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A REVIEW ON HISTORY, CONTROVERSY, TRADITIONAL USE, ETHNOBOTANY, PHYTOCHEMISTRY AND PHARMACOLOGY OF *ARTEMISIA ABSINTHIUM* LINN

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Abstract: *Artemisia absinthium Linn. (Wormwood) is an important perennial shrubby plant that belongs to the family Asteraceae. It is used as herbal medicine in Ayurveda, Homeopathy, Unani and Siddha. It has a great importance as a folk medicine in ancient history from the time of Greek.*

It is used medically with a very long tradition as anti-helminthic, but it is also used as an ingredient in the liquor absinthe. This species is globally distributed from Europe to North Asia. Flowering occurs in midsummer, pale yellow, tubular flowers develop in drooping heads in the axils of the leaves. A single plant can produce 50,000 seeds. Wormwood invades open and disturbed sites such as pastures, rangelands, crop land, stream banks, prairies .Within India; it has been recorded in the Himalayan region across Jammu & Kashmir. This review provides information on the history, ethno botany, Phytochemistry, medicinal uses, and pharmacological evaluation studies of Artemisia absinthium.

Key words: *Artemisia absinthium,Absinthe, Folk medicine, Anti-helminthic, Phytochemistry, tubular flowers,Unani.*

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INTRODUCTION

Artemisia absinthium (Wormwood) is a bitter tasting, aromatic, perennial shrub-like herb with green-grey leaves and little yellow flowers [1].Artemisia absinthium is the main ingredient of the legendary drink absinthe, which was invented in 1792 by a French doctor. Intended as a medicine, it became very popular as a recreational drink in the 18th and early19th Centuries, it acquired a reputation for triggering psychotic events; called absinthism [2].Wormwood has both a psychoactive and medicinal function. It has been employed in folk medicine at Ancient Greek timesas a cure for intestinal worms. Though whole herb of wormwood is of both medicinal and commercial importance leaves of the plant, probably the best known species have been used in medicines [3].Artemisia absinthium has been used for centuries as a moth repellant, general pesticide and as a tea/spray to repel slugs and snails. The whole plant is an aromatic tonic and formerly enjoyed a high reputation in debility of the digestive organs. It was also regarded as an anthelmintic. By distillation process it yields dark green oil having a strong odour of the plant and an acrid taste [4].

Essential oil of the plant has traditionally been used asantihelminthic, anti-inflammatory, antiseptic, antispasmodic, antitumor, neuroprotective, antifungal, antimicrobial, insecticidal,acaricidal, antimalarial ,hepatoprotective, antidepressant ,carminative (gas reliever), cholagogue (promotes bile flow),emmenagogue (promotes menstrual flow),diuretic, choleretic, hypnotic, preservative, stimulant, tonic, balsamic and depurative[5,6].The herb is also used in treating Anorexia nervosa (eating disorder), atherosclerosis (hardening of the arteries, prevention), back pain, bloating, convulsions, dropsy (water retention), fibromyalgia, hemorrhoids, herpes, improvement of mental state, insect and spider bites, jaundice, labor pains, mood, neonatal jaundice, neurasthenia (nervous breakdown), pain (pain relief), parasitic worm infections, schistosomiasis (parasite infection), skin wounds, stomach ailments, sclerosis[7].The species was cited to be used externally as cataplasm of crushed leaves for snake and scorpion bites or decoction for wounds and sores as antiseptic and antifungal [8].The purpose of this review is to understand why this herb is a source of natural products, and an alternative herbal medicine for several health disorders.

HISTORY

Artemisia has a colorful and rather dubious history: Artemisia was the wife and sister of the Persian King Mausolous. The genus artemisia was named after her and includes over 400 plants. Artemisia was a botanist and medical researcher[9]. Artemisia absinthium (Wormwood) is known from ancient times as medicinal and culinary herb. Internal parasite expelling activity of worm wood was mentioned in an Egyptian scroll that is 3,600 years old. It was later used to treat almost any complaint imaginable. Wormwood was known earlier for repelling clothes moths and other pests such as bedbugs, book worms and even rats. Absinth wormwood has a long history of human use for its intoxicating and medicinal properties[10]. Initially Artemisia absinthium was prescribed as a tonic for a variety of ailments, from headache to dysentery, the use of wormwood extract as a pharmaceutical cure for several different illnesses can be traced as far back as the Egyptian dynasty of 1600 B.C[11].

ABSINTHISM

It is an addiction to "*absinthe*", liquor flavored with the narcotic wormwood, Artemisia absinthium. This disorder is associated with the habitual abuse of absinthe. The symptoms included hallucinations, sleeplessness, tremors, and convulsions[12].

Absinthe - a cocktail of myth, conjecture and controversy

Absinthe is a formerly banned spirit drink that is made with Artemisia absinthium. During the 19th century *Absinthe* became a very popular drink because it was a favorite drink of artists, painters and writers in central Europe and USA[11].

Figure1: Preparation of absinthe using the traditional method and bottled Absinthe.

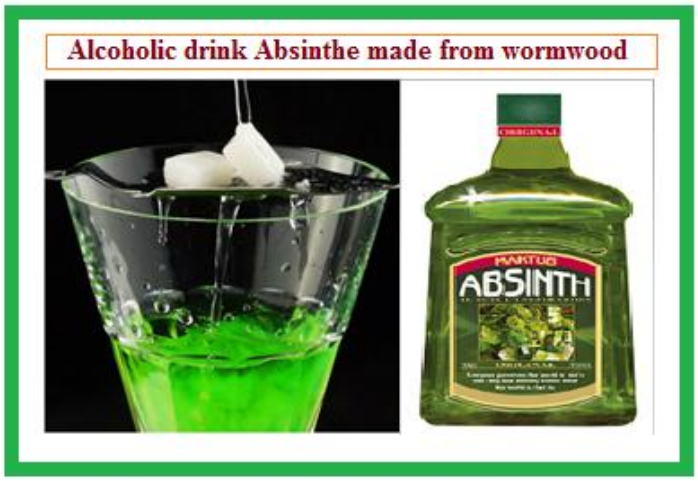

Figure 1: A schematic image representing the traditional French preparation of absinthe - involves placing a sugar cube on top of a specially designed slotted spoon, placing the spoon on a glass filled with a measure of absinthe and iced water is poured or dripped over the sugar cube slowly and commercial label of a bottled Absinthe drink.

