Journal Pre-proofs

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Please cite this article as: D. Andrews, S. Salunke, A. Cram, J. Bennett, R.S. Ives, A.W. Basit, C. Tuleu, Bitter-blockers as a taste masking strategy: a systematic review towards their utility in pharmaceuticals, *European Journal of Pharmaceutics and Biopharmaceutics* (2020), doi: https://doi.org/10.1016/j.ejpb.2020.10.017

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Bitter-blockers as a taste masking strategy: a systematic review towards their utility in pharmaceuticals.

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Abstract: Acceptable palatability of an oral dosage form is crucial to patient compliance. Excipients can be utilised within a formulation to mask the bitterness of a drug. One such category is the bitter-blockers. This term is used inconsistently within the literature and has historically been used to describe any additive which alters the taste of an unpleasant compound. This review defines a bitter-blocker as a compound which interacts with the molecular pathway of bitterness at a taste-cell level and compiles data obtained from publication screening of such compounds. Here, a novel scoring system is created to assess their potential utility in a medicinal product using factors such as usability, safety, efficacy and quality of evidence to understand their taste-masking ability. Sodium acetate, sodium gluconate and adenosine 5'monophophate each have a good usability and safety profile and are generally regarded as safe and have shown evidence of bitter-blocking in human sensory panels. These compounds could offer a much needed option to taste-mask particularly aversive medicines where traditional methods alone are insufficient.

Keywords: bitter-blocker**;** taste-modifier; bitter-blocker; excipient; palatability

1 Introduction

Oral dosage forms need to be acceptably palatable for good compliance in any given patient population [1]. Palatability is a major component of the 'acceptability' of a formulation, which encompasses a number of attributes the drug possesses, including other organoleptic properties such as smell and mouthfeel. Palatability of a pharmaceutical dosage form is a key influencer in how well patients adhere to their treatment programme [2]. Considerable progress has been made in the furthering of taste masking, not only in the form of excipients but also in novel technologies to deliver a more acceptable product such as the medicated straw which utilises coated beads within a straw for ease of administration [3] and the use of food and drink as a vehicle to administer liquid formulations [4]. However, these approaches have limitations; they are not appropriate for all dosage forms and they may require specific storage conditions and be unattractive from a commercial perspective [1].

Techniques are available to taste mask drugs by providing a physical barrier to prevent the bitter active pharmaceutical ingredient (API) interacting with the taste buds, for example, polymer coating or adding cyclodextrins to form inclusion complexes [5]. This design can limit formulation options, as encapsulating the API into a solid dosage form can be problematic for the many patient populations that experience problems swallowing medicines [6]. Polymer coating may also not be feasible depending on the properties of the API or dose requirements which may make the drug product too large to swallow. The inclusion complex approach also encounters limitations as some compounds will not form interactions with dextrins [7]. Alternatively, if inclusion complexes are formed, the encapsulated portion of the API may not be the part that confers bitter taste. These barrier approaches can alter the speed of onset of the drug and can increase production costs of the goods [8].

The addition of sweeteners and flavouring agents is commonly used to taste mask poorly palatable formulations. This simplistic approach does not always improve the perceived bitterness of highly aversive or highly soluble compounds and these excipients are often

used in combination with other taste-masking strategies This type of taste-masking aims to achieve an 'acceptable' taste profile which can be subjective, especially in children [9]. Furthermore a number of artificial sweeteners are reported to have an aversive metallic or bitter taste component [10] and have shown agonist activity at certain subsets of bitter receptors [11]. An updated approach to taste-masking may be in shifting the aim from a palatable medicinal product to a taste-neutral product by targeting bitter receptors directly. This would overcome the issues associated with personal preferences to flavours and differing perception to sweeteners. This approach would also prevent the creation of an overly palatable and attractive medicine which can lead to accidental poisoning, especially in children. This taste-neutral approach is supported by current EMA guidelines [12]. Pharmaceuticals can be unpalatable for reasons other than bitterness ; but humans have evolved to recognise bitter tastants as potentially toxic [13] and this causes a major issue with compliance, reducing the oral tolerance for pharmaceuticals. Access to bitter receptor blockers could help create an acceptable product from a previously unpalatable one and thus improve patient compliance. This approach could also reduce industry costs (both financial and time) pre-clinically when tackling the issue of taste-masking. Such bitter-blockers would act at the level of the taste cell in the oral cavity and would act independently of the co-administered compound.

1.1 The Human Taste Pathway

There are five recognised tastes; sweet, sour, umami, bitter and salty. Both sour and salty are mediated by ion channels whereas sweet, umami and bitter tastes are detected by members of two GPCR families; the taste 1 receptor family (TAS1R) and the taste 2 receptor family (TAS2R) [14]. Most bitter tastants are detected by their interaction with TAS2Rs. TAS2Rs are a large family of around 25 G-protein coupled receptors, many of which can detect a huge variety of bitter molecules. When the receptor is stimulated, the G-protein, gustducin, is activated and stimulates phospholipase C β2 which results in inositoltriphosphate activation mediating a rise in intracellular calcium levels and thus

activating transient receptor potential cation channel M5 (TRPM5). The result is membrane depolarisation, generation of an action potential and the release of ATP which then acts on purinergic receptors activating afferent nerve fibres which in turn activate the appropriate brain centres leading to taste perception [15]. This pathway is summarised in figure 1.

1.1.1 Genetic Diversity and Bitterness

Not everyone perceives medicines the same way; nuisances in genetic makeup play a role in the palatability of drugs [16]. TAS2Rs have extensive diversity across human populations around the world [17]. Over 150 single-nucleotide polymorphisms have been found in TAS2R coding regions which can result in amino acid substitutions and alter receptor functionality [18].

Most bitter compounds (including APIs) are perceived as aversive by interaction with a number of TAS2Rs [17]. Therefore, a polymorphism in a specific receptor altering its functionality is unlikely to eliminate the bitter response completely but may result in differences in sensitivity to various agonists. Once notable outlier is phenylthiocarbamide (PTC) which is perceived as highly aversive by one bitter-receptor; TAS2R38 [19]. Humans who have a 3 amino acid replacement in their TAS2R38 gene will report PTC as taste-less [20].

Given this genetic diversity in bitter receptors, it is unlikely that a bitter-blocker will have exactly the same effect in every individual; as is a limitation for traditional taste-masking methods such as sucrose [21] and the artificial sweetener acesulfame-K [22] which can be subjective in their bitter-masking efficacy due to genetic diversity of TAS2Rs.

The use of a bitter receptor antagonist will only be effective if the aversive API is hitting this receptor too. The exact role of each subset of bitter receptor, and how they influence taste perception for different medicinal compounds, is not yet fully understood. Databases such as BitterDB [23] are beginning to fill these gaps by collating information on bitter molecules and their receptors. As more knowledge is generated, the use of bitter-blocking compounds can be better directed and make the art of taste-masking more precise.

As many API interact with multiple TAS2Rs, a 'blocker' acting as a specific bitter receptor antagonist may not mask the aversive taste entirely but is likely to dampen it. This may be sufficient for the API to become palatable enough for improved patient compliance. For highly soluble and aversive API, significant improvement could be achieved using combinations of bitter-blockers, acting on multiple receptors, or bitter-blockers in conjunction with other taste-masking approaches.

1.2 Bitter-Blocker; An Inconsistent Term

The screening process for this review highlighted how the term 'bitter-blocker' is used inconsistently throughout published literature. It is used synonymously with terms such as 'taste-modifier'. This review defines bitter-blockers as compounds which modify bitter taste by interacting with the bitter-taste perception pathway in some way, acting at a pharmacological level; interfering with taste receptors or the taste-transduction mechanism. Blocking of bitter taste perception can occur throughout the taste signal cascade. A compound can act by directly antagonising bitter taste receptors, preventing the activation of gustducin and inhibiting taste perception. Such compounds are likely to be close structural analogues of bitter compounds allowing them to still bind, allosterically or otherwise to these receptors.

It would be useful if a bitter-blocking molecule was identified that interacts with a multitude of bitter receptors or that interacts with a late stage component of the taste transduction pathway. An ideal site of action for this is the TRPM5 receptor, as shown in figure 1, which facilitates the perception of bitterness to reach the brain. However, TRPM5 receptors also transduce the signals for sweet and umami flavours [24] and a blockade here would abolish these taste sensations leaving only sourness and saltiness to be detected via ion channels. This could result in a more prominent sour or salty taste, albeit less bitter, which could still be aversive to the patient and so little commercial progress has been made to this end.

