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Review

Plant-Derived Medicines for Sciatica: A Comprehensive Review

Narges Lavari[1,2], Niusha Esmaealzadeh[3,4], Roja Rahimi[3], Alireza Abbassian[1]*

[1]Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
[2]The Persian Gulf Tropical Medicine Research Center, The Persian Gulf Biomedical Sciences Research Institute, Bushehr University of Medical Sciences, Bushehr, Iran
[3]Department of Traditional Pharmacy, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
[4]Traditional Persian Medicine and Complementary Medicine (PerCoMed) Student Association, Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran

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Abstract

Sciatica commonly refers to radicular leg pain which is mainly caused by lumbar disc herniation (LDH) and affects the daily functional ability of many patients in the world. However, according to the side effects and short-term benefits of its treatments, new therapeutic agents such as natural products are needed. The aim of this study was to comprehensively review the effectiveness of plant-derived products for the treatment of sciatica. Electronic databases, including Medline (via PubMed), Scopus, and Web of Science, were searched from inception to 17 August 2023 for this comprehensive review. English language papers reporting preclinical and clinical evaluations of the effectiveness of herbal products, including medicinal plants, multi-component herbal preparations, and phytochemicals on sciatica, radicular pain, or LDH, were included. Studies on neuropathic pain due to reasons other than sciatica, radicular pain, or LDH were excluded. From a total of 5666 papers identified in the primary search, 16 (including 4 clinical and 12 preclinical studies) were finally included. Most of the plant-derived treatments mentioned in this review belonged to the polyphenol family or contained high concentrations of various polyphenols. From the results obtained, polyphenols relieved sciatica by reducing inflammation and oxidative stress, mainly through the inhibition of mitogen-activated protein kinases pathways. In conclusion, plant-derived medicines have the potential to improve the quality of life and functional ability of sciatica patients by relieving symptoms. However, further preclinical and clinical studies are suggested to prove the safety and efficacy of such herbal medicines for sciatica.

Keywords: Sciatica; Disc herniation; Medicinal plant; Traditional medicine; Herbal medicine

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*Corresponding Author: Alireza Abbassian
Department of Traditional Medicine, School of Persian Medicine, Tehran University of Medical Sciences, Tehran, Iran
E-mail: abbasian@sina.tums.ac.ir

Introduction

Sciatica, as a common health issue worldwide, affects patients' lives through poor quality of life, disability, and work absence [1,2]. It commonly refers to radicular pain in the sciatic nerve pathway in the leg and is sometimes accompanied by back pain, weakness, or sensory loss [3,4]. Sciatic neuralgia is a radicular pain caused by sciatic nerve pathology [5]. Spinal problems, including disc herniation, foraminal stenosis, spondylolisthesis, facet joint synovial cysts, arachnoid cysts, arachnoiditis, spinal tumors, and non-spinal causes such as gynecological conditions, piriformis syndrome, trauma, and zoster sine herpete play a crucial role in the etiology of sciatica. However, lumbar disc herniation (LDH) is a major cause of sciatica [4], and its pathophysiology may be due to upregulated immune response, inflammation, and nerve mechanical deformation [5]. The prevalence of sciatica, in terms of sciatica definition based on the duration or distribution of pain in different studies, ranges from 1.6% to 43% [6,7]. Sciatica has several treatment options, including medications, spinal injections, and surgery. Medications such as non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, benzodiazepines, anti-depressants, opioids, anti-convulsant, biological agents, and paracetamol have known adverse effects and limited effects on relieving sciatica [2,6]. Spinal injections of steroids are not recommended because of the small and short-term of their beneficial effects. The clinical results of surgery and conservative treatment are similar after one and two years [2]. In addition, surgery has complications such as recurrence, fibrosis, and infection [8]. Therefore, considering their side effects and limited improvements in patients with sciatica [4], the discovery of new treatments is necessary.

Medicinal plants as a part of complementary and alternative treatments have a long history in medicine and wide use in various diseases [9-11]. Traditional Persian medicine (TPM), Chinese medicine, and Ayurveda are amongst the traditional medicine systems which utilize different herbal remedies for the management of sciatica [12-14]. Numerous studies have suggested the beneficial effects of medicinal plants and their phytochemicals in the treatment of neuropathic pain and neuropathies [15,16]. In addition, medicinal plants have relieved sciatica and LDH which may be related to their anti-inflammatory and analgesic effects, immunomodulation, blood circulation improvement, phagocytosis of macrophages enhancement, collagen synthesis enhancement, and nerve protection [13]. Because of the availability and fewer adverse effects of medicinal plants, they are considered by patients to be the remedy of choice [10]. Therefore, the effects of medicinal plants and their secondary metabolites on sciatica have been evaluated by researchers. The aim of the present study is to review animal and clinical investigations on the effectiveness of herbal products, including medicinal plants, multi-component herbal preparations, and plant-derived chemical compounds for the treatment of sciatica.

