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Review Article

Food additives and brain complications: A risk to public health

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Abstract
Food additives comprise the amounts of xenobiotics that are known to affect the physiological metabolic pathways of living tissues. Although organic and inorganic chemicals are considered xenobiotics, organic compounds, the basic chemical entity for most constituents, are reported to be responsible for 80-90% xenobiotics-induced toxicity. Food additives have been the major source of generating these harmful toxins in the human population. Exposure to xenobiotics via dietary habits, environment or medication is inexorable in living creatures. Reports have shown the bidirectional interaction between xenobiotics and biological systems. When ingested, xenobiotics induce physiological, biochemical or pathological changes in the biological system. One study reported that exposure to titanium dioxide nanoparticles can cause cytotoxicity of glial cells and hippocampal neurons, leading to brain damage and changes in hippocampal function, which plays a vital role in the process of memory and learning. Therefore, the complexity and limited plasticity of the brain has always challenged researchers to seek solutions to neuronal and cognitive problems. Including new compounds in the food in the form of pesticides, preservatives, additives, and coloring agents in daily meals is the latest aspect of gene-environment interaction. The sporadic cause of neurodegenerative diseases and its epidemiological distribution can be better understood and countermeasures can be applied only if this relationship is represented quantitatively. Hence, this review focuses on the effect of food additives as xenobiotics, which leads to the potential for a compromised nervous system.

Keywords: Brain Health, Food Additives, Neurological Complications, Preservatives, Xenobiotics

INTRODUCTION

The manufacturing and production techniques of food and lifestyle changes lead to increased access to processed/frozen foods and limited fresh and nutritious food intake. Various scientific reports suggested the direct link of enhanced administration of food additives, with various physical and mental disorders, coordination difficulties, anxiety, impulsiveness, and disabilities with both cognitive and learning functions. Food supplements, additives like coloring agents, flavoring agents, sweeteners and preservatives contribute equally to the induction of organ-specific toxicity in humans (Bozzatello *et al*., 2016). Although food additives have been used for decades to enhance food's test and texture, they are reportedly harmful to brain health (Brown, 2018).

The brain is partly composed of major functional units known as neurons. Neurons have unique characteristics traits that allow the brain to communicate with its inner and outer nervous system channels (Luo, 2021). This connection is accomplished with the help of axons and dendrites, which are identified as branches of each neuron that are interconnected to each other. Each branch is composed of a gap where neurotransmitters are passed back and forth. These messages allow neurons to communicate information among themselves. Neurotransmitters are mainly composed of amino acids directly derived from the human diet. For example, the neurotransmitters serotonin, adrenaline, and dopamine are derived from amino acids, tryptophan and phenylalanine (Gasmi *et al*., 2022). Hence, the food we consume has the potential to affect our mental health and well-being at every stage of life (Levine *et al*., 2021). Besides the positive potency of food for the brain some diets have a detrimental effect on our thoughts and feelings; hence, it is necessary to understand these groups of foods (Diers *et al*., 2022). One group fixes the neurotransmitter release deficiency temporarily and the other group deteriorates the brain by hindering the

necessary conversion of food into the required nutrients needed by brain (Wilson, 2023). Complexity of the brain is the foremost reason for sensitivity towards food uptake. Since, the brain does not have an immediate response towards food poisoning like our stomach, it is rarely tried to investigate the relationship between brain and the dietary intake (Vojdani and Vojdani, 2021). Brain is also sensitive to the food that we consume in our daily lives. For proper functioning of brain, different essential nutrients such as carbohydrates, amino acids, and some essential fatty acids (EFAs), vitamins along with minerals and water are required by the brain. The biochemical and physiological consequences of food additive-associated chemicals have now started to come up. However, the neurobehavioral and cognitive deficiencies have been documented. Aspartame, for instance, is a widely used artificial, non-caloric sweetener pose a great threat to the mental health of the person (Pickering and Williams, 2014). It has been highlighted that aspartame indicts alterations in cognition, depression, mood, headache, working memory and spatial orientation. High-aspartame diet leads to irritable mood, more depression, and worse the spatial orientation tests when administered to volunteers (Lebda *et al*., 2017, Rycerz and Jaworska-Adamu, 2013). The purpose of this review is to illustrate the potential risks of these toxins on developing and adult brain and suggest a healthy lifestyle over the junk food and packed food material.

Overview of approved food additives

A food additive is any substance that becomes part of a food either directly or indirectly during processing, storage, packaging or manufacturing stages (Fellows, 2022). Additives can be direct or indirect, the former being the ones that are added intentionally and purposefully to the food while the latter ones, although in minor quantities, are those migrating unintended into the food as a result of growing, processing and/or packaging (Mwale, 2023). Additives perform some important functions in food preparation and can be eliminated only at the cost of loss of aesthetics, nutrients, and taste benefits and involve increased labor.

