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A Review of Theoretical Approach to Sweetness in Chemical Compounds

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ABSTRACT: *The relationship between humans and the sweet sensation is a challenge in itself. The concept of taste undergoes dynamic transformations throughout human civilization, reflecting individuals evolving preferences and experiences. Taste, as an experiential phenomenon, intricately involves the physiological aspects of the human body, with a direct correlation to signal transmission within the brain. The primary objective of this study is to unravel the chemical characteristics that contribute to the generation of sweet flavours. The research investigates the complex interplay between chemical structures and taste perception by utilizing a comprehensive review of literature from diverse sources, including books and scholarly articles from various publishers. Various analytical techniques, such as ligand-based glucophore modeling, quantitative structure-activity relationships, and the prediction and discovery of sweet receptors, are employed to understand the effects of chemical structures on sweetness. By exploring how the chemical composition of substances influences taste, this research aims to provide valuable insights into the molecular foundations of flavour, advancing our understanding of the complexities that underlie the human gustatory experience.*

Keywords: *glucophore; sweetness; sweet receptor; taste; QSAR*

1. Introduction

The history of human civilization has never been separated from food. Not only as a source of nutrition, but humans also tend to choose foods that will provide pleasurable sensations to their taste buds [1]. This instinct has been ingrained in our identity since the time of our ancestors, where it was used to distinguish and select which food sources are nutritious and safe for the body [2]. This concept is known as taste. Taste is a multidimensional phenomenon involving a combination of various physiological elements in the body. In theory, taste impulses captured by the taste buds will be transmitted to the brain through several cranial nerve pathways [2]. However, the perception of taste also heavily depends on other senses and tends to be integrated, such as with aromas detected by the nose and textures sensed by the somatosensory system [3]. Until the early 20th century, scientists believed that there were four primary tastes: sweet, sour, salty, and bitter. In 1908, Kikunae Ikeda discovered the concept of the fifth taste, umami [4]. Some experts proposed the addition of taste concepts like spicy, astringent, fatty, or metallic. However, the concept of the five basic tastes is still commonly used to this day [5].

The sense of sweetness is also a product of evolution as a human effort to detect easily digestible sources of glucose and other carbohydrates [6]. The concept of sweetness is believed to be known by all cultures and civilizations of humans and is intertwined with power dynamics [7]. A real-life example of this can be seen in the impact brought about by the cultivation of sugarcane (*Saccharum officinarum*) and sugar production. For hundreds of years, this commodity brought prosperity to European colonial empires but proved to be highly destructive to their colonial lands [8]. Natural sources of sugar are not only used as sweetening agents in food, but they also have other uses such as food preservation [9] and medicinal purposes [7]. For instance, honey has been long recognized for its potential as a therapeutic substance [10,11]. Interestingly, sugar was also used to be applied as a medicine, even during the Renaissance era in 16th-century Europe [12].

With the emergence of organic chemistry in the 19th century, more organic compounds were synthesized with the purpose of being used as therapeutic agents [13]. This led to the decreasing use of natural substances as primary therapeutic options [14]. On the other hand, the industrial revolution successfully promoted the more effective and efficient production of sugar. This era was also marked by the emergence of an alternative sugar source derived from beets (*Beta vulgaris*), which became quite popular and even dominated the sugar consumption market share by 1880 [15]. Towards the end of the century, the world's first artificial sweetener, saccharin, was discovered by Constantin Fahlberg and Ira Remsen [16]. This discovery raised the question, "What are the chemical characteristics that make a substance taste sweet?". At that time, the chemical structures of most naturally occurring sweet compounds had been identified, such as carbohydrates which possess distinctive chemical structures consisting of polyol groups with aldehyde or ketone groups. It is evidently different from saccharin, which had a benzene scaffold with a cyclic sulfonamide group (Figure 1). This then gave rise to a research field aimed at understanding the structure-activity relationship of molecules in providing sweetness, which we try to describe in chronological order.

2. Early theory of sweetness

The concept of structure-activity relationship was first proposed by Alexander Crum Brown and Thomas R. Fraser [17] (Crum Brown & Fraser, 1868), and it was quickly applied in various applications such as its influence on lipophilicity and toxicity [18]. This concept was later applied to taste prediction by Georg Cohn in the early 20th century. He hypothesized that a compound would impart a taste if it contained spe-

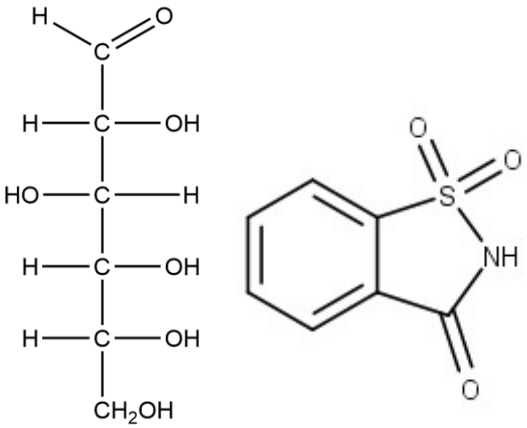
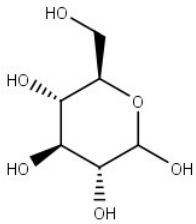
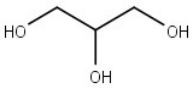
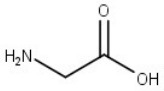
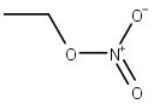


