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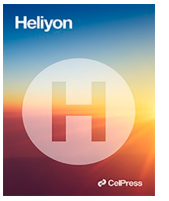

Suppression of sweet taste-related responses by plant-derived bioactive compounds and eating. Part I: A systematic review in humans

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ABSTRACT

The taste of food plays a crucial role in determining what and how much we eat. Thus, interventions that temporarily block sweet taste receptors offer a promising approach to addressing unhealthy behaviours associated with sugary foods. However, the relationship between reduced sweet taste response and food consumption remains unclear, with contradictory findings. Certain studies suggest that a diminished perception of sweetness leads to a sense of fullness and results in reduced food intake, while others suggest the opposite effect. To shed some light, our systematic review looked into the relationship between diminished sweet taste response and food consumption by examining the effects of bioactive compounds that experimentally inhibit sweetness in healthy individuals. This review was registered in the International Prospective Register of Systematic Reviews and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and the Scottish Intercollegiate Guidelines Network, and covered original papers included in Web of Science, PubMed, Scopus, Food Science Source and Food Science and technology abstracts. We identified 33 peer-reviewed English-language studies that fit the topic and met the inclusion criteria. The current literature predominantly focuses on the immediate impact of oral gymnemic acids, failing to provide preliminary evidence in support of the specific threshold hypothesis, above which food consumption decreases and below which the opposite effect occurs. Additionally, there was inconsistency in the findings regarding the short-term desire to eat following sweetness inhibition. Considering the downstream effects on energy intake and their clinical applications, further research is needed to clarify both the acute within-session effects (i.e., not wanting any more now) and the longer-term effects (i.e., deciding not to start eating) linked to oral sweet-taste-suppressing compounds.

1. Introduction

Sweet substances (especially sugar) as a source of calories are essential for caloric intake and in food selection to meet physiological needs [1,2]. The innate preference for sweet-tasting foods arises early in mammalian development [3] and is mediated by two different

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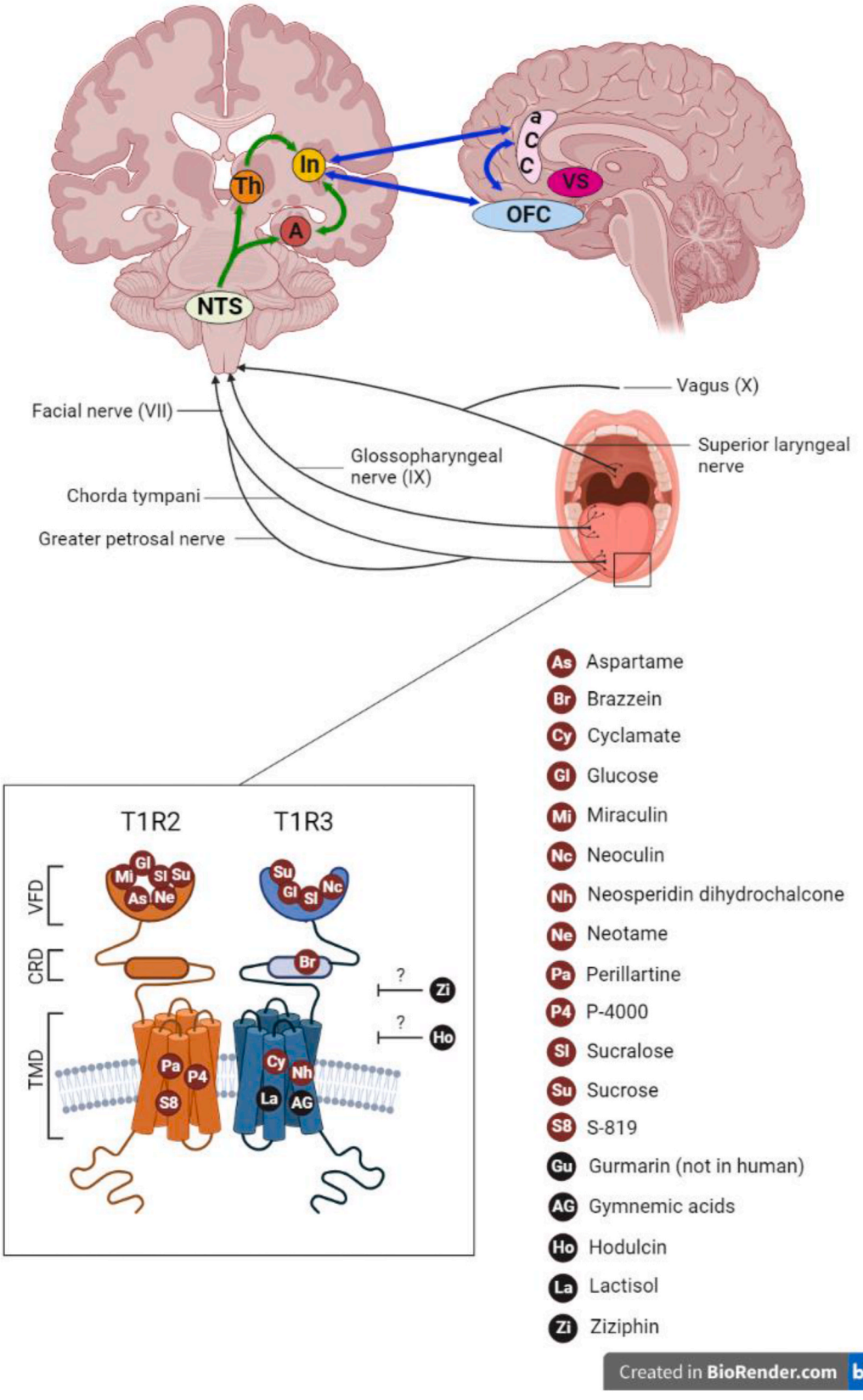

(caption on next page)

Fig. 1. Structure of the sweet taste receptor and depiction of representative ligands, including sweeteners (red circles) and sweet-taste inhibitors (black circles) [13–18]. The sweet receptor is composed of two different subunits, T1R2 and T1R3, which contain three distinct domains: the Venus Flytrap Domain (VFD), the cysteine-rich domain (CRD) and the 7-transmembrane domain (TMD). These ligands interact in these different domains, although the specific binding site of many of them is still unclear. When the T1R2/T1R3 receptors are activated, the signal travels along the primary sensory axons of the facial (VII), glossopharyngeal (IX) and vagal (X) cranial nerves to the central nervous system, specifically to the nucleus of the solitary tract (NTS). Then, the information is transmitted to the thalamus (Th) and the insula (In). The insula is also connected to limbic structures that process affective and reward value such as the amygdala (A), the orbitofrontal cortex (OFC), the anterior cingulate cortex (ACC) and the ventral striatum (VS). Sweet taste receptor inhibitors reduce the transmission of taste information to the central nervous system. The brain regions that process sensory and affective/reward dimensions of sweet taste are connected by green and blue arrows, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

systems: a canonical, T1R-dependant pathway, and an alternative metabolic pathway, a T1R-independent pathway [4,5]. The T1R-indepentent pathway is more specific for glucose and monosaccharides and is mediated by glucose transporters, ATP-gated K^+ (K_{ATP}) and sodium glucose cotransporters [6]. By contrast, the T1R-dependent pathway is activated by most sweet compounds through a heterodimeric G-protein-coupled receptor composed of the subunits Taste type 1 Receptor 2 (T1R2) and Taste type 1 Receptor 3 (T1R3) in oral bud cells and parts of the peripheral gastrointestinal tract [7]. Not only natural sugars activate this sweet taste receptor but also ligands with very different chemical structures including amino acids, proteins and non-caloric sweeteners may bind to T1R2/T1R3 (see Fig. 1). After binding to the receptor, the G-protein subunit α-gustducin leads to the activation of the gustatory nerve

