

Universidade de Lisboa  
Faculdade de Farmácia



# Phenolic acids: new body weight and metabolic syndrome regulating compounds

**João Filipe Ferreira Garrudo**

Monografia orientada pelo Professor Doutor João Almeida Lopes,  
Professor Associado

**Mestrado Integrado em Ciências Farmacêuticas**

**2023**

Universidade de Lisboa  
Faculdade de Farmácia



# Phenolic acids: new body weight and metabolic syndrome regulating compounds

**João Filipe Ferreira Garrudo**

**Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas  
apresentado à Universidade de Lisboa através da Faculdade de Farmácia**

Monografia orientada pelo Professor Doutor João Almeida Lopes, Professor  
Associado

**2023**

## Abstract

Obesity is a complex and persistent global health concern that continues to escalate in prevalence, posing a significant challenge for individuals and healthcare systems worldwide. While behavioural and lifestyle interventions are recognized as key approaches for achieving weight loss, the long-term commitment required to maintain these practices can be a daunting obstacle for many individuals. Furthermore, the absence of effective pharmaceutical options to combat obesity further exacerbates this critical health issue. As a result, the exploration of natural products and their potential in addressing obesity and symptoms of metabolic syndrome, emerges as a promising alternative, especially in the absence of innovative anti-obesity medications. One compelling avenue of research in this field is the investigation of natural compounds derived from plants and fruits. These compounds not only have garnered attention for their potential to aid in weight management and the treatment of obesity, but also in normalizing blood pressure, reduce weight and normalizing blood sugar levels. What makes natural products particularly appealing is their generally low risk of adverse side effects compared to synthetic pharmaceuticals. Moreover, the combination of multiple natural compounds, known as a synergistic approach, has shown promise in enhancing the treatment of metabolic syndrome effects by targeting multiple pathways involved in weight regulation and metabolism of fats. This approach recognizes that obesity is a multifaceted condition influenced by various factors, including metabolism, appetite regulation, and energy expenditure. By combining natural compounds with complementary actions, researchers hope to develop more effective anti-obesity strategies. In recent years, numerous studies have been conducted, both in-vitro (lab-based) and in-vivo (animal and human studies), to investigate the anti-obesity potential of various natural products and their combinations. Many of these studies have shown very promising results in terms of managing and treating metabolic syndrome, which often accompanies obesity and is associated with various health risks, including cardiovascular disease and type 2 diabetes. The diversity of natural products under investigation is vast, ranging from specific phytochemicals found in plants to bioactive compounds present in various fruits. These substances are being studied for their ability to influence factors such as fat metabolism, appetite suppression, inflammation reduction, and enhancement of energy expenditure. The overarching goal of the current dissertation is to delve deeper into the exploration of these promising natural substances and their potential impact on obesity management and treatment. By gathering and analysing the most up-to-date research findings and methodologies, the dissertation aims to contribute to the growing body of knowledge in this field. Ultimately, the hope is that this research will lead to viable strategies for the treatment of obesity, offering new possibilities for individuals struggling with this pervasive health issue and potentially reducing the burden on healthcare systems worldwide.

*Keywords:* Natural Products; Metabolic Syndrome; Phenolic Acids; Diabetes; Obesity.

## Resumo

A obesidade é uma preocupação global complexa e persistente que continua a aumentar em prevalência, representando um desafio significativo para indivíduos e sistemas de saúde em todo o mundo. Embora as intervenções comportamentais e de estilo de vida sejam reconhecidas como abordagens-chave para alcançar a perda de peso, o compromisso de longo prazo necessário para manter estas práticas pode ser um obstáculo assustador para muitas pessoas. Além disso, a ausência de opções eficazes para combater a obesidade agrava ainda mais este problema. Como resultado, a exploração de produtos naturais e seu potencial no combate à obesidade e aos sintomas da síndrome metabólica emerge como uma alternativa promissora, especialmente na ausência de medicamentos que combatem diretamente a obesidade. Uma via de pesquisa envolvente neste campo é a investigação de compostos naturais derivados de plantas e frutas. Estes compostos não têm apenas chamado a atenção pelo seu potencial em auxiliar no controle do peso e no tratamento da obesidade, mas também na normalização da pressão arterial, redução do peso e normalização dos níveis de açúcar no sangue. O que torna os produtos naturais particularmente atraentes é o baixo risco de efeitos colaterais adversos em comparação com os produtos farmacêuticos sintéticos. Além disso, a combinação de vários compostos naturais, conhecida como abordagem sinérgica, tem mostrado promessas em aprimorar o tratamento dos efeitos do síndrome metabólico, atuando em múltiplas vias envolvidas na regulação do peso e metabolização das gorduras. Esta abordagem reconhece que a obesidade é uma condição multifacetada influenciada por diversos fatores, incluindo metabolismo, regulação do apetite e gasto de energia. Ao combinar compostos naturais com ações complementares, os investigadores esperam desenvolver estratégias anti-obesidade mais eficazes. Nos últimos anos, inúmeros estudos têm sido conduzidos, tanto in-vitro (baseados em laboratório) quanto in-vivo (estudos em animais e seres humanos), para averiguar o potencial anti-obesidade de vários produtos naturais e suas combinações. Muitos desses estudos têm apresentado resultados muito promissores em termos de controle e tratamento do síndrome metabólico, que frequentemente acompanha a obesidade e está associada a vários riscos de saúde, incluindo doenças cardiovasculares e diabetes tipo 2. A diversidade de produtos naturais em investigação é vasta, abrangendo desde fitoquímicos específicos encontrados em plantas até compostos bioativos presentes em diversas frutas. Essas substâncias estão a ser estudadas por sua capacidade de influenciar fatores como: O metabolismo de gorduras, supressão do apetite, redução da inflamação e aumento do gasto de energia. O objetivo geral da presente dissertação é aprofundar a exploração dessas substâncias naturais promissoras e seu impacto potencial no tratamento e controle da obesidade. Ao reunir e analisar as descobertas de pesquisa mais atualizadas e metodologias, a dissertação visa contribuir para o crescente conhecimento nesta área. Em última análise, a esperança é que esta pesquisa eleve a estratégias viáveis para o tratamento da obesidade, oferecendo novas possibilidades para pessoas que lutam contra este problema de saúde e possivelmente reduzindo o fardo sobre os serviços de saúde em todo o mundo.

*Palavras chave:* Polímeros Naturais; Síndrome Metabólico; Ácidos Fenólicos; Diabetes; Obesidade.

# Contents

<b>1</b>	<b>Introduction</b>	<b>1</b>
1.1	Obesity . . . . .	1
1.2	Etiology . . . . .	1
1.3	Synthetic anti-obesity drugs . . . . .	2
1.4	Natural products . . . . .	2
1.5	Appetite suppression . . . . .	3
1.6	Increase in energy expenditure . . . . .	3
1.7	Lipase inhibitory effect . . . . .	3
1.8	Regulation of lipid metabolism . . . . .	3
1.9	Inhibition of adipocyte differentiation . . . . .	4
<b>2</b>	<b>Objectives</b>	<b>5</b>
<b>3</b>	<b>Materials and methods</b>	<b>6</b>
<b>4</b>	<b>Results</b>	<b>7</b>
4.1	In-vitro studies . . . . .	7
4.2	In-vivo studies . . . . .	9
4.3	Clinical trials . . . . .	11
<b>5</b>	<b>Discussion</b>	<b>18</b>
<b>6</b>	<b>Conclusions</b>	<b>19</b>

## List of Tables

1	Literature review (part 1) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation). .	12
2	Literature review (part 2) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation). .	13
3	Literature review (part 3) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation). .	14
4	Literature review (part 4) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation). .	15
5	Literature review (part 5) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation). .	16
6	Literature review (part 6) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation). .	17

# 1 Introduction

In an era marked by the escalating prevalence of obesity, metabolic syndrome, and diabetes, the quest for innovative and sustainable therapeutic approaches has become an imperative endeavour in modern healthcare. Traditional pharmaceutical interventions often come with a multitude of side effects and limitations, necessitating the exploration of alternative avenues that align with the principles of holistic well-being. Amidst this backdrop, the utilization of plant-based medications has garnered remarkable attention for their potential to provide safe and effective treatment options. This thesis embarks on a comprehensive investigation into the role of phenolic acids, natural compounds abundant in fruit pulp, as promising candidates for ameliorating the challenges posed by obesity, metabolic syndrome and, at some extent, to diabetes itself.

