Obesity mechanisms and importance of bioactive compounds from fruits in its regulation – a narrative review

Mecanismos da obesidade e importância dos compostos bioativos de frutas em sua regulação – uma revisão narrativa

Mecanismos de la obesidad e importancia de los compuestos bioactivos de la fruta en su regulación – una revisión narrativa

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Abstract
A balanced diet is essential in obesity control. Fruits stand out for the presence of various bioactive compounds, which represent promising tools in the prevention and treatment of various pathologies. In obesity, fruits phytochemicals present are related to different important mechanisms of action, such as antioxidant and anti-inflammatory activity. This narrative review aims to understand the main physiological alterations of obesity and the effects of bioactive compounds in fruits on them, identifying the best-known substances and their likely mechanisms of action on the main biomarkers. The research was carried out in the *Google Scholar*, *Scielo*, *Pubmed* and *Science Direct* databases, considering reviews published since 2015 and experimental studies since 2010. Inflammatory cytokines and adipokines are considered primary biomarkers of obesity, and are currently also considered the insulin resistance, lower glucose tolerance, oxidative stress, gut microbiota, nutrients and microRNAs. Three groups of fruits stood out for their effects: Citrus fruits, berries and tropical fruits, sources mainly of flavonoids, anthocyanins and carotenoids. Experimental results indicate that fruits and their compounds can help in the prevention and treatment of obesity through the regulation of inflammatory cytokines and adipokines involved in the mechanisms of this disease, as well as antioxidant properties and modulation of lipogenesis. More clinical studies are needed to understand the biochemical mechanisms involved, in order to favor not only the production of specific supplements but also the best clinical dietary prescription.
Keywords: Obesity; Biomarkers; Phytochemicals; Fruits; Bioactive compounds.

Resumo
Uma dieta equilibrada é essencial no controle da obesidade. As frutas destacam-se pela presença de variados compostos bioativos, que representam ferramentas promissoras na prevenção e tratamento de diversas patologias. Na obesidade, fitoquímicos presentes nas frutas são relacionados a diferentes mecanismos de ação importantes, como atividade antioxidante e anti-inflamatória. Esta revisão narrativa visa entender as principais alterações fisiológicas da obesidade e os efeitos dos compostos bioativos de frutas sobre elas, identificando as substâncias mais conhecidas e seus prováveis mecanismos de ação sobre os principais biomarcadores. A pesquisa foi realizada nas bases de dados *Google Acadêmico, Scielo, Pubmed* e *Science Direct*, considerando revisões publicadas a partir de 2015 e estudos experimentais a partir de 2010. As citocinas inflamatórias e adipocinas são consideradas biomarcadores primários da

obesidade, sendo considerados atualmente também a resistência insulínica, a menor tolerância à glicose, estresse oxidativo, microbiota intestinal, nutrientes e microRNAs. Três grupos de frutas destacaram-se por seus efeitos: as frutas cítricas, "*berries*" e frutas tropicais, fontes principalmente de flavonoides, antocianinas e carotenoides. Resultados experimentais apontam que as frutas e seus compostos podem auxiliar na prevenção e tratamento da obesidade através da regulação de citocinas inflamatórias e adipocinas envolvidas nos mecanismos desta doença, bem como propriedades antioxidantes e modulação da lipogênese. Mais estudos clínicos são necessários para entender sobre os mecanismos bioquímicos envolvidos, a fim de favorecer não só a produção de suplementos específicos como também a melhor prescrição clínica dietética.

Palavras-chave: Obesidade; Biomarcadores; Fitoquímicos; Frutas; Compostos bioativos.

Resumen

Una dieta equilibrada es fundamental para controlar la obesidad. Las frutas se destacan por la presencia de diversos compuestos bioactivos, que representan herramientas prometedoras en la prevención y tratamiento de diversas patologías. En la obesidad, los fitoquímicos presentes en las frutas están relacionados con diferentes mecanismos de acción importantes, como la actividad antioxidante y antiinflamatoria. Esta revisión narrativa pretende comprender las principales alteraciones fisiológicas de la obesidad y los efectos de los compuestos bioactivos de las frutas sobre las mismas, identificando las sustancias más conocidas y sus probables mecanismos de acción sobre los principales biomarcadores. La investigación se realizó en las bases de datos *Google Scholar, Scielo, Pubmed* y *Science Direct*, considerando revisiones publicadas a partir de 2015 y estudios experimentales a partir de 2010. Las citocinas y adipocinas inflamatorias se consideran biomarcadores primarios de la obesidad, y actualmente también se consideran la resistencia a la insulina, menor tolerancia a la glucosa, estrés oxidativo, microbiota intestinal, nutrientes y microARN. Tres grupos de frutas se destacaron por sus efectos: cítricos, "*berries*" y frutas tropicales, fuentes principalmente de flavonoides, antocianinas y carotenoides. Los resultados experimentales indican que las frutas y sus compuestos pueden ayudar en la prevención y tratamiento de la obesidad a través de la regulación de citoquinas y adipoquinas inflamatorias involucradas en los mecanismos de esta enfermedad, así como propiedades antioxidantes y modulación de la lipogénesis. Se necesitan más estudios clínicos para comprender los mecanismos bioquímicos involucrados, a fin de favorecer no solo la producción de suplementos específicos sino también la mejor prescripción dietética clínica.

Palabras clave: Biomarcadores; Fitoquímicos; Frutas; Compuestos bioactivos.

1. Introduction

In a healthy diet, macronutrients, micronutrients and water are consumed in adequate proportions to energy and physiological needs, without excessive intake. To achieve this balance, the diet should consist mostly of fresh vegetables, whole grains, legumes, seeds and nuts, with smaller portions of animal-derived foods such as meat, milk, eggs and cheese (Cena & Calder, 2020; WHO – World Health Organization, 2020). However, despite the recommendations established in many food guides and international guidelines, the consumption of fruits and vegetables by the world population reaches, on average, only two thirds of the required amounts. Thus, the Food and Agriculture Organization of the United Nations (FAO) declared 2021 as the International Year of Fruits and Vegetables, bringing up reflection on the consumption of these foods and their importance for health and sustainable food systems (*Food and Agriculture Organization of the United Nations* - FAO, 2020; Kadouh & Acosta, 2017).

Among vegetables, fruits stand out for their fresh consumption and the presence of a wide variety of bioactive compounds. These substances are not nutrients, but it has been correlated with several benefits to the human body, representing a simple and affordable alternative for the prevention and treatment of many diseases. Due to the presence of these compounds, some fruits are currently called "superfruits", due to their high antioxidant potential and functional properties, such as berries, for example. From the most common to the most exotic fruits it is possible to find different phytochemicals, with different properties. The enormous biodiversity existing in nature's biomes brings the cultivation and consumption of different fruits by country or region, representing a huge range of promising tools in the prevention and treatment of various pathologies (Chang *et al.*, 2019; Karasawa & Mohan, 2018; Nile & Park, 2014).

Poor diet is one of the main factors that contribute to the chronic non-communicable diseases development. Cardiovascular diseases, cancer, chronic respiratory diseases and diabetes are the main. In this context, obesity is also included, reaching crescent alarming levels (Budreviciute *et al.*, 2020; *Food and Agriculture Organization of the United*

Nations - FAO, 2020). According to the World Health Organization (WHO), "obesity is defined as the abnormal or excessive fat accumulation that may impair health". The Body Mass Index (BMI) is used as an important tool for diagnosis. BMI indicates obesity when it reaches values greater than or equal to 30 kg/m² (WHO, 2021). Other measures are also used in this evaluation, such as the waist circumference or the body fat percentage. However, this pathological condition is associated with much more complex changes in human metabolismo, beyond the physical consequences. The exacerbated expansion of adipose tissue deregulates levels of cytokines and adipokines, being able to significantly altering many physiological mechanisms through a state of low-grade chronic inflammation that can lead to complications (Ikeoka *et al.*, 2010; Nimptsch *et al.*, 2019; WHO - *World Health Organization*, 2008; Wu & Ballantyne, 2020).

Due to its relationship with other chronic diseases, mortality and a significant increase in incidence, obesity has been considered a huge global health problem. With a 50% increase in its prevalence from 2000 to 2016, it now affects about 13.9% of the world population. (WHO - *World Health Organization*, 2021). Some studies show a strong worsening of this panorama. In a meta-analysis of more than 280 population-based studies worldwide, Wong *et al.* (2020) estimated about 41.5% prevalence of obesity based on waist circumference data in the world population aged 15 years and over, with rapid growth between 1985 and 2014 (Wong *et al.*, 2020). Janssen et al. (2020) studied a long-term projection of obesity prevalence for 18 countries in Europe and the United States. From 1975 to 2016, there was an increase in obesity in all countries included in the study. In 2016, obesity affected between 22.7% and 29.3% of men and 19.5% to 31.3% of women in European countries. In the United States, 37.5% of men and 39.5% of women were affected at the same time. Obesity is estimated to reach peak levels between 2026 and 2054, potentially reaching about 31.0% of the European population and 44.0% of the North American population. Although this increase is expected to slow or stagnate by 2060, outcomes depend on effective and continued public health actions (Janssen *et al.*, 2020).

Obesity occurs in a multifactorial manner, with biological, environmental and behavioral factors being recognized in its etiology, such as sedentary lifestyle, genetic predisposition, emotional factors and unbalanced diet (Kadouh & Acosta, 2017). In this scenario, the phytochemicals present in fruits are related to different mechanisms of action that help in the prevention and treatment of obesity, such as antioxidant and anti-inflammatory activity, inhibition of proliferation and increase in the rate of adipocyte apoptosis, and reduction of triglyceride absorption. by reducing the formation of pancreatic lipase (Sung *et al.*, 2018; Williams *et al.*, 2013).

There is still much to be studied to understand all about phytochemicals, as well as their interactions with the human organism and also with each other. Even so, the synergism existing in the food matrix and in the varied consumption of fresh fruits brings many possibilities for health promotion through food. While many studies focus on the development of new drugs or supplements, dietary intervention can be quite affordable and effective for disease prevention and treatment, also avoiding side effects associated with drug treatment. By understanding the composition of foods and the action of the phytochemicals present, it would be possible to propose consumption strategies by food groups or compounds for different situations (Balaji *et al.*, 2016; Konstantinidi & Koutelidakis, 2019; Phan *et al.*, 2018).

Therefore, the present study aims to gather the existing knowledge in the literature about the bioactive compounds from fruits and their effects on obesity, identifying the main compounds that act on the corresponding biomarkers and their probable mechanisms of action.

