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FIVE CHEMICALS DESTROY BRAIN CELLS: HARMLESS OR VILLAIN

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ABSTRACT

There are five chemicals [monosodium glutamate, aspartame, sucralose, diacetyl and aluminum] which are being used in culinary purpose as taste makers which gives yummy feelings to tase buds to make the ingestible food delicious. The taste makers produce organoleptic properties [coloring, flavoring, sweetening agents] to some extent but they can produce harmful adverse effects in body especially to brain cells.

KEYWORDS: MSG, aspartame, sucralose, diacetyl, aluminum, brain damage.

INTRODUCTION

Monosodium glutamate (MSG) [IUPAC: Sodium 2-aminopentanedioate; CAS: 142-47-2; Molecular Formula: $C_5H_8NO_4Na$; Molecular Weight: 169.111 g/mol] is a flavor enhancer commonly added to Chinese food, canned vegetables, soups and processed meats.[1]

Figure-1: Monosodium glutamate & Kikunae Ikeda [inventor]

The Food and Drug Administration (FDA) has classified MSG as a food ingredient that's "generally recognized as safe," but its use remains controversial. Monosodium glutamate (MSG), also known as sodium glutamate, is the sodium salt of glutamic acid. MSG is found naturally in some foods including tomatoes and cheese.[2] MSG is used in cooking as a flavor enhancer with an umami taste that intensifies the meaty, savory flavor of food, as naturally occurring glutamate does in foods such as stews and meat soups. MSG was first prepared in 1908 by Japanese biochemist **Kikunae Ikeda** [Kikunae Ikeda (8 October 1864 – 3 May 1936) was a Japanese chemist and Tokyo Imperial University professor of chemistry who, in 1908, uncovered the chemical basis of a taste he named umami. It is one of the five basic tastes along with sweet, bitter, sour and salty], who was trying to isolate and duplicate the savory taste of kombu, an edible seaweed used as a base for many Japanese soups. MSG balances, blends, and rounds the perception of other tastes. MSG is commonly used and found in stock (bouillon) cubes, soups, ramen, gravy, stews, condiments, savory snacks, etc. Brain Menace number one is called MSG or monosodium glutamate. This is a very questionable contaminant that can impact the health

of the body; it causes headaches, high blood pressure, and it can cause the demise of brain cells. What's even worse is now food manufacturers are trying to hide this ingredient on the label with clever and innocent-sounding names like; hydrolyzed protein, natural flavoring, autolyzed yeast extract, and that's just the tip of the iceberg.[3]

Monosodium glutamate (MSG) is a flavor enhancer commonly added to Chinese food, canned vegetables, soups and processed meats. The Food and Drug Administration (FDA) has classified MSG as a food ingredient that's "generally recognized as safe," but its use remains controversial. For this reason, when MSG is added to food, the FDA requires that it be listed on the label. MSG has been used as a food additive for decades. Over the years, the FDA has received many anecdotal reports of adverse reactions to foods containing MSG. These reactions — known as MSG symptom complex — include: Headache, Flushing, Sweating, Facial pressure or tightness, Numbness, tingling or burning in the face, neck and other areas, Rapid, fluttering heartbeats (heart palpitations), Chest pain, Nausea, Weakness.[4]

Figure-2: Chinese culinary & Blood Brain Barrier.

Cerebral capillary endothelial cells form the BBB that surrounds the entire central nervous system. These powerful secondary active transporters couple with the energy of the Na^+-gradient to move glutamate and glutamine into endothelial cells, whereupon glutamate can exit to the blood on the luminal facilitative glutamate transporter. In most regions of the brain, the uptake of glutamate and other anionic excitatory amino acids from the circulation is limited by the blood-brain barrier (BBB). Glutamate transport at the BBB has been studied by both *in-vitro* cell uptake assays and *in-vivo* perfusion methods. Monosodium glutamate is added to foods as a taste enhancer, but it is a well-established excitotoxin. MSG slowly enters the brain, bypasses the blood-brain barrier and reaches peak concentrations in the brain three hours after ingesting it.[5]

