REVIEW

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A hypothesis: Bitter taste receptors as a therapeutic target for the clinical symptoms of SARS-CoV-2

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The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has paralysed the livelihood of the global population by inflicting higher mortality among the affected patients. Nearly the entire human physiological system can get disrupted by the virulence of SARS-CoV-2, which exemplifies the significance of discovering a potential drug target. Similar to angiotensin-converting enzyme 2 (ACE2), bitter taste receptors (T2Rs) unequivocally expressed on all vital human organs, particularly on nasal/oral respiratory tract, gastrointestinal organs, innate immune cells, heart, brain and urogenital cells are susceptible to SARS-CoV-2 virulence. Activation of T2Rs by bitter agonists restores vital functions to these organs via activation of large conductance, Ca^{2+}-dependent potassium (K^+) channels (BK_{ca}), and inducible nitric oxide synthase. T2R activation in the gustatory system can act as the first defence mechanism, primarily preventing or mitigating SARS-CoV-2 entry to the respiratory tract. Moreover, T2R activation is crucial for the improved vasodilation accompanied by the attenuation of systemic inflammation; hyper-innate immune responses; gastrointestinal disorders; defective neurological functions; acute kidney injury; and impotency witnessed in severe SARS-CoV-2 cases. This review discusses the potential for bitter taste receptors to act as drug targets for SARS-CoV-2 symptoms and the use of existing bitter agonists to restore T2R function.

1. Introduction

In December 2019, the first clinical case of the novel coronavirus 2019, defined as "COVID-19" by the World Health Organization (WHO), was recorded in Wuhan, Hubei Province of China. With its unprecedented sustainment of human to human transmission, the COVID-19 outbreak reached a pandemic status affecting all major developed and developing countries worldwide (Cevik et al. 2020). Clinical cases of both extremities from asymptomatic to fatally severe conditions have surfaced among the affected global population (Hu et al. 2020; Lescure et al. 2020). Though symptomatic COVID-19 patients can develop common symptoms of fever, cough and dyspnea during their initial stages, in the later critical stages, patients are susceptible to developing detrimental symptoms such as pneumonia, pulmonary oedema, acute respiratory distress syndrome (ARDS), acute kidney failure, and multiple organ dysfunction syndromes preceding to death (Hu et al. 2020; Huang et al. 2020; Mo et al. 2020). Patients recorded with other comorbidities such as type 2 diabetes, cardiovascular and cerebrovascular complications also become extremely vulnerable to COVID-19 virulence (Hu et al. 2020).

Clinicians across countries have been struggling to attenuate the recurrence of human to human transmission chain; however, no prominent therapeutic strategies have been developed to combat COVID-19 due to the varied clinical characteristics. Furthermore, the basic reproduction number (r0) and transmissibility of COVID-19 is considerably higher than the coronaviruses of the same genus, severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV), because of its higher binding affinity for the host-based human angiotensin-converting enzyme 2 (ACE2) receptor (Petrosillo et al. 2020; Tai et al. 2020). Henceforth, it is essential to find a remedy that is prophylactic by strengthening the innate immune response of the human host.

Toll-like receptors (TLRs) are widely targeted to ameliorate the systemic innate immune response associated with inflammatory cytokine production and other anti-viral intermediates, including phagocytosis and apoptosis. On the other hand, the idea of stimulating the bitter taste receptors (T2Rs) has gathered wide attention in strengthening systemic innate immune response for the past one and a half decades. The interest in T2Rs is largely due to its quick immune response and its associated intermediates that take about a few seconds to minutes to be expressed compared to TLRs, which require about 12 hours for a steady innate immune response to establish against any invading foreign pathogen (Hume et al. 2001; Maina et al. 2018; Patel et al. 2018).

T2Rs are comprising ~25 isoforms of G-protein coupled receptors (GPCRs) and widely expressed on the surface membrane of chemosensory cells that are prevalent on the taste buds of the tongue, regulating bitter taste sensation (Patel et al. 2018). Additionally, T2Rs have been adequately expressed on other internal body organs such as the respiratory tract, gastrointestinal tract, endocrine and genitourinary system (Luddi et al. 2019; Sternini et al. 2008). Apart from its role for bitter taste sensation, T2Rs play a vital role in regulating other crucial physiological functions such as bronchodilation, mucociliary clearance, nitric oxide (NO) production, and the synthesis of anti-microbial peptides with the concomitant reduction of airway-inflammation and adaptive-immune system activation, crucial for attenuating COVID-19 virulence in the respective patients (Lee and Cohen 2014; Lu et al. 2017; Sharma et al. 2017; Workman et al. 2015). Activation of

T2Rs using potent bitter taste agonists have been adopted to treat the inflammation-linked respiratory ailments like asthma, chronic rhinosinusitis, and chronic obstructive pulmonary disease (Nayak et al. 2019; Sharma et al. 2017; Workman et al. 2015).

GPCRs such as histamine receptors; 5HT (serotonin) receptors; muscarinic acetylcholine; and adrenoreceptors are engaged with the entry of dreadful Ebola and Marburg (Filoviruses). Cheng et al. (2015) proposed the likely mechanisms paving the entry of Filoviruses that included 1) direct contact of the glycoprotein of the viruses with GPCRs and 2) stimulation of signalling cascades of the GPCRs upon viral invasion. Stone et al. (2002) showed the facilitation of α-gustducin of rat-taste receptor cells in transferring recombinant genes using the herpes simplex virus-1 and adenoviral vectors in taste cells. Stimulation of G-protein signalling was also associated with the emergence and release of influenza virus (Hui and Nayak 2002). These reports have confirmed the direct association of GPCRs, including G-protein taste receptors with the viral entry and pathogenesis.

As T2Rs are G-protein coupled receptors expressed on all vital organs of the human physiological system, it can be utilised as a gateway for the SARS-CoV-2 infiltration alike the known ACE2 receptor (Bloxham et al. 2020). To support this hypothesis, we discuss all vital functions of the human physiological system that are regulated by T2Rs (Jaggupilli et al. 2016), which in turn are likely attenuated by SARS-CoV-2 virulence (Lu et al. 2017; Maina et al. 2018; Patel et al. 2018). Also discussed is the clinical significance of rejuvenating vital organ functions that are susceptible to SARS-CoV-2 virulence via activation of T2Rs using available bitter medicines or other natural bitter bioactive compounds (Li et al. 2020; Patel et al. 2018; Sharma et al. 2017).

2. Gustatory dysfunction and sinonasal cavity

Gustatory dysfunction is one of the noticeable clinical symptoms among emerging COVID-19 patients (Lechien et al. 2020; Vaira et al. 2020). Although the clinical mechanism by which SARS-CoV-2 impairs the gustatory response remains unclear, it is possible that SARS-CoV-2 intervenes with taste receptors, including stimulation of the T2R G protein, gustducin, in the upper and lower respiratory tracts of the infected patients (Ming et al. 1999). Additionally, patients witnessed with defective sensation of taste and smell for more than 10 days were more likely to be affected by acute lung injury due to a compromised innate immune response in the respiratory system (Lu et al. 2017; Vaira et al. 2020). Thus, the amelioration of a dysfunctional gustatory response with an improved innate immune defence is crucial to attenuate the acute lung injury inflicted by SARS-CoV-2 virulence in the upper and lower respiratory system (Carey and Lee 2019; Patel et al. 2018; Sharma et al. 2017).

