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Plant Polyphenols in Obesity and Obesity-Associated Metabolic Disorders: A Narrative Review of Resveratrol and Flavonoids Upon the Molecular Basis of Inflammation

Rosangela Passos de Jesus[1], João Felipe Mota[2], Pedro González-Muniesa[3], Dan Linetzky Waitzberg[4], Monica Marques Telles[5], Allain Amador Bueno[6*]

[1]Department of Nutrition Sciences, School of Nutrition, Universidade Federal da Bahia, Salvador, Brazil

[2]Clinical Nutrition and Sports Research Laboratory (LABINCE), Faculty of Nutrition, Universidade Federal de Goias, Goiania, Brazil

[3]University of Navarra, Department of Nutrition, Food Science and Physiology, School of Pharmacy and Nutrition, Pamplona, Spain

[4]Department of Gastroenterology, School of Medicine, Universidade de São Paulo, São Paulo, Brazil

[5]Department of Biological Sciences, Universidade Federal de São Paulo, Diadema, Brazil

[6]Department of Biology, Institute of Science and the Environment, University of Worcester, Worcester, United Kingdom

[*]**Corresponding author:** Allain Amador Bueno, Department of Biology, Institute of Science and the Environment, University of Worcester, Worcester, United Kingdom. Tel: +441905542525 Email: a.bueno@worc.ac.uk

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Abstract

Background: The epidemic of obesity, metabolic syndrome, type 2 diabetes and non-alcoholic fatty liver disease is currently unsustainable for Public Health systems, and preventive and therapeutic approaches are urgently sought to improve health outcomes for affected individuals.

Aim: In this study, we aim to further explore and synthetize available evidence on the effects of selected Plant Polyphenols (PP) upon molecular mechanisms associated with oxidative stress and inflammatory pathways. We also aim to briefly discuss PP supplementation as therapeutic tool for the prevention and management of prevalent obesity-associated metabolic disorders.

Methods: This narrative review was performed in the PubMed database in June 2018 without restriction of publication period.

Results: PP influence a broad range of cell signalling pathways; by modulating the activity of nuclear transcription factors, PP modulate gene expression and antioxidant responses, as well as inflammation and its resolution. Several interventional studies have investigated the effects of PP supplementation in a variety of sample populations, but no consensus has yet been reached regarding composition, dosage or course of treatment for therapeutic purposes. However, overall results tend to suggest a positive effect of PP in either improving metabolic profile or minimizing negative disease outcomes. Careful consideration on PP supplementation is paramount; adverse effects have already been described.

Conclusion: The successful prevention and management or treatment of obesity-associated metabolic disorders may be achieved through an effective multidisciplinary approach to tackle their modifiable risk factors. A balanced diet, which includes naturally occurring sources of PP associated with lower consumption of ultra-processed foods, is a relevant approach for the positive health outcomes desired.

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Keywords: Plant Polyphenols; Inflammation; Obesity; Metabolic syndrome; Non-alcoholic fatty liver disease; Diabetes

Introduction

Amassing amounts of epidemiological data confirm the positive associations and common risk factors between obesity and Non-Alcoholic Fatty Liver Disease (NAFLD) with other chronic metabolic conditions such as metabolic syndrome, Type 2 Diabetes (T2D) and cardiovascular diseases [1,2]. These arguably preventable chronic metabolic disorders are known to reduce life expectancy, and their combined burden to the global Public Health system is currently unbearable. Their prevalence is believed to be increasing [3], and their negative impact upon the quality of life and wellbeing of affected individuals is highly detrimental. Metabolic syndrome covers a cluster of comorbidities including hypertension, dyslipidaemia, hyperglycaemia and obesity, particularly visceral obesity [3], which in turn are also major risk factors for cardiovascular disease and T2D [4]. In the USA, the prevalence of Metabolic Syndrome is believed to be at approximately 22.5% of the adult population [5]; but other studies have found higher prevalence, for example in 56.3% of individuals aged 50 years or older [6].

NAFLD covers a broad term of conditions affecting the liver, but their common manifestations include excessive accumulation of fat in hepatocytes, insulin resistance and metabolic syndrome [7]. The prevalence of NAFLD is estimated at 10 to 40% of adults worldwide, and approximately 40% of the affected individuals show increased levels of pro-inflammatory biomarkers [7]. As the prevalence and costs of obesity-associated metabolic disorders are predicted to increase, modern societies welcome new and affordable approaches for the effective prevention, management and possibly treatment of such conditions. Recent studies have suggested that resveratrol and flavonoids, molecules belonging to the large family of Plant Polyphenols (PP), have beneficial effects against the development and manifestations of metabolic disorders [8,9,10].

Plant Polyphenols (PP) are organic compounds characterized by the presence of phenolic structural units, highly relevant in plant biology for their properties in defence against ultraviolet radiation and pathogens [11]. PP include heterogeneous families of over 8,000 molecules commonly classified as phenolic acids, stilbenes, lignans and flavonoids [12]. In specific regards to flavonoids, these are members of a large subfamily of PP featuring over 6,000 compounds including flavones, flavonols, flavanols, flavanones, isoflavones, anthocyanins and chalcones, which are found in a vast range of fruits and vegetables [13,14]. Fruits rich in PP may contain up to 200 to 300 mg of PP per 100 g wet weight, whilst up to 100 mg of PP can be found in a cup of tea, coffee or a glass of red wine [13].

