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Posted Date: 5 August 2025

doi: 10.20944/preprints202508.0270.v1

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 doi:10.20944/preprints202508.0270.v1

Review

Toxicological Effects of Tartrazine Exposure: A Review of *In Vitro* and Animal Studies with Human Health Implications

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Abstract

Tartrazine (TZ, also known as FD&C Yellow No. 5 or E102) is a synthetic, water-soluble yellow food dye widely used in the food and pharmaceutical industries. Some studies have associated TZ with allergic reactions, especially among people with dye sensitivities or pre-existing allergies. Recent research also suggests a possible link between TZ consumption and the worsening of behavioral disorders, especially in children, including symptoms such as hyperactivity, irritability, restlessness, and sleep disturbances. Experimental studies in laboratory animals have highlighted potential risks associated with prolonged or high-dose exposure, including toxic effects on the nervous system and liver function. In addition, increasing evidence indicates that TZ can induce oxidative stress (OS) by increasing the production of reactive oxygen species (ROS), which can contribute to cellular damage and inflammation. Although the evidence remains inconclusive, there are recommendations to limit the intake of synthetic food dyes especially in children's diets. The purpose of this review is to examine the potential toxic effects on health of tartrazine by analyzing findings from experimental studies in cell cultures and laboratory animals, as well as correlations observed in humans. We focus on documented adverse reactions, including possible neurotoxic, hepatotoxic, oxidative, and behavioral effects. Through this, we aim to contribute to a more comprehensive understanding of the risks associated with exposure to this synthetic food dye.

Keywords: tartrazine; health; zebrafish; toxicity; hyperactivity; oxidative stress

1. Introduction

 doi:10.20944/preprints202508.0270.v1

Tartrazine is an azo dye commonly used to impart color to food products [1–5]. Approximately 65% of azo dyes are used as food additives and are found in various products such as candies, jams, and soft drinks, as well as in pharmaceuticals, cosmetics, and textiles. Although TZ adds no nutritional benefit and has no nutritional value, it remains the most widely used food dye, with a significant presence in the global food industry [6–9]. According to the World Health Organization (WHO), since 2016, the acceptable daily intake (ADI) has been set at 0–10 mg/kg body weight [10]. Although it was one of the first food additives to raise concerns regarding the possibility of causing adverse reactions, it is still used in the EU and other parts of the world [11].

Moreover, some research has suggested a possible association between TZ exposure and allergic reactions such as urticaria, asthma, migraines, blurred vision, itching, or sleep and behavioral disorders, including hyperactivity in children [12–17]. In particular, children appear to be more sensitive to this additive, with possible links reported between food dyes and behavioral disorders such as attention deficit hyperactivity (ADHD), and even mutagenic or carcinogenic pathologies [18,19]. In a double-blind placebo-controlled study, a group of children was exposed to several doses of TZ. Some of them exhibited clear behavioral reactions such as irritability, restlessness, and sleep disturbances [20].

In recent decades, numerous experimental studies, both *in vitro* and on animal models, have investigated the effects of TZ on cellular functions, tissue integrity, and behavior. The results suggest this food additive may be involved in inducing OS through the generation of ROS [21,22], activating the inflammatory response through the overproduction of proinflammatory cytokines interleukin-1 (IL-1) and interleukin-6 (IL-6) [23,24], modifying enzymatic activity, and contributing to the onset of neurobehavioral disorders [25], including impairments in learning and memory processes [26,27]. From the perspective of the biological mechanisms involved, OS has been identified as a pathway through which TZ exerts its toxic effects, contributing to the imbalance between pro-oxidants and antioxidants in cells [28,29]. This imbalance has been reflected in elevated levels of malondialdehyde (MDA), a byproduct of lipid peroxidation, indicating enhanced oxidative damage. Concurrently, a significant reduction in the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT) has been observed, further supporting the pro-oxidant shift induced by TZ exposure [30].

However, the data available in scientific literature are heterogeneous, and translating results from preclinical experiments into the context of human exposure remains challenging. At the same time, the food industry is increasingly exploring natural alternatives to mitigate the health side effects of synthetic dyes. Therefore, replacing them with natural alternatives represents a much better option [19]. Some well-known natural alternatives include turmeric, carotenoids, annatto, saffron, and paprika extracts. For example, the azo dye TZ can potentially be replaced with carotenoids extracted from pequi (*Caryocar brasiliense*) using high-performance ionic liquids as extractants, a modern and sustainable method that offers both safety and efficiency benefits [31,32].

The aim of this review is to provide a critical and integrative analysis of experimental data from *in vitro* and animal model studies regarding the effects of TZ exposure, with a focus on the toxicological mechanisms involved (including OS, neurotoxicity, and inflammatory response). By correlating these findings with existing observations of side effects in humans, the paper aims to offer a comprehensive perspective on the potential risks to human health. Thus, the study contributes to clarifying a current issue regarding the safety of synthetic food additives and supports the need to reassess TZ exposure, particularly among children.

