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Review Article

ALCOHOL DEPENDENCE AND WITHDRAWAL: A COMPREHENSIVE REVIEW OF THERAPEUTIC APPROACHES

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ABSTRACT

Major clinical and public health issues related to neuroadaptation, compulsive alcohol use, cravings, relapse, and potentially severe withdrawal symptoms are alcohol dependency and withdrawal. Major neurotransmitter systems, including GABA, glutamate, dopamine, serotonin, opioid, and noradrenergic pathways, are dysregulated by prolonged alcohol exposure, which causes hyperexcitability in the central nervous system during abstinence. Benzodiazepines, Disulfiram, acamprosate, baclofen, and naltrexone are examples of current pharmaceutical methods that are helpful but may have drawbacks in terms of hepatic safety, dependency, side effects, or effectiveness.

This review examines the therapeutic potential of medicinal plants and their bioactive phytoconstituents while summarizing the neurobiological processes driving alcohol dependency and withdrawal. Numerous medicinal plants, such as Pueraria lobata, Hovenia dulcis, Panax ginseng, Hypericum perforatum, Salvia miltiorrhiza, Rhizoma coptidis, Scutellaria radix, Zingiber officinale, and others, have anti-alcohol, anti-withdrawal, hepatoprotective, antioxidant, and anti-craving effects, according to data from human and experimental research. ADH/ALDH-mediated alcohol metabolism, GABAergic and glutamatergic signalling, dopaminergic reward pathways, inflammatory mediators, oxidative stress, and molecular targets including SIRT1/p53 and GDNF/ERK pathways are all affected by their actions.

The reviewed evidence highlights medicinal plants as promising sources of bioactive compounds for the management of alcohol dependence and withdrawal and provides a basis for further mechanistic, pharmacological, and clinical investigations.

Key words: Alcohol dependence, Alcohol withdrawal syndrome, Neurotransmitter modulation, Medicinal plants, Phytoconstituents

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1. INTRODUCTION

Alcohol:

Alcohol is a commonly used and misused drug that may lead to a variety of financial and health issues [Lerner, Fallon et.al., 1985]. Long-term, continuous, excessive ethanol use leads to tolerance and dependence on the drug, which can harm organs and tissues. In addition to being the most widely used substance worldwide, alcohol is legal and socially acceptable in many countries [Basavarajappa and Hungund et al., 2005].When alcohol is present continuously, it constantly challenges regulatory systems and causes a range of neuroadaptations, which is known as an allosteric state. The brain's reward and stress systems are altered as a result of these changes [Weathermon and Crabb et al ., 1999].The prefrontal cortex, amygdala, hippocampus, and numerous other regions undergo

neuroadaptations as a result of these effects. Neurotransmitter systems like dopamine, glutamate, serotonin, gamma-aminobutyric acid (GABA), and a few neuropeptides become dysregulated as a result of prolonged drinking and alcohol misuse. [Culyer and Newhouse et al., 2000]. It depresses the central nervous system since it is a psychotropic substance. Long-term alcohol use can harm a number of organs, resulting in:

Physical Health Issues:

- Pancreatitis and gastritis
- Livercirrhosis and malnutrition
- Hypertension, heart rhythm problems, and congestive heart failure
- Increased risk of liver, pancreas, and oesophageal cancer
- Infertility and weakness

Mental Health Issues:-

- Depression
- Memory loss
- Emotional and sleep disturbances

Other Risks:

- Impaired motor skills and reflexes
- Fetal alcohol syndrome during pregnancy

Responsible alcohol consumption is crucial to preventing these serious health consequences [Eze et al., 2017].

2. ALCOHOL DEPENDENCE

Alcohol dependence, an acknowledged psychiatric condition, is defined by a continuous, maladaptive compulsion for alcohol intake. This illness has serious detrimental effects on a person's performance at work, relationships with others, and general physical health, among other areas of their life.Various neurobiological and environmental elements influence the motivation to consume alcohol[Jiloha RC et al., 2007].

The craving for alcohol is believed to stem from the equilibrium between its positive reinforcing effects, like euphoria and anxiety alleviation, and its adverse effects, typically linked to the negative consequences of drinking, such as hangovers or withdrawal symptoms [National Collaborating Centre for Mental Health 2011].

3. ALCOHOL WITHDRAWAL SYNDROME

A distinctive withdrawal symptom occurs when an alcohol-dependent person suddenly stops drinking or drastically cuts back. Alcohol generally suppresses central nervous system (CNS) function. As with other CNS depressants, the withdrawal symptoms that come with stopping long-term alcohol use are the reverse of the effects of intoxication. Alcohol withdrawal symptoms include, [Lerner, Fallon et.al., 1985]. Manifestations of alcohol withdrawal syndrome encompass autonomic hyperactivity, exacerbated hand tremors, insomnia, nausea or emesis, fleeting visual, tactile, or auditory hallucinations or illusions, psychomotor agitation, anxiety, or generalized tonic-clonic seizures. These symptoms should manifest within several hours to a few days following the discontinuation of extensive and prolonged alcohol consumption [American Psychological Association, 2013]. According to the WHO, it ranks as the third primary cause of untimely mortality and disability worldwide [WHO 2001].

Up to 50% of individuals with alcohol use disorder may experience alcohol withdrawal symptoms when their alcohol consumption is reduced [Long et al., 2017].Chronic alcohol consumption affects the central nervous system in a neuroadaptive way, down regulating GABAergic receptors and upregulating glutamatergic receptors, which is linked to the development of alcohol withdrawal syndrome[Schuckit et al., 2014].As a result, the central nervous system stays hyper excitable and exhibits excitatory signs and symptoms after stopping alcohol usage suddenly. Withdrawal symptoms often appear 6–24 hours after alcohol restriction Up to 5% of people with alcohol withdrawal syndrome may experience these symptoms, which can vary in intensity from anxiety and tremors to more serious symptoms including seizures and delirium tremens [Schmidt et al., 2016].

4. EPIDEMIOLOGY

WHO research states that 75.9 million of the 2 billion persons who consume ethanol suffer from an alcohol use disorder [Saxena et al., 2006]. According to another report, alcohol causes about 1.8 million deaths annually, or 3.2% of all fatalities worldwide. Additionally, it results in 58.3 million disability-adjusted life years, or DALYs, which account for 4% of the global illness burden. [Rehm et al., 2003].An estimated 18% of people have an alcohol use disorder. Every year, 5% of people suffer from alcohol consumption disorder. In circumstances, the number is significantly larger. Twenty percentage of patients with alcohol use disorders who visit emergency rooms. It is estimated that up to 50% of patients with AUD may have withdrawal symptoms, however only a small percentage need official medical therapy [Alsaeed et al., 2019].

In primary care populations, the incidence of hospitalizations with alcohol withdrawal syndrome (AWS) is estimated to be 169 per 100,000 person-enrolled-years; however, this number increases to approximately 15,000 per 100,000 for patients who already have diseases related to alcohol. AWS makes up around 0.28% of all interactions in the ED environment; this percentage has been increasing over time [Steel et al., 2024]. While general AWS mortality is estimated at about 2% with prompt, protocol-based treatment, it can reach 15% if left untreated. Factors linked to increased mortality include advanced age, hepatic cirrhosis, bacteremia, and respiratory infections [Perry et al., 2014].

