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Artemisia herba alba: A Popular Plant with Potential Medicinal Properties

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Abstract: *Artemisia herba alba* (Asteraceae), commonly known as desert or white wormwood, is used in folk medicine for treatment of various diseases. Phytochemical studies of this plant revealed the existence of many beneficial compounds such as herbalbin, cis-chryanthenyl acetate, flavonoids (hispidulin and cirsilineol), monoterpenes, sesquiterpene. The aerial parts are characterized by a very low degree of toxicity. This study reviews the main reports of the pharmacological and toxicological properties of *Artemisia herba alba* in addition to the main constituents. It would appear that this plant exhibits many beneficial properties. Further studies are warranted to more integrate this popular plant in human health care system.

Key words: *Artemisia herba alba,* ethnopharmacology, phytochemistry, toxicity

INTRODUCTION

The role of active principles present in medicinal plants and their mode of action in human and animal systems have been identified leading to elevating their status (Dutta, 1973). More importantly, herbal formulations are gradually taking a very important place due to their efficacy against a large repertoire of diseases and ailments without any notable derogatory effects (Kirtikar and Basu, 1984); and are readily available at affordable prices (Sharma *et al*., 2008). In addition, more than 70,000 species of the plant kingdom have been used as herbal medicine at one time or other (Purohit and Vyas, 2004).

The genus of *Artemisia* (Asteraceae family) has been used extensively in folk medicine by many cultures since ancient times (European medicine, North Africa and Arabic traditional medicine).

Several studies have reported many pharmacological activities of *Artemisia herba alba* (Ah), the main medicinal properties of Ah include anti-diabetic (Al-Khazraji *et al*., 1993), anti-spasmodic (Goze *et al*., 2009), antimicrobial (Zouari *et al*., 2010), antimalarial and antioxidant effects (Kadri *et al*., 2011). Many of the claimed folk medicinal uses of this plant have been tested. This study tries to present a brief overview of the available literature on the main phytochemical, pharmacological and toxicological properties of *Artemisia herba alba*.

DESCRIPTION AND ECOLOGY

Among 400 species of *Artemisia* genus, *Artemisia herba alba* (Ah) is a perennial shrub. The leaves are hairy, silvery, small and deeply, bi-pennated with linear strips. The flowering starts from September to December and basically develops at the end of the summer with many basal, erect and leafy stems covered by woolly hairs. This plant grows commonly on the steppes of northern Africa (Morocco, Algeria and Tunisia), Egypt, Sinai desert, Middle East, western Asia, the Canaries and south-eastern Spain.

The white wormwood develops in bioclimatic stages which range from the upper semi-arid to the lower Saharian prevailing on salt soils and poorly drained areas (Wengler and Vernet, 1992). It has a seasonal dimorphism, losing its wide winter leaves at the beginning of the dry season and replacing them with smaller summer leaves whose anatomical structure is different.

PHARMACOLOGICAL PROPERTIES

Ah has been described to be used in folk herbal medicine around the world for the treatment and prevention of a number of diseases. During the past two decades, many ethnopharmacolocal surveys as well as phytopharmacological studies conducted in different regions have reported the importance of this plant in the traditional medicine (Table 1).

ANTIDIABETIC EFFECT

In the folk medicine many plants are used to control diabetes (Eddouks *et al*., 2002; Tahraoui *et al*., 2007; Almasad *et al*., 2007; Ziyyat *et al*., 1997). In Morocco, *Artemisia herba alba* locally called "*chih*" is used as flavoring for tea and is considered as an important medicinal plant used for the treatment of some diseases such as diabetes (Twaij and Al-Badr, 1988; Abu-Irmaileh and Afifi, 2003; Jouad *et al*., 2001; Hudaib *et al*., 2008; Alzweiri *et al*., 2011; Azaizeh *et al*.,

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Table 1: Main medicinal properties of *Artemisia herba alba*