The digestion, absorption and metabolism of flavonoids are heavily dependent on their molecular presentation, whether monomeric, also known as aglycones, or glycosylated forms. The digestion of flavonoid glycosides begins with the process of mastication, supported by the action of the oral microbiota, which is known to secrete β-glucosidase [15,16]. Only approximately 5% to 10% of flavonoid glycosides are absorbed in the small intestine [16,17]; the largest proportion usually reaching the intestinal colon undigested, where they are partially hydrolysed by enterobacteria, with the corresponding aglycones subsequently released for absorption [16]. Glycosylated flavonoids are poorly absorbed by the gastrointestinal tract due to their hydrophilic properties [18].

Once digested and absorbed by the gastrointestinal tract, a complex process heavily dependent upon the gut microbiota [15-17], flavonoids are metabolized in the liver by complex hydroxylation, methylation, glucuronidation and sulphation reactions [16]. Their conjugated metabolites are released into the bloodstream and target extra-hepatic tissues; it is however understood that any excess of circulating conjugated flavonoid is reabsorbed by the liver and excreted with bile into the small intestine, subsequently being either re-hydrolysed and reabsorbed by enterocytes or excreted in the faeces [19].

Resveratrol is a polyphenol belonging to the class of stilbenes [20] with several reported beneficial effects for human health [8,9]. Resveratrol is found abundantly in purple grapes, red wine and other products derived from grapes, blueberries, gooseberries, blackberries and pomegranate [13,14]. Resveratrol appears to show high absorption rate but low bioavailability [21], possibly due to a range of bioconversion events involving hydroxylation [22], glycosylation, methylation [23], and hydrolysis [24], not only in the liver but also in other peripheral tissues.

The Influence of Plant Polyphenols in Signal Transduction Pathways

PP can act as receptor ligands, promoting interactions with various cell-signalling pathways, and disturbances in these pathways may be associated with the aetiology of chronic diseases. For example, the binding of dihydroxyflavone, a PP commonly found in flowering plants, to Tropomyosin Receptor Kinase (TRK) triggers autophosphorylation and subsequent activation of these receptors [25]. This particular signalling system not only is relevant for the activity of brain-derived factors for maintenance of neural tissue homeostasis, but also may be involved in neurodegeneration. The activation of the Adenosine Monophosphate-Activated Protein Kinase (AMPK) triggers intrahepatic fatty acid oxidation, inhibits lipogenesis and cholesterol synthesis, and modulates insulin secretion by pancreatic beta cells [26]; pathways constitutively activated as result of decreased energy availability for the cell [27].

It has been described that PP, including anthocyanins and others, can stimulate AMPK activation [13,28]; consequently, PP-AMPK interactions may be potential molecular targets for metabolic disarrangements.

The Mitogen-Activated Kinase (MAPK) and the Kinase Regulated by Extracellular Signals (ERKs) proteins are intracellular signalling proteins constitutively activated by various growth factors, leading to activation of pathways involved in control of proliferation, differentiation, survival, apoptosis and cell migration [25,29]. Flavonoids are known to interact with MAPK and ERKs [30], possibly modulating inflammatory mechanisms, and also likely to modulate the risk of metabolic disarrangements related to these pathways. ERKs belong to the superfamily of MAPKs, and are responsible for phosphorylation of the cyclic Adenosine Monophosphate (cAMP)-Responsive Element-Binding Protein (CREB) [25]. CREB is a transcription factor that recognizes the sequence of nucleotides located in its target genes, known as Cyclic AMP-Response Elements (CRE). CRE can be found in the regulatory regions of genes such as tyrosine hydroxylase, somatostatin, corticotropin-releasing hormone, as well as in genes involved in circadian rhythms such as the Period Circadian Protein Homolog 1 and 2 (PER1 and 2). When CREB binds to the CRE domain, the newly formed dimer acts as a transcriptional regulator of genes related to cell protection, modulated by the nuclear factor-erythroid 2-related factor 2 (Nrf2) pathway [25], which will be discussed in more detail later.

It is understood that CRE is responsive to resveratrol, but it does not present the very same level of response to other phytochemicals such as quercetin, curcumin and naringenin [31], which suggests not all PP can act as signalling molecules and activate CREB-mediated gene transcription. The effects of resveratrol in the positive regulation of CRE-mediated gene transcription, as well as its potential for transcriptional activation of CREB and Activating Transcription Factor 2 (ATF2) [31], suggest this polyphenol may have important functions in cell protection. The activation of Protein Kinase B (Akt) is induced by cAMP, which is also involved in the activation of the Exchange Protein Activated by cAMP (Epac1) [32,33]. It has been shown in High Fat Diet (HFD)-fed obese mice that resveratrol supplementation induces effects similar to those of calorie restriction, inhibiting the cAMP-degrading Phosphodiesterase (PDE) activity, as well as activating the cAMP-Akt pathway, leading to Epac1 activation [34]. Epac1 activation may provide protection against metabolic manifestations induced by obesity and glucose intolerance induced by diet.

Resveratrol administration to murine 3T3-L1 pre-adipocytes has not only increased the expression of the Sirtuin 1 (SirT1) gene and protein levels, but also reduced the expression of Survivin [35], a protein involved in inflammatory and apoptotic pathways and whose overexpression is positively related to tumour progression [36,37]. The modulation of AMPK, Akt and Survivin pathways by resveratrol suggests the possible therapeutic applications of PP in the prevention and possibly treatment of obesity and related metabolic disorders [35,38].