2. Methodology

The present study composes a narrative literature review. According to Ferrari (2015), narrative literature reviews describe the current knowledge about a specific subject through a synthesis, seeking new areas of knowledge, study and foundations for future research. This type of review consists of a non-systematic, more simplified way, aiming at updating in a

short period of time, through a broader and more relevant search about a theme, not presenting a specific methodology for the elaboration of its stages (Casarin *et al*., 2020; Ferrari, 2015). In this study, the review was composed of the following steps: problem definition; choice of databases; establishment of criteria for inclusion and exclusion of studies; discussion and presentation of findings.

For this narrative review, the *Google Academic, Scielo, Pubmed*, and *Science Direct* databases were used. The following publications were included: full text available in English, Spanish and/or Portuguese; paid and/or free access; articles. Thesis and dissertations, abstracts of any kind, papers presented at conferences, symposia, and included in proceedings, course completion papers, and papers out of the defined language were not considered.

At first, the search considered publications from 2015, based on associations between the keywords: "obesity", "pathogenesis", "etiology", "biomarkers", "oxidative stress", "inflammation" and names of the main biomarkers found. The results were compiled into an objective text about the main mechanisms of obesity.

For the second part of the paper, the following keywords were associated: "obesity", "fruits", "bioactive compounds", "phytochemicals", "nutritional composition", scientific and popular names of fruits, "trial", "clinical trial" and "supplementation". The fruits were selected according to their mention in other reviews on the subject, as well as the quantity and relevance of the experimental studies found for each of them. Only experimental studies and meta-analyses with humans and animals in normal health status, obesity or situations associated with this pathology, published between 2010 and October 2021 were included. Considering the data found, the main studies were selected, prioritizing trials with minimal processing and without association with other elements. The selected studies were used to make a table for better evaluation of the results.

3. Results and Discussion

3.1 Obesity Mechanisms

Obesity susceptibility genes have already been identified, and it has been found that a small proportion of the obese population is affected by a monogenic mutation that causes this pathology. It is possible to consider that obesity consists of the interaction of genes and environment, which results in damage to brain circuits and neuroendocrine feedback, usually associated with excessive food intake and physical inactivity. (Kadouh & Acosta, 2017; Oussaada *et al.*, 2019).

The complex system responsible for energy management in the body involves central and peripheral mechanisms that occur in the microbiome, in the cells of the adipose tissue, stomach, pancreas, and other organs. In regions of the brain outside the hypothalamus occurs sensory signals, cognitive processes, hedonic effects, memory, and attention, which interfere with food consumption (Heymsfield & Wadden, 2017). When energy consumption exceeds energy expenditure, about 60 to 80 percent of the energy is stored in the form of fat. Over time, this positive balance generates excess adiposity, which translates into several consequences (Boron & Boulpaep, 2017).

Excessive adipose tissue exerts mechanical stress that can compress the kidneys, block the airway during sleep, and overload the joints, increasing the risk for complications such as hypertension. The higher concentration of macrophages and other immune cells in this tissue increases the secretion of pro-inflammatory cytokines, which are accompanied by elevated levels of free fatty acids and lipid intermediates in non-adipose tissues, contributing to impaired insulin signaling. This whole situation further reflects a constant low-grade inflammatory state in the obese individual (Heymsfield & Wadden, 2017; Zorena *et al.*, 2020).

Besides advances in knowledge about the mechanisms of obesity and well-established anthropometric tools for clinical diagnosis, other biomarkers related to the development of this disease have been investigated. Inflammatory cytokines and adipokines are considered primary biomarkers. Insulin resistance and impaired glucose tolerance are two additional indices

frequently evaluated. It is also possible to find in the literature factors related to oxidative stress, gut microbiota, nutrients, microRNAs, and blood cell profile (Endalifer & Diress, 2020; Nimptsch *et al.*, 2019).

The increased amount and size of adipocytes present in obesity modifies adipokines secretion, mainly leptin and adiponectin, which are responsible for metabolic and inflammatory consequences. More recently, other adipokines have also been mentioned in this context, such as resistin, fatty acid binding protein 4 (FABP-4), omentin, lipocalin-2, apelin, and chemerin. As well as these proteins are close related with other diseases, Plasminogen Activator Inhibitor-1 (PAI-1) is also mentioned to be an independent risk factor for obesity-related metabolic disorders, although it needs further investigation on its mechanisms of action (Endalifer & Diress, 2020; Nimptsch *et al.*, 2019).

Leptin has a cerebral action by the interaction with cells of specific hypothalamic nuclei, controlling appetite and energy expenditure. The vicious cycle of the higher serum concentration of leptin, fat mass increase and greater propagation of inflammatory cytokines in the brain generates resistance to the effects of leptin, hindering the food intake control by the perception of satiety. This scenario also stimulates the proliferation of immune system cells, which have leptin receptors, further increasing the release of tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and monocyte chemoattractant protein (MCP-1) (Francisco *et al.*, 2018; Taylor, 2021).

In contrast to the other adipokines, adiponectin has its secretion reduced in the adipose tissue of obese individuals, as well as in cases of diabetes, coronary artery disease, insulin resistance, and atherosclerosis. This protein acts in the moderation and regulation of glucose and fatty acids, besides having anti-inflammatory effects. Adiponectin has an inverse relationship with TNF-α, IL-6, and C-reactive protein (CRP) levels, stimulate the production of IL-10 and antagonize the IL-1 receptor in macrophages (Nguyen, 2020; Nimptsch *et al.*, 2019; Taylor, 2021).

The inflammatory triggers of obesity are related to intestinal permeability, dysbiosis, hypoxia, adipocyte hypertrophy and dysfunction, mechanical stress and dietary components, leading to local and systemic effects (Karczewski *et al.*, 2018). The higher inflammatory cytokines release, mainly TNF-α, IL-6, and IL-1β, stimulate the secretion of acute phase proteins, such as CRP, which is an important inflammatory marker considered as a reference in several pathologies. IL-6 also has an influence on glucose metabolism, since as increased levels can directly affect gastric emptying, glucagon-like peptide 1 (GLP-1) secretion, and hepatic insulin sensitivity (Wueest & Konrad, 2020; Zorena *et al.*, 2020). Other cytokines and inflammatory molecules also reach higher levels, such as IL-8, IL-34, ICAM-1, V-CAM-1, MCP-1 (Endalifer & Diress, 2020; Nimptsch *et al.*, 2019). Figure 1 summarizes the main changes in inflammatory biomarkers and adipokines in obesity, as well as their metabolic and pathological consequences.

Figure 1: Mechanisms of obesity and its consequences.
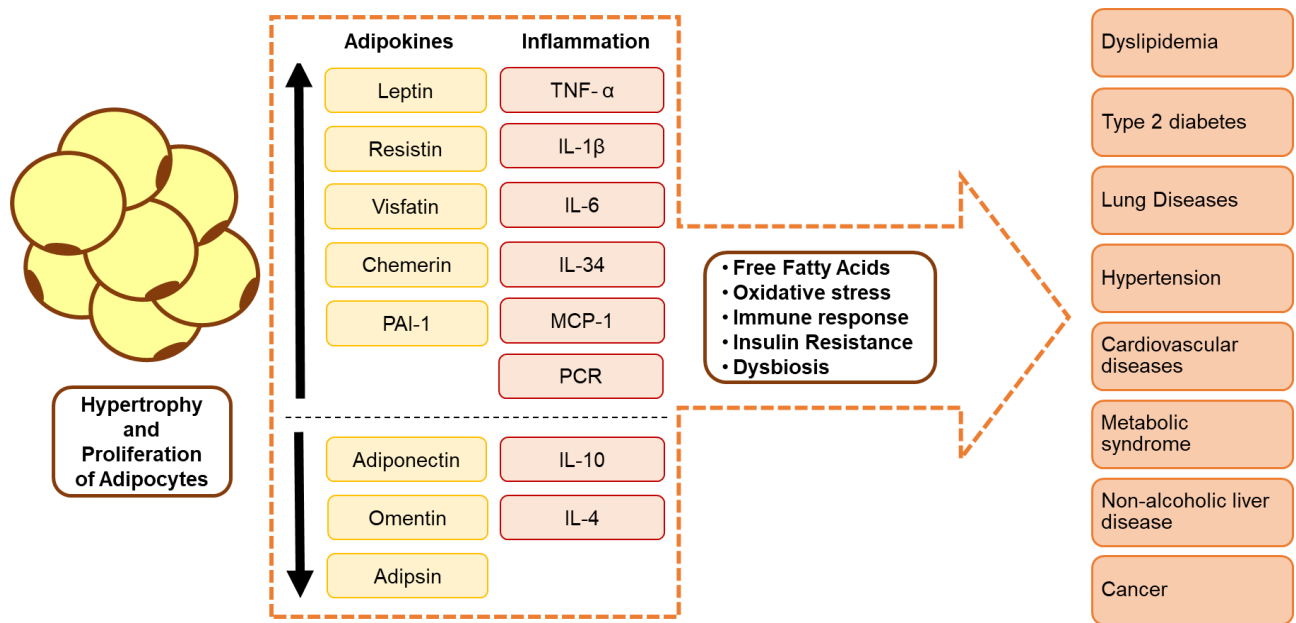
Source: Authors.

As indicated in Figure 1, the main biomarkers of obesity are adipokines and inflammatory proteins, due to the increase or decrease in their secretion caused mainly by the exacerbation of adipose tissue. This signaling dysregulation interacts with parallel changes in free fatty acid levels, oxidative stress, immune response, insulin resistance and dysbiosis, and may result in the emergence of consequences such as dyslipidemia, diabetes, cardiovascular disease, and even cancer.

The obesity complexity hinders to determine which metabolic alteration occurs first, since the affected signaling signals modulate each other, creating a vicious cycle that keeps the pathological picture in constant progress. The increase in free fatty acids tends to generate accumulation in liver and adipose tissues, inducing the production of free radicals, imbalances in glucose metabolism, and mitochondrial DNA damage. Higher levels of oxidative stress also occur due to increased insulin and inflammation, and reduced adiponectin (Nijhawan *et al.*, 2019).

The global concept of oxidative stress is defined as "an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage" (Sies, 2020). This condition may impact the obesity onset or exacerbate the disorders. Being another point favorable to insulin resistance, reactive oxygen species may favor the inactivation of signaling mechanisms between insulin receptors and the glucose transport system. Hyperglycemia, in turn, induces the generation of superoxide ions in endothelial cells at the mitochondrial level, increasing oxidative stress again (Sharifi-Rad *et al.*, 2020).

