Artificial sweetening agents as alternative of natural sweeteners – Chemistry and related Pharmaceutical aspects

Amitesh Chakraborty[1], Deep jyoti Shah[1], Tushar Adhikari*[1]
[1] *Division of Pharmaceutical Chemistry, Department of pharmacy, Guru Nanak Institute of Pharmaceutical Science and Technology, Sodepur, Kolkata, India,*
Amitesh Chakraborty: d.amitesh0017@gnipst.ac.in
Deep jyoti Shah: d.deepjyoti0023@gnipst.ac.in
**Tushar Adhikari: tushar.adhikari2022@gnipst.ac.in*

Abstract
In today's generation, due to increased sedentary life, life-style related disorders have become more prominent. This makes people more conscious about the food they consume and how the food impacts the health of an individual. Wise use of sweetening agents can reduce the impact of sweeteners on our health in daily basis. Sweetening substances are mostly metabolized by our liver and stored as glycogen for future use. But, this rapidly increases blood glucose level, which is of great harm for diabetic or pre-diabetic patients. This review critically aims at different types of natural and artificial sweeteners that are used in food preparations and their health impacts. Literature review suggests several uses and health benefits of artificial sweeteners. Keywords like 'Sweetener', 'Aspartame', 'Health benefits', 'Metabolic disorders' and other similar types were explored. Different literatures ranging from 2019 to 2024 were considered to prepare this review work. Articles in languages other than English, before 2019 and those not in Elsevier, Springer, PubMed were excluded. Products obtained from nature shows less complexities with respect to artificially synthesized product. Artificial intense sweeteners due to high sweetness potential are required in less amount, but when consumption levels are higher, there is chance of developing cancer. The health effect, either beneficial or harmfulness is independent of the potency of the sweetening agent with respect to sucrose. The health effect depends on the chemical structure and the affinity of metabolites of the sweetener to various receptors.

Keywords: *Sweetening agents; Bulk sugar; Intense sugar; Aspartame; Saccharine; Sucralose*

1. Introduction
Taste is an important factor which enhances it's palatability. One of the most important taste amongst all is sweet, which increases palatability of multiple foods and are even used to mask bitter taste of drug formulations. To impart sweet taste to foods like cooked foods, braverages or packaged foods sweetening agents are used. Sweetening agent can be defined as a substance of natural or synthetic origin which are used to impart sweet taste to the food to make it consumable [1]. Based on the origin sweetening agents can be classified broadly into natural and artificial sweetening agents. Natural sweeteners like sucrose, Fructose, glucose are obtained from nature while artificial sweetening agents are mostly synthesized in laboratories like aspartame and saccharine.
Nowadays due to increase in technology and due to the demand of generation sedentary lifestyle has become more prominent. Reduced physical activity and increase in screen time have lead progression of several metabolic diseases like cardiovascular disease obesity and diabetes mellitus [1,2].

Sweetening agents especially natural sweetening agents contain high calorie than the synthetic ones. It has been found that Sugars or sweetening agent have led to elevated progression of multiple metabolic disorders. One table spoon of sucrose contains about four calories [3,4].

Sweetening agent causes metabolic disorders by the following pathways. Consuming foods or drinks which contains Sugars increases the activity of α amylase and α-glucosidase in gastrointestinal tract for absorption of glucose, which are simplest form of sugars. This absorption of sugar in form of glucose rapidly increases blood sugar level and causes blood glucose spike. The sudden increase in blood glucose level reduces GLP synthesis in islets of Langerhans. It in turn reduces insulin production by pancreatic beta cell. Moreover, excess glucose in blood causes insulin resistance psreventing glucose to enter the cells from blood. This is the case where cells become insensitive to insulin [5,6].

This increase in insulin resistance has multifold effect. In liver, glucose is converted to glycogen for storage for later use. Insulin resistance reduces glucose concentration in cell. This activates positive feedback system. So, glucose production by body increases by upregulating gluconeogenesis in liver causing increased formation of glucose from glycogen. This further elevates blood glucose level. Secondly it increases Lipogenesis where glucose is converted to fatty acid by de novo synthesis. Hence formation of adipocyte increases. This increases fat deposition in visceral organs and abdominal region and leads obesity. Excess glucose consumption increases dopamine level which increases of craving for sweets. Levels of ghrelin or hunger hormone also increases [7,8].

Thus, consumption of sweetening agents and sugar is responsible for obesity and increase in progression of diabetes mellitus. To prevent and manage these metabolic disorders, the focus of shifting from natural sweeteners to low calorie artificial sweeteners have emerged. This review aims to discuss how and why natural sweeteners are replaced by artificial sweeteners, their potential health benefits when consumed for a prolonged period of time including both beneficial and hazards.

2. Bulk and Intense Sweeteners

Agents which impart sweetness to food are called sweetening agents. The sweetening agents are mainly classified in the following heads [9,10]:

a) Based on chemistry: Sugar (Sucrose, glucose, maltose, lactose); Sugar Replacer/ Sugar alcohol (Sorbitol, mannitol, maltitol, xylitol); Low calorie sugar (aspartame, saccharine, sucralose, cyclamate)
b) Based on source: Natural and artificial (Synthetic and semi-synthetic)
c) Based on sweetness potential: Bulk and intense
d) Based on nutrition content: Nutritive (High caloric value); Non-nutritive (Low caloric value)

In food industry, when using different types of sweeteners, the concentration of sweeteners to be added changes. This is because, the sweetening capability of different types of sweeteners are different. This is measured with respect to sweetening ability of sucrose, and is considered as 1.

