Title: COMPOSITIONS AND METHODS FOR MASKING TASTE

Abstract: Provided herein are methods and compositions for masking the taste of products who have an undesirable taste. An exemplary composition for masking taste is an oral rinse comprising miraculin in an effective amount to mask the taste of a dental product that is administered to the oral cavity of the subject. In certain embodiments, a subject who will receive dental care, e.g., in a dental office, receives an oral rinse comprising miraculin, swirls it in his mouth for 1 - 60 seconds and spits it out, prior to the start of the dental treatment.
COMPOSITIONS AND METHODS FOR MASKING TASTE

BACKGROUND

Although much progress has been made in dental care, the visit to the dentist or other oral care provider can still be improved. In particular, numerous dental products used during dental care have an undesirable taste. Eliminating the taste of such products would render an oral care visit, e.g., a visit to the dentist, more comfortable.

SUMMARY

Provided herein are methods and compositions for masking the taste of a product having an undesirable taste in a subject. In one embodiment, the method comprises administering to a subject in need of an oral product with undesirable taste an effective amount of a composition comprising miraculin (a "miraculin composition"). In certain embodiments, an undesirable taste is not a sour taste. The miraculin composition may be administered prior to or concomitantly with the product having the undesirable taste.

In one embodiment, the method is for masking the taste of one or more dental products in a subject receiving dental care, e.g., in a dental office, and may comprise administering to the subject an effective amount of a composition comprising miraculin to mask the taste of the one or more dental products. The composition comprising miraculin may be a liquid composition, such as an oral rinse or mouthwash. In certain embodiments, a subject who will receive dental care may, prior to (e.g., immediately prior to) rinse his/her oral cavity with a solution comprising miraculin. The subject may, e.g., swirl the solution in his/her oral cavity for about 5-30 seconds and then spit it out.

In certain embodiments, the oral cavity of a subject, or at least the upper portion of the tongue, is sprayed with a composition comprising miraculin. In other embodiments, a miraculin composition is a solid, e.g., a tablet or a powder.

The miraculin composition may be administered to the subject prior to or simultaneously with administration of a first dental product. For example, a composition comprising miraculin may be administered to the oral cavity of a subject from 1 second to 2 minutes prior to administration to the subject of the first dental product. The first dental product may be a local analgesic, e.g., novocaine, procaine, benzocaine and lidocaine. Methods disclosed herein may also comprise administering a second dose of a composition comprising miraculin during the dental care.

In certain embodiments, miraculin is essentially the sole active ingredient or the predominant active ingredient in the composition comprising miraculin, e.g., by weight or concentration. In certain
Further provided herein are compositions, e.g., oral rinse and mouthwash compositions, comprising miraculin in an amount effective to mask the taste of a dental product.

Provided herein are methods for masking the taste of one or more dental products in a subject receiving dental care in a dental office, comprising administering to a subject in need of dental care in a dental office an effective amount of a composition comprising miraculin ("miraculin composition") to mask the taste of the one or more dental products. The miraculin composition may be a liquid composition, such as an oral rinse. The miraculin composition may be exposed to the oral cavity of the subject for a time period ranging from 5 seconds to 1 minute. In certain embodiments, the miraculin composition is administered to the oral cavity of the subject, the subject swirls the miraculin around his mouth and spits it out. The miraculin composition may be administered to the oral cavity of the subject and the subject ingests at least a portion of the miraculin composition. The composition comprising miraculin may be administered to the subject prior to or simultaneously with administration of a first dental product to the subject. The composition comprising miraculin may be administered to the subject from 1 second to 20 minutes prior to administration to the subject of the first dental product. In certain embodiments, the at least one dental product does not have a sour taste. The first dental product may be a local analgesic, such as a local analgesic selected from the group consisting of novocaine, procaine, benzocaine and lidocaine. A method may comprise administering a second dose of a composition comprising miraculin during the dental care. In certain embodiments, miraculin is essentially the sole active ingredient in the composition comprising miraculin. In certain embodiments, the miraculin composition does not comprise a flavoring agent or is not a sustain release formulation. Also provided herein are oral rinse compositions comprising an effective amount of miraculin to mask the taste of a dental product.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the amino acid sequence (SEQ ID NO: 2) of the precursor of the four monomers that are present in the miraculin protein.

Figure 2 shows the nucleotide sequence encoding the protein having SEQ ID NO:2.

