

METHOD FOR SELECTING SWEETENERS

BACKGROUND

Field

[0001] The present disclosure relates to methods of selecting sweetener compounds and compounds selected using the methods provided for herein.

Description of the Related Art

[0002] The taste system provides sensory information about the chemical composition of the external world. Taste transduction is one of the most sophisticated forms of chemical-triggered sensation in animals. Signaling of taste is found throughout the animal kingdom, from simple metazoans to the most complex of vertebrates. Mammals are believed to have five basic taste modalities: sweet, bitter, sour, salty, and umami (the taste of monosodium glutamate, a.k.a. savory taste).

[0003] For centuries, various natural and unnatural compositions and/or compounds have been added to ingestible compositions, including foods and beverages, and/or orally administered medicinal compositions to improve their taste. Although it has long been known that there are only a few basic types of “tastes,” the biological and biochemical basis of taste perception was poorly understood, and most taste improving or taste modifying agents have been discovered largely by simple trial and error processes.

[0004] With respect to the sweet taste, diabetes, and cardiovascular disease are health concerns on the rise globally and are growing at alarming rates in the United States. Sugar and calories are key components that can be limited to render a positive nutritional effect on health. High-intensity sweeteners can provide the sweetness of sugar, with various taste qualities. Because they are many times sweeter than sugar, much less of the sweetener is required to replace the sugar.

[0005] High-intensity sweeteners have a wide range of chemically distinct structures and hence possess varying properties, such as, without limitation, odor, flavor, mouthfeel, and aftertaste. These properties, particularly flavor and aftertaste, are well known to vary over the time of tasting, such that each temporal profile is sweetener-specific.

[0006] There has been significant recent progress in identifying useful natural flavoring agents, such as for example sweeteners such as sucrose, fructose, glucose, erythritol,

isomalt, lactitol, mannitol, sorbitol, xylitol, certain known natural terpenoids, flavonoids, or protein sweeteners. *See, e.g.*, Kinghom, et al., *Noncariogenic Intense Natural Sweeteners*, Med. Res. Rev. 18 (5) 347-360 (1998) (discussing discovered natural materials that are much more intensely sweet than common natural sweeteners such as sucrose, fructose, and the like.) Similarly, there has been recent progress in identifying and commercializing new artificial sweeteners, such as aspartame, saccharin, acesulfame-K, cyclamate, sucralose, and the like. *See, e.g.*, Ager, et al., *Angew. Chem. Int. Ed.* 37, 1802-1817 (1998). The entire contents of the references identified above are hereby incorporated herein by reference in their entirety.

[0007] Sweeteners such as saccharin and 6-methyl-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide potassium salt (acesulfame potassium) are commonly characterized as having bitter and/or metallic aftertastes. Products prepared with 2,4-dihydroxybenzoic acid are claimed to display reduced undesirable aftertastes associated with sweeteners and do so at concentrations below those concentrations at which their own tastes are perceptible. Also, high intensity sweeteners such as sucralose and aspartame are reported to have sweetness delivery problems, i.e., delayed onset and lingering of sweetness. *See* S. G. Wiet, et al., *J. Food Sci.*, 58(3):599-602, 666 (1993).

[0008] There is a need for new sweetening compounds and compositions containing such compounds, having improved taste and delivery characteristics. In addition, there is a need for foods containing new sweetening compounds with such desirable characteristics.

SUMMARY

[0009] The present disclosure provides for methods of identifying, uses of, and compositions including sweetener compounds.

[0010] In a first aspect, the disclosure provides for a method of identifying a sweetener for inclusion in an ingestible composition. The method can include measuring one or more sweet receptor binding properties of a candidate sweetener, the binding properties comprising one or more of a K_D or EC_{50} value, a halftime occupancy, and a dissociation halftime of the candidate sweetener with respect to a human sweet taste receptor; and including the candidate sweetener in an ingestible composition if the one or more sweet receptor binding properties include: a K_D or EC_{50} value greater or equal to 50 μM ; a halftime occupancy within a range of 4×10^{-6} s to 20 s at K_{on} values ranging from $10^6 \text{ M}^{-1}\text{s}^{-1}$ to $10^2 \text{ M}^{-1}\text{s}^{-1}$; and a dissociation

halftime within a range of 2×10^{-5} s to 30 s at K_{on} values ranging from $10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $10^2 \text{ M}^{-1} \text{ s}^{-1}$.

[0011] In a second aspect, the disclosure provides for use of a sweetener molecule to sweeten an ingestible composition. The sweetener molecule for use in the ingestible composition may, with respect to a human taste receptor, have: a K_D or EC_{50} value of at least 50 μM ; a halftime occupancy within a range of 4×10^{-6} s to 20 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $10^6 \text{ M}^{-1} \text{ s}^{-1}$; and a dissociation halftime within a range of 2×10^{-5} s to 30 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ and $10^6 \text{ M}^{-1} \text{ s}^{-1}$.

[0012] In a third aspect, the disclosure provides for a sweetened ingestible composition. The composition may include a non-caloric sweetener molecule, wherein, with respect to a human sweet taste receptor, the sweetener molecule may have a K_D value of at least 50 μM ; a halftime occupancy within a range of 4×10^{-6} s to 20 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $10^6 \text{ M}^{-1} \text{ s}^{-1}$; and a dissociation halftime within a range of 2×10^{-5} s to 30 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ and $10^6 \text{ M}^{-1} \text{ s}^{-1}$.

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The following drawings are provided for purposes of illustrating various embodiments of the compositions and methods disclosed herein. The drawings are provided for illustrative purposes only, and are not intended to describe any preferred compositions or preferred methods, or to serve as a source of any limitations on the scope of the claimed inventions.

[0014] **FIGs. 1A–1D** plot simulated association kinetics of two example sweeteners at various association rate constants.

[0015] **FIGs. 2A–2D** plot simulated dissociation kinetics of two example sweeteners at various association rate constants.

DETAILED DESCRIPTION

[0016] The present invention disclosure describes preferred sweetener properties having preferred sweetness temporal profiles, methods of identifying sweeteners having these properties, and compositions with said sweeteners.

[0017] Without being bound by any particular theory, there may be a correlation between assay potency of non-caloric sweeteners (NCSs) at the receptor level and delayed

sweetness onset and lingering of the NCS at the receptor. The more potent a sweetener is (i.e., the greater its affinity for the receptor), the more likely it may exhibit either a delay in sweetness onset and/or linger at the receptor. NCSs may engage and disengage the sweet taste receptor within time intervals that agree with their delayed and extended sweetness temporal properties. Lower use level of higher intensity NCSs and higher affinity could therefore play a role in delayed sweetness onset and sweetness linger, respectively. Novel NCSs exhibiting sucrose-like sweetness temporal profile, on their own, may be of lower affinity and exhibit defined association and dissociation half-time values.

[0018] This description sets forth various aspects and embodiments provided herein. The description is to be read from the perspective of the person of ordinary skill in the relevant art. Therefore, information that is well known to such ordinarily skilled artisans is not necessarily included.

