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Sugars and Sweeteners: Structure, Properties and *in silico* Modeling

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Abstract: Several studies report the effects of excessive use of sugars and sweeteners in the diet. These include obesity, cardiac diseases, diabetes, and even lymphomas, leukemias, cancers of the bladder and brain, chronic fatigue syndrome, Parkinson's disease, Alzheimer's disease, multiple sclerosis, autism, and systemic lupus. On the other hand, each sugar and sweetener has a distinct metabolic assimilation process, and its chemical structure plays an important role in this process. Several scientific papers present the biological effects of the sugars and sweeteners in relation to their chemical structure. One important issue dealing with the sugars is the degree of similarity in their structures, focusing mostly on optical isomerism. Finding and developing new sugars and sweeteners with desired properties is an emerging research area, in which *in silico* approaches play an important role.

Keywords: monosaccharides; disaccharides; glucose isomers; carbohydrates; diet; quantitative structure-taste relationships (QSTR).

1. INTRODUCTION

Clinical studies show that consumption of sugar and sugar-sweetened beverages increase the risk of excessive weight and obesity [1,2], cardiac diseases [3,4], diabetes [5] or other chronic diseases such as periodontal disease [6]. Despite this fact, the consumption of sugar and sugar-sweetened beverages remains a controversial topic because it is practically impossible to control all variables in clinical studies [7,8]. Furthermore, consumption of sugars could not be controlled essentially since up to 75% of all foods contain added sugar in different forms [9] and sugar could be a contributor to foods and overall diet patterns [10,11]. The potential linkage between consumption of sugars and/or sweeteners and chronic diseases has had effects on both public health and public policies. Guidelines issued by different organizations recommend different upper limits of added sugar. The World Health Organization (WHO) and the Scientific Advisory Committee on Nutrition (SACN) in England [12,13] recommend a limit of added sugars up to 5% of overall caloric consumption while the Dietary Guidelines Advisory Committee in USA [14] recommends an upper limit of 10%. The highest upper limit of carbohydrates intake of 25% reported to the overall calories is considered safe by both the European Food Safety Authority (EFSA) [15] and the Institute of Medicine (IOM) of the USA [15].

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A significant scientific effort was aimed at development of (non-caloric) artificial sweeteners (NAS) such as aspartame (E951, European Union [17]), sucralose (E955, [18]), saccharin (E954, [19]), neotame (E961, [20]), acesulfame K (E950, [21]), and cyclamate (E952, [22]). The food additives belonging to low or non-caloric sweeteners are regulated in the European Union by the European Commission, Parliament and Council, with an E number in the range of E900-999. Several examples of NAS with their main characteristics including Acceptable Daily Intake (ADI, according with Food and Drug Administration (FDA) in the US and respectively Joint FAO/WHO Expert Committee on Food Additives (JECFA), and the European Food Safety Authority (EFSA) in the EU) are presented in Table 1.

The Introduction section should include the background and aims of the research in a comprehensive manner, for the researchers.

Table 1. Low (LAS) or non-caloric (NAS) artificial sweeteners (NAS) characteristics

Name	E index	Discovered in	Used in EU since	ADI adults (mg/kg body weight)	
				EU [23-26]	US [27,28]
saccharin	E954	1879	1887	5	5
steviol glycosides	E960	1901	2011	4	12
cyclamate	E952	1937	1954	11	7
aspartame	E951	1965	1983	40	50
acesulfame-K	E950	1966	1983	9	15
sucralose	E955	1976	2000	15	5
neotame	E961	1990	2010	2	0.3

The hypothesis of a link between diet and several diseases (such as cardiovascular [29,30], excessive weight and obesity [31,32], diabetes [33,34]) has been investigated by researchers worldwide. However, the link appears to be related to the quantity of refined carbohydrate and sugar [35] not with their presence in the diet given that the intake has

increased over the years. For example, in the Greenland Eskimos, the intake of refined carbohydrate increased 5–7-fold from 1855 (18 g/day from bread) to the 1970s (84–134 g/day from bread, biscuits and rye flour) [36]. An increase of up to ~135% in the consumption of sugar-sweetened beverages between 1977 and 2001 has been reported in the US [37].

