A Review on Medicinal Plants Used in Animal Models and Clinical Trials concerning Drug Addiction

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Abstract

Addiction to drugs, such as heroin, cocaine and alcohol, exacts great human and financial costs on society. Various evidence-based pharmacological and psychosocial interventions are currently used in the treatment of drug addiction but they do not produce adequate therapeutic benefits in every patient. Further, barriers such as financial cost, lack of availability, or perceptions of existing treatments as unappealing may limit rates of treatment uptake. Thus developing new treatments may attract a larger number of drug addicts into treatment. The use of herbal medicines within a pluralistic treatment model fits well within a range of existing theoretical frameworks for treating drug dependence. Here, the effects of *Hypericum perforatum, Valeriana officinalis, Passiflora incarnata, Rosmarinus officinalis, Papaver rhoea, Tabernanthe iboga, Ginkgo biloba, salvia miltiorrhiza, Pueraria lobata, Opuntia ficus-indica, Cynara scolymus, Panax ginseng,* melatonin, ibogaine and its derivative 18-methoxycoronaridine and some other plants active constituents in animal models and clinical trials concerning drug dependence as well as alcohol intake and hangover are reviewed. At this stage, there remains insufficient evidence to support the use of medicinal plants or their active constituents as a primary intervention for pharmacotherapy of drug addiction. Further clinical trials are required to clarify the potential role of particular agents.

Keywords: **Medicinal plants, Drug addiction, Alcohol intake, Alcohol hangover**

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Introduction

Addiction can be defined as a compulsion to take a drug with loss of control over drug taking, despite adverse consequences. The initial events that lead to addiction involve acute effects at a specific site (or sites) of action of a drug of abuse (on its target protein and neurons that express that protein). These sites of action typically activate neural networks that are associated with positive reinforcement. Repeated on-off exposure to a drug of abuse progressively leads to stable molecular and cellular changes in neurons, which alter the activity of neural networks that contain these neurons. This eventually results in complex physiological changes and related behaviors that characterize addiction, such as tolerance, sensitization, dependence, withdrawal, craving and stress-induced relapse. These drug-induced changes are, in part, counter adaptive, and they contribute to dysphoria and dysfunction, which promotes continued drug use through negative reinforcement mechanisms.

In the treatment of addiction, there are three main time points at which pharmacological interventions could be valuable. First, would be during active use of the drug itself. Second, would be to facilitate and/or ameliorate the signs and symptoms of withdrawal, if detoxification or achieving abstinence is considered to be the main initial goal. Third, would be relapse prevention once a state of abstinence from the drug of abuse is reached, such as chronic maintenance or replacement treatment [1].

Many existing pharmacological and physiological interventions for drug addiction are solidly evidence-based. Yet, there is a need to identify additional treatments. There is growing recognition that evidence-based treatments do not produce adequate therapeutic benefits in every patient. Additionally, barriers such as financial cost, lack of availability, or perceptions of existing treatments as unappealing may limit rates of treatment uptake. Developing new treatments within a pluralistic treatment model may attract a larger number of drug addicts into treatment. The use of natural and complementary therapies fits well within a range of existing theoretical frameworks for understanding and treating drug dependence. They could fulfill a variety of roles:

(1) As adjunctive treatments to existing pharmacological or psychosocial interventions.

(2) As treatment alternatives for drug users who are not eligible for existing treatments or who refuse existing treatments.

(3) As treatment options in countries or regions where evidence-based interventions are not routinely available.

(4) As treatment options for disorders where there is no current gold standard treatment.

It has been estimated that up to 45% of drug users employ natural and complementary therapies [2]. Surveys suggest that more than three-quarters of drug users contacting treatment services find complementary or alternative treatments acceptable [3, 4]. Natural and complementary therapies are a diverse and heterogeneous group of treatments; many, such as relaxation therapies, are already widely utilized within drug use treatment settings. This review will focus on medicinal plants rather than behavioral therapies and other modes of treatment. Although there are many addictive plants, relatively few have been identified as having the potential to counter addiction.

