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Tartrazine; the Toxic Food Additive

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Abstract

Food color is a feature that makes the food attractive and recognizable, particularly in modern societies. Tartrazine is one of the most widely used food additives and synthetic color applied to the food to attract vision of customers. It can, however, be the cause of many harmful effects on the long run. This study aimed to provide an outline of the existing evidence on the side effects of tartrazine on different body systems. The methods included updated search for the relevant databases. The studies focused on the impact of tartrazine on the nervous system, behavior, hypersensitivity, cardiovascular system, gastrointestinal system, liver, and kidney, reproductive system in both male and female, endocrinal, hematological, metabolicand developmental toxicity and cancer risk. It can be concluded that there is a need for professional assistance for consumers regarding food safety issues.

Keywords: *Food additives, Tartrazine, Oxidative stress, Brain, Liver, Kidney.*

I. Introduction

For centuries, food additives have been used to maintain the nutritional quality of food, make food more attractive, improve stability with a resulting reduction in waste, and provide efficient aids in processing, packaging and transportation. These include: colors, preservatives, antioxidants, acids, flavors, artificial sweeteners and stabilizers. It is often the additives that are most widely used to give a food a marketable quality, such as color, that cause adverse reactions (Baig and Kasim, 2018).

For a long time human beings use a variety of color additives where most of the colors are of synthetic origin. Without knowledge of their safety, many food industries started using synthetic food coloring. Artificial food colorants are considered safe if consumed within the acceptable daily intake (ADI) limit. However, increased consumption of these colorants may result in many hazards especially in children due to their low body weights. Children, especially in the developing countries, are the major consumers of colored food products so they are at high risk because they most often exceed prescribed ADIs (Reza et al., 2019).

Tartrazine (E102) is a monoazo dye which is commonly used as a colorant in food, medicines, and industrial products intended for human use. Through its metabolites it could cause many toxic effects particularly on the nervous system (Mahfouz and Al-Shammrani, 2013).

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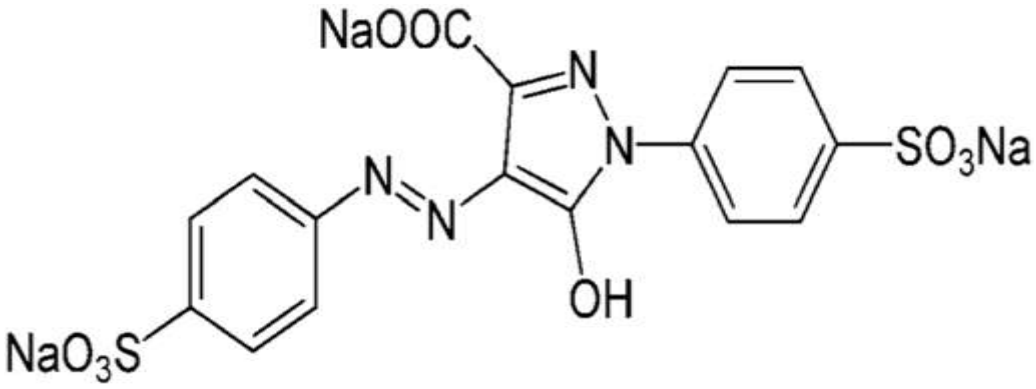

Figure (1): Structure of tartrazine(Balta et al., 2019)

Tartrazine is one of the most common azoic colorants (Shibamoto and Bjeldanes, 2009). It was approved as a "Food, Drug, and Cosmetic" (FD&C) color additive in the United States, and labeled as FD&C Yellow No. 5. In the EU, tartrazine is a permitted color additive with E number 102 (E102), while it is internationally identified with International Numbering System (INS) number 102 (INS 102) in the Codex Alimentarius (CA) (Bastaki et al., 2017).

Uses of Tartrazine

Tartrazine is frequently used in a wide range of products as a yellow coloring agent;

- Food products such as ice cream, pastries, hard candy, cotton candy, soft drinks, alcoholic beverages, sports drinks, chewing gum, chocolate snacks, cereals, cake mixes, soups, sauces, jam and jelly (Bonciu et al., 2020),
- Non-food products such as cosmetics (lipstick, face powder, eye shadow and foundation), soaps, shampoo goods. It is also used in cooking as a replacement for saffron in developing countries (Mehedi et al., 2009).