An *in vitro* study showed a dose response effect of resveratrol administration on differentiation of vascular smooth muscle cells, involving various signalling pathways. After low dose (3-5 μM) resveratrol, cell differentiation occurred via SirT1 and Akt activation, independently of AMPK. However, after higher dose (30 μM), the stimulus for differentiation occurred via a more complex signalling pathway, involving not only AMPK activation but also inhibition of the Mammalian Target of Rapamycin Complex 1 (mTORC1) pathway [39]. SirT1 and Akt activation induced by resveratrol improved insulin sensitivity and decreased the gene transcription and activity of pro-inflammatory proteins [40]. The inhibition of the mTOR pathway induced by higher doses of resveratrol is particularly relevant in obesity-associated metabolic disorders as this pathway is involved in a range of intracellular events, including regulation of gene transcription and protein translation, energy homeostasis, ribosome biogenesis and cell response to hypoxia [41].

HFD-fed mice supplemented with 0.1% resveratrol showed significantly increased mRNA expression of Uncoupling Protein 1 (UCP1), PGC-1α, Cytochrome C and Pyruvate Dehydrogenase [42]. In the same study, adipocytes harvested from these animals and incubated with resveratrol showed higher phosphorylation of AMPKα1 and increased fatty acid oxidation [42]. In another study with HFD-obese mice, 0.4% resveratrol supplementation significantly reduced the expression of key genes involved in adipogenesis, including Peroxisome Proliferator-Activated Receptor Gamma 2 (PPARγ2), Sterol Regulatory Element-Binding Protein 1c (SREBP-1c), Fatty Acid Synthase, Lipoprotein Lipase (LPL) and Adipocyte P2 Protein (aP2), as compared to control mice fed the HFD only [43]. Collectively, these results suggest resveratrol may ameliorate metabolic disarrangements induced by obesity.

As resveratrol increases the bioavailability of cytosolic cAMP, it amplifies signalling transduction cascades involving Epac1, Ca^{++}/calmodulin-dependent protein kinase kinase β (CaMKKβ) and AMPK. The Epac1/CaMKKβ/AMPK pathway is controlled by the SirT1/PGC-1α signal [34] and is known to regulate metabolic processes including energy metabolism, fatty acid oxidation, gluconeogenesis, mitochondrial biogenesis and respiration [27]. In a relatively small randomized double-blind crossover study involving obese men, resveratrol supplementation for 30 days increased Citrate Synthase activity in skeletal muscle, favouring mitochondrial metabolism via AMPK-SIRT1-PGC1α activation [44].

A combined *in vitro* and *in vivo* study showed that resveratrol treatment increased cAMP, SirT1, phosphorylated Protein Kinase A (pPKA), AMPK and SirT activity in HepG2 cells. In mice with induced hepatic steatosis, resveratrol administration reduced palmitate-induced lipid accumulation, increased fatty acid β-oxidation in harvested hepatocytes, and ameliorated hepatic steatosis, results partially attributed to induction of hepatocyte autophagy via activation of the cAMP-pPKA-AMPK-SirT1 signalling pathway [45]. In summary, these results suggest resveratrol may have a potentially preventative role, and possibly a therapeutic one, in the pathogenesis and manifestations of obesity, NAFLD, metabolic syndrome, T2D and cardiovascular disease. The effects of PP, obtained either from diet or supplementation, upon the modulation of metabolic disarrangements is a relatively new field of research worth of further detailed investigation.

Plant Polyphenols Modulate Inflammation and Oxidative Stress

Recent evidence suggests PP can influence gene expression by binding to specific transcription factors, influencing metabolic pathways related to the modulation of inflammation and Oxidative Stress (OS). The well documented NF-kB pathway, which transcribes pro-inflammatory mediators and is involved in various cell processes such as apoptosis and differentiation [46], is activated by a variety of endogenous and exogenous triggers of inflammation, including monosodium glutamate, fructose, alcohol, tobacco, glucocorticoids, Lipopolysaccharide (LPS), ultraviolet radiation, inducible Nitric Oxide Synthase, Cyclooxygenases 1 and 2 (COX-1 and COX-2), pro-inflammatory cytokines such as interleukin 1 (IL-1) and Tumour Necrosis Factor alpha (TNF-α) [47,48], and others.

Procyanidin, a potent PP belonging to the family of flavonoids and found in grape skin, grape seeds and green tea, appears to regulate NF-kB at various steps of its signalling cascade. In the earlier steps of this pathway, procyanidins may modulate IkappaB kinase activity as well as cytoplasmic retention of the dimer p65: p50. In the subsequent steps, procyanidins appear to inhibit the nuclear translocation of NF-kB pro-inflammatory dimers, and their subsequent binding to the promoter regions of target genes [49]. It has been demonstrated that microglial cells submitted to hypoxia and supplemented with resveratrol significantly decrease NF-kB activation and increase Brain-derived Neurotrophic Factor (BDNF) and IL-10 gene expression [50]. In a similar way, activation of the SirT transcription factor by resveratrol induces deacetylation of the NF-kB-p65 active dimer, inhibiting its binding to DNA, consequently suppressing the expression of cyclooxygenases, peroxidases and lipoxidases associated with various inflammatory pathways.

