Review paper

Bitter evolution to diet and health

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Abstract
Our ability to taste is primarily mediated by taste receptors that reside in our tongues. Throughout human evolution, the gene that encodes for the bitter taste receptor, TAS2R, has undergone significant diversification and expansion. This may have arisen due to the importance of detecting and avoiding potentially harmful or toxic substances. TAS2R38, a receptor responsible for the detection of an artificial bitter compound, phenylthiocarbamide (PTC), has two common variants caused by single-nucleotide polymorphisms (SNPs): proline-alanine-valine (PAV) and alanine-valine-isoleucine (AVI). Intriguingly, this variation in TAS2R38 has been shown to potentially shape both individual and population food preferences, agricultural farming, and health-associated behaviors. Tasters, who are sensitive to bitterness, have been shown to be less likely to consume vegetables, compared to non-tasters, which engender links to obesity. Bitter sensation also influenced cultivation of certain crops, such as potatoes, by distinct populations like the Andean farmers. Remarkably, alcohol consumption and smoking behaviors, both of which have bitterness associated, have been shown to be less adopted by tasters who are more sensitive to bitter compounds. Despite the name, the bitter taste receptor, TAS2R, is expressed not only on the tongue but also throughout the body; the TAS2R38 variations (PAV and AVI) have been suggested to be involved in a variety of cellular processes, such as the regulation of carcinogenesis, the ability of cells to resist bacterial infections and immune resistance to the SARS-CoV2 virus. This essay will discuss how bitter sensing mechanisms mediated by TAS2Rs influenced our diet and health throughout human evolution and history.

Keywords
Taste receptors, TAS2R, TAS2R38, PAV, AVI, Bitterness, Bitter taste, Bitter taste receptor, Phenylthiocarbamide, Tasters

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Introduction

Human taste sensation has been shaped through evolution and changes in the dietary repertoire (1). Of note, one might imagine how bitter sensation, in particular, would have been critical for survival and health by allowing one to avoid potentially lethal or toxic compounds. Human detection of bitterness is mediated by a family of type 2 taste receptors (TAS2Rs), which have undergone remarkable evolutionary expansion and diversification through many different single nucleotide polymorphisms (SNPs). Individual and population differences in TAS2Rs may explain personal and population food preferences and diet; and therefore the metabolic diseases associated with differential consumption of food categories. Furthermore, TAS2Rs are also associated with the immune system and susceptibility to pathogens.

Discussion

Taste receptors are G-protein-coupled receptors (GPCRs) (2). Compared to the ligand-gated ion channels, GPCRs significantly amplify the signal by engaging second messenger signal cascades. Taste associated GPCRs are so far recognized as TAS1R and TAS2R (3). While umami and sweet tastes have been shown to be perceived uniquely through TAS1Rs, bitterness is mainly transduced by receptors of the TAS2R family (3). Bitter tastants, such as alkaloids that are commonly found in plants, bind to TAS2Rs to elicit the taste of bitterness (4).

When stimulated by compatible compounds, TAS2Rs trigger a transduction cascade composed of two parallel pathways (5). The first operates through the activation of phospholipase C β2 (PLCB2) by the β and γ subunits of TAS2Rs' cognate G protein. In the second modulatory pathway, phosphodiesterase 1A (PDE1A) is activated by the G protein's α subunit, α-gustducin. Subsequent downstream ATP release is facilitated by activation of a calcium homeostasis modulator channel, CALHM1/3. Together these pathways depolarize the receptor cell, producing a signal that is conveyed to the central nervous system (6).

