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THE PHARMACOLOGICAL IMPORTANCE OF *BELLIS PERENNIS* - A REVIEW

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ABSTRACT

The literature reveals that the chemical constituents of *Bellisperennis*(Asteraceae) included saponins, triterpenes, several anthocyanins, polyphenols, flavonoids and polyacetylenes. The different parts of the plant exerted many pharmacological activities including antimicrobial, nervous system, dermatological, anti-inflammatory, cytotoxic, antioxidant, hypolipidemic, antihemorrhagic, hemolytic and many other effect. This paper will highlight the chemical constituents and the pharmacological effects of *Bellis perennis*.

Key words: *Bellis perennis*, Constituents, Pharmacology.

INTRODUCTION

Bellis perennis (Asteraceae) contained many secondary metabolites included saponins, triterpenes, several anthocyanins, polyphenols, flavonoids and polyacetylenes. The different parts of the plant exerted many pharmacological activities including antimicrobial, nervous system, dermatological, anti-inflammatory, cytotoxic, antioxidant, hypolipidemic, antihemorrhagic, hemolytic and many other effect.

Synonyms

Aster bellis E.H.L.Krause, *Bellis alpina* Hegetschw., *Bellis armena*Boiss., *Belliscroatica* Gand., *Bellis hortensis* Mill., *Bellis hybrida* Ten., *Bellis integrifolia* DC., *Bellis margaritifolia* Huter, *Bellis perennis* var. *caulescens* Rochebr., *Bellis perennis* f. *discoidea* D.C.McClint., *Bellis perennis* var. *fagetorum* Lac., *Bellis perennis* var. *hybrida* (Ten.) Fiori, *Bellis perennis* subsp. *hybrida* (Ten.) Nyman, *Bellis perennis* var. *margaritifolia* (Huter) Fiori, *Bellis perennis* var. *microcephala* Boiss., *Bellis perennis* f. *plena* Sacc., *Bellis perennis* f. *pumila* (Arv.-Touv. &Dupuy) Rouy, *Bellis perennis* var. *pusilla* N.Terracc., *Bellis perennis* f. *rhodoglossa* Sacc., *Bellis perennis* var. *strobliana* Bég., *Bellis perennis* var. *subcaulescens* Martrin-Donos, *Bellis perennis* var. *tubulosa* F.J.Schultz, *Bellis perennis* f. *tubulosa*A.Kern., *Bellispumila* Arv.-Touv. &Dupuy, *Bellis pusilla* (N.Terracc.)Pignatti, *Bellis validula* Gand., and *Erigeron perennis* (L.) Sessé & Moc [1].

Nomenclature and Common names

There are several theories surrounding the Latin name of Bellis, as some authors believe it wais derived from the latin word (bellus) meaning pretty, whereas others believe that it derives from the word (bello), which is latin for (war), this association may be due to the plant's long standing reputation as a wound herb, as well as the fact that it grew on most battlefields. This association may perhaps partially explain the dichotomy between the assorted deities the plant was associated with. There was also the possibility that the name derives from the myth of the water meadow nymph named Belidis, who, being pursued by the lustful orchard god Vertumnus, turned herself into a daisy in order to escape. The plant's name has also been associated with the Celtic sun God,

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Belenos. The name (daisy) derives from the Anglo Saxon name for the plant, (daegeseage), which means (day's eye), meaning the plant's tendency to only open during sunlit hours [2].

Common names

Arabic: Zahrat El rabee, Zahrat El lolo, Loloiah, Shash El kadhi, Bakerat El hokool, Bless Moamer; Chinese: Chu ju; English:Bruisewort, Bairnwort, Llygad y Dydd (Eye of the Day Welsh), Flower Of Spring, Gowan, Open Eye, Day's Eye, Banwood, Banewort, Ewe-Gowan, Little Star, Silver Pennies, Billy Button, Measure Of Love, Herb Margaret, Bainswort, Bruisewort, Child's Flower, Field Daisy, Maudlinwort, Moon Daisy; French: Pâquerette; German:Gänseblümchen, Maßliebchen; Russian:margaritka; Spanish: Vellorita; Swedish:Tusensköna[2-3].

