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REVIEW PAPER

Plant raw materials as a source of antioxidants in treatment of rheumatoid arthritis

RENATA GAJ[1], ADAM BOGACZ[2*]

[1]Department of Agricultural Chemistry and Environmental Biogeochemistry
Poznań University of Life Sciences
Wojska Polskiego 71F
60-625 Poznań, Poland

[2]Department of Biophysics
Faculty of Pharmaceutical Sciences in Sosnowiec
Medical University of Silesia in Katowice
Jedności 8
41-200 Sosnowiec, Poland

*corresponding author: phone: +48 32 364-11-64, e-mail: abogacz@sum.edu.pl

Summary

Patients with rheumatoid arthritis struggle with inflammation, oxidative stress and pain. This review paper aims to present selected plant materials with antioxidants used in the treatment of rheumatoid arthritis. The symptoms and treatment methods were presented. The role of reactive oxygen species in oxidative stress is discussed. This work includes extracts and other forms of substances with medicinal properties containing plant raw material. Example compositions of herbal mixtures recommended in this disease are presented. The medicinal properties and antioxidants were found in plant materials as follows: mountain arnica (*Arnica montana* L.*)* (flowers), Devil's claw (*Harpagophytum procumbens*) (root), meadowsweet (*Filipendula ulmaria* L.) (root and herbs), turmeric (*Curcumae longae* L.) (rhizome), white mustard (*Sinapis alba* L.), and willow (*Salix* L.) (bark), were characterized and discussed. Due to oxidative stress, accompanied by increased production of free radicals, plant materials containing antioxidants that neutralize free radicals are used in the supporting treatment of rheumatoid arthritis.

Key words: ***plant raw materials, rheumatoid arthritis, inflammation, antioxidants, free radicals, oxidative stress***

Słowa kluczowe: ***surowce roślinne, reumatoidalne zapalenie stawów, stan zapalny, antyoksydanty, wolne rodniki, stres oksydacyjny***

INTRODUCTION

Rheumatoid arthritis – general characteristics and treatment

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease [1-4]. Although the likelihood of developing this condition increases with the patient's age, rheumatoid arthritis is also observed in middle-aged individuals. Patients experience inflammation of symmetrical joints, which leads to joint deformation and disability of the patient [2–6]. The flexibility of joints decreases. Cartilage destruction results in joint dysfunction. Additionally, lesions manifest around the joints and impact the bursa, tendon, tendon sheath, ligament, muscle, and bone [2]. During the disease, exacerbations and remissions occur [2–4]. Rheumatoid arthritis can negatively affect the heart, lungs, and blood vessels, and can also cause general fatigue. Pharmacological treatment and rehabilitation are used [1–4, 7]. Examples of suitable conventional drugs include methotrexate, a folic acid analog, leflunomide, and teriflunomide (pyrimidine synthesis inhibitors), sulfasalazine (anti-inflammatory and immunosuppressive), and chloroquine and hydroxychloroquine (immunomodulatory effects) [7]. Biological drugs are also used in rheumatoid arthritis, including abatacept, adalimumab, anakinra, etanercept, golimumab, infiximab, rituximab; nonsteroidal anti-inflammatory drugs and glucocorticosteroids [8]. Rehabilitation includes stretching, strengthening, aerobic and non-weight-bearing exercises, that improve mobility and muscle strength. In the case of rheumatoid arthritis, treatments using physical methods are recommended, such as hydrotherapy [9], cryotherapy [10], magnetotherapy [11], laser irradiation [12] and exposure of diseased tissues to ultrasound [13].

Oxidative stress in rheumatoid arthritis

Rheumatoid arthritis is characterized by an imbalance in the production and neutralization of free radicals [14-17]. Inflammation of the synovial membrane and the production of a significant quantity of free radicals are the primary causes of rheumatoid arthritis, which results in the destruction of periarticular and joint tissues [14–17].The disease's severity and progression are attributed to reactive oxygen species. Oxidative stress influences the formation of immunoglobulin aggregates [14, 16]. Increased reactive oxygen species synthesis causes damage to the tissues in the joint structure [14, 16]. Reactive oxygen species cause a reduction in the viscosity of hyaluronic acid in synovial fluid [14, 16]. The reactive oxygen species include the superoxide anion radical $O_2^{\bullet}$, the hydroperoxide radical $HO_2^{\bullet}$, hydrogen peroxide H_2O_2, and the hydroxyl radical $^{\bullet}OH$ [17].

