REVIEW ARTICLE

# Mechanism of Narcotic Addictions and Its Treatment by Medicinal Plants: A Detailed Review

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**SUMMARY**

Drugs such as heroin, methamphetamine, cocaine, cannabis, alcohol, and opioids are examples of substances that have the potential to cause substance abuse and addiction. This is since each of these chemicals has a distinct mechanism of action to increase levels of dopamine and produce euphoria. To battle the effects of these narcotics, the primary focus of this review is on medicinal herbs that offer anti-narcotic qualities. The utilization of medicinal plants as a method for the treatment of substance abuse disorders has been a component of traditional medicine for some centuries. These natural antinarcotic compounds have the potential to be employed in an effective and risk-free manner to treat addiction. A class of substances known as phytochemicals has the potential to be utilized in the treatment of addiction. The development of appropriate treatment solutions that are effective over the long term is getting more challenging as a result of the fact that there is still a lack of study on the neurobiology of addiction.

**Keywords:** *Narcotics, Medicinal, Opioids, Plants, Reward Narcotics Syndrome.*

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## Introduction

Narcotics are drugs that are considered to be harmful because they induce an effect on the brain and spinal cord that results in euphoria. The repeated use of these substances results in psychological and physical dependence. The Ventral Tegmental Area (VTA) is one of the brain's regions involved in the mesolimbic reward system. It projects to the Nucleus Accumbens (NAc), the Prefrontal Cortex (PFC), the Amygdala (AMY), and the Hippocampus (HPC of the brain).[1] Dopamine acts as a neuromodulator; it modifies the sensitivity of other neurotransmitters. In individuals who are addicted to opioids, the excessive dopamine signaling causes a change in the expression of the genetic code, which ultimately results in maladaptive changes in the brain. Burst release of dopamine is responsible for the development of long-term memories associated with the stimulation of reward; a tonic release of dopamine is associated with the urge to respond to similar signals. Consuming narcotics regularly leads to a reduction in the expression of dopamine receptors in the brain, which results in a diminished interest in activities.[2]

Opioids, cocaine, cannabis, alcohol, heroin, and methamphetamine are all addictive substances. Although they target different neurological

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pathways, these chemicals typically raise dopamine levels, which induces euphoria. The traditional approaches to treating narcotics addict individuals are ineffective, and new methods must be investigated to treat patients.[3,4]

This review provides an in-depth analysis of addiction, the numerous stages of addiction, and reward deficiency syndrome. It examines how drugs that are deemed harmful induce euphoria and addiction through their impact on the body's physiological processes. Based on this review, it is possible that in the future, individuals who have become habituated to drugs could be treated using medicinal plants. Antinarcotics has the potential to cure narcotic addiction; but in order to ensure that patients successfully adhere to therapy, innovative delivery methods are required. Appropriate treatment for the physiological and psychological aspects of opioid addiction requires the utilization of multidisciplinary techniques.[5]

**Reward Deficiency Syndrome and Addiction**

The brain reward center consists of VTA, NAc, and SN. Dopamine is the principal neurotransmitter that activates this reward center, leading to euphoria. The repeated stimulation of dopaminergic neurons and the high rate of metabolism result in dopamine depletion, which leads to the dysphoric effects of substance abuse craving, as shown in figure 1. These disruptions in neurochemicals by narcotics are consistent with physical addiction. At the mesolimbic brain region, neurot-ransmitter interaction induces the reward where dopamine serves as an anti-stress neurotransmitter and interacts with D-2 dopamine receptors in the NAc (reward site). The cascade of neurotransmitters controls the reward system; the serotonin release causes the stimulation of enkephalins, which inhibits the Gamma-Ammino butyric acid (GABA) at SN and VTA; GABA is responsible for the release of dopamine at the NAc. The brain of an addictive individual needs dopamine, and a decrease in dopamine release makes an individual at risk for multiple addictive, compulsive, and impulsive attitudes.[6]