The effects of NAS on human health are controversial due assignment to randomized controlled studies [38]. Suez *at al.* demonstrated that the consumption of NAS induces compositional and functional alterations to the intestinal microbiota and finally leads to development of glucose intolerance [39,40]. Lakhan and Kirchgessner hypothesized an association between fructose consumption and cognitive decline [41] but Chiavaroli, Ha, de Souza, Kendall, and Sievenpiper showed that this hypothesis cannot be confirmed because of the lack of high quality evidence directly assessing the role of fructose in cognitive decline [42]. Brunkwall, Chen, Hindy, Rukh, Ericson, Barroso, Johansson, Franks, Orho-Melander, and Renström concluded that the relation between sugar-sweetened beverages and body mass index is stronger in people genetically predisposed to obesity [31]. Positive effects (such as anticonvulsant effect [43], analgesia [44], prebiotic effect [45]), as well as negative effects (such as carcinogenicity, genetic damage, changes in body weight [46,47], and preterm delivery [48]) of artificial sweeteners, have also been reported.

Despite the fact that the acceptable daily intake of the low or non-caloric artificial sweeteners is known and stipulated in nutrition guidelines, only the name in several cases is available on the labels of the food products, and there is no specification of the amount.

In the contentious and controversial debate related to sugars and sweeteners, it is of the utmost importance that researchers have a firm grounding in their chemical structures and properties. The chemical structure and properties of sugars and sweeteners is basic for *in silico* modeling, the first step in the identification of new desired calories possessed by sweeteners. This manuscript aims to present concisely the knowledge related to sugars and artificial sweeteners, from structural features to sweetness and characterization of the links between them by *in silico* approaches.

2. CARBOHYDRATES

Sugars are short chain carbohydrates, a biological molecule consisting of carbon (C), hydrogen (H) and oxygen (O) atoms (general formula $Cm(H_2O)_n$). Carbohydrates are a structural component of cell walls in plant and algae such as cellulose [49], of DNA - deoxyribonucleic acid [50] or RNA - ribonucleic acid [50], or of tissues (lyxose). Carbohydrates are divided in four main groups as shown in Table 2 [51].

Table 2. Main groups of carbohydrates and their characteristics

Group	Name	Atoms/Group	Remarks
monosaccharides	simple sugars	3 to 9 carbon atoms	Sharing the same formula $C_6H_{12}O_6$ but with different structural arrangements (structural isomers): • Glucose: 'blood sugar' • Fructose: 'fruit sugar' • Galactose: milk and yogurt sugar
disaccharides	double sugar		• Sucrose: glucose + fructose • Lactose (milk sugar): glucose + galactose • Maltose: glucose + glucose
oligosaccharides		3 to 6 monosaccharides	• Human milk oligosaccharides: 200 discovered, ~100 characterized [52-54] • Soybean oligosaccharides (neutral sugar, galactose, xylose, rhamnose, arabinose, mannose, glucose, fructose) [55,56] • Other sources with different characteristics: inulin [57], raffinose and stachyose [58]
polysaccharides	many sugars	large molecule that may contain hundreds of monosaccharides	Hundred of distinct types were identified. • Cellulose, callose, pectin: plant cell wall [59-61] • Starch and glycogen: reserve polysaccharides [62,63] • Chitin (α, β, γ) [64,65] and glycosaminoglycans [66]

The simplest carbohydrates are the monosaccharide whose general formula is $(CH_2O)_n$, where n ranges from 2 (diose, H-(C=O)-(CH_2)-OH, $C_2O_2H_4$) to 7 (n = 3 triose - e.g. glyceraldehyde, n = 4 tetrose, n = 5 pentose - e.g. ribose and deoxyribose, n = 6 hexose - e.g. fructose, glucose and galactose, n = 7 heptose) (see Table 3). However, not all compounds of this class follow this general formula; see for example deoxyribose ($C_3O_4H_{10}$).

The monosaccharides with fewer atoms (e.g. n = 3 and n = 4) may cyclize by dimerization forming cyclic monosaccharides with n=6 and n=8, respectively (Figure 1).

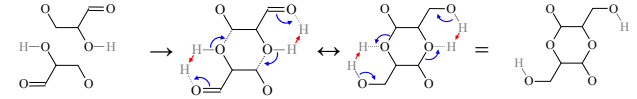


Figure 1. Dimerization of monosaccharides by example

Table 3. Monosaccharides from triose to hexose (*oses for aldose and *ulose for hetoses)

n=	Formula	Aldoses				Ketoses	
3	$C_3H_6O_3$	D-glyceraldehyde				D-dihydroxyacetone	
4	$C_4H_8O_4$	D-erythose		D-threose		D-erythrulose	
5	$C_5H_{10}O_5$	D-ribose	D-arabinose	D-xylose	D-lyxose	D-xylulose	D-ribulose
6	$C_6H_{12}O_6$	D-talose	D-gulose	D-altrose	D-glucose	D-psicose	D-tagatose
		D-galactose	D-idose	D-mannose	D-allose	D-sorbose	D-fructose

From n = 5, the monosaccharides are also stable in their cyclic tautomeric form (see Figure 2), the lactol being more common in nature, compared with aldose.