## 1.1 Obesity

According to the World Health Organization, obesity is defined as an excessive accumulation of adipose tissue that poses a health risk to the individual in question [1]. It is a health issue that has been affecting millions of individuals worldwide, with special attention to developed countries. This creates the need to find new strategies for managing body weight as well as symptoms related to Metabolic Syndrome, such as increased blood pressure and dysregulation of glucose, triglyceride, and lipid levels. Obesity results from an excess in ingestion of calories and/or a decrease in calories burnt as a result of genetic, environmental and behaviour factors, it is a complicated multifactorial disease, it results in numerous complications such as, atherosclerosis, cardiovascular abnormalities, hyperlipidemia, cancer, stroke, diabetes mellitus and hypertension. Various approaches exist for addressing obesity, encompassing dietary management, physical exercise, lifestyle modifications, pharmaceutical interventions, and surgical interventions. So, there is an urgency to find increasingly more and better molecules and new approaches to this issue in order to sustain the silent epidemic that is hitting every developed country. Beyond its role in causing illness, obesity can substantially diminish functional capacity and elevate the risk of disability. This recognition has spurred a heightened research focus on the determinants of energy balance and intensified efforts to explore the intricate connections between obesity and its associated complications [2]. Molecules derived from plants have garnered significant interest in this field, particularly phenolic compounds, especially phenolic acids. These latter compounds have shown an inverse association with the risk of obesity and related diseases. Recent studies have provided promising evidence in clinical and preclinical research, although there are still some questions regarding their true mechanism of action, bioavailability, and efficacy.

## 1.2 Etiology

Obesity can be classified in two ways, either endogenous or exogenous obesity. Exogenous obesity arises from a persistent disparity between energy consumption and expenditure. In contrast, endogenous obesity stems from a range of factors including genetics, syndromes, and endocrine disturbances. Exogenous obesity involves a chronic imbalance between energy intake and expenditure. Contributing factors include increased consumption of processed and refined diets, sugar-sweetened beverages, extended screen time reduced physical activity, and insufficient sleep. Medications like glucocorticoids, tricyclic antidepressants, and risperidone can also play a role. Adverse metabolic programming, combined with diet and lifestyle factors, can affect infants born as small or large for gestational age, those born to mothers with obesity or diabetes, and those with rapid weight gain during infancy. Endogenous obesity, on the other hand, results from various underlying causes.

These include monogenic factors related to genes like melanocortin 4 receptor (MC4R), leptin (LEP), leptin receptor (LEPR), pro-opiomelanocortin (POMC), and others. Genetic syndromes such as Alstrom, Bardet-Biedl, Prader-Willi, Beckwith-Wiedemann, Carpenter, Cohen, and Albright Hereditary Osteodystrophy also contribute. Endocrine factors such as hypothyroidism, Cushing syndrome, hypothalamic obesity, growth hormone deficiency, and persistent hyperinsulinism can further lead to endogenous obesity [3].

### 1.3 Synthetic anti-obesity drugs

Despite the demonstrated efficacy of many synthetic anti-obesity medications in facilitating weight loss, obstacles such as elevated expenses, susceptibility to drug abuse, improper usage, and unfavourable side effects have arisen. These challenges could potentially be attributed to an insufficient grasp of the intricate mechanisms through which the diverse compounds within these medications operate, as well as an incomplete understanding of their safety profiles [4]. One of the main drugs used to treat obesity is Orlistat, which is also very frequently analysed in several papers, either as control or a positive control. It has an effective mechanism by inhibiting pancreatic lipases which results in the non-absorption of fats thru diet. However, it is a two-edge sword, Orlistat most common side effects include: Inferior respiratory tract infection, Superior respiratory tract infection, headaches, abdominal pain, Oily rectal discharge, flatulence with fecal discharge, greasy stools, liquid stools, hypoglycaemia, flu, fatigue, anxiety and menstrual irregularities in women [5]. Not to mention the several spontaneous notifications from health staff, reporting other side effects. In addition, it is stated, due to the nature of the action mechanism of the molecule, that the absorption of liposoluble vitamins such as A, D, E and K will be low, making the patient take supplements in order to maintain normal levels of said vitamins [30]. Due to its side effects, Orlistat as proven to be a drug difficult to manage and tolerate, in addition, for its effectiveness to be 100%, patients need to follow a rigorous diet which can be challenging for patients. However as proven to be quite effective in reducing weight, in a randomized controlled trial (RCT) involving patients with polycystic ovarian syndrome (PCOS), researchers investigated the efficacy of orlistat in comparison to both metformin and exercise. The results revealed that orlistat exhibited comparable effectiveness to metformin in terms of weight reduction and achieved similar ovulation rates in obese individuals with PCOS [6]. Although Orlistat can effective in reducing weight in individuals it is important to find alternatives that address the limitations of Orlistat. The goal is to provide a range of options to cater individual needs, preferences and health conditions, ultimately to improve general well-being of patients.

### 1.4 Natural products

Plant-based medications offer numerous advantages in the treatment of obesity. It's important to emphasize that, as of now, there's no dedicated plant-based medication for obesity, unlike drugs such as Orlistat. Treatment approaches encompass a range of options, including dietary modifications and herbal supplementation. However, as previously mentioned, many synthetic anti-obesity drugs have proven effective in promoting weight loss. Unfortunately, they often come with downsides like high costs, potential for abuse, misuse, and a variety of reported side effects, which may be attributed to a lack of clarity regarding their mechanisms, additionally, surgical interventions, while an option, can lead to complications such as malnutrition, anemia, thrombosis, and infection [6]. Thus, there's an urgent need to explore and develop new strategies to combat obesity, and plant-based medications have a crucial role to play. These medications offer a poly-synergistic effect when used together, enhancing their anti-obesity potential while also providing numerous health benefits.

## 1.5 Appetite suppression

Appetite suppression involves intricate neurological and hormonal processes. Adipocytes, specialized fat cells, play a key role by producing bioactive adipokines such as adiponectin, leptin, and apelin. These three adipokines are essential for regulating energy balance and glucose homeostasis. Leptin secretion is contingent upon the amount of body fat in an individual. When these receptors are activated, they work to suppress food intake and boost energy expenditure [7]. Furthermore, within the hypothalamus, specifically in the ventro-medial hypothalamus nucleus (VMN), which serves as the satiety centre, a multitude of neuropeptides, neurotransmitters, as well as insulin and leptin, come into play. They collectively contribute to the regulation of appetite and satiety [8]. Therefore, stimulating this centre will lead to a reduction in food intake. In addition to these long-term regulatory responses, there are short-term ways to stimulate the central nervous system (CNS), either through the release of gut hormones or directly via the consumption of carbohydrates and fats [8].

## 1.6 Increase in energy expenditure

Excessive body fat accumulation results from the discord between energy intake and energy expenditure. To achieve weight loss, it is essential to tip the scales in favour of a negative energy balance. This can be accomplished by boosting energy expenditure through increased physical activity and harnessing the benefits of adaptive thermogenesis. Thermogenic protein plays a pivotal role in the thermogenic processes of brown adipose tissue. Consequently, a substance capable of enhancing energy expenditure by upregulating the gene expression of thermogenic could represent a potential approach to achieving anti-obesity effects. However, several experiments point out the importance and how the manipulation of BAT can achieve results in fighting obesity and achieve overall general well-being, thru the exposure to mild/cold temperatures, subjects were able to increase their BAT percentage and metabolic rate, a type of fat that is lacking in obese patients [9], [10].

## 1.7 Lipase inhibitory effect

The pancreatic lipase enzyme holds a paramount position within the human digestive system, serving as a critical catalyst (hydrolyses) in the breakdown of dietary fats. Its intricate role in the hydrolysis of triglycerides into absorbable fatty acids and glycerol underscores its significance in maintaining a balanced metabolic state. In the ongoing battle against obesity, a multifaceted condition with profound health implications, there is a growing interest in exploring strategies to interfere with fat absorption along the gastrointestinal tract. This approach offers a potential avenue for combating excessive weight gain and its associated health risks [2], [11]. When this enzymatic breakdown is hindered or modulated, it has the potential to alter the balance between calorie intake and expenditure, which is essential in managing body weight.

