

# ***Agrimonia* – biological activity and perspectives for medicinal application. Part I**

## ***Rośliny rodzaju Agrimonia – ich biologiczna aktywność i perspektywy zastosowania w medycynie. Część I***

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### **Summary**

The menopause-related alteration in a woman's body may include a variety of disorders, such as obesity, metabolic syndrome, changes in immune response or haemostatic parameters, and oxidative stress. Some plant-derived substances have been used for many years as an alternative for oestrogen therapy in the treatment of various menopausal symptoms. Among these compounds, the best known are isoflavones. However, also other biologically active compounds, that are present in herbs, should be taken into account as potential therapeutic agents. The growing number of reports has confirmed favourable effects of plants belonging to the *Agrimonia* genus. Three species of them occur in Poland: *Agrimonia eupatoria* L., *Agrimonia pilosa* Ledeb., and *Agrimonia procera* Wallr. In the present review, the available data and recent findings on the potential use of different plants from *Agrimonia* genus in prevention and therapy of various disturbances of the inflammatory system and cardiovascular disorders are described. One of the most important aspects of the medicinal application of *Agrimonia* plants is their possible role in the protection of the cardiovascular system against changes associated with menopause.

**Key words:** *Agrimonia*, biological activity, medicinal application.

### **Streszczenie**

Zaburzenia hormonalne pojawiające się u kobiet w okresie okołomenopauzalnym prowadzą do szeregu zmian zachodzących w ich organizmie, w tym do zakłóceń metabolicznych, otyłości, rozchwiania systemu immunologicznego, zaburzeń układu hemostazy oraz zmian statusu *red-ox*. Znane są substancje pochodzenia roślinnego, które są stosowane w hormonalnej terapii zastępczej w celu łagodzenia skutków wielu symptomów menopauzalnych. Pośród tych związków najlepiej poznane są izoflawony, jednak istnieje szereg roślin leczniczych i ziół zawierających wiele aktywnych biologicznie substancji, których działanie można rozpatrywać jako potencjalnych środków terapeutycznych pod kątem łagodzenia i/lub zapobiegania objawom menopauzy. Rośnie liczba doniesień dotyczących prozdrowotnych właściwości roślin należących do rodzaju *Agrimonia* obejmującego trzy gatunki występujące w Polsce: *Agrimonia eupatoria* L. (rzepik pospolity), *Agrimonia pilosa* Ledeb. (rzepik szczeciniasty) oraz *Agrimonia procera* Wallr. (rzepik wonny). Prezentowana praca przedstawia przegląd dostępnych danych dotyczących potencjalnych właściwości leczniczych różnych odmian rzepiku w ochronie i terapii zaburzeń związanych z powstawaniem i rozwojem stanu zapalnego oraz zmian w układzie sercowo-naczyniowym. Jednym z najważniejszych aspektów wykorzystywania roślin z rodzaju *Agrimonia* w profilaktyce i leczeniu zaburzeń wywołanych zmianami menopauzalnymi jest ochrona układu sercowo-naczyniowego kobiet w okresie malejącej produkcji hormonów estrogenowych.

**Słowa kluczowe:** rośliny rodzaju *Agrimonia*, aktywność biologiczna, zastosowanie w medycynie.

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## Introduction

It is known that young women during their fertile life are at lower risk of cardiovascular events compared with men, being protected by oestrogen action in their premenopausal life. The incidence and death from cardiovascular events dramatically increase in women after menopause. A growing number of reports have suggested the important role of oxidative stress in female patients as a pathology regarding female cardiovascular disease (CVD). In general, oxidative stress is higher in men than in premenopausal women, but after menopause the risk of experiencing cardiovascular events rapidly rises in women, in conjunction with a parallel increase in oxidative stress biomarkers. The menopausal status appears to enhance the development of CVD by several unfavourable changes in metabolism and haemodynamic parameters. Menopause and oestrogen deficiency lead to vasomotor symptoms, such as hot flushes and night sweats, insomnia and cognitive dysfunction. Both aging and menopause are also associated with osteoporosis as well as increased risk of cardiovascular disease. It is well known that the incidence of CVD rapidly rises after the menopause [1]. Menopausal disorders are usually treated with synthetic oestrogens. Nevertheless, the conventional hormone replacement therapy (HRT) is supposed to increase the risk of breast cancer, uterine cancer, thromboembolism, heart disease and stroke [2]. Therefore herbal/phytochemical supplements are of increasing interest as potentially useful in the prophylaxis or in clinical routine. Some plant-derived substances are widely studied as potential alternatives for oestrogen therapy that is administered to treat menopausal symptoms [3]. Plant extracts have been used for many years to cure or to moderate the vasomotor symptoms of menopause, partly due to natural phytoestrogenic agents (isoflavones) occurring in these plants. However, it should be underlined that phytoestrogens are only a part of biologically active compounds that are present in herbs. Furthermore, menopause-related alteration in a woman's body may include a variety of disorders, such as obesity, metabolic syndrome, changes in immune response or haemostatic parameters, and oxidative stress [4]. Therefore, studies on new plant extracts with wide biological activity and beneficial effects are intensively developed.

