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Review article

Targeting T2Rs, a feasible approach for natural bitter agents from traditional Chinese medicine modulate ABC transporters to treat respiratory diseases

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ABSTRACT

Background: It's known that respiratory diseases are the top of the list of systemic diseases, and accumulating evidence suggests that one of the important reasons for the high incidence of respiratory diseases is the difficulty in delivering drugs effectively to the respiratory system.
Purpose: In this review, we summarized the potential roles of targeting T2Rs in combination with bitter compounds for the treatment of respiratory diseases, and also discussed the potential of ABC transmembrane transporter proteins to deliver bitter compounds to cells to combat drug resistance, providing a reference for future studies on bitter receptor therapy related to respiratory diseases.
Results: The airway epithelium cells serve as a lung barrier against the invasion of various harmful substances in the respiratory system, and many receptors have been found to exist in the airway epithelium cells. Interestingly, it's reported that lots of bitter compounds (quercetin, resveratrol, etc.) can reduce oxidative stress and other responses in respiratory diseases via bitter taste receptors (T2Rs).
Conclusion: Collectively T2Rs, seem as feasible drug targets and alternative treatment option for for natural bitter agents from traditional Chinese medicine to respiratory diseases in the future.

1. Introduction

Respiratory diseases are reported to be one of the leading causes of death worldwide (Greene et al., 2011; Troeger et al., 2018). In particular, with the sudden outbreak of the Corona Virus Disease 2019 (COVID-19), our focus has intensified towards optimizing therapeutic approaches for respiratory ailments. The main lesions of respiratory diseases are in the trachea, bronchi, lungs and chest, and the common respiratory diseases include asthma, chronic obstructive pulmonary disease (COPD), chronic rhinosinusitis (CRS) and cystic fibrosis (CF) (McMahon et al., 2022). Clinical symptoms of respiratory diseases mostly manifest as coughing, wheezing, chest tightness, chest pain, even respiratory distress and hypoxia in severe cases, eventually leading to death from respiratory failure (Khattak et al., 2021). Most of the above symptoms are associated with smoking, indoor air pollution from solid fuels, ambient particles, and lysozyme or other bacteriocins (Soriano et al., 2020). Currently, most of available therapeutical methods for respiratory diseases are bronchodilators, inhaled glucocorticoids and antibacterial drugs (Celli and Wedzicha, 2019). In addition, monoclonal antibody therapies (biologics) are introduced to target specific cytokines and their functions (Nayak et al., 2019). Although these methods can alleviate acute exacerbations of respiratory diseases, the toxic side

Abbreviations: COVID-19, Corona Virus Disease 2019; COPD, chronic obstructive pulmonary disease; CRS, chronic rhinosinusitis; CF, cystic fibrosis; T2Rs, bitter taste receptors; ABC transporters, ATP-binding cassette transporters; GPCR, G-protein coupled receptor; c NMP, Cyclic nucleotide; c AMP, Cyclic adenosine monophosphate; IP3, Inositol (1,4,5) triphosphate; DAG, Diacylglycerol; T1Rs, taste 1 receptors; GLP-1, glucagon-like peptide 1; PD, Parkinson's disease; PTC, phenylthiocarbamide; IL-4/5/13/33, Interleukin 4/5/13/33; 6-PTU, 6-n-propyl 2-thiouracil; GPT, generative pre-trained transformer; P-g p, P-glycoprotein; MRP1, Multi-drug resistance associated protein; RCT, reverse cholesterol transport; LXRs, liver X receptors; BLM, bleomycin; EMT, epithelial mesenchymal transformation; TNF-α, Tumor necrosis factor-α; HASM, human airway smooth muscle; SNPs, single nucleotide polymorphisms; Ach E, Acetylcholinesterase; VEC, Vascular endothelial cells; CHOP, CCAAT/enhancer binding proteins homologous protein; AHR, Airway hyperresponsiveness; BALF, Bronchoalveolar lavage fluid.

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effects such as drug resistance, high cost limit the extensive and long-term use of the current available drugs. Therefore, finding more feasible drugs with fewer side effects and better efficacy is still a challenge for respiratory diseases.

It's reported that bitter taste receptors (T2Rs) play important roles in the development of oral diseases. Besides, T2Rs are also expressed in extraoral tissues and exhibit in various thereby garnering escalating attention from researchers as novel therapeutic targets against diverse diseases. Previous studies have shown that T2R10 can promote the chemosensitivity of pancreatic cancer cells (Stern et al., 2018), thereby increasing the drug resistance in these cells. Addiyionally, some bitter compounds such as flavonoids have shown therapeutic effects on respiratory diseases (Hui et al., 2013; Mocanu et al., 2015b). These lipophilic (Duarte et al., 2022b) and trans-biofilm agents possess the ability to stimulate T2Rs, facilitating their entry into the cell membrane, for example, the antimalarial drug artesunate stimulates T2R14 to improve bronchodilation. There are also many bitter compounds that can improve bioavailability by modulating ATP-binding cassette transporters (ABC transporters). For example, quercetin could downregulate the expression of ABCA3, thereby reducing oxidative stress and improving its own bioavailability. ABC transporters are specific proteins located on cell membranes, and abnormal expression of the protein family is an important contributor to the development of drug resistance in many cells. These proteins utilize the energy generated by ATP hydrolysis to transport many chemotherapeutic drugs into and out of respiratory cells. Therefore, this review aims to summarize recent advancements in T2Rs, explore how bitter compounds targeting T2Rs can effectively treat respiratory diseases, elucidate the regulatory effects of bitter compounds on ABC transmembrane and shed light on the collective involvement of all three components in respiratory diseases. The ultimate goal is to provide valuable insights for future studies investigating the diverse roles played by T2Rs.

2. T2Rs and bitter compounds in traditional Chinese medicines

The T2Rs are a subset of G-protein coupled receptors (GPCRs), which play a crucial role in cancer by regulating tumorigenesis, proliferation, migration, and invasion of cancer cells. GPCRs and their ligands serve as significant therapeutic targets for cancer treatment. After binding to T2Rs, bitter compounds can be transduced through the following three pathways: (1) Bitter receptors are stimulated to activate the α-taste conductor-PDE-cyclic nucleotide (c NMP) pathway, resulting in a decrease in cytoplasmic cyclic adenosine monophosphate (c AMP) and an increase in calcium ion (Ca^{2+}) levels, finally calcium ions depolarize the membrane. (2) Activation of β, γ-isosin- PLC-1,4,5-triphosphate inositol (IP3), Phosphatidylcholine β activation produces IP3 and diacylglycerol (DAG), resulting in the release of intracellular calcium ions (Ca^{2+}) (Bufe et al., 2002; Chandrashekar et al., 2006). (3) Pathways independent of GPCR/G protein mechanism (Fig. 1).