2. Health Implications of Tartrazine Exposure

TZ is a synthetic yellow dye widely used in food, pharmaceutical, and non-food products (Table 1). Although it enhances the appearance of products, several studies have reported its potential to trigger allergic reactions, asthma, or skin hypersensitivity. These adverse effects have led to growing interest in natural alternatives such as annatto or beta-carotene [2,25,33–45].

 doi:10.20944/preprints202508.0270.v1

Tabel 1. Common Uses of Tartrazine and Relevant Toxicological Concerns

Category	Product examples	References
Food products	TZ is widely used to impart an intense yellow color in various food products such as bread, beverages, cereals, peanuts, candies, jellies, chewing gum, flavored chips, creams, ice cream, yogurts, cakes, instant desserts, soups, sauces, jam, flavored rice, and pasta, but due to its potential side effects, there is a growing tendency to replace it with natural pigments like annatto or beta-carotene.	[2,35,37,40–43,45]
Pharmaceuticals	TZ is used as a coloring excipient in multivitamins, gelatin capsules, tablets, syrups, and pediatric medicines, but in some cases it may cause allergic reactions or asthma in sensitive individuals.	[33,36,38–40]
Non-food products	TZ is also present in non-food products such as soaps, cosmetics, shampoos, hair conditioners, pastels, crayons, and stamp dyes. It may cause hypersensitivity reactions upon skin contact.	[25,34,44,45]

TZ – Tartrazine.

From a chemical perspective, TZ is an anionic acid dye that, in an acidic environment, is converted into tartrazic acid [46]. In the body, TZ is reduced to an aromatic amine, a structure that is strongly stabilized due to its nitroso derivative [47]. This compound can trigger a wide range of immunological reactions, including fatigue, irritability, clinical depression, headaches, and sleep disturbances. Figure 1 illustrates the main pathways through which TZ may affect human health: OS, chronic inflammation, genotoxicity, and neurobehavioral disorders. These mechanisms are especially triggered under repeated or chronic exposure and may contribute to the development of systemic conditions, particularly in children and sensitive individuals. Both ingestion and simple skin contact with products containing this substance may cause hypersensitivity reactions. Some researchers suggest that symptoms may occur even at low exposure levels, with manifestations appearing up to 72 hours after contact [45].

Although there are no conclusive studies proving that TZ directly causes anxiety in humans, there is sufficient evidence from animal studies indicating that this additive may increase OS, negatively affect liver and kidney function, alter lipid levels, and consequently raise the risk of cardiovascular disease. The results regarding its impact on behavior and neurotoxicity are often contradictory or inconclusive.

TZ has been associated with various adverse reactions in some individuals, including migraines, agitation, asthma attacks, blurred vision, eczema, and other skin rashes. Additionally, some studies have suggested a possible increased risk of thyroid cancer [47,48]. In a randomized, double-blind, placebo-controlled study, the administration of a mixture of food colorants (5 mg E110, 2.5 mg E122, 7.5 mg E102, 5 mg E124) along with 45 mg E211 was linked to negative effects on concentration, hyperactive behavior, and attention in children aged 3 and 8–9 years [49]. Another study reported that TZ was responsible for approximately 1% of acute urticaria and/or angioedema cases [50].

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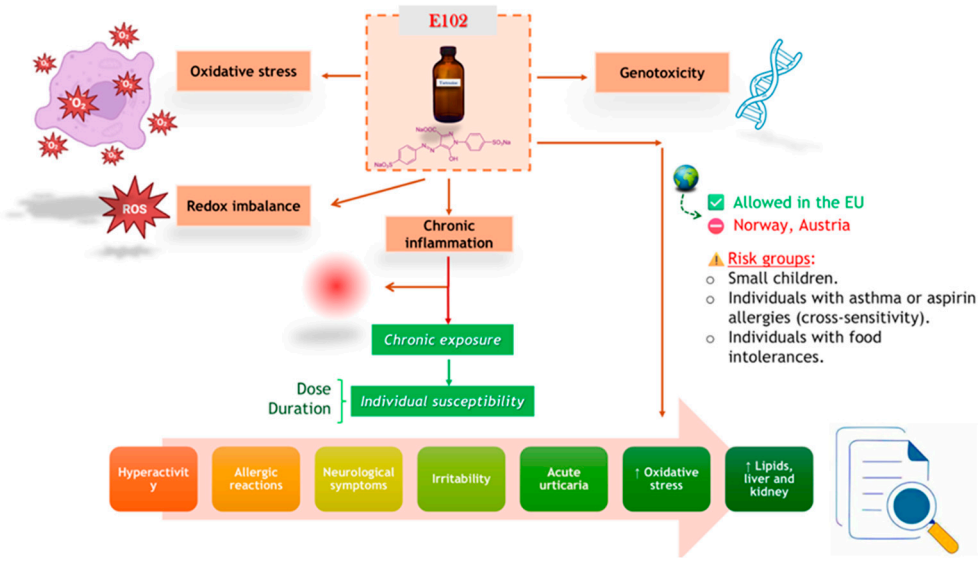

Figure 1. Toxic Mechanisms Involved in Tartrazine Exposure (Figure partially created using BioRender resources)

The effects of TZ on the behavior of children with suspected hyperactivity included irritability, restlessness, and sleep disturbances, and these reactions intensified with increasing dosage, indicating a dose-response relationship [20]. The administration of TZ in atopic patients triggered allergic reactions, predominantly cutaneous and respiratory, which were significantly more frequent compared to placebo. These included angioedema, nasal congestion, rhinorrhea, wheezing, skin rashes, and pruritus, and approximately 5% of participants showed elevated levels of TZ-specific IgE [51].