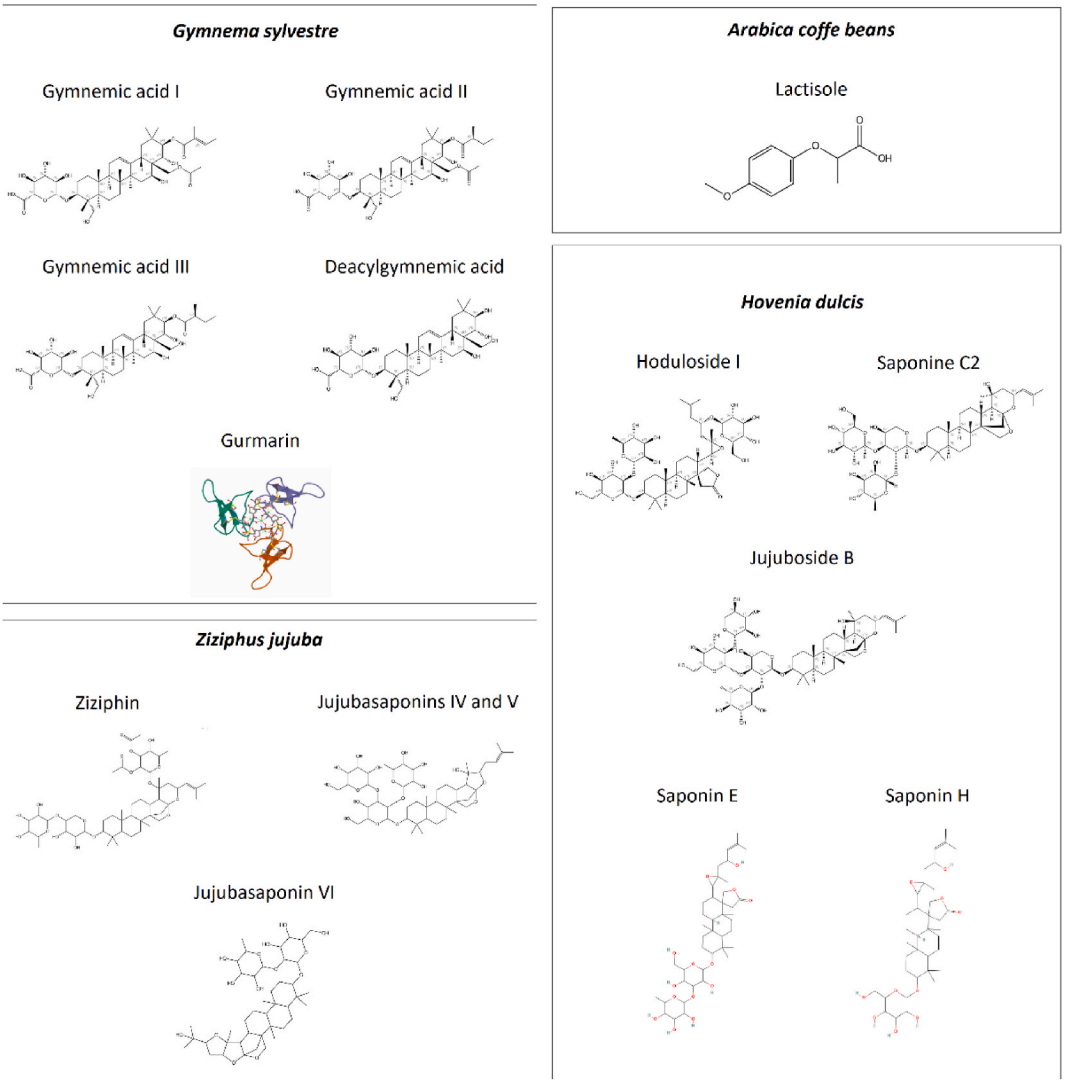

Fig. 2. Principal sweetness inhibitor chemical structures and their origin plants. Images taken from CAS SciFindern (https://scifinder-n.cas.org/), PubChem (https://pubchem.ncbi.nlm.nih.gov/) and Protein Data Bank (https://www.rcsb.org/).

fibres through signal transduction, transmitting sensory and affective information to the primary and secondary gustatory cortex of the central nervous system [8]. Thus, the sweet taste is fundamental to the genesis of the hedonic (i.e., pleasant) attribute as well as the desire to eat (i.e., appetite) [9,10]. In particular, sweet attraction is driven by the activation of brain affective-reward pathways [11, 12]. In this way, sweetness increases the attractiveness of foods and encourages consumption.

To the extent that taste is considered a primary driver of food choice and intake, several authors have highlighted the potential of targeting taste receptors as a novel strategy to address weight- and eating-related problems [19,20]; particularly considering the limited availability of effective interventions for chronic conditions associated with sweet food intake. Such conditions encompass diet-induced obesity, bulimic-spectrum eating disorder and addictive-like eating behaviour, which are highly prevalent and characterized by an increased preference for sugar [21–23]. Unfortunately, understanding the intricate relationship between diminished sweet taste response and eating behaviour is a complex matter that continues to present conflicting evidence [24].

For instance, correlational studies and observations based on sweet taste disorders suggest that reduced sweet perception can lead to a faster feeling of fullness, resulting in decreased food intake and unwanted weight loss. These studies include normal ageing [25], idiopathic or post-tonsillectomy dysgeusia [26,27] and the syndrome of inappropriate secretion of antidiuretic hormone [28]. Moreover, experimental data involving healthy subjects with decreased perception of sweetness via *Gymnema sylvestre* extracts have shown that they consumed fewer total and sweet calories compared to individuals with normal perception [29]. In contrast, other experimental studies conducted with *Gymnema sylvestre* extracts in healthy subjects and clinical research point out that a blunted sweet taste sensation may also be linked to an increased appetite and body weight gain [24,30,31]. In this case, a reduced taste perception might initially cause less satisfaction after a meal, triggering compensatory responses that drive some individuals to increase food intake to satisfy these desires. Observations of taste alterations in diabetic patients [32], as well as in overweight and obese individuals [33], also support the association between taste changes and weight gain, although whether these gustatory changes are a cause or a consequence of obesity remains uncertain [33].

To reconcile these conflicting results, insights from studies on chemosensory disorders can shed light. For instance, Schechter [26] reported that when patients initially experienced taste loss, they commonly ate many different foods in an effort to find a food that would produce any pleasurable taste sensation. Thus, some of them gained body weight during the initial stages of this illness due to what they described as compulsive overeating. However, once they realized that most foods and drinks were devoid of taste, they limited their intake and subsequent weight loss was a common outcome. Similarly, Merkonidis et al. [34] indicated that more than half of the patients with chemosensory conditions changed their eating behaviour following onset of the disorders. Interestingly, a higher proportion of patients reported eating less (18.6%) rather than eating more (7.3%). In particular, gradual onset and hypogeusia favoured weight gain, whereas weight loss was more common in those with sudden onset of symptoms and ageusia. In this sense, we posit the existence of a threshold for sweet taste suppression above which a decrease in food intake is anticipated, while the opposite effect is presumed to take place below such threshold.

To test this hypothesis, we conducted a systematic review examining the relationship between various degrees of experimentally decreased sweet taste perception and changes in eating behaviour. To do so, we first examined the primary effects of sweet-inhibiting compounds on sweet taste perception and on eating behaviour separately, using mouth rinses containing plant-derived bioactive compounds known for their ability to temporarily suppress oral sweet sensations (see Fig. 2) [35–37] in healthy subjects. Finally, we analysed studies that included the effects of both factors. Use of this methodology should be capable of minimizing confounding factors related to patient issues and provide more robust explanations about the relationship among sweet taste perception inhibition, eating behaviour and body weight under highly controlled conditions [30,38].

2. Materials and methods

2.1. Protocol and registration

This systematic review was performed following the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) [39]. It was registered in the *International Prospective Register of Systematic Reviews* (PROSPERO, CRD42021248971, 15.05.2021).

