Review

Sensory Nutrition and Polyphenols; Regulation of Homeostasis through Chemosensory Receptor Interaction with Bitter or Astringent Taste

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Sensory Nutrition and Polyphenols; Regulation of Homeostasis through Chemosensory Receptor Interaction with Bitter or Astringent Taste

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Abstract: Recent studies suggest that the interaction of dietary constituents with taste and olfactory receptors and nociceptor expressed in the oral cavity, nasal cavity and gastrointestinal tract may regulate homeostasis through activation of the neuroendocrine system. Polyphenols, of which 8,000 have been identified to date, represent the greatest diversity of secondary metabolites in plants, most of which are bitter and some of them astringent. Epidemiological studies have shown that polyphenol intake contributes to maintaining and improving cardiovascular, cognitive and sensory health. However, because polyphenols have very low bioavailability, the mechanisms of their beneficial effects are unknown. In this review, we focus on the taste of polyphenols from the perspective of sensory nutrition, summarize the results of previous studies on their relationship with bioregulation, and discuss their future potential.

Keywords: polyphenol; sensory nutrition; bitter; astringency; central nervous system

1. Introduction

In recent years, attention has focused on sensory nutrition, a field of study that examines how the senses conveyed by what people eat and drink act on the brain and how these signals affect human behavior and homeostasis [1]. In 2019, the National Institutes of Health (NIH) hosted a workshop on 'Sensory Nutrition and Disease'. The workshop invited a diverse group of researchers from neuroscience, food science, psychology, nutrition, and health sciences to understand how chemosensory influences affect eating. The workshop encouraged people to explore how these influences impact their choices and health [2]. Three topics were discussed at the conference: a) the need to optimize chemosensory testing and assessment in humans, b) the plasticity of the chemosensory system, and c) the interplay between chemosensory signals, cognitive signals, dietary intake, and metabolism, providing some guidance in advancing sensory nutrition research.

Chemosensory receptors expressed in the oral-nasal trigeminal system have been well studied to transmit signals from food to the brain and determine feeding behavior, such as ingestion or rejection [3,4]. Olfactory receptors respond to thousands of different types of volatiles [5–7]. Taste receptors respond to salts, sugars, amino acids, alkaloids, acids and fats [8,9]. In addition, stimuli such as temperature, osmotic pressure, pH, pungency and menthol are recognized by transient receptor potential (TRP) [10–12]. Flavor perception is formed by integrating signals from various

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chemosensory systems in the oral and nasal cavities within the brain [13,14]. Flavor perception is thought to be shaped by neural processes occurring in chemosensory regions of the brain, including the anterior insula, frontal operculum, orbitofrontal cortex and anterior cingulate cortex, and by interactions with other heteromodal areas including the posterior parietal cortex and ventral lateral prefrontal cortex. In recent years, it has been discovered that chemoreceptors responsible for flavor formation are expressed outside of the oral-nasal trigeminal system [4,15,16]. For instance, it is known that olfactory receptors are in sperm regulated their motility [17], in skeletal muscle controlled differentiation and regeneration [18], in adipocytes [19] and liver [20] regulated energy metabolism, and involved in gastrointestinal hormone secretion in the intestinal tract [21]. The sweet taste receptor 2/3 (T1R2/3) is expressed in various parts of the body, including the gut, pancreas, brain, bladder, bone, and adipose tissue and plays a role in energy metabolism [22]. In addition, it has been shown to induce strong relaxation in the bladder [23]. The bitter taste receptor, the taste receptor 2 (T2R) receptor, is expressed in several tissues, including the lungs, gastrointestinal tract, kidneys, genitals and brain. Xie et al. described the identification of numerous T2Rs in the gastrointestinal tract [24], and they are also expressed in the brain [25], heart [26], respiratory tract [27], reproductive system [28], bone marrow stroma and the vascular wall [29]. T1R2/3 and T2R are believed to act antagonistically in regulating innate immunity in the respiratory tract [30]. Heterodimers of the taste receptors Taste receptor 1 and Taste receptor 3 (T1R1/3) regulate gastrointestinal hormones in the gastrointestinal tract [31]. It has also been reported that it controls the fertilization ability of sperm [32]. Salt-taste channels, epithelial sodium channels (ENaCs), are known to be expressed in the kidney, distal colon, bladder, stomach and lungs [33]. Almost every cell in the body expresses at least one member of the TRP channel family, which has distinct biophysical, mechanical, and pharmacological properties [34]. In particular, TRP channels involved in sensory signaling are the best characterized and have been used as experimental models to understand functional aspects.

Sensory receptors are located in different organs and are thought to have different functions, but many details remain unknown. In particular, it is not well understood how these sensory receptors in the gut react to the nutrients and phytochemicals in food, and how the subsequent signals from these food components are transmitted to the central nervous system (CNS). Recent reports suggest that food signals may contribute to homeostasis via sensory receptors in the gastrointestinal tract. For example, in the gastrointestinal tract, by the activation of GPCRs, olfactory receptors and sweet/umami/bitter taste receptors, secrete gastrointestinal hormones. These gastrointestinal (GI) hormones have been reported to activate the vagus nerve, and the stimulation is transmitted to the CNS, affecting eating and cognitive function [35,36]. As such reports accumulate, there is a growing need to investigate the importance of sensory nutrition, that is, how chemosensory signals from food contribute to maintaining homeostasis and reducing disease risk via the gastrointestinal-brain axis.

Polyphenols are the largest and most diverse group of plant secondary metabolites, with 8000 identified to date [37]. Polyphenols are known to be coloring [38], bitter [39,40]and astringent [41,42] and have a significant impact on food palatability. In addition, daily consumption of these beverages can transform astringency and bitterness, which are inherently aversive perceptions, into pleasurable stimuli [43–45]..These results suggest that changes in taste preference and avoidance due to long-term taste exposure can be considered as adaptations accompanied by neuroplasticity. However, the mechanisms by which taste preferences change over time are not yet understood. Epidemiological studies have reported a negative correlation between polyphenol intake and cardiovascular disease [46], neurodegenerative diseases [47,48], age-related deterioration of sensory organs [49]. There are reports that people who are regular consumers of astringent and bitter drinks may be less at risk of type 2 diabetes and cardiovascular diseases, such as coffee and tea [50,51]. Large-scale intake studies of polyphenols from cocoa have also shown reduced cardiovascular deaths [52] and hippocampus-dependent cognitive improvements in the elderly [53]. In general, polyphenols are rarely absorbed from the upper gastrointestinal tract and move to the lower gastrointestinal tract, where they are partly broken down by intestinal bacteria, but mostly excreted in the feces [54]. Their beneficial mechanism of action is not known because it is very unlikely to be distributed in the blood or organs, including the brain. Recent studies have reported that polyphenols ingested from the diet can alter

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the composition of the gut flora [55]. It has been reported that the composition of secondary metabolites in the colon changes accordingly and that these may be absorbed and affect cardiovascular disease and cognitive function [56]. On the other hand, it is extremely difficult to elucidate these causal relationships because the type and quantity of polyphenols ingested vary greatly with diet, and the quality and quantity of polyphenol metabolites produced by the gut microbiota and themselves vary widely between individuals.

