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# Artificial sweeteners and their safety

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**ABSTRACT**

The desirable taste for sugar is innate but too much consumption of sugar can cause tooth decay and some health complications such as obesity and diabetes, which lead to the prevalence of the sugar substitutes (sweeteners). Sugar substitutes are alimentary additives which have a sweet taste like sugar and can be either natural sweeteners or artificial sweeteners. Natural sweeteners have nutritional value so they are called nutritive sweeteners. However, synthetic (artificial) sweeteners do not have nutritional value so they are known as non- nutritive sweeteners. Polyols or sugar alcohols are also sugar substitutes. They are considered as natural and nutritive sweeteners.

On the contrary, artificial sweeteners are gaining very popular because they help reduce calories, control weight, manage diabetes, and prevent cavities. However, their safety has been controversial. In general, artificial sweeteners undergo a safety evaluation to assess their benefits and risks before using them. A health organizations such as FDA evaluating all scientific studies and determines the maximum amount that can be eaten on a day without causing any adverse effects for each sweetener. The approved artificial sweeteners are: saccharin, acesulfame-K, sucralose, aspartame and neotame. In past cyclamate was considered safe. Alitame is not yet approved.

The aim of this paper is to give an idea about the sweeteners, artificial sweetener, their chemical structure and properties. In addition to some published studies about their safety.

**KEY WORDS:** Sweeteners, Natural Sweeteners, Artificial Sweeteners, Sugar Alcohols, Saccharin, Acesulfame-K, Sucralose, Aspartame, Neotame, Cyclamate, Alitame, ADI.

## 1. INTRODUCTION

Sweeteners are food additives that are used instead of sugar to sweeten and enhance the taste of foods, drinks and pharmaceutical preparations. Depending on their origin and production they can be categorized into natural and artificial sweeteners. Natural sweeteners have great nutritional value and supply body with energy, thus they are called nutritive sweeteners. Artificial sweeteners have no nutritional value since they cannot be absorbed in the digestive system so they are known as non- nutritive sweeteners.

There is a third type of sweeteners called Polyols (sugar alcohols) or sugar relatives, they are natural compounds and considered as nutritive sweeteners because they supply body with energy but less than sugar. (Mehtani, 1993; Sudan, 2016; Fitch and Keim, 2012).

**Natural Sweeteners:** Natural sweeteners are sweeteners that are exist and extracted from natural products without any chemical change on their structure. (Lebedev, 2010) They can be divided depending on the main structure to saccharides and non-saccharides sweeteners. Saccharides are carbohydrate (sugar). Non- saccharides sweeteners can be terpenoids, sweet protein, steroidal saponine and dihydroisocumarines (Priya, 2011) (figure.1). They are absorbed in the digestive system and metabolized to produce adenosine three phosphates (ATP), which means providing body cells with energy. (Sudan, 2016; Sadava, 2007). Natural sweeteners may be used to sweeten foods, drinks and may also be found in medications. Some of the commonly used natural sweeteners are: Honey; Maple Syrup; Molasses; Sucrose; Stevia; High fructose corn syrup (HFCS) (Neacsu, 2014).

**Side effects of natural sweeteners:** Natural sweeteners are safe in general. But they can increase the levels of blood sugar blood fats and aloo weight. So consuming too much may lead to health complications such as increasing the risk for obesity, poor nutrition, prediabetes, type 2 diabetes, and cardiovascular disease (Fitch and Keim, 2012). Also, honey shouldn't be given to children younger than one year old because it can contain botulism toxin (Mehtani, 1993; Sudan, 2016; Lebedev, 2010).

**Sugar Alcohols/ Polyols:** Sugar alcohols can be found in fruits and vegetables. The main structure of them is sugar but the aldo or keto group of it, is reduced to the corresponding hydroxyl group (Bieleski, 1982). Only a portion of sugar alcohols is absorbed in the digestive system. Therefore, they may cause digestive discomfort such as gas and diarrhea when too much is consumed. They have calories but less than sugar and do not have a major effect on blood glucose. The FDA has determined that consuming sugar alcohols is safe. They can be found in foods labeled with sugar free and medications. Some of the commonly used sugar alcohols are: Lactitol; Maltitol; Mannitol; Xylitol; Sorbitol (Lebedev, 2010).

