Review article

Safety of tartrazine in the food industry and potential protective factors

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A B S T R A C T

Tartrazine belongs to the colors raising significant concerns regarding consumer safety at low doses relevant for real-life human exposure. Scientific literature continues to grow after the European Food Safety Authority (EFSA) re-evaluation in 2009 and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2016. Therefore, this review aims to collect recent knowledge on the toxicity issues of tartrazine, namely its genotoxicity, cytotoxicity, carcinogenicity, reproductive, developmental, and neurotoxicity, alterations of blood biochemical parameters, and hematotoxicity. The second part of the review covers the potential protective factors against the toxic effects of tartrazine based on the hypothesis of mitigation of oxidative stress induced by the color. The reviewed protective factors are crocin, royal jelly, fish oil, honey, acetylsalicylic acid, black caraway, blackthorn, turmeric, vitamin E, and riboflavin. This review concludes that tartrazine seems safe under the current acceptable daily intake (ADI) and the evidence on the potential protective factors is insufficient to reach any conclusion regarding their use.

1. Introduction

Tartrazine (E 102) is a yellow water-soluble anionic azo-dye commonly used in processed cheese, canned or bottled fruit and vegetables, processed fish and fisheries products, aromatized wines, and wine-based drinks [1]. This color is used worldwide. Its population exposure varies across different world regions, with European children having exposure levels ranging from 0.4 to 7.3 mg/kg of body weight (bw) per day at the 95th percentile, US children from 0.03 to 0.09 mg/kg bw per day, and children in India and Indonesia facing much higher exposures of 1.1–3.1 mg/kg bw per day and 0.21–0.64 mg/kg bw per day, respectively [2]. There are some natural alternatives such as turmeric, carotenoids, annatto, saffron or paprika extracts [3], but the demand for its use is steady [2].

European Food Safety Authority (EFSA) evaluated its safety most recently in 2009. It confirmed the previously set acceptable daily intake (ADI) of 0–7.5 mg/kg of body weight per day [4]. Expected intake in the human population was estimated by the less refined but more conservative budget method to be 8.1 mg/kg in adults and 13.1 mg/kg of body weight per day in children, while more realistic maximum reported levels intake estimates are below the ADI of 7.5 mg/kg [4]. Conversely, Joint FAO/WHO Expert Committee on Food Additives (JECFA) assessed tartrazine toxicity in the 2016 and increased ADI from 0–7.5 mg/kg to 0–10 mg/kg based on a long-term toxicity study in rats [2]. Food and Drug Administration confirmed ADI of 5 mg/kg in the 2011 for the use in the US market

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[5].

Tartrazine belongs to the colors that raise significant concerns regarding consumer safety at low doses, which is relevant for real-life human exposure [6,7]. Therefore, it is the subject of many experimental studies aiming to assess its genotoxicity, cytotoxicity, carcinogenicity, developmental toxicity, and, recently, potential neurological, reproductive, and endocrine effects. The toxicity of tartrazine can result directly from the toxicity of the molecule itself or metabolites. Tartrazine has very low oral bioavailability [8]. However, it is extensively metabolized by intestinal microflora to absorb metabolites easily, and reductive biotransformation of the azo bond occurs in the skin and liver, too [9]. Tartrazine does not affect the activity of P-glycoprotein [10]. This non-degradable dye can lead to bioaccumulation in the organism and inflict various disorders [11].

Recently, the idea of protecting the affected organs and body functions with substances known for their antioxidant properties has been based on the toxicity of azo dyes when administered in high doses. This notion was extensively tested in a preclinical setting in the case of tartrazine, but apart from one study focusing on the protective effect of curcumin in coadministration with sunset yellow. There is no data for other synthetic food dyes. Co-administration of protective factors may become a viable option for mitigating consumer risks associated with tartrazine.

2. Tartrazine-induced toxicity

Hence, this review aims to gather the recent literature regarding the toxicity of tartrazine and identify the types of toxicity causing the most concern, mainly at ADI-relevant dosing. Another aim was to collect evidence of potential protective factors that may mitigate tartrazine-induced toxicity. To this end, a Google Scholar search for "tartrazine toxicity" was performed, limited to studies from 2015 and newer. The following text is divided by the cluster of toxicity issues related to tartrazine use, and a separate chapter is dedicated to the potential protective factors.