Humans have a total of 25 functional TAS2R genes, in addition to 11 TAS2R pseudogenes, which are nonfunctional segments of DNA that resemble genes (7). Such expansion of pseudogenes, and subsequent evolutionary lineage-specific loss of function, suggests a potential diversification of the bitter receptors in humans throughout evolution (7). Indeed, when compared to other human genes, the TAS2R family shows exceptionally high levels of genetic variation (8). Of the different TAS2R variants, TAS2R38 is responsible for detecting phenylthiocarbamide (PTC) and is the most well-studied (8). PTC is commonly used to identify tasters (those who find the compound bitter), as contrasted with non-tasters. This phenotypic difference in the ability to perceive PTC as bitter resides in the SNPs in the gene encoding for TAS2R38 that ultimately change the amino acid sequences of the

functional receptor (9). The two most common variants of TAS2R38 are proline-alanine-valine (PAV), which are carried by tasters, and alanine-valine-isoleucine (AVI), which are carried by non-tasters. Additional rare variants include the AAV and AAI; however, PAV and AVI are most commonly found in humans (10). Collectively, the genetic variations in the bitter taste receptors, TAS2Rs, that greatly expanded with human evolution raise the question as to how they might be involved in shaping our diet and health.

Senses such as smell and taste have a significant effect on the diet as they allow one to interpret the chemical properties of foods as being palatable as well as their underlying nutritional value (2). Although a clear correlation between bitterness and toxicity has yet not been established, the ability to taste bitter compounds may have been an evolutionary selective advantage as it would have allowed avoidance of ingesting potentially harmful food that could be spoiled or toxic (11). In addition to the evolutionary advantage, the extensive variations of the TAS1R and TAS2R may be associated with a wide range of food preferences across different regions and ethnic groups. In fact, there are 19 amino acid variations of the TAS2R38 gene alone, that have been recorded globally across diverse populations (8). It has been hypothesized that different ethnic groups may have evolved to acquire different variations due to diet-related selective pressures (3). Interestingly, an analysis of patterns of variations of the TAS2R pseudogenes, in contrast to the functional genes, in both African and non-African populations revealed a similar worldwide distribution of allelic variation, except for the TAS2R6P and TAS2R18 loci, both of which presented with an unexpected higher frequency outside of Africa (7).

Variations of the bitter-tasting receptor, TAS2R38, have been shown to partially explain differences in immediate food preferences at the individual and population levels. The tasters (associated with the PAV haplotype) were shown to significantly avoid bitter-tasting fruits and vegetables, being more sensitive to their bitter taste (12). A study of the Finnish population concluded that TAS2R38 taste receptor variation was associated with the consumption of vegetables and sweet food among adults. Females who were tasters (with homozygous PAV variation) consumed fewer vegetables than did the non-tasters with homozygous AVI variation (13). Another study by Choi et. al. found that a particular variation in TAS2R38; *viz.* rs10246939; was associated with the differences in the dietary intake and risk of obesity in a Korean population and suggested that the genetic variation in the bitterness receptor may have a significant effect in the prevention and treatment of obesity (14). At the population level, human diets have been significantly influenced by crops domesticated in the last 10,000 years (15). Although most crops, such as rice, corn, and wheat, originated from non-toxic species, some crops, such as

potatoes, are derived from the wild varieties that produce alkaloids, which elicit bitter tastes that render them inedible. One of the most significant examples of how bitterness relates to agriculture and diet is the cultivation of cassava (*Manihot esculenta*) throughout the tropics since the degree of bitterness of cassava directly predicts toxicity (15). Only the experienced growers of the crop are able to assess the toxicity based on taste, to select which strain to grow and minimize the downstream efforts to eliminate toxicity, ensuring that the produce is safe to eat. In addition to cassava, the traditional cultivation of potato (*Solanum tuberosum*) in Andean populations also showed that bitter taste played a critical role in agricultural farming and diet (15). Taste receptors could hence influence crop selection; which in turn could modulate metabolic diseases such as obesity. Obese populations were reported to present with gut microbiota dysbiosis due to abnormal AVI expression and sensitivity of TAS2R in the Paneth and goblet cells of the gut epithelium. The same study found that bitter compounds affected food intake and triglyceride metabolism by regulating the expression of GDF15, ADM2, with TAS2R activity.