Figure 1. Chemical structure of glucose (using Fischer projection) (left) and saccharin (right)

Table 1. The functional groups that act as glucophores and auxoglucs based on Oertly-Myers

Compound	Glucophores	Auxoglucs
 Glucose	R-CO-CHOH-R’	-CH_2OH
 Glycerine	CH_2OH-CHOH-R	-CH_2OH
 Glycine	H_2N-CH-CO_2H | R	-H
 Chloroform	R-CCl_3	-H
 Ethyl Nitrate	R-CH_2-ONO_2	-CH_3

cific functional groups, called “sapophore”. Based on several observations, it was concluded that polyhydroxy compounds or compounds containing chlorine groups tend to provide a sweet taste [19]. Further studies conducted by Ernest Oertly and Rollin Myers stated that a sweet taste would only emerge in a compound if it had a combination of glucophore groups like 1,2-dihydroxy,

amino acids, haloalkanes, or alkyl nitrates, as well as auxogluc groups [20] (Table 1). This theory closely resembles the chromophore-auxochrome concept previously introduced by Otto Witt and is still commonly implemented in UV/Vis spectrophotometry methods [21].

Nevertheless, the Cohn-Oertly-Myers theory is still far from perfect. Many phenomena remain unexplained, such as the sweet taste produced by saccharin or the impact of stereoisomers on the sweetness level of certain carbohydrate compounds. Another subsequent theory that emerged is the influence of molecular resonance energy on sweet and bitter taste proposed by Yojiro Tsuzuki [22]. Moving into the mid-20th century, more general correlation models began to be developed. Aetius Lawrence and Lloyd Ferguson initiated this by exploring the influence of physicochemical property parameters on sweetness. Parameters such as surface tension, potential energy, and the difference in melting points between the solid and dissolved phases were used to find the best model that could describe the biological response of taste buds [23]. Several years later, Corwin Hansch and Toshio Fujita formulated the concept of the Linear Free Energy Relationship (LFER) based on parameters related to lipophilicity, steric effects, and electronic effects for biological activities [24]. This concept was then extended to predict the sweetness level of 2-amino-4-nitrobenzene derivatives [25,26], resulting in the following mathematical equation 1:

$$\text{LogRS} = 0.119\ \pi^2 + 1.485\ \pi - 1.848\ \sigma + 1.742$$

Where LogRS represents the logarithmic value of the relative sweetness level, π is the Hansch lipophilic constant, and σ is the Hammett electronic constant. This equation highlights the significant role, particularly of hydrophobic and electronic parameters. Additionally, that research stated that a compound needs to be ionized in water to interact with receptors on the tongue in order to elicit a sweet taste. Other influencing parameters include hydrophobic interactions, degree of polarity, charge distance, and electron density [26]. However, the model has limitations in terms of global application, as the data used only applies within a specific compound framework. Up to this point, a sufficiently satisfying model correlating molecular structure to sweetness taste has not been found.

3. Ligand-based glucophore modelling

The next approach developed by researchers involved elaborating on the glucophore concept through three-dimensional models of sweet-tasting compounds. In 1967, Robert Shallenberger and Terry Acree formulated the AHB (Acceptor-Hydrogen-Bond-Donor) system, which was assumed to play a role in providing a sweet taste. This system consists of A and B, which are electronegative atoms, where AH acts as the hydrogen bond donor and B as the hydrogen bond acceptor. According to their theory, the distance between AH and B in a molecule should be within a range of 3 Å to provide a sweet stimulus. This model can explain the sweet taste phenomenon of various types of compounds, including carbohydrates, amino acids, saccharin, and chloroform [27] (Figure 2). The model was later modified by adding steric hindrance factors to explain the enantiomer phenomenon, where mirror-image molecules have different taste responses, as seen in amino acids and sugars [28].

This theory was further developed by Lemont Kier. Building upon the concept of pharmacophore mapping for various classes of drugs that had already been developed [29], Kier proposed that the Shallenberger-Acree glucophore model should require an additional feature to improve the prediction of interactions with binding points on taste receptor proteins. He referred to this additional electron-rich feature as a dispersion point (X) [30]. This conclusion was in line with (Equation 1) that showed the contribution of electronic parameters [26] (Figure 2). This ap-

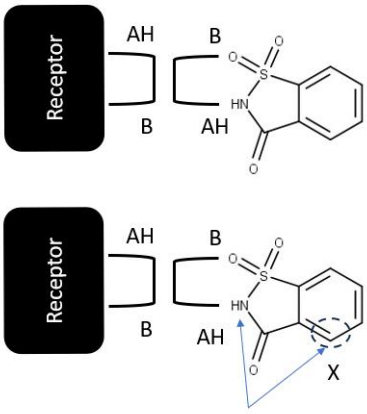


Figure 2. Two-dimensional map of glucophore hypothesis according to Shallenberger-Acree (above) and its modification by Kier (below), depicted by saccharin

