



Quercetin as a Complementary Therapy in Substance Use Disorder: A Narrative Review

Masoud Soltaninejad^{1,2} , Mehran Ilaghi^{2*} , Reza Saboori Amleshi¹ , Mohammad Shabani^{1*}

¹Institute of Neuropharmacology, Kerman Neuroscience Research Center, Kerman University of Medical Sciences, Kerman, Iran

²Student Research Committee, Kerman University of Medical Sciences, Kerman, Iran

*Corresponding Authors: Mohammad Shabani, Emails: shabanimoh@yahoo.com; shabani@kmu.ac.ir; Mehran Ilaghi, Emails: mehranila@gmail.com; m.ilaghi@kmu.ac.ir

Abstract

Substance use disorder (SUD) is a pervasive public health concern characterized by compulsive drug use despite adverse consequences. SUD treatment strategies aim to help addicts stop obsessively seeking and consuming drugs. These approaches could be provided in a variety of venues, utilizing a range of behavioral and pharmacological techniques. Emerging research explores alternative treatments for SUD, including the use of medicinal plants. Quercetin, a natural flavonoid present in various fruits and vegetables, exhibits promising pharmacological properties. This naturally occurring pharmaceutical component has shown promise as a preventive measure against a wide range of disorders. It shields the user against neurodegeneration, oxidative stress, and inflammation, offering hope for central nervous-system-related disorder treatment. Regarding substance abuse, quercetin shows substantial promise. It demonstrates the ability to mitigate the adverse effects of substances, including methamphetamine, nicotine, morphine, heroin, and alcohol, through various mechanisms, including antioxidant, anti-inflammatory, and neuroprotective pathways. This review synthesizes recent evidence supporting quercetin as a complementary approach to conventional addiction treatments.

Keywords: Quercetin, Substance use disorder, Addiction, Antioxidant, Complementary therapy

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Introduction

Substance use disorder (SUD) is a long-lasting disorder defined by compulsive drug use, even when doing so endangers the individual's health and well-being. In other words, SUD is often referred to as the "disease of the 5 Cs," which includes continued compulsive taking of drugs despite adverse consequences, loss of control, and ongoing drug craving (1,2). The majority of drugs of abuse activate reward circuits in the brain to produce their initial reinforcing effects. However, while initial drug use is largely a voluntary behavior, continued drug use impairs brain function by hindering the ability to exercise self-control over drug-seeking behaviors and making the brain more sensitive to stress and negative moods (3).

Addiction treatment strategies aim to assist addicts stop obsessively seeking and consuming drugs. These approaches could be provided in a variety of venues utilizing a range of behavioral and pharmacological techniques (4). Recent years have witnessed an increase in interest in the usage of and research into medicinal plants for the treatment of drug addiction, as seen by the rise in publications examining the effects of herbal plants in the treatment of addiction or alleviating the consequences of SUD (5).

Quercetin, a naturally occurring pharmaceutical component, has shown promise as a preventative measure against a wide range of disorders. Researchers find quercetin to be a fascinating subject of study in the context of addiction, given its expanding range of properties. In this review, we seek to investigate quercetin's neuroprotective properties in addiction medicine. First, we will provide persuasive evidence showing the newly discovered advantages of quercetin in treating a variety of disorders, with a focus on neuropsychiatric disorders. Then, we will conduct an extensive and exhaustive examination of quercetin's neuroprotective effects against several addictive drugs.

Quercetin: A promising multifaceted player in medicine

The word "quercetin" (3,3',4',5,7-pentahydroxyflavone) is derived from the Latin word *quercetum*, which means "oak forest." It is a type of flavonol not made by the human body. It is a yellowish substance entirely soluble in lipids and alcohol, completely insoluble in cold water, and slightly soluble in hot water. Quercetin is the primary polyphenolic flavonoid present in a variety of fruits and vegetables, including berries, lovage, capers, cilantro, dill, apples, and onions (6,7).



