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Review article

Unraveling the protective effects of curcumin against drugs of abuse

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ABSTRACT

Curcumin, a natural compound derived from the turmeric plant (Curcuma longa), has garnered significant attention for its diverse neuroprotective properties. Curcumin has been widely recognized for its remarkable anti-inflammatory, antioxidant, and anti-apoptotic effects, which have shown great potential in the treatment of various disorders, encompassing psychiatric and neurodegenerative diseases. In this review, we delve into the protective effects of curcumin against drugs of abuse, including morphine, methamphetamine, cocaine, nicotine, and alcohol, with a particular focus on the underlying mechanisms from a neuroscience perspective. Overall, curcumin demonstrates promising effects against the neurotoxicity induced by abused drugs through a wide range of mechanisms. These include the modulation of inflammatory cytokines, maintenance of ion homeostasis, epigenetic regulation, enhancement of antioxidant capacity, as well as the activation of the cAMP response element-binding protein (CREB) and brain-derived neurotrophic factor (BDNF) signaling pathways. These findings suggest that curcumin emerges as a promising therapeutic agent in combatting the detrimental effects induced by drugs of abuse, and further research is warranted to fully comprehend the molecular pathways and optimize its utilization for the prevention and treatment of substance abuse-related neurotoxicity.

1. Introduction

The term addiction is occasionally used to refer to the phenomenon of unrestrained, obsessive use of a substance or behavior that harms both the individual and those around them [1]. Among all types of addiction, drug addiction is a chronic, relapsing disorder with high prevalence around the globe. The development of drug addiction and relapse following drug withdrawal is influenced by a number of neural networks in the brain, including the reward system (such as the mesocorticolimbic system), the anti-reward/stress system (such as the extended amygdala), and the central immune system [2]. Besides their rewarding effects, it is well established that abused drugs could exert various adverse cognitive and behavioral consequences on the individual. These drugs could potentially disrupt various neurocircuitry pathways and harm brain structures through diverse mechanisms [3]. Therefore, the continuous endeavor to discover neuroprotective compounds against the outcomes of abused drugs persists.

Curcumin, being a natural medicinal constituent, has demonstrated potential as a protective agent against a multitude of diseases [4]. The burgeoning properties exhibited by curcumin have rendered it a captivating subject of study among researchers, particularly within the context of addiction [5,6]. In this review, we aim to elucidate the neuroprotective effects of curcumin against drugs of abuse

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from a neuroscience perspective. Initially, we present compelling evidence highlighting the emerging benefits of curcumin in diverse diseases, with specific attention to neuropsychiatric disorders. Subsequently, we undertake a thorough and comprehensive investigation of the neuroprotective effects of curcumin against distinct substances of abuse.

2. Curcumin: an emerging jack-of-all-trades in medicine?

Turmeric (Curcuma longa) is an herbaceous plant native to Asia that is widely used as a color, culinary spice, and traditional natural medicinal ingredient [7]. The rhizome of this plant is rich in yellow compounds known as curcuminoids. Curcumin is regarded as one of the most important constituents in this group of compounds [8]. Curcumin's chemical formula is 1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione [9]. The ability of curcumin to interact with different proteins facilitates selective modulation of multiple cellular signaling pathways associated with various chronic diseases [10]. Therefore, numerous studies have been conducted to investigate the therapeutic impact of curcumin in the management of a wide array of diseases [4,11].

The effects of curcumin in the field of cancer medicine have garnered significant attention, resulting in its widespread recognition [12,13]. Curcumin has demonstrated its viability as a potential therapeutic option for cancer treatment by selectively targeting diverse cell signaling pathways encompassing growth factors, cytokines, transcription factors, and genes that regulate cellular proliferation and apoptosis [14]. Extensive investigations have explored the beneficial effects of curcumin in numerous cancer types, encompassing breast cancer, lung cancer, cancers affecting the digestive system, as well as hematological cancers [15]. In addition to its therapeutic attributes, curcumin has been proposed as a prospective agent in cancer prevention, primarily attributed to its antioxidant and immunomodulatory properties [16].

