REVIEW

Put "gender glasses" on the effects of phenolic compounds on cardiovascular function and diseases

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Abstract

Introduction The influence of sex and gender is particularly relevant in cardiovascular diseases (CVD) as well as in several aspects of drug pharmacodynamics and pharmacokinetics. Anatomical and physiological differences between the sexes may influence the activity of many drugs, including the possibility of their interaction with other drugs, bioactive compounds, foods and beverages. Phenolic compounds could interact with our organism at organ, cellular, and molecular levels triggering a preventive action against chronic diseases, including CVD.

Results This article will review the role of sex on the activity of these bioactive molecules, considering the existence of sex differences in oxidative stress. It describes the pharmacokinetics of phenolic compounds, their effects on vessels, on cardiovascular system, and during development, including the role of nuclear receptors and microbiota.

Conclusions Although there is a large gap between the knowledge of the sex differences in the phenolic compounds' activity and safety, and the urgent need for more research, available data underlie the possibility that plant-derived phenolic compounds could differently influence the health of male and female subjects.

Keywords Phenolic compounds · Sex–gender · Microbiota · Cardiovascular diseases

Introduction

Until now, women have been underrepresented or excluded in medicine, except in the field of female reproduction, leading the male body to be considered the "norm". Currently, there are relevant clinical examples of the impact of the variables sex (biological differences between males and females in terms of genetics, epigenetics, endocrinology, etc.) and gender (sociocultural aspects), including cardiovascular diseases (CVD), diabetes mellitus, autoimmune diseases, and

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alcoholism ([1, 2] and cited literature). As it is very difficult to separate sex and gender because of their multiple and varied interactions in the time and in different countries and societies, the simultaneous use of the two terms is more appropriate. The influence of sex and gender is particularly relevant in CVD [3, 4] as well as in several aspects of drug pharmacodynamics and pharmacokinetics [5]. There are, in fact, numerous anatomical and physiological differences between the sexes (body dimension and composition, gastric and intestinal differences, metabolism, renal functions) that may influence the activity of many drugs, including the possibility of their interaction with other drugs, bioactive compounds, foods and beverages [6].

Although investigations on sex-related differences have recently increased, and sex and gender are pivotal determinants of health [3], the awareness of their relevance and importance is still lacking. Little is known, for example, about the influence of sex and gender on the imbalance between oxidants and antioxidants, i.e., the so-called oxidative stress [7], although some sex differences have emerged [4, 8, 9].

Oxidative stress is a known hallmark of many diseases, including CVD (ischemic diseases, cardiac hypertrophy,

stroke, etc.), and cardiovascular risk factors (CVR), such as hypercholesterolemia, hypertension, diabetes, and atherosclerosis [10, 11]. Moreover, it is important to recall that cardiovascular homeostasis depends on the balance between the generation of nitric oxide (NO) and reactive oxygen species (ROS): NO has beneficial effects against damage induced by ROS, and vice versa, ROS reduces the effect of NO [11].

Oxidizing agents include $O_2\cdot$, peroxynitrite, hydroxyl radicals, and non-radicals, such as hydrogen peroxide (H_2O_2). They are physiologically generated intracellularly, extracellularly, or in specific intracellular compartments [12] through the activity of numerous enzymes, such as xanthine oxidase, cyclo-oxygenases, lipo-oxygenases, myeloperoxidases, cytochrome P450 mono-oxygenases (CYP), uncoupled NO synthase, peroxidases, and NADPH oxidase [12]. However, the human body has evolved different physiological defences against ROS [7], including superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione transferases (GST), albumin, bilirubin and glutathione (GSH) [8], which act as ROS scavengers. In addition, ROS activate the intracellular molecular pathway of Nrf2/ARE-mediated antioxidant gene expression [7, 13]. However, under pathophysiological conditions, production of ROS might exceed the natural antioxidant defence of the cells. Although oxidative stress plays a crucial role in CVD, antioxidant therapy with supplements of micronutrients, such as vitamin E, has not resulted, to date, in a clear efficacy in the prevention of CVD [14, 15]. Notably, some authors report a slight elevation in the risk of angina pectoris [14].

Another class of food-derived bioactive molecules that acts as antioxidants and thus may have health benefits for CVD is phenolic compounds, which are a ubiquitous class of secondary plant metabolites. Some phenolic compounds are responsible for colour and others for the organoleptic properties of fruits and vegetables. The potential health benefits of phenolic compounds are attributed, in part, to their antioxidant activity [16, 17]. In vitro, they scavenge O_2 as well as hydroxyl, peroxyl, alkoxyl radicals, and NO [18], and some of them may also chelate transition metal ions, inhibiting the iron- and copper-catalysed formation of initiating radical species [18]. However, phenolic compounds act through multiple pathways and may interact with different cellular functions at concentrations much lower than that required for effective antioxidant activity [19]. In brief, phenolic compounds bind to both oestrogen receptors (ER), ERα and ERβ [19, 20]. Regrettably, very few papers have addressed the effects of these substances on the androgen receptor (AR) [21].

