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Review Article

MEDICINAL PLANTS OF RENISUS WITH ANALGESIC ACTIVITY

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ABSTRACT

Pain is an unpleasant sensory and emotional experience associated with real or potential tissue damage. The incidence of pain may result in the risk of developing some limitations in daily activities, overload in the use of health services, abuse of controlling medication, among other factors. This systematic review aimed to quantify the preclinical and clinical studies that reported the analgesic potential of plants listed in the National List of Medicinal Plants of Interest to the Unified Health System (RENISUS), published between 2010 and 2013 in two scientific databases (SciELO, Science Direct) and one publisher of scientific journals (Springer). A total of 21,357 publications were found in the initial search. The final analysis resulted in the selection of 14 publications examining 11 plants of the RENISUS list. The present study can contribute to further discussions on alternative therapies to conventional treatments for pain, using plants as an adjuvant.

Keywords: Pain, Natural products, Folk medicine, Health

INTRODUCTION

Pain is the most common reason people seek medical attention. It can be defined simply as an undesirable physical or emotional experience and it can be classified as acute or chronic. Treatment for chronic pain is a major public health problem due to the recurrent use of available drugs that have undesirable side effect [1].

For thousands of years, various forms of natural products have been used for treating pain disorders, such as the use of opium, extracted from *Papaver soniferum* L. From the nineteenth century; bioactive compounds began to be isolated and identified. Then, the action of such molecules was enhanced, such as salicin, a compound extracted from the bark of the white willow tree (*Salix alba* L.), from which the acetylsalicylic acid is produced [2]. Whereas morphine remains as the most potent analgesic drug, which was first isolated in 1803 by Friedrich Sertürner [3]. Research in pain management and drug addiction are focused on natural products. Analog compounds have been produced from natural substances, and synthetic compounds based totally on natural pharmacophores have been introduced in the market [2].

There are various forms of analgesics that contribute to reducing pain. They are classified into three categories: opioid analgesics (*e. g.* morphine and codeine); non-opioid analgesics, such as nonsteroidal anti-inflammatory drugs (NSAIDs) among which stands out aspirin and diclofenac; and adjuvant analgesics, which are compounds commonly administered for other reasons than pain, but can control it in certain situations. Antidepressant medications can act as analgesics in the treatment of many chronic pain states. Opioid analgesics cause a maximal analgesia; they are considered broad-spectrum drugs in the treatments of acute pain because of their great efficacy [4]. However, the clinical use of these drugs suffers from disadvantages because they have adverse effects such as hypertension, hyperglycemia, increased susceptibility to infection, osteoporosis, cardiovascular disease, among others [5].

One factor that has emphasized the importance of discovering new compounds for treating pain has been the fundamental understanding of complex mechanisms of pain transmission in the nervous system because nociceptive processing/pain receptors involves many classes of receptors, enzymes and signaling pathways [6]. The identification of new classes of compounds from natural sources can lead to a clearer understanding of these underlying pharmacological mechanisms. Thus, it is considered the potential of medicinal plants for the discovery of new compounds with the optimal pharmacological profile (fewer side effects and nontoxicity), especially in the treatment of pain disorders [2].

The plant-based preparations are commonly used, but the real effectiveness and the relevant active ingredients are often unknown. Nevertheless, they are drugs and as such, they have drawbacks and side effects if they are not properly administered. For these reasons, it is interesting to determine whether the use of a plant that has been applied as a medicine is supported by real pharmacological effects [7].

In 2007, the Brazilian public health system started to make available to the population, herbal remedies derived from plants. Currently, Brazil's Ministry of Health provides the use of 12 herbal medicines in the public health system (*i.e.* espinheira-santa, guaco, artichoke, mastic, cascara, devil's claw, soy isoflavones, cat's claw, mint, aloe, willow, plantago), derived from plants belonging to the Brazilian National List of Medicinal Plants of Interest to the Unified Health System (RENISUS) [8]. The list was published in February 2009 in order to encourage the use of complementary therapies in the Unified Health System (SUS), thus promoting research on medicinal plants to establish the correct and safe use of these plants [9]. The preliminary list included 237 plant species that were preselected by regions that alluded to its use by folk medicine and according to the categories of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) [10]. Lastly, 71 plants were selected prioritizing the inclusion of native plants of different biomes, which could address the most common diseases in Brazil [9]. Therefore, this study systematically searched and reviewed the amount of scientific publications about medicinal plants listed in RENISUS that have analgesic potential.