Figure 3 shows the amino acid sequence (SEQ ID NO:4) of the mature form of the four monomers that are present in the miraculin protein, and the nucleotide sequence (SEQ ID NO:3) encoding it.
Provided herein are methods for masking the taste of a product in a subject's oral cavity (mouth). In certain embodiments, the method comprises administering to a subject, e.g., a human, an effective amount of a composition comprising miraculin. The invention is based at least in part on the discovery that miraculin masks the taste of oral care products used in a dental office, such as novocaine, thereby increasing the comfort of the patient during dental care or treatment. Surprisingly it was found that miraculin masks the taste of substances or products that are not necessarily sour, but merely of an uncomfortable or undesirable taste, e.g., a bitter taste. In addition, it was found that masking occurs without the concomitant production of a sweet sensation; rather, masking of an undesirable taste occurs essentially without the production of any taste. Thus, the invention differs from the prior art in that it is not based on the change of sour to sweet taste by miraculin.

A method for masking the taste of a product in the oral cavity of a subject may comprise administering to a subject in need of an oral product an effective amount of a composition comprising miraculin. An oral product may be any product that has an unpleasant taste, such as a product that is given to a patient in the context of an oral procedure, e.g., a dental procedure. Exemplary products include analgesics, such as novocaine and lidocaine. Other products include those that are used to make imprints or molds for crowns.

A miraculin composition may be provided in various ways to the oral cavity of a subject. In certain embodiments, the miraculin composition or at least a portion of it is ingested. In certain embodiments, the miraculin composition is not ingested or at least mostly not ingested. For example a miraculin composition may be administered to the oral cavity of a subject, and removed from the oral cavity without being ingested, e.g., the miraculin composition or at least a significant portion of it is spit out by the subject. In certain embodiments, the miraculin composition is contacted with the oral cavity of the subject, or a portion thereof, such as the upper portion of the tongue, for a time sufficient for masking the taste of a product that is applied to the oral cavity of the subject.

Definitions

For convenience, the meaning of certain terms and phrases used in the specification, examples, and appended claims, are provided below.

"Amino acid modification" refers to one or more amino acid deletion, addition or substitution to an amino acid sequence. Amino acid sequence insertions include amino- and/or carboxyl-terminal fusions ranging in length from one residue to polypeptides containing a hundred or more residues, as well as intrasequence insertions of single or multiple amino acid residues. Intrasequence insertions may range generally from about 1 to 10 residues, e.g., 1 to 5, e.g., 1 to 3.
A substitution may be a conservative substitution, as defined below.

"Conservative substitution" or "conservative amino acid substitution" refers to the replacement of one or more amino acid residues in a protein or a peptide with, for each particular pre-substitution amino acid residue, a specific replacement amino acid that is known to be unlikely to alter either the confirmation or the function of a protein or peptide in which such a particular amino acid residue is substituted for by such a specific replacement amino acid. Such conservative substitutions typically involve replacing one amino acid with another that is similar in charge and/or size to the first amino acid, and include replacing any of isoleucine (I), valine (V), or leucine (L) for each other, substituting aspartic acid (D) for glutamic acid (E) and vice versa; glutamine (Q) for asparagine (N) and vice versa; and serine (S) for threonine (T) and vice versa. Other substitutions are known in the art to be conservative in particular sequence or structural environments. For example, glycine (G) and alanine (A) can frequently be substituted for each other to yield a conservative substitution, as can be alanine and valine (V). Methionine (M), which is relatively hydrophobic, can frequently conservatively substitute for or be conservatively substituted by leucine or isoleucine, and sometimes valine. Lysine (K) and arginine (R) are frequently interchangeable in locations in which the significant feature of the amino acid residue is its charge and the differing pK's of these two basic amino acid residues are not expected to be significant. The effects of such substitutions can be calculated using substitution score matrices such as PAM120, PAM-200, and PAM-250. Other such conservative substitutions, for example, substitutions of entire regions having similar hydrophobicity characteristics (e.g., transmembrane domains), are well known.

"Isolated," in reference to polypeptides or proteins, means that the polypeptide or protein is substantially removed from polynucleotides, polypeptides, proteins or other macromolecules with which it, or its analogues, occurs in nature. Although the term "isolated" is not intended to require a specific degree of purity, typically, the protein will be at least about 75% pure, more preferably at least about 80% pure, more preferably at least about 85% pure, more preferably at least about 90% pure, more preferably still at least about 95% pure, and most preferably at least about 99% pure.

