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Potential of Wormwood (*Artemisia absinthium* Linn.) herb for use as additive in livestock feeding: A review

Yasir Afzal Beigh and Abdul Majeed Ganai

Abstract
Artemisia absinthium Linn. (Wormwood) is an important perennial shrubby plant, belongs to the genus Artemisia with more than 500 species, distributed in the temperate areas across the globe and within India has been recorded in the Himalayan region. It is used as herbal medicine in Ayurveda, Homeopathy, Unani and Siddha; besides, has been incorporated as feed additive in livestock nutrition for augmenting nutrient utilization and animal performance. It has a great importance as a folk medicine in ancient history from the time of Greek as an antiseptic, anthelminitc, antipyretic, antimalarial, antioxidant, hepatoprotective and neuroprotective. This review provides information on the phytochemistry, medicinal uses and pharmacological evaluation studies along with preliminary investigations in the direction for use of *A. absinthium* L. in animal nutrition. Improving the feeding value of animal diets using bioactive and highly nutritious medicinal plants such as wormwood can be an important factor not only to enhance animal production, product quality but also to lower feed cost in developing nations especially temperate zones; however, feeding wormwood may have very powerful actions in animals including ruminants, and should be used with care.

Keywords: Feed additive, Livestock, Wormwood

1. Introduction
Artemisia absinthium L. is a highly medicinal plant and almost mentioned in all the books of herbal medicine, distributed mainly in the temperate zones of Asia, Europe and North America. *A. absinthium* is one of the important specie among the 45 members represented by genus Artemisia in the Indian flora, and is naturally distributed in the Himalayan region across Jammu and Kashmir at an altitude range of 1500-2700 m [1].
A. absinthium L. is a hardy perennial sub-shrub. Erect, woody stems (over 1 m) bear alternate, much divided, silvery ovate to obovate leaves with silky soft hairs on each side. Tiny, rayless yellowy-green flowers occur in late summer in loose panicles which arise from the woody stems. It has a distinctive fragrance, thrives in sunny positions in poor soils and can become very woody.

Taxonomic hierarchy
A. absinthium L. belongs to the genus Artemisia, which is one of the largest and most widely distributed genera of the family Asteraceae (Compositae). It is a heterogenous genus, consisting over 500 diverse species. The species are perennial, biennial and annual herbs or small shrubs [2]. Asteraceae is the largest family of angiosperms.

Taxonomy		
Kingdom	:	Plantae – Plants
Sub-kingdom	:	Tracheobionta – Vascular plants
Super-division	:	Spermatophyta – Seed plants
Division	:	Magnoliophyta – Flowering plants
Class	:	Magnoliopsida – Dicotyledons
Sub-class	:	Asteridae
Order	:	Asterales
Family	:	Asteraceae – Aster family
Genus	:	*Artemisia* L. – sagebrush
Species	:	*Artemisia absinthium* L. – absinthium

Artemisia absinthium L. is known by different vernacular names. Afsantin (Urdu); green ginger, absinthe, absinthium, wormwood (English); Apsinthion (Greek); *A. absinthium* (Latin); Afsanteen, Damseeh (Arabic); Ku ai, Yang ai (Chinese); Vermouth, Genepi (French); Wermut, Absinth (German); Afsantine (Iran); Anjenjo (Mexican); Majri, Karmala, Majtari, Mastiyarah (Hindi); Afsanteen (Unani), Absinthium (Hemopathy) [3], and locally known as 'Tethwen' in Kashmir.

Related species

A similar specie, native to Britain, is sea wormwood *Artemisia maritima* L. which is widespread on coasts in Britain and northern Europe. It is smaller (to 60 cm) with strongly scented woolly divided leaves with blunt, narrow segments. Oval yellow-orange florets occur in late summer season. Other resembling species includes mugwort (*Artemisia vulgaris* L.), Roman wormwood (*Artemisia pontica* L.), tarragon (*Artemisia dracunculus* L.) and southernwood (*Artemisia abrotanum* L.) [4].

Medicinal uses

The herb has always been of a great botanical and pharmaceutical interest and is used in indigenous systems of medicine as a vermifuge [5], an insecticide [6], acaricide [7], cardiac stimulant [8], antispasmodic, antiseptic and diuretic, and for the treatment of chronic fevers and hepatitis [9], stomach aches [10, 11], restoration of declining mental function and to improve memory [12]. Its essential oil has antimicrobial [13], antifungal [14], neuroprotective [15], antimalarial [16], and antidepressant [17] activity. Volatile oil of *A. absinthium* is rich in thujone (α and β) having anthelmintic activity [18]. In addition, the herb is used to make a tea for helping during pain of labor and in treating leukaemia and sclerosis [19]. Moreover, the organic extract of this herb revealed toxic and anti-feedant effects [20]. Recently, the aerial part of *A. absinthium* L. has shown to possess anti-snake venom activity [21]. Anticancer activities are among the prominent biological effects reported for different species of the genus Artemisia [16, 22]. It is commonly used in food industry in the preparation of aperitifs, bitters and spirits [23]. *A. absinthium* is used as whole plant in ruminant feeding.