Aspartame: Aspartame [IUPAC: Methyl L-α-aspartyl-L-phenylalaninate: CAS: 22839-47-0; Molecular Formula: $C_{14}H_{18}N_2O_5$; Molecular Weight: 294.307 $g{\cdot}mol^{-1}$] is an artificial non-saccharide sweetener 200 times sweeter than sucrose, and is commonly used as a sugar substitute in foods and beverages.[6]

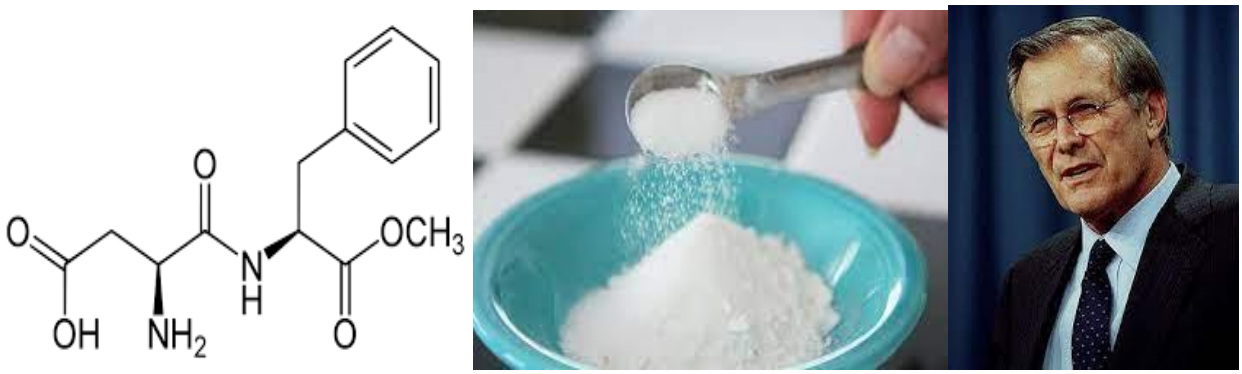

Figure-3: Aspartame & James M. Schlatter [inventor]

It is a methyl ester of the aspartic acid/phenylalanine dipeptide with the trade names NutraSweet, Equal, and Canderel. Aspartame was first made in 1965 and approved for use in food products by the United States Food and Drug Administration (FDA) in 1981. Aspartame is one of the most rigorously tested food ingredients. Reviews by over 100 governmental regulatory bodies found the ingredient safe for consumption at current levels. As of 2018, several reviews of clinical trials showed that using aspartame in

place of sugar reduces calorie intake and body weight in adults and children. Aspartame was discovered by accident by scientist **James M. Schlatter** in 1965. As Schlatter was researching an anti-ulcer drug, he licked his finger to get a better grip, and the sweetness he tasted was aspartame.

The safety of aspartame has been studied since its discovery and it is one of the most rigorously tested food ingredients. Aspartame has been deemed safe for human consumption by over 100 regulatory agencies in their respective countries, including the United States Food and Drug Administration (FDA), UK Food Standards Agency, the European Food Safety Authority (EFSA), Health Canada, Australia, and New Zealand. As of 2017, reviews of clinical trials showed that using aspartame (or other non-nutritive sweeteners) in place of sugar reduces calorie intake and body weight in adults and children. A 2017 review of metabolic effects by consuming aspartame found that it did not affect blood glucose, insulin, total cholesterol, triglycerides, calorie intake, or body weight. While high-density lipoprotein levels were higher compared to control, they were lower compared to sucrose.[7]

