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REVIEW

Therapeutic Targets for Phenolic Compounds from Agro-industrial Byproducts against Obesity

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Abstract: Background: Obesity is considered a global epidemic. This disorder is associated with several health effects, such as metabolic disturbances that need both prevention and treatment actions. In this sense, bioactive secondary metabolites can be obtained from cheap sources such as agro-industrial waste, providing a sustainable alternative against obesity. Among these secondary metabolites, phenolic compounds present a common chemical structure core with different substitutions that provide them with biological properties such as antioxidant, inflammatory, and anti-aging capacities. Objective: The aim of this review is to compile anti-obesity therapeutic targets for phenolic compounds from agro-industrial by-products. Method: Scientific information has been obtained from different databases, such as Scopus, PubMed and Google Scholar, in order to select the available full-text studies conducted in the last few years. Results: This review shows that peel, seed, pomace and other by-products from agro-industry have different effects inhibiting enzymes related to lipid or glucose metabolism and modulating biomarkers, genes and gut microbiota in animal models. Conclusion: Revalorizing actions of agro-industrial byproducts in the prevention or treatment of obesity or associated disorders can be considered to develop new high value products that act on lipid, glucose and energy metabolisms, oxidative stress, inflammation, adipose tissue or gut

microbiota. However, further human studies are needed in order to establish the optimal administration parameters.

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1. INTRODUCTION

Overweight and obesity, defined as abnormal or excessive fat accumulation, are considered as a global epidemic of the developed world by the World Health Organization (WHO) [1]. In 2016, more than 1.9 billion adults were reported as overweight and around 650 million as obese [1]. The major risk involved in this multifactorial disease is the negative health effects due to the development of other related disorders such as hypertension, diabetes mellitus, coronary heart diseases, and some types of cancers, among others [2].

As obesity is a multifactorial disease, the causes that contribute to its development are different. Among the main factors that contribute to the development of obesity is energy imbalance in the first place, and the body's efforts to store excess energy rather than limiting intake or increasing expenditure, which leads to net weight gain as the most common form of energy imbalance.

Physiological and genetic factors are also considered to be responsible for the development of the disease, for example, hormonal imbalances, changes in the microbiota and expression of certain genes related to obesity. Finally, cultural and contextual factors such as socioeconomic status, geography, food preferences, physical and social environment, gender, age, cultural identity and family composition greatly contribute to the development of the pathology [3,4]. Among the main targets that have been considered, promising novel therapies are brown adipose tissue thermogenesis, the influence of the microbiome, miRNAs, genetics and epigenetics, nutrigenomics and nutri-epigenetics, brain function in relation to intake and food choices, biological control of physical activity, food and dietary components, and nutrition in early life [5]. Taking into account that obesity is influenced by genetic, behavioral and environmental factors, prevention and treatment actions need to be directed towards multifactorial actions. Among these, healthy

lifestyle habits, based on diet and physical activity, is one of the most important aspects. However, it is important to note that eating patterns differ not only across countries but also between socio-economic statuses. In this scenario, functional food and nutraceuticals are relevant since nutritional strategies are crucial for the management of obesity [6]. The link between diet and human health has been repeatedly mentioned since ancient years and proven by extensive scientific evidence, although it was not until the mid-1980s when the Japanese government supported research focused on the potential of some foods in physiological targets, giving rise to a term “functional food” [7]. In current times, many studies report immense interest in functional food and nutraceuticals to prevent various diseases related to obesity, such as hypertension [8]. In fact, these products have been considered at the interface between nutrition and pharma [7].

In chronic diseases, conventional medical treatments with effective results can also bear adverse side effects. For this reason, the identification of cost-effective approaches for obesity management is challenging. In this sense, dietary phenolic compounds, which are reported to possess anti-obesity potential, present as an innovative alternative for obesity prevention and treatment [6]. These secondary metabolites are the largest classes of bioactive phytochemicals, and are widely present in fruits and vegetables. Their common chemical structure core is characterized by one or more aromatic rings with hydroxyl

groups, which provides them with pharmacological properties [2], such as anti-obesity effects [9]. Figure 1 shows the chemical structures of most reported phenolic compounds. These bioactive compounds may increase energy expenditure but also inhibit lipolytic enzymes, reduce plasma glucose levels or activate 5'-AMP-activated protein kinase (AMPK) [6]. For example, green tea epigallocatechins are responsible for anti-diabetic, anti-obesity and anti-hypertensive effects [8].

- Insert Figure 1 -

It is worth noting that the concentration of phenolic compounds is usually higher in fruit and vegetable by-products, such as peels, seeds, pomace or leaves, compared to their edible parts [10]. This is a very important point since it is estimated that almost 50 % of the food produced is lost or wasted before and after reaching the consumer [11]. The high content of these valuable phytochemicals can be obtained from agri-food wastes. These by-products, rich in bioactive compounds, can be revalued into high-value products, such as cosmetics, food or pharmaceuticals, which can show anti-obesity properties but also may reduce waste and provide economic benefits. For this reason, several authors have previously discussed this subject. Rodriguez-Perez *et al.* encompassed *in vitro* and in animal

studies about the anti-obesity effect of polyphenols from natural sources [6]. Other authors have also reviewed the potential against obesity of these bioactive compounds from plants [9,12,13] or food [14-16]. However, regarding agro-industrial byproducts, the most studied sources to convert into value-added anti-obesity products are fruits, vegetables and cereals, above all, citrus and tropic fruits and olive byproducts [11,17-19].

In this review, a comprehensive overview of anti-obesity therapeutic targets for phenolic compounds from agro-industrial byproducts is presented. The data-bases used, Scopus, PubMed and Google Scholar, were searched for studies published between January 2016 and May 2021, and reporting on the anti-obesity effects of the major phenolic compounds contained into agro-industrial byproduct extracts. Moreover, for punctual statements we included other year references. Keywords included obesity, phenolic compound, food byproduct, (lipid, glucose and energy) metabolism, oxidative stress, inflammation, gut microbiota and adipose tissue, as well as the corresponding synonyms and associated terms for each word. Table 1 summarizes the main details of the scientific articles discussed in this review.

