

# TAS2R38 Polymorphism and Bitter Taste Perception: Implications for Satmaya and Upashaya-Anupshaya Beyond Prakriti

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## TAS2R38 Polymorphism and Bitter Taste Perception: Implications for *Satmaya* and *Upashaya-Anupshaya* Beyond *Prakriti*

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### Abstract

**Background:** In Ayurveda, bitter (*Tikta*) formulations are prescribed for the resolution of inflammatory conditions. Genetic variation in the taste receptor *TAS2R38* influences both taste perception and inflammatory responses by differentially activating ligands, a phenomenon widely observed in Ayurvedic herbs. **Objective:** Given differences in dosage calibration based on *Prakriti*, we explored whether *Prakriti*-based stratification correlates with *TAS2R38* genetic variation and bitter taste perception thresholds. **Method:** A total of 326 *prakriti*-assessed healthy individuals were phenotyped for bitter taste using phenylthiocarbamide (PTC) with the Bartovation® taste kit on a 0–5 intensity scale, and participants were categorized as non-tasters, recessive tasters, or dominant supertasters. Genotyping of three canonical *TAS2R38* SNPs (rs713598, rs1726866, and rs10246939) was performed using Sanger sequencing and SNaPshot assays. Haplotypes (PAV-taster; AVI-non-taster) were inferred and analyzed for Hardy–Weinberg equilibrium (HWE), and associations with *Prakriti* were assessed using chi-square, Kruskal–Wallis, and Cramér’s V tests. Additionally, *in silico* docking of bitter phytochemicals (BitterDB) was conducted using an AlphaFold-derived *TAS2R38* structure. **Results:** PTC phenotypes and genotypes were concordant and in HWE. Distribution included 10.6% PAV/PAV, 46.6% PAV/AVI, and 36.5% AVI/AVI, corresponding to supertaster and non-taster phenotypes. No significant variation was observed across *Prakriti* groups. Docking analysis of compounds selected from IMPPAT plants revealed some Ayurvedic phytochemicals that showed potential affinity for *TAS2R38*. **Conclusion:** Interindividual variability in therapeutic response is observed even among patients of the same *prakriti*. Integrating taste phenotyping and genetic markers could refine *Dashavidha Pariksha*, enabling personalized selection and dosing of *Tikta* formulations while minimizing *Anupashaya*.

# 1. Introduction

In Ayurveda, bitter (*Tikta*) herbs and polyherbal formulations are prescribed for regulating a variety of conditions like elevated *Kapha*, *Kapha-Pitta*, *Kapha-Vata*, *Aama*, *Aam-Vata*, and *Meda* and also for the resolution of inflammatory conditions (*Shotha*) arising primarily from *Pitta Dosha* imbalance (Supplementary Verses 1, 2). Individuals with a *Pitta*-predominant *Prakriti*, who exhibit an inherent susceptibility to heat associated with inflammatory dysregulation, are traditionally prescribed bitter formulations with cooling properties to restore physiological homeostasis (Supplementary Verse 2). In contrast, the administration of bitter formulations in *Vata*-dominant individuals requires careful titration, as higher doses may exacerbate dryness and catabolic tendencies (*Rukshata*) (Supplementary Verse 3). Conversely, *Kapha*-dominant individuals are typically recommended more potent and concentrated bitter interventions to counteract inherent metabolic heaviness (*Gurutva*) and achieve therapeutic efficacy (Supplementary Verse 2). While this *Prakriti*-based framework provides a phenotypic rationale for the use of bitter formulations, the molecular mechanisms underlying their systemic anti-inflammatory effects in a *Prakriti*-specific context remain largely unexplored. Conventional bitter herbs such as *Swertia chirata* (*Chirayata*), *Momordica charantia* (*Karela*), *Adhatoda vasica* (*Vasa*), and *Berberis aristata* (*Daruharidra*) are widely utilized for metabolic, inflammatory, and infectious conditions; pharmacological studies further validate their antioxidative, anti-inflammatory, antidiabetic, and anticarcinogenic properties (Saha and Das, 2010; Rohini et al., 2025; Virdi et al., 2003).

At the genetic level, the *TAS2R* family of G-protein coupled receptors is primarily involved in bitter taste perception (Sequeira et al., 2023). These receptors are expressed in various extra-oral tissues beyond the tongue, including the respiratory system, brain, reproductive tissues, small intestine, airway epithelia, thyroid, and lungs (Kim and Drayna, 2005; Carey et al., 2022; Choi and Kim, 2019; Shaw et al., 2018; Mennella and Bobowski, 2015). The *TAS2R38* gene, located on chromosome 7q34, is one of the most extensively characterized members of this family. This single-exon gene (1,143 bp) encodes a 333-amino acid protein with a molecular weight of approximately 37.4 kDa. Single-nucleotide polymorphisms (SNPs) in *TAS2R38* alter amino acids at positions A49P (rs713598), V262A (rs1726866), and I296V (rs10246939), giving rise to two major haplotypes: PAV and AVI. These haplotypes correlate with distinct bitter-taste phenotypes: PAV/PAV individuals are dominant supertasters, AVI/PAV individuals exhibit intermediate sensitivity, and AVI/AVI individuals are non-tasters (Kim and Drayna, 2005; Choi and Kim, 2019). Beyond oral perception, *TAS2R38* participates in chemosensory signalling, calcium-dependent pathways, and the modulation of innate immune responses (Shrungeswara and Unnikrishnan, 2019; Cui et al., 2024; Ren et al., 2025a). Notably, berberine, a bitter alkaloid prevalent in Ayurvedic medicinal plants, exerts anti-inflammatory effects through *TAS2R38*, though the magnitude of this response varies markedly across the taster-status spectrum (Cui et al., 2024).

In this study, we explored whether *TAS2R38* polymorphisms exhibit significant differences between *Prakriti* types given their differential response to *Tikta* formulations. We combine clinical assessment of *Prakriti* with objective phenylthiocarbamide (PTC) taste and *TAS2R38*

genotype assessments along with potential binding of bitter ligands from medicinal plants, including those used in Ayurveda, through molecular docking onto AlphaFold-derived structure of *TAS2R38*. Our findings reveal that *TAS2R38* allelic variants are stable in the population as estimated by HWE with no significant difference amongst the *Prakriti* groups. This suggests that receptor-driven variability in inflammatory resolution operates independently of constitutional types. The bitter taste response phenotype and associated genotype in *TAS2R38* could be used in clinical settings as a proxy for *Satmya* (suitability) (Supplementary Verse 4) and also for calibration of dosage of bitter formulations to prevent adverse effects (*Upshaya-Anupshaya*) (Supplementary Verse 5). Integration of cost-effective PTC/genotype-based assessments in Ayurveda clinics could enable the judicious selection of *Tikta* formulations for optimal compliance and response.

## 2. Methods

### 2.1 Study Population

This study was conducted in 326 healthy individuals from Western India. During sample collection, details such as sex, height, weight, age, BMI, and other relevant information were documented. The sample had near-equal representation of males and females, with a mean age of 27.49 and WHR and BMI means of 1.17 and 23.49, respectively. The subject recruitment protocol was adopted from the ICMR National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (2017). The study was approved by the Institutional Ethics Committee of the Indian Institute of Technology, Jodhpur, and samples were collected only after consent from every participant.

### 2.2 *Prakriti* Assessment

The *Prakriti* assessment was carried out by expert Ayurveda practitioners using a standardized questionnaire adopted from Health and Wellness HWC centers governed by the Ministry of AYUSH, Government of India, and a structured data collection protocol. This comprehensively captures the anatomical, physiological, and psychological attributes of an individual (Thottapillil et al., 2021) and classifies individuals into seven constitutional *Prakriti* types, representing combinations of the three *Dosha*: *Vata* (*V*), *Pitta* (*P*), *Kapha* (*K*), *Vata-Pitta* (*VP*), *Vata-Kapha* (*VK*), *Pitta-Kapha* (*PK*), and *Vata-Pitta-Kapha* (*VPK*) (Sethi et al., 2011) (Prasher et al., 2017). The samples were a subset of a training set of data of over 1000 individuals for a larger study that is being conducted to build AI and computer vision-based models for objective assessment of *Prakriti*. The cumulative scoring pattern, normalized by the mean values of *Vata*, *Pitta* and *Kapha* in a population data set of 1000 individuals, was used to determine the *Prakriti* of the individual. The *prakriti* independently assessed by Ayurveda practitioners and the questionnaire, were concordant.