Phenylalanine: High levels of the naturally occurring essential amino acid phenylalanine are a health hazard to those born with phenylketonuria (PKU), a rare inherited disease that prevents phenylalanine from being properly metabolized. Because aspartame contains a small amount of phenylalanine, foods containing aspartame sold in the United States must state: "Phenylketonurics: Contains Phenylalanine" on product labels. In the UK, foods that contain aspartame are required by the Food Standards Agency to list the substance as an ingredient, with the warning, "Contains a source of phenylalanine". Manufacturers are also required to print "with sweetener(s)" on the label close to the main product name on foods that contain "sweeteners such as aspartame" or "with sugar and sweetener(s)" on "foods that contain both sugar and sweetener". In Canada, foods that contain aspartame are required to list aspartame among the ingredients, include the amount of aspartame per serving, and state that the product contains phenylalanine. Phenylalanine is one of the essential amino acids and is required for normal growth and maintenance of life. Concerns about the safety of phenylalanine from aspartame for those without phenylketonuria center largely on hypothetical changes in neurotransmitter levels as well as ratios of neurotransmitters to each other in the blood and brain that could lead to neurological symptoms. Reviews of the literature have found no consistent findings to support such concerns, and while high doses of aspartame consumption may have some biochemical effects, these effects are not seen in toxicity studies to suggest aspartame can adversely affect neuronal function. As with methanol and aspartic acid, common foods in the typical diet such as milk, meat, and fruits, will lead to ingestion of significantly higher amounts of phenylalanine than would be expected from aspartame consumption.[8]

Cancer: Reviews have found no association between aspartame and cancer. This position is supported by multiple regulatory agencies like the FDA and EFSA as well as scientific bodies such as the National Cancer Institute. The EFSA, FDA, and the US National Cancer Institute state that aspartame is safe for human consumption.

Neurotoxicity symptoms: Reviews found no evidence that low doses of aspartame would plausibly lead to neurotoxic effects. A review of studies on children did not show any significant findings for safety concerns with regard to neuropsychiatric conditions such as panic attacks, mood changes, hallucinations, ADHD, or seizures by consuming aspartame.[9]

Headaches: Headaches are the most common symptom reported by consumers. While one small review noted aspartame is likely one of many dietary triggers of migraines, in a list that includes "cheese, chocolate, citrus fruits, hot dogs, monosodium glutamate, aspartame, fatty foods, ice cream, caffeine withdrawal, and alcoholic drinks, especially red wine and beer," other reviews have noted conflicting studies about headaches and other studies lack any evidence and references to support this claim.

That brings me to Brain Menace number two. This potential brain invader masquerades as a health food because it’s low-glycemic. Yet it may be the most potent Brain Invader of them all. It’s called Aspartame and it’s sold under the label NutraSweet or Equal. It’s a 100% synthetic substance not found in nature that has absolutely no nutritional value.

Plus, aspartame accounts for over 75 percent of the adverse reactions to food additives reported to the FDA. Many of these reactions are very serious, including seizures and sadly — far worse conditions. Aspartame and MSG are both “excitotoxins” because they “excite” or stimulate the brain cell to its demise.[10]

Sucralose: Sucralose [IUPAC: 1,6-Dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-D-galactopyranoside; CAS: 56038-13-2; $C_{12}H_{19}Cl_3O_8$; 397.64 g/mol] is an artificial sweetener and sugar substitute. The majority of ingested sucralose is not broken down by the body, so it is noncaloric.[11]

Figure-4: Aspartame & Tate & Lyle [inventor]

In the European Union, it is also known under the E number E955. It is produced by chlorination of sucrose, selectively replacing three of the hydroxy groups in the C1, C4, and C6 positions to give a 1,6-dichloro-1,6-dideoxyfructose–4-chloro-4- deoxygalactose disaccharide. Sucralose is about 320 to 1,000 times sweeter than sucrose, three times as sweet as both aspartame and acesulfame potassium, and twice as sweet as sodium saccharin.[12] Evidence of benefit is lacking for long-term weight loss with some data supporting weight gain and heart disease risks. While sucralose is largely considered shelf-stable and safe for use at elevated temperatures (such as in baked goods), there is some evidence that it begins to break down at temperatures above 119 degrees Celsius. The commercial success of sucralose-based products stems from its favorable comparison to other low-calorie sweeteners in terms of taste, stability, and safety. It is commonly sold under the Splenda brand name. Canderel Yellow also contains sucralose, but the original Canderel and Green Canderel do not. Sucralose was discovered by **Tate & Lyle** and researchers at Queen Elizabeth College, University of London, in 1976. Tate & Lyle subsequently developed sucralose-based Splenda products in partnership with Johnson & Johnson subsidiary McNeil Nutritionals, LLC.[13]

