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Review Article: Tramadol-Induced Organ Toxicity via Oxidative Stress : A Review Study

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ABSTRACT

Background: Tramadol (TR) is a synthetic opioid-like centrally acting analgesic used for moderate to severe pain management in various diseases. Numerous investigations have supported the association between tramadol use and increased levels of oxygen-free radicals. Mass production of reactive oxygen species produces secondary toxic compounds. This could damage the internal components of the cell and ultimately causes organ damage. There exists a growing trend of tramadol abuse and the increasing reports of poisoning, abuse, and mortality due to this drug. Thus, the present study aimed to review the animals and human studies on the effects of acute and chronic exposure of tramadol in inducing organ toxicities through oxidative stress.

Methods: Pubmed, Google Scholar, and Scopus bibliographic databases were searched for studies that investigated oxidative stress as a mechanism of toxicity by tramadol. A manual search of reference lists of the retrieved articles was conducted. Data were collected from 2000 to 2021 (up to June 2021).

Results: From 28 articles concerning experimental and human studies of TR-induced oxidative stress organ damage, which included in this review, the occurrence of lipid peroxidation, alteration in the levels of total antioxidant capacity, and other oxidative stress biomarkers in many organs such as the brain, liver, kidney, adrenal and lung in the experimental studies of tramadol exposure have been observed.

Conclusion: Oxidative stress could be considered the most critical toxic mechanism in TR-induced tissue damage.

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1. Introduction

Tramadol (TR) is a centrally acting analgesic used to manage moderate to severe acute and chronic pain. Furthermore, it is used to manage opiate withdrawal and premature ejaculation [1]. TR exerts its analgesic effects through partial agonist effects on the mu-opioid receptor. It also inhibits the reuptake of serotonin and norepinephrine neurotransmitters [1, 2]. Cytochrome P450 enzymes metabolize TR to O-desmethyl tramadol as a more potent analgesic metabolite [3]. Repeated consumption of TR leads to active metabolites accumulation in the body, reducing its clearance and increasing its toxicity [4, 5]. TR abuse/poisoning seems to be a worldwide health problem with a rising trend, especially in young adults due to self-treatment of sexual dysfunction [6, 7]. Death following TR overdose is mainly through resistant shock, cardiorespiratory depression, asystole, and liver failure [8]. The concomitant use of TR with other medications, such as barbiturates, propranolol, benzodiazepines, and ethanol, can cause the fatal toxicity of TR [9, 10].

Several experimental studies indicated that the Reactive Oxygen Species (ROS) production should be considered a TR-induced toxicity mechanism. Therefore, Oxidative Stress (OS) following TR exposure induces toxicity and damage in different organs [11-15]. OS is defined as overproduction and accumulation of free radicals, including ROS in cells and tissues, and the inability of the biological system to detoxify these reactive products. Free radicals are generated by endogenous pathways such as infection, inflammation, ischemia, cancer, aging, and exogenous sources, including heavy metals, environmental pollutants, chemical solvents, toxins, and drugs [16]. Accordingly, OS is considered the primary mechanism in the pathophysiology of several poisoning, substance abuse, and diseases [17-19]. Previous studies reflected that the primary mechanisms for inducing oxidative damage in TR exposure are the involvement of the dopaminergic system and the decrease of electron transport chain complexes activity in the mitochondria [20, 21]. TR could increase the Malondialdehyde (MDA), Nitric Oxide (NO), and monoamine neurotransmitter levels [20]. Moreover, it can reduce the activity and expression of antioxidant defense anti-apoptotic agents and alter apoptotic and inflammation gene expression [21]. This review aims to present the animals and human studies about acute and chronic exposure to TR-induced OS as toxic mechanisms of organ damage.

2. Materials and Methods

Search strategy for the identification of studies

PubMed, Scopus, and Google Scholar electronic bibliographic databases were searched for studies investigating OS and lipid peroxidation mechanisms of action of toxicity by TR. The necessary data were collected from 2000 to 2021 (June 2021). The applied keywords were: “tramadol” AND “oxidative stress“ OR “Reactive oxygen species” OR “lipid peroxidation” OR “organ damage”. After the initial search, related articles were identified. Each article was reviewed to evaluate title and abstract content and eliminate duplicates and those not related to our purposes.

