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A Holistic Review On Sugar Substitutes

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ABSTRACT

Sugar substitutes have emerged as popular alternatives to traditional sugar due to their perceived health benefits, including weight management and reduced risk of diabetes and dental cavities. However, the benefits of sugar substitutes remain controversial, with conflicting evidence regarding their impact on weight regulation. Some studies suggest that sugar substitutes may facilitate weight loss by reducing calorie intake, while others indicate a potential for weight gain through metabolic and behavioral responses. Concerns have also been raised regarding the risk of cancer associated with artificial sweeteners, contrasting with findings of potential anti-tumor effects attributed to natural sweeteners. Market research indicates a consumer preference for natural sweeteners over artificial alternatives, driven by perceptions of safety and healthiness. This review article explores the scientific evidence surrounding sugar substitutes, examining their implications for weight management, dental health, and cancer risk, while addressing consumer perceptions and preferences shaping the sweetener market landscape.

Introduction

In recent years, advances in the medical industry and a growing emphasis on healthier lifestyle choices have spurred significant interest in finding alternatives to traditional sugar consumption. Various types of low-calorie sweeteners have become increasingly prevalent in modern diets to replace table sugar, i.e. sucrose. These sweeteners offer sweetness without the calorie load of sugar, appealing to individuals seeking to manage weight and reduce sugar intake. However, the use of said sweeteners has also sparked significant debate and scrutiny due to concerns regarding their potential health effects. In this review, the terms non-nutritive sweeteners (NNS), no-to low-calorie sweeteners (LCS), and sugar substitutes are used interchangeably. We delve into the multifaceted landscape of various types of sweeteners, examining their association with obesity, cancer, and dental health. By exploring these critical aspects, we aim to provide a comprehensive understanding of the scientific evidence and consumer perceptions surrounding the use of artificial sweeteners in contemporary dietary practices.

Types of Sweeteners

Sweeteners are defined as substances used to sweeten food or drinks, especially one other than table sugar (sucrose). Sweeteners can be categorized into three main types: artificial sweeteners, sugar alcohols and natural sweeteners. Artificial sweeteners, such as saccharin, sucralose, and aspartame, are entirely synthesized in laboratories. Sugar alcohols, such as xylitol, sorbitol, erythritol, and mannitol, are naturally present in small amounts, however most sugar alcohols found in packaged foods are manmade or manufactured. Lastly, natural sweeteners including stevia, monk fruit extract, and d-allulose are sourced from plants and other natural food sources. However, they undergo additional processing steps such as extraction and purification to isolate the sweetening components.

Saccharin, the oldest artificial sweetener, was initially synthesized in 1879 by a Russian chemist named Constantine Fahlberg. This compound is about 400 times sweeter than sucrose (table sugar) and is not absorbed or metabolized by the body. Over time, saccharin has been largely replaced by newer sweeteners due to its characteristic metallic aftertaste. (Mahmood & Aljuboori, 2020)

Aspartame is a widely used artificial sweetener found in over 6000 products, including soft drinks, dessert mixes, frozen desserts, yogurt, chewable multivitamins, and breakfast cereals. It is 200 to 300 times sweeter than sugar and unlike saccharin, provides a clean, sugar-like taste without any undesirable metallic or bitter aftertaste.(Choudhary & Pretorius, 2017)

Sugar alcohols, despite their misleading name, are neither sugars nor alcohols. They are low-digestible carbohydrates obtained by substituting aan aldehyde group with a hydroxyl group. Sugar alcohols are often less sweet than sugar and are used in combination with other sweeteners to achieve the desired level of sweetness and flavor in products. They have a potent laxative effect and other gastrointestinal symptoms such as flatulence, bloating and abdominal discomfort when consumed in excess.(Grembecka, 2015)

Stevia is a natural sweetener derived from the Stevia rebaudiana plant native to South America. It is produced by extracting steviol glycosides from the leaves of this plant. Stevia is known to be 50-350 times sweeter than sugar. Importantly, steviol glycosides are not digested in the upper gastrointestinal tract; they undergo hydrolysis or degradation only upon contact with microbiota in the colon. This means they do not contribute to calorie intake and are considered a low-calorie alternative to sugar. (Samuel et al., 2018)