Insulin resistance is mainly favored by increased amounts of IL-34 and TNF-α. This last one increases lipolysis, leading to a higher circulation of free fatty acids (Zorena *et al*., 2020). Meanwhile, free fatty acids further contribute to vasoconstriction of blood vessel cells, increasing the risk of fat and cholesterol plaque formation in the artery wall, which can explain the association between obesity and coronary artery disease (Coats & Martirosyan, 2015).

Different compositions of the gut microbiota in obese humans and mice suggest that multiple microorganisms may influence body weight variation (Gérard, 2016). There is increasing evidence that disturbances in the gut microbiota contribute to metabolic disorders. A reduced microbial diversity is related to increased insulin resistance, adiposity, and inflammation (Cornejo-Pareja *et al.*, 2019; Cuevas-Sierra *et al.*, 2019). Among specific microorganisms, *Helicobacter pylori* is studied for its

possible correlation with leptin and ghrelin. Furthermore, it shows more frequently in obese individuals than in individuals with healthy BMI (Baradaran *et al.*, 2021; Endalifer & Diress, 2020).

More recently, MicroRNAs have also been described as potential biomarkers of obesity, because they are stable and accessible molecules in the bloodstream, being non-invasive indicators. These markers are altered in obese individuals, when compared to healthy people. They consist of classes of short non-coding RNAs with 19-22 nucleotides involved in post-transcriptional regulation of genes, which act as key regulators of several endocrine functions. This deregulation of the microRNA profile may target adipokines and their modulating receptors, affecting the process of adipogenesis and possibly leading to the development of obesity-associated disorders (Engin, 2017; Ji & Guo, 2019; Landrier *et al.*, 2019; Alves *et al.*, 2019). In addition, they can balance the cellular redox state in metabolic disorders by regulating numerous signaling pathways associated with glucose metabolism, lipids, inflammation, and enzymes for generation and elimination of reactive oxygen species (Murri & el Azzouzi, 2018; Włodarski *et al.*, 2020).

3.2 Bioactive Compounds in Fruits

Bioactive compounds are natural secondary metabolites present in food that come from the defense system of plants against ultraviolet radiation or injuries, such as lesions in the cell matrix by insects or pathogens attacks. Many factors can impact the content of these substances in fruit, such as genetic factors, differences in agronomic and environmental conditions, such as seasonality, temperature, water availability, ultraviolet radiation, nutrient addition, pollution, mechanical damage and pathogen attack. These compounds are generally of low molecular weight, presenting a very wide chemical structure and biological functions, in addition to provide a health protective action when available in significant quantities in the diet (Patil *et al.*, 2009; Manach *et al.*, 2004; Moreira-Araújo *et al.*, 2019).

Recently, studies have shown that the bioactive compounds present in fruits have potential health benefits by reducing inflammation and oxidative stress, as well as anticancer, anti-diabetic and anti-obesity effects (Chaudhary *et al.*, 2018; Fraga *et al.*, 2019; Shahidi & Yeo, 2018;). Among several actions that these substances can exert from the biological point of view are the regulation of the production of reactive oxygen species, the expression of phase I and phase II detoxification enzymes, the immune system, the gene expression, the activation of nuclear factor kB (NF-kB) and apoptosis; reduction of platelet aggregation; inhibition of angiogenesis; anti-inflammatory, antiviral and antibacterial effects. Due to these effects, these compounds have been described as capable of reducing the incidence of several chronic diseases (Dembitsky *et al.*, 2011; Fachinello *et al.*, 2011; Patil *et al.*, 2009; Pratheeshkumar *et al.*, 2012).

Bioactive compounds are divided into three main chemically distinct groups: terpenes, phenolic compounds and nitrogen compounds. The first two are the most found in fruits, mainly in the form of carotenoids and flavonoids. Meanwhile, phenolic compounds are divided into flavonoids and non-flavonoids (Fraga *et al.*, 2019; Martínez-Navarrete, Vidal & Lahuerta, 2008; Verruck et al., 2018).

Flavonoids are a huge class of substances that constitute natural pigments, wich are formed by fifteen carbons with two aromatic rings linked by a three-carbon bridge. They are classified into flavonols, flavones, flavonones, catechins, anthocyanins and isoflavonoids. The main sources of flavonoids are fruits. Among the flavones, quercetin and myricetin are the most commonly found in this group of foods, as well as in apples, pomegranates, grapes, cocoa, and apricots (Hollman & Arts, 2000; Kris-Etherton *et al.*, 2002; Scalbert *et al.*, 2005; Verruck et al., 2018). *Citrus* fruits are examples of flavanones sources, such as naringenin and hesperitin, and also contain flavones represented by apigenin and luteolin. Catechin, among the flavans, is the compound most often found in fruits such as apple, pear, pomegranate, and cherry (Poyrazoglu *et al.*, 2002; Tomás-Barberán, 2003). Anthocyanins are the most studied flavonoid. It is a group of water-soluble natural pigments, widely distributed in plants that are responsible for the red to blue coloration exhibited by flowers and fruits. Bilberry, blackberry,

strawberry, raspberry, jamelon, jabuticaba and grape are sources of these compounds (Smeriglio *et al.*, 2016; Tsuda, 2012; Yildiz *et al.*, 2021).

The non-flavonoid phenolic compounds are divided into phenolic acids, stilbenes, coumarins, and tannins. When it comes to fruit sources, gallic and ellagic acids can be found in strawberry, pomegranate and raspberry (Poyrazoglu *et al.*, 2002); coumarins in *Citrus* fruits and stilbenes, most commonly in the form of resveratrol, in grapes, apricot and blackcurrant (Kris-Etherton *et al.*, 2002; Tomás-Barberán, 2003; Sergent *et al.*, 2012).

Carotenoids belong to the terpene group, they are fat-soluble pigments, hydrophobic and exhibit a range of colors from yellow to red in plants. This substances are present in plastids and chloroplasts, where they help to stabilize the structure and functioning of the complex involved in the photosynthetic process (Zia-Ul-Haq *et al.*, 2021). Carotenoids can be divided into two groups according to their chemical structure: carotenes (hydrocarbons) and xanthophylls, which also contain oxygen and are therefore less apolar than carotenes. Carotenoids containing an unsubstituted β-ionone ring are called provitamin A, as they can be cleaved by animals to release retinal, that can subsequently be converted to retinol (Mounien *et al.*, 2019). The carotenoids commonly found in fruits are β-carotene, present in apricots, melon, orange, and mango; β-cryptoxanthin, in papaya, mango, tangerine, orange, peach, and persimmon; and lycopene, in watermelon, guava, grapefruit, papaya, and red orange (Zia-Ul-Haq *et al.*, 2021). Besides its relationship with vitamin A, the intake of carotenoids in the diet plays an important role in reducing oxidative stress and modulating the immune response, LDL levels, atherogenic processes, and many physiological processes, thus reducing the risk of developing chronic diseases, especially some types of cancer, cardiovascular and metabolic diseases (Chaudhary *et al.*, 2018; Rao & Rao, 2007).

In Table 1 are some fruits and concentrations of the main compounds observed in their composition. It is important to remember that each fruit has a complex matrix that includes several nutrients and phytochemicals, some of them being major compounds. The properties that these fruits demonstrate are usually associated with these main compounds, but studies show that the synergy between them can modify the bioavailability, bioaccessibility and bioactivity, as well as interactions with the human body and the gut microbiota (Dima *et al.*, 2020; Rakariyatham *et al.*, 2018; Andrade *et al.*, 2022).

Table 1: Concentration of bioactive compounds in fruits.

	Fruit	*mg/100g*	*Study*
Flavonoids	Orange	157 mg - 242 mg	Park *et al.* (2020); Ávila *et al.* (2020)
	Cocoa	189 mg - 329 mg	Jean-Marie *et al.* (2021); Maciel *et al.* (2017)
	Pomegranate	104 mg - 521 mg	Mottaghipisheh *et al.* (2018); Radunić *et al.* (2017)
	Tangerine	376 mg - 874 mg	Kim *et al.* (2021); Chen *et al.* (2020)
Anthocyanins	Blueberry	55 mg - 386 mg	Rokayya *et al.* (2021); Singh *et al.* (2021); Tsuda (2012)
	Strawberry	38 mg - 66 mg	Sirijan *et al.* (2020); Martinsen *et al.* (2020)
	Açaí	45 mg - 159 mg	Carneiro *et al.* (2020); Bezerra *et al.* (2020)
	Grape	120 mg - 311 mg	Tsuda (2012); Nile *et al.* (2015)
Carotenoids	Avocado	2,5 mg - 13 mg	Jimenez *et al.* (2020); Oliveira *et al.* (2017)
	Peach	12 mg - 42 mg	Mihaylova *et al.* (2021); Saini *et al.* (2015)
	Damascus	150 mg - 173 mg	Fan *et al.* (2018); Saini *et al.* (2015)
	Banana	9,4 mg - 19,7 mg	Ashokkumar *et al.* (2018); Saini *et al.* (2015)

Source: Authors.

Table 1 shows the presence of some of the most commonly found bioactive compounds in fruits: flavonoids, anthocyanins, and carotenoids. The amounts are similar to the micronutrient content, ranging in higher or lower levels depending on the substance. Carotenoids are present in smaller quantities, while flavonoids are more abundant.

3.3 Anti-Obesity Effects of Bioactive Compounds from Fruits

3.3.1 Citrus fruits

The *Citrus* genus belongs to the family *Rutaceae* and it is responsible for originating the called *Citrus* fruits, which are the most important fruit crop in the world, with an annual production of approximately 123 million tons. Out of the most produced species are *Citrus aurantium* (sour orange), *Citrus* sinensis (L.) Osbeck (moro orange), *Citrus* sinensis (sweet orange), *Citrus reticulata* (tangerine), *Citrus limon* (lemon), *Citrus paradisi* (grapefruit) and *Citrus maxima* (pomelo). These fruits are sources of various bioactive compounds and have several beneficial effects on human health (Alam *et al.*, 2014). They are sources of anthocyanins (cyanidin and cyanidin-3-O-glucoside) and rich in flavonoids, such as flavanones (7-O-glucosylflavanone, hesperidin, naringin, hesperetin, and naringenin), flavones (polymethoxyflavone, apigenin, and luteolin), and flavonols (rutin, quercetin, dihydrokaempferol-7-O-rutinoside, and dihydroquercetin-7-O-rutinoside) (Wang *et al.*, 2020). Flavanones, especially 7-O-glycosyl flavanone, are the predominant flavonoids in *Citrus* fruits (Tripoli *et al.*, 2007). Hesperetin and naringenin are the aglycone forms of the major *Citrus* flavonoids. Hesperidin (hesperetin-7-rutinoside) and narirutin (naringenin-7-rutinoside) are found in tangerines, oranges, and lemons; and naringin (naringenin-7-neohesperidoside) and narirutin are the major flavanones in grapefruit (Zhang *et al.*, 2021). However, the concentration and distribution of each of these compounds within the fruit may vary due to environmental factors (Sun *et al.*, 2013).