Fructose-fed diabetic rats treated with resveratrol showed decreased activity of the NF-kB-p65 molecular pathway, as well as attenuated OS, in heart tissue [51]. These results further suggest that the anti-inflammatory properties of PP appear to occur mainly via inhibition of the NF-kB pathway [52], with consequent reduction of gene expression, translation and secretion of several pro-inflammatory mediators. The Early Growth Response Gene-1 (EGR1) transcribes a superfamily of nuclear transcription factors named EGR-1 proteins, which act as modulatory factors for cell differentiation, mitogenesis, haematopoiesis, angiogenesis and tissue repair [53,54], but are also involved in carcinogenesis, atherosclerosis, liver fibrosis, OS and inflammation [54]. Turmeric is rich in curcumin, a PP known for its anti-inflammatory properties [55,56] and discussed later in this review. The main inflammatory signalling pathway inhibited by curcumin is believed to be the one controlled by EGR1 [55]. Curcumin is also believed to suppress the EGR1 gene activity by interruption of the ERK signalling pathway [53]. A study employing Caco-2 and HT-29 cells, which are non- and low-mucus producing colorectal adenocarcinoma cells, respectively, treated with curcumin showed reduced binding activity of the EGR1 transcription factor to its Epidermal Growth Factor Receptor (EGFR), which also functions as a responsive element to curcumin [53].

PP have been recently described as inhibitors of the gene expression of Oestrogen Receptor, EGFR and ERK, as well as modulators of ERK phosphorylation and modulators of the Phosphatidylinositol 3-kinase / Protein Kinase B (PI3K/Akt) pathway [57]. These pathways are involved in vital cell functions such as growth, proliferation, differentiation, mobility, survival and intracellular transport [57]. The Serine/Threonine Kinase PI3K/Akt pathway can be induced by OS, which in turn induces pro-inflammatory responses. However, the excessive activation of this pathway is linked to the pathogenesis of chronic diseases that feature a pro-inflammatory component, such as NAFLD, atherosclerosis and myocardial infarction [58].

The transcription pathway modulated by Nrf2 is an important mechanism employed by the cell to control OS levels. When bound to the Kelch-like ECH-Associated Protein (Keap1), Nrf2 is inactivated, sequestered in the cytosol and degraded via ubiquitin-proteasomes. Molecular insults of oxidative nature induce Nrf2 phosphorylation, which releases Keap1 for degradation by ubiquitin proteasomes, with subsequent translocation of the activated Nrf2 to the cell nucleus. Once in the nucleus, Nrf2 heterodimerizes with Small Musculoaponeurotic Fibrosarcoma (small Maf) proteins, facilitating its specific binding to the Antioxidant Response Element (ARE) promoter regions, transcribing antioxidant and phase II detoxifying enzymes that combat the original molecular insults [46,59,60]. OS levels modulate the activity of the Keap1/Nrf2 pathway, and more recently, it has been found this pathway

can also be activated by PP [61]. Because the Keap1/Nrf2 heterodimer induces the expression of detoxifying and antioxidant enzymes, PP supplementation could be relevant to minimize the biochemical disarrangements observed in the pathophysiology of obesity-associated inflammatory metabolic disorders.

In NAFLD for example, the activation of pro-inflammatory signalling pathways in hepatocytes due to translocation of lipopolysaccharides from the gut lumen, or due to the higher influx of pro-inflammatory cytokines secreted by the excessive amounts of adipose tissue, are some of the molecular mechanisms known to induce OS in various cell compartments [62]. In that regard, it is known that NF-kB can supress the transcription of ARE-dependent genes [46], and both Nrf2 and NF-kB compete for binding to the CREB. The upregulation of Nrf2 by PP may reduce the activity of the pro-inflammatory NF-kB [63], which reinforces the hypothesis that PP have relevant anti-inflammatory and anti-oxidant properties. PP may exert not only a direct effect stimulating the formation of the small Maf-Nrf2 dimer, but also pre-transcriptionally, activating kinases such as PI3K, p38, ERK, PKC and JNK, which in turn release the Nrf2 transcription off its inhibitory complex Keap1/Nrf2. It is understood PP not only can act in the ubiquitin-proteasome pathway inhibiting proteolytic degradation of the Nrf2 and thereby prolonging its half-life, PP can also promote Nrf2 translocation to the nucleus and its binding to ARE, consequently inducing the transcription of target genes [64,65].

The promoter regions ARE and Xenobiotic-Responsive Element (XRE) are found in various target genes regulated by Nrf2. Constitutively, Nrf2 binds to ARE and induces upregulation of anti-oxidant systems, whilst XRE is activated by the transcription factor Aryl Hydrocarbon Receptor (AhR), leading to the same effect [46]. Both harmful xenobiotics and PP, including resveratrol and curcuminoids, can lead to the activation of AhR. Consequently, PP consumption favours the elimination of xenobiotics and carcinogens such as dioxin, once all these molecules compete for binding to the AhR [66-70].

Resveratrol Supplementation in Obesity-Associated Metabolic Disorders

Recent evidence suggests that resveratrol, via its antioxidant and anti-inflammatory actions on various metabolic pathways, may positively influence outcomes associated with the management of obesity-associated metabolic disorders [71]. A meta-analysis study involving 388 individuals supplemented daily with doses ranging from 8 to 1,500 mg of resveratrol showed significantly improved glycaemic control and insulin sensitivity in the T2D participants included in the study [41]. A case-control study involving patients with uncomplicated T2D and patients with proliferative and non-proliferative diabetic retinopathy found significantly decreased levels of BDNF and Lipoxin A4 (LXA4), and increased IL-6, in relation to healthy control subjects [72]. Whilst IL-6 is pro-inflammatory, LXA4 is heavily involved in the resolution of inflammation. It is believed resveratrol supplementation may be employed as adjunctive therapy in T2D; several studies have found evidence of BDNF increased levels with resveratrol supplementation [50,73-75].

