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Review

A Personalized Approach to Phytotherapy for Pain and Inflammation in Patients with Intervertebral Disc Degeneration: Prospects and Limitations

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Abstract: Phytotherapy, as a traditional medicine method, has diverse therapeutic properties that can be used for disease-modifying therapy of intervertebral disc degeneration (IDD) in humans. Of particular interest are herbal remedies for the correction of chronic inflammation (primarily cytokine imbalance). The aim of this descriptive review is to update knowledge about herbal methods that are promising or traditionally used for the correction of cytokine imbalance in IDD. The results of preclinical and clinical studies and publications of historical interest on the traditional use of herbal remedies in Eastern and Western medicine were analyzed. Most herbal remedies for the correction of cytokine imbalance in IDD have evidence classes C and D, while the number of herbal remedies with evidence classes A and B is still small, despite many years and even centuries of experience in traditional medicine. In recent decades, there has been a trend toward increased research interest in this topic, with a growing number of preclinical studies of herbal remedies in animal models of IDD and arthritis (including arthritis of the facet joints of the spine). This review has demonstrated that traditional herbal medicine has not lost its clinical significance and can be used as a component of disease-modifying therapy for IDD in humans. Planning and conducting new preclinical and clinical studies of herbal remedies for this disease are necessary to increase the level of evidence for their use in clinical practice in accordance with modern requirements.

Keywords: *phytotherapy; cytokines; cytokine status; disk degeneration; biomarker; chronic inflammation.*

1. INTRODUCTION

According to the WHO, traditional medicine is "a body of knowledge, skills, and practices based on theories, beliefs, and experiences common to different cultures, whether explicable or not, used to maintain health, prevent disease, diagnose, ameliorate, or treat physical and mental illnesses" [1]. Phytotherapy, as a separate method of traditional medicine, is used for treatment and prevention and is based on the use of whole plants, mixtures, and their individual components in various forms (infusions, decoctions, extracts, and others). Different plants have a variety of therapeutic properties [2]. Phytotherapy includes the use of complex phytochemical mixtures in an attempt to improve pathophysiological processes in many pathological conditions. However, to correctly provide information on their molecular mechanisms of activity, studies of isolated components and individual herbal extracts are necessary, which explains the limitation for the practical use of herbal remedies due to the custom of dispensing medicinal herbs in the form of mixtures [3]. The administration of a complex mixture of

chemicals is important for achieving a therapeutic effect, as the effect is additionally mediated by co-compounds [4]. The broad specificity and low affinity of multi-component compounds found in herbal remedies may be more effective than compounds with high affinity and high specificity [5]. The use of whole plants, rather than isolated chemicals, may offer a safer clinical strategy for disease-modifying therapy of intervertebral disc degeneration (IDD) [6,7]; multimodal molecular activity is an integral aspect of IDD herbal therapy [4,8]. IDD, as a multifactorial disease, affects the spinal motion segments (SMS), starting from the nucleus pulposus (NP) to the annulus fibrosus (AF), and extends to adjacent SMS. It is a common spinal pathology responsible for the development of chronic back pain. Among the pathogenetic mechanisms of IDD and vertebrogenic pain syndrome development, inflammation (in particular, cytokine imbalance) plays one of the main roles, determining the direction of the immune response [9]. Moreover, cytokine imbalance in IDD can have various variants, influencing the tactics of herbal therapy (Figure 1).

2.