### 2.3 Phenotypic Data Collection (Bitter Taste Perception Collection through Bartovation Kit)

Phenotype analysis was conducted in 289 samples from the subjects recruited above. For bitter taste testing, we used the Bartovation® taste test kit, which includes four strips:

phenylthiocarbamide (PTC), sodium benzoate, thiourea, and a control (chemical-free). PTC tasting perception is associated with the *TAS2R38* gene polymorphism. Sodium benzoate, often used as a preservative in foods and beverages, is used as a positive control. The sodium benzoate strips may taste tasteless, sweet, salty, or even bitter, depending on the individual. Thiourea, though similar to PTC, does not evoke similar responses – some people may be able to taste PTC but not thiourea, or vice versa. The control contains no chemicals and serves as a placebo. Each participant after a mouth rinse was given taste strips to place on the tongue and hold for 15-20 seconds and was to rate each strip on a scale of 0-5. Between each strip, volunteers had to do a water rinse to ensure they did not have any aftertaste after tasting each strip.

**Scoring Interpretation:** Scores are self-reported intensity (0 = tasteless; 5 = unbearable). Invalid if control > 0. Dominant supertasters are scored 5 on the PTC strip and can discriminate between all strips and scored positive for sodium benzoate and thiourea but not for the control paper. Recessive supertasters are those who had scores of 1, 2, 3, or 4 on the PTC strip and may or may not be able to taste all the strips and have given no score to the control paper. In the case of non-taster individuals, a score of 0 was assigned to the PTC strip, and scores of 0, 1, 2, or 3 were assigned to thiourea and sodium benzoate depending on their relative perception.

## **2.4 Genotypic Data Collection (Blood Collection and DNA Extraction):**

DNA isolation and genotyping of the *TAS2R38* polymorphism were carried out on all 326 samples. These were collected using the standard blood collection procedure outlined in the [WHO guidelines](#). A total of 3 mL of blood was collected from participants in K2-EDTA vacutainers. Genomic DNA extraction was carried out using a modified protocol described by Miller et al. (Miller et al., 1988) and eluted in 300-500 µL of TE buffer (pH 8.0), and DNA was quantified using NanoDrop™ 2000c Spectrophotometer (Thermo Fisher Scientific).

## **2.5 PCR preparation, QC, and cleanup**

The *TAS2R38* gene region encompassing all three SNPs (rs713598, rs1726866, and rs10246939) was amplified as a single 1.3-kb amplicon using the TaKaRa Ex Taq® Hot Start Version kit. The PCR was set up with 10 µL of reaction mix using the final 1X Ex Taq Buffer, 0.2 mM dNTPs, 300 nM of each forward primer (5'-GTGAGGAATCAGAGTTG-3') and reverse primer (5'-CTATGATAAGCTCTTACGTG-3'), 0.25 U of TaKaRa Ex Taq HS enzyme, and 30 ng of template DNA. The PCR conditions were standardised to: Initial denaturation at 95°C for 30 s; 33 cycles consisting of 94°C for 30 s, 55°C for 30 s, 72°C for 60 s, and final extension at 72°C for 7 min, followed by a quality check with 3 µL of product using a 2% agarose-TAE gel system. The PCR product was treated with 4 µL of ExoSAP-IT™ reagent (Applied Biosystems) to remove excess dNTPs and primers. Quality control was ensured through concentration estimation and gel electrophoresis.

## **2.6 Genotype analysis of *TAS2R38* polymorphisms**

We followed two approaches to comprehensively analyse the genotypes at all the three loci of *TAS2R38*. The genotypes were primarily ascertained through the SNaPshot method (Figure 1),

which adds a single fluorescently labelled base (single-base extension reaction) at the SNP position and halts the reaction. The fluorescence is then captured in the form of peaks. These SNPs were further validated by Sanger sequencing (Figure 1), which uses the dideoxy chain termination reaction to halt the growing chain with fluorescently labelled ddNTPs, and the resulting reads are further analysed by capillary electrophoresis.

### SNaPshot assay for SNP detection

Genetic variation in the *TAS2R38* receptor was characterized by genotyping three canonical SNPs (rs713598, rs1726866, and rs10246939) using a multiplex SNaPshot primer extension assay to infer major haplotypes. The SNaPshot primers were designed for all three SNPs, just one base before the SNP position (rs713598: 5'-GACACAGCAGCACACAATCACTGTTGCTCAGTG-3'; rs1726866: 5'-GGCACAGAGATGAAGGCA-3'; rs10246939: 5'-ACTTGGCATTGCCTGAGATCAGGA-3'). The reaction mix was prepared according to the manufacturer's instructions provided with the SNaPshot™ Multiplex Kit (Applied Biosystems). Two reaction mixes were set for each sample (one reaction with rs713598 and rs10246939 SNaPshot primers and another reaction with rs1726866 SNaPshot primers). The data (.fsa) files were analyzed using GeneMapper software (Sagong et al., 2014).

| rs ID     | SNaPshot Primer Sequence (5'-3')      | Length (bp) | Mutation |
|-----------|---------------------------------------|-------------|----------|
| rs713598  | GACACAGCAGCACACAATCACTGTTGCTCA<br>GTG | 33          | G>C      |
| rs1726866 | GGCACAGAGATGAAGGCA                    | 18          | C>T      |
| rs1024693 | ACTTGGCATTGCCTGAGATCAGGA              | 24          | A>G      |

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### Sanger Sequencing:

The cycle sequencing was performed using the BigDye™ Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems) as per the manufacturer's instructions using the same PCR amplification primers (either forward or reverse). The sequencing products were purified using the optimised sodium acetate-EDTA cleanup method and dissolved in 10 µl of Hi-Di™ formamide (Applied Biosystems). Finally, the product was given a heat shock (95°C) for 5 min and snap-chilled (on ice) for 5 min prior to loading in an automated sequencer (SeqStudio Flex, Applied Biosystems) with a 36 cm length capillary and POP-7™ polymer. Analysis and alignment with the reference genome were performed using Benchling software (<https://www.benchling.com/>).

## 2.8 Statistical Analysis and Hardy–Weinberg equilibrium

Data associations with *Prakriti* were evaluated using Pearson's chi-square tests, Kruskal–Wallis tests, and Cramér's V. To evaluate the agreement between phenotypic bitter taste perception and *TAS2R38* genotypes, individuals were categorized into three groups: non-taster,

recessive taster, and dominant supertaster based on both PTC taste strip responses (phenotype) and genotyping results. A total of 255 individuals were included in this analysis.

Concordance between PTC phenotypic responses and genotype frequencies was assessed via the Kolmogorov–Smirnov test. To determine the genetic and phenotypic stability and independence of the markers, HWE analyses were performed across the total population and within individual *Prakriti* strata. Allelic frequencies were calculated based on the number of supertasters (PAV/PAV), moderate tasters (PAV/AVI) and non-tasters (AVI/AVI) and the genotype distribution when the population in equilibrium was estimated from this distribution of phenotypes (genotypes). HWE was evaluated using a chi-square goodness-of-fit test between observed and expected genotype distribution with one degree of freedom. The relationship between *TAS2R38* genotype and Ayurveda *Prakriti* was evaluated using Pearson's chi-square test and Fisher's exact test with Monte Carlo simulation. Categorical variables were summarized as frequency distributions. To control for potential confounding by anthropometric and demographic factors, we fitted multinomial logistic regression models with Ayurveda *Prakriti* as the outcome variable. Genotype categories (PAV, AVI, and PAV/AVI), age, sex, WHR and BMI were included as predictors.

## **2.9 Identification and Mapping of Bitter Phytocompounds from BitterDB and IMPPAT and Construction of Chemical Feature Space and Dimensionality Reductions of IMPPAT-BitterDB data:**

The chemicals from the BitterDB 2024 version were downloaded for the analysis (<https://bitterdb.agri.huji.ac.il/dbbitter.php#Download>). BitterDB is a repository of bitter molecules and their receptors (Ziaikin et al., 2025). It had a total of 2250 chemicals based on their compound identifiers. IMPPAT 2.0 is a database of secondary metabolites of Indian medicinal plants, comprising 17967 chemicals (Vivek-Ananth et al., 2023). The overlap of these two sets of chemicals was done based on the names of the chemicals. We considered common names, synonymous names, and IUPAC names of the chemicals, whichever were available in the two datasets. We got a total of 417 chemicals based on this name-based overlap method to be used as the ligand set.

