

*Persian Medicine***Gastrointestinal effects of *Artemisia absinthium* Linn. based on traditional Persian medicine and new studies**

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Highlights

In this study, researchers reviewed the pharmacological effects of *Artemisia absinthium* Linn. (AAL), an herbal medicine from the *Asteraceae* family used for solving digestive problems, specifically parasites and intestinal worms, by concentrating on the gastrointestinal (GI) effects. Then the traditional Persian medicine (TPM) applications of this herb were compared to recent studies.

Traditionality

ALL, commonly known as wormwood and absinthe, is a species of *Artemisia* genus that belongs to *Asteraceae*. The name ALL is termed from the ancient Greek *Artemisia*, which means “the Goddess” and *absinthium*, which means “unenjoyable” or “without sweetness.” The name “wormwood” refers to the plant’s anthelmintic effects, which were recognized by the ancient Egyptians. The first documented medical use of wormwood dates back to the *Ebers Papyrus*, an ancient Egyptian medical text (1552 B.C.E.), which is recognized as the oldest preserved medical document. Wormwood syrup exhibits a hot and dry temperament and has been repeatedly used for the treatment of digestive diseases. TPM textbooks such as *Avicenna's Canon of Medicine*, *Kholase-Al-Hekmat (Summary of Wisdom)* by Aghili Khorasani, and *Al-Shamil fi al-Tibb (Comprehensive Medicine)* by Ibn al-Nafis have reported numerous GI indications for wormwood. Pharmacological studies have also confirmed a number of TPM GI benefits of wormwood.



Abstract

One of the most extensively used herbs in traditional Persian medicine (TPM) used in the treatment of gastrointestinal (GI) disorders, is the plant *Artemisia absinthium* Linn. (AAL). It also has a wide range of activities such as analgesic and anti-inflammatory, anti-oxidant, anti-fungal, and anti-bacterial activities, hepatoprotective, and neuroprotective activities in addition to having gastroprotective effects. This article is a review comparing TPM resources with new medicines. This review investigates this herb in major TPM sources and strives to extrapolate the exact function it serves in the digestive tract and compares the collected information on the function of AAL with information found in new medical resource databases such as ISI, Pubmed, Scopus, Google Scholar, and Scientific Information Database. AAL from the *Asteraceae* family of TPM, known as Afsentin, was used in the treatment of GI weaknesses, stomach pains, swellings, intestinal parasites, diarrhea, and vomiting. AAL increased appetite, so it was used for insect repellents and insecticide. Recent studies have indicated that the effects of this plant improved the symptoms of Crohn's disease and played a role in reducing inflammatory factors. It also has strong anti-parasitic, anti-insect, hepatoprotective, and antioxidant effects. Given the widespread use of AAL as a traditional medicine currently in use in different countries, particularly in the treatment of GI diseases, further clinical studies that focus on the therapeutic qualities of this plant are required in the future.

Key words: Medicinal plants, Persian medicine, Iranian traditional medicine, *Artemisia absinthium* Linn., Gastrointestinal disorder

Abbreviations:

TPM, traditional Persian medicine; AAL, *Artemisia absinthium* Linn.; GI, gastrointestinal.

Competing interests:

The authors declare that they have no conflict of interest.

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Background

In recent years, using medicinal plants has been one of the most controversial issues in pharmaceutical and medical studies [1]. Medicinal plants have been used for a long time in many countries to alleviate various human ailments. Thus, this extended usage has provided an invaluable database on the efficacy and safety of a vast number of plant species [2].

Artemisia absinthium Linn. (AAL) usually known as wormwood, and absinthe is a species of the *Artemisia* genus that belongs to *Asteraceae*. This plant has been used from antiquity to treat many human diseases, including hepatic, gastrointestinal (GI) disorders, central nervous system problems (headache, Bell's palsy, stroke, epilepsy, and mental disorders). Accordingly, various medicinal uses have been identified in numerous traditional medicine systems [3]. The first recorded medical use of wormwood dates back to the *Ebers Papyrus*, a primeval Egyptian medical text (1552 B.C.E.) that is recognized as the oldest preserved medical document [4, 5].