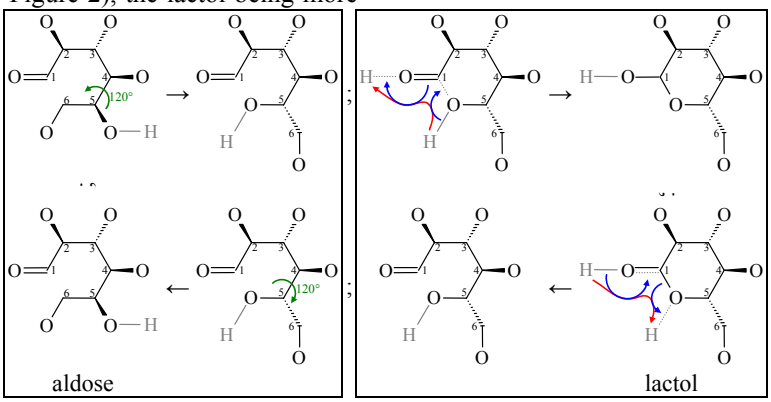
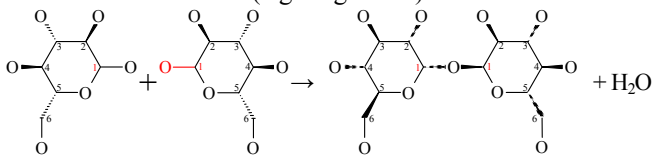


Figure 2. Transition states in tautomerization of a monosaccharide (e.g. D-glucose)

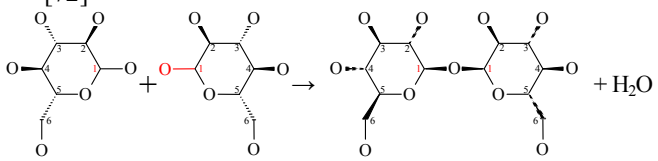
Living organisms use monosaccharides as a source of energy [67,68]. When the available monosaccharides are not needed, they are converted into glycogen and lipids in animals and humans [69,70] and into starch in plants [62,63].

A disaccharide is formed whenever two monosaccharides (identical or not) are joined. Two identical monosaccharides can form disaccharides: several examples are depicted below:

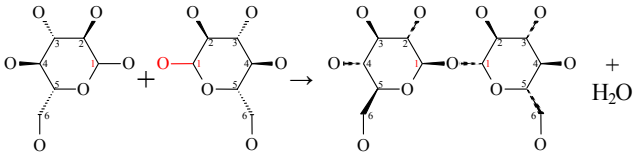
1. 2×Glucose in alpha-alpha 1-1 linkage → α,α-trehalose (natural alpha-linked disaccharide) [71]



2. 2×Glucose in alpha-beta 1-1 linkage → α,β-trehalose [72]

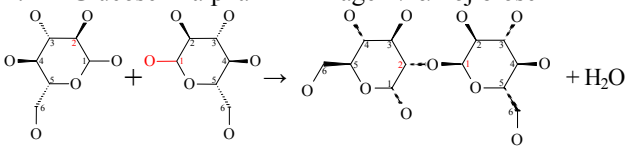


3. 2×Glucose in beta-beta 1-1 linkage → β,β-trehalose



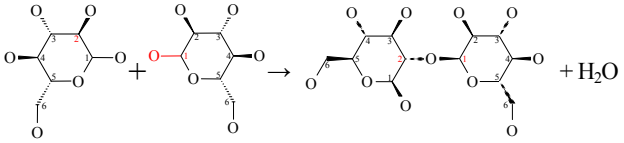
Trehalose ($C_{12}H_{22}O_{11}$) is a soluble disaccharide derived from glucose. It has three isomers and is found in microorganisms and invertebrate animals as well as in plants where it is a source of energy or has a protective role during stress, such as freezing or dehydration [73-76].

4. 2×Glucose in alpha 1-2 linkage → α-kojibiose



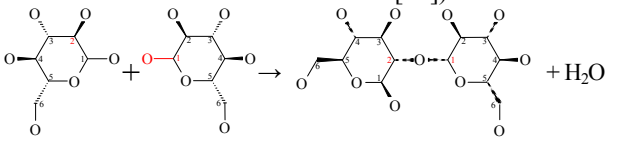
Several roles have been attributed to trehalose, such as inhibition of the glucose transporters in the plasma [77], inducing of autophagy [78], antidepressant-like properties [79], reducing aggregation of pathologically misfolded proteins [80], with utilities that need to be tested on humans.

