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Medicinal plants used on arthritis treatment: An overview through patent analysis

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Abstract

Arthritis is a chronic disabling disease that usually affects the joints. Conventional drugs have restrictions with side effects and high cost of treatment; therefore the search for newer medicinal agents both safe and cheaper is crucial. A significant proportion of the population in the world currently uses medicinal plants and there is an increasing trend in the use of herbal preparations to treat several diseases. Since patent documents are the most important source of technological information, in the present study we analysed granted patents claiming the use of medicinal plants in arthritis treatment. China was the leader in the number of patents, and the top list of granted patents includes mainly companies. Different preparations for the treatment of the most common types of arthritis were claimed. The development of standardized products with low cost, high efficacy and safety of use is of great clinical significance and market value.

Keywords: Arthritis, medicinal plants, natural products, patent

Introduction

According to a report from the World Health Organization (WHO), ischemic heart disease, stroke, chronic obstructive lung disease and lower respiratory infections have remained the top major killers during the past decade, responsible for about 20 million deaths (World Health Organization 2017) [1]. A substantial body of evidence now supports the conclusion that inflammation can predispose to all these diseases.

The inflammatory response is a physiological process aiming to restore tissue homeostasis. However, uncontrolled or unresolved inflammation may cause tissue damage and contribute to the pathogenesis of chronic inflammatory and autoimmune diseases, including arthritis, asthma, atherosclerosis, diabetes, and cancer (Nathan *et al.* 2010) [2].

Although the term arthritis is applied to a large variety of inflammatory and non-inflammatory disorders, arthritis means chronic inflammation of a joint, whether the result of a disease, an infection, a genetic defect, or some other cause. Arthritis inflammation causes pain, stiffness, and swelling in the joints and surrounding tissues (Choy 2012) [3].

Arthritis is usually seen as a disease that only affects the elderly, but it affects people of all ages, and nearly two-thirds of people with arthritis are younger than 65. This condition is more common among women (26%) than men (19%), and it affects members of all racial and ethnic groups (National Centre for Chronic Disease Prevention and Health Promotion 2016) [4]. By 2040, the number of US adults with arthritis-attributable activity limitation will increase 52% to 34.6 million (11.4% of all adults) (Hootman *et al.* 2016) [5].

Steroidal or non-steroidal anti-inflammatory drugs, along with the conventional disease-modifying anti-rheumatic drugs or biologics can be utilized in arthritis treatment, although in some cases their prolonged use is frequently associated with some critical side effects or high cost of treatment. Therefore there is a need for the development of safer and cheaper drugs and traditional medicines and natural products could be an attractive option.

Traditional medicinal herbs have served as a potential source of alternative medicine for different diseases, especially for millions of people in developing countries. According to WHO, nearly 75-80% of the world population still depend on herbal medicines (Sen *et al.* 2010) [6] and about 25% of the drugs prescribed worldwide come from plants (Rates 2001) [7]. In most societies today, even in developed countries, allopathic and traditional systems of medicine occur side by side in a complementary way. The former usually treats acute conditions while the latter is used for chronic illnesses, to reduce symptoms and improve the quality of life in a cost-effective way (Gurib-Fakim 2006) [8].

Patent documents are the most important source of technological information, a valuable and unique source of data on technological effort, which is an aspect of innovative activity (Myrick *et al.* 1993) [9]. Medicinal plants and related products are important targets of patents since they

have become of great interest to the pharmaceutical industry (Kartal 2007) [10]. The present study aims to present an overview of the latest developments using medicinal plants in the treatment of arthritis by analysing granted patent documents.

Methods

The search of documents was performed using the Derwent Innovations Index database, which covers more than 11 million patent documents filed, published - and eventually granted - in different areas, from 1963, in more than 40 countries, and is available at federal institutions in Brazil through the CAPES Journal Portal (<http://www.periodicos.capes.gov.br/>). There was not time delimitation and documents indexed from 1963 to 2017 were recovered. The strategy was based on the use of keywords combined with the International Patent Classification (IPC), which allows the assessment of the technological activity, and the Derwent Manual Code (MAN), which categorizes patent documents in groups, classes, and subclasses for all technologies, according to the patent contents. The strategy was divided into two parts. On the first part the keywords used were “natural product” or “plants” or “herbs” together with the IPC classes A61K-36/00 or A61K-125/00 or A61K-127/00 or A61K-129/00 or A61K-131/00 or A61K-133/00 or A61K-135/00 [1] and MAN codes B04-A09A or B04-A09B or B04-A09D or B04-A09F or B04-A09H or B04-A09K or B04-A10 or B04-A10B or B04-A10C or B04-A10D or B04-A10F or B04-A10G or B04-A10J or B04-A10K [2]. Next, the keyword “arthritis” and the MAN codes B12-D03 or B14-C09* or C14-C09* or C12-D03 [3] were used.

