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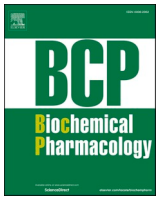

Review

Bitter taste receptors: Key target to understand the effects of polyphenols on glucose and body weight homeostasis. Pathophysiological and pharmacological implications

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ABSTRACT

Experimental and clinical research has reported beneficial effects of polyphenol intake on high prevalent diseases such as type 2 diabetes and obesity. These phytochemicals are ligands of taste 2 receptors (T2Rs) that have been recently located in a variety of organs and extra-oral tissues. Therefore, the interaction between polyphenol and T2Rs in brain structures can play a direct effect on appetite/satiety regulation and food intake. T2Rs are also expressed along the digestive tract, and their interaction with polyphenols can induce the release of gastrointestinal hormones (e.g., ghrelin, GLP-1, CCK) influencing appetite, gastrointestinal functionally, and glycemia control. Intestinal microbiota can also influence on network effects of polyphenols-T2Rs interaction and vice versa, impacting innate immune responses and consequently on gut functionally. Furthermore, polyphenols binding to T2Rs present important effects on adipose tissue metabolism. Interestingly, T2R polymorphism could, at least partially, explain the inter-individual variability of the effects of polyphenols on glucose and body weight homeostasis. Together, these factors can contribute to understand the beneficial effects of polyphenol-rich diets but also might aid in identifying new pharmacological pathway targets for the treatment of diabetes and obesity.

1. Introduction. Bitter taste receptors

Humans have developed through evolution a sophisticate sense of taste to survive in a complex environment eating an omnivorous diet. Sweet, salty and umami tastes allow to evaluate the nutritional content (monosaccharides, minerals and amino acids, respectively) of foods whereas bitter and sour perception helps to avoid the intake of potentially harmful substances and recognize fermented, spoiled, or unripe foods. Bitterness is sensed by at least 25 subtypes of the Taste type 2 Receptor (T2Rs) [1]. The ligands that activate these receptors include plant-derived metabolites such as alkaloids, polyphenols, bacterial quorum-sensing molecules, chemicals secreted by bacteria and/or by-products of cell metabolism and synthetic compounds such as pharmaceutical drugs.

Bitter taste perception begins when bitter taste-eliciting compounds interact with the taste receptor proteins i.e., G-protein coupled receptors that are expressed in type II taste receptor cells in taste buds present in the tongue and oropharynx. T2Rs are generally considered to function as monomers, although evidence suggests that are also formed as heterodimers [2]. T2Rs can detect thousands of bitter molecules, as each T2R can bind to a range of ligands. Certain receptors are broadly tuned and respond to several bitter agonists (“generalists”, as T2R14), others have a narrow range of ligands (“specialist”, as T2R38), while the ligands for others remain unidentified (Fig. 1). On the other hand, more than 150 single nucleotide polymorphisms have been discovered in human T2Rs coding regions [3]. T2R38 together with T2R3, T2R4, T2R5 and T2R16 present high level of polymorphism [4], resulting in a variety of phenotypes. Consequently, T2Rs exhibit a large threshold variability, a fact

Abbreviations: BMI, body mass index; CKK, cholecystokinin; GLP-1, glucagon like-peptide 1; HGNC, HUGO Gene Nomenclature Committee; INS, insulin; PROP, 6-n-propylthiouracil; PTC, phenylthiocarbamide; SNP, single nucleotide polymorphisms; T2Rs, taste type 2 receptors.

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that impacts on bitter taste sensitivity [5]. For example, three single-nucleotide polymorphisms (SNPs) in T2R38 have been identified, giving rise to five different haplotypes. The most common two haplotypes are proline-alanine-valine (PAV) and alanine-valine-isoleucine (AVI), being PAV homozygotes the individuals that perceive the greatest bitterness from e.g., phenylthiocarbamide (PTC) and 6-*n*-propylthiouracil (PROP) [6]. Thus, subjects can be classified as "supertasters" or "tasters" when present high or medium taste sensitivity (low or medium taste thresholds), or "non-tasters" when virtually do only recognise specific T2R38 ligands at high concentration levels.

T2R polymorphisms influence oral detection and might be involved in food preference and intake [7,8]. Therefore, bitter receptors may also play a role in modulating dietary intake of healthful foods, including many vegetables that contain bitter compounds such as isothiocyanates, polyphenols or other bioactive compounds [9]. Additionally, the expression of these receptors is not only limited to the taste buds in the oral cavity. Indeed, their ectopic expression has been reported in a variety of organs and extra-oral tissues such as lung, brain, and heart [10–12], suggesting additional functions for these receptors beyond taste perception [13]. Numerous drugs taste bitter because of activating T2Rs, including analgesic, anti-inflammatory, antibiotics, anti-asthmatic, antithyroid, immunosuppressives, antitussives, muscle relaxants, laxatives, antiemetics, antispasmodic, antipsychotics, antiarrhythmics or antimalaria drugs. On the other hand, polyphenols [9] and other bitter-tasting phytochemicals [14] could similarly exert some of their physiological actions via interaction with extra-oral T2Rs if target concentrations are high enough. For example, genistein activates T2R14 and T2R39 between 4 and 8 μM [15], concentrations that can be reached into the intestine in determined conditions [16]. While useful databases of bitter ligands are available [17,18], in the absence of selective/specific pharmacological reagents, defining the exact actions of the systemically expressed T2Rs has been challenging. Nevertheless, the association of T2R activity with respiratory function, innate immunity or cardiac depression are exciting and provocative, suggesting that these T2Rs play a role in the maintenance of homeostasis, as well as providing an additional defence against pathogens. Thus, as ancient traditional wisdom says, "Good medicine always tastes bitter". Now, this could be verified through scientific research.