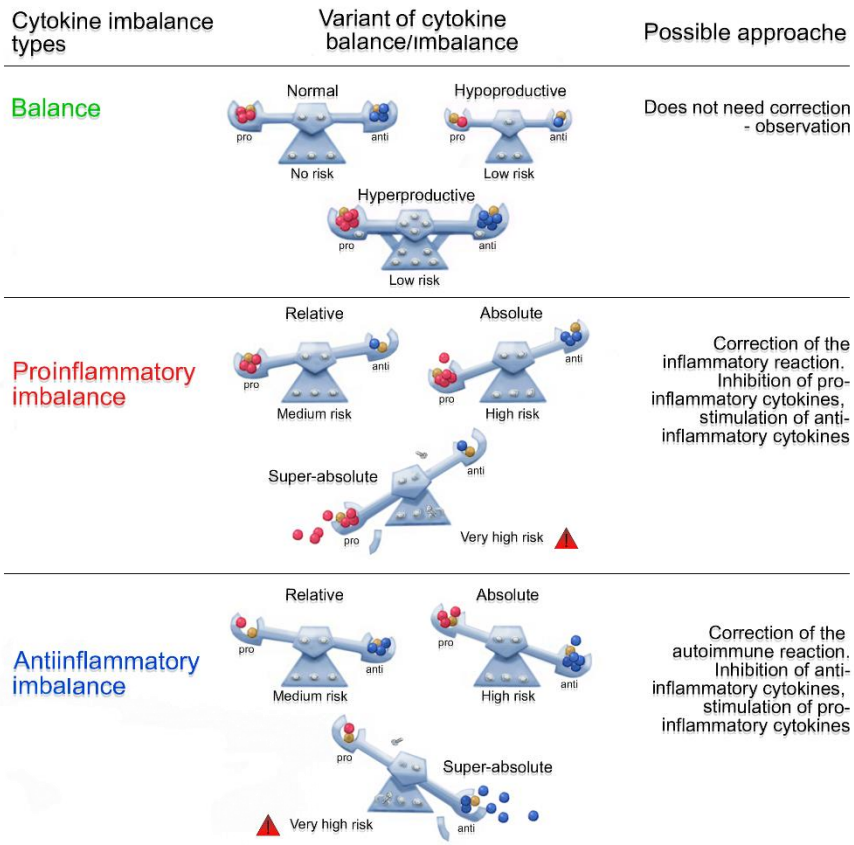

Figure 1: Variants of the balance of anti-inflammatory and pro-inflammatory cytokines as pathogenetic mechanisms of the inflammatory response in degenerating intervertebral discs.
Note: IDD – intervertebral disk degeneration; pro – proinflammatory; anti -anti-inflammatory. Pro-inflammatory cytokines are marked in red; anti-inflammatory cytokines are marked in blue; modulator cytokines are marked in yellow.

Phytotherapy of cytokine imbalance in IDD, carried out by prescribing both well-known ("classical") and new herbal preparations [9], can have various effects, including: (1) anti-inflammatory effect (directing the protective immune response in patients with IDD towards reducing chronic inflammation); and (2) regenerative effect (directing the protective immune response in patients with IDD towards recovery). Modern high-level pharmacological interventions for severe common IDD include the use of cytokines in antagonist, agonist, inhibition and stimulation models [9,10]. However, as a new emerging direction of therapeutic strategy, the occurrence of adverse events

creates barriers to their successful therapeutic application. Such adverse drug reactions (ADRs) as transient lymphopenia caused by interferons (IFN), interleukin 2 (IL-2) and tumor necrosis factor (TNF), monocytopenia with the use of interferon-gamma (IFN-γ) and TNF, neutrophilia with the use of IL-2, interferon alpha (IFN-α) and TNF, flu-like symptoms with the use of interferons, depression with the use of IL-2 and interferon-alpha (IFN-α) [11, 12, 13]. As for herbal remedies, many of their immunomodulatory characteristics are also due to the modulation of the cytokine balance, dynamic regulation of the level of cytokines. They may have better safety. Furthermore, phyto-immunomodulators are capable of altering the activity of the immune system through the dynamic regulation of other bioactive molecules—hormones, neurotransmitters, and other peptides [14]. Combinations of phytochemicals and cytokines and their regulators will allow for another approach in clinical medicine. Thus, phytotherapy as an additional method for correcting cytokine imbalance and the inflammatory response in degenerating IVDs remains relevant in modern neurology and orthopedics (Figure 2).

