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Exploratory Bioinformatics and Molecular Docking Analysis for Personalized Flavour Profiling in Illness-Associated Dysgeusia

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ABSTRACT

Nutrigenomics examines the interaction between genetic variation, nutrients, and their influence on health and disease. Taste receptors have been investigated in multiple biological contexts, but molecular findings from extraoral tissues cannot be assumed to represent human taste dysfunction. This exploratory study combined differential gene-expression analysis, protein-association networks, pathway analysis, and molecular docking to investigate taste-receptor-related experimental models. Two public datasets were analysed: GSE186509, involving human intestinal crypt cells exposed to bitter agonists, and GSE97677, involving brain tissue from T1R3-knockout and wild-type mice. Network analysis identified highly connected genes associated with broad cellular functions, including ribosomal and mitochondrial processes. Pathway analysis highlighted translation, tRNA aminoacylation, and other cellular processes whose relevance to gustatory dysfunction remains uncertain. An exploratory docking analysis examined ten compounds against TFRC and TAS2R4. Among the compounds evaluated, 5′-GMP and 5′-IMP received the most favourable reported docking scores for both targets; these scores do not establish binding, receptor modulation, or sensory benefit. No individual genetic variants, patient-specific information, or genotype-dependent compound rankings were incorporated into the analysis. The study provides preliminary hypotheses for further investigation, rather than a validated model of illness-associated dysgeusia or personalised flavour profiling. Overall, the study demonstrates the potential of integrating transcriptomic, network, pathway, and structural analyses to investigate taste-related molecular mechanisms. The identified compounds provide testable candidates for future experimental validation and personalised nutrigenomic investigation of remedying taste dysfunction.

INTRODUCTION

Nutrigenomics is the study of the interaction between the genome, nutrients, and their influence on gene expression, health, and disease risk [1]. A vital part of this field is taste receptors. They play a key role in influencing taste modalities (bitter, sweet, umami, sour, and salty). Taste buds, embedded within the papillae tissue of the tongue, form the primary foundation of flavor perception. These taste buds contain groups of cells, in which the expression of various receptor proteins plays a major role in taste perception; for example, the TAS2R family mediates bitter taste perception [2]. One factor that influences flavor

perception is the genetic polymorphisms within taste receptors [3]**.** Situations in which flavor perception is altered, such as during diseases or treatments for the disease, are due to a condition termed dysgeusia. For example, dysgeusia is one of the most prevalent side effects of chemotherapy [4]. In a systematic review, dysgeusia was reported in a wide range, from 14% to 100% of cancer patients [5]. In another study, which was conducted with 4805 head and neck cancer (HNC) patients, the total incidence of dysgeusia was 42.7% [6]. While an alteration to taste may seem innocuous, it poses a detrimental risk to patients' health. Due to a disturbance in taste, patients may avoid meals, resulting in excessive weight loss; or, due to lower sensitivity in their taste buds, they may add superfluous amounts of salt and sugar, causing overweight. Overall, it could incur nutrient deficiencies and an overall reduction in the quality of life of the patient [7].

Several research studies have been carried out in this domain, for which previous literature exists. To begin with, a study by Benish and Choi examined whether the TAS2R38 rs10246939 single nucleotide polymorphism (SNP) affects daily micronutrient intake and bio-clinical markers, like blood pressure, in a Korean adult population. The findings showed that the variant had a significant relationship with micronutrient intake in females only and no significant associations were found between the SNP and any bio-clinical markers in either sex. These findings demonstrate how the TAS2R38 genotype directly influences micronutrient intake and dietary outcome [8]. Building on the relationship between taste receptor genotype, diet, and health, another study investigated the consequences of TAS2R38 genotype on a broad range of phenotypes. The study concluded that TAS2R38 variants have an influence on food preferences, such as saltiness or even some alcohols like red wine. It also showed novel associations between the bitter-sensitive alleles and bipolar disorder, renal function, and the gut microbiome. Thus, this study demonstrates the significance of taste receptor genotype on dietary and health outcomes [9]. Expanding into the link between diseases and taste receptors, one study investigated bitter taste dysfunction in long COVID (LC) patients. It found that gene expression of Type II Taste Receptor Cells (TRC) in LC patients was decreased, showing that it is a contributing factor to bitter taste dysfunction [10]. Further discussing the relationship between taste receptors and diseases, another study explored the link between variations in TAS1R and TAS2R gene expression and cancer prognosis. They found significant connections between the expression of taste receptor genes and cancer prognosis. For example, increased TAS1R1 expression was associated with better survival in lung adenocarcinoma. Overall, the study concluded that there was a notable association between variations in the expression of the taste receptor genes and survival outcomes in 12 different solid tumor subtypes. Thus, demonstrating the potential scope of taste receptor genes in cancer prognosis [11].

Exploring more specifically the effect of diseases on taste receptors, one study investigated the effect of inflammation using lipopolysaccharide (LPS) on bitter taste sensitivity. It was found that LPS upregulated the expression of many TAS2R genes, and that an epigenetic mechanism may link inflammation, taste receptor gene regulation, and varied bitter taste sensitivity, explaining why amplified bitter taste may be experienced during illnesses and cancer treatments [12]. Taste receptors have also shown relevance in the field of drug development and repurposing. One study explored the genetic connection between the taste receptor TAS2R38 and Alzheimer's disease (AD) with the purpose of discovering whether it is relevant

and could aid in developing or repurposing drugs for treatment. It was found that TAS2R38 supertasters are associated with a lower risk of AD with the advancement of age and that MGAM could be a potential novel drug target, further demonstrating the clinical importance of research into taste receptors [13]. Lastly, a study investigated how umami peptides influence taste perception, and is also interconnected with neural, endocrine, and immune pathways. Through the identification of several pathways, the study found that there is a link between umami signalling and satiety, feeding behavior, immune function, and that there is significant crosstalk between umami signalling and the gut-brain axis [14].

