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Chemical Constituents and Pharmacological Activities of Milfoil (Achillea santolina) . A Review

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Abstract : *Achillea santolina* used traditionally as antidiabetic, anti-inflammatory and to relieve pain or dryness of the navel and stomach pain. The concentration of the essential oil in the dry *Achillea santolina* ranged from 0.11-0.20 % in ten genotypes of this species. It contained 54 volatile components. The major components were 1,8-cineole, fragranol, fragranyl acetate and terpin-4-ol. Achillea santolina also contained flavones, particularly flavonoids and sesquiterpene lactones. Many methoxylated flavones were isolated from *Achillea santolina.* The plant possessed many pharmacological activities, these included antidiabetic, anti-inflammatory, analgesic, antimicrobial, anti-arrhythmic, anti-platelet aggregation, antispermatogenic, insecticidal, insect repellent, and many other pharmacological effects . The present review will highlight the chemical constituents and the pharmacological and therapeutic effects of *Achillea santolina*.
Key words: Milfoil, *Achillea santolina.*

Introduction:

Plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives.

Medicinal plants are the Nature's gift to human beings to help them pursue a disease-free healthy life. Plants have been used as drugs by humans since thousands of years ago. As a result of accumulated experience from the past generations, today, all the world's cultures have an extensive knowledge of herbal medicine. Two thirds of the new chemicals identified yearly were extracted from higher plants. 75% of the world's population used plants for therapy and prevention. In the US, where chemical synthesis dominates the pharmaceutical industry, 25% of the pharmaceuticals are based on plant-derived chemicals[(1)].

The genus *Achillea* L. (Asteraceae) is represented by about 115 species found in the Northern Hemisphere, mostly in Europe and Asia. The genus name *Achillea* may have been derived from Achilles of Greek mythology and its historical reputation for healing wounds made it popular among the military and this association led to many of its common names: knight's milfoil, herba milifaris, staunch weed, soldiers' bloodwort and nosebleed [(2-4)].

Antimicrobial, antioxidant, anti-inflammatory, spasmolytic, antidiabetic, antiulcer, antitumor, choleretic and hepatoprotective activity, and cytotoxic effects of different *Achillea* species have been previously reported[(5)]. However, *A. santolina* was distributed in temperature regions of the northern hemisphere, especially in Europe and Asia[(6-7)]. The dried aerial parts and flowers of the plant were used traditionally as antidiabetic and as anti-inflammatory. It also used to relieve pain or dryness of the navel, stomach pain or gas and to relieve the

symptoms of common cold[7-8]. The chemical analysis showed that *A. santolina* contained oil, terpenoids, lignans, flavonoids, and other compounds. The oil of *A. santolina* contained 54 volatile components. The major components were 1,8-cineole, fragranol, fragranyl acetate and terpin-4-ol[9-10]. *Achillea santolina* possessed antimicrobial, anti-inflammatory, antidiabetic, antioxidant, cardiovascular and many other pharmacological effects. The objective of the present review is to highlight the chemical constituents and the pharmacological and therapeutic effects of *Achillea santolina*.

Chemical constituents:

The member of *Achillea* genus contained terpenoids (monoterpens, sesquiterpenes, diterpenes, and triterpenes) , lignans , flavonoids , and other compounds[9] .

Achillea santolina contains flavones, particularly flavonoids and sesquiterpene lactones[11]. Ahmad *et al* isolated two methoxylated flavones from the aerial parts of Achillea santolina were identified as 5-hydroxy-3,6,7,3′,4′-pentamethoxyflavone and 7-hydroxy-3,6,3′,4′-tetramethoxyflavone[12].

Khan found that the extract of *Achillea santolina* containe santoflavone, artemetin, a- santonin, b- sitosterol , lupeol and leukodin[7].

The concentration of the essential oil in the dry *Achillea santolina* ranged from 0.11-0.20 % in ten genotypes of this species[13]. Ahmadi et al found that the essential oils of Achillea santolina included alpha-pinene , camphene, sabinene , P-cymene, 1,8 cineole , 3-2-ocimene , linalool, chrysanthenone, camphor, pinocarvone , borneol, chrysanthenylactate, thymol, eugenol, (+)spathulenol, caryophyllene oxid, and beta-eudesmol . According to this study, camphor was the major compound of the essential oils[14].

