

The Use of *Harpagophytum Procumbens* (*Martynia Fragrans*) in Rheumatology: a Look through the Prism of Comorbidity (Literature Review)

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The objective: is to highlight the scientific achievements of the use of *Harpagophytum procumbens* in patients with osteoarthritis and other rheumatic diseases, including the aspect of comorbid processes inherent in this pathology.

Materials and methods. The authors conducted a research in printed and electronic publications, science research bases, the State Register of Medicinal Products of Ukraine using methods of analysis, comparison and synthesis of information data, as well as the results of their own initial studies of the efficacy of *Harpagophytum procumbens* in patients with osteoarthritis with phenomena comorbid processes.

Results. Materials of scientific researches carried out in different countries of the world testify that the extract of *Martynia Fragrans* has a multifaceted therapeutic effect of patients with osteoarthritis and age-old comorbid processes due to the properties of this plant like hypotensive, cardiostimulant, disaggregant, hypoglycemic, choleric, which improves the digestive system and kidneys qualities.

The indicated properties of drugs with *Martynia Fragrans* are important in terms of a possible beneficial effect on comorbid diseases of the cardiovascular, digestive, genitourinary systems and diabetes mellitus, which occur in patients with osteoarthritis. A further prospect of clinical research in this direction is presented, which will be in line with the main principles of the «Strategy of the World Health Organization in the field of traditional medicine for 2014–2023».

Conclusions. Preparations of *Martynia (Harpagophytum procumbens)* root have a multifaceted mechanism of action and are effective and safe in the treatment of patients with osteoarthritis, arthritis, mild and moderate pains. Achievements of traditional medicine and the latest studies of the effects of the extracts of *Martynia Fragrans* on metabolism, other organs and systems provide prospects for their positive impact on comorbid diseases in osteoarthritis and improve the overall results of treatment of such patients, being the prospects for further research.

Keywords: *Martynia Fragrans*, rheumatic diseases, comorbid processes, prospects of application.

Використання мартинії запашної (*Harpagophytum procumbens*) в ревматології: погляд крізь призму коморбідності (Огляд літератури)

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Мета дослідження: висвітлення наукових здобутків з використання мартинії запашної у хворих на остеоартрит (ОА) та інші ревматичні захворювання, у тому числі в аспекті властивих цій патології коморбідних процесів.

Матеріали та методи. Здійснено науковий пошук у друкованих та електронних виданнях, пошукових наукових базах, Державному реєстрі лікарських засобів України із застосуванням методів аналізу, порівняння й узагальнення інформаційних даних, а також наведені результати власних початкових досліджень ефективності мартинії запашної у хворих на ОА з явищами коморбідних процесів.

Результати. Матеріали наукових досліджень, проведених в різних країнах світу, свідчать, що екстракт мартинії запашної чинить багатогранну лікувальну дію у хворих на ОА. Зроблено акцент на нещодавно виявлені інші властивості цієї рослини, а саме: гіпотензивне, кардіотонічне, дезагрегантне, гіпоглікемічне, жовчогінне, покращення діяльності системи травлення і нирок.

Зазначені властивості мартинії запашної важливі в аспекті можливого сприятливого впливу на коморбідні захворювання серцево-судинної, травної, сечостатевої систем та цукрового діабету, що фіксують у хворих на ОА та інші ревматичні недуги. Вбачається подальша перспектива поглиблених клінічних досліджень у цьому напрямку, що відповідає основним положенням «Стратегії Всесвітньої організації охорони здоров'я в галузі народної медицини на 2014–2023 рр».

Заключення. Препарати кореня мартинії запашної (*Harpagophytum procumbens*) володіють багатогранним механізмом дії, ефективні і безпечні у лікуванні хворих на остеоартрит (ОА), артрити, біль легкого та помірного ступеня різного походження. Надбання народної медицини та новітні дослідження особливостей дії екстрактів кореня мартинії запашної на метаболізм та інші органи і системи передбачають перспективи позитивного впливу на коморбідні захворювання при ОА та покращення загальних результатів лікування таких хворих, в чому і полягають перспективи подальших досліджень.

Ключові слова: мартинія запашна, ревматичні хвороби, коморбідні захворювання, перспективи застосування.