Total flavonoid consumption in Brazil is estimated around 56 mg/day to 64 mg/day. The main contributor of the class are flavanones, mainly from oranges (Anacleto *et al.*, 2019). Likewise, in North America and Europe it is estimated around 20 mg/day to 70 mg/day, from consumption *in natura* or *Citrus* fruit juices in general. Despite this, *Citrus* flavonoids have limited bioavailability and may vary depending on the structure of the compound and the cultivation of these fruits (Mulvihill *et al.*, 2016; Chun *et al.*, 2007).

Several studies point to the potential health benefits of *Citrus* fruit consumption. *In vitro* and *in vivo* studies have shown that the consumption of flavonoids present in *Citrus* fruits has been associated with a protection against metabolic syndrome and cardiovascular diseases, just like antioxidant, anti-inflammatory, neuroprotective, anti-diabetic, anticancer, and anti-obesity effects. (Salehi *et al.*, 2019; Mulvihill *et al.*, 2016; Hwang *et al.*, 2012; Li *et al.*, 2009; Tripoli *et al.*, 2007).

Citrus sinensis (L.) Osbeck (or *Citrus aurantium dulcis*) is a reddish sweet orange variety, usually grown in Italy, around Mount Etna in eastern Sicily (Cardile *et al.*, 2015). These oranges are known as moro or red oranges, popularly marketed as functional foods or as dry extract in dietary supplementation to help promote body weight maintenance and obesity prevention. (Farag *et al.*, 2020; Russo *et al.*, 2021). The moro orange has a large amount of antioxidants, associated to anti-inflammatory, anti-diabetic, anticâncer and anti-obesity effects (Dosoky e Setzer, 2018; Gandhi *et al*, 2020; Lv *et al.*, 2015; Montalbano *et al.*, 2019), have a higher concentration of vitamin C and bioactive compounds, such as anthocyanin (cyanidin-3-O-β-glucoside) and flavanones (naringenin and hesperetin), when compared to yellow oranges (Cardile *et al.*, 2015; Kaneko e Shirakawa, 2018). Additionally, dried extract of moro orange is appointed as a new therapeutic approach to aid in the reduction of abdominal and waist fat (Silva & Filho, 2020).

A randomized controlled clinical trial conducted by Kaneko & Shirakawa (2018) evaluated the effects of moro orange juice extract supplementation (400 mg) for 12 weeks in overweight or obese individuals. Individuals with BMI between 25 and 35 kg/m² were distributed into control (30 individuals) and treated (30 individuals) groups. After 12 weeks, the treated group showed a reduction in body weight, BMI, waist and hip circumference when compared to the control group. Cardile *et al.*

(2015) conducted another randomized clinical trial, with 60 overweight individuals (BMI > 25 kg/m²) without comorbidities. Through the control (30 individuals) and treated (30 individuals) groups, the effects of supplementation of 400 mg of the moro orange juice extract for 12 weeks were evaluated. After the intervention, the treated group showed a significant reduction in BMI, body weight, waist and hip circumference when compared to the control group. Azzini *et al.* (2017) monitored 11 obese women with the evaluation of parameters associated with obesity, lipid profile, metabolic and inflammatory biomarkers during a 12-week period with daily administration of 500 ml in two doses (250 ml) of moro orange juice. The results show that daily intake of moro orange juice had no significant effects on body weight, but indicated a decrease in total and LDL cholesterol values. The clinical study develop by Silveira *et al.* (2015) about the influence of consumption of moro orange juice in healthy individuals revealed that there was no change in the anthropometric parameters of the participants, whereas it reduced some risk factors related to metabolic syndrome such as plasma levels of total cholesterol, LDL cholesterol, C-reactive protein and blood pressure, in addition to increasing antioxidant activity and improving the index of insulin resistance (HOMA-IR) in some individuals.

Citrus sinensis is native to Asia and cultivated throughout the Pacific and warm areas of the world. This species is known as sweet orange, widely consumed by several countries in the *in natura* form, juices, aside from other products. This fruit has an orange and yellowish color, as an excellent sources of antioxidants, vitamin C, and bioactive compounds such as carotenoids, anthocyanins, and flavonoids. (Farag *et al.*, 2020). The main flavanones present in sweet orange are hesperidin (hesperetin-7-O-rutinoside) and narirutin (naringenin-7-O-rutinoside), which are biologically active in suppressing inflammation and oxidative stress, as well as modulating various cell signaling pathways (Tripoli *et al.*, 2007). Regarding the biological response, the ingestion of orange juice has demonstrated blood pressure lowering activities, in addition to being associated with an improvement in insulin sensitivity, besides presenting antidiabetic, hypocholesterolemic and anti-obesity effects in *in vitro* and *in vivo* studies (Lima & Barbosa, 2021; Ghandhi *et al.*, 2020).

In a randomized clinical trial by Ribeiro *et al.* (2017), 78 obese individuals were evaluated with a combination of a low-calorie diet and 500 ml of orange juice daily for 12 weeks. Compared to the control group, the group receiving the orange juice had weight loss, improved insulin sensitivity, lipid and inflammatory profile, and also contributed to a better quality diet. Rangel-Huerta *et al.* (2015) conducted a 12-week double-blind randomized clinical trial with 100 overweight or obese subjects. They evaluated the effects of orange juice ingestion containing normal or high concentrations of polyphenols (299 and 745 mg/d, respectively) on the antioxidant defense system, biomarkers of oxidative stress, and clinical signs of metabolic syndrome. Intake of both orange juices protected against DNA damage and lipid peroxidation, decreased BMI, waist circumference, blood pressure, and leptin. The juice with the highest concentration of polyphenols also increased superoxide dismutase activity. In the Aptekmann & Cesar (2010) studies, the effects of consuming 500 ml of orange juice associated with 1 hour of aerobic training, three times a week in overweight women, for three months, were verified. The trial was divided into 13 women who consumed orange juice and did aerobic training, and the control group consisted of other 13 women who did the same aerobic training program but did not consume orange juice. At the end of the study, both groups showed weight loss. However, the group that consumed the orange juice had reduced LDL cholesterol, increased HDL cholesterol, and less muscle fatigue compared to the control group.

Citrus paradisi is known as grapefruit, the result of the natural crossing of sweet pomelo (*Citrus maxima* Burm) and sweet orange (*Citrus sinensis*), a process that occurred on the island of Barbados during the eighteenth century. The grapefruit is grown in tropical and subtropical regions, widely consumed around the world *in natura* or in juices, and has a red and orange color. Although some *in vitro*, *in vivo*, and clinical studies demonstrate that this species is a source of antioxidants, vitamin C, and bioactive compounds, such as carotenoids, citric acid, and flavonoids, some attention should be paid to the interactions of various drugs with concomitant consumption of grapefruit due to the inhibition of enzymes, mainly CYP3A4

and others, which can alter the metabolism of drugs such as chemotherapy and some modulators of the nervous system (Cristóbal-Luna *et al.*, 2018; Akamine *et al.*, 2015; Liu *et al.*, 2012; Won *et al.*, 2012; Kelebek, 2010). The main bioactive compounds present in grapefruit are flavonoids (narirutin, naringin, hesperidin, neohesperidin, didimin, poncerin), limonoids (limonin), ascorbic and citric acid, besides furanocoumarins, phenolic compounds, carotenoids (lycopene and β-carotene) and different types of organic acids (Cristóbal-Luna *et al.*, 2018; Uckoo *et al.*, 2012). *In vitro* and *in vivo* studies point out that *Citrus paradisi* presents antioxidant, anti-inflammatory, anticancer effects, blood pressure lowering activities and prevention of cardiovascular and metabolic diseases, besides presenting antidiabetic, hypocholesterolemic and anti-obesity effects (Cristóbal-Luna *et al.*, 2018; Khan *et al.*, 2016; Mallick e Khan, 2015).

Dallas *et al.* (2014) evaluated the effects of extracts of moro orange, grapefruit, and sweet orange in capsule form (2 times daily) in a randomized, clinical trial on body weight and metabolic parameters in overweight individuals (95 participants) without comorbidities for 12 weeks. There was a reduction of waist circumference, hip circumference and body weight, as well as inflammatory markers (CRP and fibrinogen), improvement of oxidative stress markers (malondialdehyde, superoxide dismutase and glutathione) compared to placebo. A randomized, clinical trial conducted by Dow *et al.* (2012) aimed to evaluate the effects of fresh grapefruit comsumption (1.5 units) on body weight, blood pressure, and lipid profile in overweight adults for 6 weeks. Participants were divided into a control group (32 subjects) and a grapefruit group (42 subjects). Fruit consumption was associated with reduced body weight, waist circumference, blood pressure, as well as improved plasma total cholesterol and LDL cholesterol compared to the beginning of the study. In another clinical and randomized study by Fujioka and collaborators (2006), the effects of the *in natura* consumption of grapefruit and products from it (juice and capsule) on body weight and metabolic syndrome in adult individuals (91 participants), during 12 weeks, were evaluated. It was seen that the individuals who consumed the grapefruit *in natura* and as a juice presented significant loss of body weight, improvement of resistance to insulin action in comparison to grapefruit capsule or placebo.

3.3.2 Berries

Botanically, berries are defined as fleshy fruits produced from a single ovary. However, the term is associated with small edible fruits of different botanical genera, with colors in shades of red-blue-purple and pitted, although they may contain seeds. This group is associated with a rich nutritional composition, especially vitamins C and E. Because the presence of anthocyanins and other bioactive compounds, these fruits provide antioxidant properties associated with several human health benefits (Gündeşli *et al.*, 2019; Joseph *et al.*, 2014). Berries have been increasingly studied for their anti-inflammatory, antioxidant, anticancer, anti-obesity, cardiovascular protection, regulation of microbiota and blood glucose effects. It is possible to affirm that the results found are due not only to the presence of a single substance, but to the complex combination of compounds and synergy between them (Calvano *et al.*, 2019; Kristo *et al.*, 2016; Yang & Kortesniemi, 2015).

