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Tramadol toxicity phytotherapy: The protective role of medicinal plants against tramadol toxicity

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ABSTRACT

The side effects of chronic exposure to synthetic drugs such as tramadol have become a concern for the health system. Medicinal plants can be used as rich sources of natural compounds with therapeutic properties to reduce the side effects of synthetic drugs such as tramadol. Hence, this study sought to review the published research concerning the protective role of medicinal plants against tramadol toxicity. This systematic review was conducted according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement. This study included all published articles evaluating the efficacy of the medicinal plants against tramadol toxicity until December, 2021. For this systematic review, search was performed using keywords including tramadol, toxicity, poisoning, overdose, medicinal plants, and herbal medicines from reliable databases such as PubMed, Google Scholar, Web of Science, Wiley, Elsevier, and Science Direct. The risk of bias tool for animal intervention studies (SYRCLE's RoB tool) criteria and the OECD guidelines and the WHO Good Laboratory Practice (GLP) handbook were used for quality assessment of animal and *in vitro* studies, respectively. This review determined 18 medicinal plants and one multi herbal formulation against tramadol toxicity. Plants such as *Nigella sativa* (Black Seed), *Moringa Oleifera* (Drumstick tree), and Aloe Vera, pomegranate, wheat, barely, pumpkin, walnut, kiwi fruit, turmeric, apple, fennel, and garlic also displayed therapeutic effects against tramadol toxicity. This review exhibits a wide range of medicinal plants with therapeutic effects such as antioxidant, anti-inflammatory and anti-apoptotic properties which could protect the organs of the body against toxicity caused by tramadol. Hence, the use of these plants or their compounds can be effective in reducing the complications caused by many diseases.

Keywords: Herbal Medicines, Medicinal Plants, Natural Compounds, Phytotherapy, Toxicity, Tramadol.
Article type: Review Article.

INTRODUCTION

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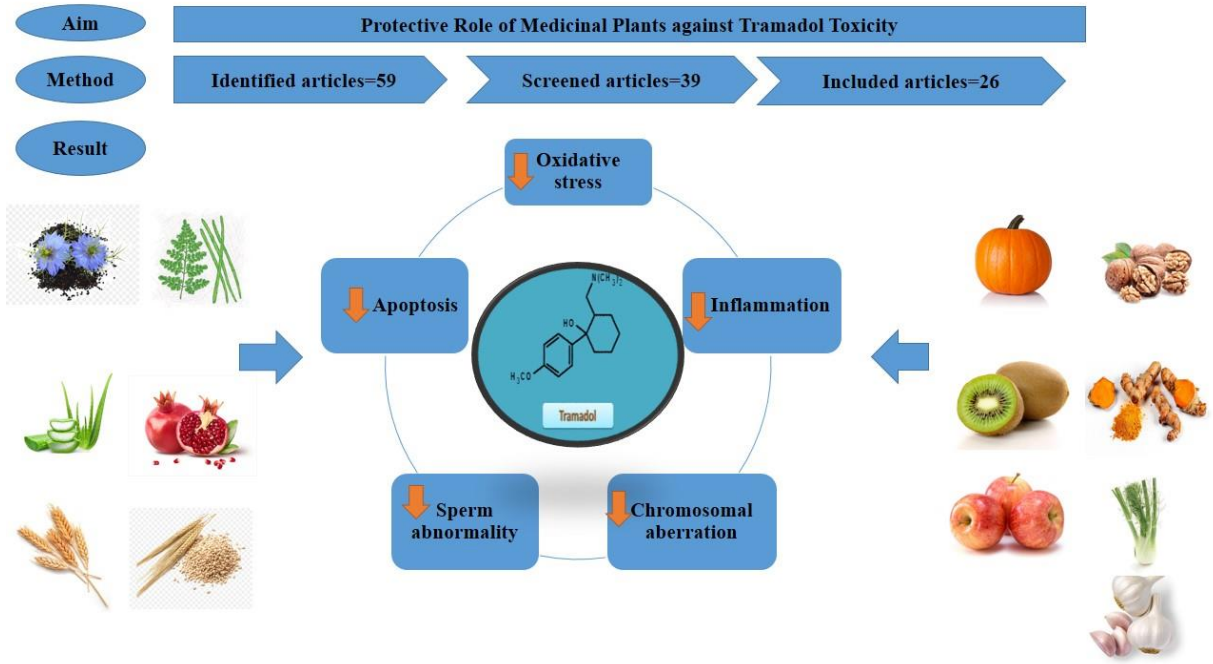
Graphical abstract



Tramadol is known as an opioid analgesic that is prescribed to relieve moderate to severe pain. Tramadol is one of the most widely used painkillers prescribed worldwide which was developed in the 1970s (Madukwe & Klein 2019). It is a 4-phenylpiperidine codeine analogue which acts through the μ-opioid receptors (MOR), the noradrenergic, serotonergic and gamma-aminobutyric acid-ergic (GABAergic) systems (Grond & Sablotzki 2004; Fig. 1).