The inclusion criteria of studies

All types of articles, including experimental and observational studies, case reports, reviews, and commentaries addressing the oxidative stress due to TR exposure, were included for this review. The search is restricted to English-language articles.

3. Results

The search yielded a total of 102 articles. Of them, 58 articles that met our inclusion criteria were selected for further review. Finally, 27 articles about experimental studies and one human study on TR-induced OS organ damage were included in this review. Table 1 summarizes the experimental studies evaluating oxidative stress induced by TR administration.

4. Discussion

Neurotoxicity

The brain tissue is liable to oxidant agents due to its high polyunsaturated fatty acid content, increased oxygen demand, and low antioxidants [22]. The neurotoxicity of TR administration on albino rats was investigated at therapeutic (25 mg/kg), double therapeutic (50 mg/kg), and 4 times therapeutic (100 mg/kg) doses for one month. TR causes an increase in brain serotonin, MDA levels, and a substantial decrease in reduced Glutathione (GSH) content, Catalase (CAT), and Superoxide Dismutase (SOD) activities in a dose-related manner. Additionally, the results demonstrated that TR by elevation of 8-hydroxy-2’ -deoxyguanosine (8-OHdG) levels could induce DNA oxidative damage in the rat’s brain [13].

The neurotoxicity effects of TR administration due to oxidative damage were investigated in animal models. Albino rats were exposed to therapeutic doses (42 mg/kg) and progressively increasing doses (42, 84, & 168 mg/kg: abuse dose) of TR for one month. The obtained results indicated that TR in abuse doses inhibited the brain mitochondrial electron transport chain complexes (I, III, and IV) that increased ROS production. However, it could not inhibit succinate dehydrogenase enzyme (complex II) activity [23].

The experimental studies indicated that the chronic TR administration altered neurotransmitter levels and oxidative stress in the brain [20, 24-27]. For example, in an experimental study, chronic tramadol administration (30 or 60 mg/kg via oral gavage; for 8 weeks) revealed a significantly increased lipid peroxidation and NO, and decreased GSH level and antioxidant enzymes activity and expression in the cerebrum. Tramadol administration resulted in increased serum TNF-α and interleukin-6 (IL-6). Furthermore, an increase in monoamine neurotransmitters, 8-OHdG, and gene and protein expression levels of apoptotic markers (e.g. p53 & Bax) in the cerebrum of tramadol-induced rats were observed [20].

Hussein et al. argued that the administration of TR in therapeutic (22.5 mg/kg) and overdoses (30, 60, & 90 mg/kg) levels for 9 weeks in albino rats induced a significant increase of MDA and 8-OHdG levels, DNA fragmentation, and caspase-3 activity. Also, a significant decrease of SOD and CAT activities occurred in the brain tissue in therapeutic and overdose groups [25].

Zhuo et al. documented that chronic TR exposure induced abnormal behavior and body /brain weight loss in zebrafish. The results demonstrated that 30 differential proteins were identified using proteomic analyses. Numerous TR responsive proteins have functions related to oxidative stress, including creatine kinase BB, ubiquitin carboxy-terminal hydrolase L-1, ATP synthase, tubulin, actin, and synaptosome-associated protein. Besides, the ultrastructural changes of mitochondria and cytoskeletal structure with the disruption of oxidative damage, apoptosis, energy metabolism, and signal transduction pathways were determined [26].

Raj et al. suggested that the long-term administration of TR in rats (50 mg/kg, intraperitoneal injection for 28 days) altered oxidative stress markers (including lipid peroxidation, nitrite, GSH, Glutathione Peroxidase (GPx) activity, SOD, CAT, mitochondrial complex I, IV, and cyclic Adenosine Monophosphate (cAMP)), neuroinflammatory markers (TNF-α, IL-1β, and IL-17), and neurotransmitters (dopamine, norepinephrine, serotonin, GABA, and glutamate) in rats brain (striatum) leads to motor deficits [27].