Table 2. Sites and points of glucophore according to MPA theory

Glucophore sites	Glucophore points	Interaction types	Example
B	B1, B2	Ionic and/or hydrogen bond	Anion (COO^-, SO_3^-), hydrogen bond acceptor (N, O, F)
AH	AH1, AH2	Ionic and/or hydrogen bond	Cation (NH^+), hydrogen bond donor (NH, OH)
XH	XH1, XH2	Ionic and/or hydrogen bond	Cation (NH^+), hydrogen bond donor (NH, OH)
G1	G1, E1	Steric (G) and hydrogen bond (E)	Steric (CH_3, CH_2, CH, F, Cl, Br), hydrogen bond acceptor (N, O, F)
G2	G2, E2	Steric (G) and hydrogen bond (E)	Steric (CH_3, CH_2, CH, F, Cl, Br), hydrogen bond acceptor (N, O, F)
G3	G3, E3	Steric (G) and hydrogen bond (E)	Steric (CH_3, CH_2, CH, F, Cl, Br), hydrogen bond acceptor (N, O, F)
G4	G4, E4	Steric (G) and hydrogen bond (E)	Steric (CH_3, CH_2, CH, F, Cl, Br), hydrogen bond acceptor (N, O, F)
D	D	Hydrogen bond	CN functional group (optional)

proach complemented the Shallenberger-Acree theory in depicting the sweet taste across different compound classes, primarily focusing on amino acids in their zwitterionic form.

Kier's study marked the beginning of application of computational chemistry methods to glucophore mapping, with the use of the semi-empirical Extended Hückel Theory to depict the conformations of several amino acids [30]. This three-point glucophore model was then applied to several derivatives of sweet-tasting compounds, yielding reasonably good correlations [31-33], although different assumptions were used regarding the definition of the X group. Robert Shallenberger and Michael Lindley concluded that the X group represented an intramolecular hydrogen bond [33], while Yasuo Ariyoshi suggested that it played a role in forming hydrophobic interactions [32].

Furthermore, glucose-binding models specific to certain compound derivatives or functional groups have also been developed. A research group from Université Claude-Bernard conducted a study focusing on several sweet-tasting functional groups, such as nitro, cyano, and carboxylate [34,35]. Based on the information from these glucose-binding models, combined with the structural information of two artificial sweete–

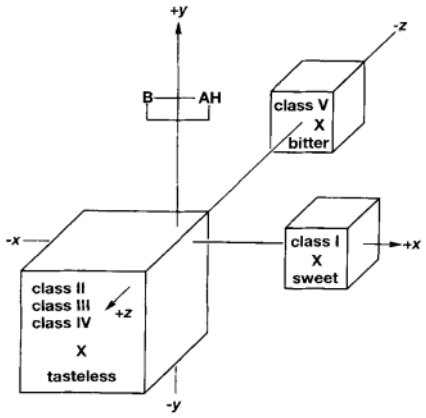


Figure 3. Structure-taste relationship based on three-dimensional molecular orientation of AH, B, and X moiety. α carbon of the second residue is located on (0,0,0). (Reprinted with copyright permission [40]).

ners, namely cyano-suosan and aspartame, they successfully discovered a new sweetener (superaspartame) with a sweetness level 14,000 times that of sucrose. This achievement was further pursued by designing new glucose-binding models based on the superaspartame model. By modifying the carbonyl group with N-alkyl imine, they managed to obtain several derivatives of superaspartame with even higher sweetness levels, reaching up to 200,000 times that of sucrose [36]. Based on these findings, Claude Nofre and Jean-Marie Tinti proposed the multi-point attachment (MPA) hypothesis [37]. They argued that for a compound to impart a sweet taste, 7-8 glucose-binding sites are required, each component involving ionic interactions, hydrogen bonding, and steric factors (Table 2).

Another specific glucose-binding model that has captured attention is the one developed based on aspartame and its derivatives. Since its accidental discovery in 1969 [38], various studies have been conducted to draw conclusions about the correlational model of peptide structure and the resulting sweet taste. Yasuo Ariyoshi initially proposed the hypothesis of aspartame derivative glucose-binding using Fischer projections and confirmed the validity of Kier's three-point glucose-binding theory, where the third group would form hydrophobic interactions [30,32]. Subsequent studies have also confirmed similar results [39]. This aspartame glucose-binding theory was further refined by the research group led by Murray Goodman, who combined X-ray crystallography data, NMR spectra, and molecular modelling to generate a comprehensive model. This model not only predicts sweetness but can also be used to explain the phenomena of derivatives that provide bitterness or have no taste at all [40] (Figure 3).