Materials and Methods

Electronic databases, including Medline (via PubMed), Scopus, and Web of Science were screened from inception until 17 August 2023 with the following formula: ("sciatica" OR "sciatic" OR "lumbosacral radicular syndrome" OR "lumbosciatic pain" OR "radicular Leg pain" OR "radicular pain" OR "radiculopathy" OR "nerve root pain" OR "lumbago" OR "sciatalgia" OR "discogenic pain") [title/abstract/keywords] AND ("herb" OR "plant" OR "extract" OR "herbal") [all fields]. Only English full-text articles and preclinical/clinical studies evaluating the effectiveness of herbal products, including medicinal plants, polyherbal preparations, and phytochemicals on sciatica, radicular pain, or LDH, were included. Studies on neuropathic pain due to reasons other than sciatica, radicular pain, or LDH were excluded. The cellular or observational studies, and studies on the combination of herbal products with non-herbal material, were also excluded. Two independent investigators screened all papers, which were exported into version X8 of EndNote software, based on the title and abstracts of the studies. Then, relevant studies were evaluated based on their full-text. The reference lists of included studies were also checked to find further relevant studies.

The included papers were reviewed for single and combined herbal preparations/phytochemical names, the dose and route of administration, study design, phytochemical category, duration of study, type of animal and disease induction model, and outcomes in animal studies. For clinical studies, single and combined herbal preparations/phytochemical names, administered dose, duration of study, concomitant therapy, outcomes, and adverse effects were collected.

The outcomes of clinical studies were extracted as follows:

- Change in pain score on visual analog scale (VAS);
- Oswestry disability index (ODI) to determine the disability;
- 36-item short form health survey (SF-36) questionnaire to determine the quality of life;
- The straight leg raise (SLR) test to identify disc pathology or nerve root irritation;
- Other outcomes, i.e., muscular power (MP), muscular spasm (MS), sitting test (ST), walking time (WT), anxiety, and functional connectivity between the brain areas.

The results of animal studies were extracted as follows:

- Pain, allodynia, and hyperalgesia;
- Inflammatory factors, e.g., interleukin (IL)-1β, IL-6, etc.;
- Oxidative factors, e.g., superoxide dismutase 2 (SOD2) and heme oxygenase-1 (HO-1).

To evaluate the quality of clinical trials, the Jadad score with a range of 0 to 5 was used. A score greater than or equal to three indicates high quality, and a score less than three indicates low quality [17].

All processes of study selection, data extraction, and quality assessment were assessed by two independent researchers. Any disagreement between investigators was resolved by consulting with the third author.

Results

From a total of 5666 articles, 5646 results were excluded primarily on the basis of duplication, non-English full-text, review, and title/abstract. From the 20 remaining papers, 4 reports were excluded: because of *in vitro* study (n=1), focusing on the induction of a neuropathic pain model rather than the treatment of sciatica (n=1), and study on the combination of plants with the non-herbal materials (chemical material and animal origin) (n=2). The final studies consist of 16 preclinical (n=12) and clinical reports (n=4). The study selection diagram is represented in figure 1, and the final included papers are summarized in tables 1 and 2.

Medicinal plants

1. Vitex negundo L.

Nirgundi Ghan Vati (NGV), a preparation from dried aqueous extract of *Vitex negundo* leaves, is basically an oral Ayurvedic treatment for osteoarthritis and rheumatoid arthritis. The significant effect of NGV for pain relief sparked the idea of a clinical trial performed by Mumtaz Ali et al. A total of 102 patients with radicular pain and irritation in terminal lumbar discs were included. In this 30-day trial, NGV along with an oil enema could reduce pain and improve the scores in the SLR test as well as the popliteal compression test [19]. NGV had possibly diminished the expression of prostaglandins. The definitive pathway involved pathway is not entirely clear [34].

2. Ligustrum lucidum W.T.Aiton

Fructus Ligustri Lucidi (FLL) or the fruit of *Ligustrum lucidum* is used for aging complications such as osteomyelitis and bone fractures. The ethanolic extract of this fruit has the ability to enhance calcium reabsorption by increasing serum levels of vitamin D-depen-