Recipe of *Absinthe*liquor

The recipe for the drink was developed during the time of the French revolution.It is documented that in 1797, a Frenchman known as M. Pernod brewed the original concoction known as absinthe. He distilled an herb preparation of wormwood, anise, fennel, lemon balm, hyssop, angelica, star anise, dittany, juniper, nutmeg, and veronica. It is said this original recipe, using the above herb mash, caused the green fairy to have a very bitter taste. The drink definitely has a much more pleasant taste when only the essential oil of wormwood is used[10, 14].

Controversy, ban & repeal

The spirit was banned in many countries and United States at the beginning of the 20th century, because it was believed to be hallucinogenic. Thujone an important chemical present in the essential oils of Artemisia absinthium was blamed for the hallucinogenic action of *Absinthe*liquor. The early 2000s saw the repeal of absinthe bans around the world, just a century after the bans were put in place and a little over two centuries after the modern recipe was popularized. In 2005, Switzerland repealed its ban, once again making absinthe legal in its country of origin, and as of 2007, at least two brands of absinthe were being legally bought and sold in the United States[11,14].

Figure 2: Symbolic image of Absinthism.

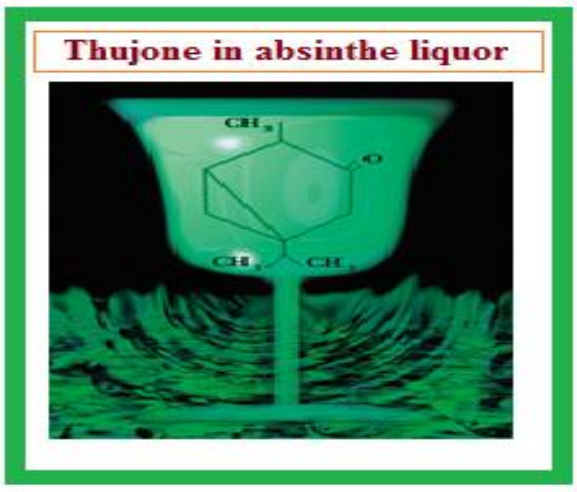

Figure 2: A schematic image representing the symbolic portrayal of blaming Thujone for Absinthism.

ABSINTHE AFICIONADOS

Following celebrities were popular for their addicted love towards Absinthe

Marilyn Manson (1969 -):A uniquely American celebrity, musician and artist, Marilyn Manson is by far today's most famous absinthe devotee[11,14].

Oscar Wilde (1854 – 1900): Oscar Wilde was one of the English language's most quotable writers, Wilde was a professed alcoholic and devotee of absinthe[11,15].

Charles Cros (1842-1888): CharlesCros was a renaissance man: painter, poet, physicist, chemist, musician, and inventor. He regularly drank up to 20 absinthes a day, and was known to regulars at Paris' legendary absinthe cafés as a bon vivant, partying long into the next day[11,16].

Charles Baudelaire (1821 – 1867): Baudelaire's main accomplishments are in the fields of poetry and art criticism,dramas, and novellas.Baudelaire's best known work includes a poem entitled "Get Drunk!" that mentions the use of absinthe [11, 17].

Thujone

Thujone is the major active constituent of wormwood oil (Artemisia absinthium).Thujone is bicyclic ketone terpene that has gained notoriety over the years. In the banned period of *Absinthe*liquor, thujone was blamed for the alleged misbehavior and hallucinogenic character of absinthe drinkers [18, 19 and 21].Thujone is one of the principle active ingredients in wormwood which was used to make absinthe, however, it was discovered by analysis that there was not enough of the thujone in absinthe to cause the hallucinations and brain damage suffered by its regular drinkers [18-20]. It was more likely the excess of the alcohol that did the damage. It has been proved that thujone is not inherently dangerous, psychically or physically, except in extremely high doses [18, 21 and 22].

Figure 3: Chemical structure and IUPAC nomenclature of Thujone.

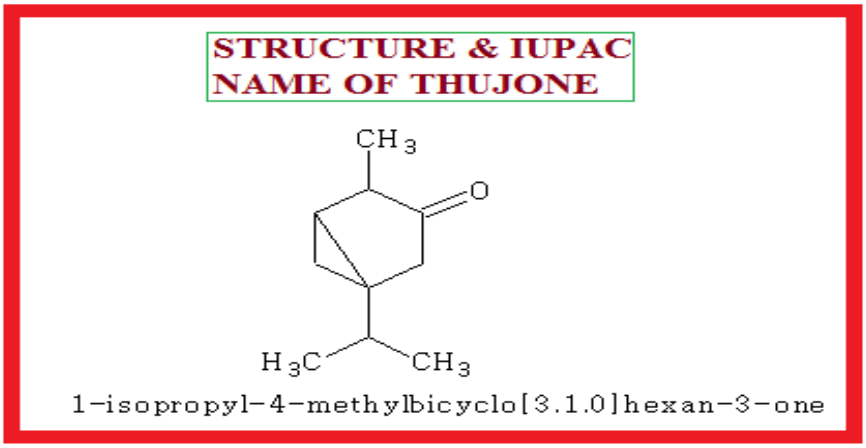

Figure 3: A schematic diagram representing the IUPAC name and chemical structure ofThujone.

Toxicity

Artemisia oil contains mainly thujone [23].The acute oral LD50 in rats was reported as 960 mg/kg; the acute dermal LD50 in rabbits exceeded 5 g/kg [24].The true appeal of thujone is that it is the chemical compound found in wormwood that gives wormwood its healing properties. Thujone is a close organic cousin of menthol, and in its purest form, thujone does in fact carry the minty aroma known to menthol. Wormwood oil is still commonly used today as a natural healing agent; the active ingredient thujone makes up about 60% of most common wormwood oil preparations sold in modern drug stores[11].

Figure 4: Isomers of Thujone.

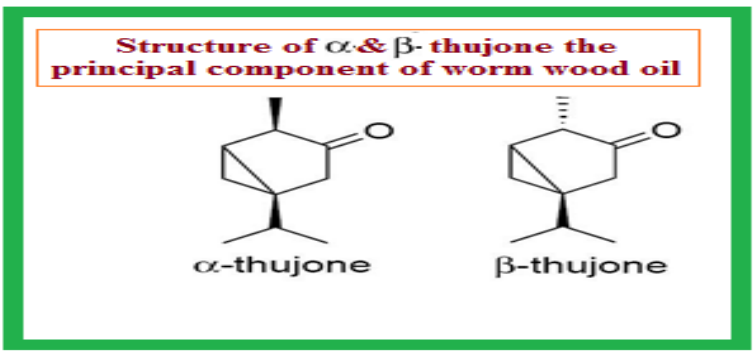

Figure 4: A schematic diagram representing the anomeric forms of Thujone.