2.2. Inclusion and exclusion criteria

The inclusion criteria to select the articles were: 1) publications on compounds with anti-sweet taste capacity; 2) human studies; 3) oral application; 4) the effects in behavioural, neural and/or metabolic terms; 5) original research articles, including controlled trials, cohort study, case-control study, cross-sectional study, crossover study, case report, and case series reports; and 6) publications in English. All published papers were searched regardless of the date of publication.

Studies were excluded if they were: 1) not based on original quantitative data such as reviews, commentaries, meta-analyses, book chapters, opinion reports, guidelines or editorial articles; 2) pharmaceutical medications; 3) substances with a synthetic origin; 4) focused only on the purification, structures, cellular activity, molecular biology or food development of substances with anti-sweetness activity; 5) based only on other-than-sweet-taste suppressions (such as bitter-taste inhibition); 6) forms without available full-texts; and 7) duplicate papers.

2.3. Search and selection of studies

Searches were conducted in six electronic bibliographic databases: Web of Science, PubMed, Scopus, Food Science Source (FSS),

and Food Science and technology abstracts (FSTA), which includes EMBASE, Medline and other open access sources; from May 2021 to January 2022. First of all, two preliminary searches were performed in the Web of Science and Scopus databases. In both databases, the detailed search strategy with all used terms is outlined in Tables S1 and S2 (see Supplementary Materials). The following search terms were used: "bioactive", "plant", "herbal", "sugar", sweet*, inhibit*, suppress*, block* and "taste". All selected words and index terms were applied in all databases in order to conduct the formal screening of search results against eligibility criteria; and Boolean operators "AND" and "OR" were employed.

In order to identify bioactive sweetness inhibitors derived from plants, we considered the term *bioactive compound* as a broader array of non-nutritive substances that have demonstrated activity in biological systems, usually animals and/or humans, and refers to plant- or animal-derived components [40].

After running the systematic search, duplicate citations were removed. Then, two reviewers independently performed the screening of the title and abstract, and the inclusion and exclusion criteria were applied in order to exclude irrelevant citations. The process was facilitated using the Rayyan Platform (https://rayyan.qcri.org; [41]), allowing for independent and anonymous review and analysis of searched literature. Following this, two reviewers obtained full-text papers, conducted the screening and assessed their eligibility. Any discrepancies underwent further review until a consensus was reached. Finally, a citation analysis on the process of the retrieved articles was carried out to find additional relevant studies from other authors, which were noted as "identified from other sources". Those articles meeting the criteria were used for data extraction and analysis.

2.4. Data extraction

For each eligible study, a data list was extracted into a Microsoft Excel (2016) worksheet using a coding template that included the following items: characteristics of the subjects (age, gender), characteristics of the bioactive compounds (studied plant, plant of origin, commercial product name, preparation, administration route, concentration and time of administration), outcomes of interest, and standard information about the study (participant, study type, measure, control stimuli, evidence level or days of treatment).

2.5. Evidence and quality assessment

An evaluation of quality of the study was conducted in order to minimize the potential for bias and ensure the accuracy of the overall conclusion. It is worth noting that low quality studies may produce deceptive outcomes, underscoring the importance of conducting such an assessment in a review. The hierarchy of research designs and levels of scientific evidence were based on the evidence assessment classification proposed by Forrest and Miller [42]. Thus, a seven-level classification was applied to assess the level of evidence strength of articles included (Table S3 in Supplementary Materials). Moreover, the algorithm for classifying study design for questions of effectiveness (https://www.sign.ac.uk/assets/study_design.pdf) and the checklist of the Scottish Intercollegiate Guidelines Network (SIGN) for randomised controlled trials were used to review quality of the articles. It should be noted that Criterion 1.10 ("Where the study is carried out at more than one site, results are comparable for all sites") was not applicable to any and, therefore, not considered for the final rating. Items checked were appropriate and clearly focused on the question addressed, randomized assignment of subjects to treatment groups, adequate concealment method, blinding, similarity between control and treatment groups, measure of the outcomes in a reliable way, dropout percentage and intention to treat analysis. Those items were qualified as "well covered", "adequately addressed", "poorly addressed", "not addressed", "not reported" or "not applicable". Qualifications "well covered" and "adequately addressed" were considered as positive, while "poorly addressed" was considered as neutral and the rest of the qualifications were considered as negative. If the majority of criteria were qualified as positive, the article was given a high rating (high quality, ++). If almost half of the criteria were qualified as positive, acceptable quality (+) was provided. Otherwise, the study was rated low quality (0) or unacceptable (−). No articles were rejected due to their quality. These criteria were applied on a study-by-study basis.

2.6. Outcomes

The primary outcome of this study was to investigate the relationship between the level of sweetness inhibition and eating behaviour. To do so, we first examined the individual effects of sweet-inhibiting compounds on sweet taste perception and eating behaviour as secondary outcomes. The parametric changes in sweet taste perception during oral stimulation with suppressors were assessed via behavioural and neural techniques, which included evaluating intensity, hedonic and temporal characteristics of sweetness. Eating behaviour was assessed following oral stimulation with suppressors, specifically examining appetite, desire to eat, motivation to eat, and actual intake or consumption.

2.7. Statistics

Data were synthesized qualitatively. Then, descriptive analyses were utilised to present the results, and the most important findings were summarized in tables. In the manuscript, the study results were presented with "0" if the study failed to show a statistically significant difference ($p > .05$) and "+" if the bioactive compound tested achieved a significant difference ($p \leq .05$) compared with control conditions, when possible, in at least one outcome.

3. Results

3.1. Study selection

The systematic literature search produced 899 eligible studies. After manual and automatic deduplication, 344 studies were excluded. Then, through screening for title and abstract, 527 studies were eliminated. The full text of the remaining 28 publications was reviewed following inclusion and exclusion criteria and quality assessment. Thereafter, full text of 2 articles was not found, so they were also rejected. Lastly, 26 papers were included. After screening full-text manuscripts, a total of 16 papers were eligible. 17 additional articles were retrieved through reference screening of selected papers, making a total of 33 articles. A detailed systematic flowchart is shown in Fig. 3.

3.2. General description of data

Regarding the study overview, all relevant characteristics of the participants, bioactive compounds and procedure are summarized in Table 1. The most common plant and bioactive compounds found were active principles derived from *Gymnema sylvestre* (Asclepiadaceae): gymnemic acids were used in 7 papers and potassium gymnemate in 1 study. *Gymnema sylvestre* is mentioned without further specification in 8 papers. Other phytochemicals were extracted from *Ziziphus jujuba*, *Hovenia dulcis* (3 studies), *Stephanotis luchuensis* var. *japonica* (3 studies), *Gymnema alternifolium* (2 studies) and *Styrax japonica* (1 study). Finally, synthetic lactisol identical to the natural analog of coffee beans was also used in one study.

3.3. Study outcomes

A total of 29 studies (87.9%) reported the individual effects of sweet-inhibiting compounds on sweet taste perception or eating behaviour (2 of them about eating behaviour and the rest about taste perception). The remaining papers reported both of the outcomes (see Table 2).

