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Existing bitter medicines for fighting 2019-nCoV-associated infectious diseases

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Abstract

The sudden outbreak of COVID-19 has led to more than seven thousand deaths. Unfortunately, there are no specific drugs available to cure this disease. Type 2 taste receptors (TAS2Rs) may play an important role in host defense mechanisms. Based on the idea of host-directed therapy (HDT), we performed a negative co-expression analysis using big data of 60 000 Affymetrix expression arrays and 5000 TCGA data sets to determine the functions of TAS2R10, which can be activated by numerous bitter substances. Excitingly, we found that the main functions of TAS2R10 involved controlling infectious diseases caused by bacteria, viruses, and parasites, suggesting that TAS2R10 is a key trigger of host defense pathways. To quickly guide the clinical treatment of 2019-nCoV, we searched currently available drugs that are agonists of TAS2Rs. We identified many cheap, available, and safe medicines, such as diphenidol, quinine, chloroquine, artemisinin, chlorpheniramine, yohimbine, and dextromethorphan, which may target the most common symptoms caused by 2019-nCoV. We suggest that a cocktail-like recipe of existing bitter drugs may help doctors to fight this catastrophic disease and that the general public may drink or eat bitter substances, such as coffee, tea, or bitter vegetables, to reduce the risk of infection.

KEYWORDS

2019-nCoV, coronavirus, COVID-19, cytokine storm, infectious disease, type 2 taste receptors (TAS2Rs)

1 | INTRODUCTION

In December 2019, there was an outbreak of a pneumonia-like disease of unknown etiology that originated from Wuhan China.[1] Clinical systemic symptoms and person-to-person spread were confirmed, and the novel coronavirus 2019-nCoV was suggested to cause this outbreak.[2-4] This coronavirus disease was officially named COVID-19 by the World Health Organization (WHO). By commercial air travel, international spread is occurring.[5] On 30 January 2020, WHO declared

Abbreviations: AMPs, antimicrobial peptides; GPCR, G-protein-coupled receptors; HDT, host-directed therapy; KEGG, Kyoto encyclopedia of genes and genomes analysis; PHEIC, public health emergency of international concern; RMA, robust multichip average; TAS2Rs, type 2 taste receptors; TCGA, the cancer genome atlas; TLR, toll-like receptor; TNF-α, tumor necrosis factor alpha; WHO, World Health Organization.

Xiangqi Li, Chaobao Zhang, Lianyong Liu and Mingjun Gu contributed equally to this work.

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2019-nCoV a Public health emergency of international concern (PHEIC). In mainland China, 37 626 confirmed and 21 675 suspected cases were reported, and among them, 7333 were severe, and 1016 people have died (2020.02.10 24:00, http://www.nhc.gov.cn/). There were also more than 90 thousand cases in 116 other countries (17 March 2020). The outbreak is still progressing and is now considered as a pandemic. The morbidity, mortality, and transmissibility of this novel coronavirus remain unresolved.[6,7] Without the availability of effective antiviral therapies, compulsory measures have to be taken to prevent person-to-person transmission. However, for those severe cases, the chances of death are very high.

Despite some suggestions, there are no drugs available to cure the patients affected by this catastrophic disease.[8] A new drug was just reported to fight 2019-nCoV,[9] but it is still in the early stages of development. The identification of effective medicines to fight this disease is urgently needed. Existing host-directed therapies (HDTs), which have proven to be safe, were suggested to help fight 2019-nCoV infections.[10-12] To identify more therapeutic drugs, we focused on a special G-protein-coupled receptor (GPCR) family named type 2 taste receptors (TAS2Rs), which was shown to play a critical role in host defense pathways.[13,14] Originally, TAS2Rs, whose ligands are bitter substances, were thought to be only expressed in the tongue. However, recent studies revealed that they are widely expressed in extraoral tissues, such as the central nervous system, respiratory tract, breast, heart, gastric and intestinal mucosa, bladder, pancreas, testes, and others.[15,16] This suggests that TAS2Rs might have functions other than bitter taste perception. Indeed, they were suggested to be involved in appetite regulation, the treatment of asthma, the regulation of gastrointestinal motility, and the control of innate immunity.[14,16-18] TAS2Rs can be classified into broadly, narrowly, and intermediately tuned receptors according to the agonist spectra.[19] TAS2R10 is one of the three broadly tuned receptors that can recognize about one-third of the bitter components tested so far.[20] As such, it may largely contribute to the overall bitter tasting ability and exert broad effects on the human body. Despite several functional studies,[21,22] the detailed functions of TAS2R10 are not fully understood.