Curcumin has also demonstrated its potential as an agent in the regulation of obesity and metabolic processes [17,18]. Curcumin has been shown to be effective in treating outcomes linked to obesity through promoting the expression of antioxidants and directly slowing preadipocyte development [17]. In addition, curcumin aids in the management of metabolic syndrome and hyperlipidemia [19]. It has also shown promise as a robust endocrine system modulator, boosting or controlling the release of several hormones, including insulin [20]. Regardless of health status, adding curcumin to one's diet lowers circulating levels of pro-inflammatory biomarkers and raises levels of anti-inflammatory mediators [21].

Curcumin has also exhibited beneficial effects in various pulmonary disorders, highlighting its potential in the management of respiratory system-related conditions. Studies have demonstrated the possible benefits of curcumin in chronic obstructive pulmonary disease (COPD), through attenuation of airway inflammation and remodeling [22]. Moreover, the relaxant effects of curcumin on tracheal smooth muscle indicate its bronchodilatory properties, suggesting its potential advantage in the treatment of diverse respiratory and allergic disorders [23]. On the other hand, curcumin also exhibits the capacity to attenuate the natural response of the body to cutaneous wounds, including inflammation and oxidation. This evidence supports its ability to promote crucial aspects of wound healing, such as collagen deposition, granulation tissue formation, tissue remodeling, and wound contraction [24,25]. Consequently, numerous topical formulations of curcumin, including emulsions, fibers, hydrogels, and various nanoformulations, have been developed to facilitate targeted delivery of curcumin specifically to the wounded sites [26].

Several clinical studies have demonstrated the safety of curcumin, even at elevated doses [27,28]. However, a challenge associated with curcumin has been its low bioavailability [29]. This constraint is primarily attributed to poor absorption, rapid metabolism, and rapid elimination from the systemic circulation, leading to low plasma and tissue concentrations of curcumin [27]. However, curcumin, when combined with other compounds or as formulations, has demonstrated increased bioavailability [30]. Therefore, studies suggest that bioavailability is not a significant limitation in the curcumin-mediated treatment of disorders [31].

The protective effects of curcumin observed in diverse diseases imply its potential utility in addressing disorders of the central nervous system. In the following sections, we present an overview of curcumin's protective effects in various neurodegenerative diseases and psychiatric disorders. This framework sets the stage for discussing its potential implications in the context of drug addiction.

3. Protective effects of curcumin in various neuropsychiatric diseases: a succinct overview

Neuropsychiatric diseases represent a significant global burden in terms of morbidity and disability [32,33]. Medicinal plants, in light of their biological safety, are increasingly being explored as complementary treatments for various neuropsychiatric disorders [34,35].

Depressive disorders are often considered the most common mental health condition among the general population [36]. Based on numerous preclinical studies, curcumin may have antidepressant-like effects in animal models, with effects resembling those of traditional antidepressants like fluoxetine and imipramine [37]. Curcumin can influence the signaling of serotoninergic and dopaminergic systems, which are widely involved in the pathogenesis of depression [38,39]. Another potential mechanism of action of curcumin on depressive symptoms is linked to the inhibition of transcription signaling pathways of some nuclear factors, including nuclear factor kappa B, which is necessary for the production of pro-inflammatory cytokines and is consequently involved in the pathogenesis of neuroinflammation [40]. Furthermore, curcumin has been shown to boost levels of brain-derived neurotrophic factor (BDNF), a neurotrophin linked to the etiology of depression [41]. Findings from a meta-analysis study on human subjects affected by depression have also revealed that curcumin might improve depressive and anxiety symptoms in these individuals [42], suggesting that it can be utilized as an adjunct treatment for depressive disorders.

In addition to its therapeutic effects on depressive disorders, curcumin has exhibited potential as a therapeutic intervention for delusional disorders. Psychotic patients exhibit notable alterations in the activity of various brain regions, particularly those

implicated in dopamine-related processes [43]. Dopamine receptors, which are abundantly present throughout the brain and are blocked by antipsychotic drugs, are widely used to treat delusional disorders; however, long-term use of antipsychotic drugs causes severe extrapyramidal side effects [44]. Preclinical studies indicate the potential of curcumin in mitigating extrapyramidal and metabolic side effects when used as an adjunct to antipsychotic medications [45,46]. Furthermore, in human clinical trials, curcumin has demonstrated promise as an adjunctive agent for improving the negative and cognitive symptoms of schizophrenia. Importantly, these trials have indicated that curcumin supplementation is well-tolerated and safe [47,48].