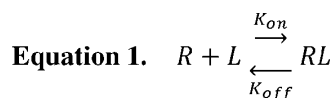
[0019] Identification of suitable NCSs has been a challenge. Though hundreds of different sweeteners have been identified over the last 200 years, none of them fully reproduce the taste of sugar (sucrose). DuBois et al., *Chemistry of Gustatory Stimuli*, In: FIRESTEIN, S. & BEAUCHAMP, G. K. (eds.) *THE SENSES: A COMPREHENSIVE REFERENCE*, San Diego: Academic Press (2008). Many previously identified NCSs have undesirable traits such as a bitter, metallic or licorice off-taste, lack of mouthfeel or bulkiness, astringency, a cooling sensation, and/or perceptible temporal issues including a delay in sweetness onset of a few seconds and a sweetness linger lasting from a few seconds to minutes. DuBois, *Molecular mechanism of sweetness sensation*, *Physiology & Behavior*, 164, 453-463 (2016). Sweetness onset describes the time needed to reach maximum sweetness intensity after sampling and linger describes the sweetness duration perceived after expectoration or ingestion. Karl et al., *Structure-dependent effects of sweet and sweet taste affecting compounds on their sensorial properties*, *Food Chem X*, 7, 100100 (2020); Deck et al., *Impact of lactisole on the time-intensity profile of selected sweeteners in dependence of the binding site*, *Food Chem X*, 15, 100446 (2022). Temporal issues may be more perceptible for so-called “high intensity” NCSs. For example, high intensity NCSs may have a relatively slow onset of sweetness sensation after tasting and a longer duration of taste. (Birch, *Sweetness*, *Arch. Dis. Childh.*, Lond., 61, 1153-1154 (1986). A delay in sweetness onset and sweetness linger may tend to co-occur. DuBois et al., *Non-caloric sweeteners, sweetness modulators, and sweetener enhancers*,

Annual review of food science and technology, 3, 353-80 (2012) (“DuBois 2012”). These temporal issues have been detected with sucralose, NHDC, stevioside sweeteners including rebA, mogroside sweeteners, monoammonium glycyrrhizinate, aspartame, neotame, advantame, thaumatin, brazzein, and monatin. DuBois 2012; Lindley, *Natural High-Potency Sweeteners*, John Wiley & Sons, Ltd. (2012); and Carniel Beltrami et al., *Sweeteners and sweet taste enhancers in the food industry*, Food Science and Technology, 38, 181-187 (2018). The relationship between delayed sweetness onset and sweetness linger may be due to non-specific interactions of NCSs with cellular membranes within the oral cavity. In such interactions, the cellular membranes may temporarily trap the sweetener molecules away from the receptor and cause delay in sweetness onset, on one hand, and creating a sweetener reservoir for molecules that have already dissociated from the receptor and allowing them to rebind, resulting in lingering, on the other hand. Certain NCSs may interact with the receptor desensitization machinery in taste receptor cells and impair signaling attenuation, resulting in a sweet taste linger.

[0020] Different NCSs’ binding kinetics at the sweet taste receptor could theoretically influence their sweetness temporal profile. However, this explanation had previously been criticized using calculations with taste-test derived affinity value for the stevioside sweetener rebA, and strict assumptions for association rate constants. *See* DuBois 2012.

[0021] The development of sweet taste receptor assays has allowed determination of sweeteners’ apparent binding affinity at the receptor and an investigation into pharmacological mechanisms underlying the temporal issues observed with these molecules. *See* Guy Servant et al., *Positive allosteric modulators of the human sweet taste receptor enhance sweet taste*, 107 PNAS 10, 4746–51 (March 9, 2010) and Nicole Servant et al., *A Dynamic Mass Redistribution Assay for the Human Sweet Taste Receptor uncovers G-Protein Dependent Biased Ligands*, 13 Frontiers in Pharmacol. 832529 (February 17, 2022), both of which are incorporated herein by reference in their entirety.

[0022] With reference to Equation 1 below, the law of mass-action applied to pharmacology describes conditions leading to all ligand-receptor interactions, including, as illustrative examples, low affinity mM carbohydrate (CHO)-sweeteners interactions with their receptor and high affinity pM antibody interactions with their antigens:



At fixed receptor levels R , increasing the ligand concentration L will favor the formation of the ligand-receptor complexes RL , or that conversely, decreasing the ligand concentration L will reduce the formation of ligand-receptor complexes RL . The dissociation rate constant, K_{off} , dictates how long the ligand remains bound to the receptor, and potentially prolongs signaling. As discussed herein, low affinity sweeteners may have a relatively high dissociation rate constant K_{off} while high affinity sweeteners may have a relatively low dissociation rate constant K_{off} .

[0023] As an example, a lower affinity sweetener may need high use levels (i.e., a high amount of the sweetener to achieve a given sweetness response, corresponding to a high L in the equation). The use levels of the low-affinity sweetener, and therefore ligand concentration L , may be so high that the interaction between the sweetener and the sweet taste receptor should be highly favored and extremely fast. Conversely, higher affinity sweeteners may take longer to achieve binding equilibrium relative to low-affinity sweeteners, as the higher affinity sweeteners require of lower use levels and relatively slower dissociation kinetics (low K_{off}) from the receptor-ligand complexes. These slower dissociation kinetics may stabilize the ligand-receptor complexes over a longer time relative to low-affinity sweeteners. With high affinity of an NCS to the sweetness receptor, and associated lower use levels of the NCS, formation of receptor-ligand complexes within the very first few seconds after sampling may not be favored, relative to lower affinity sweeteners. This time period may correspond to the time period when taste sensation is recorded and transmitted by taste bud cells. The higher affinity of very potent NCSs may lead to extended perceived effect, because of a relatively longer residence time on the receptor.

[0024] The present disclosure provides for a novel analysis of sweetener binding kinetics for identifying suitable NCSs and/or other sweeteners. Such NCSs and other sweeteners may be included in ingestible compositions.

Definitions

[0025] The following terms and phrases have the meanings indicated below, unless otherwise provided herein. This disclosure may employ other terms and phrases not expressly

defined herein. Such other terms and phrases have the meanings that they would possess within the context of this disclosure to those of ordinary skill in the art. In some instances, a term or phrase may be defined in the singular or plural. In such instances, it is understood that any term in the singular may include its plural counterpart and vice versa, unless expressly indicated to the contrary.

[0026] As used herein, “use level(s)” refer to the amount of a particular sweetener needed to achieve a given sweetness receptor response. Use levels may commonly be discussed with reference to the sweetness of a standard equivalent amount of sucrose (e.g., in degrees Brix). For instance, a use level of a given sweetener may be with reference to 5 degrees Brix equivalents (i.e., the sweetness of a solution having 5 Brix sucrose).

[0027] As used herein, “rebA” refers to rebaudioside A. Rebaudioside A can be found in the stevia leaf.

[0028] As used herein, the singular forms “a,” “an,” and “the” include plural referents unless the context clearly dictates otherwise. For example, reference to “a substituent” encompasses a single substituent as well as two or more substituents, and the like.

[0029] As used herein, “for example,” “for instance,” “such as,” or “including” are meant to introduce examples that further clarify more general subject matter. Unless otherwise expressly indicated, such examples are provided only as an aid for understanding embodiments illustrated in the present disclosure, and are not meant to be limiting in any fashion. Nor do these phrases indicate any kind of preference for the disclosed embodiment.