Plant materials, particularly those with analgesic and anti-inflammatory properties, are employed in the treatment of rheumatoid arthritis [18]. The objective of this review paper is to describe specific plant raw materials and the antioxidant compounds they contain, which are beneficial in the treatment of rheumatoid arthritis.

SELECTED PLANT MATERIALS USED IN RHEUMATOID ARTHRITIS

Mountain arnica – a medicinal raw material rich in antioxidants with anti-inflammatory properties

Mountain arnica (*Arnica montana)* belongs to the *Asteraceae* family, and grows in mountain and foothill areas Europy [19, 20]. This plant is found in Poland in the Sudetes, Western Bieszczady Mountains, Świętokrzyskie Mountains, Lower Silesia and the Masurian Lake District. Mountain arnica grows in the mountains in herbaceous stands, and in the lowlands, mainly on the edges of forests, clearings, meadows, and moors. Mountain arnica blooms from June to August. Mountain arnica is a protected plant.

The medicinal raw material comes from the cultivated plant. Mountain arnica is cultivated for medicinal purposes mainly in mountain and foothill areas of Europe. The medicinal properties of mountain arnica include anti-inflammatory, analgesic, anti-edematous, antiseptic and antithrombotic effects [20-22]. The anti-inflammatory effect of this raw material is based on inhibiting the release of pro-inflammatory factors: NF-κB, NF-AT and metabolic products of arachidonic acid [22].

The medicinal raw material used in rheumatoid arthritis is the flower baskets of the mountain arnica (fig. 1) [21, 22]. Flowers of mountain arnica are rich in antioxidants such as flavonoids (including glycosides, apigenin, kaempferol, betuletin, hispidulin) and phenolic acids: dicaffeoylquinic acids (1,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, 3,4-dicaffeoylquinic acid, 1-methoxy-oxaloyl-3,5-dicaffeoylquinic acid), chlorogenic acid, caffeic acid, gallic acid, *p*-coumaric acid, *p*-hydroxybenzoic acid, gentisic acid, ferulic acid and vanillic acid [21-25]. The flower heads of mountain arnica also

contain polyacetylenes and carotenoids (α-carotene, β-carotene, cryptoxanthin, lutein), coumarin derivatives (umbelliferone, scopoletin), phytosterols (arnisterine), bitter compounds (arnicin), triterpenes, α-amarine derivatives, arnidiol, faradiol, resins and pyrrolizidine alkaloids (tussilagin, isotussilagin) [22].

The anti-inflammatory effect of mountain arnica is mainly due to the sesquiterpene lactones it contains, which include helenalin and its derivatives [22]. Flavonoids and pigment flavonoids – anthocyanins protect lipids against oxidation by scavenging free radicals, have anti-inflammatory and antimutagenic properties [26]. Pro-oxidant enzymes are inhibited by catechins.

Carotenoids, including lycopene, effectively inhibit lipid oxidation, neutralize reactive oxygen and nitrogen species, have the ability to bind metal cations that play a role in free radical reactions, and also have the ability to inhibit enzymes responsible for the formation of reactive oxygen species [26]. Carotenoids neutralize singlet oxygen and thiol radicals (RS•), sulfonol radicals (RSOO•), nitrogen dioxide ($NO_2^{\bullet}$) and react with hydrogen peroxide (H_2O_2) [26].

Figure 1.

Mountain arnica (*Arnica montana*) (flowers)
(photo A. Bogacz)

For rheumatoid arthritis, extracts are primarily derived from mountain arnica flowers, but extracts of the entire plant are also used. These extracts are used as ingredients in ointments, gels, and medicinal tinctures. Arnica flower infusions are obtained by pouring boiling water over the raw material and keeping it covered for 30 minutes. Arnica flower decoctions are obtained by pouring water over the flowers, bringing them to a boil, and cooking for 5 minutes. Mountain arnica infusions and decoctions, are used in compresses to relieve pain and swelling. Mountain arnica products in rheumatoid arthritis should be used externally.