Therefore, we think that TAS2R10 is a useful model to identify the functions of bitter taste receptor agonists. Since we hypothesized that bitter agonists may help to fight COVID-19, we performed negative co-expression analysis using big data of 60 000 Affymetrix expression arrays and 5000 The Cancer Genome Atlas (TCGA) data sets. Surprisingly, the results matched our predictions. We found that the main functions of TAS2R10 involved controlling infectious diseases caused by bacteria, viruses, and parasites. However, it is unrealistic to develop new drugs based on TAS2Rs to address the current emergency. To immediately guide the clinical treatment of COVID-19, we searched for clinically approved drugs that are agonists of TAS2Rs.[20,23,24] Members of the TAS2R family may have similar functions, so we also reviewed medicines for two other broadly tuned receptors, including TAS2R14 and TAS2R46, which can also be stimulated by many bitter substances.[25] We identified many cheap, available, and safe medicines, which may provide good options for doctors to fight against 2019-nCoV. Furthermore, we suggest to the general public that we can drink coffee or tea and eat bitter vegetables to reduce the risk of infection.

2 | METHODS AND ANALYSIS

2.1 | Data collection and analysis

Gene expression data were retrieved from the EBI database, and incorporated CEL files were preprocessed using a robust multichip average (RMA) normalization method. The cutoff value of the standard deviation level was 0.25 to guarantee the high quality of data and capture significantly correlated transcriptome information. We collected and preprocessed 60 000 Affymetrix expression arrays and 5000 TCGA data sets. Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to enrich the top items. The analysis of biological pathways was implemented for the genes that showed the highest negative correlation with TAS2R10 expression. Pearson's correlation between the TAS2R10 probe and other probes was calculated, and the P values were unmodified P values. The q value package in R was used for multiple testing corrections. Genes with q values lower than 0.05 were recognized as significant negative co-expression genes of TAS2R10. The measurement of related parameters and statistics analyses were performed as previously described.[26]

2.2 | Medicine screening

Bitter agonists and TAS2Rs were retrieved from references openly published in the NCBI database. Bitter agonists for TAS2R10 or other TAS2R members were analyzed based on available references. Three main studies were referred to.[20,23,24] Mechanisms of action of the selected drugs were retrieved from the DRUGBANK database.

3 | RESULTS

3.1 | Potential functions of TAS2R10 in inhibiting infectious diseases caused by bacteria, viruses, and parasites

Based on 60 000 Affymetrix expression arrays and 5000 TCGA data sets, we performed KEGG analysis to identify

diseases that TAS2R10 may be involved in (Figure 1). By enrichment analysis, we found that the top items were focused on the infectious diseases caused by bacteria, viruses, and parasites, in addition to various cancers and neurodegenerative diseases. For infectious diseases, TAS2R10 might be involved in controlling legionellosis, pertussis, toxoplasmosis, shigellosis, tuberculosis, and HTLV-I infections. Besides these top items, TAS2R10 might also control other infectious diseases (Figure 2), such as pathogenic *Escherichia coli* infections, bacterial invasion of epithelial cells, *Salmonella* infections, *Vibrio cholerae* infections, epithelial cell signaling in *Helicobacter pylori* infections, Epstein-Barr virus infections, hepatitis C, hepatitis B, prion diseases, herpes simplex infections, influenza A, measles, viral myocarditis, Chagas disease (American trypanosomiasis), amebiasis, and leishmaniasis. These results suggest that TAS2R10 may be a key trigger of the host response to a wide variety of infectious diseases.