For some people, it may raise blood sugar and insulin levels. It may also damage the bacterial environment in your gut, but this needs to be studied in humans. The safety of sucralose at high temperatures has also been questioned. You may want to avoid cooking or baking with it, as it may release harmful compounds. That brings me to the third Brain Menace, Sucralose. Sold under the label Splenda.[14]

It's very important to realize that Splenda also called sucralose is NOT sugar, despite its marketing slogan "Made from sugar, so it tastes like sugar." It's actually a chlorinated artificial sweetener in line with aspartame. What's happening is, they take an ordinary sugar molecule and then add 3 chloride ions. Any time chlorine is combined with carbon, it becomes an unwanted contaminant. This is how pesticides and herbicides are created.[15]

Diacetyl: Diacetyl is known to cause inflammation, scarring and constriction of the tiny airways in the lung (bronchioles), which significantly reduces air flow. Although the chemical is considered to be safe when eaten, it may be hazardous when inhaled over a long period of time, according to the Occupational Safety and Health Administration (OSHA).[16]

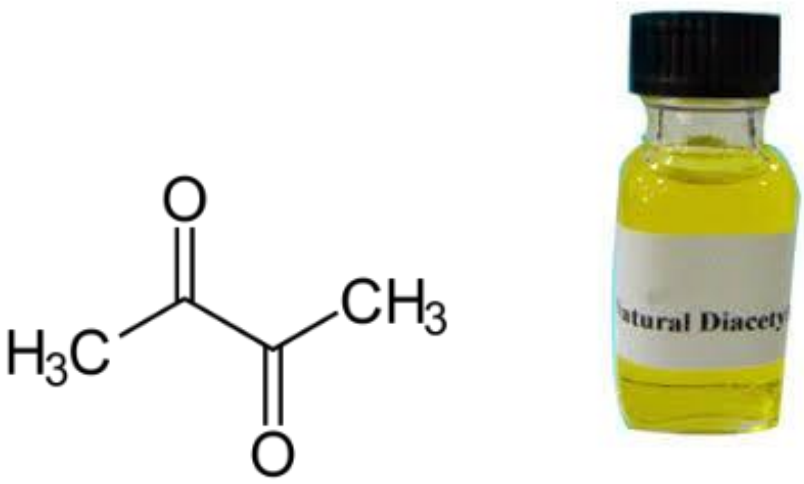

Figure-5: Diacetyl

There is currently no known cure for popcorn lung except for a complete lung transplant. The Harvard researchers said "urgent action" is needed to "evaluate this potentially widespread exposure via flavored e-cigarettes." IUPAC: Butane-2,3-dione; CAS: 431-03-8; Molecular Formula: $C_4H_6O_2$; Molecular Weight:

86.090 g·mol^{-1}. Diacetyl is an organic compound with the chemical formula $(CH_3CO)_2$. It is a yellow or green liquid with an intensely buttery flavour. It is a vicinal diketone (two C=O groups, side-by-side). Diacetyl occurs naturally in alcoholic beverages and is added to some foods to impart its buttery flavour. Diacetyl is known to cause the lung disease bronchiolitis obliterans in those individuals exposed to it in an occupational setting. A distinctive feature of diacetyl (and other vicinal diketones) is the long C–C bond linking the carbonyl centres.[17] This bond distance is about 1.54 Å, compared to 1.45 Å for the corresponding C–C bond in 1,3-butadiene. The elongation is attributed to repulsion between the polarized carbonyl carbon centres. Diacetyl has been shown to alter the amino acid arginine which could interfere with protein structure and function. Additionally, diacetyl can bind to DNA and form guanosine adducts which can cause DNA uncoiling and cell death. The chemical can bypass the blood brain barrier and interfere with cognitive functions, namely causing memory decline in older brains.[18] *In-vitro* studies on human cells also suggest that diacetyl alters the structure and function of the extracellular matrix and modifies epithelial cell responses to growth factors. Human cells exposed to diacetyl also increase secretion of substance P which causes mucus hypersecretion, airway smooth muscle contraction, and oedema. Studies in rats have demonstrated significant airway epithelial damage and necrosis after exposure to diacetyl. The diacetyl contained in e-cigarettes and vapes may increase the risk of the following serious side effects: Bronchiolitis Obliterans (aka Popcorn Lung), Fixed Airway Obstruction, Chronic Bronchitis, Asthma, Diseases of the Small Airways, Seizures, Pneumonia, Congestive heart failure (CHF), Hypotension, Additional health problems.[19]