2. EFFECTS ON LIPID METABOLISM

Lipid metabolism disorders are one of the most common risk factors for chronic diseases that have a strong connection to obesity. Therefore, the therapeutic targets of lipid metabolism could be directly related to alleviate this disorder. In this sense, many drugs, such as statin or structural

analogs of cholesterol precursors, have been shown to reduce blood lipid levels, although their long-term use can cause adverse effects [20]. Therefore, innovative alternatives with effects on lipid metabolism, such as bioactive compounds from natural sources, are being explored.

The main targets of the anti-obesity effects on lipid metabolism of phenolic compounds are related to pancreatic lipase, lipid profile, such as cholesterol levels, fatty acids (FA) and expression of genes associated with this metabolism. Pancreatic lipase is a triacylglycerol acylhydrolase that plays a key role in the hydrolyzation and absorption of triglycerides. Inhibition of this enzyme can then reduce the absorption of dietary fat. Orlistat ($IC_{50} = 0.064$ mg/mL) is currently the only drug that inhibits this lipase, but its use is related to adverse effects. As a possible alternative to drugs, in recent years there have been numerous studies focused on phenolic compounds from vegetable sources [21]. For instance, Noorolahi *et al.* in 2020 reported on the effect of pistachio green hull extract on porcine pancreatic lipase activity [22]. The results showed the highest activity of the pistachio byproduct extract ($IC_{50} = 2.26$ mg/mL) in the tannin fraction rich in polyphenols and flavonoids [22]. Moreover, others agro-industrial residues as potent pancreatic activity inhibitors have been described such as peanut skin (PS) and red (RGP), white (WGP) and mixed grape pomace (MGP) [23]. A 100 % inhibition was found for the PS extract at 10 mg/mL, being 1.14, 1.44 and 1.92 times greater than that of RGP, WGP and MGP, respectively. In

addition, the highest value of total phenolic content, determined by Folin-Ciocalteu assays, was obtained for the PS extract, followed by RGP, WGP and MGP, respectively. These results may explain the structure-activity relationship in the inhibition of pancreatic lipase [23]. On the contrary, Fabroni *et al.* in 2016 studied the effect of different food extracts rich in phenolic compounds and anthocyanins on pancreatic lipase inhibition [24]. In this study, black rice husks and ‘Moro’ and ‘Doppio sanguigno’ orange (flavedo) peels were tested. These matrices obtained lower IC_{50} values (11.04, 7.85 and 7.95 mg/mL, respectively) compared to orange and pomegranate juices (0.46 and 0.55 mg/mL, respectively), which contained the highest amount of anthocyanidins and phenolic compounds [24].

Table 1. Summary of therapeutic targets for phenolic compounds from agro-industrial byproducts against obesity

Mechanism involved	Source	Byproducts	Extract type or isolated compounds	Effective dose	Type of assay	Effect/ Mechanism of action	References
Lipid metabolism	Coffee	Silverskin and husk	Aqueous extract	31– 500 µg/mL	<i>In vitro</i>	Reduced lipid accumulation and increased mitochondrial activity in 3T3-L1 adipocytes	[25]
	Mandarin (<i>Citrus reticulata</i>)	Peel	70% methanol aqueous extract	1 mg/mL	<i>In vitro</i>	Inhibition of 3T3-L1 cell differentiation into adipocytes	[26]
	Carob (<i>Ceratonia siliqua</i>)	Seed peel, germ and pod	Flour	0.5, 0.1, and 0.05 mg/mL	<i>In vitro</i>	Reduction of the capacity of TGs	[27]
	Walnut (<i>Juglans regia</i>)	Septum	50% acetone aqueous extract	Different doses	<i>In vitro</i>	Inhibitory activity against lipase	[28]
	Coffee (<i>Coffea arabica</i>)	Pulp	Aqueous extract	<i>In vitro</i> : 200 mg/ml <i>In vivo</i> : 1000 mg/kg per day for 12 weeks	<i>In vitro</i> (Human colorectal adenocarcinoma (Caco-2) cells) and <i>In vivo</i> (Wistar rats)	Inhibition of intestinal cholesterol absorption by down-regulating NPC1L1 mediated LXRα activation and interfering with micellar complex	[29]

						formation	
Rambutan (<i>Nephelium lappaceum</i>)	Peel	Aqueous extract	30 mg/kg body weight once every two days for 12 weeks	<i>In vivo</i> (obesity rat model)	Diminution of FABP4, PPAR- γ and ERK1-2 expression		[30]
Satsuma (<i>Citrus unshiu</i>)	Peel	Pellet	For 4 weeks	<i>In vivo</i> (humans)	Decreased levels of LDL-C, and TGs		[31]
Mandarin (<i>Citrus reticulata</i>)	Peel	Aqueous extract	800 mg/daily for 8 weeks	<i>In vivo</i> (humans, obese adolescents)	Decreased body mass index, body fat percentage and waist circumference, as well as a better lipid profile criteria. In addition, a significant decrease in TC and TGs is observed		[32]
Grape (<i>Vitis vinifera</i>)	Seed	Proanthocyanidin extract	25, 100 and 200 mg/kg/day for 12 weeks	<i>In vivo</i> (Wistar rats)	Increase in the number of adipocytes and preventive decrease in the size of adipocytes through the positive		[33]

Cocoa (<i>Theobroma cacao</i>)	Husk	Pericarp flour	25 mg of (-)-epicatechin equivalents per day for 8 weeks	<i>In vivo</i> (humans)	regulation of PPAR- γ and Sirt1 TGs, LDL-C, and the TGs/HDL ratio decreased	[34]
Dragon fruit (<i>Hylocereus undatus</i>)	Peel	Betacyanins	50, 100 and 200 mg/kg/day for 14 weeks	<i>In vivo</i> (C57Bl/6 mice)	Induction of fatty acid oxidation, decreased fatty acid biosynthesis and improved sensitivity to FGF21. Improvement of adipose tissue hypertrophy Prevent weight gain and adiposity.	[35]
Jaboticaba (<i>Myrciaria jaboticaba</i>)	Peel	Aqueous extract	2% of extract for 6 and 12 weeks	<i>In vivo</i> (Wistar rats)	Supplementation for 12 weeks increased HDL-C. Long-term supplementation prevented hepatic steatosis	[36]