Использование мартинии душистой (*Harpagophytum procumbens*) в ревматологии: взгляд сквозь призму коморбидности (Обзор литературы)

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Цель исследования: освещение научных достижений по использованию мартинии душистой у больных остеоартритом (ОА) и другими ревматическими заболеваниями, в том числе в аспекте свойственных этой патологии коморбидных процессов.

Материалы и методы. Осуществлен научный поиск в печатных и электронных изданиях, поисковых научных базах, Государственном реестре лекарственных средств Украины с применением методов анализа, сравнения и обобщения информационных данных, а также приведены результаты собственных начальных исследований эффективности мартинии душистой у больных ОА с явлениями коморбидных процессов.

Результаты. Материалы научных исследований, проведенных в различных странах мира, свидетельствуют, что экстракт мартинии душистой обладает многогранными лечебными свойствами у больных ОА. Сделан акцент на недавно обнаруженные другие свойства этого растения, а именно: гипотензивное, кардиотоническое, дезагрегантное, гипогликемическое, желчегонное, улучшающее деятельность пищеварительной системы и почек качеств.

Указанные свойства средств из мартинии душистой важны в аспекте возможного благоприятного влияния на коморбидные заболевания сердечно-сосудистой, пищеварительной, мочеполовой систем и сахарного диабета, которые отмечают у больных ОА и пациентов с другими ревматическими болезнями. Представляется дальнейшая перспектива углубленных клинических исследований в этом направлении, что соответствует основным положениям «Стратегии Всемирной организации здравоохранения в области народной медицины на 2014–2023 гг».

Заключение. Препараты корня мартинии душистой (*Harpagophytum procumbens*) обладают многогранным механизмом действия и являются эффективными и безопасными в лечении больных остеоартритом (ОА), артритом, болью легкой и средней степени различного происхождения. Опыт народной медицины и новейшие исследования особенностей действия экстрактов корня мартинии душистой на метаболизм и другие органы и системы предусматривают перспективы положительного их влияния на коморбидные заболевания при ОА и улучшение общих результатов лечения таких больных, в чем и заключаются перспективы дальнейших исследований.

Ключевые слова: мартиния душистая, ревматические болезни, коморбидные заболевания, перспективы применения.

Rheumatic diseases are one of the most common ailments of humanity. Among them, osteoarthritis (OA), an age-dependent disease of a degenerative-inflammatory character, holds a prominent place [2]. The increase in life expectancy of the planet and the prevalence of obesity – one of its leading risk factors – will lead to an increase in the number of such patients and the problems associated with their medical care. It is generally accepted that osteoarthritis is characterized by a significant and increasing level of comorbidity, which significantly complicates, increases the cost of the treatment process and reduces its effectiveness [1, 2, 36]. In the spectrum of comorbid diseases, lesions of the cardiovascular system (arterial hypertension, various forms of coronary heart disease, heart failure), digestive system (gastritis, duodenitis, peptic ulcer, cholecysto-pancreatopathy, entero-colonopathy, etc.), and diabetes with obesity as one of risk factors dominate [1, 36]. In all these diseases, the non-specific pathogenetic role of systemic low-level inflammation, oxidative, nitrosative stress, hemocoagulation disorders, etc., has been established [2, 30]. In the complex treatment of such patients, it is difficult to make the correct selection of medicines, taking into account the spectrum of existing diseases and non-specific general pathological changes, and there arises a situation of forced polypragmasia, possible incompatibility of medicines, threat of side effects and complications [1, 2]. Therefore, until now, world medicine has not yet developed treatment protocols for these patients. Even in the context of OA treatment, there are currently differences between the European and North American Rheumatology Associations regarding the feasibility of using chondroprotectors (CP) in this pathology. In particular, the American Rheumatology Association considers the use of chondroprotectors in OA doubtful [22]. Based on the results of our long-term observations of repeated course of chondroprotectors use in the same patients with OA under 60 years of age, CP efficiency was good, but with increasing age of patients, their effectiveness decreased, especially in the presence of significant systemic lesions of the digestive system of the pancreatic entero-colopathy [1]. However, recent ESCO recommendations (2019) state that no oral non-steroidal anti-inflammatory drug (NSAID) should be prescribed to patients with concomitant cardiovascular diseases [8]. In this regard, the world's medicine continues to search for medicines and technologies for the treatment of such patients. One of the most promising ways to solve these problems is to use herbal remedies from the arsenal of the past. In this respect, the WHO is focusing on a document of particular importance on the «Strategy of the World Health Organization in the field of traditional medicine for 2014–2023» [4].

