effects on lipid levels (Aslani et al., 2016; Bhalla et al., 2012; Delaney et al., 1996; Augusti et al., 1996). The probable mechanism can be that, garlic may reduction the level of LDL-C by diminution of hepatic cholesterol 7α-hydroxylase, HMG-CoA reductase, pentose-phosphate pathway activities, gain of bile acid excretion, microsomal triglyceride transfer protein, cholesteryl ester transfer protein activity, bile acid excretion, and preventing hepatic fatty acid synthesis, which was conducted by allicin and/or other parts in garlic (Sun et al., 2018; Qureshi et al., 1983; Gebhardt et al., 1993).

Furthermore, the levels of CRP (-23%) were decreased after prevention with six-week of garlic receiving. There are some studies which agree with our results about the effect of garlic on CRP levels such as Varshney et al. (2016), Mirzavandi et al. (2020), Koushki et al. (2021) Taghizadeh et al. (2019), Darooghegi et al. (2019), and van Doorn et al. (2006). In two meta-analyze studies, have been showed that supplementation with garlic could reduce the level of circulating CRP (Mirzavandi et al., 2020; Darooghegi et al., 2019). In a study by Taghizadeh et al. (2019), they confirmed that garlic supplementation would reduce serum CRP levels. However, the changes were related to the supplemental doses and baseline levels of serum. Similarly, Moosavian et al. (2020) were investigated the effect of garlic supplement effects on serum levels of some inflammatory biomarkers, clinical symptoms, and fatigue in women with active rheumatoid arthritis and found that after 8 weeks intervention with garlic supplementation, serum levels of CRP ($p = .018$) decreased significantly in the garlic group as compared with the placebo group. Moreover, after six-week of lemon receiving, cholesterol (-31.8%), glucose (-32.1%), TG (-66.4%), LDL (-19.9%), GOT (-42.4%), GPT (-42.4%), ALP (-58.7%), CRP (-23.2%), Cr (-39.7%), U. A (-51.2%), and urea (-19.3%) values were decreasing significantly. People with hyperlipidemia have an increased need for antioxidants and adding some antioxidant supplementation to their diet or medication may reduce their hyperlipidemia. Vitamin C in lemon, as an antioxidant, reduces fat peroxidation and oxidative damage of blood vessels. Vitamin C and the use of diets rich in these antioxidant vitamins maintain good health and reduce the risk of heart disease (Byers et al., 1992). Two main mechanisms are answerable for the changes in cholesterol levels. 1: By exerting an antioxidant effect that reduces LDL oxidation and extends its recognition by its receptors. 2: By applying a competitive effect) scheduled to constitutional similarity (with glucose in the process of glycation, HDL and LDL contribute to increased LDL catabolism and decreased HDL excretion (Khan et al., 2002).

In the present study, lipid profile and liver enzymes were significantly changed after 6 weeks of intervention with garlic and lemon. The mixture of garlic with lemon juice has been suggested as a potential supplementation therapy to non-alcoholic fatty liver, which is a disease characterized by hyperlipidemia and liver enzyme imbalance (Aslani et al., 2016). Due to the vitamin C in lemon and the fatty acid synthesis such as HDL and reduction in cholesterol absorption and the antioxidant properties of garlic, it is thought that the combination and simultaneous use of the two as an herbal medicine can strengthen the effect of each alone, with fewer side effects than chemical drugs on fat reduction. Have lipid profiles and liver enzymes in patients with hyperlipidemia. All these positive effects of garlic and lemon supplementation can be enhanced with the addition of aerobic exercise, as shown in our results. In similar research in line with the present study, the outcomes confirmed that the combination of lemon and garlic significantly effect on serum total cholesterol, LDL-C, and blood pressure (Aslani et al., 2016). Another mechanism of lemon is its contains copious amounts of nutrients, including vitamin C, flavonoids, phenolic compounds, and citric acid (Diab et al., 2016; Oboh et al., 2014; Ahmadet al., 2013). Lemon contains various beneficial properties, such as anti-oxidation, anti-cancer, immune function regulation, regulation of blood lipids and blood pressure, and the ability to promote wound healing (Wu et al., 2021). Therefore, lemon juices are confirmed as a protection against hypercholesterolemia, and it also can decrease total cholesterol, TG and the levels of LDL and increasing HDL (Oboh et al., 2015; Trovato et al., 1996). It is reported that fermented lemon juice can prevent hepatic injury by decreasing GOT and GPT levels, hepatic lipid peroxidation, splenomegaly, and liver water (Wu et al., 2021; Chen et al., 2018). Additionally, it could keep mitochondrial integrity and decrease oxidative stress damage by expanding the mitochondrial membrane potential (Wu et al., 2021; Hsieh et al., 2020). Similar with our study, Chen et al. (2018) in a study with the subject of (fermented lemon juice produces a variety of important biological activities, containing anti-inflammatory and antioxidant capabilities), they found that the contents of plasma GPT and GOT, hepatic lipid peroxidation, and splenomegaly are reduced significantly in rats under Fermented lemon juice treatment, and pathological examination of liver fibrosis is improved. It is reported that the use of lemon can also prevent hepatic injury by decreasing liver enzymes like GOT and GPT levels (Chen et al., 2018). Wu et al. (2021), in an animal study find the lemon fermented product declined lipid profile, cell proliferation and inhibited the lipid accumulation of 3T3-L1 adipocytes. Further, decreased body weight and fat tissue weight of rats, decreased serum TG, glucose, and increased serum HDL, lemon fermented product adjusted the mRNA expression of genes associated to lipid metabolism

(PPARγ, C/EBPα, SREBP-1c, HSL, ATGL, FAS, and AMPK). In another study by Trovato et al. (1966), reported that lyophilized citrus juices can decrease TG and LDL levels in rats.

In line with these findings, previous research has reported preventive effects of garlic, lemon (Wu et al., 2021; Trovato et al., 1996; Oboh et al., 2015; Hsieh et al., 2021; Jing et al., 2013; Hashemi et al., 2017; Chen et al., 2018), and aerobic exercise in fatty liver, atherosclerosis, and metabolic syndrome (Wu et al., 2021; Seo et al., 2012; Aslani et al., 2016; Batsis & Lopez-Jimenez, 2010; Sohn et al., 2012). Previous studies have reported similar beneficial effect with the garlic supplementation in the lipid profile (Banerjee &Maulik, 2002; Budoff et al., 2009; Durak et al., 2004; Mohammadi&Oshaghi, 2014).

Exercise alone or in combination with garlic or lemon supplementation can be useful in the treatment of patients experiencing from obesity and fatty liver (Khoobkhahi et al., 2019; Warshafsky et al., 1993). Physical activity enhances the secondary messenger substances in the skeletal muscles, which contributes to better glucose consumption and a reduction in insulin resistance (Kim et al., 2017; Torkamaneh et al., 2016). Studies in humans and rodents indicate that exercise has a positive effect on fatty liver and liver functions, independent of weight reduction. Exercise strengthens the activity of the liver glucagon, a stimulant for the glucose-producing pathways. The exercise-induced increase in glucagon activity is also responsible for some changes in the expression of those liver genes that are compatible with the increase in fat oxidation (Shamsoddini et al., 2015). All these properties of the exercise help in the control of hyperlipidemia and hypercholesterolemia, among other benefits. In line with our results in terms of liver enzymes reduction, Shamsoddini et al. (2015) reported exceptional liver enzyme and liver fat decreases with aerobic exercise. On the other hand, exercise at high intensities may produce oxidative stress (Ascensao et al., 2008). In this regard, garlic extract, and lemon juice have proven benefits to enhance antioxidant potential against exercise-induced oxidative stress, in part by modulating the activity of oxidizing enzymes, which may also serve as a beneficial agent on cardiovascular disease (Yoon et al., 2006).

These findings suggest that the use of garlic and lemon supplementation combined with aerobic exercise may help in the prevention of hyperlipidemia and hypercholesterolemia, being both associated with obesity and risk factors for cardiovascular disease.

CHAPTER 7.

STUDY APPLICATIONS

Due to the industrialization of societies and the subsequent sedentary lifestyle, obesity is one of the most important diseases of the 21st century and future centuries. Therefore, addressing the problem of obesity in parallel with the rising level of social welfare and mechanization of many human activities seems an inevitable necessity. As a result of the increasing trend of this disease and enduring the individual and social financial burden of this disease, determining the most appropriate treatment method with the least side effects, recommends physical activity with the use of medicinal plants.

Physical exercise, including aerobic and resistance training, is an effective way to improve the lipid profile and liver enzymes in overweight people, and accompanying, it is an effective and inexpensive strategy to control obesity. Further, the use of some medicinal plants with antioxidant properties and blood lipid-lowering effects can also be useful. Therefore, it suggests that the use of herbs such as berberis vulgaris L, cornus mas, lemon, and garlic along with any physical activity, including aerobic exercise or resistance is a key element, cheaper, more accessible and with fewer side effects in control and treatment of obesity.

CHAPTER 8.

STUDY LIMITATIONS

As with any scientific study, there were limitations to the research undertaken in this thesis and it is important to acknowledge these.

- The present study was performed only on male Wistar rats. Therefore, it is recommended to use female mice for further research and observe the difference between the sexes.
- There is the possibility that a longer duration training program would have shown more significant differences between the experimental groups.
- In the present study, in the first six weeks period, the animals used high-fat diet and then, for the second six weeks which was an intervention part, they used normal food during the intervention, it can be possible that changing the diet could affect the results.
- The limitations of our study must be considered. The number of subjects studied is small, and this means they may not be representative of the general population. Also, this limited statistical power to detect significant differences between groups.

CHAPTER 9.

FUTURE LINES OF THE RESEARCH

Taken together, these studies provide new insights into the role of some herbal medicine, dietary intake and exercise on lipid profile and liver enzymes. This will increase our understanding of the changes that after intake of herbal medicine and physical activities on obesity. At the end of this study, we can propose future lines of work to develop in relation to the effects of physical exercise in combination with some herbal medicine such as berberis vulgaris L, cornus mas, lemon and Garlic on lipid profile and liver enzymes, which has its origin in it:

- Considering that the present study was performed on 6 weeks of aerobic and resistance training, it is expected that conducting research with a longer duration between 8 to 12 weeks will have different effects. Therefore, it is recommended that research be conducted for a longer period.
- In this regard, research has been done on non-human subjects (male Wistar rats). It is recommended that aerobic and resistance exercises with herbal medicine consumption be performed on human subjects in all sexes (male and female).
- Based on the theoretical foundations of the research, it is recommended to be used with other different doses of berberis Vulgaris L, cornus mas, lemon, and garlic and for a longer period.
- Investigating in the difference between all sexes.
- It will be useful if we were able to measure muscle changes, also measure and look, heart, liver, and kidney tissues to detect any differences among the study.
- From the experience obtained in these studies, it could be interesting and necessary to design studies in humans that allow corroborating the transfer of the findings reached in this doctoral thesis.

CHAPTER 10.

CONCLUSIONS

Preliminary and summarized conclusion

The present study reveals that have regular exercise (aerobic or/and resistance exercise) and using herbal medicine (berberis vulgaris L, cornus mas, lemon, and garlic) could be a suitable alternative method for decreasing lipid profile and liver enzymes.

The results provided can be utilized to prevent and help to treat cardiovascular and fatty liver disease.

Article/study I

Use of regular exercise (aerobic and/or resistance) in combination with berberis vulgaris L extract intake can reduce blood lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity. In the present study, the best results were reached by combining berberis Vulgaris L with aerobic or resistance training. Finally, the hypothesis is confirmed in all parameters after six-week aerobic and/or resistance training in combination with berberis vulgaris L extract intake can reduce blood lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity.