Phytochemical constituents

The active constituents present in *A. absinthium* L. are the bitter substances, essential oils and other compounds. Bitter constituents (0.15-0.4%) consists of sesquiterpene lactones, a class of natural compounds with several proved medicinal effects and includes guanolide dimmers as absinthin (0.2–0.28%) and its isomers anabsinthin, anabsin, artabsin (0.04–0.16%), and absintholide [24]; germacrene type as artabin [25]; matricin (0.007% in the drug); beta-santonin and ketopepenolid-A [26].

Essential oils (EO), mixtures of natural volatile compounds isolated by steam distillation from *A. absinthium* vary qualitatively and quantitatively according to geographical location and environmental conditions [27]. The yield of essential/wormwood oil (max. 0.2-1.5% in the drug) increases from arid to humid climate [28]. The 4 main components described are: α-thujone, (Z)-epoxy-ocimene, trans-sabinylacetat and chrysanthenyl-acetate [29]. α -thujone is typical for plants grown in areas below 1,000 m above mean sea level and is present at levels of approximately 40-70% of the wormwood oil [30]. (Z)-epoxy-ocimene is the main component in plants grown in Europe at altitudes higher 1,000 m above mean sea level. In France, there are different chemotypes with trans-sabinyl-acetate and chrysanthenyl-acetate as main components, while plants from eastern Europe are mostly mixed types [31]. Other constituents present at significant levels include myrcene (< 35%), α- pinene (6%) and nerol (3%) in wormwood oil of Russian origin [32]; p-cymene (16.5%), β-pinene (7.3%) and 7-ethyl-5,6-dihydro-1,4-dimethylazulene (5.5%) in Iranian wormwood oil [33]; cis-chrysanthenyl acetate (7.7-17.9%), a dihydrochamazulene isomer (5.5-11.6%), germacrene D (2.4-8.0%), linalool acetate (trace-7.0%), α-phellandrene (1.0-5.3%, and linalool (5.3-7.0%) in Tajikistanish wormwood oil [34]. High levels of thujanol and thujyi acetate (60-70%), myrcene(35%), camphor and 1,8-cineole were also determined in the wormwood oil [35]. Thujones, trans-sabinyl acetate, cis-chrysanthenyl acetate and cis-epoxyimene are the most common constituents in wormwood oils [13].

Other compounds present in *A. absinthium* L. are phenolic acids (2.6%) including chlorogenic, caffeic, syringic, coumaric, salicylic and vanillic acids; flavonoids (1.3%) including quercetin, rutin and glycosides, carotenoids, coumarins, homo-diterpen peroxides and thiophene [19], tannins [36]; lignans [37].

Biological activities of wormwood in animal production

Digestive effects

Enhance palatability

A. absinthium has strong flavor, which may alter feed sensory characteristics and therefore affect feed intake. Constituent phytochemicals impart strong flavors to wormwood that may increase palatability and feed intake of diets in animals. Although, the freshly cut wormwood is typically distasteful to ruminants; however, drying the plant increases its attractiveness to ruminants. Kim *et al*. [38] reported 18% increase in dry matter and organic matter intake in sheep fed diets containing wormwood relative to those fed the diet without wormwood. Also, Kim *et al*. [39] reported higher intake of diets containing wormwood silage compared to the control diet in sheep, which was partly attributable to the lower fibre and higher protein concentration and higher digestibility of diets that contained wormwood silage. Replacing rice straw with wormwood silage in ruminant diets can improve dietary nutrient supply and digestion, and enhance the content of health-promoting compounds in beef [40].

Hyper-secretary activity

Bitter constituents of wormwood stimulate the gustatory nerves in the mouth and increase the secretion of gastric juice and bile [41], thereby promote appetite and digestion. An intra-venous injection of decoctions of *A. absinthium* (equal to 5 g herbal substance) caused a threefold increase of bile secretion in dogs [42]. Liquid preparations of *A. absinthium* stimulated gastric secretion in humans when it was given orally five minutes before meal [43]. Again, Bone [44] reported dramatic increase in duodenal levels of pancreatic enzymes and bile by oral dosing of liquid *A. absinthium*. The essential oil of wormwood acts antispasmodic in small amounts; however, at high dosages or after longer-lasting intake the essential oil acts as a convulsant poison.

Digestibility enhancement activity

A. absinthium is used in indigenous systems of medicine as appetite stimulant and to facilitate the digestion process. Improvement in the secretion of gastric juice and bile by supplementation of *A. absinthium* or its extracts result in enhanced digestibility of feed in animal system. Kim *et al*. [38] reported that digestibility of DM and TDN value were significantly increased ($p<0.05$) in sheep fed diets containing the three levels (@ 3, 5 and 10% substitution of rice straw) of dried wormwood inclusion compared with the un-supplemented control. Digestibilities of crude protein and fibre in the 5% dried wormwood inclusion highly increased ($p<0.05$) upto 8.2 and 5.5% respectively relative to the control treatment. Ko *et al*. [45] reported that substituting wormwood for rice straw in the sheep diets increased *in vivo* nutrient digestibility, N retention and microbial N yield, particularly at the medium and high levels of wormwood inclusion. The reason for higher digestibility of the diets might be related to the presence of 6, 7-dimethylesculetin, capillarisin and coumarin in wormwood, which stimulate the secretion of bile salts and lipolytic enzymes in the small intestine [46].