Data from the literature on the cytotoxic, mutagenic, and genotoxic effects of TZ remain unclear and often contradictory. Although Soares et al. [52] did not identify significant cytotoxic effects, the authors highlighted the potential health risk posed by TZ, suggesting that prolonged use may contribute to carcinogenic process.

3. Oxidative Stress Induced by Tartrazine

Several studies on rats have correlated the action of TZ with the induction of OS [21,48,53–56] (Table 2). OS represents an imbalance between the production of ROS and the capacity of endogenous antioxidant systems to neutralize them, leading to damage to cellular components such as lipids, proteins, and DNA [57,58].

Table 2. Evidence of Oxidative Imbalance Following Tartrazine Exposure in Rodent Models.

Experimental organism	n=	About species	Dose	Time	Method of administration	Sample	Effect	References
Rats	18	Young male albino rats (28 days, 60–80 g)	320 mg/kg tartrazine in 1 ml distilled water, daily	4 weeks	oral gavage	Brain	↓ GPx ↑ MDA	[59]
	50	Wistar male albino rats	7.5 mg/kg	90 days	Diets containing dry mass	Liver	↑ MDA ↓ GSH	[30]

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					Serum	↓ SOD ↓ CAT ↓ GPx	
24	Male Wistar rats (10–12 weeks, 180–200 g)	2, 6, 10 mg/kg (erythrosine + TZ 50:50 mix)	6 weeks	oral gavage	Brain tissue	↑ MDA ↓ GSH ↓ CAT ↑ ACHe.	[60]
18	Male albino rats	10 mg/kg (+3.75 mg/kg sulfanilic acid)	8 weeks	oral administration	Serum, liver and kidney tissue homogenate	↑ MDA ↓GSH ↓ SOD ↓ CAT ↓ GR	[61]
18	White albino rats of either sex	Low (10 mg/kg) and high (50 mg/kg) doses	15 and 30 days	oral administration	Serum	↓ SOD	[1]
30	Sprague-Dawley male albino rats (150-200 g)	75 mg/kg	90 days	Oral administration by orogastric gavage	Hepatic and renal tissue homogenate	↑ MDA ↓ GSH ↓ SOD ↓ CAT	[62]
18	Male albino rats (10–15 weeks, 190–250 g)	400 mg/kg	30 days	oral administration	Serum	↑ MDA ↓ GSH ↓ SOD ↓ CAT ↓ GPx	[29]
40	Female Wistar albino rats (225–250 g)	500 mg/kg	21 days	oral gavage	Tissue homogenates	↑ MDA ↑ SOD ↑ TOS ↓ GSH ↓ CAT ↓ TAS	[63]
40	Adult female Wistar rats (225–250 g, 8–10 weeks)	500 mg/kg	3 weeks	oral gavage	Tissue homogenates	↑ MDA ↑ TOS, ↓ GSH ↓ SOD ↓ CAT	[56]

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						↓ TAS	
30	Adult male Sprague Dawley rats (120-150 g)	200 mg/kg	60 days	oral administration	Tissue homogenate	↑ MDA	[64]
40	Female Wistar rats, (225–250 g)	500 mg/kg	3 weeks	oral gavage	Tissue homogenate	↑ MDA ↑ TOS ↓ GSH ↓ TAS ↓ SOD ↓ CAT.	[65]
20	Male Wistar rats, (130 ± 40 g)	300 mg	30 days	oral administration	Tissue homogenate	↑MDA ↑CAT ↑GST	[55]
36	Young male albino rats (60–80 g)	low doses of TZ 15 mg/kg bw	30 days	oral administration	Liver tissue homogenate	↑ MDA ↓ CAT ↓ SOD	[54]
		high doses were 500 mg/kg bw				↑ MDA ↓ CAT ↓ SOD ↓ GSH	
40	Sprague–Dawley rats (70 ± 10 g)	175, 350, and 700 mg/kg bw	30 days	oral gavage	Brain tissue	↓GSH ↓SOD ↑MDA	[48]

ACHe – Acetylcholinesterase; bw – Body Weight; CAT – Catalase; GPx – Glutathione peroxidase; GR – Glutathione reductase; GSH – Glutathione; GST – Glutathione S-transferase; MDA – Malondialdehyde; SOD – Superoxide dismutase; TAS – Total Antioxidant Status; TOS – Total Oxidant Status; TZ – Tartrazine, ↑ - significantly increased; ↓ - significantly decreased.

