MEDICAL IMPORTANCE OF ANTHEMIS NOBILIS (CHAMAEMELUM NOBILE) - A REVIEW

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ABSTRACT

Anthemis nobilis (Chamaemelum nobile), the so-called Roman chamomile, is a perennial herb of the Asteraceae family. It possessed antibacterial, antifungal, insecticidal, hypotensive, anti-platelet aggregation, anti-inflammatory, hypoglycaemic, antioxidant, nervous, cytotoxic, bronchodilatory, endocrine and many other effects. This review highlights the chemical constituents and pharmacological effects of Anthemis nobilis.

Key words: Chemical constituents, Pharmacology, Anthemis nobilis.

INTRODUCTION

Since the dawn of civilization, man utilized plants for their medicinal and edible value. Recent reviews showed that plants produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of many drugs [1-42]. "Anthemis nobilis" (Chamaemelum nobile), the so-called Roman chamomile, is a perennial herb of the Asteraceae family. It possessed antibacterial, antifungal, insecticidal, hypotensive, anti-platelet aggregation, anti-inflammatory, hypoglycaemic, antioxidant, nervous, cytotoxic, bronchodilatory, endocrine and many other effects. This review will highlight the chemical constituents and pharmacological effects of Anthemis nobilis.

Synonyms: Chamaemelum nobile (L.)

TAXONOMIC CLASSIFICATION


COMMON NAMES

Arabic: babonaj Romani, babanq Romani, babanaq Itri, babanaq shareef; English: chamomile, common chamomile, corn chamomile, English chamomile, garden chamomile, noble chamomile, Roman chamomile, Russian chamomile, sweet chamomile; French: camomille romaine; German: römische Kamille; Spanish: camomila de jardin, manzanilla fina, manzanilla romana, Swedish: romersk kamomill [43].

Distribution: It was widely distributed in Asia, Europe, Africa and Northern America. The plant cultivated in Africa: Algeria, Morocco; Europe: Ireland, United Kingdom, France, Portugal, Spain, Austria, Belarus, Moldova, Ukraine, Bulgaria; Italy; Serbia, Belgium; Czech Republic; Germany; Slovakia; Switzerland; Australasia: Australia, New Zealand; Northern America: United states [44].

Traditional use: The cold infusion was used in gastric debility, with flatus; the hot infusion was used as diaphoretic, emetic, to relieve colds due to sudden cutaneous chilling, in dysmenorrhea to decrease pain and facilitate the flow, as antiemetic, antispasmodic, and sedative. The oil was used as carminative, and for intestinal cramps and colic due to flatulency [45-47].

DESCRIPTION

"Anthemis nobilis" is a low-growing plant, creeping or trailing, its tufts of leaves and flowers a foot high. The root is perennial, jointed and fibrous, the stems, hairy and freely branching are covered with leaves which are divided into thread-like segments, the fineness of which gives the whole plant a feathery appearance. The blooms appear in the later days of summer, from the end of July to September, and are borne solitary on long, erect stalks, drooping when in bud. With their outer fringe of white ray-florets and yellow centers, they are remarkably like the daisy. There are some eighteen white rays arranged round a

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conical center, botanically known as the receptacle, on which the yellow, tubular florets are placed- the centre of the daisy is, however, considerably flatter than that of the Chamomile. All the Chamomiles have a tiny, chaffy scale between each two florets, which is very minute and has to be carefully looked for but which all the same is a vital characteristic of the genus Anthemis. The distinction between A. nobilis and other species of Anthemis is the shape of these scales, which in A. nobilis are short and blunt. The fruit is small and dry, and as it forms, the hill of the receptacle gets more and more conical. The whole plant is downy and grayish green in colour. It prefers dry commons and sandy soil [48,49].

CHEMICAL CONSTITUENTS

A. nobilis contained 80% water , 6-7% mineral materials , volatile oil, sesquiterpenes, hydroperoxides, flavonoids, catechins, coumarins, polyacetylenes, phenolic acids, triterpenes and steroids and polysaccharides [46, 50]. However, many authors [47, 51, 52] mentioned that different parts of the plant contained:

Volatile oils (0.4-1.75%): angelic and tiglic acid esters (85%) and 1,8 cineole, 1-trans-pinocarveol, 1-trans-pinocarvone, chamazulene, farnesol, and nerolidol. Flavonoids: apigenin, luteolin, quercetin and their glycosides (apigen, luteolin-7-glucoside and rutin); Coumarins: scopoletin-7-glucoside; Germacranolide-type sesquiterpene lactones(0.6%): nobilin, 3-epinobilin, 1,10-epoxy-nobilin, and 3-dehydro-nobilin; Various alcohols: amyl and isobutyl alcohols.