This review therefore focuses on the interaction of bitter and astringent tastes of polyphenols with sensory receptors, particularly with those that are expressed extra-oral cavity. In addition, we summarized the results of previous studies on how signals produced by polyphenols affect the CNS via gastrointestinal sensory receptors and how such signals affect peripheral organs, and explored the mechanisms involved.

2. Bitter Taste Receptors and Polyphenols

2.1. Bitter Taste Receptors Expressed Extra-Oral Cavity and GI Hormones.

Most pharmaceuticals are considered to present a bitter taste, and it is also known that bitter substances such as alkaloids and humulones are known to be present in plant food [57]. It has been well studied that these bitter substances are recognized by T2Rs, one of the G protein-coupled receptors (GPCRs), which are seven transmembrane receptors expressed on taste buds [58–60]. In human, 25 members of the 291-334 amino acid long T2R superfamily are involved in the perception of bitter taste [61,62]. As mentioned above, T2Rs are known to be distributed in various organs outside the oral cavity [24–29]. In recent years, research has increasingly focused on the relationship between bitter taste receptors expressed in the gastrointestinal tract and gastrointestinal hormones released by endocrine cell [63,64]. Typical gastrointestinal hormones involved in these are glucose-dependent insulinotropic polypeptide (GIP), which is derived from K cells located in the upper small intestine, and glucagon-like peptides, which are secreted mainly by L cells located in the distal small intestine. Incretins such as -1 (GLP-1) [65–67]. Another hormone of particular interest is cholecystokinin (CCK), which is produced by I-cells in the upper part of the small intestine [68]. These hormones have been reported to be motility modulators of the gastropyloric duodenum that delay gastric content evacuation [68,69]. The peptides secreted by neuropodal cells inhibit the gastric inhibitory vagal motor circuit (GIVMC) via the vagus nerve and nucleus tractus solitarius (NTS), resulting in delayed gastric emptying. This mechanism is suggested to reduce appetite and thus energy intake [69,70].

In addition, the secreted incretin stimulates insulin secretion, which has been extensively studied for its ability to reduce the increase in blood glucose levels after a meal [70,71]. GLP-1 has glucagonostatic effects, and its analogue and receptor agonists are commonly used to treat type 2 diabetes [72–74]. GLP-1 receptor agonists in particular are widely used in clinical practice but are known to cause gastrointestinal complications. Therefore, it can be difficult to use this medicine as a preventative measure. On the other hand, GLP-1 secretion has been reported to be induced by oral administration of typical bitter substances such as quinine [75,76] and denatonium benzoate [77]. This has led to increased interest in drug discovery based on the interaction between bitter substances and T2Rs [78,79].

2.2. Interactions between Bitter Taste Receptors and Polyphenols

Polyphenols are chemically classified as flavonoids (Figure 1a) including flavanols, flavanones, flavones, flavonols, flavanols, isoflavones, anthocyanins), chalcones, tannins (proanthocyanidins, hydrolysable tannins, fluorotannins, complex tannins) and phenols [55,80]. Polyphenol compounds are commonly associated with a bitter taste. However, there is limited practical evidence on the degree of bitterness associated with specific compounds as determined by human sensory evaluation. The specific sub-chemical structure of polyphenols that contributes to the bitter taste remains unclear. The interaction between polyphenols and T2R has been validated by *in vitro* experiments [81]. Most of the experiments have involved the expression of human T2R in HEK293 cells, the addition of

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polyphenols and the detection of calcium influx into the cells using fluorescent probes. A comprehensive survey of these previous studies was conducted in the following method.

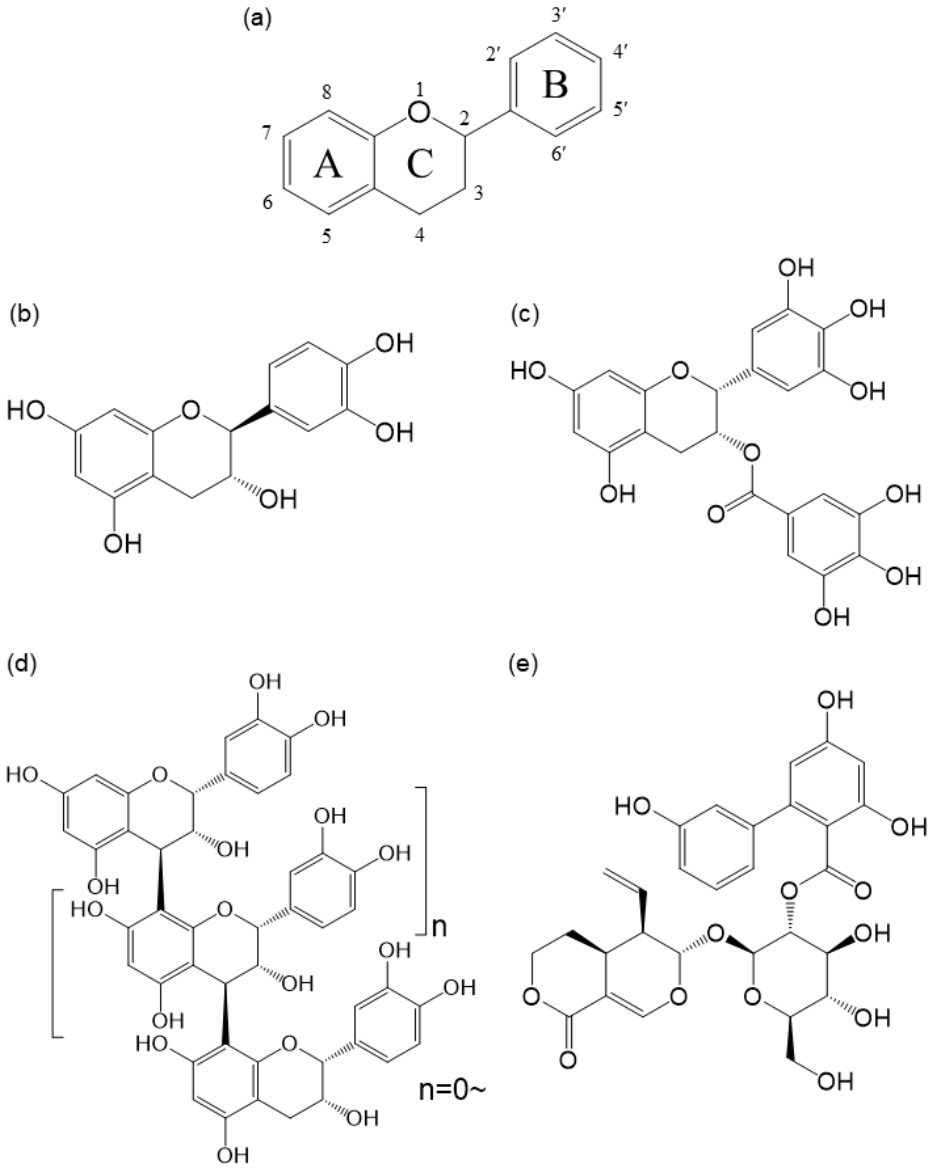

Figure 1. Chemical structure of flavonoid (a), (-)-epicatechin(b), epigallocatechin gallate (c), procyanidin(d), amarogentin (e).

