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Article

PREDICTION OF BIOLOGICAL EFFECTS OF SOME NATURAL SWEETENERS

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ABSTRACT

This study presents predictions concerning the pharmacokinetics and biological effects of the most commonly used natural sweeteners. Investigated sweeteners have favorable pharmacokinetic profiles as they are not able to affect the central nervous system, are not considered as inhibitors of the cytochromes P450 that are involved in the metabolism of xenobiotics and have not the ability to penetrate the skin. Our results also reveal some possible side effects of natural sweeteners: hyperuricemia, acidosis, hematotoxicity, cyanosis and toxicity through respiration. These data sustain that much more research is needed to fully understand the biological effects of dietary natural sweeteners in humans.

Keywords: sweeteners, biological effects, pharmacokinetics;

1. INTRODUCTION

Sweeteners are used in numerous food processes, and the effect of the ingesting of these kinds of compounds may affect health status and microbiota composition [1]. They are considered sugar alternatives that mimic the sweet taste of sugar but have an insignificant impact on energy intake [2].

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When people consume sweet foods, the taste buds receive different impulses and their response is different from one sweetener to another. The interactions that they form in the buccal cavity stimulate the brain through the neurons. The sensation of sweetness depends on the dextrogyre conformation of the sweetener that is why D-glucose is sweet, and L-glucose emanates a salty taste.

Sweeteners are often found in food ingredients and they are recommended for consumption, examples of commercial foods where we find the most common sweeteners being sweets, juices, sauces, chewing gum [3]. Sweeteners are also found in pharmaceutical preparations and drugs as excipients, the pharmaceutical industry uses lactose and saccharose as inactive ingredients of drugs tablets because of their compressibility properties. [4,5]. The effects of sweeteners on the organism can be toxic and lead to oxidative stress and allergies [6]. Furthermore, it is considered that by reducing the number of sweeteners in food, people would prevent diseases like caries, diabetes and obesity [2].

From the point of view of origin, the sweeteners are divided into two groups: natural and synthetic, the natural ones being glycosidic or non-glycosidic. To be accepted on the market, the natural sweeteners must have a good taste and not be toxic, and for this, that compound has to be soluble in aqueous solutions. Besides this, their price must be acceptable for the majority of consumers. The most common natural sweeteners are sucrose (a disaccharide formed from units of glucose and fructose), maltose (another disaccharide made from two units of glucose), lactose (the disaccharide made from one unit of glucose and one of galactose) and the monosaccharides, among glucose and fructose are the most familiar (Figure 1). Galactose is a monosaccharide similar to glucose and fructose, but the three molecules have distinct stereochemistry [7].

