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Review Article

A PHARMACOGNOSTIC REVIEW ON *ARTEMISIA ABSINTHIUM*

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ABSTRACT

Artemisia, being the widely distributed genus of the plant family Asteraceae encompasses about 500 species. Among them, *Artemisia absinthium* (*A. absinthium*) is a well-known herb commonly known as Wormwood and Afsanteen. *A. absinthium* reported to possess several therapeutic benefits in fever, inflammation, epilepsy, gastric problems and urinary disorders. Review of literature included PubMed, Science Direct searches *with 'A. absinthium'* and 'Wormwood' as initial key words. The search was further refined by looking for terms such as 'Constituents' (or composition) and 'Activity' (or effect) within the results. The major bioactive constituents of *Wormwood* are mono and sesquiterpenes. The present review comprises up to date information of traditional uses, phytochemistry and pharmacology of *A. absinthium*. The *A. absinthium* is a rich source of chemically novel compounds and needs elaborate screening strategies to dwell into the pharmacological effects of its phytoconstituents at the molecular level. This review article provides preliminary information and gives a direction for the basic and clinical research on *A. absinthium*.

Keywords: *Artemisia absinthium*, Asteraceae, Traditional uses, Phytochemistry, Pharmacology.

INTRODUCTION

Artemisia is a large, diverse genus of plants with about 500 species belonging to the daisy family Asteraceae. Some species of *Artemisia* are *Artemisia abrotanum* L., *A. afra*, *A. annua* L., *A. arborescens*, *A. arenicola*, *A. maritima*, *A. capillaris*, *A. dracunculus*, *A. stricta*, *A. laciniata*, *A. wallichiana*, *A. Japonica* and *A. siversiana*[1].

Artemisia absinthium Linn. is a very important member of this genus and recognized as the source of a Unani drug "*Afsanteen"*. *A. absinthium* is commonly called wormwood, and is locally known as 'Tethwen' in the Kashmir Valley, India[2]. It is used in indigenous medicine as a vermifuge, an insecticide, an antispasmodic, an antiseptic, and in the treatment of chronic fevers and inflammation of the liver[3]. Its essential oil has antimicrobial[4] and antifungal activity[5]. Chemical analysis of *A. absinthium* extracts has shown that its volatile oil is rich in thujone, which has been reported as an anthelmintic[6]. In Turkish folk medicine, *A. absinthium* has been used as an antipyretic, antiseptic, anthelmintic, tonic, diuretic, and for the treatment of stomachaches[7]. *A. absinthium* has been used as herbal drug throughout Asia, Middle East, North Africa and Europe[8]. The lack of a comprehensive review on the phytochemistry and pharmacology of *A. absinthium* prompted us to compile a review on the traditional uses, phytochemistry and pharmacology of *A. absinthium.*

VERNACULAR NAMES

Hindi: Vilayathi afsanthin
English: Absinthe, wormwood
Bengali: Mastaru
Gujrati: Mastaru
Marathi: Serpana
Unani: Afsanteen
Sanskrit: Damar, tartiha

Figure 1: Aerial parts of *A. absinthium*

GEOGRAPHICAL DISTRIBUTION

Wormwood is native to temperate region of Eurasia, Northern Africa and widely found in the United States and Canada.[8] It is found in Kashmir, up to an altitude of 2100 m[1].

MORPHOLOGICAL CHARACTERS

A. absinthium is a shrubby plant having hairy and ribbed stem. The leaves are 2-3 pinnatifidly cut into spreading linear-lanceolate, obtuse segments, hairy on both the surfaces. The heads are heterogamous, ray flowers female and disc flowers hermaphrodite. The receptacle is covered with long hairs. The macroscopy of the drug *Afsanteen* available in the market consists of grayish white material having broken stem twigs, leaves and

flower heads. The branch and twigs have prominent ridges and furrows covered by white hair. The leaf twigs are silvery hairy on both surfaces. The flower heads show the receptacle with long white hair. Besides this *A. siversiana* are found mixed in the drug. The characteristic differences noted in the two species of *Artemisia* viz. *A. absinthium and A. siversiana* present in the drug are given in Table 1[9].