T2Rs expressed throughout the gastrointestinal tract (Table 1) are thought to be involved in the gastrointestinal functionality [19] and glucose homeostasis [20]. In addition, functional T2R variants are associated with obesity via the modulation of dietary intake and/or by the regulation of gastrointestinal hormones [21], and consequently the modulation of appetite and satiation [7,22]. The development of metformin for treating type 2 diabetes originated from a traditional herbal remedy (*Galega officinalis*) serves as a successful example for bitter herbal medicine-based drug discovery with important clinical implications [23,24]. Despite this, the complete picture of the physiological, pathophysiological, and pharmacological implications of intrinsic bitter characteristics of some compounds for treating type 2 diabetes and obesity remain undefined. This review aims to grow the understanding of bitter receptors and bitter agonists in health and disease conditions. Here, we hypothesize that T2Rs constitute an unrecognized chemosensory network that can be intentionally targeted with bioactive compounds (e.g., polyphenols) or drugs, or that could be involved in the basis of off-target effects of bioactive compounds in food and pharmaceutical agents. Interestingly, the genetic variance of T2Rs (polymorphism), coupled with their key roles in health and disease, makes T2Rs an important subject of investigation that may open the door for novel therapeutics in the future.

Table 1
Expression of T2Rs along the gastrointestinal tract.

Organ	Expression of T2Rs
Oral cavity	T2R1, T2R3, T2R4, T2R5, T2R7, T2R8, T2R9, T2R10, T2R13, T2R14, T2R16, T2R20, T2R30, T2R31, T2R38, T2R39, T2R40, T2R42, T2R43, T2R44, T2R45, T2R46, T2R47, T2R49, T2R50, T2R60
Stomach	T2R38
Duodenum	ND
Jejunum	T2R4, T2R5, T2R7, T2R8, T2R10, T2R13, T2R14, T2R20, T2R30, T2R31, T2R38, T2R39, T2R43, T2R46
Ileum	ND
Colon	T2R1, T2R3, T2R4, T2R5, T2R10, T2R13, T2R14, T2R16, T2R30, T2R38, T2R39, T2R40, T2R42, T2R43, T2R44, T2R45, T2R46, T2R47, T2R49, T2R50, T2R60

ND, non detected. This table contents have been elaborated from references [85,90,98,99,100,101].

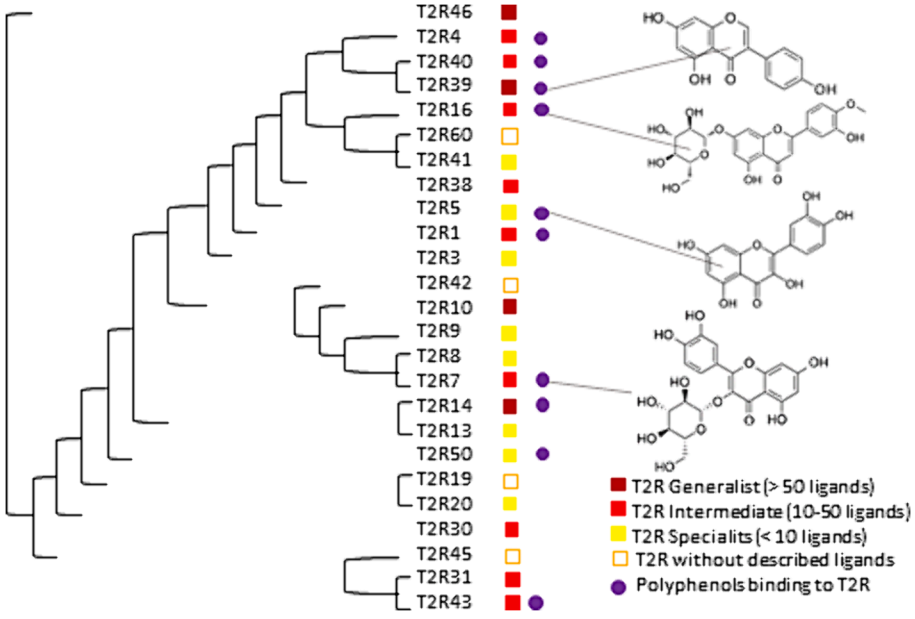

Fig. 1. T2Rs are clustered according to their mRNA sequence identity. Squares colours indicate the number of ligands that can bind to each T2R. Violet dots indicate the T2Rs that have been described as polyphenols receptors. Finally, the figure includes several polyphenolic structures that are ligands of specific T2Rs. This figure has been prepared considering references [3,56,110,111].