It also contained: angelic and tiglic acid esters, anthetic acid, choline, phenolic, phytosterols, inositol and fatty acids. The essential oil of A. nobilis is a light blue color due to the terpenoid chamazulene [53]. The amount of the constituents isolated were differ according to the origin and the age of the flowers . The essential oils of the aerial parts of the plants were included: isobutyl isobutanoate (4.4%), 2-methylbutyl isobutanoate (4.3%), isobutylangelate (24.5%), 2-butenylangelate (7.3%), 2-methylbutylangelate (17.4%), trans-pinocarveol (4.5%), isoamylangelate (7.6%) and estragol (5.0%) [53-55].

C. nobile proved to be an equilibrated valuable herb rich in carbohydrates and proteins, and poor in fat, providing tocopherols, carotenoids and essential fatty acids. Moreover, the herb and its infusion are a source of phenolic and organic acids (oxalic, quinic, malic, citric and fumaric acids) [56]. Six octulosonic acid derivatives were isolated from the flower heads of Roman chamomile (Chamaemelum nobile) [57]. Six new hydroperoxides were isolated from the ethanol extract of the blossoms of Anthemis nobilis L., besides the known 1 beta-hydroperoxyisonobilin [58].

PHARMACOLOGICAL EFFECTS

The biological activity of chamomile was mainly due to the flavonoids apigenin, luteolin, quercetin, patuletin and essential oil constituents such as α-bisabolol and its oxides and azulenes [59].

Antimicrobial effect

The extract and essential oil of Roman chamomile flower head showed antibacterial activity against P. gingivalis. The antimicrobial effects were evaluated by disk diffusion method. The results indicated that the means of inhibition zone for chamomile extract and essential oil were 13.33±3.4 and 20.5±0.5 respectively [60]. Azulenes and bisabolol were anti-inflammatory and antispasmodic, reducing histamine-induced reactions, including hay fever and asthma. Flavonoids, especially anthemidin, were also antispasmodic. Valeric acid and cyanogenic glycosides were sedative [61]. Two hydroperoxides compounds isolated from Anthemis nobilis showed a medium antibacterial activity. In a clinical study, Anthemis nobilis showed a good result in the treatment of recurrent aphthous stomatitis as estimated by the time of pain elimination and the duration of the healing [62].

The antimicrobial activity of an essential oils of the flower of Anthemis nobilis from the Provence (France) was tested against various strains of Gram-positive bacteria (Staphylococcus aureus and Enterococcus faecalis) and Gram-negative bacteria (Escherichia coli, Pseudomonas aeruginosa, Proteus vulgaris, Klebsiella pneumoniae and Salmonella sp.) as well as against the yeast Candida albicans using a modified agar dilution and agar diffusion method. In addition, some pure main and minor compounds (chemical composition obtained by means of GC and GC/MS measurements), such as isobutylangelate (32.1%), 2-methylbutylangelate (16.2%), isobutylisobutyrate (5.3%), methyl 2-methylbutyrate (1.8%), prenol acetate (1.4%), 2-methylbutyl 2-methylbutyrate (1.2%) and 2-methylbutylacetate (1.2%), were also studied for their antimicrobial effects. The Roman chamomile sample showed high antimicrobial activity against all strains of tested microbes. A similar result was found for 2-methylbutyl 2-methylbutyrate, 2-methylbutyl acetate and prenol acetate [63]. The volatile oil of Anthemis nobilis showed activity against Gram-positive bacteria, especially Bacillus subtilis, B. anthracis, Micrococcus glutamicus, B. saccharolyticus, B. thuringiensis, Sarcina lutea, B. stearothermophilus, Lactobacillus plantarum, Staphylococcus aureus, Staphylococcus sp. and L. casei, whereas the oil showed no activity against Gram-negative bacteria species including Salmonella group B, Citrobacter sp., Enterobacter sp., Esheria coli, Pseudomonas sp., Salmonella saintpaul and Salmonella weltevreden. The volatile oil also inhibited the growth of dermatophytons, Alternaria sp., Aspergillus fumigatus and A. parasiticus. Volatile oil was inactive against Candida albicans, Cryptococcus neoformans, Histoplasma capsulatum and Aspergillus niger. Hydroperoxides [Z-2-methyl-2-butyric acid-(2-hydroperoxy-2-methyl-3-butenyl) ester, and Z-2-methyl-2-butyric acid-(3-hydroperoxy-2-methylidenebutyl)
ester], isolated from the ethanolic extract of the *Anthemis nobilis* flowers, showed antibacterial activity against *E. coli*, *P. aeruginosa* and *E. faecalis*. The MIC values of first compound were 256 μg/ml against *E. coli* and 512 μg/ml against *P. aeruginosa*. The MIC values of the second compound were 512 and 128 μg/ml against the same microorganisms, respectively [64].

