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Review

Toxicological and safety assessment of tartrazine as a synthetic food additive on health biomarkers: A review

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Recently, progressive use of synthetic food additives increase the attention paid on their benefit and toxicity in food, especially for the young. One of these additives is artificial azo dyes tartrazine. This study aimed to provide an outline of the existing evidence on the beneficial and side effect of food additive with special reference to tartrazine on different organ health. The methods include updated search for the relevant databases. The studies included a description of the types of food additives and products containing tartrazine and focused on the effect of tartrazine on liver, kidney function, lipid profile, oxidative stress biomarkers, nervous system, hyperactivity, behavior, cancer, reproductive and developmental toxicity and some bioelement levels of tartrazine. Several studies were identified and some investigated advantage and disadvantage of tartrazine. Summary of the study provides potentially harmful effects of tartrazine on liver, renal function, lipid profiles, behavior, carcinogenicity and forthcoming research recommendation are outlined. This review gives a broad evaluation of the safety and various toxicity effects of tartrazine. It can be concluded that there is a need for professional assistance for consumers regarding food safety issues. Cumulative indications have been increased, demonstrating the potential danger of tartrazine, and the possibility to avoid its consumption.

Key word: Food additives, tartrazine, liver, kidney, oxidative stress, cancer.

INTRODUCTION

Varoius kinds of food additives (more than 2,500 substances) have been employed to improve the taste, tint, constancy, quality and price of foods. These are the result of industrialization and advances in the technology of food processing and treatment (NRC, 1983).

Acute, subacute and chronic toxicity are investigated before food additives are ready for customer consumption. However, post-marketing investigations of food additives properties needs to be reserved for an extensive period. Evidence regarding the security of the long-term usage of such substances, their pooled impact, and variability within the organism is uncommon. Several papers reviewed the effect of tartrazine including *in vivo* and experimental studies, while there is scarce literature on clinical aspect. The aims and concerns of this review are to assess the role of tartrazine as coloring food

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Table 1. Field report on food additives present in the hypermarket (frequently consumed by kids).

Product name	Company name	Label found
Tito wefer	Candy makers food industry	Flavors food grade
Beco-biski	EL-Jawhara for food industry	Edible flavors
Sposa Cake	Over seases Co. for food products	Food flavors
Fruity, juice powder	Dream A.S.E.	Allowed artificial colorants (E102-E110)
Ice man, ice cream	Egyptian Co. for food industries	Healthy allowed flavors
Lika, Gum	Sima Food industry	Healthy allowed artificial color (E132).

additive in hepatic function, lipid profile and biomarkers of oxidative stress and bioelement contents in blood and different tissue. Its role in the nervous system, hyperactivity and behaviour is also discussed.

FOOD ADDITIVES

Importance and disadvantages of food additives

Many people consume various food additives every day, which have both advantages and disadvantages. Food additives have an important effect in currently abundant and nourishing food sources, and allow people to appreciate a diversity of nutritious, delicious and safe foods over the year. Food additives have different beneficial effects on foods. However, food additives may contain several metabolites, such as monosodium glutamate and nitrous compounds that are found to be carcinogens. Toxicity or benefit depends on the extent to which the food components interrupt absorption, elimination or metabolism. Description of the appropriate safety limits for human ingestion is further complicated due to the interaction between several substances.

In nutrition, the probability of toxicity of chemical compounds means that all new compounds should be regarded as toxic until their safety is confirmed. Food additives sometimes destroy vitamins in food (adding caramel to a food is found to cause a deficiency of vitamin B6), are used to make bad quality food look good and can cause allergy in many people like diarrhoea, skin irritation, stomach disorders, vomiting or an increase in the body heat. Also, it may destroy the nutritional value of food. Several food colourings have been banned due to their tendency to cause cancers and tissue injuries. Tartrazine as a food additive has been proven to cause many different side-effects and allergic responses in individuals. These may comprise migraines, nervousness, asthma attacks, hazy vision, eczema, other skin rashes and thyroid cancer.