Accumulating evidence has shown that quercetin has therapeutic potential for the prevention and treatment of different diseases (8) due to its extensive pharmacological properties, including anti-inflammatory (9), anti-atopic (10), pro-metabolic (11), antiviral (12), and antimicrobial (13) activities. In addition, numerous studies have shown the protective effects of quercetin against respiratory toxic agents (14), and its effectiveness in preventing cancer (15), as it possesses a broad spectrum of anticancer characteristics (16). Additionally, quercetin has been shown to inhibit platelet aggregation (17), reduce capillary permeability (18) and lipid peroxidation (19), and increase mitochondrial biogenesis (20). Additionally, quercetin reduces the effects of psychosocial stress on passive coping behavior by restoring normalcy to the hypothalamic-pituitary-adrenal (HPA) axis, controlling neurochemical release, boosting brain-derived neurotrophic factor, and reducing oxidative/nitrogenous stress, neuroinflammation, and apoptotic pathways in the brain (21,22).

Due to its numerous protective effects in various disorders, quercetin has been found to be useful in treating disorders of the central nervous system. In the following section, we summarize the protective advantages of quercetin in various neurodegenerative diseases and psychiatric disorders, thereby establishing a potential avenue for its application in disorders related to addiction.

The neuroprotective effects of quercetin

Regarding morbidity and impairment, neuropsychiatric disorders place a heavy burden on affected individuals worldwide. Due to the biological safety of medicinal plants, they are increasingly being studied as supplemental therapies for a range of neuropsychiatric disorders (23). Quercetin has become a well-known substance that has recently drawn significant interest from researchers due to its noteworthy neuroprotective benefits.

Quercetin and Alzheimer's disease

Alzheimer's disease (AD) affects predominantly elderly people (65 years of age or older) and accounts for 60% to 80% of all dementia cases (24). As the most significant cause of dementia in the world, AD gradually impairs cognitive function and has a significant impact on daily life. Neurofibrillary tangle accumulation and β -amyloid ($A\beta$) plaque deposition are the two pathological characteristics that traditionally define AD. Memantine and other symptomatic medications like cholinesterase inhibitors have improved quality of life. However, they have not been able to stop the progression of the disease or slow down the rate of loss of cognitive function (25,26).

Additionally, AD is linked to a reduction in acetylcholine (ACh) levels, particularly in the hippocampus and neocortex. Therefore, cholinesterase inhibitors are clinically useful for treating AD symptoms (27). In a

range of *in vitro* and *in vivo* models, quercetin shows therapeutic qualities against fundamental processes underlying AD pathogenesis. By reducing oxidative stress and neuroinflammation, it safeguards neuronal cells. Quercetin has anti-AD effects that include inhibiting tau phosphorylation and $A\beta$ aggregation. It raises ACh levels by preventing the AChE enzyme from hydrolyzing ACh (28,29). Moreover, quercetin protects neurons against the cytotoxicity, protein oxidation, lipid peroxidation, and apoptosis caused by $A\beta$ and regulates the activity of antioxidant genes (30).

Quercetin and Parkinson's disease

Following AD, Parkinson's disease (PD) is the second most prevalent neurodegenerative and the most prevalent neurodegenerative movement disorder. PD is characterized by the cardinal motor symptoms of tremor, stiffness, bradykinesia/akinesia, and postural instability. However, the clinical picture also includes both motor and non-motor symptoms (31). The pathogenesis of PD involves both hereditary and environmental variables (31). The first familial instances of PD were found to have an α -synuclein gene mutation.

Additionally, the aberrant inclusion of α -synuclein was discovered in the brains of sporadic and hereditary PD instances as an important component of Lewy bodies, a pathological characteristic of PD (32). Several studies have shown that quercetin could exert therapeutic potential in PD (33). For instance, quercetin could provide cognitive-enhancing effects in a rat model of PD induced by 6-hydroxydopamine (34). Recent *in silico* findings have also suggested that quercetin and its metabolites could exhibit neurotherapeutic effects in PD (35).