3.4. Changes in taste perception after anti-sweet treatment

3.4.1. Behavioural studies

A wide variety of psychophysical and sensory tests were used with absence of a single standardized measure: taste recognition

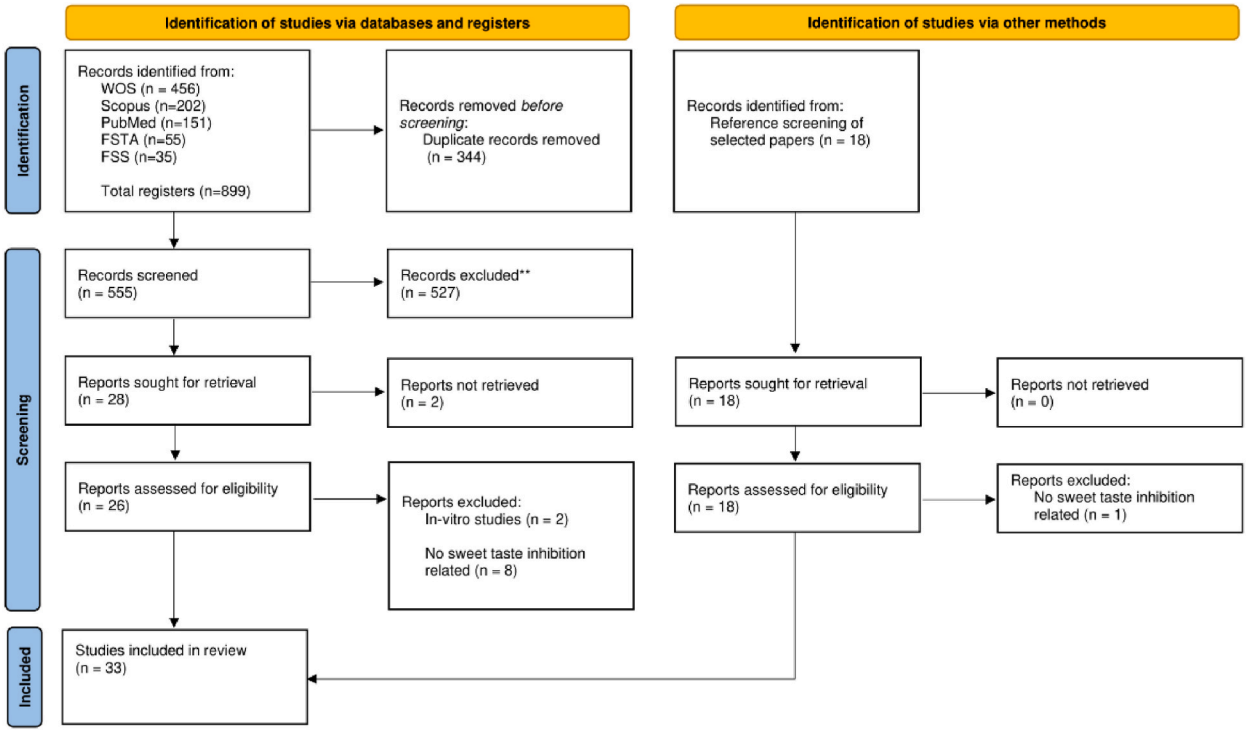

Fig. 3. PRISMA 2021 flow diagram and selection of original articles. Source: Page et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. International Journal of Surgery, 88, 105906.

Table 1
Summary of participants' characteristics, compound and procedure employed. Note: n.a.: not applicable; n.r.: not reported. w/v: weight/volume.

Biocompound/plant	Sample size	Female percentage (%)	Age (years)	Concentration	Oral administration (form)	Time administration	Days of treatment	Author (year)
Alternosides I - X/ Gymnema alternifolium	3	n.r	n.r	1 mmol	Buccal (solution)	3 min	1	Yoshikawa et al. (1998)
Alternosides XI - XIX/ Gymnema alternifolium	3	n.r	n.r	1 mmol	Buccal (solution)	3 min	1	Yoshikawa et al. (1999)
Gymnema sylvestre	118	55.9	n.r	2% solution	Buccal (solution)	90sec +60sec	1	Brala & Hagen (1983)
Gymnema sylvestre	6	66.6	26–54	0.2 g/ml and 0.4 g/ml	Lingual (solution)	2 min	1	Diamant et al. (1964)
Gymnema sylvestre	18	35.7	n.r.	0.5 g/ml	Buccal (solution)	60 s	6	Frank et al. (1992)
Gymnema sylvestre	8	40	21 ± 3	2.5% solution	Buccal (solution)	30 s	2	Kashima et al. (2017)
Gymnema sylvestre	9	77	22 ± 3	2.5% solution	Buccal (solution)	30 s	4	Kashima et al. (2019)
Gymnema sylvestre	15	60	22 ± 3	2.5% solution	Buccal (solution)	30 s	2	Kashima et al. (2020)
Gymnema sylvestre	11	0	n.r.	0.05%	Buccal (solution)	3 s	n.a	Meiselman & Halpern (1970)
Gymnema sylvestre	6	n.r.	26–54	0.2 g/ml and 0.4 g/ml	Lingual (solution)	2min	1	Oakley (1985)
Gymnema sylvestre	6	n.r.	n.r.	GS extract	Buccal (solution)	10 s	3	Warren et al. (1969)
Gymnemic acids	20	50	20–55	0.5%	Buccal (solution)	2 min	1 and 2	Gent et al. (1999)
Gymnemic acid A1, A2, A3	4	n.r.	n.r.	n.r (5 ml)	Buccal (solution)	2 min	1	Kurihara (1969)
Gymnemic acids	44	50	18–65	n.r	Buccal (lozenge)	Unlimited	2	Nobel et al. (2017)
Gymnemic acids	10	n.r.	n.r.	0.03, 0.06, 0.12, 0.25 and 0.5 g/l	Buccal (solution)	60s	6	Riskey et al. (1982)
Gymnemic acids	40	72.5	21.6 ± 4	3.5 mg of gymnemic acids	Buccal (solid food)	Unlimited	2	Stice & Yokum (2018)
Gymnemic acids	67	62	21.6 ± 3.5	3.5 mg of gymnemic acids	Buccal (solid food)	Unlimited	1	Stice et al. (2017)
Gymnemic acids	56	64.3	23.2 ± 5.7	4 mg of gymnemic acids	Buccal (solid food)	Unlimited	2	Turner et al. (2020)
Hodulcin/Hovenia dulcis	6	33.3	n.r	1% w/v	Buccal (solution)	n.r	9	Kennedy et al. (1988)
Hodulosides I–V, saponine C2, saponine E, saponine H and jujuboside B/ Hovenia dulcis	3	n.r	n.r	1 mmol	Buccal (solution)	3 min	1	Yoshikawa et al. (1992a)
Hoduloside VI - X/ Hovenia dulcis	3	n.r	n.r	1 mM	Buccal (solution)	3 min	1	Yoshikawa et al. (1993)
Jegosaponins A - D/ Styrax japonica	3	n.r	n.r	1 mM	Buccal (solution)	3 min	1	Yoshikawa et al. (2000)
Jujubasaponins IV, V and VI/Zizyphus jujuba	3	n.r	n.r	1 mM	Buccal (solution)	3 min	1	Yoshikawa et al. (1992b)
Lactisol	29	0	28 ± 5	60 ppm	Buccal (solution)	directly swallowed	4	Schweiger et al. (2020)
Potassium gymnemate	5	60	n.r.	5% KG	Buccal (solution)	1 min	2	Warren & Pfaffmann (1959)
Sitakisoside I–V/ Stephanotis lutchuensis	3	n.r	n.r	1 mM	Buccal (solution)	3 min	1	Yoshikawa et al. (1994a)
Sitakisoside VI - X/ Stephanotis lutchuensis	3	n.r	n.r	1 mM	Buccal (solution)	3 min	1	Yoshikawa et al. (1994b)

(*continued on next page*)

Table 1 (*continued*)

Biocompound/plant	Sample size	Female percentage (%)	Age (years)	Concentration	Oral administration (form)	Time administration	Days of treatment	Author (year)
Sitakisoside XI - XX/ Stephanotis lutchuensis	3	n.r	n.r	1 mM	Buccal (solution)	3 min	1	Yoshikawa et al. (1997)
Ziziphus jujuba	5	60	23–36	3.5% w/v	Lingual (solution)	3 min	5	Kennedy & Halper (1980a)
Ziziphus jujuba	5	60	n.r	1 mM	Buccal (solution)	3 min	n.r	Kurihara et al. (1988)
Ziziphus jujuba	10	20	21–26	–	Buccal (solution)	3 min	6	Meiselman et al. (1976)
Ziziphus jujuba	14	50	19–26	3.5% w/v	Buccal (solution)	10 s	4	Smith & Halpern (1983)
Ziziphus jujuba	n.r	0	n.r.	n.r/0.2%	Lingual (solution)	n.r/3min	n.a	Yamada & Imoto (1987)

[43–49], taste detection threshold [50–52] or subjective taste intensity [29,43–45,53–55]. Moreover, the specific method employed to assess sweetness suppression was not reported in 10 studies [6,56–64]. This information is shown in more detail in Table 2. We found 7 studies concerning affective experiences related to hedonics, pleasantness or liking. Specifically, labelled hedonic magnitude scales were applied in 4 studies [55,65–67], a hedonic category in 1 study [29], and hedonic visual analogue scales in 2 studies [68,69].