5. CLINICAL SPECTRUM

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), AWS is diagnosed when both of the following are true: [Kocsis, R.N et al., 2013]. There is proof that the person stopped or reduced heavy and long-term alcohol use; The withdrawal symptoms are not caused by a problem or another mental or behavioral disorder. AWS is a set of symptoms that typically appear 1 to 3 days after the drink; occasionally the symptoms appear when the blood alcohol level is still above zero (0.5 or higher).

Alcohol withdrawal is a complicated procedure. In order to better predict results, several have attempted to categorize the symptoms of alcohol withdrawal syndrome based on their severity or when they manifest. The symptoms of alcohol withdrawal syndrome are typically restricted to autonomic indications, tremor, hyperactivity, headache, and insomnia. Patients who are in withdrawal always maintain their orientation and are completely aware. Six hours after quitting or cutting back on alcohol consumption, the symptoms of alcohol withdrawal syndrome start, and they can last up to four to forty-eight hours (early withdrawal) [Mainerova et al., 2015 and Kattimani and Bharadwaj et al., 2013].Moderate withdrawal manifests as tactile or auditory hallucinations and illusory experiences while conscious. The duration of the symptoms is up to six days. Six to 48 hours following the last drink, symptomatic seizures may manifest as part of the alcohol withdrawal syndrome [Beghi et al., 2010]. The withdrawal symptoms of delirium tremens (DT), which begins 48 to 72 hours after quitting alcohol, can last for up to two weeks (late withdrawal) [Mainerova et al., 2015]. A reduced seizure threshold is the hallmark of the alcohol withdrawal seizure, a symptom that primarily manifests during the withdrawal period. Within 48 hours of quitting heavy drinking, about 90% of acute symptomatic seizures occur [Victor and Brausch et al., 1967 and Furo et al., 2023]. Alcohol withdrawal symptoms are frequently absent from seizures. Recurrent seizures affect more than half of the population. Up to 5% of seizures can progress to status epilepticus [Pieninkeroinen et al., 1992]. More than half of withdrawal seizures occur in conjunction with risk factors, such as prior epilepsy, abnormalities of the brain's structure, or drug use [Fleming and Mundt et al., 2004]. It is noteworthy that the death rate is four times higher when symptomatic seizures occur during an alcohol withdrawal episode due to severe consequences from alcohol use disorders rather than the seizures themselves. Up to 30% of withdrawal instances might result in DT, and the appearance of a seizure during withdrawal is a risk factor for entering a hazardous withdrawal condition [Victor and Brausch et al., 1967]. If an unexplained seizure occurs more than 48 hours after the last drink, it may be due to a head injury or the effects of stopping several medicines at once [Beghi et al., 2010, and Furo et al., 2023]. Confusion, odd emotions, and physical symptoms indicating nervous system issues are all indicators of delirium [Fleming and Mundt et al., 2004]. One type of mental disorder that occurs during withdrawal is hallucinosis. It may begin while a person is still drinking or after they have stopped. The person initially appears to be mentally ill, but it frequently worsens and develops into DT, a kind of delirium characterized by rapid movement and agitation. This type of delirium manifests during the withdrawal phase [Mainerova et al., 2015].

6. BIOMARKERS

Biochemical markers of heavy alcohol consumption are only somewhat helpful in making a definitive diagnosis when historical data is either unavailable or unreliable and alcohol dependence is suspected. Carbohydrate-deficient transferrin and gamma glutamyl transferase (GGT) [Takase et al., 1985]. are both sensitive indicators of excessive alcohol consumption, particularly when combined [Wurst et al., 2006]. Furthermore, GGT is comparatively non-specific and frequently elevated in patients taking medications that induce liver enzymes, such as carbamazepine and phenytoin. Additionally, macrocytosis (an increased mean corpuscular volume) may be observed [Takase et al., 1985]. This condition can have several causes because alcohol-dependent individuals may have vitamin B12 and folate deficiencies as a result of poor nutrition.Both alanine amino transaminase and aspartate aminotransferase are found to be elevated in alcohol-dependent individuals who have acute or chronic hepatitis due to excessive alcohol consumption. In the future, direct ethanol metabolites, like ethyl sulfate, may be measured as indicators of recent ethanol intake [Bleich et al., 2005]. Raised homocysteine levels are associated with alcohol withdrawal seizures in non-abstinent alcoholics [Lipton et al., 1997]. The seizure threshold may be lowered by both homocysteine and homocysteic acid, a substance produced from its metabolism, overstimulating NMDA receptors [Bleich et al., 2000]. A homocysteine level has been regarded as a helpful biomarker of the risk of alcohol-withdrawal seizures because it has been demonstrated that patients who are currently drinking and have a history of withdrawal seizures have significantly higher homocysteine levels than patients who are currently drinking but do not have such a history [Bleich et al., 2006]. However, its clinical utility has been hindered by the challenge of determining a cut-off value that would offer sufficient sensitivity and specificity. [World Health Organization, 2004]. (As given in Fig.1)

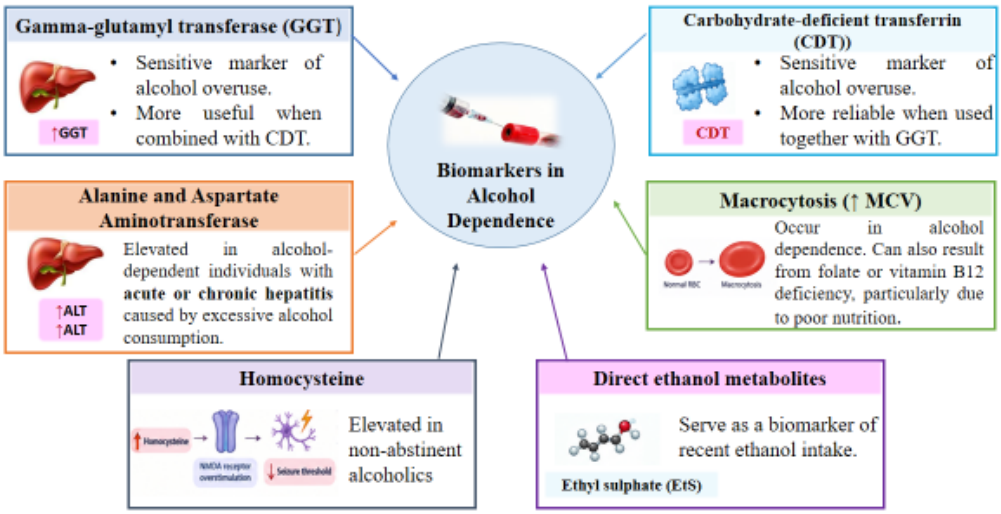

Fig.1: Biomarkers

7. THE PROGRESSION FROM ALCOHOL USE TO ALCOHOL DEPENDENCY AND REINFORCING

Research shows that individuals tend to repeat behaviors that produce pleasurable outcomes, although the reasons for such repetition are not fully understood. This behavior is associated with reinforcement, which enhances the probability of those behaviors recurring. Scientists aim to comprehend the motivations driving repeated alcohol consumption, as this is vital for understanding chronic drinking, dependency, and relapse among recovering alcoholics. Reinforcement is categorized into positive and negative types, each affected by how stimuli influence behavior repetition [Cho et al., 2019].