Tartrazine is a part of the manufacture of dyes for wool, silk, nylon, leather and paper, ink production, soap and plastic dyeing. It is also used in some medical preparations, such as vitamins, antacids and certain prescription drugs (Al-Shabib et al., 2017).

The Acceptable Daily Intake of Tartrazine

Many countries, including the European Union (EU) and the United States of America (USA), have strict regulations regarding the use of food colorants (Oplatowska-Stachowiak and Elliott, 2017).The Food Standards Agency (FSA) has adopted policy to ban the use of azo dyes in food industry. It is now mandatory in the EU to put this warning on any food and drink product that contains any of these colors ('may have an adverse effect on activity and attention in children') (Wrolstad and Culver, 2012).

According to Sierra-Rosales et al. (2017), the acceptable daily intake (ADI) is defined as "the amount of a food additive, which can be ingested daily during an entire lifetime without appreciable health risk". It is usually expressed in mg per kg of body weight per day (mg/kg body weight (bw)/day). The Food and Drug Administration has estimated the ADI of tartrazine for humans as 0 – 7.5 mg/kg body weight/day (Velioglu et al., 2019).

Unfortunately, children consume more colored food products than the regulatory authorities would expect (Stevens et al., 2015). Children can't control their feeding and are more easily attracted to color than adults. They consume these additives in chocolates, candy, cookies and beverages many times a day and care little about its health impact (Amin and Al-Shehri, 2018).

The Lethal Dose 50 (LD_{50}) of tartrazine is about 6250 mg /Kg BW. It is the mean lethal dose that kills 50 percent of the experimental animals under declared conditions (Ai-Mashhedy and Fijer, 2016).

Physical and Chemical Properties of Tartrazine

Tartrazine is the most common name for the compound: trisodium 5-hydroxy- 1-(4-sulfonatophenyl)-4-(4 sulfonatophenylazo)-*H*-pyrazol-3-carboxylate (Li et al., 2013). It comprises two sulphonic groups, one functional carboxylic group and one azo (N=N) bond (Al-Shabib et al., 2017).

The chemical formula of tartrazine is C_{16} H_9 N_4 Na_3 O_9 S_2 (Ngah et al., 2010). It is water soluble, orange-yellow powder dye that forms gold-yellow colored solutions. It has a molecular weight of 534.37 g / mol with a melting point of 300 ° C (Erdemli et al., 2017).

Synthesis of Tartrazine

Tartrazine is prepared from 4-aminobenzenesulphonic acid. It is dissolved in a diazotate compound by using hydrochloric acid (HCL) and sodium nitrite. The diazo compound is then coupled with 4, 5-dihydro-5-oxo-1-(40-sulphophenyl) - 1H-pyrazole-3-carboxylic acid. It may also be coupled with methyl ester, ethyl ester or with a carboxylic acid salt (Leulescu et al., 2018).

Another way of preparation is from phenylhydrazine-4-sulphonic acid. It is condensed with dioxosuccinic acid or with oxalacetic acid derivatives. The resulting colorant dye is then filtered and separated as a sodium salt (Jain et al., 2009).

Pharmacokinetics of Tartrazine

After oral intake of tartrazine, nearly 5 percent of the ingested amount is absorbed intact while the remaining part undergoes extensive metabolism by the gastrointestinal microflora(Boussada et al., 2017).On reaching the intestine, tartrazine is acted upon by azoreductases from intestinal bacteria and the liver's cytosolic and microsomal enzyme fraction leading to reduction of the azo bond and production of aromatic amines (Velioglu et al., 2019).The principle aromatic amines produced are sulphanilic acid and aminopyrazalone. They are absorbed and distributed to different body systems leading to various adverse reactions (Khayyat et al., 2017).

Mechanism of Action of Tartrazine

Tartrazine toxicity results from the metabolic reductive biotransformation of theazo bond (Chequer et al., 2011). The resulting aromatic amines interact with nitrite or nitrate-containing foods or in the stomach (El Golli, 2016) resulting in production of reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), hydroxyl radical and superoxide anion (Bhatt et al., 2018).

Reactive oxygen species can promote peroxidation of lipids and inhibition of endogenous antioxidant enzyme system which, in turn, accelerate oxidative stress (Bansal et al., 2005). So it seems rational to use anti-oxidant compounds to guard against the side effects of tartrazine(Rafati et al., 2017).