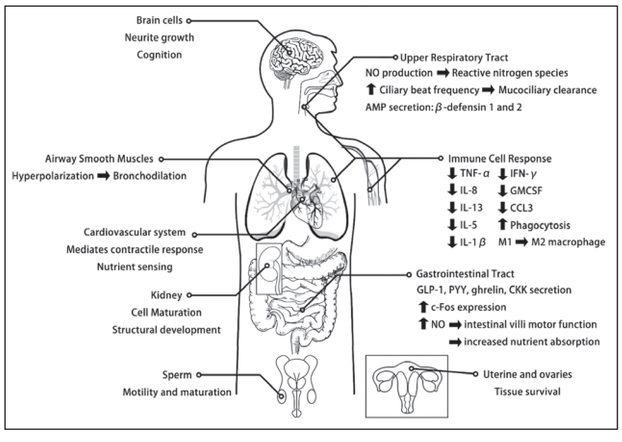

Fig. 1: Physiological functions of bitter taste receptors (T2Rs) activation in susceptible human organs of SARS-CoV-2 virulence. NO, nitric oxide; TNF-α, tumour necrosis factor-alpha; IFN-γ, interferon-gamma; IL-8, interleukin 8; IL-13, interleukin 13; IL-5, interleukin 5; IL-1β, interleukin 1beta; GM-CSF, granulocyte macrophage colony stimulating factor; CCL3, Chemokine (C-C) motif ligand 3; GLP-1, glucagon-like peptide one; PYY, peptide hormone YY; CKK, cholecystokinin.

Triggering the innate immune response using T2R agonists could possibly efface acute lung injury caused by enhanced lung inflammation and increased pro-inflammatory cytokine production during the early incubation stages of SARS-CoV-2 replication in the upper respiratory tract (Lu et al. 2017; Tufan et al. 2020). Attenuation of inflammatory damage of the nasal olfactory nerves with the controlled innate immune response via T2Rs activation could ameliorate the gustatory sensitivity on SARS-CoV-2 patients. Activation of ciliary beating in ciliated epithelial cells and phagocytosis by macrophages are two primary innate defence mechanisms regulated by the activation of T2Rs in the upper respiratory tract (Gopallawa et al. 2020) (Fig. 1).

Out of the 25 T2R isoforms, the stimulation of T2R4, T2R14, T2R16 and T2R38 through oral bitter compounds or bitter antimicrobial metabolites (Table 2 and 3) in the cilia of sinonasal epithelial cells can enhance intracellular nitric oxide (NO) production by activating calcium-dependent endothelial nitric oxide synthase (eNOS) production (Carey and Lee 2019) (Fig. 1). With this increased NO production, the ciliary proteins get phosphorylated by NO-dependent protein kinase G (PKG), accelerating ciliary beat frequency and the concomitant mucociliary clearance (Carey and Lee 2019; Stout et al. 2007). Moreover, infiltration of NO into the upper airway surface liquid can profusely trigger the production of the NO derivates, the reactive nitrogen species (RNS), exhibiting proficient anti-microbial activity by degrading the bacterial and fungal cell walls, as well as virus coat proteins (Carey and Lee 2019; Workman et al. 2017) (Fig. 1). This T2R-mediated innate immune response via calcium-dependent NO/RNS synthesis occurs swiftly and shortly, taking seconds to minutes to transpire compared to the known Toll-like receptors (TLRs) that take hours to exhibit a strong innate immune response through enhanced defensin production in the upper airway (Hariri and Cohen 2016; Lee et al. 2012; Maniscalco et al. 2007).

Additionally, the stimulation of T2Rs (T2R-10, 46 and 47) in nasal solitary chemosensory cells (SCCs), using bitter compounds, could efface pathogen invasion by neurogenic inflammation and protective airway reflexes (Saunders et al. 2014; Tizzano et al. 2011). *In-vitro* studies have shown the efficacy of T2Rs in SCCs in secreting anti-microbial peptides β-defensins 1 and 2 in ciliated and goblet cells upon its activation using bitter compounds (Carey and Lee 2019; Lee and Cohen 2014). In all, T2R activation using potential T2R agonists can reverse gustatory dysfunction by preventing the SARS-CoV-2 colonization in the human respiratory system by the pronounced mechanisms shown in Fig. 1.

3. Severe respiratory ailments

Acute respiratory distress syndrome is one of the detrimental clinical symptoms in SARS-CoV-2 patients, which inflicts higher mortality among elderly SARS-CoV-2 patients (Duca et al. 2020; Li and Ma 2020). SARS-CoV-2 entry occurs predominantly via the nasal route, carried by the patient's nasal droplets/saliva and gets colonized in the upper respiratory tract. The virus later becomes populated in the lower respiratory tract causing severe respiratory ailments on the affected patients (Lin et al. 2020; Umer et al. 2020; Zhang et al. 2020b). Among the 25 isoforms of T2Rs, T2R38 spotted on nasal epithelial cells of the upper respiratory tract; T2Rs 4, 38, 43, and 46 on bronchial epithelial cells of the lower respiratory tract; and T2Rs 10, 14, 19 and 31 on airway smooth muscle cells of the lower respiratory tract (Devillier et al. 2015) (Table 1 and Fig. 2). These T2Rs of the upper and lower respiratory tract play a crucial role in regulating the innate immune response, airway inflammation, and controlling the pathogenesis of any foreign antigens, including bacteria and viruses (Devillier et al. 2015; Workman et al. 2017) (Fig. 1).

Stimulation of T2Rs by its agonists is crucial for its interaction with the heterotrimeric gustducin G-protein receptor that is comprised of the three subunits α, β, and γ (Jaggupilli et al. 2016; Ueda et al. 2003). T2R interaction with gustducin splits its three major subunits into the α-subunit (classified as $G\alpha_{gust}$) and βγ subunit (classified as Gβ3 and Gγ13) of which the βγ subunits plays a crucial role in activating the bitter taste receptor signalling cascade

Table 1: Bitter-receptor (T2R) agonists and its biological significance on human organs vulnerable to SARS-CoV-2 virulence