2.1. Taste receptors

Taste is an important perceptual response for people, which is known as the body's "nutritional gatekeeper", maintaining the balance of nutrients in the body (Liu et al., 2017b). Taste is detected by taste cells in the upper epidermis (Yang, 2004) of the tongue, which transmit taste signals to the brain. There are five basic taste responses: sweet, sour, bitter, salty and umami (L-glutamic acid taste). Sweetness indicates the presence of carbohydrates; sourness indicates the presence of food spoilage and unripe fruit; bitterness can prevent mammalian poisoning by avoiding the intake.

of some toxic substances; saltiness controls the intake of sodium ions and maintains the body's water balance; Umami is thought to be associated with protein-rich foods. Taste cells were divided into four types: I, II, III and IV, bitter, sweet and umami tastes were sensed by type II cells (Lajtha et al., 2007).

Taste receptors are involved in a variety of important physiological processes in living organisms and are also important drug targets, and can be divided into the first family of taste 1 receptors (T1Rs) and the second family of T2Rs, and the first family of taste can be divided into three conformations, T1R1, T1R2 and T1R3. Umami receptor is a heterodimer composed of T1R1 and T1R3, which is mainly co-expressed in type II cells of taste buds in the anterior part of the tongue. Sweet taste receptors are composed of T1R2 and share T1R3 with umami taste

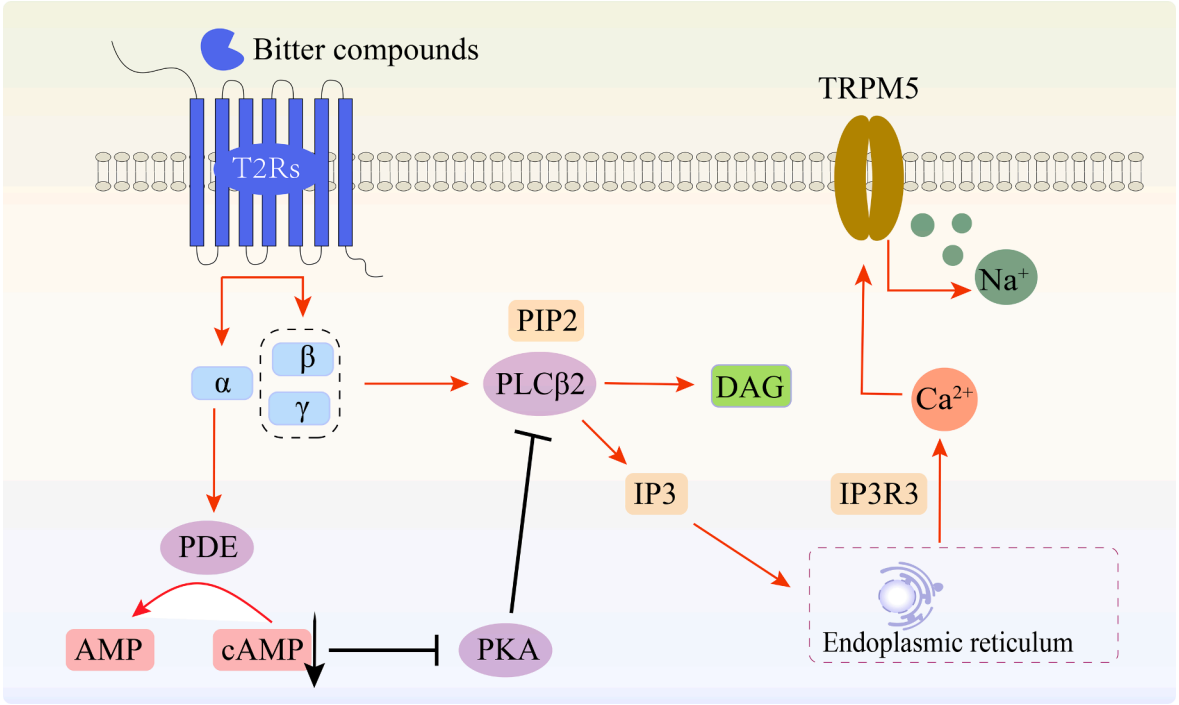


Fig. 1. Signal transduction pathway of bitter compounds.

receptors (Nelson et al., 2002; Nelson et al., 2001). Bitter taste receptor cells were mainly distributed in the vallate papillae, foliate papillae and fungiform papillae (Rozengurt and Sternini, 2007), and each cell contained a variety of T2Rs (Gabriel, 2015); The Ca^{2+} channel was activated by activating TRPV1. The nerve fibers that transmit salty taste signals are mainly distributed in the dorsal and ventral parts of the tongue (Caterina et al., 1997). Sour taste is sensed primarily by taste receptor cells on the tongue and palate epithelium (Liman et al., 2014).

Outside the oral cavity, only umami, sweet, and bitter taste belong to GPCRs, and Wauson et al. (2012) conducted a comprehensive investigation on the distribution of T1R1/T1R3 receptors and demonstrated their presence in various tissues, organs, and cells. There is already evidence suggesting that sweet taste receptors may play a role in immune regulation and response. Moreover, these receptors are expressed in gastrointestinal enteroendocrine L-cells and K-cells, which exert physiological effects through the secretion of glucagon-like peptide) and glucose-dependent insulinotropic peptide (Kojima and Nakagawa, 2011). Additionally, Deshpande and Liggett were the first to report the expression of T2Rs in airway smooth muscle cells as well as their involvement in T2Rs-mediated bronchodilation induced by bitter taste agonists. The potential use of T2Rs as screening targets for asthma treatment has garnered significant attention (Deshpande et al., 2010).

2.2. Structure and function of T2Rs

Bitter taste receptor, a member of GPCRs (Behrens and Meyerhof, 2011), is encoded by a gene family consisting of 30 genes. Its structure consists of a protein with an extracelluar N-terminus, 7 transmembrane α-helices, and intracellular C-terminus. It contains three corresponding intracellular loops and three extracellular loops (Chandrashekar et al., 2000), which can convert extracellular stimuli into intracellular stimuli. The three loops are highly conserved within cells and function as the region responsible for G-protein coupling, while the extracellular N-terminus is short and polymorphic. The diversity observed in bitter taste receptors enables them to bind to various bitter substances. T2Rs encompass 25-1, -3, -4, -5, -7, -8, -9, -10, -13, -14, -16, -38, -39, -40, -41, -42, -43, -44, -45, -46, -47, -48, 49, 50, 60), accounting for approximately 4% of human GPCRs (Pydi et al., 2012) (Fig. 2).

The expression and distribution of T2Rs have developed rapidly from early gastrointestinal endocrine cells to respiratory epithelial cells (Finger et al., 2003), pancreas, thymus, heart (Foster et al., 2013), brain, testis and other tissues. The study showed by Singh et al. (2011). used reverse transcriptase polymerase chain reaction to reveal the presence of T2R4, T2R107 and T2R38 transcripts in the brain stem of mice, the results showed that endogenous of functional T2R4 occurs in these cells. Wu et al. (2005). confirmed by reverse transcriptase polymerase chain reaction that gene expression for T2Rs was detected in the gastrointestinal mucosa of mice. Similarly, immunostaining and galactoside staining demonstrated T2R5 expression in the testis (Fehr et al., 2007).