Mung bean (<i>Vigna radiata</i>)	Hulls	Xylitol	100 and 200 g/kg per day for 21 days	<i>In vivo</i> (Sprague Dawley rats)	Cholesterol and TGs levels were decreased depending on xylitol intake level	[37]
Roselle (<i>Hibiscus sabdariffa</i>)	Calyces	Aqueous extract	10.1 g /100 g diet for 18 weeks	<i>In vivo</i> (Wistar rats)	Reduction in body weight gain, adipocytes hypertrophy and hepatic steatosis	[38]
Onion (<i>Allium cepa</i>)	Peel	60% aqueous ethanol extract	170 mg (50 mg of quercetin) two times a day for 12 weeks	<i>In vivo</i> (humans)	Weight reduction and body fat percentage	[39]
Coffee (<i>Coffea arabica</i>) and (<i>Coffea canephora</i>)	Silverskin	Aqueous extract	25, 50 and 100 µg/ml	<i>In vivo</i> (<i>Caenorhabditis elegans</i>)	Prevention of body fat accumulation	[40]
Kiwifruit (<i>Actinidia chinensis</i>)	Seed oil	n- hexane extract	1 or 3 mL/ kg per day for 8 weeks	<i>In vivo</i> (C57Bl/6 J mice)	Reduction in body weight gain, inguinal fat tissue weight and blood glucose. Increase in HDL-C levels and decrease in TGs and LDL-C levels	[41]

Jaboticaba (<i>Myrciaria jaboticaba</i>)	Ripe fruit	Aqueous extract	50 and 100 mg/kg/day for 28 weeks	<i>In vivo</i> (C57Bl/6 J mice)	Decrease in adipocyte hyperplasia, reduction in FBG. In addition, decreased plasma levels of TC and LDL-C, liver levels of TC and TGs	[42]
Walnut (<i>Juglans regia</i>)	Septum	50% acetone aqueous extract	Different doses	<i>In vitro</i>	Inhibitory activity against α -glucosidase	[28]
Onion (<i>Allium cepa</i>)	Peel	60% aqueous ethanol extract	170 mg (50 mg of quercetin) two times a day for 12 weeks	<i>In vivo</i> (humans)	Increased FBS level and decreased blood leptin level	[39]
Dragon fruit (<i>Hylocereus undatus</i>)	Peel	Betacyanins	50, 100 and 200 mg/kg/ day for 14 weeks	<i>In vivo</i> (C57Bl/6 mice)	Improvement of glucose intolerance and insulin resistance	[35]
Jaboticaba (<i>Myrciaria jaboticaba</i>)	Peel	Aqueous extract	2% of extract for 6 and 12 weeks	<i>In vivo</i> (Wistar rats)	supplementation for 6 weeks increased insulin sensitivity	[36]

Glucose and energy metabolism	Mung bean (<i>Vigna radiata</i>)	Hulls	Xylitol	100 and 200 g/kg per day for 21 days	<i>In vivo</i> (Sprague Dawley rats)	Serum glucose decreased depending on xylitol intake level	[37]
	Roselle (<i>Hibiscus sabdariffa</i>)	Calyces	Aqueous extract	10.1 g /100 g diet for 18 weeks	<i>In vivo</i> (Wistar rats)	Reduction in insulin resistance	[38]
	Watermelon (<i>Citrullus lanatus</i>)	Rind, skin and pulp	Dried watermelon products	8% pulp and 2.25% rind and skin of the energy consumed in the diet	<i>In vivo</i> (C57Bl/6 J mice)	Improved FBG, circulating serum insulin concentrations, and changes in hepatic metabolite accumulation	[43]
	Mango (<i>Mangifera indica</i>)	Pulp	Flour	5, 10 and 15 g/ 100 g of fed for 30 days	<i>In vivo</i> (Wistar rats)	Decreased blood glucose levels and increased serum insulin levels	[44]
	Pomegranate (<i>Punica granatum</i>)	Flower, peel and seed oil	Flower and peel methanol extract; Seed oil Soxhlet extract	Flower and peel extracts: 250 mg/kg/day for 4 weeks; Seed oil: 2	<i>In vivo</i> (C57Bl/6 mice)	Improves insulin sensitivity	[45]

			ml/kg/day for 4 weeks			
Kiwifruit (<i>Actinidia chinensis</i>)	Seed oil	n- hexane extract	1 or 3 mL/ kg per day for 8 weeks	<i>In vivo</i> (C57Bl/6 J mice)	Reduction in blood glucose and improves thermogenesis (PPAR- γ , UCP1, PGC1- α and PRDM16)	[41]
Jaboticaba (<i>Myrciaria jaboticaba</i>)	Ripe fruit	Aqueous extract	50 and 100 mg/kg/day for 28 weeks	<i>In vivo</i> (C57Bl/6 J mice)	Decrease in glucose intolerance, insulinemia and insulin resistance and modulation of the Akt/mTOR pathway in liver, skeletal muscle and white adipose tissue, as well as increased expression of GLUT4 in skeletal muscle	[42]
Bacupari (<i>Garcinia brasiliensis</i>)	Peel	Ethanol extract	42 mg/kg/day for 8 weeks	<i>In vivo</i> (Wistar rats)	Antioxidant and anti- inflammatory effect, increased expression of PPAR γ and IL-10, decreased expression of	[46]

						LPL and FAS and reduced TNF- α , blood levels of glucose, alanine aminotransferase, and adipocyte hypertrophy	
Oxidative stress and inflammation	Carob (<i>Ceratonia siliqua</i>)	Seed peel, germ and pod	Flour	0.5, 0.1, and 0.05 mg/mL	<i>In vitro</i>	High antioxidant capacity	[27]
	Walnut (<i>Juglans regia</i>)	Septum	50% acetone aqueous extract	Different doses	<i>In vitro</i>	Antioxidant and anti-inflammatory activity (reduction of IL-6, IL-8, IL-1 β)	[28]
	Jaboticaba (<i>Myrciaria jaboticaba</i>)	Peel	Aqueous and methanol extract	25 mL/ day during 6 and 12 weeks	<i>In vitro</i> and <i>in vivo</i> (Wistar rats)	High antioxidant potential <i>in vitro</i> and <i>in vivo</i>	[47]
	Grape (<i>Vitis aestivalis</i>)	Pomace	80% ethanol aqueous extract	250 mg/kg per day for 12 weeks	<i>In vivo</i> (C57Bl/6 J mice)	Reduction of CRP levels, revealing a possible anti-inflammatory effect	[48]
	Pomegranate (<i>Punica granatum</i>)	Peel	60% ethanol aqueous extract	150 and 300 mg/kg/ day for 12 weeks	<i>In vivo</i> (rats)	Decreased elevated circulating pro-inflammatory cytokines,	[49]

