Polyphenols and Stroke

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Polyphenols are an important family of molecules of vegetal origin present in many medicinal and edible plants, which represent important alimentary sources in the human diet. Polyphenols are known for their beneficial health effects and have been investigated for their potential protective role against various pathologies, including cancer, brain dysfunctions, cardiovascular diseases and stroke.

polyphenols flavonoids stroke

1. Polyphenols: Definition and Classification

Polyphenols are molecules chemically characterized by the presence of at least one aromatic ring with one or more hydroxyl groups attached [1][2]. Polyphenols are plant secondary metabolites that are thought to help plants to survive and proliferate, protecting them against microbial infections or herbivorous animals, or luring pollinators [3]. Polyphenols are found in many medicinal and edible plants which represent important alimentary sources, including fruits, vegetables, beverages (such as tea and red wine) and extra virgin oil [4].

This group of natural products includes a broad number of different compounds, ranging from simple molecules with low molecular weight to complex and large derived polyphenols [1][2]. According to their chemical structure, polyphenols can be classified into various classes including flavonoids, phenolic acids, stilbenes, curcuminoids, lignans, ellagitannins and ellagic acid and coumarins [1][2]. Flavonoids are structurally based on a skeleton of fifteen carbons, with two aromatic rings connected by a three-carbon bridge. They are the most numerous of polyphenols and are widely distributed through the plant kingdom [1][2]. The main subclasses of dietary flavonoids include flavonols, flavan-3-ols, flavanones, flavones, isoflavones, anthocyanins, dihydrochalcones and proanthocyanidins [1][2]. Among the non-flavonoid polyphenols, phenolic acids can be further divided into hydroxycinnamic acids and hydroxybenzoic acids [1][2]. Figure 1 depicts the classification of polyphenols and describes some known food sources for each molecular class.

