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Pharmacological Activities of *Achillea santolina*: A Review

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Abstract

Objectives: The plant of *Achillea* genuses are traditionally used for digestive problems, liver and gall-bladder conditions, menstrual irregularities, cramps, fever and wound healing. These plants are explored for their antioxidant and anti-inflammatory properties and showed significant results on the analgesic, anti-ulcer, choleretic, hepatoprotective and wound healing activities. The essential oil, proazulenes and other sesquiterpene lactones, dicaffeoylquinic acids and flavonoids are mainly responsible of these pharmacological activities. These plants can also be used as an insect repellent. This review covers the traditional and pharmacological properties of *Achillea santolina*.

Keywords: *Achillea santolina*; Medicinal use; Pharmacology; Traditional use

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Introduction

From thousands of years *Achillea* species have been utilized for various ethnopharmacological uses. The name of the genus might originate from 'Achilles' the Greek mythology since he used this plant checking the blood-stream and treat his wounds during the Trojan War. Staunchweed, bloodwort, nosebleed and military herb are some of the ethnobotanical names also reveal the former utilization of the herb [1]. It is one of the most important genres of the Asteraceae family and comprises 115 species, which are mainly distributed in Europe, Asia and North Africa [2]. Traditionally *Achillea* species are used against liver and gallbladder conditions, digestive problems, inflammation, cramps, menstrual irregularities, fever, in wound healing, and to increase urine flow [3] and mainly contains flavones, particularly flavonoids and sesquiterpene lactone [4].

The aerial parts of different species of the genus *Achillea* are widely used in folk medicine due to various purposes and pharmacological properties in various biological activities, such as, anti-inflammatory [5], antimicrobial [6,7] antispasmodic [8], antiulcer [9], and antiradical activities [10,11]. Furthermore, this plant is also used as treatment for cancerous cells [11, 12].

The dried aerial parts and flowers of this plant were used traditionally used as ant diabetic and as anti-inflammatory. It relieves pain or dryness of the navel, stomach pain or gas and to relieve the symptoms of common cold [13]. Various workers confirmed the different biological and antioxidant activities of this plant [13-25]. The volatile oil of *A. santolina* produced insecticidal and insect repellent activities on both domestic flies and honeybees [26]. The available information on this species was collected from scientific databases such as PubMed, SciFinder, Science Direct, Scopus, Web of Science, and Google Scholar. The search terms used for this review included *Achillea santolina*, phytochemical composition, essential oils, medicinal uses, activity, pharmacology, and toxicity. No limitations were set for languages.

Chemical Constituents

Various terpenoids i.e., diterpenes, monoterpens, sesquiterpenes, and triterpenes, flavonoids, lignans, and other compounds are identified in several members of genus *Achillea* in various studies [27]. Flavones, particularly sesquiterpene lactones and flavonoids are the main chemical constituents of *A. santolina* [4] along with the artemetin, santoflavone, b-sitosterol, a-santonin, leukodin and lupeol [28]. Ahmadi and coworkers concluded that camphor is the main compound of essential oil along with the (+) spathulenol, 1,8 cineole, 3-2-ocimene, alpha-pinene, borneol, camphene, caryophyllene oxid, chrysanthenone, chrysanthenylactate, eugenol, linalool, P-cymene, pinocarvone, sabinene, thymol and beta-eudesmol [29]. Khan studied the chemical constituents of *Centaurea iberica* and *A. santolina* and identified 54 volatile components in which 1,8-cineole, fragranol, fragranyl acetate and terpin-4-ol were the major components [28]. 1, 8-cineole, camphor, 4-terpineol and trans-carveol are some other essential oil compounds of *A. santolina* from Jordan [30].