The clinical utility of curcumin extends to the realm of neurodegenerative diseases and dementia as well. Alzheimer's disease (AD) is the most prevalent form of dementia among all other types, which is characterized by the production of intracellular neurofibrillary tangles and the extracellular deposition of amyloid-β (Aβ) plaques [49]. Moreover, AD is associated with a decrease in the amount of acetylcholine (ACh), particularly in the hippocampus and neocortex; therefore cholinesterase inhibitors possess clinical utility in the treatment of AD symptoms [50]. Curcumin works to treat AD primarily by inhibiting inflammation, oxidative stress, and apoptosis as well as inhibiting Aβ production and promoting its clearance [51,52]. Moreover, hybrids of curcumin and other agents such as galantamine and tacrine have shown efficacy as antioxidant and cholinesterase inhibiting agents in the treatment of AD [53,54].

Following AD, Parkinson's disease (PD) is the second most prevalent neurodegenerative condition. PD is a slowly progressing multisystem disorder that involves extensive neuropathological degradation in dopaminergic neurons of the Substantia Nigra pars

Table 1
Neuroprotective effects of curcumin against drugs of abuse.

Drug of abuse	Species	Curcumin dose	Protective effects	Reference
Morphine	Male Wistar rats	10, 20 and 40 mg/kg	Antiapoptotic and antioxidant effects in rat hippocampus	[65]
Morphine	Male C57BL/6J mice	100 mg/kg	Inhibition of morphine-induced upregulation of BDNF gene transcripts and morphine analgesic tolerance	[68]
Morphine	Male albino mice	10, 20 and 40 mg/kg	Decrease in morphine withdrawal syndrome symptoms	[71]
Morphine	Male Wistar rats	2.5, 5 and 10 mg/kg	Attenuation of the morphine withdrawal syndrome symptoms, inhibition of neuroinflammation and decrease in prefrontal μ-opioid receptor expression	[66]
Morphine	Male Wistar rats	10 mg/kg	Prevention of morphine-induced memory impairment through modulation of NO and CREB signaling	[69]
Morphine	Male ICR mice	200 and 400 mg/kg	Amelioration of opioid tolerance and dependence by inhibiting CamKIIα activity	[5]
Morphine	Male Sprague-Dawley rats	5, 20 mg/kg	Attenuation of morphine's rewarding effects	[70]
Morphine	Male Wistar rats	2.5, 5 and 10 mg/kg	Reduction in morphine dependence through suppression of activated microglial cells and reduction of inflammatory cytokines levels in the spinal cord	[67]
Cocaine	Male OF1 mice	100 mg/kg	Inhibiting the increase in the conditioned reinforcing effects of cocaine	[79]
Cocaine	PC12 cells	1, 3 or 5 μM	Preventing the cocaine-induced up-regulation of mu opioid receptor protein levels	[78]
Cocaine	Male Sprague-Dawley rats	Not specified	Inhibition of the cocaine-induced conditioned place preference	[77]
Nicotine	Adult male rats (species not specified)	40 and 60 mg/kg	Neuroprotection against nicotine-induced oxidative stress, inflammation, and apoptosis through *p*-CREB/BDNF signaling	[88]
Nicotine	Male Wistar rats	10, 30, and 60 mg/kg	Protecting the nicotine-induced in the CA1 region hippocampus through enhancing antioxidant capacity and neuronal dendritic spines	[89]
Nicotine	Male Wistar rats	12.5, 25, and 50 mg/kg (free curcumin)– 4 mg/kg (curcumin-loaded lipid-core nanocapsules)	Preventing the memory impairment, the redox imbalance and the alterations in the ATPases activity of tobacco-exposed mice	[90]
Methamphetamine	PC12 cells	0.1, 1, 10 μM	Clearance of methamphetamine induced α-synuclein accumulation	[95]
Methamphetamine	Male Wistar rats	40 and 80 mg/kg	Attenuation of methamphetamine-induced apoptosis, oxidative stress, and inflammation through the activation of *p*-CREB and BDNF signaling pathway activation	[96]
Methamphetamine	Male Wistar rats	100 and 200 mg/kg	Attenuation of methamphetamine-induced spatial memory impairment through antioxidant and anti-inflammatory effects	[97]
Alcohol	Male Wistar rats	10, 20, 40 and 80 mg/kg	Reduction in the alcohol-induced apoptosis, oxidative stress and inflammation probably via activation of CREB-BDNF pathway	[106]
Alcohol	Male Wistar rats	15, 30 and 60 mg/kg	Prevention of ethanol-induced behavioral deficits through antioxidative and anti-inflammatory signaling	[107]
Alcohol	Male C57BL/6 mice	100 mg/kg	Amelioration of cognitive deficits and reversal of the inflammatory response induced by alcohol	[109]
Alcohol	male Kun-Ming mice	40 mg/kg	Amelioration of ethanol induced-memory deficit through suppression of NOS activity	[110]