Food additives are eventually leading the food market in all the possible ways to accomplish the taste of different regions under one roof and thus, the food industries make foods that meet the ever-growing challenging demands. Food additives often become food adulterants during these desirable/undesirable advancements (Sen, 2021). This proclaims the need of the rules and regulations to keep food non-toxic while meeting the demands of modern times (Kumar *et al*., 2023) . There are country-specific regulatory bodies worldwide, such as USFDA (United States Food and Drug Administration) in the USA (Otsuki *et al*., 2001). In India, FSSAI (Food Safety and Standard Authority of India) regulates the nature and amount of particular food additives for specific food stuff. They have a set of key points that act as the framework to monitor food additives such as Acceptable Daily Intake (ADI) (DEMİR *et al*., 2022), food in which additives either can be added or not, maximum use level, Good Manufacturing Practice (GMP) (Hasnan *et al*., 2022), carryover of food additives into food etc.

In most cases, it is clearly defined what is an ingredient and, what an additive and where adulteration starts. The regulation hopefully limits or bans some of the additives. But sometimes, their definition became imprecise. For example, salt, vinegar, and lemon juice are ingredients of common food items, but characteristic acetic acid (in vinegar) and citric acid (in lemon juice), if used, must be declared as additives. These and other food additives listed in Table 1 play a variety of roles as food additives and can be categorized as organic and inorganic. These food additives are also reported as causing agents of many diseases. They generally have two main functions: first, to preserve food from pathogens or prevent oxidation or other chemical changes, to make food tasty, look better or give more pleasant feeling in the mouth. Besides, being foreign compounds (xenobiotics) to the human body, their excessive use (acute dose) or regular use over a long period (chronic dose) may impart adverse mental health effects (Lalani *et al*., 2023; Kraemer *et al*., 2022) .

Food additives as xenobiotics

Although organic and inorganic chemicals are considered xenobiotics, organic compounds, the basic chemical entity for most of the constituents, are reported to be responsible for 80-90% of the toxicity of xenobiotics. Apart from numerous sources of xenobiotics, food had been the major origin for generating these harmful toxins in biological systems, which consequently affects human populations with numerous disorders/diseases, including metabolic, autoimmune disorders and compromised nervous system (Schjenken *et al*., 2021) (Counihan and Van Esterik, 2012). Food supplements, additives like coloring agents, flavoring agents, sweeteners and preservatives contribute equally to the induction of organ-specific toxicity in humans (Berdanier *et al*., 2007) (Sambu *et al*., 2022). Despite the beneficial effects of food and additives on human health, there are several toxic chemical compounds consumed by the people in their daily lives through food. US FDA efficiently assures the minimum toxicity of food, and many regulatory companies have fixed the parameters. Manufacturers also set a limit on edible/food substances for a threshold for establishing toxicity (Campanale *et al*., 2020). Despite setting parameters, the consumption of small traces of food toxins is becoming unavoidable. Setting a precise limit point for daily human consumption poses a rigorous challenge amidst the array

of food items, their additives, and social preferences. We know that everything is toxic in an excessive amount. Only dose decides the gap between toxic and non-toxic effects (Schupp, 2022). Even water is reported to be toxic at a certain level (Organization, 2004). The water intoxication results in the hypernatremia, which is followed by cerebral edema and seizure (Papadopoulos and Verkman, 2007). Generally, the labeling requirements provided by the regulatory authorities guide the consumer with helpful information about the fat, protein, carbohydrate, caloric value, potential allergens, etc., but do not mention additives or toxins intrinsic in the foods or formed during processing/ manufacturing.

Approval of food additives for human consumption needs a prior submission of the results of use and animal feeding studies to the US FDA (Bren, 2007). After evaluating the safety, US FDA publishes a public notice about the name of the additive and its proposed use and may ask for further testing if there remains an issue of the risk after reviewing the data. A regulation permitting is issued if the US FDA concludes the safety of an additive to be used or added to the food. US FDA uses "Philosophy of the Minimum Rule" to determine food additive levels. First, the lowest and the maximum level limit at which a substance will produce its desired effect and at which it does not produce harmful effects is determined, and then the use level of the additive is decided, which should be no more than 1/100th of the "no effect" level of safety. So, there is a minimum 100-fold margin of safety imposed on the additive. Despite, all the rules, the risk of food additive-induced neurotoxicity is increasing day by day just because of speedy changes in food habits and lifestyle (Dey *et al*., 2022).