2. Bitter taste and the glucose and body weight homeostasis

Wine infused with bitter herbs (vermouth), a drink which dates to Roman times, is usually drunk before dinner to prepare the gastrointestinal system to digest foods and uptake/use nutrients. On the other hand, moderate consumption of habitual well-known bitter beverages, such as tea, coffee, and beer, might provide metabolic health benefits with decreased risk of type 2 diabetes or improved cardiometabolic markers [25,26]. Moreover, several experimental and clinical studies have reported that administration of bitter compounds led to decreased hunger scores and food intake [27,28], as well as reduced body weight in obese mice [19]. These three comprehensive examples encompass the concept of bitter compounds playing a potential role in homeostasis and interfere with physiological mechanisms via endocrine signalling, independently on their absorption, degradation, or distribution to the relevant organs of the body [29].

Taste perception is an important factor for food preference and choice, and bitterness can be the main cause of food rejection or appeal [30]. As an example, bitterness sensory properties add to the rejection or appeal of popular foods such as chocolate, coffee, or beer. Theoretically, bitter food dislike grows in proportion as the taste threshold for bitter compounds decreases [31]. A study among children observed that PROP tasters had higher body mass index (BMI), but not different intake of vegetables [32]. Authors discussed that the inability to detect this relationship may have been because vegetable intake measure did not allow to separate cruciferous vegetables intake for the analysis. Indeed, cruciferous vegetables such as broccoli, brussels sprouts, cabbage, kale, radishes, and arugula have been frequently cited as examples of taste rejection because they contain glucosinolates that give them a strong bitter taste. High sensitivity to isothiocyanates and PROP has been associated with reduced preference and acceptance of these vegetables in some studies [14,33]. In addition, wide range of factors such as age and sex are reported to modify the relationship between this bitter perception and food choices [34].

Recently, a cross-section observation of 2129 adults aged 40–80 years of the National Health and Nutrition Examination Survey (NHANES) 2013–2014 showed that high quinine reported intensity rating was associated with lower consumption of cruciferous vegetables and a high likelihood of obesity, which may mediate its association with diabetes [35]. Another study found that the average BMI of PTC supertaster females and males was significantly lower compared to PTC non-tasters. In addition, the PTC taster status was a predictor of lower scores for other basic taste RTs, but not for cruciferous hedonic perception and consumption [36]. Overall, the defined PTC supertaster cohort could be differentiated from the non-tasters by variables related to weight control such as BMI and sucrose recognized thresholds [36]. Consumption of cruciferous vegetables had been also associated with reduced risk of developing diabetes among prospective population studies [37]. These findings suggests that T2R phenotype and their signalling pathways may influence food choices and/or nutrient metabolism and consequently energy and glucose homeostasis as proposed Jeruzal-Swiatecka et al. [38]. Pham et al. [39] hypothesized that bitter components of food that can activate the T2Rs can become promising therapeutic candidates, “a bitter pill” for these diseases. However, the mechanism that links bitter taste, cruciferous vegetables intake, and obesity/diabetes are not clear yet.

Taste can interact with other senses and different tastes may interact with each other. Thus, Duffy and Bartoshuk [40] proposed that PROP supertasters may avoid high-fat food due to their intense sensation. In contrast, non-tasters were less sensitive in discriminating fatty acids in a high-fat food [41]. Furthermore, PROP non-tasters were found to have high adiposity [42]. Thus, high BMI was associated with higher PROP and linoleic acid detection thresholds [43]. These findings suggest that bitter taste might interfere with oleogust (lipid) taste perception, fat ingestion and the risk of suffering from obesity. In this way, Khan et al. [44] recently hypothesized that there is a crosstalk between T2Rs and fatty acid receptors (CD36). Chronic activation of T2R108 (T2R8, in humans), the most abundant T2R along the gut, attenuated body weight gain via reduction of fat mass, which is related to the increase of plasma GLP-1 levels in diet-induced obese mice [45]. In addition to the impact on body weight and adiposity, T2Rs are central players in maintaining glucose balance too. Thus, T2R9 is involved in glucose homeostasis and specific T2R9 polymorphisms increase the risk of developing type 2 diabetes [22].

3. Polyphenols effects on glucose and body weight homeostasis

Polyphenols are secondary metabolites that exist widely in plant and plant-based foods constituting by more than 8,000 structures ranging from low molecular weight (e.g., phenolic acids) to high molecular weight (e.g., proanthocyanidins). These molecules are characterized by the presence of at least one phenol group in their structure. These compounds can be grouped into flavonoids, non-flavonoids, and tannins according to their chemical structure. Flavonoids are classified into 14 different families such as flavanols (e.g., procyanidins), flavones (e.g., apigenin), anthocyanidins (e.g., malvidin), flavonols (e.g., quercetin), flavanones (e.g., naringenin), or isoflavones (e.g., genistein), whereas non-flavonoids include small molecules such as phenolic acids (e.g., gallic acid), lignans (e.g., secoisolariciresinol) and stilbenes (e.g., resveratrol) [46]. Humans consume 0.3–1 g/day of polyphenols. Certainly, the amount and type of polyphenols ingested are mainly related to our daily dietary choices, and many of these polyphenols, whether absorbed or not, undergo metabolism by either the host or the intestinal microbiota before being excreted [47]. As we mentioned above polyphenols are ligands to several T2Rs “generalists” such as T2R14 or T2R39 but also to T2R “specialists” such as T2R5 or T2R50 (Fig. 1). Furthermore, each polyphenol group can bind to one or more specific T2Rs. Fig. 2 summarizes the actual knowledge about the role of polyphenols as T2R ligands.