Natural sweeteners are those compounds, which are obtained from nature, and have sweetness potential less than sucrose. So, generally bulk sweeteners have sweetness potential less than 1 and hence, are called bulk sweeteners. Because of their less sweetness, more amount is required to impart the sweet taste. Hence, normally more caloric value intake occurs. Some bulk sweeteners include sucrose (standard), fructose, galactose, glycosides like stevia; sugar alcohols like maltitol, mannitol, xylitol, sorbitol and erythritol. Despite of the high calorific value, it is found that natural sweeteners should be used crude over refined sugars. This is because sucrose is obtained from sugar cane stem, but refined sugar contains

99% sucrose, while sugar cane stem extract contains 70% sucrose, thus reduces the sucrose intake [11].

When sweetening potential of a sweetener is more than 1, the amount of sweetener required to make similar sweetness is lesser. These are called intense sweeteners. Generally, these are artificial sweeteners, because more of their natural origin, they are obtained mostly from synthetic sources. Artificial sweeteners includes both synthetic and semi-synthetic compounds based on their origin. Aspartame, Sucralose, Saccharin and Acesulfame potassium (Ace-K) are some of synthetic sweeteners. Neohesperidine dihydrochalcone is a semi-synthetic sweetening agent [12]. Basically, artificial sweeteners are non-sugar alternative of sugars. They generally have sweetness potential of 30 – 13000 [13].

Artificial sugars are generally called Low calorie sugar (LCS), because of multiple reasons. The calorific value of an artificial sweetener with respect to sucrose is quite less. More over due to the intense sweetness, very less amount is required. This further reduces the calorie intake. The natural sugar in liver undergo metabolism to produce glucose, which is stored as glycogen for further use. Instead, artificial sweeteners like sucralose has found to remain unmetabolized and hence, has less impact on blood glucose levels. Because of lesser metabolism, these LCS are also called non-nutritive sugars [14,15].

Table 1 as shown represents the chemistry and chemical features of different natural and artificial sweeteners. For showing biological effect, the agents need to be metabolized. The metabolized and their concise health impacts both beneficial and hazardous are shown in Table 1.

Table 1: Different natural and artificial sweeteners used in food and their potential health impacts

Sl. No.	**Sweetener**	**Source (mainly commercial)** [16]	**Chemical properties [Molecular formula, sweetness potential]** [12,17,18]	**Metabolites in human body** [19]	**Health effects (in low levels and excessive level of intake)**	**ADI (mg/kg body weight per day)** [16,19]	**Reference**
Natural Sweeteners – Bulk sweeteners							
1.	Sucrose (table sugar)	Sugarcane (70% - *Saccharum officinarum*); Sugar beet (30% -*Beta vulgaris*)	Disaccharide (glucose and fructose); Reference for sweetness potential [$C_{12}H_{22}O_{11}$, 1.00]	Glucose and fructose	Sudden blood sugar spikes; Provide instant energy to do work; Higher calorie intake; increases glycolysis; reduces insulin secretion; insulin resistance; increase formation of glycosylated hemoglobin; increase weight; increase; increase tissue lipid accumulation; increase leptin levels	40	[9,20]
2.	Fructose	Fruits (apple, date, fig and other sweet fruits)	Monosaccharide; Sweetest natural sugar [$C_6H_{12}O_6$, 1.2 – 1.8]	Fructose-1-phosphate	Lower glycemic index; less blood glucose boost than sucrose. Excessive intake causes metabolic disorders like insulin resistance and high TG levels; hyperlipidemia	ND	[21]
3.	Stevia	*Stevia rebaudiana* leaves	Stevia glycoside [$C_{38}H_{60}O_{18}$, ND]	Steviol	Steviol and stevioside increase glycogen storage, insulin production by calcium influx in pancreatic beta cell, reduces insulin sensitivity and glycosylated hemoglobin; inhibits α-amylase;	4	[22]

4.	Maltitol	Cereal starch (corn, wheat etc.)	α-D-glucoside (α-D glycosyl at C4 of D-glucitol) [$C_{12}H_{24}O_{11}$, 0.97]	Mostly remain unmetabolized	Unlike other natural sugars, it does not react in oral cavity; reduce 30% calorie intake than sucrose; low glycemic and insulin response than sucrose; use permitted in USA	9	[23]
5.	Sorbitol	Berries; corn syrup	Monosaccharide [$C_6H_{14}O_6$, 0.6]	D-glucitol	It is used as food sweetener in USA. Improves pancreatic morphology, delay gastric emptying, α-amylase and α-glucosidase inhibition, negligible effect on obesity	ND	[24]
6.	Xylitol	Birch bark and corn cob	Sugar alcohol [$C_5H_{12}O_5$, 0.63]	Xylitol-5-phosphate	Better alternative than sucrose; pancreatic cell regeneration; no effect on glucose absorption; delay absorption of glucose from intestine	ND	[25,26]
7.	Erythritol	Fermentation of corn and yeast	Sugar alcohol [$C_4H_{10}O_4$, 0.87]	Mostly remain un-metabolized	Similar effect of xylitol; not so effective in showing anti-hyperglycemic effect; reduce insulin resistance; pancreatic cell induction to produce insulin	500	[25,26]
Artificial sweetener (Synthetic) – Intense sweeteners							
8.	Saccharin	o-toluenesulfonamide and potassium permanganate	1,2-benzisothiazole derivative; [$C_7H_5NO_3S$, 250 – 550]	Mostly remain unmetabolized	First artificial sweetener; Banned by FDA in 1997 due to chances of bladder cancer; re-allowed due to less evidences; Fluid retention and chances of constipation, mostly no effect on blood glucose; prolonged use might cause little weight gain and increase oxidative stress	5	[16,27]