2.1. Genotoxicity

In the evaluation of tartrazine, the EFSA expressed concerns about potential genotoxicity based primarily on the positive findings from the comet *in vivo* test on mice [4,12], that, however, was not conducted according to the Organization for Economic Co-operation and Development (OECD) technical guidelines [13]. In 2013, the EFSA's Panel on Food Additives and Nutrient Sources (ANS) assessed new scientific information and concluded there was no reason to revise the ADI. Nevertheless, EFSA requested new data. Later, an *in vivo* study confirmed that no significant response to tartrazine was found in this micronucleus bone marrow assay [14]. In 2016, The Joint WHO/FAO Committee on Food Additives (JECFA) reviewed new data performed by the internationally validated experimental protocol. It also concluded that there is no justified concern about the genotoxicity of tartrazine [2].

The genotoxicity of tartrazine and its metabolites still deserves attention, as the results of some new studies are inconsistent with the current conclusion of no concern. A large body of literature used *in vitro* models. Tartrazine was shown to cause mitotic spindle disorders in different eukaryotic cell lines unrelated to its oxidizing activity [15]. The genotoxic potential of a very high dose of tartrazine (2500 μg/mL) has been observed in cultured human lymphocytes, which was attributed to the significant decrease in the mitotic index [16]. However, even lower doses were found to be genotoxic, depending on the duration of exposure. A short period of exposure (3 h of incubation) caused DNA damage while testing in all testing concentrations of tartrazine ranging from 0.25 to 64.0 mM, i.e., 0.116–29.79 μg/mL [17]. The same result was achieved with prolonged exposure (72 h) but only with a concentration of 70 μg of tartrazine. A dose-dependent cytotoxic effect (not reaching the inhibitory concentration 50 - IC_{50} - at its ADI concentration) and no DNA damage were observed in the *in vitro* model of human leukemia cells [18]. The most recent *in vitro* short-term (24 h) study did not show the genotoxicity of tartrazine on the human mammary gland adenocarcinoma cell line [19]. Genotoxicity was not confirmed at lower or higher concentrations (5–500 μg/mL) in the long period [20] nor in the middle period (47 h) of exposure to tartrazine in the range of 2.5–10 mM [21]. A possible explanation is the initiation of repair mechanisms in the leukocytes during longer exposures [20].

Furthermore, tartrazine was tested in Drosophila in ADI-relevant concentration, where it did not induce any *in vivo* toxicity and significantly improved the longevity of the flies [18]. However, tartrazine at concentrations of 25, 50, and 70 mg/mL had a detrimental effect on the development of wing spot cells during the embryonic development of Drosophila larvae in a concentration-dependent manner [22,23]. However, these studies were conducted at high doses and in the Drosophila model, which largely limits their usefulness for regulators.

Rodent studies report conflicting results. Although Bastaki et al. (2017) dismissed tartrazine genotoxicity in rats, Khayyat et al. (2017) reported the potential of tartrazine in ADI dose to induce structural and functional aberrations and genotoxic effect in leucocytes in rats [14,24]. Tartrazine at a very high dose of 500 mg/kg has been shown to increase serum markers of oxidative stress after three weeks of administration to rats [25,26], which may or may not lead to DNA damage.

Hence, it seems that the genotoxic effect of tartrazine is exerted by high doses only and it is not of concern in the dietary exposure levels, which do not reach the ADI limit [2].

2.2. Cytotoxicity

Several new studies have assessed the cytotoxicity of tartrazine. They mainly provide results about the oxidative potential (due to decreased antioxidants and increased prooxidants) of tartrazine and its effect on biochemical profiles and inflammatory processes, which can lead to organ damage, particularly the liver and kidney. *In vivo* studies have also shown cytotoxicity to other organs, such as the pancreas or brain. The overview of the rodent studies is presented in **Table 1**. These studies differ in the dose (from 2 mg/kg/day to

500 mg/kg/day), duration of administration (from 30 days to 8 weeks), and the species to which tartrazine is administered (primarily rats, but also mice). The route of administration is commonly oral, and the results consistently show increased oxidative stress markers in serum, liver, brain, and kidney tissues due to tartrazine treatment.

In experimental fish (Carassius carassius), tartrazine exposure resulted in histological damage to the gill and intestine, enhanced oxidative stress, immune impairments, and gut microbiota dysbiosis [27]. Cytotoxicity studies on human cells have, in most cases, negative results. No cytotoxicity on cultured human lymphocytes has been shown in a range of concentrations of tartrazine [17,20,21]. Likewise, skin cytotoxicity in human foreskin fibroblasts has not been demonstrated [28]. On the other hand, moderate cytotoxicity has been shown in the human mammary gland adenocarcinoma cell line [19].