METHODS

Electronic literature searches were carried out in Science Direct, SciELO and Springer Link (journal issues from 2010 to 2013). Scientific articles published since the creation of RENISUS, from January 2010 to February 2013, were analyzed. All scientific papers available as full and open access texts regardless of language were considered. The keywords used in the query were the scientific names of the 71 medicinal plants listed in RENISUS.

The criteria of selection were to include publications showing preclinical or clinical evidence of the analgesic potential of plant(s) listed in RENISUS, regardless of the part of the plant used, or even the type of extraction employed. It is noteworthy that communications, digests, reviews and studies that addressed only the chemistry of the plant were not included. Papers that only mentioned the empirical use of plants as well as works carried out from semi-structured interviews were also excluded. Papers were counted only once even if they were doubled in databases.

The analysis of the collected publications was performed in three steps (fig. 1). First, the search consisted in reading the title of the publications and selecting the papers that presented terms related to analgesic potential. Second, the previous chosen papers were selected by the abstract that mentioned some kind of effective treatment with the plant of interest. Third, the articles that mentioned some form of analgesic activity were fully read and qualitatively analyzed.

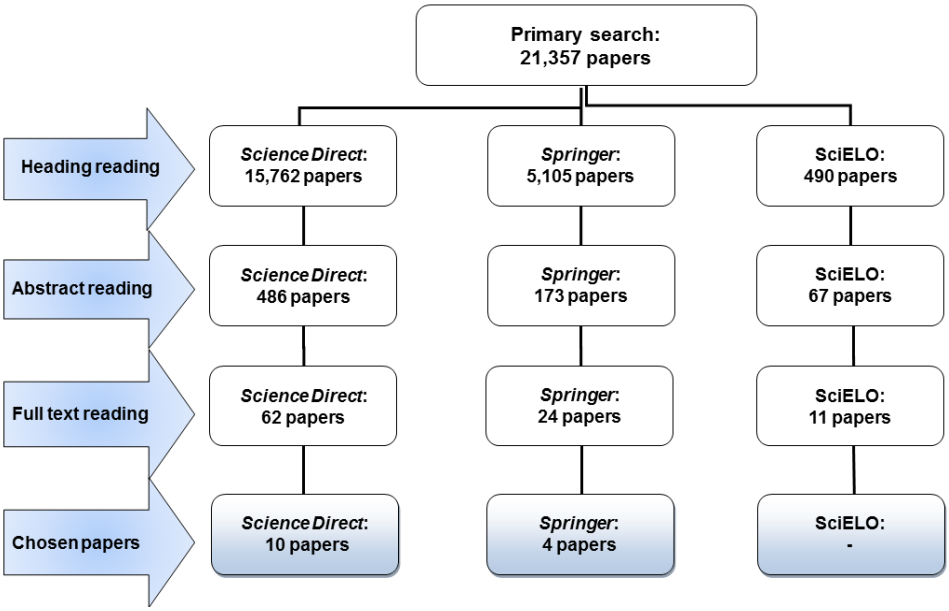

Fig. 1: Flow chart of the literature searching and study selection

RESULTS

The literature search of the two databases and the scientific publisher identified 21,357 publications. The majority were ineligible on reading the titles resulting in the selection of 726 publications that had a relationship with analgesic potential. After reading the abstracts, 629 irrelevant or duplicated papers were excluded. The remaining 97 articles were identified for full-text review. In addition, more attention was dispensed to address the results in order to highlight which studies, in fact, have proven therapeutic potential. Finally, 14 papers were included (0.07% of all searched articles). Table 1 shows the amount of analyzed papers and the number of articles selected for each medicinal plant.

