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Natural Compounds Modulating Bitter Taste Receptors: Implications for Multisystem Health and Disease

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ABSTRACT: Bitter taste receptors (TAS2Rs), a subfamily of G protein-coupled receptors, have been recently recognized for their regulatory roles beyond gustation. They are widely expressed in the oral cavity, gastrointestinal (GI) tract, respiratory system, cardiovascular system, endocrine organs, reproductive tissues, and nervous system, playing crucial roles in immune modulation, metabolic homeostasis, microbiota interactions, and cancer progression. This review systematically summarizes the physiological functions and implications of TAS2Rs across multiple organ systems and microbial environments, emphasizing their roles in health. Specifically, we highlight the key role of TAS2R38 in maintaining oral microbiota balance and preventing dental caries. TAS2Rs are abundantly expressed in the GI tract. They regulate gut microbiota, promote hormone secretion, maintain intestinal barrier function, and influence metabolic processes. TAS2Rs and their subtypes play key roles in various tissues, regulating immune responses, cell signaling, and organ function, such as TAS2R38 in respiratory defense, TAS2R14 in cardiovascular regulation and metabolic control, TAS2R14 and TAS2R43 in reproductive health. Natural compounds can regulate health by influencing different subtypes of TAS2Rs, either promoting or inhibiting their activity. Recent studies suggest that TAS2Rs could serve as promising therapeutic targets for many diseases. Understanding the intricate interactions between TAS2Rs and diverse physiological pathways may pave the way for regulating appetite and metabolism, dietary intervention.

Key words: TAS2Rs, immune modulation, metabolic regulation, GI health, natural agonists and antagonists

1. Introduction

Bitter taste receptors (TAS2Rs) are a subclass of type II taste receptors within the G protein-coupled receptor (GPCR) family. TAS2Rs were first identified in type II taste receptor cells within the taste buds of lingual papillae, where they mediate bitter taste perception^[1]. Structurally, TAS2Rs consist of a single polypeptide chain, featuring seven transmembrane helices, an extracellular amino terminus (N-terminus) responsible for ligand recognition, and an intracellular carboxyl terminus (C-terminus) involved in signal transduction. These transmembrane helices are interconnected by three extracellular loops and three intracellular loops, which contribute to the unique conformation^[2]. Among the identified TAS2R genes, human TAS2Rs (hTAS2Rs) are predominantly located on the short arms of chromosomes 5 and 12 and the long arm of chromosome 7, comprising 25 subtypes, as illustrated in Figure 1^[3]. In contrast, mouse TAS2R

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(mTAS2R) genes are concentrated on chromosomes 2, 6, and 15, with 35 subtypes identified^[4]. Similarly, rat TAS2R (rTAS2R) genes are primarily distributed on chromosomes 2, 3, and 4, with a total of 37 subtypes^[5, 6].

Although TAS2Rs were initially thought to be restricted to bitter taste perception in the oral cavity, subsequent research has demonstrated their widespread expression across multiple tissues and organs, including the respiratory tract, gastrointestinal (GI) system, and immune system^[7]. TAS2Rs play critical roles beyond taste perception, contributing to airway defense, metabolic regulation, and immune responses, as illustrated in Table 1. As research on TAS2Rs has advanced, their physiological and pathological roles have become increasingly evident.

This review aims to provide a comprehensive overview of TAS2R functions across different tissues and their associations with various diseases. Additionally, TAS2R agonists and antagonists are categorized based on their sources. By summarizing current findings, this study seeks to provide broader research perspectives for the potential application of TAS2Rs in the food industry, including their roles in taste modulation, influencing consumer dietary preferences and health outcomes.

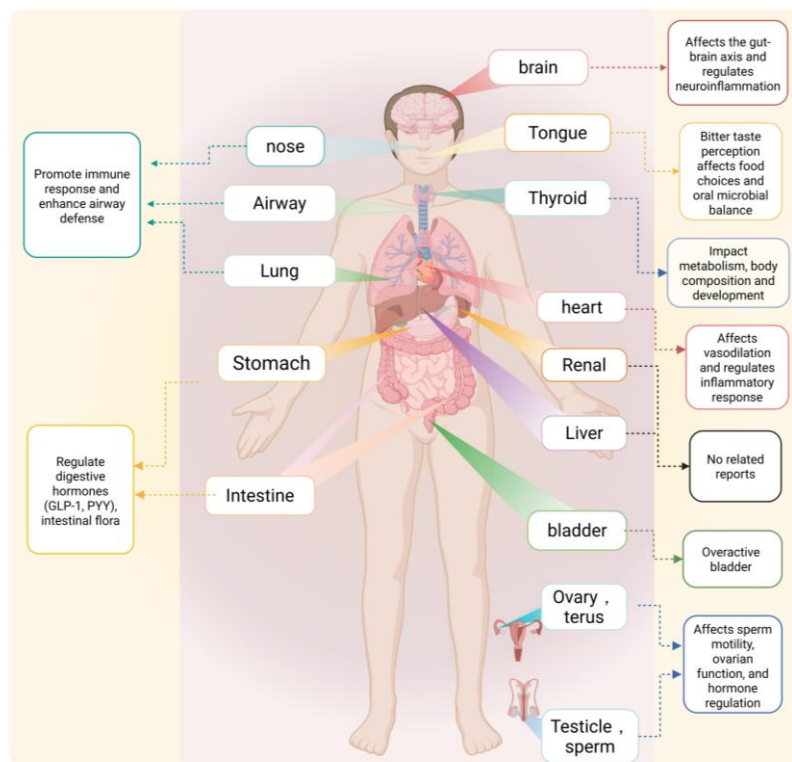


Figure 1 Health regulation of TAS2Rs in human tissues

Table 1 Distribution and health regulation of TAS2Rs in human tissues or system.

Tissues or system	Cells	TAS2Rs subtypes	Health regulation	References
Brain	Astrocytes	3,4,5,7,8,9,10,14,16,39,40,41,42,43,44,48,50	Neurodegenerative diseases, Neuroinflammation	[8]
	Human choroid plexus	1,3,4,5,7,8,9,13,14,16,20,38,39,41,42,43,44,45,46,48,50,60		[9]
Nose	Ciliated epithelial cells	38	Chronic rhinosinusitis	[10]
	Solitary chemosensory cells	4,14,46		[11]
	Human sinonasal epithelial cells	4,16,38		[11, 12]
Oral	Type II taste cells	All TAS2Rs subtypes	Dental caries, periodontitis	[5]

	Gingival fibroblasts	16,31,38,39,43		[13]
	Gingival epithelial cells	14		[14]
Thyroid	Thyroid follicular cells	1,3,4,5,7,8,9,10,13, 14 ,16,20,30, 31,38 ,39,40,41, 42,43 ,45,46,48,50,60	Impact metabolism, body composition and development	[15]
Airway	Airway smooth muscle	1,3,4,5,7,8,9, 10 ,13, 14 ,19,20,30, 31,38 ,39,42,43,45,46,50	Asthma	[16, 17]
Lung	Macrophages	3,4,5,7,8,9,10,14 ,19,20,31,38, 39,40 43,45,46	Chronic obstructive pulmonary disease	[18]
	Bronchial epithelial cells	3,4,5 ,10,13, 14 ,19,20,30, 50	Asthma	[19]
	Pulmonary artery smooth muscle cells	1,3,4,5,7,8,9, 10 ,13, 14 ,16,19,20, 31,38 ,39,40,41,42,50,60	Chronic obstructive pulmonary disease	[19]
Heart	Cardiac myocytes and fibroblasts	3,4,5,9,10,13, 14,19 ,20,30, 31 ,39,43,45,46, 50,60	Arrhythmic	[20]
	Human Aortic Endothelial cells and coronary artery endothelial cells	1,3,4,5,7,8,9, 10 ,13,14,16,19,20,30,31, 38 ,39,40,41,42,43,45,46,50,60	Cardiac inflammation	[21]
Liver	/	4,5,10,13,14,19,20,30,31,43,46	/	[22]
Renal	Renal epithelial cells	16,38	/	[23]
Pancreas	Cancer-associated fibroblasts	9,10	Type 2 diabetes	[24]
	Endocrine cells	3,4,5,10, 14 ,19,20,31		[22]
	Islets of langerhans	3,4,5, 9 ,10,13, 14 ,19,31,43,45,46,50, 60		[6]
Stomach	GI smooth muscle cells	3,4,10	Gastric cancer, chronic gastritis	[25]
	Parietal cells	8,9,13,16,20,42, 50,60		[26]
Intestinal	Human intestinal smooth muscle cells	5,7,8,9,10,13, 14 ,16,19,30,31, 38,39 ,40,41,42,43,45,46,50,60	Inflammatory bowel disease, irritable bowel syndrome	[27]
	Enteroendocrine cells	3,4,5, 38		[5, 28]
Bladder	Detrusor smooth muscle	1,4,5, 7,8 ,9,10, 13 ,14,20,30,31,38,39,40,45,50	Overactive bladder	[29]
Reproduc tive system	Placenta trophoblast cell	14,38 14	Polycystic ovary syndrome, preterm birth, ovarian cancers	[30, 31] [31]
	Human myometrium tissue	4,5,10,13, 14		[32]
	Fallopian tube tissue and uterine tissue	1,4,10, 14,38		[33]
	Granulosa cells and cumulus cells	3,4,14,19,43		[34]
	Testis and sperm	3,4, 14 ,19, 43	Sperm chemotaxis, prostate cancers	[35]
Adipose tissue	/	38	/	[36]
Skin	/	1,3,4,5,7,8,9, 10 ,13, 14 ,16,19,20,30,31, 38 ,39,40,41,42,43,45, 46,50,60	Skin cancer, psoriasis	[30, 37, 38]