There is a lot of evidence for beneficial effects of plants from the *Agrimonia* genus. *A. eupatoria* extract has been used traditionally in Europe as an astringent, cholagogue, diuretic and antidiabetic agent [5]. *A. japonica* has been used in Japan as an anti-diarrhoeal and haemostatic [6]. In some countries, *A. pilosa* has been administered for treating cough and colds, and the powder of the root, suspended in hot water, has been given to relieve stomach disorders [7]. This plant has been used in the treatment of abdominal pain, sore

throat, headaches, bloody and mucoid dysentery and heat stroke [8]. In addition, the aerial parts of *A. pilosa* were listed in the Chinese Pharmacopoeia as an astringent haemostatic for treating various types of bleeding, including bloody dysentery, and also to counteract toxins and reduce swelling for treating boils and sores [9]. Pharmacological studies on the extracts prepared from the aerial parts of *A. pilosa* demonstrated a wide range of biological properties, such as anti-hemorrhagic [10], antiplatelet [11], antioxidant [12], nitric oxide scavenging [13], and acetylcholinesterase inhibitory [14] activities. Antiviral and antimicrobial action of *Agrimonia* species has been observed for hepatitis B virus (HBV) [15], herpes simplex virus (HSV), and respiratory syncytial virus (RSV) [16]. Moreover, *A. eupatoria* reveals an inhibitory effect on *Bacillus cereus* and *Bacillus subtilis* [17].

## Antioxidative and anti-inflammatory properties of *Agrimonia* plants

Chronic inflammation and the subsequent oxidative stress are associated with the increased risk of human cancers and with the pathogenesis of various disorders of the circulatory system [18]. The disease preventive abilities of numerous plants (including herbs) are attributed mainly to their high content of flavonoids. *Agrimonia eupatoria* L. has been reported to possess a high concentration of flavonoid antioxidants: flavan-3-ols, flavonols, flavones and phenolic acids. As it was estimated by Correia et al. [19], in the aerial parts of *A. eupatoria* L. ethyl acetate fraction, flavan-3-ols are present at a high concentration (18.96%), and contain catechin and catechin-type oligomers (i.e. procyanidins), that are the major flavan-3-ols in the fraction. Another study of these scientists showed that *A. eupatoria*-derived extract revealed a strong antioxidative activity. Both the hydroalcoholic extract and polyphenol-enriched fraction from *A. eupatoria* scavenge superoxide anion, hydrogen peroxide, hypochlorous acid, and peroxyxynitrite. The authors suggest that the demonstrated significant scavenging capacity of reactive species by polyphenols from *A. eupatoria* might be a part of the anti-inflammatory effects of the extracts from this plant [20]. Procyanidins isolated from *A. eupatoria* in the ethyl acetate fraction also revealed antioxidant and anti-inflammatory properties. In addition, procyanidins may cause inhibition of blood platelet aggregation; probably, this activity is associated with the antioxidant activity of these compounds [21, 22]. Recent studies on antioxidative properties of *A. eupatoria* showed the significant neuroprotective effects of the extract obtained from this plant against glutamate-induced toxicity of hippocampal HT22 cells [23]. Moreover, some of the available data on *A. eupatoria* physiological action indicate that even the seeds of this plant may reveal beneficial effects, such as antibacterial and free radical scavenging activity [17].