Human physiology System	Organs/cells subjected to SARS-CoV-2 virulence	T2R expression	Biological functions/ properties	Adverse clinical symptoms of SARS-CoV-2 virulence
a) Respiratory	Motile cilia of airway epithelia (Bloxham et al. 2020)	T2R1, 3, 4, 7, 8, 9, 10, 13, 14, 16, 38, 43, 46 (Bloxham et al. 2020)	Increased ciliary beat frequency, mucociliary clearance (Shah et al. 2009)	Cough Dyspnea Acute respiratory distress syndrome
	Airway smooth muscle cells (Bloxham et al. 2020)	T2R1, 3, 4, 5, 8, 9, 10, 13, 14, 19, 20, 30, 31, 42, 45, 46, 50 (Bloxham et al. 2020)	Bronchodilation (Deshpande et al. 2010)	
	Bronchial epithelial cells (Bloxham et al. 2020)	T2R38, T2R46 (Bloxham et al. 2020)	Increased ciliary beat frequency, mucociliary clearance (Cohen et al. 2012)	
	Upper respiratory/sinonasal epithelial cells (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	Antimicrobial NO production, mucociliary clearance, detection of gram-negative quorum-sensing molecules (Lee et al. 2012)	
	Bronchi (Bloxham et al. 2020)	T2R3, 4, 5, 7, 8, 9, 10, 14, 19, 20, 31, 38, 39, 43, 45, 46 (Bloxham et al. 2020)	Bronchodilation (Grassin-Delyle et al. 2013)	
b) Gastrointestinal	Enteroendocrine cells, human colon, HuTu-80 and NCI-H716 cell lines (Bloxham et al. 2020)	T2R4, 5, 10, 13, 20, 30, 31, 38, 39, 40, 42, 43, 45, 46, 50, 60 (Bloxham et al. 2020)	- (Rozengurt et al. 2006)	Vomiting Abdominal pain Diarrhoea
	Enteroendocrine NCI-H716 cells (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	- Glucagon-like peptide 1 (GLP-1) secretion (Yu et al. 2015)	
	Cecum, NCI-H716 cell line (Bloxham et al. 2020)	T2R9 (Bloxham et al. 2020)	Glucose homeostasis (regulation of glucose and insulin levels), physiological consequences in T2R9 polymorphism (Dotson et al. 2008)	
	Large intestine (Bloxham et al. 2020)	T2R1, 4, 38 (Bloxham et al. 2020)	– (Kaji et al. 2009)	
	Epithelial colorectal cell line Caco-2 (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	Elevation of efflux transporter ABCB1 mRNA and protein levels, limits absorption of noxious substances (Jeon et al. 2011)	
	Saliva (Bloxham et al. 2020)	T2R43 (Bloxham et al. 2020)	Functional genetic variant protective towards Balkan Endemic Nephropathy (Wooding et al. 2012)	
	HuH7 cells, pancreatic ductal adenocarcinoma biopsies (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	– (Gaida et al. 2016a)	
	Enteroendocrine HuTu-80 cells (Bloxham et al. 2020)	T2R7, 14 (Bloxham et al. 2020)	Cholecystokinin (CCK) secretion (Le Neve et al. 2010)	
	Gastrointestinal mucosa, ducts of parotid gland (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	- (Wolfle et al. 2016)	
	Gastric epithelial cells of corpus/fundus, HGT-1 cells (Bloxham et al. 2020)	T2R1, 3, 4, 5, 7, 9, 10, 13, 14, 16, 19, 20, 30, 31, 38, 39, 41, 42, 43, 46, 50 (Bloxham et al. 2020)	Gastric acid secretion (Liszt et al. 2017)	
c) Immune	Leukocytes (Bloxham et al. 2020)	T2R4, 5, 10, 13, 14,19, 20, 45, 46, 50(Bloxham et al. 2020)	Higher expression in children with severe asthma (Orsmark-Pietras et al. 2013)	Fever Hyper-innate inflammation Cytokine storm Pro-inflammatory cytokine production
	Mast cells (Bloxham et al. 2020)	T2R3, 4, 5, 10, 13, 14, 19, 20, 46 (Bloxham et al. 2020)	Inhibits histamine and prostaglandin D2 release (Ekoff et al. 2014)	
	Neutrophils, monocytes (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	Biofilm sensing (Gaida et al. 2016a)	

Human physiology System	Organs/cells subjected to SARS-CoV-2 virulence	T2R expression	Biological functions/ properties	Adverse clinical symptoms of SARS-CoV-2 virulence
	Monocyte derived macrophages (Bloxham et al. 2020)	T2R4, 14, 38, 46 (Bloxham et al. 2020)	Increases phagocytosis (Gopallawa et al. 2020)	
	Lung macrophages (Bloxham et al. 2020)	T2R3, 4, 5, 9, 10, 14, 30, 39, 40 (Bloxham et al. 2020)	Inhibits TNF-α, CCL3, CXCL8 (Grassin-Delyle et al. 2019)	
	Lymphocytes (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	Inhibits TNF-α (Tran et al. 2018)	
d) Nervous	Frontal cortex (Bloxham et al. 2020)	T2R5 10, 13, 50(Bloxham et al. 2020)	Downregulation of T2R5 and 50, upregulation of T2R10 and 13 in Parkinson disease patients (Garcia-Esparcia et al. 2013)	Headache Dizziness Mental instability Acute stroke Ataxia Seizures
	Neuronal tissue, neuroblastoma cell line SH-SY5Y (Bloxham et al. 2020)	T2R16 (Bloxham et al. 2020)	Promotes neuronal differentiation and neurite growth via ERK and CREB phosphorylation (Wolfle et al. 2015)	
	Dorsolateral prefrontal cortex (Bloxham et al. 2020)	T2R4, 5, 10, 13, 14, 50 (Bloxham et al. 2020)	Cognition, downregulated in schizophrenia with reduced T2R expression (Ansoleaga e t al. 2015)	
	Purkinje cells of cerebellum (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	– (Wolfle et al. 2016)	
e) Cardiovascular	Left ventricle tissue(Bloxham et al. 2020)	T2R3, 4, 5, 9, 10, 13, 14, 19, 20, 30, 31, 43, 45, 46, 50(Bloxham et al. 2020)	Nutrient sensors (Foster et al. 2013)	Myocarditis Acute myocardial infarction Cardiomyopathy Dysrhythmias Dysosmia Dysgeusia Acute myelitis Miller Fisher syndrome Polyneuritis cranialis Atonia Paresis
	Vascular smooth muscle cells(Bloxham et al. 2020)	T2R46(Bloxham et al. 2020)	Increased intracellular calcium release and vasodilation (Lund et al. 2013)	
	Pulmonary arteries (Bloxham et al. 2020)	T2R3, 4, 10, 14 (Bloxham et al. 2020)	Increased endothelium-independent relaxation and vasodilation (Manson et al. 2014)	
	Pulmonary artery smooth muscle cells (Bloxham et al. 2020)	T2R1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 19, 20, 30, 31, 39, 42, 43, 45, 56, 50, 60 (Bloxham et al. 2020)	Increased calcium responses with the improved pulmonary arterial constriction and relaxation of airway rings (Upadhyaya et al. 2014)	
	Mesenteric, cerebral and omental arteries (Bloxham et al. 2020)	T2R3, 4, 7, 10, 14, 39, 40 (Bloxham et al. 2020)	Relaxation of arteries in concentration-dependent manner (Chen et al. 2017)	
f) Urogenital	HEK 293T cell line, testis(Bloxham et al. 2020)	T2R14, 16, 38, 43(Bloxham et al. 2020)	Members of RTP and REEP gene family are cofactors for functional expression of a few T2Rs expressed on urogenitals (Behrens et al. 2006)	Acute kidney injury Orchitis
	HeLa cells (cervical cancer cell line), DU145 cells (prostate cancer cell line) (Bloxham et al. 2020)	T2R13 (Bloxham et al. 2020)	Knockdown of gene caused cytokinesis failure (Zhang et al. 2012)	
	SKOV-3 cells (ovarian cancer cell line) (Bloxham et al. 2020)	T2R38(Bloxham et al. 2020)	– (Gaida et al. 2016b)	
	Placenta, JEG-3 cells (Bloxham et al. 2020)	T2R38(Bloxham et al. 2020)	Calcium influx (Wolfle et al. 2016)	

Human physiology System	Organs/cells subjected to SARS-CoV-2 virulence	T2R expression	Biological functions/ properties	Adverse clinical symptoms of SARS-CoV-2 virulence
	Kidney, cervix (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	– (Wolfle et al. 2016)	
	Sperm (Bloxham et al. 2020)	T2R3, 4, 5, 7, 8, 10, 13, 14, 31, 39, 42, 43, 45, 50 (Bloxham et al. 2020)	Homozygous carriers of T2R14 polymorphism had decreased sperm motility with limited normal acrosome (Gentiluomo et al. 2017)	
	Genitourinary, multiple ovarian and prostate cancer cell lines (Bloxham et al. 2020)	T2R1, 4, 10, 14, 38, and 43 (Bloxham et al. 2020)	Expression of T2R4 and 10 increased with the concomitant reduction of T2R14 and 38 expression on genitourinary cancer cells. Activation of T2R14 affects its cell survival (Martin et al. 2019)	
Skeletomuscular	Bone marrow derived stem cells, osteocytes, chondrocytes (Bloxham et al. 2020)	T2R46 (Bloxham et al. 2020)	T2R46 activation increased the intracellular calcium release accompanied by decreased cAMP levels and increased extracellular ATP release in human bone marrow stromal-derived cells (Lund et al. 2013)	Muscle pain, body aches
	Osteoclasts (Bloxham et al. 2020)	T2R38 (Bloxham et al. 2020)	Biofilm sensing (Gaida et al. 2016a)	

Table 2: Potential bitter medicines and effective dosages to tackle SARS-CoV-2 virulence.