Table 1: Diagnostic characteristic of *A. absinthium* and *A. siversiana*.

Plant Species	*A. absinthium*	*A. siversiana*
Growth	Perennial	Annuals and biennials
Stem	The stem and branches are white much downy with ridges and furrows and finely silky and hairy, glandular throughout.	The stem and branches are dirty yellow, ridges and furrows less prominent and sparsely hairy.
Flower	The flower heads are in large cymes. The heads are comparatively smaller in size.	The flower heads are bigger in size and distant on long lax racemes.
Receptacle	The receptacle bears soft long white hair.	The receptacle bears light brown colored thick hair.

MICROSCOPIC CHARACTERS

The young stem twigs shows outer single layer of epidermis which consists of cubical cells. Many of the epidermal cells are extended outwards to form trichomes. The trichomes are formed of cells arranged in single row or the lower being 2-5 celled. In the mature stem the endodermis has casparian strips while the cortex and pith are parenchymatous. The stem bears the usual structure. The winged petiole in T.S. shows a wavy outline. The trichomes are present all along the margins. The middle vascular bundle is larger in size showing prominent xylem and phloem layers. Glandular trichomes are present on both the surfaces. The stomata are present on the lower surface. The flowering heads are surrounded by 8-10 bracts. The anthers are yellow in color. The powdered drug is brownish yellow in color and characteristic non- lignified hair are found to be T- shaped[9].

TRADITIONAL USES OF *A. ABSINTHIUM*

A. absinthium is the main source for the Unani drug *Afsanteen* used in chronic fever, swellings, and inflammation of liver. In Europe, the tincture of the plant is used as tonic, digestive, febrifuge and anthelmintic[1]. *A. absinthium* is also used in epilepsy, gastric problems, and enlargement of spleen, urinary disorders and for wound healing[10-12]. The flowers are used in stomach diseases, and as vermifuge[13]. The leaves are used in fever[14].

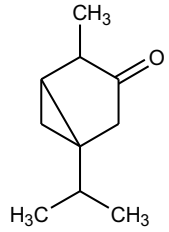
PHYTO-CHEMISTRY OF *A. ABSINTHIUM*

The chemical structures of phytoconstituents isolated from *A. absinthium* are summarized in Figure 2. The dry leaves and flowering tops collected from Gulmarg in Kashmir yielded a pleasant smelling essential oil in a yield of 0.2%. The oil contained mostly the esters of thujyl alcohol, *α*-thujone (1), *β*-thujone, thujane (2), camphene (3), cadinene, and guaiazulene.[15] The essential oil from shade dried leaves was found to contain *α*-thujene, camphene, *α*-pinene, *p*-cymene, 1,8-cineol, methylheptenone, *β*-phelandrene, caryophyllene oxide, *α*-terpineol, thujyl alcohol, geraniol (4), thujyl acetate, caryophyllene, α-himachalene, α- cadinene and elemol besides certain unidentified compounds[16].