**Insecticidal effect**

Volatile oil of *Anthemis nobilis* showed high activity against the whitefly (*Trialeurodes vaporariorum*) nymphs at 0.0047 and 0.0093 μg/ml using an impregnated filter paper test, whereas it was ineffective against the adult or egg forms [65].

**Hypotensive effect**

The hypotensive effect of *Chamaemelum nobile* aqueous extract (CNAE) in spontaneously hypertensive was studied in rats. Single oral administration of CNAE (140 mg/kg) produced a significant reduction (p < 0.05) in systolic blood pressure (SBP) after 24 h of the administration. Daily oral administration of CNAE (140 mg/kg) during 3 weeks produced a significant reduction in SBP in the day 8 (p < 0.01) of treatment. Furthermore, CNAE produced a significant increase in urinary output and electrolytes excretion (p < 0.01) from the day 8 to the end of treatment [66]. The in vitro vasorelaxant effect of *C. nobile* aqueous extract was evaluated using aortic ring isolated from Wistar rats. *C. nobile* aqueous extract at doses of 5, 10 and 20 mg/ml possessed in vitro vasorelaxant effect. Incubation of aqueous *C. nobile* extract for 30 minutes produced a significant shift of the dose-response curve to norepinephrine (NE) (10⁻⁸ to 10⁻⁵ M (p < 0.001) [67].

**Anti-inflammatory effect**

The anti-inflammatory effect of the polysaccharides isolated from the aqueous extract of Roman chamomile flowers and herb was investigated in rats. Inflammation was induced with subplantar injection of viscarine. The flower and herb polysaccharide was given ip as 10 mg/kg dose. They reduced the inflammation of the paw by 36.2 and 37.7%, respectively compared with untreated control [68,69].

The volatile oil have been documented as having anti-inflammatory activity (carrageenan rat paw edema test ) and produced antidiuretic and sedative effects following intraperitoneal administration of doses up to 350 mg/kg to rats. The mechanism of antiallergic and anti-inflammatory effects of azulenes is thought to involve inhibition of histamine release [70].

Two varieties of *Anthemis nobilis*, named (white-headed) or double flowered and (yellow-headed) yield essential oils with different composition. These essential oils proved to possess interesting anti-inflammatory and sedative properties, especially that derived from the (White-headed) variety. The oils caused 22.8 to 38.7% inhibition of the carrageenan induced increase in paw volume [71].

Six octulosonic acid derivatives were isolated from the flower heads of Roman chamomile (*Chamaemelum nobile*). The biological activity of the isolated compounds was evaluated toward multiple targets related to inflammation and metabolic disorder such as NAG-1, NF-κB, iNOS, ROS, PPARα, PPARγ, and LXR. Similar to the action of NSAIDs, all the six compounds increased NAG-1 activity 2-3-fold. They also decreased cellular oxidative stress by inhibiting ROS generation. Three of the compounds activated PPARγ 1.6-2.1-fold, while PPARα was activated 1.4-fold by compounds two compounds. None of the compounds showed significant activity against iNOS or NF-κB.

**Hypoglycemic effect:**

The effect of both a single dose and daily oral administration dose (20mg/kg body weight) for 15 days of the aerial part of *Chamaemelum nobile* aqueous extract on blood glucose concentrations and basal insulin levels in normal and streptozotocin-induced diabetic rats (STZ) were studied. Single oral administration of *C. nobile* aqueous extract reduced blood glucose levels from 6.0 ± 0.3 mmol/l to 4.9 ± 0.09 mmol/l (P < 0.05) 6h after administration in normal rats and from 21.1 ± 1.3 mmol/l to 14.5 ± 0.9 mmol/l (P < 0.001) in STZ diabetic rats. Furthermore, blood glucose levels were decreased from 6.1 ± 0.06 mmol/l to 4.6 ± 0.17 mmol/l (P < 0.01) and from 21.1 ± 1.31 mmol/l to 13.7 ± 0.9 mmol/l (P < 0.01) in normal and STZ diabetic rats, respectively, after 15 days of treatment. Basal plasma insulin concentrations remain unchanged after treatment in both normal and STZ diabetic rats, which means that the mechanism of this pharmacological activity seems to be independent of insulin secretion [72]. Flavonoid glucoside chamaemeloside, has been determined to have in vivo hypoglycaemic activity [73].

**Nervous effect**

In mice, apigenin had a clear affinity for central benzodiazepine receptors. Apigenin competitively inhibited the binding of flunitrazepam, a benzodiazepine, but had no effect on muscarinic receptors, alpha 1-adrenergceptors, or the binding of muscimol to GABA receptors. Apigenin had clear anxiolytic activity in mice without incidence of sedation or muscle relaxation effects at doses similar to those used for classical benzodiazepines; no anticonvulsant action was detected. Increasing dosages produced mild sedation and a reduction in ambulatory locomotor activity [71,74].