The databases BitterDB (https://bitterdb.agri.huji.ac.il/dbbitter.php), Phenol explore (http://phenol-explorer.eu/) and the database of natural TAS2R agonists (https://github.com/dipizio/Natural_TAS2R_agonists) were used. Search formulae were "polyphenols" "flavonoids" "flavanols" " flavanones" "flavones" "flavonols" "flavanols" "isoflavones" "anthocyanins" "chalcones" "tannins " "pro(antho)cyanidins" "hydrolysable tannins" "fluorotannins "complex tannins" "phenols" and "taste receptor 2" "T2R" "TAS2R". The survey was conducted in June 2023.

The results showed that 102 polyphenolic compounds have been tested to present using the methods described above. The findings are summarised in Table 1. Most of the compounds interacted with T2R14 and T2R39. However, (-)-epicatechin (Figure 1b), epigallocatechin gallate (EGCG, Figure 1c) and procyanidins (Figure 1d), oligomers of epicatechin, specifically interacted with T2R5 [81]. Additionally, procyanidins were found to interact with T2R7 [81]. Castalagin, grandinin, and vescalagin are hydrolyzable tannins that interact with T2R7. These tannins have a strong bitter taste similar to procyanidin, a condensed tannin [81]. The results indicate that T2R7 may have a significant

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impact on the bitterness experienced by humans. Among these polyphenols, green tea's EGCG and amarogentin (Figure 1e), a type of secoiridoid glycoside, were found to interact with multiple T2Rs. EGCG was found to interact with T2R4, T2R5, T2R30 and T2R43 [39,81]. Amarogentin is a constituent of Gentian root, which has traditionally been used as a bitter stomachic. It has been reported to interact with eight T2Rs: T2R1, T2R4, T2R10, T2R30, T2R39, T2R43, T2R46, and T2R50 [82]. In these *in vitro* experiments, attempts have been made to calculate the EC_{50} of polyphenols that activate the T2R. The concentration range varied from a few micromoles to several tens of micromoles [39,40,82–89]. The EC_{50} values were similar to those of well-known bitter substances, such as absinthin, acetylthiourea, chloroquine, denatonium benzoate, ethylpyrazine, and methylthiourea [59]. The above suggests that polyphenols have high potential as a seed for drug design using bitterness.

Table 1. The interaction of polyphenols and T2R in vitro studies.

Table 1 The interaction of polyphenols and T2R in vitro studies

T2R	compounds
1	Isoxanthohumol（122）Resveratrol(14) Xanthohumol（122）Amarogentin(125)
3	ND
4	(-)-Epicatechin（119）Epigallocatechin gallate(46) Amarogentin(125)
5	(-)-Epicatechin（119）Epigallocatechin gallate(46) Procyanidin B1（46）Procyanidin B2g（46）Procyanidin B4（46）Procyanidin B7（46）Procyanidin C2（119）PGG(pentagalloylglucose)（119）Punicalagin（46）
7	Procyanidin B1（46）Malvidin-3-glucoside（119）Castalagin（46）Grandinin（46）Punicalagin（46）Vescalagin（46）
8	ND
9	ND
10	Amarogentin(125)
13	ND
14	(+)-Catechin（118）(-)-Epicatechin gallate（121）Epigallocatechin gallate(121) Eriodictyol（118）Flavanone（118）Hesperitin（118）Homoeriodictyol（118）Liquiritigenin（118）Naringenin（118）8-Prenylnaringenin（122）Pinocembrin（118）Luteolin（118）Nobiletin（121）Scutellarein（118）Apigenin（118）Chrysin（118）Chrysoeriol（118）Datiscetin（118）5,4-dihydroxyflavone（118）6,4-dihydroxyflavone（118）5,7,2-trihydroxyflavone（118）3,7,4-trihydroxyflavone（118）3,6,3,4-tetrahydroxyflavone（118）5,7-dimethoxyflavone（118）6,7-dimethoxyflavone（118）5,7,4-trimethoxyflavone（118）4-hydroxy-6-methoxyflavone（118）6-methoxyflavone（118）7,4'-dihydroxyflavone（118）6-methoxyluteolin（118）Flavone（118）Herbacetin（118）Isorhamnetin（118）Kaempferol（118）Morin（118）Myricetin（118）Quercetagetin（118）Quercetin（122）Taxifolin（118）Fustin（118）(±)-equol（124）Biochanin A（118）Daidzein（118）Formononetin（124）Genistein（124）Glycitein（124）Isoflavone（124）Prunetin（124）7-hydroxyisoflavone（124）7,3,4-trihydroxyisoflavone（124）6,7,4-trihydroxyisoflavone（124）7,8,4'-trihydroxyisoflavone（124）7,4-dimethoxyisoflavone（118）Cyanidin chloride（118）Pelargoninidin chloride（118）Isoxanthohumol（122）Tangeretin（121）4-hydroxychalcone（118）2,2',4'-trihydroxychalcone（118）3,2-dihydroxychalcone（118）4,2,5-trihydroxychalcone（118）Butein（118）Chalcone（118）Eriodictyol chalcone（118）Isoliquiritigenin（118）Resveratrol(118)Xanthohumol（122）Procatechuic acid（46）Ferulic acid（46）Vannillic acid（46）Coumestrol（124）Sulfuretin（118）Umbelliferone（14）Silibinin（118）
16	Arbutin（126）catechole(126)
19	ND
20	ND
30	Epigallocatechin gallate(46) Procatechuic acid（46）Amarogentin(125)
31	ND
38	ND
39	(+)-Catechin（118）(-)-Epicatechin（119）(-)-Epicatechin gallate（120）(-)-Epigallocatechin(46) Epigallocatechin gallate(46) Procyanidin B2g（46）Eriodictyol（118）Hesperitin（118）Homoeriodictyol（118）Liquiritigenin（118）Naringenin（118）Pinocembrin（118）Genkwanin（118）Luteolin（118）Scutellarein（118）Tricetin（118）Apigenin（118）Chrysin（118）Datiscetin（118）4-hydroxyflavone（118）5,2-dihydroxyflavone（118）5,4-dihydroxyflavone（118）6,4-dihydroxyflavone（118）5,7,2-trihydroxyflavone（118）3,7,4-trihydroxyflavone（118）3,6,3,4-tetrahydroxyflavone（118）5,7-dimethoxyflavone（118）6-methoxyflavone（118）7,4-dihydroxyflavone（118）6-methoxyluteolin（118）Flavone（118）Fisetin（118）Gossypetin（118）Herbacetin（118）Isorhamnetin（118）Kaempferol（118）Morin（118）Myricetin（118）Quercetagetin（118）Taxifolin（118）Fustin（118）(±)-equol（124）acetylgenistin（124）Biochanin A（118）Daidzein（118）Formononetin（124）Genistein（124）Genistin（124）Glycitein（124）Glycitin（124）Malonylgenistin（124）7-hydroxyisoflavone（124）7,3,4-trihydroxyisoflavone（124）6,7,4-trihydroxyisoflavone（124）7,8,4-trihydroxyisoflavone（124）Cyanidin chloride（118）Pelargoninidin chloride（118）2,2',4'-trihydroxychalcone（118）3,2-dihydroxychalcone（118）4,2,5'-trihydroxychalcone（118）Butein（118）Chalcone（118）Eriodictyol chalcone（118）Isoliquiritigenin（118）Resveratrol(118) PGG(pentagalloylglucose)（119）Amarogentin(125)Coumestrol（124）Sulfuretin（118）Silibinin（118）
40	Isoxanthohumol（122）Xanthohumol（122）
41	ND
42	ND
43	Epigallocatechin gallate(46) Amarogentin(125)
45	ND
46	Nobiletin（121）Tangeretin（121）Amarogentin(125)
50	Amarogentin(127)
60	ND