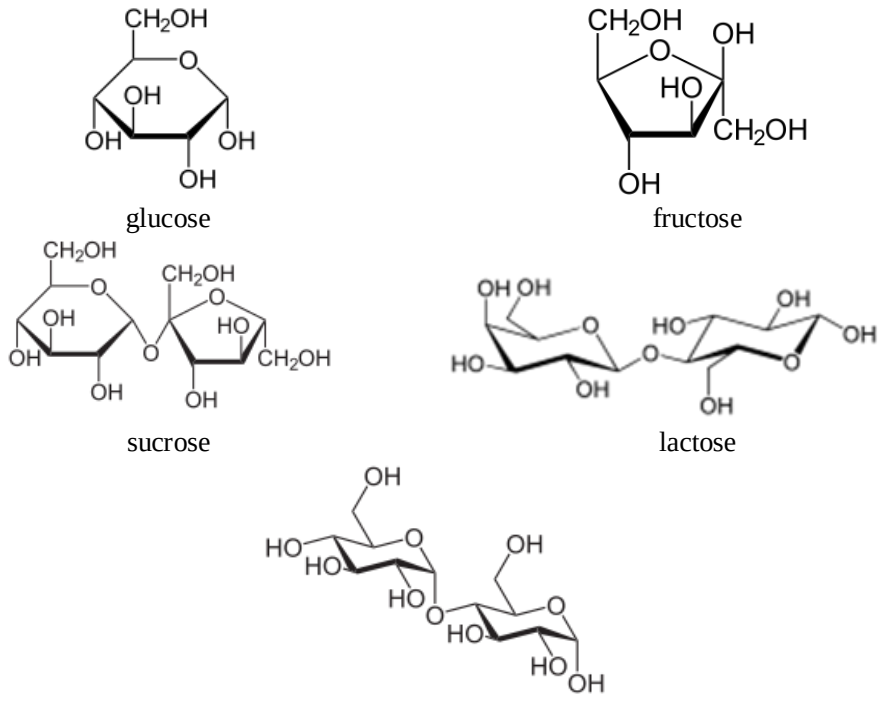

Figure 1. Structural formulas of the most common natural sweeteners

Many foods and drinks we consume every day have added natural sweeteners. Scientific literature data reveal some biological effects of these natural sweeteners, especially eating disorders and obesity [8]. Sucrose, used as the source of sugar, conducted to important effects on eating motivation and preferences [9] and some addictive effects [10] Glucose intake have shown suppression of feeding [11], can induce oxidative stress, activates protein kinase C, endorses the formation of advanced glycation end-products, enhances hexosamine biosynthetic pathway and alters gene expressions [12]. Furthermore, high glucose intake contributes to the development of insulin resistance and dysfunction of insulin secretion, mediates irreversible cell damage and encourages the proliferation of cancer cells, potentiates a suitable environment for infections and conducts to development of osteoarthritis [12]. Other studies revealed that fluctuations in glucose levels have a negative metabolic impact on *Diabetes mellitus* and might impact the development of complications [13]. Fructose is considered by humans sweeter than glucose, fructose sweetness being perceived earlier than that of sucrose or glucose [14]. Like glucose, fructose might also induce modifications in eating motivation and eating disorders [8,15] High consumption of fructose has been associated to prevalence of metabolic diseases (dyslipidemia, insulin resistance, hepatic steatosis and nonalcoholic fatty liver diseases, high blood pressure) effects on the gut microbiota conducting to impairment in intestinal mucosa integrity [16].

A high fructose intake may also induce advanced glycation end-products accumulation in the liver causing lipogenesis and intracellular lipids deposition conducting to a proinflammatory response [16]. Galactose intake is linked with the risk of ovarian cancer [17], oxidative stress, hormonal disturbances and spermatotoxic effect [7]. Maltose is the major product resulting from starch digestion by the enzyme beta-amylase (SAPHIRO et al, [18]. Some people manifest lactose intolerance meaning that they are not able to break lactose into its constituents because of insufficient lactase production. People characterized by lactose intolerance may experience allergic reactions, pain, bloating or swelling of the abdomen, diarrhea, nausea, production of gas [5].

Most of the studies revealing the effects of the investigated sweeteners have been performed in rodents, being considered that they display anatomical and physiological similarities to humans [19], but the transfer of information obtained through animal tests to humans strongly depends on the ability to measure the same endpoints in animals. Considering the expenses and the ethical concerns on using both animals and humans for testing purposes, the role of computational approaches in hazard assessment turns out to be recognized. The quantity and variety of data obtained through experimental toxicity studies permitted the building of truthful models and tools for computational toxicology assessment. Computational approaches are recognized by the Organization of Economic and Co-operation Development (OECD) [20] and European Food Safety Association [21] and are regularly used in assessing the toxicological effects of various chemicals on humans [22-29].

Taking into account the lack of data concerning the human health effects of the most used natural sweeteners (glucose, fructose, galactose, sucrose, lactose, maltose), the aim of this study is to use a computational approach to assess their biological effects on humans.

2. METHOD

Specific literature is abundant in computational tools available for predicting the biological effects of various types of chemicals. These tools are used to predict, analyze, simulate and/or visualize the biological and or side effects of chemicals. The outcomes of the computational methods object to complement and/or guide toxicity tests and prioritize chemicals. We have selected for this study SwissADME [30] and PASS [31] free accessible online computational tools, that are also robust and continuously updated and have the accuracy of predictions higher than 70%.