Pharmacological activity	Materials or patients	Part of plant used	References
Antidiabetic	Wistar rats	Aerial parts	Al-Khazraji *et al.* (1993)
	Rats, rabbits		Al-Shamaony *et al.* (1994)
	Rabbits		Twaij and Al-Badr (1988)
	C57BL/6J mice		Hamza *et al.* (2010)
	Rats		Wang and Ng (1999) and Al-Khazraji *et al.* (1993)
	Patients		Al-Waili (1986)
	Rabbits		Twaij and Al-Badr (1988)
Antihypertensive	Rats	Aerial parts	Skiker *et al.* (2010)
	Aorta of SH* rats		Farid *et al.* (2009)
	SH rats		Zeggwagh *et al.* (2008)
Antioxidant	Rats	Aerial parts	Abid *et al.* (2007)
	DPPH and ABTS assays	Shoot aerial parts	Al-Mustafa and Al-Thunibat (2008) and Kadri *et al.* (2011)
Antifungal activities	*Penicillium citrinum* and *Mucora rouxii*	Leaves	Saleh *et al.* (2006)
Against *Enterobius vermicularis* infection	Patients	Aerial parts	Al-Waili (1988)
Neurological	*In vitro*	Aerial parts	Salah and Jager (2005a), Salah and Jager (2005b)
Anti-malarial	*Leishmania tropica* and *Leishmania major*	Aerial parts	Hatimi *et al.* (2001) and Rocha *et al.* (2005)
Antispasmodic	Wistar Rats	Aerial parts	Goze *et al.* (2009)
	Rabbits	Aerial parts	Yashphe *et al.* (1987)
Immuno-modulatory	Patients	Aerial parts	Messaoudene *et al.* (2011)
Antimycoplasmal	*In vitro*	Aerial parts	Al-Momani *et al.* (2007)
Against the larvae	Larvae of Chrysomyia albiceps	Whole plant	Abdel-Shafy *et al.* (2009)

*SH: Spontaneously hypertensive

2003). A previous study has demonstrated that the aqueous extract of the aerial parts of Ah caused a significant fall in plasma glucose levels in both normoglycemic and alloxanized rabbits (Twaij and Al-Badr, 1988). In addition, another study has demonstrated that the Ah extract had a clear preventive effect on the appearance and development of insulin resistance without affecting body weight (Hamza *et al.*, 2010). In the last study, Ah seems to act as antidiabetic by restoring insulin sensitivity. Furthermore, aerial parts of Ah have been shown to act as an anti-diabetic agent and exerted a significant hypoglycaemic action (Wang and Ng, 1999). The same result has been shown by Al-Shamaony *et al.*, (1994) who confirmed that the aqueous extract of the aerial parts of Ah for 2-4 weeks caused a significant reduction in blood glucose level and prevented a significant elevation of glycosylated haemoglobin level without any body weight loss in diabetic animals. These results appear to be different with those shown by Marrif *et al.* (1995) who reported that the aqueous extract of Ah caused an initial and transient hyperglycaemic effect in normal mice and rabbits. Another study has shown that the oral administration of the aqueous extract of the leaves or barks of Ah produced a significant reduction in blood glucose level. However, the same result has not been obtained by the use the ethanolic and chloroform extract of whole plant (Al-Khazraji *et al.*, 1993).

CARDIOVASCULAR ACTION

On the other hand, Ah is widely used in the folk medicine as antihypertensive (Ziyyat *et al.*, 1997; Eddouks *et al.*, 2002; Tahraoui *et al.*, 2007; Skiker *et al.*, 2010). The antihypertensive activity of aqueous Ah extract has been demonstrated in spontaneously hypertensive rats with an increase in urinary volume and electrolyte output (Zeggwagh *et al.*, 2008). In addition, it has been shown that the aqueous Ah extract at a dose of 20 mg mL^{-1} possess *in vitro* vasorelaxant effect in aortic rings isolated from spontaneously hypertensive rats (Farid *et al.*, 2009). Recently, a study has demonstrated that aqueous Ah extract exhibited an endothelium dependent relaxation of the isolated rat aorta (Skiker *et al.*, 2010). In addition, it has been shown that 100 μg mL^{-1} of Ah essential oil exhibited an inhibitory activity on Angiotensine Converting Enzyme (ACE) *in vitro* (Zouari *et al.*, 2010). ACE inhibition is considered to be a useful therapeutic approach in the treatment of high blood pressure and hypertension complications.

ANTIMICROBIAL, ANTIOXIDANT AND ANTIRADICAL ACTIVITIES

The antimicrobial activity of Ah has been tested. For example, it has been noted that all examined essential oils of Ah had a great potential on antimicrobial activity against strains of *Staphylococcus aureus*, *Micrococcus luteus, Escherichia coli, Salmonella typhemirium, Bacillus cereus, Enterococcus faecalis.* In addition, the antimicrobial activity of Ah has been confirmed in some yeast strains of *Candida* (*C. albicans, C. glabrata, C. tropicalis* and *C. sake*) (Mighri *et al.*, 2010a). The antimicrobial and antifungal activities of Ah have been demonstrated by measuring the diameter of the zones

inhibition of several microorganisms, the results obtainedwere significant and comparable to the Gentamicin antibiotic (Mighri *et al*., 2010a). Furthermore, a stronger growth inhibitory activity of the plant on many fungi has been demonstrated; the antifungal activities were tested using *Fusarium solani, Fusarium sp*, *Aspergillus oxysporum* and *Candida albicans* (Zouari *et al*., 2010).