Article/study II

According to the results of this paper, cornus Mas extract intake in combination with aerobic or resistance training may be recommended to improve fatty liver and obesity by improving the blood lipid profile, metabolic parameters, and liver enzyme levels. Therefore, the Cornus mas extract, and the exercise may be a viable alternative or adjuvant to the use of chemical medicine. Eventually, the hypothesis is confirmed in all parameters after six-week aerobic and/or resistance training in combination with cornus mas extract intake can decline metabolic parameters, and liver enzymes, and blood lipid profile in rats with diet-induced obesity.

Article/study III

Supported by the results achieved, this study argues strongly in favor of the use of aerobic exercise and herbal supplementation such as garlic and lemon in the prevention of earned obesity or cardiovascular disease and related factors such as hyperlipidemia or hypercholesterolemia. The combination of exercise and garlic and lemon intake indicated slightly (non-significantly in various cases) better results than their isolated use, which represents that their combination could provide additional benefits and that further research is needed on this matter. Ultimately, the hypothesis is confirmed in all parameters after six-week aerobic training in combination with garlic extract and lemon juice intake can prevent in increasing metabolic parameters, liver enzymes, and blood lipid profile in rats with diet-induced obesity.

Widely, it can be pointed out that aerobic and/or resistance training in combination with some herbal medicine such as berberis Vulgaris L, cornus mas, lemon and garlic is an effective method to improve lipid profile, metabolic syndrome and liver enzymes in rats with obesity, On the other hand, although the varied forms of intervention alone, are effective in improving lipid profile, liver enzymes and metabolic parameters, aerobic and/or resistance training in combination with use of herbal medicine (berberis Vulgaris L, cornus mas, lemon and garlic) has provided superior benefits in these parameters.

CHAPTER 11.

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Chapter12

ANNEXES

Annex I. Authorization of the ethics committee

Ref: P/18/155
Date: 25, 4, 2022
Appendix:

SKUMS
Shahrekord University of Medical Sciences

Shahrekord University of Medical Sciences
Vice Chancellor of Research and Technology

To whom it may concern

This is to certify that, Ms. Sara Torkamaneh as an investigator of the research project approved by Shahrekord University of Medical Sciences has collaborated. After studying the research project entitled: "The effect of consumption of Berberis Vulgaris L, Cornus mas, limon and garlic extract along with six weeks of aerobic and/or resistance training on liver enzymes and lipid profile serum of rats with fatty liver" This university approved the relevant project with ethical code in research 2-1-94, with the project management of Dr. Mahmoud Rafieian-Kopaei. This certificate issued upon her request.

Dr. Esfandiar Heydarian
Vice Chancellor of Research and Technology Deputy

MINISTRY OF HEALTH AND MEDICAL EDUCATION
ISLAMIC REPUBLIC OF IRAN
INTERNATIONAL RELATIONS DEPARTMENT
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Annex II. Study process pictures

1.Herbal extraction process

2. Animal treadmill

3.Animal ladder

4. Animal ladder

5. Gavage extract and/or juice process

Annex III. Publications of this Doctoral Thesis.

Proceeding

Supplementary Issue: Autumn Conferences of Sports Science. Costa Blanca Sports Science Events, 18-19 December 2020. Alicante, Spain.

Effects of black Berberis vulgaris L combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes in obese rats

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ABSTRACT

Purpose: The aim of this study was to investigate the effects of a six-week intake of Berberis vulgaris L in combination with resistance and aerobic exercise on the lipid profile, metabolic parameters, and liver enzymes of obese male rats. Methods: 56 male Wistar rats were divided into seven groups: 1) healthy control (n = 8); 2) hypercaloric fatty-food-based diet (n = 8); 3) aerobic exercise (AE, n = 8); 4) resistance exercise (RE, n = 8); 5) black Berberis vulgaris L extract intake (n = 8); 6) Berberis intake combined with aerobic exercise (BAE, n = 8); and 7) Berberis intake combined with resistance exercise (BRE, n = 8). All the rats (except the controls) were induced fatty liver by six weeks of a hypercaloric diet before the intervention. After six weeks of intervention, blood samples were taken to obtain cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), glucose of c-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and urea. Differences between groups were evaluated using the Kruskal Wallis test with post-hoc pairwise comparisons. Results: All the intervention groups significantly ($p < .05$) improved the parameters compared to the hypercaloric group in almost all the assessed parameters, reaching in many cases significantly better values than the healthy group (control). Similar results were obtained between the experimental groups; however, the outcomes were slightly better (non-significant differences) for the combination of the Berberis extract and both exercise methodologies. Conclusion: The use of herbal medicines such as Berberis vulgaris L in combination with aerobic or resistance exercises may be useful in the prevention of cardiovascular disease by improving risk factors such as blood lipid levels.

Keywords: Aerobic; Resistance training; Physical activity; Fatty liver; Cardiovascular disease; Wistar rats.

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INTRODUCTION

According to the latest report from American Heart Association, cardiovascular disease (CVD) is one of the leading causes of mortality worldwide, accounting for 30% of deaths caused annually (Mazidi & Speakman, 2018). Obesity and overweight are among the most important risk factors for CVD. Previous studies have reported that mortality from CVD is more than three times higher in obese people than in normal-weight people (Aslani et al., 2016). Excessive adipose tissue increases obesity, overweight, and also CVD risk factors (Atkins et al., 2014). Increasing liver enzymes as a result of obesity and overweight may lead to liver cirrhosis and hepatocellular carcinoma associated with non-alcoholic fatty liver disease (NAFLD) (Maliakkal, 2020).

Due to these facts, it is necessary to continue the efforts to control NAFLD and CVD risk factors such as obesity and overweight (Liu et al., 2019). Low concentration of high-density lipoprotein (HDL) and high levels of total cholesterol, triglycerides, very-low-density lipoprotein, low-density lipoprotein (LDL), and increased body mass index (BMI) are associated with CVD (Yang et al., 2011). One of the best ways to reduce obesity and control blood lipoproteins is a proper diet and regular exercise (Wood et al., 1991; Shamsoddini et al., 2015). The use of medicinal herbs is one of the new approaches in the treatment of many diseases (Zhan et al., 2017). Diet, lifestyle, and genetic and environmental factors can increase obesity and chronic diseases. Behavioural interventions and healthy lifestyles are the best ways to lose weight; however, lifestyle changes could be difficult and challenging for many obese people (Haselgrübler et al., 2019). Over the years, many strategies such as drug treatments have been used to lose weight and control obesity. However, several anti-obesity drugs have serious adverse effects such as anxiety, depression, and increased CVD risk. Therefore, some medicinal herbs could be used as an alternative strategy to manage obesity with less toxic side effects than chemical medicine (Haselgrübler et al., 2019; Kang & Park, 2012).

One of these herbs with antioxidant properties is Berberis vulgaris L, a shrub of the genus Berberis, which is mainly cultivated in the region of South Khorasan in Iran and is one of the few plants whose root, peel, stem, leaves, flower, and fruits are used for various nutritive and medicinal purposes (Taheri et al., 2012). This plant is cultivated in many regions of the world and has a long history of use in traditional medicine (Dulić et al., 2019; Tabeshpour et al., 2017). Some of the alkaloids in black barberry when chemically analysed include berberine, palmatine, oxyaconthine, and berbamine, having each medicinal benefit. Berberine, the most significant compound of all, has a plethora of therapeutic benefits, including antibacterial, anti-tumoral, and anti-inflammatory properties, ameliorative effect on neural disorders, and preventive effect in coronary artery disease (Cao et al., 2020; Imenshahidi et al., 2019; Zarei et al., 2015).

On the other hand, recent reviews and meta-analyses have shown that physical exercise (both aerobic and resistance) has a significant effect on CVD (MacDonald et al., 2016). It has also been shown to reduce cardiac morbidity by 5%, stroke by 8-14%, and all-cause mortality by 4% in the average population (Schroeder et al., 2019). Improving metabolically active lean muscle mass is important for improving glucose metabolism (Kamada et al., 2017; Yang et al., 2014). Short-term randomized trials reported that resistance training reduces weight and also plays a role in improving CVD risk factors such as lipid profile (Miyachi, 2013). According to the current physical activity guidelines, it is recommended to perform resistance and aerobic exercises more than two times per week (Kamada et al., 2017; World Health Organization, 2017). Therefore, physical exercise is considered effective in weight loss and maintaining a reduced weight (Wang & Xu, 2017). They may also be effective in reducing lipid aggregation in fatty liver disease. Exercise leads to increased functional levels of glucagon (a stimulant for glucose production pathways) in the liver. The increased functional level of glucagon caused by exercise can lead to changes in the expression of this particular gene corresponding to increased fat oxidation (Bernhardt et al., 2016; Torkamaneh et al., 2016). Exercise leads to a decrease in body fat levels and leads to long-term improvement in fatty liver disease. The combination of herbs having antioxidant properties and some exercises could likely reduce cardiovascular risk factors.

Therefore, the present study aimed to investigate the effects of a six-week daily intake of black Berberis vulgaris L, physical exercise (aerobic and resistance training), and their combination on the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, c-reactive protein [CRP], urea), and liver enzymes (alanine aminotransferase [ALT], aspartate aminotransferase [AST]) in obese male rats. We hypothesized that the combination of physical exercise and black Berberis vulgaris L extract will improve to a greater extent the assessed parameters, with no big difference between the aerobic and resistance exercise.

MATERIAL AND METHODS

Participants

In this study, 56 male Wistar rats (age: six weeks; average weight: 200g) were selected and divided into seven groups: 1) control following a normocaloric diet and no treatment (n = 8); 2) hypercaloric (n = 8) following a fatty-food-based diet and no treatment; 3) aerobic exercise (AE, n=8); 4) resistance exercise (RE, n = 8); 5) ingestion of black Berberis vulgaris L extract (B, n = 8); 6) ingestion of Black Berberis in combination with aerobic exercise (BAE, n = 8); and 7) ingestion of Black Berberis in combination with resistance exercise (BRE, n = 8). All the groups were homogeneous in terms of number, breed, age, and weight. All ethical considerations and working protocols of this study were approved by Shahrekord's committee for monitoring Laboratory Animal Rights in Medical Sciences University with code 2-1-94.

The rats were kept for 12 weeks in the Shahrekord University Animal Laboratory Medical Sciences at a temperature between 22 and 27ºC. The room was illuminated in a controlled manner (12 hours off and 12 hours on). Six weeks were used to induce hyperlipidemia and hypercholesterolemia in the rats and six weeks to carry out the intervention. The hypercaloric, AE, RE, B, BAE, and BRE groups (n = 48) were induced with hyperlipidemia and hypercholesterolemia by diet (see below "*Diet formulation*" section) and 8 control rats remained healthy following a normocaloric diet.

Intervention

Diet formulation

During the six weeks before the intervention, Persintra-M emulsion was included in the diet of the 48 selected rats to induce them with hyperlipidemia. This emulsion was prepared from egg yolk and contained 1g of cholesterol, palm oil of 80% purity, and intralipid liquid per 100g of egg yolk. To produce hypercholesterolemia, 25mg of cholesterol were concentrated on 2ml and daily administered to the rats. In addition, palm oil, sugar, and cow fat were added to the rat's meal to bring it to 1% cholesterol and 20% sugar.

During the intervention period (six weeks) only the hypercaloric group continued with the above explained hypercaloric diet and the rest of the groups switched to a normocaloric animal diet. The controls remained all the 12 weeks with a normocaloric diet. Food and water was freely available to all the rats throughout the study.

