Section A-Research paper

Brief Overview about Tartrazine Effects on Health

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Abstract

Background: Tartrazine (E 102) is an artificial azo dye derived from coal tar. It is orange-colored powder known as synthetic lemon yellow. It is used worldwide as food additives to color several foods, drugs, and cosmetics. Human can be exposed to tartrazine through oral & dermal exposure, oral exposure includes food products, drugs, cosmetics, and pharmaceuticals. In food, Tartrazine used in soft drinks, juices, jellies, candies, cakes, cereal, soups, and other products. The safety and efficacy of increasingly common synthetic food additives have been under increased scrutiny in recent years, particularly in relation to their impact on developing bodies. Tartrazine, an artificial azo colour, is one of these ingredients. This research set intended to summarise the findings of previous studies on the effects of food additives like tartrazine on human health, focusing on the many systems in the body. Studies were conducted on the effects of tartrazine on the liver, kidney function, lipid profile, oxidative stress biomarkers, nervous system, hyperactivity, behaviour, cancer, reproductive and developmental toxicity, and some bioelement levels, as well as a description of the types of food additives and products containing tartrazine. Tartrazine's benefits and drawbacks were the subject of several of the studies uncovered. Potentially adverse effects of tartrazine on the liver, renal function, lipid profiles, behaviour, carcinogenicity, and recommendations for future research are summarised in the study's conclusion. This article provides a comprehensive assessment of tartrazine's safety and numerous adverse consequences. We can draw the conclusion that customers require expert guidance on matters of food safety. Indications have accumulated to show that tartrazine is harmful, and that avoiding it could be a good idea.

Keywords: Tartrazine, effects, health, Food additives

Introduction

Many different additives (now numbering over 2,500 chemicals) have been used to enhance foods in many ways, including flavour, colour, consistency, quality, and cost. Industrialization and improvements in food processing and treatment have led to them (NRC, 1983). Before being released to the public, food additives must undergo testing for acute, subacute, and chronic toxicity. However, there should be a long window set aside for studying the effects of food additives after they have been introduced to the market. Rarely is there evidence to support claims about the safety of chronic exposure, cumulative effect, or intra-organism variation. While there are many papers discussing the effects of tartrazine, both in vivo and in the lab, there is surprisingly little written about the drug's therapeutic application.

Each food additive has its own set of benefits and drawbacks, but many people use them regularly. Food additives play a crucial role in modern agriculture, allowing people to enjoy a wide variety of healthy, delicious, and safe foods throughout the year. The positive effects of food additives vary from one type of additive to another. However, numerous metabolites, like monosodium glutamate and nitrous compounds, have been identified as carcinogens, and they may be present in food additives. Whether or whether a food is toxic depends on how much of the absorption, excretion, or metabolism it disrupts. The interplay between many chemicals further complicates the description of recommended safety limits for human intake. Until their safety is verified, all novel chemicals in nutrition should be treated as potentially harmful because to the high probability of toxicity of chemical compounds. Many people are sensitive to food additives, which can lead to symptoms such as diarrhoea, skin irritation, stomach disorders, vomiting, or an increase in body heat. Furthermore, some food additives destroy vitamins in food (adding caramel to a food is found to cause a deficiency of vitamin B6), are used to make low-quality food appear more appetizing, and are used to mask the flavour of less desirable ingredients. Food's nutritional content may be lost in the process as well. Due to their link to cancer and other tissue damage, certain food dyes have been banned. It is well established that tartrazine, a common food additive, can trigger a wide variety of adverse reactions in humans. In this category, you may find headaches, anxiety, asthma attacks, blurred vision, eczema, various skin rashes, and even thyroid cancer.

Tartrazine (*E 102*) is an artificial azo dye derived from coal tar. It is orange-colored powder known as synthetic lemon yellow. It is used worldwide as food additives to color several foods, drugs, and cosmetics (Mehedi et al. 2009).