Plants often contain wide variety of antioxidant molecules, such as phenolic acids, flavonoids and other natural antioxidants. Generation of free radicals may be, at least partially, the basis of many human diseases and conditions. Therefore, the antioxidant action of Ah may explain its claimed usefulness in folk medicine. Ah yields an aromatic essential oil which is rich in monoterpenes and sesquiterpene lactones widely distributed in plants and possess anti-inflammatory and anticarcinogenic activities.

It has also shown that Ah essential oils were found to have some antioxidant abilities for preventing the linoleic oxidation and to reduce DPPH radicals (2,2-diphenyl-l-1-picrylhydrazil) and stable ABTS radicals (2,20 azinobis-3-ethylbenzthiazoline-6- sulphonic acid). This effect seems to be due to the rich phenolic compounds in Ah (Al-Mustafa and Al-Thunibat, 2008; Kadri *et al*., 2011; Tawaha *et al*., 2007). Additional studies have confirmed the antioxidant effect of Ah (Zouari *et al*., 2010; Akrout *et al*., 2010).

ANTI-SPASMODIC ACTIVITY

Phytochemical study has demonstrated that the essential oil of Ah exhibited antispasmodic activity (Yashphe *et al*., 1987). The Ah essential oils have showed marked antispasmodic effects on rabbit jejunum and contain also eucalyptol, this natural molecule had a potent antispasmodic activity (Yashphe *et al*., 1987). This type of antispasmodics is used for smooth muscle contraction, especially in tubular organs of the gastrointestinal tract. Both dicyclomine and hyoscyamine are known to be antispasmodics due to their anticholinergic action (Yashphe *et al*., 1987). Both of these drugs have general side effects and can worsen gastroesophageal reflux disease (Yashphe *et al*., 1987).

The antibacterial and the antispasmodic effects may explain the extensive use of Ah in folk medicine.

Neurological action: Recently, medicinal plants are traditionally used to treat neurological disorders such as Alzheimer's disease, epilepsy and affective disorders like depression. The neurological activity was tested by evaluating the inhibition of acetylcholinesterase and affinity to the GABA (A)-benzodiazepine site and to the serotonin transporter.

Alzheimer's disease, the major degenerative disorder of the elderly, causes millions of victims worldwide. This disease and other nervous disorders are traditionally treated by Ah (Salah and Jager, 2005a, b). For example, ethanolic extract of Ah had good affinity to the GABA (A)- benzodiazepine receptor site. Dinatin and skrofulein, two flavones extracted from Ah, inhibited the binding of [methyl-3H] diazepam to rat brain membranes *in vitro* with IC_{50} of 1.3 and 23 μM, respectively. The GABA ratios (the ratio of IC_{50} values in the absence/presence of GABA in the binding assay) were 1.1 and 1.2 for dinatin and skrofulein, respectively (Shen *et al*., 1994). Both flavones induced a slight increase in [^{35}S] *TBPS* binding. The data suggest that the flavones are antagonists of benzodiazepine receptors (Shen *et al*., 1994).

TOXICOLOGICAL PROPERTIES

The toxic effects of *Artemisia herba alba* have been studied by evaluating the effect of acute and chronic administrations of aqueous Ah extract on the reproductive system (Almasad *et al*., 2007). In the last study, the toxic effects of Ah were measured in terms of number of pregnant rats, implantation sites, viable fetuses and resorption site. The results suggested that ingestion of Ah by adult female rats (Sprague-dawley Rats) did not have a negative effect on fertility without the increase in ovarian weights and a decrease in viable fetus's number. Another study has found that the LD_{50} of the aqueous extract of the aerial parts of the plant was 4.4 g kg^{-1} b.wt (Al-Khazraji *et al*., 1993).

Some studies concerning renal toxicity insist that there is no case of renal injury caused by Ah, but recently, another study revealed an exceptional case of acute renal failure (Aloui *et al*., 2010). The mechanism by which the plant constituents injure the kidney is still unknown.

