

Leveraging the Potential Benefits of Medicinal Plants in the Management of Substance Abuse

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Abstract

There is a global increase in the number of reported cases of drug misuse and addictions. In addition to several health issues, the addict-forming substance affects society economically. Cocaine, heroin, opium, alcohol, nicotine, and marijuana are a few of the major substances that are abused. These agents' inexpensive cost and wide availability contribute to their abuse. Many conventional medications are available to treat substance abuse-related disorders, but they come with several side effects. One potential treatment option for the issues experienced by addicts is the use of alternative medications obtained from natural sources. The current study provided an overview of a few published studies that suggested herbal medication may be effective in reducing withdrawal symptoms. The information was obtained from the Web of Science, NCBI, PUBMED, EMBASE, and Google Scholar. The retrieved data were analyzed to determine the active constituent present in the plant material, the type of addict substance tested, and the possible mechanism identified. The research identified some of the plants that have been reported to be effective in the management of substance abuse complications. Information analysis revealed that plant-based medications helped lessen anxiety, pain, insomnia, and deviant conduct, among other consequences of substance usage. Withdrawal as well as dependence liabilities due to addictive agents were found to be reduced. The plant-based medicines exhibited their action on brain centers involving dopaminergic, serotonergic, and adrenergic transmission. The observations from the study revealed that herbal medicines were effective in the management of substance abuse complications. However, most of the investigations were conducted using pre-clinical testing models. Therefore, it can be said that while herbal medications showed promise in treating drug abuse-related problems, further study is necessary to pinpoint the exact safety and effectiveness of these agents.

Key words: Complications, drug screening, herbal medicines, management, substance abuse

INTRODUCTION

Substance abuse, also referred to as drug abuse, is the use of a substance in quantities or ways that are hazardous to the user or other people. It is a type of disorder linked to substances.^[1] Under the influence of these substances, people might behave criminally or antisocially and long-term abusers

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are associated with personality changes.^[2] Certain drug usage carries a potential risk of criminal penalties in addition to potential physical, social, and psychological harm. Alcohol, amphetamines, barbiturates, benzodiazepines, cannabis, cocaine, hallucinogens, methaqualone, and opioids are important substances that are being abused by populations in different countries.^[3]

When an individual loses control over their drug use despite being aware of the negative effects, they are said to have an addiction.^[4] Initially, acute effects occur at specific sites of action of the substance, followed by the activation of multiple brain networks associated with positive reinforcement.^[5] Chronic drug use leads to complex physiological changes, including withdrawal symptoms, cravings, tolerance, desensitization, dependence, and stress-induced relapse. Ultimately, these consequences culminate in dysphoria and dysfunction, triggering the body's negative reinforcement processes.^[6]

The literature claims that using plants as medication might help people cope with life's stressors, alleviate illnesses, and even change their consciousness.^[7] In many areas, these naturally produced chemicals are still widely used to treat disease conditions, either in addition to or as an alternative to conventional medical therapy.^[8] However, because of their ability to produce a wide range of therapeutic effects, including sedative, euphoric, anticholinergic, psychotic, and stimulant, some of these medicinal herbs have a propensity to be overused due to their actions on the brain centers.^[9] All age groups abuse these plant products, but mostly teenagers do so since they are inexpensive and simple to get.^[10]

Cocaine, heroin, meth, opium, marijuana, alcohol, and nicotine are regarded as some of the main substances that lead to addiction.^[11] Substance addiction is a significant issue that societies worldwide are dealing with. Drug addiction is said to have negative effects on society from a variety of angles, including health, economics, and family mistrust.^[12] Research estimates that there are over 284 million drug addicts globally, with 12,000,000 being chronic users and 6,000,000 being infrequent users.^[13] Research has shown that several commonly prescribed drugs for addiction treatment are linked to several negative side effects, which can occasionally make patients' health conditions worse.^[14]

Natural plants have been utilized to address some of the issues associated with drug addiction.^[15] According to a study of the literature, several medicinal plants have been used for centuries to treat symptoms associated with substance addiction overdoses, including withdrawal.^[16] The main advantages of employing plants in de-addiction treatments have reportedly been identified as the presence of many active ingredients in herbal medications with distinct mechanisms and inherent lack of toxicity.^[17] The current analysis focuses on the significant substitutes and explores possibilities made from plants that may be used to treat substance abuse-related difficulties.

SEARCH METHODS

A search for relevant literature was done using keywords such as "Potentiality," "Plants," "Management," "Substance abuse," "Addiction," and "Withdrawal symptoms" on the websites of PubMed, Google Scholar, and ScienceDirect. The review of the literature was completed in April and September of 2023. The review produced a total of 981 papers. Only 36 papers, nevertheless, were chosen for this investigation. The paper titles, abstracts, methodology, findings, and content were all subjected to an independent assessment by the authors. Critical factors for content evaluation included information on the English language, scientific content, research design, administration route, chemical analysis, biochemical estimate, and statistics. The review only contained papers with this information.^[18] Figure 1 represents the approach adopted to retrieve the scientific information from the literature. A summary of the action of plant-based medicine in the management of substance abuse is represented in Figure 2, whereas important characteristics are in Table 1.