In the context of medicinal plants useful for the patients with rheumatological diseases in recent decades, particular attention has been paid to *Harpagophytum procumbens* (also known as *Martynia fragrans*, *grapple plant*, *wood spider*, *devil's claw*, *African field buttercup*).

The objective: is to highlight the scientific achievements of the use of *Harpagophytum procumbens* in patients with osteoar-

thritis and other rheumatic diseases, including the aspect of comorbid processes inherent in this pathology.

MATERIAL AND METHODS

The authors conducted a research in printed and electronic publications, science research bases, the State Register of Medicinal Products of Ukraine using methods of analysis, comparison and synthesis of information data, as well as the results of their own initial studies of the efficacy of *Harpagophytum procumbens* in patients with OA with phenomena comorbid processes.

RESULTS AND DISCUSSION

Harpagophytum procumbens is dated 1904 by G. Mehnert, a former soldier and later – an African farmer, who was at war on the territory of present-day Namibia, and noticed the widespread use of this plant by African natives in various diseases [6]. In the early 20th century, this plant was imported to Europe, Asia, Australia, and later – to North America. In recent decades, in these countries *Harpagophytum procumbens* being included into official medicine and pharmacy is gaining popularity. This is proved by the availability of information about it in the pharmacopoeias of Germany, France, Great Britain, Sweden (*Harpagophyti radix*) and the decision of the European Commission ESCOP to publish a special monograph on this plant use [6, 13].

What else is known about *Harpagophytum procumbens*?

Harpagophytum procumbens (*Martynia fragrans*) is a perennial plant of the genus *Harpagofitum*, of the Martyniaceae family, native to South Africa. Tropical overgrowths are common in Angola, Botswana, Namibia, Zimbabwe, the Kalahari Desert, and Madagascar. It is industrially cultivated in African countries on the border with the Kalahari Desert and the steppe regions of Namibia [6, 7, 19, 32].

The plant having branched stems up to 100 cm in length, spreading on the ground and roots with large tuberiform thickening is the main pharmaceutical raw material [20, 25].

The chemical composition of the roots of this plant is now rather well known. Harpagoside, iridoid glycoside (1–3%), is considered to be the main active ingredient of the Martynia root. Other important constituents found in it in smaller quantities are: procumbide iridoids, harpagid, verbascoside, phenol glycosides – asteoside and isoasteoside, a mixture of phytosterols – β -sitosterol and sigmasterin, flavonoids – kaempferol and luteolin-glucoside, free caffeic and cinnamic acids, unsaturated fatty acids and triterpenes, alkaloids, waxes and a large percentage of carbohydrates, the major constituent of which is trisaccharide-stachyose (46%), macro- and microelements Ca, Mg, Fe, P, K, Co, Sn [6, 13, 27].

The study of the chemical composition of the Martynia root enabled to understand the mechanism of therapeutic action of extracts from it in various pathological states and to outline the prospects for further widespread use.

In South African traditional medicine, medicines from Martynia (tea, decoctions, ointments, powders) were used for gall

bladder, liver, kidneys, bladder diseases, and malaria; as a bitter tonic – for digestion disorders, exhaustion, pain of different localization (joints, muscles, head), for external use – in case of skin damage, skin diseases [6, 32].