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Furthermore, it should be noted that the *in vitro* experiments only targeted a limited number of the 25 T2Rs, therefore the interactions with all T2Rs remain unknown. Also, due to the different experimental conditions in each report, it was unclear to what extent the calculated EC_{50} was correct. The specific sub-chemical structure of polyphenols that contributes to the bitter taste remains unclear. The unclear steric structure of T2R was partly responsible for the uncertainty involved. In 2022, Xu et al. revealed the conformation of T2R46 for the first time using cryo-EM [90]. This paper showed that when the ligand strychnine binds to T2R46 in the apo state and activates the receptor, Y241 acts as a 'toggle switch'. Meanwhile, DeepMind has developed an AI system so called "AlphaFold" predicts the 3D structure of proteins, including an estimated structure of 25 T2Rs in humans "https://www.proteinatlas.org/search/tas2r". Docking simulation methods and/or molecular dynamics simulation methods, etc. can be used to calculate the binding mode and binding energy of T2R and the ligand polyphenol based on available information. These methods would reveal the partial structure of polyphenols and their respective affinities for bitter taste receptors. Subsequent results could be applied to the discovery of bitter-based medicines.

3. Astringent Taste Receptors and Polyphenols

3.1. Mechanisms of Astringent Taste Perception

Astringency is a taste that is specific to polyphenols, and bitter compounds can be either synthetic chemicals, such as pharmaceuticals, or natural products. Astringency is a sensory attribute that is often described as a drying, roughening, and puckering sensation in the mouth. Astringency is a common characteristic of anthocyanins, flavanols (including catechins, gallated catechins, and procyanidins), and hydrolyzed tannins [41,91]. Furthermore, it is a crucial factor in determining the quality of foods and drinks such as berries, red wine and chocolate. However, the mechanisms by which astringent polyphenol stimuli are recognized remain unclear. Taste refers to the sensation resulting from direct stimulation of taste receptors in the taste buds. The taste sensation is transmitted centrally via the sensory branches of the facial nerve (VII), the glossopharyngeal nerve (IX) or the vagus nerve (X) [92]. In contrast, somatosensation is transmitted by the general sensory branches of the trigeminal (V), glossopharyngeal (IX) or vagus (X) nerves [93]. Astringency, rather than taste, has been reported to be transmitted as somatosensory information via the trigeminal nerve [94]. The mucosa surrounding taste buds contains various somatosensory receptors, such as mechanoreceptors, temperature receptors, and nociceptors [95]. It is thought that humans perceive "flavor" through complex multisensory inputs in the oral cavity and olfactory inputs from the back of the nose that are transmitted to the CNS. Previous fMRI studies in humans have reported that the primary taste cortex, the insular cortex, is activated not only by sweet taste stimuli but also by somatosensory capsaicin and astringent taste stimuli, and that these three types of stimuli activate overlapping subregions [96]. Astringency has been reported to activate not only the insular cortex, a transient taste area, but also the superior orbitofrontal cortex, the cingulate cortex and frontal inferior triangularis with the intensity of activation being greater than that of sweet taste or capsaicin [96]. On the other hand, astringency was attributed to oral friction caused by the interaction of polyphenols with proline-rich proteins in saliva, which are recognized by mechanotropic receptors [41,42]. This theory is explained by a three-stage model in which a reversible bond between the hydrophobic face of the aromatic ring of the polyphenol and the pyrrolidine ring of the proline residue of the protein first forms a soluble complex, additional polyphenols cross-link these peptides to form a larger insoluble complex, which then aggregates further [97]. However, it is not known whether such complex reactions take place in the oral cavity in the short time between food ingestion and swallowing. It has also recently been reported that interactions with mucins in saliva may also be involved in the formation of astringent taste sensations [98]. But the target molecules that recognize this phenomenon are not at all clear. According to this theory, salivary proteins or mucins are essential for mammals to recognise astringent tastes. However, recent reports have shown that astringent polyphenols can activate GPCRs [94] or TRPs [99–101] and trigger the activity of the trigeminal nerve independently of saliva and mucins. In summary, the perception of astringency

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does not necessarily require the presence of saliva or mucin, suggesting that it is not a taste, but rather a type of somatosensory perception.