The current evidence demonstrates that tartrazine increases oxidative stress markers in animals and some human cell lines. Notably, many animal models were exposed to doses relevant to the ADI. However, oxidative stress is a non-specific toxic effect of many xenobiotics and pathological states.

2.3. Carcinogenicity

The EFSA review of available carcinogenicity studies concludes that tartrazine does not have a potential to induce benign or malignant neoplasias [4]. On the other hand, there is an ability of tartrazine to enhance the development of estrogen-dependent tumors. Due to its oxidative potential, tartrazine can act as a carcinogen promoter when administered at 50 mg/kg for 20 weeks with a carcinogen DMBA (7,12-dimethylbenz(a) anthracene). It induced breast tumorigenesis in rats [38]. An *in vitro* study reported similar results. Tartrazine caused a proliferative effect in breast cancer cells [39]. However, such doses are not of concern when using tartrazine as a food color.

2.4. Reproductive toxicity

Tartrazine has been classified as a xenoestrogen that can activate estrogen receptor (ER alpha) in an *in vitro* cell model [40], which was later disproved in an *in vivo* study. Tartrazine does not bind to ER alpha or ER beta [41]. Studies show that the effect of tartrazine on reproductive hormones depends mainly on the time of administration. Twenty-four hours after acute tartrazine administration (2.5

Table 1
Markers of oxidative stress induced by tartrazine in rodents.

Animals	Tartrazine dose	Length of treatment	Sample	Results	Author
mice, 21 and 35 days old	2.5 and 5 mg/kg	prenatally and the first 15 days after delivery to the mother	cerebrum, cerebellum, and medulla oblongata homogenates	↑ malondialdehyde ↓ glutathione, superoxide dismutase (all brain regions, both doses)	[29]
rats	7.5 mg/kg	90 days	serum, liver homogenate	↑ malondialdehyde (liver) ↓ glutathione (liver), superoxide dismutase (serum), catalase (serum), glutathione peroxidase (serum)	[30]
rats	7.5 mg/kg	30 days	serum	↑ malondialdehyde, nitric oxide ↓ total antioxidants	[24]
rats	2, 6, 10 mg/kg (erythrosine + tartrazine 50:50 mix)	6 weeks	striatum	↑ malondialdehyde ↓ glutathione, catalase	[31]
mice	10 mg/kg (+3.75 mg/kg sulfanilic acid)	8 weeks	serum, liver, and kidney tissue homogenate	↑ malondialdehyde ↓ glutathione, superoxide dismutase, catalase, glutathione reductase (in serum, liver, and kidney)	[32]
rats	10 mg/kg	15 and 30 days	serum	↓ superoxide dismutase (after 30 days)	[33]
rats	50 mg/kg	15 and 30 days	serum	↓ superoxide dismutase (after 15 and 30 days)	[33]
rats	75 mg/kg	90 days	liver and kidney tissue homogenate	↑ malondialdehyde ↓ glutathione, superoxide dismutase, catalase	[34]
rats	400 mg/kg	30 days	serum	↑ malondialdehyde ↓ glutathione, superoxide dismutase, catalase, glutathione peroxidase	[35]
rats	500 mg/kg	21 days	kidney homogenate	↑ malondialdehyde, total oxidant status ↓ glutathione, superoxide dismutase, catalase, total antioxidant status	[36]
rats	500 mg/kg	21 weeks	serum, liver homogenate	↑ malondialdehyde, superoxide dismutase, total oxidant status ↓ glutathione, catalase, glutathione peroxidase, total antioxidant status	[26]
rats	500 mg/kg	3 weeks	pancreas tissue homogenate	↑ malondialdehyde, total oxidant status, oxidative stress index ↓ glutathione, superoxide dismutase, catalase, total antioxidant status	[37]

g/kg to 20 mg/kg orally), female rats showed significantly higher progesterone and estradiol concentrations. Male rats showed considerably lower testosterone levels than control rats [42]. Likewise, in an *in vitro* study, short-term exposure (24 h) to tartrazine induced significant estrogenic activity in breast tissue cells [19]. However, with chronic treatment for 30, 60 and 90 days, the difference in hormone levels was not confirmed [42]. Furthermore, histopathological changes in testes and ovarian cells were found in the short-term test, and only mild changes after 90 days were observed [42]. However, the combination of tartrazine with Erythrosine induces changes even in chronic exposure. After 23 days of administering these two dyes, the follicle–stimulating hormone (FSH), luteinizing hormone (LH), and testosterone values increased (in doses below and above the ADI). Notably, testicular tissue damage was observed at a high dose of 20 mg/kg [43]. High doses of tartrazine (300 mg/kg) also altered sperm characteristics, accompanied by a significant decrease in testosterone levels were significantly decreased [44].