Plant-chemical associations from IMPPAT -BitterDB were converted into a binary plant × compound presence matrix. The compound degree (number of plants containing each compound) was calculated, and compounds occurring in a very low ( $\leq 5$ ) or very high number of plants ( $\geq 50$ ) were excluded to remove noise and overly generic chemistry. The filtered matrix was transformed using TF–IDF normalization with `tfidftransformer` from `scikit-learn` in Python 3.14.3 to identify plant-specific chemical signatures, and less weightage was given to the ubiquitous compounds (Sammut and Webb, 2011). Principal component analysis (PCA) was applied to the TF–IDF matrix to identify global chemical structure, and k-means clustering was used with  $k = 4$  to identify groups that share significant similarity in terms of bitter

chemical signatures (Maćkiewicz and Ratajczak, 1993). PCA coordinates were used to define major chemical classes based on optimum silhouette score. To resolve finer, non-linear structure, Uniform Manifold Approximation and Projection (UMAP) was applied to the same TF-IDF-normalized data (McInnes et al., 2020).

## 2.10 Cluster identification and chemical enrichment:

Density-based clustering of UMAP embeddings was performed using HDBSCAN with a minimum cluster size of 20 and a minimum sample size of 10 to identify stable local chemical phenotypes (McInnes and Healy, 2017). Chemical enrichment analysis was conducted using Fisher's exact test on binary presence-absence data to identify compounds over-represented in each cluster. All codes are available at [link to github codes](#).

## 2.11 *TAS2R38* Protein and Ligand Preparation

### Protein and Ligand Preparation

The three-dimensional structure of the human bitter taste receptor *TAS2R38* was obtained from the AlphaFold Protein Structure Database (AlphaFold ID: AF-P59533-F1), corresponding to the UniProt entry P59533. The library of chemicals to be docked with this protein was obtained from two databases. In addition to this bitter molecule library, phenylthiocarbamide (PTC), a well-established *TAS2R38* agonist, was included as a biological reference. These chemicals were pre-processed (salt and duplicate molecule removal) and converted to PDBQT using MayaChemTools (Sud, 2016) and Open Babel (O'Boyle et al., 2011).

### Binding Pocket Prediction

Putative ligand-binding pockets for the *TAS2R38* AlphaFold model were identified using the DoGSiteScorer web server (DoGSite3) (Volkamer et al., 2010). DoGSite3 automatically detected surface cavities and reported a druggability estimate along with key pocket descriptors, including geometric features. The top-ranked pocket with favourable druggability and suitable pocket size/shape descriptors was selected for defining the docking region.

### Molecular Docking

The docking search space for *TAS2R38* was defined around the top-ranked binding pocket predicted by DoGSite3. The grid box centre coordinates were defined within the top-ranked DoGSite3 pocket and refined around the reported PTC-associated residue pocket (W99, M100, N103, F255, S259 and V296) (Biarnés et al., 2010). The final grid box was centred at  $x = 8.022$ ,  $y = 7.326$ , and  $z = 0.972$  Å, with dimensions  $42 \times 48 \times 46$  Å, and molecular docking was carried out using AutoDock4 (Morris et al., 2009). For each ligand, the best-ranked pose (lowest predicted binding energy) was extracted. The selected poses were checked using PoseBusters v0.5.1 (Buttenschoen et al., 2024) to flag severe steric clashes and strained ligand geometries, and the final protein-ligand complexes were used for interaction analysis. Protein-ligand interaction diagrams were generated using LigPlot+ v2.2.9 (Laskowski and Swindells, 2011). In addition to the bitter molecule library (cluster 4 drugs), phenylthiocarbamide (PTC), a well-

established *TAS2R38* agonist, was included as a reference ligand to guide binding-site focusing and to enable qualitative comparison of interaction patterns.

### 3. Results

#### 3.1 Phenotype-Genotype correlation of bitter taste perception with *TAS2R38* polymorphism

The distribution of bitter-taste phenotypes within the study cohort (n = 289) revealed 49.5% (n = 143) of the population as recessive tasters (heterozygous), followed by the homozygous non-tasters at 41.9% (n = 121) and dominant supertasters at 8.6% (n = 25). The frequency distribution from the observed data of the non-tasters for the major phenotype was 0.666 and the minor was 0.333. HWE analysis revealed no significant deviation from expected values ( $\chi^2 = 3.64$ , p value = 0.057), suggesting a lack of strong selective pressure or non-random mating patterns influencing bitter taste perception in this healthy cohort.

Comprehensive genotyping of the *TAS2R38* locus was carried out on 326 individuals. The cohort was characterized by a predominant heterozygous frequency, with PAV/AVI (recessive supertasters) accounting for 47.23% (n = 154) of the population. Homozygous AVI/AVI (non-tasters) and PAV/PAV (dominant supertasters) represented 36.19% (n = 118) and 9.81% (n = 32) of the cohort, respectively. A small subset of individuals (6.74%, n = 22) exhibited rare allelic variants. The estimated frequency based on the primary taster (PAV) and non-taster (AVI) haplotypes for the minor PAV allele (p) was 0.359, while the AVI allele (q) frequency was 0.641. HWE analysis yielded a chi-square value of 3.12 (p = 0.077), indicating that the distribution of *TAS2R38* genotypes in this population also does not significantly deviate from equilibrium. To support this, we also performed cohort-level and SNP-wise analyses of phenotype and genotype data (Supplementary Tables 1–5).

**Table 1. Phenotypic and Genotypic Distribution of *TAS2R38* and HWE Analysis**

| Category                       | Genotype Distribution (N=326) | Phenotype Distribution (N=289) |
|--------------------------------|-------------------------------|--------------------------------|
| Phenotype (Genotype)           | n (%)                         | n (%)                          |
| Non-taster (AVI/AVI)           | 118 (36.19)                   | 121 (41.9)                     |
| Recessive taster (PAV/AVI)     | 154 (47.23)                   | 143 (49.5)                     |
| Dominant Supertaster (PAV/PAV) | 32 (9.81)                     | 25 (8.6)                       |
| Rare Variants                  | 22 (6.74)                     | —                              |
| Total                          | 326 (100.0)                   | 289 (100.0)                    |
| ---                            | ---                           | ---                            |
| Hardy–Weinberg Parameters      |                               |                                |
| Allele Frequency (p PAV / q    | 0.359 / 0.641                 | 0.334 / 0.666                  |

|                         |       |       |
|-------------------------|-------|-------|
| AVI)                    |       |       |
| Chi-square ( $\chi^2$ ) | 3.12  | 3.63  |
| p-value                 | 0.077 | 0.057 |

**Note:** Phenotype (N = 289) and genotype (N = 326) sample sizes differ due to data availability. Allele frequencies (p and q) were estimated from observed phenotype- and genotype-inferred counts, respectively. Expected genotype frequencies under HWE were calculated using  $p^2$ ,  $2pq$ , and  $q^2$ . The chi-square ( $\chi^2$ ) goodness-of-fit test with 1 degree of freedom was applied to evaluate deviation from HWE.