D-allulose is a low-calorie rare sugar that naturally occurs in small amounts in figs, raisin and wheat. It is approximately 70% as sweet as sugar but contains only one-tenth of the calories of sugar. Similar to sugar alcohols, excess intake may entail gastrointestinal discomfort. (Zhang et al., 2023)

Association Between Obesity and Sugar Substitutes

Definition of Obesity and Its Causes

Obesity is defined as the accumulation of excess fat in the body that leads to dysfunction of adipose tissue and abnormal fat mass physical forces.(Faruque et al., 2019) The increasing rates of obesity pose a significant public health threat, as it is a well-established risk factor for a wide range of health conditions, including but not limited to cardiometabolic disease, musculoskeletal diseases, obstructive sleep apnoea, and cancer.(Laviada-Molina et al., 2020) While low-fat diets have been recommended for weight management, it was revealed that diets high in added sugar was another significant factor contributing to obesity.(Laviada-Molina et al., 2020) It was found that the US population was consuming more than 300% of the daily recommended amount of added sugar and that the increase in total sugar consumption correlated to the increase in obesity.(Laviada-Molina et al., 2020) Therefore, it has been suggested that reducing sugar consumption may be the solution to the annual increase of obesity.

Replacing Sugar with Sugar Substitutes Promotes Weight Loss

The use of sugar substitutes has been suggested as a way to reduce sugar consumption and excess calories.(Sørensen et al., 2014) In fact, multiple animal and human studies have demonstrated the weight loss effect of replacing sugar to sugar substitutes. Sørensen *et al.* investigated the effects of sucrose and artificially sweetened beverages and foods on energy intake in overweight subjects for 10 weeks. The results demonstrated a weight gain in the sucrose group while a decreased in the sweetener group.(Sørensen et al., 2014) The sucrose group had a higher energy intake yet feeling less full, suggesting the satiating effect of sweeteners.(Sørensen et al., 2014) Another research group compared the effects of regular coke, diet coke, milk and water on changes

in total fat mass and ectopic fat deposition in the liver and muscle tissue.(Maersk et al., 2012) While the total fat mass was not significantly different between each beverage group, the research team found significantly higher liver fat, muscle fat, visceral fat, blood triglyceride, and total cholesterol in individuals given regular coke compared to than in the other three groups. In fact, diet cola reduced blood pressure by 10-15% compared with regular cola, indicating that replacing sucrose-sweetened beverages to noncaloric drinks may prevent cardiovascular and metabolic diseases, independent to weight loss.(Maersk et al., 2012) In another cross-sectional study conducted over a period of 11 years, the relationship between water and no-and low-calorie sweetened beverage (LCSB) intake with nutrient intake was evaluated.(Leahy et al., 2017; Sørensen et al., 2014) The results of the study revealed that higher LCSB intake was associated with significantly lower consumption of carbohydrates, total sugars, and added sugars than those associated with higher water intake.(Leahy et al., 2017) These results suggests that sugar substitutes beverages may be better than water at weight management.

Replacing Sugar with Sugar Substitutes Does Not Prevent Obesity, but in Fact, Promotes Weight Gain