Improve rumen fermentation

A. absinthium have potential benefits of using as a forage/feed additive source for ruminants, particularly in promoting the rumen fermentation pattern for efficient utilization of diets. Previous studies have shown that feeding dried wormwood, instead of rice straw, did not affect rumen pH [38]. However, Kim *et al*. [39] reported that ruminal fermentation characteristics were improved by substituting wormwood silage for rice straw in sheep diets with decreased ruminal pH. This decreases ruminal biohydrogenation of poly-unsaturated fatty acids (PUFA), and increase transfer of 18:3 and 18:2 PUFA from the diet to muscle tissue, thereby enhancing concentration of health-promoting fatty acids in the muscle of the steers [40].

Antiulcer activity

A. absinthium is traditionally being used to treat dyspeptic complaints, including gastritis and gall bladder ailments [47]. Shafi *et al*. [48] reported that various solvent extracts of *A. absinthium* (ethanol, hexane, chloroform, CCl_4 and methanol) has antiulcer effects on acetylsalicylic acid induced ulcers in rats. Significant antiulcer effects recorded during the study were reduction in ulcer index, increase in level of mucin, reduction in peptic activity and decrease in gastric juice volume.

Hepatic effects

Hepatic ailments are one of the major serious health issues throughout world nowadays, but regardless of remarkable advances in the modern medicine, their prevention options and treatments still remain inadequate. The blockage or retardation of the chain reactions of inflammatory process and oxidation is considered as efficient therapeutic approach for prevention as well as treatment of hepatic injuries. In recent times, the most frequent and well recognized *in vivo* model used for the investigation of novel hepatoprotective agents is rodent model of hepatic disorders induced *via* carbon tertrachloride (CCl_4) which is a hepatotoxin that triggers hepato-cellular damage mediated by free radicals [49]. Phytochemicals (sesquiterpene lactones, flavonoids, phenolic acids and tannins) present in *A. absinthium* L. and its extracts reveal strong antioxidant and/or immune modulatory potential, and thus exhibit hepatoprotective activity in animal based models. Furthermore, caffeoyl and dicaffeoylquinic acids present in *A. absinthium* are hepatoprotective in nature.

Aqueous-methanolic extract of *A. absinthium* exhibited hepatoprotective effect against acetaminophen and CCl_4 induced hepatic damage [9], and thereby scientifically support its traditional usage against various liver diseases like hepatitis and other hepatobiliary ailments [50]. The mechanism of action may be associated with inhibition of hepatic microsomal drug metabolizing enzymes, antioxidant activity, and/or blocking calcium channels. Mohammadian *et al*. [51] reported that administration of hydroalcoholic extract of *A. absinthium* would improve the liver function and the level of oxidative stress parameters such as total thiol groups in blood. *A. absinthium* extract seems to be able to preserve the structural integrity of the hepatocellular membrane leading to reduction of serum aspartate aminotransferase and alanine aminotransferase activities. Beigh *et al*. [52] reported that supplementation of *A. absinthium* L. herb alone or in combination with exogenous fibrolytic enzymes cocktail as feed additive to complete feed is possible for intensive rearing of lambs without any adverse effect on hepato-renal functioning. However, hepatoprotective effects of wormwood is possible at doses lower than 200 mg/kg [53], but at high doses *A. absinthium* plays a prooxidant and inflammatory role such as gallic acid [54], thereby induce hepatotoxicity by inflammation and oxidation depending on its thujone content, drying and harvesting conditions or climate that the plant was growing in [55].

Neurologic effect

A. absinthium has both neuroprotective as well as neurotoxic effects depending upon the intake amount of the active phytoconstituent into the animal system.

Neuroprotective activity

A. absinthium has a long history of use as restorative of lost or declining cognitive functions in traditional medicine. It 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*. [56]. Moreover, it has been reported that ethanolic extract of *A. absinthium* enhanced neurite outgrowth by potentiating nerve growth factor and PC12D cells [57]. *A. absinthium* exhibited neuroprotective effects against focal ischemia and reperfusion-induced cerebral injury in rats [58]. Neuroprotection is also exhibited by its extract as it is evident from the reduction of brain infarct volume and oxidative stress, restoration of endogenous antioxidants, and also significant improvement in behavioral outcome during cerebral ischemia and reperfusion injury. The mechanism by which *A. absinthium* normalized the damage, inhibited lipid peroxidation and neurological deficits, and restored the endogenous antioxidant defense enzymes, is probably by its antioxidant properties, suggesting that *A. absinthium* may prove to be useful adjunct in the treatment of stroke (Bora and Sharma, 2010). Also, Zeng *et al*. [59] reported that a natural sesquiterpene dimer Caruifolin D from *A. absinthium* L. considerably suppressed the production of intracellular reactive oxygen species that displayed its neuroprotective mechanism.