4. Quantitative structure activity relationships Approach

Since the formulation of the linear free energy equation model [24] and its application in predicting sweetness [26], several similar statistical approaches have been developed for various compound classes. Utilizing the same dataset [25], modifications have been made to the previously obtained quadratic regression model (Equation 1) by replacing σ Hammett parameter with the σ+ Brown-Okamoto parameter [41] and achieved a more optimal correlation [42]. This was done considering the resonance effects caused by nitro substituents and electron-donating groups positioned para to each other. However, various other studies on different structural frameworks also indicated the significance of lipophilic and steric parameters [39,43-46]. Based on observations of several variables utilized in these studies (Table 3), it can be noted that some variables describe

molecular bulkiness in a more directed manner. Among them is the STERIMOL Verloop parameter, which characterizes the three-dimensional nature of a molecule by evaluating the values of substituent lengths, minimum widths, and maximum widths. The calculation of STERIMOL values is computer-assisted, making it one of the earliest tools in computational chemistry applications [47]. Another parameter that serves a similar function is the Cartesian coordinate value of the substituent using the Corey-Pauling-Koltun spatial filling approach [48,49].

Complexity in formulating a correlational model is often encountered, where the Hansch equation model frequently fails to provide satisfactory results. This has led to the emergence of various new parameters beyond the three main variables in the free energy equation [24]. These various descriptors have been comprehensively summarized elsewhere [50]. However, we will focus on one example of a parameter commonly utilized in several modelling approaches, namely graph-based descriptors. This descriptor, also named topological descriptor, operates on the assumption that a molecular structure (excluding hydrogen atoms) is equivalent to a graph consisting of nodes (vertices) and edges. The molecular graph can be transformed into a matrix representing atom connectivity, which can then be converted into a single value and used as a descriptor. Unlike lipophilic, steric, and electronic variables that often require experimental data, topological descriptors only need structural information about the compound. Moreover, topological descriptors can yield a universal statistical model that encompasses various compounds, even from different structural frameworks [51]. Several types of topological descriptors have been applied in various studies (Table 3) [52-55], such as the Kier molecular connectivity index, the Randić index, and the Wiener index [56-58].

Approaching the 1990s, various new algorithms in the field of Quantitative Structure-Activity Relationship (QSAR) methods began to

Table 3. Various QSAR studies on sweetening class of compounds

Method and output	Class of compounds	Important variables*	References
Hansch linear equation to predict sweetness level	Nitroaniline	π, π^2, σ	[26]
Hansch linear equation to predict sweetness level	Nitroaniline	σ^+, Es	[42]
Hansch linear equation to predict sweetness level	Aspartame	f, P, B_5	[39]
Hansch linear equation to predict sweetness level	Perillartine	Log P, L, W_l, W_u	[43]
	Nitro and Cyanoaniline	L, W_l	[43]
Hansch linear equation to predict sweetness level	Amides of aspartic acid	σ^*, InA, $(Wu)_1$, $(Wu)_2$, $(Wr)_1$, $(Wr)_2$	[44]
	Aspartyl amino ester	σ^*, L_2, L_2^2, $(Wu)_1$, $(Wu)_1^2$, L_1	[44]
	Aspartyl amino propionate	σ^*, L_2, L_2^2, $(Wu)_1$, $(Wu)_1^2$, L_1, $(Wr)_2$, $(Wr)_2^2$	[44]
	Aspartyl amino acetic	σ^*, L_2, L_2^2, InM, L_1, L_1^2, InA, $(W_l)_2$	[44]
Clustering to classify sweet taste	Sulfamate	Molecular volume, Substituent length (x)	[45]
Discriminant analysis to classify sweet taste	Sulfamate	Substituent length (x), substituent width (z), $^1\chi_v$	[46]
Pattern recognition to classify sweet taste	Perillartine	Log P, $^1\chi_c$, $^1\chi_j$	[52]
Pattern recognition to classify sweet taste	Sulfamate	weighted path, self-returning walks	[53]

Method and output	Class of compounds	Important variables*	References
Discriminant analysis to classify sweet taste	Sulfamate	sum of atomic polarizability, X component of dipole moment, E LUMO, E HOMO, Log P, Z component principal of moment inertia, principal moment of inertia, $^{0}\chi_{v}$, $^{3}\chi_{v}$, B_2, B_4	[54]
PCA (Principal Component Analysis) to classify sweet taste		sum of atomic polarizability, molecular volume, E LUMO, E free dissolvation (in water), superdelocalizability, $^{3}\chi_{v}$, Z component of dipole moment, L, B_3	[54]
Genetic Algorithm based linear regression (GA) to predict sweetness level		X component of dipole moment, $^{0}\chi_{v}$, $^{1}\chi_{v}$	[54]
Neural Network to predict sweetness level		sum of atomic polarizability, Molecular volume, E LUMO, E free dissolvation (in water), superdelocalizability, $^{3}\chi_{v}$, Z component of dipole moment, L, B_3	[54]
Molecular Field Analysis (MFA)/ 3D-QSAR to predict sweetness level		probe H^+ & OH^-	[54]
Genetic Algorithm (GA) based linear regression to predict sweetness level	Disaccharide	Molecular weight, Chi-V-1, ROG, IAC-Total, Dipole-Y, Kappa-2	[55]
Molecular Field Analysis (MFA)/ 3D-QSAR to predict sweetness level		probe H^+, CH_3^+, CH_3^-	[55]
Partial Least Square (PLS) based linear regression to predict sweetness level	Guanidine	Wiener index, rotatable bonds, radius of gyration, JX, CIC	[55]
Molecular Field Analysis (MFA)/ 3D-QSAR to predict sweetness level		probe H^+, CH_3^+, CH_3	[55]
Partial Least Square (PLS) based linear regression to predict sweetness level	Various compounds	Wiener index, SC-3-C, SC-0, Chi-V-0, ALogP, Dipole-Y	[55]
Molecular Field Analysis (MFA)/ 3D-QSAR to predict sweetness level		probe H^+, CH_3^+, CH_3^-	[55]
Genetic Algorithm (GA) based linear regression to predict sweetness level	Isovanillin	radius of gyration, E HOMO, E LUMO, Vm, Shadow_XY	[61]
Molecular Field Analysis (MFA)/ 3D-QSAR to predict sweetness level		probe H^+, CH_3^+, CH_3^- , CH_3	[61]
Pattern recognition to classify sweet taste	Sulfamate	Molar refractivity, L, B_1, B_0	[63]