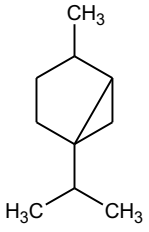
Absinthin (5) a dimeric sesquiterpene lactone isolated from the plant *A. absinthium* by using HPLC-solid phase extraction technique[17]. The plant contains volatile oil absinthe or wormwood oil. The yield of oil varies from 0.12 to 0.51 % (fresh basis) according to the source from which it is obtained. The freshly extracted oil from the air - dried leaves is dark-brown in color. The essential oil has following characteristics: specific gravity-0.9346, acid value- 2.47, and saponification value-146.6, saponification value after acetylation-193.5, ketone (thujone)-4.07 %.[15] The seeds yield an oil (33.4 %) having the following constants, iodine value-118, saponification value-186. The fatty acid composition of the oil has following constituents: oleic acid-24%, linoleic- 45%, saturated acids (palmitic and stearic)- 18%, and oxirane as epoxyoleic acid- 23%. The seeds contain mixture of 9- hydroxyl-trans-trans, 10, 12-octadecadienoic acid and 13-hydroxy-trans, trans, and 9, 11-octadcadienoic acid in the ratio of 2:1. Fresh wormwood is considered the best source of azulene. The yield of azulene has been reported to vary between 40-70 mg percent. The epigeal part and the roots of *A. absinthium* were collected in the period of flowering of the plant (June) and extracted with chloroform. 50 kg of the epigeal part gave 2900 g (5.8%) and 7.5 kg of the roots gave 525 g (7.0%) of total extractive substances. The extract contains 5-hydroxy-3, 6, 7, 3, 4,-penta methoxyflavone (artemetin), artabsin, and 3, 4, 5-trimethoxybezoic acid[18].

Two new diastereometric homoditerpeneperoxides have been isolated from aerial parts of *A. absinthium.* The mixture of both compounds showed antimalarial activity *in vivo* with an EC_{50} of 1 µg/ml. The homoditerpenes, 1-(*E*)-8-isopropyl-1,5-dimethyl-nona-4,8-dienyl-4-methyl2,3-dioxa-bicyclo[2,2,2] oct-5-ene and iso-1-(*E*)-8-isopropyl-1,5-dimethyl-nona-4,8-dienyl-4-methyl-2,3-dioxa-bicyclo[2,2,2]oct-5-ene have been reported earlier[19].

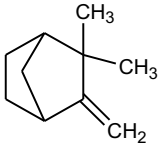
Ahamad et al.,[20] isolated four new glycoside esters from the methanolic extract of the aerial parts of *A. absinthium* characterized as stigmast-5,22-dien-3β-ol-21-oic acid-3β-glucopyranosyl-2'-octadec-9"-enoate (6); lanost-24-en-3β-ol-11-one-28-oic acid-21,23 α-olide-3β-D-glucopyranosyl-2'-dihydrocaffeoate-6'-decanoate (7); tricosan-14-on-1,4-olide-5-eicos-9'-enoate (8) and 3,11-dimethyldodecan-1,7-dioic acid-1-β-D-glucopyranosyl-6'-octadec-9"-enoate (9). Ahamad et al.[21] further isolated new isoflavone glycosides from the methanolic extract of the aerial parts of *A. absinthium* and the compounds are characterised as artemisia bis-isoflavonyl dirhamnoside (10) and artemisia isoflavonyl glucosyl diester (11).