Conventional Chinese medicine practitioners utilize *A. absinthium* to deal with neurodegenerative disorders [60]. The herb might be beneficial for the treatment of the glial and neuronal alterations observed during chronic lead intoxication in adult rat [61]. Hallal *et al*. [62] reported that treatment with *A. absinthium* L. show a significant amelioration in activity of antioxidant enzymes (superoxide dismutase, catalase and glutathione peroxidase), which may be associated with the level of non-enzymatic antioxidants than the activity of enzymatic antioxidants and protects brain dysfunction induced by mercuric chloride ($HgCl_2$), suggesting that this molecular approach can be a strategy to a possibly therapeutic action of *A. absinthium* in the treatment of neurodegeneration produced by $HgCl_2$.

Neurotoxic activity

Chronic use of *A. absinthium* has been reported to have some neurotoxic effect due to presence of thujone and its derivatives [63]. Also, Juteau *et al*. [13] reported that the constituent essential oil of *A. absinthium* contains high concentrations of thujone, thujyl alcohol and other terpene-derivatives, which are neurotoxic (hyperactivity, tremors, tonic seizures) at high doses. Thujone is a $GABA_A$ receptor antagonist that can cause epileptic-like convulsions [64] by rapidly modulating the GABA-gated chloride channel. The effect appears to be due to the parent compound, while metabolism leads to detoxification. Intraperitoneal injection of thujone was convulsant in mice [65] and the action was blocked by earlier intraperitoneal administration of diazepam or phenobarbital.

Anti-parasitic effect

Parasitic conditions of varied etiologies viz. helminthic, protozoan and arthropods, constitute major constraint to productivity, performance and profitability of livestock farming. Additionally, several of them are capable of causing human disease (zoonoses). Prior to the era of industrial chemicals (synthetic drugs), traditional medicines of plant origin (herbs/botanicals) formed the backbone of healthcare of humans as well as livestock. The advent of synthetic chemicals in the 20th century, found ready consumer preference due to their spectacular and "quick fix" actions, and rule the market even today. However, the last 3-4 decades have seen erosion of their efficacy due to large-scale emergence of resistance in parasites. At the same time, increasing concerns about their toxicity for animal, man and environment, compelled a relook at alternative control strategies. Till such time that immunization procedures could be developed against major parasitic diseases, a renewal of interest in the safe, sustainable and effective (yet relatively inexpensive) resource, that is, medicinally active plants/herbs, seems a viable option. There has been resurgence in the use of medicinal plants to treat cases of parasitism in livestock and much of the success has been achieved in this direction against a variety of parasites.

Anthelmintic activity

In indigenous systems of medicine, *A. absinthium* has been used as a vermifuge, and is considered to be an effective natural alternative remedy for parasite control both in humans as well as in animals. Volatile oil rich in thujone (α and β) from *A. absinthium* has been earlier reported to have an anthelmintic activity [18]. The genus is a rich source of sesquiterpene lactones (like artemisinin) and flavonoids that also might have anthelmintic activity with low risk of mammalian toxicity [66]. Singh *et al*. [67] reported that an aqueous extract of fresh leaves of *A. absinthium* L. given with sugar solution on empty stomach for 8-10 days, expelled out round worms completely. Also, it has been reported that crude aqueous and ethanol extracts of the aerial parts of *A. absinthium* exhibit significant anthelmintic activity in comparison to albendazole against the gastrointestinal nematodes in sheep, without apparent toxicity to the animals. *In vitro*, both extracts reduced the motility of *Haemonchus contortus* at 25 mg/mL, and both aqueous and ethanolic extracts were effective *in vitro* and *in vivo*, but ethanolic outperformed the aqueous extracts [5]. These results agree with others [68] who found that ethanolic extracts of *A. absinthium* significantly reduced egg development and juvenile (L3) larval motility of *Ascaris suum in vitro*. In contrast, Worku *et al*. [69] did not observed gastrointestinal nematicidal activity *of A. absinthium* aqueous extract in goats. Also, Squires *et al*. [70] reported that crude ethanolic extract of *A. absinthium* did not have anthelmintic activity against *H. contortus* in gerbils. While, methanol extract of the aerial parts of *A. absinthium* at a dose of 300 mg/kg reduced numbers of *Trichinella spiralis* larvae in the muscle of rats [71] as well as its essential oils caused 66% reduction of intestinal *T. spiralis* adult parasites in mice [72]. These discrepancies in results emphasize the difficulties associated with efforts to evaluate and standardize antiparasitic effects of the plant and plant-derived products. Studies have reported that polar extracts obtained with water or ethanol have a greater anthelmintic activity than non-polar extracts obtained with hexane, which usually have low or no anthelmintic activity.