"Percent identical" or "% identical" refers to two or more polypeptide sequences or subsequences that are the same (100% identical) or have a specified percentage of amino acid residues that are the same, when the two sequences are aligned for maximum correspondence and compared. To align for maximum correspondence, gaps may be introduced into one of the sequences being compared. The amino acid residues at corresponding positions are then compared and quantified. When a position in the first sequence is occupied by the same residue as the corresponding position in the second sequence, then the sequences are identical at that position. The percent identity between the two sequences is a function of the number of identical positions shared by the sequences (e.g., %...
embodiments, the two sequences are the same length. The determination that one sequence is a measured % identical with another sequence can be determined using a mathematical algorithm. A non-limiting example of a mathematical algorithm utilized for such comparison of two sequences is incorporated in the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program e.g., for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 may be used. Additional algorithms for sequence analysis are well known in the art and many are available online.

"Portion" or "fragment" (e.g., of a domain) of a reference protein refers to a discrete part of the whole reference protein (e.g., domain, e.g., a naturally occurring domain) that is at least, or at most 10% 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95%, 98%, or 99% of the size of the reference protein.

"Product having an undesirable taste" includes products or compositions that have a bitter taste. Generally, taste falls within 5 categories: sweetness, bitterness, sourness, saltiness, and umami. Sweetness, usually regarded as a pleasurable sensation, is produced by the presence of sugars, some proteins and a few other substances. Bitterness is the most sensitive of the tastes, and is perceived by many to be unpleasant, sharp, or disagreeable (e.g., quinine present in tonic water). Sourness is the taste that detects acidity. Saltiness is a taste produced primarily by the presence of sodium ions. Umami is an appetitive taste and is described as a savory or meaty taste. In certain embodiments, an undesirable taste is not a sour taste or not a predominantly sour taste.

"Similarity" or "percent similarity" in the context of two or more polypeptide sequences, refer to two or more sequences or subsequences that have a specified percentage of amino acid residues that are the same or conservatively substituted when compared and aligned for maximum correspondence. By way of example, a first amino acid sequence can be considered similar to a second amino acid sequence when the first amino acid sequence is at least 50%, 60%, 70%, 75%, 80%, 90%, 95%, 97%, 98% or even 99% identical, or conservatively substituted, to the second amino acid sequence when compared to an equal number of amino acids as the number contained in the first sequence, or when compared to an alignment of polypeptides that has been aligned by a computer similarity program known in the art.

A "subject" may be a patient and includes pediatric, adolescent, and adult subjects.

Miraculin compositions

Miraculin is a naturally occurring protein from the miracle fruit (Richardella dulcifica; Synsepalum dulcificum) (see, e.g., Kurihara et al. Science. 1968 Sep 20;161(847): 1241-3). It is
(Matsuda et al. Gene 161 (2), 175-177 (1995)). The naturally occurring protein is a homotetramer of a 191 aa long (mature) polypeptide. The polypeptide is expressed as a 220 amino acid long precursor protein having a 29 amino acid signal sequence. The precursor of miraculin consists of the amino acid sequence set forth as SEQ ID NO: 2 and shown in Figure 1 and is provided under Accession No. P13087 in UniProtKB/Swiss-Prot and BAA07603.1 in GenBank. The signal peptide corresponds to amino acids 1-29 and the mature protein corresponds to amino acids 30-220. The amino acid sequence of the mature protein is set forth as SEQ ID NO: 4 (Figure 3). The region of miraculin from amino acid 35 to 261 of SEQ ID NO: 2 has homology to Soybean trypsin inhibitor (Kunitz) family of protease inhibitors (see GenBank Accession No. BAA07603.1).

The miraculin precursor is encoded by a nucleotide sequence set forth as SEQ ID NO: 1 and shown in Figure 1 (GenBank Accession No. D38598.1; GI:1109651; Matsuda et al. Gene 161 (2), 175-177 (1995)). In SEQ ID NO: 1, nucleotides 1-6 correspond to a 5’ untranslated sequence; nucleotides 7-669 correspond to the open reading frame; nucleotides 7-93 encode the signal peptide; nucleotides 94-666 encode the mature polypeptide and nucleotides 670-759 correspond to a 3’ untranslated region. The nucleotide sequence encoding the mature miraculin protein is set forth as SEQ ID NO: 3 and shown in Figure 3.

The miraculin homotetramer is formed of two dimers of the 191 amino acid long monomers, wherein each dimer comprises two monomers that are linked through one disulfide bridge (at Cys-138 in the mature monomer). The mature miraculin monomer also forms three intrachain disulfide bridges: Cys-47-Cys-92, Cys-148-Cys-159 and Cys-152-Cys-155 (Igeta et al. Biochim Biophys Acta. 1991 Sep 20;1079(3):303-7).