compacta (SNpc) and their terminals in the striatum [55]. Due to its free radical scavenging, mitochondrial protecting, anti-inflammatory, and iron-chelating properties, curcumin is regarded as a promising therapeutic and nutraceutical agent for the treatment of PD [56]. Accordingly, several studies have indicated that curcumin prevents the dopaminergic neuronal loss in models of PD [57,58], which provides further evidence for a potential neuroprotective role for curcumin in PD.

Given the potential of curcumin to enhance behavioral and cognitive function, as well as its neuroprotective properties against neurodegenerative diseases, it is plausible that curcumin may exhibit protective utility against the adverse consequences of drug abuse on the brain. In the subsequent section, we provide a comprehensive review of studies that demonstrate the protective effects of curcumin against abused drugs.

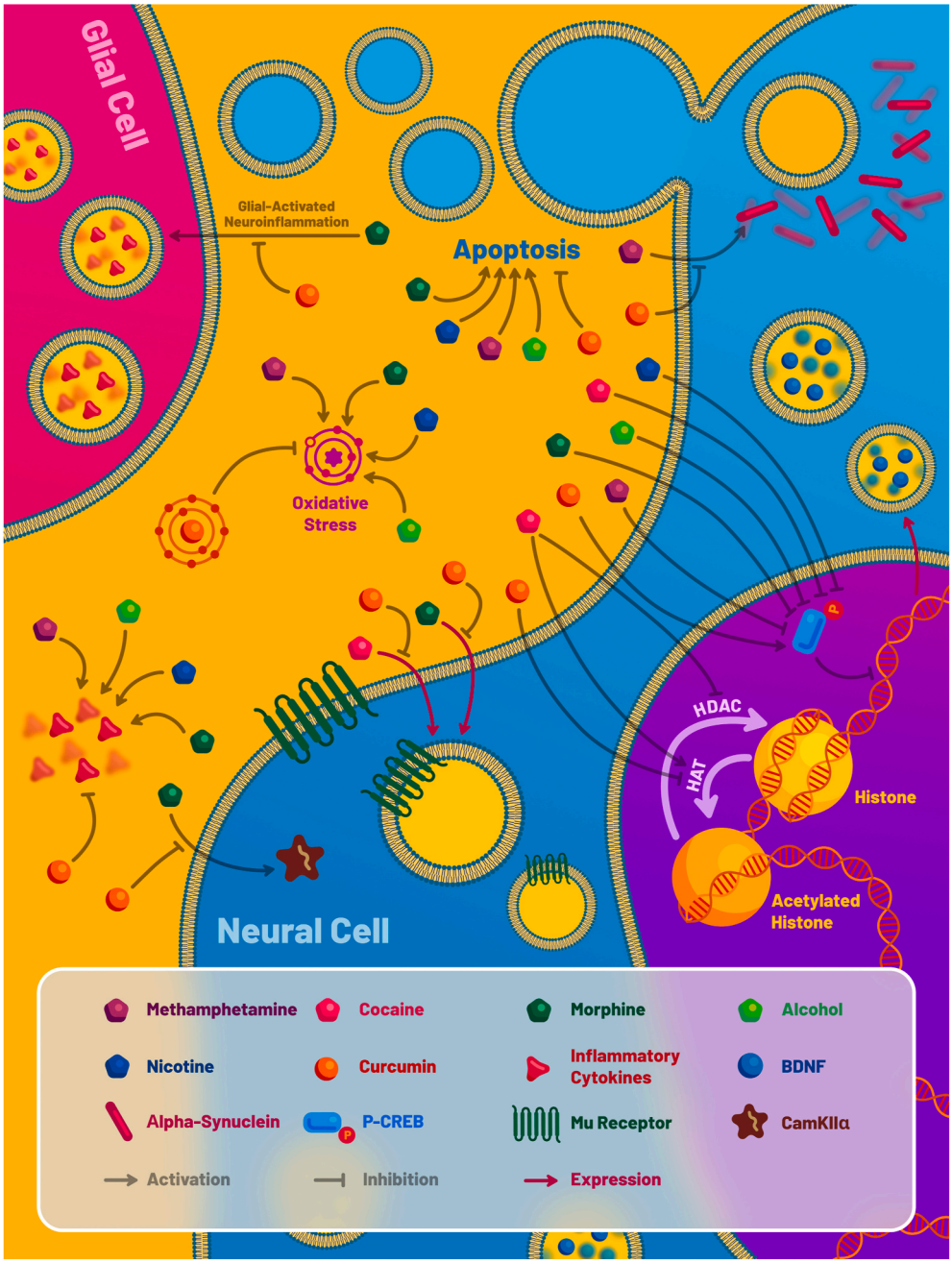

Fig. 1. Overview of the neuroprotective mechanisms of curcumin against drugs of abuse. Curcumin exerts its neuroprotective effects against drugs of abuse, such as methamphetamine, cocaine, morphine, nicotine, and alcohol, through various mechanisms. These mechanisms include inhibition of neuroinflammation, promoting antioxidative responses, decreasing apoptosis, facilitating alpha-synuclein clearance, decreasing opioid mu receptor expression, epigenetic regulation, and activating the CREB/BDNF signaling pathway.

4. Curcumin and drugs of abuse: insights into neuroprotective mechanisms

Several studies have so far explored the effects of curcumin in mitigating the adverse consequences associated with substance abuse. Evidence suggests that curcumin possesses properties that may counteract the damaging effects of various drugs, including morphine, cocaine, nicotine, methamphetamine, and alcohol (Table 1). Subsequent sections will delve into the specific mechanisms through which curcumin exerts its protective actions against each drug (Fig. 1), highlighting the potential therapeutic implications of this compound in the context of addiction.

4.1. Morphine