Antiprotozoal activity

The antiparasitic drugs which have been evaluated against the pathogenic protozoa often have severe side effects. In this context, medicinal plants as a source have attracted a considerable attention in the development of new antiprotozoal drugs. *A. absinthium* and its extracts besides anthelmintic properties have antiprotozoal activities too. *A. absinthium* extracts have been reported as exhibiting antiprotozoal potential against *Trypanosoma brucei*, *T. cruzi* and *Leishmania infantum* [73]. The antileishmanial activity is due to its constituent flavonids whose action depends on the presence of two hydroxyl groups in the molecule at C-3 and C-4 and that activity is lost with a methoxy at C-3 [74]. Besides, the oxygenated monoterpene camphor present in *A. Absinthium* shows antileishmanial activity against promastigote and axenic amastigote forms of two *Leishmania* strains (*L. aethiopica* and *L. donovani*) [75]. Also, Bailen *et al*. [76] reported that the essential oils of *A. absinthium* showed antiparasitic effects against *Leishmania infantum* at all the lowest dose tested, while these essential oils were active against *Trypanosoma cruzi* at 800 and 400 µg/mL under *in* *vitro* experimentation. Leishmanicidal and trypanocidal activities of *A. absinthium* essential oils have also been reported by Gonzalez-Coloma *et al*. [77] and Martinez-Diaz *et al*. [78]. A constituent sesquiterpene lactone- artemetin has been described as a synergist for the trypanocidal effects of other flavones [79]. Ethanol and aqueous extract of *A. absinthium* showed growth inhibitory effects against brain-eating amoeba *Naegleria fowleri* due to its constituent sesquiterpene lactone- artemisin [80].

A. absinthium also shows antimalarial activity. The aqueous and alcoholic leaf extracts of *A. absinthium* showed antimalarial activity against a strain of *Plasmodium berghei* in mice [81]. While the aqueous extract as well as a sesquiterpene lactone fraction of *A. absinthium* has inhibited the growth of *P. falciparum* known to cause malaria in humans [73]. Maximum percentage of inhibition of growth (89.9%) was shown by aqueous extract at a dilution of 1:35. The LD_{50} value of the sesquiterpene lactone fraction was 31.4 µg/ml [82, 83]. The constituent sesquiterpene lactones- artemetin and casticin enhanced the antiplasmodial action of artemisinin. Both the flavones showed *in vitro* antimalarial effects against *P. falciparum* [84].

Coccidiosis is one of the most important infections in livestock caused by Eimeria species and is of greater economic importance due to high morbidity. In order to develop alternative, safer and environmental friendly anti-coccidial agent, potent medicinal benefits for *Artemisia* species have been reported. Anticoccidian activity of *A. absinthium* and its extracts have been reported in ruminants as well as in poultry; however, the activity depends on the number of oocysts and the type of *Eimeria*. Aqueous extract *A. absinthium* at a dose of 3 mg/kg of feed per day reduces the number of oocysts in broiler chicken infected with *E. tenella* and can be used for the prophylaxis of moderate coccidiosis [85]. Tests have been conducted on different breeds of chickens, using different concentrations of extracts in correlation to the number of artificially entered Eimeria oocysts [86, 87, 88]. However, Iqbal *et al*. [89] observed that *A. absinthium* was not effective against coccidian infection in goats and recommended further studies with different dosages, concentrations and solvent preparations of *A. absinthium* extracts to arrive at a certain conclusion about its efficacy against goat coccidian.

Anti-feedant activity

Arthropod parasites such as mosquitoes, fleas, flies and ticks, apart from their direct ill-effects of discomfort, blood loss and dermatitis to their hosts, are highly important vectors of a variety of disease-agents affecting both human and animals. The active ingredients of several plants and herbs are known to possess insect repellent, insecticidal, growth inhibitory and anti-moulting activities. These natural products included in ethnoveterinary practice offer the poor livestock farmers, a cheaper, eco-friendly and sustainable alternative to synthetic conventional insecticides.

A. absinthium is famous for its anti-feedant properties [90]. Ethnobotanical studies refer to its insect repellent properties and external use of its aerial parts in cattle skin disorders [91]. The plant's characteristic odor makes it useful in companion planting to suppress weeds, because its roots secrete a substance called absinthin (sesquiterpene lactone), that inhibit the growth of surrounding plants [92]. 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. The activities of *A. absinthium* is due to its essential oil that has been shown to have acaricidal [7], insecticidal [93, 94] and repellent effects against fleas, flies, mosquitoes [95] and ticks [96]. Parveen *et al*. [97] reported that 5, 10 and 20% concentrations of *A. absinthium* ethanolic extracts showed 100% inhibition for hatching of cattle tick (*Rhipicephalus microplus*) eggs *in vitro*, suggesting that *A. absinthium* could form alternatives to commercially available synthetic acaricides. The phytochemical of *A. absinthium* - artemisinin is thought to exert its effect by reacting with the heme groups of the haemoglobin molecules digested by parasites, altering the cell structure and its functions through the free radicles derived from artemisinin, thus affecting the growth and reproduction [98]. The essential oils of *A. absinthium* L. were found to be toxic to adults of granary weevil *Sitophilus granarius* L. (Coleoptera). The oils showed about 80-90% mortality of these insects after 48 h of exposure [94]. Additionally, its organic extracts exhibited anti-feedant effects and were toxic to *Leptinotarsa decemnlineata* [20], and *Rhopalosiphum padi* [99]; however, the extraction method play an important role when evaluating the potential anti-feedant applications of *A. absinthium* extracts [100].