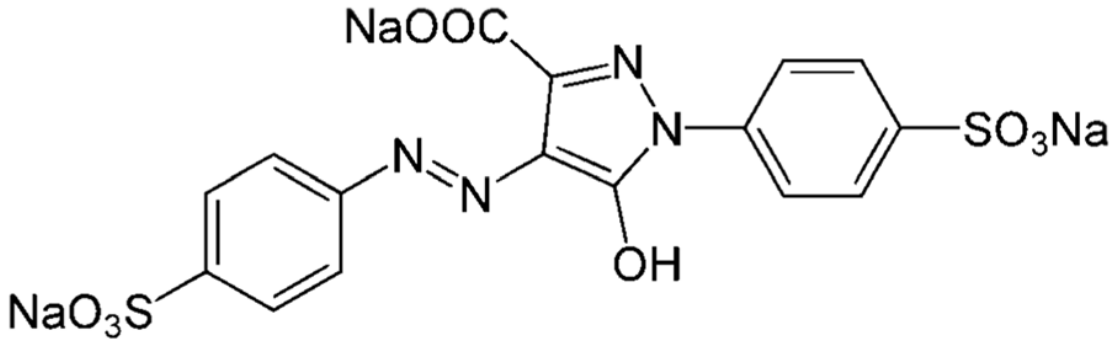

Fig. (1): Molecular structure of tartrazine. (Balta et al., 2019)

Tartrazine-Infused Goods Foods: Tartrazine can be found in a variety of foods, with amounts varying from product to product and chef to chef. These days, people try to avoid using it altogether or opt for natural dyes like annatto, malt colour, or beta carotene instead. Tartrazine is found in many common foods and drinks, including sugary treats, cotton candy, cereals (corn flakes and muesli), flavoured chips (Doritos and Nachos), cake combinations, soups, jams, sauces, ice cream, some rice, candy, chomping gum, marzipan, jelly, gelatins, mustard, marmalade, yoghurt, noodles, fruit pleasant and product, chips, and a number of quick-prep foods like.

Non-food products: Tartrazine may be found in nonfood products like soaps, cosmetics, shampoos and other hair products, conditioners, pastels, crayons and stamp dyes.

Metabolism And Biological Effects Of Tartrazine

Since tartrazine is a nitrous derivative, it is converted into a highly sensitive aromatic amine once it enters

a living organism (azo class). Sulfanilic acid has been identified as the primary metabolite. Because of its metabolic conversion into aromatic amine (sulfanilic acid) via the gut microbiota, tartrazine is known to produce allergy symptoms like urticaria and asthma, in addition to the focus of studies on its carcinogenesis and mutagenesis. (Moutinho et al., 2007) after ingestion, and perhaps via mammalian azo reductase in the liver or intestinal wall (Chequer et al., 2011). These azo dyes are oxidised to N-hydroxy derivatives by the P450 enzyme system once they have been completely reduced to aromatic amines.(Demirkol et al., 2012). This mechanism of biotransformation takes place in many species including humans (Chequer et al., 2011), which is responsible for various disorders including anemia, pathological lesions in the brain, liver, kidney and spleen, beside allergic reactions, tumor and cancer. However, tartrazine has no possibility to induce malignant or benign neoplasias. Moreover, Tanaka (2006) did not determine any adverse role of tartrazine in the development of neurobehavior, also, harmful impact on reproductive markers were not established at tartrazine dose of 1225 and 773 mg/kg BW/day for females and males, respectively. In earlier assessments, there were no suggestions of Tartrazine-linked contrary effects on reproduction. However, superoxide anion, hydroxyl radical and H2O2 reactive oxygen species (ROS) might be formed in the nitrosamines metabolism and raise oxidative stress (Bansal et al., 2005).

Role of tartrazine on sensitivity A diversity of immunologic reactions has been recognized in tartrazine consumption, comprising general fatigue, nervousness, migraines, clinical depression, purple skin spots, and disruption in sleep. Either consumption or cutaneous contact with a material containing tartrazine can produce symptoms of sensitivity. Some claim involvement signs of tartrazine sensitivity even at minor dosages, and until 72 h following its exposure. In kids, asthma attack and rashes have been claimed, as well as possible links with chromosomal injury, thyroid cancer and hyperactivity. Particular investigators have related tartrazine with infantile obsessive-compulsive disturbances and hyperactivity. Some common food additives including tartarzine, monosodium glutamate have been suggested as risk factors for exacerbations of asthma. Tartarzine is also used in many medications, and may increase asthma severity only in a few susceptible individuals, while MSG may exacerbate asthma severely (Romieu, 2005). Food additives examinations revealed that tartrazine increased sulphido-leukotriene released by peripheral leucocyte in patients with confirmed intolerance to food additives (atopic dermatitis). The mechanism of these changes may be due to a pathophysiological involvement of food additive that facilitated exaggeration of atopic dermatitis (Worm et al., 2001).