With respect to traditional Persian medicine (TPM), wormwood has a hot and dry temperament and has been repeatedly considered for the treatment of digestive diseases [3–9]. TPM textbooks such as *Avicenna's Canon of Medicine*, *Kholase-Al-Hekmat (Summary of Wisdom)* by Aghili Khorasani, and *Al-Shamil fi al-Tibb (Comprehensive Medicine)* by Ibn al-Nafis have reported numerous GI indications for wormwood. Pharmacological studies have also confirmed a number of TPM GI effects elicited by wormwood. AAL herbal extract and wormwood have been used as commercial clinical medicines from medieval to now in multiple countries. For instance, AAL is widely used in Unani medicine for the treatment of liver disease in India. Furthermore, in Iran, different herbal compounds use AAL for the treatment of anorexia and gastritis. In this review, the traditional uses of wormwood in TPM are compared to the collected information regarding the function of AAL, which is now available from new medical resources.

Morphology

AAL, commonly known as wormwood, *absinthium*, absinthe, absinthe wormwood, and grand wormwood, is an important species from the genus *Artemisia* (*Asteraceae*). Also, wormwood is known as Afsantin in TPM [10].

AAL is an aromatic, herbaceous perennial plant with straight, branched, grooved, and silvery-green stems, which grows up to 1.2 m on fibrous roots. The leaves have greenish-grey above and white below. The basal leaves are up to 25 cm long, pinnate tripinnate with long petioles. Flower heads (capitula) are hemispherical and nodding and are found in a

paniculate inflorescence. Flowers are yellowish-white and are found in bunches. Involucre contains oblong outer bracts and inner ovate bracts. Receptacles are hairy, but the corolla is glabrous [10–13] (Figure 1).

This plant can easily be cultivated in dry soil. Accordingly, it should be planted in an area with bright sun exposure and fertile mid-weight soil. This plant prefers soil rich in nitrogen and can be propagated by ripened cuttings taken in spring or autumn in temperate climates. AAL also possesses the ability for generous self-seeding. Therefore, it is naturalized in some areas outside of the native range, including many parts of North America and the Kashmir valley of India [14]. AAL plant growth sites are found in Iran, Mazandaran, Gilan, Azerbaijan, Kurdistan, Tehran, and Khorasan [1, 15].

Phytochemistry

Essential oils are significantly affected by geographical origin, and this variability in AAL species has been highlighted by several previous studies [16]. In Iran, the main components of the AAL essential oils are β -thujone (18.6%) and β -pinene (23.8%); while AAL oils of French origin contain chrysanthenyl acetate and (Z)-epoxyocimene as the major components. Moreover, in India, the main compounds include borneol, methyl hinokiate, and isobornyl acetate [16].

Growth conditions such as the elevation above sea level also affect the phytochemical properties, essential oils, and phenolic compounds in the plant [16]. The polyphenol components are herbal antioxidants and prevent free-radical-mediated diseases [17]. However, the concentration of flavonoids, phenolics, and tannins are more significant than the aqueous and chloroform extracts [18].

Phenolic compounds

Phenolic compounds present in the AAL are syringic acid, fisetin, isorhamnetin, and kaempferol [14]. The AAL phenolic acids include caffeic acid, chlorogenic p-hydroxyphenylacetic, protocatechuic, ferulic acid syringic gallic acid, p-coumaric, vanillic, and other phenols [19].

Sesquiterpene lactones

Sesquiterpene lactones elicit the characteristic bitter taste of this herb, which is ascribed to several sesquiterpene lactones, of which absinthin and artabsin are the main compounds. Furthermore, the activity of this AAL also relies on sesquiterpene lactones and their components, which include artabsin, absinthin (bitter glucoside), anabsinthin, artemetin, arabsin, artabinartabsinolides, matricin, isoabsinthin, artemolin, artenolide, parishin B, and parishin C, 24X-ethylcholesta-7,22-dien-3b-ol [14]. Most terpenes are antimicrobial and antiparasitic. Sesquiterpenes are also found in AAL and include α -bisabolol, matricin

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β -curcumen, and spathulenol.