2. TAS2Rs in the oral cavity and their role in health regulation

2.1 Distribution of TAS2Rs in the oral cavity

In the oral cavity, TAS2Rs exhibit diverse distribution patterns beyond their presence in type II taste receptor cells within taste buds. They are also expressed in various non-gustatory cells. Within taste buds, TAS2Rs are primarily located in lingual papillae, soft palate, and pharyngeal regions, where they play a direct role in bitter taste perception^[39]. The bitter taste signaling cascade begins when bitter compounds bind to TAS2Rs on type II taste receptor cells in lingual papillae, leading to G protein activation and subsequent release of the G protein beta-gamma subunits (Gβγ). This, in turn, activates phospholipase Cβ₂ (PLCβ₂),

which catalyzes the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP₂), generating inositol triphosphate (IP₃) and diacylglycerol (DAG). IP₃ binds to IP₃ receptors (IP₃R) on the endoplasmic reticulum, triggering calcium (Ca²⁺) release and activating the transient receptor potential cation channel subfamily M member 5 (TRPM5). This cascade results in Na⁺ influx, membrane depolarization, and ATP release, ultimately transmitting the bitter taste signal to the central nervous system (CNS) for taste perception^[40].

Beyond taste buds, TAS2Rs are also expressed in oral epithelial cells, gingival fibroblasts, immune cells, and spindle-shaped taste receptor cells^[41]. The expression levels of TAS2R subtypes vary across different cell types. In human gingival fibroblasts, TAS2R16, TAS2R38, TAS2R31, TAS2R39, and TAS2R43 exhibit high mRNA expressions, while TAS2R3, TAS2R4, TAS2R19, and TAS2R20 are also detectably expressed^[13]. TAS2R14 is prominently expressed in human gingival epithelial cells^[14]. In mouse gingival junctional epithelium, TAS2Rs expressed spindle-shaped taste receptor cells have been identified. These cells express ten TAS2R subtypes (TAS2R105, TAS2R108, TAS2R118, TAS2R119, TAS2R126, TAS2R134, TAS2R135, TAS2R137, TAS2R138, and TAS2R143) along with key gustatory signaling molecules, including G α , PLC β ₂, and TRPM5^[42].

TAS2Rs are widely distributed in the oral cavity, particularly in non-gustatory cells, where their function extends beyond bitter taste perception. They may play a role in regulating local signaling pathways, influencing oral immunity, inflammatory responses, and disease progression.

2.2 Regulation of oral microbiota by TAS2Rs

TAS2Rs play a crucial role in the regulation of oral microbiota, primarily by detecting bacterial signaling molecules and activating innate immune responses. TAS2R14 interacts with competence-stimulating peptides secreted by Gram-positive bacteria, facilitating the internalization of *Staphylococcus aureus* (*S. aureus*) by gingival epithelial cells. Upon bacterial stimulation, these cells secrete human β -defensin-2 (h β D-2), an antimicrobial peptide that effectively inhibits the growth of *S. aureus* and contributes to bacterial suppression^[14]. Additionally, TAS2R4, TAS2R20, and TAS2R38 recognize N-acyl homoserine lactones (AHLs) secreted by Gram-negative bacteria, activating GPCR signaling pathways^[43]. This activation leads to intracellular Ca²⁺ elevation, stimulating the secretion of antimicrobial peptide h β D-2, which directly inhibits bacterial growth, and pro-inflammatory cytokine interleukin-1 α (IL-1 α) secretion, which promotes inflammatory responses, collectively facilitating pathogen clearance^[44].

TAS2Rs also contribute to microbial homeostasis by modulating the composition of the oral microbiota. TAS2R38 single nucleotide polymorphisms determine individual sensitivity to 6-N-propyl-2-thiouracil (PROP), a bitter compound, and this variation is correlated with differences in lingual microbial communities. Compared to PROP-insensitive individuals, PROP-sensitive individuals not only exhibit higher taste sensitivity but also possess a greater relative abundance of Gram-positive *Actinomyces*, *Escherichia coli*, and Gram-negative *Campylobacter* species on their tongue surfaces^[3].

Genetic polymorphisms of TAS2Rs influence individual taste sensitivity and susceptibility to certain diseases. The TAS2R38 genotype-related differences in lingual microbial communities may not only

metabolically influence taste perception but also affect oral health, including susceptibility to caries and periodontal disease. The causal relationship between TAS2R38-mediated taste variation and lingual microbial ecology requires further investigation. TAS2R38 polymorphisms are strongly associated with the occurrence of dental caries. *Streptococcus mutans* (*S. mutans*), a major cariogenic bacterium, induces dental demineralization and caries formation through acid production and biofilm formation^[43]. In primary dentition, individuals with the PAV/PAV genotype (functionally active TAS2R38 variant) showed a 4.3-fold increase in TAS2R38 expression upon *S. mutans* stimulation, compared to only 1.2-fold in AVI/AVI carriers (non-functional variant)^[45]. This suggests that the functional genotype may enhance bacterial sensing and host defense, thereby reducing the risk of dental caries. Upon TAS2R38 activation, its downstream signaling pathway is triggered, leading to the dissociation of G α and G $\beta\gamma$ subunits. G α stimulates inhibit adenylate cyclase (AC), reducing cyclic adenosine monophosphate (cAMP) levels, which are subsequently degraded via phosphodiesterase (PDE)-dependent pathways, reducing protein kinase A (PKA) expression. This results in attenuated calmodulin-dependent protein kinase II (CaMKII), ultimately regulating the expression of h β D-2 and IL-1 α . In PAV/PAV genotype gingival epithelial cells, h β D-2 secretion significantly increases upon *S. mutans* exposure, enhancing innate immune defense against bacterial growth and reducing the risk of dental caries^[46].

TAS2R38 polymorphisms may also influence dietary preferences. Studies indicate that individuals with the AVI/AVI genotype exhibit reduced sweet taste perception compared to other genotypes, whereas PAV/PAV individuals are more sensitive to bitterness and possibly more perceptive to sweetness, possibly as a compensatory mechanism to counterbalance heightened bitter sensitivity^[47]. This heightened sweet preference in bitter-sensitive individuals may lead to increased sugar consumption, which is associated with a higher risk of dental caries, highlighting the potential health implications of TAS2R38-mediated taste perception.

2.3 Relationship between TAS2Rs and oral inflammation

TAS2Rs in non-gustatory cells influence oral inflammation through multiple mechanisms. The Ca²⁺ signaling mediated by TAS2Rs in type II taste receptor cells of lingual papillae is not only involved in taste perception but also plays a role in activating the NOD-like receptor pyrin domain-containing protein 3 (NLRP3) inflammasome, which in turn triggers the nuclear factor-kappa B (NF- κ B) signaling pathway, leading to the release of pro-inflammatory cytokines^[48].

In human gingival fibroblasts, TAS2R16, when activated by salicin, can initiate innate immune responses by downregulating intracellular cAMP, thereby inhibiting the NF- κ B signaling cascade. This suppression reduces the expression of lipopolysaccharide (LPS)-induced pro-inflammatory cytokines, helping control excessive inflammation and maintain immune homeostasis, ultimately alleviating periodontitis symptoms^[13]. However, in chronic or dysregulated inflammatory conditions, where TAS2R16-mediated signaling is insufficient or overridden by persistent pathogenic stimuli, the continued release of pro-inflammatory cytokines may lead to immune system overactivation, resulting in localized tissue damage

and exacerbation of periodontal inflammation. Additionally, spindle-shaped taste receptor cells in the junctional epithelium of mouse gingiva express multiple TAS2Rs, such as TAS2R105 and TAS2R108, and their associated signaling pathway proteins, PLC β_2 and TRPM5, which have been shown to enhance the secretion of antimicrobial peptides, thereby contributing to periodontal inflammation relief^[13, 49].