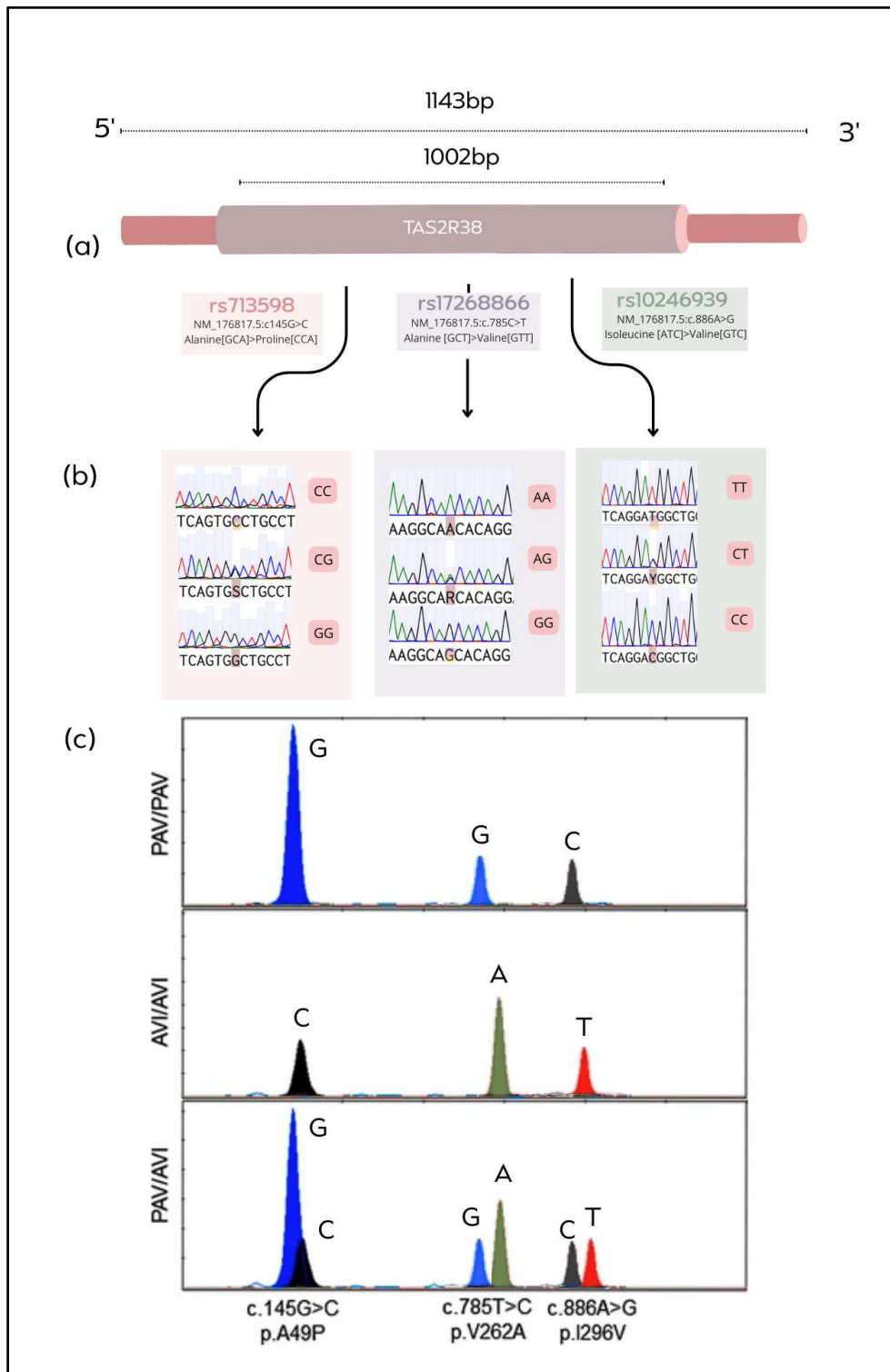


**Figure 1.** Sanger and SNaPshot sequencing profiles of *TAS2R38* genotypes. (a) Schematic representation of the three single-nucleotide polymorphisms (SNPs) in the *TAS2R38* gene: rs713598, rs17268866, and rs10246939. (b) Representative Sanger sequencing chromatograms spanning all three SNP loci. (c) Representative SNaPshot sequencing electropherograms showing allele-specific peaks for each SNP.

The chromatograms illustrate distinct allele-specific peak patterns corresponding to non-tasters (AVI/AVI), recessive tasters (PAV/AVI), and dominant supertasters (PAV/PAV) at key polymorphic sites of the *TAS2R38* gene. These characteristic peak signatures confirm accurate genotype discrimination and their concordance with bitter-taste phenotypes.

Individual SNP analysis was carried out to see if there was any significant association of the SNPs with *Prakriti*. These were also tested with respect to the bitterness score as a phenotype. SNP allele frequencies were calculated manually. Individual SNP analysis revealed no significant associations: rs713598 ( $p = 0.71$ , Cramér's  $V \approx 0.06$ ), rs1726866 ( $p = 0.81$ , Cramér's  $V \approx 0.05$ ), and rs10246939 ( $p = 0.73$ , Cramér's  $V \approx 0.06$ ) were all non-significant across classified *prakriti* groups. However, the bitterness score as a phenotype was strongly associated with individual genetic variations, though not with *Prakriti* classification. SNP allele frequencies were calculated manually. Haplotype and diplotype frequency distributions were tabulated based on the assigned *Prakriti* (Supplementary Table 6). Genotype frequencies at rs713598, rs1726866, and rs10246939 did not differ across KP, PV, and VK groups (all  $\chi^2$   $p$ -values  $> 0.70$ ; FDR-adjusted  $p = 0.81$ ), with uniformly small effect sizes (Cramér's  $V < 0.06$ ). All genetic association analyses were performed using the base package of R (version 4.4.3)

### 3.2 Phenotype and Genotype Concordance

The PTC bitterness scores showed a strong association with genotype, distinguishing tasters from non-tasters. Individuals carrying homozygous PAV and PAV/AVI genotypes ( $p < 2 \times 10^{-16}$ ) demonstrated significantly higher bitterness perception compared to non-tasters with the homozygous AVI genotype, even after adjustment for anthropometric measures. This finding served as an internal validation of our phenotypic assessment.

The concordance between phenotypic and genotypic distributions assessed using the Kolmogorov–Smirnov (K–S) test yielded  $D = 0.33$  with  $p = 1.0$ , indicating no statistically significant difference between the cumulative distributions of phenotype-based and genotype-based classifications. This result demonstrates a strong concordance between observed bitter taste perception and *TAS2R38* genotypes. These findings support the reliability of PTC taste strip-based phenotyping as a practical surrogate for genotypic classification of *TAS2R38*, validating its use for large-scale screening where molecular genotyping may not be feasible.

**Table 2. Cumulative distributions of phenotype based on PTC strips and genotype based on *TAS2R38* bitter taste gene classification.**

|                             | Phenotype | Genotype |
|-----------------------------|-----------|----------|
| <b>Non-Taster</b>           | 105       | 102      |
| <b>Recessive taster</b>     | 131       | 125      |
| <b>Dominant Supertaster</b> | 19        | 28       |
| <b>Total</b>                | 255       | 255      |

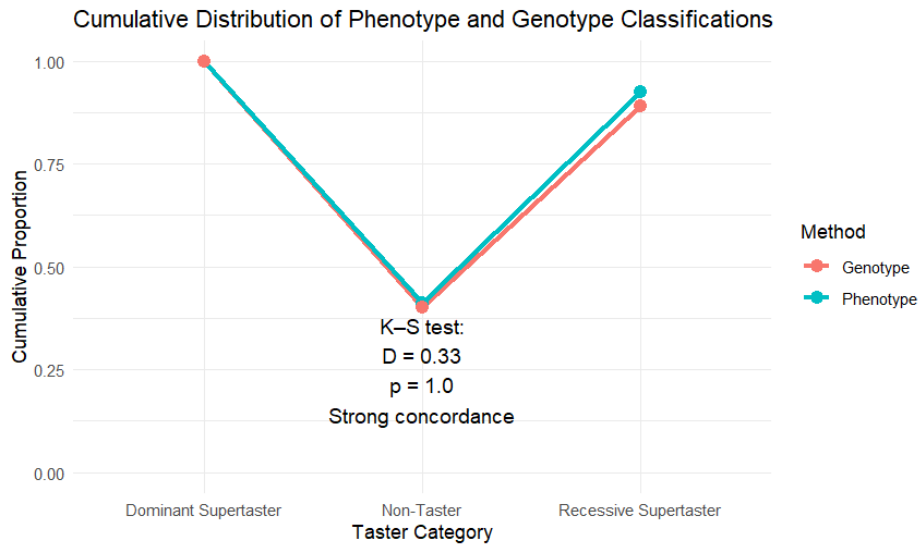


**Figure 2.** The Kolmogorov–Smirnov test revealed no significant difference between the two distributions ( $D = 0.33$ ,  $p = 1.0$ ), indicating strong concordance between PTC-based phenotyping and *TAS2R38* genotyping.

### 3.3 Association of bitter taste perception with *Prakriti*

The PTC test was carried out on a total of 289 individuals whose *Prakriti* types were also assessed (Supplementary Table 9). There was a dominance of *Kapha Pitta* (46.6%) in the cohort. In our analysis, mixed *Prakriti* groups were considered for analysis due to the limited sample size of individuals belonging to single *Prakriti* categories (*V* (8), *P* (5), and *K* (6)) and the *VPK* (2) groups. When we examined whether *Prakriti* was associated with bitterness scores after controlling for relevant variables, we found that perception scores were not significantly related to Ayurveda *Prakriti* classification ( $p > 0.05$ ). Although genotype emerged as the strongest predictor of bitterness perception, with PAV and PAV/AVI genotypes showing significantly higher scores ( $p < 2 \times 10^{-16}$ ). Gender also remained a significant factor, with males exhibiting lower bitterness scores than females ( $p < 0.01$ ). BMI and WHR were not significantly associated with bitterness scores after adjustment.

The distribution of *TAS2R38* genotypes across *KP*, *PV*, and *VK* *Prakriti* groups is presented in Table 3. Pearson's chi-square test did not reveal a significant association between *TAS2R38* genotype and *Prakriti* category ( $p = 0.43$ ). Effect size estimation using Cramér's *V* indicated a weak association (Cramér's *V* = 0.099). Similarly, Fisher's exact test with Monte Carlo simulation also showed no significant association between genotype distribution and *Prakriti* classification ( $p = 0.429$ ). Together, these results suggest that *TAS2R38* genotype frequencies do not differ meaningfully across the three *Prakriti* groups.