A randomised double-blind placebo-controlled study involving 50 NAFLD patients investigated the effects of 500 mg resveratrol supplementation for 12 weeks [76]. All participants were professionally advised to follow a lower calorie / lower fat diet and encouraged to adopt positive lifestyle changes, and a subgroup was additionally supplemented with resveratrol. Significant reductions in anthropometric markers and blood AST were found in both groups, but the resveratrol-supplemented group showed reduced ALT, pro-inflammatory cytokines, cytokeratin-18, NF-κB activity and lower steatosis, as compared to the participants receiving nutritional and lifestyle advice only [76]. This study showed that resveratrol supplementation in combination with nutritional and lifestyle advice was more effective than advice alone in reducing liver inflammation, steatosis and apoptosis.

A more recent placebo-controlled randomised clinical study, this time employing a higher dose of resveratrol for a longer period of time, was conducted with overweight individuals diagnosed with NAFLD and increased transaminases [77]. In this study, volunteers were given 1.5 g resveratrol supplementation daily for six months. Resveratrol supplementation promoted a small but statistically significant decrease in intrahepatic lipid content. On the other hand, resveratrol was ineffective in improving the other biomarkers of liver pathology, insulin sensitivity and metabolic profile measured. The authors also report adverse effects were seen in one participant [77]. The studies of [76,77] report different results regarding the outcomes of resveratrol supplementation in NAFLD, however it is worth highlighting specific methodologies employed for each study.

Although the results described above suggest a beneficial, and promising, effect of resveratrol supplementation for the management and treatment of obesity-related metabolic disorders, caution is advised regarding possible side effects. In a clinical study involving healthy individuals receiving a daily supplementation of 1 g resveratrol for four weeks, the activity of the Cytochrome P450 (CYP) isoenzymes CYP1A2, 2D6, 2C9 and 3A4 were measured through metabolism of its specific compound targets caffeine, dextromethorphan, losartan and buspirone, respectively [78]. It was found that resveratrol supplementation induced the activity of CYP1A2 but inhibited the activity of 2D6, 2C9 and 3A4. As the CYP isoenzymes metabolize over three quarters of the drugs

currently approved and commercially available for administration in humans [71], the aforementioned study of [78] suggests a relatively high dose of resveratrol has the potential to adversely affect drug pharmacokinetics and pharmacodynamics in a wide context. In light of such observation, due care is recommended when co-administering resveratrol and drugs due to the risk of altering drug bioavailability and efficacy.

Another possibly detrimental effect of resveratrol must be noted. The effects of resveratrol on hepatitis viral replication was investigated in an *in vitro* model employing hepatocellular carcinoma cells and in an *in vivo* model of hepatitis B. Resveratrol treatment was found to promote deacetylation of PGC-1α via activation of SirT1, subsequently increasing the transcriptional activity of PPAR-γ, which induced further replication of Hepatitis B virus (HBV) [79]. Similarly, the effects of resveratrol on Hepatitis C virus (HCV) replication potential was also investigated. Cultured hepatocytes infected with HCV and treated with resveratrol showed increased viral replication and reduced response to the antiviral drugs ribavirin and Interferon gamma (IFNγ) [80]. If these experimental results can be applied to humans, it may be suggested resveratrol supplementation could increase HBV and HCV replication and consequently exacerbate the manifestations of viral hepatitis. Substantial scientific evidence has so far demonstrated beneficial effects of resveratrol supplementation for metabolic diseases; however, resveratrol may not be recommended for the nutritional therapy of patients with hepatitis. The nutritional advice given to NALFD patients without viral hepatitis should carefully consider the resveratrol dosage and the supplementation period, and should always prioritize a nutritionally balanced diet.

Grape Polyphenol Supplementation in Obesity-Associated Metabolic Disorders

Resveratrol is found abundantly in purple and dark grapes, but the plant polyphenols normally found in grape extract, which comprises seeds, skin and juice, comprise a mixture of other compounds including phenolic acids, anthocyanins, quercetin, myricetin, and other flavonoids in various concentrations [81,82]. It is therefore reasonable to suggest that the health benefits attributed to the consumption of grape-derived products are the result of a combined effect of all the polyphenols consumed, rather than resveratrol alone. In that regard, the effects of grape polyphenols on cardiovascular function have been the aim of substantial research in recent times. A double-blind study involving men with metabolic syndrome and supplemented with a freeze-dried grape polyphenol powder or a placebo for 30 days showed that the supplemented group had reduced levels of cell adhesion molecules, as well as improved vascular function and blood pressure, at the end of the supplementation period [83]. A meta-analysis which evaluated 572 articles and filtered out 24 clinical studies for further analysis demonstrated that supplementation with grape polyphenols at daily doses ranging from 150 mg to 1400 mg significantly reduced systolic blood pressure, but to a lower extent than antihypertensive medications [84].