Drug withdrawal syndrome

The traditional aim of detoxification is to achieve a safe and humane withdrawal from a

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drug of dependence. Although unlikely to produce long-term abstinence in itself, detoxification is an attractive treatment option for many drug users and may permit individuals to reduce their drug use or prepare them for other treatment programs [5].

Pharmacological interventions

Pharmacological management of drug withdrawal is standard practice in many countries and an important component of comprehensive treatment provision. Use of herbal medicines with relevant pharmacological properties fits well within existing models of withdrawal management.

Many users of herbal medicines do so in conjunction with conventional treatments rather than take them as a true alternative.

Ginkgo biloba has an emerging evidence base to support its use as a cognitive enhancer in disorders of cognitive impairment such as dementia. Hypothesizing that improved cognitive function would improve treatment engagement, a double-blind clinical trial in dependent cocaine users receiving outpatient psychological treatments has been conducted. Participants were randomly allocated to one of three groups: ginkgo (standardized extract Egb761, 120 mg daily), piracetam (another nootropic agent, 4.8 g daily), or placebo. After 10 weeks there were no differences between the three interventions on any outcomes, including relapse rates, positive urine drug screens and craving or addiction severity scores. In fact there was a trend in some comparisons for placebo to be superior to other treatments. Although small sample size may have contributed to lack of observed effects for ginkgo or piracetam, the trend for effects to be in the opposite direction to what was hypothesized suggests that results do not reflect a type II error. However the negative finding highlights the need for efficacy to be tested in a controlled setting [6].

Hypericum (*Hypericum perforatum* or St John's Wort) is widely used as an herbal antidepressant with large number of controlled trials supporting its use in the treatment of mild (but not severe) depression [7, 8]. Hypericum has also been investigated for its effects on nicotine withdrawal. Similar pharmacological effects to existing treatments such as bupropion has partly contributed to the interest in hypericum. An animal study also reports that high doses of hypericum attenuated effects of nicotine withdrawal in mice [9]. This effect was the greatest when hypericum was initiated prior to nicotine cessation rather than delayed until emergence of withdrawal symptoms. Serotonin (5-HT) receptors could be involved in the beneficial effects of hypericum on nicotine withdrawal signs in mice [10]. Further, hypericum stimulates dopaminergic neurons similar to bupropione [11].

In a clinical study, 45 adult smokers were randomized to receive an oral spray containing hypericum or placebo spray in addition to brief counseling sessions and nicotine replacement patches. Although abstinence rates were similar in each group after 1 month, hypericum was associated with lower craving scores and less anxiety, restlessness and sleeplessness compared with controls [12].

Two uncontrolled trials have evaluated the effect of hypericum in smoking cessation. In one, 24 participants took 900 mg daily of hypericum for 1 week prior to and 12 weeks after quit day and 54% were continuously abstinent at 4 weeks and 38% at 12 weeks; abstinence rates that imply possible effectiveness [13]. In another study, 28 participants were randomized to 300 mg or 600 mg from 1 week prior to quit day for 12 weeks. Continuous abstinence rates at 4, 12

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and 26 weeks were 21%, 18% and 0% [14]. In a recent study, smokers with stopping smoking were randomized to 900 mg daily hypericum extract or placebo. Treatment started 2 weeks prior to quit day and continued for 14 weeks. Participants and researcher were blind to treatment allocation. All participants received weekly behavioral support. 6/71 (8.5%) participants on hypericum and 9/72 (12.5%) on placebo achieved prolonged abstinence at 4 weeks. At 6 months, 3 (4.2%) hypericum and 6 (8.3%) placebo participants were still abstinent. Taking together the absolute quit rates, the small difference between hypericum and placebo, and lack of effects on withdrawal shows that hypericum is ineffective for smoking cessation. Thus in view of the afore-mentioned clinical trials concerning hypericum, it is believed that further trials of hypericum for smoking cessation are unnecessary [15].