There are evidences, although not unequivocal, that link high consumption of fruits and vegetables to a lower risk of CVD [22–25]. Multiple factors could be used to explain the heterogeneity of the results in the literature, and among them, are the gut microbiome, body mass index, age, genetics, the country where people live and the sex [26–29].

The goal of this review is to demonstrate the effect of sex on the activity of these bioactive molecules.

Phenolic compounds

Phenolic compounds classification

Phenolic compounds are among the most important and abundant phytochemicals in plants and are found in many foods and beverages, such as beverages made from fruits, vegetables and chocolate, as well as in coffee, tea, beer, and wine ([30] and cited literature). Chemically, phenolic compounds are characterized by one or more phenolic rings and are classified into different groups (mainly flavonoids, phenolic acids, stilbenes and lignans) as a function of the number of phenol rings that they contain as well as of the structural elements that bind these rings to others [31] (Fig. 1). In plants, phenolic compounds are mainly conjugated with sugars, forming glycosides. The most studied class, due to its potential and preventive role in degenerative diseases, is that of flavonoids, which are characterized by two aromatic rings connected through an oxygenated heterocycle (Fig. 1). They can be further subdivided into six main subclasses, isoflavones, flavones, flavanols, flavanones, anthocyanidins, and flavonols (catechins and proanthocyanidins) ([30] and cited literature), which differ in the characteristics of the heterocyclic ring.

Sex-dependent bioavailability of phenolic compounds

In foods and beverages, phenolic compounds are mainly stored as a glycone or, mostly, as glycosidic conjugates. In the organism, they are widely metabolized [32]. Briefly, their metabolism starts in the oral cavity, where they come into contact with saliva and bacteria, which may possess glycosidases that induce hydrolysation of glycosylated phenolic compounds [33]. In the intestine, they are further hydrolysed [34] by lactase phlorizin hydrolase and by β-glucosidases of intestinal bacteria (microbiome; the importance of sex on microbiome is described below). The resulting aglycones generally enter into the enterocyte by passive diffusion. However, some particular flavonoids might also be transported into intestinal epithelial cells by the active sodium-dependent glucose transporter SGLT1 and hydrolysed inside the cell by a cytosolic β-glucosidase [35]. Furthermore, some phenolic compounds, such as genistein and daidzein, can also be biotransformed by CYP, which are responsible for the oxidative metabolism of various and numerous endogenous and exogenous
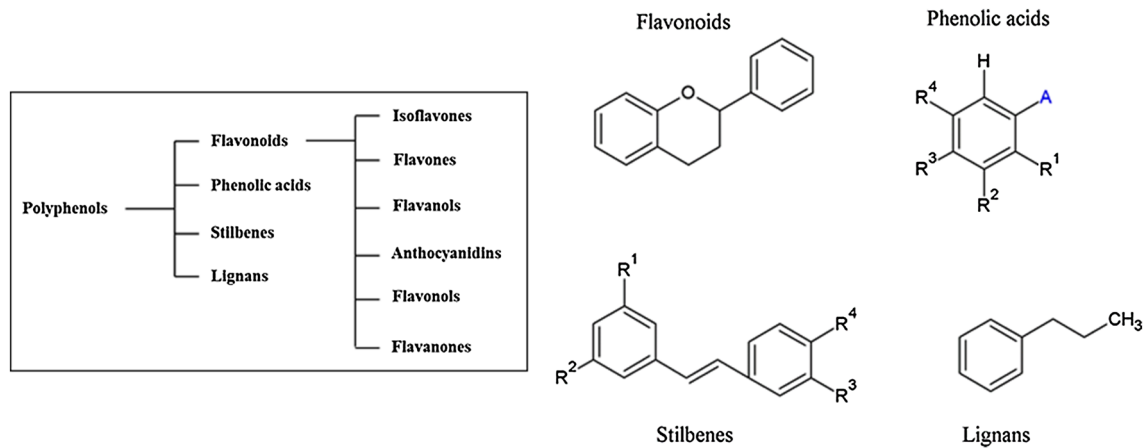
Fig. 1 Plant phenolic compounds' chemical classification and general structure. In phenolic acids, residue A should be represented by a hydroxycinnamic, a hydroxybenzoic or an aldehyde residue