Despite the number of studies suggesting sugar substitutes as the healthier alternative for sugar, there are also studies demonstrating against it. For example, the San Antonio Heart Study examined over 3000 adults over a seven to eight-year period and found out artificially sweetened beverages drinkers consistently had higher BMIs.(Yang, 2010) Moreover, in a cohort study of 1454 participants from 1884 to 2012, participants who consumed artificial sweeteners had a significantly higher BMI and increased waist circumference compared to non-users.(Chia et al., 2016; Pearlman et al., 2017) The risk of obesity is not restricted to adults but also to infants of mothers who consumed artificially-sweetened beverages during pregnancy. The study assessed the artificial sweetener and sugar-sweetened beverage consumption of 3033 pregnant women and found that the babies of mothers who consumed artificially-sweetened beverages every day were twice as likely to be overweight than of non-users.(Azad et al., 2016) There are several hypotheses why sugar substitutes promote weight gain, despite them being low to zero-calories. Since artificial sweeteners stimulate oral taste receptors but do not contain caloric energy, they fail to fully activate the post-ingestion pathway. The partial engagement in the food reward pathway triggers an increase in appetite, greater food craving and ultimately result in a rise in caloric intake.(Pearlman et al., 2017) In fact, animal studies reveal that mice that were fed artificial sweetener supplements, consumed more calories and gained more weight compared to control groups that were fed sugar.(Pearlman et al., 2017) Another hypothesis is that individuals actively overcompensate. Tey *et al.* discovered that once participants knew that they were having artificially sweetened beverages consciously chose to eat more during subsequent meals, possibly due to the idea that they are saving calories in drinks.(Tey et al., 2017) Lastly, growing evidence demonstrates the effect of artificial sweeteners on gut microbiota dysbiosis, by altering the gut microbiota composition and function. Specifically, low microbiome diversity has been linked to obesity and it was found that artificial sweeteners disturb the diversity.(Nettleton et al., 2016)

Collectively, despite extensive studies from the scientific community, there still lacks a unanimous consensus that can accurately define the effects of sugar substitutes on obesity.

Association Between Cancer and Sugar Substitutes

Artificial Sweeteners May Cause Cancer

Sugar substitutes, particularly artificial sweeteners like aspartame, have been associated with an increased risk of cancer based on various studies. In fact, the use of aspartame has been suspended in the US from 1970 to 1981 due to suspicions of causing cancer.(Czarnecka et al., 2021) Animal research has indicated that aspartame

can lead to liver and lung cancer in male mice, as well as leukemia and lymphoma in both male and female mice.(Soffritti et al., 2006; Soffritti et al., 2010; Soffritti et al., 2007) Additionally, a long-term study tracking 125,000 adults for up to 20 years found that men who consumed at least one diet soda daily had a slightly higher risk of multiple myeloma and non-Hodgkin lymphoma compared to those who did not consume diet soda.(Schernhammer et al., 2012) In another large cohort study involving over 100,000 French adults, researchers discovered an association between aspartame intake and an elevated risk of breast cancer and cancers related to obesity.(Debras et al., 2022) Moreover, prenatal exposure to aspartame has been shown to heighten cancer risk in rodent offspring.(Landrigan & Straif, 2021) Recent research has proposed a potential explanation for the carcinogenic effects of artificial sweeteners. The study revealed that mice fed sucralose experienced a decrease the function of T cells, immune cells that play a crucial role in eliminating cancerous cells.(Zani et al., 2023)

Natural Sweeteners Do Not Cause Cancer, And May in Fact Prevent Tumorigenesis

Regarding natural sweeteners such as stevia, they are generally considered safe for consumption by the FDA (Food and Drug Administration). Numerous studies have evaluated the safety of stevia, and there is no strong evidence linking their consumption to an increased risk of cancer. In fact, a recent study suggests the potential anti-cancer effect of stevia.(Iatridis et al., 2022) Similarly xylitol, a type of sugar alcohol, was found to induce the apoptosis of cancer cells.(Tomonobu et al., 2020) Another study demonstrated that mice with tongue cancer that were given xylitol survived longer than those given glucose, thus suggesting xylitol as a promising candidate sweetener in food products for cancer survivors. (Sahasakul et al., 2022) However, it must be noted that cancer research on natural sweeteners is not as extensively investigated as that on artificial sweeteners.