3.2. Astringent Polyphenols and Stress Response

Consumption of cocoa extracts, which are rich in flavanols, a type of astringent polyphenol, can significantly reduce risk of cardiovascular diseases [52]. A significant reduction in the number of cardiovascular events and deaths from cardiovascular disease was observed when elderly people were given an average of 500 mg of flavanols per day for 3.6 years. Repeated flavanols are also known to improve blood pressure a risk factors for cardiovascular disease [102,103]. Furthermore, a lot of intervention trials have demonstrated that two hours following a single intake of flavanol, there was a significant increase in blood flow-dependent vasorelaxation (FMD) levels [104]. There are also reports of an optimal dosage for these effects, known as hormesis, where the effects are attenuated at low or high doses [105–107]. The hormetic concept is based on the idea that low levels of stress up-regulate adaptive responses that not only precondition, repair and restore normal function to damaged tissues/organs, but also modestly over-compensate, reducing ongoing background damage [108–110]. We have focused on the results of this study and developed an evaluation system to reproduce this effect in experimental animals [111]. A marked increase in blood flow in skeletal muscle arterioles was observed immediately after ingestion of the cocoa-derived flavanol fraction in rats [112]. In addition, it was found that at doses generally taken by humans from food (10 mg/kg), this blood flow-increasing effect was observed, but at doses 10 times higher, the effect disappeared [113]. In experimental animals, hormesis was also observed, similar to that found in humans regarding hemodynamic alterations. It is widely recognized that exposure to stress in mammals leads to an increase in sympathetic nerve activity, causing alterations in the circulatory system [114,115]. There were several experiments conducted using adrenergic receptor inhibitors to investigate the relationship between these effects and the sympathetic nervous system. The results suggests that the rapid changes in hemodynamics after a single dose of flavanols were mediated by adrenergic receptors [113,116]. Furthermore, it has been suggested that the haemodynamic absence seen with high doses of flavanols compared to low doses was due to activation of α2 receptors, the central autoreceptor [113,116]. Similarly, single doses of anthocyanins, polyphenols with an astringent taste, showed circulatory changes via sympathoadrenergic receptors [117]. Increased sympathetic activity is also known to promote white to beige fat cell conversion and skeletal muscle protein formation [118]. After being administered a flavanol fraction from cocoa for two weeks, browning was shown in mice inguinal adipose tissue. This was characterized by polycytosis of fat, a marked reduction in adipocyte size, and increased expression of the heat-producing protein, uncoupling protein 1 (UCP-1) [119]. Repeated administration of the flavanol cinnamomycin A2 (A2) for two weeks also resulted in significant activation of the Akt/mTOR pathway and a marked increase in mean muscle cross-sectional area in the soleus muscle [120]. It has also been observed that after a single dose of flavanol, blood catecholamine levels were significantly increased [121] and urinary catecholamine excretion was also elevated [119]. Sympathetic nerve activity is known to be increased by stress. Examples include spicy substances such as capsaicin [122], temperature changes [123] and exercise [124]. It is known that when mammals are exposed to stress, activation of the hypothalamic-pituitary-adrenal axis (HPA) occurs along with hyperactivation of sympathetic nervous [125]. To confirm that the effects of astringent polyphenols on circulatory dynamics are a stress response response, we administered a single dose of flavanols and observed their effects on the HPA axis. The results showed a significant increase in the expression of the stress hormone corticotropin-releasing hormone (CRH) mRNA in the paraventricular nucleus of the mouse hypothalamus [126,127]. It was found that the duration of CRH mRNA expression onset shortened as the doses increased. A subsequent increase in blood cortisol (or corticosterone in rodents) levels was confirmed. The administration of astringent polyphenols leads to hyperactivation of sympathetic nervous and activation of the HPA axis in mammals, indicating that astringency is perceived as a stressor.

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3.3. Astringent Polyphenols and TRP Channels

According to the research results to date, it seems that astringency is likely to be a somatic sensation [94,95]. Schöbel et al. reported that the sensation of astringency is not impaired in human subjects when the taste nerve is denervated or blocked by local anaesthesia. In addition, they showed that salty, sweet, sour and bitter tastes were almost completely lost in these subjects, and that subjects lost the sensation of astringency only when both trigeminal and gustatory nerves were blocked [94]. In 1997, it was demonstrated that the somatic sensation caused by capsaicin stimulation is recognized by Transient Receptor Potential V1 (TRPV1), which is one of the nociceptors [128]. In mammals, there are 28 different TRP channel proteins expressed, which are classified into seven subfamilies based on amino acid sequence homology [34]. TRP channels are involved in a variety of sensory responses, including heat, cold, pain, stress, vision and taste, and are activated by a number of stimuli. These channels are composed of six transmembrane polypeptide subunits that assemble as a tetramer to form a cation-permeable pore [129]. TRP vanilloid 1 and ankyrin 1 (TRPV1 and TRPA1) are expressed mainly in sensory neurons and are also distributed in the oral and gastrointestinal tracts [130,131]. It is widely recognized that capsaicin activates sympathoexcitation via the CNS by activating TRPV1 expressed on sensory nerves, thereby promoting heat production [132] and altering hemodynamics [133]. The astringent polyphenol flavanols have been observed to have the same effect described as above. Interactions between TRP channels and astringent polyphenols have been reported in several cellular experiments [99–101]. In Ca^{2+} imaging experiments, it has been reported that EGCG, an astringent and bitter polyphenol, activates the mouse enteroendocrine cell line STC-1. TRPA1 receptor inhibitors canceled this effect [100]. We investigated whether astringent polyphenols activate TRP channels and investigated the involvement of TRP channels in the effect of increasing blood flow in rats. The rats were administered flavanol, A2, and TRPV1 or TRPA1 channel inhibitors simultaneously through single oral doses. The marked increase in blood flow observed with A2 alone was eliminated by the combined use of TRP channel inhibitors [134]. These findings suggest that TRP channels contribute to the sympathetic hyperactivity of flavanols as a stress response. The interaction between A2 and each TRP channel was then observed using modeling simulation methods. The binding energies of the A2 and ligand binding sites for each TRP channel were relatively high. These results suggested that there was no direct interaction between them [134].

Polyphenols are stored in vacuoles within plants, which have a weakly acidic pH of 4-5, and are stable [135]. However, when consumed by mammals, they are exposed to neutral pH conditions in gut such as the mouth, small intestine, and large intestine. It is widely recognized that flavanols [136] and anthocyanins [137], which are astringent polyphenols, undergo rapid oxidation and decomposition or condensation under neutral pH. In our study, (-)-epicatechin (EC) and its tetramer, A2, also showed superoxide radical ($O_2^{\cdot -}$) scavenging activity at acidic pH but significantly enhanced $O_2^{\cdot -}$ production under neutral pH [134]. Furthermore, an *in vitro* study conducted on TRP channel-expressing HEK293 cells has demonstrated that oxidized EGCG, which was incubatied at neutral pH for several hours, significantly enhances calcium influx [101]. In contrast, freshly dissolved, non-oxidized EGCG showed no such effect. In measuring peripheral vascular blood flow in rats after co-administration of $O_2^{\cdot -}$ scavengers and A2, the blood flow increasing effect observed with A2 alone was nullified [134].

It was reported that TRPV1 and TRPA1 can be activated by reactive oxygen species (ROS) through cytoplasmic side cysteine residues [138]. In hTRPV1, Cys-258 is highly oxidizable, leading to the formation of a disulfide bond between Cys-258 and Cys-742, which opens the channel [139]. In TRPA1, mutational analysis has reported the presence of multiple reactive oxygen species domains, including Cys421, Cys621, Cys641 and Cys665 [140]. These findings suggest that orally ingested flavanols and anthocyanins produce ROS in the neutral pH environment of the gastrointestinal tract, which are oxidatively degraded by successive oxidative reactions in the molecule, and the produced ROS may interact with the ROS recognition domain of the TRP channel and become activated (Figure 2). Furthermore, the responses of ROS-TRP channels on sensory nerves could be perceived in the

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CNS as an astringent taste. However, further research is needed on how TRP channels are involved in the mechanism of astringent taste perception.