Then we have the fourth Brain Menace, Diacetyl. I don't know about anyone else, but I love to eat warm buttery popcorn, especially while I watch a movie. There's something about the smell and the mixture of the salty goodness with the buttery flavor that I just can't get enough of. Here's the kicker: That same buttery flavor in home popcorn is actually Diacetyl. A brain toxin that can cross the blood-brain barrier, a defense mechanism that prevents harmful substances from entering the brain. And diacetyl is bad news for our memory, because when ingested, it often passes through the blood-brain barrier and can form plaques on the brain. This is often the cause of memory decline… again it's NOT always age, as most people think. We won't see diacetyl on the labels, but if we see "artificial butter flavor" or "natural flavors" we should avoid it at all costs.[20]

Figure-6: Brain.

Aluminum: $_{13}Al^{27}$ Aluminum (aluminum in American and Canadian English) is a chemical element with the symbol Al and atomic number 13. Aluminum has a density lower than those of other common metals, at approximately one third that of steel. It has a great affinity towards oxygen, and forms a protective layer of oxide on the surface when exposed to air. Aluminum visually resembles silver, both in its color and in its great ability to reflect light. It is soft, non-magnetic and ductile. It has one stable isotope, Al^{27}; this isotope is very common, making aluminum the twelfth most common element in the Universe. The radioactivity of Al^{26} is used in radio dating. Chemically, aluminum is a weak metal in the boron group; as is common for the group, aluminum forms compounds primarily in the +3-oxidation state. The aluminum cation Al^{3+} is small and highly charged; as such, it is polarizing, and bonds aluminum forms tend towards covalency. The strong affinity towards oxygen leads to aluminum's common association with oxygen in nature in the form of oxides; for this reason, aluminum is found on Earth primarily in rocks in the crust, where it is the third most abundant element after oxygen and silicon, rather than in the mantle, and virtually never as the free metal.[21]

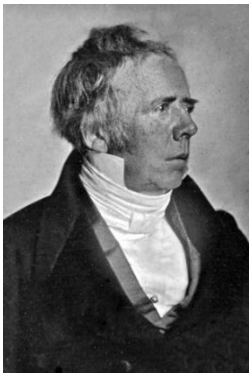

Figure-6: Hans Christian Ørsted.

The discovery of aluminum was announced in 1825 by Danish physicist **Hans Christian Ørsted** [14 August 1777 – 9 March 1851]. The first industrial production of aluminum was initiated by French chemist Henri Étienne Sainte-Claire Deville in 1856. Aluminum became much more available to the public with the Hall–Héroult process developed independently by French engineer Paul Héroult and American engineer Charles Martin Hall in 1886, and the mass production of aluminum led to its extensive use in industry and everyday life. In World Wars I and II, aluminum was a crucial strategic resource for aviation. In 1954, aluminum became the most produced non-ferrous metal, surpassing copper.[22] In the 21st century, most aluminum was consumed in transportation, engineering, construction, and packaging in the United States, Western Europe, and Japan. Despite its prevalence in the environment, no living organism is known to use aluminum salts metabolically, but aluminum is well tolerated by plants and animals. Because of the abundance of these salts, the potential for a biological role for them is of continuing interest, and studies continue. And finally, there's the fifth Brain Menace, Aluminum. Aluminum is a known neurotoxin. In the 1970's, autopsies revealed that people that had a larger than normal concentration of aluminum in the brain were more likely to have serious brain issues. Unfortunately, aluminum is everywhere.[23] It's in drinking water, supplements, antacids, anti-perspirants, cans, foil, and is commonly used in cookware. Our best bet is to look for aluminum-free deodorants, baking powder and antacids. And always ensure the supplements we take have been 3rd party tested for heavy metals. Aluminum is classified as a non-carcinogen by the United States Department of Health and Human Services. A review published in 1988 said that there was little evidence that normal exposure to aluminum presents a risk to healthy adult, and a 2014 multi-element toxicology review was unable to find deleterious effects of aluminum consumed in amounts not greater than 40 mg/day per kg of body mass. Most aluminum consumed will leave the body in feces; most of the small part of it that enters the bloodstream, will be excreted via urine; nevertheless, some aluminum does pass the blood-brain barrier and is lodged preferentially in the brains of Alzheimer's patients. Evidence published in 1989 indicates that, for Alzheimer's patients, aluminum may act by electrostatically crosslinking proteins, thus down-regulating genes in the superior temporal gyrus.[23]