A fascinating and tantalizing hypothesis of reducing the incidences of obesity emerges from these observations. It may be that differential organ expression of AVI and PAV; the two different variants of the TAS2R38 gene; in the oral mucosa/tongue and the Paneth/goblet cells of the gut epithelium respectively could simultaneously gravitate obese populations to consume a vegetarian diet and decrease their gut microbiota dysbiosis. Such an approach has not yet been presented in the public domain and may be worthwhile of therapeutic pursuit.

In addition to being a safety measure against ingesting toxic food, the presence of bitter receptors may have significantly influenced important lifestyle choices such as smoking and the consumption of alcohol. Multiple studies have reported potential associations between individual variations in the bitter responses and traits, including smoking habits and susceptibility to different disorders (8). Tobacco smoke contains a complex mixture of chemical substances of varying structure and functionality, some of which activate bitter taste receptors. Accordingly, it has been suggested that non-taster individuals with the AVI variant of TAS2R38 may be more likely to smoke because of their inability to taste bitter compounds present in tobacco smoke (7); the conclusive effect of the TAS2R38 variant on smoking behavior has yet to be determined. Risso *et al.* also found that TAS2R38 haplotypes are associated with smoking status in European-Americans but not necessarily in African-American populations and suggested that TAS2R38 variation may play a role in protecting individuals from cigarette smoking in specific populations (7). Another study found that the functional protein expression of TAS2R on the tongue was significantly lower among smokers than non-smokers, which

suggested that the presence of the bitter receptor may determine individual smoking behavior (16). TAS2R38 haplotypes have also been implicated in alcohol consumption behavior. It has been reported that AVI homozygotes, who are considered less sensitive to bitterness, consume more alcohol than heterozygotes and PAV homozygotes (17). In a cross-sectional study among the Mexican-Mestizo population, the frequency of AVV homozygotes, who do not respond to the bitter taste compound, PTC (non-taster), was significantly higher in the drinkers than the nondrinkers group. The study also found that AVV homozygosity led to an increase in alcohol intake when compared with heterozygotes and PAI homozygotes, who strongly responded to the bitter compounds (taster) (17). Collectively, variations in TAS2R38 may be involved in diverse health-related behaviors, such as smoking and alcohol consumption. However, further research is required to elucidate a clear link between different TAS2R38 haplotypes and behavior and whether different ethnicity and culture also contribute to the difference and variations.

Ironically, the bitter "taste" receptor, TAS2R, is not uniquely expressed on the tongue but is also found throughout the body, including in the respiratory, immune, and digestive systems. Due to the variety of physiological effects of TAS2R, there is growing interest in understanding the precise biochemical mechanisms that link TAS2R and disease. In addition, in some instances, the bitter receptors are being recognized as potential targets for disease intervention. Recent studies using mouse models reported that inflammation resulted in bitter taste over sensitization due to epigenetic changes in TAS2R gene clusters (18). This study found that the majority of TAS2R subtypes were overly expressed in bacterial infection LPS induced inflammation. The modulatory relationship between inflammation and TAS2R suggested broader relationships with other diseases. Currently, it is thought that TAS2R bitter receptors can regulate thyroid function (19). TAS2Rs negatively regulate thyroid-stimulating hormone (TSH)-dependent Ca2+ increases and TSH-dependent iodide efflux in thyrocytes. Immunohistochemical Tas2r-dependent reporter expression and real-time PCR analyses found that human and mouse thyrocytes and the Nthy-Ori 3-1 human thyrocyte line expressed several TAS2Rs. TAS2R agonists also inhibited basal and TSH-dependent iodide efflux. Therefore, TAS2Rs could serve as new druggable targets for therapeutic treatment of hypo- or hyperthyroidism. Tas2R10 and Tas2R14 receptors found in human airway smooth muscle are critical for airway relaxation (20). Therefore, these receptors could be a target for asthma treatments.