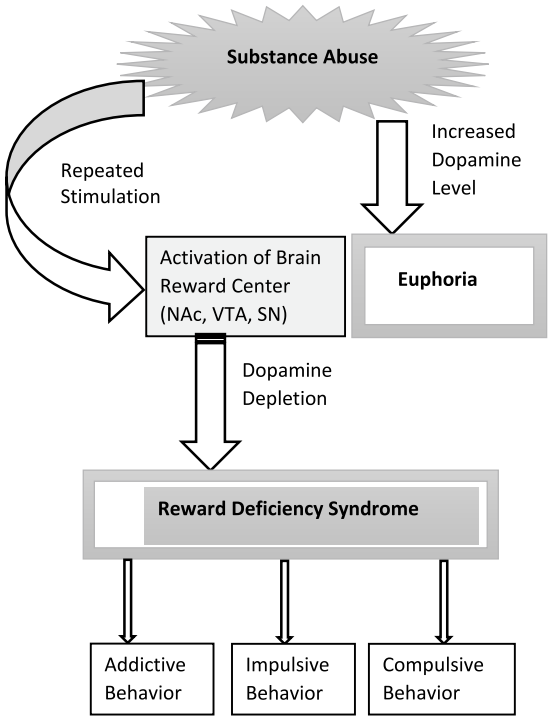


**Fig.1: Dopamine Depletion and reward deficiency Syndrome (NAc; Nucleus Accumblens, ETA Ventral Tegmental area, SN; Substantia Nigra)**

**Stages of Addiction**

Addiction usually occurs in three different stages: (1) recreational phase, administration of the narcotics is occasional; (2) intensified/ sustained drug use, habitual use of narcotics; and (3) addiction: intake of the narcotics becomes the principal activity for person.

Narcotic reinforcement is due to dopamine in NAc, VTA region, substantia nigra compacta, and dorsal striatum. Addiction is a pathological condition that reflects reward deficiency syndrome, stress, and functional deficiency. The dysfunction of cognitive behavior during addiction is visualized in the following stages: formation of preferences by the decision-making options, implementation of choice by motivation, self-regulation, and the inhibitory processes, and by process of feedback implication.[7] This review covers the mechanism of addiction induced by narcotics, including opioids, cocaine, cannabis, alcohol, heroin, and methamphetamine.[8]

**Narcotics (Substances Responsible for Addiction)**

Narcotics include illicit drugs and street drugs; the pharmacological effects of these abusive

drugs include physical dependence, tolerance, and addiction.[9] Narcotics responsible for addictive potential include opioids, cannabis, methamphetamine, alcohol, cocaine and heroin. The effects produced by Narcotics on different regions of the brain are mentioned in the table.1 below.

**Table-1: Pathophysiological effects of Narcotics on different regions of brain**

| Narcotics | Induced effect | Brain region alterations | References |
|---|---|---|---|
| Opioids | Increases dopamine release in the striatum and PFC | NAc, brain stem, chemoreceptor trigger zone (CTZ) | 10 |
| Cocaine | Dopaminylation on histone H3 glutamine in mid-brain | Mesocortico-limbic system (NAc and VTA) | 11 |
| Cannabis (marijuana) | Endocannabinoid system (cannabinoid receptors) | Cerebellum, Striatum (decreased dopamine synthesis) | 12 |
| Alcohol | Down-regulation of GABA- type A receptors and the upregulation of NMDA receptors. | Mid-brain, PFC. | 13 |
| Heroin | Alteration in the thalamocortical network and impairment of cognitive function. | Dysfunction of PFC region | 14 |
| Methamphetamine (ice) | Increased motor activity, neurotoxicity and impairment in memory | Increased dopamine release in NAc | 15 |

**Opioids**

The opioid derived from opium poppy *Papaver somniferum* used for treatment of pain and hedonic effects, morphine is a common example. Other examples include codeine, heroin, hydromorphone, oxycodone, and fentanyl. Opioids are potent analgesics but induce addiction. Opioids affect the brain stem which regulates heart rate, breath rate, and sleep, it leads to depressed breathing and even death.[16] By long-term opioid use, adaptive changes occur at the cellular level, which promotes tolerance that induces dependence, and upon cessation withdrawal symptoms appear. At systematic level, distinct processes are required for the possession of analgesia, tolerance, and dependence. Prescription opioids include both natural, semisynthetic (codeine and morphine) and synthetic opioids (methadone, tramadol, and fentanyl). Some synthetic opioids such as fentanyl, are prepared and distributed illegally.[17]