In addition, various bitter compounds can activate a bitter taste receptor (Meyerhof et al., 2010), and different bitter taste receptors can also be activated by a single bitter compound (Reichling et al., 2008), which may be different from the concentration threshold of receptor activation induced by bitter compounds. As mentioned above, T2R14 can be activated by compounds such as the active ingredient of absinthine, woodruff bitter toxin, sodium benzoate, and 1,8-naphthalaldehydic acid (Behrens et al., 2004), in contrast, aristolochic acid can activate T2R44 and T2R46(Pronin et al., 2004). Many bitter compounds such as alkaloids, flavonoids and polyphenols have significant effects in the treatment of respiratory diseases. After the interaction between bitter compounds and T2Rs, bitter signal transduction makes the brain feel bitter taste. Therefore, the combination of bitter compounds with T2Rs has become a new avenue to treat diseases.

2.3. Bitter compounds in traditional Chinese medicines

Bitter compounds are mainly derived from plants (such as phenyl thiourea, blue sheen, aloin, etc.), animals, or result from aging and deterioration during food processing food produced by microorganisms (e.g., acyl homoserine lactone produced by gram-negative bacteria Pseudomonas aeruginosa, erythromycin sugar derived from actinomycetes, postpartum fungus, etc.) (Drewnowski and Gomez-Carneros, 2000; Kingsbury, 1964; Murata and Sata, 2000).). Although there is no clear correlation between bitterness and toxicity (Glendinning, 1994), its unpleasant taste can prevent the ingestion of some toxic substances.

There are many naturally occurring bitter compounds in traditional Chinese medicines. Denatonium, commonly known as “bitter essence”, is currently recognized as the most bitter compound in the world and is mainly found in lotus (*Nelumbo nucifera Gaertn*)(Civantos et al., 2021); Citrulline belongs to terpenoids, which are generally enriched in citrus fruits (*Citrus reticulata* Blanco), especially in the highest concentration within the seeds (Ji et al., 2014). Limonin has been reported to activate T2Rs and play an anti-inflammatory role in the airways; Quercetin, naringin and kaempferol are flavonoids with a bitter taste that mainly found in *Alpinia officinarum* Hance, *panax ginseng*, *ginkgo biloba* L. and other plants; Aristolochic acid is another bitter compound found in *Asarum* plants, its derivatives aristolochic acid I and II are toxic and can bind to T2R43 and T2R44, activating them. Furthermore, familiar traditional Chinese medicines such as *Aloe vera*, *Artemisia annua* and *Andrographis paniculata* are rich in aloin, chloroquine and andrographolide (Shimizu et al., 2021), which are ligands for T2Rs and have been validated in vivo experiments. *Oregano* has shown beneficial effects on

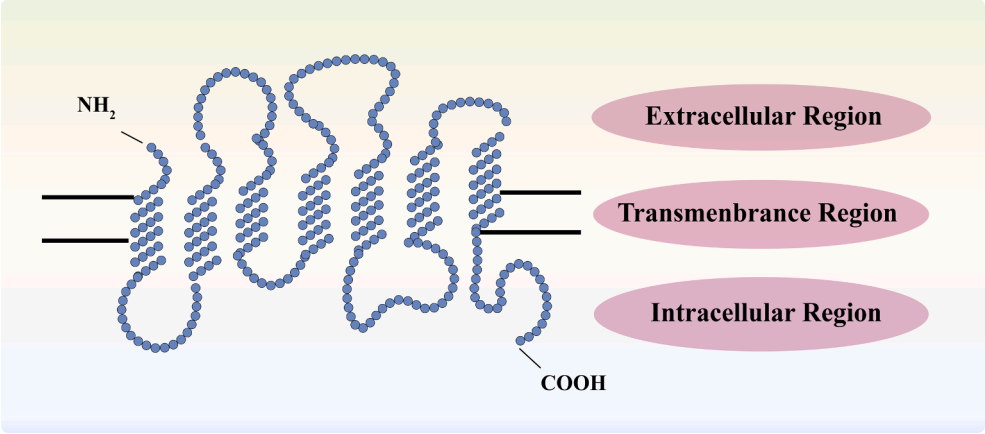


Fig. 2. Structural diagram of T2Rs.

improving symptoms of CRS as well as treating asthma (Erenler et al., 2016; Hoang et al., 2023).

There are various kinds of bitter compounds, which can be roughly divided into flavonoids, alkaloids, salts, terpenoids, hydroxyl fatty acids, amino acids, amides, N-heterocyclic compounds, thiourea, urea, esters, carbonyl compounds, phenols, crown ethers, steroids, halogenated or acetylated sugars, and metal ions (Dubois et al., 2008; Hans-Dieter and Herbert, 1985). Among them, flavonoids are natural plant secondary metabolites with a phenyl benzopyrans structure. They possess the characteristics of few side effects and low toxicity and are preferred in the drug molecules for cancer prevention (Hui et al., 2013; Mocanu et al., 2015a). Some naturally occurring bitter compounds such as bitter gourd extract have been shown to inhibit breast genes and promote apoptosis (Ray et al., 2010). Alkaline compounds consisting of pyridine, tetrahydropyrrole, quinoline, and isoquinoline. Nearly all of them possess a bitter taste, with the intensity of bitterness increasing in proportion to the strength of the alkaloid.

2.4. Application of T2Rs-bitter compounds in human diseases

Recently, the expression of T2Rs has been increasingly found in extra-oral tissues, including the brain (Santos et al., 2019), gastrointestinal tract (Lee et al., 2019), and urogenital system (Kumar and Cheng, 2021; Li, 2013; Xu et al., 2013) (Fig. 3).

In brain, bitter compounds have shown to ameliorate cognitive impairment and improve behavioral performance in mouse (Wei et al., 2019) and disease (Corpas et al., 2019; Pierzynowska et al., 2019; Sabogal-Guáqueta et al., 2015; Yang et al., 2017). These compounds mediate reduced apoptosis by regulating expression and activity (Du et al., 2018; Ghofrani et al., 2015; Wang et al., 2017a; Zhang et al., 2018); Moreover, T2Rs may play a relevant role in Parkinson's disease (PD) by their bitter compounds such as naringenin (Garcia-Esparcia et al., 2013), Singh et al. (2011) used RT-PCR and immunohistochemistry to analyze the expression of bitter taste receptors in brain cells, finding that T2R4 binds to the bitter compounds like denatonium benzoate and quinine, leading to increased intracellular calcium levels. This suggests that T2Rs are expressed in multiple regions that the of T2R14 by resveratrol facilitates ABCG2 transport (Duarte et al., 2020), thereby modulating the neural activity of resveratrol. Various bitter receptors found in the gastrointestinal tract also play a crucial role in regulating gastrointestinal motility and gastric acid secretion (Depoortere, 2014), particularly within the large intestine and colon. Kaji et al. (2009) studied the expression of T2Rs in the human intestine through various molecular biotechnology techniques, discovering that T2Rs mediate colonic epithelial anion secretion induced by a bitter compound called6-PTU in rats while promoting rapid increases in Ca^{2+} concentration through other bitter compounds such as Cycloheximideand Denatonium (Wu et al., 2002). In addition, phenylthiocarbamide (PTC) activated T2R38 in colorectal adenocarcinoma model Caco-2 cells, increasing the expression and activity of ABCB1 in intestinal cells and mouse gut (Jeon et al., 2011).