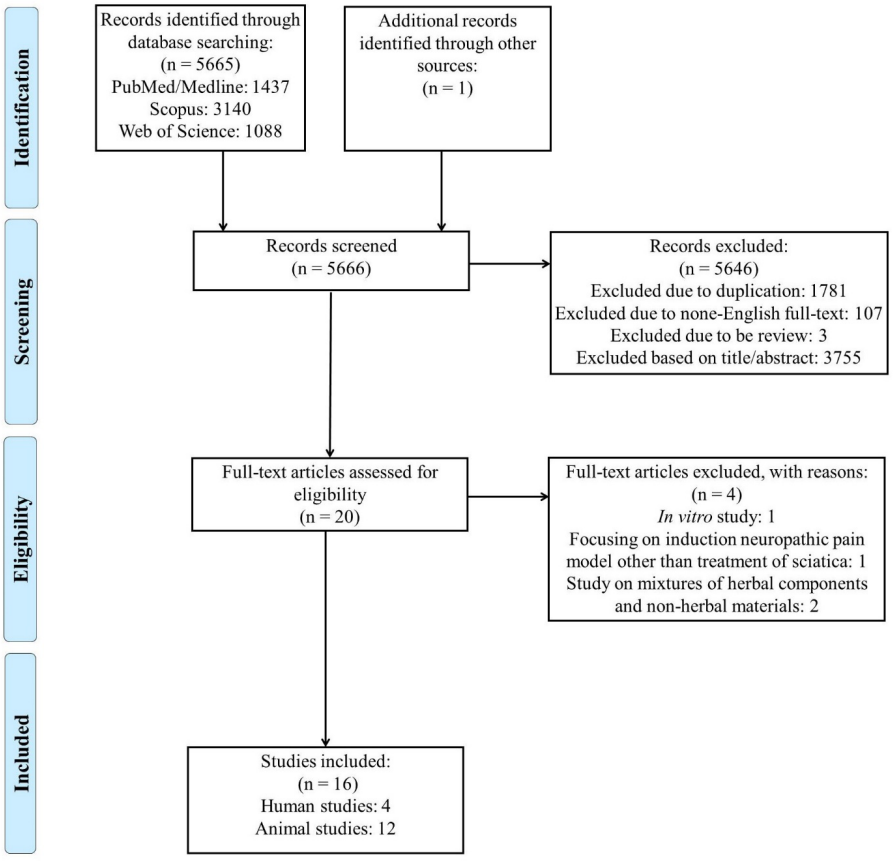

Figure 1. Study selection diagram.

Table 1. Clinical studies on the use of plant-derived medicines for the treatment of sciatica

Single & combined herbal preparations/ phytochemical	Administered dose	Study design/ duration of study	Concomitant therapy	Outcome (s)	Jadad score	Adverse effect (s)	Reference
δ-9-tetrahydrocannabinol (THC)	0.2 mg/kg of oil (THC dosage = 15.4 ± 2.2 mg), sublingual	Randomize, double-blind, placebo-controlled clinical trial in 15 patients with chronic radicular neuropathic pain/ 2 sessions divided by 3 weeks	NR	↓VAS ACC–sensorimotor cortex FC Sensorimotor-affective pain related areas FC Chronic pain network connectivity and DLPFC ↔Anxiety CVD measures (HR and BP)	2	NR	[18]
Vitex negundo L.	0.3 mg/day (2 tab, 3 times/day), p.o.	Randomized clinical trial in 102 patients with sciatica/ 30 days	Matra basti (Fat enema)	↓MS ↑SLR WT Ankle jerk Knee jerk PC ST MP	2	NR	[19]
A patch contains essential oils of *Thymus vulgaris* L., *Citrus medica* L., *Sambucus nigra* L., *Rosmarinus officinalis* L., *Matricaria chamomilla* L., and *Laurus nobilis* L.	NR, topical	Prospective randomized placebo controlled clinical trial in 79 patients with LDH/ 24 hours	NR	↓PVMS-VAS PVMS-ODI ↑SLR	2	Short-term pain increase. Bullous lesions	[20]
Lawsonia inermis L.	1.5 ml/day (0.5 ml, 3 times/ day), topical	Randomize, double-blind, placebo-controlled clinical trial in 78 patients with chronic sciatica/ 28 days	NR	↓VAS ODI ↑Total SF-36	5	Mild and localized pruritus	[21]

ACC, anterior cingulate cortex; BP, blood pressure; CVD, cardiovascular disease; DLPFC, dorsolateral prefrontal cortex; FC, functional connectivity; HR, heart rate; LDH, lumbar disc herniation; MP, muscular power; MS, muscular spasm; NR, not reported; ODI, Oswestry disability index; PC, popliteal compression; p.o., per os (orally); PVMS, paravertebral muscle spasm; SF-36, 36-item short form health survey; SLR, straight leg raise; ST, sitting test; VAS, visual analog scale; WT, walking time; ↑, significant increase; ↓, significant decrease; ↔, no significant difference.

dent calcium binding proteins (CaBP) and vitamin D3 [35]. Moreover, FLL could efficiently inhibit tumor necrosis factor α (TNF-α) and other inflammatory cytokines in an LDH rat model; however, the underlying mechanism remains to be fully explored [30].

3. Lawsonia inermis L.

Lawsonia inermis (henna) belongs to the Lythraceae family [36]. Henna leaves have been used for androgenetic alopecia, skin disorders, and wound healing [21,36-38]. In TPM, one of the traditional medicinal uses of henna is pain relief in patients with sciatica [21,39,40]. In a double-blind, randomized clinical study, the topical henna oil (aqueous extract of henna leaves in sesame oil) significantly decreased pain intensity and disability, and increased the quality of life,

Table 2. Animal studies on the use of plant-derived medicines for the treatment of sciatica.