Importantly, all the studies reporting potential reproductive risks used high doses, which cannot be ingested from food sources. Tartrazine does not seem to exert any reproductive toxicity under the current ADI.

2.5. Developmental toxicity

In 2009, EFSA assessed tartrazine as non-risk for development based on studies where no adverse effects on reproduction or development were observed for tartrazine when administered at doses equivalent to or exceeding the ADI level, namely doses of 773 and 1225 mg/kg of body weight per day [4,45,46]. This finding was later confirmed in an *in vitro* study where Tartrazine showed no adverse effect on fetal development [47].

However, recent preclinical studies have found adverse effects of tartrazine on fetal neurodevelopment when the dye is administered to pregnant females and newborns. Tartrazine in doses 2.5 mg/kg and 5 mg/kg administered p.o. during pregnancy and the first 15 days after birth caused oxidative stress and neurobehavioral and hematological alterations in mice offspring. There were histological alterations and neuronal damage in the brain, specifically in the cerebrum, medulla oblongata, and cerebellum [29]. Likewise, in rat offspring, morphological, visceral, and skeletal malformations were found when tartrazine was administered at a dose of 0.45 or 4.5 mg/kg for ten days in gestation [48]. The teratogenicity of tartrazine has also been assessed in non-mammals. Tartrazine is not embryotoxic or teratogenic for zebrafish embryos up to the dose level of 10 mM concentration. All other higher doses correlate with higher toxicity [49]. One single amount of tartrazine (0.375 mg/egg, which corresponds with 14 times the ADI) *in ovo* caused malformations in the endoskeleton (reduction in the weight and length of embryos, malformations in feathers, head, and limbs). It led to a higher mortality rate of chicken embryos [50]. However, even a dose corresponding to the ADI (7.5 mg/kg) causes a neural tube defect in the chicken embryo model [51]. Administration of tartrazine (in a concentration of 0.1 g/kg or 1.0 g/kg body weight) to a larval *Tenebrio molitor* reduced its weight [52].

Consumption of high-dose tartrazine in early life may lead to neurodegenerative changes, as evidenced by a study on rat pups (in weight 45–55 g) who were administered tartrazine in a dose of 500 mg/kg for 30 days. Their neurotransmitter levels (GABA – gamma aminobutyric acid, DA - dopamine, 5-HT - serotonin) and antioxidant biomarkers were reduced. In addition, markers of lipid peroxidation and apoptotic cells were increased in the brain cortex [53]. The neurodegenerative effect of tartrazine was also confirmed at a later age. In young male albino rats (28 days old), tartrazine (320 mg/kg for four weeks) induced severe brain damage in the form of affection of the general architecture of the brain associated with increased oxidative stress [54]. However, such high doses of tartrazine do not reflect the real-life situation, so the value of these studies is limited.

The new evidence on developmental toxicity is not conclusive. Still, the developmental toxicity of tartrazine may represent a real problem as many studies used low doses relevant to the current ADI limit.

2.6. Neurological and neurobehavioral alterations

Neurological changes after chronic exposure to tartrazine also affect adults in animal studies. Tartrazine administered daily for 30 days in doses of 7.5 mg/kg, 15 mg/kg, or 100 mg/kg caused histopathological degenerative changes in the *cerebellum*, while the degree of damage correlates with the dose [55]. Tartrazine administered daily for 40 days in doses of 7.5 mg/kg resulted in a reduction of anti-oxidant enzyme levels and increased pro-oxidants in brain regions, specifically in the frontal cortex, corpus striatum, hippocampus, and cerebellum [56]. A recent study reached very similar results in the cerebral cortex and cerebellum of male rats after four weeks of administration of the ADI dose of tartrazine [57]. In addition, tartrazine has shown an effect on neurotransmitter levels. Brain acetylcholine and gamma-aminobutyric acid (GABA) were elevated, while dopamine was depleted in tartrazine-treated rats [57]. Furthermore, exposure to 50 mg/kg of tartrazine for seven weeks caused a reduction in the volume of the medial prefrontal cortex, decreased the number of neurons and glial cells, and led to memory impairment in rats, while 5 mg/kg only caused behavioral deficits [58].

