



THE PHARMACOLOGICAL AND THERAPEUTIC IMPORTANCE OF *AGRIMONIA EUPATORIA*- A REVIEW

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ABSTRACT

The phytochemical analysis of *Agrimonia eupatoria* revealed the presence of carbohydrates, glycosides, tannins, terpenoids, phenolic compounds (flavonoids), agrimony, agrimony lactone, oils and many other bioactive chemical groups. It exerted antibacterial, antiviral, antitumor, analgesic, antioxidant, immunomodulatory, antidiabetic, gastrointestinal, hepatoprotective, wound healing and many other pharmacological effects. This paper will highlight the chemical constituents and the therapeutic potential of *Agrimonia eupatoria*.

Key words: *Agrimonia eupatoria*, Constituents, Pharmacology.

INTRODUCTION

The phytochemical analysis of *Agrimonia eupatoria* revealed the presence of carbohydrates, glycosides, tannins, terpenoids, phenolic compounds (flavonoids), agrimony, agrimony lactone, oils and many other bioactive chemical groups. It exerted antibacterial, antiviral, antitumor, analgesic, antioxidant, immunomodulatory, antidiabetic, gastrointestinal, hepatoprotective, wound healing and many other pharmacological effects.

Synonyms

Agrimonia adhaerens Gilib., *Grimonia adscendens* Andr., *Agrimonia alba* hort. ex Gizycki, *Grimonia bracteosa* E.Mey., *Agrimonia canescens* Dumort., *Agrimonia elata* Salisb., *Agrimonia eupatoria* subsp. *eupatoria*, *Agrimonia eupatoria* var. *fallax* Fiek, *Agrimonia eupatoria* var. *humilis* (Wallr.) Asch. & Graebn., *Agrimonia eupatoria* var. *longifolia* Wallr., *Agrimonia eupatoria* var. *major* Mutel, *Agrimonia eupatoria* var. *major* K.Koch, *Agrimonia eupatoria* var. *minor* (Mill.) Sol., *Agrimonia eupatoria* var. *ochroleuca* Ostenf., *Agrimonia eupatoria* subsp. *officinalis* (Lam.) Gams, *Agrimonia eupatoria* var. *rotundifolia* Wallr., *Agrimonia eupatoria* var. *sepium* Br,b., *Agrimonia eupatoria* var. *sylvatica* Čelak., *Agrimonia humilis* Wallr., *Agrimonia minor* Mill., *Agrimonia odorata* auct., p.p.408, *Agrimonia officinalis* Gaterau, *Agrimonia officinarum* Lam., *Agrimonia*

sulcata Dulac, *Agrimonia vulgaris* Gray, *Eupatorium dioscoridis* Bubani [1].

Taxonomic classification

Kingdom: Plantae; Subkingdom: Viridiplantae; Infrakingdom: Streptophyta; Division: Tracheophyta; Subdivision: Spermatophytina; Infradivision: Angiospermae; Class: Magnoliopsida; Superorder: Rosanae; Order: Rosales; Family: Rosaceae; Genus: *Agrimonia*; Species: *Agrimonia eupatoria* [2].

Common names

Arabic: Ghafith, Ghafith Gowlani, Agramon, Fatron, Hasheesha Shulghafiz, Shajrat-el-baraghis, Shaukat-el-muntined; English: Agrimony, Stickle wrote, Cocklebur, Stickwort; French: Agrimoine, Aigremoine, Eupatoire des Grecs, Eupatoire des anciens; German: Ackermennich, Adermennich, Beerkratu; Greek : Iporian Indochina: Chi hao, Long gia, Long nha thao; Hindi: Ghaafis Gujarati: Tiryamau; Italian: *Agrimonia*, *Eupatorio de Greci*; Persian: Ghafat; Roumanian: Turice, Turilamure; Russian: Reneinik, Reniashok; Sanskrit: Tiryatika, Loadev, Balbhada; Unani: Ghaafis; Urdu: Ghaafis [3-4].