A number of compounds which have the ability to alter perceived bitterness were compiled by Walsh et al [25], focussing on paediatric medicines. Some of these compounds interact with the bitter-perception pathway as bitter-blocking taste-modifiers but the list also included excipients which were reported to convey bitter suppression due to their sweetener properties, for example neohesperidin dihydrochalcone. This work stated the known limitations of each compound and their regulatory status but did not claim to be an exhaustive list of bitter-blocking agents. In fact, there is no complete review available of all known bitter-blockers nor is there a thorough risk assessment of such compounds for their use in medications. Such an assessment would evaluate their utility as potential excipients by compiling and considering the information known about them in terms of their safety, practical usability and demonstrable efficacy. The compounds can then be assigned a score according to each category to establish their potential. This structured approach would begin to fill the gaps in current knowledge around this taste-masking approach and highlight ways in which bitter-blockers could be applied. Once this knowledge is gathered, medicine regulatory bodies can be consulted to better understand the classification of bitter-blockers in pharmaceutical dosage forms. It is likely that these compounds would still fall under the label 'excipient', and not API, even though they act to block bitter receptors; just as is the case for sweeteners which also act on receptors to influence palatability but are still classified as excipients. Furthermore, the World Health Organisation describes an API as 'a substance… intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings' and bitter-blocking agents do not come under this definition [26].

1.2 Review Objectives

The aim of this work is to establish an up to date literature review on bitter-blockers and to evaluate their potential utility as excipients by critically assessing the available information.

Improved understanding of the potential benefits and limitations of these compounds would be a useful addition to the formulation toolbox of taste-masking.

The questions this review addresses are; what is the current knowledge of bitter-blockers which act at a molecular level to disrupt bitter perception? How appropriate are these bitter-blockers for use as excipients in medicinal compounds in terms of usability, safety and efficacy? To answer these questions a systematic literature review of bitter-bitter blockers (acting on TAS2Rs) was conducted and a scoring system drawn up to quantitatively assess their practical potential in medicines. This was carried out in accordance with the PRISMA guidelines [27]

2 Data Search and Collection Methodology

2.1 Data Sources and Search Strategy

Publications were screened from the following databases; Scopus, PubMed, Embase and Web of Science. All subject areas and years were included in the initial search. The term 'bitter-blocker' is not used consistently in the literature and so search terms included other key words which may have been used synonymously. The search terms selected were; 'taste modifier', 'bitter blocker', 'bitter antagonist' alongside either 'medicine', 'drug', 'formulation' or 'dosage form'. The search terms were also hyphenated to prevent excluding relevant material.

2.3 Inclusion and Exclusion Criteria

Duplicate publications were removed before conducting a review of the remaining work according to PRISMA guidelines (figure 2). Abstracts containing information pertaining to 'taste-modification by bitter blocking' were retained. From here the full texts were screened and excluded if the bitter-blocker was not a compound but a technique, such as hot-melt

extrusion, or a genetic modification, for example to bitter receptors. Papers were also excluded if the bitter-blocker did not meet the definition laid out in this review but instead offered sweetening properties or interacted directly with the bitter molecule.

2.4 Criteria of Interest for Bitter-Blockers

Utility as a potential excipient can be evaluated by understanding different compound characteristics, namely safety, efficacy (including quality of evidence) and usability.

2.4.1 Safety

Knowing an excipient is safe is vital before use with any medicine to reduce the likelihood of their contribution to adverse events. Adverse events linked to excipients have been reported [28] but these tend to occur when excipient levels exceed recommended acceptable daily intake (ADI) [29]. It is now widely understood that many excipients are not inert as was once thought. This means excipients must be deemed safe and supported by robust data. Novel excipients must be subjected to full toxicological evaluation [30]. Knowledge of the current regulatory status and any precedence of use of the excipient is also important information.

2.4.2.1 Efficacy

It is key to consider how effective a bitter-blocker has been shown to be in previous research and it is important to understand its mechanism of action. For example, if the compound reduces aftertaste or initial bitterness and to understand in what population it has shown efficacy – bitter blocking abilities have been shown to differ according to age [6]. Further understanding of the mechanism of action of a bitter-blocker could help predict how efficacious it is likely to be [9] for example, if a specific mechanism is identified, such as the blockade of one or two bitter receptors, this information can be useful to appropriately tailor its use to taste-mask certain bitter substances.

2.4.2.2 Quality of Evidence

The models used to demonstrate the efficacy of different bitter-blocking agents varies greatly. The platform used to assess the compounds can be evaluated for reliability and scored according to how rigorous the level of testing was that they received. For example, palatability testing can take many forms, the most simple of which are cell-based models [31] and lipid membrane sensors [32] such as the electronic tongue (E-tongue) [33]. An alternative way to assess the palatability of a given substance is the in-vivo brief access taste aversion (BATA) model which uses the lick response of trained rats to ascertain the aversiveness of a compound compared with bitter controls and water [34]. The gold standard test for predicting palatability for human use is human sensory testing [31]. Regardless of the model or methodology used, it is important to highlight any inconsistencies with the research, which may cast doubt over the findings. An example of this is the use of a human panel with a small participant number.

2.4.3 Usability

An excipient must be able to be practically used in a formulation intended to be given to patients. As such, it must have good compatibility with potential API [35] and should exhibit appropriate stability characteristics. If the excipient needs to be in solution to achieve bitter-blocking action, it should have a reasonable solubility, without the need for a solubilizing aid, in an acceptable vehicle appropriate for dosing (for example not in ethanol) and have acceptable stability in the formulation. Also, the quantities required to produce the desired taste-masking effects would further indicate how appropriate a bitter-blocking excipient would be for use in drug products, especially for use in solid oral dosage form or for children where small volumes of liquid are administered. The nature of its use should be considered; whether it can be incorporated into the dosage form during manufacturing, or if the bitter-blocker must be administered directly prior to taking the medication or if extemporaneous preparation is required. The practical aspects of obtaining the compound must be

highlighted, for example if it is readily available or if it requires a number of in-house synthesising steps. It is also important to consider if the compound itself has a taste or smell which could impact its acceptability and use, for example saltiness or sourness.

2.5 Development of a Scoring System

In order to best score the bitter-blockers for their potential use as excipients, it is first important to identify the significance of each of the scoring criteria.

2.5.1 Criteria Weighting

For an excipient of any sort to be incorporated into a formulation it must be safe, therefore safety is a crucial factor and should be given a weighting reflecting this when scoring. Demonstrable efficacy, including quality of the evidence, is considered equally important as without this the bitter-blocker will not be useful as a component of the formulation toolbox. Usability is the next level down of importance as the use of the bitter-blocker can be tailored according to its characteristics, for example if it does not have long-term stability in solution it could be used for extemporaneous preparation. Such factors may make an excipient less desirable but does not mean they cannot succeed as an excipient given the appropriate conditions. With this in mind when calculating the final score, both safety and efficacy/quality of evidence will carry a weighting of 3 as both are fundamental requirements for use in formulations. Usability will carry a weighting of 2 as this can be tailored.

2.5.2 Scoring Each Criteria

Each bitter-blocker will be scored from 0-3 against safety, efficacy (including quality of evidence) and usability (table 1). The score for each criterion will reflect the nature of the information available but also highlight any gaps in information. A score of 3 implies complete information is available on the bitter-blocker's safety/efficacy/usability and that the evidence suggests excellent characteristics.

The score assigned to the bitter-blocker for each criterion will be multiplied by the weight of that category (example in figure 2). This scoring system will be used to assign a mark to each of the bitter-blocker by a number of independent assessors, 3 from academia and 3 from pharmaceutical companies.