While contemporary research in this domain comprises the associations between taste receptor genetic variation, dietary outcomes, and the influences of disease and treatment on taste perception, certain gaps still exist. For example, some studies are still limited by population specificity or small cohorts. To add on, certain studies exploring the effect of illness-induced taste distortion are limited by their exclusion of the impact on genetic variations in the taste receptor genes and personalization to patients. Thus, there is a need for research using bioinformatics to combine genetic variations, receptor expression, and illness-associated molecular pathways, forming a unified model to predict potential candidates that can bring back normal flavor perception. Thus, it was hypothesized that by studying the relationship between genetic variations, taste receptor genes, and diseases, a flavour profiling framework could be developed to tackle altered flavour perception. The present study aimed to explore whether publicly available expression datasets involving taste-receptor-related perturbations could identify cellular processes and candidate molecular interactions for further investigation. An exploratory workflow combining differential gene-expression analysis, protein-association networks, pathway analysis and molecular docking was applied. The selected datasets represented human intestinal crypt cells exposed to bitter agonists and brain tissue from T1R3-knockout mice. Accordingly, the study investigated these experimental contexts rather than clinically characterised human dysgeusia. The working hypothesis was that the analyses could generate testable molecular hypotheses; restoration of taste perception and personalised compound selection were not evaluated.

METHODS

Data collection

Data collection involved searching public repositories: NCBI dbSNP, ENSEMBL, NCBI Gene Expression Omnibus (GEO), BioStudies, BitterDB, RCSB Protein Data Bank (RCSB PDB), PubChem, DISGENET, and KEGG PATHWAY database. Fields of data from the repositories included: genomic and genetic variation data; publicly available experimental and gene expression datasets; structural and molecular information on biomolecules and chemical compounds, respectively; information on associations between genes, genetic variants, and human diseases; information on biological pathways, molecular interactions, and cellular processes. Key databases selected, such as BitterDB, NCBI dbSNP, and NCBI GEO, were scanned for relevant information. The analyses reported in this study used gene-expression data from NCBI GEO, ligand structures from PubChem, and protein structures from RCSB-PDB. STRING, Cytoscape, and Reactome were used for network and pathway analyses. Other

resources, including BitterDB and dbSNP, were consulted during preliminary exploration. However, downloaded variant information was not incorporated into the reported expression analyses, network construction, or docking-based compound rankings. No individual-level genotype, clinical phenotype, or sensory-response data were used to generate personalised predictions.

Differential Gene Expression Analysis

To identify the upregulation or downregulation of certain taste receptor genes, differential gene expression analysis was carried out. Gene expression data were found from NCBI GEO through a search with the keyword "taste receptor". From the 24 results shown, 10 relevant studies were identified, out of which 2 were selected to run analysis on. The GEO2R tool, which allows researchers to compare different groups of samples and observe the differential gene expression in different experimental conditions, was utilised in analyzing the studies. The first study (GSE186509) investigated how, in obese individuals, innate immune responses and metabolic regulators may be modulated by intestinal bitter taste receptors. The study examined the effect of bitter taste receptor agonists Denatonium benzoate and Aloin on the taste receptor TAS2R43, which was also divided into two groups based on the presence of a deletion polymorphism. In the GEO2R analysis, two sets of two groups were made: DMEM (control) and Denatonium benzoate, and DMEM (control) and Aloin. The respective volcano plots were taken, and any significant genes were downloaded. Similarly, this process was carried out for the other study: GSE97677 used T1R3 knockout mice and wild-type mice to investigate the link between sweet taste signalling and neural dysfunction, in which two groups were formed based on genotype - T1R3 knockout (T1R3K0) and WT. Differential-expression analyses were conducted separately for each specified comparison using GEO2R. Statistical significance was defined as a Benjamini–Hochberg-adjusted p-value <0.05. An absolute log2 fold-change threshold of $|2|$ was additionally applied. Positive log2 fold changes indicated higher expression in the treatment or knockout group relative to its corresponding control.

Network and Pathway Analysis

A list of unique genes was compiled from the genes present in the gene expression studies by combining them and removing duplicate genes. Identifiers were standardised within each dataset before integration. Mouse genes were mapped to human orthologues using BiodbNET with actual one-to-one unmapped identifiers. Duplicate entries were resolved using Microsoft Excel. The resulting human identifiers were combined as a union for exploratory network analysis, while dataset provenance and expression direction were retained separately. This integration did not represent a pooled expression analysis or evidence of concordant regulation between the two models. The unique gene list was imported into the multiple proteins tab in the STRING database (version 12.0), and the *Homo sapiens* organism was selected to create a Protein-Protein Interaction (PPI) network. In the network, the nodes represented proteins and edges represented the protein-protein associations. A confidence score threshold of >0.400 was used, corresponding to a medium confidence and indicating that the predicted associations are supported based on integrated evidence. Using the Cytoscape software (version 3.10.4) the interaction data was visualized. The network was mainly analyzed on four factors: degree, betweenness centrality, closeness centrality,

and clustering coefficient. Primary hub genes, which are the highly connected and centrally positioned genes in a biological network, were identified. This was done by ordering the genes in descending order of degree and then selecting the top 10 genes. Pathway analysis was conducted using the Reactome database, into which the complete unique gene list was entered, and a network of pathways was created. The top 25 pathways were identified in ascending order of p-value to identify the key biological pathways that were the most statistically significant and least likely to have occurred by chance. Reactome pathways were ranked by nominal enrichment p-value for exploratory inspection. Nominal ranking alone was not interpreted as evidence of significance after multiple-testing correction. The pathway results should be evaluated alongside their false-discovery-rate values, mapped-gene counts and analysis background. Next, the genes present in the top 25 pathways were cross-referenced with the top 10 genes listed to identify the primary hub genes present in the top 25 pathways.