Quercetin, depression, and anxiety

Depression is a prevalent mental disorder with detrimental effects on an individual's physical and mental health. Depression and anxiety are linked to persistent stress (36). Numerous studies have demonstrated that quercetin treatment significantly reduces oxidative and inflammatory stress and prevents neural damage by regulating oxidative stress indicators, including thiobarbituric acid reactive substance (TBARS) and nitric oxide (NO), antioxidants such as total thiol and catalase, and pro-inflammatory cytokines in the hippocampus (37). It has been demonstrated in several studies that quercetin significantly reduces depressive symptoms in animal models of depression. For instance, quercetin has been shown to have antidepressant effects through the regulation of antioxidant defenses and the glutamatergic and oxido-nitrergic signaling pathways (38). Moreover, experimental studies show the effect of quercetin on anxiety. Kosari-Nasab and colleagues' study showed that in mice with mild traumatic brain injury, quercetin greatly reduced anxiety-like behaviors. In addition,

quercetin treatment reduced the dysregulation of the HPA axis, resulting in lower levels of corticosterone and adrenocorticotrophic hormone in these animals (39).

It is conceivable that quercetin may have protective benefits against the negative effects of drug misuse on the brain, given its capacity to improve behavioral and cognitive function as well as its neuroprotective properties against neurodegenerative disorders.

Quercetin and substance abuse

Quercetin's potential to mitigate the negative effects of substance abuse has been the subject of numerous studies to date. To address the protective effects of quercetin against substances of abuse, we did a comprehensive search of databases, including PubMed/Medline, Google Scholar, Scopus, WoS, and Embase using appropriate keywords, such as "quercetin," "substance abuse," "substance use disorder," and "drug abuse," or in combination with each type of abused drug, such as "methamphetamine," "nicotine," "heroin," "morphine," "alcohol," "ethanol," etc., using appropriate AND/OR syntax from inception to October 2023. We finally included original papers that have explored the potential effects of quercetin on the outcomes of drug abuse. Although we searched for a

complete list of potentially abused substances specifically, the following sections are based only on the substances with at least one published study on the protective effects of quercetin at the time of study.

Evidence suggests that quercetin has abilities that may alleviate the negative effects of several substances, including methamphetamine, nicotine, heroin, morphine, and alcohol (Table 1). An overview of the involved mechanisms is provided in Figure 1. The exact processes by which quercetin protects against each drug will be covered in more detail in the following sections, with an emphasis on the possible therapeutic applications of this substance in the context of addiction.

Methamphetamine

Methamphetamine consumption has significantly increased during the past decade, particularly in East and Southeast Asia (53). Methamphetamine use patterns on a global scale, particularly those for crystal methamphetamine, are now recognized as a serious health concern with high mortality and morbidity rates (54). Dopamine and serotonin axons and termini in the frontostriatal region deteriorate with repeated use of methamphetamine, which causes these monoamines

Table 1. Studies on protective effects of quercetin against abused drugs

Drug of abuse	Species	Quercetin dose	Protective effects of quercetin	Reference
Methamphetamine	Advanced glycation end products biomarkers	3.2 mM	Decreased methamphetamine-induced fluorescent advanced glycation end products formation indicating antioxidant effects	(40)
Methamphetamine	C57BL/6J mice	50 mg/kg	Ameliorated mitochondrial dysfunction and mitigated methamphetamine-induced anxiety-like behavior	(41)
Nicotine	Male Balb/C mice	50 mg/kg	Reduced the risk of nicotine dependence in the conditioned place preference paradigm	(42)
Nicotine	Male albino rats	40 mg/kg	Effects on nicotine-induced lung and liver toxicity through antioxidant effects (altering superoxide dismutase, catalase, and glutathione peroxidase)	(43)
Morphine	Male albino mice	5, 10, and 25 mg/kg	Prevention of the development of morphine tolerance and dependence in mice, possibly through nitric oxide inhibition	(44)
Morphine	Albino mice (Laka strain) of either sex	25 and 50 mg/kg	Reversed development of tolerance to the analgesic effect of morphine and morphine-induced delay in gastric transit	(45)
Heroin	Male Sprague Dawley rats	50 mg/kg/d	Attenuated heroin addiction and lowered IL-6 concentration	(46)
Heroin	Kunming mice of either sex	0.5 mg/g/day	Restrained oxidative stress and ameliorated the withdrawal syndrome in heroin-administered mice	(47)
Alcohol	Male Wistar rats	10, 20, and 40 mg/kg	Neuroprotective effects against alcohol-induced neuropathy through modulation of membrane-bound inorganic phosphate enzyme and inhibition of oxido-inflammatory markers	(48)
Alcohol	Male Sprague–Dawley rats	100 mg/kg	Protective effects on long-term alcohol-consumption-induced oxidative stress through decreasing plasma thiobarbituric acid reactive substance, protein carbonyls, TNF- α , INF- γ , and ALT levels	(49)
Alcohol	Male Laka mice	10, 25, and 50 mg/kg	Reversal of aging and chronic ethanol-induced cognitive dysfunction through modulation of plasma thiobarbituric acid reactive substance, glutathione, and catalase levels	(50)
Alcohol	Albino mice (Laka strain) of either sex	25 or 50 mg/kg	Protective effects on alcohol-abstinence-induced anxiety and convulsions	(51)
Alcohol	Male Swiss albino mice	10, 30, and 100 mg/kg	Effects on the rewarding property of ethanol through attenuating ethanol-induced conditioned place preference	(52)