**Opioid Receptors**

Opioid receptors, G-protein coupled receptors, present in the brain, spinal cord, gastrointestinal tract, and skin. Their stimulation results in brain sedation, analgesia, euphoria, and respiratory depression. Among chronic opioid user's tolerance and dependence develop rapidly, while diarrhea, bone aches, and goose bumps develop as withdrawal symptoms appear. The opioid receptors are linked with reward processing. Alterations in opioid receptor sensitivity are linked to the evaluation of opioid dependence, especially when the patient is

receiving treatment against narcotics.[18] When opioids bind to opioid receptors, a number of cytoplasmic reaction cascades are eventually triggered, including activation of phospholipase C, inhibition of adenylyl cyclase, activation of potassium channels, and closure of voltage-gated calcium channel for inhibition of neurotransmitters. Three classical opioid receptors distributed in the PNS and CNS are the mu-opioid receptor, delta opioid receptor, and kappa opioid receptor, as shown in figure 2. Mu-opioid receptors are found in the cerebral cortex and thalamus; they possess an affinity for endorphins and induce euphoria, physical dependence, and respiratory depression. The mu-opioid receptors are distributed in NAc and basolateral amygdala. They are typically involved in the brain reward system, and their effect changes with age, particularly during

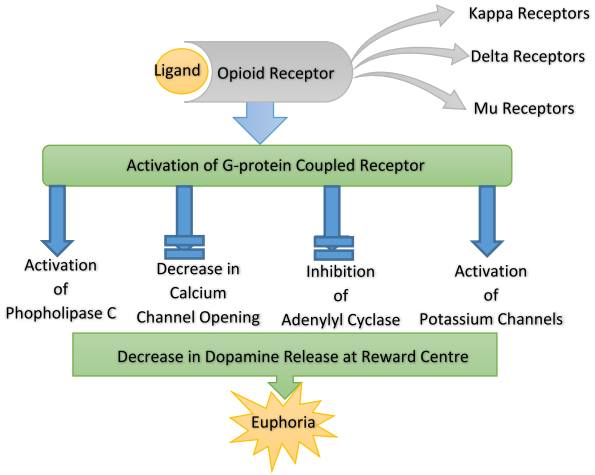


**Fig.2: Euphoria induced by the activation of Opioid receptors**

adolescence. The kappa-opioid receptors located in the hypothalamus bind to dynorphins, stimulate anti-reward action, and induce sedation. Prolonged exposure to illicit drugs increases kappa-opioid receptor function by stimulation of corticotrophin-releasing factor that promotes relapse. The stress induced by long-term drug exposure can produce a depressant effect. The delta-opioid receptors present in basal ganglia bind to enkephalins and produce anxiolytic actions; their activation decrease decreases anxiety levels and reduces depression symptoms. Opioid antagonists reverse the opioid effect by binding at opioid receptors.[19]

## Cocaine

Cocaine is a psychostimulant and illicit drug used in America, Western Europe, and Australia. Genetic and environmental factors contribute to the development of cocaine use disorder. Use of cocaine, both acute and chronic, changes epigenetic expression, leading to alterations in neuronal adaptations and brain circuits that are associated with cocaine dependence. Cocaine blocks the reuptake of dopamine, serotonin, and noradrenaline, resulting in increased levels of these neurotransmitters at the synaptic cleft. The euphoric effects of cocaine are attributed to the increased dopamine in the limbic system. Chronic cocaine uses leads to changes in the neurotransmitter system and the functioning of various brain circuits, including the mesocortical limbic system (NAc and VTA).[20]

By cocaine exposure dopamine accumulates in neurons of VTA, association of dopamine within chromatin initiate an epigenetic regulation called Dopaminylation. The histone H3 glutamine 5-dopaminylation is critical for cocaine-induced transcriptional changes in the midbrain, as shown in figure 6. Rats suffering from cocaine withdrawal showed an accumulation of H3 glutamine 5-dopamine in the VTA producing impact on the function of VTA.[21]