Exposure to TZ, even at concentrations considered environmentally relevant (50 mg/L), has been shown to cause significant biochemical changes, such as increased levels of MDA and nitric oxide (NO), along with a decrease in antioxidant enzyme activities (SOD, CAT, glutathione (GSH)) and acetylcholinesterase (AChE), suggesting neurobiochemical dysfunctions [66]. Daily administration of higher doses, such as 320 mg/kg for four weeks, exacerbates oxidative imbalance in the brain by reducing glutathione peroxidase (GPx) activity and increasing lipid peroxidation, reflected in elevated MDA levels [59]. Even significantly lower doses (7.5 mg/kg), administered over a longer

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period (90 days), induce severe OS, associated with increased MDA and reduced activities of endogenous antioxidant enzymes (CAT, SOD, GPx) and GSH levels [30].

Moreover, the combination of TZ and erythrosine has demonstrated synergistic effects in inducing OS in brain structures such as the striatum, where increases in MDA, AChE, and nitrites, along with reductions in GSH and CAT, suggest disruption of cerebral redox balance and a potential role in neurotoxicity [60].

Repeated exposure to TZ at doses ranging from 10–75 mg/kg over periods of up to 8 weeks has been associated with marked alterations in oxidative balance in key organs such as the liver, kidneys, and pancreas. This occurs through decreased levels of endogenous antioxidants (GSH, SOD, CAT, glutathione reductase (GR)) and increased MDA, reflecting a significant contribution to metabolic and endocrine dysfunctions [1,61,62].

Additional studies have shown that high doses (200–500 mg/kg) exacerbate systemic OS, affecting the liver, kidneys, spleen, and blood. Marked increases in MDA [29,55,56,63–65] were observed, along with decreases in GSH, CAT, and SOD [29,56,63,65], TOS, and TAS [65], as well as alterations in histopathological parameters [29,55,56,63,65]. However, Golli et al. [55] reported increases in CAT and GST levels. These imbalances are correlated with marked histopathological changes in the liver, kidneys, and intestines, supporting the idea of systemic toxicity via oxidative mechanisms.

Also, the studies by Amin et al. [54] and Gao et al. [48] highlight the impact of doses ranging from 15 to 700 mg/kg on the liver and brain, through the inhibition of GSH, SOD, CAT, and the increase of lipid peroxidation [48,54], reflecting the impairment of cognitive functions and potential neurotoxicity. These effects are attributed to the formation of free radicals during the metabolism of TZ, which promotes the activation of inflammatory pathways and increased expression of IL-1 and IL-6, reinforcing the role of chronic inflammation in the toxicity of this substance [48].

4. *In Vitro* Studies on Tartrazine Toxicity

In vitro studies provide a controlled experimental framework to evaluate the direct effects of TZ on cells, thus allowing the identification of the molecular mechanisms of toxicity. Several *in vitro* studies have assessed the cytotoxic and genotoxic effects of TZ in different types of human cells and experimental models (Table 3). In human lymphocytes exposed to concentrations ranging from 0.25 to 64.0 mM, TZ did not show cytotoxicity, but induced significant genotoxic effects at all tested concentrations, with only partial DNA repair observed [52]. Similarly, human leukocytes exposed to TZ at 5–500 µg/mL showed no cytotoxic or mutagenic effects; however, DNA damage was observed at concentrations ≥70 µg/mL, consistent with in silico toxicity predictions [67].

Table 3. Summary of Experimental Studies Assessing the Cytotoxic and Genotoxic Effects of Tartrazine in Different Human Cell Types and Assays.

Cell Type	Concentration Tested	Tests Performed	Key Findings	References
Human lymphocytes	0.25 – 64.0 mM	MTT assay, alkaline comet assay	No cytotoxicity; genotoxic at all doses; partial DNA repair.	[52]
Human leukocytes	5 – 500 µg/mL	Trypan Blue viability, Micronucleus test, Comet assay, Cytogenetics, In silico	No cytotoxicity/mutagenicity; DNA damage at ≥70 µg/mL; supported by in silico models.	[67]
Human foreskin fibroblasts	10, 100, 250, 500, 1000, and 2000 µg/ml for various dyes	MTT assay, ROS, lipid peroxidation, LDH	TZ: no effect; indigo carmine/chlorophyllin cytotoxic at high doses	[68]
Yeast assay, MCF-7 breast cancer cells	Not specified (short-term)	Estrogenic activity, LDH release, micronucleus test	8-PN showed the strongest estrogenic effect, followed by TZ and genistein; all exhibited low cytotoxicity and no genotoxicity.	[69]
Human lymphocytes, GR-M melanoma cells	2.5, 5and 10 mM	Chromosome aberration, CBMN assay, trypan blue test	**No genotoxicity in lymphocytes; low cytotoxicity in lymphocytes; high cytotoxicity in melanoma cells**	[70]
HaCaT HepG2 A549	20 µM, 40 µM și 80 µM	qRT-PCR Alkaline Comet Assay	Upregulated DNMT and HDAC genes with increased DNA fragmentation, indicating epigenetic and genotoxic effects.	[71]

8-PN – 8-Prenylnaringenin; CBMN assay – Cytokinesis-Block Micronucleus Assay; DNA - Deoxyribonucleic Acid; DNMT – DNA Methyltransferase; HDAC – Histone Deacetylase; HepG2 – Human liver cancer cell line; LDH - Lactate Dehydrogenase; MTT - Methyl Thiazolyl Tetrazolium; qRT-PCR – Quantitative Real-Time Polymerase Chain Reaction; ROS - reactive oxygen species; TZ – Tartrazine.