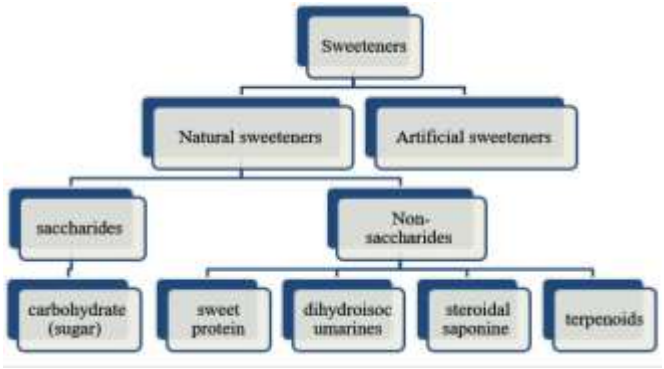


**Figure.1. Classification of sweeteners**

**Artificial Sweeteners:** Artificial sweeteners are ingredients that are used instead of sugar (sucrose). They are chemically produced and can be derived from herbs or sugar itself. Artificial sweeteners are also called high intensity sweeteners because they are much more sweeter than sugar (sucrose), thus smaller amounts are needed (Lebedev, 2010). Artificial sweeteners are not carbohydrate and have no calories. Therefore, they sweeten products without adding calories (Christina, 2008). Unlike sugar, they do not cause dental caries, do not increase the levels of blood sugar and blood fats. This may be helpful for people with diabetes and have to be careful with consuming too much sugar. They also may be helpful for diet (Tandel, 2011; Bellisle, 2007; Mattes, 2009; Bentley, 1993; Mackie, 1995; Mann, 2004). However, they aren't without side effects, they may cause digestive discomfort and headache.

Some studies refer to possible adverse effects arising from consuming artificial sweeteners but in general the FDA recognized them as safe. This means that the FDA reviews scientific evidence to ensure the safety of using artificial sweeteners and also determines the maximum amount that can be eaten on a day without causing any adverse effects over the course of lifetime, which is also known as the acceptable daily intake (ADI) (Christina, 2008). Products with artificial sweeteners are usually labeled with "light" and "sugar-free".

To date the approved artificial sweeteners are: aspartame, saccharin, acesulfame-K, neotame and sucralose. Cyclamate is banded while alitame (aclamate) is not yet approved yet.

**Uses for artificial sweeteners:** Artificial sweeteners may be used in a lot of manufactured products (liquid, solid and semi-solid products) and they also can be used at home as a substitute for sucrose (table sugar) (Tandel, 2011).

**Health effects of artificial sweeteners:** They don't generate tooth cavities (Tandel, 2011; Bentley, 1993; Mackie, 1995).

- They are non-nutritive and have no calories, so they may be used for diet and weight control by reducing calorie intakes (Bellisle, 2007; Mattes, 2009).
- They can be used in diabetes mellitus because artificial sweeteners are not carbohydrates, so they don't increase the level of blood sugar (Mann, 2004).

**Table.1. Artificial sugar substitutes (Kroger, 2006)**

| Artificial sweetener | Potency (times sweetener than sucrose) | Approved by FDA | ADI (mg/kg of body weight/day) |
|---|---|---|---|
| aspartame | 160-200 | 1981 | 40 |
| saccharin | 300 | 1985 | 5 |
| acesulfame-K | 200 | 1988 | 15 |
| neotame | 7000-8000 | 2002 | 18 |
| sucralose | 600 | 1998 | 5 |
| Alitame | 350 | -- | -- |
| Cyclamate | 30 | Banded in 1969 | -- |

**Popular artificial sweeteners and potential toxicology:**

**Aspartame:** Aspartame was found in 1965 and consented in 1981. It is a combination of 2 amino acids: L-aspartic acid and L-phenylalanine. Aspartame has the chemical formula $C_{14}H_{18}N_2O$, and the molar mass is 294.3 g/mol (Christina, 2008) (figure.2). It is much more sweeter than sucrose by 200 times and can be used in many products. In high temperatures aspartame breaks down into its amino acids and loses its sweet taste. Therefore it shouldn't be used in cooking. (Christina, 2008; Kroger, 2006; Shallenberger, 1975).