### Alterations in the Gene Expression Level

The gene expression level analyzed among cocaine abusers in postmortem brain and samples found that some of the genes expressed differentially by the transcription regulation, as shown in table-2 below. The gene expression changes in the PFC were assessed in two studies analyzing postmortem samples of dorsolateral and anterior PFC among cocaine abusers. The alteration in gene expression in the anterior PFC among cocaine, cannabis, and phenyl-cyclidine abusers reflects the genes linked to calmodulin functioning, golgi, and endoplasmic reticulum-related genes. The genes involved in mitochondrial function and oligodendrocyte function in the dorsolateral PFC are mutated in cocaine abusers.[22] Gene expression is altered in cocaine abusers, affecting myelin and glial function-related genes in the NAc. The PLP-1 gene, which encodes the major component of myelin, is also altered. In the hippocampus, gene expression changes occur in cellular and mitochondrial functional genes, as well as genes involved in neurogenesis. Dopaminergic cells in the midbrain of cocaine abusers show altered gene expression levels, impacting metabolic

**Table-2: Brain regions involved and particular gene mutation during cocaine addiction**

| Brain region involved | Addiction source | Gene mutation | References |
|---|---|---|---|
| Dorsolateral PFC | Cocaine abusers | Mitochondrial genes, Genes for oligodendrocyte function | 23 |
| Anterior PFC | Cannabis and phenyl-cyclidine abusers | Calmodulin functioning, Golgi and endoplasmic reticulum-related genes | 24 |
| NAc | Cocaine abusers | Glial function genes, PLP-1 gene, and myelin-related genes, Increased expression of PLCB-1 | 25,26 |
| Hippocampus | Cocaine | Cellular and mitochondrial functioning genes and genes involved in neurogenesis were altered, KTD20 gene altered | 27 |
| Midbrain | Cocaine | Genes involved in dopamine metabolism altered | 28 |

cascade and neuronal differentiation. Neuronal progenitor cells also experience altered gene expression, affecting genes involved in immune and inflammatory processes. Convergent analysis of studies performed on animals and human gene expression among cocaine abusers reveals alterations in ERK/MAPK signaling pathway genes, genes involved in dopamine and serotonin function (slc1a2, aldoa, aldoc, calm3, and eno2), and genes involved in brain plasticity (APP, KCNA2, GRIN2A, GRIN2B, MAP4, SNCB, PCDH10, SV2C, and PPP3CA). Acute exposure to cocaine increases NFAT transcription through the upregulation of NFAT5, a transcription factor in dopaminergic neuronal cells. Cocaine exposure leads to the downregulation of microRNAs mir-9, mir-153, and mir-124, which are responsible for cocaine dependence. The PLCB1 protein (phospholipase c beta 1) possesses genetic variations linked to cocaine dependence, and its expression is increased in the NAc of cocaine abusers.[29]

**Cannabis (Marijuana)**

Cannabis addiction is linked to reward, emotional regulation, cognitive behavior, and stress through interaction with cannabinoid receptors. Cannabis use is a pathological disorder with a genetic basis in adolescents and individuals associated with psychiatric disorders. Marijuana acts on the endocannabinoid system, modulating behavioral, endocrine, immune, cognitive, and motor functions. Genetic factors, sex, and environment influence cannabis use disorder, and the neurobiological mechanisms of addiction correspond to increased drug craving, anxiety, and negative withdrawal effects. Certain epigenetic changes contribute to neurobiological changes associated with molecular and cellular processes linked to cannabis addiction. Preclinical investigations of human brain structure are limited, but the cerebellum shows differences after cannabis use disorder. Cannabis use is known to cause depression, particularly among girls, as well as anxiety, psychological problems, and suicidal thoughts, as shown in figure 7. Impairment in the opioid genes potentiates effects on cognition and emotions, similar to findings of prenatal cannabis exposure in animals, which causes alterations in the limbic encephalic system.[30]