Numerous herbal medicines are utilized for their putative sedative properties. Some such as valerian (*Valeriana officinalis*) has evidence to support their use in insomnia. Sedative compounds have a potential role in the management of agitation, insomnia or anxiety associated with drug withdrawal. Pilot studies have reported beneficial effects of some sedative herbal medicines in the treatment of withdrawal syndrome. Passionflower (*Passiflora incarnata*) (with a daily dose of 60 drops of the extract) plus clonidine tablet with a maximum daily dose of 0.8 mg each administered in three divided doses was effective in the management of opiate withdrawal in the opiate addicts as compared to placebo drop plus clonidine tablet in the control group in a 14-day double-blind placebo-controlled clinical trial [16]. One review discusses the mechanisms of passionflower in the treatment of drug addiction focusing on one particular constituent, a benzoflavone moiety which animal studies have shown to reduce withdrawal severity from cannabis, benzodiazepine and nicotine addiction in mice. Unfortunately this review does not address the comparative effects between this constituent and whole plant preparations typically utilized for sedative and anxiolytic effects [17]. Melatonin (found in some algae and also secreted by the pineal gland) (0.3 mg orally) administered 3.5 h after the nicotine withdrawal in regular smokers significantly counteracted the acute effects of smoking cessation on mood but had no significant effect on performance compared to placebo [18]. In another double-blinded, placebo-controlled clinical trial, melatonin (2 mg in a controlled-release formulation) given nightly to benzodiazepine dependent patients with insomnia facilitated discontinuation of benzodiazepine therapy while maintaining good sleep quality [19]. Further, valerian extract (at the dose of 100 mg) improved sleep in patients withdrawing from benzodiazepine use in a double-blind, placebo-controlled clinical trial [20]. The potential to reduce morphine withdrawal signs in mice has been reported for rosemary (*Rosmarinus officinalis*) [21] and the corn poppy (*Papaver rhoea*), which may possess opioid and anticholinergic effects [22].

Ibogaine is a naturally occurring, psychoactive indole alkaloid derived from the roots of the rain forest shrub *Tabernanthe iboga* (TI). Indigenous people of Western Africa use TI in low doses to combat fatigue, hunger and thirst and in higher doses as a sacrament in religious rituals. The stimulating effects of TI have been well known for centuries. Ibogaine has been claimed to be effective in treating multiple forms of drug abuse including morphine, cocaine, heroin and nicotine [23, 24].

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Reducing hazardous alcohol intake

A series of animal studies has examined the potential for various plant derived compounds to reduce alcohol intake.

It has been proposed that ibogaine exerts its anti-craving effects by stimulating dopaminergic and serotonergic systems [25]. Accordingly, *Tabernanthe iboga* (TI) seems to be able to markedly reduce voluntary alcohol intake in alcohol-preferring rats [24]. This was not related to a possible interaction between TI and alcohol as shown by the virtually equal blood alcohol levels in both ibogaine- and placebo-treated rats. It is also of interest that the reducing effect on alcohol intake has been observed only when ibogaine was injected intra-peritoneally or intra-gastrically but not when it was injected subcutaneously. This feature suggests that the active principle of ibogaine could be a metabolite produced by the liver [26]. The therapeutic value of ibogaine is limited as it is highly neurotoxic and can cause irreversible cerebellar damage. As a result, further clinical studies have been abandoned. Because ibogaine at high doses can be toxic and cause side effects that may limit its therapeutic applications, an attempt has been made to design an ibogaine analog with no toxicity but with the same inhibitory action on reinforcing drugs. 18-Methoxycoronaridine (18- MC) appears to be such an analog. In animal models, 18- MC reduced intravenous morphine, cocaine, methamphetamine and nicotine self-administration, oral alcohol and nicotine intake and attenuated signs of opioid withdrawal, but had no effect on responding for a non-drug reinforcer and produced no apparent toxicity in comparison to ibogaine [27]. Another study showed that a single intraperitoneal injection of 18-MC significantly reduced alcohol intake and preference in a dose-dependent manner in preferring rats [28].