[0030] As used herein, “comprise” or “comprises” or “comprising” or “comprised of” refer to groups that are open, meaning that the group can include additional members in addition to those expressly recited. For example, the phrase, “comprises A” means that A must be present, but that other members can be present too. The terms “include,” “have,” and “composed of” and their grammatical variants have the same meaning. In contrast, “consist of” or “consists of” or “consisting of” refer to groups that are closed. For example, the phrase “consists of A” means that A and only A is present.

[0031] As used herein, “optionally” means that the subsequently described event(s) may or may not occur. In some embodiments, the optional event does not occur. In some other embodiments, the optional event does occur one or more times.

[0032] As used herein, “or” is to be given its broadest reasonable interpretation, and is not to be limited to an either/or construction. Thus, the phrase “comprising A or B” means that A can be present and not B, or that B is present and not A, or that A and B are both present. Further, if A, for example, defines a class that can have multiple members, e.g., A1 and A2, then one or more members of the class can be present concurrently.

[0033] A “sweetener,” “sweet flavoring agent,” “sweet flavor entity,” or “sweet compound” herein refers to a compound or ingestibly acceptable salt thereof that elicits a detectable sweet flavor in a subject, e.g., a compound that activates a T1R2/T1R3 receptor in vitro.

[0034] Other terms are defined in other portions of this description, even though not included in this subsection.

Methods of Identifying Sweeteners

[0035] In certain aspects, this disclosure provides for a method of identifying a sweetener for inclusion in an ingestible composition, the method comprising: measuring one or more sweet receptor binding properties of a candidate sweetener, the binding properties comprising one or more of a K_D or EC_{50} value, a halftime occupancy, and a dissociation halftime of the candidate sweetener with respect to a human sweet taste receptor; and including the candidate sweetener in an ingestible composition if the one or more sweet receptor binding properties include: a K_D or EC_{50} value greater or equal to 50 μM ; a halftime occupancy within a range of 4×10^{-6} s to 20 s at K_{on} values ranging from $10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $10^2 \text{ M}^{-1} \text{ s}^{-1}$; and a dissociation halftime within a range of 2×10^{-5} s to 30 s at K_{on} values ranging from $10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $10^2 \text{ M}^{-1} \text{ s}^{-1}$.

[0036] In some examples, the candidate sweetener has a halftime occupancy ranging from 4×10^{-2} s to 20 s at a K_{on} value of from $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a halftime occupancy ranging from 4×10^{-3} s to 2 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a halftime occupancy ranging from 4×10^{-4} s to 0.2 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a halftime occupancy ranging from 4×10^{-5} s to 2×10^{-2} s at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a halftime occupancy ranging from 4×10^{-6} s to 2×10^{-3} s at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate

sweetener has a dissociation halftime ranging from 0.2s to 30s at a K_{on} value of $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a dissociation halftime ranging from $2 \times 10^{-2} \text{ s}$ to 3 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a dissociation halftime ranging from $2 \times 10^{-3} \text{ s}$ to 0.3 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a dissociation halftime ranging from $2 \times 10^{-4} \text{ s}$ to $3 \times 10^{-2} \text{ s}$ at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the candidate sweetener has a dissociation halftime ranging from $2 \times 10^{-5} \text{ s}$ to $3 \times 10^{-3} \text{ s}$ at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$. In some examples, the measuring comprises quantification of the human sweet taste receptor activity by cell-based assay. In further examples, the cell-based assay is a dynamic mass redistribution (DMR) assay or a calcium mobilization assay. In some examples, the human sweet taste receptor is a T1R2/R3 sweet receptor heterodimer.

[0037] Some example assays for quantification of human sweet taste receptor activity are discussed by Guy Servant et al., *Positive allosteric modulators of the human sweet taste receptor enhance sweet taste*, 107 PNAS 10, 4746–51 (March 9, 2010) and Nicole Servant et al., *A Dynamic Mass Redistribution Assay for the Human Sweet Taste Receptor uncovers G-Protein Dependent Biased Ligands*, 13 Frontiers in Pharmacol. 832529 (February 17, 2022), each incorporated herein in their entireties. In some examples, the assay includes the human sweet taste receptor (e.g., T1R2/T1R3). In such examples, the human taste receptor can be coupled to the promiscuous G protein $G\alpha 15$ to induce PLC activation, which may cause a net increase in calcium mobilization inside cells. The calcium mobilization can be measured, for example by addition of fluorescent calcium indicator and imaging. Such assays may be implemented as a fluorometric imaging plate reader (FLIPR) assay. In other such examples, the human taste receptor can be coupled to a chimeric G protein containing the C-terminal tail 25 residues of the physiologically relevant G protein subunit $G\alpha_{\text{gustducin}}$. In such examples, cellular response to a candidate sweetener can be measured by DMR assay.

Methods of Using Sweeteners

[0038] In other aspects, the disclosure provides uses of any identified or selected sweetener of the foregoing aspects, including any embodiments or combination of embodiments thereof, as set forth above.

[0039] In a certain aspect, the disclosure provides uses of any identified or selected sweetener of the screening methods disclosed herein to increase a sweet taste of an ingestible composition.

Sweetened Ingestible Compositions

[0040] The identified or selected sweeteners can be included in the ingestible compositions in any suitable amount. In some embodiments, the identified or selected sweeteners are present in an amount sufficient to enhance the taste (e.g., by increasing sweetness) of the compositions. In some embodiments, the ingestible composition comprises the identified or selected sweetener in a concentration no less than 10000 ppm, or no less than 5000 ppm, or no less than 2500 ppm, or no less than 1000 ppm, or no less than 500 ppm, or no less than 250 ppm, or no less than 100 ppm. Thus, in some embodiments, the ingestible composition comprises the identified or selected sweetener compound in a concentration ranging from 100 ppm to 250 ppm, or from 100 ppm to 500 ppm, or from 100 ppm to 1000 ppm, or from 100 ppm to 2500 ppm, or from 100 ppm to 5000 ppm, or from 100 ppm to 10000 ppm. In embodiments where a sweetener, such as sucrose or fructose, are present, the weight-to-weight ratio of sweetener to the identified or selected sweetener compound in the ingestible composition ranges from 5000:1 to 2000:1, or from 1000:1 to 500:1, or from 250:1 to 100:1.

[0041] The ingestible compositions can, in certain embodiments, comprise any additional ingredients or combination of ingredients as are commonly used in food and beverage products, including, but not limited to:

acids, including, for example citric acid, phosphoric acid, ascorbic acid, sodium acid sulfate, lactic acid, or tartaric acid;

bitter ingredients, including, for example caffeine, quinine, green tea, catechins, polyphenols, green robusta coffee extract, green coffee extract, potassium chloride, menthol, or proteins (such as proteins and protein isolates derived from plants, algae, or fungi);

coloring agents, including, for example caramel color, Red #40, Yellow #5, Yellow #6, Blue #1, Red #3, purple carrot, black carrot juice, purple sweet potato, vegetable juice, fruit juice, beta carotene, turmeric curcumin, or titanium dioxide;

preservatives, including, for example sodium benzoate, potassium benzoate, potassium sorbate, sodium metabisulfate, sorbic acid, or benzoic acid;

antioxidants including, for example ascorbic acid, calcium disodium EDTA, alpha tocopherols, mixed tocopherols, rosemary extract, grape seed extract, resveratrol, or sodium hexametaphosphate;