						colonic tissue damage, and depressed colonic tight junction protein expression level	
	Pomegranate (<i>Punica granatum</i>)	Flower, peel and seed oil	Flower and peel methanol extract; Seed oil Soxhlet extract	Flower and peel extracts: 250 mg/kg/day for 4 weeks; Seed oil: 2 ml/kg/day for 4 weeks	<i>In vivo</i> (C57Bl/6 mice)	Reduction of plasma levels of the pro-inflammatory cytokines: TNF- α and IL-6 and improves insulin sensitivity	[45]
	Kiwifruit (<i>Actinidia chinensis</i>)	Seed oil	n- hexane extract	1 or 3 mL/ kg per day for 8 weeks	<i>In vivo</i> (C57Bl/6 J mice)	Decrease in inflammation (TNF- α , IL-6, IL-1 β , COX-2 and iNOS)	[41]
White/brown adipose tissues	Onion (<i>Allium cepa</i>)	Peel	60% aqueous ethanol extract	<i>In vitro</i> : 50, 100 and 150 μ g/ml <i>In vivo</i> : 0.5% of the diet for 8 weeks	<i>In vitro</i> (3T3-L1 cells) and <i>In vivo</i> (C57Bl/6 mice)	Change the characteristics of white adipocytes to those of brown-like adipocytes in the white	[50]
	Pomegranate (<i>Punica</i>)	Peel	Aqueous ethanol extract	50 mg/kg per day for 14	<i>In vivo</i> (C57Bl/6 J)	Activation of complex IV activity and preservation	[51]

	<i>granatum</i>)			weeks	mice)	of mitochondrial ridge structure in brown adipose tissue	
Grape (<i>Vitis vinifera</i>)	Seed	Proanthocyanidin extract	5, 25 or 50 mg/kg body weight per day for 21 days	<i>In vivo</i> (Wistar rats)	Modulation of the functionality of the brown adipose tissue	[52]	
Lotus (<i>Nelumbo nucifera</i>)	Seedpod	Procyanidin extract	150 mg/kg body weight per day for 12 weeks	<i>In vivo</i> (ICR mice)	Improved heat generation in brown adipose tissue	[53]	

NPC1L1: Niemann–Pick C1-Like 1; LXR α : liver X receptor alpha; FABP4: fatty acid binding protein, ERK1/2: extracellular signal-related kinase; Sirt1: sirtuin 1; FGF21: fibroblast growth factor 21; UPC1: uncoupling protein 1, PRDM16: PRdomain-containing 16

Regarding the lipid profile, natural bioactive compounds have been shown to be effective against fat deposition, increase fat metabolism and improve the lipid profile in plasma by increasing levels of high-density lipoprotein cholesterol (HDL-C) and low-density protein (LDL) oxidation [54]. Total cholesterol (TC), triglycerides (TGs), HDL-C, LDL-C, triacylglycerol (TAG), non-esterified fatty acid (NEFA) and long-chain FA (LCFA) are the serum parameters commonly determined in supplementation studies with phenolic compounds. In one study, Sprague Dawley rats with diet-induced obesity were treated with 800 mg/kg body weight/day of *Moringa olifera* seed oil extract by intragastric administration for the last 8 weeks [55]. The results showed that the intake of the extract produced a decrease in TC, TGs, LDL-C, VLDL-C, NEFA and an increase in HDL-C [55]. On the other hand, jaborcaba peel extract, a great source of fibers and phenolic compounds, such as anthocyanins and ellagic acid, did not show any anti-obesity effects on TC and HDL-C in Wistar rats, although the authors reported that prolonged intake could have a protective effect due to a decrease in LDL-C [36]. Recently, Abdulmalek *et al.* have reported the effective amelioration of the lipid profile in rats, with a high-fat diet, using *Lepidium sativum* L. seed aqueous/ethanolic extracts [56]. In this study, treatment with two doses of ethanolic extract (200 and 400 mg/kg BW) and one dose of aqueous extract (200 mg/kg BW) caused a significant reduction in serum TC, TG, LDL-C, and total lipids with a considerable

increase in HDL-C levels compared to the high-fat diet group. Interestingly, at the same concentration level, the best results were obtained with the ethanolic extract, which contains a higher content of phenolics and flavonoids [56]. Moreover, the effects of a guava leaf hydroalcoholic (ethanol:water, 80:20) have also been studied. This extract at 5 mg/kg was provided to obese male mice (C57BL/6J), which resulted in a significant reduction of TGs, TC, LDL-C and HDL-C [57]. On the other hand, aqueous extracts have also shown positive effects on the lipid profile. For instance, tomato and broccoli aqueous extracts were administered to male albino rats at doses of 200 and 400 mg/kg [58]. The groups that ingested the extracts showed lower values of TC, TGs and LDL-C, and higher HDL-C values than those of the high-fat diet group. Between both extracts, the aqueous tomato extracts were the most active probably due to their lycopene content [58]. It is worth noting that supplementation with microencapsulated pomegranate peel extract prevents increased TC with better results than non-microencapsulated extract in obese male C57BL/6J mice [51].

Human epidemiological studies have also reported the benefits of some byproducts rich in bioactive compounds [6]. In this regard, the aqueous phase obtained in the industrial production of olive oil industry is considered an important waste that has to be managed due to the large quantities produced. However, this byproduct has been characterized by containing more phenolic compounds than the oil itself because this retains