Blumberg et al. [85] conducted a literature review appraising studies which investigated the effects of pure grape juice of the Concord cultivar, and compared these results to other studies which investigated similar effects, but this time induced by a wider range of polyphenol-rich foods and drinks. The authors found associations between Concord grape polyphenol intake and improved flow-mediated vasodilation, blood pressure, platelet aggregation, and also a positive association with resistance of LDL-cholesterol to oxidation [85]. Grape polyphenols appear to have beneficial effects on different constituents of metabolic syndrome, reducing glycaemia, pro-inflammatory biomarkers and LDL oxidization, as well as preventing plasma postprandial oxidative stress and increasing total antioxidant capacity [86]. The daily doses of grape seed extract often used in clinical trials were in the range of 150 to 600 mg/kg, which appeared to be powerful enough to promote positive outcomes for the metabolic syndrome sufferers included in those investigations [86].

Olive Oil Supplementation in Obesity-Associated Metabolic Disorders

Olives are known for their antioxidant properties and rich composition of polyphenols, including flavonols, lignans, glycosides, hydroxytyrosol and several phenolic alcohols [87,88]. The antiobesogenic and antidiabetic properties of olive oil, which is considered a major ingredient of the traditional Mediterranean diet, have been investigated in several epidemiological studies and clinical trials. [89] observed in a Spanish population-based study a lower incidence of obesity in individuals who consumed proportionally more olive oil and less sunflower oil, in relation to the opposite, over the course of six years. A study involving overweight non-insulin-treated T2D patients found that the ingestion of polyphenol-rich extra-virgin olive oil equivalent to 577 mg of phenolic compounds / kg of body weight (BW) for 4 weeks significantly reduced fasting plasma glucose, HbA1c, serum visfatin, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT) and Body Mass Index (BMI) [90].

Biomarkers of cardiovascular function have also been investigated in studies on olive oil. For example, [91] investigated the effects of polyphenol-rich olive oil supplementation for 3 weeks on LDL cholesterol, apolipoprotein B-100 (ApoB-100) and atherogenicity, measured as number of small LDL particles and LDL oxidizability, in a controlled trial involving healthy men. Atherogenesis biomarkers, ApoB-100 and Very Low-Density Lipoprotein (VLDL) were significantly lower, and LPL gene

expression was significantly higher, in the group supplemented with polyphenol-rich olive oil. There appears to be, however, a dose-dependent effect. In a randomized double-blind crossover-controlled trial, [92] supplemented 33 hypercholesterolemic, but otherwise healthy, volunteers with 25 mL/day of a standard raw virgin olive oil (80 ppm of phenolic compounds), virgin olive oil enriched with its own polyphenols (500 ppm), and virgin olive oil enriched with its own polyphenols plus thyme polyphenols (totalling 500 ppm). Volunteers who received olive oil enriched with its own polyphenols, as well as those who received olive oil enriched with its own polyphenols plus thyme polyphenols, improved their lipoprotein subclass profile, decreased the total LDL particle/total High-Density Lipoprotein (HDL) particle, small HDL/large HDL, and HDL-cholesterol/HDL-P ratios, and decreased the lipoprotein-to-insulin resistance index after 3 weeks of supplementation.

Curcumin Polyphenols in Obesity-Associated Metabolic Disorders

Curcumin, a yellow-orange plant polyphenol found in turmeric, has drawn attention for its antioxidant, anti-inflammatory, hypoglycaemic and neuroprotective properties [93]. The effects of 500 mg or 750 mg curcumin daily supplementation for 12 weeks on protein oxidation and BDNF levels were tested in a controlled trial involving 40 non-diabetic obese men [94]. Despite not having any effect on BDNF serum levels, curcumin decreased protein oxidation at the end of the trial. In another study employing 1 g curcumin daily supplementation for 8 weeks in a group of metabolic syndrome sufferers, adiponectin levels were significantly increased and leptin significantly decreased at the end of the supplementation period [95].

The effects of curcumin supplementation on NAFLD have been investigated in a randomized double-blind placebo-controlled study. NAFLD patients who received daily doses of 70 mg curcumin for 8 weeks showed significantly reduced BMI, total cholesterol, LDL-cholesterol, triglycerides, AST, ALT, glycaemia, HbA1c and liver fat content as compared to the control group [96]. In a trial involving nephropathic diabetic patients, turmeric oral supplementation equivalent to 22.1 mg curcumin daily for 2 months reduced proteinuria, IL-8 and Transforming Growth Factor-Beta (TGF-β) without observed side effects [97].

A meta-analysis of randomized controlled trials found reduced IL-6 levels following curcuminoid supplementation [98]. This study did not suggest a significant association between circulating IL-6 and the alleged beneficial effects of curcuminoids related to supplementation dose or duration; however, a significant association between the IL-6-lowering effects of curcumin and IL-6 concentration at baseline was found. The authors suggest the positive effects of curcumin lowering IL-6 may be more evident in individuals with the highest levels of systemic inflammation. On the other hand, a systematic review and meta-analysis of randomized controlled trials found that curcumin supplementation did not influence serum total cholesterol, LDL-cholesterol, triglycerides and HDL-cholesterol levels [99]. This review considered heterogeneous populations and concluded that further trials involving specific target populations are necessary for a more conclusive opinion.