Single & combined herbal preparations/ phytochemical	Dose & route of administration	Phyto-chemical category	Type of animal & model	Duration of study	Outcome (s)	Reference
Curcumin	50 mg/kg of solution, every other day, i.p.	Diaryl-hepta-noid	Balb/C mice/ M & F, model of radiculopathy induced by LDH	11 days	↓Mechanical hyperalgesia TNF-α-induced neuroinflammation IL-6 PGE2 COX-2 SP CGRP ROS Neuron apoptosis ↑HO-1 Catalase SOD2 Regeneration of ECM proteins extracellular matrix in herniated disc	[22]
Osthole	50 µL of 2% solution , e.i., POD6	Coumarin	SD rats/ M, model of NP-induced radicular inflammatory pain	21 days	↓MPH MWT COX-2 mRNA expression of p-ERK	[23]
Osthole	100 µg/ml, e.i., POD6	Coumarin	SD rats/ M, model of NP-induced radicular inflammatory pain	28 days	↓Expression of ASIC3 Hyperalgesia MP	[24]
Osthole	50 µL of 2% solution, POD (2, 6, 13, and 20), e.i.	Coumarin	SD rats/ M, model of sciatica induced by LDH	20 days	↓Hyperalgesia NOS COX-2 ↑Long-term effect on pain	[25]
Resveratrol	0.1 ml of 50µM, epineurium underlayer injection	Stilbene	SD rats/ F, model of autologous NP radiculopathy	1 day	↓Pain Expression of TNF-α and IL-1 DRG pathological changes	[26]
Puerarin	100 mg/kg/ day, i.p.	Isoflavonoid	SD rats/ M, model of LDH induced by autologous NP implantation	7 days	↓Expression of microglia marker (Iba1) ↑Expression of p-ERK Pain thresholds	[27]
α-Asarone	20 mg/kg, bid, p.o.	Anisole	SD rats/ M, model of sciatica	21 days	↓Thermal hyperalgesia Serum levels of IL-1β, IL-6, TNF-α, & CRP The mRNA levels of IL-1β, TNF-α, TRPV1-4, TRPA1 & TRPM8 in DRG neurons The protein levels of TRPs (TRPV1-4, TRPM8 & TRPA1) & p-p38 MAPK inflammatory cell infiltration Schwann cell apoptosis cleaved-caspase3 cleaved-caspase7 TLR4 ↑IL-10 Bcl-xl Bcl-2	[28]

Ferulic acid	50 mg/kg, bid, p.o.	Cinnamate	SD rats/ M, model of sciatica	21 days	↓Thermal hyperalgesia mRNA levels of IL-1β, IL-6, TNF-α & CRP in DRG neurons Rock1 Rock2 Iba-1 iNOS, IL-1β RhoA, RhoA-GTP, COX-2 TRPV1 TRPA1 p-p38 MAPK Serum levels of CRP, PGE2 & SP CD32 ↑IL-10 CD206 Arg-1	[29]
The fruit of *Ligustrum lucidum* W.T.Aiton	200 mg/kg, p.o.	-	SD rats/ M, model of mechanical allodynia & thermal hyperalgesia	30 days	↓Mechanical allodynia IL-2 IL-6 IL-8 TNF-α MMPs (MMP-1, -3, -8 & -9) ↑Withdrawal latency	[30]
Demethoxycurcumin	15, 30, or 60 mg/kg/day, p.o.	Diarylheptanoid	SD rats/ M, model of LDH (DRG)	21 days	↓IL-1β IL-4 IL-6 TNF-α Activation of MAPKs (p-ERK, p-JNK, and p-p38) & NF-κB	[31]
Piperine	NR, p.o.	Alkaloid	SD rats/ M, model of non-compression LDH	15 days	↓IL-1β TNF-α ↑IL-10 TGF-β1	[32]
GCSB-5 (*Saposhnikovia divaricata* (Turcz.) Schischk., *Achyranthes bidentata* Blume, *Eucommia ulmoides* Oliv., *Cibotium barometz* (L.) J.Sm., *Glycine max* (L.) Merr., and *Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.)	300 mg/kg/day, p.o. in saline solution	-	SD rats/ M, model of LDH	56 days	↓Allodynia MWT Iba1 GFAP CGRP TRPV1	[33]

