Artificial Sweeteners: A Review
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Abstract:
Sugar gained a bitter name regards to health. Consumption of more sugars involves risk of more calories which leads to diseases like obesity, diabetes and cardiovascular problems in human body. These days food which is sugar free acquired much more reputation because of their low or no calorie content. So as a result many food industries use different low calorie artificial sweeteners instead of sugars. Food and Drug Administration (FDA or USFDA) accepted the use of six sugar substitutes (aspartame, saccharine, sucralose, neotame, acesulfame-k and stevia) safe human consumption. Advantame and extract from swingle fruit have recently discovered and added to the list of nonnutritive sweeteners. These artificial sweeteners or sugar substitutes are extensively applied in the fields of processed foods, dairy and therapeutic industries. The main aim of this review is to discuss the different types of artificial sweeteners, their history, synthesis, metabolism, uses, toxicity, therapeutic use, nontherapeutic use, health benefits and toxic effects.

Keywords: Artificial sweeteners, diabetes, nonnutritive sweeteners, obesity, sugar substitutes.

I. INTRODUCTION

In the recent and current years people are very much conscious about their health and showing a great concern on quality of life. Imbalanced consumption of excess calories and saturated fats is leading most of the population to obesity.

Obesity became a notable subject all over the world (Serdula et al., 1999, Scott et al., 2006). Studies show that most of the individuals are disturbed by overweight and well-being associated consequences (type II diabetes) (Sorensen et al., 2003).

The frighten prevalence of obesity has been impute to diversification of social-economic components like food habits and lifestyle (Story et al., 2008).

Responsibility on sugar consumption have taken into consideration from 1970s where obesity outbreak has started (Kavey, 2010). These days the ultimate target of diabetes is to control the glucose or sugar levels in blood.

By raised interest of customers in reducing sugars in foodstuffs having non-sugar sweeteners (NSSs) instead of simple sugars have become more popular (Sakurai et al., 2013).

Sweeteners are categorized as nutritive and non-nutritive sweeteners. Nutritive sweeteners are further classified into sugars, modified sugars, sugar alcohols and natural caloric sweeteners.

Non-nutritive sweeteners (NSSs) classification includes artificial sweeteners and natural non-caloric sweeteners (Grembecka, 2015) (fig 1).

Many of Non-nutritive sweeteners (NSSs) have been manufactured, but intense research and development in natural NSSs is expanding (Toews et al., 2019).

Non-nutritive sweeteners (NSSs) vary from sugars not only in their properties of taste, but also in metabolic rate and physiological processes (Ferrazzano et al., 2015).

Non-nutritive sweeteners (NSSs) are sweeter than sucrose and have very few calories. All of these sweeteners are distinctive in intensity and persistence sweetness (Mortensen, 2006).

In few situations, the word “artificial sweeteners” is considered as a synonym for Non-nutritive sweeteners (NSSs).

In this review we use NSSs as artificial sweeteners / Artificial sweeteners (non-nutritive sweeteners) are sugar substitutes which are several times sweeter than normal sugar.

These food additives gives sweet taste same as sugar while having no food energy making it no calorie sweeteners (Whitehouse, Boullata and McCauley, 2008).

Non-nutritive sweeteners (artificial sweeteners) are produced from extracts of plants or by safe chemicals (Wani and Bhat, 2019).

These sugar substitutes are extensively used in processed foods (powdered drinks, soft drinks, carbonated beverages, baked foods, canned foods, dairy products, jams and jellies) (Zeynep and Sifa, 2014).

Artificial sweeteners used in processed foods are aspartame, acesulfame potassium, sacralose, saccharin, cyclamate, neotame, alitame, rare sugars, xylitol and D-allose (Whitehouse, Boullata and McCauley, 2008). Characteristic attributes of artificial sweeteners are shown in Table 1.
### Table 1. Characteristic features of artificial sweeteners (Whitehouse, Boullata and McCauley, 2008).