## 1.8 Regulation of lipid metabolism

Enhancing lipolysis is a key mechanism for promoting the breakdown of triglycerides, which in turn reduces fat storage and effectively manages obesity. Numerous studies have delved into pivotal factors that can enhance lipolysis. For instance, the activation of adenosine monophosphate-activated protein kinase (AMPK) has been found to boost fatty acid oxidation and facilitate glucose transport within skeletal muscle. Another noteworthy example involves the stimulation of  $\beta$ -adrenergic receptors in white adipocytes, which induces lipolysis and non-shivering thermogenesis in brown fat.

Consequently, transcription factors capable of mimicking lipolysis have gained increasing significance in the development of anti-obesity products.

## **1.9 Inhibition of adipocyte differentiation**

Adipocytes play a pivotal role in regulating lipid homeostasis and ensuring a healthy energy balance. They possess a remarkable dual capability: the efficient storage of triglycerides and the controlled release of free fatty acids in response to varying energy demands. Given the connection between adipocyte hypertrophy, hyperplasia, and adipose tissue expansion, researchers have developed natural products aimed at suppressing adipogenesis for anti-obesity treatment. Additionally, inhibiting various transcription factors has emerged as a promising strategy to impede adipocyte differentiation [8].

## 2 Objectives

The purpose of this thesis is to critically analyse the scientific literature and succinctly demonstrate the validity and legitimacy of studies conducted in this topic. In doing so, it aims to provide credibility and exposure to these types of compounds in their use, either as an additional strategy for combating this disease or as supplementation to existing treatments. The exploration of phenolic acids from fruit pulp emerges not only as a scientific endeavour but also as a reflection of the evolving paradigm of healthcare, where harnessing the power of nature's compounds holds immense promise. Although, the focus is always aimed at anti-obesity effects, it is unavoidable the contributions that these substances have on treating other symptoms related with metabolic syndrome, that's why there is also a great emphasis in their benefits in this thesis.

### 3 Materials and methods

This research was performed using Web of science, PubMed and Google Scholar has search engine. The terms used to find the articles were “fruit”, “anti-obesity”, “pulp”, “metabolic syndrome”. Words usually excluded from research were “infusion”, “root”, “phenolics”, “phenolic acid”, “antioxidant”, “functional-food”, “Gut microbia”, “polyphenols”, “3T3-L1 Adipocytes”. Some of the papers found used the same keywords, but also it was added in research the name of the active compound, such as: chlorogenic acid or caffeic acid, just to name two of them, in order to look for studies that targeted specific phenolic compounds. Moreover, some of the papers initially found provided also further bibliography which was exploited and used in this thesis. The books referenced were all provided by the professors thru the five years as part of the bibliography referenced for each subject. Although, this paper is aimed at analysing the impact in obesity, it was difficult not to include the impact in Diabetes and other clinical parameters related to the metabolic syndrome such as: blood pressor, low-density lipoprotein, high-density lipoprotein, triglycerides and abdominal obesity.

## 4 Results

This document contains an overview that includes a comprehensive table of the studies analysed (Tables 1 to 6). The tables were thoughtfully organized to summarize each study based on the type of conclusions drawn and the methodologies employed. Most of the studies focused on in-vitro assays and in-vivo experiments conducted on mice. However, a limited number of studies investigated the impact of phenolic acids on obese humans. Fortunately, the provided tables encompass a wide range of extracts and active compounds, offering valuable insights with great variety.

The primary objective of the reviewed studies was to examine the effects of phenolic acids in the treatment or supplementation of obesity and metabolic syndrome. Additionally, other relevant studies were considered, particularly those investigating the therapeutic potential of these substances in managing type II diabetes, controlling and treating high blood pressure, regulating cholesterol levels, triglycerides, hepatic disorders, renal conditions, and other parameters associated with dyslipidaemia.

Although some studies may not directly address the main topic of this overview, they are nonetheless consequential to obesity, either directly or indirectly, the formation of free radicals is linked with several diseases, not only obesity itself, but also cancer, cardiovascular diseases, degenerative disorders and chronic inflammation which all are also age-related. Therefore, it was deemed appropriate to include such studies, especially those that analysed effects beyond body weight and fat content.

### 4.1 In-vitro studies

In-vitro studies have consistently demonstrated significant potential across various research studies, and these studies were no exception. Different approaches, cell types, methods, and active substances were employed in these studies. However, a common thread among them was the simulation of the digestive tract in-vitro.

Many studies utilized already differentiated adipocyte cells from mice to bypass the differentiation step, making the studies more feasible and mimicking tissue conditions [12], [13], [14]. The use of mice pre-adipocytes was also common in the studies identified [15], [16]. Some studies evaluated the effects on MIN6 cells [17], while others simulated the digestive tract [18], [19], [13]. In one instance, researchers utilized mice fibroblasts to differentiate them into pre-adipocytes [20], while in another, renal Vero cells and Chang hepatic cells were used for the study.

The objective of these studies consistently focused on the antioxidant activities, which play a crucial role in obesity as it leads to the formation of various oxidative factors associated with obesity-related conditions. The evaluation of antioxidant capabilities of the extracts and phenolic acids often involved methods such as hydroxyl radical scavenging ability [19], [21], 2,2-diphenyl-1-picrylhydrazyl (DPPH) and scavenging activity [22], nitric oxide radical-scavenging activity [22],  $\text{Fe}^{3+}$  reducing antioxidant power (FRAP) [22], modified ABTS radical cation decolorization [19], [12], [14], [16], and measurement of superoxide anion [16]. In one study mentioned previously, fibroblasts of mice were used to differentiate them into adipocytes, allowing for the examination of the phenolic acid's effects on adipocyte differentiation, angiogenesis prevention, and retardation [20].

While most of the analysed fruits were processed into extracts for examination, some studies focused on isolated molecules. The molecules analysed in-vitro studies included:

- Ellagic Acid [12]
- Curcumin [20]
- Galotanin [15]

These molecules were subject to in-vitro studies to investigate their effects and potential in relation to obesity and associated conditions. The remaining ones were either ethanolic extracts of the pulp, acetic extract or with distilled water. Overlooking each study: When analysing the extract of *Ziziphus mistol* [18], firstly the constitution of it was majorly Phenolic content and secondly it demonstrated that reduced greatly the oxidative-stress. Also, demonstrated to be a moderate inhibitor of the Lipase enzyme (IC<sub>50</sub>: 5.9–9.0 mg GAE/mL) to Orlistat (IC<sub>50</sub>: 0.08 mg GAE/mL). In regards to the inhibition of alfa-glucosidase and alfa-amylase it also showed moderate inhibition, although higher towards alfa-glucosidase. In the second study was evaluated *Citrus junos sieb* [19] where was produced an gelatine extract of the fruit showed potential to be used as an antioxidant with low caloric potential.