The genetic polymorphism of TAS2R38 plays a key role in susceptibility to periodontitis and inflammation modulation. *Porphyromonas gingivalis* (*P. gingivalis*), a major pathogenic bacterium associated with periodontitis, induces inflammation and periodontal tissue destruction. In response to *P. gingivalis*, individuals with the AVI/AVI genotype exhibit a 4.3-fold increase in TAS2R38 expression, whereas other genotypes show no significant changes. When TAS2R38 is silenced, the secretion of IL-1 α and interleukin-8 (IL-8) is significantly reduced in AVI/AVI genotype cells, suggesting that higher levels of pro-inflammatory cytokines in TAS2R38 AVI/AVI individuals correlate with a lower prevalence of periodontitis^[13, 50]. Furthermore, in response to *S. mutans* stimulation, PAV/PAV genotype cells with silenced TAS2R38 exhibit a 77% reduction in h β D-2 secretion and a 50% decrease in IL-1 α expression. This indicates that TAS2R38 in PAV/PAV genotypes enhances innate immune function, reduces IL-1 α release, and consequently lowers inflammation levels, thereby protecting periodontal tissues from bacterial infection^[51]. These findings suggest that individual variations in TAS2R38 expression may affect oral immune defense mechanisms, thereby altering periodontal health outcomes.

3. Expression and health implications of TAS2Rs in the GI tract

3.1 Expression of TAS2Rs in different regions of the GI tract

Although the expression profile of TAS2Rs in the GI tract remains incompletely understood, current studies indicate that their distribution is highly complex, with significant differences among species and across different GI segments. The expression patterns of TAS2Rs in human and rodents (mouse and rat) GI tracts exhibit both common characteristics and species-specific variations, suggesting that TAS2Rs play diverse roles in both localized functions and systemic regulation. Compared to their broad expression in taste papillae of tongue, TAS2R subtypes exhibit more restricted expression in the intestines. These variations in expression patterns lead to distinct TAS2R profiles in each species and across different GI segments^[52]. As illustrated in Table 2, a comparative analysis across species and intestinal regions is essential for a deeper understanding of their functional roles. Based on their expression characteristics, TAS2Rs in the GI tract can be categorized into three groups: (1) TAS2Rs are widely distributed throughout the GI system, (2) TAS2Rs localized to specific GI segments, and (3) TAS2Rs exhibiting region-specific expression across species.

In the human GI tract, hTAS2R4, hTAS2R5, hTAS2R20, and hTAS2R31 are expressed in all GI regions, making them the most widely distributed TAS2Rs^[52]. Additionally, hTAS2R10, hTAS2R14, hTAS2R19, hTAS2R20, and hTAS2R31 are present in all intestinal segments except the duodenum. Compared to the stomach and duodenum, the jejunum and colon exhibit a more diverse TAS2Rs expression profile, with hTAS2R4, hTAS2R5, hTAS2R10, and hTAS2R14 detected in both regions. However, hTAS2R7 and hTAS2R8 are exclusively expressed in the jejunum^[7]. The colon harbors the highest number of TAS2Rs

subtypes in the human GI system, with nearly all identified receptors expressed in this region. Some TAS2Rs found in the colon are shared with other intestinal segments, but several, including hTAS2R1, hTAS2R42, hTAS2R45, hTAS2R50, and hTAS2R60, are uniquely expressed in the colon. This specificity suggests a potential link between TAS2R expression and colonic microbiota, as bitter-tasting metabolites produced by gut microbiota may act as endogenous TAS2Rs ligands^[53].

In mice GI tract, mTAS2R135 and mTAS2R137 are the only receptors expressed throughout all segments, whereas other TAS2Rs display region-specific expression. For instance, mTAS2R109 and mTAS2R115 are restricted to the stomach, mTAS2R134 to the duodenum, and mTAS2R129 to the ileum^[52]. The colon represents the most receptor-rich region, including mTAS2R117, mTAS2R118, mTAS2R125 and other subtypes exhibiting specific expression in this segment^[52]. Additionally, mTAS2R131 has been identified in a subset of intestinal Paneth cells, suggesting a potential role in gut immune responses and antimicrobial peptide regulation^[54, 55]. In contrast, no single TAS2R subtype in rats is expressed across the entire GI tract. Instead, rat TAS2Rs exhibit distinct site-specific patterns. rTAS2R110 is confined to the stomach, while the duodenum exhibits the highest receptor diversity, including rTAS2R104, rTAS2R106, rTAS2R107 and other subtypes^[55]. To date, no subtype-specific expression has been reported in the jejunum or ileum, whereas rTAS2R109 is exclusively present in the colon^[53]. Overall, TAS2Rs in rats are predominantly distributed in the stomach and duodenum, with more limited expression in the jejunum, ileum, and colon.

Table 2. Distribution of TAS2Rs in the GI tract of humans, mice, and rats.

GI tract	hTAS2Rs/ mTAS2Rs / rTAS2Rs	References
Human		
Stomach	3,4,5,8,9,10,13,14,16,19,20,31,42,50,60	[26]
Duodenum	4,5,14,20,38	[7]
Jejunum	3,4,5,7,8,9,10,13,14,19,20,30,31,38,39,40,43,45,46,50,60	[56]
Ileum	3,4,5,10,14,19,20,31,38,43	[52]
Colon	1,3,4,5,10,13, 14,19,20,30,31,38,39,40,42,43,45,46,50,60	[57]
Mice		
Stomach	108,109,113,115,140,143,126,135,137,138	[25]
Duodenum	108,119,126,134,135,137,138,143	[54]
Jejunum	108,119,126,135,137,138,143	[58]
Ileum	108,119,126,129,135,137,138,143	[52]
Colon	108,135,137	[54]
Rat		
Stomach	102,105,108,110,114,118,119,121,123,126,134,138	[53]
Duodenum	102,104,105,106,107,108,114,118,119,121,123	[53, 59]
Jejunum	/	/
Ileum	/	/
Colon	108,109,119	[52]

In the GI tract of humans and rodents (rats and mice), the expression of TAS2R exhibits significant differences. While some receptors, such as hTAS2R4, are widely distributed throughout the human intestinal tract, their homologous receptors in rodents do not necessarily follow the same expression pattern. There are notable differences in the specific regions and abundance of their expression. mTAS2R126 is expressed

throughout the entire GI tract in mouse, whereas in rats, rTAS2R126 has been detected only in the stomach and duodenum. Among TAS2R subtypes, only mTAS2R135/rTAS2R135, mTAS2R134/rTAS2R134, and mTAS2R143/rTAS2R143 are expressed in the duodenum of both mice and rats. However, these receptor subtypes are not detected in the corresponding segments of human GI tract^[53].

Some TAS2Rs exhibit conserved expressions across species. hTAS2R4/mTAS2R108/rTAS2R108 is expressed in the stomach of both humans and rodents, while hTAS2R38/mTAS2R138/rTAS2R138 is expressed in the duodenum of both species, and hTAS2R1/mTAS2R119 and TAS2R4/mTAS2R108/rTAS2R108 are found in the colon of both humans and rodents^[60, 61]. However, certain receptors exhibit substantial interspecies differences. In the human intestine, only a single isoform of TAS2R10 and TAS2R14 is expressed, whereas in rodents, the corresponding TAS2R10 and TAS2R14 can be divided into multiple receptor subtypes with distinct expression profiles^[62]. Moreover, hTAS2R16/rTAS2R118/mTAS2R118, and hTAS2R41/rTAS2R126/mTAS2R126 have not been detected in the human intestine, yet they are widely distributed in rodents.

These expression differences may reflect evolutionary adaptations to distinct dietary structures and metabolic demands between species, highlighting the unique expression profiles of TAS2R receptors in humans and rodents. This variation provides key insights into the functional roles of TAS2Rs and their physiological significance across different species.

3.2 The role of intestinal TAS2Rs in gut diseases

TAS2Rs in the intestinal tract play a crucial role in maintaining gut health and regulating disease progression. Enteroendocrine cells are the primary sites of TAS2Rs expression, and these cells function by sensing taste stimuli, transmitting signals to neurons, and secreting GI hormones such as glucagon-like peptide-1 (GLP-1), peptide YY (PYY), and cholecystokinin. These hormones are essential for appetite control, metabolic homeostasis, and blood glucose regulation^[63]. Notably, TAS2R14 activation significantly enhances GLP-1 secretion, which subsequently stimulates insulin release and suppresses appetite, thereby improving glucose metabolism^[64]. Similarly, TAS2R5 activation not only elevates GLP-1 secretion but also promotes PYY release, prolonging satiety and alleviating gut dysfunctions associated with metabolic disorders.

