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ORIGINAL ARTICLE

Asperugo Procumbens: a Review of Botany, Traditional Uses, Phytochemistry and Pharmacology

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ABSTRACT

Asperugo procumbens is a medicinal plant widely distributed in the world, which is commonly used in the traditional medicine of the Middle East, while currently overlooked in European pharmacopoeias. The aim of the study is to present a comprehensive overview of A. procumbens in botany, traditional medicine, phytochemistry and pharmacology according to the up-to-date data. Scientific literature on the species was collected based on publicly available databases such as: PubMed, Web of Science, Scopus, Google, Google Scholar as well as monographs and PhD theses. In traditional medicine the aerial part of A. procumbens is used for treatment of skin infections, herpes, liver and respiratory tract diseases, to strengthen the heart and the nervous system, and others. Contemporary studies on the pharmacological activity of A. procumbens revealed that it exhibits a wide range of pharmacological properties, including antioxidant, antidepressant, sedative-hypnotic, antibacterial, as well as chemopreventive and antihypertensive properties. Despite many proven medicinal properties, the species does not have a developed phytochemical profile and its chemical composition is very poorly understood. The species is known to contain tannins, flavonoids and phenolics. Only the content of fatty acids is recognised in detail. The species is a good source of omega-3 fatty acids – stearidonic acid (SDA), α-linolenic acid (ALA), and omega-6 fatty acid – γ-linolenic acid (GLA). This article, based on the available literature, highlights the traditional uses, phytochemistry and pharmacological properties of A. procumbens, which may provide a foundation for further pharmacological study as well as clinical application of the species.

Keywords: Asperugo procumbens, German madwort, Boraginaceae, traditional uses

INTRODUCTION

Asperugo procumbens L. (German madwort) is a flowering plant included in the Boraginaceae family. There are many species in this family that are used in pharmacology and cosmetology. The therapeutic effect of plants of the Boraginaceae family is extensive and depends on the content of biologically active compounds. These mainly include flavonoids, terpenoids, naphthoquinones as well as phenols, which may have i.a. antimicrobial, antitumor, antiviral, anti-inflammatory effects[1, 2].

Despite abundant evidence from ethnobotanical research into the traditional use of the plants from the Boraginaceae family, the medical properties of many of them remain undiagnosed or not fully known. Therefore, attention should be paid to unexamined or poorly studied species from the borage family, such as Asperugo procumbens, in order to recognise their phytochemical composition and determine their therapeutic effect. The results of such research can provide knowledge about new sources of natural biologically active compounds and their potential use in medicine[2]. Ethnobotanical data from mainly Iranian traditional medicine, preliminary phytochemical studies and experimental studies suggest a broad therapeutic effect of A. procumbens, which is hardly ever found in Western medicine.

The traditional use and pharmacological properties of A. procumbens have been summarised. The available phytochemical data were also presented, indicating the need for research on the chemical identification of the species. The presentation of current data on the phytochemistry and pharmacology of the species is intended to provide the basis for further, more detailed research on its high therapeutic potential.

MATERIAL AND METHOD

Botanical description: Morphological characterisation

Asperugo procumbens is an annual from monotypic genera Asperugo L. The species has a procumbent or climbing stem (up to 70 cm) with stiff and deflexed hairs. Leaves are lanceolate, subacute to obtuse, entire or slightly dentate. Corolla is infundibuliform, initially purplish during development, turns violet, and has white scales in the throat. The calyx is lobed almost to the base, the lobes are life-like, dentate, accrescent and deltate in fruit to form a 2-lipped valves covering the nutlets[3, 4, 5].

Phytogeography: The natural range of A. procumbens covers Europe with the adjacent part of North Africa (from the Mediterranean coasts to the Urals; in the north – to central Scandinavia), Siberia and Central Asia. It was also introduced to North America[6]. However, in some regions of Europe (e.g. in the central-eastern part), A. procumbens is considered to be a naturalised archaeophyte[7, 8].

A. procumbens usually occurs in anthropogenic habitats like waste sites and farmyards, cultivated fields and their margins, hedges, gardens, weedy shrubs, resting places for cattle in mountainous locations, below cliffs in lower mountain belts, roadside, embankments and rubble sites. It grows in fertile, clay and sometimes rocky soils[3, 4, 5, 7, 9].