The hydrodistilled oil of *Achillea santolina* contained 54 volatile components. The major components were 1,8-cineole, fragranol, fragranyl acetate and terpin-4-ol[7]. Bader et al showed that the essential oil of *Acillea santolina* collected in Jordan contained mainly 1,8-cineole, camphor, 4-terpineol and trans-carveol[15] .

Antimicrobial effects :

Achillea santolina exerted antimicrobial activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Candida albicans*. MICs of *Achillea santolina* extracts against these microorganisms were 40, 60 and 12 ppm respectively[16] .

Ahmadi et al found that the standard strains of *Staphylococcus aureus* presented the greatest sensitivity to the stem extract and leaf extract in MIC(mg/l) > 0.573 and MBC> 1.146, respectively and to the flower extract in MBC> 1.663 and MIC> 0.831, respectively. In addition, it presented an intermediate sensitivity to standard strains *E.coli* with MBC> 2.293 and MIC> 1.146, respectively to the stem and leaf extract and MBC> 6.650 and MIC> 3.325 respectively to the flower extract. However, the standard strains of *Candida albicans* and *P.aeruginosa* did not show a significant sensitivity to the extracts[14]. However, methanolic extracts of *Achillea santolina* was inactive against *Candida albicans* , *Candida glabrata*, and *Candida krusei* strains[17].

Antiinflammatory effects :

A. santolina ethanol extract exerted anti-inflammatory and antidiuretic activity[10,18]. Tekieh *et al* showed that methanolic extract of *A. santolina* caused significant reduction in the edema, hyperalgesia and serum IL-6 level in complete Freund's adjuvant induced inflammation in hind paw of rats[19]. Zaringhalam *et al* found that the methanolic extract of *A. santolina* exhibited significant antihyperalgesic and anti-inflammatory effects during pretreatment and short-term treatment at dose of 200 mg/kg and there was no significant difference between 200 and 400 mg/kg doses of this extract. Defatted extract of *A. santolina* did not show significant effect on CFA-induced inflammation during different stages of treatment ($P>0.05$). Short-term treatment with methanolic extract at dose of 200 mg/kg was found more effective than indomethacin in edema, hyperalgesia and serum IL-6 level reduction ($P<0.01$, $P<0.01$ and $P<0.05$ respectively)[20].

Antidiabetic and antioxidant effects :

An acute administration of the aqueous extract of *Achillea santolina* (in a dose of 150 and 250 mg/kg body weight orally) resulted in significant reductions of serum glucose level in streptozotocin -induced diabetic rats. Chronic administration of the aqueous extract of Achillea santolina in a dose of 250 mg /kg orally for 28 days also showed marked hypoglycemic effects in streptozotocin -induced diabetic rats in comparison with diabetic control group[21] .

Ardestani and Yazdanparast evaluated the effect of *Achillea santolina* extracts on lipid peroxidation, protein oxidation and antioxidant defense system (superoxide dismutase (SOD), catalase(CAT) and reduced glutathione) in the liver of streptozotocin -induced diabetic rats. The extract of *Achillea santolina* (ethanol-water, 7:3 v/v) was given orally in a dose of 100 mg/kg of body weight/day to the STZ- induced diabetic rats for 30 consecutive days . The elevated levels of liver malondialdehyde and protein carbonyls were significantly reduced in diabetic rats fed the extract. In addition, the decreased levels of antioxidant enzyme (SOD and CAT) and glutathione were significantly improved with the extract. *Achillea santolina* extract decreased serum glucose level and modulated serum ALP (alkaline phosphatase), ALT (alanine transaminase), and AST (aspartate transaminase) in streptozotocin -induced diabetic rats[22] .