2.5.3 Scoring Limitations

The compounds identified had differing amounts of information available about them and this review leveraged information from many sources, depending on the available evidence. This is most apparent when reviewing the level at which the bitter-blocker has been assessed; some have been assessed in paediatric panels whereas others have been assessed in adult panels or in non-human models. In reality, the target patient population's age will affect the safety parameters and efficacy. For example, if the excipient is intended for use in children, but the information regarding safety is only available in adults then further testing would be required for these patients who have underdeveloped organs and a more limited metabolism [39]. This is particularly crucial for neonates who may require a new formulation altogether or a tailored dilution. Safety of excipients is of the utmost priority across all patient populations but their inclusion in paediatric medicines require further risk assessment focusing on any potential age-related safety concerns [40]. Also if a compound has shown bitter blocking ability in adult sensory panels, it will not necessarily confer the same affect in children as demonstrated by Mennella et al [6]. However, if a bitter-blocker does work in children, it is likely to work in adults as children are more sensitive to bitter taste. Children and adults have different preferences, for example children prefer salty solutions [41] so this could also affect their usability.

In this review, two separate tables of results are presented. The scores of bitter-blocking agents which have shown efficacy in a human panel are drawn up separately to those where an alternative method of assessment was used. This is to draw attention to compounds which have been assessed more rigorously but which may fall down due to other reasons of

safety or practical use compared with non-proven bitter-blocking compounds which might show potential but about which relatively little is known and evidence is only based on non-human methods of evaluation.

Those assessed using a human panel (of sufficient participant number) will be given the highest score for quality of evidence regardless of the age of the panel, but the patient population investigated will be stated and the safety scores will reflect the age. For example, if assessed in children it is important to know the safety for children. Furthermore, the results from the different human panels were expressed in a number of ways; for example, some gave a percentage inhibition of bitterness, some just quoted a significant reduction in bitterness and importantly the human studies used various concentrations of bitter controls (for example quinine). To avoid penalising studies which may have used a higher concentration of quinine or to unfairly reward those which did not detail the exact percentage inhibition, a score of 3 was given for efficacy if the human panel reached the criteria for participant number and demonstrated significant bitter blocking - regardless of how this data is presented.

With regards to safety, it is important to note that, as with any novel excipient, bitter-blockers would need to undergo a full battery of safety assessments before being considered for use in a pharmaceutical formulation. This is especially important due to their functional role as receptor blockers.

2.4.4 Reducing Bias

In order to reduce bias in this work, the initial scoring system was drawn up before the literature search. The risk of bias associated with the literature screen were minimised by setting inclusion criteria (figure 3) beforehand. After the literature search was conducted and the bitter-blockers identified, each assessor marked and ranked the compounds independently according to their interpretation of the scoring system. The scoring system was then only updated to improve clarity if there were discrepancies in interpretation.

3   Literature Screen Results

From the literature screen, 21 papers were identified which met the inclusion criteria [6,41–60]. The rationale for the studies included are laid out in figure 3 according to PRISMA guidelines [27].

Two tables of bitter-blockers were compiled, one containing those compounds assessed in human sensory panels (table 2a) and those assessed using other methods (table 2b). Compounds were grouped by class, for example salts.

4   Scoring System Results

Using the scoring system laid out in table 1 the bitter-blockers were assessed and ranked accordingly, again separated by method of assessment (table 3a & 3b).

5   Other Reported Compounds

Many cited bitter-blockers in the literature reference sweeteners or sweet proteins. Examples include thaumatin [114], aspartame [49], monellin [115] and neotame [116]. Some sweeteners are ligands for bitter receptors, acting as agonists and resulting in bitter aftertastes in the patient. For example saccharin and acesulfame K activate hTAS2R43 and hTAS2R44 at millimolar concentrations [11]. It is known that particular combinations of sweeteners can be added together to offset the bitterness of the other. For example, both saccharin and cyclamate have bitter 'off-tastes'. Saccharin activates the bitter receptors TAS2R31 and TAS2R43 at millimolar concentrations (0.17 and 0.08mM respectively) [11] whereas the half-maximal effective concentration (EC50) for the sweet receptor target (the TAS1R2/TAS1R3 heterodimer) is approximately 0.2mM saccharin. This means that saccharin is eliciting a bitter taste-response before reaching signal saturation of the sweet

receptor [117]. Cyclamate can modify the bitter-taste response to saccharin, primarily by acting on TAS2R43, a receptor partially responsible for saccharin's bitter off-taste. However, the concentrations of cyclamate required to significantly impact upon saccharin induced TAS2R43 bitterness are relatively high (half-maximal inhibitory concentration of 19.0 ± 4.6 mM) [117]. Furthermore, cyclamate itself activates certain bitter receptors, (TAS2R1 and TAS2R38) at 30mM [118], a concentration far higher than the 2.2mM EC50 of the sweet receptor target [119] but a concentration that may be required to fully block saccharin's bitterness. Such sweeteners are not included in this review as bitter-blocking agents as their primary taste-masking action is on sweet receptors.

Miraculin, is not a sweetener as such but a glycoprotein extracted from the miracle berry that is known to make sour taste appear sweet [19]. Interestingly, it was shown to improve the perception of food and drink reported as metallic in a small group of patients with altered sense of taste undergoing chemotherapy [39]. It has not been assessed against bitter compounds in sensory trials however, and it's primary effect is as a sweet receptos agonist [120] [121].

Other taste-masking agents cited in the literature as bitter blocking taste modifiers include cyclodextrins, ion-exchange complexes [116], and fatty-acids [122]. Additives which coat the mouth and prevent interaction with the taste receptors such as lipophilic vehicles [123] and surfactant compounds [124] were also excluded from this review.

5.1 Compounds Which Influence Other Taste Perceptions

Other commonly reported 'bitter blockers' include 3β-Hydroxydihydrocostunolide and 3β-hydroxypelenolide which can be extracted from wormwood and inhibit TAS2R46. However, they are agonists at a number of other bitter receptors [125] and therefore are unsuitable for addition to pharmaceutical compounds. GIV3727 was included in this review even though it has been reported to be an agonist at T2R14 [126] because it has shown to be promising in

human sensory trials. Other compounds have been shown to inhibit bitter perception but effect other taste sensations, for example $ZnSO_4$ reduced the perceived bitterness of quinine in a human sensory experiment but also reduced the panellists' perception of sweetness [127]. Zinc salt solutions also have a prominent astringency that makes them unappealing as excipients for medicines [128]. Other salts that have been reported as bitter-blocking include $MgSO_4$, which is also act as a bitter stimulus at higher concentrations [56] and has bitter inhibiting effects at lower concentrations [129] but has not shown consistent results. Both γ-aminobutryic acid (GABA) and $N\alpha,N\alpha$-bis (carboxymethyl)-l-lysine (BCML) have been shown to act as bitter blockers to 1mM quinine, with an IC50 of 3.2±0.3 µM and 59±18 nM respectively [126]. Aside from the fact GABA is a neurotransmitter and so is not an ideal excipient to add to medicines, amino acid derivatives have their own umami taste which seems to be key to their bitter suppression. Peptides which are tasteless, such as Gly-Gly, did not have any effect on bitter perception in an in vitro model of TAS2R16 [130]. Using umami flavour as a taste-masking excipient does not provide an ideal solution to bitter blocking as this taste preference is subjective and may not increase the acceptance of medicines in many patient populations.

5.2 Compounds With Other Limitations

Probenecid has been shown in vitro to inhibit the activation of TAS2R16, 38 and 43 and this correlates in humans with 10mM probenecid rinse significantly reducing the bitter perception of 10mM salicin, a TAS2R16 ligand, in a human panel of 15 people [131]. Its utility as a bitter-blocker has been shown by using it as a 10mM pre-treatment rinse and not as an excipient. Furthermore, Probenecid is an FDA approved treatment for gout and, like most medicinal compounds, is associated with side effects [132] making it an undesirable excipient choice. Other rinse approaches have shown success; pre-treatment with Chlorhexidine antiseptic can alter bitter perception of tastants given directly after [133]. However, not only is this rinse approach unsuitable but Chlorhexidine is bitter in itself.

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Other modifiers that have been reported include flavan-3-ol-spiro-C-glycosides reaction products [134] and 1-carboxymethyl-5-hydroxy-2-hydroxymethylpyridinium inner salt [135]. These have shown some bitter blocking effect in small human panels. However, these are produced by long chemical reactions, not readily available to purchase and therefore not ideal excipient candidates.