The *Viburnum opulus* [17] was a study that aimed mostly to the properties of the extract on diabetes. Used MIN6 cells to assess the release of insulin, however it was found interesting findings relating to obesity patients. The extract showed the capacity to be lipotoxic and antioxidant. The following study used extract of various of parts of plants in their essays, however there always been a reference in each test to Ellagic Acid [12], the fruit used was the Strawberry *Fragaria × Ananassa* var. *Amaou*. It showed better activity in inhibiting lipase enzyme and inhibition of adipocyte differentiation, using Orlistat has a positive control. In another study was use Oranges and Tangerines, *Citrus sinensis* L. and *Citrus reticulata* L. [21]. Ethanolic extract was used so it could be evaluated its antioxidant potential, which was confirmed by the capacity to abduct hydroxyl radicals. Vitamin C and di-terc-butyl methyl phenol as positive controls. *Antidesma bunius* L. was analysed as an ethanolic extract [13], in this study it was possible to determine its antioxidants properties, anti-lipase enzyme and anti-obesogenic capabilities in high concentrations, using Orlistat as a positive control. Curcumin was also investigated in this context but following a different approach [20]. Fibroblasts from mice were obtained in order to see the effects of Curcumin in the differentiation process of adipocytes and in angiogenesis. Results showed the inhibition of the differentiation of pre-adipocytes in adipocytes, activated the programmed death cell mechanism in adipocytes and raised the expression of the P-AMPK and P-ACC enzymes. Inhibiting the P-AMPK enzyme attenuates the synthesis of glycerol lipids and augments fatty acid oxidation by downregulating GPAT- 1 and upregulating CPT-1 expression, respectively, which lead to diminution of the cytosolic long-chain fatty acyl CoA. The activation of AMPK by curcumin downregulated ACC through phosphorylation of this enzyme, which in turn downregulated the flow of acetyl CoA to malonyl CoA. These effects of curcumin on the activation and expression of enzymes involved in adipocytes energy metabolism. The next Active substance portrait in the table in terms of in-vitro studies is Galatonin, investigators were able to extract this molecule from mango (*Mangifera indica* L.) [15]. They used 3T3-L1 cells and showed that Galatonin was able to modulate the metabolism of lipids thru a series of events that mainly involves the AMPK enzyme, such mechanism was already explained when using Curcumin. Using Pomegranate has been long associated with its antioxidant activities *Punica granatum* L. [22]. In this experiment the investigators used different cell types than the others presented in the table, using Vero renal cells and Chang Hepatic cells it was demonstrated that the extract was able to alleviate the oxidative stress upon liver cells and shown general antioxidant activity. It was speculated that it may have the potential to prevent the digestion of carbohydrates, which in practical terms means that cannot be absorbed into the body. Another paper was on the plant *Vaccinium vitis-idaea* L. [14], commonly known for the bush where mulberry's sprout. 3T3-L1 and RAW 264.7 were used to establish a reduction in biomarkers related to inflammation and oxidative stress thru the downregulation of genes pro-inflammation and upregulating anti-inflammatory genes in the adipose cells. Lastly, *Schisandra chinensis* [16] was used in this research was used the fruit peel and its extract was assessed on 3T3-L1 mice cells, where was established its anti-obesogenic effects through the phosphorylation of GSK3-Beta and Akt genes. In conclusion, it is safe to assume that

having antioxidant activity is a common property among phenolic acids whether is in a form of an extract or pure form. It's molecule form presented far stronger evidence than as an extract, however as an extract the antioxidant properties may also be due to the presence of other components such as flavonoids and terpenoids. Most of the extracts and molecules examined also presented very positive results in combating biomarkers of inflammation, oxidative stress and obesity, not only being able to reduce the number and differentiation to adipocytes but also having the capability of inhibiting lipase enzyme, this last is responsible to allow the absorption of fats into the blood.

## 4.2 In-vivo studies

In-vivo studies composed the large majority of articles analysed in this paper. The animals portrayed in all of the studies were mice of different types. Usually most of the essays required the inducement of obesity in otherwise normal mice, once the mice became obese, the treatment and experiment were assessed. In some studies, it was common the use of positive control groups in order to further analysed the effect of the extracts, either with ascorbic acid or Orlistat. There has been no preference towards the gender of the mice, however only one study performed testing in an all-female mice population.

*Morinda citrifolia* L.: Supplementation of a high-fat diet with phenolic extract from noni fruit in healthy rats showed restructuring of gut microbiota, prevention of intestinal barrier dysfunction, suppression of inflammatory reactions, and reduced weight gain and lipid accumulation in blood vessels [23].

*Syzygium cumini* L. Skeels: The supplementation of a high-fat diet with dried frozen Duhat extract in rats demonstrated regulation of lipid accumulation in adipocytes and hepatocytes, as well as hypotriglyceridaemic effects [24].

*Citrus junos* Sieb.: 40 rats 4 weeks old were subjected to this experimentation. Supplementation with citrus extract in in-vivo studies prevented obesity and demonstrated antioxidant effects in rats. It was also considered a low-calorie snack with antioxidant potential [19].

*Eriobotrya japonica*: To a group of 96 healthy mice was induced obesity and then treated with extracts from the leaves, seeds, and fruit. It effectively reduced plasma levels of LDL, triglycerides, and total cholesterol, while increasing HDL levels. It also reduced glucose levels and improved liver and kidney function in obese rats [25].

*Rubus idaeus* (Raspberry): Several masculine mice were divided into groups where they were put in a high caloric diet to induce obesity, each group would have different concentrations of the extract. Raspberry extract supplementation in male obese rats resulted in reduced adipose tissue and decreased levels of ghrelin, therefore reducing the hunger feeling in the mice [26].

No plant referenced – active compound: Piceatannol: The mice were divided into two groups, one of them was subjected to a chow diet alongside supplementation with Piceatannol and other group was subjected to a high caloric diet also with supplementation to Piceatannol. it was found that supplementation with Piceatannol reduced weight gain compared to rats on the same highly caloric diet without supplementation. Additionally, Piceatannol was shown to stabilize the intestinal microbiota, bringing it closer to the control group. Moreover, the study revealed a reduction in adipose tissue mass. These findings suggest the potential of Piceatannol as a promising intervention

in managing weight-related conditions [27].

No plant referenced – active compound: Curcumin: 18 mice were divided into three groups: one with low caloric values, the second one with high caloric value and the last one a diet with high caloric value supplemented with Curcumin. The supplementation reduced weight, fat mass, and liver weight in rats on a high-calorie diet [20].

*Plinia jaborcaba*: In the study, thirty C57BL/6 mice were divided into three equal groups and induced to develop obesity. The groups consisted of: Control group, received a highly-caloric diet. Supplementation group, in addition to the highly-caloric diet, received supplementation of the fruit extract along with gallic acid. Extract group, received the highly-caloric diet along with supplementation of the fruit extract. The study showed that the extract had a direct influence on anti-inflammatory actions related to obesity, such as reducing adipose tissue weight, protecting against dyslipidaemia, and preventing insulin resistance [28].

*Solanum macrocarpon* and *Solanum aethiopicum*: 42 female Wistar rats were divided into groups and induced to obesity, with different groups receiving a high-calorie diet, supplementation of extract, or Orlistat. The study demonstrated a reduction in weight gain, improved biochemical parameters, including increased albumin concentration, reduced LDL, cholesterol, and triglyceride levels, and decreased expression of fat synthesis-related enzymes [29].

No plant referenced – active compound - Resveratrol: Thirty male C57BL/6J mice were divided into groups with a normal diet, a high-calorie diet, and a diet supplemented with 0.4% Resveratrol. The Resveratrol showed potential in inhibiting visceral adipogenesis, suppressing galanin-mediated signalling cascade, and attenuating cytokine production by suppressing pro-inflammatory signals TLR2 and TLR4 [30].

No plant referenced – active compound - Resveratrol: Forty-two female FVB/N mice were divided into different diet groups: normal diet, normal diet + Resveratrol, high-fat diet, high-fat diet + Resveratrol, high-protein diet, and high-protein diet + Resveratrol. The study showed a reduction in lipogenesis and metabolic markers in the high-protein diet group. It also demonstrated a reduction in total cholesterol in both the high-fat and high-protein diet groups [31].

No plant referenced – active compounds – Caffeic Acid and Chlorogenic Acid: Thirty-two male mice were divided into four groups, each with different diets: normal diet, high-fat diet, and two groups that supplemented the high-fat diet with either caffeic acid or chlorogenic acid. The study demonstrated anti-obesity effects in rats induced with obesity, including reduced adipokine levels, improved body fat distribution, and decreased cholesterol biosynthesis. It also showed that chlorogenic acid was more effective and potent than caffeic acid [32].

*Schisandra chinensis*: Forty Sprague-Dawley mice were divided into four groups: one with a normal diet, one with a high-fat diet, and two groups with the same high-fat diet but supplemented with the plant extract and L-Ascorbic Acid (positive control). The results showed the decreased of lipids and body fat of the mice [16].

### 4.3 Clinical trials

In terms of clinical trials, it was clearly the area that lacked the most in research, however the majority of the papers found showed interesting outcomes and good prospects to the future.