A cytokine storm is a very important event that is responsible for the death of patients infected with coronavirus. As such, inhibiting overactive immune responses is a necessary step to stop a cytokine storm. Indeed, we found that TAS2R10 may have such a function because it can modulate natural killer cell-mediated cytotoxicity, chemokine signaling pathways, T cell receptor signaling pathways, tumor necrosis factor (TNF) signaling pathways, B cell receptor signaling pathways, Fc gamma R-mediated phagocytosis, Fc epsilon RI signaling pathways, leukocyte transendothelial migration, antigen processing and presentation, and NF-kappa B signaling pathways (Figure 3). A cytokine storm is not only initiated by our immune system to attack the virus, but it also causes damage to our cells. By KEGG analysis, we found that TAS2R10 can modulate autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis (Figure 2).

3.2 | Clinical drugs that act as TAS2R agonists for battling infectious diseases

From the above analysis, we conclude that TA2R10 may be very important to control infectious diseases caused by bacteria, viruses, and parasites. Therefore, TAS2R10 agonists are potential candidates for battling infectious diseases. We reviewed the available references related to TAS2R10 and other TAS2R members to identify clinical drugs that activate bitter taste receptors. We also analyzed the clinical applications of these drugs in DRUGBANK. We found many drugs that can activate TAS2Rs. Interestingly, many drugs can stimulate multiple TAS2Rs. Considering gene expression, these medicines may be powerful for the defense against infectious diseases in clinical applications. The first drug based on the number of responsive TAS2R members is diphenidol, which can stimulate 15 members of the TAS2R family. Clinically, diphenidol is an antiemetic and is commonly used to treat motion sickness or seasickness.

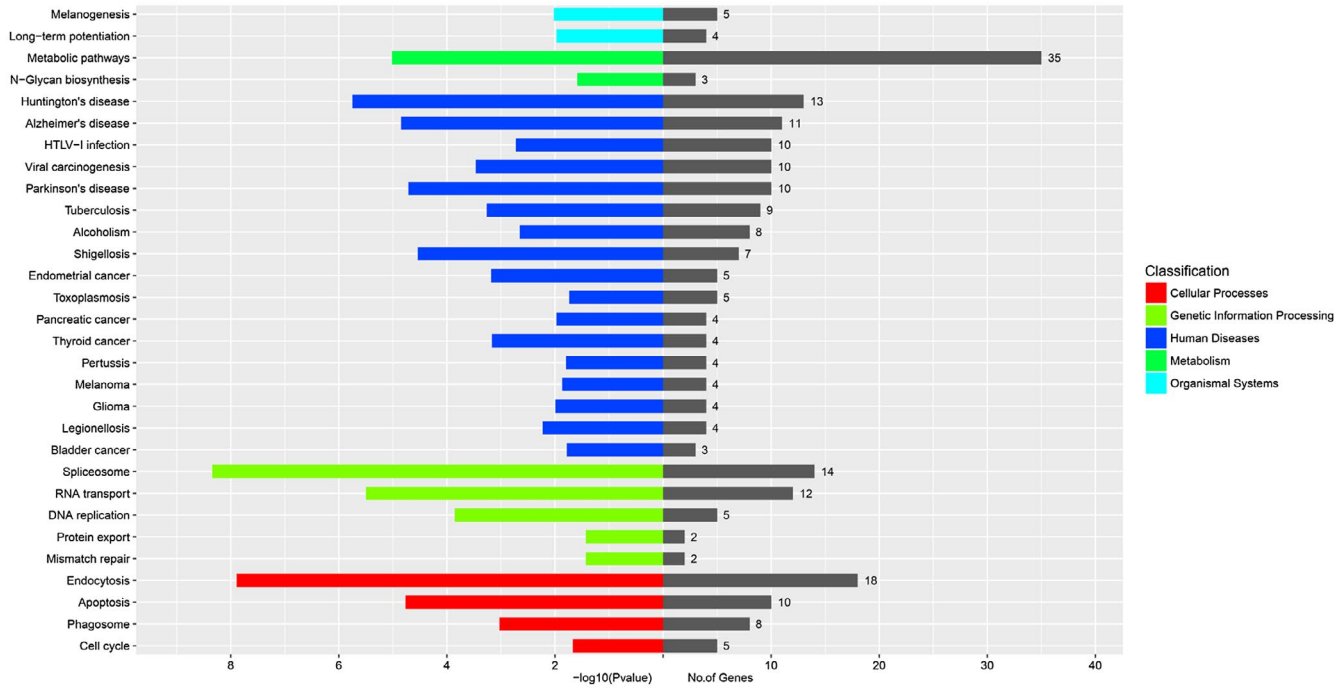

FIGURE 1 The top functional pathways for TAS2R10 determined by the Kyoto encyclopedia of genes and genomes analysis (KEGG) analysis indicated by classification. Enrichment analysis of genes negatively co-expressed with TAS2R10 was performed based on 60 000 Affymetrix expression arrays and 5000 datasets from the cancer genome atlas (TCGA). TAS2R10 was shown to play a role in the prevention of several human diseases. TAS2R10, type 2 taste receptor 10