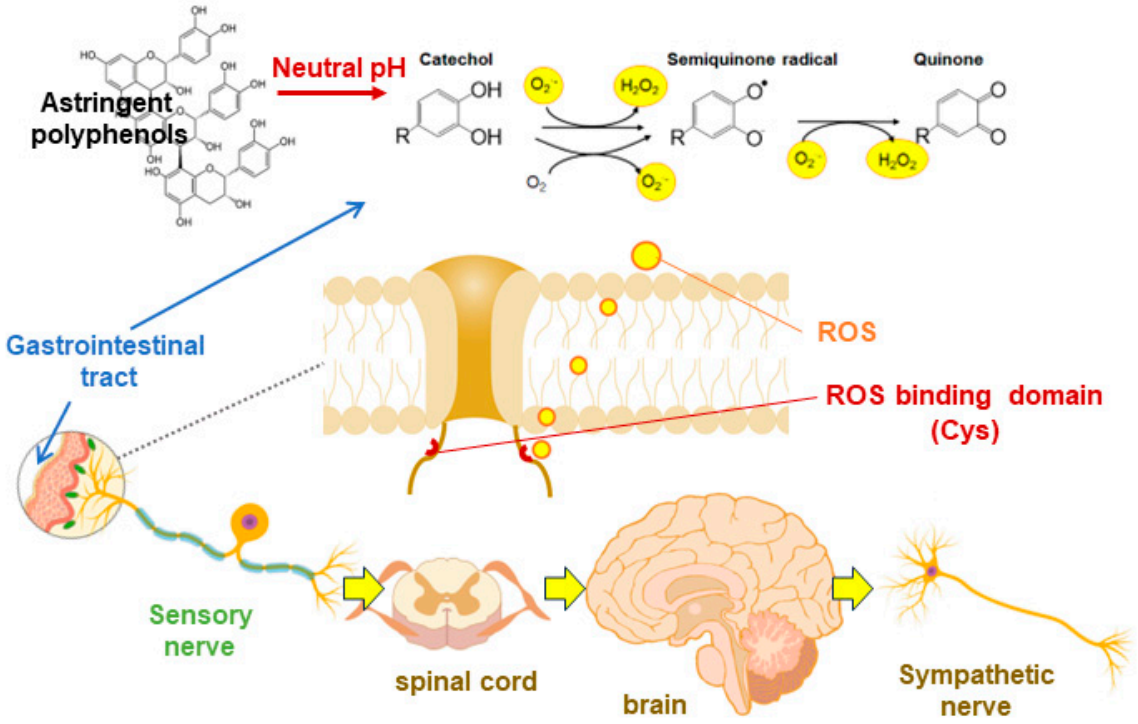

Figure 2. Hypothetical recognition mechanism of astringent polyphenols by TRP channel.

4. Bioavailability of Polyphenols

Numerous studies have been conducted on the bioavailability of polyphenols [141–143]. Although a proportion of ingested polyphenols are absorbed in the small intestine, the rate and total amount of absorption of polyphenols are known to be strongly influenced by their chemical structure. Compared to their bioavailability in humans, the urinary excretion of most polyphenols is a few percent, whereas the excretion of astringent polyphenols such as anthocyanins and flavanols is quite low [144]. Flavonoids as one of the main polyphenols are compounds with a 3,4-dihydro-2-phenyl-2H-1-benzopyran structure and there might be an inverse correlation between the number of hydroxyl groups in the B-ring and bioavailability. For example, in an intervention study, the urinary excretion rate of pelargonidin, an anthocyanin aglycon with a single hydroxyl group on the B-ring, was reported to be 1.8% [145]. In contrast, cyanidin, which has two hydroxyl groups, is around 0.1% [146]. Methylated flavonoids, which have methoxy groups on the B ring, are also known to be highly absorbable [147]. These differences in absorption may depend on the chemical stability of polyphenols in the neutral to slightly alkaline conditions of the small intestine. For example, cyanididins are readily degraded under neutral pH conditions to protocatechuic acid (PCA) and phloroglucinaldehyde (PGA), and it has been reported that blood concentrations of the degradation product PGA were four times higher than those of cyanidin [148]. Most polyphenolic compounds are known to be glucuronidated or sulfated by the small intestine or liver and exist as metabolites in the blood [54]. These metabolites have difficulty penetrating cell membranes because they are more water soluble. Ingested polyphenols pass through the upper gastrointestinal tract and reach the large intestine. Ingested polyphenols pass through the upper gastrointestinal tract and reach the large intestine. A part of ingested polyphenols is known to be degraded by intestinal bacteria in the colon. Several comprehensive reviews of these have been reported so far [149–151]. However, the amount and type of metabolic degradation of polyphenols by gut bacteria relative to the total polyphenols consumed, and the kinetics of this degradation, is not well understood. Unlike nutrients and easily absorbed chemicals, such as fat-soluble substances, ingested polyphenols are present in high

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concentrations in the oral cavity, stomach, small and large intestines. Therefore, until they are excreted from the body as feces, they keep in contact with I-, K- and L-cells that express bitter taste receptors, or with gastrointestinal sensory nerves and epithelial cells that express TRP channels for an extended period. Considering these behaviours in the gastrointestinal tract, it is likely that polyphenols exert their various physiological effects via sensory receptors expressed in the gastrointestinal tract.

5. Biological Regulation through Bitter and Astringency of Polyphenols

Polyphenols have been shown in epidemiological studies to have the potential to prevent cardiovascular disease, neurodegenerative diseases, and age-related sensory organ deterioration [46–49]. Large-scale intervention trial of flavanols have also reported reduced cardiovascular mortality [52] and hippocampus-dependent improvements in cognitive function [53]. As previously discussed, the nervous system including CNS plays a significant role in controlling obese, hyperglycaemia, dyslipidaemia, and hypertension, all of which are risk factors for cardiovascular disease [152]. However, it is important to note that polyphenols are poorly absorbed and, even if absorbed, are only present in the blood as metabolites. Therefore, it is unlikely that they can pass through the blood-brain barrier (BBB) and be distributed in the brain. There is no discussion of how bitterness and astringency contribute to these effects. In considering the mechanisms of these beneficial effects of polyphenols, we proposed to discuss the involvement of afferent and efferent nerve. The following is a review of the various physiological effects of polyphenols reported so far and how they contribute to bitter and astringent tastes.