Table 1: Total number of eligible and selected articles about plants with analgesic potential

Plant species	Science direct		Springer		Scielo		TOTAL	
	Eligible	Selected	Eligible	Selected	Eligible	Selected	Eligible	Selected
Aloe L.	171	0	41	0	1	0	1132	1
-*Aloe barbadensis* Mill.	160	0	16	0	3	0		
-*Aloe vera* (L.) Burm. f.	644	1	90	0	6	0		
Arrabidaea chica (Bonpl.) B. Verl.	9	1	2	0	2	0	13	1
Chamomilla recutita (L.) Rauschert	411	1	137	0	12	0	560	1
Cordia L.	64	0	44	0	1	0	161	1
-*C. curassavica* (Jacq.) Roem. & Schult.	10	0	4	0	3	0		
-*C. verbenacea* DC.	26	1	6	0	3	0		
Curcuma longa L.	847	1	282	1	10	0	1139	2
Justicia pectoralis Jacq.	7	1	3	0	5	0	15	1
Kalanchoe pinnata (Lam.) Pers.	55	1	13	0	3	0	71	1
Phyllanthus L.	108	0	38	0	0	0	564	1
-*Phyllanthus amarus* Schumach.	182	1	43	0	0	0		
-*Phyllanthus niruri* L.	126	0	24	0	0	0		
-*Phyllanthus tenellus* Roxb.	8	0	3	0	0	0		
-*Phyllanthus urinaria* L.	40		11		0			
Schinus areira L.	5	0	2	0	4	0	122	1
Schinus terebinthifolius Raddi	59	0	37	1	15	0		
Uncaria tomentosa (Willd. ex Roem. & Schult.) DC.	77	0	16	1	4	0	97	1
Zingiber officinale Roscoe	559	2	188	1	10	0	757	3
Total	3568	10	1000	4	82	0	4631	14

Of the total articles selected, 8 studies were published in 2011, 5 were published in 2012 and one study was conducted between January and February 2013. Four studies were conducted in Brazil [11-14]. Among the 71 plant species of RENISUS list, 11 species presented studies within the scope of the search, and 6 species were native to Brazil (*i.e. Arrabidaea chica* [crajiru], *Cordia verbenacea* [erva-baleeira], *Justicia pectoralis* [tilo], *Phyllantus amarus* [stonebreaker], *Schinus terebinthifolius* [Brazilian peppertree] e *Uncaria tomentosa* [cat's claw]). Of the 11 plants with analgesic activity, three species are available in the SUS as herbal medicines (*i.e. Aloe vera* [aloe], *S. terebinthifolius* and *U. tomentosa*). It was also evaluated which therapeutic activities are associated with the analgesic potential (table 2).

All selected studies related to analgesic potential were well distributed among the medicinal plants of interest. *Z. officinale* had three publications of interest [15-17], *Curcuma longa* (saffron) presented two studies referring to some level of analgesic activity [18, 19]. The other nine plant species were the subject of one study each: *Aloe vera* [11], *Arrabidaea chica* [12], *Matricaria chamomilla* (chamomile) [20], *Cordia verbenacea* [13], *Justicia pectoralis* [21], *Kalanchoe pinnata* (life plant) [22], *Phyllantus amarus* [23], *Schinus terebinthifolius* [14] and *Uncaria tomentosa* [24].

We can highlight that this screening evaluated so only a period of scientific production after the creation of RENISUS. However, before and after that period, several plant species have been scientifically proven as to its analgesic potential, among which: *Cannabis sativa* L. (cannabis)[25], *Baccharis trimera* (broom)[26], *Foeniculum vulgare* (fennel)[27], *Artemisia absinthium* (wormwood)[28], *Punica granatum* (pomegranate)[29] and *Plantago major* (plantago)[30]. For more details about the performed bioassays, the original references should be consulted.