vitamins or functional ingredients including, for example resveratrol, Co-Q10, omega 3 fatty acids, theanine, choline chloride (citocoline), fibersol, inulin (chicory root), taurine, panax ginseng extract, guanana extract, ginger extract, L-phenylalanine, L-carnitine, L-tartrate, D-glucoronolactone, inositol, bioflavonoids, Echinacea, ginko biloba, yerba mate, flax seed oil, garcinia cambogia rind extract, white tea extract, ribose, milk thistle extract, grape seed extract, pyrodixine HCl (vitamin B6), cyanoobalamin (vitamin B12), niacinamide (vitamin B3), biotin, calcium lactate, calcium pantothenate (pantothenic acid), calcium phosphate, calcium carbonate, chromium chloride, chromium polynicotinate, cupric sulfate, folic acid, ferric pyrophosphate, iron, magnesium lactate, magnesium carbonate, magnesium sulfate, monopotassium phosphate, monosodium phosphate, phosphorus, potassium iodide, potassium phosphate, riboflavin, sodium sulfate, sodium gluconate, sodium polyphosphate, sodium bicarbonate, thiamine mononitrate, vitamin D3, vitamin A palmitate, zinc gluconate, zinc lactate, or zinc sulphate;

clouding agents, including, for example ester gun, brominated vegetable oil (BVO), or sucrose acetate isobutyrate (SAIB);

buffers, including, for example sodium citrate, potassium citrate, or salt;

flavors, including, for example propylene glycol, ethyl alcohol, glycerine, gum Arabic (gum acacia), maltodextrin, modified corn starch, dextrose, natural flavor, natural flavor with other natural flavors (natural flavor WONF), natural and artificial flavors, artificial flavor, silicon dioxide, magnesium carbonate, or tricalcium phosphate; or

starches and stabilizers, including, for example pectin, xanthan gum, carboxymethylcellulose (CMC), polysorbate 60, polysorbate 80, medium chain triglycerides, cellulose gel, cellulose gum, sodium caseinate, modified food starch, gum Arabic (gum acacia), inulin, or carrageenan.

[0042] The ingestible compositions can have any suitable pH. In some embodiments, the identified or selected active compounds enhance the sweetness of a sweetener under a broad range of pH, e.g., from lower pH to neutral pH. The lower and neutral pH includes, but is not limited to, a pH from about 2.5 to about 8.5; from about 3.0 to about

8.0; from about 3.5 to about 7.5; and from about 4.0 to about 7. In certain embodiments, compounds as disclosed and described herein, individually or in combination, can enhance the perceived sweetness of a fixed concentration of a sweetener in taste tests at a compound concentration of about 50 μ M, 40 μ M, 30 μ M, 20 μ M, or 10 μ M at both low to neutral pH value. In certain embodiments, the enhancement factor of the compounds as disclosed and described herein, individually or in combination, at the lower pH is substantially similar to the enhancement factor of the compounds at neutral pH. Such consistent sweet enhancing property under a broad range of pH allow a broad use in a wide variety of foods and beverages of the compounds as disclosed and described herein, individually or in combination.

[0043] In certain aspects, the disclosure provides flavored products comprising any compositions of the preceding aspects. In some embodiment, the flavored products are beverage products, such as soda, flavored water, tea, and the like. In some other embodiments, the flavored products are food products, such as yogurt.

[0044] In embodiments where the flavored product is a beverage, the beverage may be selected from the group consisting of enhanced sparkling beverages, colas, lemon-lime flavored sparkling beverages, orange flavored sparkling beverages, grape flavored sparkling beverages, strawberry flavored sparkling beverages, pineapple flavored sparkling beverages, ginger-ales, root beers, fruit juices, fruit-flavored juices, juice drinks, nectars, vegetable juices, vegetable-flavored juices, sports drinks, energy drinks, enhanced water drinks, enhanced water with vitamins, near water drinks, coconut waters, tea type drinks, coffees, cocoa drinks, beverages containing milk components, beverages containing cereal extracts and smoothies. In some embodiments, the beverage may be a soft drink.

[0045] In certain embodiments of any aspects and embodiments set forth herein that refer to a flavored product, the flavored product is a non-naturally-occurring product, such as a packaged food or beverage product.

[0046] Further non-limiting examples of food and beverage products or formulations include sweet coatings, frostings, or glazes for such products or any entity included in the Soup category, the Dried Processed Food category, the Beverage category, the Ready Meal category, the Canned or Preserved Food category, the Frozen Processed Food category, the Chilled Processed Food category, the Snack Food category, the Baked Goods category, the Confectionery category, the Dairy Product category, the Ice Cream category, the

Meal Replacement category, the Pasta and Noodle category, and the Sauces, Dressings, Condiments category, the Baby Food category, and/or the Spreads category.

[0047] In general, the Soup category refers to canned/preserved, dehydrated, instant, chilled, UHT and frozen soup. For the purpose of this definition soup(s) means a food prepared from meat, poultry, fish, vegetables, grains, fruit and other ingredients, cooked in a liquid which may include visible pieces of some or all of these ingredients. It may be clear (as a broth) or thick (as a chowder), smooth, pureed or chunky, ready-to-serve, semi-condensed or condensed and may be served hot or cold, as a first course or as the main course of a meal or as a between meal snack (sipped like a beverage). Soup may be used as an ingredient for preparing other meal components and may range from broths (consommé) to sauces (cream or cheese-based soups).

[0048] The Dehydrated and Culinary Food Category usually means: (i) Cooking aid products such as: powders, granules, pastes, concentrated liquid products, including concentrated bouillon, bouillon and bouillon like products in pressed cubes, tablets or powder or granulated form, which are sold separately as a finished product or as an ingredient within a product, sauces and recipe mixes (regardless of technology); (ii) Meal solutions products such as: dehydrated and freeze dried soups, including dehydrated soup mixes, dehydrated instant soups, dehydrated ready-to-cook soups, dehydrated or ambient preparations of ready-made dishes, meals and single serve entrees including pasta, potato and rice dishes; and (iii) Meal embellishment products such as: condiments, marinades, salad dressings, salad toppings, dips, breading, batter mixes, shelf stable spreads, barbecue sauces, liquid recipe mixes, concentrates, sauces or sauce mixes, including recipe mixes for salad, sold as a finished product or as an ingredient within a product, whether dehydrated, liquid or frozen.

[0049] The Beverage category usually means beverages, beverage mixes and concentrates, including but not limited to, carbonated and non-carbonated beverages, alcoholic and non-alcoholic beverages, ready to drink beverages, liquid concentrate formulations for preparing beverages such as sodas, and dry powdered beverage precursor mixes. The Beverage category also includes the alcoholic drinks, the soft drinks, sports drinks, isotonic beverages, and hot drinks. The alcoholic drinks include, but are not limited to beer, cider/perry, FABs, wine, and spirits. The soft drinks include, but are not limited to carbonates, such as colas and non-cola carbonates; fruit juice, such as juice, nectars, juice drinks and fruit flavored drinks;

bottled water, which includes sparkling water, spring water and purified/table water; functional drinks, which can be carbonated or still and include sport, energy or elixir drinks; concentrates, such as liquid and powder concentrates in ready to drink measure. The drinks, either hot or cold, include, but are not limited to coffee or ice coffee, such as fresh, instant, and combined coffee; tea or iced tea, such as black, green, white, oolong, and flavored tea; and other drinks including flavor-, malt- or plant-based powders, granules, blocks or tablets mixed with milk or water.