One of the most common neurotoxicity mechanisms following drug abuse is oxidative stress, mitochondrial dysfunction, apoptosis, Endoplasmic Reticulum stress (ER-stress), and the inhibition of neurogenesis. Sarhan et al. demonstrated that TR exposure (40 mg/kg) in male Sprague Dawley rats and thyme extract (500 mg/kg) for 30 days a significant increase in MDA level and decrease of CAT and SOD activity in the frontal motor and cerebellar cortex specimens in TR group. Histologically and ultrastructurally, the examination of glial and neuronal cells has shown marked apoptotic and degenerative changes. Oxidative stress and ER stress-mediated PERK/apoptosis pathway mediated TR neurotoxicity. Further, this study established that thyme extract had protective effects on oxidative status in the rat brain [28].

Ghoneim et al. treated rats with TR (50 mg/kg) for 4 weeks. An increase in MDA level and reduction in the gene expression of SOD, CAT, and GPx were observed in the brain tissue [29].

Oxidative damage and the activation of apoptosis were studied by an acute dose of TR, including analgesic dose (10 mg/Kg), intermediate dose (25 mg/Kg), and the maximum recommended daily dose (50 mg/Kg) in the rat brain tissue. Oxidative damage was not observed in the brain cortex at the low dose. TR at the low dose (10 mg/Kg) has a protective effect by reducing lipid peroxidation in the brain tissue. Protein Carbonylation (PC) decreased in all experimental doses. No change in SOD, CAT, and caspase-3 activity was observed at all tested doses in the brain [30].

Barbosa et al. studied the effect of repeated administration of TR in recommended daily doses (10, 25, and 50 mg/kg) on MDA and PC levels in the rat's brain tissue. After exposure (14 days), an elevation in MDA level was observed at the brain's highest dose (50 mg/kg). A repeated administration of TR in three studied doses could not induce PC in the rat brain [31].

Albrakati evaluated the neuroprotective effect of physical exercise on TR neurotoxicity in rats. Wistar albino rats were treated with TR (40 mg/kg) for 28 days. This study results showed that the administration of TR could induce neurotoxicity by elevation of MDA level and reduction in GPx and GSH content in the brain. Physical exercise could attenuate oxidative damage and promote antioxidant capacity in the rat's brain tissue [32].

Table 1. Experimental studies evaluating tramadol-induced oxidative stress in different organs

Study	Experimental Model	Dose of Tramadol	Route of Administration / Exposure Duration	Protective Substance (Dose)	Tissue(s)	Main Outcomes	Reference No.
Ali et al. (2020)	Rat	25 mg/kg	Orally/ 30 days	-	Brain, Liver, Kidney	↑MDA,↑ 8-OHdG, ↓GSH, ↓SOD, ↓CAT, ALT, ↑AST, ↑TIMP-1, ↑CYP4502E1	13
		50 mg/kg				↑MDA,↑ 8-OHdG, ↓GSH, ↓SOD, ↓CAT	
		100 mg/kg				↑MDA,↑ 8-OHdG, ↓GSH, ↓SOD, ↓CAT	
Mohamed et al. (2015)	Rat	42, 84, and 168 mg/kg	Orally/ 30 days	-	Brain	Inhibit ETC mitochondria, ↑ROS	23
Mohahamad and Mahmoud (2019)	Rat	30 and 60 mg/kg	Orally/ 8 weeks	-	Brain	↑LPO, ↑NO,↑8-OHdG, ↑P53, ↑Bax, ↓GSH	20
Hussein et al. (2017)	Rat	22.5 mg/kg	Orally/ 63 days	-	Brain	↑MDA, ↑NO,↓CAT, ↓SOD,↑8-OHdG, ↑DNA-fragmentation,	25
						↑caspase-3 activity	
		30, 60, and 90 mg/kg				↑MDA, ↑NO,↓CAT,↓SOD, ↑8-OHdG, ↑DNA-fragmentation,↑Caspase-3 activity	
Zhuo et al. (2012)	Zebrafish	25 and 65 mg/kg	IM/ Acute injection	-	Brain	↑Creatine kinase BB, ↑Ubiquitin carboxy-terminal hydrolase L-1, ↑ATP synthase, ↑Tubulin, ↑ Actin, ↑Synaptosome-associated protein	26
Raj et al. (2012)	Rat	50 mg/kg	IP/ 28 days	-		↑LPO, ↑GSH, ↑GPx, ↑TNF, ↑IL-1β, ↑IL-17, ↓CAT, ↓SOD, ↓cAMP activity, ↓Mitochondrial complex activity (I, IV)	27
Sarhan et al. (2018)	Rat	40 mg/Kg	Orally/ 30 days	Thyme extract (500 mg/kg)	Brain	↑MDA, ↓CAT , ↓SOD	28
Ghoneim et al. (2014)	Rat	50 mg/Kg	IP/ 30 days	-	Brain	↑MDA, ↓expression of CAT, SOD, and GPx in brain	29
Faria et al. (2017)	Rat	10 mg/kg	IP/ Acute	-	Brain Lung, Heart	↓LPO, ↓PC ,↓MDA, ±SOD, ±CAT in Brain	30
		25 mg/kg				↓PC, ±SOD, ±CAT, ± Caspase-3 activity in Brain	
		50 mg/kg				↓PC, ±SOD, ±CAT, ± Caspase-3 activity in Brain ↓Caspase -3 activity in the heart ↓PC in the lung and heart	
Barbosa et al. (2021)	Rat	10 mg/kg	IP/ 14 days	-	Brain	±MDA, ±PC	31
		25mg/kg				±MDA, ±PC	
		50 mg/kg				↑MDA, ± PC	
Albrakati (2020)	Rat	40 mg/kg	Orally/ 28 days	-	Brain	↑MDA, ↓GSH and ↓GPx	32
Samadi et al. (2019)	Mice	25 mg/mL	IP/ Until seizure threshold	Caffeine (8 mg/kg)	Brain	↑ROS, ↑MDA, ↑PC, ↓GSH in brain	33

