

Effects and mechanisms of medicinal plants on dopamine reward system to reduce complications of substance abuse: A systematic review

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Abstract

Substance abuse is one of the problems that many countries are currently dealing with and it imposes several complications on our communities. The dopamine reward system is one of the regions of the brain that plays important roles in the pleasure and persistence of addiction. This review was conducted to investigate the effects and action mechanisms of medicinal plants on the dopaminergic reward system in preventing substance abuse. The key words "dopamine*" in combination with "substance abuse", "drug abuse", "addiction" or "medicinal plant", "herb*", and "phyto*" were used to retrieve relevant publications indexed in the Institute for Scientific Information (ISI) and PubMed using the EndNote software. After examining the studies, we included 23 of them in final analysis. Medicinal plants and their derivatives can exhibit anti-addiction effects in substance use disorders mainly through influencing dopamine receptors (D1 and D2). They can also serve as appropriate alternatives to drugs and to help treat relapse due to stimulating the dopamine reward system. Because substance abuse is multifactorial, it should be taken into account that phytotherapy alone cannot be effective in treating it but instead a combination of different therapies should be adopted to fight it.

Key words: Medicinal plant; Dopamine; Neurotransmitter; dopamine reward system

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Introduction

Substance use disorders (SUDs) represent one of the problems that have engaged global communities in terms of both morbidity and mortality with stupendous costs on them (1). Substance abuse can lead to increased risk of chronic diseases, family breakdown, job loss, reduced longevity, crime and increased violence (2). The dopamine reward system of the brain is one of the most important mechanisms that arouses SUDs and prevents substance abuse withdrawal. In other words, stimulation of this system in the brain is misused and substance abuse occurs as an associated complication (3). Dopamine (DA) is considered one of the most important neurotransmitters in the dopamine reward system. The reward reinforcement circuitry modulates certain physiological and instinctive activities in humans including eating, water drinking, and sexual behaviors (4, 5). The disorders that involve the dopaminergic system impair cognitive functioning, and certain drugs are helpful to treat schizophrenia or attention deficit hyperactivity disorder (ADHD) in children (6), schizophrenia, Parkinson's disease, bipolar disorder, and Huntington's disease through targeting dopaminergic neurotransmission and its receptors (7-9).

Currently, despite the availability of several psychotherapies and behavioral therapies, chemical treatments for various disorders remain particularly important (10-16). Meanwhile, medicinal plants are being increasingly welcomed because of fewer side effects and lower costs (17-24). Medicinal plants can serve as effective treatments for different disorders and diseases (25-32).

Given the physiological and psychological significance of DA, we conducted this review to identify and investigate the action mechanisms of medicinal plants and their derivatives on the dopamine reward system, to decrease SUDs.

Materials and Methods

The search terms of interest and Endnote software were used. The key words "*dopamine**" in combination with "*substance abuse*", "*drug abuse*", "*addiction*" or "*medicinal plant*", "*herb**", and "*phyto**" were used to conduct this review. Relevant articles were retrieved from the databases Institute for Scientific Information (ISI) and PubMed. Then, the plants and the plant-based products that were effective on dopamine reward system in substance abuse were selected according to the comments of two colleagues. The articles included in this review were published between 2010-2017. The articles whose full text were not accessible, studies with non-positive effects, articles written in non-English languages and irrelevant to the purpose of this study were excluded after the authors' agreement was achieved. Finally, 23 articles were included in the study.

Results

Plants and plant-based compounds can be used to treat SUDs through relatively similar mechanisms, mainly influencing dopamine receptors (Table 1 - next page).

Controlling mental pressures contributes greatly to treating and preventing substance dependence. Choi et al. reported that the plant combination extract of *Elsholtzia ciliata*, *Shinchim*, *Angelicae gigantis Radix*, and *Eugenia caryophyllata* was helpful to reduce withdrawal complications through increasing dopamine function of the brain and affecting dopamine transporter (DAT) protein (50). An-jun-ning is the other herbal formulation that returns dopamine D2 receptor (D2R) and DAT to normal levels and decreases dopamine system with opioids in mice with addiction (51). In a study with alcoholic mice, the other herbal combination made up of *Tianma* (*Rhizoma Gastrodiae*), *Gouteng* (*Ramulus Uncariae Rhynchophyllae cum Uncis*), and *Baishao* (*Radix Paeoniae Alba*), called *Pingan Fingan*, was shown to decrease DA and glutamate (Glu), and a-aminobutyric acid (GABA) in the dopamine system of the brain and therefore can be effective in alcohol withdrawal (52). Kudzu is a Chinese herbal combination that can decrease the scores on Alcohol Use Disorders Identification Test in people with alcoholism due to daidzin (53). In two studies, patients with heroin addiction were administered with *Jitai* tablet. These studies showed that 6-month treatment with *Jitai* tablet led to increase in striatal DAT availability and DAT (54,55).