5. 2×Glucose in alpha 1-2 linkage → β-kojibios

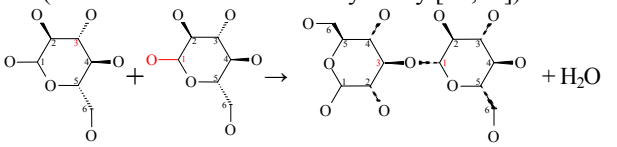


Kojibiose ($C_{12}H_{22}O_{11}$) [81] was identified in 1959 in honey [82] but is also found in small quantities in beer [83], sake and koji [84], and it is used as prebiotic [85-87]. Enzymatic synthesis is an efficient means of production of kojibiose [88,89].

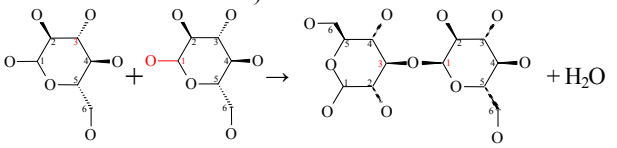
6. 2×Glucose in alpha 1-2 linkage → α-sophorose ($C_{12}H_{22}O_{11}$, identified in 1962 and proved an inducer of cellulase for *Trichoderma viride* [90])



7. 2×Glucose in beta (α,β) 1-3 linkage → laminarabiose (isolated and characterized by Barry [91,92])

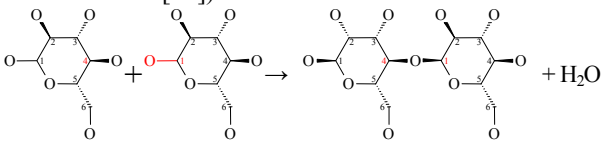


8. 2×Glucose in alpha (α,β) 1-3 linkage → nigerose (also known as sakebiose)

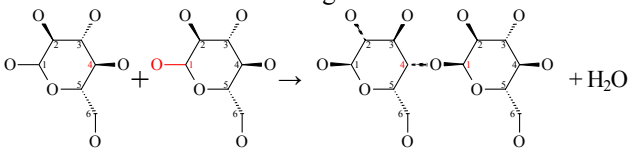


Nigerose is formally called sakebiose due to its presence in Japanese sake where it contributes to the distinctive taste. Chemical synthesis of nigerose was accomplished by Gakhokidze in 1946 [93] and was further studied by other researchers [94]. Different methods are used in the synthesis of nigerose, Konish and Shindo for example used enzymatic synthesis to obtain nigerose [95].

9. 2×Glucose in alpha 1-4 linkage → D-maltobiose (also known as maltose or malt sugar, discovered in 1872 by O'Sullivan [96])

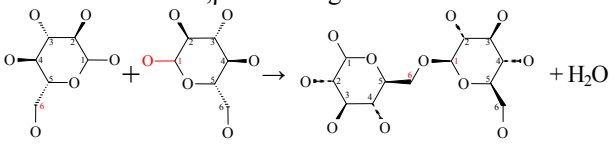


10. 2×Glucose in beta 1-4 linkage → D-cellobiose



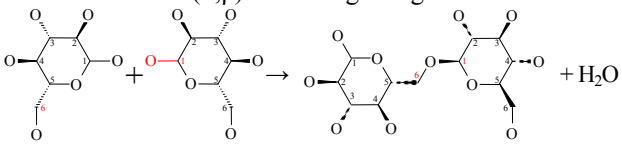
Cellobiose was first synthesized by Haskins, Hann, and Hudson in 1942 [97] and was proved to be a repeating disaccharide of cellulose [98].

11. 2×Glucose in α,β 1-6 linkage → isomaltose



Information related to isomaltose has been available since 1904 [99] but its isolation was first reported in 1949 [100]. The congenital sucrase-isomaltase deficiency was reported in 1964 [101] and induces sucrose and isomaltose intolerance by their malabsorption due to the deficiency of the enzyme required for digestion of disaccharides [102].

12. 2×Glucose in (α,β) 1-6 linkage → gentiobiose



The synthesis of gentiobiose has studied by researchers since early of 1900s. Hudson and Johnson reported in 1917 new derivative of gentiobiose [103] while Helferich published in 1926 brief information on synthesis of gentiobiose [104]. Gentiobiose is identified along with nigerose in the ripe tomato fruit and has a relatively rapid turnover rate [105]. This disaccharide was generated by hydrolysis of fungal polysaccharides [106] and isolated from bacteria [107].