a) **Positive Reinforcement** The positive reinforcement effects of alcoholism are considered essential motivators of drinking behavior in the early stages of alcoholism. Alcohol dependence is caused by positive reinforcement that tends to make people crave to consume more because it has a euphoric and hallucinatory effect [Koob et al., 2013]. Alcohol's pleasantly reinforcing characteristics are primarily mediated through indirect effects on mesolimbic DA, which are released in reaction to alcohol. These alcohol-induced positive reinforcement effects are most likely crucial in the early phases of addiction, especially in those genetically predisposed to addiction. In these circumstances, alcohol-related cues are an indication that alcohol is having a positive reinforcement impact, which may contribute to "reward-seeking [Berenz et al., 2021]. Among people without AD, positive reinforcement correlates more strongly with alcohol consumption than negative reinforcement [Tsai et al., 1995].

b) **Negative Reinforcement** It is the process by which an unpleasant experience has been removed the probability of a response increases with a stimulus [Tsai and Coyle et al., 1998]. The negative impacts of chronic alcohol use in symptoms of withdrawal and detrimental drinking-related effects encourage continued alcohol use to relieve such symptoms [Jesse et al., 2017]. Abstinence from alcohol causes the amygdala's glutamatergic neuronal synaptic transmission to become overexcited, which causes anxiety marked by an increased negative emotion. Resumption of alcohol consumption is caused by enthusiastic adverse reactions resulting from ethanol withdrawal, which are accompanied by a strong desire to consume ethanol [Grant et al., 2015]. Long-term excessive alcohol use gradually activates and sensitizes brain stress systems, increasing alcohol use and relapse risk [Berenz et al., 2021]. In contrast to positive reinforcement, negative reinforcement is more strongly linked to AD [Tsai et al., 1995].

8. PATHOPHYSIOLOGY

The effects of alcohol on various brain neurotransmitter systems have been investigated by pharmacological, electrophysiological, and genetic research, which has also established the mechanisms underlying alcohol withdrawal syndrome (AWS). Acute alcohol consumption has been demonstrated to have both an excitatory effect on GABA receptors and an inhibitory effect on N-methyl-D-aspartate (NMDA) receptors [Nutt et al., 1999 and Lingford-Hughes and Nutt et al., 2003]. This results from alcohol's detrimental effects on glutamate, the primary excitatory neurotransmitter, as well as its binding to the NMDA receptor, which activates the GABA inhibitory system. Long-term alcohol use has been demonstrated to alter the brain's neurochemical systems in a compensatory manner. [Knapp et al., 2007 and Mirijello et al., 2015]. Many of the symptoms and indicators of AWS result from the roles being reversed during abstinence, with increased NMDA receptor function, decreased GABAergic transmission, and dysregulation of the dopaminergic system [McKeon et al., 2008 and Wackernah et al., 2014]. The development of anxiety-like behavior brought on by

repeated ethanol intoxications and withdrawals is likewise dependent on GABAA and GABAB pathways [Finn and Crabbe et al., 1997]. GABA-associated receptors are downregulated and glutamate-associated NMDA receptors are upregulated in order to restore homeostasis. This reduces the CNS effects of alcohol use and leads to tolerance.

Long-term alcohol consumption can cause neurochemical alterations that patients are unaware of. Patients with these modifications experience astounding CNS effects if and when they cut back on or stop drinking alcohol. The GABA inhibitory pathway nearly completely decreases and the glutamate excitatory pathway increases in the absence of alcohol's direct interaction with the neurotransmitter systems. Seizures, delirium, and hallucinations are more likely to occur as a result of this imbalance [Barnard et al., 1992]. Early alcohol withdrawal can negatively affect an EEG and cause abnormalities like an increase in the QT interval and dysfunction of the HPA axis. Both acute and prolonged withdrawal symptoms may be prolonged by this release of corticotropin-releasing hormone [Roberto et al., 2003]. A decrease in dopamine may also be the cause of other withdrawal symptoms, such as dysphonia or anhedonia. The symptoms that arise when alcohol's inhibitory effects are no longer present are collectively referred to as alcohol withdrawal. The brain's attempt to operate normally in the absence of inhibitory alcohol is reflected in the symptoms of hyperactivity during withdrawal. These symptoms only arise in the absence of alcohol [Kang et al., 1998].

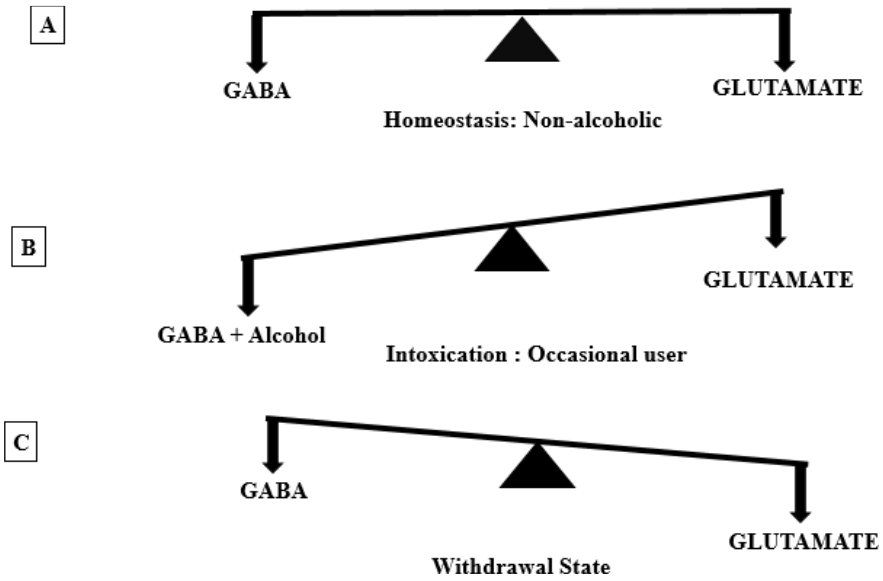

Fig.2: Pathophysiology of Alcohol Withdrawal Syndrome

9. NEUROBIOLOGY BEHIND ALCOHOL WITHDRAWAL SYNDROME AND ALCOHOL DEPENDENCE

9.1 Gamma-aminobutyric acid

The primary inhibitory neurotransmitter in the human central nervous system is GABA , acting through various receptors (GABAA, GABAB, and GABAC) with a strong depressive effect via chloride ion influx. Alcohol enhances GABA activity, influencing ethanol consumption; GABAA receptor antagonist's decrease, while agonists increase, alcohol intake, linking GABAA activation to alcohol use. These receptors are associated with anxiety, epilepsy, and depression and are modulated by sedatives like benzodiazepines [Lambert et al., 2001]. Variations in GABAA receptor subunits alter their functions. Chronic alcohol use initially boosts GABAergic neurotransmission but eventually diminishes it, resulting in anxiety and seizure susceptibility during withdrawal, as shown by impaired GABAA receptor function in the hippocampus and increased neuronal activity in the VTA. Benzodiazepines can help mitigate withdrawal effects by targeting specific GABAA subtypes [Harvey et al., 2002, Finn, Finn and Crabbe, 1997].