Anti-inflammatory effect

All drugs that are used for the management of pain and inflammatory conditions have well known side and toxic effects. In indigenous system of medicine, various medicinal plants/herbs are being presently in use for their potent analgesic and anti-inflammatory activities. For the reason, *A. absinthium* has a rational basis for its traditional use in some painful and inflammatory conditions. *A. absinthium* and its extracts have been demonstrated to possess a strong anti-inflammatory activity in animal model. Its phytoconstituents *viz.* flavonoids [101, 102] and sesquiterpene type molecules [103, 104, 105, 106] are well known to possess anti-inflammatory activity through the mechanism associated with synthesis or release of inflammatory mediators such as the histamine, serotonin, bradykinins and prostaglandins. Tetramethoxy hydroxyl-flavone isolated from *A. absinthium* has been reported to exhibit anti-inflammatory activity by inhibition of inflammatory mediators via cyclo-oxygenase-2 (COX-2), prostaglandin (E-2 and PGE-2) and nitric oxide in lipo-polysaccharide-stimulated RAW 264.7 cells [107]. Furthermore a chalcone cardomonin isolated from wormwood has been shown to exhibit anti-inflammatory activity in cellular models of inflammation [108].

Ahmad *et al*. [109] have evaluated the analgesic and anti-inflammatory activities of alcoholic extracts of *A. absinthium*. Hadi *et al*. [110] reported that the essential oil and aqueous extract of *A. absinthium* possess significant anti-inflammatory effect in laboratory animals at the doses investigated with more activity for the essential oil compared to the aqueous extract. Zeng *et al*. [59] reported that natural sesquiterpene dimer caruifolin D was a major anti-inflammatory component from *A. absinthium* L. which has potent anti-neuroinflammatory effects and suggested that caruifolin D might be developed as a drug candidate for neuro-inflammation-related diseases. Nalbantsoy *et al*. [21] studied the anti-snake venom activities of *A. absinthium* L. in comparison with carrageenan-induced acute inflammation model in rats and reported for the first time the toxicity and inflammatory actions and cytotoxic actions of crude *Montivipera xanthina* venom as well as inhibition of venom-induced inflammation by methanolic extract of *A. absinthium*.

Anti-oxidant effect

Reactive oxygen species (ROS) are highly reactive and cause oxidative damage to various biomolecules (DNA, proteins, lipids and lipoprotein) which is considered to be a crucial etiological factor implicated in different chronic diseases such as atherosclerosis, inflammatory injury, cancer and cardiovascular disease [111]. The conventional therapeutic approaches for these diseases often have severe side effects such as strong host immune response and cytotoxicity to normal cells that impresses for requirement of usefulness of antioxidant, which are considered as chemical substances that lessen and prevent oxidation. Antioxidants have the ability to protect from the damaging effects of radicals in tissue.

In this context, the use of plants and herbs as a source of natural antioxidant and biologically active compounds has attracted a great deal of scientific interest. The anti-oxidant properties of these medicinal plants is mainly attributed to their constituent phytochemicals produced as part of their normal metabolic activities. Among different classes of secondary metabolites, plant polyphenols constitute the largest group of natural antioxidants [112]. Antioxidant activity have been reported for essential oil of *A. absinthium* L. [6, 113, 114] and its extracts [19, 115], which is possibly due to its constituent flavonoids (rutin and quercetin), thymol and carvacrol as well as other phenolic compounds [116]. Artemetin (flavone) has been described as an antioxidant that neutralizes peroxide radicals [117], while Azizuddin *et al*. [118] reported weak radical scavenging activity for casticin and inactivity for artemetin; however, similar weak antioxidant effects for these flavonoids and stronger ones for the sesquiterpene lactone has been reported by Gonzalez-Coloma *et al*. [77]. Some researchers have even reported that essential oils rich in non-phenolic compounds also have antioxidant potential [13]. These pharmacophores have been known to possess anti-inflammatory, potent antioxidant and free radical scavenging activity on their own or have synergistic effects with other medicinal compounds present in the plant, increasing their absorption, pharmacological activity and permanence in the human or animal subject consuming the plant or extract.

The antioxidative activity of *A. absinthium* extracts have been tested by measuring their ability to scavenge stable 2,2-diphenyl-1-picrylhydrazyl (DPPH) free radical and reactive hydroxyl radical during the Fenton reaction trapped by 5,5-dimethyl-1-pyrroline-N-oxide, using electron spin resonance spectroscopy [119]. The DPPH free radical scavenging activity of *A. absinthium* in callus cultures has been found to be independent on biomass accumulation, but it is dependent on secondary metabolites production during the culture growth. Highest antioxidant activity (63.3%) and maximum accumulation of total phenolics (1.48 mg GAE/g DW) and total flavonoids (0.48 mg QE/g DW) were recorded in 35 day old calli which declined thereafter representing a positive correlation of phenolic compounds and antioxidant activity in callus cultures of *A. absinthium* L. [120].