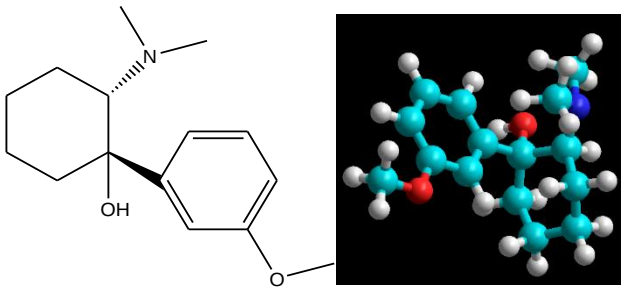


Fig-1. Tramadol structure.

Tramadol affects the noradrenergic system by inhibiting the reuptake of norepinephrine in the central nervous system (CNS) and by inhibiting the reabsorption of serotonin. It also upraises the level of serotonin in the CNS. Tramadol could also affect the GABAergic system via increasing the level of GABA in the brain (Nakhaee *et al*. 2021) and also exhibited a hepatic metabolism by cytochrome P450 pathway. It has been revealed that 85% of the oral dose of this drug is metabolized in the liver. Approximately 90% of the oral dose is excreted by the kidneys (Kaye 2015). some investigators have been reported that tramadol exhibits many side effects, the most common are vertigo, nausea, seizure, hypoglycemia, depression, xerostomia and sweating with a frequency of 2.5 to 6.5% (Vazzana *et al*. 2015). Tramadol is considered as the first cause of death due to drug poisoning among narcotics. In recent years, tramadol poisoning has increased significantly in the world (Rostam-Abadi *et al*. 2020). Tramadol poisoning can lead to acute kidney failure. Kidney dysfunction severely affects the excretion of tramadol and metabolism and also causes severe side effects. It is also observed that nephrotoxicity is possible not only in the overdose of tramadol, but also even in its therapeutic dose (Mike *et al*. 2021). Various organs of the body, including the kidneys, liver, heart, lungs, brain,

testes and muscles are damaged by tramadol intoxication (Nakhaee *et al*. 2021). The toxicity of synthetic drugs such as tramadol has become a serious challenge in the process of drug treatment of diseases (Subedi *et al*. 2019). Previous observations has suggested various strategies to reduce the toxic effects of synthetic drugs. Medicinal plants and their active compounds have long been considered for the treatment of various diseases (Sedighi *et al*. 2019). Recently, some investigators have suggested using medicinal plants in the treatment of diseases due to their low side effects, inexpensiveness and availability (Amirzargar *et al*. 2020). Hence, this study sought to review the published studies concerning the protective role of medicinal plants against tramadol toxicity.

METHODS

To guarantee the consideration of significant data, the present study was carried out according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA).

Study Design

This systematic review considered all studies conducted on the protective role of medicinal plants against tramadol toxicity. Subjects of study were animals (rats and mouse), and cell lines. Interventions were included medicinal plants as whole or their parts: leaf, root, seed and flower. Medicinal plants were used regardless of their preparation (extracts, essential oil and powders). The records were not restricted on concentration, dosage form, dose, duration or frequency of administration. The essential outcomes were considered as effectiveness of medicinal plants (at safe concentrations) on tramadol toxicity.

Eligibility criteria

Inclusion criteria: Published *in vivo* or *in vitro* studies in English until December, 2021, that represented effectiveness of medicinal plants against tramadol toxicity.

Exclusion criteria: Reviews.

Information sources, searching and selection of studies

Electronic databases such as Scopus, PubMed/Medline and Google Scholar were searched for collection of the information. All available articles containing descriptors in English until December, 2021 were chosen. The lexical terms of each database were used for creation of structured search strategies to target the "title" and "abstract" fields. Search terms including tramadol, toxicity, poisoning, overdose, medicinal plants, herbal medicines and other related words or phrases were used. After searching the electronic database, all records were transferred to EndNote reference management software. Then, skimming of the titles and abstracts was performed by two authors according to the criteria for screening of the articles. To check the inclusion criteria, the full text of articles were read.

Data extraction

To extract data, a researcher-made form was used by two authors. The below required data were extracted as follows: scientific and local names of the plants, family name, plant adjuncts, types of plant preparations, dose of treatment, dose of tramadol, type of study (*in vivo* and *in vitro*), type of participants (rat, mouse, cell line), number of animals, study duration, time of administration, dose/kg and therapeutic effect.

Outcomes measured

The key outcomes were the treated participants with the medicinal plants. The response was defined as the hepato-protective, nephron-protective, cardio-protective and fertility protective effects of the medicinal plants on tramadol toxicity. For the *in vitro* studies, the primary outcomes was cyto-protective effect of the medicinal plants.