Publication search: An extensive search of the literature related to A. procumbens was carried out to gather all relevant information on its traditional uses, phytochemistry and pharmacological properties. Publicly available databases and primary sources were searched, including PubMed, Web of Science, Scopus, Google, Google Scholar, as well as monographs and PhD theses. Literature was reviewed regardless of the year of publication. The search for information about A. procumbens was carried

out using Latin names, using the phrases “Asperugo procumbens”, “A. procumbens”, “Asperugo”. The selected data involved traditional uses, phytochemicals, and pharmacological activities. The species name is given according to The Plant List (www.theplantlist.org).

RESULTS

Traditional uses: In the traditional medicine of the Middle East (Iran, Iraq), A. procumbens is considered a medicinal plant with a wide therapeutic effect (Table 1). In traditional Iranian (Persian) medicine, the aerial part of the species is used to strengthen the nervous system and the heart, counteract dementia, as an antispasmodic and tranquilliser. A. procumbens is also applied as medicine for the treatment of skin infections and herpes[10, 11, 12, 24], the different liver diseases, asthma as well as mean of improving digestion and stomach strengthening[16, 17, 18]. It is also useful in all kinds of phlegmatic, hiccup, refreshing and mouth aromatics[14]. In Pakistan, the decoction of A. procumbens is considered a medicine for respiratory tract diseases like throat infections and chest problems[25].

[Table 1]: Finding the remains of the species in medieval monastic gardens in Iceland and Norway suggests that the species was also treated as medicinal herb in Europe[26]. Nineteenth-century German authors treated A. procumbens as a medicinal plant, which was rarely used even then (considered as obsolete). The aerial part of the plant was applied, referred to as Herba Asperuginis. Moreover, it was used as food (eaten as a vegetable)[27, 28]. In Poland, the species has been used in folk medicine, but its properties have not been specified[29].

Table 1. Traditional uses of the Asperugo procumbens.

Country	Traditional uses and literature sources
Iran	for treatment of skin infections, to strengthen the nervous system; refreshing, tranquillising and mood-elevating activities, as well as antispasmodic[10, 11, 12, 13] used as a mild sedative with mood-elevating activities, for treatment of skin infections and herpes, to strengthen the heart and the nervous system, for all kinds of phlegmatic, hiccup, refreshing and mouth aromatics[14] nerve system relaxant, antispasmodic, menstruate[15] asthma[16] stomach-strengthening, improving digestion[17] liver diseases[18] sedation[19] antihypertensive, diuretic, cardiotonic activity[20, 21] dementia[22] treatment of diabetes[23]
Iraq	skin infections[16, 24]
Pakistan	respiratory tract diseases (including throat infections and chest problems) and nausea[25]

Phytochemistry: In recent years, several studies have been carried out to confirm the therapeutic effects of A. procumbens known from traditional medicine. Despite the growing interest in the species, its phytochemical profile has not been studied so far. Only preliminary studies informing about the general chemical composition can be found. The phytochemical analysis confirmed the presence of, among others, flavonoids, phenolics and tannins in the extract[12, 14, 18, 21]. Only the fatty acids present in the plant have been studied in detail[30].

Fatty acids: Selected plants (including A. procumbens) were tested by Guil-Guerrero et al.[30] for new sources of γ-linolenic acid (18: 3ω6, GLA). Relatedly, the profiles of fatty acids from the seeds, stems, roots, flowers and leaves of the species were determined. Stearidonic acid (18:4ω3, SDA) was found to be abundant in the seeds, flowers, leaves, stems, roots of A. procumbens (11.75, 10.0, 17.7, 8.64, 8.80 % saponifiable oils, respectively). A high content of leaf saponifiable oils in this species (4.89% of dry wt) leads to a value of 0.86% of SDA in this organ. The results of the analyses (Table 2) show that individual organs of A. procumbens are a good source of some health-promoting fatty acids: omega-3 fatty acids – stearidonic acid (18:4ω3, SDA – in all examined organs), α-linolenic acid (18:3ω3, ALA – in seeds and roots); omega-6 fatty acid – γ-linolenic acid (18:3ω6, GLA – in seeds); omega-9 fatty acid – oleic acid (18:1ω9, OA – in seeds and flowers).