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An *in vitro* study on human foreskin fibroblasts evaluated the effects of several dyes, including TZ. Testing revealed that TZ did not induce significant cytotoxic effects, even at high concentrations. In contrast, indigo carmine and chlorophyllin exhibited marked cytotoxicity at elevated doses. Moreover, chlorophyllin also triggered increased ROS production, indicating potential OS. These findings underscore the importance of further research into the safety of dyes commonly used in pharmaceutical and cosmetic formulations [68].

Investigations into the estrogenic, cytotoxic, and genotoxic potential of TZ compared to phytoestrogens, using yeast assays and MCF-7 breast cancer cells, demonstrated that TZ possesses moderate estrogenic activity, with low cytotoxicity and no genotoxicity detected in short-term exposures [69]. Finally, TZ tested at concentrations of 2.5, 5, and 10 mM again showed no genotoxicity and negligible cytotoxicity in human lymphocytes but confirmed significant cytotoxic effects in melanoma cells [70] Exposure to TZ was associated with increased activation of enzymes involved in epigenetic regulation in human cells such as HaCaT, HepG2, and A549. These changes may influence cell proliferation and survival processes, favoring the activation of oncogenic pathways. Additionally, significant DNA fragmentation was observed, indicating a potential genotoxic effect. These results suggest that TZ may contribute to epigenetic disruptions and increased cancer risk [71].

These studies suggest that, although TZ presents limited cytotoxicity in normal human cells, it may induce genotoxic effects and exhibit notable cytotoxicity in certain cancer cell lines. The cell type-specific responses emphasize the importance of using diverse cellular models in assessing the safety profile of this widely used azo dye.

5. Tartrazine Toxicity in Experimental Animal Models

Experimental studies conducted on experimental models indicate a significant toxic potential of TZ, especially under chronic exposure or at high doses (Table 4). Data obtained from *Danio rerio* show increased sensitivity to TZ during embryonic development. According to the study by Joshi and Katti [72], exposure to concentrations ≥10 mM was associated with the occurrence of deformities, edema, cardiovascular dysfunctions, delayed hatching, and increased mortality. At concentrations ≥75 mM, embryonic development was completely inhibited, highlighting the significant toxic potential of the substance on embryonic development. Similar results were reported by Jiang et al. [73], who noted reduction in embryonic survival, delayed hatching, swelling of the heart, and deformities along the body axis, with estimated effective concentration for 50% of the population and lethal concentration for 50% of the population values of 42.66 millimolar and 47.10 millimolar, respectively. Furthermore, Gupta et al. [74] observed that exposure to TZ in embryonic water, especially at concentrations of 0.5% and above, caused a significant increase in hatching rate and changes in SOD1 gene expression during early developmental stages. Additionally, Thanh et al. [75] identified a vascular toxicity profile, manifested by hemorrhages, edema, and abnormal vessel branching, correlated with altered migration and proliferation of endothelial cells. Adverse effects were also observed under chronic exposure conditions. Linskens et al. [76] demonstrated that prolonged administration of TZ (22 μM) caused cognitive deficits in adult fish, reflected by decreased learning capacity and cognitive flexibility. These changes were not present with limited exposure during the early post-embryonic period, suggesting a duration-dependent manifestation of neurotoxicity.