Oral Health and Sugar Substitutes

Sugar Substitutes Do Not Cause Tooth Decay

The development of dental cavities is primarily due to bacteria in the mouth that metabolize sugar, producing acid that leads to enamel demineralization and decay. Unlike sugar, artificial sweeteners, sugar alcohols, and natural sweeteners are not metabolized by oral bacteria, thus preventing the formation of acid and protecting against dental caries.(Tuncer et al., 2014) Xylitol is particularly noted for its beneficial effects on dental health. Chewing gums containing xylitol are advertised to prevent dental cavities (Figure 1). While research results are mixed, it can be argued that the act of chewing accompanied by the gustatory reflex stimulate saliva production which helps prevent dental caries.(Tuncer et al., 2014) In fact, studies showed that individuals who chewed xylitol gum had higher pH levels compared to those who chewed a placebo gum.(Kumar et al., 2013) Mutans streptococci (MS) is a predominant bacteria in the mouth. One study demonstrated a significant reduction in MS levels in individuals who chewed xylitol gum compared to those who chewed a placebo.(Caglar et al., 2007)

Figure 1. Advertising image of a xylitol gum product

Xylitol Prevents Dental Plaque Formation and Gingivitis

The beneficial effects of xylitol extend beyond dental caries. A study reported a 20% reduction in dental plaque accumulation for individuals who chewed xylitol gum for 2 weeks, and their relative abundance of pathogenic bacteria decreased while the relative abundance of probiotic bacteria increased.(Wu et al., 2022) Gingivitis, an inflammatory condition of the gums characterized by bleeding and swollen gums, has also shown improvement with xylitol-use. One study reported less bleeding upon pressure in individuals who chewed xylitol gum compared to those who had regular chewing gum.(Keukenmeester et al., 2014) Another study demonstrated significant reductions in gingival bleeding, biofilm formation, and pH increase in individuals using toothpaste containing xylitol compared to a commercial toothpaste(Rodríguez-Agurto et al., 2023), suggesting that sugar alcohols have positive effects not only on dental health but also on gum health.

Perception of Sugar Substitutes

Consumers Prefer ‘Natural’ Sweeteners Over Artificial Ones

With the development of various alternative options to table sugar, consumers now have a wide variety of sweeteners to choose from. A randomized study conducted in Canada investigated the perceived healthiness of sweeteners among adults and found that the majority of respondents perceived aspartame as less healthy than table sugar, while almost half perceived raw sugar as healthier than refined table sugar.(Goodman et al., 2021) This suggests that consumers base their perception of sweetener healthiness more on their level of "naturalness" rather than solely on energy content. In fact, many consumers have reported concerns about the safety of artificial sweeteners with 25% of the survey participants seeing them as harmful.(Parker et al., 2018) According to Kerry’s Sensibly Sweet global research, stevia is currently the third most preferred sweetener in the world after honey and sugar. In South Korea, stevia-infused tomatoes, marketed as "stevia tomato" or "stevito” (Figure 2), have entered the market and gained significant popularity among consumers. Overall, consumers are actively seeking healthier choices of sweeteners, and this trend extends beyond processed foods and beverages to include agricultural products.

Figure 2. Product image of stevia-infused cherry tomatoes, Stevito

Conclusion

In conclusion, the landscape of sugar substitutes is complex and multifaceted, presenting both promises and challenges in the search for healthier dietary choices. While sugar substitutes offer potential benefits such as weight management and dental health by reducing calorie intake and minimizing the risk of cavities, their overall impact remains subject to debate and ongoing research. The contradictory evidence surrounding the effects of sugar substitutes on weight regulation, with studies suggesting both weight loss and weight gain, underscores the need for further investigation into their mechanisms and long-term implications.

Moreover, concerns regarding the potential carcinogenicity of artificial sweeteners juxtaposed with reported anti-tumor effects associated with natural sweeteners highlight the potential shift in the sweetener industry towards a more natural source. Consumer preferences for natural sweeteners reflect evolving perceptions of safety and healthiness, driving market trends and influencing product development in the food industry.

Moving forward, addressing the gaps in knowledge and fostering transparent communication about the risks and benefits of sugar substitutes are essential for informed decision-making by consumers, healthcare professionals, and policymakers. Continued research efforts will contribute to a deeper understanding of the impact of sugar substitutes on health and guide strategies for promoting balanced dietary choices.