ANALYSIS

Asafetida

It is essentially a dried latex made from the tap root or rhizome of several *Ferula* species. The plants are perennials that reach a height of 1.5 m, and they are members of the *Apiaceae* family. About 60% resin, 25% endogenous gum, 10% volatile oils, and 5% ash are present in asafetida.^[19] Asaresinotannols A and B, ferulic acid, umbelliferone, 2-butyl-propenyl-disulfide, diallyl sulfide, diallyl disulfide, and dimethyl trisulfide are the phyto-active ingredients that have been found.^[20] Asafetida is frequently used in the creation of many cuisines as a flavoring ingredient. Asafetida has antidotes for opium as well as medicinal qualities that help with stomach, menstrual irregularities, and throat issues.^[21]

Asafetida has been shown in certain trials to prevent weight loss in rats treated with morphine and to lower the scores of abstinence responses.^[22] To assess asafetida's involvement in the treatment of drug usage issues, more research is recommended.

Berberis vulgaris

Berberis, commonly referred to as Barbery, is a member of the *Berberidaceae* family. There are several species of the plant in North America, Asia, Europe, and Africa. The plant is evergreen and deciduous, growing to a height of 1–5 m. The blooms are bright or orange in hue, and the leaves are long.^[23] Berberine and barbamine have been isolated and identified. Triterpenes, tannins, phenolic compounds, and alkaloids are additional active constituents.^[24] The herb has historically been used as an antidote for snake and scorpion