There has been an exponential growth of epidemiological, clinical, and experimental data that has supported the benefits of a diet rich in polyphenol-containing foods [48]. Adherence to an Asian diet or a Mediterranean diet seems to be associated with a lower incidence of chronic diseases such as diabetes type 2 and obesity [49], likely attributed to the high content and diverse/complex profile of polyphenols in these diets. Recently, Chen et al. [50] reviewed the more important evidence of the anti-diabetic and anti-obesity effects of polyphenols. These effects on glucose homeostasis have been explained through the action of polyphenols on the modulation of oxidative stress, the effects on the digestion, absorption, and cellular uptake of glucose, as well as the activation of pathways related to glucose and lipid metabolism. On the other hand, the action of polyphenols on the regulation of food intake and the intestinal microbiota, as well as the modulation of the lipid metabolism and the chronic low-grade inflammation are additionally mechanism proposed to explain the beneficial effects of polyphenols on body weight control. Furthermore, numerous experimental approaches demonstrated a beneficial effect of polyphenols uptake on appetite/satiety and food intake, calories utilization and the main metabolic routes involved in the management of body weight and their complications such as type 2 diabetes [51]. As an example, Greenberg et al. [52] reported that epicathechin ingestion before a meal increased satiety. On the other hand, an inflammatory process is involved in the etiopathogenesis of these high prevalence diseases that can be modulated by polyphenols through several mechanisms [46]. Resveratrol is a good example of polyphenol with marked anti-inflammatory actions [53–55] that recently has been reported to bind to T2R and consequently to modulate interleukin release [56].

The above-mentioned actions and others increase the interest and application of polyphenols as functional beverages and functional foods, and the amount of industrially extracted polyphenols was estimated at 16,000 tons in 2015 and expected to reach 34,000 tons by the end of 2024, with an estimated monetary value near of 1.5 billion dollars [57].

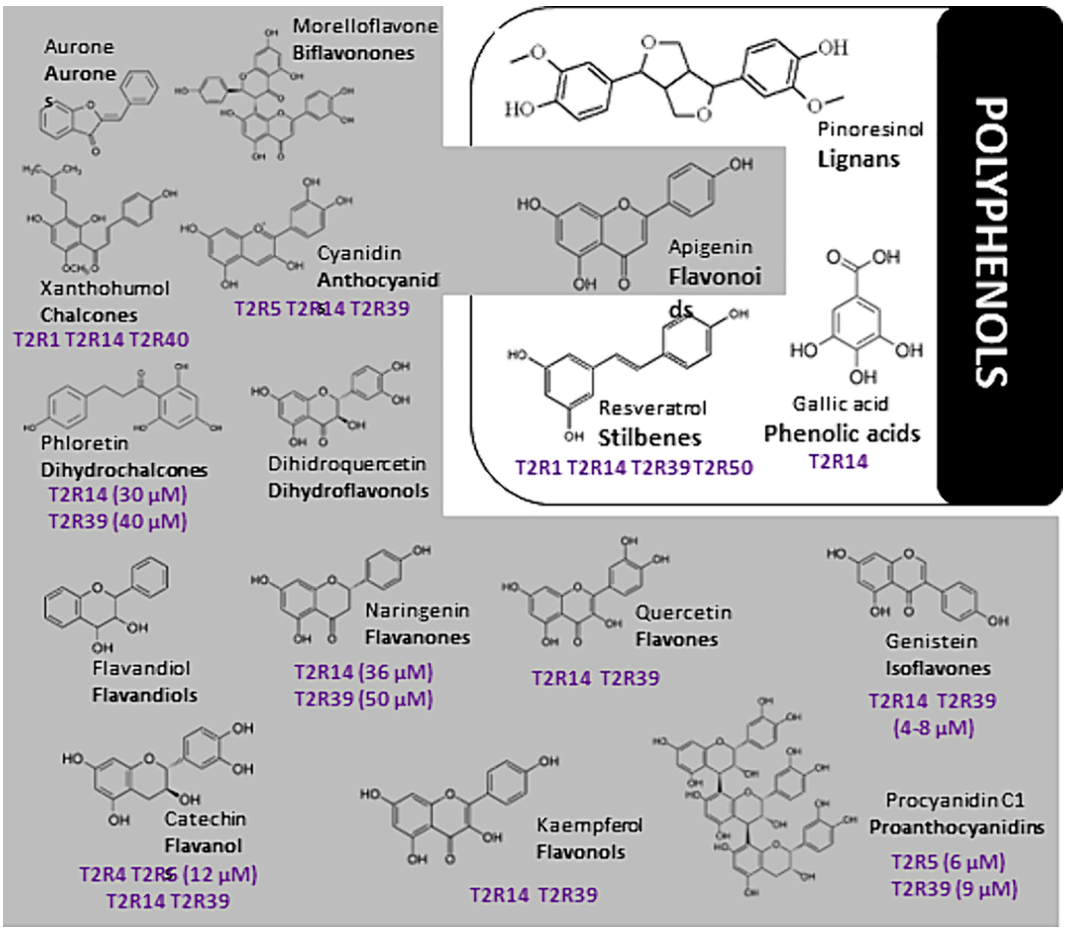

Fig. 2. Polyphenols are an extent family of bioactive compounds with diverse biological effects. Here, we summarise the main polyphenols groups and the specific T2Rs that can be actuated as their receptors. Furthermore, we include information about the concentration effective 50 to several polyphenols and T2Rs. This figure has been prepared considering references [3,56,58,96,110,111].