Sweet stimuli. Gymnema sylvestre had a general and similar effect on most sweet stimuli irrespective of chemical structure. It suppressed single primary sweet stimuli other than sugars, such as cyclamate, D-tryptophan, D-leucine, beryllium chloride, lead acetate, acesulfame K, aspartame, sodium cyclamate, fructose, glucose, stevioside and xylitol [43,56]. This also included complex taste stimuli in mixtures with sucrose as well as complex real flavours [29,43,46,55,65,70]. In the case of *Ziziphus jujuba*, the sweet stimuli evaluated were sucrose solutions [44,53,56,61], fructose, glucose, glycine, L-alanine, saccharin [50] and complex flavours such as American apple cider and apple juice [49]. In the studies with *Hovenia dulcis*, the sweetener assessed was sucrose [45,59,63]. Nevertheless, some compounds appeared to be insensitive to sweet-tasting suppressors: chloroform in the case of gymnemic acids [71] and sweet amino acids for *Ziziphus jujuba* [50].

Effectiveness in sweetness sensation. Acute suppression of sweetness with oral administration of inhibitors during a tasting or prandial phases (i.e., related to meals) was reported in every case. This result was robust and consistent across concentrations and methods (see Table 1). Findings from psychophysical investigations of *Gymnema sylvestre* have also shown selective suppression of sweet intensity with little or no reductions of other basic taste qualities (sourness, bitterness or saltiness) [46,47,55,71]. In terms of the concentration-sensory response relationship, researchers found that *Gymnema sylvestre* reduced the sweetness judgements by an average of 77%, with no evidence for a differential effect across sweeteners [48,54]. Moreover, *Gymnema sylvestre* decreased sweetness by a constant percentage independent of the concentration of the sucrose concentration tasted [48,72] and also developed in the presence of a sweetener [46,52].

Regarding gymnemic acids, although the suppression of sweetness rose with increasing acid concentration [48], the inhibitory effect was not proportional to the concentration, showing a levelling off at the higher concentrations [51]. The only study assessing the identification of sweet-tasting stimuli reported a decreased accuracy in identifying sweet items immediately following the application of gymnemic acids. Specifically, correct identification of the sweet mixtures was reduced by 23% and most misidentifications involved sucrose alone or in mixtures. Notwithstanding, gymnemic acids had no effect on the discriminability of non-sweet stimulus pairs [43]. Finally, only one study compared different gymnemic acids, which highlighted that the anti-sweet activity decreased greatly from gymnemic acid Al to A2 (the activity of A2 was less than 1/5 of the activity of an equal concentration of Al) and disappeared in A3.

Ziziphus jujuba was also able to reversibly depress the judged sweetness [44,49,50,53,63]. Studies found that 0.2% solution of the *Ziziphus jujuba* extract in the mouth for 3 min gave rise to the threshold elevation for basic sweet taste stimuli (sucrose and saccharin) [50]. With purified active components of *Ziziphus jujuba*, researchers demonstrated anti-sweet activity in 4 studies [44,53,56,63]. Kennedy and Halper [44] reported that a 3-min treatment with a 0.05% solution of ziziphin produced an initial reduction in participants' magnitude estimates of sweetness that was at least as great as the reduction produced by a 3.5% solution of crude aqueous extract of *Ziziphus jujuba* leaves. Regarding selectivity, researchers found that ziziphin depressed the sweetness perception of sugars and artificial sweeteners, but not of some sweet amino acids and other basic tastes such as the saltiness of sodium chloride (NaCl) or the bitterness of a quinine hydrochloride solution [49,50,53]. Finally, Yoshikawa, Shimono et al. [61] found suppression of sweet sensation by jujuba saponins IV-VI.

In the case of *Hovenia dulcis*, 3 studies tested the selective sweetness-reducing principle [45,59,63]. Researchers found that a 1% aqueous extract of *Hovenia dulcis* affected the perceived sweetness of sucrose, while estimates for NaCl, the sourness of citric acid or quinine were not reduced [45]. In terms of active principles, Yoshikawa et al. [59,63] preliminary showed anti-sweet activity for hodulosides I-X. Finally, using 1 mM of the compound under consideration, Yoshikawa et al. identified sweet taste suppression in sitakisosides I–V, VI-IX, XI-XIII, XVI and XVIII from *Stephanotis lutchuensis* [58,62,73], alternosides I-VII from *Gymnema alternifolium* [60,64], and jegosaponins I-IV from *Styrax japonica* [57].

Table 2
Summary of outcomes, measures and significant results. Note: T: taste perception. E: eating behaviour. "0" if the study failed to show a statistically significant difference ($p > .05$) and "+" if the biocompound tested achieved a significant difference ($p \leq .05$).

Outcome	Biocompound/plant	Measure (unit)	Statistically significant differences	Author (year)
E	Lactisole	Hunger rating (0–10 visual analogue scale), energy intake (kcal),	+	Schweiger et al. (2020)
E	Gymnemic acids	Fook intake (number of bars, total energy [kj]) and hunger, pleasantness and desire ratings (0–100 mm visual analogue scale)	+	Turner et al. (2020)
T	Gymnema sylvestre	Electrophysiological response of chorda tympani nerve (summated response)	+	Diamant et al. (1964)
T	Gymnema sylvestre	Sweetness rating (21-point category scale)	+	Frank et al. (1992)
T	Gymnemic acids	Intensity of the stimuli (10-point category scale) and taste category labelling (10-labels assignment)	+	Gent et al. (1999)
T	Gymnema sylvestre	Sweetness rating (labelled magnitude scale) and liking rating (labelled hedonic scale) under the curve), gastric emptying (pulmonary 13CO2 excretion rate), blood glucose response (mmol/L), plasma insulin responses (μIU/mL)	+	Kashima et al. (2017)
T	Gymnema sylvestre	Sweetness rating (labelled magnitude scale) and liking rating (labelled hedonic scale)	+/+	Kashima et al. (2019)
T	Gymnema sylvestre	Sweetness rating (labelled magnitude scale), liking rating (labelled hedonic scale), hunger, fullness and prospective consumption ratings (category scale)	+	Kashima et al. (2020)
T	Ziziphus jujuba	Taste category labelling (6-labels assignment) and sweetness intensity (magnitude estimation)	+	Kennedy & Halpern (1980a)
T	Hodulcin/Hovenia dulcis	Taste category labelling (6-labels assignment) and intensity of the stimuli (estimated intensity relative to the intensity of and standard solution)	+	Kennedy et al. (1988)
T	Gymnemic acids A1, A2, A3	Anti-sweet relative activity (maximum concentration of sucrose solution whose sweetness is depressed completely)	+	Kurihara (1969)
T	Ziziphus jujuba	Sweetness perception (n.r)	+	Kurihara et al. (1988)
T	Gymnema sylvestre	Sourness, saltiness, bitterness and sweetness ratings (0–10 scale)	+	Meiselman & Halpern (1970)
T	Ziziphus jujuba	Taste category labelling (salty, sour, sweet or bitter) and intensity of the stimuli (estimated intensity relative to the intensity of a standard solution)	+	Meiselman et al. (1976)
T	Gymnema sylvestre	Sourness and sweetness ratings (0–100 scale)/ electrophysiological response of chorda tympani nerve (impulses/sec, summated response)	+/+	Oakley (1985)
T	Gymnemic acids	Sourness, saltiness, and bitterness and sweetness ratings (n.r.)	+	Riskey et al. (1982)
T	Ziziphus jujuba	Sourness, saltiness, and bitterness and sweetness ratings (1–10 category scale)	+	Smith & Halpern (1983)
T	Potassium gymnemate	Threshold estimate (units of threshold change)	+	Warren & Pfaffmann (1959)
T	Gymnema sylvestre	Threshold estimate (units of threshold change)	+	Warren et al. (1969)
T	Ziziphus jujuba	Recognition threshold estimate (units of threshold change)/ electrophysiological response of chorda tympani nerve (integrated response [impulses/sec], relative response)	+/+	Yamada & Imoto (1987)
T	Hoduloside VI - X/Hovenia dulcis	Sweetness perception (n.r)	+	Yoshikawa et al. (1993)
T	Sitakisoside I–V/Stephanotis lutchuensis	Sweetness perception (n.r)	+	Yoshikawa et al. (1994a)
T	Sitakisoside VI - X/Stephanotis lutchuensis	Sweetness perception (n.r)	+/-	Yoshikawa et al. (1994b)
T	Sitakisoside XI - XX/Stephanotis lutchuensis	Sweetness perception (n.r)	+/-	Yoshikawa et al. (1997)
T	Alternosides I - X/Gymnema alternifolium (n.r)	Sweetness perception (n.r)	+/-	Yoshikawa et al. (1998)
T	Alternosides XI - XIX/Gymnema alternifolium (n.r)	Sweetness perception (n.r)	+/-	Yoshikawa et al. (1999)
T	Jegosaponins A - D/Styrax japonica	Sweetness perception (n.r)	+/-	Yoshikawa et al. (2000)
T	Jujubasaponins IV, V and VI/ Ziziphus jujuba	Sweetness perception (n.r)	+	Yoshikawa, Shimono et al. (1992)