Bitter Drugs (as agonist)	Bitter receptors (T2Rs) of target	Noticeable clinical inference of bitter drugs	*In-vitro* effective dose conc (in μM)/Precise T2Rs of target
Arborescin (Bloxham et al. 2020; Wiener et al. 2012)	T2Rs-1, 4, 10, 14, 43, 46 (Bloxham et al. 2020; Wiener et al. 2012)	-	3μM/T2R46 (Wiener et al. 2012) 30μM/T2R4 (Wiener et al. 2012) 100 μM/T2R1, 10, 14, 43 (Wiener et al. 2012)
Artemorin (Bloxham et al. 2020; Wiener et al. 2012)	T2Rs-4, 10, 14, 46, 47 (Bloxham et al. 2020; Wiener et al. 2012)	-	3μM/T2Rs-10, 14 (Wiener et al. 2012) 10 μM/T2R46 (Wiener et al. 2012) 30μM/T2R47 (Wiener et al. 2012) 100μM/T2R4 (Wiener et al. 2012)
Atropine (Bloxham et al. 2020; Wiener et al. 2012)	T2Rs10, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Antimuscarinic agent used to treat poisoning from choline esters, anticholinesterase agents, parasympathomimetic drugs. Can prevent or abolish induced reflex vagal cardiac slowing, bradycardia, asystole, cardiac arrest and counteract peripheral dilatation and abrupt decrease in blood pressure (Wishart et al. 2018).	-
Azathioprine (Bloxham et al. 2020; Wiener et al. 2012)	T2Rs4, 10, 14, 39, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Immunosuppressive agent that inhibits purine synthesis, B cells and T cells (Wishart et al. 2018).	300 μM/T2R4, 10, 46 (Wiener et al. 2012) 1000 μM/T2R39 (Wiener et al. 2012)
Azithromycin (Bloxham et al. 2020; Wiener et al. 2012)	T2R4 (Bloxham et al. 2020; Wiener et al. 2012)	Antibiotic with immunomodulatory effects used to treat mild to moderate infections caused by susceptible bacteria (Wishart et al. 2018).	-
Carisoprodol (Bloxham et al. 2020; Wiener et al. 2012)	T2R14, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Skeletal muscle relaxant that relieves pain from muscle spasms through action on the central nervous system (Wishart et al. 2018).	10 μM/T2R46 (Wiener et al. 2012) 100 μM/T2R14 (Wiener et al. 2012)
Cascarillin (Bloxham et al. 2020; Wiener et al. 2012)	T2R1, 10, 14, 46, 47 (Bloxham et al. 2020; Wiener et al. 2012)	-	10μM/T2R46 (Wiener et al. 2012) 100μM/T2R1, 10, 14, 47 (Wiener et al. 2012)

Bitter Drugs (as agonist)	Bitter receptors (T2Rs) of target	Noticeable clinical inference of bitter drugs	*In-vitro* effective dose conc (in μM)/Precise T2Rs of target
Chloroquine (Bloxham et al. 2020; Wiener et al. 2012)	T2R3, 7, 10, 14, 39 (Bloxham et al. 2020; Wiener et al. 2012)	An amino quinolone derivative used to treat bacterial/viral infections and rheumatic diseases. Inhibits heme polymerase in malarial trophozoites and inhibits terminal glycosylation of ACE2 (Wishart et al. 2018).	10 μM/T2R3, 14 (Wiener et al. 2012) 100 μM/T2R39 (Wiener et al. 2012) 10000 μM/T2R10 (Wiener et al. 2012)
Chlorpheniramine (Bloxham et al. 2020; Wiener et al. 2012)	T2R4, 10, 14, 39, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Histamine antagonist used to treat allergic reactions, hay fever, rhinitis, urticaria, and asthma and relieve symptoms of pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction induced by histamine (Wishart et al. 2018).	10μM/T2R7, 10 (Wiener et al. 2012) 30μM/T2R4 (Wiener et al. 2012) 100μM/T2R14, 38, 39, 40, 46 (Wiener et al. 2012)
Chloramphenicol (Bloxham et al. 2020; Wiener et al. 2012)	T2R10, 39, 41, 43, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Antibiotic for life-threatening infections that binds to bacterial ribosome and inhibits protein synthesis (Wishart et al. 2018).	10μM/T2R46 (Wiener et al. 2012) 30μM/T2R8 (Wiener et al. 2012) 100μM/T2R1, 10, 43 (Wiener et al. 2012) 1000μM/T2R39 (Wiener et al. 2012)
Clonixin (Bloxham et al. 2020; Wiener et al. 2012)	T2R14 (Bloxham et al. 2020; Wiener et al. 2012)	Non-steroidal anti-inflammatory drug that induces vasodilation and analgesia (Wishart et al. 2018).	2μM/T2R14 (Wiener et al. 2012)
Chlorhexidine (Bloxham et al. 2020; Wiener et al. 2012)	T2R14 (Bloxham et al. 2020; Wiener et al. 2012)	Antimicrobial biguanide used as antiseptic and for inflammatory dental conditions (Wishart et al. 2018).	0.1μM/T2R14 (Wiener et al. 2012)
Colchicine (Bloxham et al. 2020; Wiener et al. 2012)	T2R4, 39, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Reduces pain from gout and can also interfere with inflammatory pathways (Wishart et al. 2018).	100μM/T2R4 (Wiener et al. 2012) 300μM/T2R46 (Wiener et al. 2012) 3000μM/T2R39 (Wiener et al. 2012)
Cromolyn (Bloxham et al. 2020; Wiener et al. 2012)	T2R7, 20, 43, 49 (Bloxham et al. 2020; Wiener et al. 2012)	Mast cell stabilizer used as prophylactic drug for bronchial asthma and can also be used for conjunctivitis, mastocytosis, keratitis and ulcerative colitis (Wishart et al. 2018).	10μM/T2R49 (Wiener et al. 2012) 3000μM/T2R7, 43 (Wiener et al. 2012)
Dapsone (Bloxham et al. 2020; Wiener et al. 2012)	T2R4, 10, 40 (Bloxham et al. 2020; Wiener et al. 2012)	A sulfone used to treat leprosy and dermatitis herpetiformis that has anti-inflammatory, immunosuppressive, antibacterial and antibiotic properties (Wishart et al. 2018).	30μM/T2R40 (Wiener et al. 2012) 100μM/T2R4, 10 (Wiener et al. 2012)
Denatonium benzoate (Bloxham et al. 2020; Wiener et al. 2012)	T2R4, 8, 10, 13, 39, 43, 46, 47 (Bloxham et al. 2020; Wiener et al. 2012)	Bitter salt being investigated for the treatment of gastro esophageal reflux and obesity (Wishart et al. 2018).	0.03μM/T2R47 (Wiener et al. 2012) 3μM/T2R10 (Wiener et al. 2012) 30μM/T2R13, 46 (Wiener et al. 2012) 100μM/T2R39 (Wiener et al. 2012) 300μM/T2R4, 43 (Wiener et al. 2012) 1000μM/T2R8 (Wiener et al. 2012)
Dextromethorphan (Bloxham et al. 2020; Wiener et al. 2012)	T2R1, 10 (Bloxham et al. 2020; Wiener et al. 2012)	A levorphanol derivative and codeine analog used in combination with other medications to treat coughs and respiratory symptoms (Wishart et al. 2018).	10μM/T2R1, 10 (Wiener et al. 2012)
Diphenhydramine (Bloxham et al. 2020; Wiener et al. 2012)	T2R14, 40 (Bloxham et al. 2020; Wiener et al. 2012)	Antihistamine, anti-emetic, anti-vertigo, sedative and hypnotic properties used to treat respiratory systems, allergic reactions, nausea and parkinsonism (Wishart et al. 2018).	30μM/T2R14, 40 (Wiener et al. 2012)
Diphenidol (Bloxham et al. 2020; Wiener et al. 2012)	T2R1, 4, 7, 10, 13, 14, 16, 20, 30, 31, 38, 39, 40, 43, 44, 46, 47, 49 (Bloxham et al. 2020; Wiener et al. 2012)	Antiemetic and antivertigo drug used to treat vomiting and vertigo (Wishart et al. 2018).	3μM/T2R44 (Wiener et al. 2012) 10μM/T2R7, 14 (Wiener et al. 2012) 30μM/T2R10, 13, 40, 43, 46 (Wiener et al. 2012) 100μM/T2R1, 4, 16, 38, 39, 47, 49 (Wiener et al. 2012)