molecules. It is well-known that some CYPs are differently expressed in males and females: CYP2B6, CYP2A6, and CYP3A have higher activity in women than in men, while CYP2D6, CYP2E1, and CYP1A2 have slightly higher activity in men than in women ([5, 36, 37] and the references therein). The activity of CYP can be regulated by inhibitors and inducers, including nuclear receptors, such as constitutive androstane receptor (CAR), and pregnane X receptor (PXR), and peroxisome proliferator-activated receptor α (PPARα) [38]. CAR also regulates phase III transporters, such as multidrug resistance-associated proteins 2 and 3. Interestingly, androgens seem to inhibit CAR, and CAR mRNA expression is greater in females [39]. CAR-regulated CYP2B6 has higher activity in women than men and is especially higher in Hispanic females than Caucasian or African–American females [40]. In addition, genetic polymorphisms appear to be sex-specific. For example, the 1459C>T SNP and intron-3 15582C>T SNP are associated with the lowest level of CYP2B6 activity in the livers of females [40]. The above findings suggest the importance of sex and ethnicity in the regulation of CYP2B6 polymorphism. The effects of rutin, myricetin, quercetin, isorhamnetin, *p*-coumaric acid, gallic acid, and caffeic acid on CYP1A, CYP2A, CYP2E1, and CYP3A are sex-related. In female pigs, rutin, myricetin, quercetin, isorhamnetin, *p*-coumaric acid, gallic acid, and caffeic acid mainly inhibit the activity of CYP1A. Quercetin inhibition of CYP1A is not sex-dependent, but quercetin-induced inhibition of CYP2E1 only occurs in male pigs. Regarding CYP3A activity, myricetin only inhibits CYP3A in male pigs, whereas isorhamnetin is a competitive inhibitor of CYP3A activity in both sexes [41]. In humans, the sex effect is less clear [42]. Finally, it is relevant to recall that phenolic compounds may regulate the activity of transcription factors. In vitro, genistein,

daidzein, and equol can activate human and mouse PXR, with equol being more active compared to human PXR [43].

Another important aspect is that phenolic compounds can interact with the pharmacokinetics of endogenous and exogenous compounds, including drugs [44, 45]. The above results indicate that at least isoflavones may modify the metabolizing activity of CYP in a sex-dependent manner. Thus, more detailed investigations are needed, because many individuals combine drugs and isoflavone-containing supplements.

The aglycones are biotransformed by conjugation (phase II of metabolism) in the small intestine and in the liver. With only a few exceptions, the metabolism of dietary phenolic compounds leads to plasma conjugates (glucuronates or sulphates, with or without O-methylation). Rats, mice and humans differ in plasma metabolites after ingestion of phenolic compounds [46]. Moreover, the levels of these metabolites are also influenced by sex. In particular, in male rats, the main molecule is represented by disulphates, followed by 7-sulpho-4′-glucuronides, while female rats have a higher concentration of 7-glucuronides [46]. The conjugation with glucuronic acid occurs via numerous tissue-specific families of UDP-glucuronosyltransferases (UGTs) ([30] and cited literature). There is some evidence that some UGTs, such as UGTA1, may be influenced by sex [47]. For example, UGT2B17 is more expressed in men than women ([30] and cited literature); therefore, potentially, phenolic compounds might be more conjugated in males than females. In humans and animals, UGTs are induced by foods, such as citrus fruits [48], cruciferous vegetables [49], and soy (e.g., genistein) [50]. Consequentially, increased ingestion of these foods may lead to variable UGT activity, altering substrate metabolism. UGTs are also activated by the aryl hydrocarbon receptor (AhR), hepatocyte nuclear factor 4

alpha, CAR, and PXR [47]. In rodents, their activity seems to depend on steroid hormones [51]. In particular, AhR modulates ERα and ERβ and AR [52]. For example, AhR, which regulates the UGT1A gene, may interact with ERα, suppressing CYP1A1 transcription [53, 54].

Sulphate conjugation occurs through sulphatases (SULTs), which belong to two families: SULT1 and SULT 2. SULT1A enzymes preferentially metabolize phenolic substrates [55] and are regulated by PPARα, RXR, CAR, vitamin D receptor, farnesoid X receptor, retinoid-related orphan receptors, ERs, and oestrogen-related receptors (ERR) [55]. Sex plays a role in the activity of SULTs, and some isoforms are oestrogen-dependent, suggesting a variation in their activity during the menstrual cycle or oestrous phase. Indeed, in rodents, oral bioavailability of genistein appears to be dependent on the oestrous phase and ovariectomy: in ovariectomized female rats, oestrogen administration reduces the oral bioavailability of genistein, mostly via increased sulphation ([30] and cited literature). In the mouse liver, sulphation is more efficient in the female liver versus male liver, with the exception of SULT1c1, which is dominant in male mice [56]. The opposite is observed in rats [57].

Catechol-*O*-methyltransferase (COMT) plays a role in methylation, a metabolic pathway that is implicated in the metabolism of epigallocatechin and quercetin [58, 59]. Notably, COMT has lower activity (approximately 25%) in women than in men ([30] and cited literature). Considering the sexual dimorphism in COMT activity, sex differences in methylation could be plausible.

Some conjugation reactions might also involve GSH. These reactions may occur either spontaneously or be catalysed by GST [60]. Sex-specific (female mice more than male mice) induction of GST is observed with the flavone 2-phenyl benzopyrone, but not with morin, naringenin, catechin, and quercetin. Notably, the effect depends on the isozyme [61]. Sex differences are also present in the rat liver, which displays a higher expression of GST in males than in females [62]. Finally, phenolic compounds may be subjected to enterohepatic transport in the bile [63].