9.	Aspartame	L-aspartic acid and L-phenylalanine	L-aspartyl-L phenylalanine methyl ester [$C_{14}H_{18}N_2O_5$, 120 – 200]	Aspartic acid, phenylalanine, methanol	Sensitive to people with phenylketonuria; low calorie content; reduce appetite; reduce obesity; cytotoxic in nature; in excess conc. Induces angiogenesis in cancer; Bitter aftertaste	50	[28,29]
10.	Sucralose	Selective chlorination of sucrose	3-OH groups of sucrose substituted with 3Cl groups; [$C_{12}H_{19}Cl_3O_8$, 550 – 750]	Mostly unmetabolized	Bacteriostatic and increase in biofilm formation; suppress hunger and apetite; no effect on HbA1C or blood sugar; improves gut health; reduce glycemic peaks	5	[30,31]
11.	Acesulfame-potassium	diketene and sulfamic acid	Potassium salt of Acesulfame [$C_4H_4KNO_4S$, 200]	Mostly unmetabolized	Reduces bitter after taste of aspartame; increases chance of atherosclerosis; increase lipid content	15	[32]
12.	Cyclamate	Chlorination of trisaccharide raffinose	Cyclohexylsulfamic acid salt; [$C_6H_{12}NNaO_3S$, 30 – 50]	Cyclohexylamine	Narrow consumption limits; control blood glucose spike; excessive amount has risk of increase in DM and ceruloplasmin	1	[33,34]
Artificial sweeteners (Semi-synthetic)							
13.	Neohesperidine dihydrochalcone (NHDC)	Hesperetin-7-O-glucoside	Hespiridine with glycosidic linkage at 2-position; [$C_{28}H_{36}O_{15}$, 50 – 100]	NHDC-O-glycoside	Anti-oxidant and anti-inflammatory potential; blood glucose level control; suppress fat production and lipid accumulation; reduce cytokine formation	0 – 5	[35,36]

ND: Not Determined; DM: Diabetes mellitus, ADI: Annual Daily Intake

The different classes of sweetening agents discussed above are represented in Figure 1. Individual structure of each compounds are represented there.

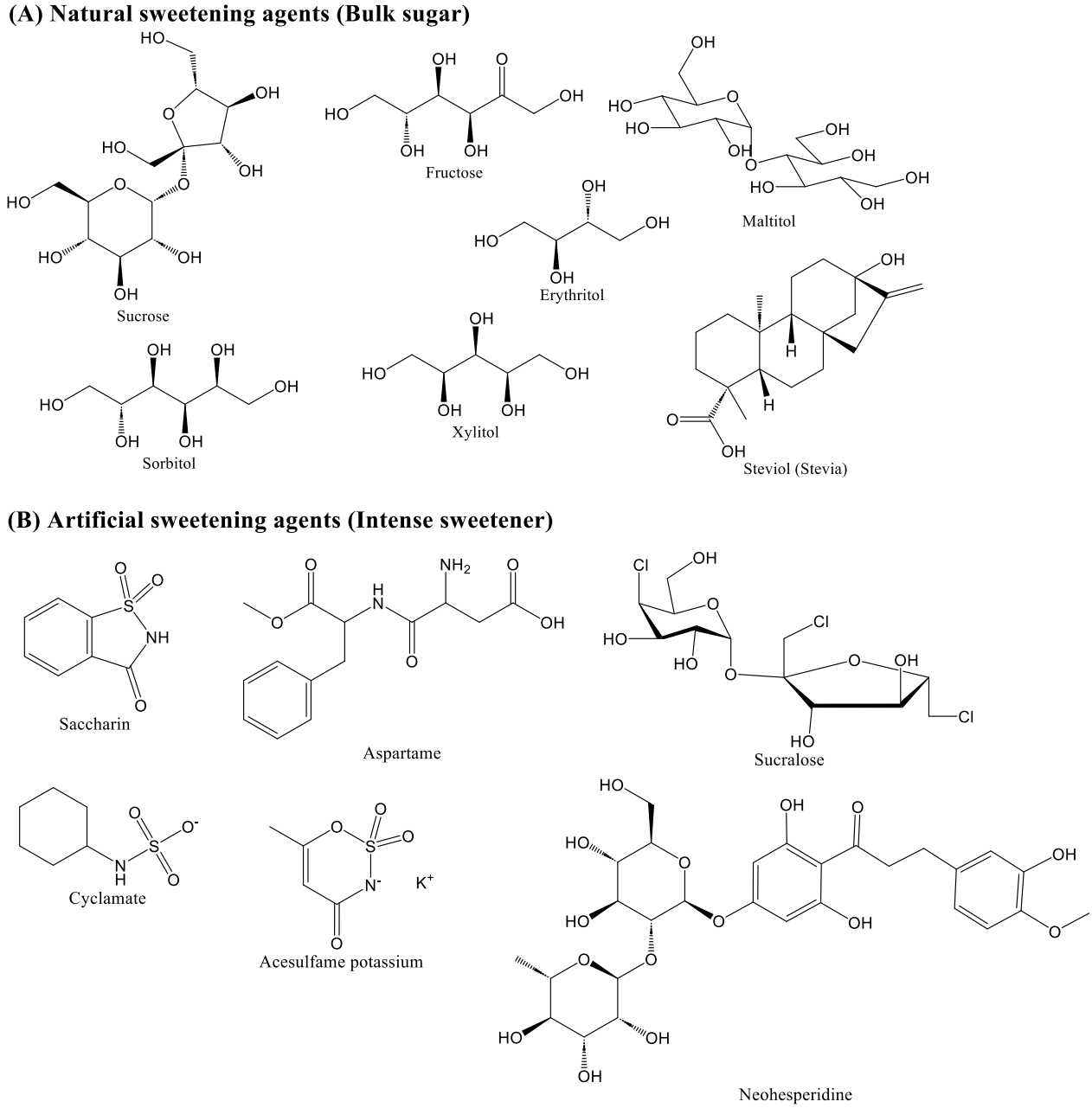

Figure 1: Chemical structure of different natural and artificial sweetening agents