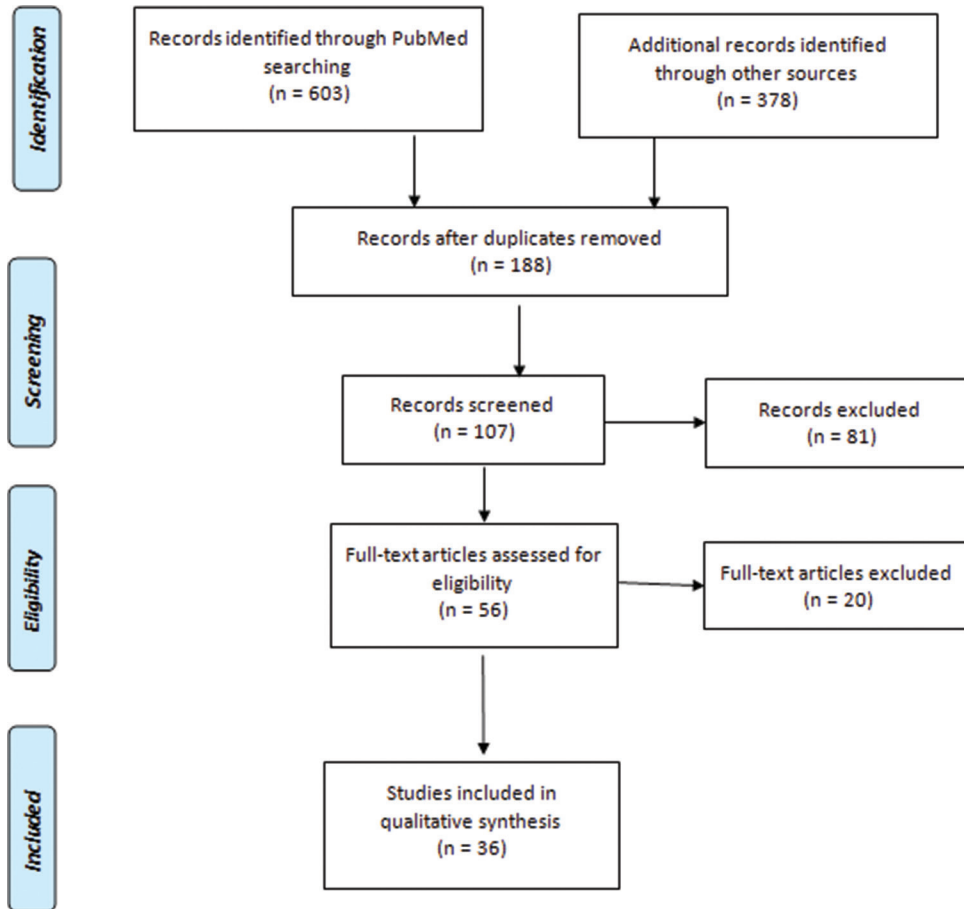


Figure 1: Flow diagram to select the scientific studies from the literature

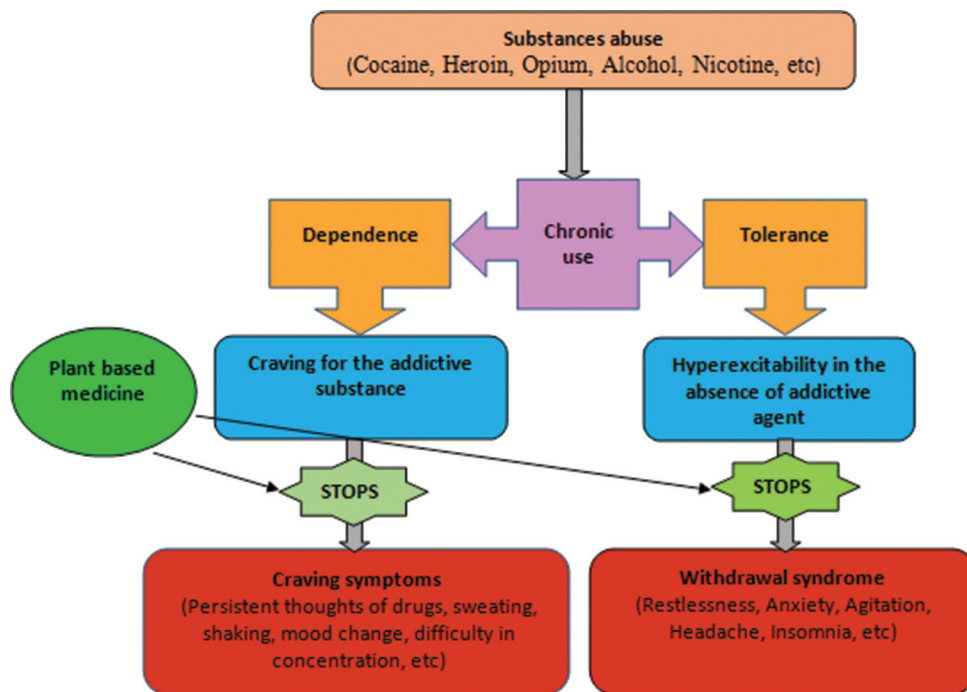


Figure 2: Actions of herbal medicine on substance abuse complications

bites, as well as a remedy for infectious illnesses, wounds, hemorrhoids, diarrhea, and uterine and vaginal issues.^[25]

Berberis is the source of berberine, an isoquinoline alkaloid. Studies on this ingredient showed anticonvulsant and

Table 1: Characteristics of some important plants being tested for management of substance abuse complications

S. No.	Name of the plant	Source	De-addiction	Major active ingredient[s]	Possible mechanism of action	References
1	<i>Asafetida</i>	<i>Apiaceae</i>	Morphine	Asaresinotannols-A and B, Ferulic acid and Umbelliferone	Unknown	[19-22]
2	<i>Berberis</i>	<i>Berberidaceae</i>	Morphine	Berberine and barbamine	Modulation of hypothalamic corticotrophin-releasing factor and the noradrenergic system in the CNS	[23-27]
3	<i>Camellia sinensis</i>	<i>Theaceae</i>	Morphine	Caffeine, theobromine, chlorogenic acid, and ellagic acid	Increased cAMP concentrations in the locus coeruleus and D-2 dopamine receptor signaling	[28-31]
4	<i>Caulis sinomenii</i>	<i>Menispermaceae</i>	Morphine	Menisperine, sinomenine, laurifoline, magnoflorine and norsinoacutin	Modulating the monoaminergic transmission and histamine levels	[32-35]
5	<i>Cynara scolymus</i>	<i>Asteraceae</i>	Alcohol	Caffeoylquinic acids and flavonoids, inulin	Through choleric and diuretic effect	[36-39]
6	<i>Chamomile</i>	<i>Asteraceae</i>	Morphine	Flavonoids, coumarins, volatile oils, terpenes, and sterols	Altering neurochemical systems of dependence in the CNS	[40-43]
7	<i>Datura</i>	<i>Solanaceae</i>	Opioids	Atropine, hyoscyne, cardiac glycosides, tannins, flavonoids, and phenolic compounds	Mainly through anti-cholinergic effects	[44-48]
8	<i>Ginseng</i>	<i>Araliaceae</i>	Morphine and alcohol	Gintonin, steroids, saponins like ginsenosides	inhibition to behavior sensitization to morphine and stimulate the microsomal ethanol-oxidizing system to promote alcohol removal	[49-55]
9	<i>Ginkgo biloba</i>	<i>Ginkgoaceae</i>	Cocaine	Myricetin, Kaempferol, Isorhamnetin, ginkgolides, and bilobalide	Unknown	[56-59]
10	<i>Hypericum perforatum</i>	<i>Hypericaceae</i>	Nicotine and alcohol	Hyperforin, hypericin, and hyperoside	Involvement of serotonin receptors for nicotine and opioid receptor antagonism for reducing alcohol intake	[60-69]
11	<i>Nigella sativa</i>	<i>Ranunculaceae</i>	Opioids	Linoleic acid, oleic acid, palmitic acid, nigellicine, nigellidine, and nigellimine	Unknown	[70-73]
12	<i>Opuntia ficus-indica</i>	<i>Cactaceae</i>	Alcohol	Palmitic acid, oleic acid, linoleic acid, and linolenic acid	Unknown	[73,74]

(Contd...)

