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Flavor misattribution: A novel approach to improving compliance and blinding in food-based clinical interventions

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ABSTRACT

Background: Clinical trials that test food-based interventions frequently suffer from ineffective blinding of study participants which can reduce the statistical power of reported outcomes, and can lead to poor compliance. This study used descriptive sensory analysis with highly trained evaluators, and well-validated statistical techniques to develop a protocol to mask the consumption of phytochemical-rich broccoli sprout extracts (BSEs[3]) for the use in clinical studies seeking to address a variety of conditions.
Methods: A trained sensory team identified foods and beverages that, when mixed with a BSE, showed promise in masking the extract's flavors. Established sensory evaluation techniques were then implemented by a group of seven trained descriptive analysis panelists to deconstruct the sensory profile of each sample (BSE suspended in a delivery vehicle). The sensory characteristics were then clustered into dimensions based upon factor analysis and principal component analysis, followed by a test-retest protocol, to match complementary flavors from liquid-based food sources that would be readily available in the cultural context of our clinical test sites.
Results: Clustering of sensory attributes (dimensions) was identified and was both negatively and positively associated with the perception of glucoraphanin-rich and sulforaphane-rich BSE. Four dimensions were able to explain 73% of the sample set variability. Pineapple juice was identified as a complementary flavor that was most effective in masking broccoli complex attributes, and lime and ginger were effective in masking other "harsh" or objectionable flavor components of the BSE.
Conclusion: Effective beverages worked by invoking "flavor misattribution", wherein a food (broccoli extract) with an objectionable sensory characteristic was paired with a vector in which that characteristic was an acceptable component of the vector's flavor profile. Further development of this concept with an unlimited palate could be used to develop optimal carriers for food product development and/or to refine the approach for clinical trials based upon local taste preferences.

1. Introduction

Food-based intervention trials often struggle to blind participants to their treatment condition because researchers are unable to mimic the sensory complexities of the food in question with an inert control [1]. For example, trials examining the antioxidant effects of long-term dark chocolate consumption have been studied frequently, yet effective controls do not exist because the active polyphenolics lend a distinctive bitter taste that is not sufficiently replicated [2]. Trials testing unpalatable treatments may additionally suffer from low compliance and may not translate to large-scale studies, if successful, without improving palatability. However, manipulation of sensory characteristics has been used successfully to mask the flavor of anti-retroviral drugs and improve compliance in children who were unable to swallow pills [3]. Recent clinical studies have evaluated broccoli sprout extracts (BSEs) for a variety of indications [1,4–10], but their pungency, bitterness, and other sensory qualities greatly influence blinding and compliance [11]. Thus, in addition to sensory acceptability of food-based interventions, development of appropriate masking agents must also be a primary and necessary waypoint in the development of efficacious treatments.

Flavor masking has been utilized in an attempt to improve the commercial acceptability of functional food products that purport to offer

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[3] BSEs: broccoli sprout extracts.

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high antioxidants as well as for bioactive phytochemical supplements with objectionable sensory qualities. For clarification, masking in this publication refers to the concealment of objectionable flavors, whereas blinding refers to the inability of participants to determine their own experimental condition. Microencapsulation, for example, has been used to mask the flavor of DHA- and EPA-rich fish oils for non-traditional food applications such as orange juice and milk without noticeable flavor changes, and a variety of other approaches have been used for pharmaceutical taste masking [12,13]. While flavor masking is frequently employed in the commercialization of functional foods, it is seldom used to facilitate evaluation of their health claims during clinical trials. Were it more commonly used in a research setting, sensory evaluation and flavor masking might lead to a stronger body of functional food research [14]. Sensory testing has been employed for over a century; initially a simple system of food grading that has become increasingly sophisticated over the past 50 years [15,16]. More recently sensory scientists have formalized and codified methodologies, creating a discipline that enables scientists to conduct reproducible tests and provide data on which robust and defensible decisions can be made [17,18]. The use of highly trained evaluators as instruments, and the application of well-vetted statistical analyses to the interpretation of results now permit very sensitive judgments to be made on the perceived sensory attributes of foods (e.g. appearance, odor, consistency, texture, and flavor).

In previous clinical trials the biologically active phytochemical sulforaphane was shown to be more bioavailable when delivered in a sulforaphane-rich (SFR) BSE than in a BSE preparation rich in glucoraphanin (the biogenic precursor of sulforaphane; GRR), but participants noted a more objectionable flavor in the SFR samples as compared to the GRR [4,5]. A number of recent clinical trials have used mango juice as a vehicle for the BSE [4,6]; as have other trials still in progress — see www.clinicaltrials.gov NCT00255775, NCT00994604, NCT00982319, NCT01008826, NCT01108003]. Acceptability of this beverage as both a masking and delivery agent is high amongst subjects in 5 separate trials in the USA, but in China it was not so well accepted. The sweetness of this juice was well tolerated in the USA, whereas Chinese subjects found it to be overly sweet and thus not as well accepted. An informal, blind survey showed a substantial preference for the GRR-BSE over the SFR–BSE beverage, indicating that masking was not entirely successful [1,4].

