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Plants and their derivatives as potential source in treatment of alcohol withdrawal syndrome and other treatment strategies: A review

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Abstract

Alcohol Withdrawal Syndrome (AWS) is a set of symptoms that develops 24 to 48 h followed by quitting drinking after a prolonged period of heavy drinking. AWS is mild to severe depending upon the duration and quantity of alcohol intake. Up to 50% of patients who use alcohol experience withdrawal symptoms. The AWS is primarily mediated by GABA and glutamate receptors. Many plants and plant derivatives are used to relieve the symptoms of alcohol withdrawal. Though, benzodiazepines serve as the first-line drugs in treating AWS, on long-term usage they develop an addiction. This review consists of plants with potential therapeutic effects against AWS, published in the literature from 1999 to 2021. The review contains plant profiles include information about the botanical name, family, animals, methodology, model, the degree of protection, and the active agents against AWS. The literature review was undertaken by searching databases such as Science Direct, Scopus, PubMed, and Google Scholar for articles using relevant keywords. Fifteen plants and nine plant derivatives were selected based on their potency in treating AWS. Studies have confirmed the effects of these medicinal plants and plant derivatives on alcohol withdrawal syndrome. The effects of these plants may prevent, reduce or treat alcohol withdrawal syndrome and other symptoms associated with it.

1. Introduction

Alcohol use disorder (AUD) is predicted to impact 18% of the total population and 5% of the population on an annual basis. 20% of adults have emergency room admission due to AWS and the frequency of AWS in patients admitted to intensive care units ranges from 8% to 40%, resulting in infectious complications and higher fatality rates. Up to 50% of patients who use alcohol experience withdrawal symptoms (Mirijello *et al.*, 2015).

Alcohol withdrawal (AW) syndrome is a set of symptoms that occurred by an individual cessation of alcohol after a prolonged period of excessive use (National Clinical Guideline Centre, 2010). The AWS is a collection of clinical signs and symptoms that occur in people who are addicted to alcohol. They usually develop 24 to 48 h after cessation of alcohol drinking or reduction in intake (Sachdeva *et al.*, 2021).The mild symptoms including nausea, vomiting, insomnia, shaky hand, anxiety occur 6 h after quitting alcohol. The more serious problems such as seizure, confusion, hallucinations, and heavy sweating arise 24 h after cessation of alcohol. Delirium tremens (a severe dysautonomic and encephalopathic state) and withdrawal seizures, both of which can be fatal occur about 1 to 5% (Mc Keon *et al.*, 2008). Commonly, the life-threatening severe symptoms are treated with drugs and also need emergency care. The drugs used to treat AW causes addiction, several side effects including withdrawal reflex. The mild symptoms are not yet treated with drugs, but it makes trouble in regular life. Hence, plant-derived compounds are especially used to treat mild AWS without causing any side effects.

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2. Pathophysiology

Alcohol is a CNS depressant. The AWS caused by an alteration in $GABA_A$ and NMDA receptor systems (Carlson *et al.*, 2012). Acute alcohol ingestion causes enhanced GABAergic neurotransmission. Whereas, in chronic alcohol exposure a reduction in number, function, and sensitivity of GABA towards the $GABA_A$ receptors (down-regulation) is observed. Acute reduction in GABA activity is responsible for AWS (insomnia and hyperreflexia) and it is caused by the cessation of alcohol (Olsen and Liang, 2017). Alcohol use reduced the brain's excitatory neurotransmitters such as a spartate and glutamate acting on both NMDA and non-NMDA receptors (Rao *et al.*, 2015). The AW increases the activation of NMDA receptors resulting in increasing entry of calcium to nerve cells.The stimulation of NMDA receptors is responsible for excitatory activity like tremors, anxiety, and seizures. Although, calcium is required for nerve cell activity, an excess of the chemical in neurons has been linked to cell death or toxicity. Repeated cycles of alcohol drinking and abstinence, on the other hand, may result in calcium-related brain damage (Valenzuela, 1997).

3. Blood alcohol level

AWS is diagnosed by physical examination and estimation of blood alcohol level. The blood alcohol level varies according to the

frequency and quantity of alcohol intake, gender, and body weight. Commonly, females have shown a high blood alcohol level compared to males, both of them consuming the same quantity of alcohol. The physiological effects produced by different blood alcohol levels are shown in Table 1 (Dasgupta, 2017).