Description

The plant: is slim, erect leafy perennial herb. The stem is about 60-90 cm long, scarcely branched. The herbs deep green, covered with soft silky hairs and when slightly bruised exhaling a peculiar, but pleasant aromatic odour. The whole plant yields a dye. **Leaves:** Leaves are pinnately

compound. Lower leaves 10-18cm; leaflets 6-21 in number coarsely toothed, hairy on both surface very unequal, large ones 5-9 elliptic, ovate or obovate rarely orbicular or minute. 1.3-3.8cm intermixed with a number of much smaller ones. Upper leaves gradually smaller and with few leaflets. Stipules adnate to the base of leafstalk. **Flowers:** Flowers very numerous 6.0mm in diameter, yellow in colour and terminal spike-like racemes. Each flower in the axial of a small, 3-cleft bract and with two smaller, 3-toothed bracteoles at the tops of stalk. Calyx-tube top-shaped, grooved, bearing outside its mouth a ring of small, hooked bristles; limb 5-lobed. Petal 5, oblong. Stamen 15, Carpels 2, free, enclosed within the calyx tube; styles thread like protruding; stigmas terminal, dilated; ovule solitary. Achenes 1 or 2, in closed in the hardened bristly calyx crowned with a ring of hooked bristles. **Fruits and Seed:** Fruits pendulous, of 1 or 2 achenes in closed in the hardened spinous calyx. Calyx of fruits encircled with a thick whorl of hooked prickles, which attach themselves to anything that comes in their way. Flowers appear in about July and August, soon after the seeds become mature. Each flower contains two seeds. It is astringent and bitter in taste (3,5-8).

Distribution: The plant is indigenous to middle and northern Europe, temperate Asia and north America [9].

Traditional uses

The name *Agrimonia* may have its origin in the Greek (*agremone*), which refers to plants which supposedly healed cataracts of the eye. The species name *eupatoria* relates to Mithradates Eupator, King of Pontus, who is credited with introducing many herbal remedies. Its ancient uses include treatment for catarrh (mucous membrane inflammation with discharge), bleeding, tuberculosis and skin diseases. It has been reported to be useful in gallbladder disorders. Numerous other reported uses include a dye, flavoring, gargle for performers and speakers, antitumor agent, astringent, cardiogenic, coagulant, diuretic, sedative, antiasthmatic and for corns or warts [10-11]. It was also used as anti-inflammatory, cholagogue, mild haemostatic, antibacterial, for irritations and infections of the intestinal tract, gallbladder diseases, hyperacidity, colic, urinary disorders (bedwetting, incontinence), sluggish liver, mucus membrane inflammations and externally for ulcerations [11].

Part used: All the parts of the herb were used medicinally [9,11-12]

Physicochemical properties

Total Ash: not more than 10%, acid insoluble ash: not more than 2% and water soluble extractive: not less than 12% [13].

Chemical constituents

The phytochemical analysis of the aerial parts of the plant revealed the presence of carbohydrates, tannins, terpenoids, phenolic compounds (flavonoids), agrimony, agrimony lactone, glycosides and oils [14-16]. Aerial parts were also contained 3% to 21% condensed tannins, polysaccharides, triterpenoid (α -amyrin, ursolic acid, euscaptic acid), silicic acid, salicylic acid, traces of essential oil, flavonoids, organic acids, ascorbic acid, nicotinamide complex (about 100-300 pg/g leaf), thiamine (about 2 μ g/g leaf) and vitamin K. The fresh herb contained agrimoniolide, palmitic and stearic acids, ceryl alcohol, phytosterols and volatile oil 0.2%. Seeds contained oil consisted of oleic, linoleic and linolenic acids [17-19].

The volatile constituents in the root and leaf of *Agrimonia eupatoria* were included (% of the total): α -Pinene 8.31, Hexanal 0.05, β -Pinene 1.27, Camphene 3.21, 3-Octanol 0.27, Cymene 0.18, D-Limonene 1.29, Eucalyptol 3.26, α -trans-Ocimene 0.51, Linalool 5.72, α -Campholenal 0.72, L-Camphor 2.11, Borneol 0.07, 4-Terpineol 1.47, α -Terpineol 4.21, p-Menth-1-en-4-ol 0.06, Pulegone 0.17, 3,4-Dimethylbenzaldehyde 0.41, 2,4-Dimethylbenzaldehyde 0.72, 2-Cyclopropylidene-1,7,7-trimethyl-bicyclo [2,2,1] heptane 0.52, 1-(2-Furyl)-1-hexanone 4.87, Bergamot oil 1.42, Nonanoic acid 0.06, 2-Methyl-4-hydroxyacetophenone 0.10, Thymol 0.82, Carvacrol 0.44, Anethole 0.07, Bornyl acetate 3.72, Neryl acetate 0.47, Geraniol acetate 0.61, Furan, 2,5-dibutyl 0.04, Decanoic acid 0.06, Eugenol methyl ether 0.52, α -Cedrene 2.87, α -Longipinene 1.42, Caryophyllene 0.81, β -Cedrene 0.14, Geranyl acetone 0.84, Copaene 0.05, Longofolene 0.11, Aromadendrene 0.42, Curcumene 0.72, β -Selinene 0.92, α -Selinene 0.47, δ -Guaiene 0.61, α -Himachalene 0.13, α -Bisabolene 0.42, Acoradiene 0.23, τ -Cadinene 0.43, Cuparene 0.37, Myristicin 0.45, α -Guaiene 0.09, trans-Nerolidol 0.22, e-Cadinene 0.92, Caryophyllene oxide 0.58, δ -Cadinene 1.53, Cedrol 14.37, epi-Cedrol 1.15, Muurolol 0.46, α -Cadinol 1.43, Patchoulol 2.17, Epiglobulol 0.08, Cubenol 0.72, Cedryl acetate 0.76, Torreyol 0.38, Farnesyl acetate 1.73, α -Eudesmol 0.06 and 14-Trimethyl-2-pentadecanone 1.24 [20].