CONSTITUENTS

Sesquiterpene lactones: Sesquiterpene lactones constitute a large and diverse group of biologically active plant chemicals which have been identified in several plant families. However, the greatest numbers are found in the Compositae family with over 3000 reported different structures. Plants containing sesquiterpene lactones have been used in some cultures to treat certain medical problems (Wu *et al*., 2006). These secondary compounds are primarily classified on the basis of their carbocyclic skeletons into germacranolides which seem to be the most abundant types of lactones found in *Artemisia* species; guainalides, eudesmanolide, pseudogua inolides and xanthonolides. There are more than 4000 Sesquiterpene lactones with known structures (Wu *et al*., 2006). The genus *Artemisia* contains this biologically active type of

Table 2: Some types of sesquiterpene lactones of Ah and geographical location

Type of sesquiterpene lactone	Country	References
Herbolides A, B,C,D,E,F,G,H and I		Segal *et al.* (1987)
Deacetylherbolides A		
3 oxo 11 β tatridine D	Palestine	Mohamed et al. (2010)
11 α-H-gallicin		
Torrentin		
Santonin		
Dihydroreynosin		
11-Epitaurin		
Vachanic acid		
α,13-Dihydrocostunolide		
11 β,13-Di-Hydrodouglanin acetate		
11 α,13-Dihydroreynosin		
11-Epiartesin		
3-Epi-erivanin		
α-Hydroxy-7 α -eudesma-4(15),11(13)-dien-12-oic acid		
1 β,8 α -Dihydroxyeudesm-4-en-6 β,7 α,11 β H-12,6-olide		
5 α H, 11 α,13-Dihydrosantamarin		
1 β -Hydroxy-11-epicolartin		
5 α H,13-Dihydro-β -cyclocostunolide		
11-Epitorrentin		
1 β -Hydroxy-4,11-diepicolartin		
1,11-Diepitorrentin		Segal *et al.* (1987)
1-Oxo-2 α,3 α,4 α,5 α-diepoxyeudesman-11 β H-12,6 α-olide		
1 β -Hydroxy colartin		
11-Epicolartin	Spain	Mohamed *et al.* (2010)
Deacetyltorrentin		
1 β -Hydroxy-3 β -propionyloxy-6 β,7 α,11 β H-eudesm-4-en-12,6-olide		
1 α -Hydroxy-3 β -propionyloxy-6 β,7 α,11 β H-eudesm-4-en-12,6-olide		
11-Epi-deacetyltorrentin,		
11-Epishonachalin A		
1-Oxo-4 α,5a-Epoxyeudesm-2-en-11 β H-12,6 α -olide		
1-Oxo-8 α -Hydroxy-4 α,5 α - epoxyeudesm-2-en-11 β H-12,6 α -olide		
1-Oxoeudesma-2,4-dien-11 α H-12,6 α -olide		
1-Oxoeudesma-2,4-dien-11bH-12,6 α -olide		
1-Oxo-8 α -hydroxyeudesma-2,4-dien-11 α H-12,6 α -olide		
1-Oxo-8 α -hydroxyeudesma-2,4-dien-11 β H-12,6 α -olide		
1-Oxo-15-hydroxyeudesma-2,4-dien-11bH-12,6 α -olide		
1-Oxo-2 α,5 α -peroxyeudesm-3-en-11 α H-12,6a-olide		
1-Oxo-2a,5a-peroxyeudesm-3-en-11 β H-12,6 α -olide		
1-Oxo-8 α -Hydroxy-2 α,5 α -peroxyeudesm-3-en-11 β H-12,6 α -olide		
1-Oxogermacra-4,10(14)- dien-6 β,7 α,11 α H-12,6-olide		
1 β -Hydroperoxy-8 α -hydroxygermacra-4,10(14)-dien-6 β,7 α,11 β H-12,6-olide		
2 β -Hydroxy-13-oxo- α -cyperene		
1 β,5,12-Trihydroxygermacra-1(10), 4(15), 11(13)-triene		
3 β -Hydroxy-8-oxo-6 β H,7aH,11 β Hgermacran-4(14),9(10)-dien-6,12-olide		
7-Hydroxy-5,6-dehydro-4,5-dihydrolyratrol		
2,6,10-Trimethyl-Cis-7,10-oxido-dodeca-3E,11-dien-2-ol-5-one		Segal *et al.* (1987)
5 α -Hydroxy-11,13-dihydroreynosin acetate	Egypt	
9 β -Hydroxy-11,13-dihydroreynosin		
5 β,9 β-Dihydroxy-1-Oxo-germacra-1(10),4(15)-dien-12,6-olide		Mohamed *et al.* (2010)
1 β -Hydroxy-6bH,7 α H,11 α H-germacran-4(5)-10(15)-dien-6,12-olide		
3 β, 8 α-Dihydroxy-6 β H,7 α H,11 β H-germacran-4(14),9(10)-dien-6,12-olide		
Santonin		
Herbalbin		
(3 R,4S,7R)-3,7-Dimethyl-4,7-epoxynon-8-enoic acid		Boriky *et al.* (1996)
1-Oxo-9 β-Acetoxygermacra-4,10(14)-dien-6 β,11bH-12,6-olide		
1-Oxo-9 β-Hydroxgermacra-4,10(14)-dien-6 β,11 β H-12,6-olide	Morocco	Mohamed *et al.* (2010)
Deacetylherbolide D		
1 β -Hydroxy-9 β -acetoxygermacra-4,10(14)-dien-6 β,11bH-12,6-olide		
1 β,9 β -Diacetoxyeudesm-4-en-6 β,11 β H-12,6-olide		
1 β,9 β -Diacetoxyeudesm-3-en-6 β,11 β H-12,6-olide	Algeria	Mohamed *et al.* (2010)