Table 1: Blood alcohol levels and their physiological effects

Blood alcohol level	Effect
10-40 mg/dl	Relaxation, mild euphoria, increased social interaction
50-70 mg/dl	Euphoria, motor impairment
80 mg/dl	Impairment in driving
80-120 mg/dl	Emotional swings and depression
120-150 mg/dl	Motor function and speech are all severely affected
150-200 mg/dl	Appear drunk. Visual impairment
200-300 mg/dl	Vomiting, symptoms of alcohol intoxication
300-400 mg/dl	Severe alcohol intoxication, total loss of consciousness
400-500 mg/dl	Fatal and may be comatose
>500 mg/dl	Highly dangerous. Fatal blood alcohol level

The mild symptoms of AWS include autonomic symptoms such as nausea, vomiting, diarrhea, elevated body temperature, elevated blood pressure, tachypnea, and motor symptoms such as tremor, ataxia, seizure, gait disturbances, hyperreflexia (Figure 1). The moderate symptoms of AWS such as anxiety, delusion, and hallucination. The severe symptoms of AWS include awareness symptoms such as insomnia, delirium, agitation, and irritability (Jesse *et al*., 2017). The alcohol withheld leads to chemical alteration in the brain and causes excessive neuronal activity (Sachdeva *et al*., 2015).

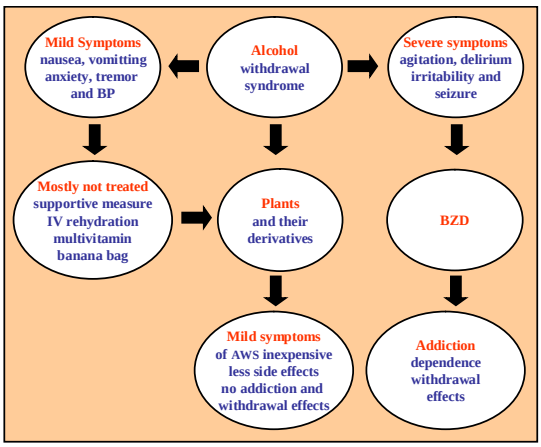

Figure 1: Alcohol withdrawal syndrome and treatment strategies (Jesse *et al*., 2017).

4. Alcohol withdrawal assessment

According to the CLAC-s (clinical institute withdrawal assessment of alcohol scale), the symptoms developed by alcohol withdrawal may be scored as (Knight and Lappalainen, 2017):

Nausea and vomiting

Score 0: No nausea and vomiting, 1-4: Mild to intermittent nausea with dry heaves, and 5-7: Constant nausea, frequent heaves, and vomiting.

Tremor

Score 0: No tremor, 1-4: Not visible tremor to moderate tremor, and 5-7: Moderate to severe tremor.

Paroxysmal sweats

Score 0: No sweat visible, 1-4: Detectable sweating, sweat on the forehead and palm, and 5-7: Drenching sweats.

Anxiety

Score 0: No anxiety, 1-4: Mild to moderate anxiety, and 5-7: Severe delirium with acute panic states or acute schizophrenia.

Tactile disturbances

Score 0: None, 1: Very mild itching, burning or numbness, 2: Mild itching, 3: Moderate itching, 4: Moderately severe hallucinations, 5: Severe hallucinations, 6: Extremely severe hallucinations, and 7: Continuous hallucinations.

Agitation

Score 0: Normal activity, 1-4: Mild to Moderately fidgety and restless, 5-7: Move forth and back.

Auditory and visual disturbances

Score 0: Not present, 1: Very mild sensitivity, 2-3: Moderate sensitivity, 4: Moderately severe hallucinations, 5: Severe hallucinations, 6: Extremely severe hallucinations, and 7: Continuous hallucinations.

Headache and fullness in head

Score 0: Not present, 1: Mild, 2: Moderate, 3: Moderately severe, 4: Severe, 5: Very severe, and 6: Extremely severe.

Orientation

Score 0: Oriented, 1: Cannot do serial additions, 2: Disoriented on a date 3: Disoriented on a date and more than 2 days, and 4: Disoriented for place.

5. Risk factors and treatment

The alcohol withdrawal seizure occurred by a reduction in the seizure threshold potential in the early stage of alcohol withdrawal. Acute seizures approximately 90 % occurs within 48 h of cessation of prolonged alcohol use. The seizures often occur without other symptoms of AWS. AWS especially repeated seizures occurred in 50% of individuals among 5% in status epileptics.