Chronic administration of tartrazine in combination with Erythrosine (2 mg/kg, 6 mg/kg, and 10 mg/kg of 50:50 mixture) caused memory impairment, increased anxiety, and depression-like phenotype in behavioral tests, and increased levels of acetylcholinesterase, pro-inflammatory cytokines, and pro-oxidants. In contrast, the endogenous anti-oxidants were decreased in rats' prefrontal cortex and hippocampus [31]. Tartrazine has also shown neurotoxic effects in experimental fishes, demonstrated by increased lipid peroxidation products in the brain tissues and decreased acetylcholine esterase activity [59]. Although the evidence is limited, some studies used ADI-relevant dosing, and their results warrant future research to rule out the neurological risks of tartrazine.

Dietary exposure to synthetic colors, including tartrazine, was hypothesized as a risk factor affecting children's behavior, particularly attention deficit hyperactivity disorder (ADHD). This matter was extensively reviewed by Miller et al. (2022). Despite the number of clinical and animal studies, a direct relationship between exposure to food colors and ADHD has not been proven and the

mechanism of how they can cause these neurological and behavioral changes is not known. Furthermore, there appears to be considerable interindividual variability in the sensitivity to synthetic food dyes [60].

2.7. Changes in blood biochemistry

Blood biochemistry reveals the general kidney and liver functions, levels of blood lipids, electrolytes, etc. They react to many diseases or toxic insults and are routinely screened in human medicine. Therefore, such estimates may become a useful indirect biomarker of tartrazine-induced toxicity. Many studies reported an association of tartrazine exposure with increased plasma levels of liver transaminases, creatinine, urea, and uric acid. An altered lipid profile has been repeatedly shown as well. The data are summarized in Table 2. These findings indicate changes in the function of main metabolic organs (liver, kidneys) after high doses and ADI-relevant exposure. This evidence combined reveals consistent alterations without a clear dose-dependent pattern, i.e., they are already present at low doses.

2.8. Hematotoxicity

According to recent studies, tartrazine alters blood cell counts. Chronic exposure to low doses close to the ADI limit exerts decreases in red blood cell count, hemoglobin, packed cell volume, platelet count, and leukocytosis in rodents. Conversely, very high doses tend to increase the red and white blood cell counts. A detailed overview of the results is in Table 3.

3. Protective factors against the toxic effects of tartrazine

Potential protective factors are hypothesized to mitigate mainly oxidative stress induced by tartrazine on the level of various organs due to their antioxidant properties. So far, it seems that co-administration of protective factors with tartrazine can eliminate (or at least minimize) the toxic effects of low- or high-dose tartrazine. So far, there is no clinical study relevant to this issue.

3.1. Crocin

Crocin is one of the saffron carotenoid pigments from *Crocus sativus*, and it has potent free radical scavenger and antioxidant properties. In recent studies, all from one team, it has been shown that crocin has several beneficial effects in tartrazine-induced

Table 2
Effect of tartrazine on blood biochemical parameters.