5.1. Circulation and Polyphenol

The effects of cocoa astringent flavanol on the circulatory system are well studied: a meta-analysis of RCTs of adult participants at cardiometabolic risk reported between 2000 and 2021 observed a marked increase in FMD [153]. These activities on FMD of astringent anthocyanin [154] was also confirmed by the meta-analyses. On the other hand, for compounds without a pronounced taste, such as resveratrol [155] or isoflavones [156], the onset of action has been reported to depend on the study design. There are few reports of other polyphenol enhancement in FMD, it is because many experiments have been conducted with mixtures, therefore the main compounds cannot be limited. FMD-enhancing effect of a single dose of flavanols shows a non-linear hormesis response [106,107]. Anthocyanins, [105,157] or flavanol [105] have been reported to be more effective on FMD in single oral doses compared to repeated doses. In addition, repeated intake of these polyphenols is also well known to affect blood pressure [158]. In particular, meta-analyses have shown that repeated intake of flavanols significantly reduces systolic and diastolic blood pressure [54,159].

In experimental animal studies, a single oral administration of flavanols or anthocyanins also results in a significant increase in blood flow of skeletal muscle arteriole [112,113,117]. Furthermore, repeated administration of these chemicals considerably decreased the mean blood pressure in rodent [160,161]. These modifications are consistent with the changes that occur in the circulatory system as a result of exercise (Figure 3).

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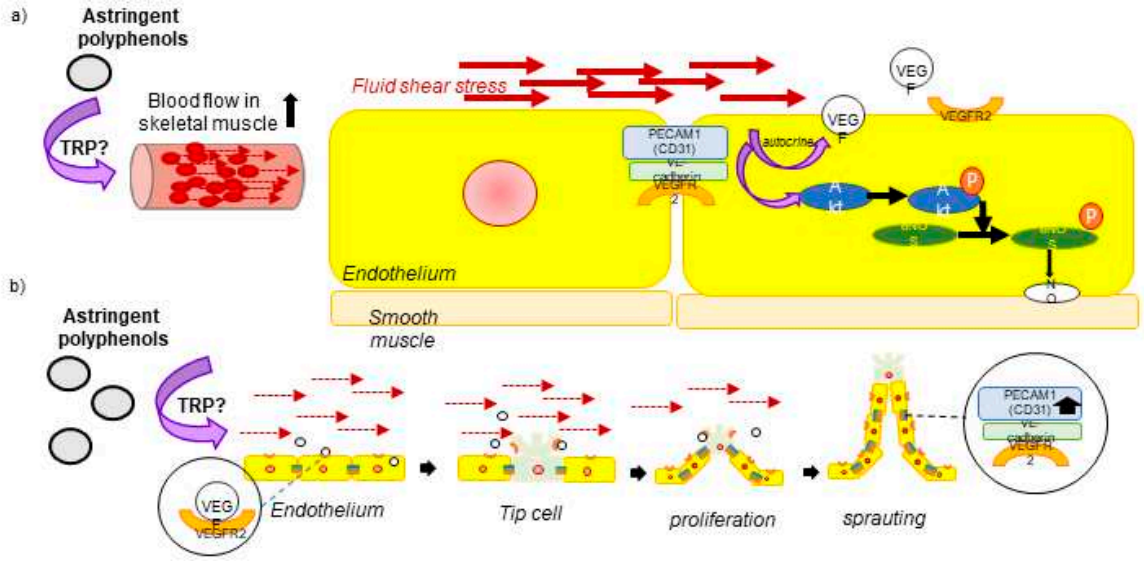

Figure 3. Illustrations of two hypotheses for the mechanisms underlying the observed effects of a single (a) and repeated oral administration (b) of astringent polyphenols on micro-and systemic circulation.

In brief, exercise induces acute changes in the microcirculation, which consequently leads to changes in the systemic circulation [159]. Exercise increases skeletal muscle blood flow through hyperactivation of the sympathetic nervous system, subsequently inducing shear stress on vascular endothelial cells [162]. Mechanosensors consisting of vascular endothelial growth factor (VEGF) receptor 2, vascular endothelial (VE) cadherin and CD31 (platelet endothelial cell adhesion molecule-1, PECAM-1) expressed on endothelial cells respond to shear stress and release vasorelaxing factor NO via the Akt /eNOS pathway, causing the vessel to relax [163]. (Figure 3a). The rise in FMD resulting from astringent polyphenols observed in intervention trials may be attributed to these alterations in hemodynamics. In addition, these alteration leads to the differentiation of vascular endothelial cells via mechanosensors, With the repetition of the exercise, these changes in hemodynamics are also repeated and are known to trigger the formation of new capillaries [164]. Continuous fluid shear stress angiogenesis through the cellular production of proangiogenic growth factors, such as VEGF. Resting endothelial cells are transformed into tip cells by the secretion of angiogenesis-promoting factors from a hypoxic or metabolically active microenvironment [165]. These tip cells proliferate to become stalk cells, which extend a growing sprout and form a lumen. Once the two spraut fuse, they form a capillary tube, which lowers the resistance to blood flow, and the endothelial cells return to quiescence. In this quiescent state, endothelial cells produce mechano-sensing complexes and form tight junctions [166] (Figure 3b). These factors lead to angiogenesis, which is an increase in blood vessel volume and a decrease in blood pressure.

In rodent studies, a single administration of astringent polyphenols induced phosphorylation of eNOS in the aorta [112,113,117,161,167]. Moreover, repeated administration of astringent polyphenols to rodents has been shown to lower blood pressure. Furthermore, repeated administration reduced blood pressure and significantly increased CD31 expression, a marker of neovascularization, in the soleus [161]. This change suggested the promotion of angiogenesis. This process of angiogenesis increases vascular capacity, reducing the risk of exposure to shear stress. Therefore, repeated ingestion of astringent polyphenols might result in a decrease in blood pressure along with a reduction in the FMD response.

5.2. Blood Glucose and Polyphenols

Interest in using bitter compounds to improve glucose tolerance by stimulating gastrointestinal hormone secretion has recently increased [78,79]. Most polyphenols have a bitter taste and low bioavailability, which makes them potentially useful for this objective. For example, interventional