Despite the enormous research and economic interest on the topic, important aspects present unclear on the mechanism involved in the polyphenol actions whether we consider the poor bioavailability of most of the polyphenols and consequently the low tissular polyphenol/polyphenol metabolite levels. However, recently the interaction of polyphenols with T2Rs expressed on intestinal epithelium has been proposed as a new mechanism to explain their biological actions.

4. Polyphenols, T2Rs and glucose and body weight homeostasis

The study of the bitterness properties of polyphenols shows that these phenomena are mediated through the activation of several T2Rs and depend on the chemical structure of the agonists. For example, catechol or galloyl group are critical feature for the interaction with T2R5, and several hydroxyl groups in the isoflavonoid ring seems to be more favourable for T2R39 activation, whereas β-glucopyranosides activate T2R16 and glucose residues seems to be important to interact with T2R7 (Fig. 1) [58]. Furthermore, each polyphenol activates different combinations of T2Rs. Thus, epicathechin activate three T2Rs (T2R4, T2R5 and T2R39), while only two T2Rs respond to pentagalloylglucose. In contrast, malvidin-3-glucoside and procyanidin trimer stimulate only one receptor, T2R7 and T2R5, respectively [58] (Table 2). Although T2R agonists are usually described as toxic sensors that protect from intoxications, a recent analysis of a database of bitter compounds, including flavonoids, demonstrated that these compounds are usually not toxic at physiological concentrations [59]. Polyphenol bound to T2Rs is involved in the glucose/body weight homeostasis through several mechanisms such as the activation of gut brain axis, the regulation of gastrointestinal hormones release, the effects on intestinal microbiota and the innate immune response, and the adipose tissue metabolism.

4.1. Role of polyphenols (and other bitter compounds) binding to T2Rs in the brain gut axis

T2Rs are expressed in several brain regions such as hypothalamus, brain stem and cortex. Indeed, Wolfle et al. [60] reported the expression of T2R16 in human brain. The administration of quinine led to an increase in brain activity in the hypothalamus and hedonic brain region. Additionally, it resulted in impaired ghrelin release, reduced food consumption scores, and decreased hedonic food intake. Considering that quinine can reach cerebrospinal fluid, it cannot be excluded a direct effect on the hypothalamic-pituitary-gut axis by bitter agonists via T2Rs. Several polyphenols such as ferulic acid and resveratrol have been reported to exert beneficial effects on body weight homeostasis through modulation of gut brain axis [61,62] but T2Rs implication in these events has not been studied yet. Interestingly, several recent studies demonstrated the presence of several polyphenols in the cerebrospinal fluid [63,64], facts that open the door to a direct modulation of hunger/satiety by polyphenols through T2Rs implication.

4.2. Effect of polyphenols (and other bitter compounds) binding to T2Rs on gastrointestinal hormones release involved in glycemia and appetite control

Endocrine cells of the gastrointestinal tract only represent 1% of the

Table 2
Main ligands of T2Rs: bitter-tasting drugs, polyphenols, and other phytochemicals.

T2R	**Agonists**: drugs, *phytochemicals* (***polyphenols***)
1	Acetaminophen, chloramphenicol, dextromethorphan, diphenidol, *gentian*, ***isoxanthohumol***, ***xanthohumol***
3	Chloroquine
4	Azathioprine, dapsone, diphenidol, ***epicatechin***, ***naringenin***, ***pentagalloyl glucose***, *quinine*
5	***Epicatechin***, ***pentagalloyl glucose***, ***procyanidin C2***
7	*Caffeine*, chloroquine, cromoglicic acid, diphenidol, ***malvidin-3-glucoside***, *papaverine*, *quinine*,
8	Chloramphenicol, denatonium benzoate
9	Procainamide, ofloxacin
10	Azathioprine, *caffeine*, chloramphenicol, chloroquine, dapsone, dextromethorphan, diphenidol, erythromycin, famotidine, haloperidol, *papaverine*, *quinine*
13	Diphenidol, denatonium benzoate
14	***Apigenin***, azathioprine, *caffeine*, carisoprodol, ***chalcones***, ***chrysin***, diphenhydramine, diphenidol, flufenamic acid, ***genistein***, haloperidol, ***hesperidin***, ***hydroxyflavones***, ***isoxanthohumol***, ***kaempferol***, ***luteolin***, ***naringenin***, noscapine, orphenadrine, *papaverine*, ***quercetin***, *quinine*, ***resveratrol***, ***xanthohumol***
16	Diphenidol, *sinigrin*
19 (48)	–
20 (49)	Cromoglicic acid, diphenidol
30	Diphenidol
31 (44)	Diphenidol, famotidine, *papaverine*, *quinine*, saccharin
38	Isothiocyanates, methimazole, phenylthiocarbamide, propylthiouracil, *sinigrin*
39	Acetaminophen, ***apigenin***, ***chalcones***, chloramphenicol, chloroquine, ***chrysin***, diphenidol, ***epicatechin***, ***flavones***, ***genistein***, ***hesperidin***, ***kaempferol***, ***luteolin***, ***pentagalloyl glucose***, *quinine*, ***resveratrol***
40	Dapsone, diphenhydramine, diphenidol, *humulone*, ***isoxanthohumol***, *quinine*, ***xanthohumol***
41	Aloin, chloramphenicol
42	–
43	Aloin, chloramphenicol, *caffeine*, cromoglicic acid, diphenidol, ***epigallocatechin***, *quinine*, saccharin,
45	–
46	Azathioprine, *caffeine*, carisoprodol, chloramphenicol, diphenidol, hydrocortisone, orphenadrine, *papaverine*, *quinine*
47	*Camphor*, denatonium benzoate, *quassin*
49	–
50	*Amarogentin*
60	–