Aerobic training program

The six-week (three sessions per week) aerobic training program was performed on a treadmill and was divided into three phases (two weeks of adaptation, two weeks of overload, and two weeks of maintenance/consolidation). A familiarization period was carried out before the aerobic training program (see Table 1) to familiarize the rats with the materials and the procedures. All the phases used no inclination (0°). A 5-minute walk at 10m/min was used as a warm-up and cool-down in every session. The control group walked five minutes once per week at 10m/min and 0º during the six weeks of the intervention.

To stimulate the rats to walk, an auditory stimulus (tapping on the wall of the treadmill) was used. For this purpose, a low-voltage electrical stimulus was initially used together with an audio stimulus. After the rats were conditioned to two stimuli simultaneously, the single audio stimulus was used in later sessions to comply with the ethics of animal experimentation.

Table 1. Aerobic training program.

	Adaptation phase		Overload phase		Maintenance phase	
	First week	Second week	Third week	Fourth week	Fifth week	Sixth week
Speed	8 m/min	12 m/min	18 m/min	20 m/min	20 m/min	20 m/min
Time	10 min	20 min	30 min	40 min	40 min	40 min

Resistance exercise

A one-meter ladder with 50 steps separated by 2cm, a width of 50cm, and an inclination of 85º was used for the resistance training. A load pouch attached to the proximal portion of the rats' tail (1-2cm after the hair growth point) was used as resistance. Prior to the six weeks of the resistance training program, a familiarization period without external weight was carried out. The number of repetitions of the training program (see Table 2) in each session ranged from 8 to 12 repetitions, with a two-minute rest in between; each repetition had to be completed in 8 seconds. At the beginning and end of the exercise, 5 repetitions without weight were used as a warm-up and cool-down. The rats were placed at the bottom of the ladder and were motivated to climb the ladder by gently pushing on their backside. No rewards or abnormal stimuli such as electrical stimulation, cold water, or air pressure were used in this study.

Table 2. Resistance training program.

	Adaptation phase		Overload phase		Maintenance phase	
	First week	Second week	Third week	Fourth week	Fifth week	Sixth week
Rats' weight average	240g	252g	260g	266g	277g	287g
Ratio overload per bodyweight	50%	75%	85%	95%	110%	120%
Average weight used	120g	189g	221g	253g	305g	344g

Black Berberis vulgaris L extraction and use

Samples of black Berberis vulgaris L extract were prepared and used after confirmation from the University's Center for Herbal Medicine Research. The Berberis root was pulverized using a mechanical mill (Moulinex, Osaka, Japan) and the powder was dissolved in 2 litres of 70% alcohol and 30% water. The solution was kept at laboratory temperature for 72 hours. It was then filtered and condensed in a rotary apparatus and kept in an incubator at a temperature of 37°C for three days. A dosage of 400 mg/kg was administered daily to the rats by gavage.

Measures

After six weeks, blood samples were taken in a single session. The rats were anesthetized by intraperitoneal injection of ketamine (70mg/kg) and xylazine (3-5mg/kg). Blood samples were taken from the rats' hearts and placed in a Sigma centrifuge (Rontgen Co., Remscheid, Germany) at 5000 revolutions. The serum was separated using Pars Azmoon kits (Pars Azmoon Co., Tehran, Iran) and transferred to a BT3000 analyser (Biotecnica Instrument S.p.A., Rome, Italy). Values of the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, CRP, urea), and liver enzymes (ALT, AST) were calculated.

Data analysis

After a basic data curation, the normality of the distribution and homogeneity of variances of each variable was assessed through the Shapiro-Wilk and Levene tests, respectively. None of the variables complied with normality and homoscedasticity assumption among the seven groups. Therefore, Kruskal Wallis testing was conducted. The effect size was reported as the eta squared (η^2) where $0.01 < \eta^2 < 0.06$ constitutes a small effect, $0.06 \leq \eta^2 \leq 0.14$ a medium effect and $\eta^2 > 0.14$ constitutes a large effect. After this, paired post-hoc tests with no adjustment evaluated significant differences. A 95% confidence level (significance $p < .05$) was accepted as statistically significant. Statistical analysis was carried out using commercial software IBM SPSS Statistics for Macintosh (Version 26.0; IBM Corp., Armonk, NY). All data are reported as the means ± the standard deviations and the 95% confidence interval.

RESULTS

Twelve weeks of fatty food diet were enough to significantly worsen almost all the variables in the hypercaloric group compared to the controls. The Kruskal Wallis test indicated that significant differences existed among the groups in all the study variables, with AST: $H(6) = 36.37$, $p < .001$, $\eta^2 = 0.62$; ALT: $H(6) = 18.83$, $p = .004$, $\eta^2 = 0.26$; CRP: $H(6) = 28.07$, $p < .001$, $\eta^2 = 0.45$; creatinine: $H(6) = 35.51$, $p < .001$, $\eta^2 = 0.60$; urea: $H(6) = 35.50$, $p < .001$, $\eta^2 = 0.60$; cholesterol: $H(6) = 38.31$, $p < .001$, $\eta^2 = 0.66$; glucose: $H(6) = 22.22$, $p = .001$, $\eta^2 = 0.33$; triglycerides: $H(6) = 20.62$, $p = .002$, $\eta^2 = 0.30$; LDL: $H(6) = 28.10$, $p < .001$, $\eta^2 = 0.45$; HDL: $H(6) = 19.15$, $p = .004$, $\eta^2 = 0.27$. Tables 3 and 4 present the outcomes of the intervention in the liver enzymes and metabolic parameters.

DISCUSSION

The purpose of the present study was to analyse the effects of physical exercise (aerobic and resistance) in combination with black Berberis vulgaris L extract on the blood parameters (lipid profile, liver enzymes, and metabolic parameters) of obese male rats. To assess this, a control group was kept healthy and the other six groups were fed with a hypercaloric diet for six weeks. After this period, one group continued with the hypercaloric diet and the other five switched to a normocaloric diet and different treatment programs (aerobic or resistance exercise, Berberis vulgaris L extract intake, and aerobic or resistance exercise combined with the intake of Berberis vulgaris L extract). The most noteworthy findings were that a six-week treatment program was enough to significantly ($p < .05$) revert the negative values raised by the hypercaloric diet, showing all the treatments improvements in almost all the assessed variables. The combination of the exercise with the ingestion of the Berberis extract provided slightly better results, although the differences between the treatments were not significant, which partially supports the study hypothesis. Concerning the comparison between aerobic and resistance training in improving the assessed parameters, not many significant differences were encountered. It is worth highlighting that none of both training methodologies significantly improved the cholesterol after six weeks and that the aerobic training did not improve urea levels compared to the hypercaloric-diet group.

Table 3. Levels of liver enzymes (AST/GOT and ALT/GPT) and metabolic parameters (CRP, creatinine, and urea) in all experimental groups (all n = 8).

Group	AST	ALT	CRP	Creatinine	Urea
1 (Control)	93.50±9.94$^{(3),4,5,6,7}$ [85.18-101.81] Median: 97.50 IQR: 17.25	41.37±7.87 [34.82-47.92] Median: 43.00 IQR: 10.50	16.55±1.47 [15.31-17.78] Median: 17.10 IQR: 0.85	0.75±0.07^{3,4,5,6,7} [0.68-0.81] Median: 0.70 IQR: 0.10	36.00±5.50^{2,3,4} [31.35-40.46] Median: 34.50 IQR: 8.00
2 (Hyper)	155.62±28.37^{3,4,5,6,7} [131.89-179.35] Median: 148.00 IQR: 52.00	72.50±17.33* [58.00-86.99] Median: 66.50 IQR: 19.75	22.93±0.96* [22.12-23.17] Median: 23.05 IQR: 1.50	0.98±0.14^{3,4,5,6,7} [0.86-1.10] Median: 1.00 IQR: 0.10	59.50±14.66$^{(4),5,6,7}$ [47.23-71.76] Median: 52.50 IQR: 19.75
3 (AE)	55.87±24.12 [35.70-76.04] Median: 51.50 IQR: 36.00	48.62±15.81 [35.39-61.85] Median: 44.50 IQR: 28.75	17.23±1.30$^{(6)}$ [16.14-18.32] Median: 17.25 IQR: 2.63	0.46±0.09 [0.38-0.53] Median:0.50 IQR: 0.10	47.75±3.65^{5,6,7} [44.69-50.80] Median: 48.50 IQR: 6.25
4 (RE)	38.87±12.63 [28.31-49.43] Median: 36.50 IQR: 9.50	50.00±8.51$^{(6)}$ [42.87-57.12] Median: 49.50 IQR: 10.00	17.32±0.93$^{(6)}$ [16.54-18.10] Median: 17.15 IQR: 1.25	0.48±0.08 [0.41-0.55] Median: 0.50 IQR: 0.17	45.87±4.29$^{(5),6,7}$ [42.28-49.46] Median: 46.00 IQR: 8.50
5 (Berberis)	36.75±8.04 [30.02-43.47] Median: 36.00 IQR: 14.25	49.50±14.18$^{(6)}$ [37.64-61.35] Median: 49.00 IQR: 27.75	17.20±1.18$^{(6)}$ [16.20-18.19] Median: 17.30 IQR: 1.40	0.46±0.05 [0.41-0.50] Median: 0.50 IQR: 0.10	40.50±5.23 [36.12-44.87] Median: 42.50 IQR: 7.75
6 (BAE)	35.75±5.14 [31.44-40.05] Median: 38.00 IQR: 8.50	40.25±3.95 [36.94-43.55] Median:40.50 IQR: 6.25	15.87±0.90 [15.11-16.63] Median: 15.57 IQR: 1.78	0.48±0.13 [0.37-0.60] Median: 0.45 IQR: 0.10	37.50±3.89 [34.24-40.75] Median: 37.50 IQR: 6.25
7 (BRE)	38.50±10.09 [30.05-46.96] Median: 37.50 IQR: 12.25	44.88±16.39 [31.17-58.59] Median: 46 IQR: 32.50	16.30±1.03 [15.43-17.16] Median: 16.40 IQR: 1.75	0.45±0.09 [0.37-0.52] Median: 0.45 IQR: 0.10	36.75±6.04 [31.69-41.80] Median: 34.50 IQR: 8.50

*Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference (p < .05) with all the rest of the groups; 1,2,3,4,5,6,7: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level 0.5 < p < 1.3); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; BAE: black Berberis vulgaris extract intake in combination with aerobic exercise; BRE: black Berberis vulgaris extract intake in combination with resistance exercise; AST: aspartate aminotransferase (also known as GOT); ALT: alanine aminotransferase (also known as GPT); CRP: C-reactive protein.*

Supporting our results, Berberis vulgaris is recognized within the scientific body of knowledge as one of the functional foods that could be beneficial for the management of hyperlipidemia and chronic inflammation in humans, having a strong protective effect on the cardiovascular system (Changizi Ashtiyani et al., 2013; Emamat et al., 2020; Fatehi et al., 2005). Previous expert literature reported that the intake of Berberis vulgaris can reduce lipid profile and liver enzymes in serum (Changizi Ashtiyani et al., 2013; Emamat et al., 2020; Fatehi et al., 2005; Lazavi et al., 2018; Iloon Kashkooli et al., 2015; Mohammadi et al., 2014; Mohammadi et al., 2011; Shidfar et al., 2012; Taheri et al., 2012; Vrzal et al., 2005). The antioxidant activity of the Berberis vulgaris and its content in berberine and polyphenolic compounds can reduce lipid peroxidation, improve lipid profile, liver function, and acid secretion (Firouzi et al., 2018; Lazavi et al., 2018).

Table 4. Levels of lipid profile in all experimental groups (all n = 8).