A number of studies in humans recorded adverse reactions such as vasculitis and urticaria following tartrazine consumption. EFSA Panel (2009) concluded that Tartrazine seems to be capable of producing intolerance responses in few exposed people and noted that sensitive persons may respond to the level of ADI dose. JECFA in 2016 and European Commission SCF (1984) evaluated tartrazine. In 2008, the EFSA Scientific Board of Food Additives, flavourings, evaluated tartrazine, against claims that it cause hyperactivity in children (EFSA, 2008c). In 2009, the EFSA ANS Panel accepted a finding on the reevaluation of tartrazine (E102) as food additives (EFSA ANS Panel, 2009). However, the Brazilian Sanitary Surveillance Agency (ANVISA) issued a consultation on the opportunity of distributing a ticket warning against rise of urticaria, asthma and allergic rhinitis in atopic patient consuming food and drugs containing tartrazine. While, Pestana et al. (2010) reported that a group of atopic subjects with asthma, nasal allergy, pseudo-allergic or urticaria responses to non-steroidal anti-inflammatory (NSAID) drugs, 35 mg of tartrazine dye, did not produce any kind of significant respiratory, cutaneous or cardiovascular responses when compared with the placebo and there were no statistical changes among the groups.

Effect of food azo dyes on liver enzymes and hepatotoxicity

Previous studies were conducted until 2015: the activities of hepatic serum enzymes (AST and ALT) increased in rats administrated food colorants particularly at high doses, suggesting elevated permeability, injuries and impairment of the hepatic cells. Also, elevation in both ALT (located in the

cytoplasm) and AST (located mainly in organelles such as mitochondria) activities indicated the injury of both the hepatic cellular and mitochondrial membranes in food azo dyes administered rats (Senthil et al., 2003). Moreover, the enzymatic activities of ALT, AST and ALP showed significant increases with consumption of an extraordinary dose of tartrazine (500 mg/kg BW) for 30 days or a high dose of carmoisine (100 mg/kg BW) when compared with control rats. While the low dose of both tartrazine (15 mg/kg BW) and carmoisine (8 mg/kg BW) displayed a significant rise in the ALT and alkaline phosphatase activities, respectively as compared to the control rats (Amin et al., 2010). In addition, Saxena and Sharma (2015) reported that consumption of food color including tartrazine induces hepatic tissue damages in Swiss Albino Rats. These effects assessed through significant increased serum total protein, albumin, ALP and hepatic MDA level and significant lowered levels of SOD, reduced GSH and CAT in the hepatic tissue. The alteration in the liver includes necrosis of hepatocytes, infiltration, vacuolation and drastic alteration in the antioxidant defense system.

The findings of Amin et al. (2010) is in agreement with that of Mekkawy et al. (1998) who specified that two low or high doses of artificial dyes contain both carmoisine and tartrazine (ponceau, carmoisine, erythrosine, sunset yellow, tartrazine, fast green, indigotine, brilliant blue and brilliant black) which revealed a significant elevation of serum ALT, AST and alkaline phosphates activities; they credited these changes to hepatocellular injury produced by the toxic properties of these artificial dyes that is associated with swelling, pyknosis, vacuolation and necrosis of the hepatic cells. The elevated activities of aminotransferases with the histopathological changes suggested that the tissue impairment of maimly liver, heart and kidney is associated with synthetic dyes.

An alternative mechanism of the significant rises in aminotransferases may be due to the biochemical and pathological state of the hepatic lobules and failure to perform vital functions, that trigger disturbance or imbalance in intermediary metabolism. Some enzymes such as ALT, AST, LDH and ALP leak out from the cells into the serum and so their serum activities determine the type and degree of destruction.