Arg-1, arginase-1; ASIC3, acid-sensing ion channel 3; Bcl-2, B-cell lymphoma-2; Bcl-xl, B-cell lymphoma-extra large; Bid, bis in die (twice a day); CD, cluster of differentiation; CGRP, calcitonin gene-related peptide; COX, cyclooxygenase; CRP, C-reactive protein; DRG, dorsal root ganglion; e.i., epidural injection; F, female; GFAP, glial fibrillary acidic protein; GTP, guanosine triphosphate; HO-1, heme oxygenase-1; Iba1, ionized calcium-binding adaptor molecule 1; IL, interleukin; iNOS, inducible nitric oxide synthase; i.p., intraperitoneal injection; LDH, lumbar disc herniation; M, male; MAPKs, mitogen-activated protein kinases; MMP, matrix metalloproteinase; MP, membrane polarization; MPH, mechanical pain hypersensitivity; MWT, mechanical withdrawal threshold; NR, not reported; NF-κB, nuclear factor-κB; NOS, nitric oxide synthase; NP, nucleus pulposus; p-ERK, phosphorylated-extracellular signal-regulated kinase; PGE2, prostaglandin E2; p-JNK, phosphorylated-Jun N-terminal kinase; p.o., per os (orally); POD, postoperative day; p-p38, phosphoinositide-38-kilodalton protein; RhoA, ras homolog family member A; Rock, Rho-associated coiled-coil containing protein kinase; ROS, reactive oxygen species; SD, Sprague-Dawley; SOD2, superoxide dismutase 2; SP, substance P; TGF-β1; Transforming growth factor β1; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRP, transient receptor potential; TRPA1, transient receptor potential ankyrin 1; TRPM8, transient receptor potential melastatin 8; TRPV, transient receptor potential vanilloid; ↑, significant increase; ↓, significant decrease.

compared to a placebo in patients with chronic sciatica [21]. The main phytochemicals of aqueous extracts of henna leaves are gallic acid, luteolin, and ferulic acid that have also shown anti-inflammatory and analgesic effects in preclinical studies [21,41].

Multi-component herbal preparations

Various herbal preparations, containing multiple active ingredients, have been investigated for their effects on sciatica. It is believed that a multi-component formulation may benefit patients more than a single-component one due to the synergistic effects of the plants contained [42].

A randomized placebo-controlled clinical trial was conducted by Uğurlu et al. in which the analgesic property of the Artcure diffusional patch was investigated. This patch was applied in patients with LDH associated with radiculopathy as a non-invasive treatment. The Artcure patch contains a high density of herbal oils obtained from thyme, rosemary, chamomile, lemon peel, elderberry, and laurel [20]. Within a month after the application of the Artcure patch, VAS and ODI score, which represents the functionality of the patients in their daily lives [43], were improved significantly. The therapeutic mechanism of the Artcure patch is believed to be the formation of an osmolarity gradient which forces the water to move from the herniated nucleus pulposus (NP) to the hyperosmolar setting. Therefore, the volume of the NP decreases and the pressure unloads. Despite the eventual amelioration of the pain through the month, the patients experienced a pain augmentation during the first 24 hours after the patch application. This might be the result of an increase in the volume of the NP due to the entrance of the oils. However, the entered oils create less osmolarity than the water and cause it to rush out of the NP, which reduces the pain conclusively [20].

In a rat model of disc herniation, the effect of 300 mg/kg of a Korean preparation called GCSB-5 was studied and compared with the therapeutic effects of aceclofenac. GCSB-5 is a mixture of six purified oriental herb extracts [44], and is safely taken for the treatment of osteoarthritis in East Asian Medicine. It has been reported to significantly decrease pain-related factors such as calcitonin gene-related peptide (CGRP), glial fibrillary acidic protein (GFAP), Ionized calcium-binding adapter molecule 1 (Iba1), and transient receptor potential vanilloid (TRPV) 1. Therefore, the pain behaviors, e.g., mechanical withdrawal threshold (MWT), enhanced notably [33]. TRPV family is a group of the transient receptor potential (TRP) channels which play an important role in dorsal root ganglion (DRG) to regulate the levels of cations, especially Ca^{2+}, inside the neurons [45]. However, some hypotonic stimuli could initiate a series of pathological cascades that increase the concentration of Ca^{2+} in the cells and stimulate the release of neurotransmitters such as CGRP and substance P (SP) [46]. This process could develop the perception of pain and cause radicular neuralgia [47]. The exact mechanism of action and the main active ingredients of GCSB-5 are not fully studied. However, the analgesic, antioxidant, and anti-inflammatory properties of some of the contained herbs, e.g., *Saposhnikovia divaricata* (Turcz.), *Eucommia ulmoides* Oliv., *Cibotium barometz* (L.) J.Sm., have been reported [48-50].

Plant-derived chemical compounds

δ-9-tetrahydrocannabinol (THC) is a cannabinoid and the main psychoactive substance of *Cannabis* spp. with promising analgesic effects [18,51]. Weizman et al. demonstrated the significant effect of sublingual THC oil on chronic radicular pain compared to placebo, correlated with altered brain connectivity, in a clinical trial. Two important cognitive-emotional modulation areas (anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC)) of the brain and their functional connections to somatosensory areas were related to the reduction of pain and were reduced by THC [18].

Demethoxycurcumin (DMC) as a kind of curcuminoid is derived from the rhizome of *Curcuma longa* L., and its pharmacological activities include anti-inflammatory, anti-hypertension, and neuroprotective effects [31,52]. The phosphorylation of mitogen-activated protein kinases (MAPKs) such as phosphorylated-extracellular signal-regulated kinase (p-ERK), phosphorylated-Jun N-terminal kinase (p-JNK), and phosphorylated-38-kilodalton protein (p-p38) release pro-inflammatory cytokines and activates inflammation [53]. Also, the nuclear factor-κB (NF-κB) pathway is involved in the inflammation regulation in cells [54]. An animal study showed that DMC reduces inflammatory reactions in LDH through inhibition of the MAPKs and NF-κB pathways. In addition, an *in vitro* study showed that DMC decreases inflammatory factors and the activation of MAPKs and NF-κB in primary human NP cells [31].