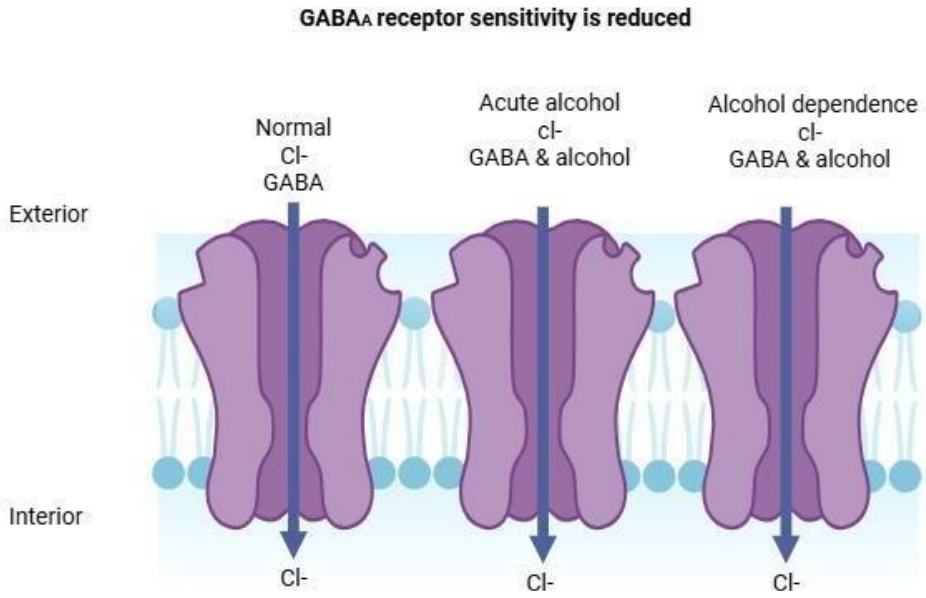

Fig. 3: The sensitivity of GABAA receptors is reduced. GABAergic inhibitory neurotransmission is reduced when alcohol use persists. GABAA receptor-chloride (Cl-) channels are activated when the synapse opens GABA channels in the absence of alcohol. Neurotransmission is suppressed as a result. Alcohol increases the effects of GABA, which increases the amount of chloride that enters the neuron and intensifies the inhibition. Both GABA and ethanol have minimal effects on GABAA receptors in alcoholism. Neurons that are already inhibited by GABA neurotransmission are amplified by low chloride [Lambert et al., 2001].

9.2 Glutamate:

One of the main excitatory neurotransmitters in the central nervous system is glutamate. It helps with cognitive processes like memory and learning. It functions by activating two primary types of receptors. There is one inotropic group. These receptors are ion channels that are gated by ligands. Ions enter and exit the cell when they open. Metabotropic is the other group. G proteins are connected to these receptors. Instead of only transporting ions, they assist in altering signals within the cell. There are three subtypes of inotropic receptors. They are kainate, NMDA, and AMPA. Every one of them has unique characteristics and activation mechanisms. Based on their genetic similarity, how they react to medications, and the signals they cause, metabotropic glutamate receptors are divided into three types. Alcohol dependence and withdrawal symptoms may be exacerbated by ethanol's primary effect on the NMDA receptor, which makes it more active and increases nerve cell excitement. Ethanol also alters how neurons communicate with one another by interfering with other glutamate receptors, such as AMPA and mGluR, which contributes to its behavioral effects. Additionally, it influences the release and uptake of glutamate, which modifies the transmission of impulses between neurons and amplifies the effects of alcohol [Tomek et al., 2013, McBride et al., 1991].Glutamate and its receptors are linked to ethanol withdrawal syndrome, which occurs when a dependent individual abruptly reduces or stops alcohol intake. The intensity of the symptoms can vary, and they could be fatal. Chronic alcohol use leads to increased glutamate neurotransmission via NMDA receptors, raising neuronal excitability and creating tolerance to ethanol. Upon cessation, heightened glutamate transmission results in central nervous system hyperexcitability and withdrawal symptoms [Koob et al., 2003]. Research indicates that NMDA receptor antagonists, like MK-801, can mitigate these symptoms in animal models. Additionally, reducing glutamate release or enhancing GABA activity can alleviate withdrawal effects, emphasizing the role of glutamate in this syndrome [Pandey et al., 1992].

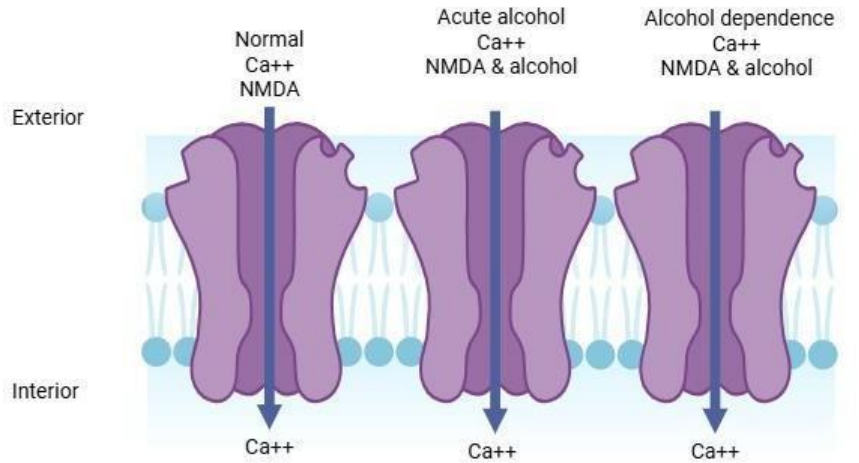

Fig. 4: The sensitivity of NMDA receptors is increased. After continuous alcoholic drinking, glutamatergic excitatory neurotransmission increases. Without alcohol, glutamate at the synapse allows calcium to enter axons through NMDA receptor carriers. Temporary exposure to ethanol reduces the amount of calcium that enters the axon through the receptor channels. When ethanol is consumed, the sensitivity of NMDA receptors to glutamate increases, resulting in an excess of calcium entering neurons and causing hyperexcitation [Lambert et al., 2001**].**

9.3 Opioid receptors:

Opioid peptides including beta-endorphin, encephalin, and dynorphins interact with opioid receptors (mu, delta, and kappa). These receptors are involved in controlling the mesolimbic dopaminergic pathway and the brain's reward system. Alcohol alters how these peptides are produced or digested, which has an impact on the system. It also affects the strength of the receptors' attachment to the peptides. Encephalin and beta-endorphin levels in the brain increase with heavy alcohol use. The emergence of alcohol addiction is linked to this rise. It has been demonstrated that drugs that block receptors, such as naltrexone and naloxone, can lower alcohol consumption, It's still unclear exactly how they operate. Some believed that these medications work by preventing dopamine from being released in the nucleus accumbens (NAc), a part of the brain involved in reward and pleasure. Nevertheless, studies reveal that naltrexone can still reduce alcohol consumption when dopamine circuits are altered. This implies that the inhibition of endorphin production may be the source of the impact. Specifically, it might stop the increase in endorphins brought on by alcohol in the NAc [Sari et al., 2011, Laine et al., 1999].

9.4 Dopamine:

Dopamine is produced and released more when alcohol is consumed. The nucleus accumbens (NAc), a crucial component of the brain's reward system, releases dopamine in response to heavy alcohol use. Alcohol consumption is decreased when dopamine receptors in the NAc are blocked. A person's mesolimbic dopamine system becomes less active after they quit drinking alcohol. The person may continue drinking in order to feel better as a result of this decreased activity. Increased calcium channel activity and decreased tyrosine hydroxylase levels were discovered to be the cause of this decrease in dopamine activity in mouse models subjected to long-term alcohol consumption. Stronger alcohol cravings were associated with decreased dopamine receptor availability in the ventral striatum and surrounding putamen in investigations including individuals who had quit drinking. These results demonstrate how alterations in the dopamine pathway contribute to the negative reinforcement associated with alcoholism [Imperato and Di Chiara et al., 1986].

