Stilbenes, Phenolic Acids and Tannin Nutraceuticals and Metabolites

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Nutraceuticals are generally defined as a food or part of a food that provides benefits to health in addition to its nutritional content. They have been receiving increasing attention due to their potential role as adjuvants against non-communicable chronic diseases (cardiovascular disease, diabetes, cancer, etc.). Positive effects have been reported associated with an average dietary consumption of several nutraceutical classes, meaning that the primary compound might not be solely responsible for all the biological effects. The in vivo activities of such biomolecules might be carried out by metabolites derived from gut microbiota fermentative transformation.

Keywords: nutraceutical ; microbiota ; metabolites ; tannin

1. Stilbenes

Stilbenes constitute a vast group of non-flavonoid plant natural defense biomolecules that act as antifungal compounds, produced especially after a lesion or a fungal infection. Among the over 400 natural stilbenes identified, *trans*-resveratrol (hereinafter simply ‘resveratrol’) is the best known and is mainly found in grape skin. Its properties—besides being a natural phytoalexin—have been extensively studied in the past years, making it the most popular polyphenol. This stilbene and stilbene alkanoic derivatives in general displayed antioxidant and antiproliferative activities on various cancer cell lines such as C2C12 (mouse muscle myoblast) and MCF7 (human breast adenocarcinoma) [1]. In particular, they can promote the activity of antioxidant enzymatic defense systems and increase the efficacy of non-enzymatic compounds, such as glutathione, in scavenging reactive oxygen species [2]. Resveratrol is not the only form of stilbene that has been investigated for its antioxidant capacity. For example, a natural oligomer of resveratrol (i.e., trans-δ-viniferin) is able to scavenge superoxide ions and inhibit lipid peroxidation efficiently. In vitro, stilbenes also act as anti-inflammatory compounds and have been shown to prevent glycation, neurodegeneration and aging [3][4]. Natural extracts rich in stilbenes showed good antimicrobial activities [5] to the point that the scaffold structure of stilbenes has been used to generate highly effective antimicrobials through biotransformation processes [6] (e.g., the so-called “duotap” dimeric stilbene compounds [7]).

The anti-inflammatory and neuroprotective effects of stilbenes, especially resveratrol, have been confirmed in rodent models, with promising results also in terms of cognitive impairment recovery and amyloid plaque reduction [3]. An additional possible use of these compounds in the future is as natural additives to preserve food from oxidation, given their efficacy in these terms [8] and their non-genotoxicity as tested in vivo [9]. Finally, resveratrol has shown promise in treating human respiratory viral infections, given the antiviral activity reported against, to name a few, influenza virus, respiratory syncytial virus and SARS-CoV-2 [10].

The structure of stilbenes exists in the following two isomeric forms: (E)-stilbene or *trans*-stilbene, and the isomer (Z)-stilbene (*cis*-stilbene), which is less stable. Natural analogues of resveratrol, such as pterostilbenes and viniferins, are higher molecular weight molecules. In particular, pterostilbenes show a higher lipophilicity, thus increasing membrane permeability and improving their bioavailability [11], whereas viniferins are the least lipophilic molecules of this class. Stilbenes can occur as free aglycones or mainly as glycoside forms (called piceids), which require enzymatic cleavage of the saccharide units to be transferred across the intestinal barrier into the circulatory system, and then undergo glucuronidation and other phase II metabolism in the liver. The catalytic action on the glycones is carried out by the gut microbiota as most of the ingested glycosides reach the colon.

To investigate the role of the gut microbiota in the metabolism of stilbenes (and therefore in determining their effectiveness), a recent study tested *Vitis vinifera* extracts by implementing M-SHIME®, a validated in vitro model of the intestinal environment [12]. Daily administration of stilbene-rich extracts (up to 1 g/L) led to significant changes in the community metabolism and composition, suggesting a role of the microbiota in the metabolism of such biomolecules. In