Histopathological examination of groups that ingested 10 mg/kg BW of tartrazine showed severe hepatic changes, swollen hepatocytes, a single large vacuole surmounting the whole cytoplasm and wide trabeculae from degenerated hepatic cells compressing and constricting the sinusoids lumen, besides, deposition of brown pigment inside the Küpffer cells and hepatic fatty degeneration with Tartrazine treatment at dose of 7.5 and 10 mg/kg BW. Also, a significant rise in the mean liver weight and congested blood vessels and areas of hemorrhage in the liver were not confirmed (Himri et al., 2011).

Meyer et al. (2017) found that initial systemic administration of tartrazine in mice resulting in a periportal recruitment of inflammatory cells, raised serum alkaline phosphatase activity and mild periportal fibrosis. Moreover, Tartrazine alone induced the colon and hepatic NF- κB activities but there was no periportal recruitment of inflammatory cells or fibrosis. Tartrazine, its sulphonated metabolites and the contaminant inhibited sulphotransferase activities in murine hepatic S9 extracts. Systemic tartrazine exposure is potentially associated with an inhibition of bile acid sulphation and excretion and not oestrogen receptor-mediated transcriptional function.

Effect of tartrazine on kidney function

Everyday consumption for 30 days, of low or high doses of tartrazine revealed a significant rise in renal function tests of urea and creatinine level when compared with control group, and the high dose indicated higher significancy in serum creatinine level (Amin et al., 2010). These results are parallel to those reported by Helal et al. (2000) on synthetic or natural food colorants. Additionally, these results are in accordance with that recorded by Ashour and Abdelaziz (2009) on organic azo dye fast green for 35 days. Also, Tartrazine presented a significant elevation in serum creatinine level in a dose response manner (Himri et al., 2011).

Impairment of renal function is closely associated with higher levels of urea and creatinine (Varely, 1987).

The renal injuries occur in all forms of renal diseases such as hydronephrosis congenital cystic, kidney renal tuberculosis, a condition in which there is calcium deposition (hypervitaminosis D). Increases in plasma creatinine in renal diseases provide a predictive importance than those of other nitrogenous substances. Concerning renal histopathological examination, Himri et al. (2011) showed tubular dilatation with thickened basement membrane, tubular degeneration and dilatation of the glomerular capillaries, and intercapillary sclerosis, atrophy of glomerulus in the group treated with 5, 7.5 and 10 mg/kg BW of Tartrazine, respectively.

For both liver and kidney phenomena represented by hepatic impairment, edema, congestion, and kidney apoptosis, with atrophy of renal corpuscles were observed. Degree and severity of histopathological aspects observed were directly proportional to the concentration of the administered dyes (Rus et al., 2009).

Hepatic GSH level and catalase activity decreased significantly in rat that ingested low and high carmoisine dose and a high dose of tartrazine (Amin et al., 2010). Also, hepatic super oxide dismutase (SOD) decreased significantly in high and low doses of tartrazine, while hepatic MDA as oxidative stress biomarker indicated significant increases with a high dose of tartrazine. Increased production of free radicals or ROS may induce autooxidation and lipid peroxidation of the hepatocytes, causing obvious hepatic injuries and subsequent release of hepatic function enzymes ALT and AST.

Tartrazine could be regarded as toxic due to its possible oxidative impairment induced by depletion of GSH, the main antioxidant for the cell, and a significant increase in MDA levels, where the researchers strongly believe that the usage of these possibly toxic colors in food needs to be re-evaluated (Demirkol et al., 2012). In a recent study, tartrazine, a widely used synthetic azo dye, induced a sharp deficiency in the biomarkers of antioxidant (SOD, catalase and GSH) and a marked rise in MDA concentration in the brain cortex in comparison with the other groups of male rat pups (Mohamed et al., 2015; Saxena and Sharma, 2015). A possible effect of frequently consuming beverages on stimulation of the risk of pathophysiology associated with ROS and peroxyl radical-facilitated events is suggested. Therefore, a healthy food consists of real food, without any artificial additives and high-quality food has no need for Tartrazine or any artificial color to maintain good health.