Kurkina found that the flavonoid content of common Agrimony herb ranged from 1.22% to 1.40% [21]. The flavonoids extracted from the plant were differ according to the source of the plant, Lee *et al.*, isolated ten flavonoids including kaempferol 3-O- β -D-(200 - O-acetyl)glucopyranoside, tiliroside, astragalin, apigenin 7-O- β -D-glucuronide, rutin, iso- quercitrin, quercitrin, luteolin 7-O- β -D-glucuronide, and luteolin 7-O- β -D-glucopyranoside [22]. However, the phenols isolated by Zhang *et al.*, were included: apigenin-7-O- β -D-glucopyranoside, catechin, quercetin, rutin, kaempferol-3-O- α -L-rhamnoside, Kaempferol-3-O- β -D-glucopyranoside, luteolin-7-O- β -D-glucopyranoside, 19 α , 24-dihydroxy ursolic acid, 3,3'-di-O-methyl ellagic acid-4-O- β -D-glucopyranoside [23]. While, Correia *et al.*, isolated flavan-3-ols (catechin

and procyanidins B1, B2, B3, B6, B7, C1, C2 and epicatechin-epicatechin-catechin), quercetin 3-O-glucoside, quercetin 3-O-galactoside, kaempferol 3-O-glucoside, kaempferol 3-O-(6"-O-p-coumaroyl)-glucoside, apigenin 6-C-glucoside [24]. Shabana *et al.*, found that the plant contained tannins (10.08%), flavonoids (0.33%) and phenolic acids (2.26%) (luteolin 7-O-sophoroside, luteolin 7-O (6"- acetylglucoside), acacetin 7-O-glucoside, luteolin 7-O-glucoside and apigenin 7-O-glucoside, protocatechuic, vanillic acids, p-hydroxybenzoic acid) [25].

Pharmacological effects

Antibacterial effect

Marked antibacterial activity against *Staphylococcus aureus* and α -haemolytic *Streptococci* has been reported for Agrimony [26]. Aqueous extracts inhibited *Mycobacterium tuberculosis*, including the strains resistant to streptomycin and p-aminosalicylate. Essential oil was antibacterial, it was active against *Bacillus subtilis* [11].

The antibacterial (against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*) and wound healing effects of the extracts of *Agrimonia eupatoria* (aqueous and ethanolic) were studied. The results showed that the ethanolic extract was more effective on inhibiting the tested bacteria than the aqueous extract. *P. aeruginosa* was the most resistant bacteria, while highest inhibition zone appeared against *E. coli* (20 mm). There was a moderate activity against *S. aureus* with inhibition zone of 15 mm [14].

Preparations of *Agrimonia eupatoria* were screened for antimicrobial activity against selected Gram-positive and Gram-negative bacteria of relevance in wounds using a 96 well plate microdilution method (200, 40 and 8µg/ml). It exerted moderate antibacterial effects [27].

Antiviral effect

Ethanolic extract of *Agrimonia eupatoria* was reported to be active against Columbia SK virus [7,11]. The Inhibitory activity of an aqueous extract of the aerial parts (stems and leaves) of *Agrimonia eupatoria* against hepatitis B virus (HBV) was investigated. The extract prepared at 60 degrees °C was found to have the greatest effect. The inhibitory activity of *Agrimonia eupatoria* extracts on HBsAg secretion varied over the growing season and was the highest at mid-July. This inhibitory activity suggest that *Agrimonia eupatoria* contain potential antiviral activity against HBV [28].

Wound healing effect

Prepared ethanolic extract ointment showed wound healing activity in rats in contrast with fucidin ointment and aqueous extract ointment, hence the wound healing was completed in 10 days by using the ethanolic extract ointment, while the healing was completed in 12 and 14 days for the aqueous extract and fucidin ointments

respectively, while, the untreated wound needed more than 16 days for healing completion [14].