Morphine, among the various opioid drugs available, is widely regarded as one of the most potent analgesics for managing post-operative and cancer-related pain [59]. The pharmacological effects of morphine primarily arise from its interaction with opioid receptors, particularly the μ opioid receptors [60]. The rewarding effects of morphine and other opioids are linked to the activation of μ opioid receptors located specifically at the GABAergic terminals within the ventral tegmental area (VTA). This results in decreased GABA release, which subsequently leads to the disinhibition of dopaminergic neurons. This disinhibition causes the release of dopamine in the nucleus accumbens, triggering feelings of euphoria and facilitating the development of drug dependence [61]. Therefore, the chronic administration of morphine is associated with high abuse potential.

It is well established that the long-term consumption of morphine induces a variety of adverse outcomes, including apoptosis, oxidative stress or alteration of blood-brain barrier function which may result in critical damage to the brain [62–64]. Curcumin has been found to exert protective effects against these outcomes. Motaghinejad and colleagues demonstrated the capacity of curcumin to function as both an antioxidant and an antiapoptotic agent in countering the detrimental effects induced by morphine dependence in the hippocampus of rats [65]. Accordingly, they showed that curcumin treatment decreased lipid peroxidation and apoptotic BAX expression, while increased superoxide dismutase activity as well as anti-apoptotic BCL-2 expression in morphine dependent rats [65]. Furthermore, another study has demonstrated that curcumin attenuates morphine dependence in rats through inhibition of glial cell-activated neuroinflammation (reduction of TNF-α and IL-6) and a decline in the prefrontal expression of μ-opioid receptors [66]. Likewise, the results of another study elucidated that the therapeutic efficacy of curcumin in reducing morphine dependence is mediated via the suppression of activated microglial cells and a subsequent decrease in the levels of inflammatory cytokines within the spinal cord [67]. These studies suggest that the antioxidant, antiapoptotic, and anti-inflammatory properties of curcumin play a pivotal role in its neuroprotection against drugs of abuse.