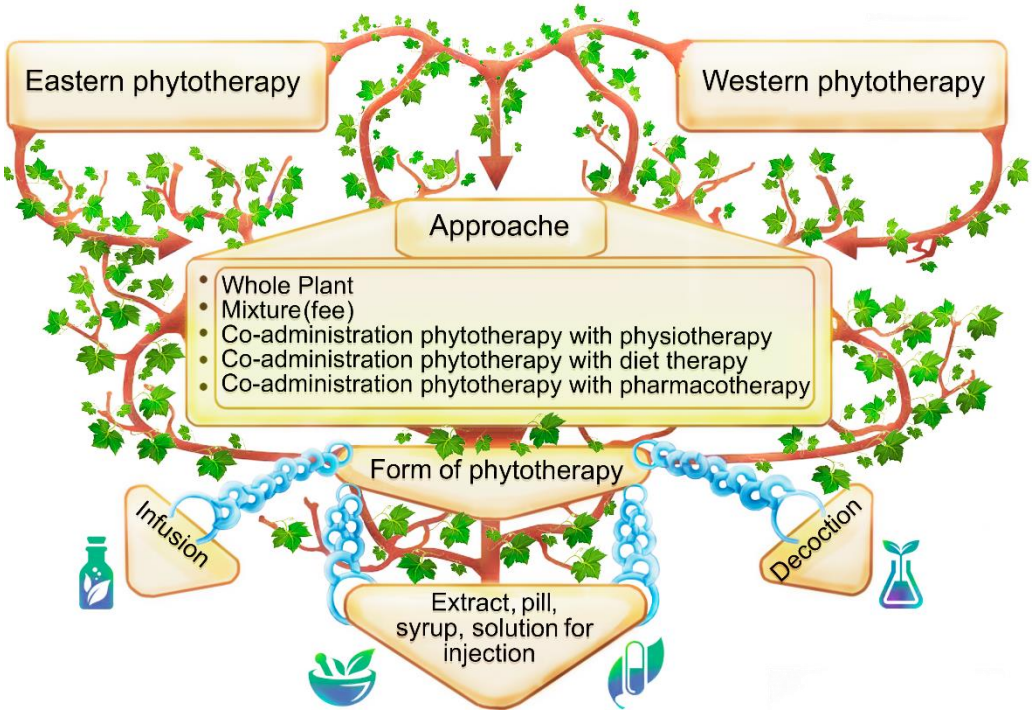

Figure 2. General approaches to herbal therapy for intervertebral disc degeneration.

The aim of this narrative review is to update knowledge on herbal therapies that are promising or traditionally used to correct cytokine imbalances in IDD.

2. THE USE OF WHOLE HERBS, MIXTURES, INFUSIONS, AND HERBAL PREPARATIONS IN THE THERAPY OF CYTOKINE BALANCE IN INTERVERTEBRAL DISK DEGENERATION

Traditional medicine varies across countries, partly due to the origins of the plants used in herbal medicine. We have conventionally identified two groups of herbal remedies, traditionally used in the East and the West. However, we acknowledge that this classification is arbitrary given the development of new technologies for their production and transportation.

2.1. Use Mainly in Eastern Herbal Medicine

2.1.1. Whole herbs

Cortex A. membranaceus (astragalus membranaceus) reduced IL-6 levels in vitro in animal models [15,16]. The possibility of using A. membranaceus in IDD models for inflammation correction has been demonstrated.

Allium sativum (allium sativum – garlic) reduced IL-6 levels in an in vitro human IDD model [17]. In addition to its hypocholesterolemic, antioxidant, and ACE-inhibiting activities [18], garlic also reduced the level of the proinflammatory cytokine IL-1β [18], exerted a hypoglycemic effect, and improved alloxan-induced diabetes mellitus in mouse models [19]. Its ability to reduce high levels of proinflammatory cytokines (IL-1, TNF, and IL-8) and stimulate the secretion of the anti-inflammatory cytokine IL-10 has also been demonstrated [17]. This explains the possibility of using Allium sativum to correct acute and chronic inflammation in IDD.

Alstonia Scholaris (Saptaparni), belonging to the Apocynaceae family, consisting of alkaloids (such as echitamin, tubotaivin, aquammicin, echitamidine, picrinin, and strictamine) and terpenes, is used as an anti-arthritic agent [20]. In animal studies, treatment with an ethanol extract of a part of the leaves of A. scholaris (100–200 mg/kg) showed a decrease in total leukocyte migration, as well as a decrease in the levels of pro-inflammatory mediators such as cyclooxygenase (COX), lipoxygenase (LOX), prostane nglandin E-2 (PGE-2), and nitric oxide (NO) [21].

Andrographis paniculata, which belongs to the Acanthaceae family, consists of andrographolide and its derivatives, which have antirheumatoid activity and inhibit the activation of the nuclear factor kappa B (NF-κB) inflammatory signaling pathway transcription factor, and play a role in the regulation of proinflammatory genes [22,23].

Boswellia serrata Linn. is a traditional medicinal resin obtained from the Boswellia tree of the Burseraceae family, used to treat rheumatoid arthritis (RA) and exhibited potent anti-inflammatory activity due to the presence of active components (terpenoids) [24]. Preclinical studies have shown the use of Boswellia serrata Linn to inhibit NF-κB, COX-2 and LOX-5 and prevent the synthesis of leukotrienes, which reduce cartilage loss, reduce the severity of synovitis and osteophyte development in humans. Clinical studies of B. serrata extract have shown significant improvement in the condition of patients suffering from osteoarthritis [25].

Cannabis sativum is oil, extracted from the seeds of Cannabis sativum, a plant belonging to the Urticaceae family, is used as an anti-inflammatory agent and is considered effective in reducing pain and inflammation. The main chemical component obtained from Cannabis sativum is a volatile resin oil consisting of canabene, canabin hydride, canabinone, and canabin, which are composed of cannabinol, pseudocannabinol, cannabinin, and several terpenes [26]. It has been shown to significantly reduce the symptoms of arthritis by inhibiting the release of TNF-α and IL-6 [27].