Assessment of risk of bias

The risk of bias was evaluated independently by two investigators for each included study. The critical appraisal process for studies involving lab animals was conducted using the Risk of Bias tool for animal intervention articles (SYRCLE's RoB tool) and Animal Research: Reporting of *in vivo* Experiments (ARRIVE) guidelines to assess the internal correctness of the studies. A low risk of bias was determined by a "yes" decision; a high risk of bias was

indicated by a "no" decision and "unclear" decision showed inadequate details to estimate the risk of bias properly. The Cochrane Risk of Bias Tool containing five domains of bias (selection, performance, attrition, reporting, and others) was used by reviewers to judge the risk of bias for separate elements. Then, reviewers included and excluded the studies. Afterward, the risk of bias criteria was classified as 'low', 'high' or 'unclear'. Finally, studies with a low and moderate risk of bias were included and studies with a high risk of bias was excluded.

Data synthesis

The *In vitro* and *In vivo* studies were used for data synthesis. Heterogeneity was assessed descriptively from the narrative synthesized data, and potential reasons for heterogeneity were found by examining individual study and subgroup characteristics. Interventional, methodological and statistical heterogeneity existed between the studies. So, statistical pooling of studies and meta-analysis could not be performed. Instead, a narrative (qualitative) summary of the studies was performed using textual descriptions of studies, grouping, and tabulation. Then, a description of the characteristics of the studies compared the effect of each plant extract relative to controls, the main parameters measured/analyzed, quality of included studies and the risk of bias of all studies were described. This has also been described in our systematic review protocol.

Quality Assessment

The Critical Appraisal Skills Programme (CASP) was used for evaluation of the quality of studies. First, the objectives of articles were identified. Then, appropriate objectives were included in the CASP checklist. In the next step, articles were divided into three levels according to their quality (low, medium and high quality). Articles that scored 4, 4-7, and above 7 were defined as low, medium and high quality articles, respectively. Articles with a score above 7 were included in the study. Fig. 1 shows the flowchart of the selecting articles process for Systematic Reviews and Meta-analyses (PRISMA; Fig. 2).

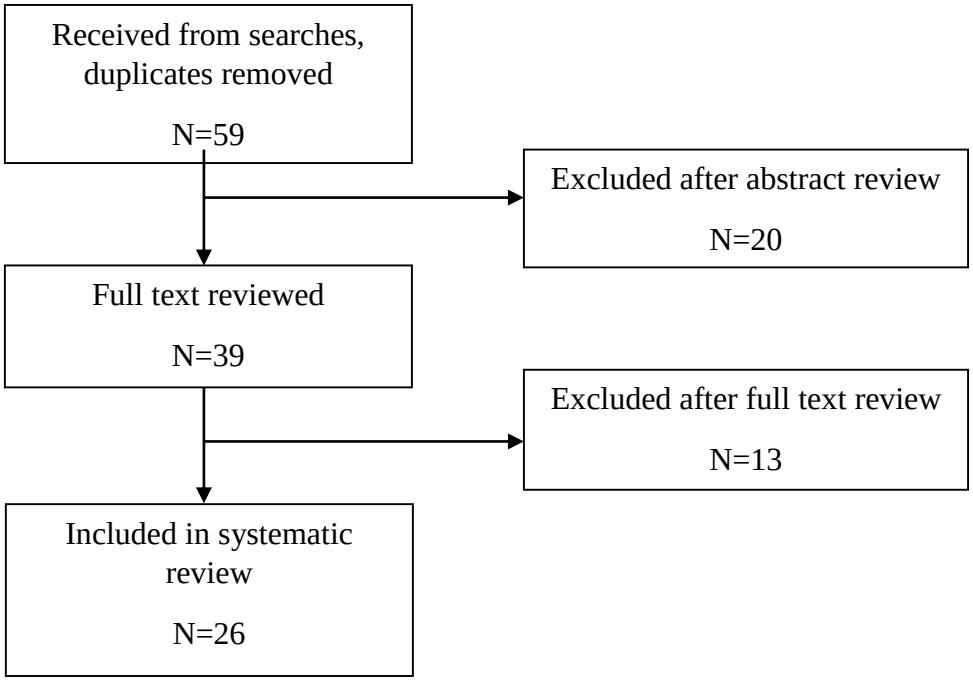


Fig-2. Flowchart of the process of articles investigation and selection based on Systematic Reviews and Meta-analyses (PRISMA) method.

RESULTS

Literature search results and description of study characteristics

A total of 75 relevant articles were independently achieved by two reviewers from electronic databases. Of these, 11 were obtained from PubMed/Medline, 14 from Scopus and 50 from Google Scholar. After reviewing relevant titles and abstracts, the duplicates were removed. The full text of 59 articles were reviewed. After a detailed review of each article, 33 articles were excluded and 26 articles were retrieved.