Results and Discussion

The result of the combined search yielded 7,169 patent documents filed and published in the world concerning the use of medicinal plants in the treatment of arthritis. Of the original applications filed, 1,330 were granted. After a full reading of the title and the abstract, 835 documents were selected. A qualitative evaluation of the patents was then performed, by analysing the “claims”, “mean plant use at the formulation”, “therapeutic secondary activity” and “mechanism of action” fields from the documents. The methodology used is itemized on Figure 1.

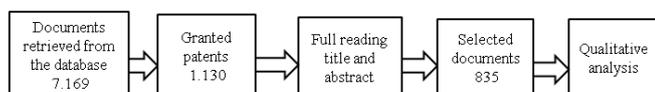


Fig 1: Flowchart of the search methodology

¹A61K 36/00 - Medicinal preparations of undetermined constitution containing material from algae, lichens, fungi or plants, or derivatives thereof, e.g. traditional herbal medicines; A61K 125/00 - Containing or obtained from roots, bulbs, tubers, corms or rhizomes; A61K 127/00 - Containing or obtained from leaves; A61K 129/00 -Containing or obtained from bark; A61K 131/00 - Containing or obtained from seeds, nuts, fruits or grains; A61K 133/00 - Containing or obtained from flowers or blossoms; A61K 135/00 - Containing or obtained from stems, stalks, branches, twigs or shoots.

²B04-A09A - Leaves; B04-A09B - Flowers and parts excluding pollen; B04-A09D - Roots; B04-A09F - Seeds, seed husks, seed meal, cereal, grain, nuts, bran; B04-A09H - Straw, hay, stems, sap; B04-A09K - Fruit; B04-A10 - Plant extracts general and other. When the use of “Chinese herbal medicine” is claimed this code is applied; B04-A10B - Leaf extracts; B04-A10C - Flower extracts and extracts from flower; B04-A10D - Pollen extract; B04-A10F - Root extracts; B04-A10G - Seed, seed husk, seed meal, cereal, grain and nut extracts; B04-A10J - Straw, hay, stem and sap; B04-A10K - Fruit extract.

³B12-D03-Antiarthritic; B14-C09 - Antiarthritic general and other; Osteoarthritis; Rheumatoid-arthritis; C14-C09 - Antiarthritic general and other; Osteoarthritis; Rheumatoid-arthritis; C12-D03 - Antiarthritic.

The analysis performed in this work included only granted patents. This is an important aspect since the sooner an applicant obtains a granted patent, the sooner the patent owner can commercialize or obtain value from the exclusive right for that technology.

Priority country

Patent applicants, which are the holders of the rights to the patented technology, may choose the countries where they want to protect their inventions. In this study, we only considered the priority countries, i.e. the first country in which the patent applications were filed. The analysis of the documents showed that over 80% of all the patents were granted in China followed by the United States and South Korea (Figure 2). This is not a surprising result since according to the World Intellectual Property Organization Indicators (2015) [11] the top offices increased their combined share of the world thanks to substantial growth in the number of patents issued by these three countries.

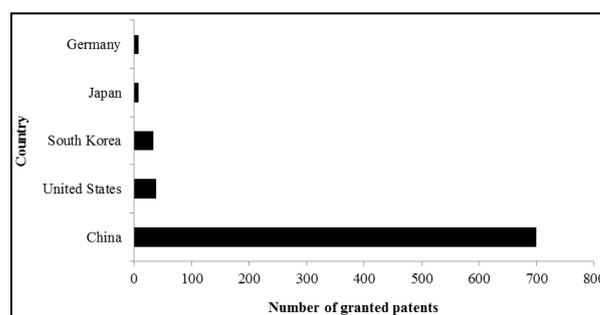


Fig 2: Priority country of granted patents related to arthritis

Main applicants

The analysis of the patenting profile from the applicants' perspective showed that the leader in patents granted in this field is the Chengdu University of Traditional Chinese Medicine. Given that medicinal plants are candidates to development pipelines over a wide range of therapeutic areas, several companies continue to bet on these products as a source of new pharmaceutical compounds. The top list of granted patents is dominated by the multinational company Nestle SA, followed by the Chinese companies Beijing Asia-East Bio-Pharmaceutical Company and Jiangsu Kanion Pharmaceutical Company.

Interestingly there were also a large number of patents (71%) granted to individual inventors, what is not unexpected given that Traditional Chinese Medicine practitioners use different plant-based medicines to treat or prevent several health problems since ancient times (Gurib-Fakim 2006; Wang 2012) [8, 12]. These applications, though, will not automatically result in technologies with commercial potential or market value, as these inventors may be sometimes simply driven by their curiosity to develop new inventions.