Osthole is mostly extracted from *Angelica pubescens* Maxim. and *Cnidium monnieri* (L.) Cusson, both from Apiaceae. Osthole is an active component widely present in Chinese cuisine for patients with discogenic low back pain [55]. Osthole, with its coumarin-like structure, bears different pharmacological activities. It has shown that osthole could inhibit cyclooxygenase (COX) enzymes, selective for COX-1, 5- lipoxygenase (LPO), and inducible nitric oxide synthase (iNOS) which prevent activated macrophage from producing further inflammatory cytokines such as nitric oxide (NO) and TNF-α [25,56]. Osthole also has a good potential for degrading allodynia and hyperalgesia. He

et al. have shown the potential of osthole for the management of pain caused by LDH. Osthole's ability to suppress overexpression of acid-sensing ion channel 3 (ASIC3), a cationic channel that activates during inflammation-induced acidosis, is the reason for the blockage of nociceptors and pain reduction, successively [24]. Wu et al. investigated another mechanism of osthole for the reduction of LDH-induced pain in a rat model. The herniation was induced by the application of the NP to DRG. The induced allodynia was assessed by an increase in the levels of expression and activation of extracellular signal-regulated kinase (ERK). ERK was proven to be responsible for producing hyperalgesia and allodynia due to nerve damage [57]. Osthole could effectively diminish the activation of ERK and expression of COX2, resulting in the minimization of pain [23].

Curcumin as a polyphenolic component is mainly obtained from the turmeric rhizome (*Curcuma longa* L.) with diarylheptanoid structure [58]. Preclinical and clinical studies have shown its safety and therapeutic effects on diseases such as arthritis, pancreatitis, and inflammatory bowel disease [22,59-61]. The systemic administration of curcumin attenuated radiculopathy due to LDH compared to the dimethyl sulfoxide (DMSO) as vehicle control, in mice. Curcumin suppressed TNF-α-induced neuroinflammation (IL-6, prostaglandin E2 (PGE2), and COX-2) through activated protein kinase B (AKT) and ERK phosphorylation pathways. It decreased nociceptive neuropeptides (SP and CGRP) in the culture of mouse DRG. It also reduced reactive oxygen species (ROS) production and neuron apoptosis, and increased the antioxidant enzymes in primary neurons. These effects of curcumin may be the cause of relieving lumbar radiculopathy in mice. Furthermore, the study has shown that curcumin promotes the regeneration effect in LDH mice [22].

Resveratrol (3,5,4'-trihydroxy-*trans*-stilbene) is a compound which is found in different herbal materials, especially grape skin [26,62]. It has represented pharmacological properties, including antioxidant, anti-tumorigenic, immunomodulatory, anti-inflammatory, and cardiovascular protective effects [26,62-65]. The anti-inflammatory and analgesic effects of resveratrol were shown by inhibiting the expression of TNF-α, IL-1, and mechanical hypersensitivity in rats with radiculopathy caused by NP. It also prevented pain behavior for two weeks, probably due to reduced expression of cytokines in the NP tissue of rats [26].

Puerarin is an ingredient derived from *Pueraria lobata* (Wild.) Ohwi (a Chinese medicinal herb) with anti-inflammatory and antioxidant effects [27,66-68]. Recent evidence exhibits that it moderates chronic pain caused by nerve injury. Several studies have indicated that pro-inflammatory cytokines (TNF-α and IL-1β), microglia as the major producers of these cytokines, and ERK activation in spinal microglia, are involved in radicular pain induced by LDH [27,69-71]. An *in vivo* study showed that it alleviates radicular pain induced by LDH in rats. The study suggested that its possible mechanism is inhibition of the spinal ERK pathway or accompaniment to spinal microglia activation [27].

Ferulic acid (4-hydroxy-3-methoxycinnamic acid) is a polyphenolic constituent that is abundantly present in herbs, whole grains, and food sources such as wheat, rice, oranges, barley, apples, coffee, and peanuts [72,73]. It displays neuroprotective effects by inhibiting neuroinflammation, nuclear translocation of NF-κB, and the microglia-mediated pro-inflammatory response [29,74,75]. It increases MI microglia markers such as IL-1β, TNF-α, iNOS, IL-6, and Cluster of Differentiation (CD) 32 and decreases M2 microglia markers, i.e., CD206 and arginase-1 (Arg-1) to inhibit neuroinflammation. In addition, ferulic acid represented analgesic properties on sciatica in rats, because it suppressed peripheral sensitization by attenuating inflammation and expression levels of TRPV1 and transient receptor potential ankyrin 1 (TRPA1) through the ras homolog family member A (RhoA)/p38 MAPK signaling pathway [29].