(*continued on next page*)

Table 2 (*continued*)

Outcome	Biocompound/plant	Measure (unit)	Statistically significant differences	Author (year)
T	Hodulosides I–V, saponine C2, saponine E, saponine H and jujuboside B/Hovenia dulcis	Sweetness sensation (n.r)	+	Yoshikawa, Tumura et al. (1992)
T/E	Gymnema sylvestre	Pleasantness rating (15-point scale), sweetness rating (25-point scale), hunger rating (11-point scale) and milkshake intake estimates (number of 280 ml cups)	+ and 0	Brala & Hagen (1983)
T/E	Gymnemic acids	Hunger rating (100-point visual analogue scale), percent of subjects who choose to eat the first candy offering (%), total candy intake, desire rating (100-point visual analogue scale) and pleasantness rating (100-point visual analogue scale)	+	Nobel et al. (2017)
T/E	Gymnemic acids	Intake (g)/neural response to anticipated high-sugar food taste and to high-sugar food taste (functional magnetic resonance imaging [blood oxygen level dependent signal])	+/+	Stice & Yokum (2018)
T/E	Gymnemic acids	Candy intake, hunger, desire and pleasantness rating (labelled magnitude scales)	+ and 0	Stice et al. (2017)

Effectiveness in hedonic attributes. Studies agree that *Gymnema sylvestre* reduced the subject's perceived taste liking of sweet stimuli [29,66,67]. Taking into account placebo-controlled single-/double-blind crossover studies, Turner et al. [69] found that participants reduced the pleasantness of eating chocolate (31.0%) while eating the first piece of chocolate following the gymnema treatment (Sweetkick) compared to the same isocaloric ingredients but without gymnemic acids. Consistently with this, Nobel et al. [68] observed that gymnema-containing lozenges reduced the pleasantness rating among subjects who ate a second candy in comparison to a placebo.

Temporal parameters. Looking at the initial post-treatment reduction of sweetness perception, at least 30 s were required for production of the full effect of gymnemic acids when held in the mouth in the administration solution [53,71], while 15 s were needed for hodulcine [45]. The degree and duration of suppressions of sweet taste intensity were differentially determined by the dose and length of exposure of the taste buds to anti-sweet blockers. Smith and Halpern [49] demonstrated that the effectiveness of ziziphins is more dependent on the time of exposure than on the dose. Indeed, brief applications of higher concentrations (in particular, 10 sec 3.5% weight/volume [w/v]) were less effective than large treatments with reduced doses (90 sec 0.88% w/v). Finally, in a series of preliminary bioassays, holding compounds in the mouth for 3 min was enough to reveal anti-sweetness properties for ziziphin [56], hodulosides, saponins, jujubosides [60,63], jujuba saponins [61], sitakisosides [60,62,73], alternosides [60,64] and jegosaponins [57].

Findings from the recovery of judged sweetness (that is, the magnitude at which response reaches the level that is not significantly different from the control) suggested that treatment with ziziphin or hodulcin was more rapid than with gymnemic acids. In particular, the time course of recovery from gymnemic acids developed within a range of 20 min to hours [46]. Studies have reported that more than 50 min were required for complete recovery from the effects of gymnemic acids, with a ~60% of the pre-gymnemic acid value at 40 min [43,46]. Riskey et al. [48] found that recovery from gymnemic acids was roughly a constant percentage of the maximum suppression, independent of both their concentration and the concentration of sucrose tasted. By contrast, after initial full depression, there is a gradual recovery over a 5-to-10-min testing period in studies with ziziphin [44,49], while this period is 1–4 min with hodulcine [45].

Undesirable effects. A within-session rebound-like effect of gymnemic acids was found by Stice et al. [65]: higher perception of sweetness and higher pleasurable sensations compared to baseline were detected when sweetness inhibition eventually disappeared during the post-tasting phase. As a result, higher pleasantness ratings of the 4th and 5th piece compared to the baseline were found.

3.4.2. Neural studies

Out of the 3 studies, we identified 2 electrophysiological studies of human gustatory response with patients undergoing otologic operations. In such studies, records of taste activity were obtained from the chorda tympani nerve discharges [47,74]. The third study was carried out with healthy subjects using neuroimaging technique in which the blood-oxygenation-level-dependent (BOLD) functional magnetic resonance imaging (fMRI) signal was assessed [70].

Effectiveness. Considering these electrophysiological studies, both consistently reported the almost complete block of responsiveness of the human chorda tympani nerve to sweeteners, but not to other non-sweet chemicals (NaCl or quinine) after a 1-to-2-minute application of 1–2% extract of *Gymnema sylvestre* to the tongue [47,74]. In the case of the fMRI, researchers found that blocking sweet taste receptors with oral administration of a lozenge containing 3.5 mg of gymnemic acids not only reduced the response of reward regions to the intake of the high-sugar foods but also reduced anticipated reward from these foods. In particular, a diminished BOLD signal to chocolate milkshake taste was observed in the left dorsolateral prefrontal cortex, as well as less recruitment of the nucleus accumbens, precuneus, orbitofrontal cortex, insula, and caudate in response to the anticipated intake of the high-sugar milkshake relative to the placebo. These effects were not moderated by participant's body mass index (BMI) [70]. Key strengths of Stice and Yokum's study were its placebo-controlled design and its sample size (n = 40) [70].

3.5. Changes in eating behaviour after anti-sweet treatment: appetite and consumption

3.5.1. Methods

Motivational dimension related to appetite, desire to eat more or prospective food consumption was measured via visual analogue scales [68,69], category scales [55] and percentage of subjects who chose to eat the first candy offering [68]. Besides self-reported measures, 6 papers included total intake or intake estimate data [29,65,68–70,75].