only a small amount of polar compounds due to its lipophilic character [59]. Peroulis *et al.* in 2019 conducted a study with thirty-five healthy participants from a rural area of Greece to explore the properties of a meat product with the microencapsulated polyphenol-rich water extract of olives [60]. All volunteers followed a Mediterranean-style free diet for four weeks and the microparticle dose was 0.5714 mg of total polyphenols per kg of body weight per day. In normolipidemic participants, the intervention did not modify lipid profiles, while in a sub-group (18 individuals) with two or more parameters related to cardio-metabolic risk, the meat product under study significantly reduced TC, TGs and LDL levels. Furthermore, oxidized LDL, which is related to oxidative damage and is involved in the formation of atheroma plaque and atherosclerosis, was also significantly reduced by the consumption of microparticles [60]. The citrus industry also generates a large amount of waste such as flavedo, seeds, peels, with a high economic and environmental impact [17]. In this scenario, a dietary intervention study was conducted on 80 obese adolescent to examine the properties of a *Citrus reticulata* peel extract rich in flavonoids, mainly hesperidin, quercetagenin, naringenin, acacetin, rutin and quercetin. In this study, the volunteers were divided into two groups: one group received 20 mL of the extract every day 30 min before breakfast or dinner and the other group 20 mL of placebo under the same conditions. Both groups followed these conditions with a low calorie balanced diet for 8 weeks [32]. The

supplementation with this extract significantly decreased TC and TG levels, thus providing an economical alternative for the management of obesity [32]. In contrast, when overweight instead of obese overweight consumed onion peel extract at 100 mg per day for 12 weeks, no [CM1]significant change in TC, TGs, LDL-C and HDL-C was observed [61][CM2]. From these results, we can infer that the experimental conditions are of utmost importance in the development of new therapeutic alternatives from agro-industrial byproducts.

On the other hand, modifications in the lipid metabolism related-gene expressions[CM3] have also been found as therapeutic targets for phenolic compounds from food byproducts [35,62-64]. A recent study has revealed that the byproducts obtained from roasted cocoa beans of the *Forastero* variety, which contain colored compounds and melanoidins, act as potent inhibitors of protein phosphatase (PTP1B) [62]. This protein is an activator of hepatic lipogenesis and its inhibition has shown a decrease in the hepatic expressions of genes involved in the synthesis of lipids and cholesterol, such as sterol regulatory element-binding proteins (SREBPs), fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC) and 3-hydroxy-3-methylglutaryl-coenzyme A synthase 1 (HMGCS1) [62]. In the case of kiwi seed oil, both the protein and the mRNA expression levels of peroxisome proliferator-activated receptor α (PPAR- α) and carnitine palmitoyltransferase 1a (CPT1a) were

significantly suppressed in liver tissues of the group of mice that ingested a high-fat diet. This CPT1 is characterized as the rate-limiting enzyme for fatty acid β -oxidation. However, compared to the high-fat diet group, CPT1b protein expression was significantly up-regulated. Furthermore, protein expression of FAS and PPAR- γ was also investigated to find out whether kiwi seed oil supplement could inhibit lipid synthesis. The results showed that the expression levels of these proteins decreased significantly in a dose-dependent manner in the mice group that ingested the extract for 12 weeks compared to the group on a high-fat diet. A similar trend was also detected in the mRNA expression of FAS, however, no significant difference were detected for the mRNA expression of PPAR- γ [63]. *Hylocereus* peel, which possesses a high content of betacyanins, similarly decreased the expression levels of AdipoR2 and PPAR- γ (lipid metabolisms-related genes) and Insig1 and Insig2 (cholesterol biosynthesis-related genes) [35]. Moreover, a reduction in the expression of FAS and lipoprotein lipase (LPL) genes was also detected in mice on a high-fat diet supplemented with 10 and 20 % red potato peels. LPL is defined as the main enzyme that hydrolyzes circulating TGs into free fatty acids and facilitates their entry into adipocytes [64]. These results suggest that the breakdown of TGs into FA was also lower, since there was a reduction in LPL transcription. In a similar way to that described previously in the cacao study, SREBP-1c and PPAR- α were also detected transcriptionally downregulated by the red potato

peel, rich in glycoalkaloids and phenolic compounds, such as caffeic and chlorogenic acids. In contrast, the expression of the liver acyl-CoA oxidase gene (ACOX1) increased for the two peel supplements. This result of the ACOX1 induction was quite interesting since its regulator PPAR- α showed the opposite expression pattern, appearing to be independently regulated in this case[64].

Considering all these results, numerous therapeutic targets (enzymatic level, lipid profile or related gene expression levels) have shown great potential to be useful for the prevention or treatment of obesity serve to prevent or treat obesity using phenolic compounds from agro-industrial byproducts.

3. EFFECTS ON GLUCOSE AND ENERGY METABOLISMS

Obesity is characterized by producing changes in lipid metabolism, but also in glucose and energy metabolism, mainly characterized by some digestive enzymes, high levels of glucose and insulin, that can result in other chronic pathologies such as cardiovascular disease or diabetes, or faulty gene expression [9]. Therefore, it is of great interest to find and exploit substances (e.g. phenolic compounds from agro-industrial by-products) that improve these metabolic parameters without producing side effects.

In this regard, α -amylase and α -glucosidase are key digestive enzymes involved in carbohydrate metabolism. The first one breaks down starch and complex carbohydrates into disaccharides, which are hydrolyzed by α -glucosidases into free glucose

that can then be absorbed [65]. Moreover, α -glucosidase is ultimately involved in the control of glucose release from polysaccharides in the gut [66]. Since some drug treatments, such as metformin, cause adverse gut effects at high doses, a combination of low-dose drugs and the intake of bioactive compounds from natural sources has been proposed as an alternative. In this context, several studies have reported evidence of the properties of phenolic compounds from vegetables for the inhibition of these obesity-related enzymes [65,67]. For example, Nowicka *et al.* in 2018 analyzed the inhibitory effect of α -amylase and α -glucosidase of aqueous extracts of peach kernel from 20 different cultivars in Poland with acarbose as a positive control. In this study, the IC_{50} values for amylase ranged from 28.26 (Madison with a high content of phenolic acids) to 141.39 mg/ml. Regarding glucosidase, the IC_{50} values ranged from 25.20 (Harrow Beauty with a high content of polymeric procyanidin) to 214.40 mg/ml [68]. Since Peruvian corn represents an important source of bioactive compounds, dried kernels of 22 different corns (12 of germplasm and 10 collected *in situ*) were tested [69]. The results showed that the samples of the Kculli race (purple grains) showed higher enzyme inhibitory activities than the other corn races. This higher activity was correlated with a higher content of total phenolic compounds and total anthocyanidins [69]. Pomegranate peel extracts have also been investigated as a vegetable source with a promising potential. For instance, the ability of its phenolic compounds to modulate glucose

metabolism by inhibiting the activity of α -glucosidase and α -amylase has been studied in a simulated *in vitro* gastrointestinal digestion system [70]. A greater effect was determined for α -glucosidase due to the content of ellagitannins, gallic acid, ellagic acid and their derivatives in the duodenum. In this sense, 0.007 mg of phenolic compounds in the duodenum extract were calculated to inhibit the activity of 1 U of α -glucosidase by 84%, while 0.036 mg for the activity of 1 U of α -amylase by 72% [70]. However, these compounds have been suggested as an effective strategy to decrease the availability of the polysaccharide substrates for glucose release in the gut [66].