Celastrus paniculatus, also known as black oil, belongs to the Celastraceae family, is traditionally used as an oil with anti-inflammatory, antioxidant, and antipyretic therapeutic activities [28]. It is a rich source of bioactive components including sesquiterpenoids, alkaloids (celastrine, celapanin, celapagin), sterols (beta-amyrin and beta-sitosterol), and polyalcohols. These components have analgesic and anti-inflammatory effects. C. paniculatus seed petroleum extract at 500 and 400 mg/kg inhibited the expression of TNF-α and IL-6 in an animal model of RA [29]. This extract has been evaluated in preclinical studies for analgesic and anti-inflammatory activity, inhibiting the release of prostaglandins, serotonin, bradykinin, histamine, TNF-α and other proinflammatory interleukins [30].

Cinnamomum verum, commonly known as *Dalchini,* belongs to the Lauraceae family. The essential oil obtained from C. verum consists of eugenol, β-caryophyllene, and eugenyl acetate, which have anti-inflammatory properties [31]. The therapeutic value of ethyl alcohol and methyl alcohol extracts using part of the plant bark has been demonstrated for the treatment of RA, resulting in a reduction in the formation of free radicals by lymphocytes along with the inhibition of the synthesis of TNF-α, type II collagen, and proteins involved in the pathogenesis of RA [32, 33].

Citrus limon belongs to the Rutaceae family. Lemon peel extract contains bioactive compounds (pyrogallic acid, caffeic acid, eugenol, and quercetin), which suppress inflammation. The use of C. limon leaf extract as a herbal therapy in an arthritis model tends to reduce free radicals, acting as an antioxidant, and inhibits xanthine oxidation [34]. A reduction in the levels of pro-inflammatory factors such as ROS (reactive oxygen species), PGE-2, IL-6, IL-1β, and TNF-α has also been shown [35].

Curcuma longa (curcumin) is an Indian spice obtained from the rhizomes of plants in the Zingiberaceae family and contains active components (campesterol, stigmasterol, β-sitosterol, cholesterol, and fatty acids). An animal study linked the anti-inflammatory effects of curcumin to the inhibition of LOX and suppression of NF-κB activation, which plays a role in inflammation, preventing the acute and chronic phases of arthritis. Also, C. longa contains the active component curcuminoid, which has potent anti-inflammatory activity [36, 37].

Glycyrrhiza glabra (also known as *licorice*) belongs to the Leguminosae family and contains glycyrrhizic acid or glycyrrhizin as the active component and the main pentacyclic triterpenoid, which has an anti-inflammatory effect [38]. Preclinical studies have demonstrated that the use of G. glabra rhizome extract inhibits leukocyte migration and autoantigen production in male Wistar rats and has anti-arthritic activity. The role of the ethanol extract of G. glabra, which inhibited the production of IL-6, TNF-α, NO, and PGE-2, has also been demonstrated [38].

Moringa oleifera belongs to the Moringaceae family. Various parts of the plant are rich in active components, including flavonoids, phenols (quinic acid and chlorogenic acid), vitamins, carotenoids, minerals, sterols (β-sitosterol), amino acids, alkaloids, and glycosides. These plant components are responsible for antioxidant protection and anti-inflammatory response [39]. They can significantly inhibit NO production by macrophage cells, reduce elevated levels of proinflammatory cytokines (IL-1, IL-6, and TNF-α), and inhibit the effects of COX2 and PGE2 in inflammation [40, 41]. Nyctanthes arbor-tristis (also known as night jasmine) belongs to the Oleaceae family. It contains phytol, eugenol, and α-terpineol [42]. The plant extract suppresses oxidative stress, reduces NF-κB levels, and regulates the expression of proinflammatory cytokine genes involved in ROS production [21,43,44].

Piper nigrum is a flowering plant in the Piperaceae family. It contains piperine as an active component and has anti-inflammatory properties. A study in an animal model of arthritis with P. nigrum extract (at a dose of 20-100 mg/kg) showed a decrease in enzymes responsible for the biosynthesis of leukotrienes and prostaglandins [45,46].

Salvia miltiorrhiza (warlike sage) belongs to the Lamiaceae family. Components of this plant can slow the development of IDD in rats due to their ability to scavenge ROS produced in degenerating IVDs [47, 48].

Strychnos nux-vomica (poison nut) belongs to the Loganiaceae family. Its alkaloids are brucine and brucine N-oxide, isolated from the seeds of the plant. These compounds have a strong anti-inflammatory effect [49]. The anti-arthritic activity is explained by the suppression of PGE-2 production and a decrease in vascular permeability, which is a key factor in the sensation of pain in arthritic joints [50, 51].

Swertia chirayita is a plant of the Gentianaceae family. It is rich in biologically active phytochemicals (xanthones, flavonoids, iridoids, secoiridoid glycosides, and terpenoids). An ethanol extract of S. chirayita leaves (200 mg/kg) suppressed elevated levels of proinflammatory cytokines (TNF-α and IL-1α) and paw edema in rats with experimental arthritis [52].