Bitter Drugs (as agonist)	Bitter receptors (T2Rs) of target	Noticeable clinical inference of bitter drugs	*In-vitro* effective dose conc (in µM)/Precise T2Rs of target
Erythromycin (Bloxham et al. 2020; Wiener et al. 2012)	T2R10 (Bloxham et al. 2020; Wiener et al. 2012)	Antibiotic used to treat respiratory tract infections, mild to moderate skin infections, gastrointestinal infections, acute pelvic inflammatory disease, syphilis, nongonococcal urethritis and symptoms caused by chlamydia (Wishart et al. 2018).	300µM/T2R10 (Wiener et al. 2012)
Famotidine (Bloxham et al. 2020; Wiener et al. 2012)	T2R10, 31, 44 (Bloxham et al. 2020; Wiener et al. 2012)	Histamine-2 receptor agonist that inhibits gastric acid secretion and is used to treat active duodenal ulcer, active gastric ulcers, symptomatic non-erosive gastroesophageal reflux disease, and erosive esophagitis (Wishart et al. 2018).	300µM/T2R10, 44 (Wiener et al. 2012)
Flufenamic acid (Bloxham et al. 2020; Wiener et al. 2012)	T2R14 (Bloxham et al. 2020; Wiener et al. 2012)	Analgesic, anti-inflammatory, and antipyretic for musculoskeletal and joint disorders (Wishart et al. 2018).	0.01µM/T2R14 (Wiener et al. 2012)
Haloperidol (Bloxham et al. 2020; Wiener et al. 2012)	T2R10, 14 (Bloxham et al. 2020; Wiener et al. 2012)	Dopamine receptor antagonist used to treat psychotic disorders (Wishart et al. 2018).	30µM/T2R10, 14 (Wiener et al. 2012)
Hydrocortisone (Bloxham et al. 2020; Wiener et al. 2012)	T2R46(Bloxham et al. 2020; Wiener et al. 2012)	Glucocorticoid used to treat immune, inflammatory and neoplastic conditions (Wishart et al. 2018).	3µM/T2R46(Wiener et al. 2012)
Levofloxacin (Bloxham et al. 2020; Wiener et al. 2012)	T2R4, 14, 20 (Bloxham et al. 2020; Wiener et al. 2012)	Fluoroquinolone antibiotic used to treat bacterial infections of the upper and lower respiratory tract, skin, urinary tract, and prostate (Wishart et al. 2018).	-
Ofloxacin (Bloxham et al. 2020; Wiener et al. 2012)	T2R9 (Bloxham et al. 2020; Wiener et al. 2012)	Fluoroquinolone used to treat bacterial infections of the respiratory tract, skin, kidney, soft tissue and urinary tract (Wishart et al. 2018).	-
Orphenadrine (Bloxham et al. 2020; Wiener et al. 2012)	T2R46 (Bloxham et al. 2020; Wiener et al. 2012)	Muscarinic antagonist used to treat acute musculoskeletal pain and drug-induced parkinsonism (Wishart et al. 2018).	30µM/T2R46 (Wiener et al. 2012)
Methoxsalen/Xanthotoxin (Bloxham et al. 2020; Wiener et al. 2012)	T2R10, 14, 20,46, 49 (Bloxham et al. 2020; Wiener et al. 2012)	Furocoumarin compound used to treat psoriasis and vitiligo by inhibiting DNA synthesis (Wishart et al. 2018).	100µM/T2R 10, 14, 46 (Wiener et al. 2012)
Noscapine (Bloxham et al. 2020; Wiener et al. 2012)	T2R14 (Bloxham et al. 2020; Wiener et al. 2012)	An antitussive investigated for treating lymphoma, leukemia, tumors and multiple myeloma (Wishart et al. 2018).	10µM/T2R14 (Wiener et al. 2012)
Papaverine (Bloxham et al. 2020; Wiener et al. 2012)	T2R7, 10, 14, 31, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Alkaloid used to treat impotence and vasospasms (Wishart et al. 2018).	10µM/T2R7, 10, 14 (Wiener et al. 2012)
Parthenolide (Bloxham et al. 2020; Wiener et al. 2012)	T2R1, 4, 8, 10, 14, 31, 44, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Anti-inflammatory agent that inhibits nuclear factor kappa B (NF-kB) activation and has been investigated for treating all allergic contact dermatitis (Wishart et al. 2018).	1µM/T2R46 (Wiener et al. 2012) 3µM/T2R14 (Wiener et al. 2012) 30µM/T2R4, 10 (Wiener et al. 2012) 100µM/T2R1, 8, 44 (Wiener et al. 2012)
Picrotoxinin (Bloxham et al. 2020; Wiener et al. 2012)	T2R1, 10, 14, 46, 47 (Bloxham et al. 2020; Wiener et al. 2012)	-	3µM/T2R14 (Wiener et al. 2012) 10µM/T2R46 (Wiener et al. 2012) 30µM/T2R46 (Wiener et al. 2012) 1000µM/T2R47 (Wiener et al. 2012)
Pirenzepine (Bloxham et al. 2020; Wiener et al. 2012)	T2R9 (Bloxham et al. 2020; Wiener et al. 2012)	Antimuscarinic agent used to treat peptic ulcers, gastric ulcers, and duodenal ulcers (Wishart et al. 2018).	-
Procainamide (Bloxham et al. 2020; Wiener et al. 2012)	T2R9 (Bloxham et al. 2020; Wiener et al. 2012)	A sodium channel blocker used to treat life-threatening ventricular arrhythmias (Wishart et al. 2018).	-
Quassin (Bloxham et al. 2020; Wiener et al. 2012)	T2R4, 10, 14, 46, 47 (Bloxham et al. 2020; Wiener et al. 2012)	-	300µM/T2R4, 10, 14, 46, 47 (Wiener et al. 2012)