The fatty acid

The fatty acid composition of the oil includes oleic and linoleic saturated acids (palmitic and stearic), and oxirane as the epoxy oleic acid. The seeds contain a mixture of acids, which includes 9-hydroxytrans, Trans,10,12-octadecadienoic acid, and 13-hydroxytrans, trans,9,11-octadecadienoic acid in a ratio of 2:1 [17].

Flavonoid compounds

Flavonoid compounds are significant components of flavonoids reported by analysis of the spectrophotometric manner of alcoholic extracts of absantin [17]. The flavonoids in the extracts include luteolin rutin, quercetin, apigenin, spinacetin, myricetin, artemitin, glycosides of quercetin (quercetin 3-glucoside, spinacetin 3-rhamnoglucoside, spinacetin 3-glucoside, quercetin 3-rhamnoglucoside, and others) [17]. *Lignans* are another group of polyphenolic substances in AAL derived from phenylalanine, include diayangambin and epiyangambinetc [17].

Volatile compounds

Volatile compounds include the volatile oils, and the most important are myrcene, sabinene, linalool, and trans-sabinyl acetate [14]. Monoterpene hydrocarbons are major compounds found in AAL and include oxygenated monoterpenes, sesquiterpene hydrocarbons, and oxygenated sesquiterpenes.

Sterolic compounds (phytosterols/sterols)

This herb is a rich source of sterols. Four types of sterols are found in AAL samples and are evaluated by chromatograms. Phytosterols in the AAL extracts are stigmasterol β -Sitosterol, campesterol, and ergosterol [14, 17]. Sitosterol and stigmasterol are the main sterols in this herb. These sterols are usually found in both the free and esterified forms.

Ethnopharmacology

The name AAL comes from primeval Greek, and *Artemis* stands for “the Goddess,” while *absinthium* represents both “unenjoyable” and “without sweetness.” The name wormwood refers to the anthelmintic effects of this plant, which have been recognized since ancient times [4, 12]. For intestinal worms, the entire plant, seeds, flowers, and roots are used to make herbal medicines in homeopathy, Ayurveda, Siddha, Unani, and even for use in modern medicine [12]. AAL was used for the treatment of hypertension and diabetes mellitus in the south-east area of Morocco (Tafilalet) [19]. It is also one of the herbs used in Mexican traditional medicine for the treatment of GI disorders [20, 21]. Also, studies have been conducted on the antipyretic effects of *artemisia* used in traditional

medicine from Pakistan [22, 23]. It is also known as an anti-cancer agent in traditional Chinese medicine [24]. Moreover, this herbal remedy is also used as an appetizer, or to treat indigestion, carminative problems, and the infusion leaves, or the flowers are used for mouth washing in Bulgaria [25].

Uses in Persian medicine

The medical and pharmaceutical uses of AAL in Persia date back to ancient times. Fruit oil and the aerial parts of AAL are among the most frequently mentioned herbal ingredients of TPM recommended remedies [26–30]. A broad spectrum of GI diseases, including GI ulcers, gastric inflammation, and swelling, diarrheal illnesses caused by gastric dysfunction, bacterial infections, and intestinal problems such as inflammatory bowel disease and colitis have been traditionally treated by Afsantin [31, 32]. In TPM, wormwood has been used to alleviate a wide range of ailments. AAL is used as an appetizer, astringent, diuretic, emmenagogue, and a cleansing agent for the pulmonary and thoracic blood vessels [33, 34]. Wormwood is also used to treat central nervous system diseases, including headache, Bell’s palsy, paralysis, tremors, epilepsy, stroke, vertigo, and nightmares. Moreover, it is used for the treatment of obstructions, hemorrhoids, anal fissures, alopecia, and otalgia [35].

Wormwood is locally applied to cure eye diseases, splenomegaly, intestinal worms, and hepatic problems. It is also used as an antidote for snake and scorpion bites and stings, hemlock, and mushroom toxicities [7]. The GI protective effects of AAL in TPM are mentioned by Razes, in his book *al Hawi (The Container)*[36].