3. SWEETENERS OTHER THAN SUGARS

The new dietary guidelines [14] and health care professionals [12,108] urge reduction of sugar intake (less than 10% daily energy intake) despite the fact that in the scientific literature there is no consensus about its effects on health. In this regard, alternative sweetening solutions are studied by researchers all over the world. The sugar intake can have different sources such as natural or artificial. The

sugar can be found in fruits, vegetable, cereals, and milk with a different glycemic index ranging from zero (natural zero calorie sweeteners, Table 4) to high (sugar, Table 4) [109].

Sweeteners are natural or synthetic compounds capable of producing a pleasant sensation. Thousands of sweet chemicals are known but few are permitted for use as sweeteners for reasons of safety and quality perception [111], so there is an interest in discovering new sweet compounds. The relative sweetness (RS), defined as the ratio of the standard sugar concentration and the iso-sweet concentration of the sweetener, is reported relative to the sweetness of sucrose (1/100%) [112]. There are several theories on the relation between chemical structure and sweet taste. In light of the research conducted by Oertly and Myers, the relationship between glucophores and auxogluc groups creates the sweet taste [113]. The AH-B theory holds that the existence of a hydrogen bond donor (AH) and a Lewis base (B, hydrogen bond acceptor) at a distance of ~3Å confirms the sweet taste [114]. It is believed that the theory of hydrophobic sites (γ in AH-B-γ and X in AH-B-X) [115] is responsible for the intensity of a sweet sensation. Nofre and Tinti described eight interaction sites between a sweetener and the sweetness receptor and introduced the multipoint attachment theory [116]. The G-protein binding theory shows that sweet taste is mediated by G-protein-coupled receptors [117]. The taste receptor type 1 family, consisting of three members, T1R1, T1R2, and T1R3, have been proposed as the universal sweet taste receptors [118] The heterodimeric T1R2+T1R3 complex is responsible in mammals for the sweet taste sensation [119-121]. Sweet tasting compounds bind differently to the extracellular venus-flytrap domain (VFT) of the T1R2+T1R3 receptor and natural and artificial sugars bind both T1R2 and T1R3 [122] while dipeptide sweetener binds just the VFT domain of T1R2 [123]. Despite the fact that the molecular basis of sweet taste has been studied using experimental models, rodents and humans differ in their perception of sweeteners [124] so such that experimental models may not be suitable.

Table 4. Characteristics of sugars and sweeteners

Category	Found/Produced …	Index		The most common are…
		Sweetness (SI)	Glycemic (GI)	
1. Sugar	naturally in fruit, vegetables, cereals, and milk	0.15-1.7	high (23-105)	Sucrose – Glucose – Dextrose – Fructose – Lactose – Maltose – Galactose – Trehalose
2. Sugar alcohols (polyols)[a]	naturally (small quantity) in plants and cereals	0.4-1	very low (1-35)	• Monosaccharide-derived: Sorbitol (E420) – Xylitol (E967) – Mannitol (E421) • Disaccharide-derived: Maltitol (E965) – Isomalt (E953) – Lactitol (E966) – Glycerol (E422) – Erythritol (E968) • Polysaccharide-derived: hydrogenated starch hydrolysates
3. Natural sweeteners	naturally	1-1.1	somewhat lower (35-50)	Honey – Maple Syrup – Coconut Palm Sugar – Sorghum Syrup
4. Natural zero calorie sweeteners	naturally	300-2000	zero	Luo Han Guo – Stevia – Thaumatin – Pentadin – Monellin – Brazzein
5. Modified sugars (such as caramel or golden syrup)	produced by converting starch using enzymes	1-1.2	high (58-65)	High Fructose Corn Syrup – Refiners Syrup – Caramel – Inverted Sugar – Golden Syrup
6. Artificial sweeteners	produced	40-8000	zero	Aspartame (E951) – Sucralose (E955) – Saccharin (E954) – Neotame (E961) – Acesulfame K (E950) – Cyclamate (E952)

[a]: lower glycemic due to incompletely absorption into the bloodstream [110]

Adapted from: http://www.sugar-and-sweetener-guide.com/all-sweetener-list.html [cited August 5, 2016]

4. *IN SILICO* APPROACHES

4.1 Methods and Assessments

Development of new sweeteners should account for several factors that affect sweetness, such as solubility, stability at different temperatures and pH, the absence of the post-flavor effect, health safety, interaction with the receptor(s), and the economics of sweetness measurements [125]. Mathematical models capable of connecting structural constitutions of chemicals with their activities/properties, or *in silico* approaches, first reported in 1868 [126] are also extensively used to estimate or predict relative sweetness (RS) [127-129]. This approach is seen as a reliable alternative to in vitro and in vivo experiments with a significant decrease of time and costs. Quantitative structure-taste relationships (QSTR) are a promising advance in the identification of new sweeteners with desired sweetness and properties. QSRT follows the following steps used in development of quantitative structure-activity/property relationships [130,131]: a) design or collect a training set of chemicals with the same experimental protocol to avoid variability; b) measure the RS experimentally and convert the structural features into theoretical descriptors; c) select

the best descriptors able to explain the sweetness. Thus, identify, evaluate and validate the QSTR models.