**Cannabis-Related Changes in Neurotransmitters**

Cannabis use disorder is developed by chronic neuroadaptations produced by repeated use. The delta-9-tetrahydrocannabinol (THC) induces euphoria, which is responsible for addiction.[31] The THC increases dopamine release in the striatum of individuals addicted to cannabis. Long-term use, on the other hand, decreases dopamine levels, which is linked to decreased attention, increased negative

symptoms, and severe addiction. In addition to abuse drugs, the function of striatal dopamine receptors D-2 and D-3 is decreased. However, in cannabis addicted individuals, the dopamine receptors are normal, resulting in unique dopamine transmission. The transmission of glutamate is regulated by endocannabinergic receptors (CB1RS), and the level of glutamate increases after acute cannabis use, which is important for inhibitory control and drug-taking behavior. However, after chronic cannabis use, the level of glutamate falls in different brain regions. This disturbs synaptic functioning in the pre-frontal motor cortex and disrupts normal brain development, contributing to drug craving.[32]

**Alcohol**

Alcohol use can be developed into abusive behavior and addiction, it is a psychiatric disorder that leads to severe health consequences. The neurobiological mechanism for alcohol addiction develops in response to environmental and genetic stimuli. Environmental factors also contribute to the development of alcohol addiction, these include exposure to different drugs, alternate reward behavior, stressful lifetime events, hopeless-ness, anxiety, depression, and adverse reinforcement effects of psychoactive drugs.[33]

**Pathophysiology of Alcohol Use Disorder**

Alcohol is the CNS depressant; it elevates gamma-aminobutyric acid (GABA) and inhibits postsynaptic n-methyl-d-aspartate (NMDA) glutamate receptors. Prolonged alcohol use, at high levels, down-regulation of GABA type A receptor and upregulation of NMDA receptors occurs. Abrupt cessation of alcohol in the blood unmasks the glutamate-mediated unmasks the glutamate-mediated excitation and produces delirium. The inhibition of the GABA system in the brain stem leads to seizure development. Alcohol withdrawal causes hyperarousal and hallucinations due to an increase in dopamine levels. The stimulation of GABA type A receptor induces hyperpolarization effects on the membrane by increasing the influx of chloride ions, causing sedation, anxiolysis, and anticonvulsant action. Alcohol addiction can be broadly divided into different stages: craving, misuse of substance, drunkenness, withdrawal, abrupt withdrawal, recovery, and prevention of relapse. The underlying addiction mechanism involves the release of dopamine in the reward pathway that connects the mid-brain to the PFC, and by the sudden release of dopamine, euphoria develops.[34]

The slow decrease in alcohol consumption, planned intervention with medicines and ultimately complete stop can decrease harmful effects of alcohol withdrawal. The agents target the GABA type A receptor and can support detoxification (examples are benzodiazepines, barbiturates, and propofol).[35]

**Heroin**

Addiction characterized by compulsory attitude toward the use of drugs and an emergent negative emotional state. The important aspect of heroin addiction is pathological memory related to modulated synapse transmission and neuroplasticity. Chronic heroin users experience impairment of cognitive function, which leads to disturbances in learning, memory, and functional losses. The dysfunction of the PFC contributes to uncontrolled use of heroin.[36]

**Disturbed Nuclear Signaling Related to Heroin**

The addictive behavior for heroin addiction seizes the normal memory in the brain circuit at the transition from drug-taking behavior to the compulsory intake of heroin. The abrupt dopamine release from VTA to the NAc and glutamate release from the basolateral area to NAc serves to be the main pathway for the mediation of conditioned cues including the restoration of heroin intake as shown in figure.3. The dorsolateral striatum, NAc, and dorsal hippocampus play an important role in the restoration of drug-taking behavior. The subdivisions of medial PFC target NAc for relapse and reflect the vital implication for which pharmacological therapies could be more beneficial.[36]

**Methamphetamine**

Methamphetamine is a transparent white

crystalline powder, soluble in water and bitter. Methamphetamine is a member of amphetamine-type stimulants having a long duration of action and increased potential to cross BBB. The non-pharmacological use of amphetamines is at high doses and administered other than the oral route (includes intranasal, intravenous, intramuscular, vaginal, and rectal route). Amphetamine is used for relaxation and for night-shift employers to enhance performance. The regular use of amphetamine is more complex than that of occasional use, and it leads to substance use disorder development.[37]