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studies have been conducted on changes in glucose tolerance and blood levels of incretin after single doses of green tea flavanol [168], coffee chlorogenic acid [169,170] or combinations thereof [168], olive oleuropein [171] and anthocyanin fraction from blackcurrant [172] in healthy subjects. Intake of 540 mg of green tea flavanol reduced the increase in blood glucose levels caused by a high-fat, high-carbohydrate diet, increased blood levels of GLP-1 and reduced GIP levels [168]. In addition, when 355 mg of chlorogenic acid was given to healthy subjects, an increase in blood levels of GLP-1 was only observed in subjects with a low insulinogenic index [170]. These combinations (beverages containing 540 mg of green tea flavanols and 150 mg of chlorogenic acid) have also been reported to reduce the rise in blood glucose, increase blood GLP-1 levels and reduce GIP levels after consumption of high-fat, high-carbohydrate cookies [168]. A single oral dose of oleuropein (20 mg) decreased blood glucose and dipeptidyl peptidase (DPP)-4 levels, which inactivates active GLP-1, and increased blood levels of GLP-1 and insulin 2 hours after consumption of the test meal [171]. These findings suggest that a single ingestion of bitter polyphenols may increase incretin secretion from gastrointestinal secretory cells, promote active incretin retention, induce insulin secretion, and suppress meal-derived blood glucose levels after a few hours. Improvements in glucose tolerance as measured by the homeostatic model assessment for insulin resistance (HOMA-IR) have been reported in studies investigating repeated administration of green tea flavanol, either alone [173] or in combination with chlorogenic acid [174], pine bark flavanol [175], acacia flavanols [176], red wine polyphenol [177], eriocitrin [178], and curcumin [179]. However, reports were suggesting that repeated intake of resveratrol can improve insulin resistance [180], or that no benefit is observed [181]. Further research is needed to determine the specific types and amounts of polyphenols that are effective in improving glucose tolerance. Yusoff et al. showed that the antidiabetic effect can depend on the chemical structure of the flavonoid [182]. It was reported that flavonoids with antidiabetic activity should have a C2-C3 double bond (C ring) in both the A and B rings of the flavonoid skeleton and hydroxyl groups in the C3', C4', C5 and C7 positions (Figure 1a). The study results demonstrate that the beneficial activity of polyphenols is highly variable, depending on the chemical structure. Therefore, for drug discovery, studies that elucidate the subchemical structures of polyphenols essential for T2R activation are crucial.

5.3. Obesity and Polyphenols

It has been suggested that consuming polyphenols may help to control obesity [183,184]. A meta-analysis of clinical trials published between 2010 and 2021 showed that polyphenols produced statistically significant reductions in body weight, BMI and abdominal circumference, but no significant reduction in body fat. Subgroup analyses showed that polyphenol intake had significant effects in subjects under 50 years of age, in the Asian population and in patients with obesity-related health problems, for more than three months and at doses of around 220 mg d-[185]. To date, the anti-obesity effects of polyphenols have been attributed to (1) appetite suppression, (2) reduced digestion and absorption of lipids and carbohydrates through inhibition of digestive enzymes, (3) adipocyte differentiation, (4) regulation of lipid metabolism, (5) stimulation of energy expenditure, (6) improvement of intestinal microflora, (7) amelioration of obesity-related mild inflammation; and (8) reduction of oxidative stress [186–188]. However, it should be noted that the bioavailability of polyphenols is very low. While they may inhibit digestive enzymes and improve gut microbiota, other effects are likely to be secondary. As mentioned above, bitter substances such as polyphenols may reduce energy intake due to suppressed appetite via the secretion of gastrointestinal hormones, resulting in vagus nervous stimulation [24,69]. Polyphenols appear to have a similar effect to GLP-1 analogues in weight loss by suppressing appetite and reducing gastric emptying [189,190]. Increased sympathetic activity after ingestion of astringent polyphenols is thought to cause fat browning as confirmed in the study using rodent [119]. In addition, this promotion of lipid oxidation induced by the consumption of astringent polyphenols has also been shown to increase HDL cholesterol levels in the blood [191,192]. Many of the hypotheses proposed as mechanisms for the anti-obesity effects of polyphenols can be explained by their bitter or astringent taste.

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5.4. Brain Function and Polyphenol

Gastrointestinal hormones secreted by the ingestion of polyphenols have been reported to activate the vagus nerve as a neurotransmitter [193]. Gastrointestinal hormones are secreted by neuropodal cells in response to bitter, sweet and umami taste stimuli, and this sensory information is transmitted directly to the mNTS within milliseconds [194–196]. Upstream of the NTS, it projects to multiple brain regions, as well as transsynaptically to the dorsal hippocampus [197] and frontal cortex [198]. These sensory transmissions have been shown to improve mood and memory in studies using severed gastrointestinal vagus nerves [194]. Recently, results from intervention studies have shown that stimulating the vagus nerve can help depression recovery [199]. The bitterness of polyphenols may play a role in the homeostasis of the brain.

Polyphenols with a markedly astringent taste have been shown to trigger the stress response and to activate the hypothalamic-pituitary-adrenal (HPA) axis with an increase in sympathetic activity [126,127]. Stress causes CRH to be secreted from the paraventricular nucleus of the hypothalamus into the pituitary portal system, stimulating the anterior pituitary to release adrenocorticotropic hormone (ACTH) [200]. ACTH subsequently circulates to the adrenal glands and stimulates the release of cortisol into the blood [201]. Cortisol readily crosses BBB and binds to receptors in the amygdala, prefrontal cortex and hippocampus [202]. Chronic stress is an allosteric load and excess cortisol is released by the adrenal glands [203]. The resulting prolonged activation of neuroendocrine, cardiovascular and emotional responses can be damaging to health with increased cardiovascular risk, cognitive dysfunction and depressive mood [204]. On the other hand, exercise has also been reported to activate the HPA axis and increase blood cortisol levels, despite its benefits for cognition, and mood and promoting adult neurogenesis [205,206]. A cortisol paradox between chronic stress and exercise on brain function has been observed [207–209]. The reason for this paradox is unclear, but one possibility is the involvement of cortisol-glucocorticoid receptor (GR)-dopamine (DA)-dopamine D2 receptors [210]; Cortisol secreted into the blood activates GR in medial prefrontal cortex and enhances glutamatergic input from mPFC to ventral tegmental area (VTA). This input to the VTA enhances the projection of DA neurons from the VTA to the mPFC. This increase in DA in the mPFC activates GABAergic neurons in the nucleus of the anterior nucleus of the terminal line (aBNST), which project to the paraventricular nucleus (PVH) of the hypothalamus. It provides negative feedback control and prevents over-reaction of the HPA axis [210]. These mechanisms suggest that exercise may have the effect of reducing excessive HPA activation and improving mood and memory function, despite increasing basal levels of glucocorticoids. In a large intervention study in elderly subjects, 3.6 years of cocoa extract, mainly composed of astringent polyphenols, was reported to restore hippocampus-dependent memory in participants in the lower tertile of habitual diet quality or flavanol intake [53]. In rodents, repeated administration of highly astringent catechin tetramers A2 has also been shown to improve spatial memory with enhanced adult neurogenesis [211]. In summary, astringent stimulation may benefit brain function via the GR-DA-DAR pathway as well as exercise, but much more research is needed to elucidate the mechanism.

6. Conclusion

The consumption of polyphenols id beneficial for the maintenance and promotion of human health. However, the mechanisms remain unclear. As most polyphenols have a bitter taste, migrate from the oral cavity to the gastrointestinal tract and interact with intestinal secretory cells, they likely regulate sugar metabolism or feeding via the T2R. On the other hand, if we consider the effects of astringent polyphenols on the circulatory system, metabolism and brain function, their effects have a great deal in common with the benefits of exercise. Astringency, which is considered a stressor, is believed to have beneficial effects due to hormesis. Research on the bio-modulation of polyphenols with taste, which has not received much attention to date, may provide a solution to the polyphenol paradox, in which polyphenols exert bio-regulatory effects despite their extremely low bioavailability.

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