Animals	Tartrazine dose	Length of treatment	Results	Author
rats	7.5 mg/kg	90 days	↑ total cholesterol, triglycerides, LDL, ALT, AST, ALP, LDH	[30]
mice	7.5 and 75 mg/kg	7 weeks	↑ total cholesterol, triglycerides, LDL, VLDL, ALT, AST, ALP, creatinine, urea, uric acid	[61]
rats	7.5 mg/kg	30 and 60 days	↑ nHDL, total creatine kinase after 30 and 60 days; no effect on total cholesterol, triglycerides, HDL, LDL, atherogenic indices	[62]
rats	7.5 mg/kg	30 days	↑ ALT, AST, ALP, urea, uric acid, creatinine	[24]
rats	7.5 mg/kg	50 days	↑ ALT, AST, ALP, GGT, urea, uric acid, creatinine, total protein, total cholesterol, triglycerides, LDL ↓HDL	[63]
rats	10 mg/kg	15 and 30 days	↑ glucose, amylase, lipase ↓ insulin, calcium, magnesium after 30 but not 15 days	[33]
mice	10 mg/kg (+3.75 mg/kg sulfanilic acid)	8 weeks	↑ total cholesterol, triglycerides, LDL, VLDL, ALT, AST, ALP, bilirubin, creatinine, urea, uric acid ↓ HDL, total protein	[32]
rats	50 mg/kg	15 and 30 days	↑ glucose, amylase, lipase ↓ insulin, calcium, magnesium at both time points	[33]
rats	75 mg in 250 mL of drinking water	7 weeks	no effect on total cholesterol, triglycerides, ALT ↑ AST, creatinine	[64]
rats	100 mg in 250 mL of drinking water	7 weeks	no effect on total cholesterol ↑ triglycerides, ALT, AST, creatinine	[64]
mice	200 mg/kg	25 days	no effect on total cholesterol ↑ bilirubin, creatinine	[65]
rats	200 mg/kg	60 days	↑ALT, AST, urea, total protein	[66]
mice	400 mg/kg	25 days	↑ total cholesterol, triglycerides, bilirubin, creatinine	[65]
rats	400 mg/kg	30 days	↑ ALT, AST, ALP, urea, uric acid, creatinine	[67]
rats	500 mg/kg	3 weeks	↑ total cholesterol, glucose, triglycerides, LDL, VLDL ↓ HDL	[25]
rats	500 mg/kg	21 weeks	↑ ALT, AST, ALP	[26]

Legend: ALT - Alanine aminotransferase, AST - Aspartate aminotransferase, ALP - Alkaline phosphatase, GGT - gamma-glutamyl transferase, HDL - high-density lipoprotein, nHDL – non-high-density lipoprotein, LDH - lactate dehydrogenase, LDL - low-density lipoprotein, VLDL - very low-density lipoprotein.

Table 3

Effect of tartrazine on hematological parameters.

Animal	Tartrazine dose	Length of treatment	Results	Author
rats	1.35 mg/kg	90 days	↓ hemoglobin, red blood cell count, packed cell volume %, platelet count ↑ white blood cell, neutrophil, lymphocyte, and monocyte counts	[68]
rats	5 mg/kg	13 weeks	no effect	[9]
rats	7.5 mg/kg	13 weeks	↓ platelet count ↑ neutrophil and basophile relative % content, mean platelet volume	[9]
rats	10 mg/kg	13 weeks	no effect	[9]
rats	75 mg in 250 mL of drinking water	7 weeks	↑ white blood cell, neutrophil, and lymphocyte relative % content	[64]
rats	100 mg in 250 mL of drinking water	7 weeks	↓ hemoglobin, platelet count, mean platelet volume ↑ white blood cell, neutrophil, lymphocyte, and monocyte relative % content	[64]
mice	100 mg/kg	72 days	↑ red blood cell count, white blood cell count, hemoglobin	[69]
mice	200 mg/kg	72 days	↑ red blood cell count, white blood cell count, hemoglobin, platelet cell volume, mean corpuscular volume	[69]

toxicity in rats. An ameliorating effect of tartrazine-induced nephrotoxicity [36], hepatotoxicity [26], pancreatic toxicity [25] and intestine toxicity [37] was reported in rats treated by a high dose of tartrazine (500 mg/kg) and crocin (50 mg/kg) for 21 days. These studies examined markers of oxidative stress such as malondialdehyde, reduced glutathione, superoxide dismutase, catalase, total antioxidant status, and total oxidant status in the kidneys, liver, pancreas, ileum, and colon tissues. Crocin alone improved these parameters and normalized the oxidative status in the tartrazine-treated cohort. These changes occurred together with evidence of tartrazine-induced histological changes and their prevention by crocin [25,26,36,37].

3.2. Royal jelly, fish oil

The royal jelly is a substance secreted by the cephalic glands of nurse bees. Cod liver oil contains, among other substances, omega-3 fatty acids. Both substances have many proven benefits, such as anti-inflammatory, antioxidant, hepatoprotective, neuroprotective, or anticancer effects [70,71]. When pregnant rats were administered tartrazine (500 mg/kg) and treated with royal jelly (300 mg/kg) or cod liver oil (0.4 mL/kg) for 30 days, the treatment provided sufficient protection against the neurotoxic effect of tartrazine on male pups brain tissue function and structure [53]. tartrazine decreased the concentration of the gamma amino butyric acid (GABA), dopamine, and serotonin, decreased levels of antioxidant biomarkers (superoxide dismutase, catalase, and the reduced glutathione), increased malondialdehyde levels, and number of apoptotic cells in the cortex. Royal jelly and fish oil administration could normalize most parameters [53]. Later, the same doses of tartrazine and protective factors were used in the same laboratory for 60 days. Researchers reached the same results regarding the beneficial effect of treatment, although the experiment targeted a different organ system, the testicular toxicity [72].