[Table 2] Pharmacology Antibacterial activity: Only one report has been found that demonstrates the antibacterial activity of A. procumbens[12]. In this study, petroleum ether, chloroform, ethanol, methanol and aqueous extracts of A. procumbens were investigated for their antibacterial activities against Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Salmonella typhi and Staphylococcus aureus with the agar-well diffusion method. The highest activity against the tested bacteria is shown by the methanol extract, which demonstrated the highest mean inhibition zone and a minimum inhibitory concentration (MIC) value of 1.56 mg/ml for K. pneumoniae, S. aureus and S. typhi, as well as 12.5 mg/ml for E. coli and P. aeruginosa. Ethanol extracts also displayed good antibacterial activities, while aqueous extracts showed weaker activity. Both the chloroform and the petroleum extracts had no antibacterial effect. The authors assume that tannin and phenolics are responsible for the antibacterial activity of the species and indicate that detailed phytochemical analyses of the species are necessary.

Table 2. Composition of the main fatty acids[a] from organs of the Asperugo procumbens[30, modified].

Organs	Oil%[b]	14:0	16:0	16:1ω7	18:0	18:1ω9	18:1ω7	18:2ω6	18:3ω6	18:3ω3	18:4ω3	20:0	20:1ω9	20:2ω6	22:0	22:1ω9	24:0	24:1ω9
seeds	19.16	0.12	8.07	0.16	1.85	15.48	0.62	15.2	5.35	36.46	11.75	0.19	2.03	0.12	0.24	0	0	0
flowers	-	-	-	-	-	1.73	-	-	-	-	10	-	-	-	-	-	-	-
leaf	4.45	-	9.51	-	-	-	-	-	-	-	17.7	-	-	-	-	-	-	-
stem	-	-	-	-	-	-	-	-	-	-	8.64	-	-	-	-	-	-	-
root	-	-	-	-	-	-	-	-	-	19.7	8.8	-	-	-	-	-	-	-

[a]Figures on a dry wt. basis.[b]g/100 g of seeds.

Antidepressant and sedative-hypnotic activity: The hydroalcoholic extract of A. procumbens was evaluated by Mirshafa et al.[13] for antidepressant and sedative-hypnotic activity in mice. Furthermore, the effect of flumazenil on the hypnotic activity of the extract was investigated. The results of the experiment point to weak antidepressant and good sedative-hypnotic effects of the hydroalcoholic extract of the aerial parts of A. procumbens in mice.

Two animal models (FST – the forced swimming test and TST – tail suspension test) were used to demonstrate the antidepressant effect of the extract. In both models, results indicated that none of the doses of the extract could reduce the immobility time in mice significantly compared with the control. The authors suppose that the low antidepressant effect of the A. procumbens hydroalcoholic extract is due to the route and duration of administration of extracts, which may affect the pharmacokinetics of the active compounds. They suggest that oral and chronic administration of the extract (according to traditional use) may give better results in humans.

The pentobarbital-induced hypnotic test was used to evaluate the sedative-hypnotic activity of the species. Hydroalcoholic A. procumbens extract in doses of 250 and 400 mg/kg, administered intraperitoneally, caused significantly prolonged pentobarbital-induced sleeping time compared to vehicle control. Furthermore, all of the doses of the extract significantly reduced the latency to sleep. Administration of flumazenil (a specific antagonist of the benzodiazepine site in the $GABA_A$) in the next stage of the experiment significantly inhibited the effects of the extract of A. procumbens on pentobarbital-induced sleeping behaviour. On this basis, the authors assume that the hypnotic activity of the extract of A. procumbens is involved in the activation of $GABA_A$ – benzodiazepine receptors. It is possible that the hitherto unidentified flavonoids of the A. procumbens contribute to the hypnotic effect of the species through benzodiazepine receptors.

In the subsequent study, the antidepressant activity of A. procumbens hydroalcoholic extract was compared with fluoxetine in the human model[14]. The double-blind study was conducted on 30 outpatients with mild to moderate depressive disorder (i.e. those who scored 18-25 on the Hamilton Depression Rating Scale, HDRS). One of the groups of outpatients received a 10 mg fluoxetine capsule, while the other group received a capsule containing 1.2 g of dried extract of A. procumbens orally per day. The recovery process was assessed by the HDRS in weeks 0, 2, 4 and 6. After the fourth week, a significant decrease in HDRS was observed in both groups. It is interesting that the onset of action of A. procumbens was faster than fluoxetine. However, after the sixth week, fluoxetine began to show greater antidepressant activity than A. procumbens ($p = 0.03$). Perhaps by increasing the dose of A. procumbens or by continuing the trial for more than six weeks, a more favourable therapeutic effect could be obtained.