Other studies have explored the correlation between longevity and functional variants of the TAS2R38 gene. A study by Melis *et al.* on cohorts from Sardinia, which has the highest percentage of people living to age 100 or above, found that the frequency of bitter tasters

(homozygous for PAV) was higher than those of non-tasters in the centenarian cohort and suggested that there may be an association between genetic variants of TAS2R38 gene (PAV and AVI) and human longevity (21). It is possible that the TAS2R38 bitter receptor is involved in the molecular mechanisms underlying the biological process of aging. It is also possible that this result was due to the differences in food preferences and health-related behaviors, as previously discussed. Indeed, one of the widely accepted hypotheses is that the non-tasters (AVI) show a reduced ability to perceive dietary fat, which can lead to an over consumption of high-fat foods (22).

Another study investigated how TAS2R may be involved in regulating the mucosal innate defense of the upper respiratory tract. Polymorphisms of the TAS2R38 gene were associated with significant differences in the ability of upper respiratory cells to clear and kill bacteria during infection (23). With regards to the recent COVID-19 pandemic, Barham *et al.* found that tasters (associated with PAV haplotype for TAS2R38) had an increased innate immune protection against the SARS-CoV-2 virus (24). Individuals with the AVI genotype (non-tasters) were more likely to not only test positive for COVID-19 but also be hospitalized and be symptomatic for a longer duration whereas bitter tasters were more resilient to the SARS-CoV-2 infection, suggesting that TAS2R, which is also expressed in the respiratory system, may be associated with the ability to resist viral infections (24). Increased susceptibility to chronic rhinosinusitis has also been associated with a non-functional (AVI/AVI) diplotype (25).

Pharmacologically, variations in TAS2Rs pose interesting questions, such as whether the effectiveness of medications depends on their bitter taste and activation of the bitter receptor, TAS2R (26). If so, the efficacy of certain drugs may differ for individual patients with different TAS2R polymorphisms. Medicines given to pediatric patients are often formulated to mask their bitter taste. This means that taste receptors in these patients; which may modulate drug efficacy; can no longer be engaged. Therefore, it may be prudent to include TAS2R screening as part of the drug development process. For example, the medication for allergic rhinitis, Azeflu®, is known to partially activate the bitter receptors TAS2Rs (27). Table 1 presents select direct and indirect effects of bitter receptors.

Table 1. Direct and Indirect effects of bitter receptors.

Pathway	Description	References
Direct		
Activation of (CALHM1) channels.	The production of IP3 and the resulting increase of $Ca2^{+}$ are associated with an increase of Na^{+} ions. The Na^{+} travels through the cation channel TRPM5. TRPM5 is the mechanism responsible for transduction of taste signals. Furthermore, cells respond to the sodium signal *via* depolarization and extracellular efflux of adenosine-5'-triphosphate (ATP), through calcium homeostasis modulator 1 (CALHM1) ion channels.	26, 28
Relaxation of airway smooth muscle	When TAS2R is activated, Gnats are dissociated from the Gβγ/Gnat complex. The released Gβγ activates phospholipase β to produce inositol 1,4,5-triphosphate (IP3). The deletion of Gnats significantly inhibited TAS2R mediated relaxation, showing their necessity for smooth muscle relaxation caused by TAS2R. Ip3 mediates the release of Ca2+ from the endoplasmic reticulum. An increase in calcium level is required for smooth muscle relaxation. Activation of TAS2R can regulate ASM (airway smooth) cell proliferation. The TAS2r exerts inhibitory action on cell cycle progression by inhibiting ERK MAP kinase activity.	20, 29, 30
Mitochondrial function	TAS2R agonists decreased the length of the mitochondria and induced mitochondrial fragmentation in airway smooth muscle cells.	15, 29
Indirect		
Longevity	TAS2R38 has multiple implications on a person's habit, including food preference, diet and nutrition, and alcoholism. These behaviors can affect human development and subsequently longevity.	21
Heart conditions	TAS2R signalling defects are involved with the pathophysiology of heart diseases. Due to the importance of TAS2R signaling in cardiac inflammation, oxidative stress, contractile dysfunction, and arrhythmia, defects in TAS2R signaling can very well result in heart diseases.	26, 31
Obesity	Extra-oral TAS2R expression could be reduced in obese subjects compared to non-obese individuals. Expression and sensitivity of TAS2Rs in other cell types are affected by obesity, particularly through the gut biome. Other studies have found that polymorphisms in TAS2R38 genes did not differ among obese and lean subjects, but there was a significant increase in TAS2R38 mRNA levels in stomach of obese subjects compared to lean subjects, signaling the connection between TAS2R38 and obesity.	32