Antitumor effect

The anti-tumor (human cervical cancer; HeLa and Rhabdomyosarcoma; RD cell lines and a primary cell culture; mouse embryo fibroblast; MEF) potentials of *Agrimonia eupatoria* L. extracts (aqueous and methanol) was studied. Five concentrations (6.0, 12.0, 24.0, 48.0 and 96.0 µg/ml) of each plant extract were assessed for three incubation time periods (24, 48 and 72 h) for HeLa and RD cell lines, or one incubation time period (48 h) for MEF cells. The results revealed that the five concentrations of plant extracts showed anti-tumor properties in a concentration-dependent manner, and the methanol extract recorded better values of percentage of growth inhibition (PGI) than aqueous extract in HeLa and RD cell lines, while, less PGI values were recorded in the MEF cells. Among these concentrations, 96.0 µg/ml was the most effective in producing PGI in RD and HeLa cancer cell lines for the three investigated time periods [29].

Analgesic effects

The peripheral analgesic and anti-inflammatory properties of Agrimony was studied in *in vivo* models. It had no central analgesia effects, but in the writhing test, the percentage of inhibition was 43.5% (single dose) and 49.8% (double dose) for the ethyl extract and 29.2% (single dose) and 46.8% (double dose) for the ethyl acetate fraction. The formalin test confirmed these results. The paw oedema test showed that both doses (single and double) of the ethyl extract and its fraction have anti-inflammatory properties, they reduced edema by 43.2% and 52.2% (ethyl extract) and 34.6% and 35.4% (ethyl acetate fraction) [30].

Immunomodulatory effect

An aqueous ethanol extract of the herb was tested for immunomodulative activity in the peritoneal cavities of mice. They produced immunostimulant activity resulted in an increase in phagocytic activity and increases in the activities of lysozyme and peroxidase [31].

Antioxidant effects

The antioxidative properties of aqueous plant extracts were evaluated using common methods such as the Rancimat and 2,2'-diphenyl-1-picrylhydrazyl (DPPH) free radical method. Moreover, a voltammetric procedure based on the protective effect of antioxidants against the oxidative DNA damage was employed using a disposable DNA biosensor fabricated as a screen-printed electrode chemically modified by calf thymus double stranded (ds) DNA [32]. Four of Agrimony flavonoids were significantly attenuated glutamate-induced oxidative stress in HT22 hippocampal cells [22].

The antioxidant potential and scavenging activity of the extract of *Agrimonia eupatoria* and fraction were

tested against the reactive species formed during inflammation and to establish a relationship between such activity and the phenolic composition. Results showed that both the extract and the fraction promptly reacted with DPPH denoting a general radical scavenger activity and produced a potential antioxidant capacity. They also reacted with superoxide anion, peroxy and hydroxyl radicals as well as with the oxidant species, hydrogen peroxide, hypochlorous acid and peroxy nitrite, strengthening their radical scavenger and antioxidant activities. In most assays, the polyphenol-enriched fraction was more efficient, pointing to a significant contribution of the polyphenols content to those activities [33].

The antioxidant activity of *Agrimonia eupatoria* (Agrimony) extracts was assessed by measuring in DPPH radical scavenging and ABTS radical decolourisation reaction systems. Radical scavenging capacity of Agrimony extracts varied in a wide range (9.1-97.5% in DPPH reaction and 6.7-79.5% in ABTS reaction) depending on the polarity of the solvent used to obtain the extract [34].

The polyphenolic profile and antioxidant activity of an ethyl acetate fraction from *Agrimonia eupatoria* aqueous-alcoholic extract was also evaluated. Flavan-3-ols catechin; and procyanidins B1, B2, B3, B6, B7, C1, C2; epicatechin-epicatechin-catechin; quercetin 3-O-glucoside; quercetin 3-O-galactoside; kaempferol 3-O-glucoside; kaempferol 3-O-(6"-O-p-coumaroyl)-glucoside; apigenin 6-C-glucoside and various phenolic acids were identified in the extract. Antioxidant activity of the *Agrimonia eupatoria* fraction containing these compounds was assessed through the 1,1-diphenyl-2-picrylhydrazyl, trolox equivalent antioxidant capacity and thiobarbituric acid reactive substances methods. Significant activity was observed for these fractions [24].