3. Artificial Sweeteners as Measure of Weight Management

Because of the capability of imparting same sweetness similar to sucrose in very small quantity, they are called low calorie sugar (LCS). Consumption of artificial sweetening agents in limited quantity can be beneficial for controlling weight and risk of Diabetes Mellitus. Studies shows correlation of weight gain and consumption of LCS shows reverse causality, such that consuming LCS reduces risk of obesity and weight gain and not the reverse. The different mechanisms of weight management and diabetes control action include [14,15,37] .Because of less amount of intense sweeteners requirement, the calorific value imparted by these sweeteners is less than that of sucrose intake. Sucrose in liver gets metabolized to glucose and stored as glycogen unlike intense sugars like saccharin, sucralose

pass unmetabolized. Appetite reduction is another mechanism of reducing the risk of developing diabetes mellitus and weight gain. Reduced in appetite causes reduced food intake followed by reduced absorption of food causes control in weight [38,39]. These artificial sugars have higher affinity than sucrose for taste bud receptors responsible for sweet taste namely T1R2 and T1R3 heterodimers. Because of strong agonistic action, in very less concentration, a sweet taste is sensed and consumption of food becomes limited [18]. These sweeteners are found to influence the release of GLP-1 and PPY, also some bulk sweeteners like sugar alcohol are found to have activities like α-amylase and α-glucosidase inhibition. Thus, inhibition of carbohydrate digestion enzymes reduces their digestion followed by absorption [26]. Due to less absorption and no metabolism, these sweeteners does not cause blood glucose spike. Moreover, it is found that some might increase the sensitivity of cells to insulin and insulin release by influencing GLP-1 secretion.

Acesulfame-Potassium, an artificial sweetener is not metabolized in out body. Though it has potassium in the structure, it has no influence on daily potassium intake [16]. The concentration or presence of glycosylated hemoglobin (HbA1C) after regular intake of sucrose were found profoundly more than after intake of artificial sweetener. Thus, artificial sweeteners have lesser effect of hemoglobin and its oxygen carrying capacity [37].

The mechanism of action of how LCS acts as an alternative of sugar for diabetic and obese patient is represented in Figure 2.

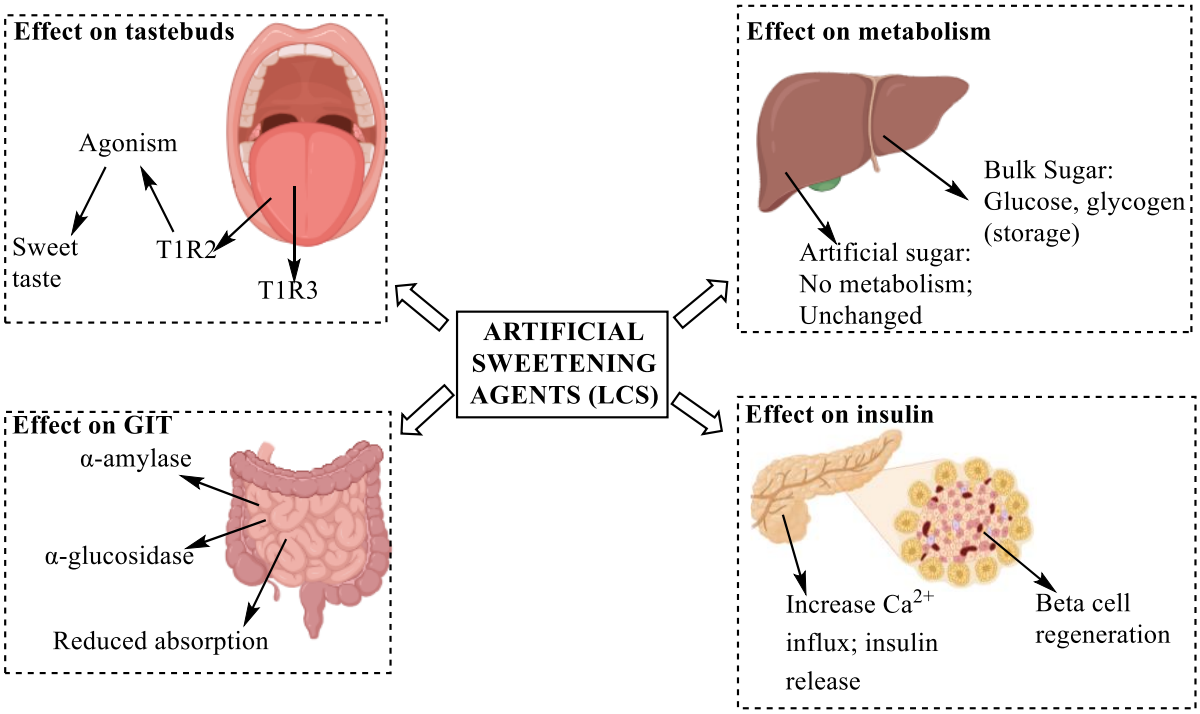

Figure 2. Mechanism of action of Intense sweeteners in maintaining blood sugar and weight management

4. Health Hazards of Artificial Sweeteners

The basic aim to shift from natural sweeteners to artificial sweetener is to reduce the calorie intake, to prevent glycemic peaks and reduce weight gain or obesity. But recent studies and ongoing projects has proven that by various mechanisms the artificial sweeteners seem to have adverse effects resulting in chronic disorders like metabolic disorders, cancer and neurogenerative disorders.

4.1. Metabolic disorders

Metabolic disorders are groups of diseases characterized with increase in waist circumference, elevated blood glucose level, increase in blood pressure or hypertension and hyperlipidemia. These are also called lifestyle related or cardiometabolic disorders. Obese people have more inclination to development of Type II Diabetes mellitus, because of the chronic low-grade inflammation hampers the insulin signaling. This makes the cells more insulin resistance, thus elevates the blood glucose level further [40].

Artificial sweeteners shows increase in metabolic disorders. These cardiometabolic disorders occur due to three main reasons:

Aspartame, which is a widely used artificial sweetening agent in our liver, is metabolized to methanol and other by products. This shows to methanol under action of alcohol dehydrogenase forms formaldehyde, which induces free radical formation and thereby reduces insulin signaling and develops more insulin resistance when used for prolonged period of time [41].