9.5 Serotonergic system:

The brain's serotonergic system is involved in mood and reward in particular. It has been demonstrated that serotonin, also referred to as 5-HT, aids in causing the nucleus accumbens to produce dopamine. Dopamine is associated with motivation and pleasure, thus this is significant. At that moment, ethanol immediately triggers the brain's release of serotonin and dopamine. Over time, how these substances are handled may change as a result of this abrupt increase. Lower levels of dopamine and serotonin may result from the brain's difficulty releasing these neurotransmitters during alcohol withdrawal. Some of the emotions observed in alcohol-dependent individuals may be explained by this lack [Mendelson and Stein, 1966].

9.6 Noradrenergic system:

The system is another crucial component of alcohol withdrawal. Noradrenaline is the neurotransmitter used in this system. The brain becomes more active after quitting alcohol, which raises nervous system stimulation. This causes the nervous system to become overactive, which results in symptoms like anxiety, perspiration, and elevated heart rate. The elevation in noradrenaline levels in the brain and spinal fluid is one explanation for this. This occurs because withdrawal causes an increase in glutamate transmission, which overstimulates neurons. The regular feedback mechanism that regulates noradrenaline levels is compromised at this point. This happens as a result of the postsynaptic alpha-adrenergic receptors losing their ability to decrease release. Noradrenaline builds up as a result,

which exacerbates emotional distress [Ramsey and Van Ree, 1993].

10. THE ROLE OF THE HPA AXIS

Stress is a daily occurrence is something that is unavoidable. It can originate from both the outside environment and our own bodies, such as when we become ill or experience a panic attack. Stress can be managed by the body. The hormone cortisol is one of these methods. It's this hormone. The adrenal glands release it. These glands are located above the kidneys. Both humans and animals cannot handle many forms of stress without cortisol. The body must regulate the amount of cortisol it uses since it has a significant impact on numerous vital organs. The pituitary gland, the hypothalamus, and the outside of each gland are these three components. The pituitary-adrenal (HPA) axis is the collective name for these three components. This system facilitates the body's and brain's reaction to stress. (As given in fig.5) [Dai et al., 2007].

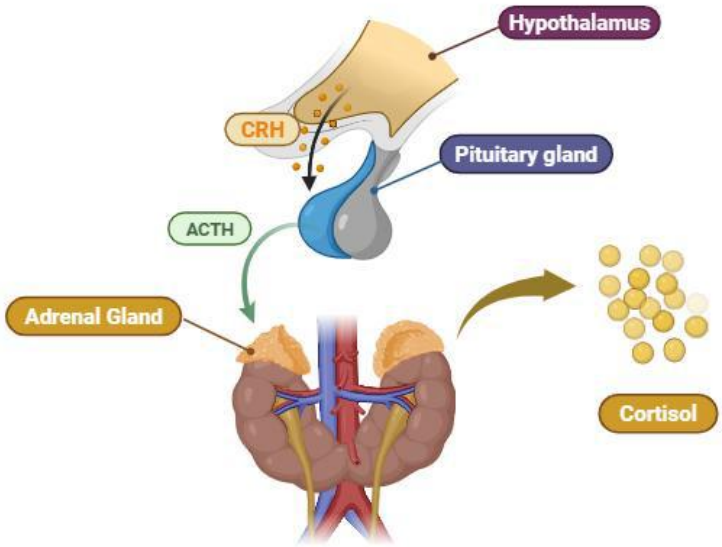

Fig.5: Role of the HPA Axis during Alcohol Withdrawal

11. REWARD SYSTEM OF BRAIN

The brain's reward system is a collection of brain regions and nerve connections that enable an individual to cider rewards, desire something, or experience happiness. When the brain's reward system is activated, people learn differently, make different decisions, and experience positive emotions like happiness and pleasure, among other things [Rassnick et al., 1993]. The dopamine pathway is part of the brain's reward system. The Nucleus accumbens (NAc) and the Ventral Tegmental Area (VTA) are part of this route. Although the VTA contains a variety of nerve cells, dopamine cells are particularly well-known. The VTA gives rise to the mesolimbic and mesocortical circuits. When an individual develops an addiction, the VTA cells travel to the nucleus accumbens, which connects these two brain regions [Kelley et al., 2004]. The reward system and the mesolimbic dopamine system link the frontal and mesolimbic regions of the brain [Trevisan et al., 1998]. The glutamine, GABA, dopamine, and natural opioid systems are all altered by alcohol. Alcohol causes the body to release endorphins, which are produced in the arcuate nucleus. These endorphins aid in the nucleus accumbens' production of dopamine. They accomplish this both directly and by preventing the VTA from producing GABA. People who are dependent on alcohol experience positive emotions due to the production of endorphins and dopamine. Drugs are used by people because they make them feel good. They wish to avoid the negative emotions that accompany quitting the drug [JT S. et. Al., 1989].The nucleus accumbens (NAc), VTA, and PFC (cortex) are the primary brain regions implicated in the effects of alcohol. These regions comprise the expanded amygdala and the dopamine system. The brain's limbic system retains all the knowledge about something that is rewarding. The HPC (Hypothalamus, Pituitary, and Adrenal) and the horizontal amygdale, which aid in processing emotions, are the brain regions that support this. The accumbens receives messages from the limbic system and the PFC. The information is processed by this area of the brain. transmits it to the motor system, causing the body to react by moving. The VTA is connected to both the NAc and the PFC [Lerner and Fallon et al., 1985].Alcohol causes these nerve cells to function more quickly, increasing the amount of dopamine in the NAc. Additionally, GABA-using nerve cells in the NAc communicate with the pallidum. The dorsal thalamus (DMT) and the VTA receive these messages. The DMT completes the system loop by sending messages to the PFC. Additionally, glutamate is used in the messages sent from the PFC to the NAc and from the AMG to the PFC. Additionally, the dopamine cells in the VTA get a glutamate message from the PFC. Addiction has been linked to these nerve cells. The NAc, striatum, and HPCs all contain

glutamate when a person quits drinking (Fig. 6) [Hall and Zador et al., 1997].