Aspartame is marketed as Equal and Nutra Sweet (Christina, 2008). The maximum amount that can be eaten on a day (ADI) is 40 mg/kg/day (Kroger, 2006).

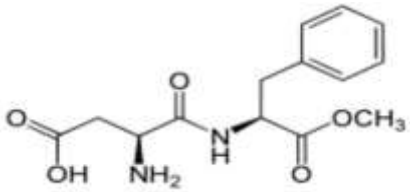


**Figure.2. the chemical structure of aspartame**

**Potential adverse effects of aspartame:** Aspartame breaks down in the body to aspartic acid, phenylalanine and methanol which also break down to formaldehyde, formic acid and diketopiperazine. (George, 2010); the use of aspartame causes a negligible change in the total intake of its components. But some people suffer from a disease called phenylketonuria (PKU) so aspartame should be avoided. Phenylketonuria a rare genetic condition in which the body is incapable of breaking down the phenylalanine (a component of aspartame) because of lacking the enzyme phenylalanine hydroxylase, which is needed to metabolism this amino acid. In this condition phenylalanine accumulates and effects human brain function (Christina, 2008).

Some studies have also presumed that aspartame metabolites have poisonous effects in elevated levels. Double-blind trials have cleared that there is no change in headache frequency, blood pressure, or blood histamine concentrations between the experimental and control groups (Schiffman, 1987).

Soffritti (2007), have demonstrated a significant increasing of malignant tumors in males Rats, increasing the chance of lymphoma and leukemia occurrence in males and females, and increase the chance of mammary cancer occurrence in females.

Other reports were demonstrated that using aspartame was linked to increasing cancer in mice (male and females). However, after intense testing both in animals and humans, aspartame has not been related to cancer or any other adverse effects (Magnuson, 2007).

**Saccharin:** Saccharin was found in 1879 and consented in 1977. It is a benzoic sulfimide, has the chemical formula $C_7H_5NO_3S$ and the molar mass is 183.2 g/mol. Saccharin is an organic acid with a pKa of 1.6 so the acid form of saccharin is insoluble in water. Therefore, saccharin is used in sodium salt form (figure.3).

Saccharine is very popular and used in a lot of products such as toothpaste and even cosmetic products. It is much more sweeter than sucrose by 300 times, but in high concentrations it can causes a bitterness taste. Like aspartame, saccharin breaks down in elevated temperatures so it cannot be used in cooking.

Saccharine is marketed as Sweet'N Low and Sugar Twin. The maximum amount that can be eaten on a day (ADI) is 5 mg/kg/day.

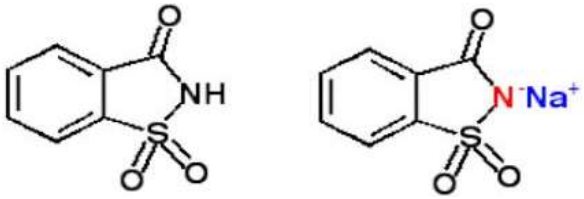


**Figure.3. The chemical structure of saccharine**

**Potential adverse effects of saccharin:** In 1960, a published study demonstrated that using saccharin in high doses can lead to bladder cancer in rats, so saccharin was banded due to the adverse effects. Later on, more research have concluded that the bladder tumors found in the rats were related to a mechanism in rats not found in humans. High doses of saccharin lead to a sediment in rat micturition which hurts the bladder cells and causes cancer. Due to these findings, it is no longer listed as a potential cancer causing agent (Elcock, 1993).

In 1994, a study of the hepatotoxicity of saccharin was published. A patient came in to the hospital with high levels of hepatic enzymes after the oral administration of three different drugs, saccharin was the only common constituent of these drugs. Further studies concluded that saccharin plays role in pathogenesis of the liver damage (Negro, 1994).