No plant referenced - active compound - Salicylic Acid: Fifty obese children with at least 6 years old. This was an interventional longitudinal observational uncontrolled cohort study which showed that dietary intake of foods rich in Salicylic Acid increased its level in the blood which in consequence led to a increase in anti-inflammatory.

*Tamarindus indica* L. – 100g of pulp: Forty overweight and obese adults. patients were randomly and equally assigned to tamarind and control groups. Both groups were instructed proper diet and maintaining physical activity for 6 weeks. Furthermore, the participants of tamarind group were instructed to consume 10 grams of tamarind fruit pulp twice daily with meals for the same period. The study did not provide evidence for the effectiveness of date pulp extract in reducing blood pressure, BMI, lipid profile, glycemic levels, or waist circumference. However, it is important to note that the study had some limitations, including the absence of consideration for calorie intake, a relatively short study duration, and the lack of a placebo group.

*Rhus coriaria* L. (Sumac) – Capsules containing 500 mg of extract or a placebo: The study involved 50 obese patients who were divided into two groups: one group received capsules containing 500 mg of Sumac pulp powder, while the other group received a placebo. The study lasted for 6 weeks. The results showed significant reductions in BMI, waist circumference, and weight in the group supplemented with Sumac. Additionally, the study demonstrated a decrease in insulin resistance among the participants[33].

*Vaccinium meridionale* Swartz - Dehydrated fruit: The study involved 25 obese men and women who were given supplementation of this fruit without making any changes to their current lifestyle, except for avoiding fruits with similar composition. Interestingly, the study did not include a control group for comparison. The results revealed a significant reduction in inflammatory parameters among the participants. However, in terms of short-term weight reduction, the supplementation did not yield a significant impact [34].

*Vaccinium arctostaphylos* – ethanolic extract: 50 obese and hypertensive patients were divided into two groups: a placebo group and a group that received supplementation with the plant's fruit extract in powdered form. The supplementation of the fruit extract, along with two hypertension medications, resulted in improved systolic and diastolic blood pressure levels. Notably, no adverse reactions or interactions were reported during the study.

Table 1: Literature review (part 1) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation).

[23]	P: <i>Morinda citrifolia</i> L., PD:09/2022, F:Noni, AS:Noni phenolic extract
In-vitro	—
In-Vivo	40 healthy rats, of which one group was induced obesity.
Clinical Trials	—
Results	It has been demonstrated that supplementation of a high-fat diet in rats with phenolic extract restructured the gut microbiota, prevented intestinal barrier dysfunction, and suppressed inflammatory reactions. It also attenuated weight gain in rats and the accumulation of lipids in blood vessels.
[24]	P: <i>Syzgium cumini</i> L. Skeels, PD:08/2021 2022, F:Duhai, AS:Dehydrated frozen Duhai extract
In-vitro	—
In-Vivo	35 rats, 6 weeks old, weighing an average of 22g +/- 2g. One group of rats was induced to become obese.
Clinical Trials	—
Results	It has been demonstrated that supplementation with the extract in high-fat diets does not prevent weight gain, but it regulates lipid accumulation in adipocytes and hepatocytes. It has shown a hypotriglyceridemic effect.
[18]	P: <i>Ziziphus mistol</i> , PD:08/2017, F:Mistol, AS:Extract of the fruit
In-vitro	Gastrointestinal tract simulation
In-Vivo	—
Clinical Trials	—
Results	Mistol has been proven to be a moderate inhibitor of the enzyme Lipase. It can be used as an alternative to existing options in the market such as Orlistat
[35]	P:Salicylic Acid, PD:05/2019, F:—, AS:—
In-vitro	—
In-Vivo	—
Clinical Trials	50 children over the age of 6 with obesity
Results	Indication of foods rich in salicylic acid in obese children with the aim of increasing their blood levels and potential anti-inflammatory effects.
[19]	P: <i>Citrus junos</i> Sieb., PD:12/2022, F:Chenpi, AS:Jelly extract of the fruit
In-vitro	The potential antioxidant activity was evaluated.
In-Vivo	40 rats at 4 weeks of age, of which one group was induced to develop obesity.
Clinical Trials	—
Results	It has been demonstrated that supplementation with the extract in in-vivo studies led to the prevention of obesity in rats and enhanced antioxidant effects. in-vitro studies have shown that it is a low-calorie snack with potential antioxidant properties.
[25]	P: <i>Eriobotrya japonica</i> , PD:09/2022, F:Loquat, AS:Fruit Extract
In-vitro	—
In-Vivo	96 healthy rats, of which one group was induced to develop obesity.
Clinical Trials	—
Results	The efficacy of the extracts in reducing plasma levels of LDL, triglycerides, and total cholesterol, and increasing HDL levels has been demonstrated. There was a reduction in plasma glucose levels. The extracts also decreased hepatic enzyme levels and improved kidney function, as evidenced by a decrease in plasma parameters of creatinine, albumin, and total protein in urine.

Table 2: Literature review (part 2) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation).

[17]	P: <i>Viburnum opulus</i> , PD:05/2020, F:Guelder rose, AS:Fruit Extract containing: Chlorogenic acid
In-vitro	MIN6 cells are used to evaluate insulin secretion
In-Vivo	—
Clinical Trials	—
Results	It has been shown to have potential antioxidant properties. However, it has also been demonstrated to be lipotoxic and capable of reducing insulin secretion.
[36]	P: <i>Tamarindus indica</i> L., PD:02/2020, F:Indian date plum, AS:Pulp
In-vitro	—
In-Vivo	—
Clinical Trials	40 overweight or moderately obese adults, non-smokers, without type 1 diabetes.
Results	The study did not demonstrate the effectiveness of date pulp extract in reducing blood pressure, BMI, lipid and glycemic profile, as well as waist circumference. However, it's important to note that the study did not take into account the calorie intake of the participants, had a short duration, and lacked a placebo control group.
[12]	P: <i>Fragaria x ananassa</i> var. <i>Amaou</i> , PD:01/2015, F:Strawberry, AS:Pulp
In-vitro	Anti-lipase activity, inhibition of adipocyte differentiation, and antioxidant activity
In-Vivo	—
Clinical Trials	—
Results	Ellagic Acid was the compound found most frequently in various extracts. Ripe fruit showed better anti-lipase activity, while green fruit exhibited anti-lipase activity and inhibition of adipocyte differentiation. The study used Orlistat as a positive control.
[21]	P: <i>Citrus sinensis</i> L. + <i>Citrus reticulata</i> L., PD:10/2020, F:Orange+Tangerine, AS:Ethanollic Extract
In-vitro	The reducing power of the extracts and the hydroxyl radical scavenging capacity were measured.
In-Vivo	—
Clinical Trials	—
Results	Based on the in-vitro assays, it can be concluded that the extracts showed good reducing power and hydroxyl radical scavenging activity. The study used vitamin C and di-tert-butyl methyl phenol as controls.
[13]	P: <i>Antidesma bunius</i> L., PD:11/2019, F:Mao Lang , AS:Ethanollic Extract
In-vitro	The anti-adipogenic effect and quantification of triglycerides were tested in 3T3-L1 adipocytes. The anti-lipase effect was evaluated through a simulation of the gastrointestinal tract.
In-Vivo	—
Clinical Trials	—
Results	The potential antioxidant activity, anti-lipase activity, and anti-adipogenic activity were demonstrated at high concentrations. Orlistat was used as a control in the study.
[26]	P: <i>Rubus idaeus</i> , PD:08/2019, F:Raspberry , AS:Fruit extract
In-vitro	—
In-Vivo	Male rats were induced to develop obesity. They were divided into several groups with different concentrations of raspberry compared to a placebo (vehicle) group.
Clinical Trials	—
Results	The study demonstrated a reduction in adipose tissue during the 4-week period. It also showed a reduction in ghrelin levels.

Table 3: Literature review (part 3) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation).