Ginkgo biloba Polyphenols in Obesity-Associated Metabolic Disorders

Ginkgo biloba extracts (GbE) have been traditionally used in the prevention and treatment of several chronic diseases, mainly due to its attributed antioxidant, anti-inflammatory, vasodilator, cardioprotective and antiedematogenic properties [100-105]. Standardized GbE contains in average a mixture of flavonoids, terpenes, bilobalides and ginkgolides, along with less than 5 ppm of ginkgolic acids, which are toxic [105,106] More specifically, GbE flavonoids are recognized as antioxidants, bilobalides are believed to present anti-apoptotic, anti-inflammatory and neuroprotective properties, and ginkgolides may play an inhibitory role on the Platelet-activating Factor [107]. It has been suggested that GbE may reduce glycaemia and insulin resistance. [108] observed that the daily intake of 120 mg of standardized GbE for 3 months significantly stimulated pancreatic β-cell function and insulin production by humans with normal glucose tolerance. The same protocol of treatment was able to reduce glycated haemoglobin in T2D patients, without affecting other parameters involved in glucose metabolism [109].

In a rodent model of diet-induced obesity, [110] observed that daily supplementation of GbE at 500 mg / Kg BW for 2 weeks increased Insulin Receptor Substrate 1 (IRS-1) and Akt phosphorylation levels, followed by inhibition of the Protein Tyrosine Phosphatase 1B (PTP-1B) - an inhibitory protein of the insulin signalling pathway - in gastrocnemius muscle. The authors also observed reduced food intake and body adiposity, as well as improved serum lipid profile, at the end of the supplementation period [110]. Another study from the same group [111] employing similar experimental procedures found reduced visceral adiposity, lowered NF-κB-p65 phosphorylation, increased insulin receptor (IR) and Akt phosphorylation in the retroperitoneal adipose tissue of diet-induced obese rats after GbE supplementation [111]. GbE supplementation was also effective in stimulating the gene expression of adiponectin receptor AdipoR1 and IL-10, with a concomitant reduction of TNF-α gene expression [111].

The anti-inflammatory properties of GbE have been investigated both *in vitro* and *in vivo*. GbE was found to significantly

reduce the nuclear translocation of NF-kB-p50 and NF-kB-p65, which are involved in the synthesis of pro-inflammatory cytokines, such as TNF-α and IL-6 [112,113]. Similarly, the potential for GbE in reducing body fat accumulation has been observed. [114] described a potential lipolytic effect of GbE flavonoids due to their inhibitory effect on the cAMP-phosphodiesterase complex in epididymal adipose tissue of rats. [115] demonstrated that GbE biflavones stimulated lipolysis in 3T3-L1 adipocyte cell culture. Taken together, these results suggest that GbE supplementation is associated with improved insulin signalling as well as suppressed pro-inflammatory pathways. Such findings highlight a potential for GbE as a possible therapeutic tool for the prevention and management of obesity-associated metabolic disorders. Notwithstanding, the lack of more significant studies in human populations, also investigating chronic use, side-effects and risks associated with toxicity, warrant further investigations.

Green Tea Polyphenols

The main compounds of Green Tea (GT) (*Camellia sinensis*) solid extracts are polyphenols belonging to the large family of catechins, the most studied ones including Epigallocatechin-3-Gallate (EGCG), Epicatechin (EC), Epigallocatechin (EGC) and Epicatechin-3-Gallate (ECG). The concentration of GT bioactive compounds can vary significantly depending on various factors, for example origin of the plant, infusion time and water temperature, but in average approximately 50 to 100 mg of catechins can be found in a typical 250 mL cup of green tea [116]. Lipid-lowering and anti-obesity properties have been attributed to GT catechins, due to their alleged effects on reducing lipid emulsification and absorption, also suppressing lipogenesis and adipogenesis [117]. Previous studies have discussed the alleged properties of GT extract upon modulation of cardiovascular function, obesity and oxidative stress [118-120].

A randomized double-blind placebo-controlled crossover study involving healthy individuals tested the effects of daily supplementation for 4 weeks with 100 mg epicatechin on cardiovascular function and insulin response [121]. Whilst epicatechin supplementation showed no significant effect on fasting blood glucose levels, lipid profile, systolic blood pressure, nitric oxide plasma levels, endothelin 1 and arterial stiffness after 4 weeks of supplementation, it did show an improvement on insulin sensitivity [121]. The effects of GT extract supplementation for eight weeks, combined or not with a programme of physical activity, were investigated in a double-blind placebo-controlled study involving overweight or obese women [122]. At the end of the supplementation intervention period, the authors observed that exercise combined with GT supplementation was more effective in reducing body fat, waist circumference, plasma triglycerides, as well as increasing resting metabolic rate, lean body mass and muscle strength, as compared to the exercised group supplemented with placebo [122].

Studies involving GT polyphenols and low-calorie diets have also been conducted. A randomized double-blind placebo-controlled study involving obese premenopausal women investigated the association between a low-calorie diet and 300 mg EGCG daily supplementation for 12 weeks. EGCG associated with the low-calorie diet was not more effective in reducing body weight, adiposity, insulin resistance, lipid profile and inflammatory biomarkers than the low-calorie diet alone [122]. However, another study following a different protocol found evidence of weight loss after EGCG supplementation: [124] conducted a randomized double-blind placebo-controlled clinical study involving women with central obesity supplemented for 12 weeks with 856.8 mg EGCG, a dose much higher than the one employed in the study of [123]. [124] found increased weight loss and reduced waist circumference in the EGCG supplemented group, as compared to its respective placebo group. Reduced plasma ghrelin and increased adiponectin were also found.