They have effect on gut microbiota. Artificial sweetening agents like saccharin and sucralose alter the gut microbiota. More than 2000 different microbes coexist in the gut, which is responsible for normal absorption followed by metabolism. Disturbance in this composition can lead to alteration in metabolic processes and development of several cardiovascular diseases [42]. Saccharin shows to affect the gut microbiota and increase in Bacteroides and a decrease in Lactobacillus bacteria. This changes fatty acid chain and glucose metabolism and leads to further glucose spike and insulin resistance [30]. Study demonstrated the ability of sucralose to adhere to gut cell and kill them. Prolonged use of sucralose reduces the concentration of Bifidobacterium in gut wall. This disrupt the microbiota in gut. Thereby the secretion of CLP-1 and 2 and PPY in pancreas reduces. This reduces cascade of event for insulin secretion from pancreatic cells [30,43]. Regular consumption of cyclamate shows increase concentration of insulin secretion, but the insulin resistance also increases, thereby reduced cellular penetration of blood glucose.

Increase in the cholesterol level causes lipid accumulation the narrow artery wall of lumen, which narrows the artery wall even more, leading to lesser blood flow with higher pressure. It has been found that excessive and prolonged use of artificial sweeteners impair the structure of apoA-1, a major protein found in HDL lipid. This alters the senescence and causes increase in incidence of developing atherosclerosis. This is found prominently by action of artificial sweetening agents like aspartame and Acesulfame-potassium [44,45].

Aspartame has found to lead “lone” atrial fibrillation, which eventually provokes series of cardiovascular disorders including hypertension, cardiac arrest and myocardial infraction [46,47].

4.2. **Increase in incidence of cancer**

Cancer is one of the deadliest diseases which potentially have very less chances of cure and very less scope for treatment has been identified. Among multiple compounds, only a few artificial sweetening agents which have been allowed by FDA due to their carcinogenicity and mutagenic potentials. Different artificial sweetening agent shows tendency to develop cancer by different mechanism:

Aspartame, which is generally used with Acesulfame-potassium to reduce its bitter after-taste, shows cancerogenic potential. Aspartame in liver when metabolized forms methanol. Alcohol dehydrogenase enzyme in liver converts methanol (CH_3OH) to formaldehyde (HCOOH). This formaldehyde is carcinogenic, since it disrupts the double strands of DNA and forms cross links. Thus, forms defective DNA. When this replicates in cell cycle, progression of cancer occurs [48].

Sucralose can induce formation of reactive oxygen species and induce oxidative stress. This ROS can subsequently oxidize and cause cellular or tissue damage [49]. Saccharin induce alteration of DNA methyltransferases enzyme and hence, in-vitro studies in rats shows

tendency of bladder cancer. Thus, FDA banned use of saccharin in the year 1981. Further lack of evidences re-allowed the use of saccharin as sweetening agent. On the other hand, acesulfame-potassium promotes histone acetylation [49].

5. Discussion

In the world of sedentary lifestyles, where India has become the diabetic capital of the world, and mostly 30% of the population is obese, the people have become conscious of their diet and the food they eat. The main goal of people is to cut off sugar and sugar-like substances from their diet. But carbohydrates and sugars, being integral part of diet should not be totally cut off. So, the focus to find alternatives of sugar has emerged. This led to development of non-sugar like sweet tasting substances called artificial sugars, which despite being sweet are not metabolized in or body. So controlled intake of these substances has minimum adverse effect in our body along with chances of management of obesity, hyperlipidemia and hyperglycemia [18]. These are also called low-calorie non-nutritive sweetening agents because of their high sweetness potential, the amount of these substances to impart sweet taste is less.

Natural sugars includes sucrose, or the reference sugar, milk sugar like lactose and galactose, sugar alcohol like mannitol, xylitol, maltitol, erythritol etc. These substances, since are obtained from nature has lesser capability of carcinogenicity and mutagenicity. These compounds, because of low sweetness potential is required in larger amount and thus causes rapid glycemic spike and over usage lead to insulin resistance and obesity [9].

Saccharine is the most widely used artificial sweetening agents used to give sweet taste to juices, beverages, cakes, biscuits and other packed food. Daily usage within the Allowed dietary intake (ADI) level is useful for management of weight and chronic lifestyle diseases, but over usage can lead to disturbance of gut microbiota causing increase in insulin resistance and reduce insulin formation. This also have risk of developing atherosclerotic plaque and cardiovascular diseases. Chances of mutagenicity and cross linking in DNA and methylation of DNA have shown chances of bladder cancer development in rats in vitro. But later, FDA allowed use of this because of lack of evidences [27,30,33].

Aspartame and sucralose are two of the most used artificial sweetening agents. Large intake of aspartame can cause two chronic diseases. Methanol production as a metabolite leads to intercalation and cross links in DNA as well as reduced insulin sensitivity. If consumed within ADI, these two are safest sweetening agents [29–31,48]. Acesulfame potassium is used with aspartame to mask the bitter aftertaste of aspartame. This substance has showed chances of development of atherosclerosis development through impairment of apoA-1 protein structure [44,45].

Role of gut microbiota has instrumental role in maintaining the blood glucose level in human body. Sucralose and saccharin, on prolonged use has shown to hamper the gut microbiota and in turn, affect glucose metabolism. It also affects synthesis of GLP-1 and PPY, and hence reduces synthesis of insulin from pancreatic beta cells.