Effect of tartrazine on the nervous system, hyperactivity and behavior

The dose levels of 125 to 500 mg/kg of tartrazine given for 30 days induced a rare adverse effects on memory and learning in animals model, this is might be because of its promotion of lipid peroxidation metabolites and ROS, preventing endogenous enzymes of antioxidant protection and the brain tissue injury (Gao et al., 2011). Taken together, because of the current evidence presented, the daily consumption of Tartrazine as agreed by the ADI rate seems to be reasonably harmless; however, exposure is unlikely to be reached after ingestion of food. Tartrazine induced hyperactivity, antisocial behavior and anxiety in male Wistar rats at 0, 1 and 2.5% doses in drinking water as recorded for different animal models of raised plus-maze, open ground and the dark-light transition experiments (Kamel and El-lethey, 2011). Moreover, Tanaka et al. (2008) found that 0.05, 0.15 and 0.45% tartrazine doses induced a few antagonistic effects on neurobehavioral markers all over generations in mice. The dose level of tartrazine induced altered neurobehavioral parameters during the lactation period in mice (Tanaka, 2006). In a clinical study, the effect of a mixture of sunset yellow, carmoisine and tartrazine on 3 to 9 years old children behavior was assessed, and it was found that synthetic colors in the diet result in exaggeration of the hyperactive behaviors (overactivities, inattentiveness, and impulsivity) in children at least up to middle infantile. Raised hyperactivity is accompanied by the development of problems in education, particularly those linked to reading, which could affect the kid's skill in school (McGee et al., 2002). These results show that adverse properties are not only seen in children with great hyperactivity but also seen in the overall population with a range of hyperactivity severities (McCann et al., 2007).

In a more recent experimental study, tartrazine was evaluated for potential neurotoxic effect, where it showed a significant decrease in gamma amino butyric acid, dopamine and serotonin levels as neurotransmitters in the brain and numerous apoptotic cells in the brain cortex were reported using an immunohistochemical staining with the anti-ssDNA antibody as apoptotic cell marker as compared to other groups (Mohamed et al., 2015). Concerning the beneficial effect of Tartrazine, it had an important inhibitory role in fibrillogenesis and showed the potential anti-amyloidogenic property of food colorants (Basu and Kumar 2017).

Effect of tartrazine on DNA and as carcinogen

Various dye applications (0.25 to 64.0 mM) revealed that tartrazine had no cytotoxic properties. Nevertheless, at all examined levels, this dye had a significant genotoxic effect. While most of the injuries were responsive to repair, some damages persisted more than +ve control following 24 h of repair. These results show that tartrazine could be harmful to health and its prolonged consumption might generate carcinogenesis (Soares et al., 2015). Investigations using spectroscopic titration for the interaction of food additives, tartrazine with DNA, showed that these dyes bind to DNA of calf thymus and different isosbestic points clearly, indicating binding of DNA with the dyes. Tartrazine as food colorants had a possible toxic effect on human lymphocytes in vitro and it seems that they bind directly to DNA (Mpountoukas et al., 2010). In a novel study, the interaction of tartrazine and endogenous compound as bovine hemoglobin was defined for the dye (Li et al., 2014). Sasaki et al. (2002) observed an extensive DNA damage in glandular stomach and the colon at doses higher than 10 mg/kg b.w. This effect may be due to the acute dye cytotoxicity or insufficient repair of DNA at the 3 h sampling time. Poul et al. (2009) verified the nonmutagenicity of tartrazine when given orally up to doses of 2000 mg/kg b.w. and reported that the dye does not increase the quantity of micronucleated colonic cells at any of the examined doses as compared to control groups. The spectroscopic and calorimetric study indicated that tartrazine induces hypochromism in DNA without any bathochromic effects. However, tartrazine improved the thermal stability of DNA by 7.53 K under saturation circumstances (Basu and Kumar, 2016b).

Reproductive And Developmental Toxicity Of Tartrazine

Tartrazine did not play a significant teratogenic toxic role at a dose of 0, 60, 100, 400 and 600 mg/kg BW in pregnant Osborne-Mendel during the 1st 19 days of pregnancy (Collins et al., 1990, 1992). Meanwhile, Mehedi et al. (2009) reported that tartrazine has toxic effects on the reproductive organs comprising, decrease in reproductive performance, reduced sperm count and increased rate of sperm anomalies in mice with doses of 0, 0.1, 1.0 and 2.5% for 13 weeks. There are particular clinical studies on assessment of the effects of various colorant mixtures, as they may be consumed in ordinary life (McCann et al., 2007). Regrettably, these works have many limitations; hence it is difficult to determine a clear conclusion on the matter (Amchova et al., 2015). The selection of a definite technique for assessing a food additive compounds can be based on expected mechanism of action and its chemistry. Moreover, there is a need for continuous estimation of novel chemicals and existing ones too, due to the contradicting data and inadequate results to conclusively classify several regularly used materials as safe or carcinogenicity.