Studies attempting to elucidate the mechanisms behind taste perception have highlighted how cascade blockers can be used to alter perception of taste sensations including bitterness. For example, U73122, a phospholipase C blocker and thapsigargin, a CA^{++}-ATPase blocker, have been shown to have efficacy in preventing bitter taste transmission by investigating nerve responses in the rat [136]. Both compounds are only soluble in unsuitable media [137,138] and their mechanism of action is non-specific, rending them unsuitable for use.

Some compounds attribute molecular action to their bitter-suppression but not on the bitter receptor pathway. For example Δ^9- tetrahydrocannabinol has been shown to enhance quinine palatability in rats by acting on CB1 receptors [139]. This mechanism of action is undesirable for use as a taste-masking excipient as it is likely to lead to off target effects [140]. TRPM8 agonists have shown promise with bitter-masking through the cooling effect they impart [141]; menthol has been shown to successfully improve the acceptability of bitter compounds in the BATA model [142] and in human sensory trials (work done in house, unpublished). The limitation with menthol is the strong smell which may be aversive to patients but other agonists which do not have the same scent need to be further investigated for their potential as taste-masking excipients.

Other bitter-blocking compounds were not discussed in this review because there is too little published data available to make any judgements on their usefulness. For example, MR15, 24A and MZ70 have been quoted to mask bitter melon's unpleasant taste using in vitro methods [143] but not there is not enough information in the public domain to evaluate them.

6 Conclusions

Palatability plays an important role in patient adherence to a medicinal regime. Bitter-blockers are a category of bitter-masking compounds which directly target the taste-pathway at a molecular level. This review highlights a number of molecules which have demonstrated, to various degrees, bitter taste-modification. The scores given to each compound based on parameters such as safety and usability put the available information in perspective. This review found that AMP and some sodium salts may be productive avenues to explore in future research to improve the palatability of bitter compounds. GIV3727 and homoeriodictyol sodium salt also scored highly but these have limited commercial viability with lack of availability and other usability issues being the major barrier for these compounds.

In order for bitter-blockers to be used more widely in pharmaceutical products it is key to understand their safety within a formulation and learn more about their use as a functional excipient. It is also important to explore factors such as length of efficacy; any effect on bitter suppression must be transient (ideally seconds, perhaps single minutes) as to not disrupt taste-perception longer than necessary. For widespread use, it may be necessary to generate new toxicological data on these compounds. It is unlikely that the promising bitter-blockers highlighted in this review would have a safety issue due to their GRAS status and the low levels required for efficacy. These compounds could offer an invaluable option to improve the palatability of medicines and help to increase patient compliance.

Funding Information

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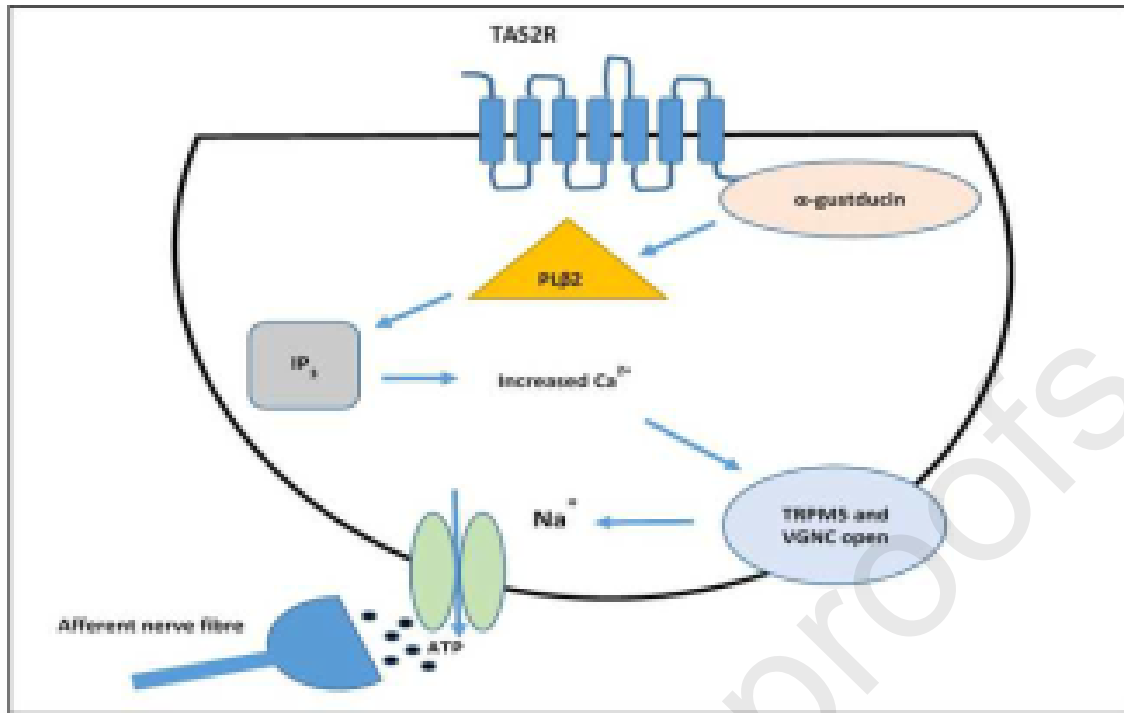
Figure. 1. Schematic representation of the human bitter taste pathway. TAS2R; taste 2 receptors, PLβ2; phospholipase C β2, IP$_3$; inositoltriphosphate, TRPM5; transient receptor potential cation channel M5, VGNC; voltage gated sodium channel.

Assessing an example taste-modifier; compound A

Known safety information: compound A has GRAS status but has no known ADI nor is it found in the human diet or patented for human use

        i)   Safety; scores 2 (weighting x3) = 6

Known efficacy information and the QoE: compound A has been shown to reduce the bitter perception of a range of different API using an animal model of palatability (n=12)

        i)   Efficacy and QoE; scores 2 (weighting x3) =6

Known usability information: compound A needs to be in solution to elicit bitter blocking of target receptors however it is not stable in suitable media for long periods of time and needs to be kept in the fridge, it is also unavailable to purchase

        i)   Usability; scores 1 (weighting x2) = 2

Total score = 14 (possible highest score is 24)

Figure 2. Worked example of scoring an example bitter-blocker against the three criteria using the different weightings. QoE; quality of evidence

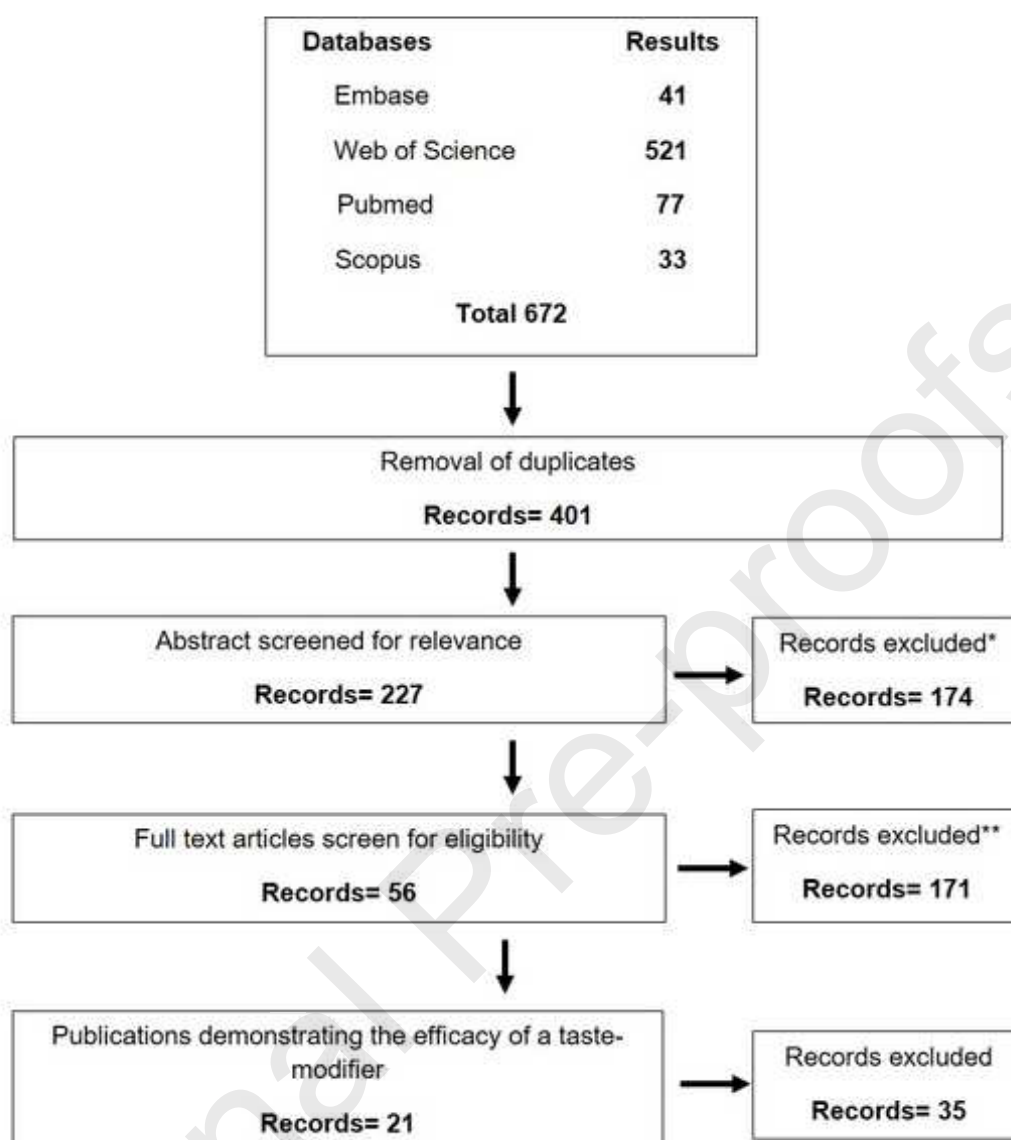Figure 3 Literature search for bitter-blockers. *Exclusion criteria for abstracts; papers were excluded at this stage if there was no relevant mention of taste-modification by bitter blocking. **Exclusion criteria for full text articles included the bitter-blocking being due to genetic modification of a model, or was describing a technique not a compound that conferred bitter-blocking or inappropriate use of the term bitter-blocker