[26]	P:Piceatannol, PD:10/2016, F:N/D , AS:Pure compound
In-vitro	—
In-Vivo	C57BL/6 mice, aged 5 weeks, were divided into control groups and test groups with the active substance under the influence of a high-calorie diet, two of which contained different concentrations of Piceatannol.
Clinical Trials	—
Results	It was demonstrated that supplementation with Piceatannol reduced weight gain compared to rats on the same high-calorie diet without supplementation. It stabilized the intestinal microbiota to levels close to the control group. It also showed a reduction in adipose tissue mass.
[27]	P:Piceatannol, PD:10/2016, F:N/D , AS:Pure compound
In-vitro	—
In-Vivo	C57BL/6 mice, aged 5 weeks, were divided into control groups and test groups with the active substance under the influence of a high-calorie diet, two of which contained different concentrations of Piceatannol.
Clinical Trials	—
Results	It was demonstrated that supplementation with Piceatannol reduced weight gain compared to rats on the same high-calorie diet without supplementation. It stabilized the intestinal microbiota to levels close to the control group. It also showed a reduction in adipose tissue mass.
[20]	P:Curcumin, PD:03/2019, F:N/D , AS:Pure compound
In-vitro	Mouse embryonic fibroblasts were used to generate pre-adipocytes and evaluate their capacity for differentiation and angiogenesis.
In-Vivo	18 C57BL/6 mice at 4 weeks of age were divided into 3 groups where they consumed 3 different diets: low-calorie, high-calorie, and high-calorie with curcumin supplementation.
Clinical Trials	—
Results	The in-vitro study showed inhibition of pre-adipocyte differentiation into adipocytes, induction of adipocyte apoptosis, and increased expression of P-AMPK and P-ACC enzymes. The in-vivo study demonstrated a reduction in weight and fat mass of the mice, as well as a decrease in liver weight, compared to the group on a high-calorie diet without curcumin supplementation.
[28]	P: <i>Plinilia jaboricaba</i> , PD:01/2021, F:Jaboticaba , AS:Fruit extract
In-vitro	—
In-Vivo	30 C57BL/6 mice, 8 weeks old, were divided equally into 3 groups and induced to develop obesity. The groups consisted of a control group receiving a high-calorie diet, a second group receiving supplementation with the extract of the fruit containing gallic acid, and a third group receiving both the high-calorie diet and supplementation with the extract.
Clinical Trials	—
Results	The study demonstrated that the extract had a direct influence on anti-inflammatory actions related to obesity, particularly in reducing LPS levels. The extract prevented weight gain in adipose tissue and protected the mice against dyslipidemia. It also prevented phenomena associated with insulin resistance.

Table 4: Literature review (part 4) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation).

[29]	P: <i>Solanum macrocarpon</i> + <i>Solanum aethiopicum</i> , PD:12/2018, F:African eggplant, AS:Acetonic extract of the fruit
In-vitro	—
In-Vivo	42 female Wistar rats were divided into groups and induced to develop obesity. The control group was fed a standard chow diet, while another group received a high-calorie diet. The remaining groups were fed a high-calorie diet with supplementation of different concentrations of the extract, and a final group received supplementation with Orlistat.
Clinical Trials	—
Results	The study demonstrated a reduction in weight gain in the rats. Obese rats treated with the extracts showed better results compared to those under the high-calorie diet alone in the following aspects: higher albumin concentrations, reduced ALP levels, decreased arthrogenic index, lower levels of LDL, total cholesterol (CT), triglycerides (TG), VLDL, increased HDL, and reduced expression of enzymes involved in fat synthesis.
[33]	P: <i>Rhus coriaria</i> L., PD:09/2019, F:Sumac, AS:Capsules containing 500g of fruit powder
In-vitro	—
In-Vivo	—
Clinical Trials	Fifty obese patients were divided into a placebo group and a group supplemented with Sumac for 6 weeks.
Results	The study demonstrated reductions in BMI, waist circumference, and weight. It also showed a decrease in insulin resistance.
[15]	P: <i>Mangifera indica</i> L., PD:04/2018, F:Mango, AS:Galotanin
In-vitro	—
In-Vivo	3T3-L1 rat pre-adipocytes were used.
Clinical Trials	—
Results	The results indicated that the active compound is capable of modulating lipid metabolism through a series of cascading reactions involving AMPK. Its potential to prevent obesity-related conditions is recognized.
[22]	P: <i>Punica granatum</i> L., PD:01/2020, F:Pomegranate, AS:Acetonic Extract of the fruit
In-vitro	Vero renal cells and Chang liver cells were used
In-Vivo	—
Clinical Trials	—
Results	Fruit and leaf substrates with a high content of phenolic acids and flavonoids have shown great antioxidant potential. They have been found to alleviate oxidative stress in liver cells. It is believed that they have the potential to inhibit carbohydrate digestion.
[34]	P: <i>Vaccinium meridionale</i> Swartz, PD:03/2022, F:N/D, AS:Dehydrated fruit
In-vitro	Vero renal cells and Chang liver cells were used
In-Vivo	—
Clinical Trials	Twenty-five obese men and women were advised to take supplementation of this wild fruit without making any changes to their current lifestyle, except for avoiding fruits with a similar composition.
Results	A control group was not included in this study. Significant reduction in inflammatory parameters was observed. However, there was no significant impact on short-term weight reduction in the patients.

Table 5: Literature review (part 5) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation).

[37]	P: <i>Vaccinium arctostaphylos</i> , PD:05/2019, F:N/D, AS:Ethanollic extract of the powder of the fruit
In-vitro	—
In-Vivo	—
Clinical Trials	Fifty obese and hypertensive patients were divided into a placebo group and a group that supplemented their treatment with the plant substrate.
Results	Supplementation of the fruit extract in conjunction with two medications indicated for the treatment of hypertension improved systolic and diastolic blood pressure without any adverse reactions or interactions.
[30]	P:Resveratrol, PD:03/2011, F:N/D, AS:Pure compound
In-vitro	—
In-Vivo	Thirty male C57BL/6J mice, 9 weeks old, were divided into groups: one group received a normal diet, another group received a high-calorie diet, and the remaining group was fed a diet supplemented with 0.4% Resveratrol
Clinical Trials	—
Results	Resveratrol has been shown to inhibit visceral adipogenesis by suppressing the galanin-mediated signalling cascade. It has also demonstrated the ability to attenuate cytokine production by suppressing pro-inflammatory signals TLR2 and TLR4.
[14]	P: <i>Vaccinium vitis-idaea</i> L., PD:01/2019, F:Blackberry, AS:Extract of the fruit
In-vitro	The ability of the extract to mitigate oxidative stress was evaluated in 3T3-L1 adipocytes and RAW 264.7 cells.
In-Vivo	—
Clinical Trials	—
Results	RIIt was demonstrated that there was a reduction of oxidation and inflammatory markers, through the regulation of pro- and anti-inflammatory genes in adipose tissue.
[31]	P:Resveratrol, PD:04/2016, F:N/D, AS:Pure compound
In-vitro	—
In-Vivo	42 Female FVB/N mice aged 8 weeks were divided into different diets: Normal Diet, Normal + Resveratrol, High Fat, High Fat Calories + Resveratrol, High Protein, High Protein + Resveratrol.
Clinical Trials	—
Results	A reduction in lipogenesis and metabolic markers has been demonstrated on a high protein diet. It also demonstrated a reduction in total cholesterol on both diets.

Table 6: Literature review (part 6) (P:Plant,PD:Publication Date,F:FRuit,AS:Preparation).

[32]	P:Caffeic acid +Chlorogenic acid, PD:01/2010, F:N/D, AS:Pure compound
In-vitro	—
In-Vivo	32 4-week-old male rats were divided into 4 groups, each on different diets. One normal, another high in fat and two others supplemented the latter with either caffeic acid or chlorogenic acid.
Clinical Trials	—
Results	Anti-obesity effect was demonstrated in rats which had been induced. Adipokines, body fat distribution and cholesterol biosynthesis values were lowered. Chlorogenic acid has also been shown to be more effective and potent than caffeic acid.
[16]	P: <i>Schisandra chinensis</i> , PD:02/2012, F:Magnolia, AS:Ethanollic extract of the fruit
In-vitro	at 3T3-L1 preadipocytes and medium anti-oxidant potential were tested.
In-Vivo	40 5-week-old Sprague-Daewley rats were divided into 4 groups: One on a normal diet, another on a high-fat diet and the other two would be like this second but supplemented with plant extract and L-Acid Ascorbic (positive control).
Clinical Trials	—
Results	In the in-vitro assays, the anti-obesity effect of the extract was demonstrated in 3T3-L1 cells and rats on a high-fat diet. Treatment of 3T3-L1 cells with the extract inhibited GSK3beta and Akt phosphorylation. The extract, in mice, was shown to decrease the amount of fat and lipids in mice subjected to a high-fat diet.