The role of intestinal TAS2Rs in inflammatory bowel disease is particularly prominent. In inflammatory bowel disease patients, TAS2R38 expression is significantly upregulated, whose activation can modulate inflammatory responses by promoting GLP-1 secretion and reducing pro-inflammatory cytokine release, thereby alleviating gut inflammation^[65]. As shown in Figure 2, TAS2Rs further enhance gut barrier function by stimulating tight junction proteins such as ZO-1 and E-cadherin, which could reduce intestinal permeability and mitigate leaky gut syndrome, thereby protecting damaged intestinal tissue. In ulcerative colitis, TAS2R activation has been shown to strengthen the intestinal mucosal barrier via the $G\beta\gamma/PLC\beta_2/IP_3$ signaling pathway, suppress mucosal inflammation, and stimulate antimicrobial peptide secretion, which in turn

prevents pathogen invasion, maintains gut microbiota balance, and improves both metabolic and inflammatory states^[66].

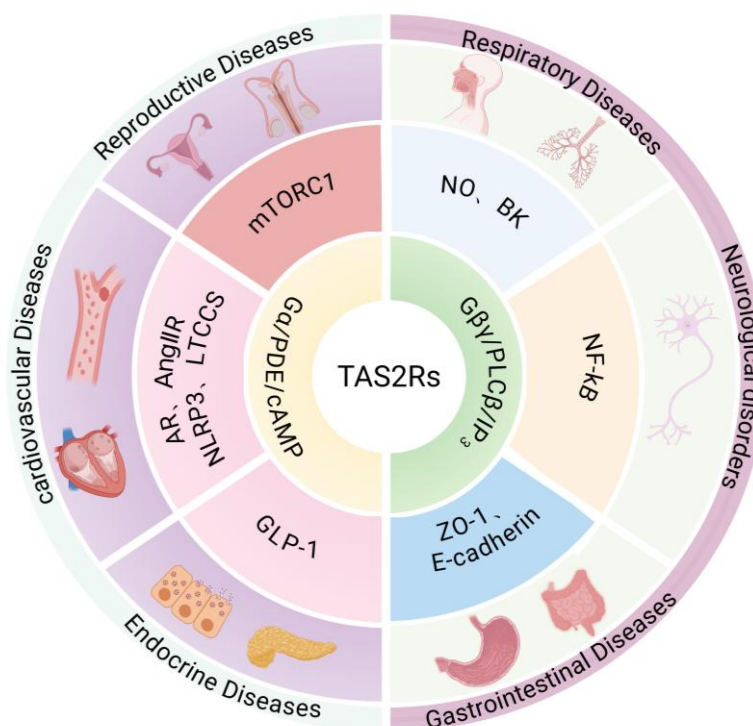


Figure 2. The relationship between TAS2Rs and key signals of various diseases.

In high-fat diet-induced gut microbiota dysbiosis, the expression levels of TAS2R138 and TAS2R116 are upregulated, which is thought to represent a stress-adaptive response to inflammation, assisting bitter taste signaling in modulating gut hormone secretion and maintaining intestinal health^[67]. Additionally, TAS2Rs interact with bacterial quorum sensing molecules, regulating hormone secretion and antimicrobial peptide release, thereby rapidly restoring gut microbiota homeostasis^[68]. AHLs, quorum sensing molecules secreted by Gram-negative bacteria, can activate TAS2R14, which triggers Ca^{2+} signaling pathways to promote antimicrobial peptide secretion^[69]. Meanwhile, TAS2R38 interacts with N-(3-oxo-dodec-12:2-enoyl)-L-homoserine lactone, a gut microbiota-derived compound, leading to immune cell activation, antimicrobial response enhancement, and inhibition of pro-inflammatory pathways.

In irritable bowel syndrome, activation of TAS2R can alleviate intestinal hypersensitivity and pain symptoms, while also modulate enteric nervous system function and regulate gut motility. Upon activation, the TAS2R signaling pathway reduces visceral nociceptive nerve excitability, thereby relieving abdominal pain and improving irritable bowel syndrome-related discomfort^[70].

3.3 The relationship between intestinal TAS2Rs and extraintestinal diseases

Intestinal TAS2Rs may contribute to extraintestinal disease processes via crosstalk with systemic hormonal and immune pathways. TAS2R38 is expressed in intestinal enteroendocrine cells, and its activation promotes the secretion of GLP-1^[71]. In addition to regulating insulin, GLP-1 can cross the blood–brain barrier and exert neuroprotective effects. Studies in Alzheimer’s disease models have shown that GLP-1 analogs, such as exendin-4, liraglutide, and lixisenatide, can reduce β -amyloid plaques, prevent synaptic damage and

memory impairment, and alleviate oxidative stress and chronic neuroinflammation in the brain^[72]. TAS2R43 is expressed in jejunal crypts, where its activation induces the secretion of antimicrobial peptides and immune factors, thereby strengthening the intestinal immune barrier. In addition, bitter agonists can activate TAS2R43 to trigger an NRF2-mediated response, leading to the upregulation of GDF15 (a gut-derived hormone that suppresses appetite) as well as genes involved in lipid metabolism. These effects collectively contribute to reduced appetite, lower energy intake, improved lipid homeostasis, and ultimately support body weight regulation^[73]. For infectious diseases, TAS2R38 detects bacterial metabolites, including AHLs and quinolones, which promotes antimicrobial peptide secretion, thereby enhancing the body's resistance to bacterial and viral infections. This function is particularly crucial in highly pathogenic infections, where TAS2R38 activation plays a key role in host defense^[74].

TAS2Rs are also implicated in cancer progression and tumor microenvironment regulation. The high expression of TAS2R genes has been shown to influence tumor cell proliferation, migration, and metastasis, indirectly affecting patient survival outcomes. Given the cell-specific nature of TAS2Rs activation and the diversity of its downstream signaling pathways, TAS2Rs may exert both tumor-promoting and tumor-suppressing effects. The TAS2R4 agonist quinine activates the pro-proliferative Ras p21-mitogen-activated protein kinase pathway in both normal mammary epithelial cells (MCF10A) and breast cancer cells (MCF7), indicating a mediating role of TAS2R4 in tumorigenesis^[75]. Interestingly, in normal cells, quinine simultaneously exerts tumor-suppressive effects by directly binding to and inhibiting RalA protein activity. However, in tumor cells, reduced Ral guanine nucleotide dissociation stimulator expression renders this RalA inhibition ineffective, allowing pro-proliferative signaling to dominate. This cell type-specific regulation demonstrates that TAS2R-mediated effects in the tumor microenvironment may shift from tumor suppression to tumor promotion due to pathway imbalance, highlighting the complex dual role of bitter taste receptors in cancer progression^[75].

3.4 Functional link between oral and gut TAS2Rs

TAS2Rs serve as chemosensory receptors in the oral cavity, where they detect potentially harmful bitter substances and trigger aversive responses to prevent toxin ingestion^[76]. In contrast, intestinal TAS2Rs detect bitter compounds derived from food and microbial metabolites through similar signaling pathways, but their activation contributes to physiological regulation. Specifically, they influence satiety and energy balance by modulating gut hormones such as GLP-1 and PYY, thereby affecting food intake^[65]. This parallel between oral taste perception and gut hormone modulation suggests that TAS2Rs form a continuous system linking bitter detection to metabolic control.

TAS2R38 exerts tissue-specific functions in the oral cavity and gut. In the oral environment, it contributes to microbiota regulation and inflammation control, notably in periodontitis^[45]. In the intestine, TAS2R38 helps maintain immune homeostasis and prevent excessive inflammation; its impaired function has been associated with aggravated inflammatory responses in inflammatory bowel disease^[43]. Through its roles across mucosal tissues, TAS2R38 participates in both local and systemic immune modulation.

Oral TAS2R activation influences taste perception and dietary choices, which in turn modulate intestinal TAS2R signaling via the gut–brain axis. This bidirectional interaction regulates gut hormone secretion, immune responses, and metabolic processes. The coordinated function of oral and intestinal TAS2Rs forms an integrated chemosensory system that links bitter taste detection to physiological regulation, supporting nutritional balance and systemic homeostasis

4. Expression of TAS2Rs in other tissues and their relationship with health

4.1 TAS2Rs in the respiratory system and disease associations

TAS2Rs are widely expressed in ciliated airway epithelial cells, brush cells, airway smooth muscle cells, and immune cells, playing a crucial role in maintaining airway defense and regulating inflammatory responses. Notably, TAS2R38, which is highly expressed in nasal cilia and tracheal brush cells, recognizes bacterial metabolites such as AHLs and initiates downstream signaling cascades that enhance mucociliary clearance and local antimicrobial defense^[77]. Air pollutants such as sulfur dioxide and ozone can also activate TAS2Rs in the respiratory tract.

In chronic rhinosinusitis, the expression of TAS2Rs in nasal epithelial cells is downregulated, although the associated signaling pathways remain functional. Upon exposure to bacterial and other external stimuli, TAS2Rs in sinus epithelial cells are activated, triggering a $G\beta\gamma$ subunit mediated $PLC\beta_2/IP_3$ signaling cascade and a localized Ca^{2+} response, which in turn promotes the synthesis of nitric oxide (NO). NO enhances mucociliary clearance and exerts bactericidal effects, suggesting a potential therapeutic role for TAS2Rs in chronic rhinosinusitis^[78]. However, in some chronic rhinosinusitis patients, TAS2R38 gene polymorphisms lead to reduced receptor function, impairing bacterial defense mechanisms and exacerbating inflammation^[10].