Group	Cholesterol	Glucose	Triglycerides	LDL	HDL
1 (Control)	49.25±10.11^{2,3,4,5} [40.79-57.70] Median: 49.00 IQR: 2.75	126.75±8.29^{2,3,4} [119.83-133.68] Median: 128.00 IQR: 9.00	64.25±17.24 [49.83-78.66] Median: 62.50 IQR: 26.25	10.88±3.48 [7.96-13.79] Median: 10.05 IQR: 6.79	37.40±4.47$^{2,(3)}$ [33.65-41.14] Median: 37.45 IQR: 8.00
2 (Hyper)	117.62±41.16^{5,6,7} [83.20-152.04] Median: 100.50 IQR: 77.00	205.75±41.71$^{(3),(4),5,6,7}$ [170.87-204.62] Median: 206.50 IQR: 58.00	117.37±26.46* [95.25-139.49] Median: 110.50 IQR: 16.50	38.30±5.35* [33.82-42.77] Median: 36.40 IQR: 8.98	26.38±5.34$^{(3),4,5,6,7}$ [21.91-30.85] Median: 27.55 IQR: 9.88
3 (AE)	85.00±15.95^{6,7} [72.16-98.83] Median: 81.50 IQR: 13.50	156.37±25.34$^{(7)}$ [135.18-177.56] Median: 156.00 IQR: 35.50	70.75±15.74 [57.58-83.91] Median: 77.00 IQR: 28.50	14.55±2.93 [12.10-17.01] Median: 14.43 IQR: 2.72	33.15±3.48$^{(5),(7)}$ [30.23-36.06] Median: 31.75 IQR: 6.47
4 (RE)	80.75±14.69$^{6,(7)}$ [68.46-93.03] Median: 79.50 IQR: 24.50	162.87±26.45^{7} [140.75-184.99] Median: 171.5 IQR: 34.75	68.87±11.51 [59.24-78.50] Median: 68.00 IQR: 23.75	15.47±2.94 [13.01-17.93] Median: 15.80 IQR: 5.25	36.98±5.33 [32.52-41.44] Median: 36.15 IQR: 5.97
5 (Berberis)	70.62±10.30^{6} [62.00-79.24] Median: 72.00 IQR: 19.75	147.75±36.51 [117.22-178.27] Median: 147.50 IQR: 61.50	75.25±19.03 [59.33-91.16] Median: 74.50 IQR: 15.50	14.46±2.78 [12.13-16.78] Median: 14.25 IQR: 5.15	37.81±8.29 [30.87-44.74] Median: 38.80 IQR: 14.20
6 (BAE)	50.12±8.25 [43.22-57.02] Median: 48.50 IQR: 9.00	149.25±17.54 [134.57-163.92] Median: 154.00 IQR: 35.50	66.62±11.09 [57.34-75.90] Median: 66.50 IQR: 21.75	12.51±2.68 [10.27-14.76] Median: 12.95 IQR: 5.73	34.53±2.88 [32.12-36.94] Median: 35.20 IQR: 5.13
7 (BRE)	63.37±12.33 [53.05-73.69] Median: 62.50 IQR: 16.00	131.75±17.33 [117.25-146.24] Median: 130.00 IQR: 9.50	70.62±16 [57.24-84.00] Median: 64.00 IQR: 32.25	12.76±1.32 [11.65-13.86] Median: 12.70 IQR: 1.12	38.25±6.33 [32.95-43.54] Median: 36.45 IQR: 9.85

*Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p < .05$) with all the rest of the groups; 1,2,3,4,5,6,7: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5 < p < 1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; BAE: black Berberis vulgaris extract intake in combination with aerobic exercise; BRE: black Berberis vulgaris extract intake in combination with resistance exercise; AST: aspartate aminotransferase (also known as GOT); ALT: alanine aminotransferase (also known as GPT); CRP: C-reactive protein.*

The usefulness of combining this nutritional supplement with physical exercise is supported by the results of our study, with significant differences (slightly better results for the combination of the extract and both exercise methodologies) or tendencies in the ALT, CRP, urea, cholesterol, glucose, and HDL (see Tables 3 and 4). Also, several previous studies have reported a beneficial effect on weight loss, NAFLD, and CVD after taking Berberis vulgaris and performing aerobic and resistance training (Schroeder et al., 2019; Torkamaneh et al., 2016). It has been also reported that regular aerobic exercise improves the lipid profile (Ghanbari et al., 2007; Kazeminasab et al., 2013; Kraus et al., 2002; LeMura et al., 2000). Regular aerobic or resistance training with caloric restriction is a common therapy to control obesity. Although the specific mechanisms of the exercise-induced improvement in the lipid profile remain unclear, previous research suggests that it is due to an increase in lipid consumption (Earnest et al., 2013; Wang & Xu, 2017). One possible mechanism is the increased activity of lipoprotein lipase (LPL), which is responsible for the hydrolysis of fasting triacylglycerol, ultra-low-density lipoproteins (chylomicrons), and very-low-density lipoprotein (Calabresi et al., 2010; Miyasita et al., 2010). Exercise can strongly develop plasma LPL activity, which promotes LPL-mediated triglycerides hydrolysis and therefore, improves the lipid profile (Kobayashi et al., 2007; Miyashita et al., 2010; Wang & Xu, 2017). Another mechanism underlying the beneficial effects of regular exercise is related to fat utilization through increased lipid oxidation during exercise (Matsuura et al., 2001).

Taken together, all the outcomes of this research suggest that restricting the calories to a normocaloric diet, altogether with the use of Berberis vulgaris extract and/or with aerobic and resistance training may be effective in the treatment of CVD and also NAFLD. Both treatments (exercise and Berberis extract) proved useful in improving the assessed parameters, however, their combination resulted in slightly better values.

CONCLUSION

In conclusion, regular exercise (aerobic and/or resistance) and Berberis vulgaris extract intake can reduce blood lipid profile, metabolic parameters, and liver enzymes in rats with diet-induced obesity. In the present study, the best results were obtained by combining Berberis Vulgaris L with aerobic or resistance training. Thus, regular aerobic or resistance training in combination with the intake of Berberis vulgaris may have a positive effect on certain risk factors to cardiovascular and fatty liver disease, such as hyperlipidemia and obesity.

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ARTICLE II

Proceeding

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Effects of Cornus mas extract combined with aerobic and resistance exercise on blood metabolic parameters and liver enzymes of obese rats

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ABSTRACT

Purpose: The purpose was to investigate the effects of six weeks of resistance or aerobic exercise combined with the intake of Cornus mas extract on the lipid profile, metabolic parameters, and liver enzymes of obese rats. Methods: 49 male Wistar rats were divided into seven groups: 1) healthy control (n = 7); 2) hypercaloric fatty-food-based diet (n = 7); 3) aerobic exercise (AE, n = 7); 4) resistance exercise (RE, n = 7); 5) Cornus mas extract intake (C, n = 7); 6) Cornus mas combined with aerobic exercise (CAE, n = 7); and 7) Cornus mas combined with resistance exercise (CRE, n = 7). All the rats (except the controls) were induced fatty liver by six weeks of a hypercaloric diet before the intervention. After the six-week intervention, blood samples were taken to obtain levels of triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), cholesterol, glucose, c-reactive protein (CRP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, and urea. A one-way ANOVA or the Kruskal Wallis tests for the non-normally distributed variables, with post-hoc pairwise comparisons, assessed differences between groups. Results: All the intervention groups significantly ($p < .05$) improved the parameters compared to the hypercaloric group in almost all the assessed parameters, reaching in many cases significantly better values than the healthy group (control). Adding the Cornus supplementation to the exercise resulted in slightly non-significant better values. Conclusion: Cornus mas extract and aerobic or resistance training may be helpful to treat fatty liver and also reduce the lipid profile levels.
Keywords: Aerobic; Resistance training; Physical activity; Fatty liver; Cardiovascular disease; Wistar rats.

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INTRODUCTION

The concurrent epidemic of metabolic diseases such as obesity, type 2 diabetes, and non-alcoholic fatty liver disease (NAFLD) has been increasing in both developed and developing countries (El Hadi et al., 2019; Tomeno et al., 2020), being a major risk factor for cardiovascular disease (CVD) (Ismaiel et al., 2019). According to the World Health Organization, CVD is the cause of 18 million deaths per year.

NAFLD is the most common liver disease (Iloon Kashkooli et al., 2015) and is a key risk factor for CVD and diabetes type 2 (Della Pepa et al., 2017). NAFLD refers to a range of liver diseases caused by abnormal fatty deposits in the liver and a comprehensive spectrum of histological liver abnormalities ranging from simple triglyceride accumulation in hepatocytes to non-alcoholic fatty liver (NAFL) and non-alcoholic steatohepatitis (NASH; Tomeno et al., 2020). Furthermore, NAFLD can lead to death if it progresses to cirrhosis and/or hepatocellular carcinoma (liver cell cancer; Reid, 2006). Previous studies show that liver enzyme levels such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST), formerly called serum glutamic pyruvic transaminase (GPT) and serum glutamic oxaloacetic transaminase (GOT), respectively (Huang et al., 2006), are some readily available factors (perhaps the best) for assessing liver status (Yıldırım et al., 2010). In this sense, the increase in ALT levels a common symptom of advanced fatty liver disease or hepatic steatosis in 80 to 90 percent of cases. ALT increases are associated with inflammation caused by fat accumulation in the liver, abdominal obesity, metabolic syndrome, dyslipidemia, hyperglycemia, hypertension, high blood pressure, and type 2 diabetes (Hallsworth et al., 2011). Determining the most appropriate treatment for NAFLD is very important due to its increasing trend and the financial, individual, and social burden of this disease.

Exercise is an important part of the overall approach to treating fatty liver disease. In many obese individuals, weight loss can be achieved through increased physical activity (Stevanović et al., 2020). Lipid profile is characterized by an increase in triglycerides and a decrease in high-density lipoprotein (HDL) levels, which is associated with other metabolic risk factors, including abdominal obesity and insulin resistance (a major cause of fatty liver) (Lehto et al., 1997). Aerobic exercise, due to the lipolysis processes involved in aerobic energy supply, reduces plasma triglycerides and increases HDL (Thompson & Rader, 2001), which is a good way to reduce liver fat and improve liver damage indicators in patients with NAFLD (Yavari et al., 2012). Based on their experiments, researchers have reported a significant inverse relationship between fitness and cardio-respiratory scores and liver fat in NAFLD patients (Nikroo et al., 2011; Zelber-Sagi et al., 2011). Resistance training can improve muscle mass, strength, and power; increase insulin sensitivity and daily energy expenditure (Dunstan et al., 2002); therefore, it is used as a health-promoting tool in the elderly and obese.

Recently, much thought has been given to the role of natural products in the treatment of various diseases such as diabetes, different microbial strains, inflammation, oxidative stress, and also cancer. Besides physical exercise for weight loss and treatment of fatty liver, the use of herbal medicines for this purpose could be a good alternative to non-toxic treatments for curing some diseases (Tiptiri-Kourpeti et al., 2019), due to their fewer side effects among other reasons (Abdollahi et al., 2014; Lietava et al., 2019). One of these herbs is Cornelian cherry. Its scientific name is Cornus mas-land and it belongs to the genus Cornaceae. Its fruits are rich in anthocyanins such as cyanidin, peonidin, pelargonidin, and petunidin, and also contain bioflavonoids, vitamin C, and ursolic acid. The anthocyanins lead to increased insulin secretion (pelargonidin increases insulin secretion up to 1.4 times), amelioration of insulin resistance, and improvement of hyperlipidemia (Dayar et al., 2020). Cornuse mas is used in Chinese and Iranian traditional medicine to treat diabetes and high blood lipids and their complications (Abdollahi et al., 2014; Lietava et al., 2019).

