RESEARCH ARTICLE

# Exploration of taste-masking functional compounds based on sequential drug therapy and their application mechanism in taste-masking products

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**The taste-masking technology refers to strategies aimed at reducing or blocking undesirable sensory experiences such as the bitterness of drugs to enhance patient medication adherence. Traditional methods for masking bitterness including the addition of sweeteners, coatings, or microencapsulation often fail to effectively mask the strong bitterness found in traditional Chinese medicine (TCM) formulations. Current research on flavor masking in TCM primarily relies on expert judgment, lacking an objective and systematic screening mechanism for functional taste-masking substances. This study aimed to identify candidate compounds with broad-spectrum taste-masking activity using a sequential administration method and explore their mechanisms of action. Using berberine hydrochloride as a model bitter drug, various functional taste-masking compounds including linalool and cinnamaldehyde were identified, which significantly reduced bitterness intensity. The extent of bitterness reduction was defined as the difference in bitterness scores between the control and treatment groups, expressed as a percentage of the control score ranging from 30 to 50%. The validation tests used aqueous extracts of TCM tablets. The results showed that these compounds exhibited a significant bitterness-reducing effect on multiple TCM formulations with the masking effect ranging from 30 to 90%. Further sodium ion fluorescence probe cell experiments showed that linalool and menthol respectively reduced intracellular sodium ion fluorescence intensity by 55% and 57% ($P < 0.01$), indicating their potential to interfere with bitterness signaling pathways and confirming their clear taste-masking potential. The findings of this study provided a systematic screening strategy and mechanism validation for the development of taste-masking agents, which might improve the clinical acceptance and patient satisfaction of bitter TCM formulations.**

**Keywords:** taste-masking; bitterness; traditional Chinese medicine; screening; fluorescent labeling.

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## Introduction

The palatability of a drug directly impacts patient adherence and therapeutic outcomes, particularly in oral formulations, where bitterness often becomes a barrier to medication compliance in children and the elderly. Therefore, improving the taste of drugs has

become a significant challenge in drug development. Traditional taste-masking methods typically rely on taste-masking agents that directly interact with bitter taste receptors. However, their effect is often short-lived and may interfere with the drug's components, potentially affecting its efficacy. With the rapid development of functional foods and oral medications, taste-masking technologies have continuously innovated, enhancing product market acceptance.

Taste-masking functional compounds are primarily classified into two categories including natural products and synthetic products. Natural taste-masking agents, due to their natural origin and high safety, are more easily accepted. Sterneder *et al*. isolated 4'-demethyl-3,9-dihydroeucomin (DMDHE) from dragon's blood resin, which reduced the bitterness of quinine by 14.8% and confirmed that its masking mechanism involved the TAS2R14 receptor [1]. Raithore *et al*. also found that citrus components such as feruloylprolamine and paclitaxel could significantly reduce bitterness [2]. Belloir *et al*. pointed out that adenosine monophosphate (AMP) in yeast extracts could significantly decrease TAS2R activation levels [3]. In terms of synthetic products, common examples include flavor modifiers, bitterness blockers, and cyclodextrin complexes. Korelc *et al*. and Atalay *et al*. confirmed that cyclodextrins could reduce the release of bitter drugs by forming inclusion complexes, thereby improving the taste [4, 5]. The perception of bitterness is primarily mediated by the TAS2Rs receptors and their signaling pathways. Bitter substances dissolve in the oral cavity and, upon binding to TAS2Rs, activate the phospholipase C (PLC) pathway, which leads to the release of calcium ions through the mediation of diacylglycerol (DAG) and inositol trisphosphate (IP3), and the signal is transmitted to the central nervous system *via* the transient receptor potential cation channel subfamily M member 5 (TRPM5) [6-8]. TRPM5 is involved not only in bitterness but also in the perception of sweetness and umami [9]. Additionally, other members of the transient receptor potential (TRP) family including TRPM8 and TRPV1 are also involved in taste regulation [10, 11]. For example, menthol as a TRPM8 agonist can mask bitterness by providing a cooling sensation [12], while capsaicin as a TRPV1 agonist interferes with the perception of bitterness through a numbing effect [13]. Despite the application of various taste-masking agents in practice, issues such as significant individual sensitivity differences, unclear mechanisms of action, and limited applicability remain. For instance, grapefruit extract has a reduced efficacy in individuals carrying CYP3A4 gene mutations [14]. Certain sweeteners and sour agents may trigger obesity or metabolic disorders, while effective in masking flavor [15]. In addition, most taste-masking products are still primarily focused on pediatric medications or dietary supplements with insufficient specificity and stability for certain drugs [16]. Although flavor modifiers and bitterness interceptors can inhibit specific TAS2Rs receptors [17], or improve drug stability and solubility through cyclodextrin complexation [18], they still fall short of meeting the broad-spectrum requirements for bitterness masking.