Vulnerability of the brain towards food xenobiotics

When mature, the brain's vulnerability during its development and rigidity to cope with any exposure makes us explore the neurotoxic effects of the chemicals used as food additives. Once the blood-brain barrier (BBB) is well-formed, a limited set of compounds can pass through it and show its adverse effect on brain cells but a developing brain in the mother's womb can be adversely affected by the mother's food intake (Denuzière and Ghersi-Egea, 2022). Therefore, ensuring a pregnant lady's food is free from such chemicals is more important. *In vitro* studies have proved food additives' independent and synergistic effects on differentiating neurons. Compounds such as brilliant blue, L-glutamate, quinolone yellow and aspartame (food additives) have reduced the neurite outgrowth during the differentiation of mouse neuroblastoma cells into neurons (Choi *et al*., 2010). Furthermore, exposure of such non-nutritional food additives during the critical brain development period has been implicated in the induction of behavioral disorders such as attention deficit hyperactivity disorder (ADHD) (Cusick *et al*., 2021). It is reported that maternally exposed coloring food additives have been found to reduce cognitive performance in rats (Ceyhan *et al*., 2013). The biochemical and physiological consequences of food additive-associated chemicals have started to come up. However, neurobehavioral and cognitive deficiencies have been documented (Contreras-Rodriguez *et al*., 2022). In the early developmental period, when neurogenesis, neuronal differentiation, neuronal migration, dendrite and axon formation, and the establishment of neuronal connectivity occurs, any adverse effect can be detrimental to the mental and cognitive functioning of the brain (Aleksandra and Alberto, 2015) (Lindeman *et al*., 2021).

In the adult stage, despite the fully formed blood-brain barrier (BBB), some chemicals can pass the BBB, enter the brain, and alter brain function. Scientific literature has some of notable examples where food additives have reached the brain cells and shown neurotoxicity(Gupta *et al*., 2020) (Giordano and Costa, 2012). Neurodegenerative diseases such as Parkinson's disease and Autism have been linked to common food additives such as benzoates, and propionic acid, respectively (Sharma *et al*., 2019). It is supposed that food additives induce brain damage, which may result from the brain's free radical generation (Sambu *et al*., 2022). Growing consumer demands for healthy, nutritious, and convenient food is a cue for improving and new technological developments in food processing. Over the last few decades, man has been exposed to many chemicals, added to fortify the microbiological and chemical safety of foods and to ameliorate its palatability, texture, flavor, and storage times. New socio-economic and technological developments lead to human exposure to new ingredients, new packaging, new foods, and new processing, which requires a more structured safety evaluation of potential human health impacts. Consequently, for human welfare, chemicals added/ food ingredients added must undergo a safety evaluation before it is ready to be used in the market (Vilas-Boas *et al*., 2021). Because brain regions develop at different times, i.e., during prenatal and post-natal life, the dominant phase of exposure to neurotoxins (toxins provoking neuronal loss) is the developmental phase (Oummadi, 2023) .

The diagrammatic representation of effect of food xenobiotics on fetus brain and adult brain is shown in Fig. 1. Conventionally, the consumption of food additives and the evaluation of unfavorable health effects to humans are reported by *in vitro* and *in vivo* toxicity studies by using the cell lines and animal species that are most tactful. Commonly, the no-observed- adverse effect level (NOAEL) are acquired from the range of doses in the tactful test species (often determined from chronic or sub-chronic feeding studies) is then used to derive

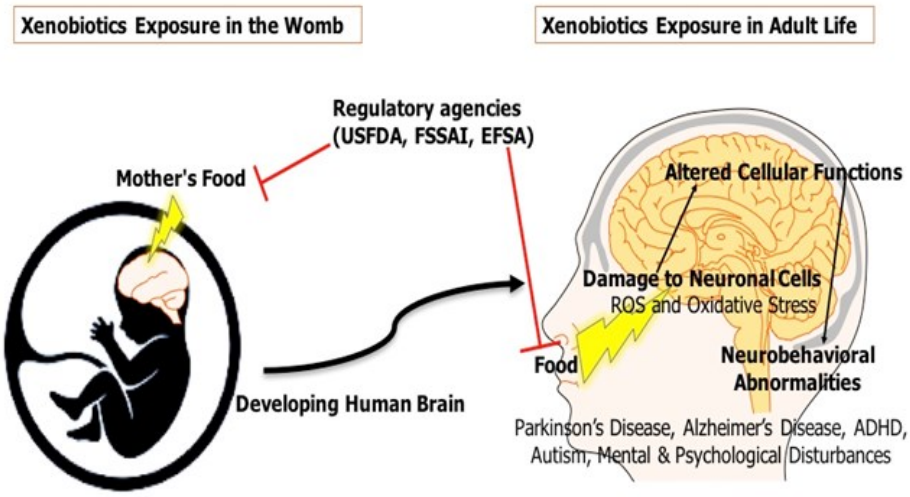

Fig.1. *Diagrammatic representation of food additives induced neuronal toxicity in developing brain and need of regulatory agencies to ameliorate dysfunctional activity (biorender.com).*