Table 2: Studies of interest spread over potential analgesic and plant used

Therapeutic activity	Medicinal plant
Analgesic activity during tissue reorganization in the sectional area of the Achilles' tendon.	*Aloe vera*
Wound healing and analgesic activity on Achilles' tendon.	*Arrabidaea chica*
Hydroalcoholic extract exerts analgesic effects in peripheral neuropathy and it is more effective in attenuating cisplatin-induced pain compared to morphine.	*Matricaria chamomilla*
Ethanol extract inhibits the *in vitro* secretion of histamine from mast cells of different animal species, thereby exerting anti-inflammatory, analgesic and anti-allergy effects.	*Cordia verbenaceae*
Exerts analgesic and protective effects on dorsal root ganglion and sciatic nerve of rats subjected to sciatic nerve crushing.	*Curcuma longa*
Analgesic effects in osteoarthritis.	*Curcuma longa*
Sedative and anxiolytic effects in the treatment of convulsion.	*Justicia pectoralis*
Analgesic activity on acetic acid-induced writhing in mice.	*Kalanchoe pinnata*
Aqueous extract decreases arthritis in the paw, mechanical hyperalgesia, and nociceptive threshold.	*Phyllanthus amarus*
The analgesic action of the mycelium of fungus Rhizoctonia sp. isolated as endophyte of plant seed.	*Schinus terebinthifolius*
Chondroprotective agent and painkiller in arthritis.	*Uncaria tomentosa*
In vivo analgesic activity of ethanol extract of rhizomes.	*Zingiber officinale*
Plant-based cream shown to be as efficient as the commercial diclofenac cream for the treatment of musculoskeletal pain.	*Zingiber officinale*
Plant extract demonstrated anti-addiction potential against chronic use of morphine.	*Zingiber officinale*

DISCUSSION

The complex relationship between pain and injury turns the perception of pain in an important research issue. It is increasingly evident that the transmission of pain to the brain is under diverse physiological control. This becomes a difficult challenge in the discovery of forms and compounds capable of inhibiting the pain feeling without causing side effects [6].

Complementary health practices are preserved over the decades by different cultures and are supported by institutions such as World Health Organization (WHO), which encourages many countries to adopt new strategies and public health policies including complementary practices in health model aiming at comprehensive care to individuals [31, 32]. The use of such practices is being gradually expanded in health services due to the biomedical model is presenting limitations such as high cost of treatment, poor problem solving, side effects and adverse drug reaction[31]. Aiming to enhance the existing precious flora in Brazil, the Ministry of Health approved in October 2014 the ordinance SCTIE/MS 1/2014. A total budget around R$ 7 million (US$ 2 million) was intended to be divided among 19 projects in the medicinal plants and herbal area. The projects are currently being developed within SUS of all Brazilian regions [32].

Resolution No. 10/2010 disposes about the notification of herbal drugs by the Brazilian National Health Surveillance Agency (ANVISA). This resolution provides 66 plant species, which are considered selling products exempt from a medical prescription for the population. Their effectiveness is supported on traditional use and available data of literature related to the subject [33].

In this respect, it is important to note that the pharmaceutical industry has sought to revitalize programs for natural products screening. Research in pain management and drug addiction are focused on natural products. Analogous compounds have been produced from natural substances. In addition, synthetic compounds completely based on natural pharmacophores have been introduced. The medical and research fields seek alternatives to undesirable side effect profiles presented by many substances. Thus, natural products are becoming increasingly studied in order to discover compounds that may interact with known analgesic targets [2]. In this sense, a study published in 2012 showed that 50% of drugs approved in 2010 were directly or indirectly derived from natural products [34].

Lastly, we would like to highlight that through all collected data, further analysis with different approaches were made. In total, 6 studies were published, aimed at the therapeutic potential of RENISUS plants against diabetes mellitus [35], the antibacterial [36], anti-inflammatory [37] and antiparasitic potential of RENISUS plants [38], the therapeutic potential of ginger [39] and finally, the amount of scientific production of RENISUS plants [40].

CONCLUSION

We can conclude through this systematic review there were few studies that showed the analgesic potential of plants listed in RENISUS that were published in the analyzed period (2010-2013). Among the 71 plants of RENISUS list, only 11 species were the subject of studies related to therapeutic potential. Regarding these plants, 3 species are available in SUS as herbal medicines (i.e. Aloe vera, Schinus terebinthifolius and Uncaria tomentosa), while 6 species are native to Brazil. The dissemination of this study will reflect and expand the perception of public health policies and thereby, provide support for the implementation of new health practices for the conscious use of herbal medicines and plants available to the population through SUS.

The results of this study present a further theoretical basis for discussions in the field of public health on alternative treatments based on medicinal plants, as an adjunct therapy. In addition, the correct use of scientifically proven medicinal plants added to conventional therapy may contribute to improving health and pain relief.

CONFLICT OF INTERESTS

Declared none

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