In modern medicine, especially in Europe and North America, *Martynia* root is widely used in the treatment of patients with lesions of the musculoskeletal system (osteoarthritis, arthritis, pain in lower back, fibromyalgia, osteochondrosis) [35, 37, 39]. Currently extensive studies have been carried out on the mechanism of anti-inflammatory and botolemic action of the *Martynia* root extract; a number of reviews and meta-analyses have been performed [3, 7, 14, 17, 37], which proved that the substances contained in this plant are capable of:

- suppressing the release of proinflammatory cytokines of tumor necrosis factor alpha, interleukin 1 β and interleukin-6 from monocytes and macrophages; suppressing the transcription of macrophage protein-1 activation factor [16, 21, 23, 25];
- activating the formation of extracellular matrix, enhancing the synthesis of chondroitin and glucosaminoglycans;
- reducing the expression of cyclooxygenase-2, 5-lipoxygenase and inducible NO synthase in fibroblasts, which minimizes the formation of prostaglandins and nitrogen oxide mediating the exudative inflammatory phase [5, 15, 16, 29, 34];
- reducing the formation of matrix metalloproteinases (MMP-1; MMP-3; MMP-9), which inhibit the activity of collagenase, cause the destruction of articular cartilage (chondroprotective effect) [26, 35].

A series of randomized studies (open, multicenter, double placebo-controlled, post-marketing ones) for the use of *Martynia* root extract in a complex application in the treatment of patients with osteoarthritis [38, 39], lumbar pain [10, 11, 12, 18], fibromyalgia [18] were performed. They show that the use of the *Martynia* root extract enables to accelerate the regression of pain syndrome and reduce the need for NSAIDs, and subsequently to stop taking the latter, using in the future only the *Martynia* extract at doses of 1000–3000 mg/day for 2 to 6 months, depending on the clinical situation [7, 9]. Some studies have shown that the *Martynia* root extract and Diacerein are equally effective in reducing the severity of joint pain [9, 12]; another study reported the same efficacy of the *Martynia* root extract in combination with a standard dose of Rofecoxib (12.5 mg), although these authors are very careful in evaluating their results because they had a rather small sampling of patients [10, 11]. Most researchers note that the use of the *Martynia* root extract reduces the intensity of joint pain by 25–50%, and increases the mobility of joints by 35–50% [12].

It is important that all researchers claim good tolerance of treatment with the *Martynia* root extract (good and very good – 98.1%), and 80% of patients with their adherence to treatment in 96.4% of cases [3, 14, 37]. Mild side effects (dyspepsia) were reported in 3%. Moreover, toxic effects are not recorded at prolonged use of this remedy [7, 9, 38].

In addition to diseases of the musculoskeletal system, the *Martynia* root extract is used for headache at cervical spine lesions, dyspeptic disorders, bad appetite, especially in cases with the elderly patients [6, 13, 19]. Antimicrobial, sedative, diuretic, antipyretic qualities characteristic of this plant should be kept in mind [6, 19, 27].

However, some sources have indicated that the *Martynia* root extract should not be used by patients with peptic ulcer disease (enhances gastric secretion, contributes to exacerbation), during pregnancy (shows some uterotonic effect) and during lactation, in children and adolescents under 18 (no experience of being used by this category of patients) [13, 14].

In general, most of the above studies indicate that the *Martynia* extract is considered to be effective, reliable and safe [7, 13].

However, our attention was attracted by other studies of the properties of this plant, which revealed previously unknown

qualities. In particular, Mncwangi et al. (2012), in addition to antimalarial and uterotonic properties, also indicate to anticancer ones [32]. Harpagosides of this plant demonstrate antimutagenic effect at environmental damages [31]. A number of researchers have reported on its ability to lower blood pressure, heart rate and increase force of contraction, promote blood thinning [18, 32, 37]. The ability of the root extract of this plant to lower blood glucose level is also important [32, 37]. Such iridoids of this plant, as bitterness, increase gastric secretion and bile excretion and raise appetite [6, 32].

But it should be noted that the *Martynia* root extract inhibits a number of cytochrome P450 isoenzymes, so there is possibility that it might change the pharmacokinetic parameters of certain drugs metabolized by these isoenzymes, including statins, certain antidiabetic and antihypertensive medical agents, as well as antidepressants, proton inhibitors and anticonvulsants [3, 37].