Types of food additives

Food additives are classified into 6 main groups: preservatives, nutritive additives, flavoring, coloring, texturizing and miscellaneous compounds. Examples of widely used food products containing target food additives and frequently consumed by children are shown in Table 1. The food additives include:

Preservatives: Preservatives are added to prolong the shelf life of foods. There are three types of preservatives. The first is antimicrobials that prevent microbial growth, which can cause life threatening illnesses such as salmonellosis or botulism, for example benzoic acid, ascorbic acid and propionic acid. This preservative can be used in cheeses, margarine and dressings, bakery products and dried fruit preparations.

The second preservative include antioxidants, which are added to oils containing unsaturated fats that are more susceptible to oxidation. Food oxidation is a damaging process, causing alterations in the chemical structure and biochemical properties result in loss of its dietary value. The antioxidant slow the degree of its oxidation, prevent them from becoming rancid and prolong food life. Natural and synthetic antioxidants provide comparable performance and they are frequently used in the mixture (Fiorentino et al., 2008). Some important antioxidants include vitamin C and E, citric acid, butylated hydroxytoluene (BHT) and butylated hydroxyanisole. The third preservative includes antibrowning which is added to fruits vegetables to prevent enzymatic browning, for example. alpha tocopherol.

Nutritional additives: They are added to increase the nutritional value of the food and comprise antioxidant vitamins, amino acids and bioelement.

Flavoring agents: Flavoring substances include the largest number of applied food additives. There are 3 main kinds of flavoring agents:

1) Sweeteners: These are substances that have a strong sweet taste but little or no caloric values. They are therefore useful for diabetics and include saccharin, sorbitol and aspartame.
2) Synthetic flavoring enhancers: They are used in general at very low level and they are synthetic, mainly esters, aldehydes and ketones.

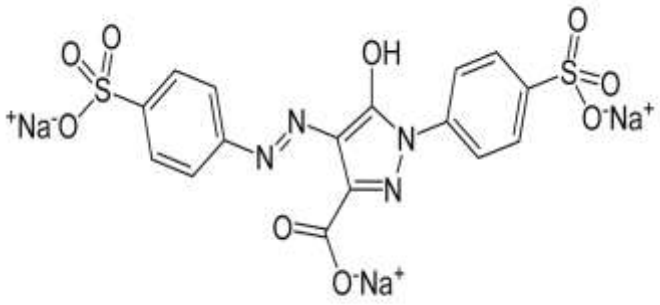

Figure 1. Structure of tartrazine.

3) Natural flavoring enhancers: They are used to modify the flavor of food without contributing any flavor on their own, for example, monosodium glutamate (MSG) and nucleotides such as disodium guanylate.

Texturizing agents: These are stabilizers and emulsifiers agents that are used to add or modify the overall texture or mouthful of food products. Emulsifiers include natural substances such as lecithin, mono-or diglycerides and several artificial byproducts. The major effect of the texturizing compound is to permit oils and flavors to be distributed through the food products. Stabilizers comprise many natural gums as carrageenan in addition to modified and natural starches. It has been used for many years in both dry and liquid form to provide the desired texture in products such as ice cream. Also, it is used to avoid deterioration and evaporation of volatile taste oils (Branen and Haggerty, 2001).

Coloring agents: These substances are added to enhance the visual appeal of food products. Some of these substances are derived from the natural colors, such as carotene and chlorophyll; others are synthetic such as indigotin, allura red, tartrazine and carmoisine.

Color additives released from authorization are intended for an extensive diversity of purposes in the foods, cosmetics and drugs (Van-Bever, 1989). Although, most color food additives are similar in relations to the FDA's monitoring description, they are controlled in 2 classes; natural (color additives exempted from certified) and the synthetic (certified) color additives. In studies from Asia and Africa, exposure to colors additives like tartrazine and sunset yellow FCF surpassed the acceptable daily intake (ADI) especially in festive and wedding times. The consumption of tartrazine and sunset yellow increased in high consumers, especially in children without control. The condition may be aggravated in an adult in developing countries (Rao and Sudershan, 2008). Tartrazine mainly affect young people because they cannot control their feeding, and are attracted to colour more easier than adult. Young people consume these additives several times daily in chocolates, gum, chips, drinks and cared little about its health effect. Moreover nervous system, behaviour and other metabolic and organ function more easily affected in young than adult .