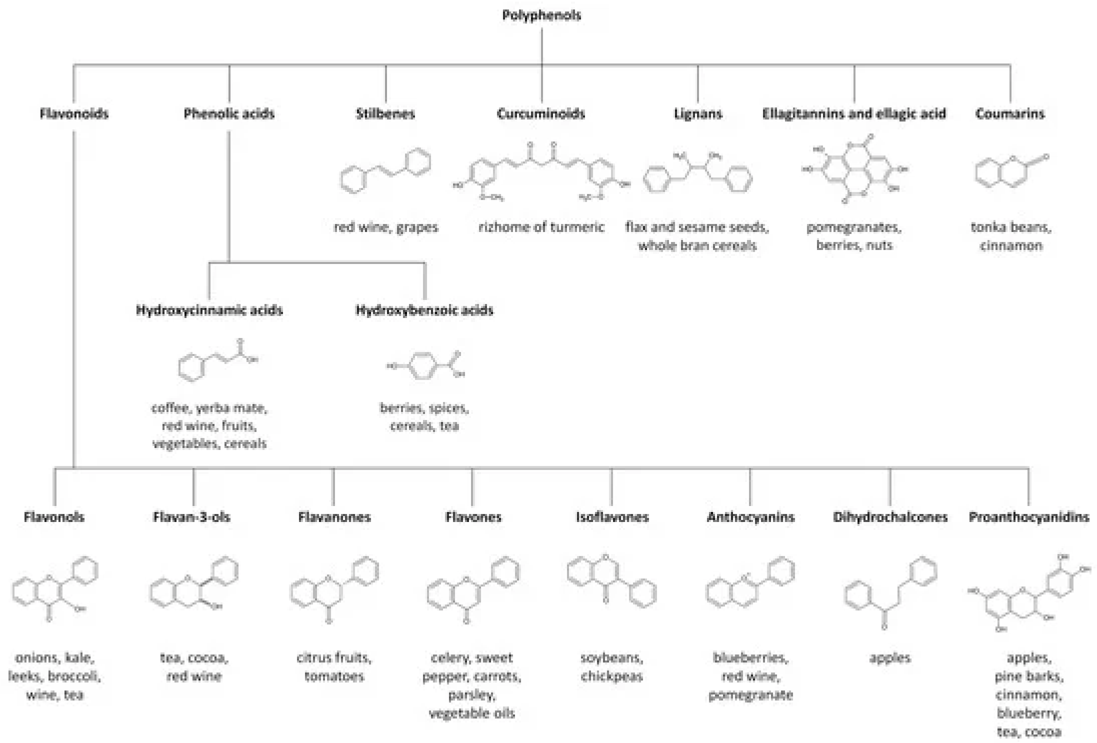

Figure 1. Major polyphenol classes and their most important food sources.

Among the many micronutrients present in plants, polyphenols are the most numerous and particularly endowed with beneficial properties [5]. For these reasons, polyphenols have been widely investigated for the prevention and treatment of several pathological conditions, including cancer, neurodegenerative disorders, metabolic and cardiovascular diseases and stroke [6][7][8].

2. Polyphenol Metabolism: Role of Gut Microbiota

Polyphenol bioavailability is generally poor, and only 1–10% of total polyphenol intake is detectable in blood and urine samples [6]. Bioavailability is particularly low for flavones, stilbenes and curcumin and is slightly higher for tea flavan-3-ols, flavanones in citrus fruits, soy isoflavones and red wine anthocyanidins [9][10][11]. However, maximum polyphenol concentration in plasma remains extremely low and rarely exceeds 1 μM, even in individuals consuming a polyphenol-rich diet [9]. How polyphenols exert their beneficial actions despite their poor bioavailability is not clear yet. A possible explanation may rely on the fact that many polyphenol metabolites exhibit a biological activity [12].

Polyphenols are generally consumed with the diet or as supplements. A proportion of ingested polyphenolic compounds can be absorbed in the small intestine and metabolized by phase II enzymes. However, the major part of polyphenols reach the large intestine where they are degraded by intestinal microbiota. A large body of evidence indicates a fundamental role of colonic microorganisms in determining the bioavailability and activity of polyphenols by transforming them into readily absorbable molecules or biologically active metabolites [5][13][14]. The relationship between polyphenols and microbiota is bidirectional and, if the intestinal bacteria modulate polyphenol metabolism, polyphenolic compounds can in their turn influence the composition of the microbial population [5][15].

Different findings suggest the gut microbiota could modulate the activity of polyphenols potentially active against stroke. For example, flavan-3-ols, phenolic compounds characterized by a generally low bioavailability, are extensively metabolized by host and gut microbiota enzymes. Phenyl-γ-valerolactones and phenylvaleric acids, the main microbial metabolites of flavan-3-ols, might be responsible for the beneficial effects attributed to their parent compounds, including neuroprotection [16]. Daidzein, an isoflavone endowed with beneficial properties enriched in soy food, is metabolized by gut microbiota to equol, which possesses higher antioxidant activity and affinity for estrogen receptors than the parent compound. The neuroprotective flavone glycoside baicalin (baicalein 7-O-glucuronide) can only be absorbed after hydrolysis by gut microbiota β-glucuronidase to the aglycone form baicalein [17]. Similarly, the neuroprotective anthocyanin cyanidin-3-O-glucoside displays a poor bioavailability, while its microbiota degradation products are more easily absorbable [18]. Ellagic acid and ellagitannins are degraded by intestinal microorganisms to form urolithins, molecules characterized by higher bioavailability and better anti-inflammatory and antioxidant properties than their compounds of origin [19].

3. Polyphenols and Stroke: Mechanisms of Action

The major mechanism of natural polyphenols in preventing stroke relies on their protective action on the cardiovascular system [7][20][21].