Molecular Docking

For the molecular docking analysis, two receptors were selected, and ten taste-active and flavour-related compounds were chosen as ligands. Two proteins with different levels of biological relevance were examined. TAS2R4 was included as a bitter taste receptor; however, its selection was not equivalent to validation by the analysed datasets, which involved TAS2R43-related agonist exposure and T1R3 deletion. TFRC was included as an exploratory target because it ranked among the highly connected proteins in the reported network. This topological observation did not establish a role for TFRC in taste perception or dysgeusia, and its docking results were interpreted separately from those for TAS2R4. The proteins Transferrin receptor (TFRC) and Taste receptor type 2 member 4 (TAS2R4) were each docked with 10 taste-active and flavour-related compounds: 6-Gingerol, Propylthiouracil, Citric acid, D-Limonene, Ethyl maltol, Guanine 5′- monophosphate (5'-GMP), Inosine 5′- monophosphate (5'-IMP), L-Glutamic acid, L-Malic acid, and Vanillin. The structures of the ligands were retrieved from the PubChem database. The structures of the receptors were downloaded from the RCSB Protein Data Bank (PDB) and saved in PDB file format. Molecular docking was performed on the Tamarind Bio website utilizing the AutoDock Vina tool, which calculated the binding affinity (kcal/mol) between the receptor proteins and the ligands. The docking box was defined on the basis of its center and dimensions. For TFRC, the docking center was positioned at X = -20, Y = -20, and Z = 150, with a width of 115, height of 100, and depth of 75. For TAS2R4, the docking center was positioned at X = 150, Y = 150, and Z = 170, with a width of 115, height of 175, and depth of 150. A standard exhaustiveness value of 8 was applied to both docking runs. Lastly, the docking results were visualized using PyMOL software to visualize receptor structures and receptor-ligand complexes. No target-specific reference-ligand benchmarking, experimentally resolved ligand redocking or decoy-based evaluation was performed in the present analysis. Therefore, the ability of the protocol to recover experimentally supported binding poses or distinguish active from inactive compounds was not established. Visualisation of a docked pose in PyMOL was not considered validation of binding.

RESULTS

Differential Gene Expression Analysis

In the differential gene expression analysis, three studies were selected and used, from which a list of significant genes was extracted, and respective volcano plots representing the differentially expressed genes for the studies were generated, as shown in Figure 1. Firstly, GSE186509 examined how TAS2R43 agonists, Denatonium benzoate (DB) and Aloin, alter gene expression in human jejunal crypts in obese individuals. The control group consisted of 17 samples of intestinal crypt cells treated with DMEM; 12 of the samples were TAS2R43(+), and 5 samples were TAS2R43(-); 13 samples were from obese individuals and 4 samples were from lean individuals. The test group consisted of 17 samples of intestinal crypt cells treated with 1mM Denatonium Benzoate; 11 samples were TAS2R43(+) and 6 samples were TAS2R43(-); 13 samples were from obese individuals, while 4 samples were from lean individuals. This study provided a direct connection between bitter compounds, taste receptor signalling, metabolism, and gene expression. Secondly, GSE97677 investigated the relationship between sweet-taste perception in the brain and the development of cognitive dysfunction. More specifically, it compared to groups of mice to analyze the role of the type 1 taste receptor member 3 (T1R3) as it is a key component of the sweet taste receptor signalling system. In the control group, 9 samples of 'WT ' wild-type mice were selected, and for the test group, 9 samples of 'T1R3 knockout' mice (do not have a functional T1R3 gene) were selected. In each group, 3 samples were taken from the cortex tissue, and 6 samples were taken from the hippocampus tissue. This study provided a model of how a disruption in a key receptor of sweet taste signalling influences downstream gene expression. To conduct the differential gene expression analysis, the GEO2R tool was utilized. The tool compared the two groups (test and control) and calculated a p-value for each gene. Then, using the Benjamini–Hochberg FDR correction to limit the number of false positives, it calculated the adjusted p-values. This statistic was used to identify the likelihood that an observed difference occurred due to chance, or whether the variation was significant. As a result of the analysis, each study provided a list of genes that were differentially expressed between the control and test groups: GSE186509 listed 17 genes, and GSE97677 listed 254 significant genes. After a combined list was created using all the genes and duplicate genes were removed, a final list of 249 unique genes was generated.