In recent years, "sequential drug therapy" has gradually gained attention as an emerging taste-masking strategy, which involves the use of taste-masking components to act on the ion channels of taste cells, particularly TRPM5, before the administration of a bitter drug, thereby interfering with taste signal transduction and reducing bitterness perception [19-21]. The advantage of this method lies in avoiding direct interactions between the drug and the masking agent, achieving a taste-masking effect with lower doses, fewer side effects, and a longer-lasting impact. Based on this, this study proposed a novel screening method for taste-masking agents using a sequential drug therapy strategy. The research followed a "masking first, then administering the bitter drug" approach and combined with sodium ion fluorescence labeling cell experiments to quantitatively assess the impact of taste-masking agents on intracellular sodium ion concentration, thereby screening for

potential taste-masking components. Meanwhile, the broad-spectrum taste-masking effect was evaluated by using aqueous extracts of bitter traditional Chinese medicine tablets as a model. The TRP channel blocker TPPO was introduced to validate the specificity and reversibility of the mechanism of action. This strategy provided a theoretical basis for the development of highly specific, low-side-effect novel taste-masking functional compounds, which would be significant for enhancing the acceptability and patient adherence to oral medications. It also offered new directions for innovation in functional foods and oral care products.

## Materials and methods

### Screening of sequential therapy compounds and volunteer selection

Commonly used and clinically safe functional bitter/taste masking products approved for clinical trials by the National Medical Products Administration (NMPA) (Beijing, China) were selected as research subjects, which included vanillic acid, peramivir, aminobutyric acid, hydroxyvanillic acid, phloretin, carvacrol, dihydrojasmonic acid, amlodipine, nifedipine, dodecalactone, trimethylcyclohexanol, decalactone, eplerenone, linalool, citral, cinnamaldehyde, eugenol acetate, menthone, monomethyl succinate, menthol, gingerol, piperine, eucalyptus oil, borneol, menthylamide, coolant ws-5, coolant ws-23, allicin, caryophyllene. All 29 products were purchased from Shanghai McLean Biochemical Technology Co., Ltd. (Shanghai, China) and numbered from 1 to 29 and made into solutions with a mass concentration of 0.1%. Berberine hydrochloride was used as a standard bitter agent. The classic sensory evaluation method was employed to assess the bitterness-masking effect. A total of 40 healthy adult volunteers including 19 males and 21 females, aged from 18 to 35 years old were recruited for this research. The procedures of this study were approved by the Ethics Committee of Zhengzhou University of Industrial Technology (Zhengzhou, Henan, China). All participants were provided with written informed consent.