<table>
<thead>
<tr>
<th>General name or common name</th>
<th>Most popular Brand names</th>
<th>Intensity of sweetness compared to table sugar</th>
<th>Kilo calories per gram (kcal/g)</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharin</td>
<td>Sweet’ N Low, Sweet Twin</td>
<td>300</td>
<td>0</td>
<td>Soft drinks, beverages, fruit drinks, powdered dessert mixes, Tabletop sweetener, Jams, Chewing gum, Baked goods, canned fruits</td>
</tr>
<tr>
<td>Acesulfame K</td>
<td>Sunett, Sweet One</td>
<td>180-200</td>
<td>0</td>
<td>Tabletop sweeteners (in packets), carbonated beverages, desserts which are frozen, Candies, Chewing gum, Dairy products, syrups and sauces</td>
</tr>
<tr>
<td>Aspartame</td>
<td>NutraSweet, Natrataste, sugar twin, Equal</td>
<td>200</td>
<td>4</td>
<td>Tabletop sweetener (in packets), chewing gums, instant coffee and tea, gelatins, puddings, Soft drinks, Yoghurt, Pharmaceuticals</td>
</tr>
<tr>
<td>Neotame</td>
<td>Same as common name (neotame)</td>
<td>10000</td>
<td>0</td>
<td>Baked goods, Soft drinks, Chewing gum, Jams, Jellies, Puddings, Processed fruit and fruit juices</td>
</tr>
<tr>
<td>Sucralose</td>
<td>Splenda</td>
<td>600</td>
<td>0</td>
<td>Tabletop sweetener (in packets), baked foods, Frozen desserts and dairy products, Fruit juices, Chewing gum, gelatins, gelatin</td>
</tr>
</tbody>
</table>

### II. TYPES OF ARTIFICIAL SWEETENERS

**Saccharin**

Saccharin is an artificial sweetener with zero food energy and no calories. This is the earliest and one of the oldest sugar substitute used for about a century in processed food and beverages industries (Zeynep and Sifa, 2014). Saccharin is 300 times more sweetener than sucrose (Whitehouse, Boullata and McCauley, 2008).

**History**

Saccharin has been identified by Fahlberg and Remsen in the year 1879 at university of John Hopkins (Baltimore). This was accidentally found by Fahlberg during the research on oxidation mechanisms of toluene sulfonamide. Saccharin was widely spread during global wars when the sugar shortage provoked (Arnold, 1983). Saccharin was banned in the year 1981, because this caused bladder cancer in rats after giving overdose of saccharin. No clear research has shown the connection between saccharin intake and risk of cancer in humans (Weihrauch and Diehl, 2004).

**Synthesis and metabolism**

Synthesis of sugar substitute saccharin includes the chemical oxidation of ortho toluene sulfonamide with reactive chemical agents like permanganate of potash, tetraoxochromic acid, electrochemically to corresponding carboxylic acid. The dehydration of ortho isomeric part gives the sweetener saccharin (Bennett et al. 1992). Saccharin is not metabolized after ingestion, it is excreted from body as it is without any change through kidneys (Whitehouse, Boullata and McCauley, 2008). Saccharin is sometimes combined with other artificial sweeteners like aspartame because of its slight bitter and metallic taste (Zeynep and Sifa, 2014).

**Uses**

Saccharin is used in various food products like carbonated soft drinks, tabletop sweeteners, and in few desserts. In hygiene oral products this sweetener hides the taste of undesirable flavor of other ingredients. Apart from its usage as sugar substitute, saccharin is used as deposition of nickel in electrolyte (Periyasamy, 2019).

**Toxicity**

Excess intake or ingestion of saccharin causes severe headache, difficulty in breathing, eruptions on skin and diarrhea (Whitehouse, Boullata and McCauley, 2008).

**Acesulfame potassium (Ace-k)**

Acesulfame potassium is used as general sweetener. This is a white crystalline material which is stable up to high temperatures (250 °C). Because of its high stability under high temperature it is used in many bakery products (Nabors, 1994).

**History**

Acesulfame potassium has been identified as sugar substitute by Hoechst (Clauss and Jensen, 1970). During the research on oxathiazinone oxides this sweetener was discovered by chance. Many other oxathiazinone oxides are sweet in taste but they have less advantageous characteristics (Clauss and Jensen, 1970).
Synthesis and metabolism
Early strategies for Ace-k preparation utilized fluoro sulfonyl isocyanate or chlorosulfonyl with propyne acetone and reacted with another chemical substances give N-chloro acetoacetamide, this is then cyclized with potassium hydroxide or caustic potash to give crystallized Ace-k. Another technique includes treating acetoacetamide with any dual equal proportions of sulfuric anhydride. As a result N-sulfoacetoacetamide is formed, the water is removed by sulfur trioxide to yield oxathiaazinone dioxide.