ETYMOLOGY

Artemisia comes from the name of the goddess Artemis in Hellenistic culture of Ancient Greek, Artemis was a goddess of the hunt, and protector of the forest and children [25-27].Absinthium comes from Ancient Greek word apsinthion[25,26],possibly meaning

"unenjoyable", and probably referring to the bitter nature of the derived beverage. The form "wormwood" is influenced by the traditional use as a cure for intestinal worms [25].The word "wormwood" comes from Middle English "wormwode" or "wermode"[25-27].

TAXANOMY

Binomial name: *Artemisia absinthium* Linn.

The accepted scientific name for absinth wormwood is Artemisia absinthium Linn. (Asteraceae) [28, 29].

Scientific classification:

Kingdom	**:**	***Plantae***
Subkingdom	**:**	***Tracheobionta***
Super division	**:**	***Spermatophyta***
Division	**:**	***Magnoliophyta***
Class	**:**	***Magnoliopsida***
Subclass	**:**	***Asteridae***
Order	**:**	***Asterales***
Family	**:**	***Asteraceae***
Genus	**:**	***Artemisia* L.**
Species	**:**	***Artemisia absinthium* Linn.**

(Source: http://www.entheology.org/edoto/anmviewer.asp?a=164)

VERNACULARS

In India and Worldwide *Artemisia absinthium* is known by the flowing names in various languages [30-34].

LANGUAGE	NAMES
Sanskrit	Damar, Indhana, Nagadamini.
Telugu	Moshipatri, Tartiha
Kannada	Davana, Urigattige, Uruvalu
Malayalam	Nilampala, Shulabandha, Tirunitri-pachcha
Tamil	Cimaimacippattiri, Machipattri, Macipattiri, Macippaccai
Marathi	Serpana, Surapeena, Surpan
Hindi	Majri, Mastiyara, Karmala, Satadu, Majtari, Vilayathiafsantin, Vilayatiafsantin
Bengali	Mastaru
Punjab	Mastiyara
Kashmir	JangliThethwan

Spiti	**Bhurse**
Greek	**Apsinthion**
Chinese	**Yang ai, Ku ai**
Latin	***Artemisia absinthium* Linn**
French	**Armoiseamere, Genepi, Vermouth**
German	**Wermut, Absinth, Bitterer Beifuss, Wurmkraut,Magenkraut**
Mexican	**Ajenjo**
Urdu	**Afsanteen Rumi, Afsantin, Qaisoom (Afsanteen)**
English	**Absinthe, Absinthium, Green ginger, Madderwort, Wormwood, Old woman,Southrenwood**
Arabic	**Ifsinteen, Afsanteen,KashuthRoomee,Damseesah,Artaamaasiyaa**
Persian	**Afsanthin,Shin,MaviBakhosha,Marwah,Afstiyun**
Tunisia	**chajretmariem**
Romanian	**Iarbă de pelin**
Polish	**Zielepiolunu**
Source:http://envis.frlht.org/botanical_search.php?txtbtname=Allium+cepa+L.&gesp=231%7CArtemisia+absinthium+L.	

In Homeopathy it is known as Absinthium and in Unani it is called as ApsinthionorAfsanteen.

WHY WORM WOOD

Artemisia absinthium is commonly called as worm wood. The name wormwood implies that it is a powerful worming agent, because of its usage for hundreds of years to expel tapeworms, threadworms, and especially roundworms from dogs, cats, and humans [35]. Although wormwood makes like miserable for parasites, it is not kind to the host also. Wormwood is a common ingredient in many herbal cleansing formulations.

HABITAT & DISTRIBUTION

Habitat

Wormwood grows naturally on uncultivated, arid ground, on rocky slopes, and at the edge of footpaths and fields. Absinth wormwood grows on disturbed sites such as along fence lines and roadsides, on borrow pits and gravel piles, and on overgrazed pastures and fields recently abandoned from cultivation .Absinth wormwood grows on a variety of soils from gravels to clay loams [36].

Global distribution

This species is globally distributed from Europe to North Asia. Absinth wormwood, native to Europe, was introduced to North America in 1841 [36]. It is now naturalized across the northern United States and in Canada [37].It grows in different parts of world like North Africa, Parts of Asia (India, Pakistan, Afghanistan, Iran and Siberia) and South America.

Distribution in India

Within India, it has been recorded in the Himalayan region across Jammu & Kashmir in an altitude range of 1500-2700 m or 5000-7000ft [38].Artemisia absinthium is one of the important one among 45 species represented by genus Artemisia in the Indian flora[39], and it is naturally distributed in Jammu and Kashmir region.*Artemisia absinthium* is distributed in Alpine to Cold Arid zone(Ladakh) (10000ft above msl) in Leh Forest Division and few locations of its distribution are Nobra, Nyoma,Choglamsar, Durbuk etc. [40].

Figure 5: Location map of Artemisia absinthium in India.

Figure 5: Schematic image representing location map of Artemisia absinthium naturaldistribution in Ladakh Division of INDIAN State Jammu & Kashmir.

CULTIVATION

The plant can easily be cultivated in dry soil, rich in nitrogen.It likes the shade and can be propagated by root division or cuttings. Sow seeds in the fall when ripe. Spacing plants about 2 feet apart, leads to growth of the plants to a heights of 4 feet.No further care is needed than to keep free from weeds. The principal producers of the plant are former USSR, Bulgaria, Hungary and Poland[41].

Regeneration &Germination

Absinth wormwood reproduces primarily by seed and is a prolific seed producer [36, 43and 44]. Although the small seeds do not have any specific morphological provision for dispersal, they are easily scattered in hay and by wind, water, and animals. The seeds retain their viability for 3to 4 years [36,42].Germination rates were measured under various

pretreatment and photoperiod conditions. Germination was best on moist soils. It occurred over a wide range of temperatures between 41 and 104 degrees Fahrenheit (5-40^{O}C) [36].

Planting Stock /Nurseries in India

One of the main herbal species grown is *Artemisia absinthium* along with other species in the nurseries and herbal gardens established by J&K Forest Department in the process of revival of old Drug Farms in phased manner for production and propagation of germplasm / nursery stock required for planting out in the field to supplement the depleting stocks of naturally growing species in the wild. Herbal garden present in Choglamsarof Leh district (Cold desert zone) is having *Artemisia absinthium* [45, 46].