It has been hypothesized that ibogaine and its analog exert their suppressant effect on alcohol intake by modulating several neuronal ways in particular dopaminergic and serotonergic systems. The true mechanism of action of these compounds in attenuating alcohol intake is not fully understood. A firm conclusion awaits further pharmacological and behavioral studies [23, 24].

The dried roots of *Salvia miltiorrhiza* (SM) **(**danshen) are used within traditional Chinese medicine for the treatment of several pathologies (e.g., insomnia). Pre-clinical data suggest that compounds from SM extract: tanshinone IIA, cryptotanshinone and miltirone are effective in reducing voluntary alcohol intake in animal models of excessive alcohol drinking [29]. One research group has published three series of controlled experiments where SM was shown to reduce acquisition of ethanol intake in rats with no prior exposure [30], reduce ethanol intake in rats with established ethanol intake [31] and prevent increases in voluntary ethanol intake occurring after a brief period of abstinence, used as an animal model of relapse [32]. Recently the same study group has found that miltirone is the possible active chemical component responsible for the reducing effect of SM extracts on alcohol intake in rats [33]. Similar to SM extracts, miltirone markedly reduced blood alcohol levels in rats when alcohol was administered intra-gastric but not intra-peritoneal, suggesting that miltirone hampered alcohol absorption from the gastrointestinal system. Finally, miltirone failed to affect the severity of alcohol withdrawal syndrome in alcohol-dependent rats. The ability of miltirone to reduce alcohol intake in rats could be explained by the anxiolytic effect previously reported in the literature [34]. Future studies are needed to clarify this mechanism. SM has not been

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subjected to any human trials and is at an early stage of research into its effects.

The Kudzu plant (*Pueraria lobata*) has been used traditionally in china to treat alcohol intoxication and hangover [35]. Recent animal research explores the potential for two isoflavone derivatives (daidzin and puerarin) to reduce alcohol intake [23, 24]. Two recent studies add to existing findings, reporting that Kudzu root extracts led to significant reductions in alcohol consumption in rats with established alcohol intake [36] and that puerarin produced reductions in alcohol intake but only temporarily [37]. According to the animal data, a preliminary clinical study explored the effect of kudzu root extract on 38 patients affected by alcohol dependence and were randomly assigned to receive either kudzu root extract (1.2 g twice daily) or placebo. Sobriety level and a visual analogic scale to assess alcohol craving were assessed. Kuduzu root appeared to be no better than placebo in reducing alcohol craving and/or promoting sobriety. Unfortunately the authors did not report the concentrations of the active isoflavones in their kudzu extract [38]. More recently a study has tested the efficacy of a kudzu extract in a group of heavy alcohol drinkers, treated with either placebo or kudzu extract (500 mg three times daily for 7 days). After the 7-day period, subjects had the opportunity to drink their preferred brand of beer in a naturalistic laboratory setting. Kudzu treatment resulted in significant reduction in the number of sips and the time to consume each beer and a decrease in the volume of each sip. These changes occurred in the absence of a significant effect on the urge to drink alcohol. The authors concluded that kudzu may be a useful adjunct in reducing alcohol intake, although the exact mechanism by which kudzu suppresses ethanol intake remains to be clarified [39]. Future research needs to identify the differences in pharmacological activity between single isolated constituents and whole plant extracts.