### Determination of bitterness rating scale and sensory correction

To establish a standardized bitterness scoring system, this study used berberine hydrochloride as a reference bitter agent and prepared five concentration gradients of aqueous solutions as 0.01 mg/mL, 0.03 mg/mL, 0.10 mg/mL, 0.30 mg/mL, and 1.00 mg/mL to cover a range of bitterness intensities from mild to strong. The concentration levels were determined based on the results of a preliminary experiment, where the bitterness perception threshold of the volunteers was assessed, ensuring that the full range of bitterness from acceptable to unacceptable was encompassed. A double-blind method was used to organize trained volunteers for sensory evaluation. The participant's subjective bitterness rating for each concentration solution was recorded, and the average score was calculated. The bitterness grading standards were established based on 5 different levels of berberine hydrochloride, where level 1 was no bitterness or almost no bitterness with the berberine hydrochloride concentration of 0.01 mg/mL and bitterness score of 0.5 – 1.5; level 2 was slightly bitter with berberine hydrochloride concentration of 0.03 mg/mL and bitterness score of 1.5 – 2.5; level 3 was bitter but acceptable with berberine hydrochloride concentration of 0.10 mg/mL and bitterness score of 2.5 – 3.5; level 4 was clearly bitter but still tolerable with berberine hydrochloride concentration of 0.30 mg/mL and bitterness score of 3.5 – 4.5; and level 5 was extremely bitter and intolerable with berberine hydrochloride concentration of 1.00 mg/mL and bitterness score of 4.5 – 5.5. This bitterness scoring system served as a reference for subsequent sensory evaluations and quantitative analysis of taste-masking effects and was used to assess the bitterness inhibition ability of various taste-masking functional compounds at the perceptual level of volunteers. When the volunteers conducted the taste evaluation, reference solutions of varying concentrations

were placed in taste cups, and the experiment was performed in ascending order of the concentrations. Volunteers received training on the definitions and levels of bitterness before the experiment. In each trial, volunteers were required to hold 10 mL of the control solution in their mouth for 15 seconds, then spit it out and rinse their mouth with water until they no longer perceived any bitterness before proceeding to the next test. The relative concentrations of berberine hydrochloride solutions and their corresponding bitterness scores were defined as 5 g/L, 4.5 for D0, 1 g/L, 3.0 for D1, 0.2 g/L, 1.5 for D2, 0.04 g/L, 0.1 for D3, respectively.

**Measurement of the impact of taste-masking drugs and data processing**

To assess the impact of taste-masking agents on bitterness, a sequential administration method was employed. The taste-masking test agent was first administered followed by the D0 concentration of the bitterness reference sample solution. Briefly, 10 mL of the D0 solution was taken, and the mouth was rinsed for 15 seconds. Then, 10 mL of the taste-masking test agent was administered, and the perceived bitterness value was recorded. Afterward, a resting period of 30 - 60 minutes was allowed until no bitterness remained in the mouth, at which point the next set of taste-masking agents was tested. To enhance the accuracy of the measurements, strategies of gradually increasing sample concentrations, randomizing the order of sample concentrations, and conducting multiple trials with the same sample were implemented. To eliminate outliers, the Grubbs' test was used to process the experimental data, which was then organized into tables and curve charts for further analysis.

**Broad-spectrum taste-masking effect of taste-masking compounds**

The taste-masking test agents were developed targeting the bitterness reference drug, berberine hydrochloride, and compounds with effective taste-masking properties for this drug were selected and formulated into 0.1% concentration solutions. Taste-masking experiments were then conducted on the water extracts of bitter traditional Chinese medicine (TCM) tablets, which effectively validated the broad-spectrum efficacy of the taste-masking agents due to their complex bitter components. The water extracts of seven bitter traditional Chinese medicinal herbs including *Forsythia suspensa*, *Gentiana scabra*, *Subprostrate sophora*, *Szechwan Chinaberry* fruit, *Radix angelicae pubescentis*, *Andrographis paniculata*, and *Plumula nelumbinis* purchased from Zhang Zhongjing Pharmacy, Nanyang, Henan, China were prepared by immersing 5 g of dried material into purified water. After decocting for 20 minutes after boiling, a decoction of 20 - 60 mL was obtained for bitterness evaluation and measurement.

**Sodium ion fluorescence labeling cell experiment based on drug sequential therapy**

The effect of taste-masking test agents on taste cells was investigated using sodium ion fluorescence labeling. Briefly, tongue samples from 10 experimental mice (Zhengzhou Huaxing Experimental Animal Co., Ltd., Zhengzhou, Henan, China.) were taken and disinfected before incubated at 37°C in a 0.25% trypsin solution for 30 minutes. The samples were then gently shaken and centrifuged to remove the digested cell clumps. Subsequently, 10 mL of RPMI-1640 complete cell culture medium supplemented with 10% fetal bovine serum, 1% penicillin-streptomycin, and 2 mM L-glutamine (Xinyanbomei Biotechnology Co., Ltd., Xi'an, Shaanxi, China) was added. The samples were incubated at room temperature for 30 minutes to allow the cells to fully recover and prepare for staining. The cell suspension was taken out, centrifuged and sedimented followed by washed 2 - 3 times with PBS. The sodium ion probe dilution solution (Shanghai Naike Biotechnology Co., Ltd., Shanghai, China) was prepared, and 1 mL of cell culture medium was mixed with 300 µL of sodium ion probe dilution solution and incubated at 37°C for 1 hour to allow the probe to fully enter the cells and label the intracellular sodium ion concentration. After staining, the cells were counted, and the cell suspension was