[0050] The Snack Food category generally refers to any food that can be a light informal meal including, but not limited to Sweet and savory snacks and snack bars. Examples of snack food include, but are not limited to fruit snacks, chips/crisps, extruded snacks, tortilla/corn chips, popcorn, pretzels, nuts and other sweet and savory snacks. Examples of snack bars include, but are not limited to granola/muesli bars, breakfast bars, energy bars, fruit bars and other snack bars.

[0051] The Baked Goods category generally refers to any edible product the process of preparing which involves exposure to heat or excessive sunlight. Examples of baked goods include, but are not limited to bread, buns, cookies, muffins, cereal, toaster pastries, pastries, waffles, tortillas, biscuits, pies, bagels, tarts, quiches, cake, any baked foods, and any combination thereof.

[0052] The Ice Cream category generally refers to frozen dessert containing cream and sugar and flavoring. Examples of ice cream include, but are not limited to: impulse ice cream; take-home ice cream; frozen yoghurt and artisanal ice cream; soy, oat, bean (e.g., red bean and mung bean), and rice-based ice creams.

[0053] The Confectionery category generally refers to edible product that is sweet to the taste. Examples of confectionery include, but are not limited to candies, gelatins, chocolate confectionery, sugar confectionery, gum, and the likes and any combination products.

[0054] The Meal Replacement category generally refers to any food intended to replace the normal meals, particularly for people having health or fitness concerns. Examples of meal replacement include, but are not limited to slimming products and convalescence products.

[0055] The Ready Meal category generally refers to any food that can be served as meal without extensive preparation or processing. The ready meal includes products that have had recipe “skills” added to them by the manufacturer, resulting in a high degree of readiness, completion and convenience. Examples of ready meal include, but are not limited to canned/preserved, frozen, dried, chilled ready meals; dinner mixes; frozen pizza; chilled pizza; and prepared salads.

[0056] The Pasta and Noodle category includes any pastas and/or noodles including, but not limited to canned, dried and chilled/fresh pasta; and plain, instant, chilled, frozen and snack noodles.

[0057] The Canned/Preserved Food category includes, but is not limited to canned/preserved meat and meat products, fish/seafood, vegetables, tomatoes, beans, fruit, ready meals, soup, pasta, and other canned/preserved foods.

[0058] The Frozen Processed Food category includes, but is not limited to frozen processed red meat, processed poultry, processed fish/seafood, processed vegetables, meat substitutes, processed potatoes, bakery products, desserts, ready meals, pizza, soup, noodles, and other frozen food.

[0059] The Dried Processed Food category includes, but is not limited to rice, dessert mixes, dried ready meals, dehydrated soup, instant soup, dried pasta, plain noodles, and instant noodles. The Chill Processed Food category includes, but is not limited to chilled processed meats, processed fish/seafood products, lunch kits, fresh cut fruits, ready meals, pizza, prepared salads, soup, fresh pasta and noodles.

[0060] The Sauces, Dressings and Condiments category includes, but is not limited to tomato pastes and purees, bouillon/stock cubes, herbs and spices, monosodium glutamate (MSG), table sauces, soy based sauces, pasta sauces, wet/cooking sauces, dry sauces/powder mixes, ketchup, mayonnaise, mustard, salad dressings, vinaigrettes, dips, pickled products, and other sauces, dressings and condiments.

[0061] The Baby Food category includes, but is not limited to milk- or soybean-based formula; and prepared, dried and other baby food.

[0062] The Spreads category includes, but is not limited to jams and preserves, honey, chocolate spreads, nut-based spreads, and yeast-based spreads.

[0063] The Dairy Product category generally refers to edible product produced from mammal's milk. Examples of dairy product include, but are not limited to drinking milk products, cheese, yoghurt and sour milk drinks, and other dairy products.

[0064] Additional examples for flavored products, particularly food and beverage products or formulations, are provided as follows. Exemplary ingestible compositions include one or more confectioneries, chocolate confectionery, tablets, countlines, bagged selflines/softlines, boxed assortments, standard boxed assortments, twist wrapped miniatures, seasonal chocolate, chocolate with toys, alfajores, other chocolate confectionery, mints, standard mints, power mints, boiled sweets, pastilles, gums, jellies and chews, toffees, caramels and nougat, medicated confectionery, lollipops, liquorice, other sugar confectionery, bread, packaged/industrial bread, unpackaged/artisanal bread, pastries, cakes, packaged/industrial cakes, unpackaged/artisanal cakes, cookies, chocolate coated biscuits, sandwich biscuits, filled biscuits, savory biscuits and crackers, bread substitutes, breakfast cereals, rte cereals, family breakfast cereals, flakes, muesli, other cereals, children's breakfast cereals, hot cereals, ice cream, impulse ice cream, single portion dairy ice cream, single portion water ice cream, multi-pack dairy ice cream, multi-pack water ice cream, take-home ice cream, take-home dairy ice cream, ice cream desserts, bulk ice cream, take-home water ice cream, frozen yoghurt, artisanal ice cream, dairy products, milk, fresh/pasteurized milk, full fat fresh/pasteurized milk, semi skimmed fresh/pasteurized milk, long-life/uht milk, full fat long life/uht milk, semi skimmed long life/uht milk, fat-free long life/uht milk, goat milk, condensed/evaporated milk, plain condensed/evaporated milk, flavored, functional and other condensed milk, flavored milk drinks, dairy only flavored milk drinks, flavored milk drinks with fruit juice, soy milk, sour milk drinks, fermented dairy drinks, coffee whiteners, powder milk, flavored powder milk drinks, cream, cheese, processed cheese, spreadable processed cheese, unspreadable processed cheese, unprocessed cheese, spreadable unprocessed cheese, hard cheese, packaged hard cheese, unpackaged hard cheese, yoghurt, plain/natural yoghurt, flavored yoghurt, fruited yoghurt, probiotic yoghurt, drinking yoghurt, regular drinking yoghurt, probiotic drinking yoghurt, chilled and shelf-stable desserts, dairy-based desserts, soy-based desserts, chilled snacks, fromage frais and quark, plain fromage frais and quark, flavored fromage frais and quark, savory fromage frais and quark, sweet and savory snacks, fruit snacks, chips/crisps, extruded snacks, tortilla/corn chips, popcorn, pretzels, nuts, other