Most common types of arthritis claimed

About one out of every five US adults has doctor-diagnosed arthritis. The term arthritis includes more than 100 different rheumatic diseases and conditions, the most common being rheumatoid arthritis, osteoarthritis, gout, psoriatic arthritis and related autoimmune diseases such as lupus. The most common types of arthritis claimed in the analysed documents are depicted on Figure 3. It is relevant to mention that almost 25% of the patents claim the use of medicinal plants in the treatment of more than one type of arthritis

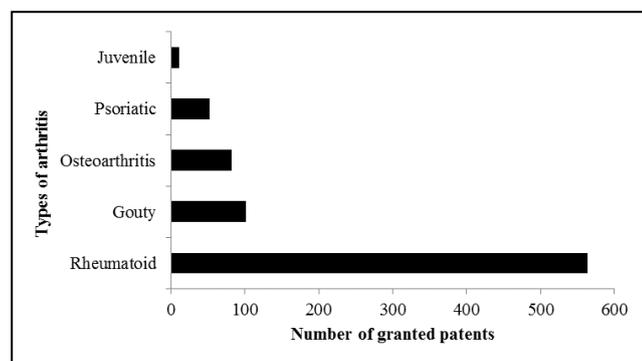


Fig 3: Main types of arthritis claimed in the granted patents

Rheumatoid arthritis is a chronic systemic disease that affects the joints, connective tissues, muscle, tendons, and fibrous tissue. It tends to strike during the most productive years of adulthood, between the ages of 20 and 40, and is a disabling condition often causing pain and deformity. The prevalence varies between 0.3% and 1% and is more common in women and in developed countries. Within 10 years on onset, at least 50% of patients in developed countries are unable to hold down a full-time job (World Health Organization 2016) [13]. The global rheumatoid arthritis market is expected to increase in value to just over US\$19 billion by 2020 (NBC News 2016) [14].

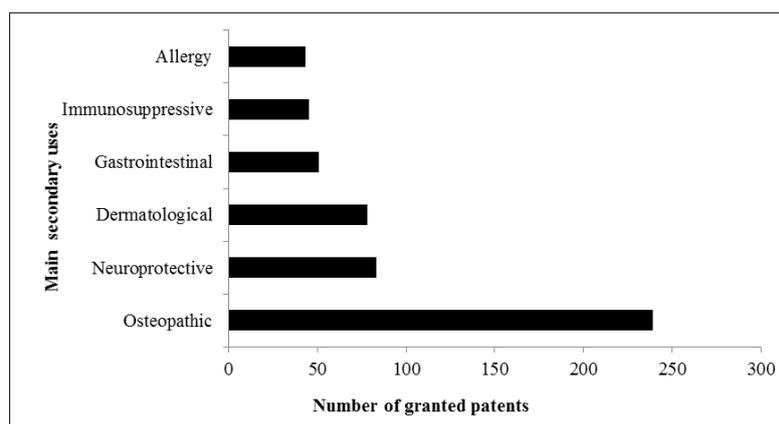


Fig 4: Other non-inflammatory uses also claimed in the granted patents related to arthritis

Natural products are important both as pharmaceutical agents and as a source of molecules with therapeutic potential. The use of new technologies, such as proteomic and genomic approaches, together with combinatorial chemistry, has led to the identification of novel bioactive structures that can be optimized generating new drug candidates for many diseases.

Main formulations claimed for arthritis treatment

The qualitative evaluation revealed that most patents (689) claim multi-herb compositions (frequently more than five herbs) for arthritis treatment. Actually, numerous phytomedicines can be found on the market as a preparation of several medicinal plants, and practitioners have always believed that synergistic interactions between the components of mixtures of plants are a vital part of their therapeutic efficacy. Only 15% (128) of the patents claimed a single herb or single herb extract, and since there were several of them, it was difficult to point out the one most widely used. The genera of plants mainly claimed in the formulations were Rose, Capparis, Acacia and Panax, all with recorded uses in phytotherapy and folk medicine. Purification of active ingredients from medicinal plants, as well as the extraction process or method for obtaining plant extracts were also

Osteoarthritis is a degenerative joint disease, which mainly affects the articular cartilage. It is associated with ageing and will most likely affect the joints that have been continually stressed throughout the years including the knees, hips, fingers, and lower spine region. Osteoarthritis is already one of the ten most disabling diseases in developed countries (World Health Organization 2016) [13].

Gout is a form of arthritis that results from disturbed uric acid metabolism and deposition of monosodium urate crystals in extra cellular space of joints, periarticular tissue, bones and other organs. Joint damage may occur, which can lead to a loss of mobility. The incidence of gout has been increasing significantly over the last years together with the understanding of its association with traditional cardiovascular risk factors (Roddy *et al.* 2010) [15].