Animal studies suggest that acute administration of hypericum can reduce voluntary alcohol intake and act synergistically with opiate antagonists [24]. Two recent studies examining the effects of hypericum on alcohol intake in rats confirm previous research and demonstrate that the constituent hyperforin contributes to observed reduction in alcohol intake [40, 41]. Hypericum extract has had alcohol intake and preference reducing effects comparable to imipramine and fluoxetine in a rat genetic model of alcoholism [42]. Hyperforin is currently considered to be the primary contributor to antidepressant effects [43]. The mechanism behind effects on alcohol intake is not established. Hypericum inhibits reuptake of various neurotransmitters including monoamines, γ-aminobutyric acid (GABA) and glutamate [43]. The antidepressant-like effect of hypericum extract in the rat forced swimming test may be mediated by interaction with σ receptors and to some extent by increased serotonergic neurotransmission. On the other hand, these mechanisms appear to be unimportant for the effect of hypericum on ethanol intake [44]. The effects on ethanol intake may also be secondary to anxiolytic or sedative activity. Thus hypericum extract may be an interesting adjunct for the treatment of alcoholism. Without human studies, these findings have little direct application to the clinical setting. However hypericum seems a likely candidate for advancing into clinical testing, given the large body of human data for other indications and availability of standardized formulations.

There are some accounts of the effects of *Panax ginseng* **(**ginseng) and its derivatives on alcohol intoxication. Early works recorded that

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ginseng saponines increased the rate of oxidation of ethanol in alcohol-fed rats [45] and red ginseng extract prevented memory failure and excitation in alcohol-intoxicated mice [46]. Later, it was demonstrated in healthy human volunteers that in 10 out of 14 cases ginseng extract (3 g/65 kg body weight) accelerated alcohol clearance by 32-51% [47]. Ginseng saponines apparently stimulate the microsomal ethanol-oxidizing system and the aldehyde dehydrogenase (ADH) enzyme action and therefore there is a faster removal of acetaldehyde with rapid shunting of excess hydrogen into lipid biosynthesis [48]. It has been also shown that rats plasma levels are lower (- 20%) when alcohol is administered orally with red ginseng extract than when alcohol is given alone. However, further studies support the idea that ginseng may promote faster disposal and elimination of alcohol from blood after drinking [49]. Obviously further studies are needed concerning the value of ginseng in the treatment of alcoholism and associated problems, e.g., memory loss and nervous reactions.

Alcohol hangover

Two clinical studies have examined plant derived products for the prevention of alcohol related hangover. The most recent of these examined the effects of an extract from the fruit of the *Opuntia ficus- indica* (also called nopal or prickly pear). Using a double blind crossover design, 64 volunteers were randomly allocated to take a single dose of nopal (1600 IU) or placebo 5 h prior to alcohol ingestion. Overall, the risk of a serious hangover was halved in the group receiving the active treatment. Additionally, nopal treatment was associated with better overall well-being and lower ratings of nausea, anorexia and dry mouth compared with placebo. After alcohol ingestion, C-reactive protein levels increased in the placebo condition. This increase was attenuated in patients receiving nopal. The investigators attribute observed therapeutic effects to the anti-inflammatory activity of nopal [50].

The second clinical study examined extracts from the globe artichoke (*Cynara scolymus*), an agent which is sometimes marketed as a hangover cure and has possible choleretic properties. Using a crossover design, 15 participants were randomly assigned to 3 capsules of standardized globe artichoke extract (320 mg) or indistinguishable inert placebo immediately before and after alcohol consumption. Artichoke extract was not effective in preventing the signs and symptoms of alcohol-induced hangover. Further the artichoke extract did not speed up recovery time. Small sample size may have contributed to lack of significant effects [51].

Safety issues relevant to the plants used in the treatment of drug addiction

Although herbal medicines are often perceived to be safe and free of unwanted effects, evidence continues to emerge that safety can not be assumed [52]. Some of the common adverse effects and drug interactions of the plants or herbal compounds used in treatment of drug addiction are cited in the Table 1 [53, 54, 55, 56].