How the sweetness (S) is measured and how these data are distributed dictates which statistical method is appropriate to be used to link S with the structural feature of the compounds. Sensory analysis evaluates the sweetness, and the variability of sensory judgments is present and increases with the intensity [132,133] which could lead to systematic bias when relative sweetness from different sources are combined because inter-individual perceptual differences exist [134]. Whenever RS is measured on ratio scale [133], parametric methods are appropriate for use in modeling if measurements follow the normal distribution – an assumption that is not always tested in QSAR/QSPR analysis [135]. The RS can be estimated or predicted using log(RS), but the logarithmic transformation of measured data will not necessarily assure their normality [136]. The sweetness could also be measured on ordinal ('non-sweet'/'semi-sweet'/'medium-sweet'/'sweet'/'very sweet'/) [137] or binary scales ('sweet'/'tasteless') [138] when non-parametric methods are applied in QSTR modeling.

Several approaches are used to calculate descriptors, from different classes of descriptors (such as 2D - topology, 3D - geometry (CoMFA - or CoMSIA [139]), 4D descriptors [139-141]) and indices (such as similarity [142], Szeged indeces calculated on matrix [143]) to families of descriptors (such as MDF - molecular descriptors family [144,145]; MDFV - molecular descriptors family on vertices [146,147], CCP - characteristic and counting polynomials [148,149], SMPI - Szeged Matrix Property Indices [150]). Regardless of the descriptors used in modeling, they must contain structural information and have distinct values for different structures. Furthermore, some assert that the descriptors in a QSTR model must not be linearly dependent on each other [151] but such dependence is not necessarily bad in classes of compounds with very similar structures.

Different statistical methods are applied to identify various QSTR models. These are mainly classified as regression methods or respectively classification methods. The most frequently used regression methods are linear models [112,152], partial least squares (PLS) approaches, and neural networks [153], genetic algorithms [139,154], and linear learning machines [137] are used to select the descriptors that best fit the model. The frequently used classification methods are linear or quadratic discriminant analysis [137,155] using Soft independent modeling by a class analogy method [156], principal component analysis [155,157], support vector machine [158], or tree inclusive classification and regression tree (CART) [137,159]. Other approaches have also been introduced. Nunes and Freitas, for example, introduced an augmented multivariate image analysis (MIA) and converted the image of a guanidine derivative into descriptors, which proved better in estimation (R^2 on training set) but gave similar performances in internal validation (Q^2) [160]. A new approach related to the MIA approach is represented by a graphical tool that uses the coefficient b from PLS regression and the variable importance in projections scores and demonstrated satisfactory prediction performance on disaccharides [161].

Different parameters are used to classify models:

- Internal (applied on training set: leave-one-out cross validation such as determination coefficient in leave-one-out analysis - Q^2, mean absolute error – MAE and mean absolute percentage error - MAPE, r^2_m(LOO)¬, Cp-statistic as a measure of overall bias, etc.) and external validation metrics (applied on test set(s): Q^2_{F1}, Q^2_{F2}, Q^2_{F3}, r^2_m(test), concordance correlation coefficient – CCC) [136,162,163]. An overall r^2_m metric has also been introduced as a metric of overall model performances in estimation and prediction [164].
- Friedman's lack of fit (LOF) which considered the least squares error ($\sum(y_{obs} - y_{calc})^2$, where y_{obs} = observed RS, y_{calc} = RS calculated by the identified model), the number of descriptors in the model and sample size [165]. The lower the LOF, the better the model is considered. Furthermore, unlike the least squares method, the value of LOF does not decrease with the increase of the number of parameters.
- Fitness score used in Double Cross-Validation as the selection of the optimal predictive MLR and PLS models [166] when genetic algorithms or neural networks are used in the identification of the best performing models.
- Error rate (ER), sensibility (Se), specificity (Sp), accuracy (Ac), false-negative rate (FNR, under-classification), false-positive rate (FPR, over-classification), positive predictivity (PP), negative predictivity (PN), probability of wrong classification as active (PWCA) or inactive (PWCI), are point estimators which along with the associated 95% confidence intervals are recommended for use in the characterization of the performance of the classification model (e.g. sweet vs. tasteless) [167,168].