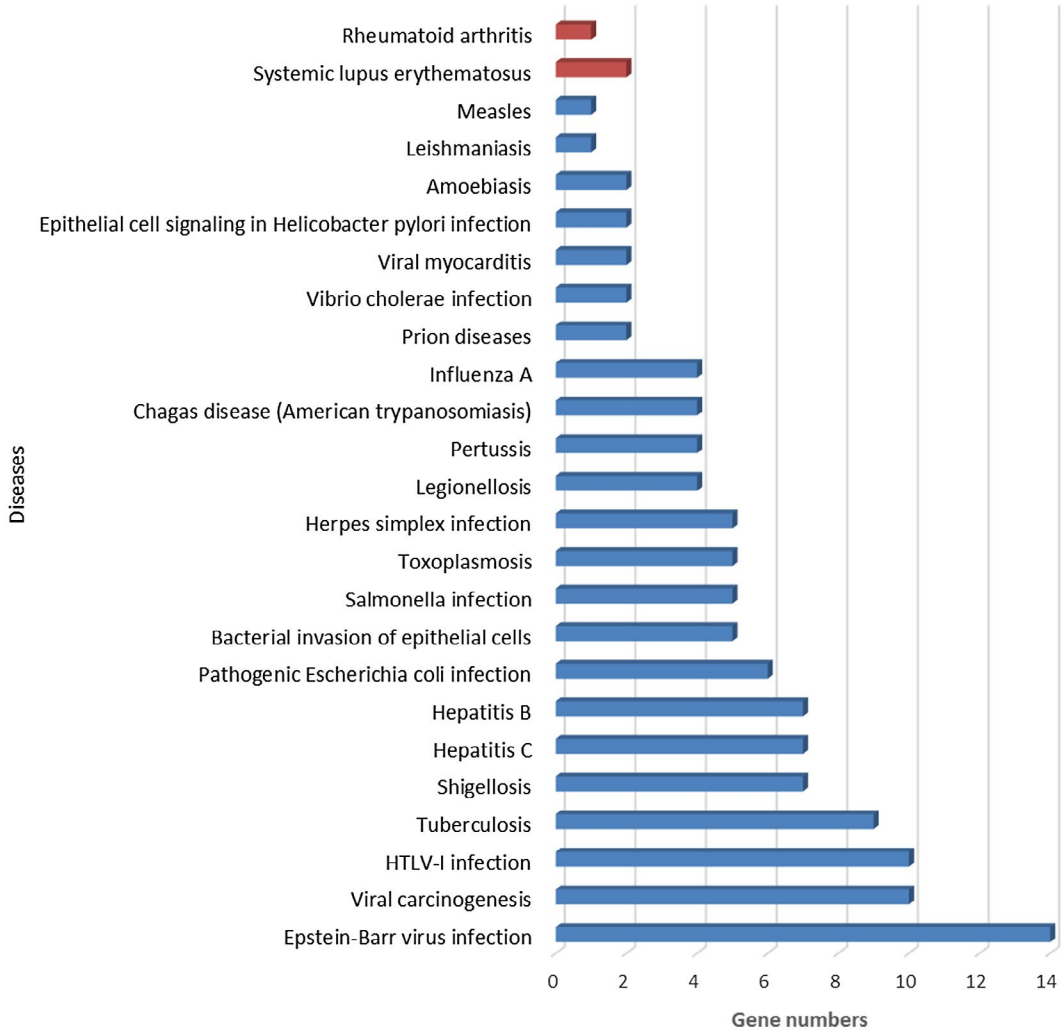

FIGURE 2 Other infectious diseases regulated by TAS2R10 determined by KEGG analysis. Enrichment analysis of genes negatively co-expressed with TAS2R10 was performed based on 60 000 Affymetrix expression arrays and 5000 TCGA datasets