Table 1: (Continued)

S. No.	Name of the plant	Source	De-addiction	Major active ingredient[s]	Possible mechanism of action	References
13	<i>Passion flower</i>	<i>Passifloraceae</i>	Opioids	Beta-carboline and passiflora	Unknown	[78-82]
14	<i>Peganum harmala</i>	<i>Nitrariaceae</i>	Opioids	Harmaline	Through influencing the opioid circuits and receptors	[83-87]
15	<i>Pueraria lobate</i>	<i>Fabaceae</i>	Alcohol	Puerarin, daidzein, tectoridin, and glycitin	Through the central nervous system, action reduces the alcohol urge	[88-93]
16	<i>Rosmarinus officinalis</i>	<i>Lamiaceae</i>	Morphine	Rosmarinic acid, luteolin, and carnosic acid	Unknown	[94-96]
17	<i>Salvia miltiorrhiza</i>	<i>Lamiaceae</i>	Alcohol	Tanshinone, cryptotanshinone, and miltirone	Through the central nervous system, action reduces alcohol intake	[97-101]
18	<i>Stephania and Corydalis</i> genus	<i>Menispermaceae papaveraceae</i>	Opioids	Levo tetrahydropalmatine	Through antagonism of dopamine receptors [D1, and D2] as well as actions at dopamine D3, alpha-adrenergic and serotonin receptors	[102-110]
19	<i>Tabernanthe iboga</i>	<i>Apocynaceae</i>	Opioids	Ibogaine	Stimulating dopaminergic and serotonergic systems.	[111-115]
20	Valerian	<i>Valerianaceae</i>	Opioids	Valerenic acid and valerenol	Allosteric modulation of GABA-A receptors that induces the anxiolytic activity	[116-120]

antispasmodic properties. By weakening the sympathetic nervous system, it also reduces nausea and diarrhea.^[24] Berberine was also shown to block calcium channels and eliminate tachycardia during the withdrawal phase.^[26] In addition, studies showed that berberine decreased feelings of anxiety and sadness that were closely linked to stopping morphine. This effect may have been caused by berberine's regulation of the noradrenergic system and the hypothalamic corticotrophin-releasing factor in the central nervous system (CNS).^[27] According to these researches, berberine may be an essential ingredient in the creation of substitute medications for the treatment of morphine withdrawal symptoms, including anxiety and sadness.^[26,27]

Camellia sinensis

The plant, which is mostly grown in mountainous areas, is a kind of tiny tree or evergreen shrub that belongs to the *Theaceae* family. Tea is commonly made from the leaves and bud leaves. The plants are indigenous to parts of Asian nations.^[28] It is said that tea, or decoction, is one of the most popular drinks in the world.^[29] It is thought that the drink has CNS stimulant effects, mostly because of the

caffeine. Theobromine, ellagic acid, gallic acid, catechins, and chlorogenic acid have all been found to be additional active components in the tea decoction.^[30] Tea leaves have been shown to have CNS stimulation in addition to immunostimulatory, anti-inflammatory, anti-stress, anti-anxiety, and anticancer properties.^[29]

Popularly known as green tea, *C. sinensis* has active ingredients that have been shown to reduce the symptoms of morphine withdrawal in a dose-dependent manner. In addition, the investigations showed that during morphine withdrawal, the phyto-components of the plant raised cAMP concentrations in the locus coeruleus, and D-2 dopamine receptor signaling.^[31]

Caulis sinomenii

Native to China and Japan, the plant is also known as sinomenine or cocculine. The *Menispermaceae* family is where the plant is categorized. This climbing plant's dried stems have long been used to treat arthritis and rheumatism because of their anti-inflammatory qualities.^[32] In addition, it was said that the extract relaxed the vascular smooth

muscles. The key ingredients found include norsinoacutin,^[33] menisperine, sinomenine, laurifoline, magnoflorine, 6-O-methyl-laundanosoline-1-O-glucopyranoside, and laundanosoline-1-O-xylopyranose.

The plant's extracts are said to have analgesic, sedative, and anxiolytic-like properties and are regarded as an essential part of Chinese medicine. It was discovered that the *C. sinomenii* extract was useful in treating drug dependency, which is linked to aberrant monoaminergic transmission.^[34] In addition, it has been observed that the plant extract inhibits the morphine-induced acquisition of place preference and modifies the amount of histamine in the CNS of mice that are dependent on morphine.^[35]

Cynara scolymus

It is also known as the globe, French, or green artichoke. The perennial plant, which is endemic to Mediterranean areas, is a member of the *Asteraceae* family. Large-headed blooms and glaucous green foliage adorn the shrub, which may reach a height of 2 m.^[36] The purple blossom features buds that are delicious. It is believed that artichokes contain flavonoids and polyphenolic chemicals, namely caffeoylquinic acids, in addition to the polysaccharide inulin.^[37] The herb has long been used to treat irritable bowel syndrome, liver dysfunction, hyperlipidemia, nausea, dyspepsia, hangovers from alcohol, and gallstone prevention. Furthermore, it has choleric and diuretic properties to encourage the formation of bile.^[38]

The plant was examined for signs of alcohol hangovers. The plant extract was thought to have a choleric impact and served as the foundation for testing against the symptoms of alcohol withdrawal.^[38,39] A small number of study data showed that the herbal remedy was acting in a promising manner, but additional investigation is required to fully comprehend the role that artichokes play in alcohol intoxication.