## 5 Discussion

The findings of the literature review provide compelling evidence regarding the effects of phenolic acids on obesity and related conditions. The comprehensive analysis covered a range of studies, including in-vitro experiments, in-vivo investigations using animal models, and a limited number of clinical trials. The collective results underscore the significant potential of phenolic acids in the treatment and supplementation of obesity and metabolic syndrome.

The in-vitro studies employed various methodologies and cell types to examine the impact of phenolic acids. Notably, the primary focus was on evaluating the antioxidant activities of these substances. The consistent findings demonstrated their remarkable ability to scavenge free radicals, reduce oxidative stress, and combat obesity-associated conditions such as chronic inflammation and related diseases. These antioxidant properties are particularly crucial in the context of obesity, where oxidative stress plays a pivotal role.

Furthermore, specific phenolic acids, such as curcumin and galatolin, were extensively studied in their pure form. These investigations revealed promising outcomes, including inhibiting adipocyte differentiation and modulating lipid metabolism. These findings highlight the potential of phenolic acids in regulating adipose tissue development, inhibiting lipid accumulation, and ultimately mitigating obesity-related factors.

Moving to the in-vivo studies, animal models, primarily mice, were utilized to explore the effects of phenolic acid supplementation on obesity and its associated parameters. The outcomes consistently demonstrated that phenolic extract or isolated compound supplementation effectively prevented weight gain, regulated lipid accumulation, improved lipid profiles, and influenced metabolic parameters. These favorable effects were attributed to the anti-inflammatory and antioxidant properties of phenolic acids, which collectively contribute to overall metabolic health enhancement.

It is important to acknowledge the limited number of clinical trials identified in the review. However, the outcomes of these studies were promising. For instance, although the supplementation of tamarind fruit pulp did not yield significant weight reduction or improvements in lipid profiles, it did lead to an increase in salicylic acid levels in the blood. This suggests that dietary intake of phenolic-rich foods may indirectly impact inflammation, which is intricately linked to obesity.

While the reviewed studies provide valuable insights, several limitations should be acknowledged. The majority of the investigations focused on animal models, primarily mice, which may not fully mirror the complexity of human obesity and metabolic syndrome. Additionally, the clinical trials were limited in number and had relatively short duration, making it challenging to draw definitive conclusions.

In conclusion, the findings of the reviewed studies strongly indicate that phenolic acids hold tremendous promise in the treatment and supplementation of obesity and metabolic syndrome. Their potent antioxidant, anti-inflammatory, and lipid-regulating properties contribute to their positive effects on various obesity-related conditions. Nonetheless, further research, including well-designed clinical trials, is warranted to fully elucidate the underlying mechanisms and unleash the therapeutic potential of phenolic acids in managing obesity and its associated disorders.

## 6 Conclusions

The use of polyphenols is considered safe due to being part of human diet, therefore its use is considered safe. Yet, there is still a need for more researches in order to determine the anti-obesity and all the mechanism that counteracts metabolic syndrome mechanisms at the molecular level, as well as to pinpoint the phytoconstituents responsible for the anti-obesity effects. Looking ahead, the primary reservoir for developing safe and efficient anti-obesity medications will be natural products. The future landscape of research in novel anti-obesity agents promises to be notably intriguing, given the wealth of unexplored plant species across the globe. Hence, scientific exploration should be actively pursued to unearth new opportunities for directly applying natural products to human use and amassing compelling evidence supporting their viability as innovative therapeutic strategies for addressing obesity.

## References

- [1] World Health Organization. *Summary of Product Characteristics - Xenical 120 mg hard capsules*. URL: [https://www.ema.europa.eu/en/documents/product-information/xenical-epar-product-information\\_en.pdf](https://www.ema.europa.eu/en/documents/product-information/xenical-epar-product-information_en.pdf). (accessed: 29.08.2023).
- [2] Christos Socrates Mantzoros. "Nutrition and metabolism : underlying mechanisms and clinical consequences". In: 2009. URL: <https://api.semanticscholar.org/CorpusID:68543905>.
- [3] Bhawana Aggarwal and Vandana Jain. "Obesity in Children: Definition, Etiology and Approach". In: *The Indian Journal of Pediatrics* 85 (2018), pp. 463–471. URL: <https://api.semanticscholar.org/CorpusID:30750628>.
- [4] Jun Goo Kang and Cheol-Young Park. "Anti-Obesity Drugs: A Review about Their Effects and Safety". In: *Diabetes & Metabolism Journal* 36 (2012), pp. 13–25. URL: <https://api.semanticscholar.org/CorpusID:2183961>.
- [5] European Medicines Agency. *Obesity*. URL: <https://www.who.int/health-topics/obesity/>. (accessed: 29.08.2023).
- [6] Pratap Kumar and Shweta Arora. "Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates". In: *Journal of Human Reproductive Sciences* 7 (2014), pp. 255–261. URL: <https://api.semanticscholar.org/CorpusID:22733373>.
- [7] Manisha Singh et al. "Managing obesity through natural polyphenols: A review". In: 2020. URL: <https://api.semanticscholar.org/CorpusID:225144595>.
- [8] Parul Singla, Animesh Bardoloi, and Anuj Parkash. "Metabolic effects of obesity: A review." In: *World journal of diabetes* 1 3 (2010), pp. 76–88. URL: <https://api.semanticscholar.org/CorpusID:6569507>.
- [9] Shingo Kajimura and Masayuki Saito. "A new era in brown adipose tissue biology: molecular control of brown fat development and energy homeostasis." In: *Annual review of physiology* 76 (2014), pp. 225–49. URL: <https://api.semanticscholar.org/CorpusID:16640348>.
- [10] Wouter D. van Marken Lichtenbelt et al. "Cold-activated brown adipose tissue in healthy men." In: *The New England journal of medicine* 360 15 (2009), pp. 1500–8. URL: <https://api.semanticscholar.org/CorpusID:477352>.
- [11] Shampa Ghosh et al. "Role of Phytomolecules in the Treatment of Obesity: Targets, Mechanisms and Limitations." In: *Current topics in medicinal chemistry* (2021). URL: <https://api.semanticscholar.org/CorpusID:232142076>.
- [12] Qinchang Zhu et al. "In vitro bioactivities and phytochemical profile of various parts of the strawberry (*Fragaria × ananassa* var. *Amaou*)". In: *Journal of Functional Foods* 13 (2015), pp. 38–49. URL: <https://api.semanticscholar.org/CorpusID:84783956>.
- [13] Ornnicha Krongyut and Khaetthareeya Sutthanut. "Phenolic Profile, Antioxidant Activity, and Anti-obesogenic Bioactivity of Mao Luang Fruits (*Antidesma bunius* L.)" In: *Molecules* 24 (2019). URL: <https://api.semanticscholar.org/CorpusID:208170382>.
- [14] Katarzyna Kowalska et al. "Inhibitory effects of lingonberry (*Vaccinium vitis-idaea* L.) fruit extract on obesity-induced inflammation in 3T3-L1 adipocytes and RAW 264.7 macrophages". In: *Journal of Functional Foods* (2019). URL: <https://api.semanticscholar.org/CorpusID:91390405>.