To control for potential confounding by anthropometric and demographic factors, we fitted multinomial logistic regression models with Ayurveda *Prakriti* as the outcome variable. Genotype categories (PAV, AVI, and PAV/AVI), age, sex, WHR and BMI were included as predictors. After adjustment, the *TAS2R38* genotype remained non-significant for *Prakriti* classification. None of the genotype categories showed statistically significant odds for

belonging to *PV* or *VK Prakriti* when compared with *KP*, confirming that the lack of association persisted even after controlling for age, sex, and BMI. Overall, *TAS2R38* genotypes did not show a direct association with Ayurveda *Prakriti* classification.

**Table 3: Distribution of Ayurveda *Prakriti* Types in our population according to *TAS2R38* genotype**

| <i>Prakriti</i> group | Non-taster (AVI/AVI) | Recessive Supertaster (PAV/AVI) | Dominant Supertaster (PAV/PAV) | Rare | Total | Frequency (%) |
|-----------------------|----------------------|---------------------------------|--------------------------------|------|-------|---------------|
| <i>K</i>              | 2                    | 4                               | 0                              | 0    | 6     | 1.8           |
| <i>P</i>              | 2                    | 3                               | 0                              | 0    | 5     | 1.5           |
| <i>V</i>              | 3                    | 4                               | 0                              | 1    | 8     | 2.5           |
| <i>KP</i>             | 57                   | 69                              | 15                             | 11   | 152   | 46.6          |
| <i>PV</i>             | 16                   | 26                              | 6                              | 7    | 55    | 16.9          |
| <i>VK</i>             | 36                   | 48                              | 11                             | 3    | 98    | 30.1          |
| <i>VPK</i>            | 2                    | 0                               | 0                              | 0    | 2     | 0.6           |
| Total                 | 118                  | 154                             | 32                             | 22   | 326   | -             |

### 3.4 Cluster identification and chemical enrichment

To further validate our findings and explore the potential impact of bitter compounds on the medicinal value of plants, we integrated bitter molecules from BitterDB with phytochemical data from the IMPPAT database. We first identified bitter compounds by comparing BitterDB with IMPPAT, a database of chemicals from Indian medicinal plants. Out of 2,250 known bitter molecules, 417 were also found in medicinal plants. After cleaning and standardizing these compounds, they were used for further analysis. We performed two kinds of analysis – (1) Clustering of medicinal plants on the basis of bitter molecules (2) Docking of molecules of a cluster enriched in compounds reported for binding to *TAS2R38* with Alphafold-derived structure of *TAS2R38*.

PCA of the TF-IDF normalized phytochemical profiles revealed a structured but compressed global organization of plant chemical space. The first two principal components explained 2.3% (PC1) and 2.1% (PC2) of the total variance, respectively. This observed low variance can be expected here because abundant common compounds get penalized due to TF-IDF normalization. This allowed variance distribution from generic compounds to plant-specific phytochemicals in the PCA. Plants formed a dense central core near the origin, accompanied

by two orthogonal extensions: a vertical axis along PC2 and a horizontal axis along PC1 (Figure 3). These extensions represent major axes of chemical differentiation. Silhouette analysis of k-means clustering on the first two principal components showed a stable high-quality clustering regime for  $k = 2-5$ , with maximal silhouette values observed at  $k = 3$  (0.936) and similarly high values at  $k = 4$  (0.917) and  $k = 5$  (0.881). A sharp decline in silhouette score beyond  $k \geq 6$  indicated over-partitioning. Based on both silhouette stability and PCA geometry, four clusters in PCA were identified and retained as PCA-based clusters.

To resolve finer-scale chemical structure beyond linear trends, UMAP embedding of the TF-IDF-normalized matrix was performed, followed by density-based clustering using HDBSCAN. This approach identified 22 non-noise UMAP clusters, alongside 354 plants ( $\approx 13.5\%$ ) classified as noise. Cluster sizes were highly heterogeneous. One dominant cluster (cluster 2) contained 1,338 plants, representing a broad, chemically generic phenotype, while several medium-sized clusters (50–170 plants) and multiple smaller clusters (20–40 plants) captured increasingly specialized chemical phenotypes. The presence of both large and small clusters supports the use of density-based clustering rather than partition-based methods. A table of plants according to their membership and coordinates on PCA & UMAP, generated by collating the information, is provided in the supplementary table 7. The phytochemicals enriched in each of these clusters are given in the supplementary table 8. Many known *TAS2R38-binding* chemicals, such as berberine, were highly enriched in cluster 4 along with other compounds like Jatrorrhizine, oxyacanthine, and Magnoflorine, with an adjusted p value  $\leq 0.01$  (supplementary table 7).

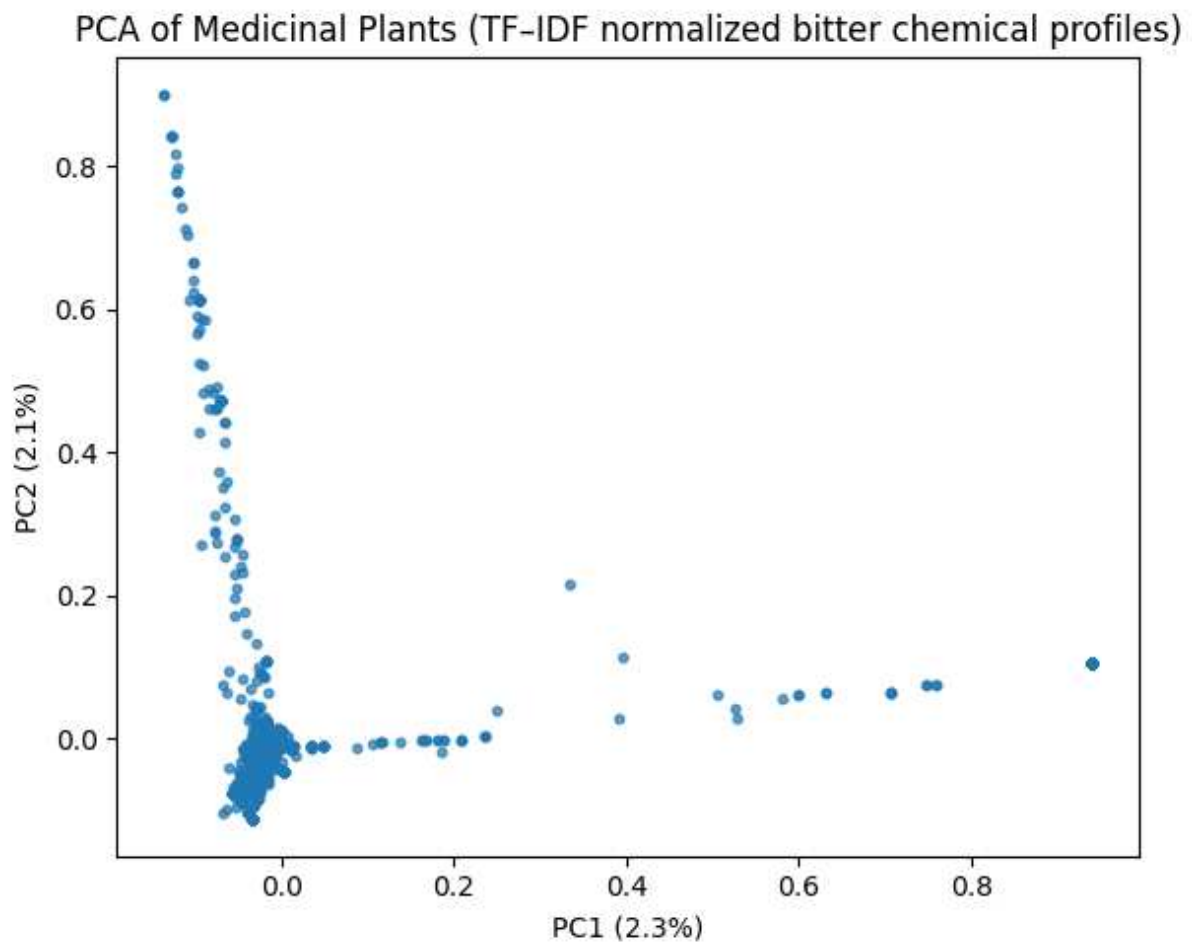


**Figure 3:** PCA of TF-IDF–normalized bitter phytochemical profiles across plant species. Each point represents a plant species; variance explained by each component is shown.

