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Effect of Artificial Sweetener Aspartame on Gut Microbiota - A Narrative Review

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Abstract: Artificial sweeteners are used widely as sugar substitutes worldwide. Aspartame is the rapidly metabolised non caloric artificial sweetener commonly used in food and beverages. Use of aspartame can leads to Type 2 Diabetes, cardiovascular diseases, colon cancer, neurological and behavioural disorders. The gut microbiota plays an important role in maintaining good health and its dysbiosis leads to metabolic disorders. The present review investigates through the existing literature the effect of aspartame on gut microbiota. There is variation in results in different studies as both positive and inconclusive results are reported. Experimental studies also indicate change in gut microbiota of the infants of pregnant and lactating mothers leading to metabolic disturbances. The literature indicates that the baseline composition of gut microbiota and habitual dietary intake affects the host response to the intervention. So, to establish the relation of aspartame intake with gut dysbiosis it is important to design studies taking into consideration the baseline composition and habitual diet of the respondents and intervention diets should be carefully controlled. Although aspartame is considered to be safe for use by regulatory authorities but taking into consideration its wide use in food industry it is important to assess its health risks regularly in interest of consumer health and more studies are warranted with appropriate study designs.

Keywords: Aspartame, Gut Microbiota, Artificial sweetener, lactating and pregnant mothers, gut dysbiosis

I. INTRODUCTION

As per report of World Health organisation 2020, over one billion adults are overweight with body mass index more than 25 kg/ m2 and 300 million people are obese, which is related to many comorbidities [1]. This concern of public health is manipulated by food industry in promoting non- nutritive artificial sweeteners (NNS) as sugar substitute. NNS are the sweetening agents which have a high sweetening intensity and no or negligible lower calorie content per gram. They can be synthetic or of natural origin. The artificial NNS approved by Food and Drug Administration (FDA) are aspartame, acesulfame-k, neotame, cyclamate and alitame while the Food Safety and Standards Authority of India (FSSAI) has approved six artificial sweeteners, namely saccharin sodium, aspartame, acesulfame potassium, sucralose, neotame, and isomaltose as food additive. In addition to be used as table top sweetener, they are widely used in soft drinks, desserts, chocolates, dairy products, jams and jellies and other confectionary items. They are not only used as sugar substitutes by diabetic people but used widely by general population also. Aspartame is the commonly used NNS particularly in diet soda. There is great debate on the negative effects of aspartame as it effects the metabolic functions. The present review investigates through the existing literature the effect of aspartame on gut microbiota and its consequences.

II. ASPARTAME

A. Chemical Nature

Aspartame ($C_{14}H_{18}N_2O_5$) (E951), an artificial sweetener, is a dipeptide composed of Aspartic acid and phenylalanine It is synthesized from L-phenylalanine or the methyl ester of L phenylalanine with L-aspartic acid. It was invented in 1965 by James M. Schlatter accidently while working on anticancer drugs The large scale production of aspartame for food industry started in 1981. It is 200 times sweeter than sugar and has no calories.. According to the FDA, the acceptable daily intake of aspartame for humans is 40 mg/kg bodyweight in Europe and 50 mg/kg bodweight [8]

B. Metabolism of Aspartame

The enzymatic digestion of Aspartame by esterases and peptidases metabolise aspartame to aspartic acid, phenylalanine and Methanol. The concenteration of these metabolites remain well below the level of toxicity [2] The toxic effect of phenyalanine occurs when it is not metabolised to Tyrosine as in metabolic disorders of Phenylketonuria. The toxic effects of methanol in humans are due to the accumulation of its metabolite formate, however it is impossible for a person to consume necessary aspartame to lead to toxic level of formate [3] So, the ingestion of even high dose , no aspartame is found in blood as it is rapidly hydrolysed in intestine.

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C. Aspartame and Metabolic disorders

Although it is considered to be safe for use by regulatory authorities but taking into consideration its wide use in food industry it is important to assess its health risks regularly in interest of consumer health. Use of Aspartame is related to many diseases like Type 2 diabetes [4] cardiovascular diseases, cancer [5], increase in lipid profile, glucose blood level, marker enzymes like alanine aminotransferase, aspartate aminotransferase and alkaline phosphatase [6-7]. The long-term use of aspartame is reported to behavioural problems, neurodegeneration and effect on learning and memory [8].