Other reports has elevated that using of saccharin may increases body weight and by affecting the homeostatic and physiological processes (Hampton, 2008).

**Acesulfame-K:** Acesulfame-K was found in 1967 and consented in 1988. It is the potassium salt of 6-methyl-1, 2, 3-oxathiazine-4 (3H)-one-2, 2, dioxide and has the molecular formula $C_4H_4KNO_4S$, molecular weight of 201.24 g/mol. (figure 4). Unlike aspartame and saccharin. Acesulfame-K does not break down in high temperatures so it can be used in cooking. It is much more sweeter than sucrose by 200 times and can causes a bitterness taste when used by itself (Kuhn, 2004).

Acesulfame-K does not break down in the body and eliminated unchanged by the kidneys. Therefore, it does not affect the potassium intake (Nabors, 2002; Horne, 2002).

Acesulfame-K is marketed as Sweet One. The maximum amount that can be eaten on a day (ADI) is 15 mg/kg/day.

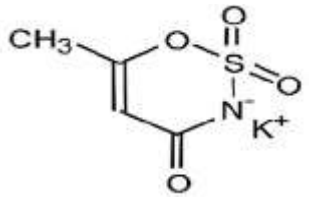

**Figure.4. The chemical structure of Acesulfame-K**

**Potential adverse effects of acesulfame-K:** Studies on genotoxicity and cytogenicity of acesulfame-K indicated that acesulfame-K reacts with nucleic acid in cells and lead to genetic damage (this damage happens at high doses), so more studies should be done.

In 2000, The FDA and other health organizations studied acesulfame-K and evaluated all of the available data, and confirmed that acesulfame-K is safe and does not cause any adverse effects like cancer.

**Neotame:** Neotame is the latest artificial sweetener, it was consented in 2002. It is a more stable molecule derived from aspartame (N-[N-(3,3-dimethylbutyl)-L-alpha-aspartyl]-L-phenylalanine 1-methyl ester) (figure.5). Its chemical formula is $C_{20}H_{24}N_2O_5$ and molecular weight of 378.46 g/mol. Neotame is much more sweeter than sucrose by 7000 times and can be used in elevated temperatures (Nabors, 2002).

Neotame is marketed as NutraSweet. The maximum amount that can be eaten on a day (ADI) is 18 mg/kg/day.


**Figure.5. The chemical structure of neotame**

**Potential adverse effects of neotame:** Neotame is metabolized and completely eliminated from the body without accumulation. The methyl ester bond hydrolysis by esterase to produce de-esterified neotame, which is the main metabolite and a small amount of methanol. The formed link between the two amino acids (aspartic acid and phenylalanine) is broken by peptidases, but in neotame the existence of the 3, 3-dimethylbutyl moiety hides this bond thus, reducing the generation of phenylalanine and makes neotame consumption safe for people who suffer from phenylketonuria.

Some studies showed variations in body weight, these variations can be explained by the undesirable teste of foods that containing neotame. This will decrease the daily food intake, resulting in long-term loss in body weight. Neotame was subjected to a lot of studies both in animals and humans. All research revealed that there is no relation between diseases and consumption of neotame (Spillane, 2006).

**Sucralose:** Sucralose was found in 1976 and consented in 1998. It is derived from sucrose, Sucralose is a chlorinated sucrose (1, 4, 6-Trichloro-galactosucrose) with chemical formula $C_{12}H_{19}Cl_3O_8$ and molecular weight of 397.64 g/mol (figure.6) (Spillane, 2006). Despite sucralose is derived from sucrose, it does not have any nutritive value like it and cannot increase the level of blood sugar because the cells cannot recognize it, thus it cannot be metabolized and eliminated unchanged (Roberts, 2000). It is much more sweeter than sucrose by 600 times and it is stable in high temperatures. Therefore it can be used in cooking.

Sucralose is marketed as Splenda. The maximum amount that can be eaten on a day (ADI) is 5 mg/kg/day.