adjusted to approximately $1 \times 10^6$ cells/mL using a hemocytometer. 10 µL (approximately $1 \times 10^5$ cells) of the labeled cell suspension was added to the center of a 96-well plate and observed and imaged under a Leica DMi8 fluorescence microscope (Leica Microsystems, Wetzlar, Germany). The visual field and parameters were adjusted to obtain a good signal-to-noise ratio. In the sequential administration experiment, 5 µL of a taste-masking test solution (10 mM menthol dissolved in 53% ethanol) was first added to the designated well. After incubating with the cells for 30 minutes, fluorescence images were captured every 1 minute for a total of 3 – 5 images to record the effect of the taste-masking agent on intracellular sodium ion fluorescence intensity. Subsequently, 5 µL of a standard bitter drug solution (5 g/L berberine hydrochloride) was added to the same well. After 20 minutes of incubation with the cells, the same imaging procedure was followed to capture 3 – 5 images at 1-minute intervals to record the fluorescence signal changes under bitterness stimulation. To ensure the accuracy and specificity of the experimental results, this study included 5 experimental groups as blank control group, positive control group, bitter drug group, taste-masking experimental group, and blocker control group. The blank control group used 5 µL of 53% ethanol solution to dissolve all test compounds to eliminate the potential impact of the solvent itself on the taste cell signals. Given the poor water solubility of many taste-masking compounds, the use of 53% ethanol as a universal solvent ensured the solubility and bioavailability. The positive control group used only 5 µL of the taste-masking compound without the bitter drug to observe the effect of the masking agent alone on the ion signals in the cells. The bitter drug group used 5 µL of 10 mM berberine hydrochloride to induce typical bitter-related ion signals. The taste-masking experimental group applied both 5 µL of 10 mM berberine hydrochloride and 5 µL of the taste-masking compound to assess the taste-masking effect. The blocker control group used 5 µL of 10 mM triphenylphosphine oxide (TPPO) (Shanghai Xinya Chemical Reagents Co., Ltd., Shanghai, China) 3 minutes prior to the taste-masking experiment followed by the addition of the taste-masking compound and berberine hydrochloride. TPPO, a non-selective TRP channel blocker, primarily affected the TRPM5 channel and was used to verify whether the taste-masking effect was mediated through TRP-related ion channels with reversible and certain selectivity. The captured fluorescence images were imported into ImageJ software (https://imagej.nih.gov/ij/) for quantitative analysis, measuring the changes in fluorescence signal intensity inside and outside the cells.

**Statistical analysis**

Statistical analysis was performed on the resulting data to evaluate the taste-masking effect of the drugs and their impact on cellular sodium ion concentration. GraphPad Prism 9.0 (GraphPad Software Inc., San Diego, CA, USA) was employed for data statistical analysis. All data were presented as mean ± standard deviation (mean ± SD). Comparisons between different groups were performed using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparisons test or the Kruskal-Wallis test for non-parametric data, depending on the data distribution and variance homogeneity. For time-series data on fluorescence intensity changes, repeated-measures ANOVA was used. *P* value less than 0.05 was defined statistically significant.