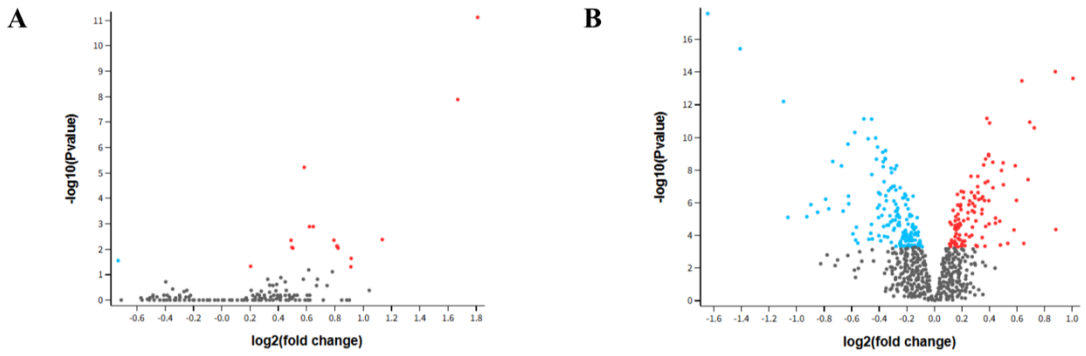


Figure 1. The figure contains the volcano plots generated by the author using the studies used in the differential gene expression analysis. The x-axis, log2(fold change), represents the direction and magnitude of expression change, and the y-axis, log10(P-value), represents the statistical significance. The red dots indicate the significantly upregulated genes with positive fold change and adjusted p-value<0.05; the blue dots represent the significantly downregulated genes with negative fold change and adjusted p-value<0.05. The grey dots represent the non-significant genes falling below the statistical threshold: adjusted p-value>0.05. (A) Volcano plot for genes in study GSE186509. The x-axis ranges from -0.6 to 1.8, and the y-axis ranges from 0 to 11. (B) Volcano plot for genes in study GSE97677. The x-axis ranges from -1.6 to 1.0, and the y-axis ranges from 0 to 16.

Network Analysis

The protein-protein interaction network was constructed with the nodes representing the proteins, and the protein-protein interactions represented by the edges, as shown in Figure 2. A total of 151 unique nodes and 240 edges were shown across the network. The network was analysed on four main topological parameters: degree of a node, which represents the number of direct connections it has with other nodes in the network; betweenness centrality quantifies how frequently a node is situated on the shortest path between other nodes; closeness centrality is, on average, how close a node is to all other nodes in the network, representing how 'central' it is in the network; clustering coefficient measures how tightly interconnected nodes are. Overall, these parameters determine how topologically important a node is. The top 10 genes were identified in descending order of degree, as shown in Table 1. RPLP0 had the highest degree in the reported network. However, high connectivity indicates a topological property of the selected network and does not establish a specific role in taste dysfunction. The prominence of ribosomal and mitochondrial ribosomal genes may reflect general cellular processes, the composition of the input list, and the coverage of existing interaction annotations.

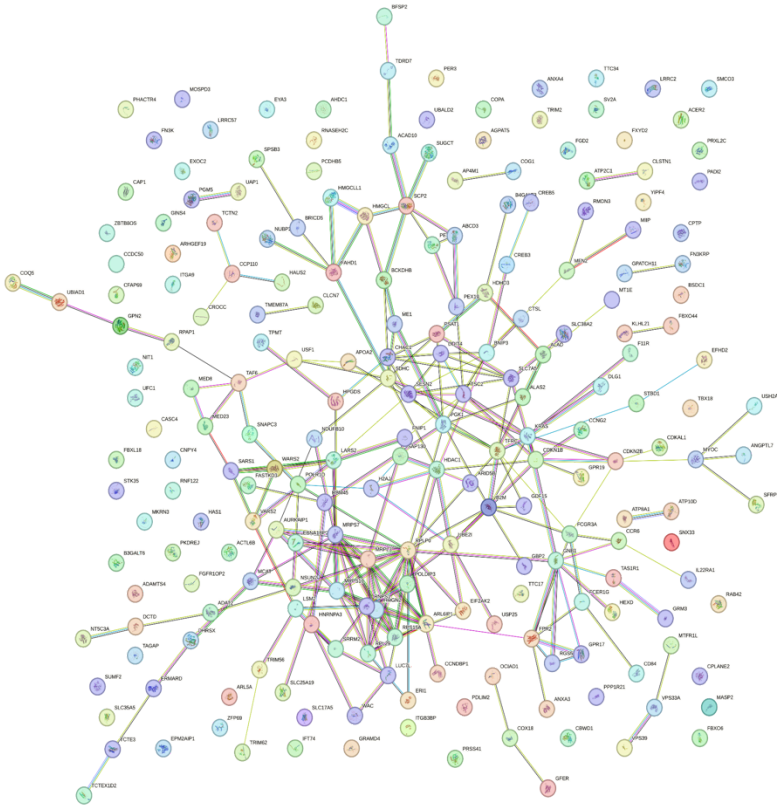


Figure. 2. Protein-protein interaction network generated by the author using STRING (version 12.0). Network nodes represent proteins, collapsed such that each node signifies all proteins produced by a single protein-coding gene locus. Colored nodes represent query proteins and the first shell of interactors, while white nodes represent the second shell. Edges represent specific, meaningful associations where proteins jointly contribute to a shared function, which does not necessitate physical binding.

Table 1. Top 10 genes of the protein-protein interaction network with corresponding topological parameters.