The essential oil of Roman chamomile decreased the mobility of male Wistar rats with 51-76% for 50 minutes, compared to untreated control, when given subcutaneously in a dose of (350, 1250 and 2500 mg/kg) and i.p in a dose of (175 and 350 mg/kg).
Antioxidant effect

Chamazulene affected free radical processes and inhibited lipid peroxidation in a concentration- and time-dependent manner [75].

The antioxidant properties of essential oils were investigated for A. nobilis from Italy. The results indicated that the volatile oils from Roman chamomile possessed high antioxidant activity [76]. The aqueous extracts (crude and decoction) of A. nobilis button flowers showed high antioxidant activity, as evaluated by ABTS, TBARS and haemolysis of red blood cells assays. Moreover, this activity was higher for the decoction extract, and it was in good agreement with its greater phenolic content. As revealed by the mass spectrometry analysis, the potent antioxidant ability of aqueous A. nobilis extracts can result from the presence of quinic acid and caffeic acid derivatives [77].

One hundred and twenty, one day old unsexed Lohman broiler chicks were used to study the effect of supplementing aqueous extract and powder of chamomile flowers to diet and drinking water on some physiological characters of broiler exposed to high environmental temperature 28 – 30 – 28 °C to alleviate heat stress. Five treatments were carried out, treatment T0 without supplementing chamomile to drinking water or diet, treatments T1 and T2 supplementing with 0.3 and 0.6% of aqueous extract to drinking water, treatments with T3 and T4 supplementing 0.6 and 0.9% of chamomile flowers powder to diet. This supplementation of chamomile to drinking water and diet had been given to birds daily for 6 hours from 1200-1800 and during the highest environmental temperature and during the experiment period from 4 – 8 weeks of age. The result revealed that body temperature reduced significantly in the group T3 and T4 compared with other treatments however heterophil lymphocyte ratio reduced significantly while hemoglobin increased in all treatments compared with T0, also glucose reduced significantly in the group T1, T2 and T3 compared with T0. The study confirmed that supplementing the aqueous extract and powder of chamomile flowers lead to alleviate heat stress. The results pointed that chamomile flowers powder supplementation gave better results than aqueous extract [78].

The antioxidant effects of Anthemis nobilis were evaluated by four different tests: DPPH radical scavenging capacity, reducing power and inhibition of lipid peroxidation using β-carotene–linoleate model system in liposomes and TBARS assay in brain homogenates. Herbal sample gave the highest β-carotene bleaching activity and lipid peroxidation inhibition (lowest EC50 values) which related to its higher content of phenolic compounds, while infusion showed the highest DPPH scavenging activity which related to their higher levels of organic acids [50].

Cytotoxic effects

The antitumour potential of Anthemis nobilis was tested in human tumour cell lines (breast, lung, colon, cervical and hepatocellular carcinomas). The plant material extract was more potent than the infusion sample in all the tested cell lines, presenting GI50 values that ranged from 82.52 to 168.40 μg/mL for the MCF-7 and HepG2 cells, respectively. Decoction preparation had no antitumour effects at the maximal concentration used (400 μg/mL), which could indicate that these effects might be related to compounds (including phenolic compounds) that are not extracted or affected by the decoction [50].

From fresh and dried herb (without inflorescences) of Anthemis nobilis L. a new sesquiterpene lactone C20H26O6 was isolated. This compound showed a cytotoxic activity at a level of ED50 HeLa 0-56 microgram/ml (1.5 x 10^6 M), and ED50 KB 1.23 microgram/ml (3.5 x 10^6 M) [79].

Nobilin, 1,10-epoxynobilin, 3-dehydronobilin and hydroxysionobilin, isolated from Roman chamomile flower, showed in vitro cytostatic activity against human HeLa (cervix carcinoma cell line) and KB (nasopharyngeal carcinoma) cell lines [80].

Effect in poly cystic ovary

The effectiveness of Anthemis nobilis aqueous-alcoholic extract was studied in polycystic ovary syndrome induced in rats by a single dose of estradiol valerate. Histological investigations revealed that the animal administered with dose of 50 mg/day showed small cysts and less inflammation, with decreasing of serum estrogen hormone(P<0.029) [82].

Contraindications and adverse effects

The US Food and Drug Administration (FDA) have classified the oil and extract of Roman chamomiles as safe substances . Large doses are emetic. Acute LD50 in rabbits (dermal) and rats exceed 5g/kg.

Dosage : Flower heads 1-4 g by infusion three times a day [47].

CONCLUSION

This review discusses the chemical constituent, pharmacological and therapeutic effects of Anthemis nobilis as promising herbal drug because of its safety and effectiveness.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.
REFERENCES

43. USDA, ARS, National Genetic Resources Program. Germplasm Resources Information Network-(GRIN). National Germplasm Resources Laboratory, Beltsville, Maryland, 2013.