sweet and savory snacks, snack bars, granola bars, breakfast bars, energy bars, fruit bars, other snack bars, meal replacement products, slimming products, convalescence drinks, ready meals, canned ready meals, frozen ready meals, dried ready meals, chilled ready meals, dinner mixes, frozen pizza, chilled pizza, soup, canned soup, dehydrated soup, instant soup, chilled soup, hot soup, frozen soup, pasta, canned pasta, dried pasta, chilled/fresh pasta, noodles, plain noodles, instant noodles, cups/bowl instant noodles, pouch instant noodles, chilled noodles, snack noodles, canned food, canned meat and meat products, canned fish/seafood, canned vegetables, canned tomatoes, canned beans, canned fruit, canned ready meals, canned soup, canned pasta, other canned foods, frozen food, frozen processed red meat, frozen processed poultry, frozen processed fish/seafood, frozen processed vegetables, frozen meat substitutes, frozen potatoes, oven baked potato chips, other oven baked potato products, non-oven frozen potatoes, frozen bakery products, frozen desserts, frozen ready meals, frozen pizza, frozen soup, frozen noodles, other frozen food, dried food, dessert mixes, dried ready meals, dehydrated soup, instant soup, dried pasta, plain noodles, instant noodles, cups/bowl instant noodles, pouch instant noodles, chilled food, chilled processed meats, chilled fish/seafood products, chilled processed fish, chilled coated fish, chilled smoked fish, chilled lunch kit, chilled ready meals, chilled pizza, chilled soup, chilled/fresh pasta, chilled noodles, oils and fats, olive oil, vegetable and seed oil, cooking fats, butter, margarine, spreadable oils and fats, functional spreadable oils and fats, sauces, dressings and condiments, tomato pastes and purees, bouillon/stock cubes, stock cubes, gravy granules, liquid stocks and fonds, herbs and spices, fermented sauces, soy based sauces, pasta sauces, wet sauces, dry sauces/powder mixes, ketchup, mayonnaise, regular mayonnaise, mustard, salad dressings, regular salad dressings, low fat salad dressings, vinaigrettes, dips, pickled products, other sauces, dressings and condiments, baby food, milk formula, standard milk formula, follow-on milk formula, toddler milk formula, hypoallergenic milk formula, prepared baby food, dried baby food, other baby food, spreads, jams and preserves, honey, chocolate spreads, nut-based spreads, and yeast-based spreads. Exemplary ingestible compositions also include confectioneries, bakery products, ice creams, dairy products, sweet and savory snacks, snack bars, meal replacement products, ready meals, soups, pastas, noodles, canned foods, frozen foods, dried foods, chilled foods, oils and fats, baby foods, or spreads or a mixture thereof. Exemplary ingestible compositions also include breakfast cereals, sweet beverages or solid or liquid concentrate compositions for preparing

beverages, ideally so as to enable the reduction in concentration of previously known saccharide sweeteners, or artificial sweeteners.

[0065] Some embodiments provide a chewable composition that may or may not be intended to be swallowed. In some embodiments, the chewable composition may be gum, chewing gum, sugarized gum, sugar-free gum, functional gum, bubble gum including compounds as disclosed and described herein, individually or in combination.

[0066] In some embodiments, identified or selected sweetener as disclosed and described herein, individually or in combination, may be provided in a flavoring concentrate formulation, e.g., suitable for subsequent processing to produce a ready-to-use (i.e., ready-to-serve) product. By “a flavoring concentrate formulation,” it is meant a formulation which should be reconstituted with one or more diluting medium to become a ready-to-use composition. The term “ingestible composition” is used herein to denote any substance that, either alone or together with another substance, can be taken by mouth, whether the ingestible composition is intended for consumption or not. The term “ingestible composition” may include any ready-to-use composition. In one embodiment, the ready-to-use composition includes a composition that can be directly consumed by a human or animal. The flavoring concentrate formulation is typically used by mixing with or diluted by one or more diluting medium, e.g., any consumable or ingestible ingredient or product, to impart or modify one or more flavors to the diluting medium. Such a use process is often referred to as reconstitution. The reconstitution can be conducted in a household setting or an industrial setting. For example, a frozen fruit juice concentrate can be reconstituted with water or other aqueous medium by a consumer in a kitchen to obtain the ready-to-use fruit juice beverage. In another example, a soft drink syrup concentrate can be reconstituted with water or other aqueous medium by a manufacturer in large industrial scales to produce the ready-to-use soft drinks. Since the flavoring concentrate formulation has the flavoring agent or flavor modifying agent in a concentration higher than the ready-to-use composition, the flavoring concentrate formulation is typically not suitable for being consumed directly without reconstitution. There are many benefits of using and producing a flavoring concentrate formulation. For example, one benefit is the reduction in weight and volume for transportation as the flavoring concentrate formulation can be reconstituted at the time of usage by the addition of suitable solvent, solid or liquid.

[0067] The flavored products set forth according to any of the foregoing embodiments, also include, in certain embodiments, one or more additional flavor-modifying compounds, such as compounds that enhance sweetness (e.g., hesperetin, naringenin, glucosylated steviol glycosides, etc.), compounds that block bitterness, compounds that enhance umami, compounds that reduce sourness, compounds that enhance saltiness, compounds that enhance a cooling effect, or any combinations of the foregoing.

[0068] In certain embodiments of any aspects and embodiments set forth herein that refer to a sweetening or flavoring concentrate, the sweetening or flavoring concentrate is a non-naturally-occurring product, such as a composition specifically manufactured for the production of a flavored product, such as food or beverage product.

[0069] In one embodiment, the flavoring concentrate formulation comprises i) compounds as disclosed and described herein, individually or in combination; ii) a carrier; and iii) optionally at least one adjuvant. The term “carrier” denotes a usually inactive accessory substance, such as solvents, binders, or other inert medium, which is used in combination with the present compound and one or more optional adjuvants to form the formulation. For example, water or starch can be a carrier for a flavoring concentrate formulation. In some embodiments, the carrier is the same as the diluting medium for reconstituting the flavoring concentrate formulation; and in other embodiments, the carrier is different from the diluting medium. The term “carrier” as used herein includes, but is not limited to, an ingestibly acceptable carrier.

[0070] The term “adjuvant” denotes an additive which supplements, stabilizes, maintains, or enhances the intended function or effectiveness of the active ingredient, such as the compound of the present invention. In one embodiment, the at least one adjuvant comprises one or more flavoring agents. The flavoring agent may be of any flavor known to one skilled in the art or consumers, such as the flavor of chocolate, coffee, tea, mocha, French vanilla, peanut butter, chai, or combinations thereof. In another embodiment, the at least one adjuvant comprises one or more bitter taste blocker, identified as described above. In another embodiment, the at least one adjuvant comprises one or more ingredients selected from the group consisting of an emulsifier, a stabilizer, an antimicrobial preservative, an antioxidant, vitamins, minerals, fats, starches, protein concentrates and isolates, salts, and combinations thereof. Examples of emulsifiers, stabilizers, antimicrobial preservatives, antioxidants,

vitamins, minerals, fats, starches, protein concentrates and isolates, and salts are described in U.S. Pat. No. 6,468,576, the content of which is hereby incorporated by reference in its entirety for all purposes.

[0071] In one embodiment, the present flavoring concentrate formulation can be in a form selected from the group consisting of liquid including solution and suspension, solid, foamy material, paste, gel, cream, and a combination thereof, such as a liquid containing certain amount of solid contents. In one embodiment, the flavoring concentrate formulation is in form of a liquid including aqueous-based and nonaqueous-based. In some embodiments, the present flavoring concentrate formulation can be carbonated or non-carbonated.

[0072] The flavoring concentrate formulation may further comprise a freezing point depressant, nucleating agent, or both as the at least one adjuvant. The freezing point depressant is an ingestibly acceptable compound or agent which can depress the freezing point of a liquid or solvent to which the compound or agent is added. That is, a liquid or solution containing the freezing point depressant has a lower freezing point than the liquid or solvent without the freezing point depressant. In addition to depress the onset freezing point, the freezing point depressant may also lower the water activity of the flavoring concentrate formulation. The examples of the freezing point depressant include, but are not limited to, carbohydrates, oils, ethyl alcohol, polyol, e.g., glycerol, and combinations thereof. The nucleating agent denotes an ingestibly acceptable compound or agent which is able to facilitate nucleation. The presence of nucleating agent in the flavoring concentrate formulation can improve the mouthfeel of the frozen Blushes of a frozen slush and to help maintain the physical properties and performance of the slush at freezing temperatures by increasing the number of desirable ice crystallization centers. Examples of nucleating agents include, but are not limited to, calcium silicate, calcium carbonate, titanium dioxide, and combinations thereof.