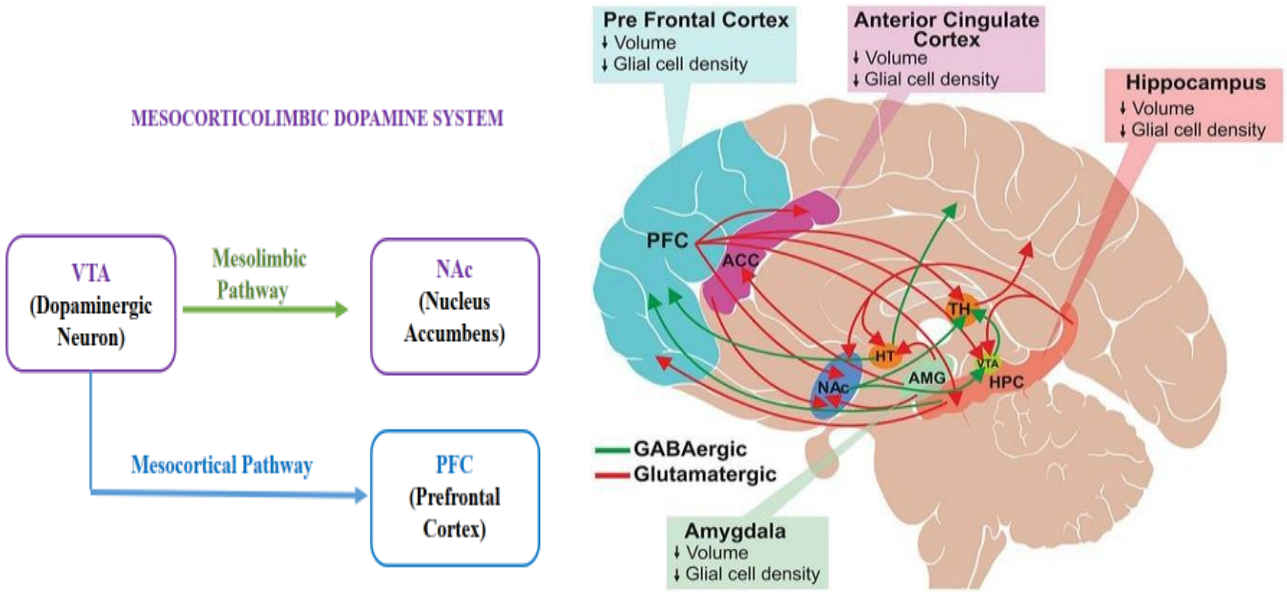

Fig. 6: Reward system of brain

12. CURRENT PHARMACOTHERAPY FOR ALCOHOL DEPENDENCE AND WITHDRAWAL

12.1 Disulfiram:

Disulfiram is a medication that does not improve people's mood. It makes drinking alcohol uncomfortable. Alcohol dehydrogenase is known to convert alcohol to acetaldehyde. Aldehyde dehydrogenase subsequently converts this acetaldehyde to acetate. Disulfiram inhibits an enzyme that breaks down aldehyde. Acetaldehyde is produced in the body as a result. Redness of the face, nausea, vomiting, and a pounding headache are all symptoms of elevated acetaldehyde in the blood. Additionally, disulfiram inhibits the brain's dopamine beta hydroxylase. This is how dopamine is converted to norepinephrine. Disulfiram also functions in this manner. This may be crucial not only for treating alcoholism but also for other substance addictions, such as cocaine. Alcohol use while taking disulfiram will cause these side effects. Additionally, the medication is unsafe for those with liver issues [Mayo-Smith et al., 1997].

Mechanism of action of Disulfiram:

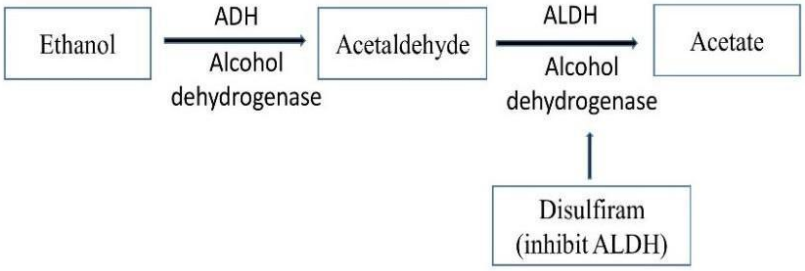

Fig. 7: Mechanism of action of Disulfiram

12.2 Benzodiazepines:

People who experience psychomotor restlessness during withdrawal are treated with benzodiazepines. Although other benzodiazepines may also be utilized, diazepam, lorazepam, and chlordiazepoxide are frequently used to treat or prevent alcohol withdrawal. When administered for a brief period of time, diazepam or chlordiazepoxide are often favored since they appear to provide a medical response with little risk of physical reliance and tolerance. Patients with severe alcoholic hepatitis or cirrhosis are typically treated with lorazepam or oxazepam.If excessive sedation occurs, the shorter half-life of lorazepam and the absence of metabolites with oxazepam may help prevent delayed effects. In patients with severe liver disease, chlordiazepoxide may be too sedative due to its unexpected half-life. Patients who are unable to take medication may require parenteral treatment, such as 18 mg of lorazepam diazepam.

Benzodiazepines inhibit neuronal movement and induce a degree of drowsiness by activating GABA receptors. Withdrawal symptoms, including as shaking, cramping in the stomach, vomiting, sweating, headaches, muscle soreness, anxiety, tension, irritability, and confusion, occur when a person stops taking benzodiazepines after becoming physically dependent on them [Zack et al., 2006, Sachdeva et al., 2015].

12.3Baclofen:

In certain clinical trials, the GABAB receptor agonist baclofen has been shown to support alcohol abstinence and prevent relapse. The GABAB receptors on clusters of neurons in the VTA that travel to limbic areas are hypothesized to be blocked by baclofen. Alcohol-induced dopamine release in the body is lessened by this mechanism. Medications that impact alcohol metabolism and a variety of neurotransmitter systems, such as the endogenous opioid system, glutamate system, dopamine system, serotonin system, and GABA system, are among the available treatments for alcohol addiction [Brennan et al., 2013].

12.4 Acamprosate:

The FDA has approved the drug acamprosate to prevent alcohol relapse. It is an analog of GABA. It has been demonstrated to attach to GABAB receptors, boosting the amount of GABA released from nerve cell terminals. It is a homotaurine derivative that decreases animal alcohol consumption and has no alcohol-related effects. It is thought to function as a glutamate antagonist, which aids in regulating the glutamate levels brought on by chronic alcohol consumption. It suppresses alcohol withdrawal by decreasing the activity of NMDA receptors. It appears to prevent calcium ions from passing via NMDA receptors and voltage-calcium channels [Harris et al., 2002].

12.5 Naltrexone and other Opioid Antagonist:

For drinkers who also suffer from depression, SSRIs seem to have an impact on preventing relapse. Although it was found to be ineffective in clinical trials, buspirone, a 5 hydroxytryptamine (5HT)-1A agonist, decreased alcohol consumption in animal tests. A 5HT-3 antagonist called ondansetron has been shown to be beneficial for drinkers, especially those with serotonergic dysfunction. It works by preventing the system's dopamine release brought on by alcohol [Roesner et al., 2010].

12.6 SSRIs:

SSRIs seem to have an impact on preventing relapse in drinkers who also suffer from depression. Although buspirone, a 5 hydroxytryptamine (5HT)-1A agonist, decreased alcohol consumption in animal tests, it was found to be ineffective in clinical trials. In drinkers, especially those with serotonergic dysfunction, ondansetron, a 5HT-3 antagonist, has been shown to be beneficial. It works by preventing the dopamine release that alcohol causes in the body [Naranjo and Bremner et al., 1993].