The antioxidant and anti-inflammatory effects of one month's consumption of *Agrimonia eupatoria* tea was evaluated in healthy volunteers. Significant elevation of plasma total antioxidant capacity was observed and interleukin 6 levels were significantly lowered at the end of the intervention. An improved lipid profile as estimated by increased high density lipoprotein (HDL) cholesterol was established upon Agrimony tea supplementation. These clinical data with Agrimony tea indicate that the plant has potential in improving markers of lipid metabolism, oxidative status and inflammation in healthy adults [35].

Antidiabetic effect

The effects of dietary administration of *Agrimonia eupatoria* on streptozotocin (STZ)-diabetic mice and on *in vitro* glucose uptake, glucose metabolism and on insulin secretion by BRIN-BD11 cells were investigated. Agrimony incorporated into the diet (62.5 g/kg) and drinking water (2.5 g/l) countered the weight loss, polydipsia, hyperphagia and hyperglycaemia of STZ-diabetic mice. Aqueous extract of Agrimony (1 mg/ml) stimulated 2-deoxy-glucose transport (1.4-fold), glucose

oxidation (1.4-fold) and incorporation of glucose into glycogen (2.0-fold) in mouse abdominal muscle comparable with 0.1 microM-insulin. In acute 20 min tests, 0.25-1 mg/ml aqueous extract of Agrimony evoked a stepwise 1.9-3.8-fold stimulation of insulin secretion from the BRIN-BD11 pancreatic B-cell line. This effect was abolished by 0.5 mM-diazoxide and previous exposure to extract did not adversely affect subsequent stimulation of insulin secretion by 10 mM-L-alanine, thereby indicating that there was no detrimental effect of the extract on cell viability. The effect of extract was glucose-independent and was not evident in BRIN-BD11 cells exposed to a depolarizing concentration of KCl. The ability of agrimony extract to enhance insulin secretion was dependent on use of heat during extract preparation. These results indicate that *Agrimonia eupatoria* exerted antihyperglycaemic, insulin-releasing and insulin-like activity [36].

Gastrointestinal effect

A compound herb preparation containing Agrimony has been used to treat 35 patients suffering from chronic gastroduodenitis. After 25 days of therapy, 75% of patients claimed to be free from pain, 95% from dyspeptic symptoms and 76% from palpitation pains. Gastroscopy indicated that previous erosion and haemorrhagic mucous changes had healed [37].

Hepatoprotective effect

The hepatoprotective effects of *Agrimonia eupatoria* water extract (AE) was studied in chronic ethanol-induced liver injury in rats. Animals were treated orally with AE at 10, 30, 100, and 300 mg/kg/day. After chronic consumption of ethanol, serum aminotransferase activities and pro-inflammatory cytokines markedly increased, and those increases were attenuated by AE. The cytochrome P450 2E1 activity and lipid peroxidation were increased after chronic ethanol consumption, while reduced glutathione concentration was decreased. Those changes were attenuated by AE. Chronic ethanol consumption also increased the levels of Toll-like receptor 4 (TLR4) and myeloid differentiation factor 88 protein expression, inducible nitric oxide synthase and cyclooxygenase-2 protein, mRNA expression, and nuclear translocation of nuclear factor-kappa B, all these effects were attenuated by AE. The results revealed that AE ameliorates chronic ethanol-induced liver injury, and that protection is likely due to the suppression of oxidative stress and TLR-mediated inflammatory signaling [38].

Other pharmacological effects

A hypotensive effect in anaesthetised cats has been documented for an Agrimony extract given by intravenous injection; blood pressure was lowered by more than 40% [39]. Significant uricolytic activity has been documented for Agrimony infusions and decoctions (15% w/v), following their oral administration to male rats at a dose of

20 ml/kg body weight (equivalent to 3 g dry plant powder) [40].

The successful treatment of cutaneous porphyria in a group of 20 patients receiving Agrimony infusions has been described. An improvement in skin eruptions together with a decrease in serum iron concentrations in urinary porphyrins was noted [41].

Adverse reactions

No health hazards or side effects are known with the proper use of the recommended doses. Agrimony is listed by the Council of Europe as a natural source of food flavouring (category N2). This category indicates that Agrimony can be added to foodstuffs in small quantities. However, because of the tannin contents, the intake of large

quantities caused digestive complain and constipation [42-43].

Dosage

Dried herb 3 (2-4) g or an infusion used three times daily. Liquid extract (1:1 in 25% alcohol) 1-3 ml three times daily. Tincture (1:5 in 45% alcohol) 1-4 ml three times daily [2, 20].

CONCLUSION

Agrimonia eupatoria is a plant with wide range of chemical constituents which exerted many pharmacological effects. There is a great promise for development of novel drugs from *Agrimonia eupatoria* to treat human diseases as a result of its effectiveness and safety.

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