[0073] In one embodiment, the flavoring concentrate formulation is formulated to have a low water activity for extended shelf life. Water activity is the ratio of the vapor pressure of water in a formulation to the vapor pressure of pure water at the same temperature. In one embodiment, the flavoring concentrate formulation has a water activity of less than about 0.85. In another embodiment, the flavoring concentrate formulation has a water activity of less than about 0.80. In another embodiment, the flavoring concentrate formulation has a water activity of less than about 0.75.

[0074] In one embodiment, the flavoring concentrate formulation has compounds in accordance with the present disclosure in a concentration that is at least 2 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 5 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 10 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 15 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 20 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 30 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 40 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 50 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is at least 60 times of the concentration of the compound in a ready-to-use composition. In one embodiment, the flavoring concentrate formulation has the present compound in a concentration that is up to 100 times of the concentration of the compound in a ready-to-use composition.

EXAMPLES

[0075] The following examples involve known sweeteners. Some sweeteners discussed are caloric sweeteners, while others are NCSs. These examples are provided for illustrative purposes and are in no way intended to limit the scope of this disclosure.

Sweetness Kinetics

[0076] Association data was obtained and fitted using the pseudo-first order association kinetics equation: $Y = Y_{max} \cdot (1 - e^{-K_{obs} \cdot t})$, where Y_{max} corresponds to the maximum binding capacity of the system, t corresponds to association time in seconds, $K_{obs} =$

$(K_{on} \cdot L) + K_{off}$, and where Y corresponds to the fraction of occupied receptors at time. Sweetener association rate constant (K_{on}) and dissociation rate constant (K_{off}) have not yet been empirically determined but can be estimated with a few assumptions for K_D and K_{on} . Measured EC_{50} values obtained in the assay are used as K_D values. K_{on} values starting at $10^2 \text{ M}^{-1}\text{s}^{-1}$ and going up to a maximum of $10^6 \text{ M}^{-1}\text{s}^{-1}$ were utilized. **FIGs. 1A–1D** plot simulated association kinetics of example sweeteners at several different association constants (K_{on}). FIGs. 1A and 1B show sucrose association kinetics. FIGs. 1C and 1D show advantame association kinetics at different K_{on} values. Table 1, below, summarizes simulated kinetic halftime at various association rates K_{on} for sucrose, advantame, and other known sweeteners. Of these, sucrose, lactose, cyclamate, D-tryptophan, acesulfame potassium, aspartame, saccharin, and rebA exhibit little to no delay in sweetness onset. Sucralose, phyllodulcin, NHDC, neotame, thaumatin, and advantame exhibit a delay in sweetness onset.

Table 1: Association halftime $t_{1/2}$ (s)

Sweetener	K_{on} : $10^2 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^3 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^4 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^5 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^6 \text{ M}^{-1} \text{ s}^{-1}$
sucrose	3.7×10^{-2}	3.7×10^{-3}	3.7×10^{-4}	3.7×10^{-5}	3.7×10^{-6}
lactose	1×10^{-2}	1.0×10^{-3}	1.0×10^{-4}	1.0×10^{-5}	1.0×10^{-6}
cyclamate	0.6	6.0×10^{-2}	6.0×10^{-3}	6.0×10^{-4}	6.0×10^{-5}
D-tryptophan	1.3	0.13	1.3×10^{-2}	1.3×10^{-3}	1.3×10^{-4}
acesulfame potassium	4.0	0.40	4.0×10^{-2}	4.0×10^{-3}	4.0×10^{-4}
aspartame	5.8	0.58	5.8×10^{-2}	5.8×10^{-3}	5.8×10^{-4}
saccharin	5.7	0.57	5.7×10^{-2}	5.7×10^{-3}	5.7×10^{-4}
rebA	20	2.0	0.2	2.0×10^{-2}	2.0×10^{-3}
sucralose	23	2.3	0.23	2.3×10^{-2}	2.3×10^{-3}
phyllodulcin	26	2.6	0.26	2.6×10^{-2}	2.6×10^{-3}
NHDC	52	5.2	0.52	5.2×10^{-2}	5.2×10^{-3}

neotame	250	25	2.5	0.25	2.5×10^{-2}
thaumatin	940	94	9.4	0.94	9.4×10^{-2}
advantame	1000	100	10	1	0.1

[0077] Dissociation data was obtained and fitted using the one phase exponential decay kinetic equation: $Y = Y_{max} \cdot e^{-K_{off} \cdot t}$, where Y_{max} corresponds to the fraction of receptor bound at equilibrium based on the K_D estimate (EC_{50} value) and the concentration of ligand used, the dissociation constant K_{off} can be obtained by multiplying K_D and K_{on} , t corresponds to dissociation time in seconds, and Y corresponds to the fraction of occupied receptors at time t . FIG. 2A–2D plot simulated dissociation kinetics of example sweeteners at several different association constants (K_{on}). FIGs. 2A and 2B plot sucrose dissociation kinetics. FIGs. 2C and 2D plot neotame dissociation kinetics. Table 1, below, summarizes simulated kinetic halftime at various association rates K_{off} for sucrose, neotame, and other known sweeteners. Of these, sucrose, lactose, cyclamate, D-tryptophan, aspartame, acesulfame potassium, and saccharin exhibited little to no sweetness linger onset. Sucralose, rebA, NHDC, thamatin, phyllodulcin, neotame, and advantame exhibit sweetness linger.

Table 2: Dissociation halftime $t_{1/2}$ (s)

Sweetener	K_{on} : $10^2 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^3 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^4 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^5 \text{ M}^{-1} \text{ s}^{-1}$	K_{on} : $10^6 \text{ M}^{-1} \text{ s}^{-1}$
sucrose	0.17	1.7×10^{-2}	1.7×10^{-3}	1.7×10^{-4}	1.7×10^{-5}
lactose	4.3×10^{-2}	4.3×10^{-3}	4.3×10^{-4}	4.3×10^{-5}	4.3×10^{-6}
cyclamate	6.5	0.65	6.5×10^{-2}	6.5×10^{-3}	6.5×10^{-4}
D-tryptophan	13	1.3	0.13	1.3×10^{-3}	1.3×10^{-3}
aspartame	20	2.0	0.2	2.0×10^{-2}	2.0×10^{-3}
acesulfame potassium	27	2.7	0.27	2.7×10^{-2}	2.7×10^{-3}
saccharin	29	2.9	0.29	2.9×10^{-2}	2.9×10^{-3}
sucralose	96	9.6	0.96	9.6×10^{-2}	9.6×10^{-3}

rebA	240	24	2.4	0.24	2.4×10^{-2}
NHDC	380	38	3.8	0.38	3.8×10^{-2}
thaumatin	1,200	120	12	1.2	0.12
phylodulcin	4,200	420	42	4.2	0.42
neotame	4,300	430	43	4.3	0.43
advantame	18,000	1,800	180	18	1.8

WHAT IS CLAIMED IS:

1. A method of identifying a sweetener for inclusion in an ingestible composition, the method comprising:

measuring one or more sweet receptor binding properties of a candidate sweetener, the binding properties comprising one or more of a K_D or EC_{50} value, a halftime occupancy, and a dissociation halftime of the candidate sweetener with respect to a human sweet taste receptor; and

including the candidate sweetener in an ingestible composition if the one or more sweet receptor binding properties include:

a K_D or EC_{50} value greater or equal to 50 μM ;

a halftime occupancy within a range of 4×10^{-6} s to 20 s at K_{on} values ranging from $10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $10^2 \text{ M}^{-1} \text{ s}^{-1}$; and

a dissociation halftime within a range of 2×10^{-5} s to 30 s at K_{on} values ranging from $10^6 \text{ M}^{-1} \text{ s}^{-1}$ and $10^2 \text{ M}^{-1} \text{ s}^{-1}$.