Due to all the aforementioned facts, the purpose of the present study was to explore the effects of physical exercise (aerobic and resistance training), intake of Cornuse mas, and their combination on the lipid profile (triglycerides, HDL, low-density lipoprotein [LDL], cholesterol), metabolic parameters (glucose, creatinine, c-reactive protein [CRP], urea), and liver enzymes (ALT, AST) in obese male rats. We hypothesized that the combination of physical exercise and Cornuse mas extract will improve to a greater extent the assessed parameters, with no big difference between the aerobic and resistance exercise.

MATERIAL AND METHODS

Participants

49 male Wistar rats (age: six weeks; average weight: 200g) were randomly assigned to seven experimental groups: [1] control (n = 7) following a normocaloric diet and no treatment; [2] hypercaloric (n = 7) following a high-fat diet and no treatment; [3] aerobic exercise (AE, n = 7); [4] resistance exercise (RE, n = 7); [5] Cornus mas extract intake (C, n = 7) following no exercise program; [6] Cornus mas extract intake in combination with aerobic exercise (CAE, n = 7); [7] Cornus mas extract intake in combination with resistance exercise (CRE, n = 7). All the groups were homogeneous in terms of number, breed, age, and weight. All ethical considerations and working protocols of this study were approved by Shahrekord's committee for monitoring Laboratory Animal Rights in Medical Sciences University with code 2-1-94.

The rats were kept for 12 weeks in the Shahrekord University Animal Laboratory Medical Sciences at a temperature between 22 and 27ºC. The room was illuminated in a controlled manner (12 hours off and 12 hours on). Six weeks were used to induce the fatty liver in the rats and six weeks to carry out the intervention. The hypercaloric, AE, RE, C, CAE, and CRE groups (n = 42) were induced with hyperlipidemia and hypercholesterolemia by diet (see below "*Diet formulation*" section) and 7 rats remained healthy following a normocaloric diet (controls).

Intervention

Diet formulation

During the six weeks before the intervention, the selected 42 rats were daily fed by gavage with a specific diet to induce hyperlipidemia and hypercholesterolemia. More concretely, Persintra-M was prepared from egg yolk to induce hyperlipidemia (1g of cholesterol, palm oil of 80% purity, and intralipid fluid per 100g of egg yolk) and 25mg of cholesterol were condensed to 2ml to induce hypercholesterolemia. In addition, the rat's meal was brought to 1% cholesterol and 20% sugar using palm oil, sugar, and cow fat.

During the intervention period (six weeks) only the hypercaloric group continued with the above explained hypercaloric diet and the rest of the groups switched to a normocaloric animal diet. The controls remained all the 12 weeks with a normocaloric diet. Water and food was freely available to all the rats throughout the study.

Aerobic training program

The six-week (three sessions per week) aerobic training program was performed on a treadmill and was divided into three phases (two weeks of adaptation, two weeks of overload, and two weeks of maintenance/consolidation). A familiarization period was carried out before the aerobic training program (see Table 1) to familiarize the rats with the materials and the procedures. All the phases used no inclination (0°). A 5-minute walk at 10m/min was used as a warm-up and cool-down in every session. The control group walked five minutes once per week at 10m/min and 0º during the six weeks of the intervention.

To stimulate the rats to walk, an auditory stimulus (tapping on the wall of the treadmill) was used. For this purpose, a low-voltage electrical stimulus was initially used together with an audio stimulus. After the rats were conditioned to two stimuli simultaneously, the single audio stimulus was used in later sessions to comply with the ethics of animal experimentation.

Table 1. Aerobic training program.

	Adaptation phase		Overload phase		Maintenance phase	
	First week	Second week	Third week	Fourth week	Fifth week	Sixth week
Speed	8 m/min	12 m/min	18 m/min	20 m/min	20 m/min	20 m/min
Time	10 min	20 min	30 min	40 min	40 min	40 min

Resistance training program

A one-meter ladder with 50 steps separated by 2cm, a width of 50cm, and an inclination of 85º was used for the resistance training. A load pouch attached to the proximal portion of the rats' tail (1-2cm after the hair growth point) was used as resistance. Prior to the six weeks of the resistance training program, a familiarization period without external weight was carried out. The number of repetitions of the training program (see Table 2) in each session ranged from 8 to 12 repetitions, with a two-minute rest in between; each repetition had to be completed in 8 seconds. At the beginning and end of the exercise, 5 repetitions without weight were used as warm-up and cool-down. The rats were placed at the bottom of the ladder and were motivated to climb the ladder by gently pushing on their backside. No rewards or abnormal stimuli such as electrical stimulation, cold water, or air pressure were used in this study.

Table 2. Resistance training program.

	Adaptation phase		Overload phase		Maintenance phase	
	First week	Second week	Third week	Fourth week	Fifth week	Sixth week
Rats' weight average	240g	252g	260g	266g	277g	287g
Ratio overload per bodyweight	50%	75%	85%	95%	110%	120%
Average weight used	120g	189g	221g	253g	305g	344g

Cornus mas extraction and use

Samples of Cornus mas were procured from reputable suppliers and used after confirmation from the Center for Herbal Medicine Research of the University. The plant was pulverized using a mechanical mill (Moulinex, Osaka, Japan) and dissolved in 2 litres of alcohol (70%) and water (30%). The solution was left to stand for 72h at laboratory temperature. It was then filtered and condensed in a rotary apparatus and kept in an incubator at a temperature of 37°C for three days. A dosage of 400mg of Cornus mas per one kilogram of body weight was administered daily to the rats by gavage.

Measures

After the six-week intervention, another session was used to extract the blood samples. The rats were anesthetized by an intraperitoneal injection of ketamine (70mg/kg) and xylazine (3-5mg/kg). Blood samples were taken from their hearts and were introduced in a Sigma centrifuge (Rontgen Co., Remscheid, Germany) at 5000 revolutions. At this point, the serum was transferred using Pars Azmoon kits (Pars Azmoon Co., Tehran, Iran) to a BT3000 analyser (Biotecnica Instrument S.p.A., Rome, Italy). Values of the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, CRP, urea), and liver enzymes (ALT, AST) were calculated.

Data analysis

After a basic data curation, the normality of the distribution and homogeneity of variances of each variable was assessed through the Shapiro-Wilk and Levene tests, respectively. Only the triglycerides complied with normality and homoscedasticity assumption among the seven groups. Therefore, a one-way analysis of variance (ANOVA) for the triglycerides and Kruskal Wallis testing for the non-normally distributed variables were conducted. The effect size was reported as the eta squared (η^2) where $0.01 < \eta^2 < 0.06$ constitutes a small effect, $0.06 \leq \eta^2 \leq 0.14$ a medium effect and $\eta^2 > 0.14$ constitutes a large effect. After this, paired post-hoc tests with Tukey adjustments for the parametric analysis and with no adjustment for the non-parametric evaluated significant differences. A 95% confidence level (significance $p < .05$) was accepted as statistically significant. Statistical analysis was carried out using commercial software IBM SPSS Statistics for Macintosh (Version 26.0; IBM Corp., Armonk, NY). All data are reported as the means ± the standard deviations and the 95% confidence interval.

RESULTS

Twelve weeks of fatty food diet were enough to significantly worsen almost all the variables in the hypercaloric group compared to the controls. The ANOVA and the Kruskal Wallis test indicated that significant differences existed among the study variables, with AST: $H(6) = 29.01$, $p < .001$, $\eta^2 = 0.55$; ALT: $H(6) = 18.09$, $p = .006$, $\eta^2 = 0.29$; CRP: $H(6) = 24.20$, $p < .001$, $\eta^2 = 0.43$; creatinine: $H(6) = 35.29$, $p < .001$, $\eta^2 = 0.70$; urea: $H(6) = 31.57$, $p < .001$, $\eta^2 = 0.61$; cholesterol: $H(6) = 34.13$, $p < .001$, $\eta^2 = 0.67$; glucose: $H(6) = 21.58$, $p = .001$, $\eta^2 = 0.37$; triglycerides: $F(6) = 14.78$, $p < .001$, $\eta^2 = 0.68$; LDL: $H(6) = 24.84$, $p < .001$, $\eta^2 = 0.45$ and HDL: $H(6) = 13.33$, $p = .038$, $\eta^2 = 0.18$. Tables 3 and 4 present the outcomes of the intervention in the liver enzymes and metabolic parameters.

DISCUSSION

This study aimed to assess the effectiveness of physical exercise (aerobic and resistance) and Cornus mas extract intake in improving blood parameters (lipid profile, liver enzymes, and metabolic parameters) of rats with fatty liver and obesity. For such purpose, a control group was kept healthy from the beginning and the other six groups were induced fatty liver and obesity by diet. Of these six groups, one continued having the hypercaloric diet and the other five joined different treatment programs (aerobic or resistance exercise, Cornus mas extract intake, and aerobic or resistance exercise combined with the intake of Cornuse mas extract). The most notable findings were that all the intervention groups after six weeks of treatment reverted their levels and significantly improved compared to the hypercaloric group in almost all the assessed parameters, reaching in many cases better values than the healthy group (control). These interesting results provide a strong foundation for the management and treatment of obesity and other associated conditions such as fatty liver, cardiovascular disease, metabolic syndrome, diabetes mellitus, atherosclerosis, and dyslipidemia (Dayar et al., 2020; El Hadi et al., 2019; Huang et al., 2009; Tomeno et al., 2020; Wong et al., 2016).

The outcomes presented are in accordance with previously published investigations that found improvements in different hepatic and lipidic parameters after intaking Cornuse mas extract both in rats (Alavian et al., 2014; Asgary et al., 2013, 2014) and humans with type 2 diabetes (Soltani et al., 2015). This beneficial effect of the Cornuse mas extract may be due to its content in antioxidants, phenolic compounds, and vitamins, which help in the prevention of inflammatory processes and oxidative stress associated with different metabolic and cardiovascular conditions (Abdollahi et al., 2014). What is new from this study, is the combination of the intake of Cornuse mas extract with aerobic and resistance exercises, which slightly improved (only significant for the cholesterol and glucose) the levels in almost all the variables compared to only performing the exercise programs or only intaking Cornuse mas extract.

Table 3. Levels of liver enzymes (AST/GOT and ALT/GPT) and metabolic parameters (CRP, creatinine, and urea) in all experimental groups (all n = 7).