Medicinal plants exhibit anti-addiction properties through several mechanisms including physiological, biochemical, psychological, and transcendent mechanisms (56). Studies have also investigated the other aspects of this issue. A study showed that medicinal plants could decrease the unpleasant complications due to long-term substance abuse such as depression and anxiety and even be useful in treating these two psychiatric disorders (55). Herbal combinations cause increase in serotonin, DA (57), and dopamine transporters (55) and are therefore effective in treating anxiety, which is the other mechanism to decrease this complication. Medicinal plants can exert their effects in regulating the dopamine system of the brain and treating the associated diseases through important mechanisms such as influencing dopamine receptor antagonism (40). Medicinal plants and their derivatives decrease oxidative stress in the body (58-60). They may control neuroinflammation and decrease dopaminergic degeneration in the nervous system (61-65). It is important to determine the active doses of medicinal plants so that they can be effective in modulating and regulating dopamine. They should be usually consumed as balanced to cause as few side effects as possible (66). In addition, it should be taken into consideration that certain medicinal plants that contribute to increasing DAT levels and can decrease lactation, and therefore should be consumed cautiously and under physician's supervision in lactation (67-70).

Table 1: Medicinal plants and phytochemicals effective on dopamine

Plants /Phytocompound names	Type of use/ Origin	Main effects and mechanisms	References
<i>Brugmansia arborea</i>	Extract	Affecting the dopaminergic and the cholinergic systems, probably providing a neurobiological substrate for treatment of morphine or cocaine abuse	(33)
<i>Black asphaltum</i> (shilajit)	Extract	Altering cortico-hippocampal dopamine in alcoholic mice	(34)
<i>Thunbergia laurifolia</i> Linn.	Extract	Stimulating dopamine release from the nucleus accumbens (reward area responsible for addiction) both in vitro and in vivo as with cocaine and amphetamine without being addictive.	(35, 36)
<i>Paecilomyces japonica</i>	Extract	Modulating brain dopaminergic systems.	(37)
<i>Scutellaria baicalensis</i> Georgi	Extract	Attenuating morphine addiction-related behavior through functional regulation of dopamine receptors	(38)
Silibinin	<i>Silybum marianum</i>	Attenuating decreases in the dopamine content of the prefrontal cortex and treating the methamphetamine (METH)- induced cognitive impairments	(39)
Tetrahydropalmatine (l-THP)	Corydalis and Stephania	Preventing substitution of the dopamine D2/D3 receptor agonist and attenuating the reinforcing and subjective effects of cocaine, therapeutic effect on METH-induced locomotor sensitization; suppressing the rewarding properties of METH and elevating extracellular dopamine (DA) levels in the nucleus accumbens shell (nAcb); treating addiction and preventing relapse in nicotine and heroin-induced reinstatement.	(40-44)
Terpenoid cannabinoids	Cannabis plant	Modulating endocannabinoid and transient-receptor-potential-channel systems for cannabinoid abuse	(45)
Sauchinone	<i>Saururus chinensis</i>	Blocking the acquisition and expression of conditioned place preference (CPP) and acute hyperlocomotion induced by METH in mouse.	(46)
Tetrahydroprotoberberine	Corydalis yanhusuo W.T. Wang	Binding dopamine D1, D2, and D5 receptors and treating cocaine addiction	(47)
L-Stepholidine	<i>Stephania intermedia</i>	Influencing dopamine D1 receptor agonist/D2 antagonist properties and treating heroin relapse	(48, 49)

It is also worth mentioning that relapse of substance abuse is a complex and multifactorial issue that is affected by certain factors such as inappropriate lifestyle, unhealthy diet, unhealthy social relationships, inadequate physical activity, and even the type of abused substance, and therefore various treatments may be required to prevent substance abuse relapse (71,72). Therefore, using medicinal plants alone cannot be sufficiently effective to treat the complications of substance abuse and a combination of different therapies such as chemical treatments and psychotherapies should be

adopted to achieve the highest possible efficiency. Certain plants and their derivatives decrease withdrawal syndrome symptoms even through fighting the opioid system (66).

Conclusion

Medicinal plants and their derivatives can exhibit anti-addiction effects in SUDs mainly through influencing D1 and D2. They can also serve as appropriate alternatives to drugs and to help treat relapse due to stimulating the dopamine reward system. Although medicinal plants and their derivatives can help withdrawal from drugs and prevent substance abuse relapse through various mechanisms including physiological, biochemical, and psychological, it should be taken into account that phytotherapy alone cannot be effective in treating a complex disease such as substance abuse because they have mainly biologically therapeutic effects.

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