Conclusion

Taken together, evidence from the literature indicates that the bitter taste receptor does not only function in tasting bitter compounds and affecting food preferences and habits, but also potentially regulates different biological processes throughout the body. These biological processes affect resistance to virus and bacteria, respiratory airway relaxation, gut microbiome dysbiosis, thyroid function and longevity. Early in the COVID-19 pandemic, chloroquine, which is widely used to treat malaria, emerged as a potential viricidal (27). Interestingly, chloroquine induces an intense bitter sensation and is used to activate the bitter receptor, TAS2R (26). Given the diverse expression and function of TAS2R, it is tempting to speculate that some of the early evidence of the therapeutic efficacy of chloroquine against COVID-19 was also mediated by TAS2R signaling in the upper airway.

It is remarkable how the molecular detector of bitterness can influence not only as trivial as the individual preference for certain vegetables but also agricultural farming and human health through history and evolution. Further investigations into how the extra-oral function of the bitter taste receptor and genetic variations confer individual differences in the immune system, cancer, and overall health will shed light upon personalized, precision medicine. Understanding the conditions in which PAV and AVI haplotypes appear is clinically promising.

References

1. Breslin, P. (2013). An evolutionary perspective on food and human taste. Current Biology, 23(9). https://doi.org/10.1016/j.cub.2013.04.010

2. Meunier, N., Briand, L., Jacquin-Piques, A., Brondel, L., & Pénicaud, L. (2021). COVID 19-Induced Smell and Taste Impairments: Putative Impact on Physiology. Frontiers in physiology, 11, 625110. https://doi.org/10.3389/fphys.2020.625110

3. Valente, C., Alvarez, L., Marques, P. I., Gusmão, L., Amorim, A., Seixas, S., & João Prata, M. (2018). Genes from the TAS1R and TAS2R Families of Taste Receptors: Looking for Signatures of Their Adaptive Role in Human Evolution. Genome biology and evolution, 10(4), 1139–1152. https://doi.org/10.1093/gbe/evy071

4. Muñoz, I.J., Schilman, P.E. & Barrozo, R.B. (2020). Impact of alkaloids in food consumption, metabolism and survival in a blood-sucking insect. Sci Rep 10, 9443 https://doi.org/10.1038/s41598-020-65932-y

5. Roper, S. D. (2007). Signal transduction and information processing in mammalian taste buds. Pflügers Archiv - European Journal of Physiology, 454(5), 759–776.

https://doi.org/10.1007/s00424-007-0247-x

6. Ma, Z., Tanis, J. E., Taruno, A., & Foskett, J. K. (2016). Calcium homeostasis modulator (CALHM) ion channels. Pflügers Archiv - European Journal of Physiology, 468(3), 395–403. https://doi.org/10.1007/s00424-015-1757-6

7. Risso, D. S., Mezzavilla, M., Pagani, L., Robino, A., Morini, G., Tofanelli, S., et. al. (2016). Global diversity in the TAS2R38 bitter taste receptor: revisiting a classic evolutionary PROPosal. Scientific reports, 6, 25506. https://doi.org/10.1038/srep25506

8. Behrens, M., Gunn, H. C., Ramos, P. C., Meyerhof, W., & Wooding, S. P. (2013). Genetic, functional, and phenotypic diversity in TAS2R38-mediated bitter taste perception. Chemical senses, 38(6), 475–484. https://doi.org/10.1093/chemse/bjt016

9. Smith, J. L., Estus, S., Lennie, T. A., Moser, D. K., Chung, M. L., & Mudd-Martin, G. (2020). TAS2R38 PAV Haplotype Predicts Vegetable Consumption in Community-Dwelling Caucasian Adults at Risk for Cardiovascular Disease. Biological research for nursing, 22(3), 326–333. https://doi.org/10.1177/1099800420913935