Anti-microbial effect

Anti-bacterial activity

In recent decades, antimicrobial herbal products have received considerable attention because of a rapid increase in antibiotic resistance in microorganisms [121]. *A. absinthium* have been reported to have a broad spectrum of inhibitory activity against a variety of microorganisms due to presence of essential oil for which the herb is most likely still used as a cure for gastrointestinal disorders and the treatment of wound infections as an antiseptic. The minimal inhibitory concentration (MIC) of the oil ranges from <0.08 mg/mL (against *Proteus mirabilis* and *Enterobacter aerogenes* isolated from human stools, and against *Pseudomonas aeruginosa* and *Staphylococcus aureus* isolated from wounds) to 2.43 mg/mL (against *Klebsiella oxytoca* from stools), while the minimal bactericidal concentration (MBC) of the oil ranges from 0.08 mg/ mL (against *E. aerogenes* from stools, and against *S. aureus* and *K. oxytoca* from wounds) to 38.80 mg/mL (against *Listeria monocytogenes* ATCC 7644) [122].

Extracts of *A. absinthium* have been shown to exhibit strong antimicrobial activity, especially against gram positive pathogenic bacteria [123] which could be attributed to the presence of the major (camphor, p-cymene, caryophyllene) or minor (α-pinene, β-pinene) components of the plant or synergy between these compounds [124]. These pinene-type monoterpenes (α-pinene, β-pinene) are well-known chemicals having antimicrobial potentials; besides enantiomers of α-pinene and β-pinene have a strong antibacterial activity [125]. Camphor, as the major constituent of *A. absinthium*, has been reported to have a strong antibacterial activity against gram positive bacteria [126]. Higher resistance in gram negative bacteria can be attributed to external phospholipid membrane that is infiltrated to lipophilic components. Lack of this membrane in gram positive bacteria causes easier entrance of the essential oil and extract components to bacterium. This process may cause increase in ionic permeability and permeation of vital inner cellular components which finally result in damage to enzyme system of bacterium. Essential oils can also inhibit the synthesis of DNA, RNA, protein, and polysaccharide in bacterial cells [127].

Ethanol extracts of *A. absinthium* possess same effects against different specific bacterial strain with inhibition zones of 10-15 mm in diameter for *Staphylococcus aureus* [128]. Habibipour and Rajabi [129] also reported higher effect of extract of *A. absinthium* on *Haemophilus influenza* which was even better than Ofloxacin. Likewise, Moslemi *et al*. [124] reported that topical application of *A. absinthium* extract on the infected wound sites produced significant antibacterial activity against *S. aureus.* Significant antibacterial activity of *A. absinthium* essential oil and its extract also suggest its capacity as a natural food preservative in the food industry for preservation of food material from degradation mainly by microorganism activity during production, storage, and marketing as an alternative to synthetic antibiotics that has lead to an increase of some pathogens' resistance and uncomfortability to patients due to their adverse drug reactions [130, 131]. These plants based secondary metabolites such as essential oil and extracts are widely used in the food industry and are considered Generally Recognized as Safe (GRAS).

Anti-fungal activity

The emerging resistance of microbes to synthetic antifungal agents has serious implications in the management of infections; besides, these antifungal compounds also act on targets found in mammalian cells which may result in toxicity or adverse drug interactions, thereby necessitating the discovery of novel antifungals. Herbs/botanicals could be a better source of medicine as compared to synthetically produced drugs. The pharmacological importance of these medicinal plants is due to the presence of active constituents known as phytochemicals or plant secondary metabolites (PSM) including simple phenols and phenolic acids, flavonoids, coumarins, quinones, saponins, xanthones, alkaloids, lectins, polypeptides, terpenoids, essential oils and others.

A. absinthium have been reported to have inhibitory activity against a variety of fungi which could be attributed to the major component of essential oil. The anti-fungal activity of essential oils of wormwood gives it an important role in the field of food, cosmetics, and pharmaceutical industries. The essential oils containing (Z)-epoxyocimene and chrysanthenyl acetate as major components distilled from the aerial parts of *A. absinthium* from France inhibited *in vitro* growth of *Candida albicans* and *Saccharomyces cerevisiae* var. chevalieri [13]. Wormwood essential oil from a Turkish population, whose main components are camphor, 1,8-cineole and chamazulene, has been described as fungicidal at a dose of 20µL against 34 species of fungi including *Fusarium solani* and *Fusarium oxysporum* [6]. *F. oxysporum* and *F. solani* were affected by essential oils (cis-epoxyocimene, chrysanthenol, and chrysanthenyl acetate) from cultivated as well as commercial oil samples of *A. absinthium* has also been reported by Bailen *et al*. [76]. Significant inhibitory activity of wormwood essential oils against the three phytopathogenic fungi *viz*. *F. graminearum*, *F. culmorum* and *F. oxysporum* has been observed by Msaada *et al*. [130]. Furthermore, *A. absinthium* essential oil from Uruguay rich in thujone showed anti-fungal effects against *Alternaria* sp. and *Botrytis cinerea* [132].

Other effects

Antipyretic activity

In Turkish folk medicine, *A. absinthium* has been used as an antipyretic herbal drug [10]. Khattak *et al*. [133] reported that hexane-, chloroform-, and water-soluble extracts of *A. absinthium* exhibit antipyretic activity comparable to potency of aspirin against subcutaneous yeast injections in rabbits. No toxic effects were documented for the plant extract at doses up to 1.6 g/kg. In another study with the ethanolic extract of *A. absinthium* which contains 24-β-ethyl p-cholesta-7, 22-dien-3 Bat, shows antipyretic activity in rats with least side effects [71].