Most T2Rs have been detected in the respiratory system (Shaik et al., 2016), indicating their respiratory diseases. In Hariri's study (Hariri et al., 2017b), T2Rs were found to be crucial regulators of sinus immune responses and potential therapeutic targets, with T2R14 influencing cytokine release in primary and cultured airway cells, thereby triggering the anti-inflammatory effects of flavonoids.

It is worth noting, however, that T2Rs may not necessarily exert their function solely within the oral cavity. Recently, Lu et al. (2021) utilized the CRISPR/Cas9 gene-editing technique to delete three bitter taste receptors - T2R143/T2R135/T2R126. The findings demonstrated that bronchiectasis does not require T2Rs, which aligns with Liu *et al.*'s study (Liu et al., 2017a) where T2R143/T2R135/T2R126 were found to be expressed in the airways of mice and other non-taste epithelial tissues instead of their canonical locations. Collectively, further to elucidate the role of T2Rs in the airway and other tissues. Subsequently, we will discuss the potential of combining T2Rs with bitter compounds for treating respiratory diseases.

3. Application of T2Rs and bitter compounds in respiratory diseases

The common characteristics of respiratory diseases encompass heightened airway obstruction, inflammation within the airways, and

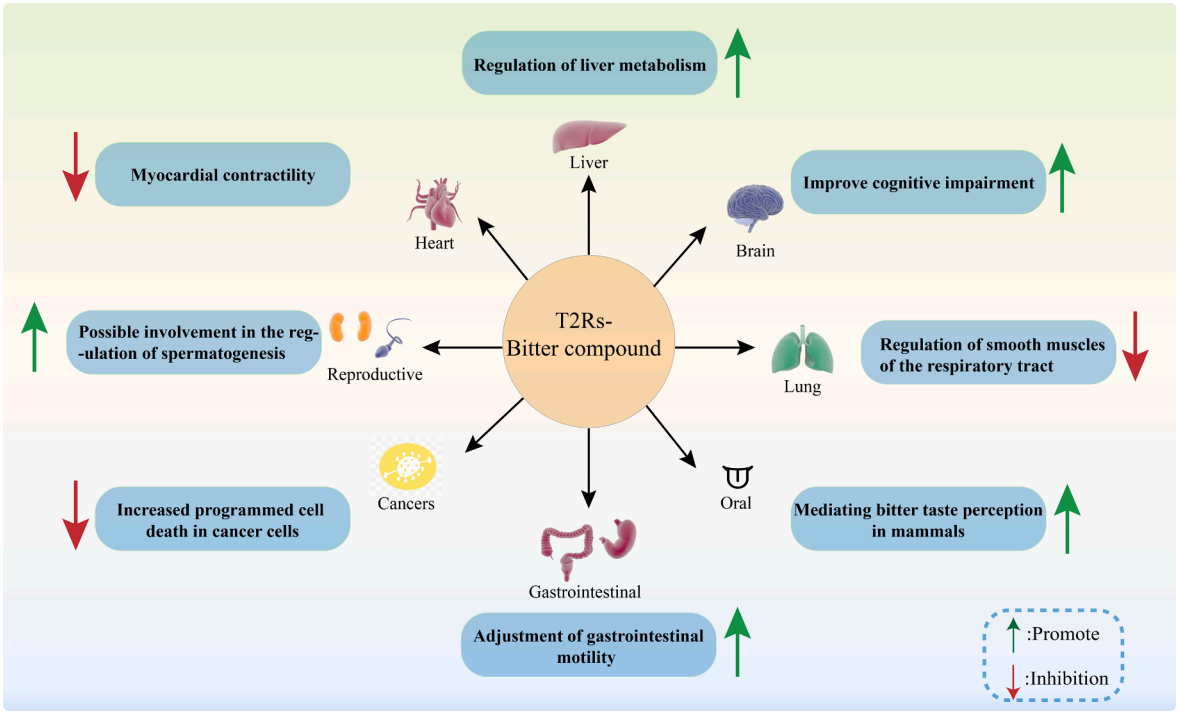


Fig. 3. Application of T2Rs-bitter compounds in human diseases.

stress. Alleviating or modifying these features constitutes the primary approach in contemporary solutions.

3.1. Application of bitter compounds in respiratory diseases

3.1.1. Application of bitter compounds in traditional Chinese medicines

Several bitter compounds have been found to inhibit the stimulation of inflammation by primary and cultured airway cells (Hariri et al., 2017a; Hariri et al., 2017b), thus showing potential as therapeutic agents for the treatment of acute respiratory viral infections (Ren et al., 2020) (Table 1). Quinine, denatonium, naringin (Ni et al., 2021), quercetin and kaempferol have all been identified as having the ability to reduce interleukin 4 (IL-4) levels in vitro and in vivo models of asthma. Among these compounds, naringin and quercetin have demonstrated significant efficacy.(Guihua et al., 2016; Park et al., 2009; Ren et al., 2021; Shi et al., 2009). Amentoflavone and quercetin have been reported to exhibit efficacy in improving bronchial inflammation (Cai et al., 2019; Nanua et al., 2006; Rogerio et al., 2010). In addition, limonin, denatonium and 6-n-Propyl-2-thiouracil (6-PTU) have demonstrated the ability to enhance smooth muscle contraction by inducing cellular apoptosis (Doggrell, 2011; Sakai et al., 2016; Wen et al., 2015a). Quinine activates T2Rs by increasing capillary frequency and stimulating NO production, which enhances respiratory innate immune defense (Workman et al., 2018) The receptors for denatonium (T2R4, T2R10) and chloroquine (T2R3, T2R10) were expressed in generative pre-trained transformer (GPT) (Pulkkinen et al., 2012), and The downstream signaling pathway of GPCR can be regulated by a regulator of G protein signal 21, which directly influences bitter-mediated c AMP formation and intracellular calcium flow in airway epithelial cells (Cohen et al., 2012). Denatonium has been demonstrated to induce apoptosis in airway epithelial cells by damaging mitochondria (Wen et al., 2015b). Moreover, it should be noted that bitter taste receptors exhibit species-specificity, making it uncertain whether a natural compound acting as an agonist in a mouse TAS receptor would elicit the same response in humans. In the upper respiratory tract, hTAS2R46 and hTAS2R38 are present, and when stimulated with phenylthiouride, these receptors display low levels of calcium response. This leads to a high intracellular production of NO, resulting in bacterial infection and bronchiectasis, ultimately contributing to asthma development (Carey et al., 2017).