Other types and inflammatory related conditions also claimed in the granted patents were ankylosing spondylitis (43); lupus (30) and fibromyalgia (07).

Secondary therapeutic activities also claimed

A patent document likely has a very broad scope of protection, including secondary uses for the protected product. The analysis of the patents granted for the treatment of arthritis also revealed that they often included claims for the treatment of other diseases as well (Figure 4)

claimed in the granted patents.

Mechanism of action claimed

The mechanism of action is an important way to identify how a drug works in the treatment of a certain disease since it refers to the specific biochemical interaction through which the drug produces its pharmacological effect. Phytomedicines exert their therapeutic effects often through the additive or synergistic action of several compounds acting at single or multiple target sites associated with a pathophysiological process (Briskin 2000) [16].

The main mechanisms claimed in the granted patents for the treatment of arthritis are illustrated on Table 1. Importantly, 755 documents did not define the mechanism of action of the protected product, at least not in the analysed fields (“claims”, “mean plant use at the formulation”, “therapeutic secondary activity” and “mechanism of action”) and therefore they were not taken into account. It is important to have in mind the significant number of individual inventors, which may have no interest or condition to evaluate the mechanism of action of their invention.

Table 1: Mechanisms of action claimed in the granted patents related to arthritis.

Mechanism of action	Number of patents
Enzyme Inhibitor	33
Protein Inhibitor	17
Receptor Antagonist	2
Others mechanisms*	28
Not described	755

Inflammation is a complex process, which is regulated by multiple signalling pathways forming an intricate network. During the past decades drug development focused on key targets considered crucial that, when antagonized or neutralized, block the output of a particular pathway. Based on the patents that mentioned the mechanism of action, approximately 41% of the documents claim products with enzyme-inhibiting properties, predominantly cyclooxygenases, lipoxygenases and nitric oxide synthase, the main known enzymes which modulate specific biochemical reactions in the inflammatory process. Enzyme inhibitors are substances which in small quantity decrease enzyme activity in a precise way.

Over the past years there has been a considerable increase in the knowledge about the immune system and new targets with potential roles in the inflammatory process have been described. For complex processes like inflammation, an interference with multiple targets is superior to targeting a single key factor regarding drug efficiency (Koeberle *et al.* 2014) [17]. Almost 35% of the documents cited other mechanisms of action, including protein inhibition, particularly chemokines; receptor antagonists in addition to cell inhibition (differentiation and proliferation). The mechanisms of action claimed for medicinal plants in arthritis treatment reflect not only classic mechanisms – enzyme inhibitors – but also recent advances in the field.

A number of clinical trials have shown that undoubtedly phytopharmaceuticals exhibit therapeutic equivalence with synthetic drugs and can also be used in the treatment of severe diseases (Wagner 2005) [18]. Even though few clinical trials have yet been performed to corroborate the safety and efficacy of herbal medicines, most plant-derived compounds have been proved to interfere directly or indirectly with different inflammation pathways (Calixto *et al.* 2003) [19] and, thus, may be used in the treatment of inflammatory disorders, including arthritis (Beng *et al.* 2011; Lü 2015) [20, 21].

Similar to other chronic and disabling diseases, arthritis must be handled over a long period of time, aiming to minimize pain, loss of function, and the social / psychological dysfunction, which are often associated with long-term illnesses (Choy 2012) [3].

While there are no signs of cures in the immediate future, advances in both conventional medical treatment and alternative therapies have made living with arthritis more manageable (Cornella *et al.* 2016) [22]. Natural products and their derivatives have formed the basis of traditional medicine systems and represent more than 50% of all the drugs in clinical use in the world today (Gurib-Fakim, 2006) [8]. Currently a significant proportion of the population in the United States uses herbal products to treat several illnesses or improve health (Briskin 2000; Bent *et al.* 2004) [16, 23].

Conclusion

It is estimated that arthritis and arthritis-attributable activity limitation will remain a growing problem for clinical and public health systems, which must create policies and resources to address these future needs (Hootman *et al.* 2016) [5].

In this work we have showed that pharmaceutical companies

and other institutions are investing in the quest for plant-derived medicines for arthritis treatment, probably driven by the rise in the number of adults with doctor-diagnosed arthritis and the chronic nature of the disease. Unquestionably the demand for phytomedicines as new therapeutic options is increasing globally and is estimated to grow even more in the years to come (Verma *et al.* 2008) [24]. Consequently the development of standardized products with low cost, high efficacy and safety of use is of great clinical significance and market value.

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Conflict of Interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

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