Study	Experimental Model	Dose of Tramadol	Route of Administration / Exposure Duration	Protective Substance (Dose)	Tissue(s)	Main Outcomes	Reference No.
Bameri et al. (2018)	Mice	25 mg/mL	IP/ Until seizure threshold	-	Brain	↑ROS, ↑MDA, ↑ LPO, ↑PC, ↓GSH	21
Baghishani et al (2018)	Rat	50 mg/kg	Orally/ 28 days	Crocin (30 mg/kg)	Brain	↑LPO, ↑Dark neurons, ↑Apoptotic cells	14
Abdel-Zaher et al. (2011)	Mice	50 mg/kg	SC/ Single dose	Nigella sativa oil (4 ml/kg)	Brain	↑NO, ↑MDA, ↑ LPO, ↓GSH, ↓GPx	37
Sadek et al. (2018)	Rat	15 mg/kg	IP/ 15 days	Lycopene (10 mg/kg)	Liver	↑LPO, ↑ MDA, ↓GSH, ↓TAC, ↑DNA fragmentation	38
Owoade et al. (2019)	Rat	10 mg/kg 50 mg/kg 100 mg/kg	Orally/ 28 days	-	Liver, Kidney	↓SOD, ↓CAT in liver and kidney, ↓GSH in liver ↑MDA,↓SOD, ↓CAT,↓GSH in liver and kidney	39
Barbosa et al. (2020)	Rat	10 mg/kg	IP/ 14 days	-	Lung, Kidney, Heart	↑PC in the kidney, ↓TAC in liver ↑MDA in lung and heart ↑MDA in liver and kidney, ↓TAC in liver and ↑TAC in kidney ↑MDA in heart	40
Abdel-Aal et al. (2016)	Rat	100 mg/kg	Orally/ 4 weeks	Camel's milk (20 mL/rat)	Kidney	↑MDA , and ↓GPx in plasma	41
Salah et al. (2020)	Rat	30 mg/kg	Orally/ 30 days	Barley and wheat grasses (30 mg /kg and 250mg/ kg, respectively)	Kidney	↑MDA, ↑NO, ↓GSH, and ↓ CAT in kidney ↑MDA, ↑NO, ↓GPx, and ↓ CAT in serum	42
Shalaby AM et al. (2020)	Rat	Dependent doses	Orally/ 30 days	-	Adrenal cortex	↑MDA,↓GPx,↓SOD	4
Abdelaleem et al. (2017)	Rat	80 mg/Kg	Orally/ 12 weeks	-	Adrenal cortex	↑MDA in adrenal,↓GPx,↓Thioredoxin reductase in blood	44
Ibrahim et al. (2019)	Rat	40 mg/kg	Orally/ 21 days	-	Testis	↑MDA, ↓GSH, ↓SOD, and ↓CAT in testis and blood	49
Ahmed et al. (2014)	Rat	40 mg/kg	SC/ 8 weeks	-	Testis	↑MDA,↑NO,↓GPx,↓SOD,↓CAT	45
Nna et al. (2017)	Rat	20 mg/kg	Orally/ 60 days	-	Testis	↓SOD, ↓GPx, ↓CAT,↓GSH,↑MDA	47
Koohsari et al. (2020)	Rat	50 mg/kg	IP/ 21 days	Melatonin (1,1.5 and 2.5 mg/kg)	Testis	↑MDA, ↑PC,↓GSH, ↑MMP, ↓Bcl-2 expression, ↓Mitochondrial dysfunction ,↓ Succinate dehydrogenase activity	48
Abd et al. (2020)	Rat	40 mg/kg	Orally/ 30 days	Moringa oleifera leaves extract (100 mg/kg)	Testis	↑MDA,↓SOD,and ↓CAT in testis	50