The use of tartrazine was focused on was because of its extensive usage in many beverages and sweets, to provide color to colorless foodstuff, make the food more attractive, appetizing and is a synthetic compound.

RESEARCH UPDATE ON TARTRAZINE

Tartrazine is an artificial lemon yellow azo dye, recognized as E102 or C.I. 19140 or FD&C Yellow 5 and used for the coloring of food. It is water soluble, derived from coal tar and its structure is shown in Figure 1.

Products containing tartrazine

Foods: Several foods have tartrazine in different quantities, relying on the industrialist or the cook administrator. Nowadays, the tendency is to prevent its addition or its replacement with a non-synthetic coloring material like annatto, malt color or beta carotene. Foodstuffs containing tartrazine include sweetmeat, soft drinks, cotton candy, cereals (corn flakes and muesli), flavored chips (Doritos and Nachos), cake combinations, soups, jam, sauces, ice cream, some rice, candy, chomping gum, marzipan, jelly, gelatins, mustard, marmalade, yogurt, noodles, fruit pleasant and product, chips and several expediency foods together with glycerin, lemon and honey products, soft drinks (Mountain Dew and Mirenda), energy drinks, prompt desserts, and some product containing tartrazine as shown in Figure 2.

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

Medications: Particular medicinal preparations comprise

Figure 2. Some products containing tartrazine.

tartrazine as antiacids, vitamins, certain prescription medications and medical capsules. Accruing research has been performed on tartrazine and its effect on the health

METABOLISM AND BIOLOGICAL EFFECTS OF TARTRAZINE

Tartrazine is reduced inside a organism to an aromatic amine which is greatly sensitized, since it is a nitrous derivatives (azo class). The chief metabolite recognized so far is sulfanilic acid. Tartrazine is identified to cause allergy such as urticaria and asthma, besides the emphasis of studies on its carcinogenesis and mutagenesis because of its metabolic conversion into aromatic amine (sulfanilic acid) via the gut microflora (Moutinho et al., 2007) and possibly by mammalian azo reductase in the hepatic or intestinal wall after consumption (Chequer et al., 2011). When these azo dyes are reduced totally into aromatic amines, they are oxidized to N-hydroxy derivatives by the enzymatic system of P450 (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 H_2O_2 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 (E-102) 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 tartrazine on albumin and hemoglobin binding

Tartrazine could result in conformational and some microenvironmental alteration of both human and bovine serum albumin, which might disturb the biological functions of serum albumins. This provides a significant understanding on the mechanism of tartrazine toxicity *in vivo* (Pan et al., 2011). The synchronous fluorescence investigation indicated that tartrazine binds with the hemoglobin central cavity, which was confirmed by a molecular demonstrating study (Li et al., 2014). Recently, the interaction of the food colorant tartrazine with hemoglobin was considered by Basu and Suresh Kumar (2016a). They found that tartrazine slaked the intrinsic fluorescence of hemoglobin by inducing conformational alterations and substantial damage in the helicity of Hb.

Effect of food azo dyes on liver enzymes and hepatotoxicity

Previous studies were conducted until 2015. The findings in Table 2 are as follows: 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 (Table 2). 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

Table 2. Effect of food colorants, tartrazine both low and high doses, on liver, renal function, lipid profile and oxidative stress.