α-Asarone is an ingredient of *Acorus* plant species with neuroprotective and anti-inflammatory activities [76,77]. Zhang et al. indicated that α-Asarone relieved chronic sciatica in rats. It attenuated Schwann cell apoptosis to promote nerve repair by suppressing the toll-like receptor 4 (TLR4)/p38 MAPK pathway and also inhibited peripheral sensitization by reducing the levels of the TRPs and inflammatory factors [28].

Piperine is the main phytochemical of *Piper longum* L. which belongs to the Piperaceae family [32,78]. It has been shown that piperine can suppress the inflammatory and oxidative factors, as well as bone destruction of the sciatic nerve [32,79]. An animal study demonstrated that oral administration of piperine could significantly improve sciatica and diminish the inflammatory response by suppressing the NF-κB signal pathway in rats with non-compression LDH [32].

Discussion

Sciatica, as a radicular pain mainly due to LDH, is a common condition that affects patients' functionality. Current treatments do not seem to be beneficial for long-term use, and most of them leave behind a huge deal of side effects [2]. Still highly favored, even in people of modern lives, plant-based products are the drug of choice for many people due to being generally safe, naturally-derived, cost-effective, and experienced for thousands of years behind them [10]. Therefore, in the current article, we aimed at reviewing *in vivo* studies, both clinical and pre-clinical ones,

to understand the mechanism by which plant-based medicament could manage sciatica. However, most of the studies focused on the mode of action rather than the mechanisms and pathways, especially with multi-component formulations. Despite this fact, the most common pathways could be recognized by concluding the obtained information from the included studies.

Three factors have been observed to be the reasons for lumbar radicular pain development in sciatica, i.e., mechanical factors, neuroimmunological responses, and inflammation. However, the core cause of lumbar radicular pain is believed to be inflammation. LDH, for example, could provoke the immune system and inflammatory process to produce diverse inflammatory factors and sensitize nociceptors [80]. Any further mechanical compression, as well as immune responses, could amplify the perceived pain. TNF-α at its increased levels in NP leads to the production of NO, which is strongly correlated with thermal hyperalgesia [81].

This study showed that herbal remedies can improve pain intensity, quality of life, and functional ability in patients with sciatica. In addition, some of these herbal products, mainly polyphenols, demonstrated beneficial effects on pain, as well as inflammatory and oxidative factors in various animal models of radicular pain or LDH.

It has been suggested that improvement of pain, functional ability, and quality of life in patients with sciatica, may be due to anti-inflammatory and analgesic effects [21]. A review of cellular and animal studies demonstrated that phytochemicals such as curcumin and resveratrol exert beneficial effects on intervertebral disc degeneration (IDD) by regulating inflammation and oxidative stress through various pathways, e.g., NF-κB and MAPKs pathways. IDD is one of the pathological bases of LDH [82].

General properties such as analgesic, anti-inflammatory, and antioxidant effects were frequently mentioned in the selected studies. These three features, however, are closely related. Oxidative reactions are the primary cause of neural tissue damage and can trigger an inflammatory cascade. This acute inflammation often leads to severe pain and has the potential to become chronic in most neuromuscular conditions due to plasticity and neuromodulation [83]. Chronic inflammation would eventually lead to deformity of the cartilage and bones, intervertebral discs, and vertebrates in the case of sciatica, respectively [80].

The mentioned multi-component products were mostly traditional formulas, either Ayurvedic or Chinese, which were composed of different parts of various plants. Most of these plants have shown anti-inflammatory and analgesic features, and it is probably their synergy which is responsible for the formula's therapeutic effect. They also have the ability to treat inflammations all through the body and thus, relieve pain. It should be noted that this procedure is the result of cytoprotective cascades and could be feasible through the whole neuromuscular system. This is in accord with the holistic traditional medicines, such as Chinese, Ayurvedic, and TPM.

Most of the herbal treatments mentioned in this article either belonged to the polyphenol family or contained high concentrations of various polyphenols. A systematic review of 17 randomized clinical trials concluded that polyphenols can improve rheumatic diseases by reducing pain and inflammation. Polyphenols are well-known for their radical-scavenging and anti-inflammatory aspects [84]. With their aromatic ring structure, polyphenols are also able to regulate the immune system and repair joints by stimulating anabolic processes such as increasing the activity of insulin-like growth factor-1 (IGF-1) [85,86]. Furthermore, an *in vivo* study demonstrated that bioactive-dietary-polyphenol-preparation (BDPP) relieved pain caused by IDD in rats by inhibiting the expression of pro-inflammatory cytokines in DRG [87]. From results obtained from the papers, polyphenols such as curcumin, DMC, osthole, resveratrol, puerarin, α-Asarone, and ferulic acid alleviated sciatica by reducing inflammation and oxidative stress, mainly through the inhibition of MAPKs pathways. The effects of polyphenols on sciatica are shown in figure 2.