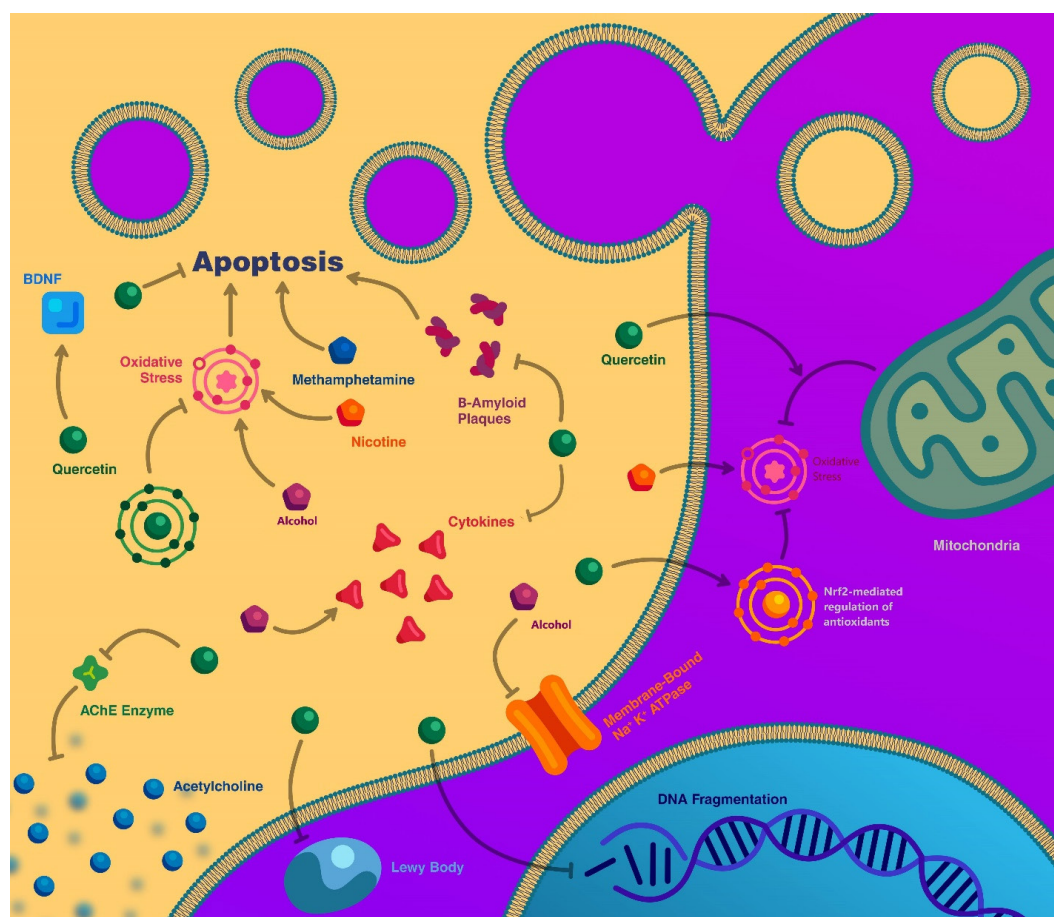


Figure 1. An overview of the neuroprotective mechanisms of quercetin against abused drugs and neurodegeneration. Quercetin exerts neuroprotective effects by enhancing brain-derived neurotrophic factor levels, inhibiting the oxidative stress induced by abused drugs, inhibiting apoptotic pathways, reducing inflammatory cytokines, and preventing DNA fragmentation. Additionally, quercetin activates the nuclear factor-erythroid factor 2-related factor 2 (Nrf2) pathway, promoting an antioxidant response against abused drugs. Quercetin also inhibits Lewy body formation, β -amyloid plaques, and acetylcholinesterase (AChE) enzyme, thereby showing potential in ameliorating neurodegenerative diseases