**Sensitization induced by Methamphetamine**

The repeated use of methamphetamine leads to increased motor activity and sensitivity; this process is termed sensitization, as shown in the figure.4 below. The continuous use of amphetamine can raise the dopamine level in Nac. Methamphetamine enters into dopaminergic pre-synapse by the dopamine transporter and promotes its release in the cytosol, and cytosolic dopamine level is raised by the vesicular monoamine transporter 2. Methamphetamine possesses the potential to inhibit the monoamine oxidase enzyme involved in the metabolism of dopamine and ultimately contributes to the behavioral deficit, amnesia, and neurotoxicity in CNS. Methamphetamine activates the brain reward pathway by activating dopamine receptors and increasing dopaminergic signaling in the brain reward pathway.[38]

**Medicinal Plants**

Addiction to narcotics is a major psychiatric and socio-economic issue in society. As the person is diagnosed with narcotic addiction, it becomes mandatory to bring the patient back to life. For centuries, man used medicinal plants for their pharmacological value, which plays an important role in treating different diseases. The phytochemicals (including alkaloids, flavonoids, terpenoids, and phenylpropanoids) present in medicinal plants possess biological activities that can upgrade the quality of human life in the pharmaceutical industries.[39]

**Nigella Sativa**

Nigella sativa is a non-opiate drug that belongs to the family Ranulaceae and is effectively used

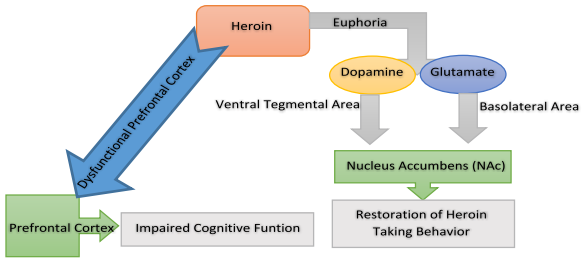


**Fig.3: Effects of heroin addiction**

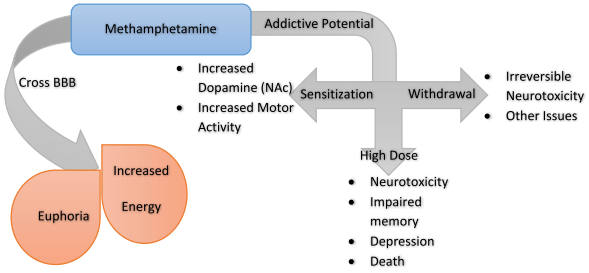


**Fig.4: Sensitization induced by Methamphetamine**

for the treatment of withdrawal symptoms. Its common name is 'kalonji', known as 'habatul saud', also called black cumin. Nigella sativa is effective for the long-term treatment of opioid dependence and for the treatment of infections. The majority of addicts suffer from infections, so it is more effective for the treatment of addiction. It is rich in nutritious amino acids, by which opioid addicts get more benefits, especially those who require nutritious supplements.[40]

**Withania Somnifera**

Withania somnifera known as ashwaganda, belongs to the family Solanaceae, used for the treatment of benzodiazepine withdrawal syndrome as it possesses GABA receptor agonist activity. It is effective for the relief of over-active nervous system and anxiety linked to withdrawal syndrome. The methanol extract of W. somnifera is effective for neural regeneration and synapse reconstruction potential and relieves the withdrawal effects of morphine. The morphological changes induced by opioid withdrawal in NAc can be prevented upon treatment with Somnifera extract.[41]

**Matricaria Recutita**

Matricaria recutita belongs to the family Asteraceae. The phytochemicals are terpenoids, flavonoids, coumarins, and spiro ethers. It possesses benzodiazepine-like ligands and

certain inhibitory effects which inhibit morphine dependence. The benzodiazepine-like compounds of M. recutita act on the gamma-aminobutyric acid (GABA type receptors, increasing the GABA effect on ligand-gated ion channel, causing hyperpolarization of neurons, decreasing the neuronal response accompanied by low action potential firing, leading to sedative effect.[42]