In the computational assessment of the biological activity of chemical compounds, predictions are usually based on the analysis of molecular properties (descriptors of chemicals) as there is a supposed relationship between chemical structures and biological activity in a chemical dataset [32]. As an example, the most used rule for predicting the oral bioavailability of chemical compounds is Lipinski's rule. It states that a compound with good oral bioavailability must meet the following criteria: molecular weight (MW) must be less than 500 daltons, the octanol-water partition coefficient (logP) must not exceed 5, there are not more than 5 hydrogen bond donors (HBD) and no more than 10 hydrogen bond acceptors (HBA) [33]. In this study, the ZINC database (https://zinc.docking.org/) was used to extract the SMILES (Simplified Molecular Input Line Entry System) formulas, the structural data file files (sdf) and the physical-chemical properties of the considered compounds. ZINC database contains information concerning 230 million chemical compounds that are commercially available and can be used in particular for molecular docking studies. This base can be accessed free of charge, is available online [34].

SwissADME (http://www.swissadme.ch/) software was used to obtain information concerning the pharmacokinetics of investigated sweeteners used in the food industry. It is a freely available web tool that allows the computation of the physicochemical properties of a chemical compound and its pharmacokinetic profile starting from the SMILES formula. The accuracy of predictions of SwissADME tools is situated between 72% and 94%. It supports studies that led to the discovery of new drugs, predicts interactions between various types of molecules, such as interactions between proteins and ligands, between human cytochromes and their inhibitors and between the glycoprotein P and its substrates. This software also predicts interactions between molecules and the body, i.e intestinal absorption and blood-brain barrier penetration) [35].

Prediction of Activity Spectra of Substances (PASS) is another software free available on-line (http://www.pharmaexpert.ru/passonline/) that has been used to obtain predictions concerning the side effects of investigated sweeteners [36]. PASS is a computational tool allowing prediction of biological activity and/or toxic and side effects of a chemical compound starting from its SMILES formula with a mean accuracy of prediction about 90%. PASS computational tool independently estimates two probabilities: the probability that the investigated compound belongs to a particular class of active compounds (Pa) or inactive compounds (Pi). The value of Pa is computed taking into account the similarity of the molecule under investigation with the structures of those molecules within the training set which are the most typical in a subset of "actives". Consistently, Pi reflects the similarity of the investigated compound with the molecules within the training set that belongs to the subset of "inactive". Activities with Pa>Pi are considered as promising for a given compound and a good accuracy of prediction is obtained for Pa>0.7.

All these methods have been developed for predicting the biological activity and/or side effects of drug candidates, but they were successfully applied for other chemicals: water-soluble derivatives of chitosan [23], cosmetic ingredients [26], parabens [25], steroids [24], pesticides [26]; [27], oligosaccharides [28].

3. RESULTS AND DISCUSSIONS

Taking into account the importance of the molecular properties for the biological activity of chemicals, the physicochemical properties of the sweeteners under investigation are extracted from ZINC database and are presented in Table 1. This table contains molecular descriptors related to the molecule dimension expressed by the molecular weight (MW), to polarity such as H-bond donors (HBD), H-bond acceptors (HBA) and topological polar surface area (TPSA), to electric charge, to lipophilicity expressed by partition coefficient (logP) and to flexibility expressed by the number of rotatable bonds (NRB) of the molecule.

Table 1: Physical and chemical proprieties of investigated carbohydrates extracted from ZINC Database: logP (partition coefficient), HBD (number of H bonds donor), HBA (number of H bonds acceptors), TPSA (polar topological area), MW (molecular mass), NRB- number of rotatable bonds

Compound	logP	HBD	HBA	Net charge	TPSA (Å^2)	MW (g/mol)	NRB
Glucose	-3.22	5	6	0	110	180.15	2
Fructose	-2.04	5	6	0	110	180.15	2
Galactose	-2.64	5	6	0	110	180.15	5
Sucrose	-3.75	8	11	0	190	342.29	5
Lactose	-3.43	8	11	0	189	342.29	4
Maltose	-4.45	8	11	0	190	342.29	4

Compounds having a small molecular weight, increased lipophilicity (high value for logP) and reduced flexibility (low number of rotatable bonds) are considered to have a better membrane permeation and a good oral absorption [36].