an ADI for a specific chemical compound (Judson *et al*., 2010). Human data is the most efficient approach to digging out the risk factor without any extrapolations in the species (Blaauboer, 2002). Although NOAEL is based on studies in human subjects for some additives like stannous chloride, erythrosine, canthaxanthin etc. This is possible only after having appropriate toxicological knowledge of the test compounds (Delgado-Vargas and Paredes-Lopez, 2002). However, it is much needed to explore more research in the context of human correlation data outcome. For food additives, the safety evaluation may be advanced by the addition of the knowledge obtained from the speedy developed scientific tools which support the toxicity studies like molecular biology, biochemistry, and pharmacological studies. To provide the continuity in the research, it is better to use the *in vitro* test system for providing scientific platform. *In vitro* studies may prove useful in bridging the gap between a test species and the human situation. The Panel on Contaminants in the Food Chain (CONTAM Panel) identified developmental neurotoxicity in young children and cardiovascular effects and nephrotoxicity in adults as the critical effects for the risk assessment (Norouzirad *et al*., 2018, Oummadi, 2023). Chemicals can be exposed to the fetus through mother by crossing the placenta and causes neurological dysfunction that prevails for the lifetime (Santosh, 2023).

Changing food habits, food additives and neurotoxic impact

It has been reported that various junk food items are made up of processed food consumed by children and adults in large quantities have food additives (Saravanan *et al*., 2023). Food additives used as preservatives, such as sulfites, nitrates/nitrites, butylated hydroxyanisole (BHA), monosodium glutamate (MSG) used in junk foods, snacks, soups, sauces, dried fruits, fruit juices and meat products, have been associated with an aggregation of symptoms in susceptible individuals. Quoting an example of MSG, a flavored enhancer used in different junk food items, has been associated with severe headache and/or asthma in susceptible individuals. MSG has also been the cause of epilepsy-type "shudder" attacks in children. MSG is also reported to damage the brain of young rodents (Kayode *et al*., 2023). BHA and sulfites used in soup mixes may cause urticaria, angioedema, and asthma in humans (Goyal *et al*., 2023) (Laura *et al*., 2019). Saccharin, widely used by the soft drink and sweet food industry, has been found to produce cancer, mutagenic and growth-inhibiting as reported in different animal studies (Azeez *et al*., 2019; Das *et al*., 2021).

Excitotoxins, defined as taste enhancers, are found abundantly in many food products and have been reported to damage human brain cells. These include MSG, hydrolyzed vegetable protein, aspartame (sold as NutraSweet) and cysteine(ZIEM'S). All these excitotoxins have a similar impact on selected neurons in the brain, i.e., overstimulation and continuous firing of neurons until they get exhausted and die. For knowing the adverse effects of food additives on health numerous experiments were carried out and various harmful effects associated with neuronal impairment are reported. Butylated hydroxyanisole (BHA) is widely used in the cosmetic and pharmaceutical industries and the food business to protect foods from lipid oxidation and the production of free radicals (BOUFTIRA, 2023). Despite the fact that the US Food and Drug Administration (FDA) has classified BHA as generally recognized as safe (GRAS), studies have linked it to malignant and benign tumors in the anterior stomach of rats. Furthermore, in the calf's thymus, tert-butylhydroquinone, the primary metabolite of BHA, promoted the production of 8-hydroxy deoxyguanosine (8-OHdG), an oxidative

stress biomarker (Karimi *et al*., 2019). The International Agency for Research on Cancer has classified the BHA as "probably carcinogenic to humans" based on toxicological studies (IARC). However, it is not classified as a cancer causing agent by the United States Environmental Protection Agency (EPA). BHA, on the other hand, is listed on the National Toxicology Program (NTP) Carcinogen List as "Reasonably Anticipated to Be a Carcinogen." Although there is inadequate evidence that BHA is a public health threat at current levels, the FDA stated that more research into its impact on various enzymes and metabolic systems is needed. Free radicals and the oxidative stress caused by xenobiotics such food additives are widely thought to be the fundamental cause of many chronic diseases (Jomova *et al*., 2023).