IMPACTS AND INVASIVE POTENTIAL

The ecological impacts and invasive potential of absinth wormwood are not well-documented .Absinth wormwood is used in companion planting to suppress weeds, because its roots secrete a substance called absinthin (sesquiterpene lactone), that inhibit the growth of surrounding plants [36, 48] .It can repel insect larvae when planted on the edge of the cultivated area. It has also been used to repel fleas and moths indoors. Studies of its effect on the germination of other plants are inconclusive [36]. Although absinth wormwood leaf extracts inhibited the germination of needle-and-thread grass (Stipa comata), they stimulated the germination of green needle grass (S. viridula) [47]. Absinth wormwood is described as unpalatable to fairly palatable for cattle [49], as it is reported to have a bitter taste. If cattle do browse the plant, it taints the milk can give an unpleasant taste to it [48].

CONTROL OF SPREAD

Absinth wormwood grows best in moist habitats. Although it spreads rapidly on disturbed sites, it is easily controlled by herbicides and/or vigorous competition from grasses [48]. Herbicides like Picloram , glyphosate, 2,4-D(2,4-Dichlorophenoxyacetic acid) and Dicamba provides the most rapid and complete control of absinth wormwood [36,48].

ETHNOBOTANY

Morphology

The herb Artemisia absinthium is a, perennial plant with fibrous roots. Its leaves are alternate, stalked, and exstipulate. The leaf blade is triangular; both sides of the leaves are densely covered with silver-hair [50]. The flowers of worm wood are pale yellow in color,

tubular, and clustered in spherical bent-down heads (capitula), which are in turn clustered in leafy and branched panicles. Flowering is from early summer to early autumn; pollination is anemophilous. The fruit is a small achene; seed dispersal is by gravity. The plant's characteristic odor can make it useful for making a plant spray against pests [51].

MICROSCOPIC CHARACTERS

1. Flowers

Flowering season of *A.absinthium is* in between July to October [35,53and 54].Flowers are tiny, small and yellow-green in color. A.*absinthium* has numerous flower heads with short stems and hangs in many flower panicles[37]. Flowers are heterogamous in nature. Each flower head is surrounded by 8-10 bracts [33, 52]. Size of single flower is like approximately 3–4 mm (0.12–0.16 in). Capitula is surrounded by involucral bracts. Capitula flowers are pale yellow and tubular [37,52].The number of stamens in the flower are 5 and its pistil is made up of 2 fused carpels. The shape of the involucre is hemispherical; they (involucral bracts) are arranged in several rows and hairy. Capitula is nodding, quite erect and seen in the form of a lax racemose cluster [33, 37and 52].

Figure 6: Inflorescence of Artemisia absinthium.

Figure 6: Image courtesy:http://www.luontoportti.com/.

2. Fruit

The type of fruit is a single-seeded dry indehiscent achene fruit that develops from a one part inferior ovary,formed by two united carpels called cypsela and it is yellowish. The fruit is about 1.5 mm long.The ripe fruits are not crowned by a tuft of hairs, or pappus **[37].**

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Figure 7: Fruit of Artemisia absinthium.

Figure 7: Image courtesy: http://www.invasive.org/.

3. Leaves

The leaves are spirally arranged, greenish-grey colored above and white below. Worm wood leaves are ovate to obovate, 2-2.5cm. They are covered with silvery-white trichomes, and bearing minute oil-producing glands. The leaf-stalks are slightly winged at the margin. The basal leaves are up to 25 cm long, bipinnate to tripinnate with long petioles, with the cauline leaves (those on the stem) smaller, 5–10 cm long, less divided, and with short petioles; the uppermost leaves can be both simple and sessile (without a petiole).T shaped trichomes are found on both leaf epidermi when seen through Microscope.The leaves and flowers are very bitter, with a characteristic odour, resembling that of Thujone [41].

Figure 8: Leaves of Artemisia absinthium.

Figure 8: Image courtesy: http://www.luontoportti.com/.

3. Stem

Stem arises from the perennial root,which has a warm and aromatic taste. The is branched, firm, leafy and sometimes almost woody at the base[4,52].The stem is about 2 to 4 feet high and whitish [4, 56].Stem is stiff and paniculatelybranched. It is erect, angular and ribbed. It is closely covered with fine silky hairs[52, 56].The leaf twigs are silvery horay on both the surfaces. The twigs of the branches are ridged and their furrows are covered by white hair[37, 55].

Figure 9: Stem of Artemisia absinthium.

Figure 9: Image courtesy: https://gobotany.newenglandwild.org/.

4. Roots

A.*absinthium has a* well-developed taproot root system with a diameter of 2 inches (5 cm) and shallow lateral branches extending up to 6 feet in all directions [43].wormwood may be weakly rhizomatous [32,48]. Interxylary bark that protects the roots from desiccation is absent in wormwood roots [36].

ETHNOBOTONICAL CLAIMS & USES OF WORMWOOD

Parts used in Herbal Medicine

A.*absinthium is a* bitter, aromatic, frutescent (shrubby) perennial plant.The useful parts are leaves, flowering tops, roots, stem and mostly all parts of the plant. They are used in chronic fevers, swellings, inflammation of liver, menstrual disorders. It is a remedy for enfeebled digestions and debility. Flowers are vermifuge, tonic in intermittent fever. Herb yields an essential oil, called wormwood oil which is used externally in rheumatism. Whole plant,

seeds, flowers and roots of the Worm wood are used to make herbal medicines in Ayurveda, Homeopathy, Unani, Siddha and even in Modern medicine [26].

Therapeutically, wormwood in dried form as well as wormwood or oil of absinthe can be an effective organic tonic for stomach ailments. A powder form is also available, known as a wormwood tincture. Tincture of the plant is used as tonic, digestive, febrifuge, anthelmintic and brain concussion. Civilizations for the past four thousand years and counting have used proper dosages of wormwood and wormwood extract to treat all manner of illness and inflammation, as we continue to do today[26].The main compounds found in A.*absinthium* are Silica ,Thujone, Tannic and resinous substances, Malic acid, Absinth and Anabsinth (two bitter substances) and Succinic acid[27].

In addition to being the star feature in the creation of absinthe, wormwood has many other naturally occurring uses in its environment. Gardeners and small-scale farmers alike use wormwood as a natural repellent of pests. In- and out-doors, wormwood can be an effective defense against insect larvae, fleas, and moths. Wormwood can also be used to inhibit the growth of weeds and other unwanted plant life when selectively planted with other crops or treasured flowers[27].