Bitter Drugs (as agonist)	Bitter receptors (T2Rs) of target	Noticeable clinical inference of bitter drugs	*In-vitro* effective dose conc (in μM)/Precise T2Rs of target
Quinine (Bloxham et al. 2020; Wiener et al. 2012)	T2R4, 10, 14, 31, 39, 43, 46 (Bloxham et al. 2020; Wiener et al. 2012)	Antimalarial drug used for malaria and leg cramps (Wishart et al. 2018).	-
Salicylic acid (Bloxham et al. 2020; Wiener et al. 2012)	T2R14 (Bloxham et al. 2020; Wiener et al. 2012)	COX inhibitor used to treat acne, psoriasis, callouses, corns, keratosis pilaris and warts (Wishart et al. 2018).	-
Strychnine (Bloxham et al. 2020; Wiener et al. 2012)	T2R10, 46 (Bloxham et al. 2020; Wiener et al. 2012)	-	0.1μM/T2R46 (Wiener et al. 2012) 3μM/T2R10 (Wiener et al. 2012)
Tobramycin (Bloxham et al. 2020; Wiener et al. 2012)	T2R14, 20 (Bloxham et al. 2020; Wiener et al. 2012)	An antibiotic effective against gram-negative bacteria, used to treat lung infections and under investigation for the treatment of sinus infections (Wishart et al. 2018).	-
Yohimbine (Bloxham et al. 2020; Wiener et al. 2012)	T2R1, 4, 10, 26, 38, 46 (Bloxham et al. 2020; Wiener et al. 2012)	A sympatholytic and mydriatic agent used to treat impotence in males (Wishart et al. 2018).	300μM/T2R1, 4, 10, 38, 46 (Wiener et al. 2012)

with increased inositol triphosphate (IP3) and diacylglycerol production in the non-gustatory airway smooth muscle (Jaggupilli et al. 2016; Kim et al. 2017; Margolskee 2002). Concertedly, this mechanism of action increases intracellular calcium concentrations and its release is accompanied by membrane hyperpolarization through the stimulation of the large conductance, Ca^{2+}-dependent potassium (K^+) channels (BK_{ca}) (Grassin-Delyle et al. 2013, 2015). This would prevent pathogen invasion in the respiratory system with increased Ca^{2+}-dependent nitric oxide (NO) production and its associated increase in ciliary beat frequency of the human airway epithelial cells leading to ameliorated mucociliary clearance and improved relaxation of bronchial smooth muscle cells (Grassin-Delyle et al. 2013) (Fig. 1). T2R activation is as significant as the β-2 adrenoreceptor activation in inducing the bronchial dilatation (Grassin-Delyle et al. 2013, 2015).

These noticeable clinical inferences of T2R activation in the upper and lower respiratory tract is crucial in tackling the severe respiratory ailments mediated by the colonization of deleterious pathogens, including SARS-CoV-2. Prolonged exposure of T2R-agonists, including quinine, has been associated with the T2R desensitization affecting its function as a vasorelaxant (Robinett et al. 2011). Prior exposure of quinine for 15 minutes drastically reduced the bronchodilation response of T2R via G protein-coupled receptor kinase (GRK)-dependent phosphorylation, which further intervened with Ca^{2+} responses to endothelin and bradykinin exposure in the airway smooth muscle cells (Robinett et al. 2011). Therefore, it is recommended to opt for a mild dose of T2R agonists in compliance with a moderate therapeutic dose of beta-adrenoreceptor agonists to treat severe respiratory ailments of SARS-CoV-2 patients.

T2Rs being widely expressed on the blood leukocytes also effectively inhibit pro-inflammatory cytokines such as IL-13, IL-5, tumour necrosis factor-alpha (TNF-α), IL-1β and interferon gamma (IFN-γ) production with the reversal of collagen and fibronectin deposition in an allergen-induced asthmatic mice model upon its stimulation using the potent T2Rs agonists such as chloroquine and quinine (Sharma et al. 2017). T2Rs linked with the regulation of airway inflammation and attenuation of pathogen invasion are shown in Table 1. Chloroquine binds specifically to T2Rs 3, 7, 10 and 39, whereas quinine binds to T2Rs 4, 7, 10, 14, 39, 40, 43, 44 and 46 (Sharma et al. 2017) (Table 2). Other well-known allopathic drugs that are classified as T2R agonists include denatonium, aristocholic acid, saccharine, erythromycin, ofloxacin, and noscapine (Jaggupilli et al. 2016; Sharma et al. 2017) (Table 2). Natural T2R agonists that target the diverse range of bitter taste receptors of the human physiology, including the T2Rs 4, 38, 43, and 46; and T2Rs-10, 14, 19 and 31 of the upper and lower respiratory tracts, respectively, are preferred along with the other classified allopathic T2R agonists to treat the severe respiratory ailments of extreme SARS-CoV-2 cases (Clark et al. 2012; Li et al. 2020) (Table 2 and 3).

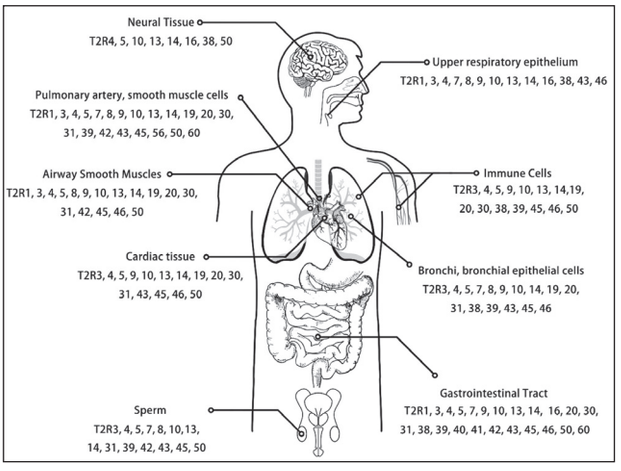

Fig. 2: Noticeable bitter taste receptors (T2Rs) of therapeutic target spotted on susceptible human organs to SARS-CoV-2 virulence

4. Gastrointestinal manifestations

Concordant with gustatory dysfunction and respiratory ailments, symptoms of vomiting, abdominal pain, and diarrhoea with the gastrointestinal complications have been observed among SARS-CoV-2 patients (Konturek et al. 2020; Zhou et al. 2020). About 26% of 254 SARS-CoV-2 Chinese patients showed adverse gastrointestinal symptoms (Zhang et al. 2020b). Alike the functional significance of the prevalence of T2Rs and its associated G-proteins, including α-gustducin, in the respiratory tract (Rozengurt 2006; Shaik et al. 2016), T2R expression in compliance with the other functional G-proteins such as α-gustducin and α-transducin in the gastric and intestinal mucosa regulates the gastrointestinal function as shown in Fig. 1 and Fig. 2 (Foster et al. 2014; Sternini 2007). By inferring to rodent-based studies, the T2Rs and α-gustducin of the human colon regulate chemoreceptive signalling followed by the regulation of glucagon-like peptide 1 (GLP-1) and peptide-like hormone YY (PYY) secretion linked with satiety and nutrient intake, which involves the secretion of cholecystokinin of the small bowel that is essential for fat and protein digestion (Chamoun et al. 2018; Rozengurt 2006; Sternini 2007).

Additionally, T2Rs along with other Gα proteins stimulates intracellular Ca^{2+} concentration upon its activation by oral bitter agonists in enteroendocrine cells (Rozengurt 2006; Sternini 2007). In response to the activation of T2R, synthesis of PYY, GLP-1, ghrelin, and cholecystokinin (CCK) are also triggered in the intestinal colon cells (Rozengurt 2006; Rozengurt et al. 2006; Xie et al. 2018). Furthermore, T2R stimulation using bitter agonists enhances c-Fos

expression, a neurostimulator protein marker that regulates the activity of extrinsic afferent neurons (Rozengurt 2006; Sternini 2007). NO production in intestinal brush cells are simultaneously increased, influencing the motor functions of intestinal villi and the absorption of nutrients (Rozengurt 2006; Steensels and Depoortere 2018; Sternini 2007). T2R activation by bitter agonists delays gastric emptying in the duodenum through the controlled secretion of ghrelin and other satiety hormones such as GLP-1 and CCK in the experimental mice model (Janssen et al. 2011). Collectively, these pronounced mechanisms of T2Rs in the gastrointestinal system are aspired to defend the absorption and digestion of any toxic metabolites or elements in the human gut (Steensels and Depoortere 2018). Likely, the function of T2Rs, especially T2Rs 1, 3, 4, 5, 7, 8, 9, 10, 13, 14, 16, 19, 20, 30, 38, 43, 46, 50, 108, 120, 131 and 138 of the human gut (Bloxham et al. 2020) (Table 1) could be hindered with the SARS-CoV-2 virulence either by direct interaction or by its genome/protein components preceding the adverse clinical symptoms of the gastrointestinal tract such as vomiting, poor food intake, indigestion, abdominal pain, and diarrhoea in SARS-CoV-2 patients (Rozengurt et al. 2006; Steensels and Depoortere 2018; Xie et al. 2018). Exposure to T2Rs agonists (Table 2) is crucial in managing gastrointestinal complications among emerging SARS-CoV-2 patients (Li et al. 2020).