Method and output	Class of compounds	Important variables*	References
Pattern recognition to classify sweet taste	Aspartame	Molar refractivity, W_r, W_l, W_u, W_d	[64]
Pattern recognition to classify sweet taste	β-(3-hydroxy-4-methoxyphenyl)ethylbenzene	Molar refractivity, L, B_1, π, σ_m, σ_p	[65]
Linear Learning Machine (LLM) to classify sweet taste	Perillartine	Log P, L, W_r, W_l, W_u, W_d	[62]
Multivariate image analysis (MIA) based QSAR to predict sweetness level	Disaccharide	Bitmap images	[70]
	Guanidine	Bitmap images	[71]
Multi-linear regression to predict sweetness level	Sucrose	Ionization potential	[72]
	Guanidine	Ionization potential, molar refractivity, heat of formation	[72]
k-Nearest Neighbor classification to classify sweet taste	Various compounds	BIC3, CATS2D_05_AL, mRNH2, GATS6v, GATS7v, AVS_B(e), SpMax_B(i), B03[O-O], F03[N-O], SM4_B(s), C-026, F01[C-N], CATS2D_04_AL	[73]
k-means clustering to predict sweetness level	Various compounds	AAC, CATS2D_02_PN, CATS2D_05_LL, ALogP, ATSC6p, B07[C-N]	[74]
N-nearest Neighbor to classify sweet taste	Various compounds	F03[N-O], Uindex, CATS2D_04_AL, CATS2D_05_AL, C-026, nCconj	[75]
Partial Least Square Discriminant Analysis to classify sweet taste		F03[C-S], MATS1s, CATS2D_02_DN, CATS2D_04_AP, ARR, D/Dtr07	[75]
Partial Least Square (PLS) based linear regression to predict sweetness level	Various compounds	Mean atomic van der Waals volume, MLogP, number of Oxygen atom, C-040, F04{C-N], number of heavy atoms, B07[N-O]	[76]
Genetic Function Approximation to predict sweetness level	Various compounds	ALogP, χ indices, κ indices, element count, electrotopological state keys, electrostatic energy, E LUMO, valence energy	[77]
Artificial Neural Network to predict sweetness level		Not available	[77]
Multiple linear regression to predict sweetness level	Various compounds	SMILES-based descriptor (DCW_H)	[78]
Multiple linear regression to predict sweetness level	Amides of aspartic acid	Vibrational spectra eigenvalues (EVA)	[79]
Multiple linear regression to predict sweetness level	Various compounds	SMILES-based descriptor (DCW_H)	[80]
Deep learning to classify sweet taste	Various compounds	Qed, molecular weight, molecular weight of heavy atoms, exact molecular weight, electron valence number, BertzCT, Kappa 3*, Labute ASAm SLogP_VSA2, TPSA, Chi 0, Hall-Kier Alpha, SMR_VSA5, Estate_VSA1, VSA_Estate9, Mol MR, fr_C_O, fr_C_O_noCOO, fr_ether	[81]
Various machine learning-based methods to predict sweetness level	Various compounds	Not available	[82]

emerge. This development was supported by the increasing capabilities of computers to process data and the availability of a growing number of software tools for molecular modelling. One significant advancement during this era was the three-dimensional QSAR modelling using methods based on Molecular Field Analysis. In this approach, a set of compound conformations in three-dimensional space would be overlaid and positioned within a box with a specific grid spacing. This grid, subsequently referred to as a grid, would serve as the point for evaluating the steric and electronic energy of the conformer ensemble. The results would yield a quantitative relationship equation based on the spatial dimension of the compound set, providing information about the areas influencing their biological activity. This method was introduced by Richard Cramer III through the CoMFA (Comparative Molecular Field Analysis) software, which also became a standard protocol in three-dimensional QSAR studies [59,60]. Numerous studies have applied this method with the goal of mapping active conformations and identifying functional groups that play crucial roles in the sweet taste contribution through both steric and electronic approaches for compound classes such as sulfamates, isovanillin, disaccharides, and guanidines [54,55,61].