The antioxidative activities of hydroalcoholic extract of *Achillea santolina* were investigated employing various established *in vitro* systems including total antioxidant activity in linoleic acid emulsion system, 1,1-diphenyl-2-picrylhydrazyl (DPPH), superoxide and hydroxyl radicals scavenging, reducing power, and inhibitory effect on protein oxidation as well as the inhibition of Fe^{2+}/ascorbate induced lipid peroxidation in rat liver homogenate. Total phenolic and flavonoid content of *Achillea santolina* extract was also determined by a colorimetric method. The results revealed that *Achillea santolina* extract has notable inhibitory activity on peroxides formation in linoleic acid emulsion system along with concentration-dependent quenching of DPPH and superoxide radicals. Furthermore, the extract showed both nonsite-specific ($Fe^{2+} + H_2O_2 +$ EDTA) and site-specific ($Fe^{2+} + H_2O_2$) hydroxyl radical scavenging suggesting potent hydroxyl radical scavenging and chelating ability for iron ions in deoxyribose degradation model. A linear correlation between *Achillea santolina* extract and the reducing power was also observed ($r^2 = 0.9981$). *Achillea santolina* extract prevented thiobarbituric acid reactive substances formation in Fe^{2+}/ascorbate induced lipid peroxidation in rat liver tissue in a dose-dependent manner. Moreover, free radical induced protein oxidation was suppressed significantly by the addition of *Achillea santolina* extract over a range of concentrations. These results clearly demonstrated that *Achillea santolina* extract possess a marked antioxidant activity[23].

Cardiovascular effects:

On isolated heart of rats as an experimental model to determine the effect of the methanol extract of *Achillea santolina* on the electrophysiological properties , the methanolic extract of *Achillea santolina* induced significant depression of WBCL, AVCT and ERP and non-significant increase in the time constant of recovery (t.rec). It may be considered a potential drug for anti-arrhythmic effect for suppression or treating supraventricular tachyarrhythmia[24].

Achillea santolina crude extract induced dose-dependently inhibition in *in vitro* ADP and collagen-induced human platelet aggregation (maximal inhibition was 34.4 ± 2.9% and 78.3 ± 2.5 % respectively). This effect was mostly exerted by diethylester extract**.** Chloroform and ethyl acetate extracts had about half the effect, and water extract was devoid of antiaggregant effect. However, when *Achillea Santolina* extracts given to rats for 10 days (10 mg/kg/day) , they produced insignificant decline in the thrombus weight[25] .

Other effects :

The hydroalcoholic extract (300 mg/kg/day intraperitoneally, for 20 days) of *Achillea santolina* caused histological alterations in the seminiferous tubules included disorganized germ epithelium, exfoliation of immature germ cells, germ cell necrosis and increased number of metaphases in germinal epithelium of seminiferous tubules in mice. The authers concluded that *Achillea santolia* exerted antispermatogenic effect[26] .

The volatile oil of *Achillea santolia* produced insecticidal and insect repellent activities on both domestic flies and honeybees. The ethanolic extract did not produce any insecticidal or repellent activity against larvae of potato tuber worm, on worker groups of honeybee and on domestic flies by applying three different methods[27].

Mustafa and Al-Khazraji investigated the effects of *Achillea santolina* extracts on the second instar of larval stage of *Culex pipiens molestus* Forskal. They found that the extracts of *Achillea santolina* caused high mortality to the larvae after 7 days of treatment[28].

Tammam et al examined the phytotoxic potential of *Achillea santolina* L. (Asteraceae) on *Vicia faba* L. and *Hordeum vulgare* L. *Achillea santolina* extract exhibited inhibitory effect on plumule and radicle lengths with a maximum inhibition at 16% concentration. The growth of radical was enhanced in broad bean and barley treated with 1 and 2% concentrations of *Achillea santolina* extract, respectively. Leaf area was significantly reduced in both crops and the percent reduction was greater in broad bean than in barley. There was a highly significant decrease in soluble protein contents in broad bean plants and a significant increase in barley plants treated with *Achillea santolina*. The number of *de novo* synthesized proteins in barley plants were more than those induced in broad bean plants [29].

Pour and Farahbakhsh also tested the allelopathic potential of an aqueous extract and powder of *Achillea santolina* on the germination and seedling growth of pea (*Cicer arietinum*), safflower (*Carthamus tinctorius* L.) and wheat (*Triticum sativum*). The concentration 50,75, and 100 g L^{-1} inhibited pea and wheat seed germination significantly, but had no inhibitory effect on the germination of safflower. The powder of mature Achillea plants affected the fresh and dry weight and shoots length in these crops negatively compared with the control in all levels[30]. The authors concluded that *Achillea santolina* may be a source of biological herbicides[29-30].

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