One of the most often used food colorants is tartrazine (TZ, E102), a synthetic azo lemon yellow color dye (Rovina *et al*., 2017). TZ is found in various food and non-food products, including soft and sport beverages, sauces, jellies, chewing gums, soaps and cosmetics products. TZ is also used instead of saffron in some areas as a low-cost substitute. An acceptable daily dose (ADI) of TZ per day has been set by the Joint FAO/WHO Expert Committee, which is 0 to 7.5 mg/kg body weight (Wu *et al*., 2021). TZ has been shown to affect experimental animals in research. Children, being primary users, are more susceptible to synthetic additives. Hyperactivity was seen in three- and eight-to-nine-year-old children who consumed foods containing artificial coloring additives in a randomized double-blind research (Rambler *et al*., 2022). In the same vein, synthetic food colorants can cause neurobehavioral abnormalities and teratogenicity in neonates if consumed during pregnancy (Albasher *et al*., 2020). In rat pubs exposed to 4.5 mg/kg of TZ from the sixth to the fifteenth day of gestation, a decrease in fetal weight, cardiomegaly, and liver and kidney damage were seen. Furthermore, rat dams exposed to 1% and 2% dietary TZ during pregnancy, lactation, and three months after weaning had normal development and no adverse behavioral or physical effects, with the exception of a small transient change in the female newborns neuromotor clinging ability and a slight increase in red blood cells (RBCs) and hemoglobin (Hb). Perinatal exposure to the azo dye TZ within the ADI range in mouse infants caused neurobehavioral changes. TZ caused histological changes and oxidative stress in diverse parts of the brain. Furthermore, perinatal TZ exposure resulted in hematological changes, altered locomotor movement, and anxiety-like behavior in neonatal mice. TZ usage during pregnancy and breastfeeding can cause teratogenic consequences and neurobehavioral changes in neonatal rats, even if it was delivered within the ADI range (Hashem *et al*., 2019). These findings suggest that azo dyes be consumed in moderation and that the public be made aware of their teratogenic potential. Food additives and associated neuronal impairments are documented in Table 1.

Nanoparticles as food additives and neurotoxicity: Evidence and impact on health

It appears that nanoparticles are not intentionally added to food today, as the EU has approved no nanosubstance for use in food. Rather, research have found that they come from a nanoscale fraction of food additives like TiO_2 (E171), which has received special focus in this section. If the statistics are true, this nano fractional might be as high as 40%, and the projected total intake of TiO_2 (as indicated by EFSA) is 1.28 mg/kg/person, resulting in a significant amount of nano TiO_2. IARC, on the other hand, has classed TiO_2 as a probable carcinogen. A potential link between particle ingestion and numerous chronic inflammatory disorders, which is also mentioned in this research, has piqued the curiosity of several groups (Rydström, 2012). To begin with, the brain coordinates cognitive, motor, and metabolic processes while also maintaining the organism's homeostasis. The blood-brain barrier (BBB) is a specific membrane that shields the brain and nervous system from harmful systemic circulation chemicals (Hwang and Kim, 2014). Gold (Au), silver (Ag), SiO_2, TiO_2, and iron oxide nanoparticles are permutated into the bloodstream and can move across the BBB in rats and mice, according to a variety of studies (Zhang *et al*., 2014). Exposure to titanium dioxide nanoparticles can cause cytotoxicity of glial cells and hippocampal neurons, leading to brain damage and changes in hippocampal function, which plays a vital role in memory and learning (Song *et al*., 2015). After long-term intragastric administration of TiO_2, the accumulation of TiO_2 in the hippocampus can be observed, leading to increased hippocampal ROS, cell apoptosis, and memory impairment of spatial recognition. TiO_2 exposure during pregnancy affects offspring's memory and learning. Pregnant rats were given TiO_2 through gavage (100 mg/kgbw) for 21 days, after which their offspring's memory and learning were assessed, revealing that the pups had reduced hippocampus cell proliferation, impaired learning and memory, and poor spatial recognition memory. Gavage was used to test the effects of TiO_2 at 10, 25, and 50 mg/kgbw in mice for 45 days. Higher concentrations of TiO_2 reduced the number of tyrosine hydroxylase neurons, which are required for dopamine generation, and increased dark neurons in the substantia nigra pars compacta, which were created after a brain injury and harmed the animals' motor skills. These findings support prior evidence that a TiO_2 intraperitoneal injection caused rippleness and slumberness in mice (Mohammadipour *et al*., 2020). Additionally, the length of exposure must be addressed when observing changes in animal behavior because

Table 1. List of food additives, which can cause the health disorders including brain dysfunction