Medicinal products derived from arnica possess antibacterial properties in addition to antioxidant potential [27]. They are effective in alleviating pain [28]. Flavonoids and phenolic acids in mountain arnica glycerol-water extracts show antioxidant activity and cytoprotective effect against oxidative damage in fibroblasts [29]. Pharmaceutical availability of hydrogels with extracts of mountain arnica was described in paper [30]. The antioxidant properties of extract from mountain arnica depend on the part of the plant from which the infusion was obtained [31]. The flower head extracts and mountain arnica herb exhibited the highest efficacy in scavenging free radicals.

Application of Devil's claw in the treatment of rheumatoid arthritis, taking into account its antioxidant activity

Devil's claw (*Harpagophytum procumbens*) is a perennial plant from the *Pedaliaceae* family, which grows on the outskirts of the Kalahari Desert in Namibia, Botswana and South Africa (including Zimbabwe, Mozambique, Zambia) [32]. The plant has a tuberous root with a bitter taste and a color ranging from gray-brown to dark brown. Dried secondary storage tubers are used as a medicinal raw material (fig. 2) [32].

Figure 2.

Devil's claw (*Harpagophytum procumbens*) (root)
(photo A. Bogacz)

Due to the content of antioxidant substances and the bioactive compounds, the root of Devil's claw is used in the treatment of rheumatoid arthritis [32–40]. The root of Devil's claw contains iridoid

glycosides, such as harpagoside, a glycoside with an ester character linked to trans-cinnamic acid, and its degradation products, 8-*p*-coumaroylharpagide and harpagide, which exhibit potent anti-inflammatory and antirheumatic properties [32–38]. Procumbid and procumboside are responsible for the anti-inflammatory and anesthetic effects of the discussed plant material. Flavonoids, luteolin and kaempferol derivatives occur in Devil's claw root [32, 33]. The presence of phenolic acids was detected: cinnamic acid and its derivative – caffeic acid, chlorogenic acid, as well as sterols and triterpenes [32, 33]. Root of Devil's claw contains phytosterols (stigmasterol, *β*-sitosterol), harpagoquinone, waxes, minerals (Ca, Cr, Mg, Mn, K, P, Se, Si, Zn) as well as glucose and fructose [33].

Devil's claw root preparations are used in the form of extracts, tinctures, tablets, capsules and ointments [33]. These preparations have anti-inflammatory effects [33, 41–45], because they inhibit the secretion of cytokines by immune system cells [33]. The analgesic effect of Devil's claw root preparations may probably be due to the anti-inflammatory action of iridoid glycosides contained in the root and the inhibition of eicosanoid synthesis and secretion [33]. The most effective relief from the effects of rheumatoid arthritis is achieved with devil's claw capsules, as they contain a high concentration of active ingredients. Ointments that reduce joint pain and inflammation are also highly effective.

Meadowsweet and rheumatoid arthritis

Meadowsweet (*Filipendula ulmaria*) belongs to the rose family (*Rosaceae*) [46]. This plant occurs in Europe, Asia and North America in moist and shady areas (near rivers, in wet meadows) [46]. Meadowsweet blooms from June to August.

Mainly flavonoids, phenolic glycosides, tannins, and essential oils are the compounds in meadowsweet that possess medicinal properties [46–49]. Rutoside, quercetin, hyperoside, spiraeoside, and kaempferol are flavonoids that are present in meadowsweet. Spiraeoside is the primary flavonoid in the flowers, accounting for approximately 3.5%. Hyperoside is present in the leaves and stem [46].

Meadowsweet herb (fig. 3) contains salicylates, which are responsible for the analgesic effect in inflammatory joint conditions [48]. This action is symptomatic, not curative. Salicylates contained in meadowsweet are also responsible for the bactericidal effect [46, 49].

Meadowsweet flower contains flavonoids, phenolic glycosides, essential oils, tannins, organic acids and mineral salts [46–49]. Decoctions and infusions of meadowsweet flowers are used in preparations for rheumatoid arthritis due to their anti-inflammatory and analgesic effects [46, 49–53]. Ointments containing extracts of meadowsweet flowers are also used.

Figure 3.