The second is quinine, which stimulates nine TAS2R members and is used for the treatment of malaria. The third and fourth drugs are chlorpheniramine and denatonium benzoate. Chlorpheniramine is an antihistamine used to relieve allergy symptoms, and denatonium benzoate is used as an antifeedant. Next is chloramphenicol (antibiotic), azathioprine (immunosuppressive medication), papaverine (antispasmodic), caffeine for resistance to anesthesia, yohimbine (a popular health supplement for men), chloroquine used to treat malaria, dapsone (antibacterial agent), dextromethorphan (antitussive), haloperidol (antipsychotic), famotidine (gastric acid inhibitor), and erythromycin (antibiotic) (Table 1). There were also some drugs whose receptor is only TAS2R14 or TAS2R46.

4 | DISCUSSION

The current outbreak of COVID-19 caused by 2019-nCoV has led to more than seven thousand deaths.[1] Cheap, available, safe, and effective medicines for fighting 2019-nCoV are urgently needed. HDT was suggested to help fight 2019-nCoV infections.[10] The TAS2R family is an important player in host defense mechanisms.[16] Here, we conducted a big data analysis of more than 60 000 data sets for TAS2R10, which can be activated by one-third of the bitter substances tested so far.[20] Exciting results were obtained by negative gene co-expression analysis. Specifically, we found TAS2R10 is mainly involved in controlling several infectious diseases caused by bacteria, viruses, and parasites, in addition to various cancers (Figures 1 and 2). This suggests that TAS2R10 may be a key trigger of host defense pathways. Previous observations showing its anticancer activities and regulation of smooth muscle relaxation are consistent with our results.[21,22] Other studies showed that TAS2Rs can activate the robust calcium-dependent secretion of antimicrobial peptides (AMPs), including β-defensin 1 and 2, from epithelial cells in the respiratory tract.[9,27,28] Furthermore, the secretion of AMPs stimulated by TAS2Rs occurred very quickly (~5 minutes), but enhanced AMP production was observed over hours in

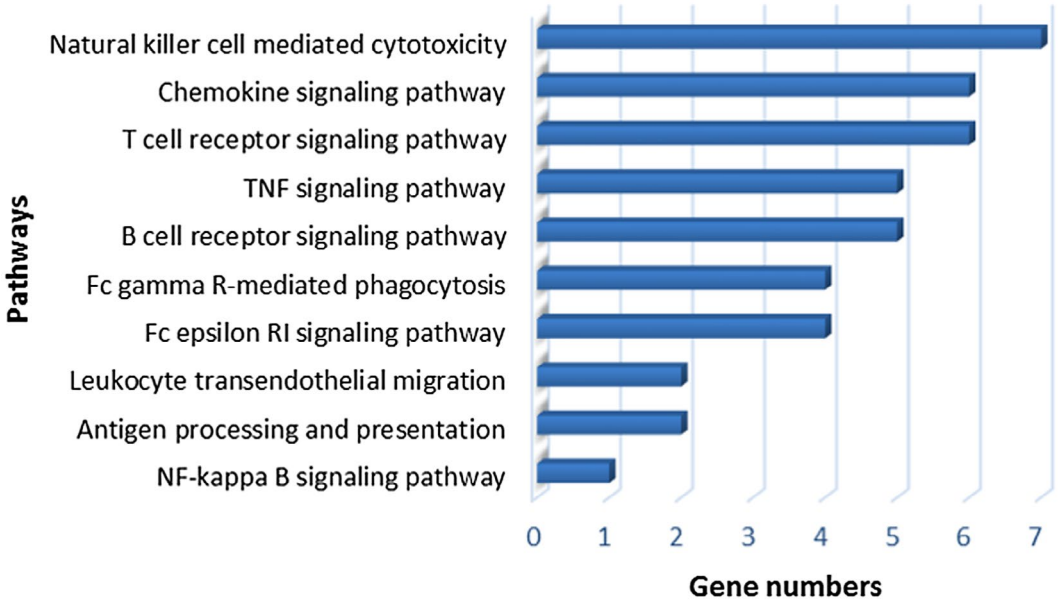

FIGURE 3 Pathways related to cytokine storms regulated by TAS2R10 determined by KEGG analysis. Enrichment analysis of genes negatively co-expressed with TAS2R10 was performed based on 60 000 Affymetrix expression arrays and 5000 TCGA datasets. TAS2R10 was showed to control cytokine storms by regulating several pathways