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References

Azad, M. B., Sharma, A. K., de Souza, R. J., Dolinsky, V. W., Becker, A. B., Mandhane, P. J., Turvey, S. E., Subbarao, P., Lefebvre, D. L., Sears, M. R., & Investigators, f. t. C. H. I. L. D. S. (2016). Association Between Artificially Sweetened Beverage Consumption During Pregnancy and Infant Body Mass Index. *JAMA Pediatrics*, *170*(7), 662-670. https://doi.org/10.1001/jamapediatrics.2016.0301

Caglar, E., Kavaloglu, S. C., Kuscu, O. O., Sandalli, N., Holgerson, P. L., & Twetman, S. (2007). Effect of chewing gums containing xylitol or probiotic bacteria on salivary mutans streptococci and lactobacilli. *Clin Oral Investig*, *11*(4), 425-429. https://doi.org/10.1007/s00784-007-0129-9

Chia, C. W., Shardell, M., Tanaka, T., Liu, D. D., Gravenstein, K. S., Simonsick, E. M., Egan, J. M., & Ferrucci, L. (2016). Chronic Low-Calorie Sweetener Use and Risk of Abdominal Obesity among

Older Adults: A Cohort Study. *PLOS ONE*, *11*(11), e0167241. https://doi.org/10.1371/journal.pone.0167241

Choudhary, A. K., & Pretorius, E. (2017). Revisiting the safety of aspartame. *Nutr Rev*, *75*(9), 718-730. https://doi.org/10.1093/nutrit/nux035

Czarnecka, K., Pilarz, A., Rogut, A., Maj, P., Szymańska, J., Olejnik, Ł., & Szymański, P. (2021). Aspartame-True or False? Narrative Review of Safety Analysis of General Use in Products. *Nutrients*, *13*(6). https://doi.org/10.3390/nu13061957

Debras, C., Chazelas, E., Srour, B., Druesne-Pecollo, N., Esseddik, Y., Szabo de Edelenyi, F., Agaësse, C., De Sa, A., Lutchia, R., Gigandet, S., Huybrechts, I., Julia, C., Kesse-Guyot, E., Allès, B., Andreeva, V. A., Galan, P., Hercberg, S., Deschasaux-Tanguy, M., & Touvier, M. (2022). Artificial sweeteners and cancer risk: Results from the NutriNet-Santé population-based cohort study. *PLoS Med*, *19*(3), e1003950. https://doi.org/10.1371/journal.pmed.1003950

Faruque, S., Tong, J., Lacmanovic, V., Agbonghae, C., Minaya, D. M., & Czaja, K. (2019). The Dose Makes the Poison: Sugar and Obesity in the United States - a Review. *Pol J Food Nutr Sci*, *69*(3), 219-233. https://doi.org/10.31883/pjfns/110735

Goodman, S., Vanderlee, L., Jones, A., White, C., & Hammond, D. (2021). Perceived Healthiness of Sweeteners among Young Adults in Canada. *Canadian Journal of Dietetic Practice and Research*, *82*(2), 90-94. https://doi.org/10.3148/cjdpr-2020-030 %M 33320777

Grembecka, M. (2015). Sugar alcohols—their role in the modern world of sweeteners: a review. *European Food Research and Technology*, *241*(1), 1-14. https://doi.org/10.1007/s00217-015-2437-7

Iatridis, N., Kougioumtzi, A., Vlataki, K., Papadaki, S., & Magklara, A. (2022). Anti-Cancer Properties of Stevia rebaudiana; More than a Sweetener. *Molecules*, *27*(4). https://doi.org/10.3390/molecules27041362

Keukenmeester, R., Slot, D., Rosema, N., Van Loveren, C., & Van der Weijden, G. (2014). Effects of sugar-free chewing gum sweetened with xylitol or maltitol on the development of gingivitis and plaque: a randomized clinical trial. *International Journal of Dental Hygiene*, *12*(4), 238-244. https://doi.org/https://doi.org/10.1111/idh.12071

Kumar, S., Sogi, S. H., & Indushekar, K. R. (2013). Comparative evaluation of the effects of xylitol and sugar-free chewing gums on salivary and dental plaque pH in children. *J Indian Soc Pedod Prev Dent*, *31*(4), 240-244. https://doi.org/10.4103/0970-4388.121822