Antioxidative and anti-inflammatory effects have also been described for *Agrimonia pilosa*. Recently (2010), He et al. [24] demonstrated the strong antioxidative action of *A. pilosa*, confirmed by the determination of reducing power, total antioxidant capacity and free radical scavenging assays. The beneficial or therapeutic properties of both aqueous and alcoholic extracts from this herb are well known. It has been estimated by the HPLC method that *A. pilosa* contains numerous biologically active compounds, including quercetin, quercitrin, hyperoside, taxifoliol, luteolin-7-O-beta-D-glucopyranoside and rutin. Therefore, this plant is considered to be a very promising source of natural antioxidants and a dietary nutritional supplement, helpful in the prevention and therapy of oxidative stress-related diseases. For example, in China, the aqueous extract from *A. pilosa* is commonly administered to combat asthenia and fatigue. Zhu et al. [12] reported that some butanol-soluble compounds present in the aqueous extract of *A. pilosa* are responsible mainly for  $\cdot\text{OH}$  radical-scavenging activity. *A. pilosa* has also been used traditionally to treat various inflammations, including those related to allergic diseases. Results obtained by Jung et al. [25] indicate that *A. pilosa* alcoholic extract has anti-inflammatory activity, mostly due to the suppression of inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS) production. The enhanced nitric oxide (NO) generation caused by iNOS induction is closely correlated with pathophysiology of cardiovascular diseases, infections, different cancer types and neurodegenerative disorders [26-28]. Under pathological conditions, the increased production of NO is responsible for the generation of peroxynitrite (ONOO $\cdot$ ), which is a strong oxidizing and nitrating agent, formed *in vivo* (i.e. in the cardiovascular system), as a result of the rapid reaction between NO and superoxide anion [29]. Therefore, the recognition of the substances capable of preventing the overproduction of NO has become an important issue in the research of treating chronic and acute inflammatory diseases. Compounds that are present in *A. pilosa* were found to scavenge NO, generated in lipopolysaccharide-induced RAW264.7 macrophages. Taira et al. [13] suggested that polyphenols may be responsible for this action. According to Park et al. [30], agrimonolide isolated from *A. pilosa* displays hepatoprotective properties due to its free radical scavenging activity. Furthermore, *Herba Agrimoniae* is able to suppress the lipopolysaccharide-induced production of proinflammatory cytokines such as tumour necrosis factor  $\beta$  (TNF- $\beta$ ), and interleukins (IL-1 $\beta$  and IL-6) in a dose-dependent manner [31].

### **Agrimonia plants and haemostasis**

The haemostatic system includes a wide range of complex interactions between blood platelets, coagulation cascade, fibrinolytic proteins and anti-thrombotic

activity of endothelium. The maintenance of haemostatic balance is essential to avoid bleeding or thrombosis; however, it may be disturbed by various factors, including circulating pro-inflammatory mediators related to chronic or acute diseases. Oxidative stress associated with the inflammatory process and diseases has been reported to be involved in the alteration of physiological functions of all components of the haemostatic system, and may lead to thrombotic complications [32]. Since a link between inflammation, oxidative stress and cardiovascular disorders has been found [33], the antioxidative properties of various plant-derived compounds have been investigated as potentially useful agents in the protection of the cardiovascular system. The available data indicate that herbs from the *Agrimonia* genus influence cardiovascular disorders. Scientific evidence of anti-haemostatic and anti-platelet properties of *Agrimonia* plants has been reported as early as in the 1980s. Studies on animals showed that *A. pilosa* caused the prolongation of the bleeding time [11]. Wang et al. [12] demonstrated that the aqueous extract from *A. pilosa* inhibited the collagen-induced aggregation of platelet-rich plasma (PRP) in a dose-dependent manner. Furthermore, the aggregation induced by ADP and arachidonate in PRP was also reduced. Significant inhibition of aggregation in washed platelet suspensions was observed, and even the increase of calcium concentration in medium could not overcome the strong inhibitory effect of *A. pilosa* extract. Moreover, hyperoside (quercetin-3-galactoside), occurring in various *Agrimonia* plants, is capable of decreasing blood pressure [34].

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