Effects: Aluminum, although rarely, can cause vitamin D-resistant osteomalacia, erythropoietin-resistant microcytic anemia, and central nervous system alterations. People with kidney insufficiency are especially at a risk. Chronic ingestion of hydrated aluminum silicates (for excess gastric acidity control) may result in aluminum binding to intestinal contents and increased elimination of other metals, such as iron or zinc; sufficiently high doses (>50 g/day) can cause anemia.There are five major aluminum forms absorbed by human body: the free solvated trivalent cation (Al^{3+}(aq)); low-molecular-weight, neutral, soluble complexes (LMW-Al0(aq)); high-molecular-weight, neutral, soluble complexes (HMW-Al0(aq)); low-molecular-weight, charged, soluble complexes (LMW-Al(L)n+/−(aq)); nano and micro-particulates (Al(L)n(s)). They are transported across cell membranes or cell epi-/endothelia through five major routes: (1) paracellular; (2) transcellular; (3) active transport; (4) channels; (5) adsorptive or receptor-mediated endocytosis.[23]

During the 1988 Camelford water pollution incident people in Camelford had their drinking water contaminated with aluminum sulfate for several weeks. A final report into the incident in 2013 concluded it was unlikely that this had caused long-term health problems. Aluminum has been suspected of being a possible cause of Alzheimer's disease, but research into this for over 40 years has found, as of 2018, no good evidence of causal effect. Aluminum increases estrogen-related gene expression in human breast cancer cells cultured in the laboratory. In very high doses, aluminum is associated with altered function of the blood–brain barrier. A small percentage of people have contact allergies to aluminum and experience itchy red rashes, headache, muscle pain, joint pain, poor memory, insomnia, depression, asthma, irritable bowel syndrome, or other symptoms upon contact with products containing aluminum. Exposure to powdered aluminum or aluminum welding fumes can cause pulmonary fibrosis. Fine aluminum powder can ignite or explode, posing another workplace hazard.[24]

Exposure routes: Food is the main source of aluminum. Drinking water contains more aluminum than solid food; however, aluminum in food may be absorbed more than aluminum from water. Major sources of human oral exposure to aluminum include food (due to its use in food additives, food and beverage packaging, and cooking utensils), drinking water (due to its use in municipal water treatment), and aluminum-containing medications (particularly antacid/antiulcer and buffered aspirin formulations). Dietary exposure in Europeans averages to 0.2–1.5 mg/kg/week but can be as high as 2.3 mg/kg/week. Higher exposure levels of aluminum are mostly limited to miners, aluminum production workers, and dialysis patients. Consumption of antacids, antiperspirants, vaccines, and cosmetics provide possible routes of exposure. Consumption of acidic foods or liquids with aluminum enhances aluminum absorption, and maltol has been shown to increase the accumulation of aluminum in nerve and bone tissues.[25]

CONCLUSION

Your taste buds crave for some foods without any instinct from your brain or stomach!! This is when we call it an addiction for any food. There is no story heard anywhere that someone got addicted to apple or broccoli. But there are some foods that make it very difficult to stop eating once you have a taste of them. The reason for this addiction is the right combination of things that make your brain give signals that you want more. These are made with a perfect ratio between refined carbohydrates and added fat. This will cause an increase in the blood sugar level, triggered by your brain. This happens with processed foods that contain harmful chemicals in the form of preservatives and additives. Generally, these foods don't have anything to do to improve your health, but the thing is, we cannot stop eating this. The main reason for the addiction to fast foods is the blood glucose imbalance that you experience after eating them. Also, there are feel-good chemicals that are produced in the body due to the action of the taste-makers and additives in the food. Let us go through some of the most addictive fast foods that we come across almost every day, which we need to avoid at any cost.