What sources of the *Martynia* root extract are available on the pharmaceutical market of Ukraine and Europe? It is sustamar, pills, registered by the Pharmacological Committee of Ukraine, as well as a dietary chondroprotective supplement Artromega, which also contains 24 components including *Harpagophytum* root powder. Currently, there is information on the use of sustamar by more than 5,000 patients who participated in the controlled clinical research. In 2016 the positive results obtained moved the European Medical Agency (similar to the US FDA) to approve the clinical use of this drug to address mild and moderate joint pain. There are several medicinal forms of *Martynia* root extract in Europe, including capsules, tinctures, decoctions, herb teas, creams, balms and even injections. Most of them are marketed as biologically active additives.

Summarizing the results of numerous studies and meta-analyses of *Martynia* root extract in patients with rheumatological profile, especially in osteoarthritis, we note that they are mainly devoted to the pathophysiological and clinical aspects of the total effect of the factors of this plant on the main manifestations of these diseases. However, the current realities of life show that these diseases due to the duration and age of patients, the impact of environmental factors and lifestyle (hypodynamia, malnutrition, obesity), gain a number of other, pathogenetically close or drug-related accompanying diseases, called comorbidity. In the most common joint disease – osteoarthritis – such accompanying comorbid diseases are arterial hypertension, various forms of coronary heart disease, including heart failure, diabetes, systemic lesions of the digestive canal (gastroduodeno-, cholecystopancreato-, enterocolonopathy, dysbacteriosis etc.), urogenital system diseases, dyslipidemias, neurotic conditions [1, 36]. At the same time, with increasing the duration of the disease and the age of patients, the spectrum and severity of these diseases increase. In this aspect, the use of extracts of *Martynia* root appears to be even more promising as a potentiating factor of action of hypotensive, hypoglycemic, cardiotoxic, diuretic, antiplatelet agents, enhancer of bile excretion and optimizer of intestinal digestion, appetite, which often occur in patients with this disease. However, in this context, only cautious warnings have been found in the literature regarding the peculiarities of the use of this plant in rheumatological patients in the above mentioned concomitant (comorbid) pathological conditions.

The differences between the recommendations of the European Rheumatology League (proposed) and the American Rheumatology Association (considered inappropriate) (2014, 2016) concerning the feasibility of using chondroprotectors in patients with osteoarthritis are also important [22, 28]. According to our long-term observations, the efficacy of chondroprotectors in 60-year-old patients with osteoarthritis is good, but in patients who are older than this age, especially in the presence of systemic lesions of the digestive canal accompanied by long-term enterocolopathies, the effectiveness of chondroprotectors really dramatically decreases.

es [1]. Perhaps in such cases, one of the reasons is the reduction of absorption of chondroprotectors in the intestine. The ability of the *Martynia* root extract to improve digestion processes on the one hand, and its local chondroprotective action mediated by inhibition of collagenase activity, production of metalloproteinases, activation of extracellular matrix formation, chondroitin synthesis and glucosaminoglycans – on the other hand, should provide the desired treatment results in such patients.

Another important aspect of treating patients with osteoarthritis is the use of NSAIDs. According to the latest recommendations of 2019 ESCEO (European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis) it is recommended to use NSAIDs in the lowest possible doses and shorter courses [8]. To some extent, it can be extrapolated to the relatively long-term use of acetylsalicylic acid preparations by them if they suffer from various forms of coronary heart disease. The use of *Martynia* root preparations enables to do so.

It should also be considered that most patients with osteoarthritis are of elderly and senile age often with a predisposition to oncopathology. This plant has antimutagenic properties in environmental damages [31].

Solving the above problems of using medical agents of the *Martynia Fragrans* root in patients with rheumatological profile in the presence of comorbid processes is one of the interesting prospects for further research as one of the options for implementation of the World Health Organization Recommendations 2014–2023 [4].

CONCLUSIONS

1. Preparations of *Martynia* (*Harpagophytum procumbens*) root have a multifaceted mechanism of action and are effective and safe in the treatment of patients with osteoarthritis, arthritis, mild and moderate pains.

2. Achievements of traditional medicine and the latest studies of the effects of the extracts of *Martynia Fragrans* on metabolism, other organs and systems provide prospects for their positive impact on comorbid diseases in osteoarthritis and improve the overall results of treatment of such patients, being the prospects for further research.

Conflict of interests. The authors declare no conflict of interest.

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Статья поступила в редакцию 10.04.2020