Anti-Microbial Activity

A. santolina showed significant antimicrobial activity against Staphylococcus *aureus* (MIC-40 ppm), *Pseudomonas aeruginosa* (MIC-60 ppm) and *Candida albicans* (MIC-12 ppm) [21]. S.

aureus showed maximum sensitivity against the stem and leaf extract (MIC>0.57 mg/l and MBC>1.12) and flower extract (MBC>1.67 and MIC>0.83) of *A. santolina* compared to *E.coli* with intermediate activity in stem and leaf extract (MBC>2.29 and MIC>1.15) and flower extract (MBC>6.650 and MIC>3.325). *C. albicans* and *P. aeruginosa* did not show any antimicrobial activity against any extract 29. The methanolic extracts were also showed no significant effected against *C. albicans*, C. glabrata, and *C. krusei* strains [31].

The essential oils of leaves, flowers and stems of *A. santolina* L. (Asteraceae) collected at complete flowering stage from Southwest of Algeria, were isolated by hydrodistillation and subsequently analyzed by means of GC and GC/MS. The essential oils were rich in oxygenated monoterpenes (65.91-79.94%). The major constituents in the flowers, leaves and stems were: camphor (68.12, 65.17, 55.72%), 1,8-cineole (8.22, 4.77, 0.7%) and α-terpineol (2.84, 5.35, 2.76%). The highest EO yields were obtained for the leaves and the flowers (0.59 and 0.49% v/w, respectively), whereas, the stems were characterized by very weak yield value (0.05%) [32].

Anti-Inflammatory Activity

Some studies reported the anti-inflammatory and anti-diuretic activity of *A. santolina* [20,32]. The methanolic leaf extract significantly decreases serum IL-6 level, hyperalgesia and edema in complete Freund's adjuvant inflammation induced paw rats [33]. Zaringhalam, et al. also observed that short-term treatment was more efficient than indomethacin in edema, hyperalgesia and serum IL-6 level reduction [25].

Anti-Diabetic and Antioxidant Activity

The aqueous extract (150-250 mg/kg) significantly decreases serum glucose level and showed hypoglycemic effects in streptozotocin-induced diabetic rats [15]. Ardestani and Yazdanparast also studied the effect of *A. santolina* on protein oxidation, lipid peroxidation and antioxidant defense system in the liver of streptozotocin-induced diabetic rats (100 mg/kg) and observed a significant reduction in the elevated levels of malondialdehyde and protein carbonyls. They also found that *A. santolina* extract decreased serum glucose level and improves the antioxidant enzyme and glutathione levels [10]. The hydroalcoholic extract of *A. santolina* possesses antioxidative activities.

Ardestani and Yazdamparast investigated total antioxidant activity in rat liver homogenate and observed notable inhibitory activity on peroxides formation in linoleic acid emulsion system along with concentration-dependent quenching of DPPH and superoxide radicals. The ethanol-water extract of the Middle-Asian species *A. santolina* showed a pronounced superoxide radical scavenging activity (IC50=39 μg/ml), a less DPPH radical scavenging activity (IC50=55 μg/ml) and a much lower hydroxyl radical (Fe^{3+}/ascorbate/EDTA/H_2O_2) scavenging activity (IC50=519 μg/ml) while in rat liver homogenate up to a 78% inhibition of lipid peroxidation could be achieved. The total phenolic content of 105 mg/g and a total flavonoid content of 49 mg/g are suggested to be responsible for the antioxidant capacity [19].

In a recent study, the ethanol-water (7:3) extract of *A. santolina* has been investigated in rat pancreatic tissue. The results showed, that the treatment in a dose of 0.1 g/kg reduced blood glucose level almost three times and serum nitric oxide to the level of the healthy control group. The level of pancreatic malondialdehyde also decreased significantly. Accumulation of protein carbonyl and the advanced oxidation of protein products were also reduced by 26 and 62% respectively, compared to the values of diabetic control animals. In addition, the activities of catalase and superoxide dismutase significantly increased and the extract restored the content of pancreatic glutathione to the normal level. The treatment inhibited weight loss compared to the diabetic untreated group [34]. It was assumed that the same group of compounds (e.g. flavonoids) was responsive for the antidiabetic and antioxidative properties of *A. santolina*.