response to Toll-like receptor (TLR) stimulation.[27] TAS2Rs can also upregulate the expression of AMPs to ameliorate periodontitis.[29] TAS2R38 was stimulated by acyl-homoserine lactones and gram-negative quorum-sensing molecules to subsequently activate nitric oxide-dependent innate immune responses.[17] Tuft cells, a type of gut epithelial cell, can detect helminth, stimulating TAS2R to trigger type 2 immune responses.[18] Moreover, some required genes for bitter-sensing, such as α-gustducin and Trpm5, are also critical to initiate a type 2 immune response.[30,31] Human lymphocytes also directly express TAS2R.[32] These reports are consistent with our results. Together, these findings suggest that TAS2Rs may robustly regulate human innate immunity and trigger host defenses to control the infection.[16] Very recently, WHO scientists reviewed currently available information about COVID-19 and concluded that 2019-nCoV replicates efficiently in the upper respiratory tract, similar to conventional human coronaviruses that are a major cause of common colds during the winter season. As such, the upper respiratory tract is the most important door to be closed for fighting against this deadly disease. AMPs can block the interaction between a virus and its receptor.[33] Therefore, we believe that using drugs to activate bitter receptors is an effective method to prevent the deadly virus from efficiently replicating in the upper respiratory tract.

When we searched for clinical medicines that acted as TAS2R agonists,[20,23,24] we found many bitter drugs, which have been proven to treat different diseases in clinical applications retrieved from DRUGBANK (Table 1). Unexpectedly, the first drug listed by the number of responsive TAS2R members is diphenidol, which is an antiemetic agent primarily used in patients with meniere disease and labyrinthopathies to treat vomiting and vertigo.[34] It is considered to be a relatively safe drug for controlling gastrointestinal discomfort, such as motion sickness or seasickness. However, an overdose may result in serious toxicity in children.[35] The second drug quinine is commonly used to treat malaria. Quinine is also a mild antipyretic and analgesic that is still useful for the treatment of babesiosis and some muscular disorders.[36] The third is chlorpheniramine, a histamine H1-receptor antagonist commonly used to relieve symptoms associated with allergic reactions, hay fever, rhinitis, urticaria, and asthma.[37] Next is chloramphenicol, an antibiotic used in the treatment of cholera and in eye drops or ointment to treat bacterial conjunctivitis.[36] Although it is linked to some adverse events,[38] azathioprine is used to treat inflammatory conditions, such as rheumatoid arthritis, and as an immunosuppressant in renal transplants. Papaverine is a safe direct-acting smooth muscle relaxant used in the treatment of impotence and as a vasodilator, especially for cerebral vasodilation.[39] Caffeine is beneficial in preventing and treating apnea and bronchopulmonary dysplasia in newborns.[40] Interestingly, yohimbine is a health product for men and is alleged to be used as an aphrodisiac and to bulk muscle.[41] Chloroquine is an antimalarial agent and is used to treat rheumatoid arthritis, systemic lupus erythematosus, and amebic liver abscesses.[42] Camphor is used topically as a skin antipruritic and an anti-infective agent but can lead to severe poisoning in children.[43] Dapsone is mainly used against mycobacterium leprae and to treat malaria.[44] Dextromethorphan is widely used as an antitussive, and more recently, for neurological and psychiatric disorders.[45]