Consensus regarding the effects of EGCG supplementation on metabolism is yet to be reached. A randomized placebo-controlled trial involving overweight and obese individuals investigated the combined effects of 282 mg EGCG and 80 mg resveratrol daily supplementation for 12 weeks [125]. The authors found no changes in plasma metabolic biomarkers, nor changes in insulin-stimulated glucose disposal, gluconeogenesis, lipolysis markers, energy expenditure or total body fat between the groups. However, a tendency for visceral fat reduction was seen in the supplemented group, as well as smaller increase in plasma triglyceride induction after a fasting-high fat refeeding meal, in relation to the respective control group [125].

The biochemical properties of *Camellia sinensis* have been described in the scientific literature; however, it is not yet fully understood whether its supplementation could lead to, or exacerbate, liver damage. Cases of hepatotoxicity associated with GT extract intake have been reported [126]. These rare cases were often individuals consuming high doses of GT extract for prolonged period of time, or in combination with synthetic drugs, or in cases of previously established liver disease. It remains unknown whether the observed cases of liver damage could be attributed to the consumption of GT extract exclusively, or to a competitive mechanism of biotransformation between drug and phytochemical, or due to tissue incompetence, for example in liver disease [127].

A systematic review investigated the affinity of GT extract with various isoforms of the CYP microsomal complex, their possible interactions with drugs and the risks associated with drug-induced liver injury [128]. It has been highlighted that despite a

weak association between GT extract and the risk of drug-induced liver injury, GT catechins may promote partial inhibition of some CYP isoenzymes responsible for detoxification reactions of phase I, and that the bioavailability of some drugs metabolized by CYP3A4 has increased when administered in combination with GT extract, which could potentially increase their concentration to toxic levels [128].

Therefore, despite the low prevalence of hepatic toxicity associated with GT, considering the worldwide popularity of this herbal tea, health professionals should always consider an individualized approach for the evaluation of benefits and potential side effects of herbal medicine therapies. Particular consideration is due to patients who already have chronic liver disease in the Child-Pugh classes B or C range. The scientific evidence so far available is not yet sufficient to assertively prove or disprove the safety and beneficial effects of GT polyphenols on management and or treatment of obesity and obesity-associated metabolic disorders.

Directions for Future Work and Final Considerations

Despite the elucidation of several molecular pathways activated or inhibited by isolated plant polyphenols, some of them briefly discussed in this review, the exact mechanisms on how other nutrients, alongside other blood borne factors, influence the molecular effects of polyphenols are yet to be fully understood. Several investigations suggest that the metabolic effects associated with the consumption of polyphenol-containing foods are not limited to a single polyphenol only, but to a mixture of compounds, which further suggests a combination of polyphenolic agents with antioxidant properties may have a potential therapeutic approach. In light of that, as new therapeutic interventions take significant time to reach the general population, the development of additional supporting strategies, including nutritional interventions that can target specific molecular pathways affected in metabolic disorders, offers a new and promising therapeutic avenue.

The successful prevention of obesity and obesity-associated metabolic disorders is heavily dependent on a range of healthy and positive lifestyle choices, including active lifestyles and healthy diets. Such diets include low consumption of ultra-processed foods and contain naturally occurring sources of flavonoids and resveratrol, as well as antioxidant nutrients such as vitamins and trace elements, found in broad variety of fruits, vegetables, whole grains, beans and seeds. If an obesity-associated metabolic disorder develops, either as consequence of biochemical disturbance or chronic positive energy balance, the prescription of complementary nutritional therapeutics should follow similar principles, which are based on the prescription of nutritionally adequate diets and lower consumption of ultra-processed foods, in combination with supplementation, when justified.

Despite the widely publicised promising effects of plant polyphenols as therapeutic options in metabolic disorders, a careful evaluation of the benefits and risks of plant extract supplementation, be it in pharmacological doses or doses higher than those found in naturally occurring foods, is mandatory. As adverse effects have already been described after phytochemical supplementation, the risk of toxicity should be always considered. This consideration is even more relevant where patients are being treated with multiple allopathic medicines, in which the risk of metabolite interaction can alter the pharmacokinetics and pharmacodynamics of all compounds administered. Phytochemicals and nutraceuticals can compete with other substrates for the same cytochrome P450 isoforms, and therefore their inappropriate prescription may jeopardize patient's health.

Due to the heterogeneity of the clinical studies so far conducted, which are understandably different in experimental procedures, frequency and duration of interventions, and specific inclusion criteria, for example severity of obesity and associated co-morbidities, the safe recommendation of the phytochemicals briefly discussed here has not yet been established. The patient's genetic background, for example their ethnicity or the presence of Single Nucleotide Polymorphisms, as well as their microbiome and phytochemical bioavailability, are additional confounding factors that should be considered when assessing the applicability of clinical trials and the interpretation of findings to real life scenarios. Therefore, nutritional interventions for the prevention and management of obesity and associated co-morbidities should address first the intake of a quantitatively and qualitatively adequate diet, which provides natural sources of dietary polyphenols including flavonoids and resveratrol. The recommendations for a healthy diet should be encouraged before the prescription of isolated phytochemical supplementation.

Ethical Statement

Not applicable as no ethical issues regarding this desk-based study have been identified

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Authors' Contributions

All authors contributed to the design, literature appraisal, critical discussion and conclusions of the study. Dr Passos and Dr Bueno were also involved in write-up and layout of the manuscript. All authors share equal responsibility for the contents of the manuscript.

Conflict of interest

None of the authors have any conflict of interest to disclose.

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