The extracts of the medicinal plants *A. santolina* and Raphanu sativus have been reported to show anti-cancer effects on different cancer cell lines ($CaCO_2$(colon adenocarcinoma) HepG2 (hepatic carcinoma), MCF7 (breast cancer) and the normal WISH (amniotic cell line)) *in vitro*. The methanolic extract of *R. sativus* seeds showed higher phenolic content (791.98 mg/d.wt) and higher antioxidant activity (93%) than those of the ethanolic extract of *A. santolina* (340.23 mg/d.wt) and (72.72%), respectively. *R. sativus* methanolic extract showed lower flavonoids contents (1.025 mg/g d.wt) than *A. santolina* ethanolic extract (24.66 mg/g d.wt). Treatment of CaCO2, HepG2, MCF7 and WISH cell lines with *A. santolina* extract showed IC50 of 17.67 μg/ml, 15.12 μg/ml, 42.19 μg/ml and 50.99 μg/ml, respectively. *A. santolina* and *R. sativus* extracts induced similar cell cycle arrest in CaCO2 at G1 phase by 42.4% [35,36].

Khori et al. isolated heart of langandrof rats to show that methanolic extract of this plant could decrease relative activity of atrioventricular node. He observed a significant depression of WBCL, AVCT and ERP and non-significant increase in time constant of recovery which makes this plant a potential drug for suppression or treating supraventricular tachyarrhythmia [22].

The crude extract dose-dependently (10 mg/kg/day) of *A. santolina* inhibited *in vitro* adenosine diphosphate and collagen-induced human platelet aggregation (maximal inhibition respectively 34.4 ± 2.9% and 78.3 ± 2.5%). The anti-aggregant property of the plant could be attributed to flavones, particularly flavonoids and sesquiterpene lactone [28-31] that are present in this plant. Several studies have shown that flavonoïds significantly inhibit platelet adhesion, aggregation, and secretion [35]. Chocolate drinks, rich in flavonoïds, also inhibit the activity of platelets [36,37].

Other Activity

Golalipour, et al. showed that administration of the hydroalcoholic extract of *A. santolina* (300 mg/kg/day; 20 days) to mice results

in an increased number of metaphases in germinal epithelium of seminiferous tubules, disarrangement in germ epithelium, exfoliation of immature germ cells and germ cell necrosis with no alteration in vacuolization of seminiferous tubules [38]. First results on the insect repellent activity of the essential oil of *A. santolina* could be promising agent against domestic flies and honeybees [24].

Tammam, et al. observed that higher concentrations of *A. santolina* extract exhibited inhibitory effect on plumule and radicle lengths of *Vicia faba* and *Hordeum vulgare* with a maximum inhibition at 16%. The growth of radicle was enhanced when treated with 1 and 2% concentrations of *A. santolina* extract, respectively. A residue bioassay experiment inhibited the growth of the two tested species [39].

Pour and Farahbakhsh investigated the allelopathic potential of an aqueous extract (0, 25, 50, 75, and 100 g L-1) and powder (0, 7.5, 15 and 30 kg-1) of *A. santolina* on the germination and seedling growth of *Cicer arietinum, Carthamus tinctorius* and *Triticum sativum*. They found that all extract concentrations of except 25 g L-1 inhibited *C. arietinum* and *T. sativum* seed germination significantly, but had no inhibitory effect on the germination of *C.tinctorius* [40].

Conclusion

In this review we have briefly summarized the traditional uses, ethnobotanical description, ethnopharmacological properties and phytochemical constituents that have been isolated from *A. santolina*. Further research should be conducted to explore new potential therapeutic agents and their ethnopharmacological properties of *A. santolina* for the treatment of life-threatening diseases.

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