There have been further distinct outcomes and mechanisms for the protective gain of curcumin against addiction, as well. Findings from a study exhibited that the chronic administration of morphine resulted in a notable escalation in the expression of exon I and IV BDNF transcripts. However, the administration of curcumin effectively nullified the upregulation of BDNF transcription and concurrently mitigated the development of analgesic tolerance to morphine [68]. This beneficial effect of curcumin was attributed to its inhibitory properties on the cAMP response element-binding protein (CREB), which is implicated in the underlying mechanism [68]. Moreover, another study has highlighted the protective effect of curcumin against morphine-induced memory impairment, possibly through the nitric oxide (NO) pathway and its downstream CREB signaling. Accordingly, the findings showed that curcumin treatment could reverse the decreased phosphorylated-CREB (*p*-CREB) expression induced by morphine [69]. Curcumin has also been shown to attenuate opioid tolerance and dependence through the inhibition of Ca2+/calmodulin-dependent protein kinase II α (CamKIIα) activity [5]. It has also been shown that curcumin disrupts the brain's reward mechanisms that are responsible for the manifestation of acute reinforcing properties associated with opioids. For instance, Katsidoni et al. demonstrated that subthreshold doses of curcuminiod mixture and curcumin could inhibit the reward facilitating effects of morphine [70]. Findings of another study by Motaghinejad and colleagues also revealed that curcumin treatment has the capacity to attenuate morphine withdrawal syndrome in a dose-dependent manner [71], suggesting that curcumin holds promise as an adjunctive treatment for mitigating both the rewarding effects and withdrawal manifestations of morphine, particularly in individuals undergoing long-term opioid therapy.

4.2. Cocaine

Cocaine is a psychostimulant drug that has emerged as a significant component of the global drug landscape, exhibiting diverse patterns of use across different countries [72]. Within the initial year of cocaine use, approximately 5 % of individuals who partake in its consumption will develop substance dependence, while nearly 20 % will progress to become long-term cocaine-dependent individuals [73]. The psychomotor stimulant effects of cocaine are primarily achieved by blocking the dopamine transporter in the striatum. Subsequent heightened dopamine receptor signaling in the nucleus accumbens contributes significantly to the rewarding effects associated with cocaine use [74]. Additionally, the signaling cascades involving CREB and its associated components, are integral in orchestrating the cocaine reward in the nucleus accumbens and the transition to compulsive use in the dorsal striatum [74].

Curcumin's neuroprotective effects against cocaine have been investigated in the context of its epigenetic effects. The extent of histone acetylation is determined by the interplay of two enzymatic groups: histone acetyltransferases (HATs) and histone deacetylases (HDACs). These enzymes govern the conformational changes in chromatin structure, thereby modulating the accessibility of DNA repair proteins and transcription factors to chromatin [75]. Curcumin has been identified as an inhibitor of HAT, suggesting its potential as an epigenetic modulator in countering the effects of drugs of abuse [76].

In a study by Hui et al., findings revealed that pretreatment with curcumin as an HAT inhibitor prior to cocaine administration, significantly inhibited the cocaine-induced conditioned place preference [77]. This study highlighted that histone modifications

represent a potentially significant mechanism underlying the conditioned effects of cocaine. Moreover, HAT may be a potential therapeutic target for cocaine addiction. Therefore, by modulating histone acetylation, curcumin may exert epigenetic regulation and help mitigate the addictive properties of cocaine, offering a potential avenue for therapeutic intervention. In another study by Winick-Ng et al., it was demonstrated that cocaine increases μ-opioid receptor expression by enhancing NO levels and decreasing HDAC activity, indicating that cocaine exposure results in histone acetylation enhancement. Notably, the administration of curcumin prior to cocaine exposure successfully blocked the increase in protein levels of μ-opioid receptors induced by cocaine [78]. Similarly, another study has exhibited that inhibition of HAT by curcumin before social defeat inhibited the increase in the conditioned reinforcing effects of cocaine [79]. Overall, these findings refer to epigenetic mechanisms as potential avenues leading to innovative treatments for drug addiction, also highlighting the potential of curcumin as an epigenetic regulator agent.