Taraxacum officinale is a plant of the Asteraceae family. It is used in traditional Chinese medicine for the prevention and treatment of various inflammatory and infectious diseases [53, 54, 55]. Thus, taraxasterol, one of the pentacyclic triterpenes isolated from

Taraxacum officinale, has significant anti-inflammatory and antioxidant activity [56,57], reducing elevated levels of TNF-α, IL-6, and matrix metalloproteinases (MMPs) by suppressing the NF-κB inflammatory signaling pathway. Furthermore, it inhibits the activation of NLRP3 (NLR family pyrin domain containing 3) inflammasomes and its modulators [56,57,58,59], which plays an important role in correcting cytokine imbalance in IDD [60].

*Terminalia chebula (*known as *Chebulic myrobalan)* belongs to the Combrataceae family. It contains various chemical components (chebulic acid, ellagic acid, chebulagic acid, chebulic acid, and gallic acid), flavonoids, resins, fixed oils, fructose, amino acids, and sterols. These compounds have strong anti-inflammatory effects [61]. A preclinical study using hydroalcoholic extract of T. chebula fruits in animal models such as formaldehyde-induced arthritis and CFA (complete Freund's adjuvant)-induced arthritis showed a significant reduction in elevated levels of proinflammatory cytokines (TNF-α, IL-6, and IL-1β) [62]. *Withania somnifera* (also known as Indian ginseng) belongs to the Solanaceae family. It contains bioactive compounds (withanolides and withaferin A) [63,64]. Clinical evaluation of W. somnifera extract (250 and 125 mg) demonstrated its efficacy in significantly reducing inflammation in a dose-dependent manner by inhibiting NF-κB activation and its regulated expression of genes playing a role in acute and chronic inflammation [65].

2.1.2. Mixtures / Charges

Bushen Huoxue Decoction reduces the expression of the proinflammatory cytokine IL-1β induced by D-galactose in a rat model of IDD and reduces the expression of TNF-α in a castrated rat model [66]. This herbal remedy can inhibit the degeneration of lumbar IVDs, as well as the expression of p38MAPK protein in a castrated rat model. It can also effectively suppress the production of β-catenin via the Wnt/β-catenin signaling pathway [66].

Duhuo Jisheng Decoction inhibits the formation of stromal cell-derived factor (SDF), which induces inflammasome expression in human degenerative NPs via the C-X-C motif chemokine receptor 4 (CXCR4)/nuclear transcription factor NF-κB pathway. This decoction can suppress the mRNA activity, expression of Fas, Fasl, Bcl2-associated protein X (Bax), Bid, caspase-3 and caspase-8, and suppress the activation of Bcl-2 mRNA expression. It also inhibits NP cell apoptosis by promoting the G1/S phase switch, a key restriction point of the NP cycle. During the IDD process, Duhuo Jisheng Decoction controls the expression of pro-inflammatory mediators and the signaling pathways of TNF and IL-17, the differentiation of Th17 cells, the signaling pathway of hypoxia-inducible factor-1 (HIF-1) and other signaling pathways [66]. Proinflammatory cytokines (IL-1β and TNF-α), as well as apoptosis-associated inflammatory mediators (MMP-2 and CASP-3), are known to be significantly elevated in NP cells after lipopolysaccharide stimulation. These inflammatory mechanisms are improved by treatment with serum containing Duhuo Jisheng Decoction [67].

Hozai is a group of Japanese traditional herbal remedies (kampo). They are used to treat chronic fatigue syndrome [68]. *Hochuekkito (HET), Juzen-taihoto (JTT),* and *Ninjin'yoeito (NYT)* are representatives of Hozai. Typically, Hozai contains five herbs: ginseng, astragalus root, Japanese angelica root, licorice, and Atractylodes rhizome or Atractylodes lancea rhizome. Kampo formulations for prescription in Japan contain components other than Atractylodes species, which contain byakujutsu (Atractylodes rhizome) or (alternatively) sojutsu (A. lancea rhizome) [69]. HET, JTT, and NYT preparations contain different components depending on the pharmaceutical company [70]. HET, JTT, and NYT did not change the percentage of CD4+ T cells, but the percentage of CD8+ T

cells tended to increase after treatment with HET, JTT, or NYT in a dose-dependent manner, whereas Tregs (regulatory T cells) were suppressed by HET, JTT, and NYT [70].