Distribution

It is native to Europe and western Asia, and introduced in north and south America [4-6].Now, it is distributed in Africa: Morocco; Asia: Afghanistan, Cyprus; Iran, Iraq, Palestine, Jordan, Lebanon, Syria, Turkey, Armenia, Azerbaijan, Georgia, Russian Federation, China; Europe: Denmark, Ireland, Sweden, United Kingdom, Austria, Belgium, Czech Republic, Germany, Hungary, Netherlands, Poland, Slovakia, Switzerland, Belarus, Moldova, Russian Federation, Ukraine, Albania, Bosnia and Herzegovina, Bulgaria, Croatia, Greece, Italy, Macedonia, Montenegro, Romania, Serbia, Slovenia, France, Portugal, Spain, Estonia, Latvia, Lithuania; Australia; Australia, New Zealand; North America: United states, Canada; South America: Argentina and Chile [3].

Traditional use

The flowers and young leaves were used as a vegetable. The plant was used traditionally as an expectorant, diuretic, anti-inflammatory, antipyretic, vulnerary, antispasmodic, astringent, ophthalmic, homeostatic**.** *Bellis perennis* was also used in the treatment of common cold, stomachache, eye diseases, eczema, skin boils, gastritis, enteritis, diarrhea, bleeding, rheumatism, inflammation, and infections of the upper respiratory tract [7-20]. In homeopathic therapy, It was said that the plant acts upon the muscular fibers of the blood-vessels and beneficial in muscular soreness, lameness, venous congestion due to mechanical causes. It was the first remedy in injuries to the deeper tissues and injuries to nerves with intense soreness and intolerance of cold bathing [21].

Description

Flower and Fruit: The flower heads are usually found singly at the end of the sharply angular stem. The flower is small to medium-sized and heterogamous. The epicalyx is semispherical to bell-shaped. The sepals of the epicalyx are more or less double-rowed. The receptacle is conical and glabrous when bearing fruit. The l- to 2-rowed female ray flowers are linguiform, white, pink, purple or bluish and distinctly longer than the epicalyx. The disc flowers are androgynous, tubular and 5-tipped. The achenes are obovate, very flattened, ribless, and have side veins. The flower has no pappus but may have short, brittle bristles. Leaves, Stem and Root:Wild Daisy is a 10- to 15-cm high perennial plant that has basal leaves in rosettes or alternate leaves at the lower part of the stem; its roots are short and cylindrical. The rosette leaves are circular to spatulate or heart-shaped, dentate and occasionally entire-margined with a single rib; they have vertical hairs on both sides [22-23].

Part used: The medicinal part is the whole flowering plant [23].

Chemical constituents

The literature reveals that the chemical constituents of *Bellis perennis*(Asteraceae) included triterpenoidsaponins, triterpenes, several anthocyanins, flavonoids and polyacetylenes**.** The chemical investigation of the essential oils from the aerial organs of *Bellis perennis* showed that polyacetylenes were one of the dominant class of compounds [28].However,*Bellis perennis* contained triterpenesaponins (2.7%) [23]. Four novel triterpenoidsaponins were isolated from the underground parts of *Bellis perennis*. The structures were elucidated as 3-O-beta-D-glucopyranosides of 2 beta,3 beta,16 alpha-trihydroxyolean-12-ene-28-oic acid-28-alpha-L- rhamnopyranosyl(1----2)-[beta-D-glucopyranosyl(1----6)]-beta-D- glucopyranoside, 2 beta,3 beta,23-trihydroxyolean-12-ene-28-oic acid-28-O-beta-D-xylopyranosyl (1----2)-[beta-D-glucopyranosyl (1----6)]- beta-D-glucopyranoside and 2 beta,3 beta,23-trihydroxyolean-12-ene-28-oic acid-28-O-alpha-L-rhamnopyranosyl(1----2)-[beta-D-glucopyranosyl(1----6)]- beta-D-glucopyranoside and as 3-O-alpha-L-rhamnopyranosyl-2 beta,3 beta,23-trihydroxyolean-12-ene-28-oic acid-28-O-beta-D-glucopyranosyl(1----2)-[beta-D-glucopyranosyl(1----6)]- beta-D-glucopyranoside [29].