The contents of this table have been elaborated from references [9,14,20,90,102,103]. T2R19 formerly known as T2R48; T2R20 formerly known as T2R49; T2R31 formerly known as T2R44.

intestinal epithelium, but they constitute the largest endocrine organ producing and releasing more of 20 hormones such as serotonin, cholecystokinin (CKK), glucagon like-peptide 1 (GLP-1), peptide tyrosine-tyrosine or glucose-dependent insulinotropic polypeptide. These regulatory hormones serve as the signalling molecules for gut-brain axis and by acting locally to ensure appropriate digestion following the food ingestion through nutrient-sensing mechanisms [65]. In addition to this above nutrient sensing, the discovery of T2Rs in the endocrine cells of gastrointestinal tract suggest that they might also sense non-nutrients such as polyphenols, contributing to the regulation of gut hormones release and motility/secretion in a similar way to taste perception (Fig. 3). Although a complex set of elements modulates gastrointestinal hormone release, bitter agonist might be also involved [19].

Iven et al. [66] reported that intragastric bitter tastants (quinine) decreases prospective and actual food intake in healthy women by interfering with homeostatic and hedonic brain circuits in a ghrelin- and motilin-mediated fashion, and more recently this research group confirmed the potential of intragastric bitter tastants to reduce hunger sensations and orexigenic gut peptides [67]. Ghrelin produced by gastric

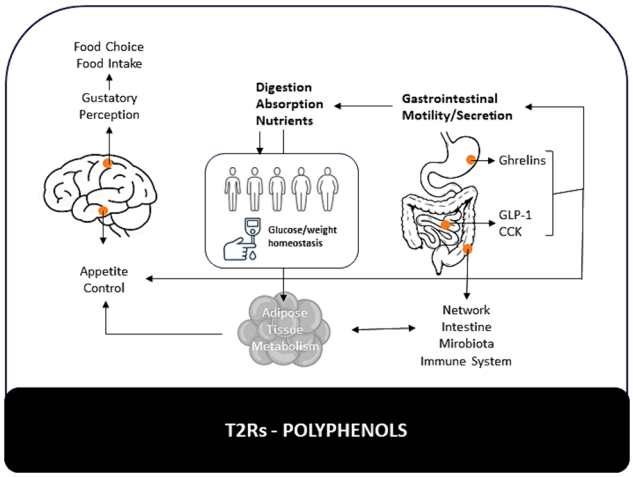

Fig. 3. Main mechanisms involved in the role of polyphenol-T2Rs interaction on glucose/body weight homeostasis. CKK, cholecystokinin; GLP-1, glucagon like-peptide 1.

P/D1 cells is the main peripheral orexigenic hormone and some polyphenols such as epicatechin gallate stimulates its secretion via T2R14 and T2R39 [68]. Interestingly, short-term treatment with bitter flavanols stimulated ghrelin secretion, while long-term treatment inhibited this hormone release. Furthermore, additional studies reported that other circulating hormones and neural reflexes may mask the local stimulatory effect of bitter agonists on ghrelin release [68].

GLP-1 and other incretins released by L enteroendocrine cells in response to the presence of macronutrients in the intestine has been proposed as key element of glucose and body weight homeostasis. Thus, several GLP-1 agonists (such as semaglutide and liraglutide) are recently used for the treatment of diabetes and obesity [69]. Parallelly, the secretion of GLP-1 can be stimulated by ingested foods with a bitter taste due to the presence of plant secondary metabolites [65]. Thus, recent evidence indicated that several specific bitter compounds present in anti-diabetic preparations (phenanthroline, berberine, Qing-Hua) interact with T2Rs (T2R5, T2R38) in enteroendocrine cells to release GLP-1 [70,71]. Furthermore, GLP-1 secretion can be enhanced by ligand activation of T2R9, which was identified as a candidate gene in a genome-wide association study of type 2 diabetes [20]. In this way, denatonium benzoate induced GLP-1 release and the subsequent insulin secretion, leading to a decrease in glycemia in diabetic mice by stimulating T2Rs [71]. The expression of T2Rs and the alpha-subunits of the G protein gustducin in the rodent gastrointestinal tract and it endocrine cells are also involved in CKK release induced by bitter compounds and its further anorexigenic effects [72]. Table 3 summarizes the effects of polyphenols on GLP-1, CKK, and insulin release. However, only two of these studies have reported the effects of these bitter ligands on glycemia [73,74]. Additionally, only one study has investigated the effects on food/energy intake [75], and one on body weight [45]. This fragmented information suggests that few studies have presented a comprehensive picture of the topic.