Furthermore, JTT stimulates the production of the anti-inflammatory cytokine IL-12 and subsequent activation of lymphoid natural killer (NK) cells [71,72]. Human lymphocyte cultures incubated with JTT produced elevated levels of IL-12, IL-18, and INF-γ [73]. JTT was found to significantly reduce the percentage of Treg cells compared to the control [74]. The largest difference in the composition of Hozai between each JTT is the inclusion of A. lancea rhizome (sōjutsu) or Atractylodes rhizome (byakujutsu). The effect of sojutsu is more potent in suppressing the percentage of Treg cells compared to byakujutsu.

HET and NYT enhance the secretion of granulocyte colony-stimulating factor [75]. NYT synergistically enhances the effect of whole-cell vaccine *in vivo*, which requires CD8+ T cells [76]. HET suppressed peripheral blood mononuclear cells and significantly increased the secretion of the anti-inflammatory cytokine IL-6 (37-fold higher than the control). JTT also increased the level of IL-6 more than HET and NYT. Also, HET, JTT increased immune activity by increasing the secretion of pro-inflammatory cytokines (IL-6, IL-10, IL-17A, IFN-γ and TNF-α). In contrast, HET, JTT and NYT decreased the percentage of Tregs and, accordingly, the secretion of TGF-β [77].

2.1.3. Herbal remedies

Fufang Qishe is a herbal remedy that suppresses catabolic factors (MMP-1, -3, -13) and activates regenerative factors of damaged IVD structures (type II collagen, proteoglycans) [78].

The herbal remedy *Liuwei Dihuang* can regulate the expression of JNK and p38MAPK and inhibit NP cell apoptosis, suppress catabolic factors (MMP-1, -3, -13), and activate regenerative factors of damaged IVD structures (type II collagen, proteoglycans) [78]. The therapeutic effect of Liuwei Dihuang decoction in IDD is mediated by controlling the levels of caspase-3, IL-1β, and other inflammatory mediators, and preventing apoptosis of degenerating IVD cells [47,48].

2.1.4. Combined herbal therapy

2.1.4.1 Combination with pharmacotherapy

A combination of *cyclophosphamide, prednisolone,* and *Qing Shen Fang* was used for disease-modifying therapy of lupus nephritis to enhance the therapeutic response to pharmacotherapy. Moreover, this combination was more effective than cyclophosphamide and prednisolone alone. After treatment, the expression of IFN-γ and IL-4 cytokines in the observation and control groups was significantly lower than before treatment, and the expression of these proinflammatory cytokines in the observation group was lower than in the control group [79]. Therefore, these results explain the promising use of Qing Shen Fang in correcting cytokine imbalance in IDD [80].

A combination of *Kampo* and *prednisolone* is used to treat autoimmune diseases, including RA [81]. *Saireito* (designated 114) is a Kampo drug that is used in combination with corticosteroids (most often prednisolone) and has a steroid-like immunosuppressive effect [82]. In a study by Yamazaki et al [83], combination therapy with prednisolone + Saireito demonstrated greater inhibition of peripheral blood mononuclear cell proliferation than monotherapy with prednisolone at a dose of 0.0001 μg/mL. This demonstrates that low doses of prednisolone may have a synergistic immunosuppressive effect when combined with Saireito, thereby reducing the risk and incidence of corticosteroid ADRs. On the other hand, the effect of higher doses of prednisolone may overshadow the effects of Saireito. Although, Saireito may potentially reduce the inhibitory effect of prednisolone on human peripheral blood mononuclear cell.

However, no statistical differences were found in the levels of proinflammatory cytokines TNF-α and IFN-γ when prescribing any dose of prednisolone in the prednisolone monotherapy or prednisolone + *Saireito* combination therapy groups. It was reported that Saireito does not affect the production of TNF-α or IFN-γ in human peripheral blood mononuclear cells at a prednisolone concentration of 100 μg/ml [84], as well as at 300 μg/ml on Th1 cells. However, the use of prednisolone in combination with *Saireito* resulted in an increase in the concentration of IL-6 in Th2 cells. Probably, this combination has the potential to restructure the composition of Th1 and Th2 cells (towards Th2 dominance) and improve the clinical condition of Th1-mediated autoimmune diseases. On the contrary, it also suggests that IL-6 may potentially worsen the clinical status of Th2 autoimmune diseases such as RA. Neither prednisolone monotherapy nor prednisolone + *Saerieito* combination therapy affected IL-17 production compared with control groups [83]. The main difference between TJ114 and KR114 (Tsumura & Co. (TJ) or Kracie Holdings (KR) formulations) is that the latter consists of a large number of *Alismataceae, Polyporus, Poria cocos*, and *Cassia bark*, and the former includes *Atractylodes Rhizome*, whereas the latter includes *Rhizoma Atractylodis Macrocephalae*. No significant differences were found between the effects of TJ114 and KR114 on the inhibition of peripheral blood mononuclear cell proliferation, changes in the ratio of CD4+ T cells, CD8+ T cells, and Tfh cells, or on the expression of proinflammatory cytokines (TNF, IFN-γ, IL-6, IL-10, IL-17A, or IL-21) [83].