Parameter	Biomarkers	Control Groups	Low and high tartrazine	References
Liver function	ALT, AST and ALP (U/l)	Normal	↑	Amin et al. (2010); Himri et al. (2011).
Renal function	Urea and Creatinine (mg/dl)	Normal	Significant ↑	Helal et al. (2000); Ashour and Abdelaziz (2009); Amin et al. (2010); Himri et al. (2011)
Lipid profile	TC and TG (mg/dl)	Normal	↑	Ashour and Abdelaziz (2009); Amin et al. (2010)
Oxidative stress/antioxidant markers	SOD (U/g)	Normal	↑	Amin et al. (2010)
	Catalase	Normal	↑	Mohamed et al. (2015)
	GSH(nmol/100 mg)	Normal	↑	Mohamed et al. (2015)
	Malondialdehyde (nmol/g/h)	Normal	Decrease	Demirkol et al. (2012); Mohamed et al., (2015)

↑ Indicates increased value of the biomarkers.

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).

Effect of food azo dyes (tartrazine and carmoisin) on lipid profile

The study of Amin et al. (2010) and Ashour and Abdelaziz (2009) indicated the reduction in serum cholesterol and triglycerides levels (Table 2) when food color azo dye (fast green) was given orally to male albino rats for 35 days.

Approximately, 50% of the intestinal cholesterol pool is reabsorbed and recirculated via the enterohepatic flow, while the rest is eliminated in the feces. The abnormality

of serum cholesterol level is considered as indicator of hepatic diseases and so, the diminished cholesterol level may suggest liver injuries.

Recently, Elbanna et al. (2017) found that rats treated with food azo dyes (sunset yellow (E110) and carmoisine (E122)) produced highly significant changes in the hematological index. Also, liver function (ALT, AST, amylase and total bilirubin), renal function (BUN and creatinine), glucose and globulins were significantly elevated. Besides, noticeable histopathological changes several body organs, and these changes and inflammation were improved by treatment with lactic acid bacteria.

Role of food colorants, azo dyes on oxidative/antioxidant biomarkers

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 non-mutagenicity 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).

The literature on the cytotoxic, mutagenic and genotoxic effect of tartrazine are controversial and unsatisfactory in some cases. In this concern, the work of Soares et al. (2015) demonstrated that tartrazine has no cytotoxic effects and concluded that tartrazine may be unsafe to health and its extended usage could generate carcinogenesis. On the other hand, infrequent studies indicated that tartrazine, erythrosine and indigo carmine are strong inhibitors of skin tumor promotion in mice treated with TPA and DMBA (Kapadia et al., 1998). Khayyat et al. (2017) found that rats administered tartrazine exhibited an obvious increased hepatic and renal function, and also increased oxidative markers and decreased total antioxidants markers. Alternatively, giving tartrazine was linked to severe histopathological and cellular changes in hepatic and renal tissues, moreover, tartrazine initiates leukocyte DNA damage as identified by comet assay.

Recently, the study of Sekeroglu et al. (2017) indicated that both tartrazine and its metabolites have possible genotoxic effect on human lymphocyte cultures with and without a metabolic activator (S9 mix) while, tartrazine can induce cytotoxicity at the highest level in culture without S9 mix under the experimental situations. These evident indicated that tartrazine had an adverse effect on health.

Concerning long-term carcinogenicity of tartrazine, some studies are now available on the chronic effect of tartrazine. Himri et al. (2011) found that a 90 daily oral dosing of 5 to 10 mg/kg b.w in Wistar rats, revealed significant dose-related high blood biochemical markers of glucose, triglycerides, total cholesterol, blood urea nitrogen, creatinine, AST and total protein, as compared to the control.

When tartrazine was given at 0, 1 and 2% in drinking water to 50 female and male rats for 2 years, carcinogenicity was not seen (Maekawa et al., 1987). Nontoxic injuries were reported at all the dye doses in the treated groups. The tumor detected, in the control and treated groups, was spontaneous in the strain of rats and the author determined that the tumors that were found in 1% of the treated group were not associated with the administration of the dye.

Collectively, these records revealed that Tartrazine might generate carcinogenesis at an extraordinary dose or accumulative exposure, however, this is improbable to occur.

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 INTERESTS

The authors declare that there is no conflict of interest.

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