secondary metabolites (Mehrdad *et al*., 2007). Interestingly, there are large differences in chemotypes of sesquiterpene lactone constitution between countries and regions according to the properties of geographical location, soil and climate. Consequently, there are many groups of sesquiterpene lactones of Ah growing in Spain, Morocco, Algeria, Tunisia, Egypt, Palestine and Jordan (Mohamed *et al*., 2010) (Table 2).

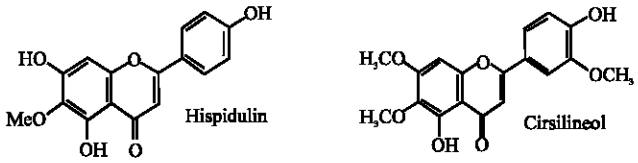

Fig. 1: Chemical structures of some major flavonoids of *Artemisia herba alba*

Phenolic compounds and flavonoids: The flavonoids detected in Ah show a large structural variation ranging from common flavone and flavonol glycosides to more unusual highly methylated flavonoids such as Hispidulin and Cirsilineol which possess an anti-proliferative activity against multiple types of cancer cells (Sheng *et al*., 2008; He *et al*., 2011) (Fig.1).

The aerial parts of the Ah contain other flavonoids such as Vicenin-2, Schaftoside, Isoschaftoside, 5`,4-Dihydroxy-6,7,3-trimethoxyflavone, Quercetin-3-rutinoside, Pultetin 3- rutinoside and Pultetin 3-glucoside.

Essential oils: The Ah essential oils, obtained by hydrodistillation from aerial parts, have been well investigated (Akrout *et al*., 2010; Bezza *et al*., 2010). There is a large diversity in oil composition from plants grown in different countries and sometimes in different localities of the same country. However, the major components of Ah oil appear to be monoterpoids mainly the oxygenated types such as 1,8-cineole, chrysanthenone, chrysanthenol (and its acetate), α and β-thujones and camphor as. In Morocco, the Ah oil is known generally to be characterized by substantial levels of ketones such as α and β thujones and camphor (Chaouch and Charrouf, 2010). More recently, a study has revealed that the essential oil of the Algerian Ah contained in majority: cis-chrysanthenyl acetate (25.12%); (2E, 3Z) 3,5-heptadienal-2-ethyliden-6-methyl (8.39%); α-thujone (7.85%); myrtenyl acetate (7.39%); verbenone (7.19%) and chrysanthenone (4.98%) (Laid *et al*., 2008). While the major components of the Tunisian Ah essential oil extracted from aerial parts are the oxygenated monoterpenes, cineole, thujones, borneol and sabinyl acetate (Mighri *et al*., 2010b; Zouari *et al*., 2010; Mohsen and Ali, 2009). In addition, in Spain, a study has revealed that monoterpene hydrocarbons and oxygenated monoterpene are the most abundant skeletons in Ah oil (Salido *et al*., 2004; Abad *et al*., 2012).

The different compounds responsible of the pharmacological activity of Ah may act individually or in a synergistic manner.

CONCLUSION

The present review reports the main and important pharmacological activities of Ah including antidiabetic, cardiovascular, antimicrobial, antioxidant, antiradical, anti-spasmodic and neurological activities. However, the precise underlying mechanism(s) of action of these pharmacological activities are still remained to be determined. In addition, the phytochemical studies have clearly demonstrated that the main constituents of Ah are sesquiterpene lactones, phenolic compounds, flavonoids and essential oils with an intraspecific variability of these constituents depending on the geographical area. The available toxicological investigations have shown generally that Ah is free from toxic effects at least at the doses used in the studies. Finally, additional investigations dealing with the study of active principle/pharmacological activity are needed in order to support the valorization of this popular medicinal plant in human health care system.

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