1. French Fries: No matter what the age is, almost everyone becomes a fan of this fried food item, once he/she tastes it. You cannot stop eating this even when your stomach is full due to the treat that you give to your taste buds.
2. Pizza Pizza is an Italian food. It is healthy if made with healthy ingredients, especially when prepared at home. But, in food courts, they are sold with added taste-makers and high-calorie ingredients like cheese.
3. Chocolate Nobody will have an opposition to the statement that chocolates are addictive. No wonder your child craves for chocolate even at mid-night. Milk chocolates are packed with a high amount of sugar that is not good for your health.
4. Ice Cream You don't have any right to scold your child if he/she asks for ice cream more frequently, when you yourself are addicted to it. Ice cream is an all-time favourite of both children and adults. This is due to the high amount of added sugar that it contains.
5. Burgers There are many famous food brands that are specialized only in burgers. No wonder these fast-food chains are opening their outlet in each and every city across the country. This is all because people are addicted to burgers, no matter what the age is.

6. Popcorns Popcorns are made with a high amount of salt in it. This is why you cannot stop eating popcorns once you taste the first piece. No worries, just make this at home. Popcorn is a healthy food when made with healthy options.
7. Carbonated Drinks There are many researches which show that carbonated drinks are unhealthy. The surprising fact is that people crave for carbonated drinks even when they know that these are not good for the health.
8. Sausage Sausage is one of the favourite foods of many people. They love to have sausages with added sauces and flavours. This is because it is one of the most addictive foods.
9. Fried Chicken Once you taste it, you will always crave for it more and more. Usually, fried chickens are served along with other calorie-rich unhealthy foods that make the cravings even stronger.
10. Potato Chips Potato chips are the all-time favourite snacks for most of the people. Once you start eating this, you will not be able to resist the temptation of having more. The craving will be more intense if it is a little spicy too.

REFERENCES

1. Yamaguchi S (1991). "Basic properties of umami and effects on humans". Physiology & Behavior, 49(5): 833–41.
2. Obayashi, Y; Nagamura, Y (2016). "Does monosodium glutamate really cause headache?: a systematic review of human studies". The Journal of Headache and Pain, 17(1): 54.
3. Yamaguchi, Shizuko, Central Research Laboratories, Ajinomoto Co., Japan; Takahashi, Chikahito, Central Research Laboratories, Ajinomoto Co., Japan. (1984). "Interactions of monosodium glutamate and sodium chloride on saltiness and palatability of a clear soup". Journal of Food Science, 49(1): 82–85.
4. Walker R, Lupien JR, School of Biological Sciences, University of Surrey, UK, and Food and Nutrition Division, FAO of the United Nations, Italy. (2000). "The safety evaluation of monosodium glutamate". Journal of Nutrition, 130(4S Suppl): 1049S–52S.
5. Freeman, Matthew (2006). "Reconsidering the effects of monosodium glutamate: A literature review". Journal of the American Academy of Nurse Practitioners, 18(10): 482–86.
6. Nahon DF, Roozen JP, de Graaf C (1998). "Sensory evaluation of mixtures of maltitol or aspartame, sucrose and an orange aroma". Chemical Senses, 23(1): 59–66.
7. Azad MB, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, Mann A, Jeyaraman MM, Reid AE, Fiander M, MacKay DS, McGavock J, Wicklow B, Zarychanski R (2017). "Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies". CMAJ., 189(28): E929–E939.
8. Rogers PJ, Hogenkamp PS, de Graaf C, Higgs S, Lluch A, Ness AR, Penfold C, Perry R, Putz P, Yeomans MR, Mela DJ (2016). "Does low-energy sweetener consumption affect energy intake and body weight? A systematic review, including meta-analyses, of the evidence from human and animal studies". International Journal of Obesity, 40(3): 381–94.
9. Trocho C, Pardo R, Rafecas I, Virgili J, Remesar X, Fernández-López JA, Alemany M (1998). "Formaldehyde derived from dietary aspartame binds to tissue components in vivo". Life Sciences, 63(5): 337–49.
10. Struck, Susanne; Jaros, Doris; Brennan, Charles S.; Rohm, Harald (2014). "Sugar replacement in sweetened bakery goods". International Journal of Food Science & Technology, 49(9): 1963–76.
11. Azad MB, Abou-Setta AM, Chauhan BF, Rabbani R, Lys J, Copstein L, et al. (2017). "Nonnutritive sweeteners and cardiometabolic health: a systematic review and meta-analysis of randomized controlled trials and prospective cohort studies". CMAJ., 189(28): E929–E939.
12. Bannach G, Almeida RR, Lacerda LG, Schnitzler E, Ionashiro M (2009). "Thermal stability and thermal decomposition of sucralose" (PDF). Eclética Química, 34(4): 21–26.
13. Grotz VL, Henry RR, McGill JB, Prince MJ, Shamoon H, Trout JR, Pi-Sunyer FX (2003). "Lack of effect of sucralose on glucose homeostasis in subjects with type 2 diabetes". Journal of the American Dietetic Association, 103(12): 1607–12.
14. Berry C, Brusick D, Cohen SM, Hardisty JF, Grotz VL, Williams GM (2016). "Sucralose Non-Carcinogenicity: A Review of the Scientific and Regulatory Rationale". Nutrition and Cancer, 68(8): 1247–1261.