Chamomile

It is a member of the *Asteraceae* family and is also known as chamomile. Most nations in Europe, Asia, and America are where it flourishes. The plant has slender, spindle-shaped roots and is an annual. The stem can reach a height of 10–80 cm and is upright and strongly ramified. The blooms are white and the leaves are bi-tripinnate.^[40] People ingest chamomile through food and drink. It is used to treat ulcers, wounds, gastrointestinal issues, sleeplessness, hemorrhoids, and wounds, among other medical conditions. It also has antipyretic and anti-inflammatory effects. Flavonoids, coumarins, volatile oils, terpenes, sterols, and polysaccharides are the active ingredients that have been identified.^[41]

Studies on rats using chamomile extract indicate that it lessened the symptoms of withdrawal brought on by morphine. Some of the morphine withdrawal symptoms, such

as grooming and raising, were sedatively affected by two active components, apigenin, and chrisin (phytoestrogen), which were extracted from the extract.^[42] The explanation for this was proposed because phytoestrogens may have reduced the symptoms of morphine withdrawal syndrome by acting on some neurochemical systems of dependency in the CNS.^[43]

Datura

Because of its deadly effects, this genus of nine species is often known as devil's trumpets. The plant, which is a member of the *Solanaceae* family, may be found growing throughout America, Africa, and Asia. With upright blooms and alternating leaves, the plant reaches a height of 2 m.^[44] According to reports, the herb has pain-relieving qualities and is used to treat hemorrhoids and Parkinson's disease.^[45] On the other hand, the plant is dangerous and can result in delirium, respiratory depression, arrhythmia, hallucinations, psychosis, and even death if consumed. Atropine, hyoscine, cardiac glycosides, tannins, flavonoids, and phenolic compounds are among the significant phyto-constituents that were identified.^[46]

Hyoscine and scopolamine are the main ingredients that give *Datura* extracts their analgesic and anti-inflammatory properties, according to research on the extracts.^[47] Of its anticholinergic properties, the plant was also shown to be useful in lowering the occurrences of opioid withdrawal symptoms. This action may have been mediated by the limbic system or by neural circuits that influence the autonomic nervous system. The two most significant withdrawal symptoms that *Datura* reduced in rats were bruxism and diarrhea.^[48]

Ginseng

Ginseng is the root of plants of the *Panax* genus, of which there are multiple known types, including American, Chinese, and Korean *Ginseng*. It is a member of the *Araliaceae* family. The plant's roots have a pale brown color and resemble a person's limbs and body.^[49] Gintosides, steroids, and other saponins like ginsenosides are the most significant phytoconstituents found in *Ginseng*. The traditional usage of *Ginseng* extract is to enhance general well-being.^[50] The extracts are frequently used to boost immunity, combat illness, and deal with stress. In addition, investigations have suggested that *Ginseng* might help cure erectile dysfunction and diabetes. Other uses include the treatment of headache, fever, indigestion, and infertility.^[51]

Previous research has shown that *Ginseng* extract blocks the analgesic effects of opioids in a non-opioid-dependent manner. *Ginseng* was also demonstrated to reduce morphine tolerance and dependency liability. According to the research, *Ginseng* can lessen the inhibitory impact of co-exposure to foot shock stress on the development of morphine tolerance,

but not the psychological stress in animal models.^[52] Several mechanisms, including suppression of behavior sensitization to morphine, methamphetamine, and cocaine, have been suggested as the mechanism behind this. In addition, it was shown that *Ginseng* inhibited the recurring phenomena of the effects of cocaine and methamphetamine.^[53]

Studies on the saponins extracted from *Panax Ginseng* (*Ginseng*) showed that the herb accelerated the rate at which ethanol was oxidized in rats given alcohol. The microsomal ethanol-oxidizing system and aldehyde dehydrogenase (ADH) enzyme activity have been observed to be stimulated by the administration of saponins; as a result, acetaldehyde is removed more quickly, and excess hydrogen is quickly shifted into lipid biosynthesis.^[54] Furthermore, the results of these investigations showed that red *Ginseng* reduced alcohol-induced mice's excitement and memory impairment. According to clinical experiments, *Ginseng* extract helped abusers remove alcohol up to 50% faster. According to these investigations, *Ginseng* may be used in the treatment of alcohol intoxication.^[55]

Ginkgo biloba

It is a member of the *Ginkgoaceae* family and is also known as ginkgo or ginkgo. The plant may be found growing in numerous Asian nations' temperate zones. Ginkgo is widely used in these areas as a dietary supplement to help maintain human health. These plants produce big trees that may grow up to 35 m in height. Dioecious blooms adorn the fan-shaped leaves.^[56] Treatments for high blood pressure, menopausal problems, tinnitus, post-stroke recuperation, dementia, tardive dyskinesia, and cognitive impairments have been used traditionally.^[57] Phenolic acids, proanthocyanidins, flavonoid glycosides (such as myricetin, kaempferol, and isorhamnetin), quercetin, trilactones, ginkgolides, and bilobalide, as well as special ginkgo biflavones, alkylphenols, and polyphenols, are among the significant phytochemicals that have been found.^[58]

According to some research, *G. biloba* may be able to help manage the negative effects of cocaine by minimizing a few minor issues.^[59] To be more specific about the effectiveness in treating withdrawal symptoms, additional study is recommended.