- [15] Chuo Fang et al. “Gallotannin derivatives from mango (*Mangifera indica* L.) suppress adipogenesis and increase thermogenesis in 3T3-L1 adipocytes in part through the AMPK pathway”. In: *Journal of Functional Foods* (2018). URL: <https://api.semanticscholar.org/CorpusID:89932644>.
- [16] Hyoung Joon Park et al. “Anti-obesity effect of *Schisandra chinensis* in 3T3-L1 cells and high fat diet-induced obese rats”. In: *Food Chemistry* 134 (2012), pp. 227–234. URL: <https://api.semanticscholar.org/CorpusID:86513639>.
- [17] Anna Podsedek et al. “Matrix Effects on the Stability and Antioxidant Activity of Red Cabbage Anthocyanins under Simulated Gastrointestinal Digestion”. In: *BioMed Research International* 2014 (2014). URL: <https://api.semanticscholar.org/CorpusID:14899607>.
- [18] Mara Eugenia Orqueda et al. “Chemical and functional characterization of skin, pulp and seed powder from the Argentine native fruit mistol (*Ziziphus mistol*). Effects of phenolic fractions on key enzymes involved in metabolic syndrome and oxidative stress”. In: *Journal of Functional Foods* 37 (2017), pp. 531–540. ISSN: 1756-4646. DOI: <https://doi.org/10.1016/j.jff.2017.08.020>. URL: <https://www.sciencedirect.com/science/article/pii/S1756464617304838>.
- [19] Mingfang Peng et al. “Development of Citrus-Based Functional Jelly and an Investigation of Its Anti-Obesity and Antioxidant Properties”. In: *Antioxidants* 11 (2022). URL: <https://api.semanticscholar.org/CorpusID:254485115>.
- [20] Asma Ejaz et al. “Curcumin inhibits adipogenesis in 3T3-L1 adipocytes and angiogenesis and obesity in C57/BL mice.” In: *The Journal of nutrition* 139 5 (2009), pp. 919–25. URL: <https://api.semanticscholar.org/CorpusID:32420901>.
- [21] Assia Bentahar et al. “Phenolic content and antioxidant activity of ethanolic extracts from *Citrus sinensis* L. and *Citrus reticulata* L. fruits”. In: *Journal of Drug Delivery and Therapeutics* 10 (2020), pp. 308–313. URL: <https://api.semanticscholar.org/CorpusID:233287125>.
- [22] Chika I. Chukwuma and authors. “Corrigendum”. In: *Journal of Food Biochemistry* 44.8 (2020), e13376. DOI: <https://doi.org/10.1111/jfbc.13376>. eprint: <https://onlinelibrary.wiley.com/doi/pdf/10.1111/jfbc.13376>. URL: <https://onlinelibrary.wiley.com/doi/abs/10.1111/jfbc.13376>.
- [23] Ruimin Wang et al. “Phenolics from noni (*Morinda citrifolia* L.) fruit alleviate obesity in high fat diet-fed mice via modulating the gut microbiota and mitigating intestinal damage”. In: *Food Chemistry* 402 (2023), p. 134232. ISSN: 0308-8146. DOI: <https://doi.org/10.1016/j.foodchem.2022.134232>. URL: <https://www.sciencedirect.com/science/article/pii/S030881462202194X>.
- [24] Carmela Jhoy G. Mercado et al. “Antioxidant, Anti-obesity, and Lipid-lowering Properties of Philippine Duhat (*Syzygium cumini* L. Skeel) Freeze-dried Fruit Flesh”. In: 2021. URL: <https://api.semanticscholar.org/CorpusID:250084566>.
- [25] Zainab R. Abdelrahman, Yasser K. Bustanji, and Shtaywy S. Abdalla. “Ethanol Extracts of *Eriobotrya japonica* (Loquat) Seeds, Leaves, and Fruits Have Anti-obesity and Hypolipidemic Effects in Rats”. In: *Pharmacognosy Magazine* 19 (2022), pp. 56–65. URL: <https://api.semanticscholar.org/CorpusID:257277512>.

- [26] Dushyant Kshatriya et al. “Phenolic-enriched raspberry fruit extract (*Rubus idaeus*) resulted in lower weight gain, increased ambulatory activity, and elevated hepatic lipoprotein lipase and heme oxygenase-1 expression in male mice fed a high-fat diet”. In: *Nutrition Research* 68 (2019), pp. 19–33. ISSN: 0271-5317. DOI: <https://doi.org/10.1016/j.nutres.2019.05.005>. URL: <https://www.sciencedirect.com/science/article/pii/S0271531719301708>.
- [27] Yen-Chen Tung et al. “Piceatannol Exerts Anti-Obesity Effects in C57BL/6 Mice through Modulating Adipogenic Proteins and Gut Microbiota”. In: *Molecules* 21 (Oct. 2016), p. 1419. DOI: 10.3390/molecules21111419.
- [28] Larissa Lages Rodrigues et al. “Phenolic compounds from jaboticaba (*Plinia jaboticaba* (Vell.) Berg) ameliorate intestinal inflammation and associated endotoxemia in obesity.” In: *Food research international* 141 (2021), p. 110139. URL: <https://api.semanticscholar.org/CorpusID:232080566>.
- [29] Kemi Feyisayo Akinwunmi and Ibukun Olamide Ajibola. “Evaluation of Anti-obesity Potentials of Phenolic-Rich Fraction of *Solanum aethiopicum* L. and *Solanum macrocarpon* L. on Diet-induced Obesity in Wistar Rats”. In: *European Journal of Medicinal Plants* (2018). URL: <https://api.semanticscholar.org/CorpusID:92283109>.
- [30] Soyoung Kim et al. “Resveratrol exerts anti-obesity effects via mechanisms involving down-regulation of adipogenic and inflammatory processes in mice”. In: *Biochemical Pharmacology* 81.11 (2011), pp. 1343–1351. ISSN: 0006-2952. DOI: <https://doi.org/10.1016/j.bcp.2011.03.012>. URL: <https://www.sciencedirect.com/science/article/pii/S0006295211001791>.
- [31] Keila Lopes Mendes et al. “Distinct metabolic effects of resveratrol on lipogenesis markers in mice adipose tissue treated with high-polyunsaturated fat and high-protein diets”. In: *Life sciences* 153 (May 2016), 66–73. ISSN: 0024-3205. DOI: 10.1016/j.lfs.2016.04.014. URL: <https://repositorio.ufmg.br/bitstream/1843/44213/2/Distinct%20metabolic%20effects%20of%20resveratrol%20on%20lipogenesis%20markers%20in%20mice%20adipose%20tissue%20treated%20with%20high-polyunsaturated%20fat%20and%20high-protein%20diets.pdf>.
- [32] Ae-Sim Cho et al. “Chlorogenic acid exhibits anti-obesity property and improves lipid metabolism in high-fat diet-induced-obese mice”. In: *Food and Chemical Toxicology* 48.3 (2010), pp. 937–943. ISSN: 0278-6915. DOI: <https://doi.org/10.1016/j.fct.2010.01.003>. URL: <https://www.sciencedirect.com/science/article/pii/S027869151000013X>.
- [33] Samira Kazemi et al. “The effects of sumac (*Rhus coriaria* L.) powder supplementation in patients with non-alcoholic fatty liver disease: A randomized controlled trial.” In: *Complementary therapies in clinical practice* 41 (2020), p. 101259. URL: <https://api.semanticscholar.org/CorpusID:226971945>.
- [34] Journal Vitae, Emerson Gallego-Peláez, and María Maldonado. “Consumption of osmo-dehydrated Andean Berry (*Vaccinium meridionale* Swartz) decreases levels of pro-inflammatory biomarkers of overweight and obese adults \*Corresponding”. In: *Vitae* 28 (June 2021). DOI: 10.17533/udea.vitae.v28n2a343810.
- [35] Giulia Vizzari et al. “Circulating Salicylic Acid and Metabolic Profile after 1-Year Nutritional–Behavioral Intervention in Children with Obesity”. In: *Nutrients* 11 (2019). URL: <https://api.semanticscholar.org/CorpusID:157066936>.

- [36] Sedigheh Asgary et al. “Evaluation on the Effects of *Tamarindus Indica L.* Fruit on Body Weight and Several Cardiometabolic Risk Factors in Obese and Overweight Adult Patients: A Randomized Controlled Clinical Trial”. In: *International Journal of Preventive Medicine* 11 (2020). URL: <https://api.semanticscholar.org/CorpusID:212729516>.
- [37] Saeed Kianbakht and Fataneh Hashem-Dabaghian. “Antihypertensive efficacy and safety of Vaccinium arctostaphylos berry extract in overweight/obese hypertensive patients: A randomized, double-blind and placebo-controlled clinical trial.” In: *Complementary therapies in medicine* 44 (2019), pp. 296–300. URL: <https://api.semanticscholar.org/CorpusID:164218173>.