



Sensory evaluation of the taste of *berberine hydrochloride* using an Electronic Tongue



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ABSTRACT

Background: The “Electronic Tongue” is an instrument that can be trained to screen the taste attributes of formulations within a rapid timeframe when used in conjunction with sensory panel taste assessment data.

Purpose: The purpose of this research was to demonstrate that a sensory instrument for taste (e-Tongue) could be used to evaluate the bitterness of *berberine hydrochloride* from Chinese medicinal herbs.

Methods: Several flavorful native compounds were tested by the e-Tongue. Data from a human sensory panel was collected to train the e-Tongue. The e-Tongue was then used to establish the correlation between data from the sensory panel, and to predict the bitterness scores of *berberine hydrochloride*.

Results: The e-Tongue showed different response patterns for different tastes or strengths of flavor compounds. No significant differences were found between the results of the e-Tongue and the sensory taste panel.

Conclusions: The e-Tongue could be used to evaluate the effect of bitterness of *berberine hydrochloride*. Therefore, e-Tongues showed potential to replace sensory panel evaluations in future experiments regarding Chinese traditional medicine.

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1. Introduction

Oral pharmaceutical products residing in the mouth long enough to be tasted should be palatable. Palatable attributes include appearance, taste, smell, and texture. Palatability could significantly affect compliance and therefore dictate whether a successful or unsuccessful therapeutic outcome is attained. Palatability of the drug product should be given careful consideration to achieve optimal efficacy, as the drug is useless if the patient does not or cannot take the medication. The current methods that can assess the bitterness of agents mainly comprise sensory panel evaluations.

At present, research into bitter receptors on human taste bud cells is a hotspot in palate research. In humans, bitter taste is mediated by G protein-coupled receptors that belong to the TAS2R gene family, which contains 25 TAS2R genes [1,2]. Researchers had investigated the molecular receptive ranges of bitter taste receptors using 104 natural or synthetic bitter chemicals to challenge all of the 25 human TAS2R genes in transfected cells [3]. The results indicated that the detection of the numerous bitter chemicals is related to the molecular receptor ranges of hTAS2Rs, which explains how the vast array of bitter compounds can be detected by such a limited number of sensors. However, these experiments were carried out on rats or in vitro, and many phenomena remain poorly understood.

The “Electronic Tongue” (e-Tongue) has recently become available [4]. This is an instrument that can be trained to screen the taste attributes of formulations within a rapid timeframe when used in conjunction with human taste assessment data.

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Several pharmaceutical laboratories are using this instrument to assess the bitterness of active pharmaceutical ingredients (APIs) and the masking efficiency. In addition, it is also used in the development of placebos, in taste matching of formulations, and in unknown-to-reference comparisons [5–11].

The first multi-sensor system for liquid analysis based on a non-specific sensor approach was a taste sensor termed the e-Tongue introduced in 1990 by Toko et al. [12]. It was followed by several other sensors based on different principles, including the Voltammetric Electronic Tongue, Biofilm Electronic Tongue and PVC Electronic Tongue. However, these studies [13–16] were conducted with pilot e-Tongue models with short life sensors, thereby significantly limiting their application. Recently, a taste analyzing system manufactured by Alpha MOS has become commercially available. The taste sensors consist of silicon transistors with an organic coating that governs sensitivity and selectivity of each individual sensor. The sensors are estimated to last up to one year.

Assessment of the taste and flavor of oral drug preparations is of major interest to the pharmaceutical industry, particularly for research-based companies. Typical tasks include evaluation of taste changes due to aging, masking of unpleasant (usually bitter) taste of active substances or the selection of the least bitter-tasting molecules from a number of new chemical entities.

Drugs used in traditional Chinese medicine (TCM) have varied tastes (predominantly sweet, bitter, pungent or astringent), some of which are particularly complex as they have several active constituents [17]. The compound *berberine hydrochloride* is a quaternary ammonium salt from the isoquinoline alkaloid group. It is found in plants including *berberis*, *goldenseal* (*Hydrastis canadensis*), and *Coptis chinensis*, and is usually present in the roots, rhizomes, stems and bark. It has a typical bitter taste. This study used the bitter score both from an e-Tongue and from a human sensory panel to establish a possible correlation between the two techniques. The bitterness scores of *berberine hydrochloride* were detected by an e-Tongue and the prediction was performed by the sensory panel data.