Alcohol withdrawal seizures (<50%) occurrence rate increased with concurrent risk factors such as brain lesions, prior epilepsy, and use of drugs (Lal, 2005). Benzodiazepines (intravenous diazepam and lorazepam) are, effectively treated against alcohol withdrawal seizures. The benzodiazepine dose is calculated based on average alcohol intake per day. The amount of alcohol consumption is calculated by using the formula (Kattimani and Bharadwaj, 2013):

Alcohol (in g) = Volume of liquor (ml) × 0.008 × (%) ethanol content in the liquor (w/v).

In the case of mild to moderate, AWS are treated with supportive therapy including intravenous rehydration, electrolyte supplements, multivitamin, and thiamine especially for Wernicke-Korsakoff syndrome (thiamine deficiency in the brain due to AW) (Muncie *et al*., 2013). A banana bag is an IV fluid containing vitamins and minerals that are preferably used to treat alcoholics. The bags contain vitamins (thiamine, folic acid), and magnesium sulfate used to correct the chemical alterations in the human body induced by alcohol (Kelsey *et al*., 2006).

Some of the treatment regimens used in alcohol withdrawal states are fixed-dose regimen (Diazepam 60 mg/ Chlordiazepoxide 125 mg), loading dose regimen (Diazepam 20 mg), symptom triggered treatment (CIWA-Ar (Ar-revised version) score 8 or more-Chlordiazepoxide), symptom monitored loading dose (Diazepam 20 mg/2 h till CIWA-Ar score becomes 10) and rapid loading with close monitoring (Diazepam) ((Kattimani and Bharadwaj, 2013).

Benzodiazepine withdrawal after prolonged usage may also lead to protracted withdrawal syndromes (Ashton, 1991). However, for severe symptoms scored 5-7 in CIWA, allopathic medicines are the first line choice of drugs. Where as, herbal medicines can be used to treat mild to moderate symptoms scored 1-4 in CIWA categories. Herbal medicines have several advantages such as minimum or no side effects, low cost can be continued for a long period (Vivekanandan *et al*., 2018; Malik *et al*., 2020; Lalitha and Sivakumar, 2018; Lalitha *et al*., 2015), and has no withdrawal effects.

Many plant and plant derivatives are proved in the treatment of alcohol withdrawal syndrome. The main purpose of this article is to highlight several effective medicinal plants used for treating alcohol withdrawal syndrome and other symptoms associated with it.

6. Materials and Methods

Publications related to the plants and their derivatives used in the treatment of AWS were collected from databases such as PubMed, Scopus, Science Direct, Wiley, and Springer. Keywords used in this study included “ethanol withdrawal”, “medicinal plants”, “alcohol withdrawal syndrome”, “treatment”, and “plant derivatives”. Articles published in the period between 1999 and 2021 were included in this review.

Table 2: Plants in treating AWS

Plant name and family	Part used	Dose (mg/kg)	Animal used	Method of induction	Evaluation	Reference
Bacopa monnieri **Plantaginaceae**	Whole plant	100,200, and 300/PO	Wistar rats	A modified liquid diet with ethanol 7.2% for 21 days	Reverse depression by tail suspension and forced swim test). Hyper locomotor activity by actophotometer.	(Sharma *et al*., 2018)
Bacopa monnieri **Plantaginaceae**	Whole plant	100, 200 and 500/PO	Male Wistar rats	A modified liquid diet with ethanol 9% for 15 days	Anxiety behaviorwas assessed by elevated plus maze and light-dark test. Alcohol markers gabra1, Gabra4, gabra5 genes of $GABA_A$ receptors.	(Gupta and Sharma, 2019)
Clitoria ternatea **Fabaceae**	Aerial parts	100,200 and 400/PO	Swiss albino mice	A modified liquid diet with ethanol 6.3% for 10 days	Antidepressant activity by forced swim test.	(Prashant *et al*., 2018)
Crocus sativus **Iridaceae**	Stigma	40,80 and 160/PO	Male mice and Male BALB/c mice	Ethanol 2g/kg (10%v/v) for 7 days	Seizure threshold by PTZ kindling. Antidepressant activity by a forced swim and open field test.	(Shoja *et al*., 2018; (Hosseinzadeh *et al*., 2004)
Hypericumper foratum **Hypericaceae**	Aerial parts	25,50,100 and 200/PO	Male Wistar rats	A modified liquid diet with ethanol 7.2% for 15 days·	Decreased locomotor hyperactivity· Reduction in the stereo type behavior.	(Coskun *et al*., 2006)
Pueraria montana **var Fabaceae**	Root	500 mg/kg/ PO	Female AP rats	15% ethanol for 50 days	Suppressed alcohol intake and AWS.	(Benlhabib *et al*., 2004)
Pueraria montana **var Fabaceae**	Flowers	200/PO	Male Kunming mice	10% ethanol for 28 days	Amelioration of depression and anxiety.· Brain hippocampal expression of BDNF. Plasma CRH, ACTH, and CORT levels.	(Jiang *et al*., 2021)