Table 4. Effects of Tartrazine on Behavior and Biochemistry in Animal Models

Experimental model	n=	Method of administration	Time	Dose	Analysis	Effect	Ref.
				Zebrafish			
Zebrafish embryo	20/concentration	Exposed to E3 medium with varying TZ concentrations in Petri dishes	24, 48, 72, 96, 120, 144, 168 hpf	0, 0.1, 1, 2, 3, 4, 5, 10, 20, 30, 40, 50, 75, 100 mM	Developmental anomalies (heart rate, edema, tail distortion, hatching, mortality) observed via bright field microscopy.	Control embryos hatched normally; ≥10 mM caused early hatching with deformities and ≥40 mM increased mortality.	[72]
	25 embryos/well	Embryos exposed in 6-well plates with E3 medium supplemented with TZ	3-4 h post-fertilization to 4 dpf	0, 5, 10, 20, 50 g/L	Zebrafish embryo toxicity and vascular defects.	Dose-dependent vascular defects: hemorrhage, edema, small eye, vessel abnormalities.	[75]
	20	Exposed in E3 medium	72 hours (hpf)	5-100 mM (various concentrations)	Developmental and cardiac toxicity parameters	TZ caused dose-dependent drops in survival, hatching, cardiac/yolk sac edema, spinal defects, and heart rate.	[73]
	9	Exposure via aquatic media	6 months to a year	22 μM	Behavioral tests: T-maze test, cognitive flexibility, memory, learning, perseverance, consistency in choices.	Learning, memory, and flexibility impaired; task completion and perseverance reduced.	[76]
	100	Exposed to varying erythrosine and TZ levels in embryo water.	Up to 10 dpf	Erythrosine: 0.001–0.1%; TZ: 0.01–0.5%	Biochemical and genetic analyses	High TZ (≥0.5%) boosted hatching (55% at 48 hpf, 100% at 72 hpf) and triggered SOD1 expression via OS.	[74]
				Mice			
KunMing mouse (20 ± 2 g)	40	Oral gavage	30 days	175–700 mg/kg body mass	Behavioral (Step-through, Morris maze) and biochemical tests	TZ negatively affects learning and memory in mice, increasing escape time and reducing reaction time in tests.	[48]
Male Swiss albino mice (4 weeks)	15	Oral administration	72 days	100 mg/kg	Hematological analyses	Increased red blood cell count, WBC count, and hemoglobin	[77]

				200 mg/kg		Increased red and WBC counts, hemoglobin, platelet volume, and MCV	
Swiss albino mice (25-30g)	15	Oral administration	25 days	200mg/kg	Physiological and biochemical analyses	No effect on cholesterol; increased bilirubin and creatinine	[78]
				400 mg/kg		Increased total cholesterol, triglycerides, bilirubin, and creatinine	
				Rats			
Sprague–Dawley rats (70 ± 10 g)	40	Oral gavage	30 days	175, 350, 700 mg/kg body mass	Behavioral tests: Open-field test. Biochemical analyses	TZ increases activity and anxiety in rats, also causing histopathological changes in the brain.	[48]
Male Wistar rats (40-50 g)	45	Dissolved in tap drinking water	16 weeks	%, 1% (low dose) and 2.5 % (high dose)	Behavioral tests: Open field behaviour test Elevated plus maze test Light-Dark transition task Forced swim test Social interaction test	The study highlights the harmful effects of TZ on anxiety and depression, highlighting the risks of long-term exposure to food dyes on mental health.	[79]
Young male albino rats (28 days old, 60-80g)	18	Oral gavage	4 weeks	320 mg/kg TZ in 1 ml distilled water, once daily.	Neurobiological and histological analysis: Brains were harvested and analyzed for histological changes.	TZ has a neurotoxic effect, evidenced by histological changes such as neuronal apoptosis and vascular congestion.	[59]
White albino rats of either sex	18	Oral administration	15 and 30 days	Low dose: 10 mg/kg High dose: 50 mg/kg	Biochemical, hormonal and histological analyses	TZ disrupts glucose balance, damages pancreas, alters endocrine function. Increases glucose, lipase; decreases insulin, Ca, Mg	[1]
Male albino rats	18	Oral administration	8 weeks	10 mg/kg (+3.75 mg/kg sulfanilic acid)	Biochemical and histological	Caused liver and kidney dysfunction with lesions.	[61]

						Increased cholesterol, triglycerides, LDL, VLDL, ALT, AST, ALP, bilirubin, creatinine, urea, uric acid. Decreased HDL, total protein.	
Wistar male albino rats	50	Diets containing dry mass	90 days	7.5 mg/kg	Biochemical and histological analyses	TZ raised lipids, liver enzymes, kidney function. Increased total cholesterol, triglycerides, LDL, ALT, AST, ALP, LDH.	[30]
Female Wistar albino rats (225–250 g)	40	Oral gavage	21 days	500 mg/kg	Biochemical analyses and histopathological examinations	Increased AST, ALT, ALP indicating liver damage.	[63]
Male albino rats (65–80 g)	12	Oral administration	7 weeks	7.5 and 75 mg/kg	Biochemical and histopathological analyses	Study showed harmful lipid, biochemical changes and liver-kidney damage. Increased cholesterol, triglycerides, LDL, VLDL, ALT, AST, ALP, creatinine, urea, uric acid.	[80]
Male Wistar albino rats (200–250 g)	40	Oral administration	50 days	7.5 mg/kg	Biochemical and histopathological analyses	TZ impaired liver/kidney, altered histology, lipids, glucose. Increased ALT, AST, ALP, GGT, urea, uric acid, creatinine, protein, cholesterol, triglycerides, LDL; decreased HDL.	[81]
Adult female Wistar rats (225–250 g, 8–10 weeks old)	40	Oral gavage	3 weeks	500 mg/kg	Biochemical and histopathological analyses	TZ caused degenerative and metaplastic changes in ileum and colon epithelium.	[56]
Wistar albino rats (146–153 g)	20	Dissolved in 1 ml of distilled water	30 days	7.5 mg/kg b.wt.	Biochemical, histological and ultrastructural analyses	TZ raised AST, ALT, ALP, uric acid, urea, creatinine, reduced antioxidants, and caused liver and kidney damage.	[26]