## Results and discussion

**Clinical trial results of taste-masking products**

To ensure the safety and efficacy of the clinical trial, taste-masking agents with high safety profiles were selected for sequential taste-masking trials. The results showed that the bitterness of the control group was reduced from an initial level of 4.5 to 4.3, demonstrating a decrease of 0.2 in bitterness. Among the other taste-masking products, linalool, citral, cinnamaldehyde, eugenol acetate, menthone, monomethyl succinate, menthol, gingerol, piperine, eucalyptus oil, borneol, menthylamide,

**Table 1.** Comparison of the changes of bitterness between different bitter mask products and the blank group.

| No. | Medications | Before the change in bitterness | After the change in bitterness | Bitterness decreases (Δ bitterness) | *P* value |
|---|---|---|---|---|---|
| | Blank group | 4.5 | 4.3 | 0.2 | - |
| 1 | Vanillic acid | 4.5 | 4.4 | 0.1 | 0..063 |
| 2 | Peramivir | 4.5 | 4.3 | 0.2 | 0.052 |
| 3 | Aminobutyric acid | 4.5 | 4.4 | 0.1 | 0.066 |
| 4 | Hydroxyvanillic acid | 4.5 | 4.3 | 0.2 | 0.071 |
| 5 | Phloretin | 4.5 | 4.4 | 0.1 | 0.099 |
| 6 | Carvacrol | 4.5 | 4.4 | 0.1 | 0.101 |
| 7 | Dihydrojasmonic acid | 4.5 | 4.3 | 0.2 | 0.095 |
| 8 | Amlodipine | 4.5 | 4.3 | 0.2 | 0.109 |
| 9 | Nifedipine | 4.5 | 4.4 | 0.1 | 0.200 |
| 10 | Dodecalactone | 4.5 | 4.3 | 0.2 | 0.055 |
| 11 | Trimethylcyclohexanol | 4.5 | 4.4 | 0.1 | 0.072 |
| 12 | Decalactone | 4.5 | 4.4 | 0.1 | 0.095 |
| 13 | Eplerenone | 4.5 | 4.4 | 0.1 | 0.062 |
| 14 | Linalool | 4.5 | 4.1 | 0.4 | 0.002 |
| 15 | Citral | 4.5 | 4.0 | 0.5 | 0.022 |
| 16 | Cinnamaldehyde | 4.5 | 4.0 | 0.5 | 0.031 |
| 17 | Eugenol acetate | 4.5 | 4.0 | 0.5 | 0.012 |
| 18 | Menthone | 4.5 | 4.1 | 0.4 | 0.003 |
| 19 | Monomethyl succinate | 4.5 | 4.0 | 0.5 | 0.011 |
| 20 | Menthol | 4.5 | 4.0 | 0.5 | 0.007 |
| 21 | gingerol | 4.5 | 4.1 | 0.4 | 0.012 |
| 22 | Piperine | 4.5 | 4.0 | 0.5 | 0.009 |
| 23 | Eucalyptus oil | 4.5 | 4.1 | 0.4 | 0.016 |
| 24 | Borneol | 4.5 | 4.0 | 0.5 | 0.037 |
| 25 | Menthylamide | 4.5 | 4.1 | 0.4 | 0.006 |
| 26 | Coolant ws-5 | 4.5 | 4.0 | 0.5 | 0.022 |
| 27 | Coolant ws-23 | 4.5 | 4.0 | 0.5 | 0.002 |
| 28 | Allicin | 4.5 | 4.1 | 0.4 | 0.003 |
| 29 | Caryophyllene | 4.5 | 4.2 | 0.3 | 0.001 |

coolant ws-5, coolant ws-23, allicin, and caryophyllene were found to markedly reduce bitterness with the reductions ranging from 0.3 to 0.5 ($P < 0.01$), indicating that their taste-masking effects were superior to the control group. Vanillic acid, peramivir, aminobutyric acid, hydroxyvanillic acid, phloretin, carvacrol, dihydrojasmonic acid, amlodipine, nifedipine, dodecalactone, trimethylcyclohexanol, decalactone, eplerenone, and other drugs demonstrated no visible change in bitterness compared to the control group with changes ranging from 0.1 to 0.2 ($P > 0.05$), indicating they did not possess taste-masking effects (Table 1). Linalool along with several other taste-masking agents significantly reduced the bitterness of berberine hydrochloride, thereby improving the patient's medication experience. In contrast, some agents did not exhibit effective taste-masking effects, indicating that in clinical applications, preference should be given to drugs with clear taste-masking properties to enhance patient compliance and satisfaction.