Miraculin is a glycoprotein, wherein each monomer is glycosylated. The molecular weight of each glycoprotein monomer is 24.6 kDa including 3.4 kDa (13.9% of the weight) of sugar constituted (on molar ratio) of glucosamine (31%), mannose (30%), fucose (22%), xylose (10%) and galactose (7½) (Theerasilp et al. (1988) J. Biol. Chem. 263 (23): 11536-9).

Forms of miraculin that differ from the naturally occurring miraculin may also be used, provided that they mask the taste of products having an undesirable taste. For example, a miraculin with one or more alternative posttranscriptional modification(s), e.g., glycosylation, may be used. In certain embodiments, a miraculin composition comprises miraculin that is aglycosylated or miraculin that is less glycosylated or contains a different glycosylation pattern relative to the naturally occurring miraculin. In certain embodiments, miraculin is produced in prokaryotes and is therefore not glycosylated.
sequence that differs from that of the naturally occurring miraculin having SEQ ID NO: 2 or 4. For example, a miraculin composition may comprise miraculin that differs from SEQ ID NO: 2 or 4 in at most 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 amino acid additions, deletions or substitutions. A miraculin composition may also comprise miraculin comprising an amino acid sequence that is at least 75%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% identical or similar to SEQ ID NO: 2 or 4. Amino acid substitutions may be conservative or non-conservative amino acid substitutions. Amino acid modifications are preferably located in portions of the protein that do not affect the secondary or tertiary structure of the protein and/or are not involved in masking taste and/or in binding to taste buds. It may also be preferred to retain the cysteines in the miraculin protein as they assure proper three- and four-dimensional folding. In certain embodiments, a miraculin composition comprises miraculin or a biologically active fragment or an analog thereof that is fused to a non-miraculin polypeptide, to, e.g., stabilize the protein. In certain embodiments, such a miraculin fusion protein is engineered so that it releases the miraculin portion of the fusion protein in the oral cavity of the subject to whom it is administered.

Miraculin may be extracted from the miracle fruit or generated synthetically or genetically. For example, it may be purified from the miracle fruit as described, e.g., in EP1 9920924876, or by NaCl at acidic pH, as described in Theerasilp et al. (1988) JBC 263:1 1536. Miraculin may also be produced in a microorganism, e.g., a prokaryote, such as bacteria (see, e.g., Matsuyama et al. J Biochem. 2009 Apr;145(4):445-50 describing the production of miraculin in E. coli, as well as Ito et al. (2007) BBRC 360:407). Miraculin may also be produced in plants, fruits or vegetables and may be extracted therefrom. For example, miraculin has been expressed in lettuce and tomato (see, e.g., Sun et al. (2006) FEBS Lett. 580:620; Kazuhisa et al. (2010) J. Agric. Food Chem. 58:9505; and US Patent publication 20090205068).

For the uses described herein, miraculin may be administered in the form of the fruit itself or a genetically engineered fruit or vegetable expressing miraculin, or a fraction, e.g., a purified fraction, or extract thereof, such as a dried extract. For example, miraculin compositions, e.g., tablets, may be made by combining the dried extract of the fruit, or of a genetically modified producer of the protein (such as lettuce or tomato) with a carrier.

Miraculin compositions, e.g., tablets, for use as described herein may also be purchased commercially. For example, Miracle fruit tablets are made by mBerry and may be purchased from Funky Food Shop through Amazon.com. Miracle fruit tablets are also produced by Sen Yuh Farm Science Co. and sold through ThinkGeek.
the type of vehicle used for delivering it. However, generally, a liquid composition may comprise miraculin at a concentration of at least 0.01 x 10^-6 grams/liter; at least 0.05 x 10^-6 grams/liter; at least 0.1 x 10^-6 grams/liter; at least 0.2 x 0.1 x 10^-6 grams/liter; at least 0.3 x 10^-6 grams/liter; or at least 0.4 x 10^-6 grams/liter. For example, a miraculin composition may comprise about 0.1 x 10^-6 grams/liter to 10 x 10^-6 grams/liter of miraculin; 0.1 x 10^-6 grams/liter to 10 x 10^-6 grams/liter of miraculin; 0.1 x 10^-6 grams/liter to 5 x 10^-6 grams/liter of miraculin; 0.1 x 10^-6 grams/liter to 1 x 10^-6 grams/liter of miraculin; or 0.4 x 10^-6 grams/liter to 0.7 x 10^-6 grams/liter of miraculin. In certain embodiments, a liquid miraculin composition comprises 0.1 x 10^-6 grams/liter of miraculin, 0.2 x 10^-6 grams/liter of miraculin, 0.3 x 10^-6 grams/liter of miraculin, 0.4 x 10^-6 grams/liter of miraculin, 0.5 x 10^-6 grams/liter of miraculin, 0.6 x 10^-6 grams/liter of miraculin, 0.7 x 10^-6 grams/liter of miraculin, 0.8 x 10^-6 grams/liter of miraculin, 0.9 x 10^-6 grams/liter of miraculin or 1 x 10^-6 grams/liter of miraculin.