Table 1 Scoring criteria for bitter-blockers

	Score of 0	Score of 1	Score of 2	Score of 3
Safety	Evidence of a hazardous nature in low/ efficacious concentrations OR No information available on safety	Incomplete or little information is known on the safety of the compound OR No information found but is a close structural analogue of another compound with 'Generally Regarded as Safe' (GRAS) status	The compound is deemed safe for example has GRAS status OR Has a known ADI that exceeds the efficacious dose OR Is found in the human diet with no concern highlighted on its use although it may be associated with allergies in some patients so requires strict labelling OR Is patented for human use	The compound is deemed safe (for example has GRAS status) AND Not associated with allergies in patients AND one of the following Is patented use for humans OR Has a known ADI that exceeds the efficacious dose, or regulatory bodies have stated there is no limit to the ADI OR Is found in the human diet with no concern highlighted on its use OR The compound has recent precedence for use in human consumables and/or pharmaceuticals
Efficacy and QoE	No demonstrable efficacy shown as a bitter blocker OR Study demonstrating efficacy has inconclusive or unreliable results	Efficacy shown in a cell-based model expressing a limited number of receptors (which gives no context to its action) or using a sensor technology (which has limitations [36] and also gives limited context) OR Transient bitter blocking shown in an animal model (e.g. BATA) against one compound OR Efficacy shown against one bitter compound in a human panel of	Demonstrates effective transient bitter blocking against one compound which has been demonstrated in a human panel of at least n=8 OR Demonstrates effective transient bitter blocking against more than one compound which has been demonstrated in a model that does not involve humans (n>8) or in a human panel of insufficient participant number (n<8)	Demonstrates effective transient bitter blocking against more than one compound with efficacy demonstrated in human sensory panels of sufficient sample size, at least n=8 (unpublished in house data shows n=8 to be sufficient to distinguish between low and high levels of bitterness)

		insufficient number (n<8)		
Usability	No known information on stability/ solubility

AND/OR

Toxic at doses required for bitter-blocking

AND/OR

Not available to purchase

AND/ OR

More than three limitations to its use, for example, specific storage is required/ it is only suitable for extemporaneous preparations/ it has a flavour in itself which may be aversive to some patients/ it is expensive to purchase | Poor compatibility with API identified or likely to occur

AND/OR

Solubility either
 - inappropriate (e.g. only soluble in ethanol/ DMSO) Or
- only partially soluble in water Or
- poor solubility; too low to convey efficacy if an efficacious concentration has been demonstrated in a human panel or, if no efficacious concentration is known, requires more than 30mL of solvent to dissolve 1g i.e. less soluble than 33.33mg/mL [37]

AND/OR

Stability either
- specific time period of stability unknown Or
- not stable in solution for at least 3 months (regardless of storage conditions required, e.g. refrigeration)

AND/OR

Not available to purchase readily/ requires a number of synthesising steps

AND/OR

This compound has up to three limitations to its use; for example, specific storage is required/ it is only suitable for | Acceptable solubility; either exceeding that required for efficacy in humans or, if not known, above 33.33mg/mL

AND

Acceptable stability of at least 3 months (regardless of storage condition required e.g. refrigeration)

AND

No demonstrable evidence of its ease of use in humans

AND

Readily available to purchase

AND

The compound may have up to two additional requirements that limits its use in some way. For example, storage; refrigeration may be necessary, or the compound may only be appropriate for extemporaneous preparations or it may have its own flavour/taste that could be aversive to some patients (e.g. sour) | Demonstrable ease of use in humans, for example if it is required to be in solution for efficacy, publications report it solubilised in appropriate media and could be administered in sensible quantities (for example 5mL total volume if administered to children [38] or 10mL if administered to adults [31])

AND

Solubility exceeding that required for efficacy in humans, or if unknown, above 33.33mg/mL and stable for at least 3 months at room temperature

AND

No aversive taste potential; it is either tasteless or pleasant tasting

AND

Readily available to purchase.

AND

The compound has no additional limitations to its use |

extemporaneous preparations/ it has a flavour in itself which may be aversive to some patients/ it is expensive to purchase

Table 2a. bitter-blockers extracted from the literature review which were tested in a human panel

Bitter-blocker and level of assessment	Mechanism of Action	Safety information	Demonstration of efficacy	Usability
Acids				
• **Citric acid** **Citric acid if found in citrus fruit** [55] **Assessed using a human panel** [55]	Calcium imaging has shown citric acid to be an antagonist at TAS2R16 [55].	Citric acid is found naturally in human consumables such as citrus fruits and is often added to food, beverages and drug formulations to adjust pH [55] There is no defined limit to daily intake [61] because it is safe and abundant in the human diet It has GRAS status.	In a human sensory panel of 11 adults, a dispersible tablet containing 2.5% (0.3M/ 57mg/mL, pH 1.84) citric acid supressed the bitterness and improved the palatability of olopatidine hydrochloride [55]	Citric acid has good solubility in water (592mg/mL) and good stability in solution (> 1 year) [62]. The dry material is moisture sensitive [63] Commercially available from Sigma 2.5% citric acid would convey the same sourness as a carton of grapefruit juice [64]
Overall score = 19 Limitations; sourness may be an issue for some patient populations		**Safety score = 3** (found in human diet and GRAS)	**Efficacy/QoE score= 2** (only tested against one bitter compound in a human panel)	**Usability score = 2** (sourness may be an issue for some patients)
• **AMP (Adenosine 5' monophosphate); nucleotide found in RNA** **Assessed as NaAMP in human panel** [56] **and as AMP in both *in vivo* and *ex vivo* assessment** [57]	AMP acts on peripheral taste inhibition. The glossopharyngeal nerve innervates taste receptor cells in the tongue and is responsive to bitter stimulus. 0.1mM AMP significantly inhibited the nerve responses to bitter compounds such as quinine and denatonium benzoate. It is thought AMP may alter the receptor G-protein coupling [57]	AMP is found in many foods and is found in breast milk [25] It has GRAS status for use in food and drinks and oral pharmaceutical dosage forms [65] AMP is patented for use in human consumables and pharmaceuticals [66] AMP has no precedence in pharmaceuticals	Human panel of 14 adults; 20mM NaAMP (7.4mg/mL) in pH 5 deionised water, on average, reduced the bitter perception of the following bitter compounds by 67%; 10mM pseudoephedrine, 4mM ranitidine, 50mM acetaminophen, 0.1mM quinine and 1.2M urea. This study did not give the bitter inhibition results for individual pharmaceuticals [56] G-protein activation assay using bovine taste cell membranes; AMP (0.01 - 5mM) dose-dependently inhibited transducin activation by bitter compounds. 2.5 mM AMP inhibits activation of transducin by 5mM denatonium benzoate and 1 mM quinine [57] Mouse two-bottle preference test; AMP had an inhibitory effect on the bitter perception of	Solubility in water of 100 mg/mL [67] which exceeds efficacious concentration AMP is stable if refrigerated at 4°C; it maintains its initial concentration after 25 weeks of storage. If exposed to room temperature, AMP solution will begin to degrade after a few days [68] Commercially available from Sigma Has a savoury taste [69]

		concentrations up to 5mM denatonium benzoate and 10 mM quinine. AMP was effective at 0.5 mM for quinine and 1 mM for denatonium benzoate [57]	
Overall score = 22 Limitations; requires refrigeration and has a slight savoury flavour		**Safety score = 3** (GRAS and in the human diet)	**Efficacy/QoE score= 3**