PHYTOCHEMICALS OF ARTEMISIA ABSINTHIUM

The major active constituents found in Artemisia absinthium are essential oil and bitter compounds. The composition of essential oil varies according to geographical source [41].Fresh wormwood is considered the best source of azulene; the yield of azulene has been reported to vary between 40 and 70 mg per cent. The freshly extracted oil from the air-dried leaves is dark brown in colour.

Fatty acid composition of the oil

The fatty acid composition of the oil are oleic, linoleic, saturated acids (palmitic and stearic), and oxirane as epoxy oleic acid. The seeds contain a mixture of 9-hydroxytrans, Trans, 10, 12- octadecadienoic acid and 13- hydroxytrans, Trans, 9, 11- octadecadienoic acid in the ratio of 2:1[57].

Sesquiterpenelactones

The bitter taste and the activity of the herb is ascribed to several sesquiterpene lactones, of which absinthin and artabsin are the main compounds. Sesquiterpene lactones found in Artemisia absinthium are Artabsin, absinthin (bitter glucoside), anabsinthin, artemetin,

arabsin, artabinartabsinolides, matricin, isoabsinthin, artemolin[58] ,artenolide, parishin B and parishin C, 24X-ethylcholesta-7,22-dien-3b-oI [59].TLC analysis of nonpolar compounds of sesquiterpene lactones using solvent system -chloroform – petroleum ether – ethyl acetate (2:2:1, v/v/v); resulted in the separation of 12 compounds from *Artemisia absinthium.*More polar compounds of sesquiterpene lactones can be separated by using solvent system chloroform – petroleum ether – ethanol (5:4:1, v/v/v), which separated 7 compounds from *Artemisia absinthium* [60].

Volatile compounds

Major components of *A. absinthium* volatile oil are Myrcene, sabinene, linalool and trans-sabinyl acetate [58].Monoterpene hydrocarbons are predominant in *A.absinthium* when compared to oxygenated monoterpenes, sesquiterpene hydrocarbons and oxygenated sesquiterpenes[60].

Flavonoid compounds

Significant content of flavonoid compounds are reported through spectrophotometric analysis of alcoholic extracts of Artemisia absinthium[57].Flavonoids seen in the extracts areRutin, Luteolin, Quercetin ,Myricetin ,Apigenin , spinacetin[61], 5,6,3',5'-tetramethoxy 7,4'-hydroxyflavone,5-hydroxy-3,3',4',6,7-pentamethoxyflavone,artemitin, glycosides of quercetin[57].

Polyphenol compounds

Polyphenols are natural antioxidants and useful for the prevention of free radicals mediated diseases [57].Phenolic compounds present in the Artemisia absinthium are -Syringicacid,Fisetin, Isorhamnetin,Kaempferol[60].

Phenolic acids

p-hydroxyphenylacetic, chlorogenic, p-coumaric, protocatechuic, syringic, vanillic, Gallic, Caffeic , Ferulic and other acids[61].

Lignans

Lignans are polyphenolic substances derived from phenylalanine and they are like diayangambin and epiyangambinetc.are seen in Artemisia absinthium[22].

Sequiterpenes

Sequiterpenes like α-bisabolol, β-curcumen, matricin and spathulenol are found in Artemisia absinthium [62].

Sterolic compounds (Phytosterols/sterols)

A.absinthium is a rich source of sterols. Chromatograms evaluated four types of sterols in *Artemisia absinthium* samples. Phytosterols present in the A.absinthium extracts are β - Sitosterol ,Stigmasterol , Campesterol and ergosterol[57,60].The main sterols are sitosterol and stigmasterol. These sterols are found in considerable quantities both in free and esterified form.

Figure 10: Content of Sterolic compounds in Artemisia absinthium.

S.no	Phytosterol	Free sterol Form	Ester Form
1	β - Sitosterol	++	++++
2	Stigmasterol	++	+++
3	Campesterol	+	++
4	Ergosterol	-	+

Figure 10: Schematic table representing quantitative comparison of sterolic compounds inboth free and esterified form.

Along with the above types of compounds A.absinthium also contains tannins andcarotenoids also.

ETHNO PHARMACOLOGICAL EVALUATION OF *ARTEMISIA ABSINTHIUM*

***in vitro* studies**

Osmotic stability of human erythrocytes

De Freitas et al. in 2008 reported that the flavonoids present in the aqueous crude extract of *A. absinthium* might be responsible for the protection of human erythrocytes (RBC) against hypotonic shock [63].

Free-radical scavenging activity

Methanol extract of A. absinthium in the in vitro assays showed significant ($p<0.05$) superoxide anion, hydrogen peroxide, hydroxyl and nitric oxide radical scavenging activities, and significant reducing power [64]. Different solvent extracts of Artemisia absinthium (extraction with ethyl acetate, methanol, petroleum ether, chloroform, n-butanol and water) were tested for their free-radical scavenging activity in *in vitro* conditions with 2, 2-diphenyl-1-picrylhydrazyl (DPPH) free radical and hydroxyl radical ($OH^{\cdot}$) (formed in the Fenton reaction) by Canadanovic-Brunet et al. in 2005 and has reported the following order of antiradical activity : ethyl acetate > methanol > n-butanol > chloroform > petroleum ether >water.At a concentration of 0.5 mg/ml the ethyl acetate extract of A.absinthium reduced

all DPPH radical molecules and also at a concentration of 0.25 mg/ml the same extract inhibited completely the formation of hydroxyl radicals (OH^-) [65].

Figure 11: Percentage of antiradical activity shown by different solvent extracts of A.*absinthium*at two different concentrations, a) 0.25mg/ml and b) 2mg/ml