Data presented in Table 1 illustrate that all of these compounds are hydrophilic and expose a high topological polar area, are not charged, have low molecular weight and reduced flexibility as the number of rotatable bonds is low. Monosaccharides totally respect the Lipinski's rule and theoretically have ideal oral bioavailability as their physicochemical parameters are associated with acceptable aqueous solubility and intestinal permeability. Disaccharides illustrate a high number of hydrogen bonds donors and acceptors, correlated to their increased TPSA and leading to poor permeability across the membrane bilayer.

The pharmacokinetic properties of the studied sweeteners have been obtained using SwissADME software and are presented in Table 2.

All investigated sweeteners illustrate poor gastrointestinal absorption and are considered as substrates of the P-gp protein, emphasizing that their systemic exposure is reduced. The poor absorbtion of disaccharides is correlated with the fact that they cannot cross the mucosa, they are hydrolyzed into monosaccharides. The glucose is able to cross the enterocytes and to reach the hepatic portal system. The fructose and the galactose are converted to glucose, being metabolized only in this form [13].

It is worth mentioning that the calculations of the probabilities of gastrointestinal absorption, or bioavailability are done without taking into account the fact that the cells have special transporters for certain molecules, such as for glucose (and the other monosaccharides). By means of these transporters, the speed of entry into the cells of the studied molecule is significantly higher than the simple passage (diffusion) through the biological membranes. In reality, the bioavailability of glucose and the rate of entry into cells is much higher than was calculated based on the descriptions used by the prediction software mentioned above.

Table 2: Pharmacokinetic properties of the studied sweeteners: GI- gastrointestinal absorption, BBB- blood-brain barrier penetration, P-gp – P-glycoprotein, CYP- cytochrome P450, LogKp- coefficient of passage through the skin

Com pound	GI	BBB	P-gps	Inhibition of				
				CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP3A4
Glucose	Low	no	yes	no	no	no	no	no
Fructose	Low	no	yes	no	no	no	no	no
Galactose	Low	no	yes	no	no	no	no	no
Sucrose	Low	no	yes	no	no	no	no	no
Lactose	Low	no	yes	no	no	no	no	no
Maltose	Low	no	yes	no	no	no	no	no

Investigated carbohydrates are not capable of penetrating the blood-brain barrier. It is not an unexpected result as it is known that the additive effect of increasing TPSA (through increase in HBA/HBD count) on decreasing passive permeability and simultaneously increasing P-gp transport efficiency is responsible for a decrease in the chemical exposure in the brain [37]. However, glucose is the essential energy substrate for the brain and supports the energy requirements of the central nervous system function, but it enters brain cells through glucose transporters [13]. It is also known that disaccharides are not able to reach the blood circulation (unless they are injected) and consequently, the predictions concerning the blood barrier penetration are not necessary for these compounds. It underlines one of the limitations of the *in sillico* tools that allow to test any molecule even for improbable biological actions and the significant role of the researchers in interpreting these predictions.

None of these sweeteners is an inhibitor of the human cytochromes and it reveals that they do not interfere with co-administrated drugs.

Figure 1 shows the logarithmic value (logKp) of the skin penetration coefficient. All the natural sweeteners considered in this study have low values of logKp, thus illustrating their reduced ability to penetrate through the skin. This result is important for people working in the factories where these sweeteners are produced and / or packaged because they are professionally exposed.