De Carmargo *et al.* optimized the extraction method of phenolic compounds from winemaking by-products (cv. Tempranillo) to obtain the extract with the greatest potential for the inhibition of α -glucosidase. They used Pronase and Viscozyme (enzyme treatments) to increase the solubility of the phenolics present in the sample [71]. These treatments increased inhibition of α -glucosidase compared to the control. Between both enzyme treatments, an inhibition of α -glucosidase by $7.35 \pm 3.1\%$ and $7.79 \pm 0.6\%$, was determined for the phenolic compounds extracted with Pronase and Viscozyme, respectively. However, two treatments only improved the amount of soluble phenolic compounds but decreased the content of insoluble-bound phenolics [71]. Therefore, both Pronase and Viscozyme could be applied for the development

of high added-value products against obesity based on soluble phenolic compounds.

The oral glucose tolerance test (GTT) is defined as the gold standard for the diagnosis of impaired glucose tolerance, a well-established risk factor related to obesity [72]. For this reason, several studies have used this method to determine the effect produced by bioactive compounds. For example, GTT was performed to study the effect of watermelon byproduct skin extract in a male C57BL/6J mouse model fed a high-fat diet [43]. A reduction in fasting blood glucose (FBG) concentrations was observed in the group supplemented with watermelon skin extract, to a level statistically equivalent to the low-fat diet group [43]. This result and the reduction in serum insulin concentrations, could be closely related to the phytochemicals present in the watermelon skin [43]. FBG was also determined in a diet-induced obese male mouse model (C57BL/6 J) treated with a phenolic extract obtained from jaboticaba [42]. This extract, rich mainly in proanthocyanidins and ellagitannins, provided a faster reduction in plasma glucose concentrations than the high-fat diet group [42]. In addition, obese animals presented the highest plasma insulin concentration, indicating elevated insulin release during oral GTT, and as result of this test, the supplemented group showed lower blood glucose levels [42]. Similarly, extracts of pomegranate peel [45], bacupari peel [46], aqueous jaboticaba peel [36], kiwifruit seed oil [41], chenpi [73] and Roselle byproducts [38] have also shown a positive effect in animal models. On the other hand, FBG has been measured in dietary

intervention studies conducted in human models. For example, a human trial was conducted to measure the direct effect of the olive water extract on FBG and insulin levels at dietary concentrations. The results showed a reduction in elevated glucose and insulin levels after administration of the extract in a food matrix [60]. The same behavior in glucose levels was revealed with an onion peel extract, rich in quercetin, in a randomized, double-blind, placebo-controlled study [39].

Taking into account other targets involved in glucose and energy metabolisms, resistin has been identified as a secreted adipocyte hormone with action in regulating glucose homeostasis, increasing blood glucose levels as well as the production of hepatic glucose [74]. Likewise, high levels of resistin can cause insulin resistance which has been linked to obesity. As an example of a study evaluating this parameter, Aborehab et al. in 2016 demonstrated that aqueous extracts of tomato and broccoli significantly reduced FBG and resistin levels in obese rats compared to those on a high-fat diet. [58]. On other hand, the PI3K/AKT pathway is an intracellular signaling pathway important in regulating cell proliferation, differentiation, metabolism, and cytoskeletal reorganization. This pathway has been associated with obesity since insulin from food is capable of activating it, increasing glucose utilization and reducing gluconeogenesis in the liver and muscle under physiological conditions [75]. Nevertheless, the mammalian target of rapamycin (mTOR) has been described as the master regulator of the cell's

growth and metabolic state in response to nutrients, and its dysregulation also contributes to obesity [76]. In this sense, the concentrations of Akt and mTOR have shown in some studies to be able to be modified by phenolic extracts from food byproducts, such as the Brazilian berry jaboticaba, rich in ellagic acid derivatives and anthocyanins [42]. In this particular study, the hepatic Akt levels were found statistically elevated in the group of mice that consumed the extract with the highest gallic acid content. In contrast, the extract with a lower content of this compound showed higher levels of Akt in white adipose tissue and muscle. Regarding mTOR, both groups supplemented with different concentrations of gallic acid showed lower concentrations in the liver, and higher in the white adipose tissue, compared to the control group on a high-fat diet group. In contrast, in muscle, the mTOR values were only statistically lower in the mice group that ingested the extract with the highest content of gallic acid. [42]. Akt activation is responsible for initiating the translocation movement of the glucose transporter GLUT4, which is encoded by solute carrier family 4 anion exchanger member 2 (SLC4A2), from the cytoplasmic vesicles to the cell membrane in adipocytes and myocytes. In fact, GLUT4 activation enhances glucose uptake and increases the amount of intracellular glucose available for metabolic conversion, promoting greater cell proliferation [77]. In the previous study of jaboticaba extracts, GLUT4 levels in muscle were also increased in the same way as Akt [42]. In another study, phenolic compounds from aqueous

coffee silverskin and husk extracts were also able to stimulate GLUT4 translocation *in vitro* [25]. 5'-Adenosine monophosphate-activated protein kinase (AMPK) is another important therapeutic target in obesity. AMPK promotes GLUT4 translocation and glucose uptake, suggesting that its activation may play a role in the regulation of energy homeostasis [78]. In a similar way to the other therapeutic targets, extracts rich in phenolic compounds have shown effects on the activation of AMPK. For example, a chenpi extract activated the AMPK signaling pathway by increasing levels of phosphorylated AMPK in adipose tissue [73]. Fermented persimmon extracts also activated AMPK in a dose-dependent manner [79]. Phenolic extracts of lotus seed and pear pomace water incremented the phosphorylated AMPK [73]. In these studies it has been revealed that the modulation of AMPK is linked to the chemical structure of phenolic compounds [82]. For this reason, bioactive extracts from agro-industrial waste, rich in these compounds, have great potential to be a cheap but powerful alternative for obesity relief.