Toxic Effects of Tartrazine on Different Body Systems

The impacts of tartrazine on different body systems vary depending on several factors, such as genetic predisposition, age, nutritional condition, concentration and length of exposure to a given dose (El-Desoky et al., 2017).

A. Effect on the central nervous system:

The neurotoxic effect of tartrazine is the result of reductive biotransformation of the azo bond during metabolism of tartrazine which produced free radicals (Elekima et al., 2019). Tartrazine can promote lipid peroxidation and ROS production. Considering that the brain tissue contains large quantities of polyunsaturated fatty acids, it is primarily the target of free radical damage (Mohamed et al., 2015).According to Bhatt et al. (2018), even at the ADI level of tartrazine, oxidative damage and alteration of biochemical brain tissue markers can occur. ^{38}S-labeled sulphanilic acid (main tartrazine metabolite) was found in the brains of developing rats by passing through the blood-brain barrier.

B. Effect on behavior:

Food colorants have always been linked to the development of attention deficit hyperactivity disorder (ADHD) in children (Vojdani and Vojdani, 2015).Studies have failed to demonstrate a direct link between food coloring and ADHD. However, tartrazine exposure in hyperactive children has led to increased irritability, restlessness and sleep disturbance (Oyewole and Oladele, 2016).Nigg et al. (2012) also noted that approximately 8 per cent of children with ADHD showed clinical improvement with dietary color limitation. The Joint Expert Committee on Food Additives (JECFA) therefore recommends the prohibition of food additives for children under the age of one (Sierra-Rosales et al., 2017).

C. Hypersensitivity reactions:

Tartrazine has been shown to cause extensive range of allergic reactions in atopic individuals. These responses include angioedema, urticaria and asthma exacerbations (Elwan and Ibrahim, 2019).Tartrazine can aggravate asthmatic episodes through the up regulation of Leukotriene B4 (LTB4) expression (Leo et al., 2018) and mast cell degranulation (Balta et al., 2019).

D. Effect on the cardiovascular system:

According to Ahmad et al. (2019) &Oyewole and Oladele (2016), elevation of serum cardiac enzymes and pathological changes of the myocardium were reported in rats treated with tartrazine.Induction of hypertension is one of the adverse effects of tartrazine. This is mediated by an increase in carotid-sinus nerve activity with mean blood pressure elevation (Alsalman et al., 2019).

E. Effect of tartrazine on the GIT:

The administration of oral tartrazine to laboratory rats resulted in gastric mucosa atrophy (El Rabey et al., 2019) as well as increase in the number of lymphocytes and eosinophils in the lining of the stomach suggesting inflammation (El Golli, 2016).

F. Effect of tartrazine on the liver:

El-Desoky et al. (2017) recorded altered liver functions and histology in rats following oral tartrazine administration. Oxidative stress was recognized as the underlying etiology of these results.Tartrazine can

activate human oestrogen receptors. Since oestrogen has cholestatic action, chronic intake of tartrazine can predispose to the development of primary biliary cirrhosis (Axon et al., 2012 &Vilas-Boas et al., 2020).

G. Effect of tartrazine on the kidney:

Erdemli et al. (2017) proposed that elevation of Blood urea nitrogen (BUN) and creatinine levels in experimental rats was the result of tartrazine-induced oxidative stress.Glomerular collapse, inflammatory cell infiltration, congested vasculature in peritubular interstitial tissue and damaged epithelium of proximal and distal renal tubules were all noted by (Ali et al., 2016) in renal tissue of tartrazine-treated animals.

H. Effect on male reproductive system:

Tartrazine intake may affect testosterone level and sperm count (Hoseinpouran et al., 2015).According to Visweswaran and Krishnamoorthy (2012), zinc is essential for normal testicular growth and functioning. Tartrazine affects spermatogenesis by mobilization of zinc from testis.

I. Effect on female reproductive system:

After acute oral and intraperitoneal administration of high doses of tartrazine to albino rats, Elekima and Nwachuku (2019) registered significant increases in progesterone and estradiol (E2) concentrations. The observed rise in E2 was attributed to tartrazine'sxenoestrogenic potential (i.e., it activates receptors of estrogen).