Usability score = 2 (requires refrigeration and may have limited use due to its umami flavour [70])

Flavanoids

• **Homoeriodictyol (HED) sodium salt is extracted from the North American Herba Santa shrub (Eriodictyon californicum)** **Homoeriodictyol sodium salt was assessed in human panels** [58,59]	Homoeriodictyol sodium salt does not affect other taste sensations such as sweet or salty. It partially blocks bitter reception for a wide variety of bitter tastants. It is likely to bind allosterically to a site common to all bitter receptors, alternatively it is possible it blocks one bitter receptor subtype which many bitter tastants have affinity for [59]	Hydroxyflavanones and their salts have been patented for their use in foods and pharmaceuticals for reducing bitter/metallic tastes [73]. At present, there is no precedence for pharmaceutical use. Homoeriodictyol sodium salt has GRAS status [74]	In a human sensory panel of 8 people homoeriodictyol sodium salt (0.31mM) reduced the perceived bitterness of 2.58mM caffeine by around 45%. HED decreased the perceived bitterness of a range of bitter tastants with various structures (guaifenesin, paracetamol, quinine, denatonium benzoate, salicin and amarogentin). The concentration of homoeriodictyol necessary to reduce the bitter intensity of each tastants varied from 0.31 to 0.77mM [59] In a separate human panel (n=12), 0.31mM homoeriodictyol sodium salt reduced the perceived bitterness of 1.1mM caffeine and 6.2mM (+)-catechin by 15% and 33% respectively [58]	Homoeriodictyol has a 0.34g/L (1.05mM) water solubility [77] which exceeds the efficacious dose and has good stability up to 40 degrees centigrade [78] however the length of time HED sodium salt is stable for is unknown Homoeriodictyol sodium salt is extracted from Herba Santa. Herba Santa can be obtained from suppliers [59]. Homoeriodictyol sodium salt itself is not commercially available
Overall score = 20 Limitations; not available to purchase		**Safety score = 3** (patented for human consumption and GRAS)	**Efficacy/QoE score= 3**	**Usability score = 1** (not available to purchase and actual stability unknown)
• **2,4-dihydroxybenzoic acid vanillylamide is a close structural analogue of homoeriodictyol** **2,4-dihydroxybenzoic acid vanillylamide**	Unknown but likely to be similar to HED sodium salt and potentially bind allosterically to a site common to all bitter receptors, alternatively it is possible it blocks one bitter receptor subtype which	No safety information found although a close structural analogue of homoeriodictyol which is safe	In a human sensory panel (n≥10), 2,4-Dihydroxybenzoic Acid N-(4-Hydroxy-3-methoxybenzyl)-amide (also known as 2,4-Dihydroxybenzoic acid vanillylamide) showed dose-dependent activity as an inhibitor of the bitter taste of 2.6mM caffeine solution. At 0.017mM the	No solubility or stability data found Not found to be available commercially. Can be synthesised [71]

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was assessed in a human panel [71]	many bitter tastants have affinity for [59]		compound inhibited caffeine's bitterness by around 12% and at 1.7M it inhibited caffeine's bitterness by around 40%. 0.017mM 2,4-dihydroxybenzoic acid vanillylamide also suppressed the bitterness of 0.015mM quinine by around 25%	
Overall score = 12 Limitations; not available to purchase and lack of information available		**Safety score = 1**	**Efficacy/QoE score= 3**	**Usability score = 0** (not available to purchase and no stability/ solubility data available)
• **Jaceosidin and sakuranetin are isolated from rice leaves** [72] **Assessed in a small human panel with inconclusive results** [60]	In vitro assays show the flavanones jaceosidin and sakuranetin to be antagonists at TAS2R31 [60]	Sakuranetin is reportedly harmful [75] as is jaceosidin due to its effect on cell apoptosis [76]	A panel of 4 tasters reviewed the effect on palatability of 1% sakuranetin dissolved in ethanol on the palatability of acesulfame K – results were documented as 'inconsistent' and due to lack of aqueous solubility no full results could be drawn [60]	Sakuranetin has very poor aqueous solubility (109.2mg/L) [79] and jaceosidin is only soluble in DMSO and ethanol [76] These compounds may be harmful at doses required for bitter-blocking
Overall score = 0 Limitations; unsafe and only soluble in ethanol/DMSO		**Safety score = 0** (unsafe substance)	**Efficacy/QoE score= 0** (inconclusive results)	**Usability score = 0**
• **GIV3727 (4-(2,2,3-trimethylcyclop entyl) butanoic acid)** **Assessed using HEK293 cells expressing various receptor subtypes and human sensory panel** [43]	GIV3727 it thought to be an insurmountable antagonist at the orthosteric binding site of TAS2R31.This mechanism of action may result in GIV3727 having a slow release profile which could render it unacceptable for use in drug products unless this proves to be a short lived effect. Molecular modelling suggests Lys^{265} in helix 7 of both hTAS2R31 and hTAS2R43 is important for GIV3727's action [43].	It is currently used as a flavouring and is patented for use to rectify off-tastes [80]. GIV3727 has no assigned ADI as it is deemed safe at levels used as a flavouring agent [81] and it has GRAS status [82] GIV3727 has no precedence in pharmaceuticals	In human sensory panel of 50 people, 150μM (0.03mg/mL) GIV3727 added to 2mM acesulfame K or to 2mM saccharin significantly reduced the perceived bitterness compared to control whilst having no effect on perceived sweetness of these sweeteners or of sucrose [43] In vitro, GIV3727 inhibits activation of six subtypes of TAS2Rs (TAS2R4, 7, 31, 40, 43 and 49) [43]	GIV3727 is very expensive even in low quantities (around £20,000 per gram) GIV3727 is stable in methanol/DMSO/ ethanol for over 2 years [83]. If this is evaporated off, GIV3727 can be resuspended in PBS; the supplier's information states that GIV3727 is soluble in PBS, pH 7.2 up to 0.25mg/mL, these solutions can only be kept for a short period of time (no longer than a working day) due to oxidation. Therefore, GIV3727 is not stable in suitable media GIV3727 in methanol

			must be stored at -20 degrees centigrade GIV3727 is commercially available from cayman chemical
Overall score = 20	**Safety score = 3** (patented and GRAS)	**Efficacy/QoE score= 3**	**Usability score = 1** (expensive to purchase, required specific storage and not stable in an appropriate media; could have use for extemporaneous preparations)
Lipoproteins • **Lipoprotein mixture, composed of phosphatidic acid (PA) and beta-lactoglobulin (LG)** **Assessed using a human panel** [44]	It is thought that PA-LG acts primarily on bitter taste-receptors directly. When PA-LG is given alone, any subsequent administration of a bitter compound is perceived as more palatable than the control [44].	PA originates from soybeans and LG originates from milk and are safe. PA-LG complexes are held by hydrophobic interactions and hydrogen-binding and hence can be hydrolysed in the digestive system easily [44]. Other combination fatty acids (FA) are patented for their use in food and drink. Linoleic acid and heptanoic acid in combination are used reduce the bitter off-taste of artificial sweeteners in beverages [84]. At present, there is no precedence for pharmaceutical use. Potential allergens are associated with PA-LG so may limit its utility [85]	In a human sensory panel, (n=8-10) 0.85% PA (12.6mM) + 2.15% LG (0.584mM) in 5mL water selectively and reversibly inhibited bitter perception of 12 compounds, in particular basic and hydrophobic substances. PA-LG reduced the bitter perception of 5mM promethazine and 10mM propranolol to almost zero and greatly reduced that of 50mM caffeine and 0.5mM quinine. PA-LG complex did not affect perception to salty or sweet stimulus [44]	This phospholipid-protein complex can be made by suspending PA and LG in water and homogenizing. The homogenate could then be freeze dried and the powder at 3% can be dispersed in 5mL deionised water (pH 5-7) [44]. Both PA and LG, in the powder form, have stability of over 1 year but in solution they have poor stability PA and LG are both available from Sigma
Overall score = 17 Limitations; not suitable for those with egg or milk allergies and used for extemporaneous preparation		**Safety score = 2** (found in human diet and FAs have been patented for human use however it is associated with allergies in some patients)	**Efficacy/QoE score= 3**	**Usability score = 1** (not reported to fully dissolve in solution but is dispersed so may be used for extemporaneous preparation)