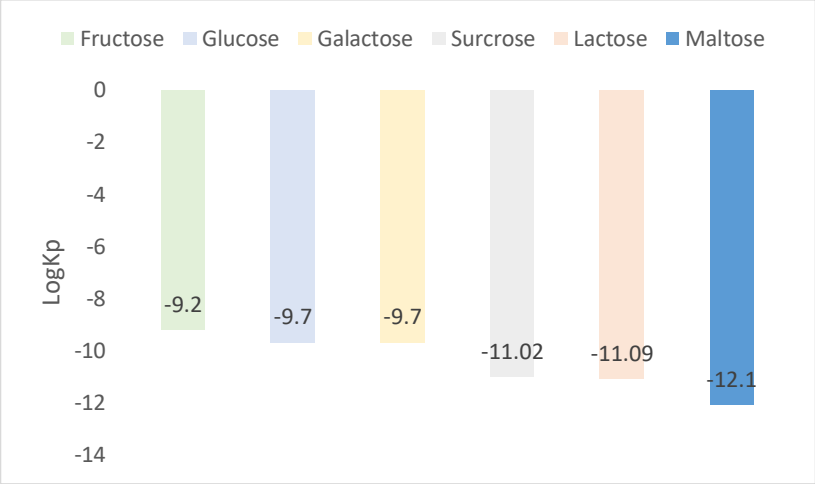

Figure 1. Logarithmic values of the skin penetration coefficients for investigated sweeteners

The use of PASS online software concerning the side effects of investigated sweeteners are illustrated in table 3.

Table 3. Predictions obtained using PASS software concerning the side effects of investigated sweeteners

Compound	**Predicted side effects and the probability for every prediction**
Glucose	Hyperuricemia (0.936), weight loss (0.930), acidosis (0.924), toxic by respiration (0.916)
Fructose	Hyperuricemia (0.778), hematotoxic (0.766), ulcer (0.760)
Galactose	Hyperuricemia (0,936), weight loss (0,930), acidosis (0,924), toxic by respiration (0.916)
Sucrose	Hyperuricemia (0.943), acidosis (0.931)
Lactose	Cyanosis (0.927), toxic by respiration (0.931), weight loss (0.917), acidosis (0.920), hyperuricemia (0.909), hematotoxic (0.905)
Maltose	Cyanosis (0.927), toxic by respiration (0.931), weight loss (0,917), acidosis (0.920), hyperuricemia (0.909), hematotoxic (0.905)

Data presented in Table 3 reveal common side effects of investigated sweeteners: hyperuricemia, acidosis, hematotoxicity, lactose and maltose illustrating the higher number of possible side effects. Some of these effects have already been noticed. High fructose intake may conduct to developing metabolic disease [38] and hyperuricemia [39] and fructose, lactose, sucrose and maltose may produce acidosis [40]. Another study revealed that galactose consumption as the only carbohydrate source promotes fat loss [41].

It is commonly known that intake of sweeteners conducts to weight gain, and it is surprising to notice that some of the investigated sweeteners may produce weight loss. A high concentration of any of investigated sweeteners in blood conducts to acidosis that further may produce weight loss. It illustrate that weight loss is a consequence of acidosis, not of the intake of sweeteners. Moreover, these predictions concern the situation of the intake of only the

sweeteners, not in combination with other compounds of diet. These results underline other limitation of computational assessment of biological effects of chemicals, these predictions do not take into account the quantity of ingested chemicals and the interactions with other compounds of the diet.

4. CONCLUSION

The results obtained within this work show that the investigated sweeteners have favorable pharmacokinetic profiles as they are not able to affect the central nervous system, are not considered as inhibitors of the cytochromes P450 that are involved in the metabolism of xenobiotics and have not the ability to penetrate the skin. The results envisaging the poor ability of natural sweeteners to penetrate the skin are important for those who work in factories that produce, pack or use these sweeteners because they are professionally exposed and can be contaminated with larger quantities of these compounds and the adverse biological effects can be pronounced.

Our results also reveal some possible side effects of natural sweeteners: hyperuricemia, acidosis, hematotoxicity, cyanosis and toxicity through respiration. Literature data reveal that only hyperuricemia and acidosis have been observed, but we must take into consideration their other possible side effects. Our data sustain that much more research is needed to fully understand the biological effects of dietary natural sweeteners in humans.

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