Moreover, QSAR methods have expanded beyond linear free energy equations. Various pattern recognition-based algorithms have also been employed in building structure-taste relationship models [52-54,62-66]. One example of a derivative class that has been extensively explored using Quantitative Structure-Activity Relationship (QSAR) methods is the sulfamate group, which was also discovered accidentally [67]. Targeted studies initially began with hypotheses specific to this compound class [68,69]. Subsequent studies aimed to refine these hypotheses using QSAR approaches. William Spillaine and Grainne McGlinchey used semi-quantitative structure-activity relationship methods to predict the characteristics of alkyl (R) groups attached to sulfamate moieties (R-NHSO3-) that would contribute to sweetness. Using a linear free energy equation approach, they concluded that the CPK volume of the alkyl group should fall within the range of 90-250 $Å^3$ A research group from Toyohashi University of Technology applied SIMCA methods to classify sulfamate compounds with sweet taste potential using descriptors such as STERIMOL [63] and connectivity indices [53]. Furthermore, a comprehensive study was conducted by William Spillaine's research group regarding QSAR of cyclamate derivative compounds, employing various statistical approaches like linear regression equations, Principal Component Analysis (PCA), Linear Discriminant Analysis (LDA), Genetic Algorithm (GA), Neural Network (NN), and MFA. The results demonstrated that the MFA method outperformed other methods in predicting the sweetness level of new sulfamate derivative compounds. Additionally, it was found that Log Kw values (lipophilicity parameter based on HPLC data) and σ* values (modified Hammett parameter for polar aliphatic groups) played roles in the structure-taste correlations, although the correlation parameters obtained were not yet optimal [54].

5. Prediction and discovery of sweet receptor

The existence of receptors involved in taste perception was known since the mid-20th century, with their discovery in animals [83]. It was later hypothesized that taste perception phenomena could be modelled as ligand-receptor interactions [84]. However, their existence in humans was not fully confirmed throughout the 20th century. Several studies were conducted during this century to map the binding points of taste receptors, such as those by Robert Cagan, who used various types of radioligands to study the interaction patterns between compounds and taste receptors [85,86]. Another approach used was conformation-based ligand modelling. Essentially, this method is identical to the glucose-binding model described earlier, where it refers to the three-dimensional

structure of several sweet-tasting ligands. This method was first introduced by creating a three-dimensional conformation model of aspartame based on NMR elucidation, Ramachandran plots, and conformational energies [87]. This model then led to the hypothesis of the binding site shape on sweet receptors, which was further developed to accommodate other compound classes like saccharin, oximes, and nitroanilines [88]. Building upon these findings, the Unilever research group also formulated a receptor binding site hypothesis model based on aspartame, referring to different conformers than those used previously [39]. However, both models were created using fairly flexible dipeptide compounds, which should be taken into consideration [89]. Another model formulated using computational molecular modeling, which used a dataset of aspartame derivative compounds constructed in three-dimensional conformations with the early version of MMFF force field [90] and the semi-empirical INDO/S method for electrostatic energy calculations [91]. The results obtained not only included the topology of the receptor binding site and locations of ionic interactions but also mapped hydrophobic regions, as well as positive and negative partial charges [92] (Figure 4).

A significant discovery occurred at the beginning of the millennium, where the receptors responsible for the perception of sweetness were successfully identified in humans and mice [93-95]. These receptors were named T1R2 and T1R3 (Taste receptor type 1 members 2 & 3) and belong to the GPCR (G-coupled protein receptors) family, along with the previously discovered bitter and umami taste receptors [96-99]. Generally, GPCRs consist of a seven-helix transmembrane protein domain (TMD) and an extracellular domain referred to as the Venus Fly Trap Module (VFTM) [100] (Figure 5). Both are connected by a Cysteine Rich Domain (CRD). However, the 3D structure of these proteins has not yet been determined. Therefore, the homology modeling approach is used to predict the 3D structure of the protein and its ligand interaction mechanism. Using amino acid sequence information and the structure of reference proteins (templates), the tertiary or quaternary structure of a protein can be accurately predicted [101]. Pierandrea Temussi used this method to predict the structures of T1R2 and T1R3 utilizing amino acid sequences obtained from previous research and referring to the structure of the mouse mGluR1 receptor available in the Protein Data Bank repository (PDB ID: 1EWV) [93,102,103]. The 3D structure of the protein obtained was then used as the interaction target for several sweet-tasting proteins (brazzein, monellin, and thaumatin) using mo-

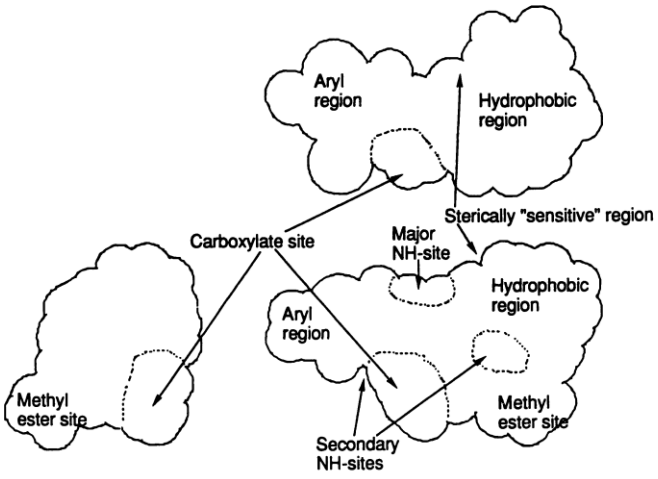


Figure 4. Van der Waals surface of the sweet receptor site model according to Culberson & Walters. (Reprinted with copyright permission [92])