• **Phosphatidic acid (PA) alone** **Assessed using a human panel** [45].	Phosphatidic acid adsorbs to the bitter compound but mostly acts directly on bitter receptors [45]	As above. Caution for use in milk allergy sufferers	14.8 mM PA supressed the bitter perception of 0.1 mM quinine in a human panel of 11 people by around 80% [45]	PA is not soluble in water but is dispersed and it does not have good stability in solution
Overall score = 14 Limitations; not suitable for those with milk allergies and used for extemporaneous preparation		**Safety score = 2** (as above)	**Efficacy/QoE score= 2** (efficacy shown against one bitter compound)	**Usability score = 1**
• **Riboflavin-Binding Protein (RBP)** **Riboflavin-binding protein is isolated from chicken egg** [86] **RBP was assessed in a human panel** [48]	RBP has been shown to bind to quinine by hydrophobic interactions to supress its bitterness but there is evidence to suggest RBP directly antagonises a number of bitter receptors (it is not known which ones) due to RBP's bitter supressing action of structurally different tastants [48].	Found in the human diet (it is in egg whites at 0.09%) [48] No current use in pharmaceuticals Unsuitable for those with egg allergies	In a human sensory panel of 4 participants, 0.2mM RBP decreased the bitterness of 0.125mM quinine by almost 100% [48]	RBP has poor solubility in water of 1mg/mL (0.03 mM) RBP powder is commercially available from Sigma RBP has been shown to inhibit sweetness from some proteins which may limit its use [87].
Overall score = 11 Limitations; poor usability		**Safety score = 2** (found in human diet but associated with egg allergy)	**Efficacy/QoE score= 1** (insufficient sample size and only one bitter substance tested)	**Usability score = 1** (solubility is insufficient for efficacy and can inhibit sweetness)
Sodium salts • **Sodium gluconate** **Assessed in paediatric sensory panels** [6,41]	Sodium ions are thought to act on specific bitter receptors directly. The exact mechanism is unknown, sodium may shield the receptor proteins, modulate ion channels or act on second messenger systems [56]. It is not a universal bitter receptor blocker or modulator as its influence on compounds differs [88,89]	Sodium gluconate is generally regarded as safe for use in pharmaceuticals and foods [90]. There are some concerns about exposing patients to excess sodium but 2mL of 0.3M sodium gluconate provides approximately 14mg sodium, the daily limit for children has been recommended to be 1,500mg per day and 2,300mg for adults [91] so this quantity is	In a paediatric sensory panel of 41 children, ages 7-10, 2mL 0.3 M sodium gluconate improved the perceived palatability of 0.5 M urea in 70% of the children. There was no difference in the palatability of urea + salt compared to salt alone. 0.3 M sodium gluconate improved the perceived bitterness of 0.08M caffeine in 68% of the children but this solution was perceived as more bitter than the salt alone. Children also ranked sodium gluconate as equally preferable to water [41]	The solubility of sodium gluconate in water is approximately 600mg/mL (2.75M) at 25°C [95] Sodium gluconate is reportedly very stable, especially in water [96] and has been demonstrated to be stable for at least 3 months as part of a medicinal cream [97] Sodium gluconate is commercially available from sigma The salty flavour may be off-putting for

	unlikely to be an issue with regulatory bodies Sodium containing compounds have been patented for bitterness inhibition in pharmaceuticals [92]	In another paediatric panel of 154 children 0.3M sodium gluconate reduced bitter perception of 0.119mM quinine [6]	some patient populations such as adults – children do not find the saltiness aversive [41]
Overall score = 22 Limitations; saltiness may be aversive		**Safety score = 3**	**Efficacy/QoE score= 3**
			Usability score = 2 (salty flavour may be aversive to some patients)
• **Sodium chloride + L-Arg** **Assessed in human sensory trial** [53]	See above	Both components have GRAS status [93,94]. 5mL of 30mM sodium chloride provides approximately 3.5mg sodium Sodium containing compounds have been patented for bitterness inhibition in pharmaceuticals [92].	Sodium chloride (30 mM) in combination with 2.87mM L-Arg has also been shown to be effective in human sensory trials, the number of participants was 6 per group, against a number of bitter tastants including quinine at 0.1mM. All samples were in 5mL [53]. However, NaCl is perceived as saltier and more aversive than sodium gluconate and so less preferable [89]	Good solubility in water [98] and individual components have good stability [99] [98] Components are commercially available from sigma Sodium chloride has a salty flavour [100]
Overall score = 19 Limitations; saltiness may be aversive		**Safety score = 3**	**Efficacy/QoE score= 2** (insufficient sample size)	**Usability score = 2** (salty flavour may be aversive to some patients)
• **Sodium acetate** **Assessed in human sensory trials** [49,56]	See above	GRAS status [90]. 10mL of 100mM sodium acetate provides approximately 23mg sodium Sodium containing compounds have been patented for bitterness inhibition in pharmaceuticals [92]	100mM sodium acetate reduced the bitter perception of a range of bitter pharmaceuticals, including 0.1mM quinine and 1.2M urea, by 55% on average in a human sensory panel of 14 participants, the solutions were in 10mL [56] 1.33M sodium acetate also reduced the perceived bitterness of a range of green vegetables by 42% in a human panel of 37 people [49]	Good solubility in water [101], 246.1g/L (3M) [102] and good stability for up to 1 year in solution [103] Commercially available from sigma Sodium acetate has a mild salty flavour [104]
Overall score = 22 Limitations; saltiness		**Safety score = 3**	**Efficacy/QoE score= 3**	**Usability score = 2** (salty flavour may be aversive to some patients)

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may be aversive

Table 2b. bitter-blockers extracted from the literature review which were tested using a non-human method