S.No.	Food additive	Occurrence	ADI	Neurological manifestations	Other complications	Refernce
1.	Sulphites	Sulfites occur naturally in many foods, especially fermented foods such as wines. In addition, sulfites have long been used as ingredients in Pharmaceuticals	0-0.7 as SO2 mg/kg BW	Neurotoxicity, Hippocampal neuron number loss	Asthmatic reactions, anaphylaxis, urticaria, diarrhea, abdominal pain and cramping, nausea and vomiting, pruritis, localized angioedema, difficulty in swallowing, faintness, a headache, chest pain, loss of consciousness, “change in body temperature,” “change in heart rate,” and nonspecific rashes.	(Choi *et al.*, 2010, Ademiluyi *et al.,* 2020, Hajihasani *et al.*, 2020, Hazzaa *et al.*, 2020, Zanfirescu *et al.*, 2019)
2.	Mono sodium Glutamate (MSG)	widely used in many commercially packed food and restaurant and household cooking	1g/day in free form	Alteration in memory -related neurons in prepubertal rats, impaired auditory brainstem structure and function, Neurotoxicity, cognitive dysfunction, nervous toxicological effects at high dosage, Short-Term Memory, Gliosis, and Oxidative Stress	MSG symptom complex (numbness of the back of the neck, general weakness, and palpitations), asthma, urticarial, hepatotoxicity, obesity, diabetes and angioedema, genotoxic effects in lymphocytes	(Mohamed *et al*., 2015)
3.	Tartrazine (FD&C Yellow No. 5)	Coloring agents in food products	7.5 mg/kg bodyweight	Neurobehavioral alterations (perinatal exposure), neurotoxicity	Reproductive toxicity	(Strużyńska, 2017, Jiang *et al.*, 2019)
4.	Sodium Nitrate and Nitrite		0-3.7 milligrams (mg) nitrate ion/ kilogram (kg) body weight	mild anxiogenic-like behavior and alters brain metabolomic profile	Methaemoglobinaemia, Congenital malformations, negative developmental outcomes during pregnancy	(Kopalli *et al.*, 2013)
5.	BHA and BHT	Used in breakfast cereals, chewing gum, snack foods, vegetable oils, shortening, potato flakes,granules and chips, enriched rice, and candy to prevent oxidation of unsaturated fatty acids.	BHA: 0-0.5mg/kg BW BHT: 0-0.05mg/kg BW	Neurotoxic	Dose-dependent forestomach and liver tumors, impairment of anticoagulant properties, immunosuppression, haematotoxic and immunotoxic, testicular dysfunction	(Abd-Ellah *et al*., 2018)
6.	Benzoates	Preservatives are found in alcoholic beverages, fruit juices, soft drinks, baked goods, cheeses, gum, condiments, frozen dairy products and relishes	0-5 mg/kg BW	Parkinson's, neurodegenerative diseases,	Premature aging and provokes cancer, kills healthy cells of human body	(Maghiari *et al.*, 2020)
7.	Parabens	Coffee extracts, fruit juices, pickles, sauces, soft drinks,processed vegetables, baked goods, fats and oils, seasonings,sugar substitutes, and frozen dairy products	0.1%	impairment in child cognitive abilities, Neurotoxicity	Allergic reactions, As endocrine-disrupting chemicals	(Rodero *et al.,* 2009)
8.	Carmine	Yogurt, candy, beverages, applesauce, baked goods, and red-colored beverages.	5-0mg/kg BW	-	Hypersensitivity reactions attributed to carmine ranging from anaphylaxis to occupational asthma	(Alhusaini *et al.,* 2020)
9.	Annatto	Natural food color extracted from the seed coat of annatto (Bixaorellana L.)	0-0.065 mg/ kg BW/day as bixin		urticaria, anaphylaxis, angioedema, asthma, and contact dermatitis	(Morland *et al.,* 2018)
10.	Allspice	Natural antimicrobial	-	Neurotoxic, incoordination, weakness, ataxia		(Thimraj *et al.,* 2019)

Table 1. *Condt*.

11.	Aspartame	Artificial sweetener	50 mg/kg BW	Cerebral cortex neurotoxicity Neurotoxic response, dopaminergic degeneration and complication	pro-angiogenic effect and a weak irritant potential at the vascular level, reproductive toxicity	(Das and Smid, 2019)
12.	Sucralose	Synthetic organochlorine sweetener	5 mg/kg BW/ day	neurotoxic, harmful effects on cognition and hippocampal integrity	Carcinogenic, teratogenic and nephrotoxic,	(Finn and Lord, 2000)
13.	Propionic acid	Preservative and 12lavouring agent in packaged foods	-	Autism, neurotoxicity	Propionic acidemia	(Al Suhaibani *et al.,* 2021)
14.	Diacetyl	Important aroma compound in butter, margarine, sour cream, yogurt, and a number of cheeses, including Cheddar, Gouda, Camembert,Swiss, Maasdam, quarg, Mexican Chihuahua, ricotta, cottage, and goat cheeses	0–50 mg/kg BW	Intrinsic neurotoxicity	Mutagenicity, bronchiolitis obliterans,chronic parenchymal lung disease, Lung injury	(Das and Smid, 2019)
15.	Saccharin	used in food as a non-nutritive sweetener	5 mg/kg BW	Behavioral toxicity and neurotoxicity	Dose-dependent hepatotoxicity, liver carcinogenesis, loss of anti-atherosclerotic activity and toxicity	(Han *et al.,* 2021)

TiO_2 amassment impacts the inflammatory response and, as a result, memory and learning ability. TiO_2 nanoparticles cause hippocampus neuro-inflammation and immurements of neurotransmitters that affect memory, learning, and motor functions, such as dopamine and serotonin, in mice after 60 and 90 days of exposure (Asghari *et al*., 2019).