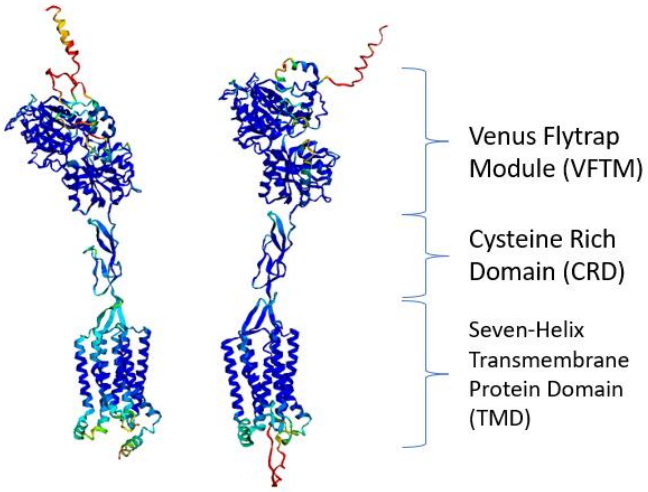


Figure 5. Model of human sweet receptors T1R2 (left) and T1R3 (right) (modelled using ColabFold 1.5.2 [113])

lecular docking methods [104-106]. The simulation results showed stable interactions with the T1R2-T1R3 receptor complex [102]. Similar studies were also conducted elsewhere using sweeteners such as neotame and superaspartame with the T1R3 receptor [107]. It was subsequently discovered that the structure of sweet receptors always exists in the form of the T1R2-T1R3 heterodimer, leading several homology modeling studies to reference both templates [108,109-112].The structure of mGluR1 receptors is known to have two conformations, namely Conformation I with an open-open shape (PDB ID: 1EWT) and Conformation II with an open-close shape (PDB ID: 1EWV), with the latter conformation being associated with ligand binding (PDB ID: 1EWK) [103]. Consequently, the heterodimer structure of sweet receptors should have four conformers, two for each T1R2 and T1R3 subunit [109]. The differences between these conformers refer to the structure of lobes 1 and 2 (LB1 and LB2) in the VFTM domain, where ligand-receptor binding sites are located. Some ligands are known to occupy these binding sites, such as aspartame, neotame, as well as various carbohydrate compounds [107,114,115]. Interestingly, findings from Senomyx indicate that in vitro tests show that both artificial sweeteners interact with the VFTM domain of the T1R2 unit only, which differs from previous predictions that suggested them as ligands for the T1R3 unit [107,114]. Furthermore, other binding sites have been successfully identified in vitro, such as in the CRD domain of the T1R3 unit for brazzein, transmembrane proteins for cyclamate and lactisole [116,118], and several allosteric modulators that enhance the sweet taste of a compound [119,120].

6. Latest development and prospects in the future

Since the formulation of the Setúbal Declaration in 2002 and its formalization by the Organization of Economic Cooperation and Development (OECD) in 2007, the quantitative structure-activity relationship (QSAR) methods must be rigorously validated based on established statistical principles [121,122]. This principle applies to all types of QSAR models, including those related to structure-taste correlations. During its implementation, the five principles of 'Good QSAR Practice' based on the OECD have presented various challenges that model makers in the field of QSAR must consider (Table 4). The majority of sweet-taste structure-activity relationship models developed over the past two decades have been in accord to these principles (Table 3). An-

Table 4. QSAR principles according to OECD [125]

Principles	Definition	Challenges
Defined end-point	Dependent variable (biological activity or physicochemical properties) should be accurately measurable.	Obtaining ideally homogeneous response data from a single testing center or at the very least from the same testing protocol.
Unambiguous algorithm	The algorithms used should be transparent, unambiguous, and reproducible.	Obtaining reproducible independent variable data, considering that descriptor calculation algorithms can significantly differ between different software tools.
Defined domain of applicability	QSAR models should be predictive for compounds with specific response values, including both biological activities and physicochemical properties.	Mapping to the extent which QSAR model can be applied to a specific group of compounds and ensuring that its implementation is not extrapolative.
Appropriate measures of goodness-of-fit, robustness, and predictivity	The importance of QSAR models lies in their ability to meet both internal and external validation parameters.	A wide range of parameters that can be used for validation, and achieving consensus among experts on the mandatory validation.
Mechanistic interpretation (if possible)	If possible, a good QSAR model should be able to explain the influence of the descriptors used on the response variable	It's not uncommon for models that are highly interpretable to provide less adequate validity.

other interesting observation in this trend is the increasing diversity of compound datasets. The so-called global model approach has the advantage of including various compounds with identical responses in a single QSAR model. This makes the resulting model more robust and applicable to a broader range of compounds compared to local models that only use compounds from a single group [123,124]. An early study using the global model approach involved 3D QSAR modeling of 149 compounds from four different groups [55]. Subsequently, research by Cristian Rojas and his team also employed high-diversity compound datasets to establish correlations between structure and sweet taste and to create classification models distinguishing sweet and non-sweet compounds [73-75]. Other studies have focused on specific descriptor usage, statistical parameters, or specific software, and have even incorporated artificial intelligence [78,79,81,82]. On the other hand, local QSAR modeling approaches have not been entirely abandoned. Some studies still focus on specific groups of sweet compounds, such as saccharides, guanidines, and dipeptides [70-72, 79].