10. Boxer, E. E., & Garneau, N. L. (2015). Rare haplotypes of the gene TAS2R38 confer bitter taste sensitivity in humans. SpringerPlus, 4, 505. https://doi.org/10.1186/s40064-015-1277-z

11. Meyerhof, W., Batram, C., Kuhn, C., Brockhoff, A., Chudoba, E., Bufe, B., Appendino, G., & Behrens, M. (2010). The molecular receptive ranges of human TAS2R bitter taste receptors. Chemical senses, 35(2), 157–170. https://doi.org/10.1093/chemse/bjp092

12. Duffy V. B, Hayes J. E, Davidson A. C, Kidd J. R, Kidd K. K, Bartoshuk L. M. (2010). Vegetable Intake in College-Aged Adults Is Explained by Oral Sensory Phenotypes and TAS2R38 Genotype. Chemosens. Percept., 3 (3-4), 137-148. https://doi.org/10.1007%2Fs12078-010-9079-8

13. Sandell, M., Hoppu, U., Mikkilä, V., Mononen, N., Kähönen, M., Männistö, S., et. al. (2014). Genetic variation in the hTAS2R38 taste receptor and food consumption among Finnish adults. Genes & nutrition, 9(6), 433. https://doi.org/10.1007/s12263-014-0433-3

14. Choi J. H. (2019). Variation in the TAS2R38 Bitterness Receptor Gene Was Associated with Food Consumption and Obesity Risk in Koreans. Nutrients, 11(9), 1973. https://doi.org/10.3390/nu11091973

15. Wooding, S. P., Ramirez, V. A., & Behrens, M. (2021). Bitter taste receptors: Genes, evolution and health. Evolution, Medicine, and Public Health, 9(1), 431–447.

https://doi.org/10.1093/emph/eoab031

16. Aoki, M., Takao, T., Takao, K., Koike, F., Suganuma, N. (2014). Lower expressions of the human bitter taste receptor TAS2R in smokers: reverse transcriptase-polymerase chain reaction analysis. Tobacco Induced Diseases, 12(August), 12. https://doi.org/10.1186/1617-9625-12-12

17. Ramos-Lopez, O., Roman, S., Martinez-Lopez, E., Gonzalez-Aldaco, K., Ojeda-Granados, C., Sepulveda-Villegas, M., & Panduro, A. (2015). Association of a novel TAS2R38 haplotype with alcohol intake among Mexican-Mestizo population. Annals of hepatology, 14(5), 729–734. https://pubmed.ncbi.nlm.nih.gov/26256902

18. Lin, C., Jyotaki, M., Quinlan, J., Feng, S., Zhou, M., Jiang, P., Matsumoto, I., Huang, L., Ninomiya, Y., Margolskee, R. F., Reed, D. R., & Wang, H. (2023). Inflammation induces bitter taste oversensitization via epigenetic changes in Tas2r gene clusters (p. 2023.02.08.527520). bioRxiv. https://doi.org/10.1101/2023.02.08.527520

19. Clark, A. A., Dotson, C. D., Elson, A. E. T., Voigt, A., Boehm, U., Meyerhof, W., Steinle, N. I., & Munger, S. D. (2015). TAS2R bitter taste receptors regulate thyroid function. The FASEB Journal, 29(1), 164–172. https://doi.org/10.1096/fj.14-262246

20. Zhou, Y.-W., Sun, J., Wang, Y., Chen, C.-P., Tao, T., et. al. (2022). Tas2R activation relaxes airway smooth muscle by release of Gα t targeting on AChR signaling. Proceedings of the National Academy of Sciences, 119(26), e2121513119. https://doi.org/10.1073/pnas.2121513119

21. Melis, M., Errigo, A., Crnjar, R., Pes, G. M., & Tomassini Barbarossa, I. (2019). TAS2R38 bitter taste receptor and attainment of exceptional longevity. Scientific Reports, 9(1), Article 1. https://doi.org/10.1038/s41598-019-54604-1