This review highlighted that the use of natural sweetener, due to their high calorific value should be limited. The instrumental factor to use artificial sweetener to reduce diabetes and obesity without any opposite effect lies on its wise use within the advised ADI by World Health organization (WHO) and Food Drug Administration (FDA). Generalizing the use of artificial sugars to all individual should not be practiced, instead focus on individual body needs should be done. The balance between benefits and potential risks should be monitored for all individual before advising these artificial sugars, especially for vulnerable groups of people like children, pregnant women and people with chronic lifestyle diseases. Future research direction should focus in animal model study about different effects of use of

multiple sweeteners in synergism and interpret their understanding for future use by common people.

6. Conclusion

From this review work, it is evident that health effects, either beneficial or hazardous is independent of the sweetness potential of the substance. The main aim to use artificial sweetener is to reduce the immediate glucose spike of the natural sweetener. Prolonged use of low calorie non-nutrient artificial can show chronic metabolic disorder, if not consumed within the allowed dietary intake limit. This review work compiles significant results and data from different research paper and no original work has been done in our lab. The choice of sweetener to be used should in individualized based on their chronic diseases, metabolic rate, consumption and gut microbiota interactions and should be done under supervision of registered medical practitioner.

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REFERENCES

[1] *D. O'Connor, M. Pang, G. Castelnuovo, G. Finlayson, E. Blaak, C. Gibbons, et al., "A rational review on the effects of sweeteners and sweetness enhancers on appetite, food reward and metabolic/adiposity outcomes in adults," Food Funct, vol. 12,* ***(2021)****, pp. 442-465, https://doi.org/10.1039/D0FO02424D.*

[2] *J.H. Park, J.H. Moon, H.J. Kim, M.H. Kong, Y.H. Oh, "Sedentary Lifestyle: Overview of Updated Evidence of Potential Health Risks," Korean J Fam Med, vol. 41,* ***(2020)****, pp. 365-373, https://doi.org/10.4082/kjfm.20.0165.*

[3] *L.C.G. Martins, M.V.O. Lopes, C.M. Diniz, N.G. Guedes, "The factors related to a sedentary lifestyle: A meta-analysis review," J Adv Nurs, vol. 77,* ***(2021)****, pp. 1188-1205, https://doi.org/10.1111/jan.14669.*

[4] *G. Raghavan, A. Bapna, A. Mehta, A. Shah, T. Vyas, "Effect of Sugar Replacement with Stevia-Based Tabletop Sweetener on Weight and Cardiometabolic Health among Indian Adults," Nutrients, vol. 15,* ***(2023)****, pp. 1744, https://doi.org/10.3390/nu15071744.*

[5] *Y. Liu, J. Cheng, L. Wan, W. Chen, "Associations between Total and Added Sugar Intake and Diabetes among Chinese Adults: The Role of Body Mass Index," Nutrients, vol. 15,* ***(2023)****, pp. 3274, https://doi.org/10.3390/nu15143274.*

[6] *M. Veit, R. van Asten, A. Olie, P. Prinz, "The role of dietary sugars, overweight, and obesity in type 2 diabetes mellitus: a narrative review," Eur J Clin Nutr, vol. 76,* ***(2022)****, pp. 1497-1501, https://doi.org/10.1038/s41430-022-01114-5.*

[7] *A. Lang, O. Kuss, T. Filla, S. Schlesinger, "Association between per capita sugar consumption and diabetes prevalence mediated by the body mass index: results of a global mediation analysis," Eur J Nutr, vol. 60,* ***(2021)****, pp. 2121-2129, https://doi.org/10.1007/s00394-020-02401-2.*

[8] *A. Sampath Kumar, A.G. Maiya, B.A. Shastry, K. Vaishali, N. Ravishankar, A. Hazari, et al., "Exercise and insulin resistance in type 2 diabetes mellitus: A*

*systematic review and meta-analysis," Ann Phys Rehabil Med, vol. 62, **(2019)**, pp. 98-103, https://doi.org/10.1016/j.rehab.2018.11.001.*

[9] *K.M. Gillespie, E. Kemps, M.J. White, S.E. Bartlett, "The Impact of Free Sugar on Human Health—A Narrative Review," Nutrients, vol. 15, **(2023)**, pp. 889, https://doi.org/10.3390/nu15040889.*

[10] *G. Maroni, L. Pallante, G. Di Benedetto, M.A. Deriu, D. Piga, G. Grasso, "Informed classification of sweeteners/bitterants compounds via explainable machine learning," Curr Res Food Sci, vol. 5, **(2022)**, pp. 2270-2280, https://doi.org/10.1016/j.crfs.2022.11.014.*

[11] *S. Arshad, T. Rehman, S. Saif, M.S.R. Rajoka, M.M.A.N. Ranjha, A. Hassoun, et al., "Replacement of refined sugar by natural sweeteners: focus on potential health benefits," Heliyon, vol. 8, **(2022)**, pp. e10711, https://doi.org/10.1016/j.heliyon.2022.e10711.*

[12] *A. Saraiva, C. Carrascosa, D. Raheem, F. Ramos, A. Raposo, "Natural Sweeteners: The Relevance of Food Naturalness for Consumers, Food Security Aspects, Sustainability and Health Impacts," Int J Environ Res Public Health, vol. 17, **(2020)**, pp. 6285, https://doi.org/10.3390/ijerph17176285.*

[13] *Z. Chen, Z. Shen, Z. Hua, X. Li, "Global development and future trends of artificial sweetener research based on bibliometrics," Ecotoxicol Environ Saf, vol. 263, **(2023)**, pp. 115221, https://doi.org/10.1016/j.ecoenv.2023.115221.*

[14] *L. Andrade, K.M. Lee, A.C. Sylvetsky, S.I. Kirkpatrick, "Low-calorie sweeteners and human health: a rapid review of systematic reviews," Nutr Rev, vol. 79, **(2021)**, pp. 1145-1164, https://doi.org/10.1093/nutrit/nuaa123.*

[15] *M. Daher, C. Fahd, A.A. Nour, Y. Sacre, "Trends and amounts of consumption of low-calorie sweeteners: A cross-sectional study," Clin Nutr ESPEN, vol. 48, **(2022)**, pp. 427-433, https://doi.org/10.1016/j.clnesp.2022.01.006.*