The authors of both articles[13, 14] conclude that further phytochemical and pharmacological analyses of the species should be performed to isolate and characterise the active compounds that produce the antidepressant and sedative-hypnotic effects.

Antihypertensive activity: A. procumbens and 134 other plants used in traditional Iranian medicine, such as antihypertensive, cardiotonics and diuretics, have been tested for the inhibitory activity of their angiotensin-converting enzyme (ACE)[21]. ACE inhibitors are widely used in the treatment of hypertension and heart failure. Aqueous and ethanol extracts of the aerial part of A. procumbens were investigated. The enzyme assay was carried out using the HPLC method. Ethanol A. procumbens extract revealed relatively high ACE inhibitory activity (52% ACE inhibition), while the aqueous extract showed no activity. The tannins found in the ethanolic extract may be responsible for the inhibitory activity of the species. Despite the relatively high ACE inhibitory activity of the ethanol A. procumbens extract, it is not indicated by the authors as a plant with high potential antihypertensive activity.

Antioxidant and chemopreventive activity: Arabsalmani et al.[18] evaluate the antioxidant and chemopreventive effects of the aqueous extract of A. procumbens (AAP) against diethylnitrosamine (DEN)-induced hepatocellular carcinoma (HCC) in rats. AAP-treated rats were pretreated with the extract intragastrically at three different doses (100, 200, and 400 mg/kg) two weeks before DEN injection. At the end of the experiment, rats pretreated with AAP showed a significant reduction of serum biomarkers of liver damage and cancer, like: alfa-fetoprotein (AFP), alanine transaminase (ALT), gamma-glutamyl transpeptidase (GGT), as well as aspartate transaminase (AST), compared to DEN-treated rats.

The authors also investigated the in vitro and in vivo antioxidant activities of APP by determining the hepatic oxidative stress markers (glutathione – GSH, malondialdehyde – MDA level in liver homogenate) and using the 1,1-diphenyl-2-picryl hydroxyl (DPPH) method. The results indicate that the A. procumbens extract counteracted DEN-induced oxidative stress and restored GSH concentrations in the liver of AAP-treated rats. German madwort extract administered to DEN-treated rats decreased MDA levels and thus liver lipid peroxidation. Lastly, the pretreatment of the German madwort extract to DEN-treated rats also caused a significant decrease in relative liver weight. The authors assumed that the preventive effect of A. procumbens against HCC may be due to the antioxidant, anti-inflammation, and anti-carcinogenic activities of the polyphenols present in the extract. Moreover, the authors suggest that further research is needed to clarify which active constituents induce the chemopreventive effect of the A. procumbens against liver cancer and to elucidate mechanisms underlying the effect.

Against urease activity: Nabati et al.[31] studied 137 traditional Iranian medicinal plants for their urease inhibitory activity, which could be used to treat Helicobacter pylori infection. Inhibition of the urease enzyme activity results in an increased sensitivity of the H. pylori in an acidic environment and thus natural elimination by the acidic conditions inside the stomach or the body's immune system. The plants were examined against Jack bean urease activity by the Berthelot reaction. Each plant was extracted using 50% aqueous methanol. A. procumbens extract revealed weak urease inhibitory activity (12.43%

inhibition against urease activity at 10 mg/ml concentration). The IC_{50} value for the species has not been determined. Therefore, the herb is unlikely to be used in the treatment of H. pylori.

CONCLUSIONS

Contemporary pharmacological studies have confirmed that A. procumbens has a wide range of pharmacological properties, including antibacterial activity, antihypertensive activity, antidepressant and sedative-hypnotic activities, antioxidant and chemopreventive activities, and others that make this species highly applicable in the pharmaceutical industry. Unfortunately, there are still no systematic extraction or separation studies to establish the phytochemical profile of the species. Aside from the fatty acids, the detailed chemical composition of the species remains unknown. In the studies of pharmacological activities of the species, total plant extracts were used and, in principle, no attempts were made to isolate bioactive constituents and thus identify molecular mechanisms. Therefore, it is necessary to intensify research on the detailed chemical composition and biological activity of individual constituents in order to fully discover and use the therapeutic potential of the species.

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