The rapid development in the field of combinatorial chemistry has enabled the rapid synthesis of diverse compounds. This has led to the creation of numerous compound databases that can be screened for bioactivity [126]. The testing of compounds in these libraries can be expedited and made more cost-efficient through virtual screening using computer-based methods. This approach is known as virtual screening and is commonly used in the discovery and development of new drugs. Virtual screening can be classified into two types: ligand-based, where information about active compounds is used as the starting point for the search, and structure-based, where information about the target receptor and

biological activity is required [127]. This method has successfully identified several new sweet compounds [128-130].

Virtual screening process, especially the ligand-based approach, has become easier to perform with the availability of various supporting sources, such as curated databases of sweet compounds from the literature, and web servers that provide modeling methods [131,132,133-136]. So far, the majority of models used still employ machine learning methods with descriptors that may not be easily correlated with compound-receptor interactions. This "black-box" approach is commonly used in various QSAR models, especially those used in prediction software and web servers. This is because one of the OECD points does not emphasize the obligation of interpretation for a model (Table 4). In the future, it would be beneficial to consider model interpretability in model construction. This can be achieved by using easily understandable descriptors (physico-chemical parameters, functional groups, etc.) and by making machine learning-based statistical models more interpretable [137]. On the other hand, significant challenges still need to be addressed in structure-based virtual screening approach. As mentioned earlier, due to the absence of a 3D structure of the human sweet receptor, the structure must be constructed from its amino acid sequences and then transformed into its quaternary form using structural references from sweet receptors in other species. Further verification is also required regarding the dynamics of their interactions over a specified period using molecular dynamics methods to obtain a representation closer to the real conditions in a biological system [138]. Over the past decade, an increasing number of homology models have been developed with improved accuracy. Some interesting findings include the orthosteric binding site volume of the T1R2-T1R3 receptor, which is approximately 4900 $Å^3$, allowing interactions with both small and large sweet compounds [139]. Various modifications in the quaternary structure construction have been made, such as comparing different software tools to obtain the best methods, using the sweet receptor from the Medaka fish (PDB ID: 5X2M) as a structural reference, and implementing molecular dynamics simulations in the receptor model [140-144].

The primary method in structure-based virtual screening is molecular docking, which simulates ligand-receptor interactions as a lock-and-key Fischer model. One way to evaluate the results of this process is by selecting compounds with the best docking scores and assessing ligand-amino acid residue interaction compatibility [145]. Before using molecular docking methods, their validity must be confirmed through various statistical parameters, such as RMSD and AUC ROC values [146]. Another challenging parameter is the linear correlation between docking scores and biological responses, in this case, the level of sweetness. A study has attempted to demonstrate a linear relationship between the two [147]. However, it still requires support from larger and more diverse sweet compound datasets and the use of various software tools. Molecular docking methods should also be supported by *in vitro* and *in vivo* testing to verify the computational results [148]. As research in the field of GPCR (G-protein-coupled receptors) continues to advance, it is highly possible that other receptors suitable as templates will be discovered [149]. Additionally, there is the potential for the T1R2-T1R3 receptor itself to be stored in the PDB repository. This would significantly aid researchers in better understanding the interactions between sweet compounds and sweet receptors.

Conclusion

This review examines sweetness in chemical compounds and the methodologies employed to analyze and forecast their sweetness levels. The primary focus of the study revolves around the concept of glucophore, incorporating diverse techniques such as the LogRS approach, three-dimensional modelling of sweet compounds, and

utilizing computational chemistry methods to map glucophores.

Various methodologies for predicting sweetness levels, including the Hansch linear equation, discriminant analysis, pattern recognition, Principal Component Analysis (PCA), genetic algorithm-based linear regression, neural networks, and Molecular Field Analysis (MFA)/3D-QSAR, are applied to a range of compounds, including Nitroaniline, Aspartame, Perillartine, Sulfamate, Disaccharide, Guanidine, and Isovanillin.

Furthermore, the research uses the three-dimensional structure of proteins as interaction targets for sweet-tasting proteins like brazzein, monellin, and thaumatin, employing molecular docking methods. Simulation outcomes reveal stable interactions with the T1R2-T1R3 receptor complex. Nevertheless, the study confronts significant challenges attributed to the absence of a three-dimensional structure of the human sweet receptor. Consequently, the structure must be constructed from amino acid sequences and transformed into a quaternary form using structural references from sweet receptors in other species. Additional verification is imperative regarding the dynamics of their interactions over a specified period using molecular dynamics methods to attain a representation closer to natural conditions in a biological system.

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