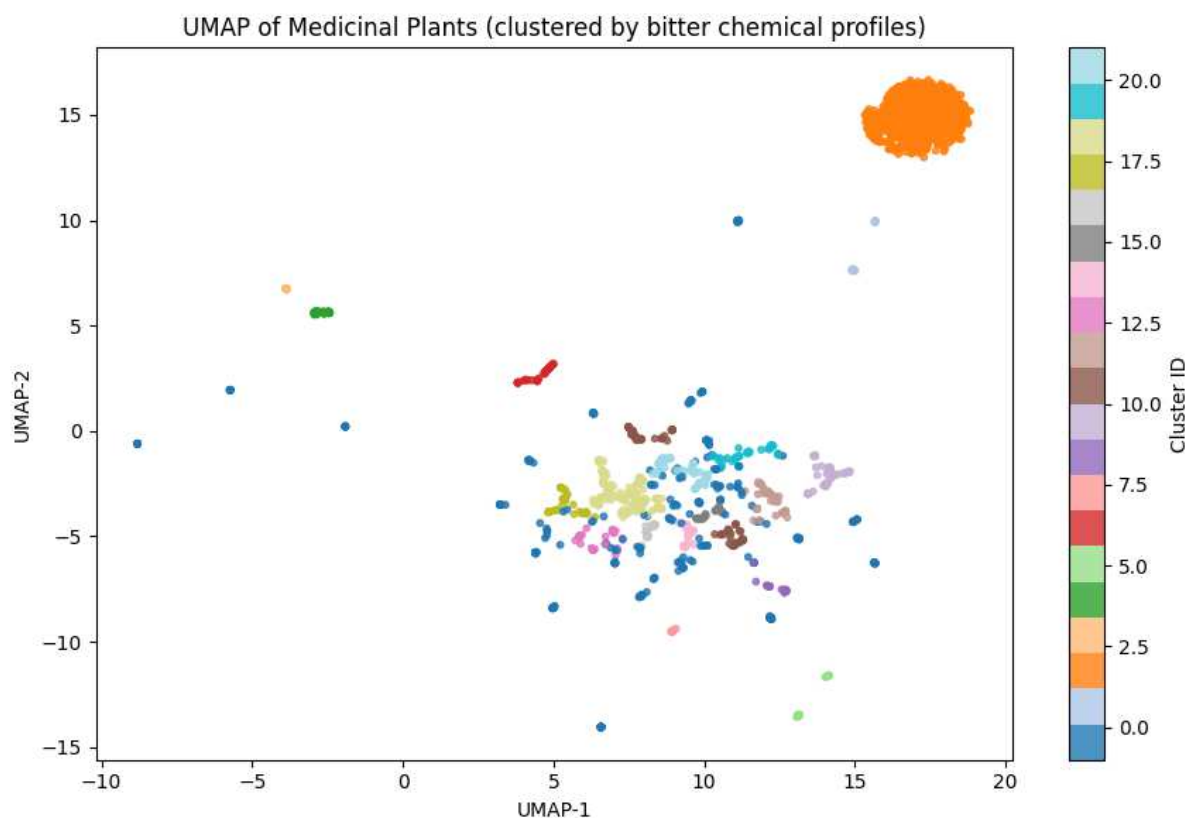


**Figure 4:** UMAP embedding of medicinal plants based on TF-IDF–normalized bitter chemical profiles. Points represent plant species and are coloured by cluster identity, reflecting similarity in shared bitter chemical composition.

### 3.5 *TAS2R38* model and Binding Pocket prediction

The AlphaFold-predicted *TAS2R38* structure (AF-P59533-F1; UniProt P59533) was downloaded, and the receptor model was then used for binding-site identification (DoGSite3) and for defining the docking search space. DoGSite3 pocket prediction identified a top-ranked cavity in the AlphaFold-predicted *TAS2R38* structure. The predicted pocket had a volume of 1833.38 Å<sup>3</sup>, a surface area of 1827.32 Å<sup>2</sup>, a depth of 28.41 Å, and a druggability score of 0.81. These values indicate a well-defined and druggable binding site. This cavity was therefore used to define the docking search space and has been highlighted in Figure 5.

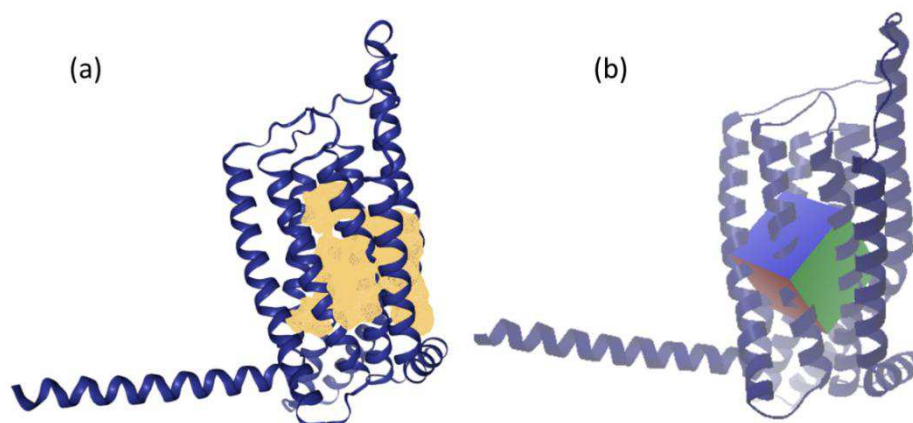


**Figure 5:** (a) Top-ranked binding cavity predicted by DoGSite3 mapped onto the AlphaFold-predicted *TAS2R38* structure (pocket surface shown in yellow). (b) AutoDockTools (ADT) docking grid box centered on the PTC binding pocket region (grid shown as a colored box), used to define the search space for docking.

### Molecular Docking

Molecular docking was performed for the Cluster 4 chemicals (Table 4). Using the DoGSite3-predicted cavity (centred on the reported PTC-interaction region), we docked the phytochemical library against the *TAS2R38* model and evaluated binding energies and pocket interactions from the top-ranked poses. The predicted binding energies of the best docked poses of the phytochemicals are seen in Table 4. Docking results identified Coptisine (-10.48 kcal/mol) as the top hit, followed by Baicalin (-9.64 kcal/mol), Berberine (-9.23 kcal/mol), Wogonin (-8.87 kcal/mol), and Picrotoxinin (-8.78 kcal/mol). The best-ranked poses for these ligands consistently were observed to be bound within the predicted binding pocket, and make interactions with the pocket as observed in the protein–ligand interaction plots shown in Figure 6.

**Table 4. Molecular Docking results from AutoDock4. The top 5 chemicals that have high binding affinity with the *TAS2R38* target protein are highlighted in grey.**

| Ligand ID   | Compound Name | Binding energy (kcal/mol) |
|-------------|---------------|---------------------------|
| IMPHY006688 | Coptisine     | -10.48                    |
| IMPHY004115 | Baicalin      | -9.64                     |

|                   |                            |              |
|-------------------|----------------------------|--------------|
| IMPHY005665       | Berberine                  | -9.23        |
| IMPHY005530       | Wogonin                    | -8.87        |
| IMPHY000986       | Picrotoxinin               | -8.78        |
| IMPHY000985       | Picrotin                   | -8.74        |
| IMPHY005607       | Baicalein                  | -8.72        |
| IMPHY011813       | Unii-kki91P85GE            | -8.69        |
| IMPHY010550       | Naringenin                 | -8.62        |
| IMPHY008905       | Magnoflorine               | -8.59        |
| IMPHY007190       | Jatrorrhizine              | -8.45        |
| IMPHY005455       | Orientin                   | -8.42        |
| IMPHY011906       | Noscapine                  | -8.27        |
| IMPHY011844       | Chlorogenic acid           | -8.19        |
| IMPHY007084       | Vanillic acid              | -8.11        |
| IMPHY014396       | Quercetin-3-glucoside      | -7.91        |
| IMPHY004388       | Kaempferol                 | -7.89        |
| IMPHY008724       | Isorhamnetin               | -7.76        |
| IMPHY004631       | Stearic acid               | -6.94        |
| IMPHY011933       | Caffeic acid               | -6.77        |
| <b>CID_676454</b> | <b>Phenylthiocarbamide</b> | <b>-6.57</b> |
| IMPHY012713       | Vitexin                    | -6.54        |
| IMPHY011797       | Oleic acid                 | -6.48        |
| IMPHY004619       | Quercetin                  | -6.42        |
| IMPHY014990       | Linoleic acid              | -6.41        |
| IMPHY005330       | Palmatine                  | -6.39        |
| IMPHY011974       | 4-Hydroxycinnamic acid     | -6.37        |
| IMPHY011802       | Ferulic acid               | -6.32        |
| IMPHY008689       | Isovitexin                 | -6.29        |
| IMPHY003578       | Oxyacanthine               | -6.22        |
| IMPHY012721       | Isoquercitrin              | -6.21        |

|             |               |       |
|-------------|---------------|-------|
| IMPHY015047 | Rutin         | -6.20 |
| IMPHY009035 | Formononetin  | -6.12 |
| IMPHY007327 | Palmitic acid | -5.96 |
| IMPHY001971 | 1-Penten-3-OL | -5.89 |
| IMPHY011985 | Nicotiflorin  | -5.83 |
| IMPHY011707 | beta-Carotene | -5.55 |
| IMPHY001801 | Isoorientin   | -5.32 |
| IMPHY000060 | Myristic acid | -5.21 |