2.1.4.2 Pharmacopuncture

Pharmacopuncture is a traditional Korean therapeutic method. Liquid extracted from medicinal herbs is injected into acupuncture points on the body using a syringe. This approach achieves the effects of both acupuncture and herbal medicine [85] and is used for a variety of conditions, particularly those of the musculoskeletal system [86], including IDD.

GCSB-5 *("Shinbaro capsule"*) is the main ingredient in Shinbaro herbal puncture and has a long history of clinical use for spinal disorders [87,88]. GCSB-5 is composed of six wild herbs including *Cibotium barometz, Bang-Poong (Sapashnikovia divaricata (Turcz) Schischkin), Eucommia ulmoides, Ogapi (Acanthopanax sessiliflorum, Achyranthes japonica* and *Glycine max*), and Shinbaro 2 is prepared by adding four herbs (*Ostericum koreanum, Angelica pubescens, Paeonia albiflora* and *Scolopendra subspinipes*) to five medicinal herbs (*Cibotium barometz, Saposhnikovia divaricata, Eucommia ulmoides, Acanthopanax sessiliflorus* and *Achyranthes japonica*) of GCSB-5 [89]. Although the main chemical components of Shinbaro have not been sufficiently studied, therapeutic activities of individual components of Shinbaro have been reported: anti-inflammatory and antioxidant effects of Eucommia ulmoides and Acanthopanax sessiliflorum [90,91], anti-inflammatory and anti-osteoporotic properties of Achyranthes japonica [92], anti-inflammatory properties of Scolopendra subspinipes mutilans, traditionally used to treat arthritis and neuropathic diseases [93], inhibitory activity of Cibotium barometz on osteoclastogenesis and strengthening of bones in the treatment of lumbago, rheumatism, radiculitis [94], anti-inflammatory role of Ostericium koreanum due to suppression of PGE-2 and NO [95], anti-cancer, anti-inflammatory, antioxidant, antibiotic and analgesic effects of three other herbs included in Shinbaro 2 [96, 97, 98, 99].

GCSB-5 administration reduces mechanical allodynia and radicular pain in patients with IDD by suppressing neuroglial activity in the spinal dorsal horn and the expression of calcitonin DRG (dorsal root ganglion), gene-related peptide (CGRP), and transient receptor potential vanilloid 1 (TRPV1) [100].

In terms of cytokine balance, Shinbaro and Shinbaro 2 suppressed high levels of proinflammatory cytokines IL-1β and TNF-α, inducible nitric oxide synthase (iNOS), and

ADAMTS-5 activity in a dose-dependent manner [101]. Shinbaro 2 suppressed inflammatory responses induced by surgical coccygeal disc autotransplantation. Consistent with previous studies, after Shinbaro 2 administration, MMP secretion was reduced at the mRNA and protein levels [102]. In a study by Chung et al [103], in an in vivo animal model, oral administration of GCSB-5 suppressed LPS-induced NO production by down-regulating mRNA and iNOS expression. GCSB-5 also suppressed the expression of cyclooxygenase-2 (COX-2) and proinflammatory cytokines (IL1-β, IFN-γ). LPS-induced NF-κB activation was also attenuated by GCSB-5, which correlated with its inhibitory effect on IκB degradation. The signaling pathway involving Akt activation was also attenuated by GCSB-5 treatment [104].

2.2. The Use of Whole Herbs Primarily in Western Herbal Medicine

Aloe barbadensis, commonly known as *Aloe vera*, belongs to the Asphodelaceae family. It consists of various chemical components such as anthraquinone, anthracene, cinnamic acid, and anthranilic acid, exhibiting anti-inflammatory and anti-arthritic activity. *Aloe vera* can be effectively used in the treatment of allergic reactions, arthritis, and rheumatoid fever due to the presence of the active compound anthraquinone alkaloid (aloe emodin), which has anti-inflammatory activity by inhibiting PGE-2 and iNOS [105,106]. Available preclinical data evaluating *Aloe barbadensis* in animals have shown inhibition of PGE-2 production, reduction of proinflammatory mediators (IL-8, TNF-α, IL-6 and IL-1) and inhibition of NF-κB translocation, p38, JNK and ERK kinases involved in mediating inflammatory signaling cascades [107].