Many polyphenols are endowed with anticoagulant and antiplatelet activities, potentially contributing to the prevention of thrombus formation, the main cause of ischemic stroke [22][23]. For example, several coumarin derivatives exert anticoagulant properties by inhibiting the vitamin K epoxide reductase complex and are widely used as clinical anticoagulant agents [24]. Among the polyphenols endowed with antiplatelet activity, the isoflavones genistein and daidzein possess a marked and physiologically relevant cyclooxygenase-1 (COX-1) inhibitory activity [25]. Other flavonoids with antiaggregant effects, including the isoflavone tectorigenin, have been reported to act as antagonists on thromboxane receptors [25][26].

Hypertension, a long-term medical condition affecting millions of individuals worldwide [27], is an important risk factor in particular for intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH) subtypes of stroke [28][29]. Dietary intake of flavonoids belonging to anthocyanin, flavone and flavan-3-ol subclasses may contribute to the prevention of hypertension [30][31]. The underlying biological mechanisms by which polyphenols regulate blood pressure include vasodilation through the regulation of nitric oxide (NO) and endothelium-derived hyperpolarizing factor (EDHF) [20][30][31].

Besides the well-documented beneficial effects of polyphenols on cardio- and cerebrovascular systems, a growing number of studies in cellular and animal stroke models indicates a direct protective effect of many polyphenols on the brain. Notably, several polyphenols exert neuroprotective actions in preclinical models even when administered after stroke induction, indicating that these molecules may be useful not only in increasing resilience to brain damage, but also for the recovery of patients suffering from stroke. Moreover, the fact that different polyphenolic compounds act on the same molecular pathways raises the possibility that they may promote synergistic effects at very low doses. Therefore, the possible synergistic effect between polyphenols with each other or with other compounds may provide the rationale to overcome the limitations caused by the poor bioavailability of these molecules.

At the mechanistic level, polyphenols exert their neuroprotective benefits by acting on several targets simultaneously. These compounds are generally strong antioxidants, working as reactive oxygen species (ROS) scavengers and metal chelators due to the presence of hydroxyl groups and neutrophilic centers [6]. Furthermore, many polyphenols are able to activate transcription factors involved in antioxidant-responsive element pathways, such as erythroid 2-related factor 2 (Nrf2), thus promoting the expression of antioxidant enzymes including superoxide dismutase (SOD), heme oxygenase-1 (HO-1), catalase, glutathione reductase and glutathione-S-transferase [32].

Apoptosis is a process that can play a primary role in various pathologies, including cardiovascular diseases and stroke [33]. Many polyphenols are able to interact with proteins regulating apoptosis, including proapoptotic (Bax, Bad) and antiapoptotic (Bcl-2, Bcl-XL) members of Bcl-2 family, p53, mitogen-activated protein kinases (MAPKs) and protein kinase B (AKT) [33]. These compounds can act as pro- or antiapoptotic agents, depending on their concentrations, cellular system and stage of pathological process [33].

The polyphenol-mediated neuroprotection not only involves a direct effect on neurons, but also modulatory effects on different inflammation players in the brain, including microglia and mast cells (MCs) [34][35]. The anti-inflammatory properties of polyphenols are based on their capability to interfere with immune cell regulation, inflammatory gene expression and the synthesis of inflammatory mediators [36]. For example, a number of polyphenols have been shown to modulate nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), toll-like receptor (TLR) and arachidonic acid pathways, suppressing the production of tumor necrosis factor α (TNF-α), interleukin (IL)-1β, IL-6, IL-1 and IL-8, as well as cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and nitric oxide (NO) [36].

Epigenetic modifications, including DNA methylation, histone modifications and RNA-based mechanisms, modify gene expression without altering the DNA sequence. Epigenetic modifications regulate important physiological processes in living organisms, but they have also been associated with the pathogenesis of various diseases, including stroke [37]. Various polyphenols can influence epigenetic mechanisms underlying stroke pathogenesis and progression by modulating DNA methylation and histone modifications through the interaction with histone deacetylases (HDACs) and DNA methyltransferases (DNMTs) [38].

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