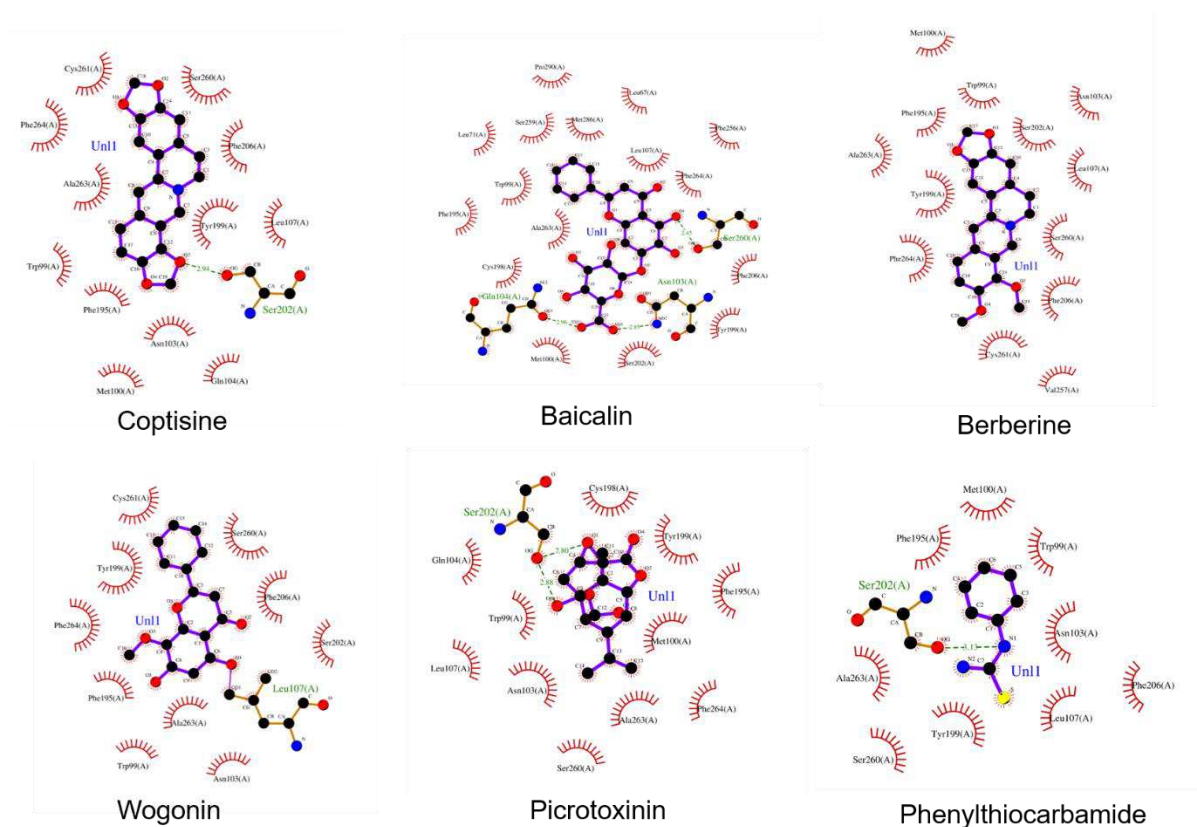


**Figure 6:** Protein–ligand interaction diagrams for the best docked poses using LigPlot+ v2.2.9 with *TAS2R38*.

## Discussion

This study provides a unique framework for integrating Ayurvedic phenotyping with taste receptor genetics. Our study reveals that beyond the variations that align with *Prakriti*-based differences, extensively reported in genetic studies, there exist stabilized functional variants across populations that could govern significant variability within *Prakriti* groups, especially in the mixed types. In this specific study, we demonstrate this in the context of responsiveness to *Tikta Rasa*, which, according to Ayurveda, is not only influenced by constitutional *Prakriti* but is more dynamically modulated by *Vikriti*. (Supplementary verses 2, 3). Our results indicate that genetic variability in the taste receptor *TAS2R38* could act as a modulator of this response. Notably, these genetic differences can be readily captured using validated taste strips to assess bitter taste sensitivity. Through non-invasive point-of-care assessments, practitioners can adopt a dual-layer model: using *Prakriti* to understand a patient's systemic constitution and *TAS2R38* status to predict specific ligand-receptor interactions. We also observed a large fraction of medicinal plants used in Ayurveda to harbour ligands that could exert their effects through *TAS2R38*, and variability around this axis could have widespread systemic effects due to the extra-oral functions reported for this bitter taste receptor (Supplementary Table 10). This could enable rational use of bitter herbs for maximizing therapeutic efficacy.

### ***TAS2R38* polymorphic states could independently modulate differential bitter taste responses across *Prakriti* groups**

The primary objective of this study was to determine if specific *Prakriti* types are associated with *TAS2R38* bitter taste genotypes and whether phenotypic taste perception (PTC) can serve as an objective clinical proxy for these differences. In Ayurveda, the administration of bitter herbs (*Tikta Rasa*) requires careful calibration; while they are essential for resolving inflammation and enhancing metabolism in *Pitta* and *Kapha* types, their inherent drying properties necessitate lower dosages in *Vata*-dominant individuals to avoid dehydration. Based on these biological differences and functional requirements as well as prior reports of pharmacogenetic studies, we hypothesized that genetic variations in bitter taste would differ significantly between *Prakriti* groups and the markers could objectively capture these differences. Noteworthy, we observed no significant difference between the *Prakriti* groups, with each group having a distribution of tasters, non-tasters and moderate tasters anticipated of a random mating population in HWE. These patterns mirror the distribution of the general population. With respect to bitter taste perception, we observe differences across gender, with males exhibiting lower perception. However, these trends were not observed at the genetic level. While there is fair concordance between genotypes and phenotypes, taste perception may be confounded by external variables; thus, genotyping may provide more definitive inference with respect to taste perception at the molecular level.

The observation of HWE across *Prakriti* groups is particularly striking. A large fraction of *Prakriti* groups are mixed types, and our analysis primarily focused on these in the cohort. Mixed types are often more difficult to assess clearly in clinical settings compared to predominant types, and the relative contributions of each dosha are vital for rational

therapeutics. So far most of the studies have been carried out in predominant *Prakriti* types that account for one-tenth of the population. Traditionally, it is suggested that *Vata-dominant* individuals exhibit lower tolerance to *Tikta Rasa* due to its *Ruksha* (drying) and *Laghu* (light) *Guna* (qualities), whereas *Pitta* and *Kapha* constitutions generally tolerate bitter substances better owing to their cooling (*Sheeta*) and drying (*Ruksha*) actions. (Supplementary Verses 4, 5). However, therapeutic dosing is determined by disease state (*Vikriti*) and digestive capacity (*Agni*) rather than *Prakriti* alone. Based on these inherent differences, mixed *Prakriti* groups, depending on the *Dosha* and *Guna* inheritance along with genetic variation, may elicit different responses to a bitter herb. For instance, a *Vata-dominant* individual with the ‘supertaster’ (PAV/PAV) genotype may exhibit stronger aversion to *Tikta Rasa*, potentially limiting its intake and possess a protective mechanism against excessive bitter intake. whereas in *Kapha-dominant* individuals, the ‘supertaster’ (PAV/PAV) genotype may be insufficient to counteract obesity driven by underlying metabolic and lifestyle factors. Conversely, a *Pitta-Kapha* individual predisposed to inflammation and obesity with a non-taster (AVI/AVI) genotype might fail to respond to bitter formulations that act through *TAS2R38*. Unlike other markers reported earlier, taster status thus cannot be considered a molecular proxy for *Prakriti*. This independence may provide a vital mechanistic explanation for the inter-individual variability in therapeutic response observed even among patients of the same *Prakriti*.