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MDA: Malondialdehyde; LPO: Lipid peroxidation; SOD: Superoxide dismutase; CAT: Catalase; GSH: Gluthatione; GPx: Gluthatione peroxidase; 8-OHdG: 8-Hydroxy-2-deoxyguanosine; ETC: Electron transfer chain; TAC: Total antioxidant capacity; NO: Nitric oxide; PC: Protein carbonyl; MMP: Matrix metalloproteinases; TNF-α: Tumor necrosis factor- alfa; IL: Interleukin; IM: Intramuscular injection; IP: Intraperitoneally injection; SC: Subcutaneous injection

↑: Increase; ↓: Decrease; ±: No effect

The protective effect of caffeine evaluated on neurotoxicity and oxidative stress induced by TR. The mice were exposed to TR (25 mg/mL) to view the seizure threshold. ROS generation significantly increased in the brain mitochondria as an indicator of oxidative stress. An increase of MDA and PC levels and a decrease of GSH content indicated oxidative damage of the brain following TR administration. These findings revealed that caffeine could modulate brain oxidative status following TR consumption [33].

The role of the dopaminergic system on the seizure and oxidative damage induced by TR was investigated by Bameri et al.. Male albino mice were exposed by TR (25 mg/mL) until observation of seizure threshold. Oxidative damage induced by TR injection is evaluated in the brain. The increase of ROS, LPO, PC, and decrease of GSH content was observed in brain tissue. This result showed that as TR substantial side effect, the seizure could increase free radicals level and disrupt oxido-redox status in the brain [21].

Learning and memory impairment

Hippocampus is among the vital areas of the brain because of its role in memory and learning [34, 35]. It is susceptible to oxidative stress due to its high metabolic activity [34, 36]. An animal study indicated that crocin has protective effects on learning and memory disorders caused by oxidative damage induced by TR in rats' hippocampus [14]. In this study, rats were treated with tramadol (50 mg/kg), tramadol, and crocin (30 mg/kg) orally for 28 consecutive days. The results revealed that the crocin improved learning and memory of tramadol-treated animals, decreased apoptotic cells in the hippocampus, and decreased the side effects of tramadol on the nervous system [14].

Tolerance and dependence

TR could induce tolerance and dependence as a result of oxidative stress. Exposure of mice to TR showed a significant increase in MDA level and decrease in GSH content and GPx activity in the brain [37]. In this study, repeated administration of Nigella sativa oil (4 ml/kg, p.o.) and tramadol (50 mg/kg, S.C.) inhibited the development of tramadol tolerance, as measured by the hot plate test and dependence. NO overproduction and increase in brain MDA level induced by repeated administration of tramadol to mice or by administration of naloxone to tramadol-dependent mice were inhibited by co-administration of the oil. Also, concurrent administration of the NO synthase inhibitor, L-N(G)-nitroarginine methyl ester (10 mg/kg) or the antioxidant, N-acetylcysteine (50 mg/kg) enhanced these inhibitory effects of N. Sativa oil. On the other hand, the use of Nigella sativa oil before drug treatment could attenuate oxidative damage induced by TR [37].