3.1.2. Application of ABC transporters and bitter compounds

The integrity of the respiratory epithelial barrier serves as the primary defense mechanism for preserving lung health. Bitter compounds exhibit distinctphobic ones permeate phosphol through diffusion within the organism, while hydrophilic ones access target cells via specific membrane transport proteins (Duarte et al., 2022a). Numerous bitter compounds possess hydrophobic properties, resulting in limited bioavailability due to restricted absorption and stability.

ABC transporters are membrane proteins found in respiratory epithelium that facilitate the transport of various substrates across biofilms using energy. They play a crucial role in protecting cells from exposure to diverse substances (van der Deen et al., 2005). Additionally, ABC transporters are essential for maintaining the bioavailability of bitter compounds within the respiratory system. Some well-studied examples of ABC transporters include P-glycoprotein (P-g p), multi-drug resistance associated protein (MRP1), ABCA1, ABCG1(Chai et al., 2017) and ABCA3(Peca et al., 2015). ABCA1 and ABCG1 play a role in reverse cholesterol transport (RCT) by facilitating the efflux of cellular cholesterol and phospholipids, and their transcriptional regulation is mediated by liver X receptors (LXRs) (Zhao and Dahlman-Wright, 2010). ABCA3 functions as a phospholipid exporter specifically involved in the synthesis of pulmonary surfactants. Studies conducted on knockout mice have confirmed that the absence of ABC transporters disrupts lipid homeostasis, reduces surfactant production, impairs respiratory physiology, and increases the expression of inflammatory cytokines in lung cells (Bates et al., 2005; McCarthy et al., 2022; Rindler et al., 2017).

Flavonoids possess the potential for treating respiratory diseases; however, their limited bioavailability in the lung hampers their advantageous health effects. Consequently, it is comprehended that flavonoids modulate the expression and activity of ABC transporters *in vivo/in vitro. In vitro* models, RLE/ABCA3 cells utilized to investigate the inhibitory effect of quercetin on ABCA3 expression, thereby suppressing bleomycin (BLM)-induced epithelial mesenchymal transformation (EMT) (Takano et al., 2020) in alveolar type II cells and reducing ntracellular ROS levels, consequently mitigating oxidative stress and alleviating inflammation. The presence and activity of these ABC transporters may also influence the delivery of pulmonary drugs to their target sites. Mice lacking ABCG1, ABCA1, and ABCA3 of inflammatory factors IL-1β (Hamilton et al., 2002) and tumor necrosis factor-α (TNF-α) in their lungs (Baldán et al., 2008). These inflammatory factors can cause inflammation,oxidative damage, airway fibrosis and mucogenesis, which affect the treatment of respiratory diseases (Mukhopadhyay et al., 2006). Furthermore, Mercier et al. (2018) established a pharmacological model using RPMI2650 cells to study nasal mucosa and observed functional activity of and MRP1 transporters at the cellular level. Apigenin directly interacts with ABC transmembrane transporter CFTR (Ferrera et al., 2007), expressed in the parietal membrane of epithelial cells. The synergistic combination of apigenin-quercetin downregulates ABC transporter expression and inhibit membrane transporter protein (P-g p) activity and phase II enzyme function, thereby reducing compound metabolism and increasing the potential bioavailability of apigenin (Ravisankar et al., 2019). This highlights the relationship between quercetin and ABC transporter expression.

Both *in vitro* and animal models have shown that bitter compounds can regulate the expression of ABC transporters, which should be further studied. Overall, novel therapeutic approaches hold promise for enhancing drug resistance and augmenting drug bioavailability.

3.2. Exploration of T2Rs as an intermediate in the treatment of respiratory diseases

The activation of T2Rs by bitter compounds leads to changes in the levels of Ca2+, NO, cAMP (Upadhyaya et al., 2014), thereby reducing oxidative stress in the respiratory tract and resulting in relaxation or constriction of the airways. However, this alteration in airway tone often exacerbates airway inflammation response observed in most respiratory diseases. Studies have shown that activation of extra-oral T2Rs (T2R4, T2R14, T2R38) can prevent inflammation (Carey et al., 2017). Therefore, it is suggested that the activation of T2Rs may be associated with inflammatory responses in respiratory diseases and these responses serve as indicators for evaluating the anti-inflammatory and antioxidant effects induced compound-mediated activation (Fig. 4).

3.2.1. Asthma and COPD

Asthma is a chronic inflammatory disease of the airway, characterized by the contraction of human airway smooth muscle (HASM) due to an increase in local bronchoconstrictor substances. This leads to airway inflammation and obstruction of airflow (Mims, 2015; Vogelmeier et al., 2017). Deshpande et al. (2010) initially reported the expression of T2Rs in human airway smooth muscle cells. Both quinine and denatonium, which are T2R agonists and bitter compounds, have been shown to improve bronchiectasis by reducing Ca^{2+} oscillation frequency (Tan and Sanderson, 2014) and Ca^{2+} sensitivity. Additionally, it has been found that artesunate, an antimalarial drug, may enhance Ca^{2+} flow through binding with T2R14(Wang et al., 2019). Flavonoids such as chloroquine, naringenin and kaempferol inhibits the expression activities of inflammatory cytokines TNF-α, IL-4, IL-5, and IL-13, reducing airway resistance in inflammatory rats and asthmatic mice (Devillier et al., 2015; Gong et al., 2012; Ren et al., 2021; Shi et al., 2009), ultimately improving cough. Cuiyuncao exerts anti-inflammatory function through the T2R10/IP3R1/NFAT1 dependent signaling pathway (Desv (Yu et al.,

Table 1
Protective role of bitter compounds in respiratory system.