***Mitragyna speciosa* Rubiaceae**	Leaves	300, and 500/PO	Male Swiss albino mice	A modified liquid diet with ethanol 7.2% for 30 days	Lowered the behavioral parameters (rearing, displacement head weaving, grooming, lip-smacking, and scratching).	(Kumarnsit *et al*., 2007)
***Ocimum sanctum* Lamiaceae**	Leaves	100,200 and 300/PO	Wistar rats	A modified liquid diet with ethanol 7.2% for 21 days	Locomotor hyperactivity by actophotometer, anxiety by elevated plus maze, and light-dark model.	(Sharma *et al*., 2018)
***Passiflora incarnata* Passifloraceae**	Plant	200/PO	Male Wistar rats	Ethanol 4 g/kg (20%v/v) for 19 days	Nociceptive activity by Tail flick latency and hot plate test).	(Schunck *et al*., 2017)
***Salsola collina* Chenopodiaceae**	Plant	200/PO	Male Albino rats days	Ethanol 5 g/kg (25%v/v) for 5 total lipids level	Phosphatidylethanolamine, phosphatidylcholine.	(Selevich *et al*., 1999)
***Schizandra-chinensis* Schisandraceae**	Fruit	100, and 300/PO	Male Sprague Dawley rats	Ethanol 3 g/kg (20%v/v) for 28 days	Anxiety behavior by Elevated plus maze, inhibition CORT· Reduction in norepine-phrine (NE) and MHPG in the paraventricular nucleus of the brain.	(Wu *et al*., 2014)]
***Sesbania grandiflora* Fabaceae**	Leaves	100, and 200/PO	Female Swiss albino mice	Ethanol 2 g/kg (10%v/v) for 7 days	Antidepressant action by Forced swim test.	(Sundarrajan and Velmurugan, 2016)
***Withania-somnifera* Solanaceae**	Root	50/PO	Male Wistar albino rats	A modified liquid diet with ethanol for 15 days	Antianxiety activity by Elevated plus-maze. .	(Gupta and Rana, 2008)
***Withania-somnifera* Solanaceae**	Root	500/PO	Albino mice	Ethanol 2g/kg (10%v/v) for 7 days	Suppress PTZ kindling seizure.	(Ruby *et al*., 2012)
***Zingiber officinale* Zingiberaceae**	Rhizome	200/PO	Male Wistar albino rats	Ethanol 2 g/kg for 42 days	Improved hyperlipidemia antinephrotoxic effect (Urea and creatinine level estimated).	(Maralla, 2013)
Ziziphi spinosae	Semen	60, and 180/PO	Male Sprague Dawley rats	(20%v/v) for 28 days	Ameliorated anxiety (Elevated plus maze and open field) by improving both CRF/CRF receptor 1 and nociceptin/orphanin FQ (N/OFQ)/ N/OFQ peptide receptor (NOP) transmissions in the central nucleus of the amygdale.	(Li *et al*., 2019)

7. Medications for AWS

7.1 Benzodiazepines

Benzodiazepines (BZD) including chlordiazepoxide, diazepam, and lorazepam are widely used as first-line medications to suppress the AWS. Long-acting BZD such as chlordiazepoxide, diazepam is superior to other BZD to treat AW delirium and seizures (Witkiewitz *et al*., 2019). Lorazepam is an intermediate-acting BZD preferably used in patients with liver problems (Girish *et al*., 2016). Alcohol use and benzodiazepines both act additively on GABA receptors and cause depressant effects and induce suicidal thoughts. Hence, care must be taken when BZD is used to treat AWS (Koh *et al*., 2021). But, BZD use leads to an increased risk of suicide due to aggression, dementia, respiratory depression, negative withdrawal effects, dependence, and BZD withdrawal syndrome. The BZD overdoses are needed in some cases of AWS, but overdose may cause unconsciousness. Moreover, it has a major risk of abuse and dependence (Guina and Merrill, 2018).