Landrigan, P. J., & Straif, K. (2021). Aspartame and cancer - new evidence for causation. *Environ Health*, *20*(1), 42. https://doi.org/10.1186/s12940-021-00725-y

Laviada-Molina, H., Molina-Segui, F., Pérez-Gaxiola, G., Cuello-García, C., Arjona-Villicaña, R., Espinosa-Marrón, A., & Martinez-Portilla, R. J. (2020). Effects of nonnutritive sweeteners on body weight and BMI in diverse clinical contexts: Systematic review and meta-analysis. *Obesity Reviews*, *21*(7), e13020. https://doi.org/https://doi.org/10.1111/obr.13020

Leahy, M., Ratliff, J. C., Riedt, C. S., & Fulgoni, V. L. (2017). Consumption of Low-Calorie Sweetened Beverages Compared to Water Is Associated with Reduced Intake of Carbohydrates and Sugar, with No Adverse Relationships to Glycemic Responses: Results from the 2001-2012 National Health and Nutrition Examination Surveys. *Nutrients*, *9*(9). https://doi.org/10.3390/nu9090928

Maersk, M., Belza, A., Stødkilde-Jørgensen, H., Ringgaard, S., Chabanova, E., Thomsen, H., Pedersen, S. B., Astrup, A., & Richelsen, B. (2012). Sucrose-sweetened beverages increase fat storage in the liver, muscle, and visceral fat depot: a 6-mo randomized intervention study. *Am J Clin Nutr*, *95*(2), 283-289. https://doi.org/10.3945/ajcn.111.022533

Mahmood, A., & Aljuboori, S. (2020). A Review: Saccharin Discovery, Synthesis, and Applications. *Ibn Al-Haitham Journal for Pure and Applied Sciences*, *3*, 43-61. https://doi.org/10.30526/33.2.2442

Nettleton, J. E., Reimer, R. A., & Shearer, J. (2016). Reshaping the gut microbiota: Impact of low calorie sweeteners and the link to insulin resistance? *Physiology & Behavior*, *164*, 488-493. https://doi.org/https://doi.org/10.1016/j.physbeh.2016.04.029

Parker, M. N., Lopetcharat, K., & Drake, M. A. (2018). Consumer acceptance of natural sweeteners in protein beverages. *Journal of Dairy Science*, *101*(10), 8875-8889. https://doi.org/https://doi.org/10.3168/jds.2018-14707

Pearlman, M., Obert, J., & Casey, L. (2017). The Association Between Artificial Sweeteners and Obesity. *Current Gastroenterology Reports*, *19*(12), 64. https://doi.org/10.1007/s11894-017-0602-9

Rodríguez-Agurto, A., Bravo, M., Magán-Fernandez, A., López-Toruño, A., Muñoz, R., Ferrer, J., & Mesa, F. (2023). Randomized clinical trial on the clinical effects of a toothpaste containing extra virgin olive oil, xylitol, and betaine in gingivitis. *Scientific Reports*, *13*(1), 6294. https://doi.org/10.1038/s41598-023-33521-4

Sahasakul, Y., Angkhasirisap, W., Lam-Ubol, A., Aursalung, A., Sano, D., Takada, K., & Trachootham, D. (2022). Partial Substitution of Glucose with Xylitol Prolongs Survival and Suppresses Cell Proliferation and Glycolysis of Mice Bearing Orthotopic Xenograft of Oral Cancer. *Nutrients*, *14*(10). https://doi.org/10.3390/nu14102023

Samuel, P., Ayoob, K. T., Magnuson, B. A., Wölwer-Rieck, U., Jeppesen, P. B., Rogers, P. J., Rowland, I., & Mathews, R. (2018). Stevia Leaf to Stevia Sweetener: Exploring Its Science, Benefits, and Future Potential. *J Nutr*, *148*(7), 1186s-1205s. https://doi.org/10.1093/jn/nxy102

Schernhammer, E. S., Bertrand, K. A., Birmann, B. M., Sampson, L., Willett, W. C., & Feskanich, D. (2012). Consumption of artificial sweetener- and sugar-containing soda and risk of lymphoma and leukemia in men and women. *Am J Clin Nutr*, *96*(6), 1419-1428. https://doi.org/10.3945/ajcn.111.030833