The objectives of this study were as follows:

- (i) To use the flavored natural products to assess the cross-sensitivity of the different flavor compounds.
- (ii) To investigate the potential use of an e-Tongue in ranking the relative bitterness of compounds, in order to screen for better taste-masking agents and their appropriate use level.
- (iii) To prove that an e-Tongue can be used to evaluate the effect of the bitterness of *berberine hydrochloride*.

2. Materials and methods

2.1. Materials

Sodium L-glutamate (MSG), NaCl, quinine and caffeine were obtained from Alpha MOS Inc. Steviol glycosides were supplied by Shanghai Kaisai Chemical Engineering Co., Ltd., China. Citric acid, Super Sweet (a compound of different sweeteners), acesulfame-K, and sucralose were obtained from Zhangzhou Shengyuan Chemical Products Co. Ltd., China. Matrine, amygdalin, and naringin were obtained from Nanjing Langze Agricultural Development Co. Ltd., China. *Berberine*

hydrochloride was obtained from Lion Biological Technology. A set of samples that contained *berberine hydrochloride* was tested by both healthy volunteers and an e-Tongue. The concentrations of *berberine hydrochloride* tested were 1.23 mg/l, 2.46 mg/l, 4.92 mg/l and 12.30 mg/l. Due to different concentrations of *berberine hydrochloride* being different shades of yellow, gardenia yellow was used to adjust the solutions to the same color.

2.2. Equipment

An α -Astree liquid and taste analyzer (e-Tongue, Alpha MOS Inc.) was connected with an LS16 auto sampler unit, taste sensors and a reference electrode (Ag/AgCl, Alpha MOS Inc.). The system was equipped with a data acquisition and analysis software package. The set of taste sensors included ZZ14601, AB11303, GA13207, BB14005, CA13602, DA10905, and JE13101.

2.3. Methods

2.3.1. General sample preparation and analysis

The compounds tested were weighed and dissolved in purified water. All testing beakers contained 80 ml of solution. When the reference electrode and sensors were dipped into a beaker containing a test solution, a potentiometer difference between each individually coated sensor and the Ag/AgCl reference electrode was measured and recorded by the e-Tongue software. Each sample was analyzed for 120 s. The liquid sensors and the reference electrode were rinsed with purified water for 10 s after each sample analysis. Using well-conditioned sensors, each sample was usually tested seven or eight times by a rotation procedure (i.e., the first round of measurements of all samples was completed before the next round of measurements was started).

2.3.2. Response of an e-Tongue to compounds and natural products – cross-selectivity test

Five different natural products or compounds were used for the cross-selectivity test, including citric acid (sourness, can be found in plants such as *Crataegi Fructus*, *Mume Fructus*, *Jujubae Fructus* and many other herbs), steviol glycosides (sweetness, can be found in *Stevia* spp.), *berberine hydrochloride* (bitterness, can be extracted from *Coptis* spp. or *Philodendron* spp.), NaCl (saltiness, in almost all plants and animals), and MSG (umami, in almost all plants and animals). All compounds in Chinese herbal medicines were prepared at the same concentration (10 mM) except *berberine hydrochloride* which was prepared at 1 mM. Solutions were analyzed using the e-Tongue as described above.

2.3.3. Response of taste sensors to different bitter substances

Six different bitter substances with the same concentration of 1 mg/100 ml in aqueous solution were detected by the e-Tongue. The substances were matrine (bitterness, extracted from *Sophora flavescens* Ait.), *berberine hydrochloride* (bitterness), amygdalin (bitterness, present in *Armeniaca semen amarum* from *Prunus armeniaca* L. var. *ansu* Maxim., *Prunus sibirica* L. or *P. armeniaca* L.), naringin (bitterness, extracted from fruits of *Citrus paradisi* Macfadyen), quinine (bitterness, extracted from *Cinchona ledgeriana*) and caffeine (bitterness,

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