Bitter-blocker and level of assessment	Mechanism of Action	Safety information	Demonstration of efficacy	Usability
Acids				
• **Chlorogenic acid** **Chlorogenic acid is an ester of caffeic acid and quinic acid. It is found in many fruits, vegetables and coffee** [25] **Assessed using an artificial-lipid membrane taste sensor; SA402B** [52]	The inhibition of taste sensor outputs is thought to occur mainly via chlorogenic acid acting on the surface of taste sensor membrane and competing with the API [52]	Chlorogenic acid is abundant in the human diet and is GRAS. It is found in coffee at approximately 0.2-0.6mg/mL (0.56-1.69mM) [105]. The concentration shown to be effective was well within this range Caffeic acid and its salts are currently patented as bitterness inhibitors in food – masking the bitter aftertaste of artificial sweeteners [25]. At present, there is no precedence for pharmaceutical use	Taste sensor outputs of bitter basic drugs tested at 0.5mM were significantly reduced by the addition of 0.1, 0.5, 1.0 mM chlorogenic acid dose-dependently. 0.5mM chlorogenic acid decreased the sensor output for these drugs by up to 46.0 ± 3.6% The sensor outputs for bitter acidic drugs tested at 0.8mM were reduced but less effectively by addition of 0.3, 0.8, 1.4mM chlorogenic acid. 0.8mM of chlorogenic acid (1:1 with drug) inhibited bitterness by up to 12.2 ± 1.3% [52]	Chlorogenic acid as a crystalline solid is stable for at least two years but it is recommended that the solution is not kept for more than one day due to poor stability [108] The solubility of chlorogenic acid in phosphate-buffered saline (pH 7.2) is 25mg/mL. Commercially available from Sigma
Overall score = 14 Limitations; not stable in solution for long period of time		**Safety score = 3** (GRAS and patented for human use and present in high quantities in the human diet)	**Efficacy/QoE score = 1** (not shown in a human panel)	**Usability score = 1** (not stable in solution for long periods of time and low solubility but could have use for extemporaneous preparations)
• **Abscisic acid** **Abscisic acid is a plant hormone** [54] **Assessed using HEK293T cells expressing TAS2Rs** [54]	Pharmacological characterisation confirms that abscisic acid acts as an antagonist at T2R4 [54]	Abscisic acid is found in fruits and vegetables such as blueberries, with a concentration of around 30 µg/g [54] which equates to 180.8 µM. It has also been reported that abscisic acid is endogenously produced by insulin	Abscisic acid antagonises 1 mM quinine at T2R4 with an IC50 value of 34.4 ± 1.1 µM. However, this study found that known T2R4 'agonists' were not able to activate the receptor so a reliable conclusion cannot be thoroughly drawn as to its efficacy [54]	Abscisic acid needs to be in solution to confer efficacy but is soluble in ethanol and DMSO and requires storage at -20 degrees centigrade [109] Commercially available from Sigma

		secreting cells in humans [106] Abscisic acid has GRAS status No ADI exists at present [107]		
Overall score = 11 Limitations; study which demonstrated efficacy came to unreliable conclusions and is insoluble in biocompatible media		**Safety score = 3** (found in human diet and GRAS)	**Efficacy/QoE score = 0** (unreliable evidence from study, with known T2R4 agonists not able to activate the receptor)	**Usability score = 1** (Needs to be in solution to have effect but soluble in inappropriate media and requires specific storage)
Flavanoids				
• **4′-fluoro-6-methoxyflavanone, 6,3′-dimethoxyflavanone, and 6-methoxyflavanone** **Assessed using HEK293 cells expressing TAS2R39 and hTAS2R14** [42]	It is likely the flavanones 4′-fluoro-6-methoxyflavanone, 6,3′-dimethoxyflavanone, and 6-methoxyflavanone are antagonists of TAS2R39 [42]	The safety of 4′-fluoro-6-methoxyflavanone is unknown No precedence of use found	In vitro assays show the flavanones; 4′-fluoro-6-methoxyflavanone, 6,3′-dimethoxyflavanone, and 6-methoxyflavanone (in order of decreasing potency) to inhibit the activation of TAS2R39 by 1.7mM denatonium, 4′-fluoro-6-methoxyflavanone eliminated the response completely. The three flavanones also inhibited the activation of hTAS2R14 but to a lesser extent [42]	Solubility/ stability data for 4′-fluoro-6-methoxyflavanone, 6,3′-dimethoxyflavanone, and 6-methoxyflavanone is not readily available Not commercially available
Overall score = 3 Limitations; not enough information available on usability or safety		**Safety score = 0** (not enough information known)	**Efficacy/QoE score= 1** (cell based model of only two bitter receptor subtypes)	**Usability score = 0** (not enough information known)
• **Substituted 3-(pyrazol-4-yl) imidazolidine-2,4-diones** • **3- (1- ((3,5-dimethylisoxazol-4-yl) methyl)-1H-pyrazol-4-yl)-1- (3-hydroxybenzyl)imidazolidine-2,4-dione** • **3- (1- ((3,5-dimethylisoxazol-4-yl)methyl)-1H-pyrazol-4-yl)-1- (3-hydroxybenzyl)-5,5-**	These compounds selectively antagonise hTAS2R8 (IC_{50}'s = 0.035 and 0.073µM) [50]	Both compounds are GRAS for use as an excipient A full toxicological report found that the no observable averse effect level (NOAEL) for each compound is orders of magnitude above the expected human exposure [110]	Both substituted 3-(pyrazol-4-yl) imidazolidine-2,4-diones have been shown to significantly attenuate the bitter taste of a variety of bitter tastants including caffeine (1mM) in cell models expressing TAS2R8 [50]	Both insoluble in water. Require ethanol to solubilise [50] Commercial availability cannot be found

dimethylimidaz olidine-2,4- dione

Assessed in HEK293 cells expressing hTAS2R8 [50]

Overall score = 11 Limitations; insoluble in suitable media and limited evidence of efficacy	**Safety score = 2**	**Efficacy/QoE score= 1** (single receptor expressing cell line)	**Usability score = 1** (insoluble in suitable media and not available to purchase)
• **Triphenylphosp hine oxide (TPPO)** **Assessed in Hek293 cells expressing TRPM5** [51]	TPPO selectively inhibits the TRPM5 receptor. TRPM5 is activated by intracellular calcium release after taste cell activation by sweet, bitter and umami tastants [2] and so by blocking here these taste signals cannot be transduced.	TPPO is reported as very toxic at high levels [111]. A reference dose of 0.02mg/kg-day has been extrapolated with safety margins from dog toxicology studies [112]. This would mean a 70kg person can be exposed to a maximum of approximately 5.03µM per day, which is well below the IC_{50}.	TPPO inhibited human TRPM5 heterologously expressed in HEK293 cells (IC_{50} = 12µM) [51]	TPPO is almost insoluble in deionized water. It is soluble in ethanol, formic acid, acetic acid, and dichloromethane [113] Unsafe to use as doses required for bitter blocking. It is commercially available from sigma
Overall score = 3		**Safety score = 0** (efficacious concentration from study could be toxic in humans)	**Efficacy/QoE score= 1** (efficacy shown in model of only TRPM5 and this will affect other taste sensations)	**Usability score = 0** (insoluble in suitable media and unsafe at required doses)

Table 3a Bitter-blocking agents tested using human panels. Overall score according to 2 x usability, 3 x efficacy/quality of evidence and 3 x safety

Compound	Overall score
AMP	22
Sodium acetate	22
Sodium gluconate	22
GIV3727	20
Homoeriodictyol sodium salt	20
Citric acid	19
Sodium chloride + L-arginine	19
Phosphatidic acid + beta-lactoglobulin	17
Phosphatidic acid	14
2,4-dihydroxybenzoic acid vanillylamide	12
Riboflavin-binding protein	11

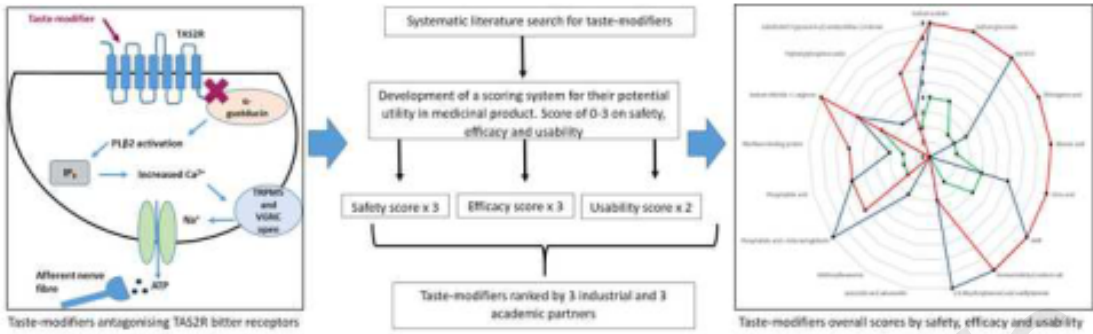| Jaceosidin and sakuranetin	0

Table 3b Bitter-blocking agents tested using non-human methods. Overall score according to 2 x usability, 3 x efficacy/quality of evidence and 3 x safety

Compound	Overall score
Chlorogenic acid	14
Substituted 3- (pyrazol-4-yl) imidazolidine-2,4-diones	11
Abscisic acid	11
Triphenylphosphine oxide (TPPO)	3
4'-fluoro-6-methoxyflavanone, 6,3'-dimethoxyflavanone, and 6-methoxyflavanone	3

Taste-modifiers antagonising TAS2R bitter receptors

Taste-modifiers overall scores by safety, efficacy and usability