TABLE 1 Human TAS2R10, TAS2R14, and TAS2R46 responsive drugs

Bitter drug	Main clinical action	Responsive TAS2R member
Diphenidol	Antiemetic (In, Wi)	1,4,7,10,13,14,16,38,39,40,43,44,46,47,49
Quinine	Antimalarial; antipyretic; analgesic	4,7,10,14,39,40,43,44,46
Chlorpheniramine	Anti-allergy	4,7,10,14,38,39,40,46
Denatonium benzoate	Anti-feedant (No)	4,8,10,13,39,43,46,47
Parthenolide	Anti-allergic contact dermatitis (In)	1,4,8,10,14,44,46
Arborescin		1,4,10,14,43,46
Chloramphenicol	Antibiotic (Ve)	1,8,10,39,43,46
Cascarillin		1,10,14,46,47
Picrotoxinin	Experimental	1,10,14,46,47
Quassin		4,10,14,46,47
Azathioprine	Immunosuppressive	4,10,14,39,46
Artemorin		4,10,14,46,47
Papaverine	Antispasmodic (In)	7,10,14,31,46
Caffeine	Anit-apnea for newborn	7,10,14,43,46
Yohimbine	Anti-impotence (In, Ve)	1,4,10,38,46
Chloroquine	Antimalarial;anti-autoimmune (In, Ve)	3,7,10,39
Camphor	Antipruritic and anti-infective	4,10,14,47
Dapsone	Anti-leprosy (In)	4,10,40
Strychnine		7,10,46
Dextromethorphan	Antitussive	1,10
Haloperidol	Antipsychotic	10,14
Brucine		10,46
Coumarin	Experimental	10,14
Cucurbitacin B		10,14
Thujon, (-)-a-		10,14
Benzoin	Experimental (proved)	10,14
Famotidine	Gastric acid Inhibitor	10,44
Cucurbitacin E		10
Cycloheximide		10
Erythromycin	Antibiotic	10
Diphenylthiourea		1,14,38
Colchicine	Anti-gout	4,39,46
Sodium benzoate	Food preservative (In)	14,16
Diphenhydramine	Antihistamine (In)	14,40
Carisoprodol	Muscle relaxant	14,46
Noscapine	Antitussive (In)	14
Benzamide		14
Chlorhexidine	Antiseptic (Ve)	14
Divinylsulfoxid		14
Flufenamic acid	Anti-inflamatory	14
4-Hydroxyanisol		14
Hydrocortisone	Glucocorticoid (Ve)	46
Orphenadrine	Antispasmodic	46

(Continues)

TABLE 1 (Continued)

Bitter drug	Main clinical action	Responsive TAS2R member
Tatridin B		46
Artemisinin	Antimalarial (In)	46

Note: All are proven, except no indications of action and special notes. Drugs were retrieved in DRUGBANK. The main references for responsive TAS2R members were as the materials and methods. (1) Wi indicates withdrawn. Diphenidol is an antiemetic agent, but an overdose may cause serious toxicity in children. (2) In means investigational. Parthenolide has been used in clinical trials studying the diagnosis of allergic contact dermatitis, but its efficacy has not been proven in clinical application. Benzoic acid is a fungistatic compound that is widely used as a food preservative and may be beneficial as an add-on therapy in schizophrenia. Diphenhydramine is used extensively for the treatment of seasonal allergies, insect bites and stings, and rashes, and it also has antiemetic, antitussive, hypnotic, and antiparkinson properties. (3) No indicates not proven. Denatonium benzoate is used as an antifeedant, so it may be unaccommodated for swallowing. It is also not proven as a drug in DRUGBANK and has potentially important health risks. (4) Ve indicates vet proved. Chlorhexidine is a broad-spectrum antimicrobial biguanide used as a topical antiseptic and in dental practice for the treatment of inflammatory dental conditions caused by microorganisms. Hydrocortisone, a glucocorticoid secreted by the adrenal cortex, is used to treat immune, inflammatory, and neoplastic conditions. (5) Benzoin is an FDA-approved color additive used for marking fruits and vegetables. (6) Colchicine has been approved for managing exacerbations of Familial Mediterranean Fever (FMF), a hereditary autoinflammatory condition. (7) Yohimbine has been used as a mydriatic and in the treatment of impotence. It is also alleged to be an aphrodisiac. (8) Artemisinin is also a bitter substance. It is especially interesting that artemisinins possessed robust inhibitory effects against viruses, protozoa, helminths, and fungi, and it could inhibit infections, cancer, and inflammation.

These clinical applications registered in DRUGBANK are consistent with our suggested functions of TAS2Rs in controlling various infectious diseases.