2. The method of claim 1, wherein the candidate sweetener has a halftime occupancy ranging from 4×10^{-2} s to 20 s at a K_{on} value of from $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.

3. The method of claim 1, wherein the candidate sweetener has a halftime occupancy ranging from 4×10^{-3} s to 2 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.

4. The method of claim 1, wherein the candidate sweetener has a halftime occupancy ranging from 4×10^{-4} s to 0.2 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

5. The method of claim 1, wherein the candidate sweetener has a halftime occupancy ranging from 4×10^{-5} s to 2×10^{-2} s at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.

6. The method of claim 1, wherein the candidate sweetener has a halftime occupancy ranging from 4×10^{-6} s to 2×10^{-3} s at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.

7. The method of claim 1, wherein the candidate sweetener has a dissociation halftime ranging from 0.2s to 30s at a K_{on} value of $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.

8. The method of claim 1, wherein the candidate sweetener has a dissociation halftime ranging from 2×10^{-2} s to 3 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.

9. The method of claim 1, wherein the candidate sweetener has a dissociation halftime ranging from 2×10^{-3} s to 0.3 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

10. The method of claim 1, wherein the candidate sweetener has a dissociation halftime ranging from 2×10^{-4} s to 3×10^{-2} s at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.

11. The method of claim 1, wherein the candidate sweetener has a dissociation halftime ranging from 2×10^{-5} s to 3×10^{-3} s at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.

12. The method of any one of claims 1 to 11, wherein the measuring comprises quantification of the human sweet taste receptor activity by cell-based assay.

13. The method of claim 12, wherein the cell-based assay is a dynamic mass redistribution (DMR) assay or a calcium mobilization assay.

14. The method of any one of claims 1 to 13, wherein the human sweet taste receptor is a T1R2/T1R3 sweet receptor heterodimer.

15. Use of a sweetener molecule to sweeten an ingestible composition, wherein, with respect to a human taste receptor, the sweetener molecule has:

a K_D or EC_{50} value of at least 50 μM ;

a halftime occupancy within a range of 4×10^{-6} s to 20 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $10^6 \text{ M}^{-1} \text{ s}^{-1}$; and

a dissociation halftime within a range of 2×10^{-5} s to 30 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ and $10^6 \text{ M}^{-1} \text{ s}^{-1}$.

16. The use of claim 15, wherein the sweetener has a halftime occupancy ranging from 4×10^{-2} s to 20 s at a K_{on} value of from $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.

17. The use of claim 15, wherein the sweetener has a halftime occupancy ranging from 4×10^{-3} s to 2 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.

18. The use of claim 15, wherein the sweetener has a halftime occupancy ranging from 4×10^{-4} s to 0.2 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

19. The use of claim 15, wherein the sweetener has a halftime occupancy ranging from 4×10^{-5} s to 2×10^{-2} s at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.

20. The use of claim 15, wherein the sweetener has a halftime occupancy ranging from 4×10^{-6} s to 2×10^{-3} s at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.

21. The use of claim 15, wherein the sweetener has a dissociation halftime ranging from 0.2s to 30s at a K_{on} value of $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.

22. The use of claim 15, wherein the sweetener has a dissociation halftime ranging from 2×10^{-2} s to 3 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.

23. The use of claim 15, wherein the sweetener has a dissociation halftime ranging from 2×10^{-3} s to 0.3 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

24. The use of claim 15, wherein the sweetener has a dissociation halftime ranging from 2×10^{-4} s to 3×10^{-2} s at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.

25. The use of claim 15, wherein the sweetener has a dissociation halftime ranging from 2×10^{-5} s to 3×10^{-3} s at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.

26. The use of any one of claims 15 to 25, wherein the human sweet taste receptor is a T1R2/T1R3 sweet receptor heterodimer.

27. A sweetened ingestible composition, comprising:

a non-caloric sweetener molecule, wherein, with respect to a human sweet taste receptor, the sweetener molecule has:

a K_D value of at least 50 μM ;

a halftime occupancy within a range of 4×10^{-6} s to 20 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $10^6 \text{ M}^{-1} \text{ s}^{-1}$; and

a dissociation halftime within a range of 2×10^{-5} s to 30 s at K_{on} values ranging from $10^2 \text{ M}^{-1} \text{ s}^{-1}$ and $10^6 \text{ M}^{-1} \text{ s}^{-1}$.

28. The composition of claim 27, wherein the sweetener has a halftime occupancy ranging from 4×10^{-2} s to 20 s at a K_{on} value of from $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.

29. The composition of claim 27, wherein the sweetener has a halftime occupancy ranging from 4×10^{-3} s to 2 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.

30. The composition of claim 27, wherein the sweetener has a halftime occupancy ranging from 4×10^{-4} s to 0.2 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.

31. The composition of claim 27, wherein the sweetener has a halftime occupancy ranging from 4×10^{-5} s to 2×10^{-2} s at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.
32. The composition of claim 27, wherein the sweetener has a halftime occupancy ranging from 4×10^{-6} s to 2×10^{-3} s at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.
33. The composition of claim 27, wherein the sweetener has a dissociation halftime ranging from 0.2s to 30s at a K_{on} value of $1 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^2 \text{ M}^{-1} \text{ s}^{-1}$.
34. The composition of claim 27, wherein the sweetener has a dissociation halftime ranging from 2×10^{-2} s to 3 s at a K_{on} value of from $1 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^3 \text{ M}^{-1} \text{ s}^{-1}$.
35. The composition of claim 27, wherein the sweetener has a dissociation halftime ranging from 2×10^{-3} s to 0.3 s at a K_{on} value of from $1 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^4 \text{ M}^{-1} \text{ s}^{-1}$.
36. The composition of claim 27, wherein the sweetener has a dissociation halftime ranging from 2×10^{-4} s to 3×10^{-2} s at a K_{on} value of from $1 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^5 \text{ M}^{-1} \text{ s}^{-1}$.
37. The composition of claim 27, wherein the sweetener has a dissociation halftime ranging from 2×10^{-5} s to 3×10^{-3} s at a K_{on} value of from $1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$ to $9.9 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$.
38. The composition of any one of claims 27 to 37, wherein the sweetener molecule is naturally occurring.
39. The composition of any one of claims 27 to 37, wherein the sweetener molecule is non-naturally occurring.
40. The composition of any one of claims 27 to 39, wherein the human sweet taste receptor is a T1R2/T1R3 sweet receptor heterodimer.