7.2 Barbiturates

Barbiturates are less commonly used in the treatment of AW seizures either alone or along with BZDs. Because it causes respiratory

failure and the need for mechanical ventilation due to its long half-life (Hammond *et al*., 2017; Martin and Kartz, 2016).

7.3 Neuroleptics

Atypical neuroleptics such as risperidone, olanzapine, and quetiapine are used in the treatment of AW hallucinations and delirium (New *et al*., 2015). Typical neuroleptics such as chlorpromazine, promazine are not used because it causes severe agitation and hypotension. All neuroleptics are only used to calm the patients, but it reduces the seizure threshold and risk of occurrence of seizure and prolongation of QT interval (Kerna, 2020).

7.4 Anticonvulsants

NBAC (Non-benzodiazepine anticonvulsants) including carbamazepine is safe and tolerable than BZD in the treatment of AWS (Leggio *et al*., 2008) and valproic acid has high efficacy and safety to control AW seizure (Farrokh *et al*., 2021). But, carbamazepine is associated with dizziness, diplopia, ataxia, nausea, and vomiting. Though, anticonvulsants have less abuse potential than benzodiazepines, they do not prevent seizures or delirium tremens (McKeon *et al*., 2008). Gabapentin was reported to treat mild to moderate AWS, but not act against severe AWS (Hammond *et al*., 2015).

8. Plant derivatives in treating AWS

8.1 Argan oil

Argan oil (10 ml/kg) administration to AWS induced male Wistar rats lower the somatic signs of ethanol withdrawal (stereotyped signs, agitation by irritability to touch, tail stiffness, and abnormal posture and gait, lower anxiety-related behavior (Elevated plus maze and light-dark model) (Figure 2) during abstinence, inhibited oxidative stress and neurodegeneration in the brain by attenuating intermittent ethanol intoxication (IEI) (ElMostafi *et al*., 2020).

8.2 Berberine

Berberine is an isoquinoline alkaloid found in plants. It is found that berberine (5, 10 and 20 mg/kg, i.p) possess inhibitory effects against ethanol withdrawal (Modified liquid diet with ethanol 10% for 10 days) induced hyperexcitability signs mediated by its neuromodulatory action in C57BL/6J mice (Bhutada *et al*., 2011).

8.3 Curcumin

The increase in fat and decrease paraoxonase-1(PON-1) activity caused by alcohol consumption and a sedentary lifestyle. A combination of short-term swimming training and curcumin administration was found to increase the activity of PON-1 in male Wistarrats (Azarbayjani *et al*., 2019).

8.4 Fluoxetine

Fluoxetine (10 mg/kg) attenuated ethanol withdrawal symptoms induced by a modified liquid diet with ethanol 7.2% for 21 days. The antidepressant activity measures the high-frequency brain wave oscillation and spontaneous motor activity in male Wistarrats. Pretreatment with fluoxetine was attenuated the physical and electrical brain wave activities induced by AW (Cheaha *et al*., 2014).

8.5 Fucoidan

Fucoidan (300 mg/kg), a polysaccharide component in brown seaweeds when administered to alcohol withdrawal (15 % ethanol for 5 days) C57BL/6J mice, regulated the gut flora of mice exposed to alcohol and reduced endotoxemia. The fucoidan down-regulated the TLR4/MyD88/NF-κB p65 pathway blocks alcohol-induced microglial cell activation, inflammation in the brain and protect against depression-like behaviors induced by alcohol withdrawal (Sucrose preference test, forced swim test, open field test, and Y-maze test) of mice (Xue *et al*., 2021).

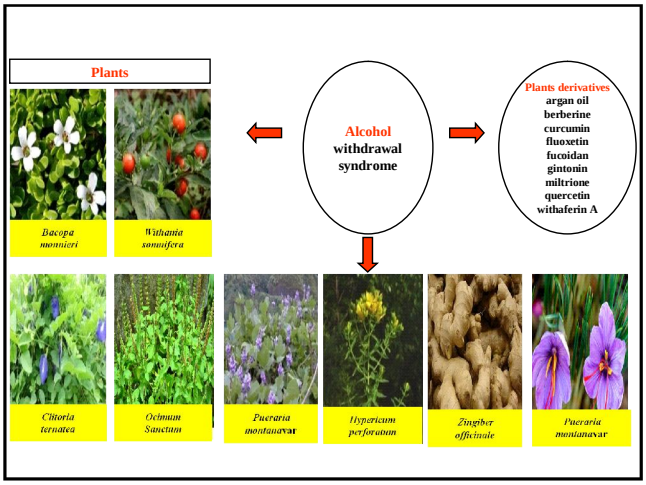

Figure 2: Plant and their derivatives used for alcohol withdrawal syndrome.