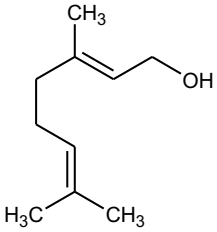
(1) Thujone



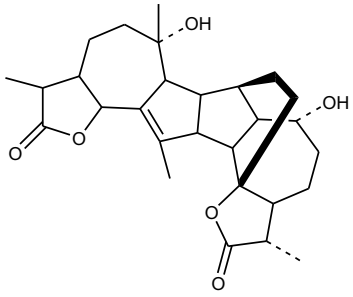
(2) Thujane



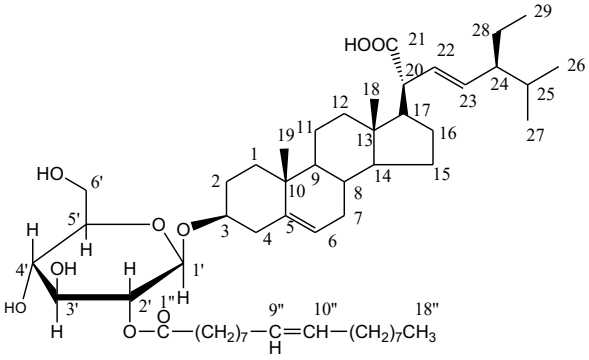
(3) Camphene



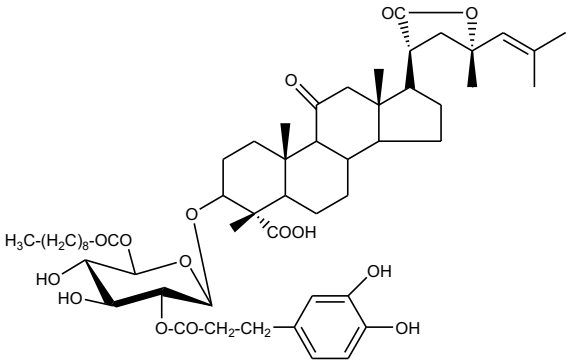
(4) Geraniol



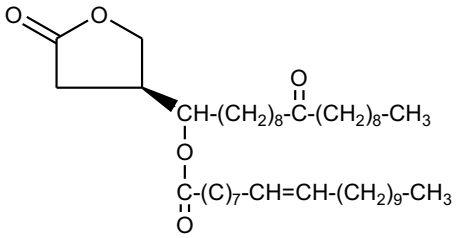
(5) Absinthin



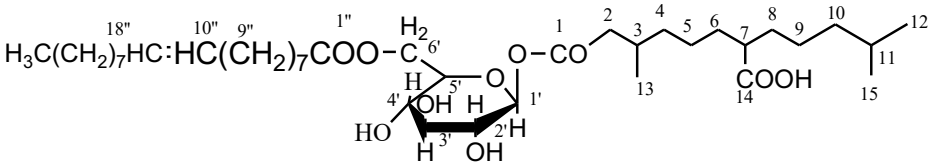
(6) Stigmast-5,22-dien-3beta-ol-21-oic acid-3beta-glucopyranosyl-2'-octadec-9"-enoate



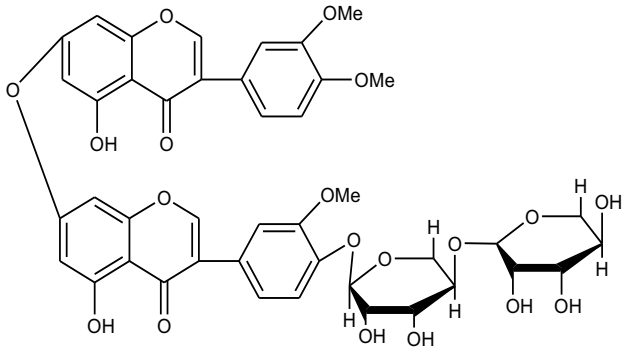
(7) Lanost-24-en-3beta-ol-11-one-28-oic acid-21,23 alpha-olide-3beta-D-glucopyranosyl-2'-dihydrocaffeoate-6'-decanoate



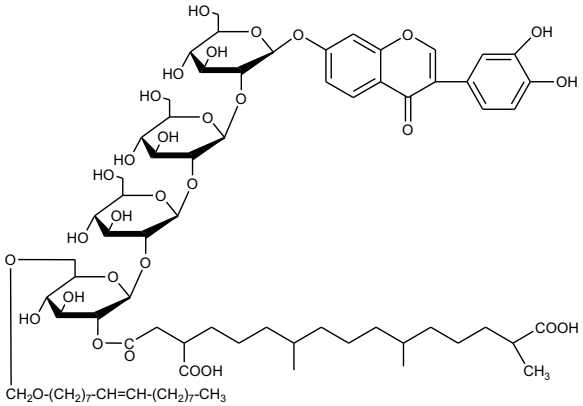
(8) Tricosan-14-on-1,4-olide-5-eicos-9'-enoate



(9) 3,11-dimethyldodecan-1,7-dioic acid-1-beta-D-glucopyranosyl-6'-octadec-9"-enoate



(10) Artemisia bis-isoflavonyl dirhamnoside



(11) Artemisia isoflavonyl glucosyl diester

Figure 2: Chemical structures of major constituents reported from *A. absinthium* Linn.