4. EFFECTS ON OXIDATIVE STRESS AND INFLAMMATION

During obesity, several oxidative stress and inflammation factors are highly produced, including reactive oxygen and nitrogen species, free radicals and proinflammatory intermediates. In addition to these, antioxidants in plasma, cellular response or protein inhibition, are considered therapeutic targets that could be

modulated by a by-product rich in phenolic compounds [9]. In fact, it is well known that organisms have developed mechanisms to reduce oxidative stress, such as non-enzymatic and enzymatic antioxidant endogenous defenses. However, after a period of overstimulation, these enzymes are depleted and cannot cope with increased oxidative stress, thus other exogenous defenses provided by the diet are needed [83].

Long-term consumption of a high-fat diet provides increased lipid peroxidation and decreased endogenous antioxidant mechanisms, including superoxide dismutase (SOD), reduced glutathione (GSH), glutathione-s-transferase (GST), glutathione peroxidase (GPx) or catalase (CAT).

Several biomarkers have been studied to assess oxidative stress caused by obesity, such as malondialdehyde (MDA), which are most measured by thiobarbituric acid reactive substances (TBARS) for lipid peroxidation, nitric oxide (NO) and xanthine oxidase (XO), among others [84]. In this sense, animals on a high-fat diet present high MDA levels, and some extracts rich in phenolic compounds, such as jacoticaba peel extract, have shown the ability to reverse this oxidative state. [47]. In addition, these bioactive extracts have also shown the ability to significantly increase the plasma levels of GSH and CAT, which are important enzymes in antioxidant defense [47]. In another study, supplementation with *L. sativum* seed extracts at 200 and 400 mg/kg body weight, decreased hepatic oxidative indicators, such as TBARS, NO

and XO [56]. Furthermore, the activity of CAT, SOD, GST, GSH and GPx was maintained at normal levels in the group of supplemented rats, in contrast to the lower values detected in the group of obese control rats. Interestingly, GSH levels were also higher after the intake of both ethanol and water seed extracts [56]. In general, the ethanol seed extract from *L. sativum* in low doses was the most potent against oxidative stress in the rat liver [56]. These extracts were also tested to ameliorate the inflammatory status in obese rats, showing an increase in adiponectin levels and a decrease in leptin levels [56]. Since the leptin/adiponectin ratio has been described as a biomarker of inflammation, supplementation with bioactive extracts of *L. sativum* showed a decrease in this biomarker [56]. Besides that, the ethanolic seed extract at 200 mg showed the greatest potential to decrease hepatic inflammatory cytokines, such as tumor necrosis factor alpha (TNF- α), interleukins (IL): IL-1 β , IL-6, inducible nitric oxide synthase (iNOS) levels, and down-regulated mRNA level of TNF- α , monocyte chemoattractant protein-1 (MCP-1) and IL-23 [56]. The effects of cocoa by-product extracts on oxidative stress and inflammation have also been studied. For example, one of these extracts, rich in products of the Maillard Reaction, was able to reduce the TBARS concentration in kidney tissue. Another cocoa extract rich in flavan-3-ol monomers showed the lowest values for the GSH:GSSG (oxidized glutathione) ratio in liver tissue, showing separate mechanisms of action [62]. In relation to the antioxidant enzymes ratios,

the SOD/CAT and SOD/GPx ratios are related to the cellular detoxification capacity, determining the degree of removal of hydrogen peroxides produced by SOD. Therefore, a higher detoxification capacity would be associated with lower SOD/CAT and/or SOD/GPx ratios. In this sense, several studies have evaluated these parameters in relation to the intake of phenolic compounds or bioactive extracts. For example, the supplementation with an anthocyanin-depleted cherry extract produced higher ratios compared to the control group of obese mice. These results suggested that the levels of oxidative stress in supplemented mice were relatively low, probably due to the antioxidant and scavenging radical capacities of phenolic compounds [85]. In another example, the administration of a methanolic extract of *Moringa oleifera* leaf to rats on a high-fat diet showed dose-dependent effects in reducing TBARS to normal state and improving GPx, CAT and SOD activity in the heart [86]. These parameters were also positively modified by a green pea hull extract in obese rats. In this particular study, the result were related to the presence of 10 phenolic compounds and 49 bioavailable metabolites in the plasma and urine samples [87]. A tart cherry extract rich in anthocyanidin also produced a significant increase in SOD activity and a reduction in leptin and IL-6 levels [88]. Another example also related to anthocyanins was based on the supplementation with a cranberry extract in mice with diet-induced obesity. That extract produced an increase in SOD and a decrease in TNF- α plasma levels [89].

Raspberry and cranberry extracts have also been studied, which increased SOD, CAT and GPx activities [90], or enhanced CAT levels in liver and adipose tissues, respectively [91]. Regarding the olive leaf potential, Zhang *et al.* reported the high antioxidant effects of Chinese olive leaf tea by enhancing SOD and GPx activities and reducing MDA levels [92]. Furthermore, the intake of extracts rich in oleuropein- or hydroxytyrosol significantly increased the antioxidant capacity and reduced the lipid peroxidation of the liver tissue of rats fed a high-fat diet towards normal values. Between both extracts, the extract rich in hydroxytyrosol showed better results against the hepatic oxidative state [93].

C-reactive protein (CRP) level has been used as an important medical biomarker of inflammation in obese population. In this sense, the effect of phenolic compounds on the level of this biomarker has also been explored, as in the case of a grape pomace extract. This extract, rich in catechin and epicatechin as the main phenolic compounds in addition to quercetin, resveratrol and gallic acid, was able to restore the normal levels of this biomarker in mice fed a high-fat diet [48]. Moreover, other parameters related to oxidative stress and inflammation have also been described, such as arachidonic acid derivatives (12- and 15-hydroxyeicosatetraenoic acids) or the relative concentrations of stearyl carnitine and palmitoyl carnitine. These metabolite indicators have been shown to decrease after

supplementation with different watermelon diets compared to a high-fat diet group [43].