Excluded studies

The eligibility of 33 studies were not confirmed and excluded because of incomplete information.

Included studies

Twenty-six studies met the criteria for inclusion and followed internationally accepted guidelines. The results of this review identified 18 useful medicinal plants and one multi herbal formulation against tramadol toxicity. Based on the Table 1, plants such as *Nigella sativa* (Black Seed), *Moringa Oleifera* (Drumstick Tree), and *Aloe Vera* were reported as the most important medicinal plants against tramadol toxicity. In addition, plants known as foods including pomegranate, wheat, barely, pumpkin, walnut, kiwi fruit, turmeric, apple, fennel, and garlic also exhibited therapeutic effects against tramadol toxicity. As shown in Table 1, the seeds with approximately 43% were the most widely used organs of the aforementioned plants. Moreover, the oil with approximately 21% were the most widely used forms of these medicinal plants. Hepato-protective, nephron-protective, and reproductive protection were also most important therapeutic effects of these medicinal plants. The further information about these medicinal plants and their effects are shown in Table 1.

DISCUSSION

Despite the widespread prescription of tramadol to relieve various pains, its inappropriate use and numerous side effects have become a major concern for investigators (Kaye 2015). Acute and even chronic exposure to tramadol carries risks for different organs of the body (Nakhaee *et al*. 2021). The CNS is known as the site of action of tramadol. The liver and kidneys are also known to be the major organs in the metabolism and excretion of tramadol, respectively. Therefore, the above organs are most damaged by the toxicity of tramadol (Elkhateeb *et al*. 2015). Investigators have shown that tramadol could induce damage caused by oxidative stress, inflammation, and apoptosis in CNS, liver, kidney and reproductive system. Some reports have revealed the provoking role of tramadol in the production of reactive oxygen species (ROS; Jiang *et al*. 2021). ROS are a type of free radical that causes a condition called oxidative stress. Under this condition, the balance between the production of free radicals and antioxidants in the body is disturbed and causes the production of excess free radicals (Turrens 2003). Limited antioxidant defenses against free radicals and subsequently oxidative stress lead to development of damage to cells via increasing lipid peroxidation and ultimately membranes injuries, modification of proteins and DNA damage (Droge 2002). It has been found that oxidative stress caused by tramadol plays a role in induction of mitochondria dysfunction. Overproduction of ROS due to administration of tramadol involves in provoking mitochondrial dysfunction and finally induces mitochondrial injury through damage to mitochondrial complex II and mitochondrial membrane including disrupted membrane pores, membrane collapse and mitochondria swelling (Mohammadnejad *et al*. 2021). On the other hand, the damaged mitochondria could produce ROS and induce oxidative stress. Finally, the production of free radicals and damage to mitochondria can cause direct damage to DNA and subsequently induce apoptosis (Mousavi *et al*. 2021). Hence, using strategies to reduce the toxic effects of drugs such as tramadol on the organs of the body can be helpful. Using synthetic drugs to treat diseases has become a regular practice in the health system. However, side effects, the unavailability of chemical drugs to all members of the community, and drug interactions have raised concerns (Solati *et al*. 2021). Hence, some investigators are looking for natural alternatives such as medicinal plants due to their availability, inexpensiveness and low side effects (Farzan *et al*. 2019). Medicinal plants have a long history in the treatment of diseases and various poisonings (Abbaszadeh *et al*. 2019). The presence of effective active ingredients compounds with therapeutic effects in medicinal plants has led to the growing tendency to use these plants (Taheri *et al.* 2019).

Table 1. Effective medicinal plants on tramadol toxicity.