13. MEDICINAL PLANTS AND PHYTO CONSTITUENTS TO PREVENT ALCOHOL WITHDRAWAL AND DEPENDENCE

13.1 Pueraria lobata (Fabaceae)

Pueraria lobata used for the treatment of alcohol-patients include the isoflavone-rich extracts of kudzu root and sometimes also of kudzu flowers. Studies confirm that these extracts significantly delay the metabolism of alcohol which leads to the formation of the products responsible for the troublesome dependence symptoms such as nausea, vomiting, headaches, face redness and quite frequently excessive sweating [Benlhabib et al., 2004]. It is the isoflavones in kudzu materials, puerarin, daidzein and daidzin among others, which are of greatest interest as they are the compounds ascribed with therapeutic properties [Delmonte and Rader, 2006]. Similar to the well-known ALDH-2 inhibitor disulfiram, it was shown that the kudzu isoflavones inhibited the enzymatic activity of both ADH and ALDH. It's also intriguing to note that throughout therapy with kudzu-based products, there was a notable decrease in alcohol consumption as well as, crucially, an increase in abstinence periods and a decrease in alcohol cravings. Similarly, the isoflavone (daidzin, 7-O-glucosyl-4′-hydroxyisoflavone) suppression of ALDH-2, which participates in the conversion of dopamine and serotonin into steroids in the brain, is responsible for the decreased urge for alcohol consumption after using kudzu.The impact of these isoflavones on alcohol-exposed brain cells, which frequently lead to impaired mental performance, is another intriguing finding. Additionally, it was discovered that the kudzu extract reduced heavy drinkers' overall alcohol consumption during a drinking session while increasing the number of little sips and the amount of time needed to finish a unit of beverage. When kudzu is eaten orally, no adverse consequences have been recorded. Hemolysis has been brought on by intravenous puerarin. Hypothermia was brought on by intraperitoneal injection of puerarin or crude Pueraria lobata extracts.

Although it hasn't been well investigated in humans, kudzu root may also help people lose weight. According to the most recent study, administering kudzu root extract has not interfered with drinkers' sleep/wake cycles. As a result, its use as an adjuvant treatment for alcohol dependency has not been shown to have any potential negative effects on sleep [Li et al.,2010].

13.2 Hypericum Perforatum (**Hypericaceae**):

St. John's Wort is the common name for Hypericum perforatum. Mood problems are frequently treated with Hypericum perforatum (HPE) extract [Carai et al., 2000]. Because to its high concentration of phenolic chemicals, including flavonoids, hyperforin, and hypericin, Hypericum perforatum has antioxidant potential. In vitro, hyperforin has NMDA-receptor-potential neuroprotective effects that may be therapeutically beneficial in preventing alcohol use disorder relapses [Bozin et al., 2013]. Hypericum perforatum had a behaviorally selective influence on the

amount of alcohol consumed by msP rats. The effects of hypericum CO2 extract were not altered by the GABAA receptor antagonist bicuculline or the GABAB receptor antagonist CGP-36742. These findings suggested that GABA agonist actions do not influence HPE's inhibitory effects on alcohol consumption. In conclusion, Hypericum perforatum may be useful in reducing alcohol consumption, but further research is required to understand the underlying mechanisms [Perfumi et al., 2002,Perfumi et al., 2003].

13.3 Salvia miltiorrhiza (Lamiaceae):

Salvia miltiorrhiza includes tanshinones, also known as abietane-type diterpenes, and acids. Salvia miltiorrhiza and its derivatives are mostly utilized in medicine to treat neurological diseases, particularly circulation issues, liver inflammation, and drowsiness [Li et al.,2010]. Salvia miltiorrhiza's salvianolic acid B may reduce acute alcohol-induced liver cell death in mice by triggering SIRT1, which eliminates acetyl groups from the p53 pathway. Acid B pretreatment increases antioxidant enzymes, decreases toxic cytokines such interleukin-6, and significantly minimizes the increase in liver enzyme levels brought on by alcohol. Additionally, salvianolic acid B increases SIRT1 activity. prevents alcohol from causing p53 to become acetylated. It cleaves caspase-3 and prevents NF-κB from rising. stops the decrease in B-cell lymphoma-extra large protein that alcohol causes. Other Salvia miltiorrhiza constituents, such as magnesium lithospermate B and cryptotanshinone, may also aid in the treatment of alcohol-related liver illnesses, such as liver cancer, due to their anti-cell-death and potential anti-inflammatory properties. Salvia miltiorrhiza may therefore be a treatment for alcohol-related injuries. Salvia miltiorrhiza's anti-inflammatory qualities may also assist cure alcohol use disorder by lowering alcohol use, preventing relapse, and shielding the liver from alcohol damage [Wang et al., 2016].

13.4 Tabernanthe iboga (Apocynaceae):

Ibogaine, an alkaloid derived from the root bark of Tabernanthe iboga, has been shown by scientists to decrease voluntary alcohol consumption in alcohol-loving rats. Cell line-derived neurotrophic factor (GDNF) levels in the ventral tegmental area and other midbrain regions are increased by ibogaine. Ibogaine activates the GDNF pathway in dopaminergic neuron-like SHSY5Y cells, as evidenced by the activation of the GDNF receptor Ret and the downstream kinase ERK1. Lastly, this effect is mimicked by injecting GDNF into the ventral tegmental area, and the ibogaine-induced decrease in alcohol self-administration is lessened by inhibiting GDNF in the same region [He et al., 2005,]. However, ibogaine is not used in therapeutic settings due to its adverse consequences [Li et al.,2010].

13.5 Rhizoma Coptidis (Ranunculaceae)

Rhizoma Coptidis has long been utilized in traditional Chinese medicine. It relieves intestinal irritation, diarrhea, and dysentery. Berberine, an alkaloid, is the primary active component. Neurotransmitter systems can be altered by berberine, particularly in alcohol use disorders. Berberine (10 and 20 mg/kg) has a similar impact to diazepam (1.25 and 2.5 mg/kg) in reducing the symptoms of alcohol withdrawal hyperexcitability in rats. Berberine's primary mechanism of action is probably neuromodulation. Alcohol's rewarding potential in mice is similarly diminished by berberine, which likewise lessens the development and expression of alcohol-induced conditioned location preference, decreases the choice of alcohol over water, and lessens the effect of alcohol and the sensitization to that effect. In both living animals and cell cultures, berberine also heals the damage alcohol causes to the gut. According to studies, berberine regulates the upstream signals TLR2 and TLR4 as well as the increase in TNFα and IL-1β in the gut lining caused by alcohol. Rhizoma coptidis's neuromodulatory effect may therefore reduce alcohol intake [Bhutada et al., 2011, Bhutada et al., 2010].