to become depleted (55). Although the exact processes of neurotoxicity are not fully understood, oxidative stress and apoptosis are involved (56). Human positron emission tomography and magnetic resonance imaging have revealed abnormalities in the brain, including inflammation (57) and decreased density of dopaminergic markers (58,59). These anomalies, brought on by injury to the cingulate, frontal, and striatal areas, mediate cognitive deficiencies in methamphetamine addicts (60).

Quercetin's neuroprotective effects against methamphetamine have been investigated. In a study conducted by Filošević Vujnović et al, it was concluded that quercetin significantly decreased methamphetamine-induced fluorescent advanced glycation end products, which are indicators of aging and neurodegenerative disorders (40). Similarly, another study by Chen et al offered proof that quercetin could ameliorate mitochondrial dysfunction and alleviate methamphetamine-induced anxiety-like behavior (41).

Nicotine

The psychostimulant found in tobacco and nicotine is pharmacologically related to stimulants like

amphetamines and has parasympathomimetic qualities, making it easy to abuse and become addicted to. Nicotine abuse causes brain cells to undergo oxidative damage, apoptosis, and inflammation (61). In addition, quercetin has been demonstrated to have several protective benefits against nicotine-induced harm to several organs, in addition to its neuroprotective properties. Accordingly, research demonstrates that quercetin guards against the harmful effects of nicotine on the lungs (43,62), liver and kidney (63), and reproductive system (64). Additionally, as quercetin binds free radicals and regulates endogenous antioxidants through nuclear factor-erythroid factor 2-related factor 2 (Nrf2) activation (42), it is anticipated to be a potential agent to lower the risk of nicotine dependence. In a study by Al Anany et al., the findings revealed that quercetin and/or curcumin prevent DNA fragmentation in the liver and lung tissues caused by nicotine by regulating the amount of lipid peroxidation, enhancing the antioxidant system, reducing oxidative stress, and blocking oxidative stress (43).

Morphine

Drugs like morphine and other opioids can cause a wide

range of pharmacological activity. Some of the effects they have on the central nervous system include strong analgesia, euphoria, sedation, endocrine dysregulation, miosis, antitussive activity, or respiratory depression. Additionally, they cause the peripheral nervous system to release histamine and cause muscle spasms (65). The stimulation of opioid receptors is linked to the pharmacological activity of acute dosages of morphine. It primarily interacts with the μ opioid receptors (66,67). In the study of Habibi Asl et al., who investigated the effects of quercetin and ACTH on tolerance and dependence caused by morphine in rats, they came to the conclusion that quercetin or ACTH pretreatment reduced the level of tolerance. Based on these findings, it may be inferred that administering quercetin or ACTH alone could stop the emergence of morphine tolerance. These effects could be attributed to quercetin's activity as an NO inhibitor (44). According to the results of another study, quercetin administration could reverse the development of tolerance and dependence on morphine (45).

Heroin

Heroin, a highly addictive illegal narcotic, is one of the major public health issues worldwide (68,69). The current pharmacological cures for heroin addiction work by targeting the μ opioid receptors with complete agonists like methadone, partial agonists like buprenorphine (which also functions as a κ -antagonist), or full antagonists like naltrexone (70,71). Heroin abuse could cause various systemic consequences, including respiratory depression (72), pulmonary edema (73), vasculitis (74), leukoencephalopathies (75,76), and myelopathy (77). Moreover, the brains of heroin addicts show a wide range of neuropathologic alterations (78). Recent studies have revealed substantial evidence for efficient pharmacologically-based therapy modalities for controlling opioid withdrawal and assisting patients in maintaining abstinence. In a recent study by ElShebiney et al, it was demonstrated that when it comes to preventing heroin relapse, quercetin and resveratrol may be useful, while quercetin and magnolol may be used to lessen the intensity of heroin withdrawal (46). According to another study, which investigated its antioxidant effects, quercetin could restrain oxidative stress and ameliorate the withdrawal syndrome in heroin-administered mice (47).