5. Hyper innate immune responses

Hyper innate immune response mediated by blood leukocytes, including macrophages and natural killer cells activation with increased pro-inflammatory cytokines production such as interferon-gamma (IFN-γ), IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α), are widely apparent among the severe SARS-CoV-2 cases (Liu et al. 2020; Merad and Martin 2020). T-Lymphocytes that diminished during the early onset of SARS-CoV-2 virulence are more likely to get rejuvenated in the later stages to mollify the hyper innate immune response, paving the recovery of severely ill SARS-CoV-2 patients (Liu et al. 2020). Coagulation of blood cells are also initiated by coagulation factor-III with increased pro-inflammatory cytokines production, especially IL-6 in SARS-CoV-2 patients (Merad and Martin 2020).

T2Rs 4, 5, 10, 13, 14, 19, 20, 31, 45, 46, and 50 are predominantly expressed on both the lymphocytes and leukocytes (Bloxham et al. 2020; Orsmark-Pietras et al. 2013). T2R10 is highly expressed on lymphocyte cells, whereas T2R5 is widely expressed on mixed leukocyte cell populations. T2Rs 31 and 43 are also widely expressed on blood leukocytes, including natural killer cells, T cells and B cells (Malki et al. 2015). T2Rs-3, 4, 5, 10, 13, 14, 19, 20 and 46 are enormously expressed on the mast cells (Bloxham et al. 2020). T2R activation of lymphocytes and leukocytes by the bitter agonists, chloroquine and denatonium were shown to attenuate pro-inflammatory cytokine and eicosanoid release by blood leukocytes with improved bronchodilatation in severe asthmatic patients (Orsmark-Pietras et al. 2013) (Fig. 1). The activation of T2Rs 3, 4, 5, 7, 9, 10, 14, 30, 38, 39, and 40 on human lung macrophages using the bitter agonists erythromycin, phenanthroline, ofloxacin, and carisoprodol attenuated lipopolysaccharide (LPS)-induced proinflammatory cytokine secretion consisting of TNF-α, chemokine (C-C-motif) ligand 3(CCL3) and interleukin 8 (IL-8), which is independent to the secretion of the anti-inflammatory interleukin 10 (IL-10) (Grassin-Delyle et al. 2019).

T2Rs being widely expressed by the human monocytes, leukocytes and lymphocytes have been therapeutically targeted using natural and allopathic bitter agonists to tackle the respiratory ailments associated with cytokine storms preceded by the hyper innate immune response in severe asthmatic and chronic obstructive lung disease patients (Meyerhof et al. 2010; Nayak et al. 2019; Vrancic et al. 2012). T2R expression on the macrophages, monocytes, leukocytes, and T and B lymphocytes (Table 1) are likely to be hindered by SARS-CoV-2 virulence either by its direct contact or by its virulent genome/proteins. Henceforth, an aggravated immune response with the cytokine storm combined with hyper-reactive macrophages, monocytes and other blood leukocytes have been largely observed among SARS-CoV-2 patients (Merad and Martin 2020). T2R stimulation in presence of natural/allopathic bitter agonists (Table 2) could profusely control the cytokine storm inflicted by the hyper reactive innate immune cells, especially the macrophages, leukocytes and monocytes in the respiratory system of the severely ill SARS-CoV-2 patients (Li et al. 2020).

6. Cardiovascular complications

Myocarditis, acute myocardial infarction, cardiomyopathy, and dysrhythmias are noticeable cardiovascular complications witnessed among SARS-CoV-2 patients (Long et al. 2020). Excluding hypertension and other co-morbid conditions, including, type 2 diabetes; systemic inflammation and its associated hypercoagulation of blood cells with abundant SARS-CoV-2 infiltration in the respiratory system, precedes these cardiovascular complications with the increased mortality in the SARS-CoV-2 patients (Chen et al. 2020; Long et al. 2020; Shi et al. 2020). ACE2 receptor contributes the most to SARS-CoV-2 infiltration in the human upper respiratory tract as well as in the heart, kidney and gut (D'Amico et al. 2020; Jiang et al. 2020; South et al. 2020). In similar to the disrupted function of ACE2 with the SARS-CoV-2 spike 1 (S1) protein binding (Jiang et al. 2020; Touyz et al. 2020; Zabetakis et al. 2020), it is highly plausible that the T2R biological functions as a G-protein coupled receptor in cardiac myocytes could be intervened by the S1 protein binding of SARS-CoV-2 (Cheng et al. 2015; Hui and Nayak 2002; Jaggupilli et al. 2016).

T2Rs, especially T2R46, that are unanimously expressed on the myocytes, vascular smooth muscle cells, pulmonary arteries, and pulmonary vascular smooth muscle cells (Fig. 2) would thus be refrained from its regular biological functions such as nutrient sensing, vasoconstriction and vasodilatation of the myocytes by interacting with the S1 protein of SARS-CoV-2 (Bloxham et al. 2020) (Table 1). Furthermore, the systemic inflammation accompanied with the hypercoagulation mediated by disturbed T2R functions of the upper respiratory tract could be preceding factors of myocarditis, acute myocardial infarction, cardiomyopathy, and dysrhythmias witnessed among the SARS-CoV-2 affected patients (Akhmerov and Marban 2020; Merad and Martin 2020; Zabetakis et al. 2020).

SARS-CoV-2 virulence inflicts musculoskeletal injury by establishing direct contact with skeletal muscle cells. T2R46 being exclusively expressed on skeletomuscular cells such as bone marrow stromal cells, osteocytes and chondrocytes (Table 1) could get affected with SARS-CoV-2 virulence in the skeletal muscle cells, inflicting rhabdomyolysis via systemic inflammation and hyper-reactive immune responses in SARS-CoV-2 patients (Ellul et al. 2020; Riquelme et al. 2014; Zhang et al. 2020a).

Therefore, it is likely that the stimulation of T2Rs with appropriate bitter agonists (Table 2) could proficiently defend these adverse cardiovascular symptoms as well as the skeletomuscular injury of SARS-CoV-2 virulence.

7. Neurological symptoms

Severe abnormalities in the central nervous system (CNS) associated with headache, dizziness, mental instability, an acute cerebrovascular accident (CVA), ataxia, and seizures have been observed among SARS-CoV-2 patients (Ellul et al. 2020; Sheraton et al. 2020). Patients also showed adverse clinical symptoms of a disturbed peripheral nervous system including dysosmia, dysgeusia, acute myelitis, Miller Fisher syndrome and polyneuritis cranialis (Sheraton et al. 2020). Moreover, severe SARS-CoV-2 cases have developed symptoms of direct skeletal muscle injury such as atonia and paresis (Sheraton et al. 2020). Severe SARS-CoV-2 cases with CNS abnormalities also showed reduced levels of lymphocytes and blood platelets with the increased blood urea nitrogen levels (Sheraton et al. 2020). ACE2 is the known gateway for SARS-CoV-2 in the CNS. Virus entry is also facilitated by the straight trans-synaptic route through olfactory bulb, mimicking the transmission of SARS-CoV and MERS-CoV beyond the blood-brain barrier of the CNS (Sheraton et al. 2020). Systemic inflammation and hyper-reactive immune responses are preceding factors of the adverse clinical symptoms of the CNS and peripheral nervous system in SARS-CoV-2 patients (Sheraton et al. 2020).