Male Wistar rats (10–12 weeks old, 180–200 g)	24	Oral gavage	6 weeks	2, 6, 10 mg/kg (50:50 erythrosine-TZ)	Behavioral (open field test, forced swimming test, tail suspension test), biochemical and enzymatic analyses	Increased nitrite, TNF-α; worsened anxiety and depression.	[60]
Sprague-Dawley male albino rats (150-200 g)	30	Oral administration by orogastric gavage	90 days	75 mg/kg	Biochemical, genetic, immunohistochemical, histology analyses	Increased AST, ALT, urea, creatinine; liver and kidney damage.	[62]
Female Wistar albino rats (225–250 g)	40	Oral gavage	21 days	500 mg/kg	Biochemical and histopathological analyses	TZ caused kidney glomerular collapse, inflammation, congestion.	[82]
Albino rats (~0.2 kg)	63	Oral administration	30 and 60 days	7.5 mg/kg	Biochemical and histopathological analyses	TZdamages heart, raises nHDL and creatine kinase, increasing cardiovascular risk.	[83]
Male rats (10–15 weeks old, 190–250 g)	18	Oral administration	30 days	400 mg/kg	Biochemical analyses	Increased ALT, AST, ALP, urea, uric acid, creatinine; decreased Na, K, Ca.	[84]
Adult male Sprague Dawley albino rats	30	Oral administration	90 days	1.35 mg/kg	Hematological, immunological, and histopathological analyses	Decreased hemoglobin, RBC, PCV%, platelets; increased WBC, neutrophils, lymphocytes, monocytes.	[85]
Female Wistar rats (225–250 g)	40	Oral gavage	3 weeks	500 mg/kg	Biochemical and histopathological analyses	Increased total cholesterol, glucose, triglycerides, LDL, VLDL; decreased HDL.	[65]
Albino Wistar rats	20	Oral administration	7 weeks	75 mg/250 mL water 100 mg/250 mL water	Biochemical, hematological and histopathological analyses	TZ damaged liver, kidneys, spleen; no change in cholesterol, triglycerides, ALT. Increased AST, creatinine, WBC, neutrophils, lymphocytes.	[86]
Adult male Sprague Dawley rats (120–150 g)	30	Oral administration	60 days	200 mg/kg	Biochemical, histological and physiological analyses	Subchronic TZ affects liver and kidney parameters and induces OS. Increased ALT, AST, urea, total protein.	[64]
	30	Oral administration	13 weeks	5 mg/kg		no effect	[87]

Male and female Wistar rats (170–200 g)				7.5 mg/kg	Hematological and histopathological analyses	Decreased platelets; increased neutrophils, basophils, and mean platelet volume.	
				10 mg/kg		no effect	
Adult male albino rats (120–150 g)	40	Oral gavage	30 days	7.5 mg/kg bw	Histopathological and Immunohistochemical analyses	TZ causes structural damage in cerebellum, glands, kidneys, with edema, congestion, neuron vacuolization, and cell deformation.	[88]
				15 mg/kg bw		ChatGPT a spus: Edema, dilated perineural spaces, and degenerating Purkinje cells.	
				100 mg/kg bw		Severe Purkinje cell degeneration, gray matter vacuolization, edema, nuclear pyknosis, vessel engorgement, increased astrocytes.	
Male Wistar rats (130 ± 40 g)	20	Oral administration	30 days	300 mg	Biochemical and histopathological analyses	Increased transaminases, LDH, creatinine, uric acid, kidney proteins; decreased total protein, albumin, globulin; HDL unchanged.	[55]
Young male albino rats (*Rattus norvegicus*), 60–80 g	36	Oral administration	30 days	Low dose: 15 mg/kg bw	Biochemical analyses	Increased ALT, AST, ALP, total protein, albumin, globulin, creatinine, urea; decreased serum cholesterol.	[54]
				High dose: 500 mg/kg bw		Increased ALP, total protein, albumin, creatinine, urea	

ALP – Alkaline Phosphatase; ALT – Alanine Aminotransferase; AST – Aspartate Aminotransferase; b.wt. – Body weight; Ca – Calcium; dpf – Days Post Fertilization, GGT – Gamma-Glutamyl Transferase; HDL – High-Density Lipoprotein; hpf – Hours Post Fertilization; LDH – Lactate Dehydrogenase; LDL – Low-Density Lipoprotein; MCV – Mean Corpuscular Volume; MPV – Mean Platelet Volume; Na – Sodium; OS – Oxidative Stress; PCV% – Packed Cell Volume Percentage (hematocrit); RBC – Red Blood Cells; SOD1 – Superoxide Dismutase 1; TNF-α – Tumor Necrosis Factor-alpha; TZ – Tartrazine; VLDL – Very Low-Density Lipoprotein; WBC – White Blood Cells.