15. Labare MP, Alexander M (1993). "Biodegradation of sucralose in samples of natural environments". Environmental Toxicology and Chemistry, 12(5): 797–804.
16. Kreiss, Kathleen (2017). "Recognizing occupational effects of diacetyl: What can we learn from this history?". Toxicology, 388: 48–54.
17. Nielsen JC, Richelieu M (1999). "Control of flavor development in wine during and after malolactic fermentation by Oenococcus oeni". Applied and Environmental Microbiology, 65(2): 740–5.
18. Lockey JE, Hilbert TJ, Levin LP, Ryan PH, White KL, Borton EK, et al. (2009). "Airway obstruction related to diacetyl exposure at microwave popcorn production facilities". The European Respiratory Journal, 34(1): 63–71.
19. Eriks K, Hayden TD, Yang SH, Chan IY (1983). "Crystal and molecular structure of biacetyl (2,3-butanedione), (H3CCO)2, at −12 and −100 °C". J. Am. Chem. Soc., 105(12): 3940–3942.
20. Kanwal R, Kullman G, Fedan KB, Kreiss K (2011). "Occupational lung disease risk and exposure to butter-flavoring chemicals after implementation of controls at a microwave popcorn plant". Public Health Reports, 126(4): 480–94.
21. Dohmeier, C.; Loos, D.; Schnöckel, H. (1996). "Aluminum(I) and Gallium(I) Compounds: Syntheses, Structures, and Reactions". Angewandte Chemie International Edition, 35(2): 129–149.
22. Magalhaes, J.V.; Garvin, D.F.; Wang, Y.; Sorrells, M.E.; Klein, P.E.; Schaffert, R.E.; Li, L.; Kochian, L.V. (2004). "Comparative Mapping of a Major Aluminum Tolerance Gene in Sorghum and Other Species in the Poaceae". Genetics, 167(4): 1905–1914.
23. Horst, Walter J. (1995). "The role of the apoplast in aluminium toxicity and resistance of higher plants: A review". Zeitschrift für Pflanzenernährung und Bodenkunde, 158(5): 419–428.
24. Andersson, Maud (1988). "Toxicity and tolerance of aluminium in vascular plants". Water, Air, & Soil Pollution, 39(3–4): 439–462.
25. Van Ginkel, M.F.; Van Der Voet, G.B.; D'haese, P.C.; De Broe, M.E.; De Wolff, F.A. (1993). "Effect of citric acid and maltol on the accumulation of aluminum in rat brain and bone". The Journal of Laboratory and Clinical Medicine, 121(3): 453–460.