Nanoparticles of TiO_2 also degrade spatial recognition memory and learning. On the other hand, investigations conducted over 30 days revealed that TiO_2 nanoparticles caused locomotor dysfunctions, despite the fact that there was no substantial change in spatial learning and memory ability. Taking all of this information into account, TiO_2 exposure could be a risk factor for neurodegenerative disorders. Increased BBB permeability was found to be increased in Primary microvessel endothelial cells in rat brain against silver nanoparticles. Along with that higher expression of pro-inflammatory cytokines, lower cell survival are also noticed. Furthermore, for showing the permeability, silver nanoparticles administered intraperitoneally or by oral gavage accumulate in the kidney, liver, and stomach as well as in

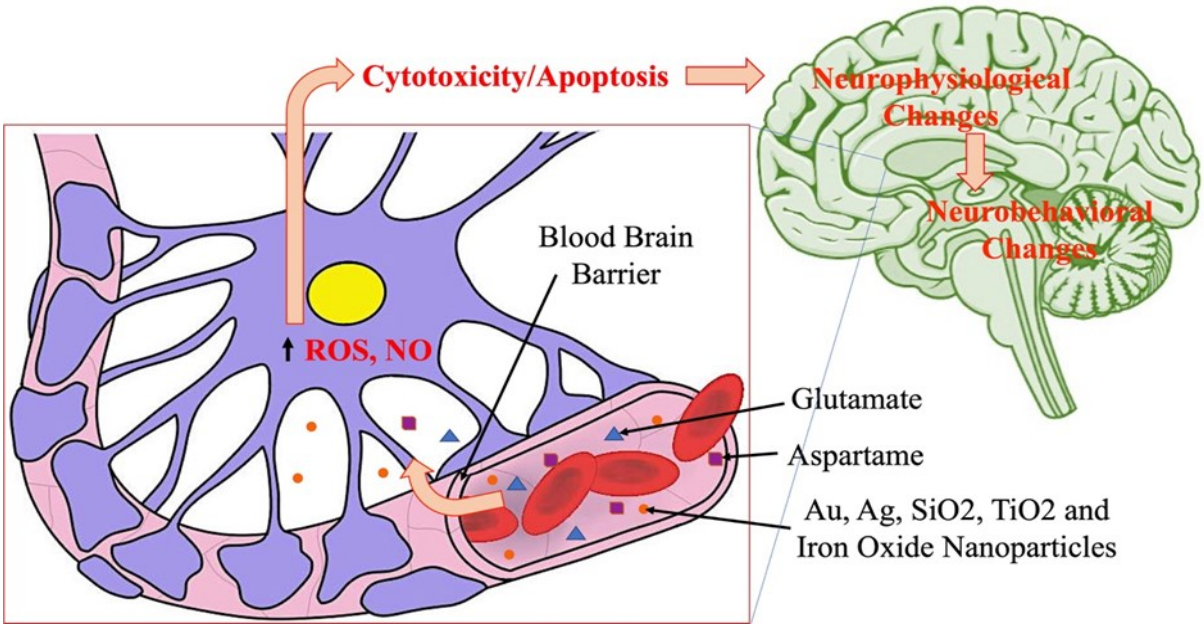

Fig. 2. *Xenobiotics including food additives such as Glutamate, Aspartame and Nanoparticles may cross blood brain barrier subsequently inducing ROS and NO in the brain cells. This stress may lead to cytotoxicity and/or apoptosis of these cells phenotypically expressed as neurophysiological changes. Neuropathological conditions may aggravate, changing normal behaviour of the individual which can alter daily life chores (biorender.com)*

the brain, demonstrating that silver nanoparticles can cross the BBB, with accumulation in the hypothalamus, hippocampus, cerebral cortex, thalamus, and cerebellum occurring after 24 hours, 28 days, and even 13 months (Báez *et al*., 2021). In addition, oral exposure to silver nanoparticles can impair long-term memory and cognitive coordination, as well as damage the plasticity of the brain. Interestingly, in vitro studies using Alzheimer cell lines (ALT, BV2 and N2a cells) have shown that silver nanoparticles can increase inflammation, oxidative stress, apoptosis and promote Aβ amyloid (Aβ1-40 and The production and deposition of Aβ1-42) indicate that exposure of silver nanoparticles may be involved in the progression of neurodegenerative Alzheimer's disease (Strużyńska, 2017).