Pharmacological research into gastrointestinal diseases

Antiparasitic

AAL extract has antiprotozoal effects against *Trypanosome brucei*, *Plasmodium falciparum*, *Trypanosome cruzi*, and *Leishmania infantum* [37]. Hydroxypelenolide, artemetin, and casticin are the most important components in AAL and are considered to have antiparasitic effects. Also, the antileishmanial action of flavonoids occurs in the presence of two hydroxyl groups on the molecule at C-3 and C-4, and this activity is missed when a methoxy is at C-3. The artemisin in the plant has antimalarial properties, and the plant has been used as anti-malarial since the distant past [38]. Oral extract of *Artemisia absentium* prepared with di-ethyl ether solvent is used in cats to reduce the excretion of the *Toxacara cati* parasite in the feces and causes cats to develop milder cases of toxocariasis [39].

Anti-worm

AAL is effective against roundworms and other types of worms [40]. The ethanolic extract of AAL causes a reduction in worm motility. Furthermore, previous studies have demonstrated via fecal egg count assay that these plant extracts affect the survival of the adult nematodes under in vitro conditions. A study on herbal remedies found that the anti-worming effect of the hydroalcoholic and alcoholic extracts of eucalyptus aqueous extracts in sheep GI nematodes was investigated in comparison with albendazole and significant anti-worm effects were found in the adult worms. Oral administration of aqueous extracts and crude ethanolic extracts of herbs administered to the sheep also significantly reduced the excretion of germinal nematodes in the stool [41].

Hepatoprotective

In a study, the hepatic effects of the aqueous extract of AAL on chemically and immunologically induced liver injuries in mice was investigated. This study strongly indicated that the protective effect of aqueous extract of AAL on acute liver injury might be due to antioxidative or immunomodulatory activity [42]. Also, an aqueous-methanolic extract of AAL (Compositae) is effective against acetaminophen- and CCl₄-induced hepatic damage [43]. Accordingly, the obtained results suggest that alcoholic extracts of *Artemisia* ameliorate liver toxicity in rats through reducing oxidative damage and the serum levels of AST, ALT [44].

Therapeutic effect on Crohn's disease

The results of using AAL in Crohn's disease-types of inflammatory bowel disease are promising [45]. In a study by Oomer et al. in 2007, AAL indicated a positive effect on the mood and quality of life of

Crohn's patients, as well as the estrogenic effects of this plant [46]. In another study on Crohn's disease, it was shown that AAL reduced the level of TNF and affected the mood of these patients [47].

Antioxidant

AAL extract has an antioxidant effect and inhibits free radicals [37]. In another study, the effect of aqueous extract of AAL on oxidative stress in lead hematotoxicity was investigated, and it indicated that aqueous extract of AAL had re-activated the enzymes that were damaged in the presence of lead and protected them against the oxidation of lipids [48]. The antioxidative activity was tested by the ability to scavenge stable 2,2-diphenyl-1-picrylhydrazyl free radical and reactive hydroxyl radicals during the 5,5 dimethyl-1-pyrroline-N-oxide, Fenton reactions, using electron spin resonance spectroscopy.

Anticancer

AAL ethanol extract selectively inhibited the growth of hepatocellular carcinoma without cytotoxic effects on the normal hepatic cells. AAL or derivatives of this herb have been introduced as potential cancer treatments that affect multiple pathways. They are known to detect the cell cycle, persuade apoptosis, and slow cell proliferation [49].

Insecticide properties

AAL prevents feeding by insects and, thus, can be used locally as an insect repellent [50]. The following types of fungus *Myzus persicae*, *Spodoptera littoralis*, and *Rhopalosiphum padi* have been isolated from this ex-fatal extract [51] (Table 1).



Figure1 Morphology of *Artemisia absinthium* Linn.

Table 1 Pharmacological activities reported from the *Artemisia absinthium* Linn.