Antidepressant activity

In medical clinical practice, depression is considered to be the second most chronic condition and upto the year 2020, it shall become the second leading cause of disability and premature birth worldwide. More or less two-thirds of the depressed and nervous victims counter to the existing treatments but it is disappointing regarding the magnitude of improvement. Although, nowadays there are various efficient antidepressant available. Traditional medicinal plants have been assessed for psychotherapeutic potential against depression in various animal models. The investigations showed the antidepressant activity in tail suspension test and forced swimming test by using *A. absinthium* at flowering stage and it considerably reduced the immobility period in both the tests [17].

Anti-cancerous activity

It has been reported that crude extract of the aerial parts of *A. absinthium* modulates intracellular signaling mechanisms, thus has the ability to inhibit cell proliferation and promote apoptosis in carcinoma estrogenic-unresponsive cell line, MDA-MB-231, and an estrogenic-responsive cell line, MCF-7. 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* [134]. Artemisetin isolated from *A. absinthium* exhibited marked antitumor activity against melanoma B16, but only weakly retarded growth of *Pliss lymphosarcoma* [135]. Shafi *et al* [22] reported that *A. absinthium* has anti-proliferative effects on human breast cancer cells, could possibly trigger apoptosis in cell lines through the modulation of Bcl-2 family proteins and the MEK/ERK pathway.

Hypolipidemic activity

Hyperlipidemia is considered to be a major risk factor for cardiovascular diseases including atherosclerosis, myocardial infarction, heart attacks and cerebrovascular diseases [136], which can be treated with *A. absinthium* extract that has been reported to reduces serum cholesterol and triglyceride by 8 and 3.5 times, respectively in rabbits [137]. *A. absinthium* ethanolic extract (500, 1000 mg/kg) have potent antihyperlipidemic activity in high cholesterol diet induced hyperlipidemia models. The possible mechanism of lipid alteration might be cholestatic effect of *A. absinthium* in liver by enhanced removal or catabolism of lipoproteins [138] and/or inhibition of lysosomal lipid hydrolytic enzymes secreted by the liver [139].

Immuno-modulatory activity

In traditional medicine, worldwide, herbal drugs are used to treat immune disorders, such as inflammatory and autoimmune diseases. Several herbal medicines have immunomodulatory effects [140]. *A. absinthium* is commonly used to modulate immune-mediated disorders in indigenous system of medicine. It has been reported that polysaccharides isolated from *A. absinthium* have immunomodulatory effects by induction of a Th1 response and stimulation of nitric oxide production [141]. In addition, *in vivo* studies indicated that *A. absinthium* suppressed tumor necrosis factor alpha (TNF-α) and accelerated healing in patients with Crohn's disease [142]. *A. absinthium* extract, at concentrations below 100 µg/mL can modulate the immune response toward a Th1 pattern, by induction of CD40 expression on dendritic cells and cytokine production with inhibition of dendritic T cell stimulating activity at high concentrations [143].

Cell stability activity

De Freitas *et al*. [144] 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.

Adverse reactions

Thujone, a characteristic component of essential oil of the *A. absinthium* L., is a known central nervous system toxin; however, the toxicological risk from use of conventional wormwood preparations is very low and aqueous extracts contain little thujone. Excessive dosing, long-term use or use of the essential oil could lead to toxicity "absinthism" -mental disorder in humans [145] with the symptoms of hallucinations, sleeplessness and convulsions. The side effects may include brain damage and even death, insomnia, intestinal cramps, nausea, restlessness, seizures, stomach cramps, tremors, urine retention, vertigo and vomiting [146]. Several animal experiments conducted with pure thujone have confirmed its properties to cause dose-dependent tonic-clonic seizures [55]. The no-effect level (NOEL) has been reported to be in the range between 5 and 12.5 mg/kg bodyweight/day [147].

Conclusion

The present review emphasizes the traditional uses, phytochemistry, ethnopharmacological and toxicological information on *A. absinthium* L. in animal and human studies. In recent years, phytochemical studies have received considerable attention to know about numerous known and unknown constituent compounds of medicinal value that can be screened for their beneficial purpose in animal and/or human system. Ethano-veterinary medicinal studies on *A. absinthium* have revealed its pharmacological potential, which is essential for its further consideration and standardization as a medicine or feed additive at safer level. *A. absinthium* have strong flavors, thus have very powerful actions in animals including ruminants, and should be used with care because elevated doses can stimulate undesirable side effects. Improving the feeding value of animal diets through supplementation of bioactive and high nutritional herbal plants such as wormwood is a viable proposition to enhance the nutrient utilization efficiency for augmenting productivity as well as product quality to have sustainable livestock production, particularly where feeding of low grade roughages is indispensable. However, it is more essential to evaluate its potential on modern scientific lines through phytochemical, pharmacological studies, and clinical and nutritional trials.

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