Hypericum perforatum

It is a blooming tree in the *Hypericaceae* family that is popularly known as St. John's Wort. It may be found in temperate regions of Australia, Africa, and America. The plant has spreading rhizomes and is perennial. With branching leaves and vivid yellow blooms, the upright stems can reach a height of 1 m.^[60] Hyperforin, hypericin, tannins, flavonoids, phenolic acids, isoquercitrin, hyperoside, quercitrin, chlorogenic acid, and rutin are the essential constituents of

the plant.^[61] It has a long history of use in the treatment of bacterial and viral infections, anxiety, depression, wounds, burns, cancer, inflammatory-related illnesses, and as an antioxidant and neuroprotective agent.^[62]

Because *H. perforatum* possesses antidepressant properties, it has been investigated for nicotine withdrawal. It has been shown that giving mice *Hypericum* beforehand has an effective way of lowering the symptoms of nicotine withdrawal.^[63] It was proposed that serotonin receptors have a role in the process.^[64] In addition, the findings from the animal research are corroborated by the clinical trials on *Hypericum*, which showed that adult smokers treated with *Hypericum* experienced fewer cravings, anxiety, restlessness, and insomnia than the control groups who did not get any therapy.^[65]

According to a different study, *Hypericum* can work in tandem with opiate antagonists to decrease voluntary alcohol consumption. A rat investigation revealed that the active ingredient, hyperforin, was responsible for both the activity and the decrease in alcohol consumption. *Hypericum*'s action is similar to that of fluoxetine and imipramine.^[66] Moreover, earlier studies revealed that hyperforin had strong antidepressant properties, which may be attributed to its interaction with σ receptors and, to a lesser degree, to elevated serotonergic neurotransmission.^[67]

One potential mechanism proposed for the activity of *Hypericum* is its capacity to decrease the absorption of several neurotransmitters, including glutamate, γ -aminobutyric acid (GABA), and monoamines.^[68] A further benefit might be the sedative and anxiolytic effects that have been documented following the intake of *Hypericum*.^[69] According to the research, *Hypericum* may be a useful medication for de-addictive sessions as well as one of the prospective agents in addressing the issues related to alcohol intoxication and nicotine misuse.

Nigella sativa

Other names for it include charnushka, black cumin, kalongi, and black caraway (Family: *Ranunculaceae*). The plant is indigenous to nations in Europe, Asia, and Africa. The plant reaches a height of 20–30 cm, and its linear, finely split leaves show this. The plant produces beautiful flowers that have a pale blue or colorless tint. Numerous cuisines employ the flower's seeds as a spice.^[70] Previous studies have shown that *N. sativa* has several therapeutic benefits against conditions such as cholesteremia, hypertension, and diarrhea. Among the significant phytochemicals that have been extracted from the seeds are nigelline, nigellidine, palmitic acid, oleic acid, and linoleic acid.^[71]

This medicinal plant has been scientifically examined for its ability to alleviate the symptoms of opiate withdrawal. It

has also been proven to be useful in treating infections and weaknesses, which are the primary sources of pain following addiction.^[72] Furthermore, when the plant extract was tested on patients, no significant negative effects were noted. In addition to being a suitable natural treatment for treating withdrawal syndrome. *N. satvia* also possesses anti-allergic, antimicrobial, sympatholytic, and nutritional qualities due to its high amino acid content.^[73]

Opuntia ficus-indica

This plant, which is a member of the cactus family, is also known as the Indian fig or *Opuntia*. It is widely distributed in parts of Asia, Africa, and America. It is a member of the *Cactaceae* family, and some species reach up to 5 m in height. The plant has an oblong stem that is succulent and has waxy epidermis. The fruits that are produced by the blooms range in color from light green to deep crimson.^[74] This herb has traditionally been used to lower elevated blood cholesterol and blood glucose levels. The essential ingredients with documented therapeutic qualities are linoleic acid, linolenic acid, oleic acid, and palmitic acid.^[75]

The plant's fruit extract has been tested to help patients avoid alcohol-related problems. It has been observed that the extract lessens symptoms including dry mouth, nausea, and anorexia.^[76] According to biochemical assessment, the extract raised C-reactive protein levels, and the anti-inflammatory effect may be connected to the therapeutic levels that were seen.^[77]

Passion flower

It is sometimes referred to as passion vines or passiflora. It is a member of the *Passifloraceae* family, which includes more than 550 species of flowering plants in the genus. The United States, South America, Mexico, and Central America are home to the majority of these plants. Southeast Asia is home to a few as well.^[78] A symmetric radical flower with five sepals and five petals is called a passiflora. A significant component found was the harmala alkaloid beta-carboline.^[79] The flowers have historically been used to treat attention-deficit hyperactivity disorders, menopausal symptoms, anxiety, and sleep disturbances.^[80]

Previous investigations have revealed sedative and anxiolytic effects from *P. flower* extract.^[81] It was discovered that passiflora, one of the active ingredients, was just as successful as clonidine in treating the psychological and physical signs of opiate withdrawal.^[82] These trials' findings suggested that passiflora could be a useful adjuvant medication for treating opiate withdrawal.