3.3. Acetylsalicylic acid (ASA)

ASA is a nonsteroidal anti-inflammatory drug that exerts its effects by an irreversible inhibition of cyclooxygenase enzymes. In addition to the analgesic, antipyretic, antiplatelet, and anti-inflammatory properties used in human medicine, it has been shown as an antitumorigenic and neuroprotective agent in clinical and preclinical studies [73,74]. Although the combination of tartrazine and ASA was previously described as risky, with administration of tartrazine to ASA-sensitive patients leading to eczema and asthma exacerbation [75], this cross-reactivity was later refuted [76]. On the contrary, ASA seems to show potential benefits. High doses of ASA reversed tartrazine-induced neurotoxic changes in rats, demonstrated as cancerogenic overexpression of proliferative factors and brain hemorrhage. Tartrazine induced these alterations at a very high dose of 700 mg/kg administered for two weeks, whereas the brain tissue of rats co-administered by ASA (150 mg/kg for three weeks) was intact [77].

3.4. Honey

Honey is an antioxidant, anti-inflammatory, and anti-tumor agent [71]. In addition, limited evidence points to its potential to protect the kidney, liver, stomach, jejunum, and testis tissues from the toxic effects of tartrazine. Tartrazine induced harmful organ alterations in rats at a relatively low dose of 10 mg/kg dose administered for eight weeks. Tartrazine exerted decreased antioxidant levels, high-density lipoproteins and increased liver enzymes, kidney indices, lipid peroxidation, triglycerides, total cholesterol, and low- and very-low-density lipoproteins together with histological changes of stomach, liver, kidney, and testis tissues. Administration of honey and tartrazine at a dose of 2.5 mg/kg ameliorated the biochemical parameters, normalized antioxidant parameters, and restored the histology of organs to nearly average values [78]. A similar rat study in a different laboratory used the same tartrazine and honey dosing but lasted 12 weeks and focused on jejunal mucosa. Tartrazine induced degenerative tissue changes, decreased proliferating cell nuclear antigen expression, and increased expression of tumor necrosis factor-α (TNF-α), while honey treatment normalized these detrimental changes [79]. Both studies were performed in male rats using a different natural honey source.

3.5. Black caraway (black cumin, Nigella sativa)

Nigella sativa is a plant commonly known as black caraway, black cumin, or black seed for spice or flavoring. It is known to possess certain anti-diabetic, antitussive, anticancer, antioxidant, hepatoprotective, neuroprotective, gastroprotective, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, and bronchodilator activity [80]. Despite numerous studies with promising results, *Nigella sativa* or its constituents have not yet been approved in any indication.

When co-administered with tartrazine, *Nigella sativa* seed oil has demonstrated a cytoprotective and antioxidant effect in male rats. Low-dose tartrazine (10 mg/kg) treatment for eight weeks decreased total serum protein, antioxidants, and high-density lipoproteins, increased liver enzyme, kidney function parameters, total cholesterol, triglycerides, low-density lipoproteins, and lipid peroxidation. These changes co-occurred with histopathological changes in the liver, kidney, testes, and stomach. Treatment with *Nigella sativa* oil (10 mL/kg) prevented all these detrimental effects of tartrazine [32]. In addition, thymoquinone, the main bioactive component in *Nigella sativa* oil, showed a hepatoprotective effect in high-dose (100 mg/kg) tartrazine-caused hepatotoxicity (oxidative and inflammatory changes) in male rats [81].

3.6. Blackthorn fruit (Prunus spinosa)

Blackthorn (Prunus spinosa) is a common bush with dark blue edible fruits despite their adstringent solid taste. Blackthorn fruits are a rich source of antioxidants and may exert a potent protective effect against toxic substances [82]. Only one preclinical study focused on the curative effects of blackthorn against the impact produced by tartrazine (75 mg/kg, seven weeks) in rats. In blood, tartrazine increased alanine aminotransferase and creatinine. Creatinine level was normalized by administration of blackthorn fruit dissolved in water. Tartrazine altered liver, spleen, kidneys, and brain histology, which was not prevented by the blackthorn fruit material [64].