Some sex differences are observed in daidzein metabolism. Daidzein can be biotransformed in equol ([30] and cited literature). However, this does not occur in all humans (on average, 30–35% among the Caucasian population). Relevantly, after 15 days of soy ingestion, only women develop the capacity to metabolize daidzein into equol ([30] and cited literature), which is more active than daidzein. This is in line with the results of a 2-year study in postmenopausal women. In particular, a major hypocholesterolemic effect is found in women who produce equol versus non-producers. Beyond equol, *O*-desmethylangolensin can also be produced, and its plasmatic level is higher in men than women [64].

Recently, it has been shown that the activity of some transcription factors may be influenced by circadian rhythms, which in turn, are influenced by sex [65], suggesting the importance of timing on the influence of sex on the metabolism of phenolic compounds.

Excretion of conjugated phenols occurs via renal (7–30%) and biliary (10%) routes ([30, 66] and cited literature). Sex differences are described for some molecules that are eliminated via the renal route: adult female rats eliminate a higher amount of the mono-glucuronoconjugate than mono-sulphoconjugate of apigenin after oral intake [67]. The basal urinary and plasma total phenolic contents are lower in women than in men [68]. Indeed, during 1 month of daily soy ingestion, women initially excreted more isoflavone conjugates in urine than men, but they also experienced a progressive decrease in urinary excretion of genistein and daidzein, unlike men [69]. Urinary isoflavone excretion following ingestion of different soy foods has been examined by Faughnan et al. [70]: they observed that women eliminate more genistein after higher ingestion of soy milk versus textured vegetable protein, while urinary excretion in men is not influenced by the food matrix. Urinary daidzein excretion does not depend on sex or on the food matrix. Finally, equol excretion (in equol producers) requires the food matrix to be higher following textured vegetable protein intake. Because women have lower renal excretion versus men [5], it is plausible that renal excretion of phenolic compounds occurs in a sex-specific manner. Thus, isoflavone metabolism and disposition are affected by the duration of soy ingestion in women, but not in men.

In conclusion, the awareness of bioavailability, metabolism, distribution and excretion of these compounds in humans should be clearly established and linked with their biological effects. The interindividual variability in their pharmacokinetics suggest an interindividual variability in biological response, but interindividual variability in efficacy has been little explored [71, 72]. The understanding of inter-individuality is necessary to clarify their role in well-being and health.

Phenolic compounds effects from a sex perspective

Effect on vascular function

The effect of genistein and quercetin on blood pressure was recently reviewed [73, 74]; however, the effect of sex was not analysed. Nevertheless, some sex differences have been described in animals and humans. In short, genistein (600 mg genistein/kg food for 4 weeks) reduces systolic blood pressure, pulse pressure, and cardiac work only in female normotensive mice [75]. The inhibitory effect of the endocannabinoid: anandamide on the contractility induced by noradrenaline is only potentiated by oral genistein in

female rats [76]. This effect is prevented by the concomitant administration of the oestrogen receptor antagonist fulvestrant. Phenolic compounds of red wine relax aortic rings, especially in female rats [77], this action is linked with redox-sensitive PI3-kinase/Akt-dependent NO-mediated relaxations, which is higher in the aorta of female than male aorta [77]. In rabbits, genistein and daidzein inhibit the formation of neointimal cells, and genistein is more active in male aortic rings [78].

A recent meta-analysis that included subjects supplemented with flavanols from 18 randomized studies (9 trials enrolled men and women, while 5 and 4 studies included only males and only female subjects, respectively) demonstrates that there are significant decreases in blood pressure, fasting plasma glucose, total cholesterol, low-density lipoproteins, and triglycerides, whereas high-density lipoproteins were significantly increased. A comparison of studies that enrolled only men or only women is inconclusive due to the low number of subjects [79].

The supplementation with flavonoids seems to improve vascular function and reduce reactive protein C, VCAM, and E-selectin, whereas the plasma NO concentration is higher, especially in men with an increased risk of CVD [80]. The SU.VI.MAX study demonstrates that there is an inverse relationship between flavonoids present in the diet and blood pressure in women [81]. These discrepancies could be attributed to the limited consumption of soy in Western populations, to short-term and small-size studies, to ethnicity, and to pharmacokinetics. For example, only 25% of non-Asians and 50% of Asians lack the intestinal bacteria that convert daidzein into equol [82], and it has been reported that individuals who do not have these bacteria may benefit from soy consumption [83]. However, other studies suggest that subjects that are able to produce more equol are more sensitive to the beneficial effects of isoflavone ingestion [84].

Uric acid is the major antioxidant of plasma and hydrophilic environments and is also able to propagate oxidative damage. Moreover, it is considered to be a CVD risk factor [85]. Blueberries are rich in phenolic compounds and are able to decrease uric acid both in men and women, even if the effect lasts for a shorter period in women than in men [86].

A recent paper shows that flavan-3-ol, which is present in dark chocolate, only reduces platelet aggregation and P-selectin expression induced by adenosine diphosphate in men. Moreover, it reduces platelet aggregation induced by thrombin receptor-activating peptide and increases thrombin receptor-activating peptide-induced fibrinogen binding in women [87]. In addition, the ex vivo bleeding time induced by collagen/epinephrine is increased both in women and men. White chocolate only reduces P-selectin expression induced by adenosine diphosphate and elevates collagen/epinephrine-induced ex vivo bleeding time in men [87].