8.6 Gintonin

Gintonin is isolated from *Panax ginseng*. It is a lysophosphatidic acid (LPA) receptor-ligand gintonin (100 mg/kg) to protect against the depressive-like behavior induced by (Forced swim test and tail suspension test) AW (6% ethanol for 14 days) in C57BL/6 mice. Gintonin elevated the plasma 5-HT levels (Kim *et al*., 2017).

8.7 Miltrione

Miltrione is isolated from the root of the *Salvia miltiorrhiza*. Miltrione binds with benzodiazepine receptors and partially blocked the increase in the mRNA in a 4 subunit of $GABA_A$receptor induced by AW in cultured brain hippocampal cells of Male SD rats (Mostallino *et al*., 2004).

8.8 Quercetin

Quercetin is a plant polyphenolic compound isolated in the various plant kingdom (Das and Gezici, 2018; Gezici *et al*., 2020). Quercetin (25 and 50 mg/kg/PO) on administration for the treatment of ethanol withdrawal syndrome (2 g/kg ethanol for 6 days) in albino mice, decreased the hyper locomotor activity (Actophotometer) and anxiety (Mirrored chamber test) and was also found to suppress PTZ kindling seizure (Joshi *et al*., 2005; Lalitha *et al*., 2021).

8.9 Withaferin A

Withaferin A is a steroidal lactone isolated from the *Withania somnifera* plant (Khare and Naharwar, 2020; Jinukuti and Giri, 2015). Withaferin A (10 and 20 mg/kg, IP) when administered during the alcohol dependence phase from day 15-21 was found to prevent the ethanol withdrawal (modified liquid diet with ethanol 7.2% for 14 days) induced elevated scores of somatic behaviors (grooming, sniffing, genital licking, head weaving, gnawing, scratching, chewing,

and body shake), hyperlocomotion (Actophotometer), depressive behavior (Forced swim test), and anxiety (Elevated plus maze) in SD rats. It also attenuated the elevated plasma corticosterone and ACTH levels in ethanol-withdrawn rats (Nandkishor *et al*., 2018).

9. Discussion

Alcohol withdrawal syndrome is a set of distressing mental and physical symptoms that arise when you stop drinking alcohol. The symptoms range from mild tremors to convulsions and hallucinations (Weaver, 2015). The GABA (inhibitory neurotransmitter) and glutamate (excitatory neurotransmitter) are found to play a major role in alcohol withdrawal syndrome (Bayard *et al*., 2004). Benzodiazepines are considered as the gold-standard treatment for AWS, but research specifies that diazepam poses the potential hazard of dependence (Ennaceur *et al*., 2010). This review compiles the description and effectiveness of some plant and plant derivatives in an alcohol withdrawal syndrome. A modified liquid diet with ethanol-induced AWS was found to be the most common and preferred method for inducing alcohol withdrawal syndrome in animals. This modified liquid diet includes cow milk 925 ml + 25-75 ml ethanol (96.5% ethyl acetate) + Vitamin A 5000 IU + Sucrose 17 g or nutritional source. 7.2% and 10% ethanol are the preferred choice of concentration for administration. Mostly male Wistar albino rats were preferred over the female (some studies were carried out in females and both sexes). A female alcohol-preferring rat transgenic animalmodel and C57BL/6 transgenic mouse that is specific to alcohol withdrawal syndrome was also used. More plants from the Fabaceae family are found to be effective against AWS. These plants and plant derivatives are found to either suppress the behavioral symptoms of AWS or alter the biochemical parameters that are involved in the ethanol withdrawal syndrome.

10. Conclusion

Currently, mild to moderate alcohol withdrawal symptoms are not treated with medications because of their side effects. The life threatened severe symptoms only treated with drugs. The plant and plant derived components especially used to treat mild to moderate AWS. Prolong use of plant medication does not produce addiction, withdrawal symptoms like benzodiazepines. The plants are cheap, easily available, and cause very less side effects.

Plants provide natural anxiolytic, antioxidant activity and serve as effective herbal medicines, in part due to their active compounds, such as flavonoids, tannins, phenolics, and alkaloids that improve the performance of the central nervous system and other peripheral organs involved in an alcohol withdrawal syndrome.More researches are needed to separate the active constituents of plants and molecular interactions of their compounds for analysis of their therapeutic and prophylactic properties against AWS.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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