All the above evidence points out that oral administration of titanium dioxide and silver nanoparticles can change cognitive brain processes related to memory and learning, and may increase the risk of neurodegenerative diseases, but more research is needed. Although there is limited evidence for the effect of SiO2 on the brain after oral exposure, it is clear that the permeability of the blood-brain barrier remains unchanged even at 1000-2000 mg/kg body weight for 28 days. In addition, 1000 mg/kgbw of SiO2 for more than 90 days will not increase the Si content in the striatum, hippocampus or cerebellum, which indicates that oral exposure to SiO2 will not damage the permeability of the BBB and will not cause obvious neurotoxic effects. An in vitro study showed that neurons exposed to SiO2 nanoparticles (PC12 cell line) had reduced viability, increased ROS production, and depletion of malondialdehyde, dopamine, and down-regulation of tyrosine hydroxylase (Wu *et al*., 2011). Although we have summarized the evidence of the effects of non-food-grade nanomaterials on the brain and animal behavior, there is still much to be explored in this field, such as whether eating food additives containing nanoparticles can cause satiety, circadian rhythms, and motor skills or changes in mental illness—disorders such as depression and anxiety-like behaviors and cognitive impairment. The diagrammatic representation regarding nano food additives and neuronal impairment is shown in Fig. 2. In conclusion, food authorities must pay greater attention to the size, changes, and toxicity of TiO_2 and other nano additives to provide wholesome food for the population securely.

Regulatory agencies to minimize side effects of food xenobiotics

Sometimes, food additives increase the risk of neuronal dysfunction and other diseases instead of imparting potential benefits to the population. Therefore, it can be postulated that changing food habits also plays a critical role in developing neurodegenerative diseases/ disorders (Popa-Wagner *et al*., 2020). Hence, it is especially important to set some acceptable limit for these food additives to be utilized in food products. Controlled measures and standards have been established by authorised regulatory agencies in some countries to minimize the health risks to the public. World Health Organization (WHO), in conjunction with Food and Agriculture Organization (FAO), have established general principles regarding the justified and unjustified conditions of use of additives, the need for adequate toxicological investigation and evaluation, and biochemical, acute, short and long-term effects and carcinogenicity. ADI is available as a food additive depending on the nature of the compound and its pharmacological/ biological actions found during pre-clinical and clinical studies. So, ADI of most of the food additives is available (Kroes *et al*., 2005, Organization, 2022). In some countries, some regulatory agencies have manifested standards and control measures to keep down the health risk to the residents (Organization, 2002). WHO, in coexistence with Food and Agriculture organization (FAO), set up general principles concerning the adequate terms for the use of additives, the need for adequate toxicological investigation and evaluation and for biochemical, acute, short and long-term effects and carcinogenicity. Chemical risk assessment follows a specific paradigm composed of four steps: hazard identification, hazard characterization, exposure assessment and finally, risk characterization (Hernando *et al*., 2006) (Felter *et al*., 2021).

Need for research to overcome the developing neuronal impairment

Research is going on to minimize the risk of additives. However, the toxicity study of chemicals and its adverse effects and risks are studied by using animal data from long-term studies. Internationally recognized guidelines for testing have been published (Guth *et al*., 2020). The testing system has two major objectives: (I) To identify the utmost toxic effects of the compound in response to the identification and examination potential of the target tissue and (II) on the toxic capacity and nature of the toxicant. It should measure the level of intake of the toxicant, which should not show any adverse toxic effect (Alexeeff *et al*., 2002). The threshold of toxicological concern (TTC) is a principle which refers to the possibility of establishing a human exposure threshold value for all chemicals, below which there is no appreciable risk to human health.

Furthermore, man is exposed to thousands of chemicals whether occurring naturally/ synthetic compounds (Munro *et al*., 2008, Piwowarska and Kiedrzyńska, 2022). Apart from this, the chemicals harming the individuals, predominantly known as xenobiotics can be easily ingested through food and drinks (Ben Seghir *et al*., 2023). Since the walls of the gastrointestinal and urinary tract are lipophilic in nature, they are poorly excreted and therefore, their concentration in plasma and

living tissues has to be crucially monitored (Lemmens *et al*., 2021). Moreover, the brain being the most complex and leading organ controlling almost all the functions of the body is also under the threat of exposure to food xenobiotics (Ruczaj and Brzóska, 2023). Therefore, more research is to be needed to further set a limit to daily uptake of food additives.

Conclusion

To protect the health of many children, youth, adolescents, adults and the health of offspring, the government must pass a law that refuses to allow the food industry to continue adding non-permissible additives to present-day daily food and beverages. Exposure to some chemicals, such as xenobiotics, is unavoidable; hence, daily dietary intake should be monitored, especially for pregnant women and neonates. Unknowingly, these substances are ingested through the food source, sometimes resulting in severe diseases, including neuron degeneration. It is believed that the expected mechanism of food additives-induced neuronal impairment may be the outcome of oxidative stress. Industries are making foods more attractive, more delicious and palliative. Frozen foods are ready to be cooked using various natural or synthetic chemicals (food additives) to modify the characteristics of food without considering their safety profile. Furthermore, labeling requirements should include the quantity or amount of food additives used in the product instead of just mentioning their names. Despite the industrial and synthetic food, a daily diet that includes natural spices, vegetables etc., should also be focused on being healthy in the present, future, and forthcoming generations.

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Conflict of interest

The authors declare that they have no conflict of interest.

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