Chronic supplementation with quercetin, one of the most potent antioxidants of plant origin, also significantly reduced systolic blood pressure [88, 89] in women with type 2 diabetes mellitus [90]. Moreover, Alonso and Martinez-Gonzalez [91] showed that the antihypertensive effect of extra-virgin olive oil is only present in men, and Nagata et al. [92] found an inverse correlation between soy intake and diastolic blood pressure in Japanese men as well as a marginally positive association in peri-and postmenopausal women. In humans of both sexes with mild to moderate hypertension, consumption of soy milk for 3 months induces a modest but significant hypotensive effect [93]. The hypotensive effect is also present in healthy normotensive men and postmenopausal women (50–76 years old), in which 3 months of soy dietary supplementation also significantly reduce the lipid profile [94, 95]. However, other authors have not confirmed hypotensive effects in either hypertensive or normotensive subjects [73]. Globally, the above data suggest that sex is important for the effects of phenolic compounds in vessels (Table 1).

In humans, the results of a placebo-controlled intervention study conducted in healthy men showed that quercetin can improve endothelial function by increasing endogenous

Table 1 Summary of the effects of phenolic compounds on cardiovascular functions of female rodents and women in comparison with their male counterparts

	Blood pressure	Heart functions	CVD prevention	LDL-cholesterol profile
Genistein	Reduction [75]	Protection [100]		
Quercetin	Reduction [88, 89]			
Flavanols	Reduction [122]			Reduction [122]
Extra-virgin olive oil phenolic compounds	No effect [91]			
Soy milk phenolic compounds	Reduction [93]			
Soy supplementation	Reduction [94, 95] No effect [73, 107]	Protection [101, 102]	Protection [109–114] Lower risk [118] No effect [108]	No effect [107]
Flavonoid enriched diet	Reduction [81]			
Wine phenolic compounds	Aortic ring relaxation [77]			

NO and reducing endothelin-1 production through inhibition of NADPH oxidase and activation of endothelial NO synthase [96].

In addition, soy products improve the lipid profile, especially in Chinese men [97], and two meta-analyses [98, 99] demonstrated that soybean isoflavones ameliorate endothelial function in postmenopausal women. Subgroup analysis shows that this effect is more evident in women who have impaired endothelial function at baseline [98].

Effect on CVD prevention

Studies conducted in animals and humans indicate a potential beneficial effect of flavonoids on heart health. In isolated guinea pig myocytes, an electrophysiological study shows that the genistein effects on the intracellular Ca^{2+} cycle differs in male and female cells [100]. The results suggest that genistein may afford greater cardioprotection in females than males.

An in vivo study performed on transgenic mice with a mutation in the alpha-myosin heavy chain gene, usually fed with a soy enriched diet, shows that while female mice preserve cardiac contractile function and continue to increase their cardiac mass, male mice develop thin ventricular walls and have poorly contractile hearts[101, 102]. When the diet of these mice were substituted with a casein-based diet, males no longer deteriorate versus cardiomyopathy [103], suggesting that the soy-based diet worsens hypertrophic cardiomyopathy more in male mice than female mice [104]. The supplementation with genistein and daidzein into casein-based diet does not recapitulate the entire cardiac phenotype of the young animals consuming the soy diet, but it augments the hypertrophy in the transgenic males and attenuates the myocardial growth in the females [105]. In addition, the hearts of female mice experience hypertrophy in response to the exercise stimulus regardless of diet [106].

Notably, these results also show that dietary manipulation of the heart can lead to adaptation. These results strongly suggest that caution should be used before recommending oestrogenic compound supplementation, at least in patients with cardiac disease [104].

The beneficial health effects of phytoestrogens are not clearly demonstrated regarding CVD prevention. The American Heart Association reversed its endorsement of soy, because it did not find a significant beneficial effect of soy on lipids, blood pressure, or menopausal changes [107], and it has been observed that dietary isoflavones do not reduce the risk of CVD or stroke in Dutch women [108]. However, some clinical studies indicate a potential beneficial effect of soy intake on cardiovascular risk factors or CVD mortality [109–115]. The Shanghai Women's Health Study shows that higher soy protein ingestion is linked with a lower risk of incident CVD in Chinese women [116], whereas there is a positive association in men [117]. In a Japanese study, total soy intake and soy isoflavones are only associated with a lower risk of CVD and stroke in women [118], but this association is not present in another Japanese cohort that included men and women aged > 35 years [119]. In a large cohort study in Chinese men and women, a soy-rich diet is not significantly associated with CVD mortality [120]. Notably, in men, the highest quartile of soy protein intake is linked with a slightly elevated risk of CVD mortality. However, a systematic meta-analysis shows little evidence of the beneficial effects of soy consumption on the risk of stroke and CVD [121].