Peganum harmala

Popular names for this plant include wild rue, African rue, harmel, and escand. It grows in the Mediterranean's temperate

deserts and is a member of the *Nitrariaceae* family. When crushed, the plants, which reach a height of around 0.8 m, have an unpleasant taste and odor.^[83] The blooms are solitary and appear to be whitish-yellow, with alternating leaves. The plant's extract has long been used for its many therapeutic benefits, including antidepressant, antihypertensive, anticancer, and antibacterial.^[84] Alkaloids including quinazoline and beta-carboline have been discovered as the major active ingredients in *P. harmala*.^[85]

According to research done on this plant thus far, it may inhibit monoamine oxidase and have antagonistic effects on serotonin.^[86] An alkaloid known as harmaline was identified as one of the active components and it was discovered to have a part in reducing a few opioid withdrawal symptoms. One theory for the potential process involved modulating the opioid circuits and receptors in the brain stem, along with the limbic and autonomic nerve systems.^[87]

Pueraria lobate

The herb is widely utilized in Chinese medicine and is native to Asian nations such as China. It is a climbing, semi-woody perennial in the *Fabaceae* family with deciduous leaves and purple-white flowers.^[88] The herb is well known for curing spasms and pyrexia. Additional therapeutic applications include reducing body temperature, eye irritation, dry mouth, high blood pressure headaches, and stiff neck issues.^[89] A few of the significant active ingredients include glycitin, tectoridin, puerarin, and daidzein.^[90]

In the Chinese medical system, this plant is one of the most well-known herbal remedies for hangovers and alcohol intoxication. Rat studies revealed that *P. lobate* root extracts reduced alcohol intake when alcohol intake was already established.^[91] Human trials indicate that the application of plant extract significantly decreased the quantity of each sip as well as the number of sips and time to drink each brand of alcohol.^[92] In addition, alcohol abusers receiving the extract treatment had a markedly decreased desire to consume alcohol.^[93]

Rosmarinus officinalis

Also called rosemary, it is indigenous to the Mediterranean area. It is a member of the *Lamiaceae* family. The plant may reach a height of 1.5 m, and its evergreen leaves and pink, white, purple, and blue blooms are its main features.^[94] Numerous active components, including carnosic acid, luteolin, and rosmarinic acid, have been found. According to reports, rosemary can help with neurological or mental conditions including sadness, anxiety, and cognitive decline.^[95]

Some morphine withdrawal symptoms may be lessened, according to a few trials on rosemary.^[96] To determine

the actual potential of herbal medications, more study is necessary.

Salvia miltiorrhiza

It is a member of the *Lamiaceae* family and is also known as red sage or tan shen. The plant is indigenous to China, Japan, and other Asian nations. The plant is a deciduous perennial with split leaves that reach a height of 60 cm. The hue of the blooms ranges from pale purple to lavender blue.^[97] Plant extract has historically been used to treat cardiovascular conditions including angina and ischemic stroke. Salvianolic acid, dihydrotanshinone, miltirone, tanshinone I, and tanshinone IIA are the significant active ingredients that were identified.^[98]

In the Chinese medical system, the plant's roots are commonly used to alleviate sleeplessness. In animal models of excessive alcohol consumption, it was discovered that the significant phytoconstituents of the herb tanshinone, cryptotanshinone, and miltirone were effective in lowering voluntary alcohol intake.^[99] According to the observation, the extract minimized the amount of ethanol consumed by rats who already had an established intake of ethanol, reduced the amount of ethanol consumed voluntarily after a brief period of abstinence, and reduced the amount of ethanol consumed by rats who had never been exposed to ethanol before.^[100] When alcohol was given intra-gastrically to rats, but not intra-peritoneally, miltirone was shown to be primarily responsible for lowering blood alcohol levels. This finding suggests that miltirone hampered the absorption of alcohol from the gastrointestinal tract. The anxiolytic effect may be connected to the reduction in alcohol consumption mediated by miltirone.^[101]

***Stephania and Corydalis* genus**

A genus of flowering plants in the *Menispermaceae* family is called *Stephania*. It grows in parts of Australia and Asia. The plant is a herbaceous perennial that reaches a height of around 4 feet. Its leaves are arranged in a spiral pattern, and its anthers resemble crowns.^[102] The plant's active ingredients include thaicanine 4-O-beta-D-glucoside, 5-hydroxy-6,7-dimethoxy-3,4-dihydroisoquinolin-1[2H]-one, and [-]-thaicanine N-oxide [4-hydroxycorynoxidine]. The herb is used as a traditional medicine to treat fever, cancer, hyperglycemia, dysentery, asthma, and TB.^[103]

The genus *Corydalis* has over 540 species. The plants are herbaceous, annual, and part of the *Papaveraceae* family. The substance is widely used in Chinese medicine to treat a variety of illnesses. The majority of African and Asian nations' temperate zones are where they thrive.^[104] It has been observed that *Corydalis* has pharmacological efficacy against diseases of the neurological system, heart, and digestive system. Coumarins, flavonoids, steroids, and organic acids are significant constituents linked to biological activity.^[105]