From the saponin fraction, seven new triterpenesaponins, perennisosides I, II, III, IV, V, VI, and VII, were isolated together with four previously isolated saponins, bellidioside A, asterbatanoside D , bernardioside B2, and bellissaponin BS6 [26].

Five new triterpene saponins perennisosides VIII, IX, X, XI, and XII were isolated from the methanol-eluated fraction of the methanolic extract from the flowers of *Bellis perennis* [30]. In addition, six acylated oleanane-type triterpene oligoglycosides, perennisaponins A, B, C, D, E, and F, were isolated from the flowers of *Bellis perennis* together with 14 saponins, nine flavonoids, and two glycosides [14].

The plant contained polyphenols and flavonoids,the variations in total phenolic and flavonoid contents of *Bellis perennis* flowers were studied. The contents of flavonoids varied from 0.31 to 0.44 mg quercetin equivalent/100 mg dry weight and from 1.37 to 2.20 mg pigenin-7-glucoside equivalent/100 mg dry weight. Total phenolics ranged from 2.81 to 3.57 mg gallic acid equivalent/100 mg dry weight. Contents of phenolics and flavonoids as well as antioxidant activity of daisy flowers vary to a relatively small extent during the year and were not dependant on the time of collection. Thus, the flowers possess comparable quality as to these characteristics over the whole flowering season of *Bellis perennis* [31-32]. The phenolic compounds of *Bellis perennis* included flavonoids (quercetin, apigenin, kaempferol, isorhamnetin, apigenin-7-O-β-D-glucoside, apigenin-7-O-β-D-glucuronide, apigenin-7-O-(6´´-*E*-caffeoyl)-β-D-glucoside, apigenin-7-O-β-Dmethylglucuronide, isorhamnetin-3-O-β-D-galactoside, isorhamnetin-3-O-β-D-(6´´-acetyl)-galactoside, and kaempferol-3-O-β-D-glucoside), anthocyanins (three glucuronylated and malonylated cyanidin-3-glucosides), phenolic acids (caffeic, ferulic, sinapic, p-coumaric, and salicylic acids) and tannins [10,12, 33-37].

PHARMACOLOGICAL EFFECTS

Antimicrobial effect

The antimicrobial effect of the aqueous and ethanolic extracts of the aerial parts of *Bellis perennis* was studied by *in vitro* method. Among the microorganisms tested, the most susceptible strains were *Staphylococcus epidermidis*MU 30 and *Staphylococcus aureus*MU 38. The antibiofilm effect of the extracts was measured by microplate biofilm method. Ethanolic extract of *Bellis perennis*did not inhibit biofilm formations of the tested microorganisms, however the aqueous extract showed limited anti-biofilm activity against *P. aeruginosa* ATCC 27853, *P. fluorescens* MU 181 and *S.epidermidis* MU 30 at 10 mg/ml concentration. Anti-Quorum Sensing (QS) activity of extracts was determined using biosensor bioassay with *Chromobacteriumviolaceum* CV026. The concentration of 100 mg/ml of aqueous extract of *Bellis perennis*showed promising anti-QS activity on *Chromobacteriumviolaceum*CV026 with zone of pigment inhibition of 10mm. Inhibition of QS-regulated violacein production in *Chromobacteriumviolaceum* ATCC 12472 and swarming motility in *Pseudomonas aeruginosa*PA01 were carried out using standard methods. Aqueous and ethanol extracts of *Bellis perennis* inhibited swarming by 9.5% and 38.1%, respectively. The results suggest that *Bellis perennis* could be an alternative source to explore for useful contents in the fight against bacterial infections [38]. Deca-4,6-diynoic acid and deca-4,6-diyne-1,10-dioic acid showed antimicrobial activity, the two compounds effective against Gram-positive and Gram-negative bacteria, respectively [28].

Bellis perenni extract showed *in vitro* and *in vivo* antifungal activity [39].Triterpenoid glycosides obtained from *Bellis perennis* inhibited the growth of human-pathogenic yeasts (Candida and Cryptococcus species). The intensity of growth inhibition is influenced particularly by the carbohydrate chains of the glycosides. Monodesmosidic as well as bisdesmosidic glycosides of polygalacic acid exert fungicidic effects [40].