Group	AST	ALT	CRP	Creatinine	Urea
1 (Control)	94.14±9.56^{2,4,6,7} [85.29-102.98] Median: 97.00 IQR: 15.00	39.71±6.77$^{(3)}$ [33.44-45.98] Median: 41.00 IQR: 11.00	16.42±1.54 [14.99-17.85] Median: 17.00 IQR: 0.80	0.72±0.04^{3,4,5,6,7} [0.68-0.77] Median: 0.70 IQR: 0.10	34.42±3.59* [31.10-37.75] Median: 34.00 IQR: 7.00
2 (Hyper)	161.00±25.60* [137.46-184.82] Median: 150.00 IQR: 45.00	74.57±17.62^{1,4,5,6,7} [58.27-9087] Median: 68.00 IQR: 20.00	23.15±0.79* [22.41-23.89] Median: 23.20 IQR: 0.80	1.01±0.13^{3,4,5,6,7} [0.88-1.13] Median: 1.00 IQR: 0.10	60.85±15.29^{4,5,6,7} [46.71-74.99] Median: 53.00 IQR:22.00
3 (AE)	83.85±14.39$^{(4)}$ [70.54-97.16] Median: 86.00 IQR: 24.00	56.71±18.04$^{(4),7}$ [40.02-73.40] Median: 60.00 IQR: 34.00	17.04±1.27$^{(5)}$ [15.85-18.22] Median: 17.20 IQR: 3.00	0.44±0.07 [0.37-0.51] Median: 0.50 IQR: 0.10	48.71±2.62^{5,7} [46.28-51.14] Median: 49.00 IQR: 4.00
4 (RE)	65.85±11.82 [54.92-76.79] Median: 66.00 IQR: 29.00	42.42±11.02 [32.22-52.62] Median: 39.00 IQR: 8.00	17.24±0.975 [16.34-18.14] Median: 16.80 IQR: 1.30	0.47±0.07 [0.40-0.54] Median: 0.50 IQR: 0.10	45.28±4.27 [41.33-49.23] Median: 45.00 IQR: 9.00
5 (C)	79.57±19.90 [61.16-97.98] Median: 88.00 IQR: 23.00	47.51±35.00 [32.61-62.41] Median: 45.00 IQR: 35.00	15.61±0.93 [14.75-16.47] Median: 15.80 IQR: 1.60	0.42±0.07 [0.35-0.49] Median: 0.40 IQR: 0.00	42.85±3.18 [39.91-45.80] Median: 42.00 IQR: 4.00
6 (CAE)	71.42±14.03 [58.44-84.40] Median: 79.00 IQR: 29.00	45.00±10.67 [35.12-54.87] Median: 43.00 IQR: 24.00	16.12±1.73 [14.52-17.72] Median: 16.20 IQR: 3.00	0.42±0.07 [0.35-0.49] Median: 0.40 IQR: 0.10	47.14±6.54 [41.09-53.19] Median: 47.00 IQR: 8.00
7 (CRE)	63.57±22.04 [43.18-83.95] Median: 61.00 IQR: 48.00	39.14±10.38 [29.54-48.74] Median:39.00 IQR: 8.00	15.47±1.76 [13.84-17.10] Median: 15.50 IQR: 3.40	0.40±0.00 [0.40-0.40] Median: 0.40 IQR: 00	42.71±3.45 [39.52-45.90] Median: 45.00 IQR: 7.00

*Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference (p < .05) with all the rest of the groups; 1,2,3,4,5,6,7: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level 0.5 < p < 1.3); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; C: Cornuse mas intake group; CAE: Cornuse mas intake in combination with aerobic exercise; CRE: Cornuse mas intake in combination with resistance exercise; AST: aspartate aminotransferase (also known as GOT); ALT: alanine aminotransferase (also known as GPT); CRP: C-reactive protein.*

Regarding the effects of the exercise on the assessed parameters, a six-week program of both exercise methodologies was enough to improve the values of almost all the assessed variables, as happened in previous research (de Piano et al., 2012; Carbajo-Pescador et al., 2019; Slentz et al., 2011; Shamsoddini et al., 2015). On the other hand, one study reported inconsistent results in this regard (Barani et al., 2014). It is worth mentioning that resistance exercise showed trends of further improving liver enzymes and HDL than aerobic exercise. In fact, the six-week aerobic training program was not enough to significantly modify the ALT, urea, and HDL levels. These positive results associated with the exercise could be due to its regulator effect on insulin resistance and glucose levels. In this regard, insulin resistance is associated with fatty liver and metabolic diseases. The main mechanisms of insulin resistance are negative regulation of deep insulin receptors and a decrease in signalling caused by excessive signalling of free fatty acids in the bloodstream (Akyüz et al., 2007). To perform muscle contractions during the exercise the levels of the glucose transporter type 4 protein, secondary messengers (Richter & Hargreaves, 2013), and insulin-1 receptors rise to increase glucose uptake in the skeletal muscle (Chibalin et al., 2000). As a result, glucose is better absorbed, and insulin resistance is reduced. Furthermore, visceral fat represents a source of free fatty acids that can be preferentially oxidized to glucose. Reducing visceral fat by decreasing abdominal obesity may be another important benefit of exercise leading to significant improvement in metabolic indicators (Albright et al., 2000; Houttu et al., 2020). Due to all these aforementioned factors, we can state that physical exercise has a positive impact on the treatment of fatty liver and metabolic diseases.

Table 4. Levels of lipid profile in all experimental groups (all n = 7).

Group	Cholesterol	Glucose	Triglycerides	LDL	HDL
1 (Control)	$47.28 \pm 9.12^{2,3,4,5,7}$ [38.84-55.72] Median: 48.00 IQR: 18.00	125.00 ± 7.18^{2} [118.35-131.64] Median: 126.00 IQR: 10.00	$64.00 \pm 18.61^{2,3,4,(5)}$ [46.78-81.21] Median: 59.00 IQR: 27.00	$10.10 \pm 2.92^{*}$ [7.39-12.81] Median: 9.70 IQR: 4.90	$37.97 \pm 6.00^{2,3}$ [32.41-43.52] Median: 37.90 IQR: 12.00
2 (Hyper)	$123.71 \pm 40.38^{(3),4,6,7}$ [86.36-161.06] Median: 108.00 IQR: 71.00	$216.85 \pm 29.65^{*}$ [189.43-244.27] Median: 216 IQR: 57.00	$142.28 \pm 24.23^{*}$ [119.78-164.69] Median: 139.00 IQR: 47.00	$39.05 \pm 5.29^{*}$ [34.15-43.95] Median: 37.20 IQR: 9.30	$28.11 \pm 6.45^{4,(5),7}$ [22.11-34.08] Median: 30.50 IQR: 12.30
3 (AE)	81.85 ± 5.45^{6} [76.80-86.90] Median: 80.00 IQR: 10.00	124.42±3.99 [120.73-128.12] Median: 125.00 IQR: 7.00	97.57±15.45 [83.27-11.86] Median: 99.00 IQR: 21.00	13.95±2.28 [11.83-16.06] Median: 14.20 IQR: 2.80	$31.84 \pm 3.20^{(4),7}$ [28.87-34.81] Median: 31.40 IQR: 3.70
4 (RE)	79.42±2.22 [77.37-81.48] Median: 79.00 IQR: 3.00	125.00±8.56 [117.08-132.91] Median: 125.00 IQR: 11.00	93.00±21.97 [72.67-113.32] Median: 91.00 IQR: 37.00	14.94±2.73 [12.41-17.47] Median: 15.20 IQR: 4.50	35.81±3.91 [32.19-39.43] Median: 36.30 IQR: 2.50
5 (C)	85.57 ± 8.99^{6} [77.25-93.89] Median: 85.00 IQR: 9.00	$132.42 \pm 12.24^{(6),(7)}$ [121.10-143.75] Median: 131.00 IQR: 21.00	89.71±10.45 [80.04-99.38] Median: 87.00 IQR: 16.00	14.06±4.12 [10.24-17.88] Median: 11.40 IQR: 7.00	35.05±4.48 [30.90-39.20] Median: 36.20 IQR: 9.70
6 (CAE)	70.00±6.75 [63.75-76.24] Median: 70.00 IQR: 11.00	119.28±10.30 [109.75-128.81] Median: 121.00 IQR: 19.00	73.85±10.33 [64.29-83.41] Median: 73.00 IQR: 18.00	13.76±2.42 [11.52-16.00] Median: 14.20 IQR: 4.70	34.52±6.84 [28.19-40.85] Median: 30.80 IQR: 8.90
7 (CRE)	78.42±6.80 [72.13-84.72] Median: 81.00 IQR: 12.00	121.85±5.61 [116.66-127.04] Median: 123.00 IQR: 7.00	78.85±15.98 [64.07-93.63] Median: 81.00 IQR: 28.00	13.87±2.14 [11.89-15.86] Median: 12.80 IQR: 4.30	37.92±4.54 [33.72-42.13] Median: 36.50 IQR: 6.00

Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p < .05$) with all the rest of the groups; ^{1,2,3,4,5,6,7}: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5 < p < 1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; RE: resistance exercise group; C: Cornuse mas intake group; CAE: Cornuse mas intake in combination with aerobic exercise; CRE: Cornuse mas intake in combination with resistance exercise; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

CONCLUSION

According to the results of this study, Cornus Mas extract intake in combination with aerobic or resistance training may be recommended to improve fatty liver and obesity by improving the blood lipid profile, metabolic parameters, and liver enzyme levels. Therefore, the Cornuse mas extract and the exercise may be a good alternative or adjuvant to the use of chemical medicine.

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ARTICLE III

Proceeding

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Preventive effects of garlic and lemon extract combined with aerobic exercise on blood metabolic parameters and liver enzymes

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ABSTRACT

Purpose: The aim of this study was to evaluate the effects of aerobic exercise in combination with garlic and lemon on the lipid profile, metabolic parameters, and liver enzymes of obese male rats. Design: Sixty-four male Wistar rats were divided into eight equal groups consisting of 1) control following no treatment (n = 8); 2) hypercaloric fatty-food-based diet (n = 8); 3) aerobic exercise (AE, n = 8); 4) garlic intake (G, n = 8); 5) aerobic exercise with garlic intake (AEG, n = 8); 6) lemon intake (L, n = 8); 7) garlic and lemon (GL, n = 8); 8) garlic, lemon and aerobic exercise (GLAE, n = 8). After six weeks of intervention, blood samples were taken to obtain cholesterol, triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and glucose. C-reactive protein (CRP), alanine aminotransferase (GPT), aspartate aminotransferase (GOT), alkaline phosphatase (ALP), creatinine (Cr), urea and uric acid (UA) were also measured. A one-way ANOVA or the Kruskal Wallis tests for the non-normally distributed variables, with post-hoc pairwise comparisons were conducted to assess differences between groups. Results: All the intervention groups obtained significantly better values compared to the hypercaloric group, although being also fed with a hypercaloric diet. In certain parameters, the intervention groups obtained equal or even better results than the control healthy group. The combination of aerobic exercise with the intake of garlic and lemon showed slightly non-significant better results. Conclusion: Aerobic exercise combined with the intake of garlic and lemon juice may influence the lipid profile, liver enzymes, and other blood parameters associated with cardiovascular disease.
Keywords: Physical activity; Lipid profile; Hypercholesterolemia; Fatty liver; Cardiovascular disease; Wistar rats.

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INTRODUCTION

Cardiovascular disease (CVD) entails high rates of mortality (25-45%; Mobaseri et al., 2003). Furthermore, when this disease is combined with factors such as obesity these mortality rates may increase three times (Aslani et al., 2015). It is important to control the levels in blood total cholesterol, triglycerides, very-low-density lipoprotein, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) among other parameters within the management and prevention of CVD (Yang et al., 2011).

In this regard, regular exercise combined with appropriate nutritional intake is considered the best way to reduce obesity and control the aforementioned blood parameters (Shamsoddini et al., 2015; Wood et al., 1991). Previous expert literature has shown that regular physical activity increases HDL and lowers LDL, which is one crucial contribution to reducing the risk of cardiovascular disease (Kelley et al., 2019). Physical exercise has attracted the attention of many researchers in the field of cellular studies, particularly in the area of heart, brain, liver, muscle, and blood cells. Although physical exercise lowers fat and can be useful in the treatment of obesity, it is usually accompanied by an increase in oxidative stress, which is a risk factor to cell damage and breakdown (Ascensao et al., 2008). Aerobic exercise increases the efficiency of energy production systems and cardiorespiratory resistance. However, this exercise methodology performed at high intensities also increases the level of oxidative stress (Aslani et al., 2015), which can damage cellular DNA from various sources (Williamson and Davison, 2020). Oxidative stress plays a key role in obesity, and associated conditions such as dyslipidemia and hypertension, which are also risk factors for CVD (Marseglia et al., 2014).