In asthma, studies using asthmatic mouse models have shown downregulated expression of TAS2R10, TAS2R14, TAS2R31 and downstream signaling molecules in airway tissues. However, the TAS2R-mediated bronchodilation pathway remains functional^[79]. Upon TAS2R activation, its activation initiates the classical G protein signaling cascade, in which G_α dissociates from $G\beta\gamma$. The $G\beta\gamma$ subunit activates the $PLC\beta_2/IP_3/Ca^{2+}$ pathway, resulting in localized Ca^{2+} currents that trigger downstream immune responses. This cascade activates large-conductance Ca^{2+} activated potassium channels, resulting in membrane hyperpolarization and relaxation of airway smooth muscle, thereby reducing bronchoconstriction^[80].

Additionally, TAS2Rs may alleviate asthma symptoms by modulating acetylcholine receptors (AChRs). When TAS2Rs are activated, G_α interacts with AChRs, weakening the action of AChR on other G-protein-coupled receptors, inhibiting AChR-mediated Ca^{2+} signaling and blocking downstream GPCR pathways, ultimately inhibit airway smooth muscle contraction and improving asthma symptoms^[81]. Figure 3 illustrates this process. Notably, in allergic asthma mouse models, sulfur dioxide (SO_2) exposure may suppress TAS2R signaling by downregulating the transcription of mTAS2R143, mTAS2R135, and mTAS2R126 in airway epithelial clusters, thereby exacerbating airway inflammation and worsening asthma symptoms^[82]. Chronic obstructive pulmonary disease is characterized by a persistent inflammatory response, coordinated through the release of cytokines and chemokines. Several TAS2Rs, including TAS2R3, TAS2R4, TAS2R5,

TAS2R9, TAS2R10, TAS2R14, TAS2R31, TAS2R39, and TAS2R40, are expressed in human macrophages. Upon activation, these TAS2Rs can attenuate lipopolysaccharide (LPS)-induced inflammatory responses by suppressing the production of key pro-inflammatory cytokines such as TNF- α and IL-1 β . This regulatory mechanism contributes to the modulation of local immune inflammation and strengthens pulmonary immune defense^[18].

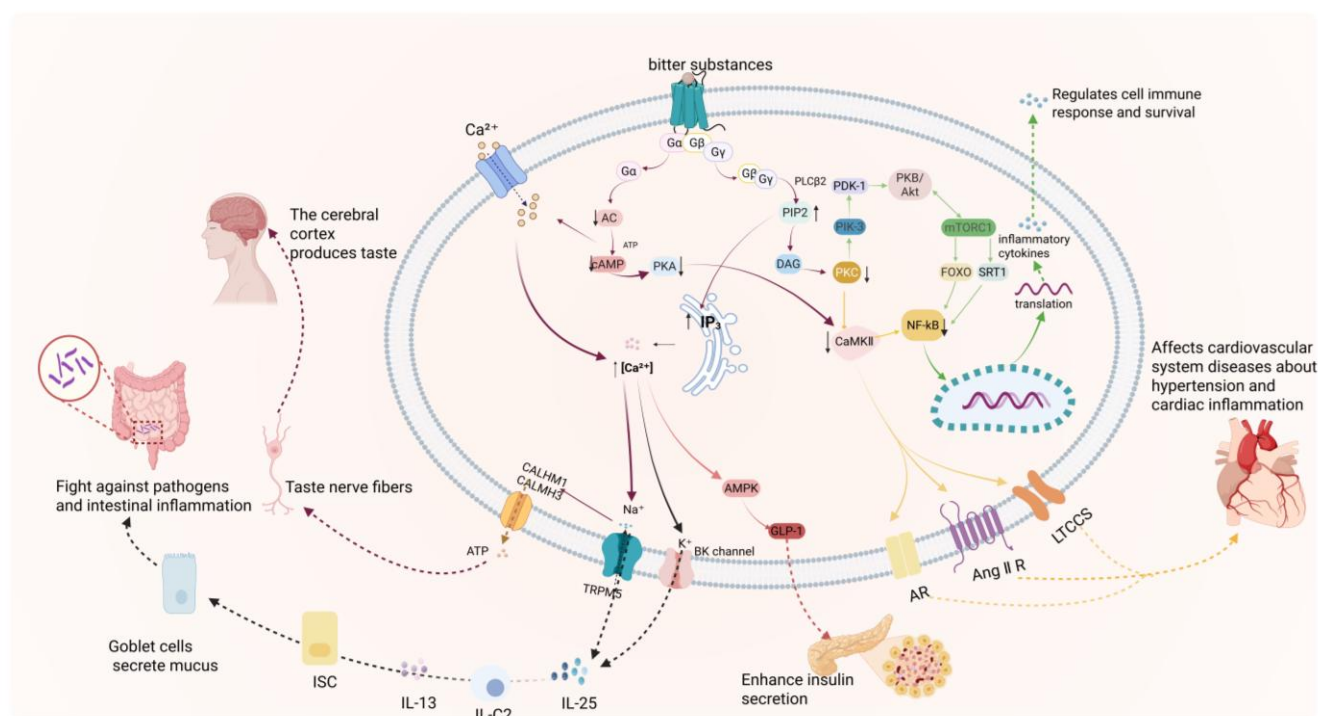


Figure 3. Schematic diagram of TAS2Rs signaling pathway.

4.2 TAS2Rs in the Cardiovascular System and Disease Associations

The expression and function of TAS2Rs in the cardiovascular system were first identified in 2013 in human and rat^[20]. Subsequent studies confirmed the presence of several key TAS2R subtypes, including TAS2R108, TAS2R126, TAS2R137, and TAS2R135 in rat and TAS2R14, TAS2R31, TAS2R50 in human, that revealed their involvement in cardiac rhythm regulation and the pathogenesis of cardiovascular diseases^[83].

TAS2R signaling is closely linked to the development of cardiac arrhythmias. In the rat left ventricle, rTAS2R120 exhibits the most abundant mRNA expression, followed by rTAS2R121 and rTAS2R143. Studies demonstrate that TAS2Rs agonists, such as quinine and chloroquine, prolong ventricular depolarization duration and attenuate sinoatrial node rhythm in a G protein-dependent manner, thereby reducing heart rate. Furthermore, these agonists counteract β -adrenergic receptor activation, effectively suppressing isoproterenol-induced tachycardia^[83]. Upon TAS2R activation reduces intracellular cAMP levels through the AC/cAMP/PKA/CaMKII pathway, ultimately dampening downstream Ca²⁺ signaling and contractile activity. Consequently, reduced expression of L-type Ca²⁺ channels, TRPM5, and adrenergic receptors (ARs) contributes to a slower sinoatrial rhythm and may help suppress arrhythmic activity.

Simultaneously, $G\beta\gamma$ signaling activates the $PIP_2/IP_3/PKC/CaMKII$ pathway, ultimately reducing the activity of TRPM5, LTCCs, ARs, and angiotensin II receptor (AngIIIR), resulting in relaxation of cardiovascular smooth muscle and aiding in the restoration of normal heart rhythm^[84].

Cardiac inflammation, including infective endocarditis, myocarditis, and pericarditis, can impair cardiac pump function, leading to systemic hypoperfusion and, in severe cases, life-threatening complications. The onset of cardiac inflammation is strongly associated with the activation of NF- κ B and NLRP3^[85]. In rodent models, TAS2R14 and their key downstream signaling molecules exhibit a downward expression trend during cardiac inflammation. Upon TAS2R activation, both the $G\beta\gamma/PLC\beta_2/PIP_2/PKC$ and $G\alpha/AC/cAMP/PKA$ signaling pathways contribute to the inhibition of CaMKII expression and the suppression of NF- κ B production. Since NF- κ B is a transcriptional activator of NLRP3, TAS2R activation indirectly inhibits NLRP3 transcription, thereby reducing the expression of cardiac inflammatory cytokines and exerting a protective effect against cardiac inflammation^[84]. Additionally, the oxidative stress sensor nuclear factor erythroid 2-related factor 2 (Nrf-2) has been found to suppress cardiac inflammation by upregulating anti-inflammatory mediators. Activated TAS2Rs can regulate Nrf-2 nuclear translocation via the $G\beta\gamma/PLC\beta_2/PIP_2/PKC$ and $G\alpha/AC/cAMP/PKA$ pathways, leading to a reduction in inflammatory cytokine levels, thereby contributing to the therapeutic modulation of cardiac inflammation^[86].