Effect on nervous system

The effects of aqueous extract of flowers from *Bellis perennis*on anxiety-like behavior and memory in Wistar rats were tested.*Bellis perennis (*20 and 60 mg/kg)administrated rats, spent more time at the center, showed less mobility and velocity. In the elevated plus maze, the high dose of *Bellis perennis* administrated rats spent more time in the open arms, spent less time in the closed arms, were less mobile, were slower and rotated less frequently. In the Morris water maze, the high dose of *Bellis perennis* administrated rats spent more of the time to find the platform. In conclusion, *Bellis perennis* may produce biphasic effects on both anxiety-like behaviour and learning performance of the rats [7]. The effect of *Bellis perennis* was investigated on viability of healthy neuronal cell line. On treatment with 90% alcohol, the cell viability was significantly decreased to 18% as compared to the negative control (only media) which was taken as 100%. The effect of alcohol was neutralized by *Bellis perennis*at 2µl/ml, 4µl/ml and 8µl/ml. It significantly increased the cell viability [41].

Effect on skin wound healing

*Bellis perennis*was used as skin lightening drug (Belides^{TM}, *Bellis perennis*flower extract). It affected the metabolic pathways involved in melanin synthesis. It inhibited tyrosinase, transcriptional control of tyrosinase expression, reduced pro-melanogenic mediators endothelin, and α MSH (melanin stimulating hormone), as well as reducing melanosometransfere keratinocyte [42]

The wound healing activity of *Bellis perennis* flowers was evaluated in Wistar albino rats. Dried *Bellis perennis* flowers were extracted with ethanol, then fractioned with n-butanol and an ointment was prepared from the n-butanol fraction. Six wounds were created for each animal by using circular excision wound model. The first two wounds were treated topically with HOTBp (hydrophilic ointment treatment containing n-butanol fraction). The second two wounds were control group and not treated with anything. The third two wounds were treated only with HOT (hydrophilic ointment treatment without n-butanol fraction). Treatments were applied once a day and lasted for 30 days. Wound samples were excised on days 5th, 10th and 30th. The percentage of wound healing was calculated by Walker's formula after measurement of the wound area and the tissue samples

were examined histopathologically. The percentages of wound closure (HOTBp: 100%; HOT: 85% and control: 87%) and histopathological observations showed that there were statistically significant differences between HOTBp, HOT and control groups ($p < 0.05$) at 30th day. The authors concluded that topically administered ointment prepared from the n-butanol fraction of *Bellis perennis*flowers has a wound healing potential without scar formation in circular excision wound model in rats [20].

*Bellis perennis*is the homeopath's first choice for deep tissue injury, it is also one of the top remedies for joint and muscular soreness, deep tissue injuries and sport occidents [43-44].

Antiinflammatory effect

In two placebo-controlled studies, Traumeel injections, (which contains *Bellis perennis*)was used in patients with hemarthrosis. It showed that Traumeel injections improved joint and mobility, and decreased intensity of pain and effusion [45-46].

Cytotoxic effect

Butanol extract of flowers of *Bellis perennis*showed antitumor activity when evaluated by potato disc tumor induction bioassay (93% inhibition). The active constituent is a saponin [3-*O*-α-rhamnopyranosylpolygalacic acid 28-*O*-{α-rhamnopyranosyl-(1→3)-β- Xylopyranosyl(1→4)-α-rhamnopyranosyl-(1→2)-[α- arabinofuranosyl -(1→3)-4-*O*-acetyl-β-fucopyranoside][(47)]. Antitumor activities of different fractions of *Bellis perennis*flowers at different concentrations were evaluated using potato Disc tumor induction bioassay. The most active fraction showed 99% tumor inhibition at 3000 mg/l [48].

Antioxidant effect

Antioxidant [1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical scavenging, reducing activity and total antioxidant activity of the plant materials were studied. The aqueous extracts of the aerial parts showed higher DPPH scavenging activity (85.8% at 102.5 microg/ml) than the methanol extract. Reducing power was also observed for both tested extracts, where the formation of linoleic acid peroxides was more for the aqueous extract than the methanol extract of the aerial parts [49].