Gene	Degree	Betweenness Centrality	Closeness Centrality	Clustering Coefficient
RPLP0	17	0.2474558538	0.3307086614	0.2132352941
MRPS7	13	0.1027497946	0.2923433875	0.3461538462
TFRC	11	0.1278659284	0.3255813953	0.1636363636
MRPS10	10	0.04462538115	0.2781456954	0.5777777778
MRPL3	10	0.01530337711	0.2739130435	0.5333333333
KRAS	10	0.1716677098	0.324742268	0.08888888889
PGK1	9	0.1572593551	0.3298429319	0.1666666667

SDHC	9	0.2397119412	0.3298429319	0.08333333333
HDAC1	8	0.09515464281	0.2923433875	0.1071428571
ARL6IP1	8	0.0203877551	0.2751091703	0.75

Pathway Analysis

Reactome is a database that maps human biological reactions, processes, and pathways. Through the analysis conducted using Reactome, with the complete list of 249 unique genes, a pathway network was created to map out the various processes the genes partake in. From the list of pathways, the top five most relevant pathways in the exploratory analysis were Translation (R-HSA-72766), tRNA Aminoacylation (R-HSA-379724), Senescence-Associated Secretory Phenotype (SASP) (R-HSA-2559582), Mitochondrial tRNA aminoacylation (R-HSA-379726), and p75NTR negatively regulating the cell cycle via SC1 (R-HSA-193670). These pathways principally represent broad cellular functions rather than taste-specific signalling. Their appearance in the analysis does not establish causal involvement in dysgeusia or indicate whether the pathways were activated or suppressed. Biological interpretation is further limited by differences in species, tissue, and experimental perturbation between the source datasets. Translation is one of the most fundamental cellular processes, in which the mRNA sequence is used to create a polypeptide to accomplish protein synthesis. Another process contributing to protein synthesis, tRNA aminoacylation, involves the specific attachment of an amino acid to its corresponding transfer RNA molecule, ensuring that the correct amino acids are brought during translation. The SASP pathway is a cellular signalling network where senescent cells release inflammatory cytokines, growth factors, and enzymes into the surrounding environment. In a chronic state, this promotes aging, fibrosis, and cancer progression. Almost exactly similar to tRNA aminoacylation, Mitochondrial tRNA aminoacylation involves the particular binding of the mitochondrial tRNA, which is present in the mitochondrial matrix, to its cognate amino acid. Lastly, involved in stopping cell proliferation, the p75 neurotrophin receptor (p75NTR) interacts with the Schwann cell factor 1 (SC1) to negatively regulate the cell cycle, leading to growth arrest. Lastly, the list of genes identified in the top 25 pathways from the genes in Table 1 were RPLP0, MRPS7, MRPL3, MRPS10, and HDAC1.

Molecular Docking Analysis

Molecular docking was used to generate possible ligand–protein poses and associated scoring-function estimates for ten compounds against TFRC and TAS2R4. More negative scores indicated more favourable predictions within the specified docking setup, but were not experimental measurements of binding affinity or thermodynamic stability. Rankings were interpreted within each target and were not used to establish receptor activation, inhibition, or clinical efficacy. The best 5 compounds for TFRC based on binding energies, in ascending order, were as follows: 5'-GMP (-9.674 kcal/mol), 5'-IMP (-8.651 kcal/mol), 6-Gingerol (-6.130 kcal/mol), Propylthiouracil (-6.020 kcal/mol), and Citric acid (-5.990 kcal/mol). The best 5 compounds for TAS2R4 on the same basis were as follows: 5'-GMP (-7.632 kcal/mol), 5'-IMP (-7.041 kcal/mol), D-Limonene (-6.393 kcal/mol), 6-Gingerol (-5.895 kcal/mol), and

Citric acid (-5.525 kcal/mol). 5′-GMP, 5′-IMP, 6-gingerol, and citric acid appeared within the five most favourably scored compounds for both targets. This overlap was descriptive and did not establish target specificity, functional activity, or likely benefit for taste dysfunction. Receptor structures and certain docking complexes were visualized using PyMOL software, as shown in Figure 3.

Table 2. Reported AutoDock Vina scores for ten compounds docked against TFRC and TAS2R4. Scores represent predictions from the specified computational setup and are not experimentally measured binding affinities.

Compound	TFRC Binding Affinity Score (kcal/mol)	TAS2R4 Binding Affinity Score (kcal/mol)
6-Gingerol	-6.130	-5.895
Propylthiouracil	-6.020	-5.220
Citric acid	-5.990	-5.525
D-Limonene	-5.532	-6.393
Ethyl maltol	-5.515	-5.441
Guanosine 5′-monophosphate	-9.674	-7.632
Inosine 5′-monophosphate	-8.651	-7.041
L-Glutamic acid	-5.587	-4.744
L-Malic acid	-5.307	-4.746
Vanillin	-5.863	-5.491