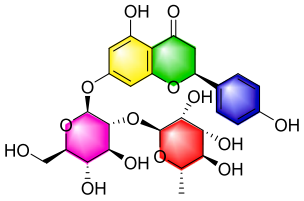
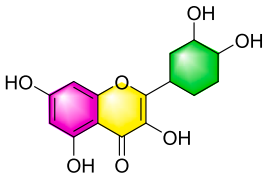
Compound	Disease	Structure	Biological activity	Cells/Animals	Ref
Naringin	Normal respiratory		Improving memory; Inhibiting TNF-α, AChE;	Wistar rats	(Kaur and Prakash, 2020)
			Inhibiting Amyloid deposits; Increasing VEC proliferation; Inhibiting endothelial cell apoptosis Inhibiting GRP78, CHOP, caspase-12 and Cyt c proteins;	Culture of Rat VEC in Vitro	(Shangguan et al., 2017)
	Asthma		Inhibiting OVA-induced eosinophil counts; Decreasing IL-4 and INF-γ; Inhibiting Th2 cells and enhancing Th1 cells; Inhibiting GABA3 and increasing T-bet.	Ovalbumin was used to establish asthma model mice	(Guihua et al., 2016)
			Inhibiting cough and AHR; Inhibiting Leukocytes, IL-4, IL-5 and IL-13 in BALF.	Guinea	(Ren et al., 2021)
			Promoting the proliferation of the 16HBE14o-, BEAS-2B, and A549 cells, Nontoxicity to the airway epithelial structure and function; Promoting ACEs proliferation	16HBE14o-, BEAS-2B, and A549 cells	(Ni et al., 2021)
			Decreasing traction gradually Decreaseing bronchial airway resistance in mice	ASMCs cultured in vitro or bronchial airways of Balb/c mice in vivo	(Wang et al., 2016)
			Decreasing levels of IL4, IL13, CCL5, CCL11 and iNOS inhibiteing pulmonary IkappaBalpha degradation and NF-kappaB DNA-binding activity	Mice were sensitized and challenged with ovalbumin	(Shi et al., 2009)
	COPD		Decreasing neutrophil/lymphocyte/platelet counts and MDA content in blood; Upregulating AQP1 in the lung tissues	LPS/CS-induced mice	(Zhang et al., 2022)
	CF		Attenuating DPM-induced injury Increasing DPM-induced CFTR, AQP1, and AQP5 mRNA and protein expression	DPM-induced mice and cell	(Shi et al., 2019)
	Chronic bronchitis		Decreasing IL-8, LTB4 and TNF-α; Increasing the content of lipoxin A4 (LXA4) in BALF	Guinea pig model	(Luo et al., 2012)
Quercetin	Normal respiratory		Inhibiting ET and NO synthesis; Decreasing NOX2, TNF-α, IL-1 and IL-6;	Lung epithelial A549 cells	(Sul and Ra, 2021)
	Asthma		Decreasing eosinophil counts in BALF, blood, and lung parenchyma; Decreasing neutrophils in blood and IL-5 in lung homogenates.	BALB/c mice	(Gong et al., 2014)
			Increasing levels of IL-4; Increasing IFN-γ.	OVA-induced asthma model mice	(Park et al., 2009)
	CRS		Increasing transepithelial Cl^- transport and CBF in MNSE and HSNE cultures;	Primary HSNE and MNSE cells	(Zhang et al., 2011)
	CF		Activating CFTR-mediated anion transport in respiratory epithelial cells; Inhibiting Cl^- conductance at high concentration.	Fisher rat thyroid and CFBE41o- cells	(Pyle et al., 2010)
	Acute respiratory distress syndrome		Decreasingd MMP-9 activity; Suppressing LPS-induced lung inflammation, and that an HO-1-dependent pathway mediated these cytoprotective effects	Mouse model of ALI were established by challenging intratracheally LPS	(Takashima et al., 2014)
			Inhibiting TNF-alpha-induced PI 3-kinase activity, Akt, NF-kB and IL-8	Human airway epithelial cells	(Nanua et al., 2006)
	Airway hyperinflammation		Inhibiting levels of IL-5, IL-4, NF-kappaB, P-selectin expression and the mucus production in the lung	Mice	(Rogerio et al., 2010)
	COPD		Corticosteroid sensitivity was restored	human monocytic U937 cells	(Mitani et al., 2017)

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Table 1 (*continued*)

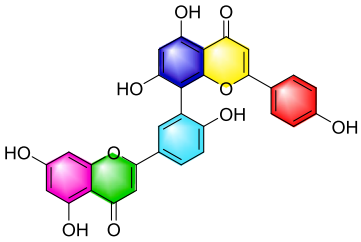
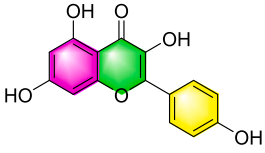
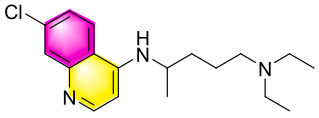
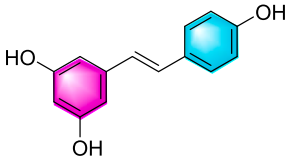
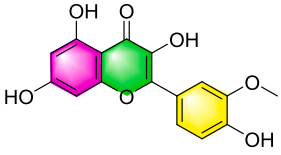
Compound	Disease	Structure	Biological activity	Cells/Animals	Ref
Amentoflavone	Asthma		Attenuating airway hyperresponsiveness and goblet cell hyperplasia; Increasing IL-4, IL-5 and IL-13, IgE, IFNγ; Reducing eotaxin, NFAT1 and c-Myc protein in lung tissue of OVA-challenged rats.	Ova-induced rats	(Ferrera et al., 2007)
	Pleurisy		Decreasing SOD and GSH depletion and MDA and MPO generation; IL-1β and TNF-α Increasing HO-1, NQO1, and γ-GCL levels, IL-10	Wild-type (WT) and Nrf2-deficient (Nrf2) mice	(Hou et al., 2022)
	Inflammation		Ihibiting of C3 and negative regulation of the B cell receptor /NF-κB signaling pathways andHMGB1	Lung inflammation from cold exposure	(Cai et al., 2019)
	Acute lung injury		Increasing Nrf2-GCLc signaling, enhancement of GSH antioxidant defense, reduction of oxidative stress and final amelioration of inflammation and histological injury of lung	CLP-induced septic rats	(Zong and Zhang, 2017)
Kaempferol	Asthma		Inhibiting TNF-α induced adhesion of molecule-1 and eosinophil integrin β2 in epithelial cells; Inhibiting eosinophils in airway and lung tissue;	Human airway epithelial BEAS-2B cells and eosinophils	(Gong et al., 2012)
			Inhibiting total white blood cell and eosinophil count in BALF; Inhibiting expression of $CD4^+$, $B220^+$, MHC class II and CD40 in BAL cells; Inhibiting Th2 cytokines (IL-5 and IL-13);	BALB/c mice	(Gong et al., 2012)
			Modulating PAR1 activation attenuates fibrotic airway remodeling through bronchial EMT; Decreasing collagen deposition, epithelial secretions and goblet hyperplasia;	BEAS-2B cells and BALB/c mice	(Medeiros et al., 2009)
	CF		Immunofluorescence demonstrated a favorable change in the intracellular distribution of CFTR	IB3-1cells	(Lim et al., 2004)
Chloroquine	Asthma		Inhibiting immunoglobulin E, IL-4/-13 and TGF-β1 in BALF to attenuate AHR, inflammation and remodeling; Inhibiting ASM cell proliferation (PCNA), hypertrophy (α-SMA) and accessory secretion (MMP-9 and MMP-13).	HDM sensitized mice and ASM cells	(Rogerio et al., 2007)
Resveratrol	Asthma		Inhibiting IL-4,IL-5; Suppressing airway hyperresponsiveness, eosinophilia, and mucus hypersecretion	OVA-induced allergic mouse	(Lee et al., 2009)
	COPD		Decreasing IL-1 and IL-8; Increasing IFN-α and miR-34	Rats Dendritic cells	(Wang et al., 2015; Wang et al., 2017b)
Isorhamnetin	Asthma		Decreasing IL-1β, IL-6, IL-8 and CXCL-10.	Human bronchial epithelial cell line BEAS-2B cells	(Ren et al., 2022)
	COPD		Decreasing IL-6	Mice	(Xu et al., 2022)