4.3 TAS2Rs in the endocrine system and diseases associations

TAS2R4, TAS2R5, TAS2R14, and TAS2R20 are relatively high expressed in pancreatic and intestinal endocrine cells, playing a crucial role in insulin regulation, glucose metabolism, and the progression of metabolic diseases. Studies have shown that TAS2R3, TAS2R38, TAS2R44, and TAS2R46 influence insulin secretion and β -cell function through Ca^{2+} and cAMP-mediated signaling pathways, suggesting their potential significance in the regulation of type 2 diabetes (T2DM) and other metabolic disorders^[24].

T2DM is primarily characterized by hyperglycemia, insufficient insulin secretion, and insulin resistance. Although TAS2R38 are expressed at relatively low levels in pancreatic β -cells, their functional relevance has been increasingly associated with the onset and progression of T2DM. There is no significant difference in the expression levels of TAS2R38 in the intestinal endocrine cells between healthy individuals and T2DM patients^[24]. Upon TAS2R activation, $G\alpha$ and $G\beta\gamma$ subunits dissociate upon TAS2R activation, initiating the $G\alpha/PDE/cAMP/AMPK/PI_3K$ signaling axis, which promotes insulin secretion and enhances β -cell sensitivity to glucose, thereby contributing to improved insulin resistance. The other pathway involves $G\beta\gamma$ activates the $PLC\beta_2/IP_3/IP_3R/Ca^{2+}$ pathway, increasing intracellular Ca^{2+} levels and promoting insulin secretion. This process also enhances the expression of Ca^{2+} /calmodulin-dependent protein kinase β , which further activates AMPK and enhances the secretion of GLP-1, promotes insulin secretion and inhibits glucagon release, thus effectively lowering blood glucose levels^[87, 88].

4.4 TAS2Rs in the Reproductive System and Diseases Associations

TAS2Rs are widely expressed in the reproductive system, playing a crucial role in sperm maturation, oocyte development, and the regulation of reproductive hormones. Studies have shown that TAS2R14 and

TAS2R43 are highly expressed in the testes and sperm, influencing sperm motility and chemotactic behavior^[89]. In the female reproductive system, TAS2Rs such as TAS2R3, TAS2R4, and TAS2R14 are expressed in ovarian granulosa and cumulus cells, contributing to oocyte maturation and follicular homeostasis^[90].

Abnormal expression of TAS2R14 and TAS2R43 in testes and sperm has been linked to male infertility. When TAS2Rs in sperm are activated, $G\alpha$ inhibits AC, while $G\beta\gamma$ activates PDE, both contributing to reduced intracellular cAMP levels. Since cAMP is a key regulator of sperm flagellar motility, its decrease results in reduced sperm motility and lower sperm vitality^[91]. Additionally, $G\beta\gamma$ activates the $PLC\beta_2/IP_3/Ca^{2+}$ pathway, leading to TRPM5 activation and the regulation of sperm chemotaxis toward the oocyte. Disruption of this signaling may impair directional movement and reduce fertilization efficiency^[92].

TAS2R signaling dysfunction is closely linked to polycystic ovary syndrome (PCOS). Patients with PCOS usually have elevated androgen levels. TAS2R14 and TAS2R108 activate guanine nucleotide-binding protein G(q) subunit alpha ($G\alpha_q$) mediated signaling pathways, regulating $PLC\beta_2$ and its downstream messengers IP_3 and DAG, triggering a Ca^{2+} signaling cascade. This process influences the expression of CYP17A1, a key enzyme in steroidogenesis, leading to a reduction in testosterone and androstenedione levels. In PCOS mouse models, TAS2R108 agonist KDT501 has been shown to restore ovarian steroidogenesis, improve follicular development, reduce insulin resistance, and limit fat accumulation. Additionally, TAS2R activation may help suppress chronic low-grade inflammation in the ovarian microenvironment, thereby alleviating PCOS symptoms^[90]. These findings suggest that TAS2Rs may serve as potential therapeutic targets for PCOS, with their signaling pathways playing a role in modulating ovarian function.

TAS2Rs are also present in smooth uterine muscle and are associated with preterm birth regulation. Myosin light chain kinase (MLCK) phosphorylation mediates uterine smooth muscle contraction. Although TAS2R126, TAS2R135, TAS2R137 and TAS2R143 expression levels do not significantly differ between preterm and normal pregnancy models in mouse uterine smooth muscle, TAS2Rs activation can reduce intracellular Ca^{2+} levels via the $G\alpha/AC/cAMP$ signaling pathway, inhibiting MLCK phosphorylation. This results in weaker and less frequent uterine contractions, maintaining uterine relaxation and reducing the risk of preterm birth^[93]. The TAS2R agonist Chloroquine activates TAS2R14, modulating intracellular Ca^{2+} signaling in human myometrial cells, thereby completely inhibiting uterine smooth muscle contractions^[32]. These findings suggest that TAS2Rs may be novel therapeutic targets for preterm birth regulation, with potential applications in pregnancy management and maternal-infant health products.

TAS2R signaling pathways also play a crucial role in inhibiting reproductive system malignancies, including ovarian and prostate cancers. TAS2R14 activation via the cAMP-PKA signaling pathway suppresses tumor cell proliferation by regulating cell cycle proteins, slowing tumor growth. This pathway also reduces mitochondrial membrane potential, triggering cytochrome C release and caspase-dependent apoptotic, thereby inducing apoptosis in cancer cells. Additionally, TAS2R14 activation downregulates matrix metalloproteinases, inhibiting cancer cell invasion and migration, reducing the likelihood of tumor

metastasis^[33]. Furthermore, TAS2R38 genetic polymorphisms may be associated with cancer risk. A study in 2024 found that the G/A and G/G genotypes of the odds ratio of 1.77 has been reported for the association between the non-bitter tasting TAS2R38 CA6 genotype and an increased risk of breast cancer. This suggests that TAS2R may play a role in breast cancer development^[33].

The role of TAS2Rs in reproductive infections has also gained attention. When the male reproductive tract is infected by bacteria or viruses, TAS2R14 and their downstream signaling molecules are downregulated, affecting antimicrobial immune responses. Studies in Sprague-Dawley male rats suggest that TAS2R activation via the $G\beta\gamma/PLC\beta_2/IP_3$ signaling pathway promotes intracellular Ca^{2+} release, leading to an increase in cytosolic Ca^{2+} levels. This stimulates nitric oxide synthase, facilitating NO production, which subsequently inhibits inflammatory cytokine release, exerting antimicrobial and anti-inflammatory effects^[94].

4.5 TAS2Rs in the Nervous System and Diseases Associations

Neurodegenerative diseases (NDDs), including Alzheimer's disease, Parkinson's disease, and multiple sclerosis, are marked by progressive neuronal loss and persistent neuroinflammation, particularly in regions such as the hippocampus, cortex, and substantia nigra. Accumulating evidence suggests that the activation of the NLRP3 inflammasome and the NF- κ B signaling pathway plays a central role in promoting the release of pro-inflammatory cytokines like IL-1 β and IL-6, which further exacerbate synaptic dysfunction and neuronal apoptosis^[48]. TAS2R14 and TAS2R39 are expressed in the choroid plexus cells of the brain and can significantly inhibit neuroinflammation through specific signaling pathways^[95]. Experimental models in Sprague-Dawley rats have shown that TAS2R activation during neuroinflammatory states triggers the $G\beta\gamma/PLC\beta_2/IP_3$ signaling axis, leading to increased CaMK β expression. This upregulation suppresses NLRP3 inflammasome assembly and reduces NF- κ B activity, thereby decreasing the production of IL-6 and IL-1 β . Such effects have been observed predominantly in the hippocampus and prefrontal cortex, brain regions crucial for memory and cognitive function. By mitigating inflammation in these areas, TAS2Rs may contribute to neuroprotection, preserve synaptic integrity, and slow the progression of neurodegenerative diseases^[48].

Beyond its role in reducing inflammation, TAS2R activation influences the PDK-1/Akt (3-phosphoinositide-dependent protein kinase-1/ protein kinase B) signaling pathway, regulating the activity of mTORC1 (mechanistic target of rapamycin complex 1) and SIRT1 (sirtuin 1). This coordinated mechanism ultimately inhibits NF- κ B activation, thereby significantly alleviating neuroinflammation-induced neuronal damage^[96]. These findings suggest that TAS2R activation may serve as a novel therapeutic strategy for neurodegenerative diseases, as its ability to modulate neuroinflammation and support cellular repair positions it as a promising neuroprotective target.

5. Agonists and antagonists effects of natural compounds on TAS2Rs

5.1 Natural substances act as TAS2Rs antagonists

When bitter compounds bind to TAS2Rs, they activate intracellular signaling pathways, transmitting signals into the cell, reducing the intracellular-extracellular potential difference, leading to cell membrane depolarization and exciting postsynaptic neurons. Subsequently, these signals are relayed to the nucleus of the solitary tract in the brainstem, where they are processed and integrated by the central nervous system, ultimately allowing the organism to perceive bitterness^[97]. TAS2Rs blockers work by either blocking TAS2Rs or interfering with bitter taste signal transduction, thereby reducing or eliminating the perception of bitterness. These antagonists' function through competitive bidding to receptor agonist sites or by inducing conformational changes upon receptor binding, thereby suppressing bitter taste perception^[98]. Such mechanisms alter individual sensitivity to bitter foods, significantly improving the acceptance of naturally bitter foods such as dark leafy vegetables, coffee, and functional plant extracts. Based on their origin, TAS2R antagonists can be categorized into three types: plant-derived, animal-derived, and microbe-derived antagonists, as illustrated in Table 3.