The investigation reported herein was therefore designed to develop beverage(s) that would better mask the flavor of BSE and facilitate its utilization in clinical trials in rural China and the USA without either interfering with its bioavailability or augmenting its chemoprotective activity. Two BSEs were evaluated, (GRR and SFR); the preparation of each has been previously described [1,4], and both were eventually used in a clinical trial in HeHe, Qidong, Jiangsu Province, PRC — a rural subsistence farming region of China near Shanghai [7]. GRR had been determined to be easier to mask and less pungent in flavor, therefore this study focused primarily on masking the SFR flavor [19]. In this novel, scientifically guided effort to develop culturally appropriate taste-masking carriers for BSE, a variety of vehicles (beverage and otherwise) were prepared and sampled by a panel of trained sensory evaluators. A preliminary screening for widespread acceptability focused upon the culinary preferences of the target trial population by using flavors and vehicles readily available in that region. The selected vehicles were then further tested using an array of standardized descriptors in order to identify sensory characteristics that masked the perception of the BSE.

2. Materials and methods

2.1. Broccoli sprout extract

Broccoli sprout extract (BSE) was produced at Johns Hopkins Medical School and supplied as one of two slightly different compositions: either a glucoraphanin-rich (GRR) BSE, or a sulforaphane-rich (SFR) BSE. A "serving" of each consisted of enough powder to deliver 100 μmol of the phytochemical of interest (glucoraphanin or sulforaphane), consistent with what has been delivered in a number of clinical trials [4–10]. This amounted to 300 mg of GRR BSE and 500 mg of SFR BSE. These powders were prepared by boiling 3 day old broccoli sprouts and lyophilizing the aqueous extracts as previously described [1,4,6]. The resultant yellow/tan powders (BSE) are hygroscopic, completely water soluble, and have a strong odor and taste that has been described by untrained consumers as broccoli-like (GRR) and radish or daikon-like (SFR). All BSE powders were stored at −4 °C until mixed with test vehicles.

2.2. Preliminary screening

Culturally appropriate beverage flavors (or "vectors") were identified by registered dietitians, based on their popularity in Asian food markets, since the initial use in a clinical trial was to be in China. These flavors included green tea, pineapple, mango, lime, grass jelly, tamarind, soy, soursop, melon, lychee, coconut, honey, and ginger (Table 1). In addition to beverages, the use of puddings, custards, and mochi was also explored. Two trained sensory panelists narrowed this preliminary group of flavors to include only those flavors with strong flavor-masking potential in two informal tasting sessions. 4 oz of each sample was mixed with a serving of BSE and evaluated for flavor-masking effectiveness. Mixtures were deemed ineffective if they were no better than water at masking the taste of BSE, based on the intensity of broccoli- or radish-related aromatics. Effective beverages successfully lowered these perceived aromatics whereas partially effective beverages elicited only a minor improvement compared to water. From this preliminary testing, ten beverages were chosen for formal sensory evaluation.

2.3. Masking beverage preparation

Both juices and flavored beverages were purchased from Asian Food Market (Piscattaway, NJ) based on their anticipated availability in rural China (near Shanghai), and based upon the assessment of trained experts on both the cuisine and logistics at the trial site. Initially, eight experimental samples were created along with 2 control samples, one that

Table 1
Preliminary sensory analysis evaluation of masking and acceptability.

Vector	Masking of GR[a]	Masking of SF	Anticipated acceptability
Green tea	NE	NE	High
Grass jelly	E	NE	Low
Soursop	E	PE	Low
Mango drink	NE	PE	High
Tamarind	NE	PE	Low
Pineapple	E	PE	High
Soy milk	E	PE	Moderate
Calpico beverage	E	PE	Moderate
Mango pudding[b]	E		High
Melon mochi[b]	E		Low
Calpico lychee[c]		PE	Moderate
melon drink[c]		PE	Moderate
coconut juice[c]		NE	Moderate
honey/ginger[c]		PE	High
Calpico/soy[c]		E	Moderate
mango/pineapple[c]		PE	High
Calpico/pineapple[c]		E	High
pineapple/ginger/honey[c]		E	High
Calpico/ginger/honey[c]		E	High
pineapple/coconut/ginger/honey[c]		NE	High
Calpico/coconut[c]		NE	Moderate

[a] NE — not effective, PE — partially effective, E — effective.
[b] Vectors were not tested for SFR masking.
[c] Vectors were not tested for GRR masking, for reasons described in the Materials and methods section.