Hepatotoxicity and nephrotoxicity

The effect of TR administration on the brain, liver, and kidney was investigated at therapeutic (25 mg/kg), double therapeutic (50 mg/kg), and 4 times therapeutic (100 mg/kg) doses for one month on adult male rats. The results highlighted a substantial increase in the MDA and 8-OHdG levels in the brain, liver, and renal tissues. Moreover, in a dose-dependent pattern, GSH content and activities of antioxidant enzymes such as CAT and SOD were significantly decreased in these organs [13]. Besides, hepatic and renal function parameters including serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), urea, and creatinine were increased in a dose-dependent manner. At the molecular levels, a significant increase in hepatic cytochrome P4502E1, Tissue Inhibitor of Metalloproteinase-1 (TIMP-1), and renal Kidney Injury Molecule-1 (KIM-1) were observed. The results suggested that TR's neurotoxic, hepatotoxic, and nephrotoxic effects are induced by the production of DNA damage and oxidative stress [13].

Sadek et al. investigated TR hepatotoxicity and the ameliorative effect of lycopene on oxidative damage induced by TR in the rat liver. Forty male Wistar albino rats were classified into 4 groups, including control, TR (15 mg/kg), lycopene (10 mg/kg), and TR and lycopene (received mentioned doses) groups. After 15 days of exposure, TR could induce lipid peroxidation and elevated liver MDA level. Moreover, GSH content and Total Antioxidant Capacity (TAC) were decreased after TR treatment. In addition, the activity and gene expression of antioxidant enzymes such as CAT, SOD, and GST decreased. DNA fragmentation was observed in TR treated group. The results indicated that lycopene had a protective effect and could prevent TR hepatotoxicity [38].

Liver and renal toxicity have been reported in TR treated (10 mg/kg, 50 mg/kg, and 100 mg/kg for 28 days) in male Wistar albino rats [39]. In rats treated with TR (50 and 100 mg/kg) for 28 days, MDA levels increased in liver and renal tissues. All TR doses could decrease SOD and CAT activity. The low dose of TR (10 mg/kg) reduced GSH content in the rat liver. In the 50 and 100 mg/kg doses, GSH decreased in the organs. This study showed that TR consumption could increase MDA lev-

els and decrease antioxidant content in hepatic and renal tissues in a dose-dependent manner [39].

The effect of TR repeated therapeutic doses on liver and kidney oxidative damage was studied by Barbosa et al.. Male Wistar rats were received 10, 25, and 50 mg/kg of TR (low analgesic, intermediate, and the maximum recommended daily doses, respectively) for 14 days. MDA as a biomarker of LPO increased only at 50 mg/kg dose of TR in the liver and kidney tissues. TR only at the lowest dose (10 mg/kg) increased PC groups in the kidney tissue and could not increase liver protein carbonylation. Furthermore, TR at all experimental doses could decrease the TAC in the liver. But at the highest dose (50 mg/kg), increased TAC in kidney tissue; thus, TR may differently affect the antioxidant status of the liver and kidney [40].

The ameliorative effect of camel's milk on TR nephrotoxicity was investigated. Rats were received TR (100 mg/kg) and TR plus Camel's milk (100 mg/kg & 20 mL/rat) for 4 weeks. TR treated rats reflected signs of nephrotoxicity by increasing MDA level and decreasing GPx activity in plasma. Treatment with camel's milk led to progress in kidney function by a significant reduction in MDA level and increase in GPx concentration [41].