Meadowsweet (*Filipendula ulmaria*) (herb)
(photo A. Bogacz)

Due to its analgesic, antipyretic, diaphoretic, and anti-inflammatory properties, the root of meadowsweet is a raw material used for rheumatic and muscular pain [46, 47, 50].

The volatile salicylic acid methyl ester and primaverose, which are composed of glucose and xylose, are produced by monotropitoside, a heteroside found in meadowsweet roots [46]. Meadowsweet contains natural salicylates, which are a precursor to aspirin. Meadowsweet root is used in tablets and alcoholic extracts to relieve joint pain.

Turmeric, white mustard, and willow (fig. 4, 5, 6) as the medicinal plants in treatment of rheumatoid arthritis

Due to their high antioxidant content and valuable bioactive compounds, turmeric (*Curcumae longae* L.) (rhizome) [54-62], white mustard (*Sinapis alba* L.) [63, 64], and willow (*Salix* L.) (bark) [49, 65, 66], are also used in the treatment of rheumatoid arthritis.

Turmenic (fig. 5) contains compounds from curcuminoids group, mainly curcumin (77%), and additionally demethoxycurcumin and bis-demethoxycurcumin (around 5%) [54]. Curcumin (diferuloylmethane) is a polyphenolic yellow pigment [55, 56]. These compounds are responsible for its antioxidant, anti-inflammatory, antimutagenic, and antimicrobial properties [55-62].

Figure 4.

White mustard (*Sinapis alba* L.)

Figure 5.

Turmenic (*Curcumae longae* L. (rhizome)

(photo A. Bogacz)

Figure 6.

Willow (*Salix* L.) (bark)

White mustard (*Sinapis alba*) (fig. 4) belongs to the *Brassicaceae* family [63, 64]. Medicinal ingredients derived from this plant exhibit antioxidant activity. Phenolic compounds, tocopherols, selenium, and magnesium are found in mustard seed. Sinigrin is responsible for anti-inflammatory, antibacterial, and antifungal properties.

Willow bark (fig. 6) is the source of polyphenols and its extracts have strong antiradical and anti-inflammatory effects [49, 65, 66]. Polyphenolic compounds, including apigenin, quercetin and salicylic acid, exist in willow bark.

The exemplary mixtures of the medicinal plant useful in rheumatoid arthritis

In the supporting treatment of rheumatoid arthritis, in addition to single herbs, mixtures of various plant materials are also recommended. Among the commonly available mixtures of plant materials for rheumatoid arthritis, you can find, for example, combinations of meadowsweet, willow bark, birch leaves, nettle leaves, knotweed herb, and blackthorn flowers. The therapeutic effect of extracts from a mixture of raw materials depends on the type and weight share of plant ingredients in the mixture. The antioxidant properties of extracts obtained from mixtures of plant raw materials are examined using EPR and UV-Vis spectroscopic methods [67-70].

CONCLUSIONS

Plant materials containing antioxidants that neutralize free radicals formed in oxidative stress are used in the treatment of rheumatoid arthritis. Plant raw materials: mountain arnica (*Arnica montana* L.*)* (flowers), Devil's claw (*Harpagophytum procumbens*) (root), meadowsweet (*Filipendula ulmaria* L.) (root and herbs), turmeric (*Curcumae longae* L.) (rhizome), white mustard (*Sinapis alba* L.), and willow (*Salix* L.) (bark), support treatment of rheumatoid arthritis. Plant products that possess antioxidant, anti-inflammatory, antibacterial, and analgesic properties are advised for the treatment of rheumatoid arthritis. These products may be in the form of single raw materials or combinations of plant raw materials. Extracts obtained from different parts of plants may have different effects. The intended use of medicinal plant extracts may be either internal or external.

Clinical trials are necessary to determine whether the utilization of diverse plant mixtures in the treatment of rheumatoid arthritis is a viable alternative to synthetic drugs. The high efficacy of plant extracts in the treatment of various diseases is supported by the available literature data [67–70]. This efficacy was demonstrated through the application of laboratory techniques such as UV-Vis spectrophotometry and EPR spectroscopy.

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Ethical approval

The research conducted is not related to either human or animal use.

Conflict of interest
Authors declare no conflict of interest.

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