particular, higher levels of short-chain fatty acids (SCFAs, i.e., the end-products of the fermentation of fibers by the gut microbiota, with a pivotal role in host physiology) and NH_4^+—overall considered a clue of wellness of the microbial population—were detected, together with a general increase in Enterobacterales and a decrease in Bacteroidales orders. Furthermore, the authors reported that Gram-negative species were less sensitive to the potential anti-microbial activity of the tested extracts. In another study, fecal samples from different healthy omnivorous donors without a history of antibiotic usage in the previous 3 months were incubated in an in vitro fecal fermentation system to evaluate the microbiota's ability to digest six stilbenes and stilbenoids [13]. According to the authors' findings, resveratrol, oxyresveratrol and piceatannol were extensively metabolized by the fecal microbiota, undergoing double bond reduction, dihydroxylation and demethylation, depending on the position of hydroxyl and methyl groups, thus generating various metabolites. For example, resveratrol fermentation resulted in dihydroresveratrol as the only metabolite, as detected by liquid chromatography followed by mass spectrometry (LC/MS). However, it should be noted that a previous study reported two additional compounds, i.e., 3,4-dihydroxy-*trans*-stilbene and 3,4-dihydroxybibenzyl, in almost—but not all—the fecal samples tested, thus suggesting that metabolic processes and end-products are strictly dependent upon individual microbiota composition [14]. The biological properties of the so far identified intermediates and end-products still have to be clearly elucidated, but they might be responsible for the positive effects (e.g., antioxidant, anti-inflammatory and antitumoral properties) observed in some studies after the administration of stilbenes [11][15]. Results obtained from resveratrol and stilbene administration might sometimes be contradictory [16][17]. It is also worth noting that several stilbene-based engineered drugs have been approved by the U.S. Food and Drug Administration agency (FDA) and the European Medicines Agency (EMA) and are effectively in use for estrogen-receptor modulating therapies such as raloxifene (osteoporosis in women), toremifene and tamoxifen (both in use for hormone receptor-positive breast cancer) [18]. Another stilbene derivate, Ramizol, is currently under preclinical investigation for the treatment of *Clostridioides difficile* infections [19][20].

2. Phenolic Acids

Phenolic acids are other non-flavonoid phenolic compounds, widespread in plants as free or saccharide-conjugated soluble and insoluble forms. Berries, cereals, legumes and oilseeds carry the highest amounts of phenolic acids. Phenolic acids exhibit marked radical scavenging capacity, resulting in a beneficial effect against cancer development, cardiovascular diseases, inflammatory diseases and other disorders [21]. In addition to the antioxidant property, quite common to polyphenols in general, as already discussed, phenolic acids possess other potentially clinically relevant properties. For example, ferulic acid showed marked antithrombotic effects in vitro and in vivo [22]; coumaric acid showed inhibitory effects on lactate dehydrogenase (LDH) release, promoting the recovery of hyperlipidemia steatohepatitis in vivo [23]; gallic acid showed anti-urolithiatic properties (inhibition of urolithiasis crystal formation), thus improving kidney health [24]; vanillic acid significantly inhibited human colorectal cancer growth in a xenograft tumor model, via the inhibition of hypoxia-induced expression of hypoxia-inducible factor (HIF)-1α, thereby inhibiting in a dose-dependent manner the vascular endothelial growth factor (VEGF) and erythropoietin (EPO) proteins, both involved in tumor graft angiogenesis [25].

Phenolic acids have also shown marked antibacterial activity in vitro against several pathogenic strains [26]. Zhang and colleagues [27] reported a synergic effect of coumaric acid and chlorogenic acid with fosfomycin in the treatment of *L. monocytogenes* infections, whilst Tan et al. [28] tested chlorogenic acid with levofloxacin, obtaining positive results on *Klebsiella pneumoniae* infections in vivo. Extracts rich in phenolic acids (e.g., from peanuts) have shown antibacterial effects against Gram-positive bacteria species, such as *Bacillus cereus* and *S. aureus*, and Gram-negative pathogens, such as *Pseudomonas aeruginosa* and *Salmonella enteritidis* [29].

According to their scaffold structure, phenolic acids can be divided mainly into hydroxybenzoic and hydroxycinnamic acids. Hydroxycinnamic acids are derived from cinnamic acid and are usually present in foods as esters with glucose units. Hydroxybenzoic acids are derived from benzoic acid and are often found in soluble moieties with various sugars such as glucose and rhamnose. Among hydroxybenzoic acids, the best known are vanillic acid, gallic acid, *p*-hydroxybenzoate and protocatechuic acid, whereas hydroxycinnamic acids are mainly represented by chlorogenic, caffeic, ferulic and coumaric acids.