Different pathways and factors have been mentioned in the current study that their regulation could effectively manage sciatica. Among these pathways, the role of the MAPK/ERK is probably the most important one. Activation of the MAPK/ERK pathway increases the ROS concentration and therefore oxidative stress. It also enhances the activity of p53, Caspase 8, and IL-1β that accelerate the senescence of the NP cells and apoptosis [88]. Besides, the ERK pathway leads to an increase in matrix metalloproteinase (MMP) which decreases the extracellular matrix (ECM) [89]. The mentioned plants and formulas, however, could notably regulate the activity of MAPK/ERK and regulate inflammatory as well as oxidative factors, i.e., TNF-α, IL-6, IL-1, iNOS, SOD2, and catalase. Therefore, pain and nerve necrosis diminished, and SLR and muscular power improved. These findings are in line with the result of a meta-analysis on LDH by Sun et al. [90].

Herbal treatments are usually accompanied by other complementary methods for the treatment of LDH in Chinese medicine. In a review article by Zhang et al., other methods such as acupuncture, massage, physical therapy, and lifestyle modifications were found to be more effective in LDH if they are co-administered with herbal drugs [91].

One of the major concerns with medicinal plants,

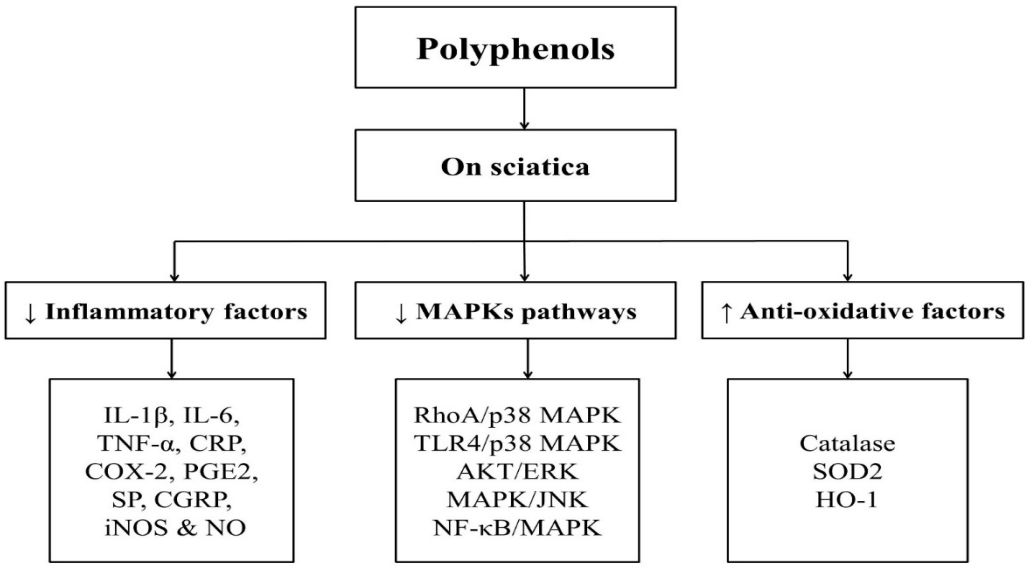

Figure 2. The effects of polyphenols on sciatica. AKT: activated protein kinase B; CGRP: calcitonin gene-related peptide; CRP: C-reactive protein; COX: cyclooxygenase; ERK: extracellular signal-regulated kinase; HO-1: heme oxygenase-1; IL: interleukin; iNOS: inducible nitric oxide synthase; JNK: Jun N-terminal kinase; MAPK: mitogen-activated protein kinases; NF-κB: nuclear factor-κB; NO: nitric oxide; p38: 38-kilodalton protein; PGE2: prostaglandin E2; RhoA: ras homolog family member A; SOD2: superoxide dismutase 2; SP: substance P; TLR4: toll-like receptor 4; TNF-α: tumor necrosis factor α.

especially the multi-component ones, is that the risk of drug-herb interactions is inevitable. Plants have the potential to alter the hepatic production of metabolizing enzymes, cytochrome P450, and intestinal P-Glycoprotein [92]. People with radicular pain have a tendency to consume NSAIDs and corticosteroids for the management of their pain and inflammation [93]. Thus, careful precautions should be considered to prevent further side effects.

The limitation was that this study encompassed only four clinical studies of the traditional formulations, due to few clinical trials on sciatica or radicular pain. Some of these studies lacked proper randomization as well as placebo control, which is rather important in studies concerning formulas based on traditional medicine. It is strongly recommended to design high-quality randomized placebo-controlled clinical trials to have more reliable research on sciatica.

The positive side of herbal preparations is that they are generally accepted, and they contain various phytochemicals that attach to their targets and exert effect via multiple pathways. Therefore, a single drug could relieve the neuromuscular symptoms by different mechanisms.

Conclusion

In conclusion, herbal medicines can be beneficial in improving the quality of life and functional ability of sciatica patients by inhibiting MAPKs pathways and offering symptomatic relief. However, further preclinical and clinical studies with high-quality designs are suggested to confirm the safety and efficacy of such herbal products as a natural treatment for sciatica.

Conflict of Interests

None.

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