Plant-derived TAS2Rs primarily include flavanone compounds. 4'-fluoro-6-methoxyflavanone and 6,3'-dimethoxyflavanone have been found to inhibit TAS2R39 and TAS2R14 activity by reducing Ca^{2+} ion release, thereby suppressing TAS2Rs activation^[99]. Flavonoid compounds extracted from *E. californicum* leaves, such as sakuranetin and 6-methoxy sakuranetin, significantly inhibit TAS2R31 activity^[100]. Eriodictyol and its derivatives, such as homoeriodictyol and naringenin, have been shown to inhibit TAS2R10, reducing the bitter perception of compounds like quinine and caffeine^[101]. Additionally, acidic dipeptides (such as Glu-Glu and Asp-Asp) and organic acids can bind to TAS2R16, suppressing its activity and reducing the bitterness of salicin. Amino acid derivatives such as glutamate (L-Glu), aspartate (L-Asp), γ -aminobutyric acid (GABA), and N-decanoyl-L-tryptophan have also been found to effectively antagonist bitter taste perception^[102].

Animal-derived TAS2Rs inhibitors include adenosine compounds, cholesterol, and amino acid derivatives. Cholesterol, as an endogenous molecule, has been found to modulate TAS2R14 receptor function by binding to orthostatic sites, serving as an allosteric regulator that modifies TAS2R14 sensitivity to agonists. Depending on its binding site and membrane concentration, cholesterol can either enhance or suppress TAS2R14 signal transduction^[103]. Additionally, L-Glu and L-Asp can directly bind to TAS2R16 in a competitive manner, preventing activation by bitter compounds, thus reducing bitterness perception^[104]. These amino acid derivatives are widely used in the food industry as sensory quality enhancers.

Microbial TAS2Rs inhibitors include lactic acid, ethanol, fermentation enzymes, yeast extracts, polysaccharides, amino acids, and their derivatives. Studies have shown that certain *Lactobacillus* species may regulate TAS2R16 and TAS2R38 activity through their metabolic products, thereby reducing bitter perception, a mechanism commonly used in fermented food production to mitigate bitterness^[105]. Yeast extracts, particularly those rich in AMP, have been shown to inhibit multiple TAS2Rs. AMP-containing yeast extracts have demonstrated inhibitory effects on TAS2R subtypes such as TAS2R3, TAS2R4, TAS2R14 attenuating responses to bitter agonists by increasing their EC_{50} values and reducing the maximal response

amplitude. These results indicate a combination of competitive and non-competitive inhibition mechanisms^[106]. Lactate and short-chain fatty acids, such as butyrate, can competitively bind to TAS2R16, reducing the binding of bitter ligands like salicin and thereby decreasing bitter taste perception^[105]. Short-chain fatty acids produced by *Bacteroides spp.* can alter the conformational structure of the TAS2R14 receptor, reducing the perception of bitter compounds (such as bitter polyphenols) and increasing food acceptability^[107]. Additionally, short-chain fatty acids metabolized by *Bacteroides* and *Clostridium* species can activate GPCR signaling pathways, leading to negative feedback regulation of GPCRs, which results in reduced TAS2R14 expression on the cell membrane and a decrease in sensitivity to bitter compounds^[108]

Table3. Natural substances act as TAS2Rs antagonists.

Compound	TAS2Rs Subtypes	Chemical Classification	Function tissue in human	Regulation method	References
Plant source					
4'-fluoro-6-methoxyflavanone	39	Flavonoid derivatives	/	Reducing Ca ²⁺ release	[99]
6,3'-dimethoxyflavanone	14,39	Flavonoids	/		[109]
Sakuranetin	31	Flavonoids	/	Inhibit receptor activity	[100]
Centaureidin	31	Flavonoids	/		[100]
Homoeriodictyol	10,14	Flavonoids		Inhibit the bitter taste of quinine,	[110]
Eriodictyol	10,31	Flavonoids	/	caffeine and bitter almonds	[100, 111]
Naringenin	10,14	Flavonoids	/		[110]
Liquiritigenin	10	Flavonoids	/		[111]
Umami peptides (Glu-Asp 、 Glu-Glu 、 Glu-Ser 、 Asp-Glu-Ser and Glu-Gly-Ser)	16	Peptides	Kidney	Inhibition of salicylate-induced Ca ²⁺ signaling	[112]
Citric acid	16	Tricarboxylic acid	/	Inhibition of salicylate-induced	[102]
Tartaric acid	16	Dicarboxylic	/	signaling and pH-related	[102]
Ascorbic acid	16	Acids Vitamin C, organic acids	/	inhibitory effect	[102]
Gluconic acid	4,31,39,40	Carboxylic acid compounds	/	Significantly reduced the bitter taste of quinine hydrochloride	[113]
3-hydroxydesacetylcynaropicrin	46、 30、 40	Sesquiterpene lactones	/	Competitive inhibitor	[114]
3-hydroxyparthenolide	46 、 30 、 31、 43	Sesquiterpene lactones	/	Competitive inhibitor, Concentration dependence	[114]
Animal source					
Cholesterol	14	Endogenous molecules	/	Mutant structural adjustment factors affect their signal transmission	[115]
Glutamate and aspartate	16	Amino acid	/	Direct competitive binding	[104]
Microbial source					
Lactobacillus metabolites	16,38	Lactate	Oral	Affecting the activity of bitter taste receptors	[105]
Yeast extracts (rich in amp)	7,9,10,14, 16,38,43	Yeast	Oral	Bitterness masking agent	[106]
Butyrate	16	Short-chain fatty acids	/	Competitively bind to TAS2R16, reducing the binding of bitter ligands	[105]
Short-chain fatty acids	14	<i>Bacteroides</i> and <i>clostridium</i>	/	Alter the conformational structure of the TAS2R14	[108]

5.2 Natural substances act as TAS2Rs agonists

Plant-derived TAS2Rs activators include various phytochemicals and bioactive compounds that specifically activate certain TAS2R subtypes in Table 4. Caffeine can directly bind to TAS2R10, TAS2R14, TAS2R43, and TAS2R46 initiate bitter taste signal transduction and influencing metabolic and immune regulation^[116, 117]. Berberine in coptis can activate TAS2R38, which stimulates the secretion of GLP-1 and regulates glycemic homeostasis, and helps alleviate T2DM^[28]. Epigallocatechin gallate from green tea activates TAS2R14, TAS2R31 and TAS2R39, thereby triggering the AMPK signaling pathway, which enhances glucose metabolism and contributes to the prevention and management of diabetes^[118]. Naringin, a flavonoid found in citrus fruits, binds to TAS2R4 and TAS2R14, activating signaling pathways that relax airway smooth muscle, helping relieve asthma. It also shows anti-inflammatory and anticancer effects^[119, 120].

Apigenin is a naturally occurring flavonoid known to activate the bitter taste receptors TAS2R14 and TAS2R39. It exhibits a wide range of pharmacological activities, including antioxidant, anti-inflammatory, anticancer, antimicrobial, antiviral, cardioprotective, and anti-obesity effects^[118]. Amarogentin can activate seven bitter taste receptor subtypes (TAS2R1, TAS2R4, TAS2R39, TAS2R43, TAS2R46, TAS2R47, and TAS2R50) and exhibits notable anti-inflammatory and anticancer properties. In skin cancer models, it has been shown to induce apoptosis and inhibit tumor cell proliferation^[118]. Chrysin is a flavonoid compound that activates the bitter taste receptors TAS2R14 and TAS2R39^[99]. It exhibits notable anti-inflammatory and anticancer activities by inhibiting the proliferation and metastasis of skin cancer cells and inducing apoptosis^[118]. Cucurbitacin B, a natural triterpenoid compound found in bitter melon, agonists of TAS2R10 and TAS2R14, exhibits potent skin-targeted anti-inflammatory and anticancer activities^[121]. It suppresses psoriasis-related cytokines such as IL-8 and c-c motif chemokine ligand 20, inhibits keratinocyte proliferation, and reduces tumor growth by impairing cancer cell proliferation and migration^[118].