Salah et al. designed a study to evaluate the protective effects of barley and wheat grasses against TR nephrotoxicity. In this study, male albino rats received TR (30 mg/kg, 1/10 of LD_{50}), TR and barley grass (30 mg/kg and 250 mg/kg), TR/ barley grass (30 mg/kg and 500 mg/kg), TR/ wheatgrass (30 mg/kg and 250 mg/ kg), and TR/ wheatgrass (30 mg/kg and 500 mg/kg) for 30 days. After exposure time, analysis of kidney samples after exposure time demonstrated that NO and MDA levels increased and GSH content and CAT activity decreased in the TR treated group. An increase of NO and MDA levels and a decrease of GPx and CAT activity were also observed in serum samples. Administration of barley grass and wheatgrass at 500 mg/kg could significantly decrease NO, MDA levels and increase CAT activity and GSH content in kidney tissues [42].

In a human study, 60 patients that received TR analgesia (in 3.9±1.2 years) for treating chronic pain and osteoarthritis in the permissible daily dose range (200-400 mg/d) were evaluated for hepatotoxicity. The results suggested that long-term use of TR in the patients with CYP2D6 gene polymorphism (CYP2D6*DUP and CYP2D6*1) causes LPO, depletion of antioxidant stores, and cell damage in the liver tissue due to the high concentration of TR metabolites. On the other hand, LPO could damage hepatocytes and promote the activities of CYP 450 enzymes [43].

The lung and heart toxicity

Oxidative damage and the activation of apoptosis due to TR administration were studied in rat lung and heart tissues. Wistar rats were treated to a single dose of TR as an analgesic dose (10 mg/Kg), intermediate dose (25 mg/Kg), and the maximum recommended daily dose (50 mg/Kg). Low, intermediate, and high doses revealed no change in MDA levels in rat lung and heart tissues. However, a high dose of TR (50 mg/Kg) significantly increased PC groups in these organs. The activity of SOD and CAT enzymes presented no change in these doses. TR at a low dose has a protective effect. The activity of caspase-3 in the heart tissue decreased at all doses, and no change in lung tissue [30].

The effect of repeated TR administration in recommended clinical daily doses (10, 25, & 50 mg/kg) for 14 days on oxidative status in the rat's lung and heart tissues was investigated [31]. In the rats treated with 25 and 50 mg/kg TR, an increase of MDA level was observed in the lung tissue. All studied doses could induce LPO in the heart organ. Therefore, the heart is more sensitive to low doses of TR. All doses could not induce protein carbonylation in lung and heart tissues [31].

Adrenal toxicity

A previous study demonstrated that the long-term use of tramadol could induce endocrinopathy [4]. The effect of TR dependency and its withdrawal was investigated on the adrenal cortex. Three experimental groups included the control group, the TR dependent group (received increasing oral TR recommended doses for 30 days), and the recovery group (received therapeutic doses of TR for 1 month followed by a one-month withdrawal period). The results indicated a significant increase in MDA level and decrease in GPx and SOD activity were observed in the adrenal gland of TR treated group. However, the decrease in MDA level and the improvement of antioxidant enzymes functions were reported in the withdrawal group [4].

In another experimental study, the effect of chronic TR consumption on the induction of OS in the rat adrenal gland has been evaluated. Wistar albino rats were exposed to 80 mg/kg TR for 12 weeks. Chronic administration of TR resulted in a significant increase in the adrenal MDA level. Furthermore, a decrease in blood levels of GPx and thioredoxin reductase and a reduction

in the genetic expression of these antioxidant enzymes were observed in the TR-treated group. TR withdrawal decreased and increased the adrenal gland's MDA level and antioxidant capacity, respectively [44].

Testicular and reproductive toxicity

TR-induced oxidative stress's possible role on reproductive system performance was evaluated in rats [45]. TR (40 mg/kg) was administered for 8 weeks. The progress of OS and the increase of MDA, NO, and the decrease of SOD, CAT, and GPx enzymes activity impairs testicular functions [45]. Moreovero, the overproduction of ROS and LPO could be detrimental to spermatogenesis and sperm motility due to its polyunsaturated fatty acids membrane and lack of its cytoplasm to generate a primary preventive and repair mechanism against oxidative stress [46].

The long-term (60 days) use of TR (20 mg/kg) could induce the increase of testicular MDA level and decrease of GSH content, SOD, CAT, and GPx activity in the rat testis [47].