3.5.2. Effectiveness in motivational attributes

Findings are inconsistent on the desire to eat. While Turner et al. [69] and Nobel et al. [68] found that participants reduced their desire to eat sweet items, Stice et al. [65] did not replicate the motivational effect for high-sugar foods despite observing reduced pleasantness rating (see also [70]). Regarding prospective consumption during early post-prandial periods (defined as the period

Table 3
Methodological assessment of studies based on the Scottish Intercollegiate Guidelines Network checklist. Note: 1.1. Appropriate and clearly focused question. 1.2. Assignment is randomized. 1.3. Adequate concealment method. 1.4. Blinding. 1.5. Groups are similar at baseline. 1.6. Treatment under investigation is the only difference; 1.7. All relevant outcomes are measured in a standard, valid and reliable way. 1.8. Percentage of drop-outs in each treatment (control/experimental). 1.9. Intention to treat analysis. 1.10. Various sites are comparable. 2.1. Risk of bias: high quality (++), acceptable quality (+), low quality (0), unacceptable (−). AA: adequately addressed. co-RCT: crossover randomized controlled trial. NAD: not addressed. NAP: not applicable. NR: not reported. PA: poorly addressed. WR: well recovered.

Type of study	Evidence level	1.1	1.2	1.3	1.4	1.5	1.6	1.7	1.8	1.9	1.10	2.1	Author (year)
Co-RCT	2	WR	WR	NR	NR	WR	NAP	WR	17/118	WR	NAP	0	Brala & Hagen (1983)
Co-RCT	2	WR	WR	NR	WR	WR	NAP	WR	0	WR	NAP	+	Frank et al. (1992)
Co-RCT	2	WR	WR	NR	NR	WR	NAP	WR	0/0	WR	NAP	0	Gent et al. (1999)
Co-RCT	2	WR	WR	NR	NR	WR	NAP	WR	0	WR	NAP	+	Kashima et al. (2017)
Co-RCT	2	WR	WR	NR	NR	WR	NAP	WR	0	WR	NAP	+	Kashima et al. (2019)
Co-RCT	2	WR	WR	NR	NR	WR	NAP	WR	0	WR	NAP	+	Kashima et al. (2020)
Co-RCT	2	WR	WR	NR	WR	WR	NAP	WR	1/5	WR	NAP	+	Kennedy & Halpern (1980)
Co-RCT	2	WR	WR	NR	NR	NAP	NAP	WR	0/0	WR	NAP	0	Kennedy et al. (1988)
Co-RCT	2	WR	PA	NR	NR	PA	NAP	WR	0	WR	NAP	+	Meiselman & Halpern (1970)
Co-RCT	2	WR	NAP	NR	NR	NR	NAP	WR	0/0	WR	NAP	0	Meiselman et al. (1976)
Co-RCT	2	WR	WR	NR	NR	WR	NAP	WR	0/0	WR	NAP	+	Nobel et al. (2017)
Co-RCT	2	WR	WR	WR	WR	NAP	NAP	WR	0	WR	NAP	++	Riskey et al. (1982)
Co-RCT	6	WR	WR	NR	WR	NAP	NAP	WR	2/29	WR	NAP	+	Schweiger et al. (2020)
Co-RCT	2	WR	WR	WR	WR	WR	NAP	WR	0/0	WR	NAP	++	Stice et al. (2017)
Crossover	3	WR	NAP	NR	NR	NAP	NAP	WR	4/6	WR	NAP	0	Diamant et al. (1964)
Crossover	4	WR	NAP	NR	NR	NAP	NAP	WR	0	WR	NAP	–	Kurihara et al. (1988)
Crossover	3	WR	NAP	NR	NR	NAP	NAP	WR	4/6	WR	NAP	0	Oakley (1985)
Crossover	3	WR	NR	NR	NR	NAP	NAP	WR	0	WR	NAP	–	Smith & Halpern (1983)
Crossover	3	WR	NAP	WR	WR	WR	NAP	WR	0/0	WR	NAP	++	Stice & Yokum (2018)
Crossover	3	WR	NR	WR	WR	NAP	NAP	WR	0	WR	NAP	+	Turner et al. (2020)
Crossover	3	WR	NR	NR	NR	NAP	NAP	AA	0	PA	NAP	0	Warren et al. (1969)
Experimental design	4	WR	NR	NR	NR	NAP	NAP	PA	0	AA	NAP	–	Kurihara (1969)
Experimental design	4	WR	NAP	NR	NR	NAP	NAP	WR	1/5	WR	NAP	0	Warren & Pfaffmann (1959)
Experimental design	7	WR	NAP	NAP	NAP	NAP	NAP	WR	0	AA	NAP	0	Yamada & Imoto (1987)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1992a)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1992b)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1993)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1994a)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1994b)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1997)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1998)
Experimental design	4	WR	NR	NR	NR	NR	NR	PA	0	WR	NAP	–	Yoshikawa et al. (1999)
Experimental design	4	WR	NR	NR	NR	NAP	NAP	WR	0	WR	NAP	–	Yoshikawa et al. (2000)

following a meal when sweet substances absorption is underway), Kashima et al. [55] reported significantly higher scores of desire for sweet taste (0–20 min) and lower satisfaction (0–80 min) in the *Gymnema sylvestre* compared to the control condition during the postprandial period.

3.5.3. Effectiveness in consumption

We found 5 studies assessing the impact of administration of the sweet taste receptor inhibitors on subsequent sweet short-term (within a session) intake/consumption. Out of these, 4 studies [29,65,68,69] reported that people whose perception of sweetness had been decreased by *Gymnema sylvestre* ate less total and sweet calories than those with normal perception. In these studies, the reduction in total intake was between 5.5% and 52.0% when snack-type foods [29] or sweet candies [65,70] were used, and 23.0% less quantity of chocolate or candy eaten compared to placebo [68,69]. Nevertheless, individual differences were found in food intake. That is, Turner et al. [69] reported that several participants did not follow the expected trend of reduced consumption of high-sugar sweet items but they ate more after consumption of the gymnemic acids. Although the exact mechanisms behind these post-treatment effects remain unclear, two hypotheses have been put forward. One was the "curiosity factor" as participants were unfamiliar with the sugar suppression effect and wanted to re-experience the anti-sweet effect [69]. The other was that the receptor might rebound into the active state resulting in a higher perception of sweetness and, in turn, higher pleasurable sensations. Finally, in the sole study using lactisole, Schweiger et al. [76] showed that a concentration of 60 ppm lactisole in combination with 10% sucrose led to a 13% increase in short-term energy intake in healthy subjects.

3.6. Relationship between sweetness inhibition and intake

Out of the 33 papers reviewed, only three collected data on taste perception and eating behaviour simultaneously [29,65,68]. Brala & Hagen found that after applying gymnemic acid, participants' perception of sweetness decreased by 6 ± 1 points out of 20 in the first test. Additionally, the group that consumed gymnemic acid consumed an average of 501 ± 237 calories, whereas the placebo group (treated with tea rinse) consumed an average of 638 ± 333 calories. This reduction is equal to almost 20% [29]. Nobel et al. reported that 74% of the participants in the placebo group consumed a second candy, whereas only 51% of the group that consumed gymnemic acid lozenges ate a second candy. This represented a 23% decrease, which is the same percentage as the decrease in pleasure experienced [68]. Finally, Stice et al. found that the group that consumed gymnemic acid lozenges showed a 25% reduction in the percentage of participants who chose and ate a second piece of candy. This reduction was associated with a 20% decrease in pleasure experienced after consuming the second piece of candy in the gymnema group [65].

3.7. Evidence assessment, quality assessment and risk of bias

Evidence levels are shown in Table 3. Only 36.3% of papers reviewed had a higher level of evidence ("+" or "++"). The checklist of the Scottish Intercollegiate Guidelines Network (SIGN) for RCTs was followed for all kinds of design and several methodological weaknesses were found (see Table 3). Regarding this analysis and taking into account the low percentage of studies with high level of evidence, the risk of bias is elevated in most of them.