Alcohol

Alcohol addiction is a global issue contributing to more than 3% of annual fatalities globally, placing a significant financial and medical strain on healthcare systems (79). The effects of alcohol on inflammation in the gut and brain are closely related. Alcohol use weakens the intestinal barrier in the gut, allowing bacteria and bacterial endotoxins to enter the bloodstream. These bacterial endotoxins can invade other organs, including the brain, resulting

in neuroinflammation and cognitive impairment (80). Alcohol can also have an immediate impact on the brain by causing immune cells like microglia to become active and generate neuroinflammatory cytokines. Alcohol has been linked to a higher risk of neurodegenerative disorders. In addition, alcohol drinking has a detrimental effect on brain stem cells, impairing adult neurogenesis and leading to hippocampal impairment (80).

Quercetin has been evaluated for its ability to treat rats with an experimental form of alcoholic neuropathy in a study by Raygude et al (48). Accordingly, allodynia, hyperalgesia, motor coordination, reduced nerve conduction velocity, and lower levels of membrane-bound Na^+/K^+ -ATPase were significantly diminished after chronic therapy with quercetin (20 and 40 mg/kg) for ten weeks. Additionally, quercetin decreased high levels of malondialdehyde, myeloperoxidase, and pro-inflammatory mediators like NO (48). Similarly, it has been demonstrated that reduced levels of TBARS, protein carbonyls, tumor necrosis factor- α , interferon- γ , and alanine transaminase in the plasma of ethanol-exposed rats, suggesting that quercetin therapy may offer protection against the oxidative damage induced by ethanol (49). In another study, mice given chronic ethanol experienced a rise in lipid peroxidation and decreased levels of the antioxidant enzymes catalase, superoxide dismutase, and total glutathione in the forebrain. These effects were markedly reversed when quercetin was administered (50).

Furthermore, in another study, ethanol withdrawal caused the mouse locomotor activity to rise significantly, indicating an anxiety-inducing reaction. Acute and long-term treatment of quercetin (25 or 50 mg/kg, po) significantly protected mice from ethanol withdrawal anxiety and convulsions (51). Likewise, another research on the effects of quercetin on the development, maintenance, and reinduction of ethanol-induced conditioned place preference in young mice showed that acquisition and reinstatement were slowed down by pretreatment with quercetin. Additionally, administering quercetin sped up the extinction of ethanol-induced conditioned place preference (52).

Conclusion

In conclusion, quercetin emerges as a promising neuroprotective agent with multifaceted potential in addiction medicine. Its ability to mitigate neurodegeneration, oxidative stress, and inflammation makes it a valuable candidate for treating neuropsychiatric disorders and substance abuse. Clinical trials are warranted to evaluate its efficacy as an adjunctive therapy in SUD treatment and neuropsychiatric disorder management. Furthermore, exploring quercetin's potential synergies with existing pharmacological interventions could provide novel combination therapies. Additionally, investigations into optimal dosing regimens and potential side effects

will be crucial for translating quercetin's therapeutic potential into clinical practice. Overall, quercetin holds promise as a versatile player in the pursuit of enhanced treatments for addiction and neuropsychiatric disorders.

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Authors' Contribution

Conceptualization: Mehran Ilaghi, Mohammad Shabani.

Investigation: Masoud Soltaninejad, Reza Saboori Amleshi, Mehran Ilaghi.

Methodology: Masoud Soltaninejad, Reza Saboori Amleshi, Mehran Ilaghi.

Project administration: Mohammad Shabani.

Resources: Mohammad Shabani.

Software: Reza Saboori Amleshi.

Supervision: Mehran Ilaghi, Mohammad Shabani.

Validation: Mohammad Shabani.

Visualization: Reza Saboori Amleshi.

Writing—original draft: Masoud Soltaninejad, Reza Saboori Amleshi, Mehran Ilaghi, Mohammad Shabani.

Writing—review & editing: Mohammad Shabani.

Competing Interests

The authors declare that they do not have any conflict of interest.

Ethical Approval

All study protocols have been approved by the Ethics Committee of Kerman University of Medical Sciences and were carried out following relevant guidelines and regulations.

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