The best known fruits in this group are strawberry, blueberry, currant, raspberry, blackberry, cranberry, goji berry, and raspberry, most commonly found in North America and Europe (Joseph *et al.*, 2014). The more intense the purple color, the higher quantities of anthocyanins are found. Cyanidin is the most prevalent in this group of fruits. The antioxidant activity can vary according to the contents of different types of compounds in this class. Cyanidin and delphinidin, for example, have greater potential than malvidin, pelargonin, petunidin, and peonin. The presence of flavonols also affects antioxidant activity, since they have greater activity than anthocyanins. (Zorzi *et al.*, 2020). The major phenolic compounds in these fruits are catechin, quercetin, rutin, chlorogenic and gallic acids. In smaller amounts, ellagic, caffeic, and ferulic acids are also frequently found. (Gündeşli *et al.*, 2019).

Ellagic acid is a phenolic compound known for its anticarcinogenic, antiviral, antibacterial, anti-inflammatory, and antioxidant potential. Gallic acid, on the other hand, has a high antioxidant capacity, about 3 times higher than vitamin C or E.

Quercetin is also a potent antioxidant, with important additional biological, pharmacological and medicinal properties, capable of inhibiting human platelet aggregation *in vitro* and manifesting anticancer properties. (Nile & Park, 2014). Anthocyanins, in turn, also have these properties. Their presence is highlighted as the main factor in the effects related to berries, especially in the context of obesity. Studies show that anthocyanins are able to help regulate metabolic control, reducing lipogenesis, oxidative stress, and inflammation. Several *in vivo* and *in vitro* studies have demonstrated the anthocyanins power to reduce body weight, adiposity and systemic inflammation, by decreasing adipokines derived from adipose tissue and by altering gut microbiota profiles. Other mechanisms related to the action of anthocyanins in obesity are the inhibition of lipid absorption, increased energy expenditure and control of food intake (Gomes *et al.*, 2019; Gündeşli *et al.*, 2019; Lee *et al.*, 2017; Yildiz *et al.*, 2021).

Concerning inflammatory mechanisms, positive effects are observed for berries supplementation in various forms, including extracts and anthocyanin components. Studies with blueberry, blackcurrant, cranberry, and strawberry have reported assorted effects, including the increase of IL-10, adiponectin, and NK cells, and decrease of IL-6, TNF-α, fibrinogen, and adhesion molecules (Joseph *et al.*, 2014). Primary mechanisms mediating the anti-inflammatory effects of berries include a reduction in NF-κB signaling that may be secondary to reduced oxidative stress, a negative regulation of TLR4 signaling and an increase in Nrf2, and negative regulation of the NLRP3 inflammasome in adipose tissue macrophages (Lail *et al.*, 2021). Long-term consumption of these fruits and derivative products is also associated with better plasma lipid profiles and reduced risk factors for metabolic syndrome and cardiovascular disease (Yang & Kortesniemi, 2015). An *in vitro* study about the influence of cranberry extract on adipocytes of embryonic lineage 3T3-L1 mice showed reduced secretion of IL-6, MCP-1, leptin and PAI-1 in the treated group at baseline and under oxidative stress, with dose-dependent effects (Kowalska & Olejnik, 2016).

There are still too few clinical studies with these fruits for the level of evidence to be sufficient to accurately determine treatment protocols. However, it is clear that the benefits that these fruits can offer are quite relevant when looking at the existing evidence, especially regarding their insertion in the daily diet. In a randomized crossover clinical trial evaluating controlled dietary intake of blackberries (600 grams per day) for one week, Solverson *et al.* (2018) found significant increases in fat oxidation and insulin sensitivity in overweight men fed a high-fat diet. In another randomized clinical trial, Hsia *et al.* (2020) evaluated the consumption of 450 mL a day of a beverage produced with cranberry extract in obese individuals for 8 weeks. The results indicated no effect on insulin sensitivity or glucose tolerance, whereas there was a reduction in serum triglyceride concentrations for the entire supplemented group, with a decrease in markers of oxidative stress (oxidized LDL, isoprostanes, LOX-1, and malonaldehyde) in subjects with elevated CRP concentrations.

Among the best known berries, blueberry is the most studied in obesity, with both animal and human studies. Table 2 lists the most recent studies with this fruit and their main results on obesity-related markers. Wu *et al.* (2013) found significant effects in rats that consumed blueberry juice instead of water. They found modulation of mRNA expression for PPARγ, FAS, IL-6 and TNF-α and the adipokines leptin and adiponectin. In this study, the results also show less weight gain and adipose tissue formation, as well as a reduction in blood glucose and the HOMA-IR index. In adults with metabolic syndrome who received a blueberry smoothie, a reduction in inflammation and oxidative stress was observed by Nair *et al.* (2017). Stull *et al.* (2010), also using a blueberry smoothie as an intervention, detected improved insulin sensitivity in obese subjects with insulin resistance. In this second study, there were no significant changes in markers of inflammation and adiposity. It was noted that the effects in animals were more promising, indicating that more studies are needed to understand the best treatment protocol to achieve the same benefits in humans, as results were observed on a smaller scale and specific situations were avaiable in each study, with a small number of participants.

More recently, other regional fruits with similar shape, color, and composition have also been studied. In Brazil, açaí, jabuticaba and camu-camu stand out. (Neri-Numa *et al.*, 2018).

The açaí fruit (*Euterpe oleracea* Martius) is a native fruit from northern Brazil and its health benefits are associated with its phytochemical composition, rich in polyphenols. Regarding polyphenols, açaí contains cyanidin 3-glycoside and cyanidin 3-rutinoside as the main anthocyanins and, in smaller amounts, peonidin 3-rutinoside, peonidin 3-glycoside, cyanidin 3-O-sambubioside, and pelargonidin 3-O-glucoside. Its main flavonoids are quercetin, orientin, and their derivatives, as well as the proanthocyanidins (Gordon *et al.*, 2012; Vasconcelos *et al.*, 2019).

Martino *et al.* (2016) showed that açaí polyphenols reduced intracellular lipid accumulation during adipocyte differentiation, achieving a reduction in the expression of transcription factors and adipogenic genes, accompanied by a decrease in leptin and total PAI, and an increase in adiponectin. The same study demonstrated cellular protection against reactive oxygen species production and decreased microRNA expression, with lower protein levels of pro-inflammatory cytokines when cells were challenged with TNF-α. Song *et al*. (2021) showed that treatment with anthocyanin-rich acai extract attenuate obesity, hepatic steatosis, and insulin resistance in mice receiving a hyperlipidic diet. Furthermore, the extract altered gut microbiota composition, decreasing the proportions of Firmicutes and Proteobacteria that had been increased by the high-fat diet, and also significantly increased *Akkermansia muciniphila*, which was inversely correlated with biomarkers of obesity complications-such as blood glucose, insulin, and triacylglycerols-and genes involved in lipid metabolism.

In light of growing evidence, açaí has been studied for the prevention and treatment of diseases related to the metabolic syndrome (Cedrim *et al.*, 2018). Checking human studies, a 90-day randomized, double-blind, controlled clinical trial concluded that the addition of 200 g of açaí to a hypoenergetic diet reduced oxidative stress and improved the inflammatory status in overweight individuals with dyslipidemia by significantly reducing the markers IL-6 and 8-isoprostane when compared to the placebo group (Aranha *et al.*, 2020). An open pilot study conducted with 10 overweight adults who ingested 100 g of acai pulp twice daily for 1 month found that there was a reduction in total cholesterol, LDL cholesterol, as well as the ratio of total to HDL cholesterol. In addition, treatment with açaí improved the postprandial rise in plasma glucose after the standardized meal (Udani *et al.*, 2011).

The jabuticaba fruit, despite being consumed mainly fresh, has its commercialization hindered by its high perishability, being more used as a potential raw material for processed products. Due to the residue generated in the industry and the concentration of compounds, its peel is in evidence in the existing literature. The jabuticaba peel consists mainly of insoluble and soluble fibers (pectin), ellagitannins (casuarinin, casuarictin, pedunculagin and casuariin), β-carotene, phenolic acids (gallic, ellagic and trans-cinnamic acids) and flavonoids. rutin, myricetin, quercitrin and anthocyanins (cyanidin-3-glucoside and delphinidin-3-glucoside). Although about 71% of the anthocyanins are concentrated in the peel, the main constituents responsible for the antioxidant capacity of the fruit are ellagitannins and galotannins (Neri-Numa *et al.*, 2018; Plaza *et al.*, 2016).

Two studies demonstrate the effects of supplemented jabuticaba peel and seed powder in mice fed a high-fat diet. Trindade *et al.* (2021) concluded that supplementation attenuated weight gain and fat accumulation, absence of mast cells in the visceral depot, and reduction in circulating and tissue levels of IL-6 and TNF-α. Supplemented mice exhibited smaller adipocyte size, reduced leptin levels and increased adiponectin levels, as well as improved glucose metabolism and insulin sensitivity. Soares *et al.* (2021) demonstrated that consumption of jabuticaba bark and seed powder promoted changes in the diversity of the intestinal microbiota of obese mice, besides favoring a reduction in metabolic endotoxemia, attenuation of hepatic remodeling by improving the expression of hepatic lipogenesis genes (AMPK, SREBP-1, HGMCoA, and ABCG8), and attenuation of dyslipidemia. In a study about the action of a phenolic-rich extract of jabuticaba fruit in obese mice it was observed that the supplemented animals showed a reduction in body weight gain and adiposity and were protected against

insulin resistance and dyslipidemia. The extract inhibited inflammatory intermediates (TNF-α, TLR-4 and NF-κB) and showed a possible partial modulation of the inflammasome pathway in the colon. Thus, the study indicated a direct anti-inflammatory effect in the gut of obese mice, suggesting an improvement of metabolic endotoxemia (Rodrigues *et al.*, 2021). Lenquiste *et al.* (2019) concluded that freeze-dried jabuticaba bark and jabuticaba tea treatments reduced weight gain and adiposity, improved insulin sensitivity, increased HDL, and prevented long-term hepatic steatosis in obese rats. Another study evaluating freeze-dried jabuticaba peel supplementation in rats fed with a high-fat diet indicated beneficial effects on triglyceride excretion and reduced hepatic lipid peroxidation index (Batista *et al.*, 2013). Although the *in vivo* study results are promising, clinical studies need to be conducted to investigate the effects of jabuticaba in humans.