Activity	Dosage form/ type of extract	Effective concentrations/ dosages	Model	Results	References
Hepatoprotective	Aqueous extract	50, 100, 200 mg/kg/day	In vivo (rat)	Decreased the lipid peroxidation in the liver tissue, hepatoprotective action through inhibiting microsomal drug metabolizing enzymes,	[42] [44]
	Hydroalcoholic extract	10,50,100mg/kg /day	In vivo (mice)	reduced the serum levels of AST, ALT, reduced the oxidative damage, and reduced hepatocellular necrosis.	
Antioxidant	Aqueous extract	200 mg/kg/day	In vivo (Human)	Repaired the activities of defense antioxidant enzymes glutathione peroxidase and SOD, disturbance by exposure to lead and had been a protective role against lipid peroxidation.	[43]
Antiparasitic	Di-ethyl ether extracts	0.3 and 0.6 mg/mL	In vitro	The fecal egg numbers per gram decreased gradually in the cats.	[39] [41]
	Aqueous extracts	300 and 600 mg/kg/day	In vivo (cat)	Treatment of GI nematodes of sheep	
	Crude ethanolic extracts	200mg/kg/day	In vivo (sheep)		
Anticancer	Ethanol extracts	25, 75, and 150 µg/mL	In vitro (hepatoma cells)	Reduced mitochondrial membrane potential ($\Delta\psi_m$), increased the release of cytochrome c and promoted the cleavage of caspase-3, caspase-9, and poly (ADP-ribose) polymerases.	[49]
Crohn's Disease	Dried powdered wormwood herb	3×750 mg/day	In vivo (human)	Increased production of pro-inflammatory cytokines like the TNF- α .	[46] [47]
		3×500 mg/day		A steady improvement in Crohn's disease symptoms.	

AAL: *Artemisia absinthium* Linn.; GI, gastrointestinal.

Prospective and conclusion

The present review summarizes the traditional ethnobotany uses and phytochemistry of AAL, particularly in the treatment of GI disorders. In traditional Iranian medicine, GI effects, such as anti-bloating, appetizer, tonic stomach, anti-parasite, and anti-fever, are mentioned for treatment with AAL [3, 9]. Further applications for this herb include hemorrhoids, fissure, and liver inflammation. To date, various types of *artemisia* have been used in local therapies to treat sputum, cough, blood circulation, worms, allergies, malaria, hepatitis, cancer, inflammation, fungal, bacterial, and viral infections

[48]. AAL, as a member of this genus, has a good hepatic protective effect, which can be attributed to the chlorogenic acid metabolites and quercetin derivatives identified in this aqueous extract. Conversely, treatment with an aqueous extract of AAL has significantly reduced the serum levels of TNF-, IL-1, and prevents tissue changes such as necrosis in the liver lobule and the infiltration of inflammatory lymphocytes, and macrophages in the tissue [47]. It has been reported that sesquiterpenes and flavonoids from the plant extract have anti-inflammatory properties [50]. Using *Artemisia* in the treatment of diseases has been applied in the past century, and the effects have been mentioned in folk medicine. Most of the articles on this plant include review articles on

ethnopharmacology and laboratory studies of the pharmacological effects and herbal substances. Considering the confirmation of the digestive effects of this plant in traditional medicine in different countries, *artemisia*-based clinical studies are expected to be accomplished on the treatment of inflammatory bowel disease, dyspepsia, and *Helicobacter pylori* treatment.

Considering the scientific findings on AAL and comparing them with Iranian sources of medicine, it can be observed that AAL has been of great importance in the treatment of many diseases, especially GI diseases. Thus, there is a need for a retrospective view of science in these resources, which would be a major task by pharmacologists and traditional pharmacists.

With respect to the above findings, use of this drug in traditional books and native medicine was found to be consistent with the new findings, and many of these studies may have roots in traditional and indigenous uses. This proves the value of this legacy from our ancestors as a potential current novel therapy or treatment

Although the pharmacological effects of *Artemisia* gastroenterology have been reported in Iranian medicine sources, there are few clinical studies that were accomplished in this area. Thus, it is necessary to design clinical trials based on this plant by combining traditional medicine resources with newer studies.

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