A cytokine storm is a nonspecific inflammatory response caused by the excessive secretion of more than 150 cytokines and chemical mediators by immune or nonimmune defense cells, characterized by rapidly proliferating and highly activated T cells, macrophages, and natural killer cells.[46] It is a last resort mechanism of our immune system. A cytokine storm is also a key event causing death in patients infected with coronavirus.[2,47] Thus, inhibiting overactive immune responses is very important for preventing cytokine storms.[48] Indeed, we found that TAS2R10 may help prevent a cytokine storm because it can regulate natural killer cell-mediated cytotoxicity, chemokine signaling pathways, T cell receptor signaling pathways, TNF signaling pathways, and others (Figure 3). A recent report confirmed our results that TAS2R members 3, 4, 5, 9, 10, 14, 30, 39, and 40 were involved in the inhibition of cytokine production, such as TNF-α, CCL3, and CXCL8, in human lung macrophages.[49] It reported that quinine, denatonium, dapsone, colchicine, strychnine, chloroquine, erythromycin phenanthroline, ofloxacin, and carisoprodol worked in this inhibition. In contrast, diphenidol did not, which indicates that it may work in other organs. It is reported that diphenidol, diphenhydramine, and caffeine might accumulate in reproductive organs,[50] and diphenidol has been shown to block voltage-gated Na (+) channels, which are associated with specific types of pain by inhibiting the expression of tumor necrosis factor alpha (TNF-α).[51] Chlorpheniramine is used for the relief of cough and upper respiratory symptoms associated with allergies or colds in adults, and it can also inhibit TNF production.[52] Yohimbine, as a selective α-adrenergic antagonist, can ameliorate lipopolysaccharide-induced acute kidney injury in rats and also inhibit cytokine production.[53] Artemisinin is widely used as an antimalarial medication and is also a bitter substance that can reduce the production of proinflammatory cytokines.[54,55] Notably, artemisinins possessed robust inhibitory effects against viruses, protozoa, helminths, and fungi and are suggested to inhibit infections, cancer, and inflammation for its established safety record in millions of malarial patients.[54,56] In short, bitter drugs are good candidates for preventing cytokine storms.

According to the abovementioned results, TAS2Rs and their agonists may not only stimulate host defenses, but may also prevent overactive immune responses. This new HDT may be a viable option for fighting COVID-19-associated infectious diseases. Based on this, we provide the following advice for fighting against COVID-19.

1. For the general public: our results indicated that bitter medicines may be helpful not only to fight against 2019-nCoV, but also for the treatment of the other infectious diseases. It is better to be safe than sorry. To strengthen body resistance and reduce our chances of infection, we suggest drinking coffee, tea, kuding tea made of the broadleaf holly leaf, or tea made of lotus seeds. We also suggest eating bitter vegetables and foods, such as bitter gourds, dandelions, and chocolate, to reduce the risk of infection.[57,58]
2. For mild symptom patients and suspected cases: as an insurance policy, they should be given bitter anti-infective drugs. Infusion with bitter amino acids, such as L-valine, L-phenylalanine, L-tyrosine, may also help to strengthen body resistance.[24,59]
3. For severe symptoms patients: bitter drugs can prevent a cytokine storm, and as such, these bitter drugs may be important for the effective treatment of severe patients. They should not only be prescribed conventional anti-infective drugs, but also given bitter drugs. The most common presenting symptoms caused by 2019-nCoV

are dyspnea, fever, cough, and fatigue.[2] Based on these clinical systemic symptoms, a cocktail-like recipe of our identified drugs may be helpful for these patients. Using a mixture may also reduce the unwanted side effects by using a lower clinical dose of each drug. For example, diphenidol is used for gastrointestinal discomfort; quinine, chloroquine, or artemisinin for helping kill microorganisms; chlorpheniramine for suppressing immune reactions; yohimbine for improving muscular strength; dextromethorphan for preventing coughs (Table 1). Caffeine may be a good option for babies infected by 2019-nCoV. Notably, a very recent report suggested that chloroquine, one of our suggested drugs, might kill 2019-nCoV at the cellular level.[60] Significantly, this result supports the findings of our investigation. Of course, personalized medical management should be performed by first-line doctors.

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AUTHOR CONTRIBUTIONS

C. Zhang, L. Liu, and M. Gu. collected data and analyzed the drugs. X. Li conceived the study. X. Li and C. Zhang wrote the manuscript with the help of all authors.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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