One of the proposed treatments for increased oxidative stress is the intake of antioxidants. For instance, garlic supplementation has an important positive effect on hypercholesterolemia (Banerjee et al., 2002; Ried et al., 2008). Garlic (Allium sativum) has strong antioxidant properties and can therefore reduce oxidative stress due to its content in polyphenols. Garlic may also protect cells and metabolic tissues (e.g., liver) from chemical damage from peripheral toxins due to its contents in s-allyl-L-cysteine and propyl-cysteine, and also reduce lipid peroxidation through cysteine sulfoxides (Aslani et al., 2016; Dhawan & Jain, 2004; Lanzotti et al., 2006). Furthermore, garlic has proven antimicrobial, antithrombotic, anticarcinogenic, antihypertensive, antiarthritic, and lipid and glucose-lowering properties (El-Sabban et al., 2009; Gorinsteina et al., 2006; Mohamed et al., 2011). Another nutritional supplement that is believed to play an important role in the prevention of cardiovascular diseases and oxidative stress is the lemon. Citrus limon, is one of the most popular fruit varieties worldwide. Previous studies have shown that the erycosytryn and hesperidin present in lemon juice can help in reducing oxidative stress due to their antioxidant properties (Aslani et al., 2015, 2016; Minato et al., 2003). Due to all these aforementioned facts, the question arises whether the specific combination of garlic and lemon supplementation altogether with aerobic exercise may play a role in parameters associated with CVD.

This study aimed at analysing the effects of aerobic exercise, the intake of garlic, lemon, and the combination of all these treatments on the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, c-reactive protein [CRP], urea, uric acid [UA]), and liver enzymes (alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST]) in obese male rats. We hypothesized that the physical exercise altogether with the combination of garlic extract and lemon juice will improve to a greater extent the assessed parameters compared to the aforementioned treatments individually.

MATERIAL AND METHODS

Participants
64 male Wistar rats (age: six weeks; average weight: 200g) were randomly assigned to eight experimental groups: [1] control (n = 8) following a normocaloric diet and no treatment; [2] hypercaloric (n = 8) following a high-fat diet and no treatment; [3] aerobic exercise (AE, n = 8) following a high-fat diet; [4] garlic extract intake (G, n = 8) following a high-fat diet and no exercise program; [5] garlic extract intake in combination with aerobic exercise (GAE, n = 8) and following a high-fat diet; [6] lemon juice intake (L, n = 8) following a high-fat diet and no exercise program; [7] intake of garlic and lemon juice (GL, n = 8) following a high-fat diet and no exercise program; [8] intake of garlic and lemon juice in combination with aerobic exercise (GLAE, n = 8) and following a high-fat diet. All the groups were homogeneous in terms of number, breed, age, and weight. All ethical considerations and working protocols of this study were approved by Shahrekord's committee for monitoring Laboratory Animal Rights in Medical Sciences University with code 2-1-94.

The rats were kept for six weeks in the Shahrekord University Animal Laboratory Medical Sciences at a temperature between 22 and 27ºC. The room was illuminated in a controlled manner (12 hours off and 12 hours on). All the groups (n = 56) were induced with hyperlipidemia and hypercholesterolemia by diet (see below "*Diet formulation*" section) and 8 rats remained healthy following a normocaloric diet (controls).

Intervention
Diet formulation
The selected 56 rats were daily fed by gavage with a specific diet to induce them with hypercholesterolemia and hyperlipidemia. More concretely, Persintra-M was prepared from egg yolk to induce hyperlipidemia (1g of cholesterol, palm oil of 80% purity, and intralipid fluid per 100g of egg yolk) and 25mg of cholesterol were condensed to 2ml to induce hypercholesterolemia. In addition, the rat's meal was brought to 1% cholesterol and 20% sugar using palm oil, sugar, and cow fat. The controls remained all the study with a normocaloric diet. Water was freely available to all the rats throughout the study.

Aerobic training program
The six-week (three sessions per week) aerobic training program was performed on a treadmill and was divided into three phases (two weeks of adaptation, two weeks of overload, and two weeks of maintenance/consolidation). A familiarization period was carried out before the resistance training program (see Table 1) to familiarize the rats with the materials and the procedures. All the phases used no inclination (0°). A 5-minute walk at 10m/min was used as a warm-up and cool-down in every session. The control group walked five minutes once per week at 10m/min and 0º during the six weeks of the intervention.

To stimulate the rats to walk, an auditory stimulus (tapping on the wall of the treadmill) was used. For this purpose, a low-voltage electrical stimulus was initially used together with an audio stimulus. After the rats were conditioned to two stimuli simultaneously, the single audio stimulus was used in later sessions to comply with the ethics of animal experimentation.

Table 1. Aerobic training program.

	Adaptation phase		**Overload phase**		**Maintenance phase**	
	First week	Second week	Third week	Fourth week	Fifth week	Sixth week
Speed	8 m/min	12 m/min	18 m/min	20 m/min	20 m/min	20 m/min
Time	10 min	20 min	30 min	40 min	40 min	40 min

Garlic and lemon extraction and use

Samples of fresh garlic and lemon from authentic providers were prepared and used after confirmation from the University's Center for Herbal Medicine Research. To prepare the garlic extract, the fresh garlic was peeled and washed and then cut into smaller pieces with an electric mill (Moulinex, Osaka, Japan). The garlic was mixed with a dilution of 70% water and 30% alcohol and kept in the laboratory for 72 hours. It was then filtered, evaporated, and placed in an incubator at 37ºC for three days. A dose of 200mg/kg was dissolved in one mL of distilled water and given to each rat daily (Ebrahimi et al., 2015). To produce the lemon juice, after washing and squeezing the lemons, the extract was diluted with a juicer based on the concentration of 50mg/kg from distilled water (Nichols et al., 2011).

Measures

After the six-week intervention, another session was used to extract the blood samples. The rats were anesthetized by an intraperitoneal injection of ketamine (70mg/kg) and xylazine (3-5mg/kg). Blood samples were taken from their hearts and were introduced in a Sigma centrifuge (Rontgen Co., Remscheid, Germany) at 5000 revolutions. At this point, the serum was transferred using Pars Azmoon kits (Pars Azmoon Co., Tehran, Iran) to a BT3000 analyser (Biotecnica Instrument S.p.A., Rome, Italy). Values of the lipid profile (triglycerides, HDL, LDL, cholesterol), metabolic parameters (glucose, creatinine, CRP, urea, UA), and liver enzymes (ALP, ALT, AST) were calculated.

Data analysis

After a basic data curation, the normality of the distribution and homogeneity of variances of each variable was assessed through the Shapiro-Wilk and Levene tests, respectively. Only the HDL and UA complied with normality and homoscedasticity assumption among the eight groups. Therefore, a one-way analysis of variance (ANOVA) for the normally distributed and Kruskal Wallis testing for the non-normally distributed variables were conducted. The effect size was reported as the eta squared (η^2) where $0.01 < \eta^2 < 0.06$ constitutes a small effect, $0.06 \le \eta^2 \le 0.14$ a medium effect and $\eta^2 > 0.14$ constitutes a large effect. After this, paired post-hoc tests with Tukey adjustments for the parametric analysis and with no adjustment for the non-parametric evaluated significant differences. A 95% confidence level (significance $p < .05$) was accepted as statistically significant. Statistical analysis was carried out using commercial software IBM SPSS Statistics for Macintosh (Version 26.0; IBM Corp., Armonk, NY). All data are reported as the means ± the standard deviations and the 95% confidence interval.

RESULTS

Six weeks of fatty food diet were enough to significantly worsen almost all the variables in the hypercaloric group compared to the controls. The ANOVA and the Kruskal Wallis test indicated that significant differences existed among the study variables, with ALP: $H(7) = 49.29$, $p < .001$, $\eta^2 = 0.76$; AST: $H(7) = 35.92$, $p < .001$, $\eta^2 = 0.52$; ALT: $H(7) = 35.63$, $p < .001$, $\eta^2 = 0.51$; CRP: $H(7) = 28.55$, $p < .001$, $\eta^2 = 0.39$; creatinine: $H(7) = 27.16$, $p < .001$, $\eta^2 = 0.36$; UA: $F(7) = 34.87$, $p < .001$, $\eta^2 = 0.71$; urea: $H(7) = 34.79$, $p < .001$, $\eta^2 = 0.50$; cholesterol: $H(7) = 39.94$, $p < .001$, $\eta^2 = 0.59$; glucose: $H(7) = 44.65$, $p < .001$, $\eta^2 = 0.67$; triglycerides: $H(7) = 43.68$, $p < .001$, $\eta^2 = 0.66$; LDL: $H(7) = 31.84$, $p < .001$, $\eta^2 = 0.44$; HDL: $F(7) = 21.37$, $p < .001$, $\eta^2 = 0.60$.

Table 2. Levels of liver enzymes (ALP, AST/GOT and ALT/GPT) and metabolic parameters (CRP, creatinine, UA and urea) in all experimental groups (all n = 8).

Group	ALP	AST	ALT	CRP	Creatinine	UA	Urea
1 (Control)	281.10±132.40^{3,5,8} [170.3-391.8] Median: 2.42 IQR: 224.00	97.12±7.82^{3,4,5,6,7} [90.58-103.66] Median: 96.0 IQR: 10.00	29.50±2.61^{3,4,5,6,7} [27.31-31.68] Median: 30.00 IQR: 4.47	15.05±1.53$^{(3),(4),(5),6}$ [1376-16.33] Median: 14.80 IQR: 2.95	0.47±0.04$^{(8)}$ [.43-0.51] Median: 0.50 IQR: 0.07	2.95±0.43^{3,4,5,6,7} [2.58-3.31] Median: 3.00 IQR: 0.45	35.12±4.01$^{2,3,4,5,6,7,(8)}$ [31.76-38.48] Median: 34.00 IQR: 4.50
2 (Hyper)	823.00±146.20* [700.7-945.2] Median: 768.00 IQR: 247.20	227.25±62.99* [147.58-279.91] Median: 191.50 IQR: 96.25	60.75±7.99* [54.06-67.43] Median: 59.50 IQR: 13.00	21.70±2.80* [19.35-24.04] Median: 31.15 IQR: 5.80	0.78±0.12* [0.68-0.89] Median: 0.80 IQR: 0.25	9.80±1.60* [8.45-11.14] Median: 9.50 IQR: 1.80	62.25±12.20^{3,5,6,7,8} [52.04-72.45] Median: 58.00 IQR: 11.75
3 (AE)	458.80±104.20^{4,7} [371.7-546.03] Median: 448.00 IQR: 150.75	132.37±18.66 [116.76-147.98] Median:135.50 IQR: 35.50	35.37±2.44 [33.33-37.41] Median: 35.00 IQR: 4.75	16.48±0.80$^{(8)}$ [15.81-17.15] Median: 16.5 IQR: 1.57	0.47±0.04$^{(8)}$ [0.43-0.51] Median: 0.50 IQR: 0.07	4.65±0.72 [5.25-4.67] Median: 4.60 IQR: 0.67	47.12±3.94^{4} [43.82-50.42] Median: 48.00 IQR: 5.00
4 (G)	234.50±33.83$^{5,(6),8}$ [206.21-262.78] Median: 228.50 IQR: 56.50	146.62±22.28$^{(8)}$ [127.99-165.25] Median: 146.00 IQR: 39.00	37.00±2.92$^{(8)}$ [34.55-39.44] Median: 37.50 IQR: 4.50	16.70±0.99^{8} [15.86-17.53] Median: 16.30 IQR: 2.05	0.41±0.09 [0.32-0.49] Median: 0.40 IQR: 0.10	4.48±0.89 [3.73-5.23] Median: 4.25 IQR: 1.30	53.50±7.55^{8} [47.18-59.81] Median: 54.00 IQR: 5.50
5 (GAE)	393.00±48.30^{7} [352.5-433.2] Median: 410.00 IQR: 80.00	127.62±23.95 [107.59-147.65] Median: 122.50 IQR: 46.00	34.87±3.27 [32.14-37.60] Median: 34.50 IQR: 2.75	16.32±1.54$^{(8)}$ [15.03-17.61] Median: 16.85 IQR: 2.35	0.45±0.09 [0.37-0.52] Median: 0.45 IQR: 0.10	4.47±1.04 [3.60-5.34] Median: 4.25 IQR: 1.40	53.62±7.89^{8} [47.02-60.22] Median: 53.50 IQR: 9.50
6 (L)	339.80±24.21$^{(7),8}$ [319.6-360.1] Median: 344.50 IQR: 32.00	131.00±29.81 [106.07-155.92] Median: 116.50 IQR: 53.00	35.00±4.00 [31.65-38.34] Median: 34.50 IQR: 5.00	16.67±0.88^{8} [15.93-17.41] Median: 16.65 IQR: 1.35	0.47±0.08$^{(8)}$ [0.41-0.55] Median: 0.50 IQR: 0.17	4.78±0.84 [4.08-5.49] Median: 4.80 IQR: 1.45	50.25±7.47$^{(7)}$ [43.99-56.50] Median: 47.50 IQR:11.00
7 (GL)	235.60±35.02^{8} [206.34-264.90] Median: 223.50 IQR: 58.50	138.37±31.13 [112.34-164.40] Median:132.50 IQR: 61.00	35.62±3.29 [32.87-38.37] Median: 35.50 IQR: 6.25	16.05±1.07 [16.94-16.05] Median: 16.15 IQR: 1.83	0.47±0.12 [0.36-0.58] Median: 0.45 IQR: 0.61	4.82±1.03 [3.96-5.68] Median: 4.80 IQR: 1.85	46.87±8.35 [39.88-53.86] Median: 47.00 IQR: 16.50
8 (GLAE)	510.80±65.50 [456.09-565.65] Median: 523.00 IQR: 105.25	122.12±20.96 [104.59-139.65] Median: 118.50 IQR: 39.75	33.62±3.29 [30.87-36.37] Median: 33.00 IQR: 6.00	15.30±1.04 [15.15-16.94] Median: 16.15 IQR: 1.83	0.38±0.09 [0.30-0.47] Median: 0.40 IQR: 0.15	4.41±0.68 [3.83-4.98] Median: 4.20 IQR: 1.20	44.62±3.24 [41.90-47.34] Median: 44.50 IQR: 6.25

*Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p < .05$) with all the rest of the groups; 1,2,3,4,5,6,7: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5 < p < 1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; G: garlic intake group; GAE: garlic intake combined with aerobic exercise group; L: lemon juice intake group; GL: garlic and lemon intake; GLAE: garlic and lemon intake combined with aerobic exercise; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; UA: uric acid.*

Table 3. Levels of lipid profile in all experimental groups (all n = 8).

Group	Cholesterol	Glucose	Triglycerides	LDL	HDL
1 (Control)	54.75±3.01^{3,4,5,6,7} [52.23-57.26] Median: 56.00 IQR: 5.50	105.62±11.10$^{3,(4),5,6,7}$ [96.3-114.9] Median: 103.50 IQR: 21.00	26.62±6.41$^{2,3,(5),6,7}$ [21.26-31.98] Median: 26.00 IQR: 11.75	19.98±2.25$^{2,3,(4),5,6,7,8}$ [17.82-22.09] Median: 19.57 IQR: 3.76	44.33±4.20* [40.82-47.85] Median: 44.80 IQR: 6.82
2 (Hyper)	110.75±26.29* [88.76-132.73] Median: 106.50 IQR: 19.50	218.00±22.27* [199.37-236.62] Median: 208.50 IQR: 24.25	148.37±26.51$^{(3),4,5,6,7,8}$ [126.21-170.53] Median: 156.00 IQR: 51.50	30.63±2.26* [28.74-32.52] Median: 29.60 IQR: 4.18	29.17±0.73$^{(4),5,8}$ [28.56-29.78] Median: 29.00 IQR: 1.20
3 (AE)	65.5±8.40 [58.47-72.52] Median: 66.50 IQR: 8.00	146.00±13.25^{8} [134.91-157.08] Median: 146.50 IQR: 17.25	60.00±16.2 [46.44-73.55] Median: 63.50 IQR: 29.25	24.93±2.17 [23.11-26.75] Median: 24.84 IQR: 2.75	31.52±3.27 [28.78-34.26] Median: 31.10 IQR: 6.57
4 (G)	66.125±4.61 [62.26-69.98] Median: 65.50 IQR: 8.00	129.75±21.86^{7} [111.47-148.02] Median: 126.50 IQR: 19.75	35.62±12.80 [24.86-46.38] Median: 34.00 IQR: 18.50	23.46±2.26 [21.56-25.35] Median: 23.35 IQR: 3.08	33.27±2.40 [31.26-3528] Median: 33.70 IQR: 3.20
5 (GAE)	64.37±9.57$^{(6),(7)}$ [56.36-72.38] Median: 62.50 IQR: 14.25	139.62±17.49$^{(8)}$ [125.00-154.24] Median: 144.00 IQR: 14. 50	39.75±8.87 [32.32-47.17] Median: 36.00 IQR: 12.75	24.00±2.08 [22.26-25.73] Median: 24.15 IQR: 4.02	34.32±2.66 [32.09-36.55] Median: 34.95 IQR: 5.15
6 (L)	75.50±13.50^{8} [64.21-86.78] Median: 78.00 IQR: 23.75	148.00±23.85^{8} [128.05-167.94] Median: 139.50 IQR: 38.00	49.87±11.0 [40.66-59.08] Median: 53.00 IQR: 18.50	24.53±2.08 [24.86-46.38] Median: 22.79 IQR: 2.95	32.61±2.44[30.56- 34.65] Median: 32.70 IQR: 2.32
7 (GL)	73.12±6.15^{8} [67.98-78.26] Median: 72.00 IQR: 8.25	155.25±11.65^{8} [145.50-164.99] Median: 160.00 IQR: 16.00	45.62±14.70 [38.10-53.14] Median: 45.50 IQR: 14.75	25.00±2.70 [23.71-26.28] Median: 25.15 IQR: 3.27	33.03±2.91 [30.60- 35.47] Median: 33.10 IQR: 3.27
8 (GLAE)	60.87±5.35 [56.39-65.35] Median: 62.50 IQR: 8.50	121.50±8.53 [114.36-128.63] Median: 122.50 IQR: 15.00	35.25±4.50 [31.65-38.84] Median: 34.50 IQR: 7.00	23.93±4.50 [21.64-26.22] Median: 23.45 IQR: 2.07	36.18±2.28 [34.27-38.09] Median: 37.10 IQR: 4.73

*Data are presented as mean ± standard deviation and 95% confidence interval for the mean [lower bound-upper bound]; median and interquartile range (IQR) are also displayed for the non-normal variables. Being *: significant difference ($p < .05$) with all the rest of the groups; ^{1,2,3,4,5,6,7}: significant difference with the group 1, 2, 3, 4, 5, 6, or 7, respectively (numbers between brackets represent statistical tendency at the level $0.5 < p < 1.3$); IQR: interquartile range; Hyper: hypercaloric group; AE: aerobic exercise group; G: garlic intake group; GAE: garlic intake combined with aerobic exercise group; L: lemon juice intake group; GL: garlic and lemon intake; GLAE: garlic and lemon intake combined with aerobic exercise; LDL: low-density lipoprotein; HDL: high-density lipoprotein.*

DISCUSSION

The main aim of this study was to analyse the potential preventive effect of garlic and lemon juice supplementation combined with aerobic exercise in the worsening of blood parameters (liver enzymes, metabolic parameters, and lipid profile) resultant from a hypercaloric diet. For such purpose, a control group was kept healthy and the rest of the groups followed a hypercaloric diet for six weeks. During these six weeks, six different treatments (i.e., aerobic exercise program; garlic supplementation; garlic supplementation and aerobic exercise; lemon juice supplementation; garlic and lemon juice supplementation; garlic and lemon juice supplementation combined with aerobic exercise) were applied to the rats and one group of rats received no treatment. It is worth highlighting that all the treatments served to prevent the worsening in almost all the assessed parameters (significant differences to the hypercaloric group), which confirms the study hypothesis. Furthermore, some values remained at the same levels as in the control healthy group, which followed a normocaloric diet. These findings suggest that the use of garlic and lemon supplementation combined with aerobic exercise may help in the prevention of hyperlipidemia and hypercholesterolemia, being both associated with obesity and risk factors for cardiovascular disease.

In line with these findings, previous research has reported preventive effects of garlic, lemon, and aerobic exercise in fatty liver, atherosclerosis, and metabolic syndrome (Aslani et al., 2016; Batsis & Lopez-Jimenez, 2010; Sohn et al., 2012). Therefore, the use of herbal medicines altogether with aerobic exercise can be a good alternative to chemical medicines (Rahman et al., 2003). Fatty acid synthesis such as HDL and reduction in cholesterol absorption may be possible mechanisms of action. Previous studies have reported similar beneficial effect with the garlic supplementation in the lipid profile (Banerjee & Maulik, 2002; Budoff et al., 2009; Durak et al., 2004; Mohammadi & Oshaghi, 2014), with other studies obtaining controversial results in the lipid profile (Turner et al., 2004) and glucose reduction (Ali et al., 2000). Also, the lemon has been associated with hepatoprotective properties (Bhavsar et al., 2007; Minato et al., 2003). The mixture of garlic with lemon juice has been highlighted as a potential supplementation therapy to non-alcoholic fatty liver, which is a disease characterized by hyperlipidemia and liver enzyme imbalance (Berman et al., 2017; Shi et al., 2012; Xu et al., 2020). All these positive effects of garlic and lemon supplementation can be enhanced with the addition of aerobic exercise, as shown in our results.

Exercise alone or in combination with garlic and lemon supplementation, can be useful in the treatment of patients suffering from obesity (Warshafsky et al., 1993) and fatty liver (Torkamaneh et al., 2016). Physical activity increases the secondary messenger substances in the skeletal muscles, which leads to better glucose consumption and a reduction in insulin resistance (Kim et al., 2017). Studies in humans and rodents show that exercise has a positive effect on fatty liver and liver functions independent of weight reduction. Exercise increases the activity of the liver glucagon, a stimulant for the glucose-producing pathways. The exercise-induced increase in glucagon activity is also responsible for some changes in the expression of those liver genes that are compatible with the increase in fat oxidation (Shamsoddini et al., 2015). All these properties of the exercise help in the control of hyperlipidemia and hypercholesterolemia among other benefits. In line with our results in terms of liver enzymes reduction, Shamsoddini et al. (2015) reported exceptional liver enzyme and liver fat decreases with aerobic exercise. On the other hand, exercise at high intensities may produce oxidative stress (Ascensao et al., 2008). In this regard, garlic extract and lemon juice have proven beneficious to enhance antioxidant potential against exercise-induced oxidative stress, in part by modulating the activity of oxidizing enzymes, which may also serve as a beneficial agent on cardiovascular disease (Yoon et al., 2006). Due to all these aforementioned factors and their relation, it could be recommended the combination of aerobic exercise with natural herb supplementation with antioxidant properties such as garlic and lemon juice looking forward to improving the values of certain blood parameters associated with obesity and cardiovascular disease progression (e.g., hyperlipidemia, hypercholesterolemia) such as those included in this research.

CONCLUSION

Supported on the results obtained, this study argues strongly in favour of the use of aerobic exercise and herbal supplementation such as garlic and lemon in the prevention of acquired obesity or cardiovascular disease and related factors such as hyperlipidemia or hypercholesterolemia. The combination of exercise and garlic and lemon intake showed slightly (non-significantly in many cases) better results than their isolated use, which suggests that their combination could provide additional benefits and that further research is needs on this matter.

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