Plant	Family Name	Part of Plant	Preparation	Dose of Treatment	Dose of Tramadol	Participant	Tissue	Therapeutic Effect	Results	Ref
Nigella sativa Linn	Ranunculaceae	Seed	Oil	1 ml/kg in 1 ml corn oil/day, orally for 30 days	30 mg/kg/day, orally for 30 days	Adult male albino rats	Kidney and liver	Hepatoprotective and nephroprotective	NsL oil treated group exhibited a significant reduction in the serum levels of liver function tests including ALT, AST, GGT, total bilirubin, urea, creatinine and kidney and liver levels of oxidative stress markers including MDA and a significant increase in GPx kidney and liver level in comparison with tramadol-treated group ($p < 0.001$). Moreover, NsL oil treated group showed recovered structure of liver and kidney and reduced collagen fibers.	(Elkhateeb *et al*. 2015)
Punica granatum L.	Punicaceae	Seed	Ethanolic extract	40 mg/kg orally for 3 weeks	20, 40, and 80 mg/kg orally for 3 weeks	adult and adolescent male Wistar rats	testes	Testicular protection	Pomegranate Seed Extract revealed ameliorating effect against hemorrhage, vacuolization, apoptosis and chromatin degeneration and malformation of sperms. Moreover, pomegranate seed extract protect the sperms through reversing elevation in collagen fibers and disruption of S phase of the cell cycle.	(Minisy *et al*. 2020)
Costus Speciosus	Costaceae	Rhizome	Methanolic Extract	200 mg/kg per day orally for 4 weeks	40 mg/kg orally for 4 weeks	male albino mice	Bone marrow	Cyto-protective	*Costus speciosus* Rhizome Extract decreased structural and numerical chromosomal aberrations. It also reduced MDA and improved antioxidant markers including SOD, CAT and GSH levels significantly.	(Daabo 2020)
Nigella sativa	Ranunculaceae	Seed	Oil	2, 4, and 8 ml/kg for 15 days orally, 30 min before each	50 mg/kg subcutaneously (s.c.) for 7 and 15 days,	Male adult Swiss–Webster mice	Blood and brain	Neuroprotective	N. sativa oil (4 mL/kg) prevented the tolerance to tramadol and its withdrawal manifestations. Moreover, N. sativa oil (4 ml/kg) decreased brain MDA levels and elevated brain GSH level and GSH-Px activity significantly.	(Abd el-Zaher *et al*. 2011)

				tramadol injection						
Morinda lucida	Rubiaceae	Root	Ethanolic extract	500, 1000 and 1500) mg/kg b. wt for 10 days	20 mg/kg b. wt daily subcutaneous for 42 days	Adult male and female albino rats	Ovaries and Uterus Testes and Epididymis	Fertility protection	*Morinda lucida* showed prophylactic effect against tramadol-induced reproduction damage through improved histopathological changes of male and female reproductive system.	(Amadi *et al.* 2021)
Triticum aestivum (Wheat grass)	Poaceae	grass	Powder (suspended in distilled water before taken orally)	250 and 500 mg/kg body weight orally for 30 days	30mg/kg/ day orally for 30 days	Adult male albino Sprague Dawley rats	Liver Serum	Hepatoprotective	Wheat grass (especially 500mg/kg) reduced the serum levels of ALT, AST, ALP, and bilirubin significantly. This powder also improved the serum levels of albumin and globulin. The serum and liver levels of MDA and NO decreased significantly and the serum and liver levels of CAT and GSH elevated significantly.	(Abd EL-Maoula 2019)
							Kidney Serum	Nephroprotective	Administration of 500 mg/kg of Wheat grass involved in remarkable significant reduction in serum creatinine, urea nitrogen and uric acid. Wheat grass also increased the serum levels of albumin and globulin. Moreover, serum and kidney levels of MDA and NO decreased and serum and kidney levels of CAT, Gpx and GSH increased significantly after treatment with Wheat grass.	(Eldamaty 2020)
							Heart Serum	Cardiovascular protection	Treatment with Wheat grass (especially 500mg/kg) depressed the serum levels of total cholesterol and TG, LDL, VLDL significantly and increased HDL significantly. This powder could decrease the serum and heart levels of MDA and NO and increase CAT and Gpx significantly.	(Ali Mohammed Ali 2021)

Hordeum vulgare L. (Barley grass)	Poaceae grass	Powder (suspended in distilled water before taken orally)	250 and 500 mg/kg body weight orally for 30 days	30mg/kg/ dayorally for 30 days	adult male albino Sprague Dawley rats	Liver serum	Hepatoprotective	Barley grass (especially 500mg/kg) could reduce the levels of ALT, AST, ALP, and bilirubin significantly. It also improved the serum levels of albumin and globulin. The serum and liver levels of MDA and NO decreased significantly compared to tramadol treated group and the serum and liver levels of CAT and GSH elevated significantly.	(Abd EL-Maoula 2019)
						Kidney Serum	Nephroprotective	The use of 500 mg/kg of Barley grass involved in remarkable significant reduction in serum creatinine, urea nitrogen and uric acid. Barley grass also elevated the serum levels of albumin and globulin. Moreover, serum and kidney levels of MDA and NO decreased and serum and kidney levels of CAT, Gpx and GSH increased significantly after treatment with Barley grass.	(Eldamaty 2020)
						Heart Serum	Cardiovascular protection	Barely grass (especially 500mg/kg) treatment depressed the serum levels of total cholesterol and TG, LDL, VLDL significantly and increased HDL significantly. This powder could decrease the serum and heart levels of MDA and NO and increase CAT and Gpx significantly.	(Ali Mohammed Ali 2021)
Epimedium brevicornum	Berberidaceae -	Extract	0.81 g/kg/day and 2.43 g/kg/day for 65 days orally	50 mg/kg/day for 65 and 130 days orally	Adult male Wistar rats	testis and epididymis serum	Testicular protection	Significant increase in sperm count, sperm motility, Tes, FSH, LH, and E2 hormones and the level of SOD and significant decrease in sperm abnormality, MDA and NO levels was observed after *E. brevicornum* extract treatment. Moreover, a significant reduction and elevation was seen in the gene expression of BAX and Bcl2 respectively. *E. brevicornum* extract treatment caused improvement in seminiferous tubules morphology and preventing necrosis of spermatogenic cells and Sertoli cells and seminiferous tubules.	(Abdelaziz *et al.* 2020)
Lagenaria siceraria	Cucurbitaceae -	Special preparation	0.5 mg/b.wt for 40	subcutaneous injection 125 µg/100 g	adult male Swiss albino mice	Kidney Liver Ileum	Nephroprotective Hepatoprotective	Treatment with *Lagenaria siceraria* could elevate nuclear volume, DNA, RNA, protein and polysaccharides content of epithelial cells in the kidney, liver and ileum. On the other hand, collagen content,	(Aref *et al.*