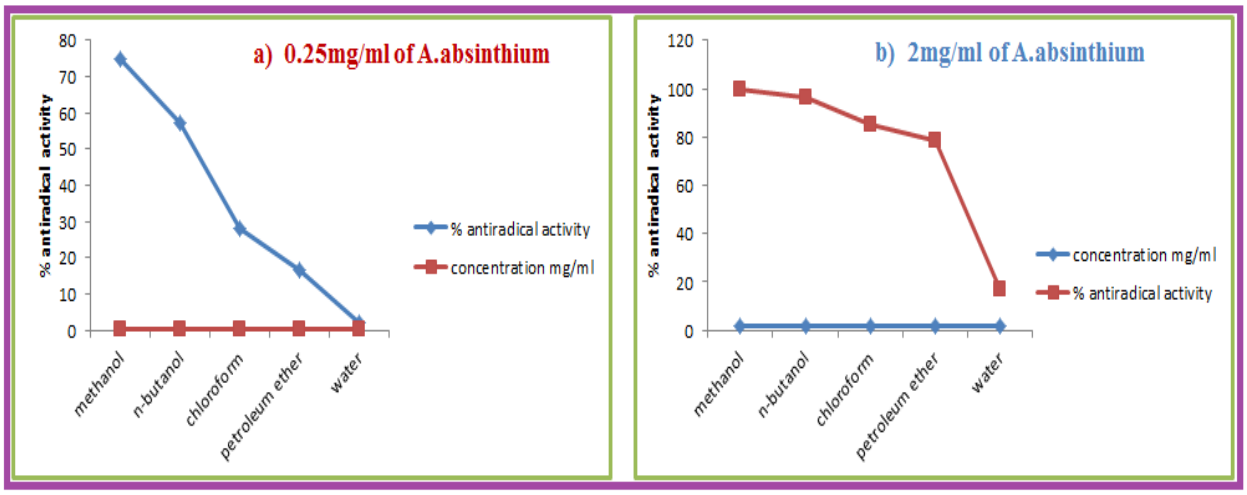

Figure11:

a) Graph showing % scavenging effect of different solvent extracts of A. *absinthium* with a concentration of 0.25 mg/ml - the methanol extract - 74.65% , n-butanol - 57.24%, chloroform -27.95%, petroleum ether- 16.64% (low scavenging effect) and water extract - 95.68% (high scavenging effect).

b) Graph showing % scavenging effect of different solvent extracts of A. *absinthium* with a concentration of 2 mg/ml - the methanol extract - 100%, n-butanol -96.06%, chloroform - 84.82%, petroleum ether- 78.26% and water extract - 95.68%.

Cognitive enhancement function

A. absinthium plant has long history of use as restorative of lost or declining cognitive functions in traditional medicine. A. absinthium has shown cognitive enhancement because of its nicotinic and muscarinic receptor activity ,which was studied and reported in homogenates of human cerebral cortical membranes by Wake et al. in the year 2000[66].

Neurite outgrowth function

Li Y, Ohizumi Y in 2004 evaluated and reported that at a concentration of 30 µg/ml different solvent extracts (methanol, ethyl acetate and aqueous extracts) of A. absinthium has enhanced neurite outgrowth by potentiating nerve growth factor and PC12D cells [67].

Figure 12: Neurite outgrowth enhancement of A. absinthium solvent extract

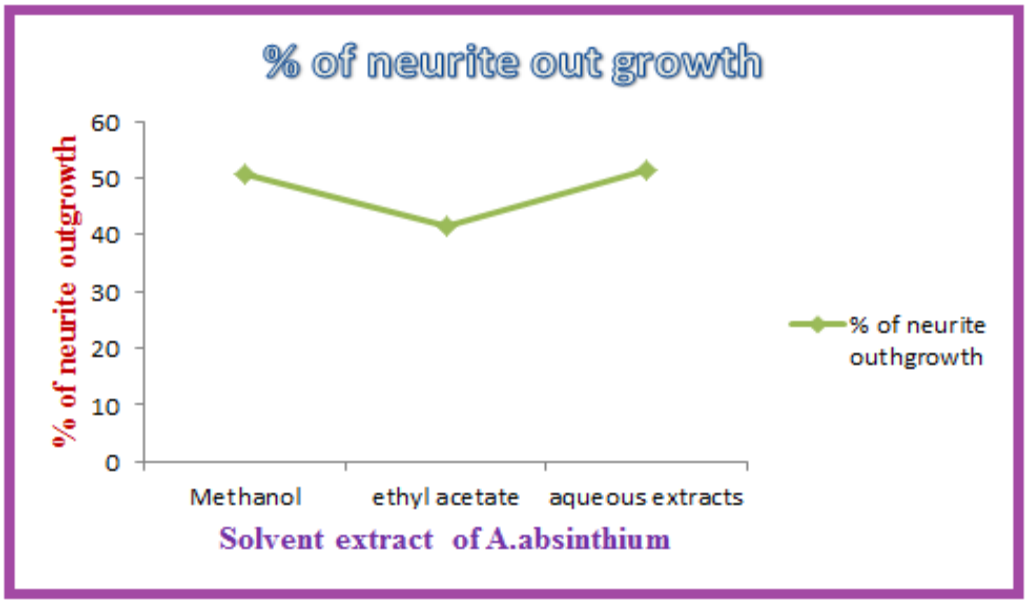

Figure 12: Graph representing enhanced neurite outgrowth induced by NGF from PC12D cells by variable solvent extracts of A. absinthium in percentages- methanol - 50.53%, ethyl acetate - 41.53% and aqueous extracts - 51.43%.

Antiprotozoal activity

Artemisia absinthium exhibit antiprotozoal activity and acts against Trypanosoma brucei, Trypanosoma cruzi, Leishmania infantum , Leishmania donovani and Plasmodium falciparum [68].The oxigenatedmonoterpene camphor, which is contained in Artemisia Absinthium, showed an antileishmanial activity against promastigote and axenic amastigote forms of two Leishmania strains (L. aethiopica and L. donovani) [70].Growth inhibitory assay reports of aqueous and ethanolic extracts of A. absinthium have shown strong inhibition against the growth of Naegleriafowleri (brain-eating amoeba) due to presence of artemisin like compound in it [69].

Antimalarial activity

Artmesia absinthium shows antimalarial activity. Aqueous extract as well as a sesquiterpene lactone fraction of A. absinthium has inhibited the growth of Plasmodium falciparum (causes malaria in humans).Maximum percentage of inhibition of growth (89.9%) .In the was shown by aqueous extract at a dilution of 1:35. The LD50 value of the sesquiterpene lactone fraction was 31.4 µg/ml [71, 72].

Figure 13: Antimalarial activity of Artemisia absinthium solvent extract in terms of %inhibitionin the growth of plasmodium falciparum.