**Broad-spectrum taste-masking effects of taste-masking agents**

The broad-spectrum taste-masking effects of the effective taste-masking compounds were further evaluated by applying them to the water extracts of bitter TCM tablets. The taste-masking effects

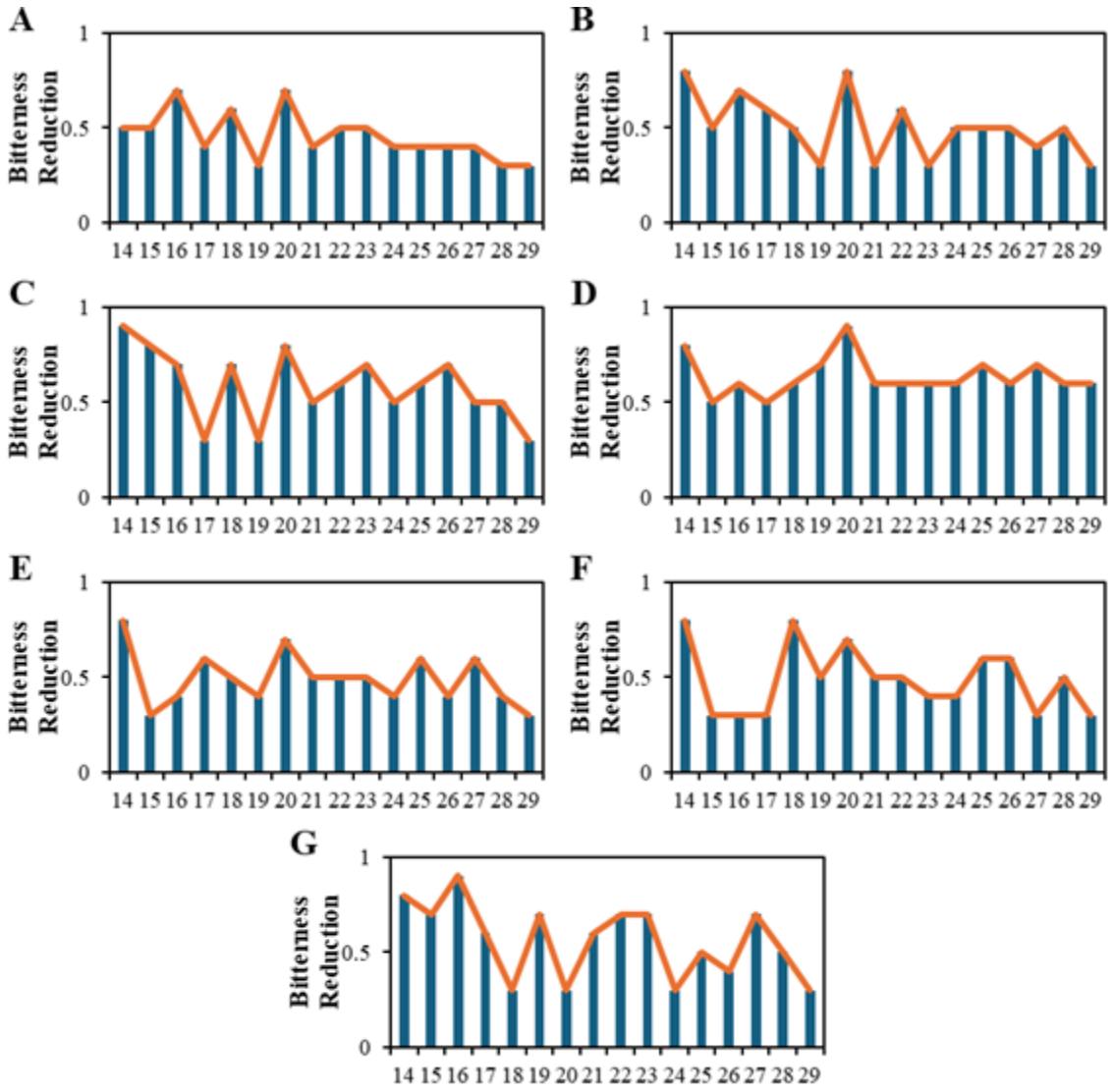


**Figure 1.** Comparison of Δbitterness before and after the application of each taste-masking compound. **A.** *Forsythia suspensa*. **B.** *Gentiana scabra*. **C.** *Subprostrate sophora*. **D.** Szechwan Chinaberry fruit. **E.** *Radix angelicae pubescentis*. **F.** *Andrographis paniculata*. **G.** *Plumula nelumbinis*. **14.** Linalool. **15.** Citral. **16.** Cinnamaldehyde. **17.** Eugenol acetate. **18.** Menthone. **19.** Monomethyl succinate. **20.** Menthol. **21.** Gingerol. **22.** Piperine. **23.** Eucalyptus oil. **24.** Borneol. **25.** Menthylamide. **26.** Flavor coolant ws-5. **27.** Flavor coolant ws-23. **28.** Allicin. **29.** Caryophyllene.

of compounds including linalool, citral, cinnamaldehyde, eugenol acetate, menthone, monomethyl succinate, menthol, gingerol, piperine, eucalyptus oil, borneol, menthylamide, coolant ws-5, coolant ws-23, allicin, and caryophyllene extracts were statistically evaluated. The change in bitterness (Δbitterness) before and after the use of the taste-masking agent was further calculated. The results showed that all water extracts of TCM tablets displayed a visible reduction in bitterness under the action of taste-masking compounds with a reduction range of 0.3 to 0.9 ($P < 0.01$), which indicated that taste-masking compounds had good taste-masking effects on the bitter components of various TCM tablets. Specific analysis revealed that the three flavor correctors had noticeable effects on the bitterness of different TCM tablets. Among them, for *Forsythia suspensa*, cinnamaldehyde and menthol had the best taste-masking effects, while linalool and menthol had the best taste-masking effects for *Gentiana*

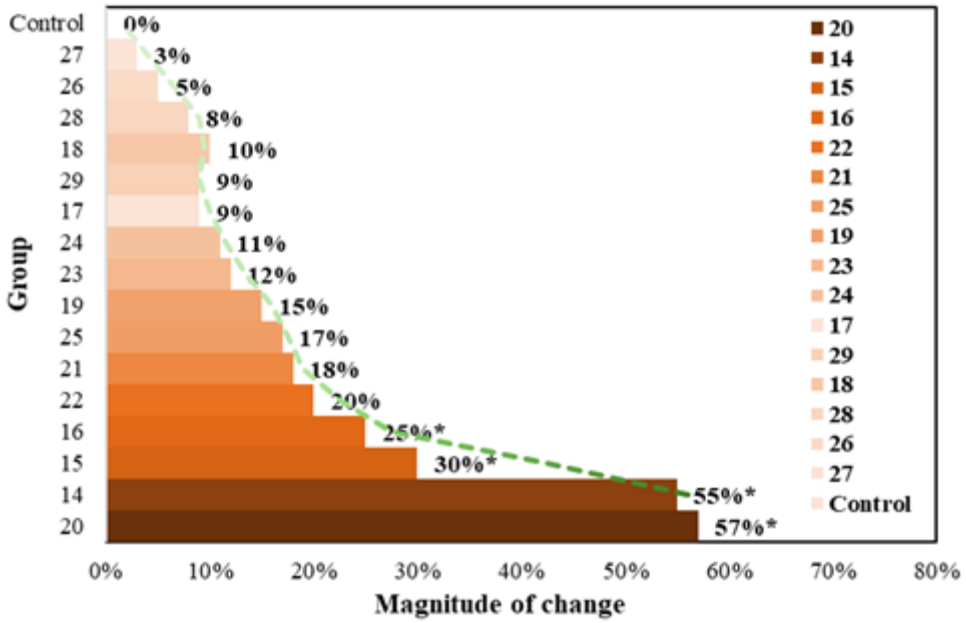


**Figure 2.** Changes in sodium ion fluorescence labeling after the application of each taste-masking compound. **14.** Linalool. **15.** Citral. **16.** Cinnamaldehyde. **17.** Eugenol acetate. **18.** Menthone. **19.** Monomethyl succinate. **20.** Menthol. **21.** Gingerol. **22.** Piperine. **23.** Eucalyptus oil. **24.** Borneol. **25.** Menthylamide. **26.** Flavor coolant ws-5. **27.** Flavor coolant ws-23. **28.** Allicin. **29.** Caryophyllene. *: $P < 0.05$ compared to the blank control group.