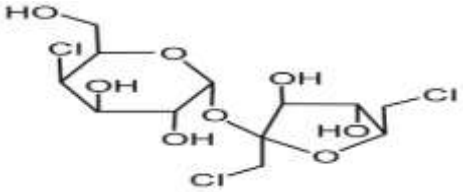

**Figure.6. The chemical structure of sucralose**

**Potential adverse effects of sucralose:** Sucralose has chlorine atoms so it belongs to the organic chlorides, which are known as toxic chemicals. Several studies have focused on these possible toxic effects including carcinogenic, reproductive and neurological effects but these influences were not proofed and sucralose was considered as safe by FDA. Sucralose metabolism suggests why it is not toxic, it is insoluble in fat and does not dechlorinates, thus it does not gather in the body fats like other organic chlorides (Daniel, 2000).

The FDA estimated hundreds of studies on human and animals and revealed that there is no proof of that sucralose can lead to cancer or other serious health problems.

**Unapproved sweeteners**

**Alitame:** Alitame is a combination of two amino acids L-aspartic acid and D-alanine with a tetra methylthietanyl-amine moiety substituted on terminal N (Figure.7). Alitame is much more sweeter than sucrose by 2000 times and does not break down under heat conditions so it can be used in cooking.

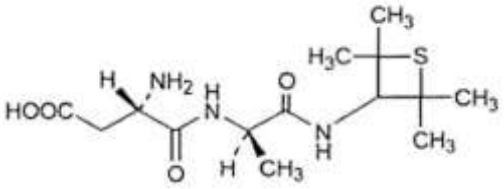

**Figure.7. The chemical structure of alitame**

**Potential adverse effects of alitame:** Alitame is absorbed in the body and metabolized to aspartic acid which is metabolized regularly and alanine amide which is eliminated unchanged.

The FDA estimated the information from numerous research studies in human and animals and revealed that there is no evidence that alitame and its components are dangerous and do not lead to any health problems like cancer. Alitame has been approved in some countries.

**Cyclamate:** Cyclamate was found in 1937 and has been banned in 1969. Cyclamate is an organic acid (Cyclohexylsulfamic acid) and it is used as sodium or calcium salt. The sodium salt has the molecular formula $C_6H_{12}NNaO_3S$ and a molecular weight of 201.22 g/mol (Figure.8). It is much more sweeter than sucrose by 30-50 times and does not break down under heating and freezing conditions so it can be used in cooking and freezing without any effect on its sweetness.

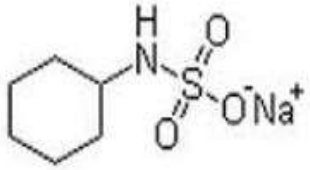

**Figure.8. The chemical structure of Cyclamate Na**

**Potential adverse effects of cyclamate:** The problems surrounding cyclamate are based on the difficult of determination the ADI for it because different people metabolize it in different ways. Some people excrete it without any change and some people metabolize it to cyclohexylamine (Figure.9), which is more toxic than cyclamate. (Bopp, 1986) so scientists must estimate this safety issue and solve it.

Another issue surrounding cyclamate is that cyclamate can lead to bladder cancer in animals. Extensive studies on the carcinogenicity of cyclamate did not show any link between cyclamate and cancer. Therefore, scientists revealed that cyclamate is not carcinogenic (Ahmed, 1992). Now there is a petition about cyclamate for approval.

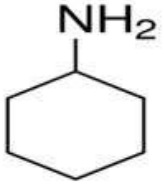

**Figure.9. The chemical structure of cyclohexylamine**

## 2. CONCLUSION

Natural sweeteners are safe. But they have calories and may cause some adverse effects, like tooth cavities, increasing body weight, increasing triglycerides and diabetes. On the contrary, artificial sweeteners don't have calories and do not cause such health problems (do not generate tooth cavities, do not effect on blood sugar). But they aren't without side effects and their safety has been controversial. Yet the health organizations have illustrated the safety and approved 5 artificial sweeteners (acesulfame-K, aspartame, neotame, saccharin, and sucralose).

More research and long-term surveys should be done to decrease harassment resulting from artificial sweeteners.

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