PHARMACOLOGICAL ACTIONS OF *A. ABSINTHIUM*

Artemisia absinthium has a long history of human use in traditional medicine throughout the world. There is plethora of reports of experimental and clinical evidences related to its different uses that are summarized in Table 1.

Antimalarial Activity

The aqueous and alcoholic leaf extracts were shown to possess definite shizonticidal activity in a 4-day test against a chloroquine - sensitive strain of *Plasmodium berghei* in mice. The aqueous extract and alcoholic extract were administered p.o., s.c. and i.p. The highest suppression of parasitaemia was observed with the alcoholic extract given orally at the 74 mg/kg dose level. The aqueous extract was less active[22]. The antimalarial activity of the various constituents of the plant viz. artemisinin, artemether, arteether, etc. was reviewed by Sukh Dev[23] and Vasanth et al. [24], The sesquiterpene lactone fraction and aqueous extract *of A. absinthium* inhibits *P. falciparum.* The aqueous extract of *A. absinthium* at the dilution of 1:35 showed maximum inhibition percentage (89.9%). The LD50 value was 31.4 µg/ml of sesquiterpene lactone fraction[25].

Anticancer Activity

Artemisia shows anti-angiogenic effects in tumor cell lines. The methanolic extract of *A. absinthium* inhibits proliferation of MCF-7 and MDA-MB231 cell. These cells were treated with different concentrations of *A. absinthium* for almost 3 days. The methanolic extract at dose of 20 g/ml caused 50% inhibition in MDAMB-231 cells and 50% inhibition in cell proliferation of MCF-7 cells at 25 g/ml as compared to the control[26].

Antimicrobial Activity

The essential oil from the air dried leaves was tested for its antibacterial activity against *Staphylococcus aureus* (sensitive and resistant strains), *Salmonella typhi, E. coli, Proteus vulgaris, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* and for antifungal activity against *Candida albicans, C. utilis* and *Aspergillus niger* by the serial dilution method. The essential oil at 1:1000 dilutions was found to be active against both sensitive and resistant strains of *S. aureus, K. pneumoniae* and *P. aeruginosa*[27].

Accordance to an investigation, ethanol extracts of *A. absinthium* branches inhibit *Staphylococcus aureus* with inhibition zones 10-15 mm in diameter, however, not shown antibacterial potential against *Candida albicans, E. coli, Streptococcus faecalis and Bacillus subtilis*[28].

Anthelmintic Activity

The water extract of the leaves showed some nematicidal activity against the second stage juveniles of *Meloidogyne incognita* (Kofoid and White) chitwood at 50 and 100% concentration after an exposure of 24 and 48 hr. The activity was higher after an exposure of 48 hr.[29] The anthelmintic efficacy of crude aqueous and crude ethanolic extracts of the aerial parts of *A. absinthium* was also evaluated by Tariq et al.,[30] in the gastrointestinal nematodes of sheep. *A. absinthium* shows significant anthelmintic effects of these extracts on live adult *Haemonchus contortus* worms.

Hepatoprotective Activity

The aqueous and methanolic extracts of wormwood was studied in acetaminophen and carbon tetra chloride induced hepatic damage. Pretreatment of rats with plant extract significantly prevented rise in serum level of transaminases like GOT and GPT. Post-treatment of rats with plant extract restricted the hepatic damage. These results indicate that the crude extract of *A. absinthium* exhibits hepatoprotective action.[31] *A. absinthium* extracts reveal strong *in vitro* antiradical activity as well as antioxidant potential and moreover anti-parasitic potential in animal based models[32].