It has been extensively demonstrated that phenolic acids are metabolized by human phase II metabolism enzymes after absorption in the gastrointestinal tract, undergoing methylation, glucuronidation and sulfation with derivates that may be (more) biologically active [30][31]. Phenolic acids as gut microbiota-derived end-products are produced in most metabolic pathways of phenolic compounds and have been shown to possess intrinsic anti-inflammatory properties, as well as synergistic anti-inflammatory effects with SCFAs [32]. Hence, the role of the gut microbiota in phenolic compound

metabolism, in general, is due to its ability to derive smaller phenolic compounds (i.e., phenolic acids) starting from complex phenolic (a)glycones, otherwise less absorbable and with lower biological activity.

3. Tannins

Tannins are a class of polyphenolic biomolecules with a high molecular weight (500 Da to 20 kDa) found in most plants, given their pivotal role in protecting from predation and regulating plant growth. The major classes of tannins are hydrolyzable tannins, condensed tannins (also known as non-hydrolyzable tannins) and phlorotannins. Hydrolyzable tannins consist of repeated units of gallic (i.e., gallotannins) or ellagic (i.e., ellagitannins) acid, or other polyhydric alcohols together with a sugar core. Tannic acid, a mixture of digallic acid esters of glucose, is one of the simplest examples of hydrolyzable tannins. Condensed tannins are mainly made of catechins together with anthocyanidin aglycone scaffolds, which explains their alternative name of proanthocyanidines. Finally, phlorotannins are oligomers of phloroglucinol, a compound mainly produced in algae. An additional group of biomolecules that are sometimes included among tannins because of their high molecular weight is polystilbenes, which, as the name suggests, are polymeric structures of stilbenoid scaffolds mainly represented by several viniferins. In vitro tannins have shown marked antioxidant properties linked to the prevention of cardiovascular diseases, cancer and osteoporosis. This potential has also aroused the interest of the food industry, which uses them as preservative agents in food [33]. In addition, tannins have shown promising results in the beef industry, reducing ammonia and methane production in rumen fermentation both in vitro [34] and in vivo [35].

In human studies, the anticancer properties of tannins have been investigated, finding interesting results, particularly for tannic acid, both in cancer prophylaxis and as an adjuvant in cancer therapy [36][37]. Tannic acid has also shown promising antibacterial activity against both Gram-positive and Gram-negative species, such as *S. aureus*, *E. coli*, *Streptococcus pyogenes*, *Enterococcus faecalis*, *P. aeruginosa*, *Yersinia enterocolitica* and *Listeria innocua* [38][39][40]. Furthermore, it has shown antiviral effects against pathogenic viruses such as influenza A virus, Papilloma virus, noroviruses, *Herpes simplex virus* type 1 and 2 and HIV [41].

The pharmacological aspects of tannins have not been investigated as thoroughly as the simpler polyphenols; however, it is clearly known that their intake is not associated with direct adsorption [42], resulting in over 90% of biomolecules entering the colon. Here, the gut microbiota plays a pivotal role in the catabolism of such polymers into their monomers, with the polymerization rate appearing to determine the fate of such compounds during digestion [43]. Gut colonizers as the genus *Akkermansia* and members of the families *Lachnospiraceae* and *Ruminococcaceae* [44], as well as the species *Butyrivibrio* spp., *Gordonibacter urolithifaciens* and *Bifidobacterium pseudocatenulatum* [45], are mostly necessary to ferment non-digestible condensed tannins into bioavailable metabolites—mainly catechins and phenolic acid scaffolds—that can exert systemic pharmacological effects as illustrated in the previous sections. At the same time, fermentation produces useful substrates (e.g., SCFAs and probably other still unknown metabolites) for the microbial counterpart, in a sort of prebiotic effect. In contrast, hydrolyzable tannins are degraded in mild acid conditions, releasing the monomers of gallic or ellagic acid directly in the upper digestive tract, which then undergo adsorption, conjugation with methyl, glucuronic or sulfate groups and finally excretion [46].

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