Camu-camu (*Myrciaria dubia*) has attracted international interest mainly for its high levels of vitamin C (about 2-50 g/kg). In addition, the fruit is considered a source of different kinds of polyphenols, including flavonols, anthocyanins, ellagic acid derivatives, ellagitannins, gallic acid derivatives, and proanthocyanidins. The contents of total ellagic acid, quercetin, and cyanidin tends to be higher than of other fruits considered to be good sources, and also other fruits of the same family (Donado-Pestana *et al.*, 2018). Anhê *et al.* (2019) used crude camu-camu extract as a treatment for mice with obesity induced by high-fat, sucrose diet. The results showed that the extract improved glucose tolerance and insulin sensitivity, increased energy expenditure, reduced weight gain and visceral and liver fat accumulation through activation of brown adipose tissue. These effects were related to a positive regulation on the expression of the uncoupling protein 1 mRNA and the membrane bile acid receptor TGR5. The authors also associated the results with changes in the gut microbiota generated by the treatment, where there was an increase in *Akkermansia muciniphila* and a reduction in *Lactobacillus*. Nascimento *et al.* (2013) conducted a study with obese rats using 25 mL of camu-camu pulp as a treatment. The results showed a reduction in their fat weights in white adipose tissues, an increase in HDL levels, and reduction of glucose levels, total cholesterol, triglycerides, LDL and insulin in the blood.

Also in South America, maqui, myrtle, and calafate are found in Chile and Argentina. These fruits also have anthocyanins as one of the most significant compounds in their composition, with greater abundance of delphinidin and cyanidin. Phenolic acids, flavonoids, and ellagitannins are also present, such as quercetin, rutin, and ferulic, gallic, and coumaric acids. (Garcia-Diaz *et al.*, 2019; Schmeda-Hirschmann *et al.*, 2019).

Obese mice supplemented with freeze-dried maqui showed decreased weight gain and improved insulin response, besides differential expression of genes involved in lipogenesis, fatty acid oxidation, multilocular lipid droplet formation, and thermogenesis in subcutaneous white adipose tissue resembling a brown adipose tissue phenotype (Sandoval *et al.*, 2019). Sandoval *et al.* (2021) noted that maqui supplementation decreased hepatic steatosis in obese mice by regulating lipid handling in the liver to counteract the metabolic impact of a high-fat diet. Changes in the metabolic profile include a negative regulation of lipogenic X receptor target genes and fatty acid oxidation gene expression, along with an increase in the expression of a co-repressor of the nuclear receptor family (Smile). In another study, Alvarado *et al.* (2016) observed that a delphinidin-rich extract of maqui reduced postprandial fasting blood glucose and insulinemia in pre-diabetic humans. The authors suggest that with the exploratory results, the extract could act by mechanisms inhibition of intestinal glucose transporters, by improving insulin sensitivity, or by an incretin-mediated effect.

In a study by Ramirez *et al.* (2021), consumption of polyphenol-rich calafate extract by obese mice prevented high-fat diet-induced obesity, in addition to increased energy expenditure, and improved mitochondrial function of brown adipose tissue. Olivares-Caro *et al.* (2020) observed by an *in vitro* study that calafate extract reduced intracellular reactive oxygen species production and inhibited LDL oxidation and malondialdehyde formation, suggesting an action of the fruit on lipoperoxidation.

3.3.3 Tropical Fruits

While some fruits are found all over the world more easily, others stand out for their more regional consumption, being considered exotic due to their lower commercialization and popularity. This is especially true for tropical fruits, grown on a small scale or growing naturally in their natural habitat. Certain fruits are associated with a medicinal use through their benefits, as in Chinese medicine and indigenous cultures. (Chang *et al.*, 2019; Cornara *et al.*, 2020; Devalaraja *et al.*, 2011). In this group, many fruits have carotenoids as one of the main bioactive compounds present, ensuring a yellowish or orange color. Some examples are: acerola, guava, kaki, buriti, pequi, carambola, cajá, physalis, pitanga, canistel (Rodrigues *et al.*, 2017).

Carotenoids play an important role in obesity and associated pathophysiological disorders, including metabolic inflammation, insulin resistance, and hepatic steatosis. Studies suggest that their action may also occur at the central level, probably preventing or reducing neuroinflammation and comorbidities associated with obesity (Mounien *et al.*, 2019). These compounds effects impact on gene expression and cell function through several mechanisms, such as interaction with receptor transcription factors PPARs and RARs, modulation of NF-kB and Nrf2 pathways, and elimination of reactive species (Bonet *et al.*, 2015). Beta-carotene, the main precursor of vitamin A and retinoic acid, is able to promote fatty acid oxidation in adipocytes and other tissues (Coronel *et al.*, 2019). By monitoring 80 adults, Harari *et al.*, (2020) correlated the presence of carotenoids, mainly α and β-carotene, lutein, and lycopene, in blood circulation and adipose tissue with favorable metabolic changes in humans, including insulin sensitivity in liver and adipose tissue.

Physalis or camapu (*Physalis peruviana* L.) is found on several continents, associated with different medicinal uses. Its composition is associated with a huge list of bioactive compounds, wich include terpenes (monoterpenes, sesquiterpenes, diterpenes, triterpenes, and carotenoids), phenolic compounds (acids, esters, aldehydes, chalcones, coumarins, flavonoids, glycosides, and cinnamic acid derivatives), carboxylic acids, and alkaloids. In the category of terpenes, the carotenoids attract the most attention in this fruit, ensuring its yellowish color. (Kasali *et al.*, 2021). This abundance of compounds provides physalis antioxidant, antimicrobial, and anticancer properties (El-Beltagi *et al.*, 2019).

Pino-de la Fuente *et al.* (2020) led an experiment with male C57/BL6 mice submitted to a hyperlipidic diet. Through gavage, a dose of 300mg/kg/day of physalis pulp was administered for 8 weeks. Supplementation reduced adipose tissue formation, but not weight gain. In this study, the fruit was shown to reduce the trend of increased blood glucose, total cholesterol, and insulin resistance, and reduced secretion of inflammatory cytokines TNF-α, IL-6, IL-1β, and TLR4 mRNA.

Another tropical fruit is the pequi (*Caryocar brasiliense* Camb.), native to the Brazilian Cerrado. Made up of a greenish-brown exocarp, an outer mesocarp formed by a white pulp, and an inner mesocarp, the edible portion of the fruit is light yellow to dark orange in color. The pequi has a high carotenoid content and it is one of the richest Brazilian fruits in this bioactive compound (Geocze *et al.*, 2021). It is a source of lipids, dietary fiber, polyphenols, zinc, magnesium and calcium, as well as phenolic compounds, mainly gallic acid, ellagic acid, and quercetin. Additionally, besides its natural form, it is often used as an ingredient in typical dishes, canned pequi, liqueur, cream and oil. (Nascimento-Silva *et al.*, 2019; Ribeiro *et al.*, 2014).

The pequi oil (pulp and kernel) is the most frequent by-product of pequi in *in vivo* studies, due to its nutritional and functional properties. It has high levels of monounsaturated fatty acids (especially oleic acid) and saturated fatty acids (especially palmitic acid). Due to its high fat composition, this fruit should be used with caution. Despite this, studies developed with pequi oil in animal models have shown antioxidant, anti-inflammatory, cardioprotective, hepatoprotective, antigenotoxic, and anticarcinogenic effects. In humans, there is evidence to support the anti-inflammatory, cardioprotective, and antigenotoxic effects (Filho *et al.*, 2021; Nascimento-Silva *et al.*, 2019).

A study conducted by Silva *et al.* (2020), evaluated the effects of supplementation with *C. brasiliense* oil in mice. For this experiment, the animals were supplemented with lipid source by gavage in different dosages (1000 and 2000 mg/kg/day).

After 90 days of supplementation with *C. brasiliense* oil, a reduction in total cholesterol, LDL-c and non-HDL-c levels was observed. Regarding visceral fats and adiposity index, the treatment with 2000 mg/kg/day showed the best result. César *et al.* (2017) observed the effects of a partial replacement of lard with pequi oil in a Western diet model on cardiovascular risk and *ex vivo* cardiac function in rats. For this experiment, animals were divided into a control diet, a lard and sucrose diet, and a diet with lard replaced by 27% pequi oil. After 12 weeks, reduced adiposity index, less accumulation of hepatic triglycerides, improved ex vivo cardiac contractility and relaxation indices were seen in the pequi oil group. There was no difference among other risk factors evaluated. Moreno *et al.* (2016), studied the effects of ingesting pequi pulp on cardiometabolic risk factors in rats. For this experiment, 16 male rats were divided into a control group and a pequi group. The control group received a standard diet and the pequi group received the same diet plus pequi pulp (3.26 g/100 g) for 15 weeks. At the end of the experiment, lipid profile, glucose, insulin, HOMA-IR, blood pressure, heart rate, liver lipids, intestinal and fecal histomorphometric parameters were evaluated. There was no difference between the experimental groups for blood pressure, heart rate, glucose, insulin, HOMA-IR, triglycerides, cholesterol, HDL-cholesterol. The Pequi group showed decreased hepatic deposition of lipids, increased fecal production, and increased height of intestinal villi.

Because of the great variety of existing tropical fruits, other numerous bioactive compounds are present, including flavonoids, phenolic acids, and alkaloids. Certain exotic fruits can be highlighted for their distinctive composition with more reports in the literature, such as pomegranate, lychee, pitaya, mangosteen, noni, and jackfruit.

The pomegranate (*Punica granatum*) is a native species found mostly in the eastern part of the globe, in regions such as India, Iran, and the Himalayas. Its bark and seeds are used medicinally for different benefits. Recognizing its rich phytochemical composition, the current literature values this fruit for its great therapeutic potential. The main bioactive compounds avaiable are anthocyanins, phenolic acids, flavonoids, and tannins, mostly in the form of ellagitannins, galotannins, and punicalagin. Citric, malic, tartaric, succinic, fumaric, and ascorbic acids are present, but this fruit is most popular by its ellagic and punycic acid content (Jacob *et al.*, 2019; Rahmani *et al.*, 2017).