*scabra* and *Subprostrate sophora*. For *Plumula nelumbinis*, linalool and cinnamaldehyde had the most visible taste-masking effects, while, for *Radix angelicae pubescentis*, linalool and menthol also demonstrated good flavor-correcting effects. Further, linalool and menthol were also the most effective taste-masking agents for Szechwan Chinaberry fruit and *Andrographis paniculata* (Figure 1). The results confirmed the broad-spectrum taste-masking effects of taste-masking compounds in various bitter TCM tablets.

**Results of sodium ion fluorescence labeling cell in drug sequential therapy**

The taste-masking effects of linalool, citral, cinnamaldehyde, eugenol acetate, menthone, monomethyl succinate, menthol, gingerol, piperine, eucalyptus oil, borneol, menthylamide, coolant ws-5, coolant ws-23, allicin, and caryophyllene were additionally investigated using sodium ion fluorescence labeling and mouse tongue tissue gustatory cells. The results showed that, compared to the blank control group, the relative expressions of sodium ions for linalool, citral, cinnamaldehyde, and menthol were markedly reduced ($P < 0.05$). The change amplitude (%) of each taste-masking compound was then calculated. The results showed that linalool and menthol exhibited the most prominent taste-masking effects, reducing the intracellular sodium ion fluorescence intensity by 55% and 57%, respectively ($P < 0.01$), indicating that these two compounds had strong potential in inhibiting bitter taste perception. Citral and cinnamaldehyde also demonstrated noticeable taste-masking effects by reducing the fluorescence intensity of 30% and 25%, respectively ($P < 0.05$), showing a promising prospect for application. Menthone, monomethyl succinate, and piperine weakened the bitter taste signals to some extent, but their effects were relatively weak with no visible change in fluorescence intensity compared to the blank control group ($P > 0.05$). Other taste-masking compounds such as coolant ws-5 and allicin also exhibited some taste-masking abilities ($P > 0.05$). The blank solvent in the control group

(53% alcohol solution) did not markedly affect the intracellular sodium ion concentration with fluorescence signal intensity remaining stable (Figure 2). By comparing with the blocker TPPO, the mechanism of action of the taste-masking compounds was further verified, indicating their effective interference with intracellular sodium ion signaling. It was observed that taste-masking compounds such as linalool and menthol demonstrated significant taste-masking effects by reducing intracellular sodium ion fluorescence signals, which suggested that these compounds might inhibit bitter taste perception by regulating the ion balance in taste cells. This study provided important experimental evidence and data to support the further development of new taste-masking agents.

## Conclusion

The history of taste-masking is extensive with early efforts aimed at altering the brain's perception of bitterness using sweeteners and modern pharmaceutical approaches involving drug encapsulation to isolate contact with taste buds. Additionally, molecular transmission blockers have been employed to mask bitterness, yet these agents often lack broad-spectrum effectiveness, leading to higher research and development costs. In comparison to traditional combination therapies, the sequential therapy proposed in this study systematically investigated the effectiveness of taste-masking drugs in reducing bitterness, providing a scientific basis for improving patients' medication experience. Clinical trial results indicated that linalool, citral, and cinnamaldehyde excelled in reducing bitterness, thereby enhancing the patient's medication experience. The broad-spectrum taste-masking effects demonstrated that linalool and menthol significantly inhibited the bitterness of multiple TCM tablets, confirming their wide-ranging effectiveness in masking bitterness. The mechanism exploration of taste-masking compounds through sodium ion fluorescence labeling revealed that taste-masking compounds might regulate the ion balance of taste cells, inhibiting bitter perception, providing important experimental evidence for the development of new taste-masking agents. This research effectively screened various taste-masking compounds and confirmed their promising prospects in improving bitter taste perception and increasing patients' medication compliance, which provided scientific evidence and data support for the optimization of clinical drugs and the improvement of patients' medication experience.

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