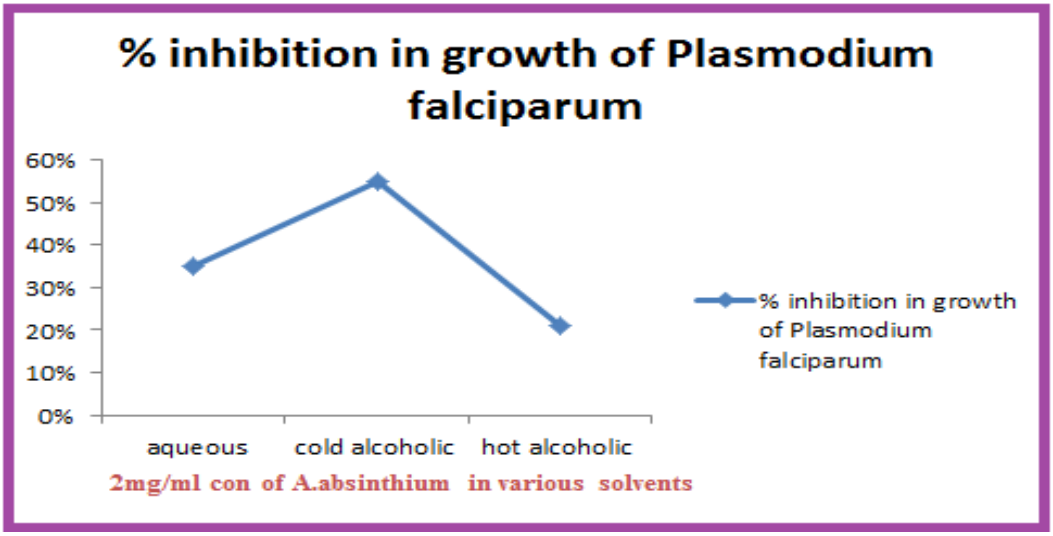

Figure13: Graph representing the inhibition percentages in the growth of Plasmodium falciparum by aqueous, cold alcoholic and hot alcoholic extracts of Artemisia absinthium (2mg/ml) as35%, 55% and 21%.

Antifungal activity

Distillated essential oils from the aerial parts of A. absinthium inhibited in vitro growth of different fungal speciesCandidaalbicans and Saccharomyces cerevisiae var. chevalieri and Microsporumcanis[73].

Antihelmintic activity

Whole plant and plant extracts of Artemisia absinthium have traditionally been used as antihelmintics against gastrointestinal nematodes . It has been observed that the crude alcoholic extract of Artemisia absinthium has got an antihelmintic activity for its tremocidal effects in vitro. Studies on anthelmintic efficacy of crude aqueous extracts (CAE) and crude ethanolic extracts (CEE) of the aerial parts of A. absinthium in comparison to albendazole against the gastrointestinal (GI) nematodes of sheep revealed that CAE and CEE have significant anthelmintic effects on live adult Haemonchuscontortus worms (Barber Pole Worm) and CEE was as effective as the reference drug-albendazole; however CEE is more efficacious than CAE. Artemisia absinthium is a natural alternative control for parasites of both animals and humans[74].

***in vivo* studies**

Antiulcer activity

Shafi N*et al*. reported that various solvent extracts of Artemisia absinthium (ethanol, hexane, chloroform, carbon tetrachloride and methanol) has shown antiulcer effects on acetylsalicylic acid induced ulcers in rats. Significant antiulcer effects recorded during the study were reduction in the ulcer index, decrease in the volumes of gastric juice (~1/3), decrease in peptic activity, and increase in mucin levels [75].

Figure 14: Reduced Ulcer index by solvent extracts of A.absinthium.

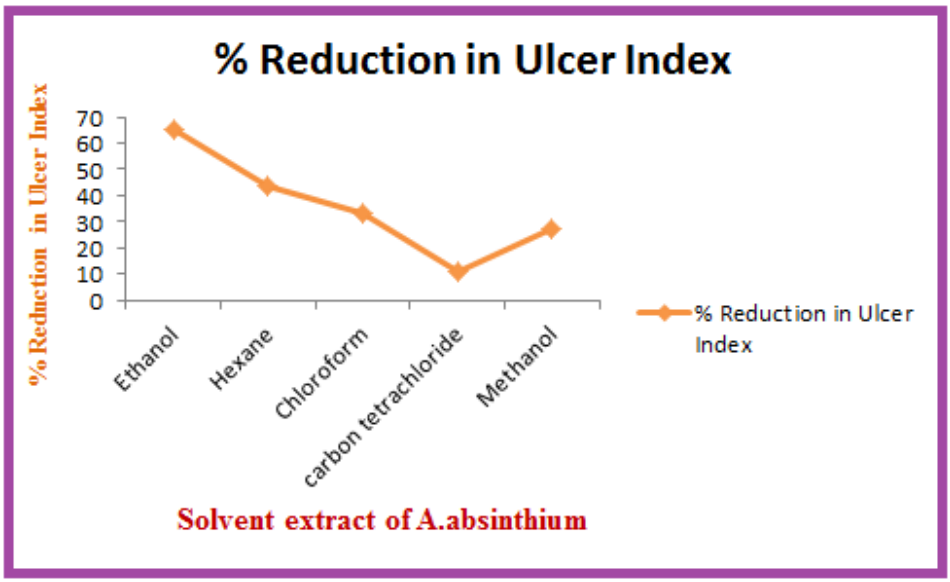

Figure 14: Graph represents the reduction of ulcer index by various solvent extracts of A.absinthium as follows – ethanol-65%, hexane-44%, chloroform-33%, carbon tetrachloride-11% and methanol-27%.

Antimicrobial activity

It was recently reported that the essential oils occurring in flowers and aerial parts from A. absinthium have antimicrobial properties[77,78].Moreover aqueous extracts of A. absinthium are rich in caffeoyl and dicaffeoylquinic acids, which are known to inhibit HIV-1 integrase from integrating the reversibly transcribed viral DNA into host cell DNA[76].

Figure 15: Antimicrobial activities of Artemisia absinthium extracts against differentmicroorganisms.