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Table 1- Common adverse effects and drug interactions of the plants or herbal compounds used in treatment of drug addiction

Plant or herbal compound name	Common adverse effects	Drug interactions
Hypericum perforatum	Similar to selective serotonin reuptake inhibitors; photosensitivity; pruritis; delayed hypersensitivity	Serotonergic antidepressants; CYP3A4, IA2 and 2C9 induction: HIV protease inhibitors, HIV non-nucleoside reverse transcriptase inhibitors; warfarin; cyclosporine; oral contraceptives; anticonvulsants; digoxin; theophylline
Valeriana officinalis	Drowsiness; GI upset; liver function abnormalities; headache; palpitations; insomnia; hepatitis	Increase in effect of sedatives; CYPA4 inhibitors
Passiflora incarnata	Dizziness; confusion; ataxia; vasculitis; nausea; vomiting; drowsiness; tachycardia; hepatic and pancreatic toxicity	Anticoagulants; increase in effect of sedatives; CYP3A4 inhibitors
Rosmarinus officinalis	Seizures (at high doses); asthma (from repeated occupational exposures); contact dermatitis; photosensitivity	None reported
Papaver rhoea	Vomiting; stomach pain	None reported
Ibogaine and its derivative 18-methoxycoronaridine	Cholinesterase inhibitor: can lead to cholinergic toxicity; bradycardia; ibogaine but not 18MC: significant cerebellar toxicity	Cholinergic and anticholinergic drugs
Ginkgo biloba	Increase of bleeding time; intracerebral hemorrhage; possibly adverse effects on male and female fertility	Antithrombotic agents
Salvia miltiorrhiza	A case of overcoagulation in a patient with rheumatic heart disease	Potentiates warfarin activity
Pueraria lobata	None reported	Theoretically with anticoagulants, aspirin, cardiovascular agents and hypoglycemic drugs
Opuntia ficus-indica	Diarrhea; nausea; abdominal fullness; headache	Hypoglycemic drugs
Cynara scolymus	Contact dermatitis	Insulin; oral antidiabetics
Panax ginseng	Promotes mastalgia; rarely causes postmenopausal bleeding; >3 g per day causes ginseng abuse syndrome consisting of morning diarrhea, nervousness, insomnia, rash, depression and amenorrhea; in cigarettes exacerbates symptoms in schizophrenic patients; induces manic state in depressive patients; palpitations; nausea; vomiting; blurred vision; hoarseness; abnormal uterine bleeding	Insulin; oral hypoglycemics; antithrombotic agents; monoamine oxidase inhibitors; loop diuretics; digoxin

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Conclusion

Despite growth in research into herbal therapies, at this stage there remains insufficient evidence to support the use of herbal therapies as a primary intervention for drug addiction. Should we discourage drug addicts from using herbal therapies? When making these judgments, it is important to consider the broader clinical context. Treatments with demonstrated efficacy should be promoted where available. However, gold-standard interventions such as methadone maintenance remain unappealing for many opiate users. Additionally, treatment options with demonstrated efficacy may not be widely available or accessible in some regions. When little evidence exists to support an intervention, patients should be told this, as part of an informed decision-making process. Monitoring changes in target symptoms such as drug consumption or drug craving is a technique commonly incorporated into existing drug addiction treatments, and is an important component of gauging treatment response. A systematic approach to treatment utilizing outcome monitoring is especially important when trialing a nonevidence-based intervention.

Continuing research is needed to clarify the potential role of particular interventions. Positive effects in animal studies do not necessarily translate to clinical effectiveness. These studies may contribute to our understanding of the pharmacology of these compounds. However without clinical research they provide little to guide treatment. Therapies which have shown promise in human studies need to be subjected to larger adequately powered controlled trials. It would be desirable for future clinical research to examine herbal medicines not in isolation, but to compare them with both existing treatments and strategies that optimize existing treatments. Drug dependence is a chronic disorder; research needs to incorporate longer-term treatments outcomes and conform to the current standards by which we evaluate conventional interventions.

In conclusion, no herbal therapies have yet been fully demonstrated to be effective for drug addiction treatment. The limitations of existing research augur well for researchers rather than clinicians. It is likely that any potential role for herbal medicines will be as part of a multi-dimensional approach to service provision rather than as sole interventions. More research is required to define this role. In the meantime, it is important that our enthusiasm for new treatments does not generate a situation where drug addiction disciplines endorse a lower standard of clinical evidence than would be acceptable in other fields of medicine.

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