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Table 1 (*continued*)

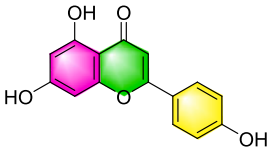
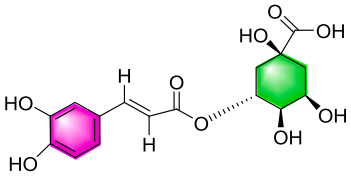
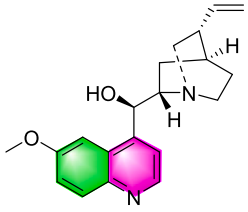
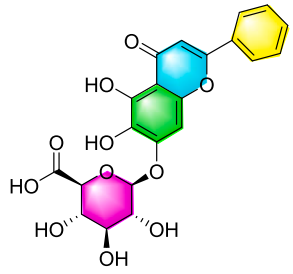
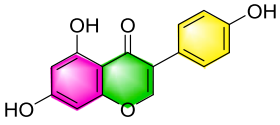
Compound	Disease	Structure	Biological activity	Cells/Animals	Ref
Apigenin	CRS		Inhibiting α-SMA, fibronectin and type I collagen; Inhibiting MAPK (p-38, JNK) and NF-κB activation induced by TGF-β1; Reducing migration and collagen contractile activity to inhibit fibroblast functional activity.	Nasal fibroblasts and isolated subnasal turbinate tissue	(Yang et al., 2018)
	COPD		Inhibiting CD38 and H2O2–induced senescence	hydrogen peroxide (H2O[Formula: see text]- or doxorubicin (DOXO)-induced senescence model	(Li et al., 2021)
Chlorogenic acid	CRS		Promoting Cl^- transport mediated by CFTR..	Mouse and human sinus epithelium	(Illing et al., 2015)
Quinine			Increasing ciliary beat frequency and NO production.	CRS patients	(Workman et al., 2018)
Baicalin	Asthma		Reversing OVA-induced oxidative stress and inflammation Upregulating miR-103 Decreasing OVA-IgE, IL-6, TNF-α and NF-kB.	OVA-induced asthmatic mouse	(Ma et al., 2014; Zhai and Wang, 2022) (Liu et al., 2016a)
	CRS		Decreasing IL-33-dependent expression of trypsin-like in mast cells.	Human airway epithelial cells and human mast cells	(Yoshida et al., 2021)
	COPD		Improving lung function and HPA axis function	36-week side stream cigarette smoke induced rat model	(Wang et al., 2018)
			Inhibiting apoptosis and TNF-α, IL-6 and IL-8 levels in MLE-12 cells; Increasing HSP72 expression	MLE-12 cells	(Hao et al., 2021)
			Increasing IL-10, SOD, GSH and level of p-IκBa/IκB; Decreasing the protein levels of MYD88, p-NF-κBp65/NF-κBp65, TLR2, and TLR4	Rats	(Ju et al., 2022)
			Inhibiting TNF-α, IL-β and NF-kB; Increasing HDAC2	Cigarette smoke (extract) (CS/CSE)-induced airway inflammation	(Li et al., 2012; Zhang et al., 2021)
Genistein	Asthma		Decreasing OVA-induced airway inflammation, Th2-type cytokines Increasing Th1-type cytokines	OVA-induced mice	(Gao et al., 2012)
	CF		Chloride ion outflow.	CF bronchial epithelium is CFBE1o-	(Andersson and Roomans, 2000)
	COPD		Inhibiting NF-κB,TNF-α and MMP	Lymphocytes	(Liu et al., 2016b)

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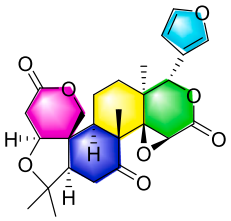
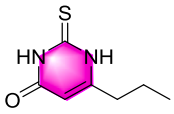
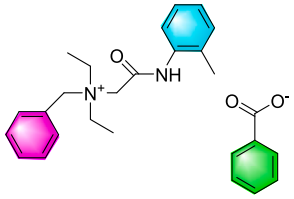
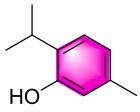
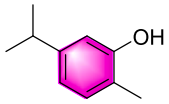
Table 1 (*continued*)

Compound	Disease	Structure	Biological activity	Cells/Animals	Ref
Limonin	CF		Reducing inflammatory factors; Increasing T2Rs in lung.	Rats	(Doggrell, 2011)
6-n-Propyl-2-thiouracil			Inhibiting smooth muscle contraction.	Rat and mouse	(Sakai et al., 2016)
Denatonium	Asthma		TAS2R4, TAS2R10 were expressed in GPT Inhiting contractions induced by carbachol.	Guinea pig	(Pulkkinen et al., 2012)
	CF		Damaging mitochondria; Inducing apoptosis in airway epithelial cells.	Airway epithelial cells	(Wen et al., 2015a)
Thymol	Asthma		Improving the most prominent inflammation characteristics of asthma	Balb/c mice	(Mohammadi et al., 2018)
	COPD		Reducing lung emphysema and inflammation in mice.	Mices	(Games et al., 2016)
Carvacrol	Asthma		Reducing the values of AEC, IgE, IL-4, IL-5, IL-13, TNF-α, IFN-γ, iNOS and MDA.	Rats	(Ezz-Eldin et al., 2020)
	COPD		Indicating a preventive effect on tracheal responsiveness and pathological changes of the lung.	Guinea pigs	(Gholami Mahtaj et al., 2015)

2017)). The above findings suggests that targeting T2Rs may be a potential therapeutic approach for asthma treatment.