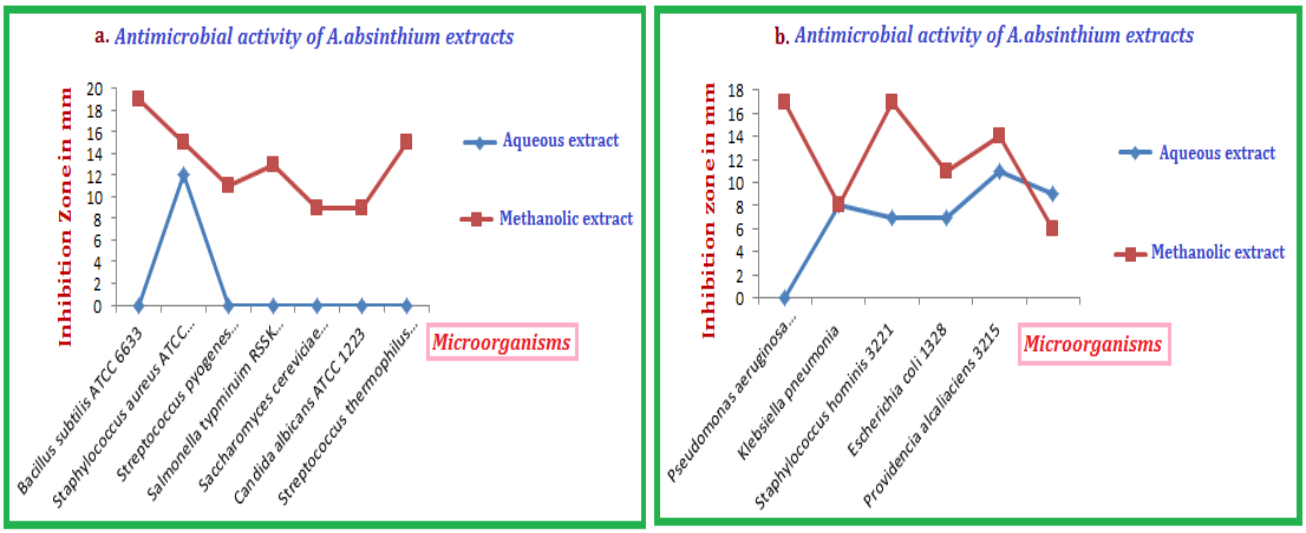

Figure 15: Graphs a and b representing antimicrobial activity of Artemisia absinthium extracts against different microbial species[78].

Anti-cancerous activity

The crude extract of the aerial parts of Artemisia absinthium (AA) modulates intracellular signaling mechanisms. it has been demonstrated that it has the ability to inhibit cell proliferation and promote apoptosis in a human breast carcinoma estrogenic-unresponsive cell line, MDA-MB-231, and an estrogenic-responsive cell line, MCF-7,when cells were incubated with various concentrations of Artemisia absinthium.Shafi G *etal* reported that A. absinthium has anti-proliferative effects on human breast cancer cells ,could possibly trigger apoptosis in both cell lines through the modulation of Bcl-2 family proteins and the MEK/ERK pathway [79].Artemisetin isolated from A. absinthium exhibited marked antitumor activity against melanoma B16, but only weakly retarded growth of Plisslymphosarcoma[80].It has been reported that chlorogenic acid (5-O-caffeoylquinic acid) of A.absinthium had inhibitory effects on carcinogenesis in the large intestine, liver, and tongue, and exhibited protective effects on oxidative stress *in vivo* [81].

Hepatoprotectiveactivity

Sesquiterpene lactones, flavonoids, phenolic acids and tannins which are contained in aqueous extract of Artemisia absinthium L. (AEAA) have got a protective effect against acute liver injury which may be attributed to their anti-oxidative and/or immune modulatory

activity.

Furthermore caffeoyl and dicaffeoylquinic acids present in Artemisia absinthium are hepato protective, anti-histaminic, hypocholesterolemic and anti-spasmodic in nature. Aqueous methanolic extract of A. absinthium exhibited hepatoprotective effect against acetaminophen- and carbon tetrachloride-induced hepatic damage [82]. Histopathology of the liver tissue showed that aqueous extract of Artemisia Absinthium (AEAA) attenuated the hepatocellular necrosis and led to reduction of inflammatory cells infiltration. Phytochemical analyses revealed the presence of sesquiterpene lactones, flavonoids, phenolic acids and tannins in the AEAA. It has got a protective effect against acute liver injury which may be attributed to its antioxidative and/or immunomodulatory activity, and thereby scientifically support its traditional use[82].

Intoxicating effects

The intoxicating effects of thujone were believed to activate receptors responsible for marijuana intoxication; however, thujone exhibited low affinity for rat cannabinoid receptors [83].

Anti nemathelminthic activity

Methanol extract of the aerial parts of A. absinthium at a dose of 300 mg/kg found effective against a trichinellosis (Trichinellaspiralis) in rats [84].

Antipyretic activity

Reports state that hexane, chloroform, and water-soluble extracts of A. absinthium exhibit antipyretic activity against subcutaneous yeast injections in rabbits. No toxic effects were documented for the plant extract at doses up to 1.6 g/kg [85].

Anti-oxidative stress function

Oral administration of methanol extract of A. absinthium (100 or 200 mg/kg) inhibited cerebral I/R-induced oxidative stress by decreasing thiobarbituric acid reactive substances (TBARS), and restoring levels of SOD and GSH[86].It is believed that high contents of total phenolic compounds and total flavonoids, present in the extract of A.absinthium contribute to the antioxidant properties and antioxidative activity, which plays an important role in protecting cells from oxidative degeneration. It has been shown that the treatment with aqueous extract of Artemisia Absinthium in animals exposed to lead reduced TBARS and carbonyl levels in liver and kidney and restored the levels of membrane-bound

enzymes(Na^{+}-K^{+}-ATPase, Ca^{++}-ATPase, Mg^{++}-ATPase) and lipid levels to near normal. These results indicate that aqueous Wormwood extract had a significant antioxidant activity and protect liver and kidney from the lead-induced toxicity[86,87].

Antibacterial Activity

Caffeoylquinic acids contained in the A.absinthium extracts are believed to be key components in killing multi-drug resistant microbial infections causing gram-positive pathogenic bacteria such as Staphylococcus aureus and Enterococcus faecalis[88].

Antioxidant activity

High phenolic acids and flavonoid content of ethanolic extract of A. absinthium has made it as a good antioxidant. At concentrations of 100 mg/L and 500 mg/L its extract is cytocompatible in NCTC cell line. This plant extract possess fibroblast protective effect against hydrogen peroxide-induced oxidative stress in cultured cells. Based on these findings the traditional use of wormwood in skin disorders treatment could be explained by their antioxidant and cytoprotective activities[89-91].

CONCLUSION

The present review emphasizes the traditional uses,phytochemical, ethnopharmacologicalreports and toxicological information on Artemisia absinthium. In recent years, phytochemical studies received much attention to know about numerous known and unknown compounds of medicinal value that can be screened for their therapeutic value for several health disorders without any side effects. Ethanomedicinal studies on Artemisia absinthium have revealed its pharmacological potential, which is essential for its further consideration andstandardization as a medicine at safer level. However, it is more essential to evaluate its medicinal potential on modern scientific lines through phytochemical, pharmacological studies and clinical trials.The information summarized here is intended to serve as a reference tool to people in the fields of developing alternative medicine from the chemistry of natural products.

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