Anti-inflammatory Activity

Methanolic extract of aerial part of *A. absinthium* shows anti-inflammatory activity. The anti-inflammatory activity was estimated volumetrically by measuring the mean increase in hind paw volume of rat with the help of Plethysmometer. Acetylsalicylic acid in the dose of 300 mg/kg is used as standard drug**.** Plant extract was given orally in the doses of 300,500 and 1000 mg/kg. Control group received 0.9% NaCl (saline) solution. *A. absinthium* showed significant anti-inflammatory activity[33].

Analgesic and Antipyretic Activity

Methanolic extract of aerial part of *A. absinthium* shows analgesic activity. The analgesic activity assessed in intact mice by tail flick latency in tail flick immersion method. Acetylsalicylic acid in the dose of 300 mg/kg is used as standard drug. Plant extract given orally in the doses of 300, 500 and 1000 mg/kg. Control group received 0.9% NaCl (saline) solution. *A. absinthium* showed significant analgesic activity.[33] Khare[34] also reported antipyretic activity of water, hexane and chloroform extract of *A. absinthium*. He also reported that wormwood extract upto 1.6 g/kg has no side effects[34].

Insecticidal Activity

The essential oil from the plant revealed no juvenile hormone activity against the *Dysdercus koenigii*.[35] The powder of the flower heads in concentration of 30 and 15 was 31.57 % and 28.38 % larvicidal in housefly *Musca domestica*, respectively. The powder did not show any activity against the third instar larvae[36].

Neuroprotective Activity

Suppression of tumour necrosis factor alpha (TNF-alpha) and other interleukins by wormwood extracts were reported recently in *in vitro* studies by Krebs *et al* [37].

The potential protective effects of wormwood on cerebral oxidative stress and damage as well as behavioral disturbances induced by cerebral ischemia and reperfusion injury was studied in rats. The brain oxidative stress and damage, and behavioral deficits were significantly attenuated by pre-treatment with the methanol extract of *A. absinthium*. These findings suggested that *A. absinthium* is neuroprotective and may prove to be useful adjunct in the treatment of stroke [38].

Antioxidant Activity

A. absinthium contains various flavonoids and phenolic compounds that are possibly involved in the mechanism of free radical scavenging activity. The 2,2-diphenyl-1-picrylhydrazyl-free radical scavenging activity in *A. absinthium* was found to be independent on biomass accumulation in callus culture but it is dependent on secondary metabolites production. Maximum accumulation of total flavonoids (1.89 mg quercetin equivalent/g dry weight), total phenolics (13.57 mg gallic acid equivalent/g dry weight) and the highest antioxidant activity (82.7%%) was observed from 35-day-old callus culture. These results indicate that cell suspension cultures of *A. absinthium* have the potential antioxidant activity[39].

Table 2: Pharmacological and clinical activities of *A. absinthium*

S. No.	Plant parts/ Extracts	Pharmacological activities	References
1.	Essential oil	The essential oil of *A. absinthium* shows antimicrobial activity	[27, 28]
2.	Leaves	The water extract of the leaves of *A. absinthium* shows showed some nematicidal activity against the second stage juveniles of *Meloidogyne incognita*	[29]
3.	Leaf	*A. absinthium* shows antimalarial effects on *Plasmodium berghei* in mice	[22]
4.	Aerial parts	Methanolic extract of aerial part of *A. absinthium* shows anti-inflammatory activity	[33]
5.	Aerial parts	Methanolic extract of aerial part of *A. absinthium* shows analgesic activity.	[33]
6.	Aqueous and methanolic extracts	Aqueous and methanolic extracts of *A. absinthium* shows hepatoprotective action against acetaminophen and CCl_4 induced hepatic damage	[31]
7.	-	*A. absinthium* show overall relief in different clinical stages of intestinal amoebiasis caused by *Entamoeba histolytica*	[42]
8.	Flower	The powder of the flower heads shows larvicidal property in housefly *Musca domestica*	[36]
9.	Sesquiterpene lactone	Sesquiterpene lactone fraction and aqueous extract *of A. absinthium* inhibits *Plasmodium falciparum*	[25]
10.	Methanolic extract	Methanolic extract of *A. absinthium* shows *in-vitro* anticancer activity	[26]
11.	Different extracts	Different extracts of *A. absinthium* shows antiulcer activity	[41]
12.	Aerial parts	The crude ethanolic extract and crude aqueous extract of aerial parts of wormwood have significant anthelmintic effects on live *Haemonchus contortus* worms	[30]
13.	-	*A. absinthium* shows antidepressants activity in tail suspension test and in forced swimming test	[40]
14.	-	Wormwood shows neuroprotective actions on reperfusion-provoked cerebral damage	[38]
15.	-	*A. absinthium* shows free radical scavenging activity in *in-vitro*	[39]