Flavanols are strong antioxidants in plant foods, and tea is a major dietary source. There is evidence from prospective cohort studies that tea and flavanols are inversely related to stroke incidence [122]. Finally, a systematic review and meta-analysis performed with apple, tea and cocoa containing flavanols in cohorts coming from different countries shows that low-density lipoprotein and body mass index are reduced in women and men, respectively [29], whereas total white cell reduction and triglycerides are not influenced by sex. These results again show a great interindividual response, indicating that beneficial effect may partially depends on sex of individual in combination with other individual characteristic such as genetical, hormonal, and metabolic status.

Phenolic compound mechanisms from a sex perspective

Oxidative stress among males and females

Sex differences in oxidative stress and inflammation have already been reviewed, and they seem to depend on species and tissues and cells ([4, 8, 9, 123–125] and cited literature). Oxidative stress and inflammation play a crucial role in the pathogenesis of atherosclerosis vascular inflammation leading to infarction and ischemia. Oxidized low-density lipoproteins (oxLDL) are internalized by macrophage, vascular endothelial and smooth muscle cells, and these cells are the source of foam cells [9, 125]. Internalization of oxLDL activates the inflammasome, which in part is regulated by sexual hormones [125] through ERα, ERβ, and G-protein-coupled receptor-30 (GPR30) (see below) as well as AR. We currently do not understand how the immune response and oxidative stress in women differ from men and in atherosclerosis. However, some differences have been found in animal models and humans.

Oxidative stress seems to be higher in male than female rats, being that the levels of SOD, GPx and lipid peroxidation are lower and higher in males versus females, respectively [126]. In rats, H_2O_2 and $O_2\cdot$ production, at baseline,

is lower in females than in males in aortic vascular smooth muscle cells (VSMCs) and isolated aortas [127–129] and lipid peroxidation is higher in male cells versus female cells [129]. In addition, male VSMCs have less SOD and CAT activity [127, 129], and the in vivo SOD levels are also lower in male rat carotid arteries than in female ones [127].

Furthermore, sex differences also emerge or persist after different treatments: exposure to NO, for example, only reduces $O_2\cdot$ and elevates SOD activity as well as gene expression in male rat VSMCs [127]. In aortic rat VSMCs, UVB radiation significantly increases production of the 4-hydroxynonenal, H_2O_2 and $O^-{}_2$, the effect of which is larger in male VSMCs than in female VSMCs. Further UVB exposure induces a higher reduction of GPx in female VSMCs [130].

SOD activity is higher in female rat hearts than in male [126], whereas male rats and mice have a higher level of GPx [126, 131]. Moreover, at the cardiac level, in young and aged male rats, cardiac protein oxidation is higher in males than in females, whereas cardiac lipid peroxidation is not different between sexes [132, 133]. In spontaneously hypertensive rats, the SOD, CAT and trolox equivalent antioxidant capacities are higher in males than in females, whereas GPx is not different, while sex-dependent differences are not observed in normotensive and borderline hypertensive rats of both sexes, with lipid peroxidation being similar in both sexes [134]. Finally, sex differences have been described in response to antioxidant therapy. Fortepiani and Reckelhoff [135] demonstrate that the antioxidant tempol decreases blood pressure only in male spontaneously hypertensive rats. In rats, sex differences are also present when enzymes that produce ROS are considered. As a subunit-specific example, Nox1 and Nox4 of NAPH oxidase are higher in male than in female rats, while Nox2 does not differ between males and females [136, 137].

In mice, SOD activity is higher in females than in males in the brain and lung, but not at the renal and cardiac levels [131]. Moreover, CAT activity is similar in the two sexes in the brain, heart, and lung of mice, but is higher in female kidneys [131]. The activities of GPx and glutamate-cysteine ligase (GCL), a key enzyme in the synthesis of GSH, are more elevated in the female mouse kidney and brain versus the male equivalents. By contrast, the activities of GCL and GPx are more elevated in the male heart than in the female heart [131]. Notably, at least in the mouse brain, age increases oxidation, which is greater in females than in males [138].

Nrf2 activates cytoprotective genes during periods of oxidative stress, and interestingly, many of cytoprotective genes are more highly expressed in the livers of female than male mice [139, 140]. Furthermore, male and female Nrf2 knockout mice have different phenotypes, because Nrf2-dependent antioxidant enzymes are only expressed in female

bones [141]. Oestrogens can up-regulate Nrf2 and increase the expression of antioxidant enzymes during ischemic and reperfusion injury [142].

In humans, at baseline, H_2O_2 production is higher in male human umbilical vein endothelial cells (HUVECs) than in female ones [143]. Clinically, the biomarkers of oxidative stress are higher in young men than in women of the same age [144], although this is not a univocal result, because another study reports that women present a higher oxidative status than males [145]. Tóthová et al. [146] demonstrated that MDA and advanced glycation end-products are significantly higher in healthy adult women, whereas advanced oxidation protein and the ferric-reducing ability of plasma are greater in men. Young fertile women present higher levels of MDA than men, whereas no differences are detected between postmenopausal women and men of the same age [147]. Interestingly, when data are corrected for body weight, the difference in the MDA levels between fertile women and young men persists and extends to postmenopausal women and men > 45 years old [147]. The same study shows that protein oxidation does not diverge between men and women, but when the body weight correction is applied to carbonyl groups, fertile and postmenopausal women have higher levels of carbonyls than men of both ages [147].