0.4 x 10^-6 grams/liter of miraculin corresponds to approximately 0.1% w/v of miraculin. In certain embodiments, a miraculin composition comprises at least 0.01% w/v of miraculin; at least 0.03% w/v of miraculin; at least 0.05% w/v of miraculin; at least 0.07% w/v of miraculin; at least 0.1% w/v of miraculin; at least 0.2% w/v of miraculin; at least 0.3% w/v of miraculin; at least 0.4% w/v of miraculin. For example, a miraculin composition may comprise 0.01% to 10% w/v of miraculin; 0.1% to 1% w/v of miraculin; 0.1% to 0.7% w/v of miraculin; 0.1% to 0.6% w/v of miraculin; or 0.1% to 0.5% w/v of miraculin.

A miraculin composition, such as a tablet, may comprise at least 0.01 x 10^-9 grams of miraculin; 0.03 x 10^-9 grams of miraculin; 0.05 x 10^-9 grams of miraculin; 0.07 x 10^-9 grams of miraculin; 0.1 x 10^-9 grams of miraculin; 0.3 x 10^-9 grams of miraculin; 0.5 x 10^-9 grams of miraculin; 0.7 x 10^-9 grams of miraculin; 1 x 10^-9 grams of miraculin; 3 x 10^-9 grams of miraculin; 5 x 10^-9 grams of miraculin; 7 x 10^-9 grams of miraculin; 10 x 10^-9 grams of miraculin; 13 x 10^-9 grams of miraculin; 15 x 10^-9 grams of miraculin; or 20 x 10^-9 grams of miraculin. For example, a miraculin composition may comprise 0.01 x 10^-9 to 10 x 10^-9 grams of miraculin; 0.1 x 10^-9 to 10 x 10^-9 grams of miraculin; 0.5 x 10^-9 to 10 x 10^-9 grams of miraculin; or 1 x 10^-9 to 10 x 10^-9 grams of miraculin.

A miraculin composition, such as a tablet, may comprise at least 0.01% w/w of miraculin; at least 0.03% w/w of miraculin; at least 0.05% w/w of miraculin; at least 0.07% w/w of miraculin; at least 0.1% w/w of miraculin; at least 0.3% w/w of miraculin; at least 0.5% w/w of miraculin; at least 0.7% w/w of miraculin; at least 1% w/w of miraculin; at least 3% w/w of miraculin; at least 5% w/w of miraculin; at least 7% w/w of miraculin; at least 10% w/w of miraculin; at least 30% w/w of miraculin; at least 70% w/w of miraculin; at least 80% w/w of miraculin; or at least 90% w/w of miraculin.
0.1% to 10% w/w of miraculin; 0.1% to 1% w/w of miraculin or 1% to 10% w/w of miraculin.

In certain embodiments, a miraculin composition comprises one or more additional active or inactive ingredients or pharmaceutically acceptable excipients. The identity of particular ingredients may depend on the particular form of the composition, e.g., liquid versus solid, however generally the following active and inactive ingredients may be added alone or in combination to a miraculin composition: emulsifiers, flavorings, coloring agents, anti-plaque agents, anti-staining compounds, excipients such as emollients, preservatives, other types of stabilizers such as antioxidants, chelating agents, tonicity modifiers (e.g., sodium chloride, manitol, sorbitol, or glucose), spreading agents, pH adjusting agents and water soluble lubricants, e.g., propylene glycol, glycerol, antibacterial agents, ethanol, menthol, eucalyptol, thiamine, methyl salicylate, cetlypyridium chloride, calcium nitrate, fluoride, zinc chloride, potassium nitrate, aloe, carnauba wax, sanguinaria extract, papain, sodium laurel sulfate, coloring agents, sodium saccharin, sodium citrate, carbamide peroxide, calcium peroxide, glyceryl peroxide, benzoyl peroxide, peppermint oil, cinnamon oil, acid compounds, stain removing agents, gelling agents, or polyethylene glycol. The concentration of each may easily be determined by a person skilled in the art. Lecithin, a natural emulsifier found in soy and other plants, and gum arabic, which comes from the sap of certain species of acacia trees, can be added for use as an emulsifier, dispersant, and/or wetting agent. Suitable preservatives may include benzalkonium chloride, parabens, chlorhexidine acetate, chlorhexidine gluconate, sorbic acid, potassium sorbitol, chlorbutanol, and phenoxyethanol. Suitable emollients are, for example, di-n-octyl ether, fatty alcohol polyalkylene glycol ether, 2-ethylhexyl palmitate, and isopropyl fatty acid esters.