3.7. Curcumin (turmeric, Curcuma longa)

Curcumin is a natural yellow dye extracted from turmeric rhizomes (*Curcuma longa*). It is marked with the code E 100 when used as a natural food color. Curcumin has extensive health benefits. In animal and clinical studies, it has shown a promising effect in the treatment of high cholesterol, diabetes, depression, anxiety, Alzheimer's disease, or cancer [83,84]. Unfortunately, it usually reaches these benefits only at very high doses. Nevertheless, curcumin did show specific protective effects when co-administered with tartrazine. Curcumin at dose ranges 1, 2, and 4 g/kg of rodent chow dependently attenuated the toxic impact of low-dose tartrazine (7.5 mg/kg of rodent chow). Specifically, it normalized higher concentrations of blood lipids, hepatic enzymes, and kidney function parameters, as well as the indicator of oxidative stress malondialdehyde [30]. A study testing the effect of tartrazine on colorectal adenocarcinoma and hepatocellular carcinoma human cancer cell lines and a normal cell line, skin fibroblast BJ-1, confirmed a potent antioxidant and anticancer effect of curcumin, mainly when used in nanoparticle formulation [85]. Recent research has confirmed that encapsulating curcumin in nanoparticles might improve its therapeutic effects and bioavailability [86]. Therefore, even in a low dose (1 or 2 g of the nanoformulation), curcumin showed a protective effect against oxidative stress, DNA damage, the imbalance in serum glucose, and the up-regulation of apoptosis-related genes induced by tartrazine (7.5 mg/kg for 50 days) in male rats [63]. Curcumin also reverses the detrimental developmental effects of tartrazine, such as the shape, length, body weight, and skeleton of chicken embryos [50].

Curcumin is the only intervention tested for protective effects against another food color, sunset yellow. The study tested a high dose of the color (200 mg/kg) and 150 mg/kg of curcumin for 28 days. The findings indicate that curcumin moderated the deleterious effects on the liver, kidney, and testicular structure and function induced by exposure to sunset yellow [87].

3.8. Vitamin E

Vitamin E is a fat-soluble and essential antioxidant in the body, protecting cell membranes from damage by free radicals. Only one study evaluated vitamin E's potential in preventing Tratrazine-induced toxicity. However, this study has one crucial strength: the use of low (5 mg/kg) and high (50 mg/kg) color doses for seven weeks. Notably, the low tartrazine dose falls within the ADI range. Vitamin E in high doses (100 mg/kg) was shown to prevent the behavioral (spatial memory) deficits caused by both tartrazine doses, the decreased volume of cortical regions exerted by the high dose, and aberrant brain cell morphology induced again by both doses [58].

3.9. Riboflavin

Riboflavin (vitamin B2) is a yellow to orange-yellow natural dye and vitamin soluble in water. In the food industry, it is marked with code E 101. There is minimal evidence, but one preclinical study using 200 mg/kg/day of tartrazine for 60 days followed by another 60 days of tartrazine recovery and riboflavin (100 mg/kg) treatment has demonstrated its reparative abilities in gastro toxicity [88]. Furthermore, another study assessed low-dose tartrazine (7.5 mg/kg for 30 days) neurotoxicity and a potential benefit of 25 mg/kg of riboflavin. Riboflavin largely prevented tartrazine-induced cerebellar cytoarchitecture impairment [89].

4. Conclusion

Tartrazine is undergoing pervasive research compared to other synthetic food colors, and concerns regarding its safety have been raised. Many studies report serious toxic effects after doses, which are irrelevant to human exposure to food sources. Hence, tartrazine seems to be safe for the human consumer under the current ADI. However, continued monitoring is crucial to ensure consumer safety, especially at ADI-relevant doses. Regarding the protective interventions against tartrazine organ toxicity, the results seem promising, but the main limitation of the research is the lack of reproduced evidence. In many cases, the quality of the studies is limited. The experiments test unrealistically high tartrazine doses, non-standardized extract or mixtures of the protective factors, making replication of the results complicated or impossible, do not provide mechanistic insights, use animals of one sex only etc. Another issue to consider is the use of non-standardized test material in these studies, particularly because some reports do not use food-grade tartrazine and do not report its purity levels. However, this approach may be proven valid by future high-quality experiments and clinical trials and become a beneficial adjuvant treatment.

CRediT authorship contribution statement

Petra Amchova: Writing – review & editing, Writing – original draft, Conceptualization. **Filip Siska:** Writing – review & editing, Writing – original draft. **Jana Ruda-Kucerova:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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