J. Endocrinal and hormonal effects of tartrazine:

Abdel-Aziz et al. (2019) found that tartrazine intake can affect the thyroid gland structure and function. Oral administration of tartrazine to rats resulted in various histological changes besides marked elevation of serum levels of thyroid hormones with decline in thyroid stimulating hormone (TSH) level. These could be the result of ROS damaging the thyroid follicular cells where thyroid hormones are stored. Increased level of thyroid hormones stimulates reduced production of TSH from the pituitary due to negative feedback mechanism.El-sakhawy et al. (2019) reported degenerative changes in the submandibular glands as cytoplasmic vacuolations and pyknosis of the nuclei of the acinar cells in tartrazine-treated rats.

K. Metabolic effects of tartrazine:

Al-Seeni et al. (2018) reported marked elevation of serum total cholesterol (TC), triglyceride (TG) and low density lipoproteins (LDL) as well as decreased level of the high density lipoproteins (HDL) following oral intake of tartrazine in rats. They also noticed elevation of serum sodium (Na^+) level and decline of serum potassium (K^+) level. It was attributed to oxidative stress-induced damage of cell membrane leading to disturbance in membrane permeability and Na^+ and K^+ pumping.

Imafidon et al. (2015) reported reduction in blood glucose level in rats after oral tartrazine treatment. Although the exact mechanism is unknown yet, hypoglycemia may be due to direct or indirect effect on insulin release and sensitivity.

High doses of tartrazine can result in decline in body weight gain (Al-Shinnawy and Elkattan, 2013). According to El-Wahab and Moram (2013), "synthetic food colorants might bind to the bacterial cell surface in the intestine, leading to a decrease in the number of the active bacterial cells and an inhibition of the food absorption capacity at the intestinal surface, leading to a [body weight] BW decrease".

L. Hematological effects of tartrazine:

Ahmad et al. (2019) noted that rats exposed to oral tartrazine showed significant decrease in hemoglobin and haematocrit values. This may be the result of oxidative stress on blood forming tissues. According to Abd-Elhakim et al. (2018), oral tartrazine given to rats caused significant decline in red blood cells (RBCs) count and platelet count.

M. Genotoxic effect of tartrazine:

According to Mpountoukas et al. (2010), tartrazine is capable of damaging human lymphocytes and binding directly to DNA (cytotoxic effect). Meanwhile, no evidence of genotoxicity was detected.Genotoxicity was encountered at a much higher dose with no evidence of cytotoxicity (Soares et al., 2015).Amchova et al. (2015) also suggested that tartrazine might trigger carcinogenesis at very high doses or on cumulative exposure.

On the contrary, Bastaki et al. (2017) excluded any genotoxic activity for tartrazine. Absence of carcinogenic activity in long term carcinogenicity studies in mice and rats supports lack of genotoxic potential. They also proposed that previous positive genotoxicity studies were defective as they used non-standard protocols and showed lack of dose-dependence.To clarify this discrepancy, more comet assay investigations must be performed according to the latest recommended protocol (Khayyat et al., 2017).

N. Teratogenic potential of tartrazine:

Hashem et al. (2019) described pathological changes in rat fetuses exposed to tartrazine during the period of organogenesis. Skeletal malformations, liver damage, necrotic renal tubules and hemosiderin deposits in the spleen were reported. Fetal resorption and death also occurred.

O. Effect on the immune system:

Tartrazine is considered immunotoxic as it results in exhaustion of constituents of innate immunity,lysozyme activity and phagocytic activity and decrease of immunoglobulin concentration inrats which is a marker of humoral immunity (Abd-Elhakim et al., 2018).

II. Conclusion and recommendations

In conclusion, tartrazineis one of the most common food colorants with harmful impacts on human health. Children are usually the most vulnerable group to develop adverse reactions from tartrazine since they are the major consumers of colored food products.On the light of the results of the present study, the following guidelines are recommended: Firstly, the use of tartrazine to color food and the consumption of such foods should be restricted as far as possible, especially for children. Secondly, further studies are needed for assessment of health impacts of tartrazine on other organs and systems in human and for identification of the cumulative effect and chronic use of tartrazine. Thirdly, improvement of health education programs for the purpose of increasing public awareness regarding the health impact of synthetic food colorants, reading the label on consumer products and avoid using those containing tartrazine.

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