				days orally	b.wt) for 20 and 40 days			Ileum protection	necrosis and infiltration of immune cells decreased after treatment with *L. siceraria*.	2021)
***Cucurbita pepo* (Pumpkin)**	Cucurbitaceae	Seed	Ethanolic extract	oral dose of 40, mg/kg body for 21 days	oral dose of 20, 40, or 80 mg/kg body for 21 days	adolescent and adult male Wistar rats	testes	Testicular protection	Pumpkin Seed extract could reverse damage to testes caused by tramadol including severe structural changes in germ cells, apoptosis, atrophic changes, hemorrhage, vacuolization, cell loss, and disorganization to normal status.	(Minisy *et al*. 2017)
Juglans regia	Juglandaceae	seed	Essential oil	2.5, 5, 10, 20, 40, 80 and 160 µg for 48 h	1 mM for 48h	PC12, rat neuron-like cell line	Cell	Anti-apoptosis (cell death)	*J. regia* essential oil caused elevation in cell viability and proliferation and reduced cell cytotoxicity and death. It also mitigated production of NO, IL-1β, IL-6, INFγ, and TNFα, disrupted mitochondrial membrane, fragmentation of DNA and caspase-3 activity.	(Elyasi *et al*. 2020)
***Silybum marianum* (Silymarin or milk thistle)**	Asteraceae	Seed	extract	100 mg /kg BW/day foe 4 weeks	40 mg/Kg BW/day orally for 4 weeks	male albino rats	Liver Serum	Hepatoprotective	Silymarin treatment could reduce the serum level of GPT, GOT, ALP and GGT and increase albumin, globulin and total protein compared to tramadol treated group. It was also observed that the liver level of MDA decreased significantly after silymarin treatment. Moreover, the liver levels of CAT and SOD, GSH (not significantly) increased significantly. Silymarin treatment also improved liver structure and decreased cell infiltration and vacuolization. Positive reactions for Proliferating cell nuclear antigen (PCNA) was also seen in silymarin treated group.	(Khalaf 2017)
***Actinidia deliciosa* (Kiwi fruit)**	Actinidiaceae	Fruit	Hemogenate	4ml / rat by using a stomach tube	25mg/kg body weight dissolved in 0.4 ml distilled water by a	ale albino rats of Sprague Dawley	Liver Serum	Hepatoprotective	It deems that Kiwi fruit induced weight gain and elevated serum HDL, albumin and total protein and depressed total cholesterol and TG, LDL, VLDL, AST, ALT, ALP, GGT and total bilirubin significantly. Kiwi fruit also decreased TNF-α, AchE, total oxidative capacity and increased SOD and total antioxidant capacity significantly.	(Elbadrawy & Elkewaw y

					stomach tube					2019)
***Curcuma longa* L. (Turmeric)**	Zingiberaceae	Rhizome	Aqueous extract	200mg/kg b.w. using a stomach tube	25mg/kg body weight issolved in 0.4 mL distilled water by a stomach tube	Male albino rats of Sprague Dawley	Liver Serum	Hepatoprotective	Turmeric caused weight gain and increase in serum HDL, albumin and total protein and depressed total cholesterol and TG, LDL, VLDL, AST, ALT, ALP, GGT and total bilirubin significantly. Turmeric treatment also led to reduction in serum levels of TNF-α, AchE, total oxidative capacity and increased SOD and total antioxidant capacity significantly.	(Elbadrawy & Elkewawy 2019)
Nigella sativa	Ranunculaceae	Seed	oil	4ml/kg/day, 30 min before each tramadol injection for 30 days orally by means of a stomach tube	intraperitoneal injections 20, 40, 80 mg/kg/day for 30 days	Male albino rats	brain	Neuroprotective (Anti-apoptosis (cell death))	It understood that Black seed oil could protect the motor area of cerebral cortex via maintenance of appearance of multiple pyramidal and granular cells and decreasing the number of p53-positive cells significantly.	(Omar & El-Hawwary 2014)
Nigella Sativa	Ranunculaceae	Seed	oil	4 l/kg/day, 30 min before each tramadol	intraperitoneal injections 20 g/kg/day in the first	Male albino rats	Liver Serum	Hepatoprotective	It concluded that NSO administration could protect hepatic histo-architecture and ultrastructure via decreasing hemorrhage, necrosis, apoptotic, and vacuolization of hepatocytes and infiltration of immune cells. Moreover, a significant reduction was observed in the number of anti-CD68 positive cells and the serum levels of AST, ALT, ALP and bilirubin.	(Omar & Mohammed