4.2 History of QSTRs

Some of the earlier models linking the structure of the sweeteners with their taste were published in the 1950s [169] and 1960s (saccharin derivatives [170], 2-amino-4-nitrobenzene derivatives [127], dipeptides [171]). Several papers were published and present the sweetness mechanism or predictive models useful to document new compounds with reference to the models published from 2004 to 2014 [172]. In this section, some QSTR models on relative sweetness, published from January 2014 to October 2016 are discussed.

Singh, Khan, and Singh investigated the sweetness, defined as log(RS) (RS being taken from the scientific literature) of sucrose (n=31) and guanidine (n=30) derivatives using molar refractivity (Lorentz-Lorentz formula) and ionization potential [173]. The best performing model regarding the goodness-of-fit showed that 86.5% in

the variation of the sweetness of sucrose derivatives could be explained by a linear relationship with ionization potential, molar refractivity and solvent accessible surface area (n=29, and 2 outliers). The most performing model on guanidine derivatives proved to be a monovariate model (the lowest difference between R^2 and Q^2); 74.5% of sweetness is explained by the changes in molar refractivity (n=27, 3 outliers excluded). The authors removed compounds from the dataset based on their contribution to the model, the increase of R^2 and incorrectly called these compounds 'outliers'. However, Dixon's [174], Grubbs' test [175], Rosner's Extreme Studentized Deviate test [176], and Iglewicz and Hoaglin's robust test [177] all failed to identify any outliner in the sucrose derivatives. In this dataset, the R^2 decreased from 86.5% (as reported in [173]) to 85.5% when the model with three descriptors is used on the whole dataset. was by The above tests identified one outlier (compound 19) in the guanidine derivatives set, with high influence on R^2 since its removal decreased the value of R^2 from 74.5% to 61.6%. This estimation is mistakenly interpreted as a prediction since no training vs. test analysis or external validation of the performing models was conducted. Such confusion is also seen in other articles (see for example [139]). Overall, the study is not reproducible. No information about the source of log(RS) as well as the geometry optimization are provided in the manuscript, and the estimation power and internal validity are moderate, so there is no utility for prediction of new compounds belonging to the class of sucrose or guanidine derivatives.

Wang, Yang, Lu, Liu, Song, and Li produced and purified five sweet mogrosides from Luo Han Guo, a Chinese sweet fruit, and in 3 of 5 compounds, the exact molecular structure was established [178]. Three of the five compounds proved to have a sweet taste (all of them have four or more glucose units) while two compounds were tasteless. The authors concluded that the sugar residues contribute to the mogroside taste, with an enhancement of the sweet taste when β-glycosidic bonds are present [178].

Rojas, Tripaldi, and Duchowicz published models with moderate predictive abilities [179]. The studied sample of natural and synthetic sweeteners consisted of 233 compounds divided into a training set and a test set by the k-means cluster approach. The most straightforward method, random assignment of compounds to the training or test sets proved able to classify the compounds [180]. This group reported a model with six descriptors, 4 positive and 2 negative contributors to the relative sweetness, which was able to explain 79.7% of the log(RS) as a linear function of descriptors in the model. The model characterized in this way had estimation (training) and prediction (internal as leave-one-out and leave-many out as well as external as a test sample) performances based on the reported statistical metrics [179]. However, insufficient details regarding the observed RS are presented in the paper (e.g. which method was used to assure the comparability of different sources of the relative to sucrose data and to reduce variability in RS), or regarding the suitability of multiple linear regression analysis. Moreover, the distribution of data-points as presented in Figure 1 in [179] raises the question about the membership of the compounds in the same population; analysis of sub-groups could be in this case more suitable than the study of the whole sample. The same pattern could also be seen in other models reported for sweeteners (see for example Fig. 3 in [181]).