4.3. Nicotine

Nicotine, the psychostimulant component of tobacco, possesses parasympathomimetic properties and shares pharmacological similarities with amphetamine-like stimulants, rendering it susceptible to abuse and addiction. Nicotine abuse leads to the induction of oxidative stress, apoptosis, and inflammation in brain cells [80]. Apart from its neuroprotective effects, curcumin has been shown to exert several protective effects against nicotine-induced damage in several organs. Accordingly, it has been shown that curcumin protects against the toxic effects of nicotine on the lung [81,82], esophagus [83], reproductive system [84,85], liver [86], and adrenal cortex [87].

Accumulating evidence suggests that curcumin plays a role in attenuating the neurotoxic effects of nicotine. It has been demonstrated that curcumin exerts its neuroprotective effects against nicotine-induced apoptosis, inflammation, and oxidative stress through the activation of the *p*-CREB and BDNF signaling pathways [88]. Further evidence also suggests that curcumin could protect the nicotine-induced damage in the CA1 region of the hippocampus, which was accompanied by enhancing antioxidant capacity and neuronal dendritic spines [89]. In a separate study, it was demonstrated that both free curcumin and curcumin-loaded lipid-core nanocapsules effectively prevented memory impairment, redox imbalance, and alterations in ATPases activity in mice exposed to tobacco [90], suggesting that curcumin's protective mechanism against tobacco-induced cognitive impairments involves the maintenance of ion homeostasis and redox balance.

4.4. Methamphetamine

Methamphetamine ranks as the second most widely used illicit drug worldwide, with an estimated global prevalence of 0.4 % on an annual basis [91]. The consumption of methamphetamine leads to toxicity in multiple organs, including the central nervous system. Specifically, this psychostimulant drug exerts detrimental effects on nigrostriatal neurons, thereby heightening the susceptibility to neurodegenerative conditions such as PD [92]. The mechanism underlying methamphetamine-induced neurotoxicity is complex and involves various pathways. Methamphetamine triggers a significant release of dopamine and excessive generation of glutamate in the brain, leading to the production of a substantial amount of reactive oxygen species (ROS), which contributes to mitochondrial dysfunction and induces endoplasmic reticulum stress, both of which play crucial roles in the neurotoxic effects of methamphetamine [93,94].

Several studies have suggested that curcumin can protect against the neurotoxicity of methamphetamine. Ryskalin and colleagues have provided evidence that in cells exposed to methamphetamine, the autophagy substrates, particularly α-synuclein, accumulate in the cytosol. However, curcumin facilitates the clearance of α-synuclein and enhances the autophagy flux, suggesting its potential to promote efficient autophagic processes [95]. In another study, Gholami and colleagues demonstrated that curcumin reduced methamphetamine-induced apoptosis, oxidative stress, and inflammation through the activation of *p*-CREB and BDNF signaling pathways [96]. Similar findings from a separate study have also indicated that curcumin attenuated methamphetamine-induced spatial memory impairment through its antioxidant and anti-inflammatory effects [97]. However, it is worth noting that the results of a previous study indicated that curcumin not only failed to inhibit the behavioral effects of methamphetamine but actually enhanced them [6]. These findings imply that further research is required to comprehensively investigate the complex interactions and potential underlying mechanisms involved in the interaction between curcumin and methamphetamine, in order to provide a more comprehensive understanding of their relationship.

4.5. Alcohol

Alcohol, known for its sedative properties, possesses neurodegenerative characteristics. Given its pharmacological similarity to sedative and hypnotic substances, alcohol has the potential to be abused. Studies have shown that alcohol abuse causes behavioral and cognitive impairments in animal models and human subjects [98,99]. Accordingly, alcohol abuse induces oxidative stress and triggers neuroapoptotic and neuroinflammatory pathways [100,101]. Long-term and excessive alcohol consumption leads to a condition known as alcoholic hepatosteatosis, characterized by the accumulation of fat in the liver. This condition subsequently triggers inflammation, necrosis, fibrosis, and eventually cirrhosis, which affects millions of individuals worldwide and represents a significant cause of mortality, particularly in developed countries [102].