22. Keller K. L, Adise, S. (2016). Thiourea Compounds: Implications for Food Acceptance, Dietary Intake, and Obesity Risk in Children. Ann. Rev. Nutrition, 36, 157-182. https://doi.org/10.1146/annurev-nutr-071715-050916

23. Lee, R. J., Xiong, G., Kofonow, J. M., Chen, B., Lysenko, A., Jiang, P., et. al. (2012). T2R38 taste receptor polymorphisms underlie susceptibility to upper respiratory infection. Journal of Clinical Investigation, 122(11), 4145–4159. https://doi.org/10.1172/jci64240

24. Barham, H. P., Taha, M. A., Broyles, S. T., Stevenson, M. M., Zito, B. A., & Hall, C. A. (2021). Association between bitter taste receptor phenotype and clinical outcomes among patients with COVID-19. JAMA Network Open, 4(5). https://doi.org/10.1001/jamanetworkopen.2021.11410

25. Tran, H. T. T, Stetter, R, Herz, C, Spottel, J, Krell, M, Hanschen, F. S. et. al. (2021). Allyl Isothiocyanate: A TAS2R38 Receptor-Dependent Immune Modulator at the Interface Between Personalized Medicine and Nutrition. Front. Immunol., 12, 669005. https://doi.org/10.3389%2Ffimmu.2021.669005

26. Tuzim, K., & Korolczuk, A. (2021). An update on extra-oral bitter taste receptors. Journal of Translational Medicine, 19(1), 440. https://doi.org/10.1186/s12967-021-03067-y

27. Bouazza, B., Ramdani, I., & Chahed, R. (2021). Chloroquine and covid-19: Role as a bitter taste receptor agonist? New Microbes and New Infections, 40. https://doi.org/10.1016/j.nmni.2021.100843

27. Ekstedt, S., Kumlien Georén, S., & Cardell, L. O. (2020). Effects of MP-AzeFlu enhanced by activation of bitter taste receptor TAS2R. Allergy, Asthma & Clinical Immunology, 16(1), 45. https://doi.org/10.1186/s13223-020-00438-w

28. Pérez, C. A., Huang, L., Rong, M., Kozak, J. A., Preuss, A. K., Zhang, H., Max, M., & Margolskee, R. F. (2002). A transient receptor potential channel expressed in taste receptor cells. Nature Neuroscience, 5(11), 1169–1176. https://doi.org/10.1038/nn952

29. Nayak, A. P., Shah, S. D., Michael, J. V., & Deshpande, D. A. (2019). Bitter Taste Receptors for Asthma Therapeutics. Frontiers in Physiology, 10, 884. https://doi.org/10.3389/fphys.2019.00884

30. Kim, D., Cho, S., Castaño, M. A., Panettieri, R. A., Woo, J. A., & Liggett, S. B. (2019). Biased TAS2R Bronchodilators Inhibit Airway Smooth Muscle Growth by Downregulating Phosphorylated Extracellular Signal–regulated Kinase 1/2. American Journal of Respiratory Cell and Molecular Biology, 60(5), 532–540. https://doi.org/10.1165/rcmb.2018-0189OC

31. Timpson, N. J., Christensen, M., Lawlor, D. A., Gaunt, T. R., Day, I. N., Ebrahim, S., & Smith, G. D. (2005). TAS2R38 (phenylthiocarbamide) haplotypes, coronary heart disease traits, and eating behavior in the British Women's Heart and Health Study2, 3. The American Journal of Clinical Nutrition, 81(5), 1005–1011. https://doi.org/10.1093/ajcn/81.5.1005

32. Chupeerach, C., Tapanee, P., On-Nom, N., Temviriyanukul, P., Chantong, B., Reeder, N., Adegoye, G. A., & Tolar-Peterson, T. (2021). The influence of TAS2R38 bitter taste gene polymorphisms on obesity risk in three racially diverse groups. BioMedicine, 11(3), 43–49. https://doi.org/10.37796/2211-8039.1175