Diet supplementation with Chardonnay grape seed flour has been reported to have an effect on different hepatic gene expression profiles in high-fat mice [94]. For example, among the genes related to oxidative stress and inflammation, iNOS trafficker, NOS2, otopetrin 1 (OTOP1), lipopolysaccharide binding protein (LPB), toll like receptor 4 (TLR4), TLR4 interactor with leucine-rich repeats (TRIL), TNF- α , TNFAIP3 interacting protein 3 (TNIP3) and IL 7 receptor (IL7R) were detected down-regulated [94]. Moreover, an up-regulation of the expression levels of different genes, such as peroxisome proliferative activated receptor γ coactivator 1 α (PPARGC1 α), flavin-containing monooxygenase 3 and 5 (FMO3 and FMO5), GPx3, GST α 4, GSTm6, and lipocalin 2 (LCN2), was also detected caused by the grape supplement [94].

In summary, phenolic compounds from agro-industrial by-products have been shown to modulate the oxidative and inflammatory conditions associated with obesity, although further human clinical trials are needed to gain a deeper understanding of these effects.

5. EFFECTS ON BROWN/WHITE ADIPOSE TISSUES AND GUT MICROBIOTA

The excessive expansion of white adipose by increasing the number or size of adipocytes has been associated with obesity, thus being a therapeutic target for phenolic compounds. Likewise, adipocyte hypertrophy promotes cell

death and inflammation, which are considered the main mechanisms related to obesity. On the other hand, alterations in the gut microbiota have also been shown to play an important role in obesity [13]. For these reasons, studies have been conducted to explore the effect of supplements rich in phenolic compounds on the gut microbiota and white adipose tissues. For instance, dietary supplementation with citrus peel extracts, at low and high doses of polymethoxyflavones and hydroxyl polymethoxyflavones (CPL and CPH, respectively), has been studied for this purpose [95]. Interestingly, both CPL and CPH extracts were able to decrease body fat by reducing perigonadal and retroperitoneal adipose tissue weight. Between them, CPH showed a greater capacity to decrease lipid accumulation, probably due to the large amount of flavones [95]. In contrast, the effects on the gut microbiota were different for these two extracts. At the phylum and genus levels, the CPH and CPL extracts showed a greater similarity in the microbiota composition with the normal diet and obese mice groups, respectively. [95]. In general, high levels of *Lactobacillus* were detected in both CHP and CPL groups but the highest levels were related to the CPH extract. In this CPH group, *Allobaculum* and *Prevotella* were found in the highest concentration, and rc4-4, SMB53, *Turicibacter*, *Akkermansia*, and *Ruminococcus* in the lowest in comparison with the CPL and high-fat diet groups [95]. Therefore, these results confirm the phenolic compound but also their concentration level play a fundamental role to exert a positive effect.

Similarly, another study evaluated the effect on adipose tissue of the following three peel onion extracts: an ethanolic (60 %) extract (OPE), an ethyl acetate fraction (OPEA) and a water fraction (OPW) [50]. The phenolic content of these three extract was based mainly on quercetin and isoquercetin in the following order: OPEA > OPE > OPW [50]. Adipocytes in the untreated control group showed the typical appearance of lipid droplets, similar to all differentiated 3T3-L1 cells. However, a higher concentration of OPE contracted the lipid droplet into multiple droplets, thereby reducing the overall lipid accumulation in adipocytes. The OPW and OPEA extracts exhibited the same browning effect on 3T3-L1 adipocytes [50]. At the gene expression level, mice on a high-fat diet treated with OPE, OPEA and quercetin showed the same behavior in the expression of several brown adipose tissue-specific genes, such as PRDM16, UCP1, FGF21, PGC1- α and cell death-inducing DFFA-like effector (CIDEA) in retroperitoneal and subcutaneous white adipose tissues, promoting the change of white adipocytes to brown-like ones by inducing gene expressions[50]. Polyphenols-rich purple maize pericarp water extracts at 200 and 500 mg/kg have also been studied in mice on a high-fat diet [96]. Both extracts showed a reduction in total visceral adipose tissue in terms of weight. In addition, the diameter of adipocytes was also significantly reduced with both extracts, especially with the 500 mg/kg one. These results suggested that purple maize pericarp extracts may act as a good alternative against obesity by

inducing a white-fat browning phenotype and a subsequent thermogenic state [96]. Regarding the gut microbiota, a study was carried out with extracts rich in phenolic compounds of the pomegranate peel, which were supplemented to rats on a high-fat diet at two doses (150 and 300 mg/kg) [49]. The changes in the gut microbiota indicated that, at the phylum level, Firmicutes, Bacteroidetes, Proteobacteria, Tenericutes and Actinobacteria were the five largest in fecal microbiota. The Firmicutes/Bacteroidetes ratio, which plays an important role in metabolic disorders, was significantly reduced by the low-dose extract compared to the high-fat diet group [49]. At the genus level, 50 genera were found. Among them, two genera of the *Prevotellaceae* family were detected in high abundance with both extracts in the same way as in the control group, although the best results were associated with the lowest dose [49]. The overall results suggested that this treatment restored the general composition of the gut microbiota community in rats on a high-fat diet similar to that of the control group [49].

Therefore, the adipose modification and the modulation of the gut microbiota by phenolic compounds from food waste could become an alternative therapeutic strategy to prevent obesity and its associated complications.

CONCLUSION

Low cost and easy availability of agro-industrial byproducts, which are considered waste, are the main reasons for considering them as a

potential source of bioactive ingredients. Numerous studies have reported that phenolic compounds have positive effects against obesity by modulating different parameters involved in lipid, glucose and energy metabolism, oxidative stress, inflammation, white adipose tissue / brown and the gut microbiota. Although the number of these studies has been increasing exponentially in recent years, most of these studies have been based on exploring these beneficial properties in extracts rich in phenolic compounds, and there are still mechanisms of action that remain unclear. For example, most studies do not exactly explore which compounds or derived metabolites are responsible for the beneficial properties or whether there is a synergistic effect between them. On the other hand, most studies have also been carried out using animal models. For these reasons, more studies, including human intervention trials, are still needed to help understand the bioavailability as well as metabolization mechanisms of the phenolic compounds. All these studies will provide a deeper understanding of the mechanisms of action, allowing monitoring of the applications for the release of these compounds in a controlled manner through encapsulation strategies. In addition, agro-industries will have more information on the properties of their by-products rich in phenolic compounds, allowing the development of potential applications of value-added products.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

All authors declare there is no conflict of interest, financial or otherwise.

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