III. GUT MICROBIOTA

Gut Microbiota refers to the microorganisms present in Gastrointestinal tract and it continues to evolve throughout life [9] More than thousand species and in one individual nearly 160 species are present [10]. The common bacteria present are *Firmicute*s and *Bacteroidetes*, *Actinobacteria* , *Proteobacteria* *Verrucomicrob*ia , and *Fusobacteria* [11] Any quantitative or qualitative disruption in composition of the normal microbiota is known as 'gut dysbiosis'. It has been postulated that the commensal microbes that reside within the gastrointestinal tract are implicated in human disease. Dysbiosis gut microbiota has been associated with obesity [12] inflammatory bowel disease [13] Type 2 Diabetes [14] and colon cancers.[15]

IV. EFFECT OF ASPARTAME ON GUT MICROBIOTA

A. Negative effects of Aspartame on Gut Microbiota

Suez et. al.[16] demonstrated the development of glucose intolerance through induction of compositional and functional alterations to the intestinal microbiota by consumption of Non caloric artificial sweeteners . McVey Neufeld et. al. [17] reported that the gut microbiota is important for normal signalling in enteric nervous system. The important transmitters produced by gut microbiota are NE produced by Escherichia, Bacillus and Saccharomyces, 5- Hydroxytryptamine by Candida, Streptococcus, Escherichia, and Enterococcus spp .[18-19] It is possible that aspartame can lead to dysbiosis and disturbance in production of neurotransmitters leading to neurological disorders[20] Aspartame increase the total bacteria with predominance of Enterobacteriaceae and Clostridium leptum in faecal matter [21]

Nettleton et. al. [22] observed that the maternal aspartame exposure in pregnancy and lactation not only alter the gut microbiota composition mother but also in offspring who were not directly exposed to aspartame. Following obesity induction, female Sprague Dawley rats were given during pregnancy and lactation high fructose and aspartame of 5–7mg/ kg/day. The offspring were weaned onto control diet and water and followed until 18 weeks. Despite no sweeteners were given to the offspring there was alteration in gut microbiota with a notable increase in *Porphyromonadaceae*. *Moreover*, Germ-free mice that received cecal microbiota from offspring at weaning had significantly greater body weight 7-, 10- and 14-days following inoculation indicating glucose tolerance in early life, despite there was no direct consumption of sweeteners by offspring. Stichelen et al. [23] exposed pregnant and lactating mice to non-caloric artificial sweeteners Sucralose and acesulfame K and reported alterations in microbiota with significant increase in *Akkermansia muciniphila* in pups which is related to metabolic dysregulations. The development of the gut microbiota in critical period in early life is important and influence the maturation of immune system and have role in occurrence of autoimmune disease [24] and as Aspartame is widely used as non-calorific sweetener so the effect of aspartame in pregnant and lactating mothers can be of concern with respect to infant health and need further investigation.

B. Proposed Mechanism Of Aspartame Action On Gut Microbiota

Shil and Chichger et. al. [25] investigated the role of aspartame on gut bacterial pathogenicity and gut epithelium-microbiota interactions, using models of microbiota (Escherichia coli NCTC10418 and Enterococcus faecalis ATCC19433) and the intestinal epithelium (Caco-2 cells). In this in vitro study Model gut bacteria were exposed to different concentrations of the aspartame, and their pathogenicity and changes in interactions with Caco-2 cells were measured. Aspartame differentially increase the ability of bacteria to form a biofilm. Co-culture with human intestinal epithelial cells shows an increase in the ability of model gut bacteria to adhere to, invade and kill the host epithelium.

Aspartame may alter the activity of intestinal enzyme alkaline phosphatase. secreted by brush border cells of duodenum .The enzyme blocks the proinflammatory endotoxins of bacteria [26], improve the gut barrier function [27] and promote commensal bacteria growth[28]) Phenyalanine which is a by product of asparatate metabolism inactivate the activity of alkaline phosphatase. The reduced intestinal alkaline phosphatase activity leads to glucose intolerance and metabolic syndrome[29]. The reduced enzyme activity also alters the pH of gut and microbial ecology [30]

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Short chain fatty acids like propionate and butyrate are the microbial metabolites produced by fermentation of unabsorbed food by gut microbiota. The consumption of aspartame by obese rat model leads to increase in total bacteria with predominance of Enterobacteriaceae and Clostridium leptum and increase in propionate and butyrate . Propionate is directly made available to liver for gluconeogenesis by enterohepatic circulation [21]

C. No effect of Aspartame on Gut Microbiota

The treatment of healthy human participants between the ages of 18 and 45 years with body mass index (BMI) of 20–25 with standard dose of 14% (0.425 g) of the acceptable daily intake of aspartame for 14 days separated by a four-week washout period also did not reflected any significant difference in gut microbiota and short chain fatty acids in faecal matter [31] No significant difference in median percent abundance of bacteria at class and order level among the consumers having 5.3-112mg/day of aspartame over four day study period [32] . Lobach et. al. pointed the limitation of study design and suggested the inclusion of an isocaloric control group for the confirmation of the reporting that aspartame is responsible for change in gut microbiota [33] The variation of results of various studies on effect of low calorie non-nutritive sweeteners on gut microbiota are reported due to confounding factors [34]. The response of host to dietary interventions varies and are affected by individual differences in gut microbiota of subjects under study [24] The baseline composition of gut microbiota and habitual dietary intake affects the host response to dietary intervention [35-38]. So to establish the relation of aspartame intake with gut dysbiosis it is important for an individual to design studies taking into consideration the baseline composition and habitual diet of the respondents and intervention diets should be carefully controlled.