An exemplary miraculin composition may comprise at least a buffering agent, at least one preservative, at least one chelating agent and at least one anti-oxidant. The buffering agent may be a phosphate buffer, the preservative may be methyl paraben or propyl paraben, the chelating agent may be EDTA, and the anti-oxidant may be citric acid or a salt thereof.

In certain embodiments, one or more mucoadhesives are included in the composition. As used herein the term mucoadhesive means a natural or synthetic substance, e.g., gels, pastes, macromolecules, polymers, and oligomers, or mixtures thereof, that can adhere to a subject's mucous membrane for a period of time sufficient to locally deliver a therapeutically-effective amount of miraculin and other ingredient, if included. The composition itself need not be mucoadhesive, as long as it can form a mucoadhesive upon contact with the mucosa. Mucoadhesives may be water soluble and a combination of mucoadhesives may be used. Homopolymers of ethylene oxide are particularly preferred in combination with a second mucoadhesive such as sodium carboxymethylcellulose. Commercially available homopolymers of ethylene oxide are sold under the trademark POLYOX by Dow Chemical Company, Midland, Mich, (see, e.g., US20070071802).
to 9, 5 to 9, 6 to 9, or 6 to 8. In certain embodiments, a miraculin composition has a pH of about 7. The pH of a miraculin composition may be maintained at the desired pH with a buffer, e.g., an acetate buffer. The pH is preferably biologically or physiologically acceptable.

All forms of miraculin compositions are preferably stable at room temperature for at least a day, a week, a month or more. However, compositions that must be stored at temperatures below room temperature, e.g., 4°C, or below freezing, may also be used. In certain embodiments, a miraculin composition is stored as a lyophilized composition (maintained, e.g., in the form of a blister pack) that is mixed with an aqueous solution prior to its use.

In certain embodiments, a miraculin composition is a liquid composition, such as an oral rinse or wash (e.g., mouthwash) solution. For example, miraculin may be added to a commercially available mouthwash, such as SCOPE, LISTERINE mouthwash, TOM’S OF MAINE mouthwash, CREST mouthwash, BIOTENE DENTAL mouthwash, NATURES ANSWER 81922 PERIOWASH mouthwash, SMART MOUTH MOUTHWASH, or Procter & Gamble PRO-HEALTH CPC ANTIGINGIVITIS/ANTIPLAQUE ORAL RINSE. In other embodiments, a miraculin composition is a liquid that is intended for ingestion. Liquid compositions may also be used in the form of sprays or aerosols.

In certain embodiments, the miraculin composition is in the form of a solid, e.g., a tablet or a pill, that the subject takes prior to, or at the same time as, the exposure to the product with the undesirable taste. The solid should be able to be solubilized in the oral cavity of the subject within a reasonable amount of time, preferably within 3, 2 or 1 minute or 45, 30, 20, 10, 5 seconds or less. Other solids that may be used include powders. After dissolution of the solid and exposure to the oral cavity of the subject, the subject may either ingest the solid or spit it out, e.g., followed by one or more rinses of a solution, e.g., water. The composition may also be in the form of a gel, e.g., which may be applied to the oral cavity or a portion thereof, such as the upper portion of the tongue. The composition may also be in the form of film or strip, e.g., a Listerine strip, that is applied to the upper portion of the tongue. Without wanting to be limited to a particular mechanism of action, it is believed that the miraculin composition must come into contact with the taste receptors, which are mostly located on the upper portion of the tongue. Solids may also first be dissolved in a liquid, e.g., water or an oral rinse, and then administered to a subject. For example, a miraculin composition may be in the form of an effervescent tablet that is added to water or a mouthwash and given to a subject prior to an oral care procedure.
Miraculin compositions preferably comprise miraculin that is at least 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% pure, i.e., essentially devoid of components that originate from the composition or organism from which the miraculin was extracted or purified. For example, when miraculin is purified from the miracle fruit, miraculin is preferable at least 70%, 80%, 85%, 90%, 95%, 96%, 97%, 98% or 99% pure, as measured based on the weight or molecular weight of the ingredients of the miracle fruit. Thus, for example, a miraculin composition that is at least 90% pure comprises less than 10% of non-miraculin ingredients of the miracle fruit.