**Saliva Officinalis**

Saliva officinalis exerts different pharmacological actions on CNS, including neuroprotective, antioxidant, analgesic, and memory-enhancing effects. Its flavone components can stimulate the chloride channels of GABA receptors, which are responsible for the anti-addiction potential. It possesses anti-inflammatory and anti-oxidant action. When administered to morphine-dependent rats, hydro-alcoholic extract of S. officinalis at doses of 400 mg/kg, 600 mg/kg, and 800 mg/kg was found to be efficacious in eliciting anti-opioid effects.[43]

**Mitragyna Speciosa**

Mitragyna Speciosea belongs to the Rubiaceae family, and its common name is ketum (biak). In southeast Asia, it is used for the treatment of pain, cough, and diarrhea and it acts as a stimulant to enhance efficiency. It possesses stimulant action at low doses and opioid-like effects at high doses. It is used in the United States as a cost-effective alternative to the self-withdrawal treatment of opioids. Kratom is used with o-desmethyl-tramadol, marketed as krypton, and can be added to synthetic cannabinoids. The phytochemicals of kratom are mitragynine and 7-OH-mitragynine which possess opioid-like actions and as partial agonists at mu-opioid receptors and competitive antagonists at kappa and delta opioid receptors. The partial agonist activity of mu-opioid receptors reduces respiratory depression in the case of overdose. 7-OH-mitragynine is 13-46 times more potent than morphine and mitragynine, respectively. Mitragynine can stimulate the alpha two adrenergic receptors accent for the sedative, analgesic action without causing respiratory depression. Mitragynine can produce effects on dopamine and serotonin receptors, and it could be used as maintenance therapy to treat addicted opioid individuals.[44]

**Albertisia Papuana Leaves**

Albertisia papuana l. commonly known as Mekai by the Dayak tribe. Due to its actions on CNS, its phytochemicals were analyzed to treat withdrawal symptoms of opioid addiction in the narcotic-dependent mouse model by psychomotor tests, light and ear nerve sensitivity tests, curiosity tests, and coordination tests. A. papuana l. proved to reduce withdrawal effects and could be used for rehabilitation in morphine addicts.[45]

**Terbenthe Iboga**

Terbenthe Iboga belongs to the family Apocyanaceae, used as traditional medicine for the treatment of opioid withdrawal. T. iboga possesses a high fraction of ibogaine alkaloids, which showed anti-addictive effects against several abusive drugs. It is a noncompetitive antagonist at nicotinic acetylcholine receptors. Pre-clinical data demonstrates decreased self-administration of morphine, cocaine, alcohol, nicotine, and methamphetamine in different animal models. In clinical settings, Ibogaine reduces craving and withdrawal from narcotics in humans.[46]

**Corydalis Species**

The Corydalis sp. belongs to the family Papavaraceae and it possesses alkaloids, coumarins, flavonoids, steroids, organic acids, and certain other chemical moieties. The protoberberine alkaloids possess analgesic, antitumor, antipsychotic, and antiplatelet action. They exert pharmacological action on the nervous, cardiovascular, and digestive systems. The most pronounced effect of Corydalis sp. is analgesia and it does not produce addiction and tolerance.[47]

**Conclusion**

The biggest indicator of addiction potential is the euphoria that narcotics provide. The brain regions are altered in addicted individuals and they are responsible for the tangled condition of addicted individuals. Although they have

different mechanisms of addiction, the activation of the brain's reward system and a rise in dopamine levels are the results. As medication therapy is effective in treating addicted individuals, relapse is still a complicated situation that occurs due to the neurological changes in the brain signaling cascade and the tolerance developed due to repeated use of narcotics. The conventional method of treating narcotic-dependent individuals may be substituted by the use of medicinal plants with no side effects and patient adherence to treatment could be elevated.

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**Authors Contribution**

**MA:** Data collection, data analysis, manuscript writing and proofreading

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**FJ:** Idea conception, data analysis, results and interpretation

**SAS:** Manuscript writing and proofreading

**ZAH:** Data collection