Testicular toxicity of TR (50 mg/kg, 21 days) and protective effects of Melatonin (MT) were evaluated in the rat [47]. The study indicated that reproductive toxicity was due to lipid peroxidation and proteins oxidation (an increase of PC) and a decrease of GSH content in testis tissue. Besides, testis mitochondrial dysfunction was diagnosed by inhibiting succinate dehydrogenase activity (complex II), MMP collapse, and mitochondrial swelling. An increase in apoptosis gene expression and abnormal sperm count, morphology, and motility was observed in testis tissue [48].

Possible effects of TR addiction and withdrawal on rat's testicles tissues and spermatogenesis were investigated by evaluating oxidative stress genes biomarkers [49]. Adult male Wistar albino rats received TR (40 mg/kg) for 3 weeks. The results showed an increase in MDA levels and a remarkable decrease in GSH content, SOD and CAT activities were observed in the rat testis tissue and blood [49].

The rat testicular tissue investigated the protective effects of Moringa oleifera Leaves Extract (MLE) on TR-induced oxidative damage. Male albino rats were separated into four groups and received TR (40 mg/Kg), MLE (100 mg/kg), and TR and MLE (mentioned doses) for 30 days. The results indicated that MDA level increased and SOD and CAT activity decreased in testes of the TR treated group. Moreover, MLE could reduce TR testicular oxidative damage [50].

The antioxidant effects of tramadol on ischemia-reperfusion injury

There are scant experimental studies that show the antioxidant and anti-inflamatory effects of TR in experimental ischemia-reperfusion models [51, 52]. TR has been revealed to decrease ischemia-reperfusion injuries in some tissues, such as myocardial, skeletal, hepatic, or brain tissues. In an experimental study, possible antioxidant effects of TR were examined in the ischemic stage via MDA level, SOD, and GPx activity in the myocardial tissue. TR generated antioxidant effects by inhibiting proxy radicals, increasing SOD and GPx activity, and decreasing MDA content in the rat heart tissue [51].

TR treatment has alleviated the metabolic injuries in the rat hind limb skeletal muscle ischemia and reperfusion in an experimental model. TR (20 mg/kg) was administered intravenously immediately before reperfusion. Ischemia was induced in anesthetized rats by left femoral artery clipping for 2 h followed by 24 h of reperfusion. Serum and tissue MDA levels in ischemia-reperfusion rats were significantly increased. The muscle tissue GSH, SOD, and CAT levels in the Ischemia-reperfusion group were significantly lower than the control group [52].

TR suggested a hepatoprotective effect against hepatic Ischemic-reperfusion injury in an experimental model. TR was administered 30 minutes before ischemia in rats. TR attenuated hepatic injury induced by Ischemia-reperfusion by reducing transaminases, structural changes, and apoptotic cell death, decreasing the level of inflammatory markers such as TNF-α, TNF-α/IL-10 ratio, and nuclear factor-κB gene expression. It also increased IL-10 levels in hepatic tissues. TR reduced oxidative stress parameters except for SOD activity [52].

5. Conclusion

This review provides a significant body of experimental evidence that oxidative stress is a toxic mechanism of TR-induced organ injury in acute and chronic administration. The increase of MDA and PC levels and decrease of the GSH content, GPx, SOD, and CAT activity in different organs and the protective effects of antioxidants against TR-induced organ damage are sufficient to confirm the involvement of OS in TR-induced toxicity. Although many experimental studies concerning the evaluation of oxidative stress on TR-induced tissue damage were observed, the number of controlled human

studies is limited. However, scant data about low concentrations of TR have a protective effect on oxidative stress biomarkers in ischemic-reperfusion experimental models.

Therefore, proving the oxidative stress alteration in TR-induced toxicity and the effects of antioxidants in the prevention and treatment of toxic organ effects in humans remains to be elucidated by performing many human studies with suitable sample sizes. Finally, antioxidant therapy with vitamin C and E may be considered an additional therapeutic modality in tramadol poisoning.

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

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Author's contributions

Conceptualization, data collection, investigation and writing original draft: Leila Mohammadnejad; Writing, review and editing and supervision: Kambiz Soltaninejad.

Conflict of interest

The authors declared no conflict of interest.

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