In certain embodiments, a miraculin composition also comprises a dental care product, e.g., an analgesic, such as novocaine, lidocaine, benzocaine, articaine, septocaine, marcaine, and mepivacaine. Additional components may also be present, such as a buffer and other active or inactive ingredients, such as those further disclosed herein or known in the art.

**Exemplary methods**

In certain embodiments, the composition is contacted with (or applied to) the oral cavity of a subject for at least 1, 2, 3, 5, 10, 20, 30, or 60 seconds or for at least 1, 2, 3, 5, 6, 7, 8, 9, 10, 15, 20, 25 or 30 minutes. In certain embodiments, the composition is contacted with the oral cavity of the subject for 1 second to 1 minute; for 1 second to 5 minutes or for 10 seconds to 1 minute. The length of the exposure of the miraculin composition with the oral cavity should be sufficient for masking the taste of a product that is subsequently or concomitantly contacted with the oral cavity of the subject. A subject may take in a composition and swirl the composition in its oral cavity (e.g., rinsing the oral cavity) for a period of time sufficient to mask the taste of a product that is subsequently or concomitantly taken into the oral cavity of the subject. For example, a miraculin composition may be maintained or swirled in the oral cavity of a subject for about 1, 2, 3, 5, 10, 20, 30, or 60 seconds or for at least 1, 2, 3, 4 or 5 minutes or for 1-60 seconds, 1-30 seconds, 5-60 seconds, 5-30 seconds, 10-60 seconds or 10-30 seconds. The miraculin composition may then be swallowed or spit out, or a combination thereof, by the subject. This step may be followed by rinsing the oral cavity with water.

In certain embodiments, a miraculin composition is contacted essentially only with the tongue of the subject, e.g., the upper part of the tongue, which contains the taste buds. For such applications, the miracle composition may be similar to a strip or film, e.g., a LISTFNE strip, that melts on the tongue.
is dissolved in water or an oral rinse that is administered to the oral cavity of a subject prior to the contact with an oral product having an undesirable taste. In certain embodiments, or a small amount of a concentrated solution of miraculin is added to the water or the oral rinse.

The methods described herein may be used prior to, or concomitantly with, the administration into the oral cavity of a subject of a substance that has an undesirable taste. In certain embodiments, an undesirable taste is not a sour or acidic taste. A miraculin composition may be administered to a subject prior to any oral procedure, e.g., dental procedure, using an analgesic or other composition having an undesirable taste, such as a bitter taste. Exemplary oral procedures include dental cavity remediation and filling, root canal, tooth extraction, oral surgery (e.g., gum surgery) or other dental or oral cavity surgery, the addition or removal of sealant, applying a molding material for making a mold for a crown or a dental implant, the addition or removal of orthodontics, the addition or removal of dentures, dental caps, or dental bridges, dental cleaning, and dental bleaching. A procedure may be conducted in the office of a dentist (e.g., a general dentist), an orthodontist, a periodontist, an endodontist, a dental hygienist or a prosthodontist.

Exemplary products whose taste may be masked by a miraculin includes analgesics, such as novocaine (also called procaine), lidocaine (also called xylocaine or lignocaine), benzocaine, articaine, septocaine, marcaine (a long-acting anesthetic), and mepivacaine. Benzocaine and novocaine are of the ester class and derived from para-aminobenzoic acid, or PABA. Therefore, it is expected that any analgesic in that class will have its taste masked by miraculin. Other products include those that are used for preparing a mold for, e.g., a crown or a dental implant.

In a preferred embodiment, an oral care provider, e.g., a dentist, applies a miraculin composition to the oral cavity of a subject, or instructs the subject to do so, prior to the start of the oral, e.g., dental, procedure, such as prior to the administration to the subject of an analgesic. An oral care provider may also reapply 1, 2, 3, 4, 5 or more times miraculin composition during the procedure, particularly if the procedure is long. For example, a miraculin composition may be reapplied after about 30, 45, 60, 75, 90, 105 or 120 minutes. Generally, the effect of miraculin on masking taste may last from about 1-3 hours. In addition, a miraculin composition may also be reapplied to the oral cavity of the subject if the subject indicates that it can still taste the product being administered.

Also provided are miraculin compositions, e.g., described herein, for use in masking the bad taste of an oral product, e.g., as further provided herein.

A subject may be an animal, such as a human. The subject may be an adult or a child.
having an undesirable taste. For example, an analgesic, such as novocaine or lidocaine, may contain miraculin.

The following examples should not be construed as limiting the scope of this disclosure.