V. CONCLUSION

Although aspartame is rapidly metabolised in body and its intake to the level of toxicity at the recommended safe by regulatory authorities. But the experimental studies have reported the gut dysbiosis and its consequences as ill health. But as gut microbiota is unique and constantly evolving so the study designs need attention and to consider the baseline gut microbiota and dietary pattern of the subjects in consideration. Moreover the effect of intake of aspartame on gut microbiota of infants of pregnant and lactating women needs investigation for prevention of metabolic syndromes in offspring.

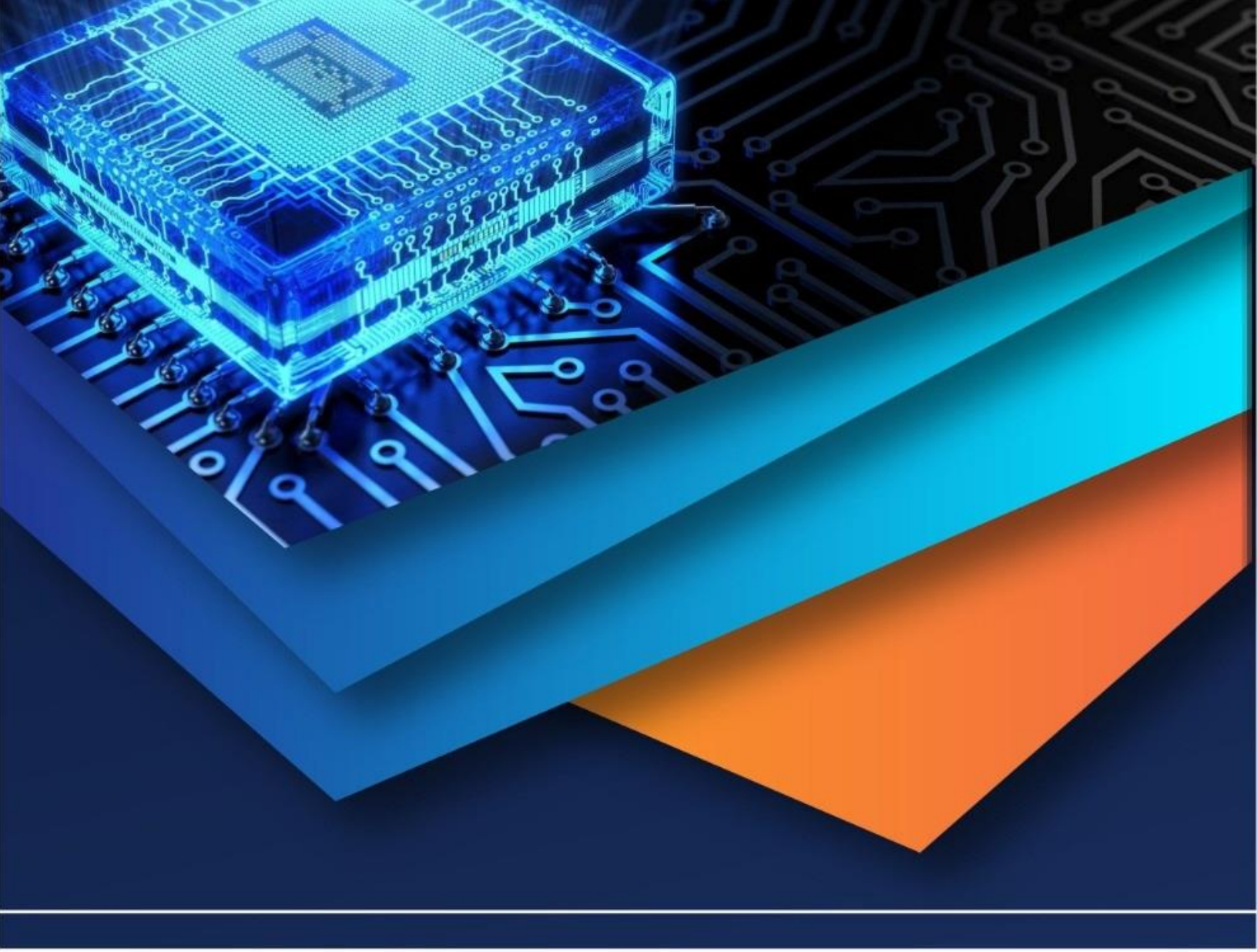
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