Pomegranate is associated with positive impacts against oxidative stress, reduction of liver damage, anticancer effects, cardiovascular and bone protection, and regulation of metabolic disorders such as insulin resistance (Fourati *et al.*, 2020; Rahmani *et al.*, 2017). In a meta-analysis of 7 studies totaling 350 individuals with insulin resistance, Jandari and colleagues (2020) concluded that there were no significant effects of pomegranate supplementation on metabolic parameters. However, the authors report that more studies are needed, considering longer intervention time and more specific design for this evaluation. It was noted that few clinical trials have been conducted to evaluate the properties of pomegranate, and other results are found in favor of this fruit. Makino-Wakagi *et al.* (2012) evaluated the effects of pomegranate extract supplementation in ovariectomized female ddY mice (30mg/kg extract weight per day for 12 weeks) and differentiated murine 3T3-L1 adipocytes incubation with extract, ellagic acid and punicic acid (50 and 100 µg/mL extract; 20, 40 and 70 µM ellagic acid; 5 and 10 µM punicic acid). A reduction in resistin secretion was seen in both models, with a greater *in vitro* action by ellagic acid. Other compounds such as catechins and puerarin are associated with this mechanism by reducing resistin mRNA expression. However, this result was associated with the action of ellagic acid in the regulation of proteins at the intracellular level, without affecting the levels of mRNA. In a clinical trial with 42 overweight and obese adults, Hosseini *et al.* (2016) evaluated the effects of supplementing 1000 mg of pomegranate extract per day for 30 days. There was greater weight loss among the supplemented group, as well as a reduction in fasting blood glucose, insulin, HOMA-IR, total cholesterol, LDL, and triglycerides. Increased HDL and reduced inflammatory cytokines were also observed. Comparing the experimental studies found (Table 2), it is noted that the effect of this fruit may be quite related to the time and amount used, requiring further studies to confirm its anti-obesity effects in humans. Thus, the rich phytochemical composition should not be disregarded.

Less exotic, but also a tropical fruit, cocoa (*Theobroma cacao*) is known around the world for its derivative products, such as chocolate. Cocoa is a fruit that stands out for its high presence of polyphenols. Among the phenolic compounds avaiable, we find tannins and flavonoids, which include flavanols, flavonols, anthocyanins, flavones, and flavanones. Among these, flavanols appear in larger quantities, with catechin and epicatechin being the main representatives of this subclass in cocoa. Epicatechin has been said to be the most abundant monomeric flavanol in cocoa, accounting for 35% of the total phenolic content. In addition, the fruit also contains a complex series of procyanidins, formed from the condensation of catechin or epicatechin units, which may also be called condensed tannins. (Efrain *et al.*, 2011; Wollgast & Anklam, 2000).

Munguía *et al.* (2015), in a double-blind randomized controlled trial using obese adults, demonstrated that a cocoa flavonoid supplement (80mg), consumed once daily for 4 weeks, reduced body weight and abdominal circumference compared to placebo. There was also a reduction in serum markers of oxidative damage (protein free carbonyls and malondialdehyde) and improvement in lipid profile, mainly by biochemical parameters of triacylglycerols and TG/HDL ratio, indicating that cocoa flavonoids can positively modulate obesity-related anthropometric and cardiometabolic risk factors. Another randomized placebo-controlled study using overweight/obese adults, reductions in vascular constriction in the brachial artery and increased magnitude of blood flow during reactive hyperemia were observed after 4 weeks of daily consumption of a cocoa beverage, coupled with dark chocolate consumption. It is suggested that these changes may have been caused by increased release of nitric oxide, a vasodilator. A reduction in the arterial stiffness marker was also observed in the women, indicating increased compliance of the conductive arteries or decreased constriction of the peripheral arterioles. From the results obtained, regular intake of natural cocoa and dark chocolate appears to be beneficial for maintaining cardiovascular health, without adverse effects on body weight or body composition (West *et al.*, 2014). Likewise, it is possible to reduce the chances of this type of obesity complication. More results obtained in cocoa trials are seen in Table 2.

Table 2: Effects of bioactive compounds from fruits on the obesity mechanisms.

		Mode	Treatment	Target Group	Anti-obesity Effects	Study
Citrus Fruits	**Moro Orange**	Orange juice extract	400 mg/day for 12 weeks	60 overweight adults without comorbidities	↓ BMI and body weight ↓ waist and rips perimeters	Cardile *et al.* (2015)
		Orange juice	750 ml/day for 8 weeks	35 obese adults with metabolic syndrome	↓ TC, LDL-c and CRP ↓ arterial presure, HOMA-IR ↑ antioxidant capacity No effects on anthropometric parameters	Silveira *et al.* (2015)
		Orange juice	500 ml/day for 12 weeks	11 obesity women	↓ CT and LDL-c No effects on anthropometric parameters	Azzini *et al.* (2017)
		Moro juice extract	400 mg/day for 12 weeks	60 overweight adults without comorbidities	↓ BMI and body weight ↓ waist and rips perimeters	Kaneko & Shirakawa (2018)
	Sweet Orange	Orange juice	500 ml/day + 1h aerobic exercise for 3 months	13 overweight women	↓ body weight ↓ LDL-c e ↑ HDL-c ↓ muscle fatigue	Aptekmann & Cesar (2010)

		Orange juice with normal (299 mg) or high (745 mg) polyphenols concentration	500 ml/day for 12 weeks	100 obese adults	↓ DNA damage and lipid peroxidation ↓ BMI and waist perimeter ↓ arterial pressure and leptin ↑ SOD activity	Rangel-Huerta *et al.* (2015)
		Orange juice	500 ml/day + hypoenergetic diet for 12 weeks	78 obese adults	↓ body weight, inflammatory and lipid profile ↑ insulin sensitivity	Ribeiro *et al.* (2017)
	Grapefruit	*in natura*, juice or encapsuled juice extract of grapefruit	1 *in natura* unit, 237 ml of juice or 200 mg of juice extract for 12 weeks	91 obese adults	*in natura* and juice: ↓ body weight ↑ insulin sensitivity	Fujioka *et al.* (2006)
		in natura grapefruit	1,5 *in natura* unit for 6 weeks	42 overweight adults	↓ body weight and waist perimeter ↓ arterial pressure, TC and LDL-c	Dow *et al.* (2012)
		Encapsulated extracts of grapefruit, moro orange and sweet orange	2 capsules/day for 12 weeks	95 overweight adults	↓ body weight, rip and waist perimeter ↓ CRP and fibrinogen ↑ MDA, GPX and SOD	Dallas *et al.* (2014)
Berries	**Blueberry**	Freeze-dried reconstituted blueberries	50g/day for 8 weeks	48 obese adults with metabolic syndrome	↓ LDL-o and MDA ↓ systolic and diastolic pressure	Basu *et al.* (2010)
		Freeze-dried blueberries smoothie	45g/day for 6 weeks	32 obese adults with insulin resistance	↑ insulin sensitivity No effects on inflammation and adiposity markers	Stull *et al.* (2010)
		Blueberry juice	*ad libitum* instead of water for 12 weeks	48 C57BL/6 male mice on a hyperlipidic diet	↓ weight gain and adipose tissue formation ↓ blood glucose and HOMA-IR ↓ leptin ↑ adiponectin ↓ mRNA expressão for PPARγ, FAS, IL-6 and TNF-α	Wu *et al.* (2013)
		Hyperlipidemic diet added with freeze-dried blueberries (5% and 10%)	*ad libitum* for 3 months	200 C57BL mice on a hyperlipidic diet	↓ blood glucose and resistin (10% diet) ↓ leptin, IL-1β, IL- 2, IL-7 TNF-α, GM-CSF and MCP-1 ↑ adiponectin No effects on leptin or insulin resistance	Mykkänen *et al.* (2014)
		Freeze-dried blueberry extract	gavage, 25 or 50 mg/kg for 14 days	36 male Wistar rats with hypercholestero-lemia	↓ weight gain	Ströher *et al.* (2015)
		Diet added with 8% freeze-dried blueberries	*ad libitum* for 8 weeks	Male Zucker rats (36 obese + 36 eutrophic)	obese: ↓ IL-6, TNF-α and CRP (serum); ↓ IL-6, TNF-α e Nf-kB (adipose	Klimis-Zacas *et al.* (2016)

				and hepatic tissue); ↑ adiponectin eutrophic: ↓ IL-6 (serum and liver) both: ↓ TNF-α and CRP (liver)	
	Freeze-dried blueberries smoothie	45g/day for 6 weeks	27 metabolic syndrome adults	↓ total ROS and superoxid radicals (serum and monocytes) ↓ mRNA expression for inflammatory cytokines ↓ TNF-α, IL-6 and TLR-4	Nair *et al.* (2017)
	Diet added with blueberry polyphenol extract (200 mg/kg)	*ad libitum* for 12 weeks	C57BL/6 mice on a hyperlipidic diet	↓ body weight gain and food efficiency ratio ↓ LDL, PPARγ, FAS, aP2, GAPDH e GLUT4 ↓ liver TC and TG ↑ HDL Changed the composition of the gut microbiota and modulated specific bacteria Returned lipid metabolism to normal	Jiao *et al.* (2019)
Açaí	Açaí pulp	100g/day por 30 days	10 overweight adults	↓ blood glucose and insulin ↓ CT, LDL and HDL/CT ratio Ameliorated the post-prandial increase in plasma glucose following the standardized meal	Udani *et al.* (2011)
	Açaí + Banana smoothie	150g açaí pulp + 50g banana, high-fat challenge breakfast	23 overweight men (30-65 years) without comorbidities	↓ Total oxidant capacity Improved vascular function No effects on arterial pressure, heart rate or postprandial glucose response	Alqurashi *et al.* (2016)
	Açaí beverage	325ml twice a day for 12 weeks	37 adults (18-65 years) with metabolic syndrome	↓ 8-isoprostane ↓ IFN-γ	Kim *et al.* (2018)
	Açaí pulp	200g/day + hypoenergetic diet for 60 days	131 overweight adults with dyslipidemia	↓ 8-isoprostane ↓ IL-6 No effects on lipid profile and blood glucose	Aranha *et al.* (2019)
	Anthocyanin-rich extract of açaí	Daily gavage, 150 mg/kg for 14 weeks	36 male SPF C57BL/6 mice + induced obesity by hyperlipidic diet	↓ TG, TC, NEFA e LDL ↓ Lipid accumulation in adipose tissue ↓ ALT and AST ↓ blood glucose and insulin ↓ lipogenesis genes ↑ fatty acid oxidation	Song *et al.* (2021)