### **Bitter taste response markers can provide molecular explanations for *Satmya* and *Upshaya-Anupshaya***

According to Ayurveda a successful treatment outcome depends on understanding the interaction between disease (*Rog*), the patient (*Rogi*) and the medicine (*Aushadha*). Though *Prakriti* baselines govern inherent susceptibility, there are other aspects to be considered (*Dashvidhpariksha*) (Supplementary Verse 6) during treatment. One of them is habituation or suitability (*Satmya*). This study suggests that variability in genes such as *TAS2R38* could provide molecular connections to *Satmya* aspects even within the same *Prakriti* groups. For the same *Prakriti* (e.g., *Pitta-Kapha*) with different haplotypes (PAV vs AVI), there could be different responses to bitter medications. A non-taster (AVI/AVI) or a moderate taster (PAV/AVI) may have a higher *Satmya* for intense bitter taste (*Tikta Rasa*), while a supertaster (PAV/PAV) would find the same herb intolerant leading to poor compliance or even a harmful effect. Also, the study on the molecular docking provides a link to the *Aushadha* axis such that certain classes of bitter (*Tikta*) drugs harbouring some phytochemicals, such as berberine, would have different efficacy due to the genetic polymorphism (*Satmya*) even though they are widely used for the resolution of inflammatory conditions. Since the medicine just does not work through systemic digestion but through specific receptor-mediated pathways, these differences could be apparent at the system-wide level. In this case the polymorphism could also explain the diagnostic logic (*Upshaya-Anupshaya*) of *Nidan Panchaka*. For example, a patient with an inflammatory condition (*Rog*) with an adverse response to the bitter herb (*Anupshaya*) might be due to not only *Prakriti* but also to their *TAS2R38* variation (*Satmya*) that prevents the herb from binding to the cognate receptor to trigger the anti-inflammatory response. Integrating constitutional traits with receptor-level sensitivity mirrors FDA-approved guidelines that mandate dose adjustments based on specific SNPs. Just as SNPs in enzymes

like CYP450 dictate precise dosage shifts in conventional medicine (Zheng et al., 2025), we propose that *TAS2R38* serves as a comparable receptor-level biomarker for Ayurvedic therapeutics. However, it might be worthwhile to mention that Ayurvedic herbs with polypharmacological compositions might have molecules that could modulate the activity of different bitter taste receptors, also through binding in allosteric sites.

### **The Bitter Taste Perception Link to Obesity and *Kapha* Management**

A bitter taste response has profound implications for the management of obesity (Liszt et al., 2022; Choi, 2019), a condition traditionally associated with *Kapha* dominance and *Medas* (fatty tissue) accumulation. *TAS2R38* is expressed in extraoral tissues, such as the enteroendocrine L-cells of the gut. When activated by bitter ligands, this receptor acts as an agonist for glucagon-like peptide-1 (GLP-1) and mediates the release of cholecystokinin (CCK) – hormones that increase satiety, slow gastric emptying, and improve insulin sensitivity (Pham et al., 2016), (Wang et al., 2024), (Wang et al., 2025).

In the context of obesity, an individual with the AVI/AVI (non-taster) genotype may lack the robust GLP-1 surge typically induced by bitter formulations. This could create a physiological mismatch in a *Kapha*-type patient who is already predisposed to a slow metabolism. Such individuals may exhibit a higher preference for calorie-dense foods and a diminished therapeutic response to bitter drugs. Stratifying obesity treatments by *TAS2R38* status could enable clinicians to identify patients who require intensified bitter therapy to overcome this receptor-level deficiency.

### **The PTC Taste Strip in clinical settings**

The strong concordance observed between PTC taste intensity scores and *TAS2R38* genotypes ( $D=0.33$ ,  $p=1.00$ ) establishes PTC-based assessment as a robust functional surrogate for genetic testing. This validation is particularly relevant for resource-constrained environments. Integration of a test that explains variability in bitter taste response, either by a kit or genetic testing, could serve as a clinical proxy for *Upashaya* and can reduce the time to arrive at the right dosage calibration by a trial-and-error approach. Thus, if a patient is a supertaster, anticipating a stronger anti-inflammatory response, a lower dosage of *Tikta* herb can be administered; else there could be a higher risk of *Anupshaya* due to oversensitivity. Also, the study highlights that integration of such variation can also enable precision treatment even within *Prakriti* groups. Earlier studies have reported the distribution of pharmacogenes between *Prakriti* groups. This work suggests *Prakriti* alone is insufficient for prescribing potent bitters like *Kutki* (*Picrorhiza kurroa*) or neem, and taste phenotyping should become a standard part of *Dashvidha Pariksha* (patient examination).

Since bitter taste receptors have extraoral effects of *TAS2R38*, polymorphism in this receptor could also have variability in response to the effect of bitter medicine in extraoral tissues. The final aspect is the clinical compliance and dosage (*Matra*). "Non-tasters" might require higher doses of bitter formulations to achieve the same physiological "trigger", whereas "supertasters" might experience the Vata-aggravating effects of *Tikta Rasa* (dryness, depletion) much faster.

Thus, by using a non-invasive, low-cost bedside test, clinicians can objectively personalise Tikta-based therapies, moving toward a tiered approach: identifying the baseline Prakriti and then integrating genetic sensitivity to refine the treatment.

### **Bitter ligands from Ayurvedic herbs could demonstrate variability in systemic responses**

Molecular Docking is usually done to predict the binding affinities of the molecules with the receptor, and it is important to know the threshold of binding affinities at which signalling is turned on. Bitter herbs from Ayurveda so far have not been extensively integrated with modern approaches for identification of better therapeutic leads (De León et al., 2021). In our study, we carried out an exploratory docking study of phytochemicals from cluster four with the *TAS2R38* receptor structure and have taken PTC as the control (Supplementary Table 10). Coptisine, baicalin, berberine, wogonin, and picrotoxinin showed the highest binding energy with the AlphaFold structure of *TAS2R38*. How these binding energies impact the response of drugs needs to be further studied in the case of both tasters (PAV) and non-tasters (AVI) through molecular dynamics simulations.

Our clustering analysis of molecules from BitterDB reveals that not all bitter plants are functionally equivalent. Phytochemicals such as berberine and jatrorrhizine (found in *Berberis aristata* and *Tinospora cordifolia*) (Kumar Verma et al., 2021) exhibit significantly higher binding affinity to taster variants in docking studies (Ren et al., 2025b) (Subramanian et al., 2025) (Chen et al., 2026) (Biarnés et al., 2010). This provides a structural rationale for why certain herbs are more effective in specific individuals. Given that *TAS2R38* is implicated in GLP-1 secretion and nitric oxide production (Wang et al., 2025), these variations likely contribute to differences in how patients manage inflammatory conditions and regulate metabolism (Cui et al., 2024).

### **Limitations and Future Directions**

Despite its foundational nature, this study has limitations, most prominently the sample size, which suffices for an exploratory study but requires validation in larger datasets. Furthermore, humans possess 25 bitter taste receptors, many of which have been reported to have functional variations. Future studies should focus on a panel of variations across different taste receptors. Given that phenotypic variability is evident across gender and age, taste strip results might not be reliable if not interpreted correctly, alongside the genotype. Finally, molecular docking does not account for all potential binding sites or the polypharmacological nature of Ayurvedic preparations, which may target different regions of the protein or compensate for activity loss by binding to other taste receptors. Another area where this could have confounding observations is when an individual has *Ama* (Supplementary Verse: 7) that compromises bitter sensation. In such cases the phenotypic responses might not reveal true tasting status, and use of the strip might be misleading. This has to be validated with the genetic data. Conversely, since the bitter response is restored upon alleviation of *Ama*, such strips could also be utilised to monitor resolution of *Ama* in clinical settings. Ruling out the possibility of true response versus confounding because of an ongoing *Ama* status is a subject of future investigation.

## Conclusion

Our results for the first time demonstrate how genetic variations, in this case polymorphisms in the bitter taste gene *TAS2R38*, can act as independent modulator rather than a part of *Prakriti* trait. This is a critical finding that highlights the possibility of discovering molecular markers of *Satmaya* (individual suitability) that exist beyond baseline *Prakriti*. These could be integrated in the objective tool kit of *Dasvidhpariksha*. Furthermore, the strong genotype-phenotype concordance highlights the potential use of non-invasive taste strips as a powerful bedside tool. These observations could help explain differences in therapeutic responses (*Upshaya-Anupshaya*) in *Vikriti*. The phenotype-genotype correlation and response could also provide a novel method to distinguish as well as monitor the status of *Ama* which often compromises bitter response during active diseases.

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**Data availability:** The data underlying this study are available in the published article and its supporting information. Sequencing data will be made available on request.

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