Flavonoids such as liquiritigenin, kaempferol, luteolin, and resveratrol act as agonists of TAS2R14 and TAS2R39^[99]. Activation of these receptors by flavonoids is associated with anti-inflammatory, antitumor, and tissue-repairing effects. In atopic dermatitis models, these compounds attenuate inflammation by suppressing inflammatory cell infiltration, downregulating pro-inflammatory cytokines, alleviating oxidative stress, and reducing serum IgE levels^[122, 123]. In skin cancer models, TAS2R14 and TAS2R39 activation inhibits tumor cell proliferation and migration, induce apoptosis, and markedly reduce tumor volume, multiplicity, and weight, underscoring their therapeutic potential in tumor suppression^[124]. Collectively, these findings indicate that TAS2R14 and TAS2R39 activation by flavonoids may contribute to both anti-inflammatory regulation and cancer prevention.

Quinine activates bitter taste receptors TAS2R4, TAS2R7, TAS2R10, TAS2R14, TAS2R31, TAS2R39, TAS2R40, TAS2R43, and TAS2R46 in the airways^[40], that enhance ciliary beat frequency and stimulate NO production, thereby boosting innate immune defenses in the respiratory tract^[125]. This mechanism suggests potential therapeutic benefits for alleviating chronic rhinitis. Gentiana activates the TAS2R1^[126]. It shows to suppress lipid accumulation and significantly decrease daily caloric intake, indicating its potential role in

metabolic regulation and obesity prevention^[127]. Quercetin is a natural flavonoid abundantly found in various fruits and vegetables, especially red onions. It has been shown to activate the bitter taste receptor TAS2R14 and exhibits neuroprotective effects^[128]. Andrographolide, the primary active compound in *Andrographis paniculata*, activates TAS2R46 and TAS2R50 to exert dual antioxidant and anti-inflammatory effects^[129, 130]. Vanillin activates TAS2R14, TAS2R20, and TAS2R39, enhancing appetite while improving GI microbiota composition^[131]. Piperine, as a specific agonist of TAS2R14, significantly promotes the secretion of GLP-1 from intestinal L cells^[132].

Bile acids are the most important animal-derived TAS2Rs activators. These compounds, primarily found in the liver and gallbladder, interact with TAS2R1, TAS2R4, TAS2R14, TAS2R39, and TAS2R46, activate the bitter taste signaling pathway, inducing bitter taste perception, and participating in fat digestion and absorption^[133]. Tauroursodeoxycholic acid, glycocholic acid, and other bile acids can activate multiple TAS2Rs. During the digestion of high-fat foods, these bile acids may act as “signaling molecules”, enhancing bitter taste perception, and regulating appetite and digestion^[133].

Microbial-derived TAS2Rs activators can either bind directly to TAS2Rs or induce TAS2Rs activation through secreted metabolites. Acyl-homoserine lactones secreted by *Pseudomonas aeruginosa* include 3-Oxo-C12-AHL and C8-AHL, which activate TAS2R4, TAS2R14, and TAS2R20, while C8-AHL specifically activates TAS2R4 and TAS2R14, triggering bitter taste receptor signaling pathways and modulating immune functions^[38]. Additionally, *S. mutans* releases competence-stimulating peptide (CSP), which binds to TAS2R14, inducing Ca²⁺ signaling and promoting the secretion of cytokines such as IL-8, TNF- α , and IL-6, thereby playing a crucial role in oral immunity, host defense, and immune regulation^[14]. Furthermore, N-acyl-homoserine lactones produced by *Pseudomonas aeruginosa* function as TAS2R38 activators, directly binding to the receptor and activating downstream signaling pathways. TAS2R38 activation enhances NO production, which can exerts antimicrobial effects by disrupting bacterial membranes, cell walls, DNA, and various essential proteins^[46]. These microbial molecules modulate TAS2R signaling pathways through different mechanisms, leading to TAS2R activation. In addition to enhancing bitter taste perception, these activators are involved in host immune surveillance and microbial quorum sensing, playing a vital role in host-microbiome interactions.

Table 4. Natural substances act as TAS2Rs agonists.

Compound	TAS2Rs subtypes	Origin	Function tissue in human	Main function	References
Plant source					
Caffeine	7,10,14,43,46	Coffea arabica	Pancreas	Influence metabolic and immune regulation	[116, 117]
Berberine	38,46	Coptis chinensis	GI	Treatment of type 2 diabetes; anti-inflammatory effects	[28, 118]
Epigallocatechin gallate	14,31,39	Green tea	Skin	Beneficial effects on skin inflammation, cutaneous tumors, satiety enhancement, and reduction of food intake	[118]
Naringin	4,14	Citrus fruits	Airway	Treat bronchiectasis, exert anti-inflammatory and anti-tumor	[119, 120]

				effects	
Apigenin	14,39	Grapefruit, lettuce, celery	Skin	Antioxidant, anti-inflammatory, anticancer, antimicrobial, antiviral, cardioprotective, and anti-obesity effects	[118]
Amarogentin	1,4,39,43,46,47,50	Various plants	Skin	Reduce inflammation, induce apoptosis, inhibit cell proliferation	[118]
Amygdalin	16	Apricot, peach, bitter almond	Oral	Multiple immunomodulatory effects on human epidermal keratinocytes	[134]
Chrysin	14,39	<i>Opuntia ficus indica</i> L, <i>Viburnum opulus</i> L, honey and propolis	Skin	Anti-inflammatory and anticancer effects	[118]
Cucurbitacin B	10,14	Momordica charantia	Skin	Anti-inflammatory and anticancer effects	[118, 121]
Genistein	14,39	Glycyrrhiza uralensis	Skin	Anticancer and wound-healing-promoting	[99]
Kaempferol	14,39	Green leafy vegetables	Skin	Anti-inflammatory and anticancer effects	[135]
Luteolin	14,39	<i>Daucus carota</i>	Skin	Anti-inflammatory and anticancer effects	[99, 118]
Resveratro	14,39	Grapes, wines, and peanuts	Skin	Anti-inflammatory and anticancer effects	[118]
Quinine	4, 7,10,14, 31,39,40,43,46	<i>Cinchona officinalis</i>	Oral, GI	Regulation of lipogenesis and treatment of chronic sinusitis	[40]
Gentiopicroside	1	Gentiana scabra	Fatty	Inhibit fat production and reducing daily energy intake	[126, 127]
Quercetin	14	Red onion	Nerve	Neuroprotective	[128]
Andrographolide	46,50	Andrographis paniculata	Nerve	Antioxidant and anti-inflammatory effects	[129, 130]
Vanillin	14, 20,39	<i>Vanilla planifolia</i>	Kidney	Appetite enhancement and GI microbiota composition improvement	[131]
Piperine	14	<i>Piper nigrum</i>	GI	Stimulation of glucagon-like peptide-1 secretion.	[132]
Animal source					
Glycocholic acid	1,4,14,39,46	liver	and GI	Fat digestive function	[133]
Tauroursodeoxycholic	1,4,14, 46	gallbladder			
Chenodeoxycholic acid	1,14				
Lithocholic acid	1				
Deoxycholic acid	1,4				
Taurocholic acid	1,4,14,39,46				
Ursodeoxycholic acid	1,4				
Microbial source					
N-3-oxo-dodecanoyl-L-homoserine lactone	4,14,20	<i>Pseudomonas aeruginosa</i>	Airway	Immune modulation	[38]
C8-AHL	4,14,	<i>Pseudomonas aeruginosa</i>	Airway		
CSP	14	<i>Streptococcus mutans</i>	Gingival	Oral immunity, host defense, and immune regulation	[14]
N-acyl-homoserine lactones	38	<i>Pseudomonas aeruginosa</i>	Airway	Antimicrobial effect	[46]

6. Challenges and prospectives

This review highlights the multifaceted roles of TAS2Rs in physiology and microbial environments and underscores their therapeutic potential. Clarifying their complex interactions with diverse pathways and bitter taste genotypes may offer new strategies for disease prevention and appetite regulation. Although TAS2Rs have been recognized as multifunctional receptors, their roles in disease regulation and clinical applications remain challenging. A variety of TAS2R agonists and antagonists have been identified, but the activation of multiple TAS2Rs by the same ligand often results in signal overlap and non-specific responses, complicating the development of dietary guidance. Understanding the specific binding mechanisms between TAS2Rs and their ligands is essential for improving drug selectivity or therapeutic precision. Additionally, TAS2R genetic polymorphisms influence taste perception, metabolism, and disease susceptibility, yet their impact on TAS2R signaling in different biological contexts is still unclear. Further studies on how genetic variations shape TAS2R functions could support the development of personalized interventions based on individual genotypes.

TAS2Rs are involved in metabolism and other diseases, making them potential therapeutic targets. Future research should focus on identifying highly selective TAS2R modulators using computational tools such as molecular docking, AI-assisted, and virtual screening^[136]. Integrating genomic profiling with TAS2R-targeted drug development could further optimize personalized nutrition and pharmacological treatments, advancing precision medicine^[137]. Overcoming these challenges will not only enhance our understanding of TAS2R functions in health and disease but also promote their use in dietary guidance development and personalized treatment strategies for a range of chronic diseases.

Disclosure statement

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