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In rodents, oral administration of TZ induces significant structural and functional changes. Meena et al. [77] highlighted hematological and hepatic alterations at doses of 100–200 mg/kg, manifested by changes in organ weights and biochemical imbalances. Similarly, Arefin et al. [78] reported evidence of hepatotoxicity and nephrotoxicity at doses of 200–400 mg/kg, including increases in bilirubin, creatinine, and body weight. TZ significantly affects glucose homeostasis and pancreatic endocrine function, being associated with increased blood glucose levels and lipase activity, as well as decreased insulin, calcium, and magnesium levels after 30 days of administration [1]. Other histopathological effects include dilation of perineural spaces and severe degeneration of Purkinje cells, edema, and increased astrocyte populations. Subchronic exposure to TZ has been correlated with alterations in hepatic and renal parameters, evidenced by increases in alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea, and total protein [64], as well as transaminases, lactate dehydrogenase (LDH), creatinine, and uric acid, with decreases in total proteins, albumin, and globulins [48,59,60].

At the neurobehavioral level, TZ induces hyperactivity, anxiety, and cognitive deficits in behavioral tests, alongside cerebral histological changes including neuronal apoptosis and vascular congestion, highlighting its neurotoxic effect [48,59,60]. In a complementary study, Kamel and El-Lathey [79] reported anxious and depressive effects, as well as decreased social interaction in male Wistar rats, suggesting a cumulative negative impact on mental health.

Chronic exposure (7.5–500 mg/kg) has been correlated with increases in hepatic enzymes (ALT, AST, alkaline phosphatase (ALP)) [26,30,54,61,63,80,81,84], renal markers (urea, creatinine, uric acid) [61,63,80,81,84], and lipid parameters (low-density lipoprotein (LDL), triglycerides) [30,61,65,80,81]. These changes were accompanied by histopathological lesions in vital organs such as the liver, kidneys, testes, stomach, colon, heart, and central nervous system [30,56,61,63,80,81,83,85,86]. Hematological and immunological alterations included leukocytosis, increased tumor necrosis factor alpha (TNF-α), and splenic changes, alongside decreases in hemoglobin and platelets [85,87]. Endocrine disorders, electrolyte imbalances, and neuroinflammation were also reported [60].

Altinoz et al. [56] documented severe intestinal lesions with losses of intestinal antioxidants and increases in lipid peroxidation. Additionally, cardiovascular impairment was suggested by elevated cardiac troponin, creatine kinase, and non- high-density lipoprotein cholesterol (HDL) cholesterol [83], indicating a myocardial risk in cases of prolonged exposure.

A significant number of studies have analyzed the protective potential of natural compounds. Curcumin, crocin, Nigella sativa oil, chlorophyll, and spinach fruit extract have proven effective in reducing OS, normalizing biochemical parameters, and alleviating tissue damage [30,56,61–63,65,81,82,85,86,89]. Al-Seeni et al. [61] reported in a study with doses of 10 mg/kg over 8 weeks hepatic and renal dysfunctions, histopathological lesions, and alterations in lipid profile and oxidative markers, with partial improvement following administration of Nigella sativa oil.

Available data consistently highlight the systemic toxic effects of TZ, manifested through hepatic, renal, hematological, metabolic, and neurological dysfunctions, confirmed by both biochemical changes and histopathological lesions. Prolonged exposure also induces hematological and immunological disorders, disturbances in glucose and electrolyte metabolism, as well as negative effects on the central nervous system, including anxiety, depression, reduced locomotor activity, and neuroinflammation [30,60,63,80,85,87,88].

6. Conclusions

Tartrazine remains a widely used synthetic food additive, yet accumulating scientific evidence raises serious concerns about its safety. Preclinical studies consistently report toxic effects such as oxidative stress, inflammation, neurotoxicity, metabolic disruption, hepatotoxicity, and potential genotoxicity. While these findings are mostly from animal models, the underlying mechanisms, including antioxidant system impairment and inflammatory pathway activation, are relevant to human disease. Although direct clinical evidence is limited, epidemiological data suggest associations between tartrazine exposure and adverse effects like hyperactivity, allergies, migraines,

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and behavioral issues, particularly in children. Given the potential for cumulative exposure, individual variability, and unclear thresholds for chronic toxicity, a re-evaluation of tartrazine's safety is both timely and necessary. Replacing tartrazine with safer, natural alternatives should be prioritized to protect public health, especially for sensitive populations.

7. Future Perspectives

For a comprehensive understanding of the risks associated with tartrazine, long-term clinical studies, identification of specific biomarkers, and clarification of the involved epigenetic mechanisms are needed. In parallel, the development of safe natural alternatives and the reevaluation of current regulations become essential priorities for protecting public health.

Author Contributions: Conceptualization, M.V., A.S. and A.C.; methodology, M.V., V.R. and C.A.; validation, V.B., M.H. and A.C.; formal analysis, M.V. and A.S.; investigation, resources, data curation, M.V., A.S., V.R., V.B., G.P., C.I., A.C., C.A., M.H; writing—original draft preparation, M.V., A.S. V.R. and I.-M.B; writing—review and editing, G.P. and C.A; visualization, V.R., C.I. and I.-M.B.; supervision, V.B. and M.H. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest: The authors declare no conflicts of interest.

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