The antioxidant capacity of the aqueous and ethanolic extracts of the aerial parts of *Bellis perennis* was also determined by the ferric thiocyanate (FTC) and the 1,1-diphenyl-2-picrylhydrazyl (DPPH) free-radical scavenging assays. Extracts showed weak radical scavenging activity with the DPPH method. IC_{50} values were found as 37.85 mg/ml for ethanolic extract and 96.98 mg/ml for aqueous extract, respectively. Results obtained from FTC assay showed 16.98% inhibition for ethanolic extract and 58.14% inhibition for aqueous extract compared with BHT (63.36% inhibition) and ascorbic acid (77.67% inhibition) [38].

Apigenin-7-O-ghicopyranoside (ApG), a flavonoid isolated from the flowers of *Bellis perennis* L., showed strong *in vitro* antioxidant potential, because of the capacity of removal of hydroxyl radicals and nitric oxide, and also prevented the formation of thiobarbituric acid-reactive substances. These parameters were inhibited at the highest concentration of ApG at rates of 77.7%, 72% and 73.4%, respectively, its inhibitory effect on acetyl cholinesterase, suggesting potential use in the treatment of neurodegenerative diseases [37].

The antioxidant activity of *Bellis perennis* flowers was determined by a 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay. The antioxidant activity expressed as IC_{50} values varied from 66.03 to 89.27 µg/ml; it is about 50, 30, 20, and 10 times lower as compared with quercetin, ascorbic acid, Trolox®, and butylhydroxytoluene, respectively, and about five times higher in comparison with apigenin-7-glucoside. There is a significant correlation between antioxidant activity and total phenolics. No correlation between total flavonoid contents and antioxidant activity was observed [32].

Hypolipidemic effect

The methanolic extract and its saponin fraction (methanol-eluted fraction) of the flowers of *Bellis perennis* were found to suppress serum triglyceride elevation in olive oil-treated mice. Among these saponins, perennisosides I and II showed inhibitory effects on serum triglyceride elevation at doses of 25-50 mg/kg orally [26]. As a result of hypolipidemic effect of saponin constituents isolated from the flowers of *Bellis perennis*, it also can be utilize as preventive drug in ischemic diseases and as an anti-obese remedy [50].

Antihemorrhagic and hemolytic effect

The effect of *Bellis perennis* on postpartum blood loss was studied by double blind, placebo-controlled, randomized, clinical trial. At 72h postpartum, mean Hb levels remained similar after treatment with homeopathic remedies (12.7 versus 12.4) as compared to a significant decrease in Hb levels in the placebo group (12.7 versus 11.6; $p<0.05$), in spite of less favorable initial characteristics of the treatment group. The mean difference in Hb levels at 72h postpartum was -0.29 (95% CI -1.09; 0.52) in the treatment group and -1.18 (95% CI -1.82; -0.54) in the placebo group ($p<0.05$) [51].*Bellis perennis* showed haemolytic activity. It has been found that the haemolytic activity of the drug changes in dependence on the time of collection of capitula during the year; it is lowest in March, then it increases, reaching the maximum in summer months (June, July and August), and then it decreases again [52].

Other pharmacological effects

The methanolic-eluted fraction of the methanolic extract from the flowers of *Bellis perennis* was found to inhibit gastric emptying in olive oil-loaded mice at a dose of 200 mg/kg, orally [30]. The plant also acts as an astringent, reduces mucous production, and also has anti-inflammatory and fever-reducing effects, possibly due to the triterpenesaponin content [23].

Contraindications and adverse effects

No health hazards or side effects are known in conjunction with the proper administration of designated therapeutic dosages [23].

Dosage

The drug is used topically as an extract, in teas and in poultices of pressed leaves for the treatment of skin diseases. A decoction can be used for wound poultices. An infusion is prepared by adding 2 teaspoonfuls of plant to 2 cups of water, then allowing it to draw for 20 minutes. The daily dose of the infusion is 2 to 4 cups per day. A decoction is made from the green leaves [23].

CONCLUSION

The paper reviewed *Bellis perennis* as promising medicinal plant with wide range of pharmacological activities which could be utilized in several medical applications because of its effectiveness and safety.

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