3.2.2. CRS

CRS is an inflammation of sinuses and nasal mucosa, thus anti-inflammatory effects of flavonoids may play a protective role against CRS (Liu et al., 2022). The role of T2Rs in sinusitis and their contribution to chronic rhinosinusitis have been extensively studied (Adappa et al., 2016; Adappa et al., 2013; Adappa et al., 2014; Carey et al., 2016; Dżaman et al., 2016; Gallo et al., 2016; Mfuna Endam et al., 2014; Rom et al., 2017). Apigenin inhibits functional activity of nasal fibroblasts by reducing the migration and collagen contractile activities (Yang et al., 2018). Numerous studies indicate that T2R38 plays a predominant role (Lee and Cohen, 2014; Lee and Cohen, 2015a; Lee and Cohen, 2015b), particularly in individuals with T2R38AVI/AVI (Hariri et al., 2017b), single nucleotide polymorphisms (SNPs) in the T2R38 gene may affect susceptibility to CRS and reduce oxidative stress. T2Rs and related signaling pathways could potentially serve as targets for treating chronic rhinosinusitis (Dżaman et al., 2016). Expression of T2R38 has been found enhance upper respiratory innate immunity (Douglas and Cohen, 2017). Baicalin has been shown to stimulate T2R14, leading to the inhibition of IL-33 expression (Yoshida et al., 2021).

3.2.3. CF

CF is characterized by the presence of chronic bacterial infections, bronchiectasis, excessive production of airway mucus, and elevated levels of intracellular (d'Angelo et al., 2014). Quercetin and genistein can reduce the conductivity of chloride ions in rats or cells (Andersson and Roomans, 2000; Pyle et al., 2010; Jaggupilli et al., 2017). Treatment with quinine in CuFi-1 cells resulted in a dose-dependent intracellular Ca^{2+} levels and bronchoconstriction, indicating functional expression of T2Rs in these cells. In addition, studies have shown that the bitter agonist denatonium can activate primary nasal epithelial cells HSP90 and reduce NO production stimulated by T2Rs, which plays an important role in airway antimicrobial. These fingdings suggest that targeting T2Rs may hold promise for the treatment of cystic fibrosis. Numerous studies have described the effects of bitter compounds against CF.

4. Summary and discussion

This review discusses that bitter compounds from plants targeting T2Rs may be a viable treatment for respiratory diseases and are considered as potential novel bronchodilators. T2Rs are important intermediates that regulate the action of bitter compounds on tissues or cells, as reflected by the reduction of inflammatory factors, and bitter compounds reduce oxidative stress and alleviate the inflammatory response by stimulating T2Rs. Notably, the low bioavailability of bitter compounds and their ability to cross epithelial cell membranes greatly limit their effective treatment of disease, whereas binding to ABC transporters not only reduces inflammation levels, but also effectively

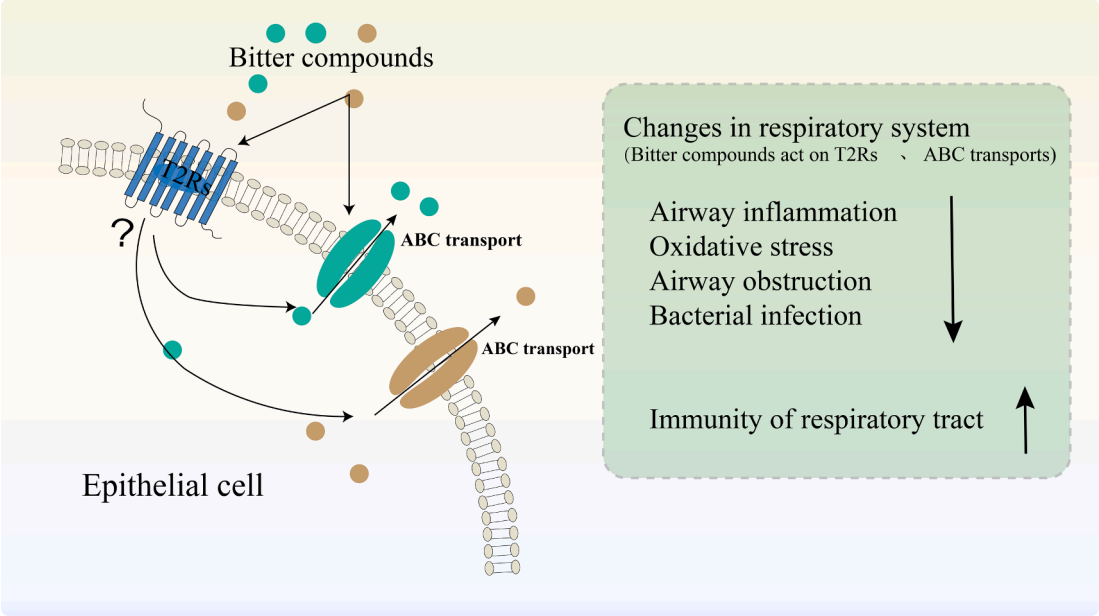


Fig. 4. T2Rs act as intermediates for the transport of bitter compounds. T2Rs act as intermediates that can bind directly to bitter compounds and may regulate ABC transporters activity at the epithelial cell membrane. In addition, bitter compounds can directly affect ABC transporters activity. It is also indicated that bitter compounds and T2Rs caused some changes in the respiratory system: airway obstruction, and bacterial infections↓; Immunity of respiratory tract↑.

reduces compound metabolism and increases bioavailability. In terms of taste, most of the active pharmaceutical ingredients with poor taste are bitter and are an important cause of poor compliance and adherence to medication in many patients, especially in children, which severely limits the development and clinical application of many formulations. Innovative taste correction and taste masking techniques can be used, such as the addition of sweeteners such as aspartame and steviol, bitter taste receptor inhibitors such as propoxur, enterodiol and γ-aminobutyric acid or direct coating of bitter compounds with acrylic resins and β-cyclodextrins, etc. Sweeteners can activate sweet taste receptors to produce sweet taste, thus balancing the bitter taste of traditional Chinese medicine substances. Bitter taste blockers can competitively bind to bitter taste receptors, thereby reducing the frequency of bitter taste signal transduction. Inclusion complexes can directly block the bitter taste from touching the mouth. The above methods effectively enable these bitter ingredients to retain their activity and improve their taste, making it easier for patients to accept the drug in the mouth to treat their diseases. In conclusion, the natural bitter compounds present in plants can continue to be studied in depth in the future to explore their potential ability to combine with T2Rs to treat diseases.

In summary, targeting T2Rs in combination with bitter compounds from plants is a promising therapeutic approach, while how to improve the bioavailability of bitter compounds in lung respiratory epithelial cell membranes remains to be addressed. When both T2Rs and ABC transporters are present in the cell membrane, it is possible to use bitter blockers (Trp-Trp (Ojiro et al., 2021) etc.) and ABC transporters inhibitors (Propofol (Greene et al., 2011)) to block the perception of bitter compounds simultaneously and separately, and analyze the degree of uptake of bitter compounds in the lung epithelial cell membrane by some indicators.

such as changes in Ca^{2+} content and changes in the level of inflammatory factors produced by the activation of T2Rs by bitter compounds. These experimental hypotheses will clarify the mechanism and bioavailability of bitter compounds through T2Rs and ABC transporters in the treatment of respiratory diseases, and are of great importance for the future treatment of respiratory diseases.

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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