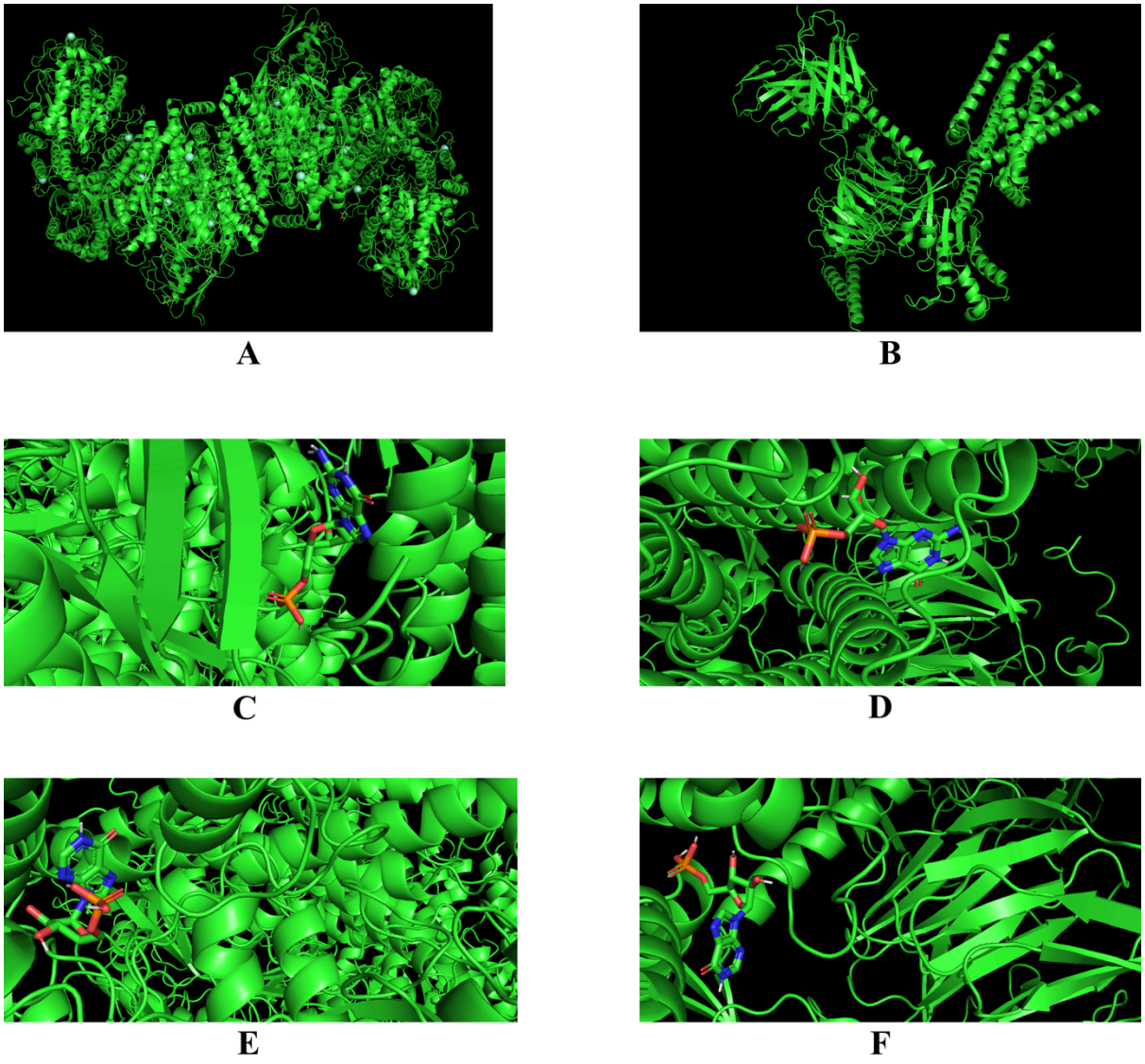


Figure 3. Molecular structures and predicted ligand–protein interactions visualised by the author using PyMOL software. Structures of TAS2R4 and TFRC and their docked interactions with ligands. (A) Visualized structure of human transferrin receptor (TFRC). (B) Structure of taste receptor type 2 member 4 (TAS2R4). (C) Close-up view of the predicted TFRC binding pocket following molecular docking of 5′-guanosine monophosphate (5′-GMP), with the ligand and key interacting residues shown as sticks. (D) Close-up view of the predicted TAS2R4 binding pocket following docking of 5′-GMP. (E) Close-up view of the predicted TFRC binding pocket following docking of 5′-inosine monophosphate (5′-IMP). (F) Close-up view of the predicted TAS2R4 binding pocket following docking of 5′-IMP. All structures were visualized using PyMOL (3.1).

DISCUSSION

The present study provides an integrated computational workflow to examine molecular changes associated with taste signalling and to identify nutritionally relevant compounds that may be promising candidates for further investigation. Differential gene expression analysis of the selected GEO datasets identified 17 significant genes from GSE186509 and 254 from GSE97677, resulting in 249 unique genes after removal of duplicates. These genes were subsequently analysed through protein-protein interaction and pathway-based approaches, where the resulting network comprised 151 nodes and 240 edges and identified highly connected genes including RPLP0, MRPS7, MRPL3, MRPS10 and HDAC1, with TFRC also ranking among the principal network genes. The pathway analysis further showed enrichment of processes related to translation, aminoacylation of tRNA, mitochondrial tRNA aminoacylation, senescence-associated secretory phenotype and negative regulation of the cell cycle. Taken together, the network and pathway findings highlighted broad cellular processes in the analysed experimental models. They did not establish that these processes were taste-specific, causally related to dysgeusia or suitable targets for restoring gustatory function. The ensuing docking analysis provided a structural screening step that linked this molecular context to taste-active and flavour-related compounds. Among the ten ligands tested, 5′-GMP and 5′-IMP showed the most favourable predicted binding affinities for both TFRC and TAS2R4, while 6-gingerol and citric acid were also among the common higher-scoring compounds. Together, these analyses generated exploratory hypotheses concerning expression changes, cellular pathways and possible compound–target interactions. They did not establish a continuous causal relationship between the experimental perturbations, the selected docking targets and human taste dysfunction.