[16] *T.A. More, Z. Shaikh, A. Ali, "Artificial Sweeteners and their Health Implications: A Review," Biosci Biotechnol Res Asia, vol. 18, **(2021)**, pp. 227-237, https://doi.org/10.13005/bbra/2910.*

[17] *A. Piekara, M. Krzywonos, A. Szymańska, "Sweetening Agents and Sweeteners in Dietary Supplements for Children-Analysis of the Polish Market," Nutrients, vol. 12, **(2020)**, pp. 2387, https://doi.org/10.3390/nu12082387.*

[18] *K. Wilk, W. Korytek, M. Pelczyńska, M. Moszak, P. Bogdański, "The Effect of Artificial Sweeteners Use on Sweet Taste Perception and Weight Loss Efficacy: A Review," Nutrients, vol. 14, **(2022)**, https://doi.org/10.3390/nu14061261.*

[19] *M.A. Farag, M. Rezk, M. Hamdi Elashal, M. El-Araby, S.A.M. Khalifa, H.R. El-Seedi, "An updated multifaceted overview of sweet proteins and dipeptides as sugar substitutes; the chemistry, health benefits, gut interactions, and safety," Food Research International, vol. 162, **(2022)**, pp. 111853, https://doi.org/10.1016/j.foodres.2022.111853.*

[20] *M. Yamakawa, K. Wada, S. Koda, F. Mizuta, T. Uji, S. Oba, et al., "High Intake of Free Sugars, Fructose, and Sucrose Is Associated with Weight Gain in Japanese Men," J Nutr, vol. 150, **(2020)**, pp. 322-330, https://doi.org/10.1093/jn/nxz227.*

[21] *M.R. Taskinen, C.J. Packard, J. Borén, "Dietary Fructose and the Metabolic Syndrome," Nutrients, vol. 11, **(2019)**, pp. 1987, https://doi.org/10.3390/nu11091987.*

[22] *V. Peteliuk, L. Rybchuk, M. Bayliak, K.B. Storey, O. Lushchak, "Natural sweetener Stevia rebaudiana: Functionalities, health benefits and potential risks," EXCLI J, vol. 20, **(2021)**, pp. 1412-1430, https://doi.org/10.17179/excli2021-4211.*

[23] *A. Saraiva, C. Carrascosa, D. Raheem, F. Ramos, A. Raposo, "Maltitol: Analytical Determination Methods, Applications in the Food Industry, Metabolism and Health*

Impacts," Int J Environ Res Public Health, vol. 17, ***(2020)****, pp. 5227, https://doi.org/10.3390/ijerph17145227.*

[24] *N.Z. Msomi, O.L. Erukainure, M.S. Islam, "Suitability of Sugar Alcohols as Antidiabetic Supplements: A Review," J Food Drug Anal, vol. 29,* ***(2021)****, pp. 1-14, https://doi.org/10.38212/2224-6614.3107.*

[25] *V. Bordier, F. Teysseire, G. Schlotterbeck, F. Senner, C. Beglinger, A.C. Meyer-Gerspach, et al., "Effect of a Chronic Intake of the Natural Sweeteners Xylitol and Erythritol on Glucose Absorption in Humans with Obesity," Nutrients, vol. 13,* ***(2021)****, pp. 3950, https://doi.org/10.3390/nu13113950.*

[26] *B.K. Wölnerhanssen, A.C. Meyer-Gerspach, C. Beglinger, M.S. Islam, "Metabolic effects of the natural sweeteners xylitol and erythritol: A comprehensive review," Crit Rev Food Sci Nutr, vol. 60,* ***(2020)****, pp. 1986-1998, https://doi.org/10.1080/10408398.2019.1623757.*

[27] *O.H. Azeez, S.Y. Alkass, D.S. Persike, "Long-Term Saccharin Consumption and Increased Risk of Obesity, Diabetes, Hepatic Dysfunction, and Renal Impairment in Rats," Medicina, vol. 55,* ***(2019)****, pp. 681, https://doi.org/10.3390/medicina55100681.*

[28] *K. Czarnecka, A. Pilarz, A. Rogut, P. Maj, J. Szymańska, Ł. Olejnik, et al., "Aspartame—True or False? Narrative Review of Safety Analysis of General Use in Products," Nutrients, vol. 13,* ***(2021)****, pp. 1957, https://doi.org/10.3390/nu13061957.*

[29] *S.A.A. Shaher, D.F. Mihailescu, B. Amuzescu, "Aspartame Safety as a Food Sweetener and Related Health Hazards," Nutrients, vol. 15,* ***(2023)****, pp. 3627, https://doi.org/10.3390/nu15163627.*

[30] *S. del Pozo, S. Gómez-Martínez, L.E. Díaz, E. Nova, R. Urrialde, A. Marcos, "Potential Effects of Sucralose and Saccharin on Gut Microbiota: A Review," Nutrients, vol. 14,* ***(2022)****, pp. 1682, https://doi.org/10.3390/nu14081682.*

[31] *J.A. Aguayo-Guerrero, L.A. Méndez-García, H. Solleiro-Villavicencio, R. Viurcos-Sanabria, G. Escobedo, "Sucralose: From Sweet Success to Metabolic Controversies—Unraveling the Global Health Implications of a Pervasive Non-Caloric Artificial Sweetener," Life, vol. 14,* ***(2024)****, pp. 323, https://doi.org/10.3390/life14030323.*

[32] *C.H. Lin, H.Y. Li, S.H. Wang, Y.H. Chen, Y.C. Chen, H.T. Wu, "Consumption of Non-Nutritive Sweetener, Acesulfame Potassium Exacerbates Atherosclerosis through Dysregulation of Lipid Metabolism in ApoE−/− Mice," Nutrients, vol. 13,* ***(2021)****, pp. 3984, https://doi.org/10.3390/nu13113984.*