Medicinal Plant	Scientific Name	Major bioactive phytoconstituents	Biological Effect and Mechanism	Ref.
Kudzu	Pueraria lobata	Puerarin, daidzin, daidzein, tectoridin	Anti-alcohol, anti-craving and anxiolytic: Modulates alcohol metabolizing enzymes and neurotransmitter systems, including GABAergic pathways, thereby reducing alcohol intake and withdrawal-associated anxiety.	[Benlhabib et al., 2004]
Japanese raisin tree	Hovenia dulcis	Dihydromyricetin (ampelopsin), myricetin, quercetin, hovenitins	Anti-withdrawal, neuroprotective and hepatoprotective: Dihydromyricetin modulates GABAA_A receptors and reduces CNS hyperexcitability; antioxidant activity helps protect against alcohol-induced oxidative damage.	[Le et al., 2018]
St. John's wort	Hypericum perforatum	Hypericin, hyperforin, flavonoids	Anti-alcohol, anxiolytic and antidepressant: Modulates monoaminergic neurotransmission and neuronal signaling involved in alcohol-seeking behavior and withdrawal-related behavioral changes	[[Carai et al., 2000].]
Danshen	Salvia miltiorrhiza	Tanshinone I/IIA, cryptotanshinone, miltirone	Anti-alcohol and neuroprotective: Modulates CNS signaling and attenuates oxidative stress and neuroinflammation associated with chronic alcohol exposure	[Wang et al., 2016]
Ginseng	Panax ginseng	Ginsenosides (Rb1, Rg1, Rg3), polysaccharides	Anti-alcohol, neuroprotective and antioxidant: Modulates neurotransmitter systems and endogenous antioxidant mechanisms, helping protect neurons against alcohol-induced injury.	[Le et al., 2018]
Purple passionflower	Passiflora incarnata	Benzoflavone fraction, flavonoids (vitexin, isovitexin)	Anxiolytic and anti-withdrawal: Modulates GABAergic neurotransmission and decreases anxiety and CNS hyperexcitability associated with alcohol withdrawal.	[Lieberman et al., 2017]
Thyme	Thymus vulgaris	Thymol, carvacrol, polyphenols	Antioxidant, neuroprotective and hepatoprotective: Reduces ROS generation and lipid peroxidation and supports endogenous antioxidant defense against alcohol-induced injury	[Shati and Elsaid et al., 2009]
Fenugreek	Trigonella foenum-graecum	Polyphenols, quercetin, naringenin, vitexin, rutin	Hepatoprotective and antioxidant: Enhances antioxidant defenses and reduces alcohol-induced lipid peroxidation and oxidative hepatic injury	[Kaviarasan et al., 2007]
Ginger	Zingiber officinale	6-Gingerol, 6-shogaol, zingerone	Antioxidant, hepatoprotective and neuroprotective: Scavenges ROS and reduces lipid peroxidation and inflammatory damage produced by chronic alcohol exposure.	[Shati and Elsaid et al., 2009]
Milk thistle	Silybum marianum	Silymarin, silybin, silychristin, silydianin	Hepatoprotective and antioxidant: Stabilizes hepatocyte membranes, enhances antioxidant defense and decreases alcohol-induced hepatic oxidative injury.	[Xu et al., 2005]

Prickly pear	Opuntia ficus-indica	Rutin, naringenin, betalains, polyphenols	Antioxidant and anti-hangover: Reduces oxidative and inflammatory responses associated with alcohol exposure through free-radical scavenging and antioxidant activity.	[Xu et al., 2005]]
Evening primrose	Oenothera biennis	γ-Linolenic acid (GLA)	Hepatoprotective and anti-inflammatory: Supports lipid mediator synthesis and reduces inflammatory and oxidative damage associated with alcohol-induced tissue injury	[Kaviarasan et al., 2007]
Iboga	Tabernanthe iboga	Ibogaine, ibogamine alkaloids	Operates on the brain's chemical systems, such as the glutamate, dopamine, and serotonin pathways, to prevent addiction and cravings. Reward and dependence are related to anti-addictive and anti-craving.	[He DY. Et al.,2005]
Asparagus	Asparagus officinalis	Flavonoids, steroidal saponins, polyphenols	Hepatoprotective and antioxidant: Enhances antioxidant defense and may support alcohol-metabolizing enzyme activity, thereby reducing alcohol-induced hepatic oxidative stress.	[Kim et al., 2009]
Evodia	Tetradium ruticarpum (syn. Evodia rutaecarpa)	Evodiamine, dehydroevodiamine, rutaecarpine	Anti-hangover and hepatoprotective: Enhances alcohol metabolism and antioxidant enzyme activity and reduces oxidative stress associated with alcohol exposure.	[Schramm and Hamburger et al.,2014]
Ashwagandha	Withania somnifera	Withaferin A, withanolide A/D	Anxiolytic, neuroprotective and anti-stress: Modulates GABAergic signaling and attenuates oxidative and neuroinflammatory stress, potentially reducing withdrawal-related anxiety.	[Ruby et al., 2012]
Green tea	Camellia sinensis	EGCG, catechins, epicatechin	Antioxidant, neuroprotective and hepatoprotective: Enhances antioxidant defenses and reduces ROS-mediated neuronal and hepatic damage associated with alcohol exposure.	[Dobrzyńska et al., 2004]
Turmeric	Curcuma longa	Curcumin, demethoxycurcumin, bisdemethoxycurcumin	Neuroprotective, antioxidant, anti-inflammatory and hepatoprotective: Activates Nrf2-mediated antioxidant defense and inhibits NF-κB-mediated inflammatory responses.	[Zhao and Qi et al., 2025]
Bacopa	Bacopa monnieri	Bacosides, bacopaside	Neuroprotective, anxiolytic and antioxidant: Modulates GABAergic and other neurotransmitter systems while reducing oxidative neuronal damage.	[Mathur et al., 2016]
Holy basil	Ocimum tenuiflorum	Eugenol, rosmarinic acid, ursolic acid	Anxiolytic, anti-stress, antioxidant and hepatoprotective: Reduces oxidative stress and modulates stress-related and neurotransmitter pathways, potentially alleviating withdrawal-related behavioral changes.	[Funde et al., 2025]
Licorice	Glycyrrhiza glabra	Glycyrrhizin, glycyrrhetinic acid, liquiritin	Hepatoprotective, antioxidant and anti-inflammatory: Reduces inflammatory signaling and oxidative hepatic injury caused by chronic alcohol exposure.	[Pastorino et al., 2018]
Garlic	Allium sativum	Allicin, S-allyl cysteine, sulfur	Antioxidant, hepatoprotective and neuroprotective: Enhances endogenous	[Ansari et al., 2022]

		compounds	antioxidant systems and reduces ROS-mediated cellular and neuronal injury.	
Amla	Phyllanthus emblica	Emblicanin A/B, gallic acid, ellagic acid, quercetin	Antioxidant, hepatoprotective and neuroprotective: Scavenges ROS and enhances endogenous antioxidant enzymes, reducing alcohol-induced oxidative tissue damage.	[Chaphalkar et al., 2017]
Andrographis	Andrographis paniculata	Andrographolide, neoandrographolide	Anti-inflammatory, antioxidant and hepatoprotective:Activates antioxidant defense pathways such as Nrf2 and suppresses inflammatory signaling, reducing alcohol-induced tissue injury.	[Sivaraj et al., 2011]
Black pepper	Piper nigrum	Piperine, volatile oils, polyphenols	Neuroprotective and antioxidant: Modulates neurotransmitter signaling and reduces oxidative stress, providing potential protection against alcohol-related neuronal dysfunction.	[Balakrishnan et al., 2023]

Table 1. Medicinal plants and phytoconstituents to prevent alcohol withdrawal and dependence:

14. CONCLUSION

Alcohol dependence and withdrawal are complex disorders involving significant neuroadaptations in GABAergic, glutamatergic, dopaminergic, serotonergic, opioid, and stress-related pathways. The therapeutic limitations of currently available pharmaceutical treatments emphasize the need for safer and more efficient complementary approaches, even though they can lessen relapse, alcohol cravings, and withdrawal symptoms.

According to the current review, medicinal plants and their bioactive phytoconstituents have a great deal of promise for treating alcoholism and withdrawal. Plants that affect alcohol consumption, withdrawal symptoms, alcohol metabolism, oxidative stress, inflammation, and liver damage include Pueraria lobata, Hovenia dulcis, Panax ginseng, Hypericum perforatum, and Salvia miltiorrhiza. Neurotransmitter systems, antioxidant pathways, ADH/ALDH activity, and particular molecular targets are all linked to these effects.

Overall, the available evidence supports medicinal plants as promising sources of therapeutic agents for alcohol-related disorders. However, more standardized pharmacological research, thorough mechanistic analyzes, toxicity assessments, and rigorously planned clinical trials are needed to determine their effectiveness, safety, and possible use as supplemental or alternative treatments.

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