The findings are consistent with previous work investigating nutritional or regenerative strategies for taste dysfunction, while differing substantially in methodological approach. A randomized, double-blind clinical trial investigating the zinc-containing compound polaprezinc reported improved gustatory sensitivity in the higher-zinc treatment group, supporting the broader concept that nutritional factors can influence taste function [15]. Similarly, a placebo-controlled study of zinc sulfate in patients receiving radiotherapy examined preservation of bitter, salty, sweet, and sour taste perception and reported beneficial effects, demonstrating a clinically measurable relationship between nutritional supplementation and taste function [16]. In contrast to these intervention-based studies, the present work begins with expression changes and network-level molecular information before prioritising candidate compounds computationally. The regenerative perspective of the present study is also comparable to work demonstrating that photobiomodulation can upregulate Sonic hedgehog signalling and promote taste-bud regeneration and recovery of taste function, as well as to studies using gingival mesenchymal stem-cell-derived exosomes that demonstrated taste-bud regeneration, reinnervation and increased regenerative markers [17,18]. These studies, however, relied on cellular and animal models rather than transcriptomic screening and molecular docking. Conversely, the computational workflow used here has strong methodological similarity to network-pharmacology and docking studies in other biological domains. The Gastrodia elata study in ischemic stroke integrated disease-associated genes with GEO-derived DEGs, followed by enrichment, PPI analysis, and molecular docking, with subsequent

experimental validation, providing a close precedent for linking transcriptomic changes to pathway-guided target selection [19]. Similarly, the melanoma-Parkinson's disease study used overlapping expression-defined genes, functional and regulatory network analyses, compound prediction, and AutoDock Vina to identify and test candidate molecular interactions [20]. Similar to these studies, the present work uses public gene-expression data, network analyses, and docking as sequential stages of candidate discovery; however, it applies this strategy to taste-related biology and nutritionally relevant compounds.

Several limitations should be considered when interpreting these findings. First, the GEO datasets incorporated different biological models and experimental contexts, including intestinal crypt cells exposed to bitter compounds and brain tissues from T1R3 knockout and wild-type mice, meaning that differences in tissue type, species, and experimental condition may contribute to the observed gene-expression patterns. The resulting 249-gene set should therefore not be interpreted as a definitive molecular signature of human taste-bud dysfunction. The analysis also did not implement personalised profiling. The presence of TAS2R43 deletion-status information in the source dataset and the comparison of knockout with wild-type mice did not constitute individualised compound prediction. A personalised extension would require an explicit analysis linking individual genetic or expression differences to altered compound rankings, followed by validation against measured functional or sensory responses. Second, pathway enrichment identifies statistical associations but does not establish that a particular pathway is causally responsible for altered taste perception. Finally, molecular docking provides predicted binding affinities under a simplified structural model and cannot establish bioavailability, tissue exposure, target modulation, taste-cell regeneration, or sensory recovery. These limitations define important directions for future work. Independent validation using additional taste-related transcriptomic datasets, ideally from human taste tissue or clinically characterized dysgeusia groups, would strengthen the biological relevance of the identified genes and pathways. Experimental validation should then examine whether the highest-priority compounds alter the expression or activity of selected targets and whether such effects translate into taste-cell regeneration or functional recovery. Future docking studies could also incorporate reference ligands, decoy controls, and more biologically supported target selection, followed by molecular dynamics and wet-lab validation as demonstrated in related computational studies [19].

CONCLUSION

Overall, this study demonstrates the potential utility of integrating differential gene expression, protein-interaction networks, pathway analysis, and molecular docking to investigate nutritionally relevant mechanisms associated with taste biology. This study combined transcriptomic, network, pathway, and molecular docking analyses to explore taste-receptor-related experimental models. The network and pathway findings primarily implicated broad cellular processes and should not be interpreted as a molecular signature of human dysgeusia. The reported docking scores identified 5′-GMP, 5′-IMP, 6-gingerol and citric acid as candidates for further computational assessment, but did not establish target binding, functional modulation or improvement in taste perception. No patient-specific or genotype-based

compound selection was performed. The principal contribution is an exploratory workflow whose biological and clinical relevance requires independent validation.

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Raahil Gore is a grade 12 student at Inventure Academy, Bangalore, India, with interests in molecular biology and bioinformatics. He hopes to pursue biomedical research, exploring the molecular mechanisms underlying disease and the applications of computational biology in healthcare.

REFERENCES

[1] V. S. Neeha and P. Kinth, "Nutrigenomics research: A review," *J. Food Sci. Technol.*, vol. 50, no. 3, pp. 415–428, 2013, doi: 10.1007/s13197-012-0775-z.

[2] S. P. Wooding, V. A. Ramirez, and M. Behrens, "Bitter taste receptors: Genes, evolution and health," *Evol. Med. Public Health*, vol. 9, no. 1, pp. 431–447, 2021, doi: 10.1093/emph/eoab031.

[3] J. Diószegi, E. Llanaj, and R. Ádány, "Genetic background of taste perception, taste preferences, and its nutritional implications: A systematic review," *Front. Genet.*, vol. 10, Art. no. 1272, 2019, doi: 10.3389/fgene.2019.01272.

[4] F. Pombo, C. Seabra, A. J. Sá, and I. Ferreira, "Chemotherapy-induced dysgeusia and its perverse consequences: A case report," *Cureus*, vol. 14, no. 8, Art. no. e27908, 2022, doi: 10.7759/cureus.27908.