Oxathiaazinone dioxide upon neutralization in presence of potassium hydroxide gives the final product Ace-k (Clauss, Schmidt-Rohr and Spiess, 1993). Acesulfame-k is not digested or stored in the human body. This is excreted through urine as unchanged. Most of the artificial sweeteners are generally excreted through urine without any modifications (Kier, 1972).

Uses
Acesulfame-k is mostly used in various fields of sugar substitutes. Commonly used fields of Ace-k are tabletop sweeteners (in packet form), sweet drinks, confectioneries, desserts, dairy products, chewing gums, oral hygiene products and pharmaceutical industries (Periyasamy, 2019).

Toxicity
Methylene chloride which is present in Ace-k is carcinogenic which leads to cancer in human body. Excess intake of this may cause severe headache, depression, nausea sensation, mental disturbance, liver and renal problems. Ace-k forms acetoacetamide in human body upon metabolism, which is highly toxic and causes tumors in thyroid glands of rats, dogs and rabbits. Few studies suggest that only 1% of acetoacetamide is collected in human body for three months (Zeynep and Sifa, 2014).

Aspartame
Aspartame is the most discussed sugar substitute which tastes like sugar. This is highly stable to hot temperatures and has modest solubility in water. This rate of solubility of aspartame is directly proportional temperature (Rencüzoğulları et al., 2004).

History
Aspartame was identified in the year 1965 by chemist G. D. Searle during the series of research on new gastric ulcers drugs. Aspartame was accidentally discovered while the synthesis of tetrapeptide. Food and Drug Administration (FDA or USFDA) accepted aspartame as artificial sweetener in the year 1981. Aspartame is mixed with other sweeteners like saccharin to maintain sweetness and other related properties (Butchko and Stargel, 2001).

Synthesis and metabolism
Aspartame is manufactured by the reaction between phenylalanine methyl ester with aspartic acid or asparaginic acid. This sweetener is metabolized into small amounts of phenylalanine, methanol, aspartic acid. Methanol (carbinol) is further break down into methyl aldehyde (formaldehyde) which in turn forms formic acid in the liver of human body. The excess formaldehyde is excreted through urine through kidney. Little quantity of ethanol is produced when aspartame is consumed in diet (Humphries, Pretorius and Naudé, 2007).

Uses
Aspartame is commonly applied as artificial sweetener in all fields of processed food.

Toxicity
The individuals who are suffering from a rare phenylketonuria genetic disorder should avoid intake of aspartame. This caution of intake should be clearly mentioned on packaging of processed foods containing aspartame (FDA). The end products (methanol, aspartic acid and phenylalanine) after metabolism of aspartame causes the following health disorders: severe headache, improper vision, tumors in brain, sight problems, loss of memory and nausea sensation (Stegink, Filer and Baker, 1977).

Neotame
Neotame is the recently discovered sweetener which is derived from aspartame. Neotame is formed when tertiary butyl group is added to amine free group of aspartic acid. The neotame was accepted as general purpose or tabletop artificial sweetener in the year 2002 except in poultry and meat by Food and Drug Administration (FDA or USFDA) (Whitehouse, Boullata and McCauley, 2008).

History
After the favourable and positive results of aspartame, many modifications such as stability to heat, low restrictions and more sweetness in aspartame are made to develop a novel sugar substitute. Hundreds and thousands of compounds were synthesized. As a result of this research, a noval sweetener with all the desirable characters neotame was produced. Neotame got approval from Food and Drug Administration (FDA or USFDA) in the year 2002 (Nofre, 2000).

Synthesis and metabolism
Neotame is synthesized when tert-butyl group added to amine part of aspartic acid. Neotame is about 60 percent more sweeter than aspartame (Nofre, 2000). Neotame is quickly digested by esterase present in the body, this esterase hydrolysis the methyl ester group during metabolism. Methanol is formed in little amount which is absorbed by the body. The de-esterified neotame is eliminated from human body through urine and fecal matter within 72 hours of intake. Neotame is safe sweetener for those who suffer from phenylketonuria (Nofre, 2000).

Toxicity
Excess consumption of neotame causes toxicity in liver. Few other toxic effects of neotame are change in human body weight, mild headache and loss of appetite (Nofre, 2000).

Sucralose
Sucralose is one of the largely consumed sugar substitute. Sucralose is highly stable, safe and even used at higher temperatures (baked food products). Sucralose is up to 1000 times more sweeter than sucrose, thrice sweet as aspartame and acesulfame potassium and sucralose is twice sweet as saccharin (Sims, Roberts, Daniel and Renwick, 2000).