[33] *H.M. Hasan, S.Y. Alkass, D.S.P. de Oliveira, "Impact of Long-Term Cyclamate and Saccharin Consumption on Biochemical Parameters in Healthy Individuals and Type 2 Diabetes Mellitus Patients," Medicina, vol. 59,* ***(2023)****, pp. 698, https://doi.org/10.3390/medicina59040698.*

[34] *M.D. Pang, G.H. Goossens, E.E. Blaak, "The Impact of Artificial Sweeteners on Body Weight Control and Glucose Homeostasis," Front Nutr, vol. 7,* ***(2021)****, https://doi.org/10.3389/fnut.2020.598340.*

[35] *S. Choi, S. Yu, J. Lee, W. Kim, "Effects of Neohesperidin Dihydrochalcone (NHDC) on Oxidative Phosphorylation, Cytokine Production, and Lipid Deposition," Foods, vol. 10,* ***(2021)****, pp. 1408, https://doi.org/10.3390/foods10061408.*

[36] *M. Kwon, Y. Kim, J. Lee, J.A. Manthey, Y. Kim, Y. Kim, "Neohesperidin Dihydrochalcone and Neohesperidin Dihydrochalcone-O-Glycoside Attenuate Subcutaneous Fat and Lipid Accumulation by Regulating PI3K/AKT/mTOR Pathway In Vivo and In Vitro," Nutrients, vol. 14,* ***(2022)****, pp. 1087, https://doi.org/10.3390/nu14051087.*

[37] *A.M. Gallagher, M. Ashwell, J.C.G. Halford, C.A. Hardman, N.G. Maloney, A. Raben, "Low-calorie sweeteners in the human diet: scientific evidence, recommendations, challenges and future needs. A symposium report from the FENS 2019 conference," J Nutr Sci, vol. 10, **(2021)**, pp. e7, https://doi.org/10.1017/jns.2020.59.*

[38] *F. Harnischfeger and R. Dando, "Obesity-induced taste dysfunction, and its implications for dietary intake," Int J Obes, vol. 45, **(2021)**, pp. 1644-1655, https://doi.org/10.1038/s41366-021-00855-w.*

[39] *M. D. Pang, G. H. Goossens, and E. E. Blaak, "The Impact of Artificial Sweeteners on Body Weight Control and Glucose Homeostasis," Front Nutr, vol. 7, **(2021)**, https://doi.org/10.3389/fnut.2020.598340.*

[40] *F. Zatterale, M. Longo, J. Naderi, G. A. Raciti, A. Desiderio, C. Miele, et al., "Chronic Adipose Tissue Inflammation Linking Obesity to Insulin Resistance and Type 2 Diabetes," Front Physiol, vol. 10, **(2020)**, https://doi.org/10.3389/fphys.2019.1607.*

[41] *S. Sabarathinam, D. Dhanasekaran, and N. Ganamurali, "Artificial Sweetener is a Growing Threat for Metabolic Syndrome: Why is Extra Attention required?" Future Sci OA, vol. 9, **(2023)**, https://doi.org/10.2144/fsoa-2023-0092.*

[42] *C. Debras, E. Chazelas, L. Sellem, R. Porcher, N. Druesne-Pecollo, Y. Esseddik, et al., "Artificial sweeteners and risk of cardiovascular diseases: results from the prospective NutriNet-Santé cohort," BMJ, **(2022)**, pp. e071204, https://doi.org/10.1136/bmj-2022-071204.*

[43] *A. Sadagopan, A. Mahmoud, M. Begg, M. Tarhuni, M. Fotso, N. A. Gonzalez, et al., "Understanding the Role of the Gut Microbiome in Diabetes and Therapeutics Targeting Leaky Gut: A Systematic Review," Cureus, **(2023)**, https://doi.org/10.7759/cureus.41559.*

[44] *S. Singh, A. Kohli, S. Trivedi, S. G. Kanagala, FNU. Anamika, N. Garg, et al., "The contentious relationship between artificial sweeteners and cardiovascular health," Egypt J Intern Med, vol. 35, **(2023)**, pp. 43, https://doi.org/10.1186/s43162-023-00232-1.*

[45] *L. V. Griebsch, E. L. Theiss, D. Janitschke, V. K. J. Erhardt, T. Erhardt, E. C. Haas, et al., "Aspartame and Its Metabolites Cause Oxidative Stress and Mitochondrial and Lipid Alterations in SH-SY5Y Cells," Nutrients, vol. 15, **(2023)**, pp. 1467, https://doi.org/10.3390/nu15061467.*

[46] *A. R. Gómez-Fernández, A. Santacruz, and D. A. Jacobo-Velázquez, "The complex relationship between metabolic syndrome and sweeteners," J Food Sci, vol. 86, **(2021)**, pp. 1511-1531, https://doi.org/10.1111/1750-3841.15709.*

[47] *N. D. McGlynn, T. A. Khan, L. Wang, R. Zhang, L. Chiavaroli, F. Au-Yeung, et al., "Association of Low- and No-Calorie Sweetened Beverages as a Replacement for Sugar-Sweetened Beverages With Body Weight and Cardiometabolic Risk," JAMA Netw Open, vol. 5, **(2022)**, pp. e222092, https://doi.org/10.1001/jamanetworkopen.2022.2092.*

[48] *P. J. Landrigan and K. Straif, "Aspartame and cancer – new evidence for causation," Environmental Health, vol. 20, **(2021)**, pp. 42, https://doi.org/10.1186/s12940-021-00725-y.*

[49] *W. Ghusn, R. Naik, and M. Yibirin, "The Impact of Artificial Sweeteners on Human Health and Cancer Association: A Comprehensive Clinical Review," Cureus, vol. 15, **(2023)**, pp. e51299, https://doi.org/10.7759/cureus.51299.*