[5] D. Munankarmi, "Management of dysgeusia related to cancer: A systematic review," *J. Lumbini Med. Coll.*, vol. 5, no. 1, pp. 3–12, 2017, doi: 10.22502/jlmc.v5i1.110.

[6] Y. Afiyanti, M. Mandasari, S. R. Lestari, L. A. Nasution, M. S. N. Gautama, I. A. M. V. Susiladewi, et al., "Prevalence of dysgeusia in head and neck cancer patients: A meta-analysis and moderator analysis," *J. Oral Rehabil.*, vol. 53, no. 4, pp. 900–915, 2026, doi: 10.1111/joor.70147.

[7] W. M. H. Rademacher, Y. Aziz, A. Hielema, K.-C. Cheung, J. de Lange, A. Vissink, et al., "Oral adverse effects of drugs: Taste disorders," *Oral Dis.*, vol. 26, no. 1, pp. 213–223, 2020, doi: 10.1111/odi.13199.

[8] Benish and J.-H. Choi, "Bitter taste receptor TAS2R38 genetic variation (rs10246939), dietary nutrient intake, and bio-clinical parameters in Koreans," *Clin. Nutr. Res.*, vol. 12, no. 1, pp. 40–53, 2023, doi: 10.7762/cnr.2023.12.1.40.

[9] C. B. Nunes, A. W.-Y. Lim, Q. Dy, J.-S. Ong, and L.-D. Hwang, "Phenome-wide investigation of dietary and health outcomes associated with bitter taste receptor gene TAS2R38," *Eur. J. Nutr.*, vol. 64, no. 5, Art. no. 218, 2025, doi: 10.1007/s00394-025-03718-6.

[10] S. Jaishankar, D. Schaeper, S. C. Janga, and M. Srinivasan, "Single-cell transcriptomic analysis of salivary epithelial cells reveals large-scale dysregulation in bitter taste dysfunction," *Int. J. Mol. Sci.*, vol. 27, no. 7, Art. no. 2953, 2026, doi: 10.3390/ijms27072953.

[11] R. M. Carey, T. Kim, N. A. Cohen, R. J. Lee, and K. T. Nead, "Impact of sweet, umami, and bitter taste receptor (TAS1R and TAS2R) genomic and expression alterations in solid tumors on survival," *Sci. Rep.*, vol. 12, Art. no. 8937, 2022, doi: 10.1038/s41598-022-12788-z.

[12] C. Lin, M. Jyotaki, J. Quinlan, S. Feng, M. Zhou, P. Jiang, et al., "Lipopolysaccharide increases bitter taste sensitivity via epigenetic changes in Tas2r gene clusters," *iScience*, vol. 26, no. 6, Art. no. 106920, 2023, doi: 10.1016/j.isci.2023.106920.

[13] C. W. Su, K. Chen, T. Wu, E. M. Reiman, Q. Wang, and Alzheimer's Disease Neuroimaging Initiative (ADNI), "TAS2R38-linked MGAM expression in Alzheimer's disease: A novel target for precision drug repurposing," *medRxiv*, preprint, 2025, doi: 10.1101/2025.09.09.25334938.

[14] S. Hemmati and A. Mohagheghzadeh, "The NeuroImmunoEndocrine circuit of umami peptides: A systems biology approach," *Nutrients*, vol. 18, no. 8, Art. no. 1299, 2026, doi: 10.3390/nu18081299.

[15] M. Sakagami, M. Ikeda, H. Tomita, A. Ikui, T. Aiba, N. Takeda, et al., "A zinc-containing compound, Polaprezinc, is effective for patients with taste disorders: Randomized, double-blind, placebo-controlled, multi-center study," *Acta Otolaryngol.*, vol. 129, no. 10, pp. 1115–1120, 2009, doi: 10.1080/00016480802552550.

[16] N. Najafizade, S. Hemati, A. Gookizade, N. Berjis, M. Hashemi, S. Vejdani, et al., "Preventive effects of zinc sulfate on taste alterations in patients under irradiation for head and neck cancers: A randomized placebo-controlled trial," *J. Res. Med. Sci.*, vol. 18, no. 2, pp. 123–126, 2013.

[17] H. Y. Lee, C. D. G. Abueva, A. Padalhin, S. Y. Park, H. S. Ryu, P.-S. Chung, et al., "Regeneration of taste through sonic hedgehog upregulation by photobiomodulation," *J. Biophotonics*, vol. 16, no. 11, Art. no. e202300043, 2023, doi: 10.1002/jbio.202300043.

[18] Y. Zhang, S. Shi, Q. Xu, Q. Zhang, R. M. Shanti, and A. D. Le, "SIS-ECM laden with GMSC-derived exosomes promote taste bud regeneration," *J. Dent. Res.*, vol. 98, no. 2, pp. 225–233, 2019, doi: 10.1177/0022034518804531.

[19] Y. Luo, P. Chen, L. Yang, and X. Duan, "Network pharmacology and molecular docking analysis on molecular targets and mechanisms of *Gastrodia elata* Blume in the treatment of ischemic stroke," *Exp. Ther. Med.*, vol. 24, no. 6, Art. no. 742, 2022, doi: 10.3892/etm.2022.11678.

[20] L. Zhang, D. Li, X. Zheng, M. Wu, Q. Yao, H. Chen, et al., "Exploring the underlying molecular connections: A bioinformatics approach to link melanoma and Parkinson's disease," *Front. Genet.*, vol. 16, Art. no. 1526018, 2025, doi: 10.3389/fgene.2025.1526018.