4. Discussion

Regarding the individual effects of sweet-inhibiting compounds on sweet taste perception or eating behaviour, we found empirical evidence of sweet taste perception modification for 7 plants (*Gymnema sylvestre, Hovenia dulcis, Ziziphus jujuba, Gymnema alternifolium, Stephanotis lutchuensis* and *Styrax japonica*) and their sweetness-inhibitory constituents. Also, anti-sweet activity was reported for the compound lactisole. Other compounds also mentioned in the literature, such as escin from Aesculus hippocastanum [77], are completely ignored so far.

In particular, we found that oral treatments with extracts of *Gymnema sylvestre* consistently depressed psychophysical and hedonic judgements, neural responses and sweet food consumption. This was irrespective of the chemical structure of the sweet stimulus, from natural/artificial to caloric/non-caloric sweeteners. In most of the studies, 2.5% of gymnema solution was sufficient to achieve an inhibition just by rinsing it in. Moreover, these results were observed across designs with little or no reduction of other basic taste qualities such as sourness, bitterness or saltiness. According to the preliminary data available so far, similar tendencies but against a smaller number of sweeteners were obtained with *Ziziphus jujuba* and *Hovenia dulcis*. However, inconclusive evidence of the impact on motivational factors (including a decrease in desire to eat) was found for these anti-sweet compounds.

The literature examining the impact of initial sweet taste loss on sweetness consumption when using temporary suppression of oral sweet sensations through plant-derived substances is scarce. Moreover, the limited data available for healthy adults were not consistent with our hypothesis that there is a specific threshold of sweet taste suppression above which a reduction in food intake occurs and below which the opposite takes place. Instead, it appears that the relationship between sweet taste suppression and food intake is not a binary response that abruptly switches on or off at a specific threshold. It is rather a continuous relationship, where the reduction in food intake is associated with the proportional degree of sweet taste suppression. This implies that, as the level of sweet taste suppression increases, the reduction in food intake also gradually increases, rather than taking place suddenly. It suggests a dose-dependent relationship, where the extent of sweet taste suppression is related to the magnitude of the acute effect on food intake.

Interestingly, various factors can also lead to temporary or permanent declines in sweet taste receptor functioning, such as genetics, nutrition (e.g., zinc deficiency), biology (e.g., elderly individuals), external factors (e.g., smoking, alcohol consumption), or viral

illnesses (like COVID-19). These conditions usually result in decreased food intake and changes in eating habits [78]. However, even in the presence of these conditions, it remains uncertain how sweet taste suppression impacts food intake and whether this response follows a binary or gradual pattern. For example, genetic variations, such as single nucleotide polymorphisms that alter the function of the T1R2-T1R3 receptor complex, have been proposed to exert a similar effect as suppressing sweet taste. This can influence ligand-receptor binding, giving rise to distinct tasting phenotypes and sugar consumption patterns among individuals. Nonetheless, ongoing studies investigating the relationship between genetic variability in the TAS1R2 subunit and the intake of sweet foods have generated conflicting reports. Some studies suggest that the link is driven by differences in oral sweet taste perception, while others propose effects in extra-oral peripheral tissues that extend beyond changes in taste perception [79]. In any case, additional research is needed to thoroughly examine the threshold hypothesis regarding the relationship between sweet taste loss and its influence on eating behaviour, taking into account larger and more diverse populations and including both typical and unusual groups such as individuals experiencing normal aging or taste disorders.

4.1. Implications for clinical practice and future research

There are several important considerations to address in order to apply sweetness inhibitors in clinical settings involving individuals with obesity or eating disorders. First, it is unclear whether the reduced consumption of sweet foods through sweetness inhibitors leads to increased intake of non-sweet (but fatty) foods, particularly in situations where both are served simultaneously [55]. Second, while these compounds have little or no effect on other basic taste qualities (such as sourness, bitterness, or saltiness), it remains to be explored whether they may modify umami perception (e.g., monosodium glutamate), which is mediated by the same subunit T1R3 of the sweet receptor [80]. Third, oral suppression of sweet sensations can be a therapeutic strategy as they curb the desire and the drive to consume sweet foods. However, previous studies suggest a rebound-like effect in which acute suppression of pleasurable sensations paradoxically leads to greater desire and intake of sweetened foods, especially when individuals are chasing a sweet sensation and failing to get it [30,55,69]. Fourthly, regarding the impact on body weight status, rinsing with sweetness inhibitors may benefit those who have difficulty restraining their sugar intake and/or regulating abnormal attraction and craving for sweetness, irrespective of their specific BMI. For instance, Turner et al. [69] found no relationship between the consumption of *Gymnema sylvestre* and BMI groups, with no differences in sweet food consumption, desire or pleasantness between overweight/obese participants and normal-weight participants. It is likely that different overweight/obese phenotypes (for instance, high-sugar diet-induced obesity versus genetic obesity) exhibit different sweetness inhibition profiles. Finally, it is crucial to thoroughly evaluate the safety of these bioactive compounds, taking into consideration potential side effects. For instance, the use of *Gymnema sylvestre* in treating diabetic patients has been associated with toxic hepatitis or drug-induced liver injury, underscoring the need for rigorous safety assessments [81].

4.2. Limitations

Methodological limitations were sample power across studies, which were typically small, with 24.2% of the studies using sample sizes n = 30 and over in every group, and 38.1% with a total sample size of fewer than 10 participants [44,45,47,51,52,66,67,71]. Further, no human studies have employed a longitudinal design to determine whether changes in sweet perception are associated with subsequent eating behavioural change or not. Moreover, the study of quality of the articles shown in Table 3 highlights their low quality. Only 12 articles can be classified as of “acceptable quality".

In order to get accurate and relevant results it is important to apply specific evaluation rules related to the preparation, serving, application of anti-sweet substances, and tasting of sweet samples under controlled conditions so that biasing factors are minimized. However, most studies did not explicitly give information about how and for how long rinsing was performed. Only a minority of studies accounted for variables that are known to affect taste perception in their design or analysis, including age (as gustatory perception decreases with increasing age), previous training, time of day, meals (sensitivity may be reduced for between 1 and 4 h after a meal), hunger (which makes people more sensitive to sweetness), smoking, BMI, diseases, medication, temperature or receptor adaptation (tasting a strong sample may affect results for a weak one). For example, studies in this review suggest that taste sensitivity may be related to BMI. The fact that it is of significance is illustrated by Brala and Hagen [29]. These authors showed that 5.5% of total caloric intake was accounted for by a gymnemic treatment in comparison to the 19.9% attributable to body size. Notwithstanding, a recent study found no association between BMI and the amount of high-sugar sweet food eaten, the desire for the next serving and the pleasantness ratings following the consumption of *Gymnema sylvestre* [70]. Finally, in terms of validity, a limitation of these studies is their focus on basic sweet tastes [48] rather than testing suppression of real complex sweet flavours present in our diet.

4.3. Conclusions

We investigated the relationship between the level of sweetness inhibition and eating behaviour. Notwithstanding limited evidence, preliminary findings do not support the hypothesis that, after oral administration of a sweetness inhibitor in healthy subjects, there is a threshold of sweet taste suppression above which a reduction in food intake occurs and below which the opposite happens. Rather, a continuous function between the level of sweetness inhibition and the reduction in sugar intake appears to be the case. On the other hand, following oral administration, three plant species, i.e. *Gymnema sylvestre*, *Hovenia dulcis* and *Ziziphus jujuba*, acutely depressed judgments of sweetness, pleasantness and consumption. Likewise, the within-session effect of sweet suppression also seemed to increase the desire to eat sweet-tasting substances, although more research is needed. Regarding eating behaviour and any potential

downstream effects on energy intake and nutritional status, the critical distinction between the acute within-session effects versus longer-term effects of oral sweet-taste-suppressing compounds remains to be explored.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Raquel Rayo Morales reports financial support was provided by Government of Spain Ministry of Universities. David Garcia-Burgos reports financial support was provided by Spain Ministry of Science and Innovation.

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Appendix A. Supplementary data

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