Soffritti, M., Belpoggi, F., Degli Esposti, D., Lambertini, L., Tibaldi, E., & Rigano, A. (2006). First experimental demonstration of the multipotential carcinogenic effects of aspartame administered in the feed to Sprague-Dawley rats. *Environ Health Perspect*, *114*(3), 379-385. https://doi.org/10.1289/ehp.8711

Soffritti, M., Belpoggi, F., Manservigi, M., Tibaldi, E., Lauriola, M., Falcioni, L., & Bua, L. (2010). Aspartame administered in feed, beginning prenatally through life span, induces cancers of the liver and lung in male Swiss mice. *Am J Ind Med*, *53*(12), 1197-1206. https://doi.org/10.1002/ajim.20896

Soffritti, M., Belpoggi, F., Tibaldi, E., Esposti, D. D., & Lauriola, M. (2007). Life-span exposure to low doses of aspartame beginning during prenatal life increases cancer effects in rats. *Environ Health Perspect*, *115*(9), 1293-1297. https://doi.org/10.1289/ehp.10271

Sørensen, L. B., Vasilaras, T. H., Astrup, A., & Raben, A. (2014). Sucrose compared with artificial sweeteners: a clinical intervention study of effects on energy intake, appetite, and energy expenditure after 10 wk of supplementation in overweight subjects. *Am J Clin Nutr*, *100*(1), 36-45. https://doi.org/10.3945/ajcn.113.081554

Tey, S. L., Salleh, N. B., Henry, J., & Forde, C. G. (2017). Effects of aspartame-, monk fruit-, stevia- and sucrose-sweetened beverages on postprandial glucose, insulin and energy intake. *International Journal of Obesity*, *41*(3), 450-457. https://doi.org/10.1038/ijo.2016.225

Tomonobu, N., Komalasari, N., Sumardika, I. W., Jiang, F., Chen, Y., Yamamoto, K. I., Kinoshita, R., Murata, H., Inoue, Y., & Sakaguchi, M. (2020). Xylitol acts as an anticancer monosaccharide to induce selective cancer death via regulation of the glutathione level. *Chem Biol Interact*, *324*, 109085. https://doi.org/10.1016/j.cbi.2020.109085

Tuncer, D., Onen, A., & Yazici, A. R. (2014). Effect of chewing gums with xylitol, sorbitol and xylitol-sorbitol on the remineralization and hardness of initial enamel lesions in situ. *Dent Res J (Isfahan)*, *11*(5), 537-543.

Wu, Y. F., Salamanca, E., Chen, I. W., Su, J. N., Chen, Y. C., Wang, S. Y., Sun, Y. S., Teng, N. C., & Chang, W. J. (2022). Xylitol-Containing Chewing Gum Reduces Cariogenic and Periodontopathic Bacteria in Dental Plaque-Microbiome Investigation. *Front Nutr*, *9*, 882636. https://doi.org/10.3389/fnut.2022.882636

Yang, Q. (2010). Gain weight by "going diet?" Artificial sweeteners and the neurobiology of sugar cravings: Neuroscience 2010. *Yale J Biol Med*, *83*(2), 101-108.

Zani, F., Blagih, J., Gruber, T., Buck, M. D., Jones, N., Hennequart, M., Newell, C. L., Pilley, S. E., Soro-Barrio, P., Kelly, G., Legrave, N. M., Cheung, E. C., Gilmore, I. S., Gould, A. P., Garcia-Caceres, C., & Vousden, K. H. (2023). The dietary sweetener sucralose is a negative modulator of T cell-mediated responses. *Nature*, *615*(7953), 705-711. https://doi.org/10.1038/s41586-023-05801-6

Zhang, W., Chen, D., Chen, J., Xu, W., Chen, Q., Wu, H., Guang, C., & Mu, W. (2023). D-allulose, a versatile rare sugar: recent biotechnological advances and challenges. *Critical Reviews in Food Science and Nutrition*, *63*(22), 5661-5679. https://doi.org/10.1080/10408398.2021.2023091