Other hormones are related to glucose/body weight homeostasis through bitter taste-T2Rs pathways. As an example, thyroid hormones production is also involved in the energy/glucose homeostasis. Clark et al. [76] reported that bitter-tasting compounds negatively regulate thyroid-stimulating hormone and consequently iodide hormones release. Interestingly, these authors reported that T2R42 specific polymorphism was associated with lower thyroid hormone levels in a human cohort [77].

Table 3
Supportive information on the effects of polyphenols and other phytochemicals on gastrointestinal hormones release through T2R interactions.

Ligand	Model	T2Rs	Gastrointestinal hormones		Reference
			GLP-1	CCK	
Ellagitannins	C57BL/6J mice	108	↑		[104]
	STC-1 cells (mice)	108, 119, 126, 138	↑		[104]
Isosinensetin	NCI-H716 cells	50	↑		[105]
Piperine	Caco-2 cells	14	↑		[106]
1,10-Phenantroline	Fischer-344 and Wistar rats	5	↑	↑	[76]
Hop bitter acids	293 T cells	1, 8, 10		↑	[74]
Cucurbitacin B	Diabetic, C57BL/6 and Gα-gust null mice	–	↑		[75]
Isohumulone	C57BL/6J diet-induced obese mice	108	↑		[45]
Berberine	STC-1 cells (mice)	106	↑		[107]
	NCI-H716 cells	38	↑		[71]
PROP	HuTu-80 cells	38	↑		[39]
PTC	Caco-2 cells	38		↑	[108]
Steroid glycoside	HuTu-80 cells	14		↑	[109]

CCK, cholecystokinin; GLP-1, glucagon like peptide 1; PTC, phenylthiocarbamide; PROP, 6-*n*-propylthiouracil; ↑ increase.

4.3. Effect of polyphenols (and other bitter compounds) binding to T2Rs on adipose tissue metabolism

The hypertrophy of adipocytes in obese subjects stimulate immune cell infiltration and pro-inflammatory cytokines release that contributes to systemic low-grade inflammation and the recruitment of obesity [78]. These pathways are involved in uncontrolled expansion of adipose tissue when caloric intake become excessive, as well as disruption of insulin signalling in the peripheral tissues leading to insulin resistance. Interestingly, overexpression of T2R126 in 3 T3-L1 preadipocytes decreases fat accumulation after induction of differentiation and reduces the expression of adipogenic genes. Furthermore, epicatechin, a ligand of T2R126 induced differentiation of mice adipocytes [79]. TAS2R38 is also more expressed in subcutaneous and visceral adipose tissues of obese than lean subjects and is involved in differentiation and delipidation processes [80].

4.4. Role of microbiota in the interconnected effects of T2Rs on the immune response

Gut microbiota plays a key role in the development of metabolic disorders [81] and influences eating behaviour [82]. Latorre et al. [83] observed that antibiotic treatment suppresses the elevation of T2R38 expression in the gut of overweight/obese subjects. The concept that the intestinal microbiota could modulate taste-receptor mediated inflammation can be contemplated when considering the role of T2Rs in the innate immunity response in the respiratory tract. Because high-fat diets are known to alter gut microbiota, it is reasonable to suspect that this could influence T2Rs expression/signalling, altering the gastrointestinal innate immunity and the metabolism of the host. In that sense, Caremoli et al. [84] reported an increased specific expression of T2R116 and T2R138 (T2R16 and T2R38 in humans) in the colon of obese mice induced by a high-fat diet, T2Rs that have been shown to be activated by quorum-sensing molecules. Furthermore, these facts were significantly associated, either positively or negatively, with bacteria belonging to 17 genera. Among these, there was Akkermansia muciniphila, a Gram-negative mucus-resident bacterium that seems to have a beneficial effect in metabolic, immune, and inflammatory diseases by attenuating intestinal mucosa damage and controlling intestinal homeostasis. Additionally, faecal transplantation from obese mice to normal mice induced the increase of T2R116 and T2R138 in the large intestine and a positive correlation between these T2Rs expression and Akkermansia abundance was observed [84]. Moreover, T2R agonists altered the expression of antimicrobial peptides, mucus proteins, and cytokines that are part of the type 2 innate immune response. Furthermore, Liszt et al. [85] identified T2R10 as potential target to alter antimicrobial peptide release in the human intestine. Furthermore, aloin induced CLCA1 release, activated oxidative phosphorylation, and affected mRNA expression of genes involved in vesicle transport and protein translation in a T2R43-dependent manner. Bitter compound denatonium benzoate ligand from T2R43 induced an NRF2-mediated stress response and an unfolded protein response that resulted in increased expression of the mitokines GDF15 and ADM2 and the LDLR genes, which control anorectic signalling and lipoprotein homeostasis. These events that are involved in immune responses and metabolic regulation in obesity. Though many questions remain to be addressed and further studies are required to establish causality in addition to association, the findings of this study provide support for a role of T2Rs in gut chemosensing and suggest that these bitter taste receptors could be explored as potential targets for treating diseases with microbiome disturbances. Additional studies about the effects of poliphenols-T2Rs interactions on the microbiota status and the glucose/body weight homeostasis are necessary.