As previously noted, plant-derived phenolic compounds might protect against heart disease through inhibition of oxidative damage [19]. Flavonoids can be used as an illustrative example of such activity. Their chemical structure is compatible with a one-electron donor activity. They function as antioxidants in vitro in both cell cultures and cell-free systems by scavenging superoxide anion, singlet oxygen, and lipid peroxy-radicals and/or by stabilizing free radicals that are involved in oxidative processes through hydrogenation or complexing with oxidizing species ([32], and cited literature). As a product of this reaction, flavonoids themselves become free radicals, but their conjugated structure allows the remaining orbital electron to be relatively inactive. Consequently, the beneficial effect of bioactive phenolic compounds has been widely attributed to the putative antioxidant capacity of these molecules. Although in vitro experiments clearly sustain the positive influence of phenolic compounds on oxidative stress, the effects of these substances in living systems are inconclusive or could not confirm the in vitro data at all [148]. More recently, the real impact of phenolic compounds as antioxidants has been reconsidered and questioned based on evidence that shows that the molecular basis of their activity is much larger than originally considered [149]. For example, it has been reported that the phenolic compounds of extra-virgin olive oil, in a sex-specific manner, increase glutathione reductase activity and GPx and GSH levels by activating the Nrf2 pathway in rat VSMCs [150]. Moreover, the effect of red wine phenolic compounds on increasing aorta ring relaxation is greater in females than

males, probably due to the high expression of endothelial NOS in females [77].

These data may, in part, provide a partial explanation for the variability in the literature that indicates the importance of sex on phenolic compounds effects. Moreover, sex differences may vary according to a specific species, organ or tissue, as well as the studied parameters. Globally, the above findings urge for future detailed studies that focus on the evaluation of the influence of sex on redox homeostasis, also considering that the deterioration of the redox status seems to be a link between psychological stress and cardiovascular risk [151].

Nuclear receptors

Although the affinity of phenolic compounds for both ERα and ERβ is lower than oestrogen, competition-binding studies have confirmed that nutritional molecules (e.g., genistein, coumestrol, daidzein, and equol) showed a distinct preference for ERβ [152]. By contrast, in comparison with genistein, 8-prenylnaringenin, which only occurs in hops, was found to be 100 times more potent as an ERα agonist [153]. The ability to modulate ER activities led to the inclusion of phenolic compounds in the class of selective oestrogen receptor modulators (SERM) [19]. However, accumulating data on phenolic compounds' action mechanisms indicate that these compounds have a very complex spectrum of activities. Thus, they should not be considered to be "natural" SERMs, which function as ER agonists in some tissues and antagonists in other organs. Rather, phenolic compounds could function as ER agonists on certain pathways (i.e., membrane-initiating pathways) in all organs, eliciting effects downstream of these pathways. We recently defined these substances as mechanism-specific ligands that differentially modify ER signalling and physiological outcomes. Although the available data are currently limited, they may be important in providing a conceptual background for the putative protective effect of phenolic compounds against CVD. Apart from the direct effect on sex-hormone receptors, phenolic compounds could affect the levels of these receptors. As example, quercetin inhibits AR protein levels in a dose-dependent manner [21], while naringenin maintains a high level of ER in cells [154].

To evaluate whether a different susceptibility of male and female sex-hormone receptors to phytochemicals exists, we evaluated the impact of naringenin on rat VSMC motility. Naringenin inhibits VSMC migration, a protective effect against atherosclerosis insurgence in both female- and male-derived cells, via ERβ [155]. Naringenin requires ERβ and p38 activation to affect female VSMC motility. Intriguingly, this naringenin effect is also present in male VSMC in which ERβ is expressed. Thus, these data indicate that ERβ signals are prone to flavonoid modulation in both male and female

VSMC [155]. In humans, ERα, ERβ, and GPR30 are differently expressed in males and females, whereas AR presents the same level of expression.

Microbiota

Numerous studies link the gut microbiota (the microorganisms living in the digestive tracts of humans and other animals) to the so-called metabolic syndrome, obesity, type 2 diabetes, and CVD [156–159]. Metabolic syndrome is also associated with autoimmune disorders, such as diabetes type I [160], depression and anxiety [161].