					Gut bacterial phylotype improvement	
Tropical Fruits	**Pequi**	Diet added with pequi	Standard diet added pequi pulp at 3,26g/100g, for 15 weeks	16 male Wistar rats	↓ lipid hepatic deposition and increased ↑ fecal output, intestinal villus height and crypt depth No effects on blood pressure, heart rate, glucose, insulin, HOMA-IR, triglycerides, cholesterol, HDL-cholesterol, and liver and heart redox status	Moreno *et al.* (2016)
		Pequi oil	High in lard and sucrose diet with 27% of lard replaced by pequi oil	36 male Wistar rats	↓ adiposity index ↓ hepatic triglyceride accumulation ↑ *ex vivo* heart contractility and relaxation indexes	César *et al.* (2017)
		Pequi oil	Gavage 5 days a week, 400 mg for 4 weeks	20 male Wistar rats with and without physical training	↓ tissue damage ↓ MDA	Vale *et al.* (2019)
		Pequi oil	Gavage, 1000 and 2000 mg/kg for 90 days	28 male Swiss mice (*Mus musculus*)	↓ CT, LDL and non-HDL-c ↓ visceral fat adiposity index (2000 mg/kg/day better result)	Silva *et al.* (2020)
	Pomegra-nate	Pomegranate seed oil	High-fat diet with 1% Pomegranate seed oil for 12 weeks	16 male C57Bl/J6 mice	↓ weight gain and fat mass ↑ insulin sensitivity ↑ respiratory exchange ratio (carbohydrate and fat oxidation) No effects on energy expenditure, food intake and blood glucose	Vroegrijk *et al.* (2011)
		Punicalagin enriched pomegranate extract (40%)	Gavage, 50 and 150 mg/kg for 8 weeks	60 male Sprague–Dawley SPF rats on a hyperlipidic diet	↓ weight gain ↓ insulin and leptin ↑ adiponectin ↓ TC and LDL Only 150mg/kg: ↓ TG and HOMA-IR ↓ mRNA SREBP-1c, FAS, ACC1, SCD1 and ACLY ↑ DGAT1 and DGAT2 ↓ CRP, TNF-α, IL-1β, IL-4, IL-6 and IGs ↓ oxidative stress	Zou *et al.* (2014)
		Pomegranate extract	1000 mg/day for 30 days	42 overweight and obese adults	↑ weight loss ↓ glicemia de jejum, insulin, HOMA-IR, TC, LDL and TG ↑ HDL ↓ MDA, IL-6 and CRP	Hosseini *et al.* (2016)
		Pomegranate juice	250 mL/day for 12 weeks	44 adults with type 2 diabetes	↓ IL-6 and CRP No effects on TNF-α, blood glucose and HOMA-IR	Sohrab *et al.* (2017)

|					
	Encapsulated pomegranate extract (210 mg punicalagin)	1 capsule/day for 8 weeks	53 adults	↓ diastolic pressure No effects on anthropometric parameters, total polyphenols and total antioxidant capacity in plasma, and MDA in urine	Stockton *et al.* (2017)
	Pomegranate juice	Daily gavage, 10 mL/kg de for 8 weeks	18 Wistar rats on a hyperlipidic diet	↓ weight gain and adipose tissue ↓ blood pressure ↓ LDL endothelial damage induced by a high-fat diet, TNF-α, IL-1β, IL-6, MCP-1 e PAI-1 ↑ HDL, TG, adiponectin and insulin	Michicotl-Meneses *et al.* (2021)
	Pomegranate fruit pulp polyphenols	Daily gavage, 200 mg/kg for 14 weeks	36 C57BL/6J mice on a hyperlipidic diet	↓ weight gain ↓ TG, CT, LDL, NEFA ↓ hepatic steatosis, TG, ALT, AST ↓ fasting blood glucose, insulin and HOMA-IR Modulated the overall structure and composition of the gut microbiota	Song *et al.* (2021)
Cocoa	Cocoa beverages	30–900 mg flavanol cocoa beverage/day for 5 days	20 obese adults with at risk for insulin resistance	↓ 8-isoprostane, CRP and IL-6 No effects on glucose regulation	Stote *et al.* (2012)
	Dark chocolate + sugar-free cocoa beverage	37 g/d of dark chocolate and a sugar-free cocoa beverage (total cocoa ¼ 22 g/d, total flavanols (TF) ¼ 814 mg/d) for 4 weeks	30 overweight or obese adults (40-64 years)	↑ basal diameter and peak diameter of the brachial artery ↑ basal blood flow volume ↓ arterial stiffness No effects on anthropometrics parameters, fasting glucose and lipid levels	West *et al.* (2014)
	Sugar-free cocoa beverage or Non-chocolate snacks + sugar-free non-cocoa beverage	Energy-restricted diet + 236 mL Sugar-free cocoa beverage + 1.45 oz dark chocolate tasting square (270 mg de flavanol)/day) for 18 weeks	60 overweight or obese premenopausal women (25-45 years)	↓ weight ↓ sistolic and diastolic pressure ↓ blood glucose and insulin No effects on blood lipids	Nickols-Richardson *et al.* (2014)
	Flavanol-enriched cacao beverage	80 mg/day for 4 weeks	15 overweight adults with threshold criteria for metabolic syndrome	↓ Body weight and waist circumference ↓ TG, TC, LDL and TG/HDL ratio ↑ HDL ↓ MDA e free carbonyls	Munguía *et al.* (2015)

| Cocoa beverage | Cocoa beverage (960 mg total polyphenols; 480 mg flavanols) or flavanol-free placebo (110 mg total polyphenols; <0.1 mg flavanols) with a high-fat fast-food–style breakfast (6h study) | 18 obese adults with elevated waist circumference and with established and stable T2D for at least 5 y | ↑ HDL and insulin
↓ large artery elasticity

No effects on TC, LDL, glucose and HsCRP

No effects on insulin resistance (except 4 h), arterial pressure and small artery elasticity index | Basu *et al.* (2015) |
| Cocoa extract | meal enriched with 1.4 g of cocoa extract (415 mg flavanols), restricted diet for 4 weeks | 24 overweight or obese adults (50-80 years) | ↓ postprandial AUC of SBP | Ibero-Baraibar *et al.* (2017) |

Source: Authors.

Table 2 shows the results of experimental studies with some of the main fruits found. By these results, it is possible to verify that the influence of the bioactive compounds from fruits impacts on the modulation of fundamental obesity biomarkers, as inflammatory cytokines and adipokines, in addition to the antioxidant potential that balances oxidative stress. Furthermore, these fruits can positively affect other mechanisms that are related to obesity complications, especially with regard to the cardiovascular system, in the case of decreased blood pressure and improvements in the lipid profile. Figure 2 explicits these main mechanisms of action.

Figure 2: Effects of bioactive compounds from fruits on the mechanisms of obesity.
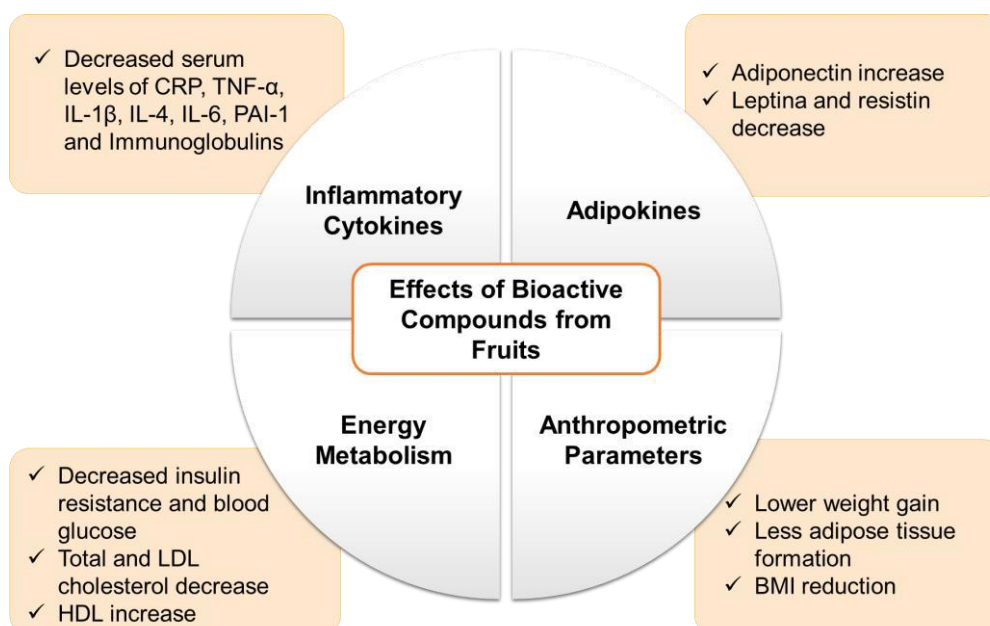
Source: Authors.

Figure 2 summarizes the effects of fruit bioactive compounds found in this review across four important obesity-related aspects: inflammatory cytokines, adipokines, energy metabolism and anthropometric parameters. The main biomarkers of obesity were regulated by increased adiponectin, decreased leptin, resistin, CRP, TNF- α and interleukins. A metabolic regulation occured through lower insulin resistance and blood glucose, besides an improved lipid profile. Less weight gain and adipose tissue formation have also been noted in some studies, favoring a reduction in BMI, quite characteristic of obesity.

Finally, the modulation of the intestinal microbiota also appears in some of the selected studies with positive results. The relationship between the microbiota and obesity has been extensively studied in recent years. Considering the possible benefits of bioactive compounds on this aspect, the interaction of these substances with beneficial microorganisms for the modulation of obesity should be relevant for further researches. As many of these results occurred in animal experiments, additional investigation is needed to state the same effects in humans and to understand how it works. (Cornejo-Pareja *et al.*, 2019; Yen *et al.*, 2020).

4. Final Considerations

Obesity is a multifactorial disease, wich imbalance between cytokines and inflammation markers, combined with a higher level of oxidative stress, assumes a vicious cycle that keeps the pathological condition in constant progress. Inflammatory cytokines and adipokines are considered primary biomarkers of obesity. Insulin resistance, lower glucose tolerance, oxidative stress, intestinal microbiota, nutrients and microRNAs are also currently considered. Food presents itself as a strong factor influencing this process, being important by not only the energy balance but also by the quality of the diet.

Fruits have an important nutritional composition for a healthy diet. Its bioactive compounds bring even more benefits, that can help in the prevention and treatment of chronic non-communicable diseases. The effects are observed not only on a single organ or tissue, but it occurs by a systemic regulatory effect on obesity mechanisms. Despite the different bioactive compounds present in each fruit, the results related to obesity biomarkers are similar, reaching regulatory mechanisms that benefits the balanced functioning of the body and promote health.

There are still few experimental studies that help to clarify the mechanisms of action of the bioactive compounds from fruits in obesity. The animal models results are more optimistic than the human models. Despite the great difficulty of controlling all aspects related to the experiment in humans, it is important to emphasize that different forms of administration and dosage used can interfere with the results.

Therefore, it is necessary to study more deeply about the action of the bioactive compounds present in fruits, since the elucidation of these interactions can be useful to supplements production and also the best clinical dietary prescription. In addition, it is important to encourage the fruits consumption, aiming at improving the population's eating habits and reducing the incidence of diseases. Since many types of fruits can be used to the obesity control, the region and food preferences can also be considered for the inclusion of these foods more easily in the daily routine.

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