Furthermore, some widely used artificial sweeteners (saccharin, acesulfame) binds T2Rs as well as T1Rs [86]. These sweeteners use is also associated with important changes in intestinal microbiota profile, decreased satiety signalling, altered glucose homeostasis, increased calorie intake and weight gain [87]. In fact, Turner et al. [88] reported that acesulphame, cyclamate, saccharin and stevia bind to specific T2Rs, induce dysbiosis and increase the risk for metabolic disorders. However, the mechanism of these events should be clarified.

5. The implication of T2R polymorphism on the individual variability of polyphenol effects on glucose and body weight homeostasis and immune response

According to the HUGO Gene Nomenclature Committee (HGNC) database there are 39 genetically diverse and highly polymorphic T2R single exon genes that encode for 29 functional T2Rs and 10 non-coding pseudogenes in human [89] whereas most authors consider the existence of only 25 functional T2Rs [90]. These T2Rs genes are located on chromosomes 5, 7, and 12. On average, T2R genes contain four single nucleotide polymorphisms (SNPs) of which many are non-synonyms mutations that encode amino acid substitutions [3]. This polymorphism is no longer thought only to account for differences in oral bitter taste perception [3,91], it is also recognized to influence multiple physiological aspects such as eating behaviour, alcohol dependence, glucose homeostasis or longevity. A Korean study identified that the T2R38 genotype associated with non-tasting status was associated with a significant higher BMI in females. However, there was no association between this polymorphism and energy intake, suggesting another biological mechanism [92]. Similar effects were reported by Trius-Soler et al. [36] which reported a relationship between T2R38 sensitivity (recognition threshold) and BMI in a healthy young cohort (Torribera

Student Taste Study).

One potentially illuminating approach is to compare the cell physiology of functional and non-functional T2R haplotypes (for example, the human T2R38 has two common haplotypes – the PAV version is a "taster" for the bitter ligand phenylthiocarbamide and secreted bacterial products, whereas the AVI is a "non-taster"). Humans with the "taster" T2R38 haplotype respond to bacterial-derived agonists and mount an anti-bacterial response to infection in the upper airway, whereas those with the "non-taster" T2R38 haplotype are more susceptible to upper respiratory infections [93]. Besides T2R38, high levels of polymorphisms have been also found in other T2Rs such as T2R3, T2R4, T2R5 and T2R16. These T2Rs are expressed along the alimentary tract and its polymorphisms can be explain differential interactions with intestinal microbiota and immune response as well as the variability of biological effects of polyphenols. The role of T2Rs on insulin sensitivity and glycaemic control is also supported by the findings of impaired glucose homeostasis, likely due to reduced GLP-1 release, in an Amish family with a functionally compromised T2R9 [20].

6. Conclusions and future perspectives

Although numerous bitter medicinal plants have been used in folk and traditional medicine and cuisine and inherited by generations, the scientific integration of modern medicine and traditional (ancient) wisdom remain limited. This review proposes that activation of T2Rs by polyphenols and other bitter compounds could modulate gut hormones secretion that regulate gastric emptying, gastrointestinal motility/secretion, may affect satiety/appetite, and enhances insulin secretion as well as bile acid release, leading to metabolic outcomes with improved glucose and body weight control. However, additional research is needed to clarify these statements.

Sensory nutrition is a novelty area of research that focuses on how the chemical senses, and oral somatosensation affects dietary choices and health [94]. The strategy of developing personalized nutritional plans through T2R genotype status study has been previously outlined by Bray and Carek [95]. Now, this could be specifically focused on diabetes/obesity prevention and treatment. Consequently, it is imperative to quantify T2Rs expression in extra-oral tissues to elucidating their normal physiological roles outside of the gustatory system. Furthermore, defining prevalence of T2Rs polymorphisms and taste phenotypes in diabetic/obese patients could assist physicians in predicting the course of the disease and facilitate treatment decisions as well as in optimizing therapies for personalized treatments of these diseases.

Bitter tastants such as polyphenols are a potential weight-loss treatment. This is a non-invasive, easy approach, which should be received with considerable enthusiasm by the public. However, literature about bitter administration lacks consistency in methods and findings. Moreover, additional research must clarify how these compounds should be given based on the site of administration, the best bitter compound to use, and at what timing in respect to the meal. This review is therefore a step towards advancing research for the further development of the "bitter pill" to the treatment of high prevalence disorders such as diabetes and obesity. Research in targeting T2Rs for clinical use is still in its infancy where in vivo studies on the efficacy of T2R agonists have mostly been conducted in pre-clinical studies. In this way, CRISPR-Cas9-edited T2Rs cell models are leading to reveal new mechanisms for polyphenols studied several decades ago [96], and it is a potent methodology to develop new T2R agonists/antagonists that can lead to the discovery of novel drug candidates.

A recent systematic review reported limited consistent conclusive evidence that bitter compounds influence hormones release, appetite and food intake [97] and stated the interest to a research agenda for clinical studies that should include continued evaluation of a range of bitter compounds, at a range of doses, genotyping participants to confirm if the targets T2Rs are functionally present, and exploring the effects of bitter substances outside of only healthy adults, for example obesity and type 2 diabetes. Another point to consider is the food matrix in which the bitter compounds enter the body. It is possible that the combination of compounds and nutrients in foods may modulate the satiating effect of bitter compounds and vice versa, where bitter compounds may act in a nutrient-specific or metabolic state-dependent manner.

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Marta Trius-Soler: Writing – review & editing. **Juan José Moreno:** Writing – review & editing.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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