Effect of tartrazine on tissues bioelement contents

In a few manuscripts on biolement and tartrazine, there were reports on significant changes in levels of bioelements in rats' liver, kidney and brain tissues exposed to tartrazine (Cemek et al., 2014). The changes include increased Cu and iron level in renal tissue, which is important because copper accumulation in the tissues leads to Wilson's disease and hepatic cirrhosis (Shazia et al., 2012); this effect may be due to binding of copper and iron to the artificial food colorants, resulting in its tissues accumulation (Stevens et al., 2013). The levels of the trace elements, aluminium and barium, reduced by consuming high and low doses of tartrazine in the brain. Moreover, low dose tartrazine induced

reduced liver zinc content and high dose tartrazine has the same result in kidney, this may be due unsaturated fatty acids peroxidation in cell membranes by ROS produced during tartrazine administration, resulting in a decrease of membrane flexibility and disturbance in cell function and integrity which affected the pumping and selection of activities of membranes and the level of bioelements may be altered in tissues (Cemek et al., 2014).

The safety effect of tartrazine as food additive

A number of subchronic and chronic feeding investigations on the role of tartrazine in mice and rats for periods of over one year without any given or significant opposing role, has been formally defined and evaluated (EFSA ANS Panel, 2009). Insignificant discoloration of fur, fecal and urinary output had been observed in doses from 10 g/kg of feed upwards (Borzelleca and Hallagan, 1988), which is greater than ADI of tartrazine. In the authors' opinion, the use of tartrazine in children's food and the presence of discoloration in body fluid demonstrated its incomplete metabolism. The authorities that confirmed its safety are now somewhat dated. On the other hand, several recent publications have been provided in this review. This is the first paper that covers most of the available literature including the relationship between tartrazine, oxidative stress biomarkers, hyperactivity, behavior, carcinogenicity, reproductive and developmental toxicity and some bioelement levels. Also, it provides some important recommendation on food additives that are vital to the health of the consumer. Various aspects of tartrazine and health, however, still demand supporting evidence.

Conclusion And Recommendations

Existing literature and accumulated evidence indicate the various harmful effects of tartrazine on several organs and health systems. It can be firstly concluded that food additives, including the colorant tartrazine, adversely affect and modify the biochemical biomarkers in important organs such as the kidney and liver, even when used in low doses. The risk increases when a higher dosage is taken and when consumed daily for 30 days, given the hepatic oxidative stress caused by the formation of ROS. Children consume these additives several times daily in chocolates, gum, chips, drinks and many other products and are susceptible to the adverse effects of tartrazine. Secondly, tartrazine can be converted by intestinal flora into aromatic amines that may be changed to nitrosamine. This releases ROS. It is therefore, essential to make consumers awareness of the side effects of these food azo dyes. Thirdly, these food additives can affect body weight and the growth of children, as normal food consumption is reduced. Furthermore, the azo dye group including tartrazine, induce hypersensitivity and allergic reactions. Consumption of tartrazine as a food additive should be limited; particularly in children. Fourthly, continuous updating of the safety evaluations of the effect of tartrazine on health is recommended using modern methodological approaches and by making available all current results that include: data from studies on the nervous system, behavior, injuries to body organs, and results concerning issues of genotoxicity, reproductive toxicity and chronic carcinogenicity/toxicity. Fifthly, many companies that produce products containing these food additives have never revealed the type or level of food additives added to their products. The public cannot determine the type of food additives or the dosage that they have consumed. Therefore, the food industry is obliged to mention the name and concentration of food additives found in their products, with reference to those foods mainly consumed by young children and, further, they should focus more when labelling products, to offer clear and detailed information; particularly to persons who are intolerant to such products. Finally, all currently available evidence highlights the potentially harmful effects of tartrazine and how it is ineffective as a nutritive additive. It is recommended that its consumption should be avoided.

Conflict of Interest: None

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