Discrimination between sweet and tasteless (396 compounds in the training set versus 170 compounds in the test set) and between sweet and bitter (356 compounds in the training set versus 152 compounds in the test set) was reported in 2016 by Rojas, Ballabio, Consonni, Tripaldi, Mauri, and Todeschini [140] using classification approaches. The models were selected based on a two-dimensional structural representation of compounds translated into descriptors by Dragon software. The reported sweet-tasteless model comprised nine descriptors with a sensibility that dropped from 0.89 (training) to 0.75 (test) and a more stable specificity, ranging from 0.78 in training set to 0.75 in the test set. They reported that the sweetness of a molecule is related to the number of NH_2 radicals on the aliphatic skeleton as with the number of N and O pairs at a topological distance of three. In contrast, negative values of average vertex sum from Burden matrix weighted by Sanderson electronegativity, the leading eigenvalues from Burden matrix weighted by ionization potential and a CATS2D acceptor-lipophilic at log_5 characterize the tasteless compounds. Moderate performances of this sweet-tasteless model are obtained in estimation (training) as well as in the internal five-fold cross-validation analysis regarding the ability to classify correctly sweet and tasteless compounds (G-mean [182] of 0.8332 for training and respectively 0.8485 for cross-validation). Unfortunately, the strength is weak on training set, where a G-mean of 0.5625 is obtained. On the other hand, ROC graph Euclidean distance (ROCED) [183] that takes values between 0 (perfect classifier for both training and test set) and 4.5 (bad classifier, >2.5 characterize a random classifier) is 0.90 arguing that the model is not a random classifier. The model able to discriminate sweet and bitter molecules comprised just four descriptors but with better performances in identification of sweet compounds (Se = 0.96 in the training set and 0.95 in the test set) and moderate abilities in identification of bitter compounds (Sp = 0.77 in the training set and with 0.63 in the test set). However, the ability to classify sweet and bitter compounds is similar to that in the previously reported model, with a G-mean of 0.8598 in the training set and of 0.5985 in the test set. The bitter compounds were characterized by the presence of C and N pair at a topological distance of one and by the presence of C linked to an electronegative atom (e.g. O, N, S, P, Se, halogens) connected to any group separately through carbon separated by an aromatic bond. The value of ROCED equal with 0.95

sustains the fair ability of the model to discriminate between sweet and bitter compounds.

CURRENT CHALLENGES AND PERSPECTIVES

Information and knowledge in science increase exponentially and this increase are observed in the publication of scientific literature. The sugar and sweeteners are of interest due to the not all the time prove the link between consumption and several chronic diseases. The reflection of sugar and sweeteners (both caloric and non-caloric) consumption on human health (such on cardiovascular and metabolic disorders - including diabetes mellitus, glycemic response, and obesity) lacks most of the time the scientific rigorousness, leading to questionable results [184,185]. Since the links are questionable, some studies on artificial sweeteners proved to promote weight loss while others show no effect or even weight gain [186], rigorous studies are needed to find the causal link [187,188]. Valid data and measurements resulted from standardized methods, along with the opportunities opened by proteomics, transcriptomics, and genomics, could lead to new scientific pathways in the investigation of sugar and sweetness fingerprints and association of their consumption with more than metabolic and cardiovascular diseases (e.g. neurological, psychiatric disorders, psychological behavior, etc.). All these activities could lead to a better understanding of the relation between sugar and sweeteners intake and their effects on the human health.

The trends and patterns in the identification of new compounds are changing and the animal models that proved unsuitable due to differences in perception of sweetness are replaced by *in silico* approaches. *In silico* approaches are by definition an interdisciplinary domain and thus an interdisciplinary team could be the key to success in this field. The main challenge in the identification of new sweet compounds with desired properties using *in silico* approaches is related to the validity and reliability of the input data, more specifically to the measurement of relative sweetness. The experimental conditions of RS measurement must be comparable to be suitable for *in silico* modeling and whenever this is not accomplished, measures taken to minimize the variability in the measurements must be clearly presented. Furthermore, the inter-observer variability must be considered with more attention especially when different populations are used to measure sweetness. This issue is not properly treated in many manuscripts that report QSTR models and thus the usefulness of these models in screening is doubtful. Additionally, the available relative sweetness data are heterogeneous and standardization of the measurement method of relative sweetness is needed. This gap opens the way to identifying new measuring methods that assure a smaller variability and higher reliability of experimental data. Moreover, the publication of QSTR models must be supplemented with the availability of experimental data to assure reproducibility. This practice could lead to an increase in the quality of the published models and will open the possibility of secondary research such as integration of a larger number of compounds and identification of those patterns that generally fall into the same class. Moving towards integrated strategies that combine standardization of relative sweetness measurements and reporting of the models (focusing on statistical methods such as Shannon entropy [189], factorial analysis [190], linear regressions other than the weel-known once [191,192], etc) with new approaches or optimization of the old ones to be applicable to sweets and sweeteters (such as spectral analysis [193], distance-based topological indices [194], logistic kinetics approach [195], similarity analysis [142], operations on mapps [196], Cluj polynomials [197], etc.) could make *in silico* modeling a promising approach.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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