				injection for 30 days orally by means of a stomach tube	10 days, 40 mg/kg/day in the second 10 days, and 80 g/kg/day in the last 10 days					2017)
Moringa Oleifera	Moringaceae	Leaves	water and chloroform extract	daily oral dose of *M. oleifera* leaves extract, (20 mg/kg/bw) for three weeks	daily intraperitoneal injection of (0.3 mg/kg/bw), for three weeks	adult albino mice	Kidney Serum	Nephroprotective	There were a significant reduction in the serum levels of urea and creatinine in *M. oleifera* treated group compared to tramadol treated group. It also was observed that the structure of kidney in *M. oleifera* treated group was similar to normal status in control group. *M. oleifera* treatment could decrease glomerular atrophy, Bowman's space, degeneration of tubules, vacuolation of cells, hemorrhage, infiltration of immune cells and congestion.	(Albrakati 2017)
Moringa Oleifera	Moringaceae	Leaves	aqueous extract	orally (100 mg/kg BW/day) for 4 weeks	orally (40 mg/kg BW/day) for 4 weeks	male albino rats	Testes Serum	Testicular protection	The results showed that *M. oleifera* leaves extract could ameliorate testicular injury via significant increasing relative body and testes weight, testosterone, FSH, and LH levels, sperm counts, sperm vitality and motility, spermatogenesis, number of Leydig cells testicular SOD and CAT. In addition, *M. oleifera* leaves extract significantly decreased sperm abnormality, immobility, testicular MDA level, seminiferous tubules degeneration.	(Abd *et al*. 2020)
Malus domestica (Apple)	Rosaceae	Seed	aqueous extract	daily oral (15mg/kg/ bw)	daily oral	Adult male Sprague–Dawley rats	Liver Serum	Hepatoprotective	It was observed that apple seed extract could prevent weight loss. Apple seed extract also significantly decreased the serum level of total lipid, cholesterol, triglycerides, LDL, VLDL, ALT, ALP, AST, GGT and total bilirubin. In addition, the serum level of HDL and albumin increased significantly. Oxidative stress markers	(Abdulhadi)

				for 2 weeks	(3mg/kg/bw) for 2 weeks				including MDA, H2O2, SOD, CAT, and GSH showed significant changes better than control group.	
Foeniculum Vulgare (Fennel)	Apiaceae	Seed	Powder	orally 10g, 20g, 30g fennel /kg diet for 6 weeks	orally (200 mg/kg bw) three times weekly for 6 weeks	male albino Sprague Dawley rats	Serum	Tramadol toxicity Protection	Fennel seed (especially 30g) elevated body weight and hemoglobin significantly nearly normal range. In addition, the serum levels of total cholesterol, TG, VLDL-c, LDL-c, and HDL-c reversed significantly similar to normal range of control group. Fennel seed (especially 30g) ameliorated kidney and liver function via significant decreasing the serum level of uric acid, urea, creatinine AST and ALT. This powder increased SOD, total antioxidants and decreased MDA and AchE.	(A Elsemelawy & OI 2018)
Aloe vera	Asphodelaceae	gel (viscous liquid)	gel (viscous liquid)	daily oral gavage of Aloe Vera gel 300 mg/kg for 4 weeks	50 mg/kg/day orally by gavage for 4 weeks	adult albino rats (50 male and 50 female)	Testes Ovaries	Reproductive Protection	*Aloe vera* gel attenuated lipid peroxidation via decreasing the serum level of MDA and increasing the serum levels of testosterone and GSH. *Aloe vera* gel also ameliorated testes and ovaries through inhibition of dilatation in seminiferous tubules and vacuolation, atrophy of testes, and spermatogenic arrest. It also inhibited follicular atresia, hyperplasia of corpus luteum and vacuolation in ovaries.	(Hindawy *et al*.2018)
Allium sativum (Garlic)	Amaryllidaceae	-	syrup	0.6mg/130g body weight of rat) orally for 28 days	1.9/130g body weight of rat)orally for 28 days	wistar rats	Liver Heart Kidney Serum	Tramadol toxicity Protection	Garlic administration induced elevation in the body weight, decrease in liver, heart and kidney weight. In addition, RBC's, Hb, PCV, MCV, MCH and MCHC levels were increased in garlic treated group compared to tramadol treated group. In contrast, WBC's level was decreased after garlic treatment.	(Ukpanukpong *et al*.)
							Liver Serum	Hepatoprotective	Garlic treatment increased significantly the serum level of HDL. In contrast, garlic could not affect the serum levels of AST, ALT, ALP, total cholesterol, TG, LDL, and VLDL.	(Eban *et al*. 2021)