The dominant phyla in the human gastrointestinal tract are *Firmicutes* (including *Clostridium, Enterococcus, Lactobacillus, Ruminococcus*, and *Faecalibacterium genera*) and *Bacteroidetes* (including *Bacteroides* and *Prevotella genera*) [162, 163], with phyla such as *Actinobacteria, Proteobacteria, Synergistetes, Fusobacteria*, and *Verrucomicrobia* is also present [162]. The human adult microbiota is relatively stable from adulthood to old age [163]. Notably, sex differences are described in the gut microbiota [164, 165] and could be implicated in sexual dimorphic patterns in energy and nutritional requirements [166–170]. In particular, an American study demonstrates that *Bacteroidetes* are lower in the gut of men than women [168]. This is line with a European study that shows that *Bacteroides–Prevotella* is more prominent in males than females [171], whereas *Bacteroides thetaiotaomicron* is higher in Chinese men in Chinese women [170]. Indeed, the abundance of the Bacteroides is lower in obese men than obese women [172]. The maternal gut microbiome varies during pregnancy, with bacterial diversity more pronounced during the third trimester, when oestrogens are at maximum levels [173].

In this context, it is important to recall that a two-way interaction exists between phenolic compounds and the gut microbiota, being that the gut microbiome is involved in the metabolism of phenolic compounds (i.e., bioavailability), and the phenols and their microbial metabolites can promote factors for proliferation of beneficial gut inhabitants and can inhibit the pathogenic species [174, 175]. Microbiota can metabolize oestrogen-like compounds, which in turn, may induce the proliferation and growth of certain types of bacteria. For instance, daidzein is metabolized by gut bacteria to *O*-desmethylangolensin and *S*-equol [176], which can activate ERα or ERβ[177, 178]. Additionally, genistein and glycitin can vary the composition of the faecal bacterial community in postmenopausal women by increasing and decreasing the concentration of the *Bifidobacterium* and *Clostridiaceae*, respectively [176, 177]. Notably, *Clostridium scindens* may convert glucocorticoids into androgens by side-chain cleavage [179]. Intriguingly, some bacteria that have β-glucuronidase activity might increase intestinal

reabsorption of oestrogens (see above). As a whole, the modulation exerted by phenolic compounds on the composition of the gut microbiota should be considered to be possible novel action mechanisms that are activated by these molecules to exert effects on cardiovascular functions.

Phenolic compounds' effect during development

Early life experiences have profound influences on health in adult life; therefore, we report the sex differences with phenolic compounds observed in early life, even if only a few studies are available. Daidzein and genistein are detected in amniotic fluid, and genistein can cross human (in vitro) and rat (in vivo) placentae [180–182]. Notably, amniotic fluid containing female foetuses can store more daidzein and genistein than amniotic fluid containing male foetuses [183]. Moreover, a mother of a female baby presents a higher total antioxidant status and lower plasma hydroperoxides than a mother of a male baby: umbilical cords obtained from female babies have, indeed, a higher total antioxidant capacity, lower plasma membrane hydroperoxides and higher CAT, GPx, and SOD activities than male samples [184]. It has been observed that HUVECs obtained from umbilical cord of males produce more H_2O_2 than female ones [143]. The importance of the perinatal environment on the development of modifying the risk profile for disease in adulthood is now well-recognized [185]. Epidemiological studies underline the association between perinatal factors, such as breastfeeding versus formula milk. It is relevant to recall that soy-based milk composes 13% of the infant formula marketed in the United States [186]. Neonates fed with soy milk have higher soy isoflavones than Japanese men consuming a soy-based diet and much higher soy isoflavones than in US adults [186, 187].

Animal studies demonstrate that ingestion of genistein in the first 22 days after birth increases the fat/lean mass ratio, fat mass, adipocyte size and number as well as decreases the muscle fibre perimeter in females [188]. These findings suggest that postnatal exposure induces sex-specific effects. Indeed, environmentally relevant ingestion of genistein may disrupt female reproductive development and function [189], as genistein is a reproductive toxicant and endocrine disruptor in rodents [190, 191]. Some consequences (irregular oestrous cycles, early reproductive senescence, infertility) appear late in life [189]. Male rats also appear to be sensitive to phytoestrogens during development, because the central nervous system-gonadal axis and male sexual behaviour are altered [192]. All of these data, as also demonstrated by others [193], suggest that differences in male and female susceptibility to phytoestrogen could be present.

Conclusions

CVD is the first cause of death in developed countries; thus, primary prevention of CVD is a major public-health priority. Regarding phenolic compounds, a recent meta-analysis shows that some phenolic compounds, such as flavanols, may be beneficial in the prevention of CVD. This is not an univocal result, because although CVD is associated with increased oxidative stress, data on the efficacy of antioxidant therapy is still lacking [14]. In addition, many, if not all, trials are of low quality, and this does not permit any firm conclusions.

Considering that dietary intake is not sufficient to reach pharmacological concentrations of phenolic compounds, the problem of dosage must be resolved. Data on the influence of sex on the activity of phenolic compounds are even scarcer; nevertheless, sex differences in the biotransformation of phenolic compounds have been described. The difficulty of reaching a firm conclusion is further aggravated by the fact that sex differences in oxidative stress and the response to antioxidants are species (mouse, rat, humans)-specific, making data not transferable from animals to men and women. It is evident that there are still large gaps in our knowledge regarding the sex differences of phenolic compounds' activity and safety, and significantly more research is urgently required.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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