The biological functions of T2R16 expressed on the cortex, cerebellum and hippocampus as well as the T2Rs 4, 5, 10, 13, 14, and 50 on the frontal cortex and dorsolateral prefrontal cortex include cognition and neurite growth (Fig. 1 and Fig. 2). Analogous to ACE2 receptors, these G-protein T2Rs are susceptible to SARS-CoV-2 virulence (Cheng et al. 2015; Hui and Nayak 2002; Stone et al. 2002). Moreover, T2R38 expressed on the Purkinje and neurons/glial cells (Table 1) could be targeted by the S1 protein of SARS-CoV-2 as the potential receptor agonists to establish its virulence in the CNS. Concomitantly, activation of T2Rs using bitter agonists of either natural or commercial drugs (Table 2) could help the SARS-CoV-2 patients overcome neurological complications (Li et al. 2020).

8. Urogenital complications

SARS-CoV-2 patients diagnosed with an acute kidney injury exhibited higher mortality compared with patients who did not develop any adverse clinical symptoms of acute kidney injury (Soleimani 2020). ACE2, which plays a major role in SARS-CoV-2 invasion in other organs, does the same for the kidney wherein the infiltration of SARS-CoV-2 occurs via ACE2 receptors expressed on proximal tubule cells (Soleimani 2020). Concertedly, cathepsins (cysteine protease) support the entry of SARS-CoV-2 into the proximal tubules by incorporating structural changes on the S1 protein of SARS-CoV-2 (Soleimani 2020). Although the pathogenesis of SARS-CoV-2 on kidney dysfunction remains poorly understood, it has been suggested that SARS-CoV-2 virulence on its own could damage kidney tubules (Soleimani 2020). Including ACE2, G-protein T2R function on renal tubular epithelial cells and M-1 (collecting tubule) cells confirmed by rodent-cell line study could get disrupted, inflicting kidney malfunction (Gheblawi et al. 2020; Hui and Nayak 2002; Liang et al. 2017). T2Rs expressed on kidney cells, particularly on renal tubular epithelial cells and M-1 cells have been exclusively engaged with its maturation through the controlled secretion of intracellular Ca^{2+} through the phospholipase C (PLC)-dependent mechanism (Liang et al. 2017).

Rodent-based cell line study (Liang et al. 2017) confirmed T2Rs 108, 116, 123, and 130 expressed at a higher level on primary renal epithelial cells, whereas the T2Rs 110, 113, 126 and 131 expressed in higher proportions on the M-1 cells. Biological stimulation of T2Rs by bitter agonists, especially T2R105 together with guanine nucleotide-binding protein G(t) subunit alpha-3 (GNAT3) that are vastly expressed on the renal tubule system, is crucial for the structural development as well as the maintenance of glomerulus and renal tubules (Liang et al. 2017; Liu et al. 2015). Also, the sustainment of T2R functions through the exposure of bitter compounds is vital for the maturation of kidney cells (Liang et al. 2017). In case of severe SARS-CoV-2 cases, it is very likely that the T2R functions of kidney cells are intervened by the infiltration of SARS-CoV-2. T2R activation using the bitter agonists could profusely rejuvenate damaged kidney cells of the SARS-CoV-2 patients (Liang et al. 2017), thus reducing the mortality rate inflicted by acute kidney injury on severe cases, particularly in elderly patients. Clinicians prefer the bitter agonists specific to the kidney T2Rs, especially T2R105 at low/moderate dose levels to treat the critical SARS-CoV-2 patients with acute kidney injury (Li et al. 2020). Equivalently, it is essential to restore the functions of T2Rs 14 and 43 expressed on sperm cells as well as T2Rs 1, 4, 10, 14, and 38 expressed on uterine tissue and ovaries using specific bitter agonists to avoid impotency (Table 1 and 2) on severely ill SARS-CoV-2 male and female patients (Bloxham et al. 2020; Sansone et al. 2020). T2Rs of sperm cells positively regulate its motility and function (Fig. 1), whereas T2Rs of ovaries and uterine tissue is vital for its survival (Bloxham et al. 2020).

9. Challenges and future direction

The SARS-CoV-2 binding affinity of T2Rs expressed on various human functional organs should be validated through *in silico* protein modelling. Concomitantly, the clinical efficacy of the bitter agonists at the low/moderate dose should be validated using the existing bitter medicines or other indigenous bitter bio-actives on the severely ill patients to control the detrimental clinical symptoms. Based on the functions of T2Rs reported in current literature, SARS-CoV-2 virulence could likely be mitigated through T2R activation, and therefore could benefit clinicians as well as patients in defending SARS-CoV-2 pathogenesis on a long-term basis. Furthermore, by activating T2Rs through exposure to bitter agonists, the natural innate immunity among the unaffected population can be enhanced, which could attenuate the human to human transmission chain of SARS-CoV-2.

Limitations of using T2Rs as drug targets involve the existence of polymorphisms, which could render certain isoforms of T2Rs insensitive to bitter agonists (Adappa et al. 2014; Mfuna Endam et al. 2014). In mind of these cases, a bitter molecule drug cocktail could be formulated to target multiple T2R isoforms. In severe or critical COVID-19 cases, a pharmacogenetic approach could be adopted wherein the drug cocktail is catered to enhance drug potency pertaining to the patient's genetic polymorphism. Another concern is the possible inhibition of T2Rs by sodium salts or by the activation of sweet taste receptors as demonstrated in gustatory bitter taste sensation (Khan et al. 2018). Therefore, it is recommended that the administration of T2R targeting drugs do not coincide with food intake. Further research is required to investigate the interaction of bitter agonists in combination with other supplements.

10. Conclusion

Host-based targets are crucial to attenuate the SARS-CoV-2 virulence that affects the entire human physiology system, especially pertaining to the respiratory system, immune response, cardiovascular system and kidney function, which can lead to higher mortality among the severely ill patients upon infliction. T2Rs may accompany ACE2 as potential receptors of the S1 protein of SARS-CoV-2 and could profusely contribute to SARS-CoV-2 infiltration in all major human organs, including the respiratory tract, heart, gastrointestinal tract, kidney and brain. By inferring into the clinical significance of T2Rs biological functions; it is more likely that SARS-CoV-2 invasion intervenes with the G-protein T2R biological functions in defending its pathogenesis in susceptible organs (Cheng et al. 2015; Hui and Nayak 2002; Stone et al. 2002). It is also obvious that ACE2 dysfunction linked with the SARS-CoV-2 virulence alone cannot contribute to all those detrimental clinical symptoms of the human physiology system. Thus, host-based T2Rs should be targeted using potential bitter agonists either of natural origin or of derived bio-actives (recommended at the low/moderate doses to avoid any desensitization of T2Rs) to attenuate the severe clinical symptoms associated with the deteriorated respiratory system, cytokine storm, hyper-reactive immune responses, kidney and cardiovascular complications on the SARS-CoV-2 patients. The application of bitter agonists must be proven with sufficient clinical trials to assure the efficacy of targeting the bitter taste receptors to manage the emerging SARS-CoV-2 outbreak and its associated virulence on the global population.

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