A multitude of studies have investigated the potential protective effects of curcumin against the detrimental outcomes associated with alcohol abuse. Numerous research findings have specifically highlighted the role of curcumin in safeguarding against alcohol-induced hepatotoxicity, indicating its potential as a therapeutic agent for protecting the liver from alcohol-related damage

[103–105]. Furthermore, curcumin has also shown potential against neurotoxicity and cognitive outcomes of alcohol abuse. Findings of a study by Motaghinejad et al. demonstrated that curcumin reduced alcohol-induced oxidative stress, apoptosis, and inflammation via activation of the CREB/BDNF pathway [106]. In another study, Tiwari and Chopra showed that ethanol exposure resulted in impaired spatial navigation, increased oxidative-nitrosative stress, and heightened inflammatory signaling. However, simultaneous administration of curcumin effectively prevented all of these negative effects at behavioral, biochemical, and molecular levels [107]. In a separate study, these authors have also pointed out that curcumin's ability to mitigate oxidative stress, neuroinflammation, and apoptosis plays a significant role in preventing cognitive deficits in rats that were exposed to ethanol during the postnatal period [108]. Another study has also shown that curcumin treatment during the peri-adolescence period enhanced anxiety and memory deficits in mice exposed to prenatal and lactational alcohol. These mice also exhibited heightened expression of pro-inflammatory mediators, which could be prevented by curcumin administration [109]. Moreover, research has demonstrated that the protective effects of curcumin against acute ethanol-induced memory deficits are mediated through the suppression of nitric oxide synthase (NOS) activity in the brains of mice [110]. Collectively, curcumin holds promise as a therapeutic agent for mitigating the detrimental effects of alcohol on multiple organ systems, particularly the central nervous system.

5. Concluding remarks and future perspectives

In conclusion, the present review provided compelling evidence supporting the neuroprotective effects of curcumin against drugs of abuse, including morphine, nicotine, cocaine, methamphetamine, and alcohol. Through its diverse mechanisms of action, curcumin has demonstrated the ability to attenuate neuronal damage, oxidative stress, inflammation, and apoptosis induced by these addictive substances. The findings presented in this review highlight the potential of curcumin as a multifaceted neuroprotective agent in the context of drug addiction. By targeting key pathological pathways associated with drug-induced neurotoxicity, curcumin holds great promise for the prevention and treatment of addiction-related cognitive impairments and neurodegenerative disorders. Furthermore, the ability of curcumin to modulate neuroplasticity and synaptic plasticity provides a rationale for its use in promoting neuronal recovery and functional restoration following chronic drug exposure.

Despite the substantial progress made in understanding the neuroprotective effects of curcumin against drugs of abuse, several avenues remain unexplored, offering opportunities for further investigation. Firstly, more detailed studies are warranted to elucidate the precise molecular mechanisms underlying curcumin's protective effects. This includes investigating its interactions with specific drug targets, signaling pathways, and cellular receptors involved in addiction-related neurotoxicity. Additionally, further research is needed to optimize the delivery and formulation of curcumin to maximize its therapeutic efficacy. Strategies such as nanoparticle-based drug delivery systems or combination therapies could be explored to enhance the bioavailability and target-specific delivery of curcumin to the central nervous system. Furthermore, while preclinical studies have provided valuable insights into the neuroprotective effects of curcumin, clinical trials are required to evaluate its efficacy and safety in human subjects. Randomized controlled trials involving individuals with substance use disorders could provide valuable evidence regarding the potential benefits of curcumin as an adjunct therapy in addiction treatment. Moreover, considering the nuanced biological responses and potential variations between males and females, it is imperative to underscore the pivotal role of sex and gender considerations. Therefore, conducting trials to take sex and gender differences into account, seems necessary. Lastly, investigating the long-term effects of curcumin administration on addiction-related behaviors and relapse is crucial for understanding its full therapeutic potential. Animal models that recapitulate the chronic and relapsing nature of drug addiction should be employed to evaluate the sustained effects of curcumin and its ability to prevent addiction-related cognitive impairments.

Ethics approval

All study protocols have been conducted under approval of the Ethics Committee of Kerman University of Medical Sciences and were carried out in accordance with relevant guidelines and regulations.

Consent for publication

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CRediT authorship contribution statement

Masoud Soltaninejad: Data curation, Methodology, Software, Writing – original draft. **Reza Saboori Amleshi:** Conceptualization, Methodology, Software, Writing – original draft. **Mohammad Shabani:** Conceptualization, Data curation, Methodology, Writing –

review & editing. **Mehran Ilaghi:** Conceptualization, Data curation, Software, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

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

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