EXAMPLES

This Example describes that administration of a miraculin composition to the oral cavity of a subject masks the taste of dental products, thereby rendering the visit at a dental office more pleasant.

During a visit with her periodontist, the inventor ingested a tablet of miraculin (Miracle Berry Fruit Tablet from Sen Yuh Farm Science Co., obtained from ThinkGeek.com) about 1-3 minutes prior to the administration of novocaine into her mouth. The inventor could not taste the novocaine at all. Then, to further test the masking of the novocaine taste by miraculin, the periodontist squirted some novocaine directly onto the inventor's tongue. Again, the inventor did not taste the novocaine at all.

On a different day, the inventor visited her dentist to have a temporary crown made. The inventor ingested a tablet of miraculin (same as above) and about 1-5 minutes later received into her mouth material for preparing a mold for a temporary crown. The inventor did not taste this product either. On the other hand, miraculin did not appear to mask the taste of the material used to make a mold for a permanent crown.

Thus, the inventor discovered that miraculin can mask (or shield) the taste of dental products having an undesirable taste, such as an analgesic and the material for preparing temporary molds, and that it does so essentially without producing any new taste, such as a sweet taste.

Equivalents

Those skilled in the art will recognize, or be able to ascertain and implement using no more than routine experimentation, many equivalents of the specific embodiments described herein. Such equivalents are intended to be encompassed by the following claims. Any combinations of the embodiments disclosed in the dependent claims are contemplated to be within the scope of the disclosure.

Incorporation by reference

The disclosure of each and every US and foreign patent and pending patent application and publication referred to herein is specifically incorporated by reference herein in its entirety.
1. A method for masking the taste of one or more dental products in a subject receiving dental care in a dental office, comprising administering to a subject in need of dental care in a dental office an effective amount of a composition comprising miraculin ("miraculin composition") to mask the taste of the one or more dental products.

2. The method of claim 1, wherein the miraculin composition is a liquid composition.

3. The method of claim 2, wherein the miraculin composition is an oral rinse.

4. The method of claims 3, wherein the miraculin composition is exposed to the oral cavity of the subject from 5 seconds to 1 minute.

5. The method of claim 2, wherein the miraculin composition is administered to the oral cavity of the subject, the subject swirls the miraculin around his mouth and spits it out.

6. The method of claim 2, wherein the miraculin composition is administered to the oral cavity of the subject and the subject ingests at least a portion of the miraculin composition.

7. The method of claim 2, wherein the composition comprising miraculin is administered to the subject prior to or simultaneously with administration of a first dental product.

8. The method of claim 7, wherein the composition comprising miraculin is administered to the subject from 1 second to 20 minutes prior to administration to the subject of the first dental product.

9. The method of claim 7, wherein at least one dental product does not have a sour taste.

10. The method of claim 7, wherein the first dental product is a local analgesic.

11. The method of claim 10, wherein the local analgesic is selected from the group consisting of novocaine, procaine, benzocaine and lidocaine.

12. The method of claim 8, comprising administering a second dose of a composition comprising miraculin during the dental care.

13. The method of claim 1, wherein miraculin is essentially the sole active ingredient in the composition comprising miraculin.

14. The method of any of claim 1, wherein the miraculin composition does not comprise a flavoring agent.
16. An oral rinse comprising an effective amount of miraculin to mask the taste of a dental product.
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FIGURE 2

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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A61K 8/18 (2006 01);A61Q 11/00 (2006 01)

USPC: 424/49

According to International Patent Classification (IPC) o r to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S.: 424/49

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

The Online Medical dictionary for the definition of mouth rinse.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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<tr>
<td>X</td>
<td>U.S. 3898323 (Fennell et al.) 5 August 1975 (5.8. 1975), see abstract and column 3, lines 3-1-4.</td>
<td>1-3, 5, 7, 9, and 13-16</td>
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<td>U.S. 5547657 (Singleton et al.) 20 August 1996 (20.8. 1996), see abstract, column 1, lines 66-67 and column 2, lines 1-3, column 4, lines 7-15, column 2, lines 25-67 and column 3, lines 1-9.</td>
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<td>U.S. 5376374 (Zelaya) 27 December 1994 (27.12.1994), see abstract and column 4, lines 8-25.</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"F" document member of the same patent family

Date of the actual completion of the international search: 12 December 201 (12.12.201)

Date of mailing of the international search report: 1 Office EB 2012

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US

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Contact Person:

Telephone No.: 571-270-5867

Form PCT/ISA/210 (second sheet) (April 2007)
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<td>With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of:</td>
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Form PCT/ISA/2 10 (continuation of first sheet(l)) (April 2007)