Antidepressant Activity

Methanolic extract of aerial part of wormwood at flowering stage was screened for antioxidant and antidepressant activities. The extract showed potent antioxidant activity. The extract also showed promising antidepressant activity in forced swimming test and it considerably reduced the immobility period both in forced swimming test[40].

Antiulcer Activity

The different solvent extracts such as carbon tetrachloride, chloroform, methanol, ethanol and hexane of *A. absinthium* was evaluated in the acetyl-salicylic acid induced ulcer model in rats. The study showed reduction in ulcer index, increase in level of mucin, reduction in peptic activity and decrease in gastric juice volume[41].

CLINICAL STUDIES ON *A. ABSINTHIUM*

Amoebiasis

In a study on 25 patients of intestinal amoebiasis, *A. absinthium* administered in the form of a capsule (500 mg) (three capsules / 6 hr for a period of 15 days) was found to show overall relief in different clinical stages with disappearance of *Entamoeba histolytica* in 70% of cases without any noticeable adverse effect[42].

Viral Hepatitis

A. absinthium was studied in viral hepatitis and to assess the myocardial function in hyperbilirubinaemic patients by computing the ejection on M-mode echocardiography in 20 patients. The drug was administered in fine powder form in the doses of 6 g in two divided doses for 4 weeks with weekly assessments. The test drug was found to shorten the clinical and biochemical recovery from the disease. In cases of viral hepatitis the ejection fraction of heart slightly decreased which was statistically insignificant needing a long term study[43].

TOXICITY OF ABSINTHE

The chronic abuse in zenith of absinthe in the nineteenth and twentieth century was made responsible for a syndrome called absinthism and was described to cause the following symptoms, after consuming absinthe, at first the well-being had been stimulated, latter hallucination had arisen followed by a depressive phase. Prolonged drinking of absinthe had caused convulsions, blindness, hallucinations, and mental deterioration. In advanced state, signs of degeneration could be observed, which could cause convulsions that even resulted in death. In comparison to β-thujone, α-thujone is believed to be 2.3 fold more toxic. The possible mechanism of action of α-thujone is interaction with GABA dependent chloride channels[44].

CONCLUSION

Phytochemical and pharmacological studies done so far on the *A. absinthium* confirm the claims of traditional use of this plant. Wormwood has immense potential for researchers and exploring it will lead to isolation and identification of new compounds which could be used as drugs for curing common and critical diseases. Pharmacological studies have demonstrated its anticancer, neuroprotective, hepatoprotective, antimalarial, anthelmintic, antipyretic, antidepressant, antiulcer, antibacterial, antiprotozoal and antioxidant activities. Looking at the broad spectrum of *A. absinthium* for various purposes, it is useful to cultivate this plant at large scale. The information congregated in this review will help researchers and industry persons to work in line to reconnoiter the potential of this plant and utilize it for the benefit of the society. *A. absinthium* is indexed in critically endangered category, so consistent efforts should be made to protect this plant species to become extinct.

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