Multi herbal formulation	-	-	Extract	400 mg/kg/day	Tramadol hydrochloride/paracetamol 1.68 g/300 ml of water	Swiss albino mice	Blood	Hepatoprotective Haematological preservation	This plant formulation made up of these plants: *Tinospora cordifolia*, *Terminalia chebula*, *Azadirachta indica*, *Andrographis paniculata*, *Aloe barbadensis* miller, Curcuma longa, *Trigonella foenum-graecum*, *Piper nigrum*, *Elettaria cardamomum*. Administration of this formulation could meliorate toxicity caused by Tramadol hydrochloride/paracetamol. Multi herbal formulation elevated body weight, the levels of RBC, HCT, MCHC, Platelets, Hb, PCV, MCV, MCH and declined the serum levels of AST, ALT and WBC.	(Darbar *et al*. 2020)

The aim of the present systematic review was to evaluate the protective role of medicinal plants against tramadol toxicity. The results of our systematic review indicated that *Nigella sativa* (Black Seed) oil as the most studied plant against tramadol toxicity exhibited hepato-protective, nephron-protective and neuroprotective effects against tramadol toxicity. The previous study expressed that *Nigella sativa* oil improves its protective role through decreasing lipid peroxidation marker and increasing antioxidant enzymes activity such as Gpx and GSH levels (Abdel-Zaher *et al*. 2011). The latter authors have been reported that black seed oil is recognized as a rich source of thymoquinone as its active ingredient. They also showed that *N. sativa* oil possess anti-oxidative effect due to the presence of thymoquinone which shows its antioxidant property through NO production and improving antioxidant capacity (Abdel-Zaher *et al*. 2011). Our results showed that pomegranate was another medicinal plant which exhibits protective effect against testicular damage caused by tramadol. Some investigators found that pomegranate improves antioxidant capacity and cellular structure due to the presence of total phenols and total flavonoids especially punicalagin. Literatures have been shown that punicalagin participates in the protection of the cells from oxidative stress (Minisy *et al*. 2020). Turmeric is known as a famous flavor in our meal. Using turmeric has been associated with liver protection. As described in Table 1, we found that turmeric represents hepato-protective effect against liver toxicity caused by tramadol. This study showed that turmeric acts as an antioxidant agent by increasing the activity of antioxidant enzymes and total antioxidant capacity along with anti-inflammatory agent by decreasing inflammatory cytokines such as TNF-α (Elbadrawy & Elkewawy 2019). Curcumin is the main active ingredient in turmeric with numerous therapeutic properties (Rathore *et al*. 2020). Some investigators have linked the therapeutic effects of turmeric to curcumin including antioxidant, anti-inflammatory and anti-apoptotic properties (Fu *et al*. 2021). This review identified a wide variety of useful medicinal plants against tramadol toxicity. Many of these plants such as pomegranate, wheat, barely, pumpkin, walnut, kiwi fruit, apple, fennel, and garlic are consumed daily as food or fruits. They have shown that edible plants, as rich sources of antioxidant compounds, can protect against a variety of diseases (Vuolo *et al*. 2019; Abbasi *et al*. 2020; Bahmani *et al*. 2020; Zarei *et al*. 2017; Ebrahimi *et al*. 2019; Rahmati *et al*. 2022; Kustiawan *et al*. 2021). As mentioned in Table1, abovementioned medicinal plants exhibit various protective effects against tramadol induced toxicity via their antioxidant, anti-inflammatory and anti-apoptotic properties. One limitation of this systematic review was that we did not search more databases. Another limitation was that we did not assess studies that were published in other languages except English and Persian. Furthermore, the inclusion criteria was chosen based on papers that had available online summaries/abstracts.

CONCLUSION

Nowadays, the tendency to the study of the therapeutic properties of medicinal plants has expanded according to the available evidence. Medicinal plants have a high potential in the treatment of various diseases due to their active ingredients. Recently, investigators have begun research about the replacement of natural compounds with synthetic drugs. Aforementioned medicinal plants in this review exhibit a wide range of therapeutic effects such as antioxidant, anti-inflammatory and anti-apoptotic properties which could protect completely the organs of the body including CNS, liver, kidney and reproductive system against toxicity caused by tramadol. Therefore, there is a need for further studies, especially studies to evaluate the toxicity and effectiveness of these plants for preparation of new drugs on people affected by tramadol.

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All the authors contributed equally to the writing of the manuscript.

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