History
Sugar substitutes sucralose was unintentionally found by Tate and Lyle in the year 1976 while series of research on sucrose. The Food and Drug Administration (FDA or USFDA) approved sucralose for use in 15 different processed foods (Sims, Roberts, Daniel and Renwick, 2000).
Synthesis and metabolism
Sucralose is synthesized by substituting three hydroxyl groups of sucrose with chlorines. This sugar substitute is not metabolized and absorbed in human body. Sucralose is excreted same as it is through fecal matter (Kroger, Meister and Kava, 2006).

Toxicity
Toxic effects of sucralose include shrinking of thymus glands, diarrhea and giddiness (Sims, Roberts, Daniel and Renwick, 2000).

THERAPEUTIC AND NON THERAPEUTIC USES

Therapeutic use
Replacement of common table sugar with less or no calorie sugar in food products allows less calories intake into the body which in turn helps in reducing weight. High sucrose containing foods may cause dental decay, in order to reduce this problem doctors prescribe to use sugar substitutes. People suffering from diabetes have fluctuations in blood sugar use of sugar substitutes or artificial sweeteners in diet instead of table sugar allows more stability in blood sugar levels (Bellisle and Drewnowski, 2007).

Non therapeutic use
Aspartame taste same as common sugar which is used as sugar substitute in various processed foods. In few beverage and food industries aspartame is used as a sugar substitute which not only gives sugar taste but also enhances and even intensifies the flavors (Bellisle and Drewnowski, 2007).

HEALTH BENEFITS
Artificial sweeteners do not increase the sugar levels in blood which is responsible for diabetes. These sugar substitutes have no calories. As these artificial sweeteners do not increase calories in body they help people to control their weight. They provide good oral health (Whitehouse, Boullata and McCauley, 2008).

TOXIC EFFECTS OF ARTIFICIAL SWEETENERS
Artificial sweeteners like saccharin, ace-k and aspartame involves in genetic change, especially in DNA of lymphatic cells. Few by-products produced from sugar substitutes cause breakage in DNA strands. These can change the metabolic properties of human body. Toxic effects of artificial sweeteners are given in Table 2.

<table>
<thead>
<tr>
<th>Name of artificial sweeteners</th>
<th>Metabolites</th>
<th>Annual Daily Intake (mg/kg)</th>
<th>Acute problems</th>
<th>Chronic problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saccharin</td>
<td>Ortho sulfamoylbenzoic acid</td>
<td>5</td>
<td>Nausea, vomiting, diarrhea</td>
<td>Low birth weight, bladder cancer, hepatotoxicity</td>
</tr>
<tr>
<td>Acesulfame-K or ace-k</td>
<td>Acetoacetamide</td>
<td>15</td>
<td>Headache</td>
<td>Thyroid tumors in rats, clastogenic, high doses cause genotoxicity</td>
</tr>
<tr>
<td>Aspartame</td>
<td>Methanol, aspartic acid &amp; phenylalanine</td>
<td>50</td>
<td>Headache, dry mouth, dizziness, nausea, vomiting, thrombocytopenia, mood swings</td>
<td>Lymphomas and leukemia in case of rodents</td>
</tr>
<tr>
<td>Neotame</td>
<td>Methanol and de-esterified neotame</td>
<td>2</td>
<td>Headache, hepatotoxic at high doses</td>
<td>Lower birth rate, weight loss, cancer in offspring, hepatotoxicity</td>
</tr>
<tr>
<td>Sucralose</td>
<td></td>
<td>5</td>
<td>Diarrhea, dizziness, stomach pain</td>
<td>Thymus shrinkage, enlargement of cecal in rodents</td>
</tr>
</tbody>
</table>

Table.2. Toxic effects of artificial sweeteners (Whitehouse, Boullata and McCauley, 2008).

III. CONCLUSION
The most common diseases like diabetes, obesity and heart attacks are increasing in people every year. Increase in sugar intake through processed food, sweets and soft drinks made people to have more concern on their good health. As a result artificial sweeteners or sugar substitutes are gaining more importance. Many countries use these sugar substitutes in various processed foods and alcoholic beverages. United States of America and European countries (including UK) have approved six low-calorie artificial sweeteners as sugar substitutes after extensive scientific research. A great number of different sugar substitutes have been synthesized and current research require developing more calorie free and safe artificial sweeteners from industrial food waste.

IV. REFERENCES