Levo-tetrahydropalmatine has been identified as one of the key ingredients in the *Corydalis* and *Stephania* genera for treating the symptoms of de-addiction. Studies carried out on this component revealed that it can lessen drug addicts' withdrawal symptoms.^[106]

L-THP's mode of action was shown to have antagonistic effects on dopamine D1, D2, and D3 receptors in addition to activities at serotonin, alpha-adrenergic, and dopamine receptors.^[107] The anti-addiction activity was caused by blocking D3 receptors and pre-synaptic autoreceptors, which enhance dopamine release and antagonize α -adrenergic and serotonin receptors.^[108] Furthermore, these effects were also crucial in the management of opiate addiction.^[109] In addition, it has been shown that this component's antagonistic action on dopamine receptors lowers locomotor activity and raises the threshold for intracranial self-stimulation, which results in tranquil and hedonistic effects.^[110]

Tabernanthe iboga

This evergreen shrub is mostly found in Africa and is a member of the *Apocynaceae* family. The plant reaches a height of 2 m, and its blossoms are either pink or yellowish-white in hue. There are reports of hallucinogenic effects from the root or bark, which is mostly associated with the active ingredient ibogaine.^[111] Other active ingredients found in the plant include harmaline, ibogamine, voacangine, tabernanthine, and coronaridine. The herb has long been valued for its hallucinogenic qualities as well as its ability to reduce weariness, appetite, and sexual effects.^[112]

Mostly prevalent in western Africa, this plant is well known for relieving thirst, hunger, and exhaustion. Ibogaine, an alkaloidal psychoactive ingredient found in the plant, is useful in treating morphine, cocaine, heroin, and nicotine addiction, among other substance misuse disorders.^[113] Research has also shown that ibogaine decreases the voluntary consumption of alcohol, and this effect is associated with its activation of the dopaminergic and serotonergic systems. The results showed that a metabolite produced by the liver may be the active ingredient in ibogaine.^[111] Ibogaine's therapeutic potential is nevertheless limited by the neurotoxicity that has been reported.^[112]

An ibogaine analog called 18-methoxycoronaridine was created and put through testing to counteract the neurotoxic impact. In contrast to ibogaine, the analog did not cause toxicity in animal trials, but it did diminish the self-administration of morphine, cocaine, methamphetamine, and nicotine as well as oral alcohol and nicotine consumption. It also lessened the indications of opioid withdrawal.^[114] Ibogaine and its counterpart have been proposed to have inhibitory effects on alcohol consumption by regulating many neural pathways, including the dopaminergic and serotonergic systems.^[115]

Valeriana officinalis

Countries throughout Europe and Asia are home to this plant. The plant may reach a height of 5 feet and is a member of the *Valerianaceae* family. The plant grows in temperate zones, and insects and flies are drawn to the flower's pleasant scent.^[116] Essential oils, iridoids, flavonoids, alkaloids, amino acids, and lignanoids have been identified as the active ingredients. Sedation, antidepressant, antianxiety, antihypertensive, antimyocardial ischemia-reperfusion damage, and blood lipid modulation are among the therapeutic qualities mentioned.^[117]

Due to its well-known sedative and tranquilizing properties, this traditional medication made from the plant's roots is frequently used to treat anxiety and sleeplessness. Valerian was found to be useful in treating tension and spasms when the dosage was raised.^[118] This was thought to be the cornerstone for managing the adverse effects of drug misuse. The identification of a potential mechanism included the induction of anxiolytic action through allosteric regulation of GABA-A receptors.^[119] Valerenol and valerenic acid are two significant active ingredients that have been linked to anxiolytic and CNS depressive effects. It has been revealed that these substances act at several types of recombinant GABA[A] receptors.^[120]

Future implications and limitations

As indicated in the literature, the incidences of substance abuse are increasing around the globe. Addiction to such agents was found to be prevalent among the younger generation of society, affecting their health as well as their education, personality development, involvement in nation-building activities, etc. The government authorities are currently spending millions of dollars on the management of substance abuse complications, leading to an economic burden. The herbal medicines commonly practiced in economically weaker nations *per se* are cheap and safe. More studies in this direction might identify potential therapeutic agents that effectively counteract substance abuse complications, besides reducing the cost of treatment.

Herbal medicines were found to act on several brain centers such as dopaminergic, serotonergic, and adrenergic pathways. These mechanisms have been established to be involved in the reward process that compels a person for addiction liabilities. However, most of the studies on these herbal medicines were conducted in animal experimental models. The findings although predict the possible action of the compound but in many instances contradict the results. Hence, more research involving different experimental models is essential to determine the actual role of these herbal medicines in the management of substance abuse-related complications.

CONCLUSION

According to the current study, several herbal remedies that have been used traditionally may be able to lessen the consequences associated with substance dependence. It has been discovered that these medications lessen withdrawal symptoms such as agitation, discomfort, anxiety, and disturbed sleep. Many people have traditionally utilized these plant-based medications daily to cure a variety of different illnesses, particularly in undeveloped or underdeveloped nations. These substances may be a safe choice for treating withdrawal symptoms because they are natural. To fully explore these compounds' potential in treating drug abuse-related disorders, further study on these plants using various pre-clinical and clinical models is necessary.

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