The genus Berberis (family Berberidaceae) comprises approximately 500 species. Several species of barberry, such as *B. crataegina, B. aristata, B. vulgaris*, and *B. calliobotrys*, have been described to possess antiarthritic activity [108,109,110]. A study by Alamgeer et al [111] found that *B. orthobotrys* has the ability to reduce thermal denaturation of albumin. The plant extract and fractions demonstrated acceptable dose-dependent stabilization of erythrocyte membranes. The protective effect on erythrocyte lysis could be considered a clear indicator of the antiarthritic activity of *B. orthobotrys*. *B. orthobotrys* significantly inhibits chronic arthritis and protects joints, which may be due to its inhibitory effects on inflammatory mediators (IFN-α, PDGF (platelet-derived growth factor) and cytokines (IL-1, IL-6 and TNF-α)) and the resulting immunological protection [112]. Treatment with B. orthobotrys extract and fractions (primarily n-butanol) showed a significant reduction in radiographic and histological damage and significantly suppressed changes in joint architecture. It can be speculated that the inhibition of CFA-induced arthritis may be due to the presence of berberine and berbamine alkaloids, which significantly improved synovial hyperplasia and inflammatory infiltration by inhibiting TNF-α, IL-1β, IL-6, PGE-2, COX-2, NF-κβ, Th17 repression, dendritic cell responses and other signaling pathways [113, 114]. An analysis conducted on B. vulgaris roots showed a significant repressive effect against CFA-induced arthritis due to the presence of berberine and oxyacanthine [115]. Extracts of various Berberis spp. (e.g. *B. aristata, B. vulgaris, B. croatica, B. microphylla* and *B. lycium*) have antioxidant activity [116, 117, 118, 119, 120] which is associated with phenols and flavonols. The active substances isolated from the n-butanol fraction are quercetin, gallic acid, caffeic acid, p-coumaric acid, P-coumaric acid, ferulic acid, trans-4-hydroxy-3-methoxycinnamic acid and sinapic acid.

Phenols and flavonoids have been previously reported to possess anti-inflammatory and antioxidant activities [121]. The bioactive phytochemical constituents of *Berberis lycium royle* act by inhibiting prostaglandin synthesis in carrageenan-induced inflammation, while inhibition of phospholipase A2 was observed in xylene-induced inflammation

[122]. The active phytoconstituent of *Berberis orthobotrys*, the phytosterol beta-sitosterol, inhibits the transcription factor NF-κB, and its involvement in gene regulation of elevated levels of inflammatory mediators is generally associated with rheumatoid arthritis [123]. Furthermore, preclinical animal studies using aqueous methanol extract such as ethyl acetate, n-butanol, and aqueous form of various parts of the plant roots and stems have shown antiarthritic activity in CFA-induced arthritis models and inhibition of the production of inflammatory mediators IFN-α PDGF and cytokines (IL-1, IL-6, and TNF-α) [124].

Borago officinalis L. is a rich source of fatty acids such as γ-linolenic acid (GLA). It has been traditionally used to reduce joint swelling [24,111], PGE levels, and inhibit pro-inflammatory mediators such as TNF-α and other cytokines [125]. GLA is a precursor of anti-inflammatory mediators (arachidonic acid) and modulators of inflammatory responses, including eicosanoids (prostaglandins and leukotrienes) and cytokines (interleukins), and GLA also inhibits NF-κB, ERK1/2, and JNK1, which play roles in the pathogenesis of arthritis. Borage oil contains GLA, thus exhibiting anti-arthritic activity [126]. *Caragana pruinosa*, a deciduous shrub belonging to the legume family, contains active phytochemicals such as flavonoids, stilbenes, and terpenoids. Recent studies have demonstrated that herbal remedies from the root portion of the plant are rich sources of flavonoids such as purinosanone D and purinosanone E, along with other analogs such as 2,4-dihydroxy-3'-methoxy-4'-ethoxychalcone, 7,4-dihydroxyflavanone, butin, and scutellaprostin C, which tend to reduce NO production and suppress the synthesis of IL-1β, IL-6, IL-10, and CRP by macrophages [127, 128].

The genus Caralluma R. Br. belongs to the family Apocynaceae and includes approximately 120 species. These are succulent perennial edible herbs used in folk medicine as a potent remedy for the treatment of pain of various localizations [129,130]. Pregnane glycosides, terpenoids, flavonoid glycosides and sterols are the main classes of compounds found in Caralluma species, and all of them confirm their medicinal value. Caralluma quadrangula (Forssk.) is a succulent shrub of this genus traditionally used for the treatment of ulcers, diabetes and rheumatoid arthritis [130]. Treatment with Russeolyside B, the active component of Caralluma, significantly suppressed inflammation by reducing paw volume, swelling and arthritic index, especially at the higher dose (50 mg/kg), compared to the control group [131]. This effect was consistent with the results obtained for carumbelloside-II and -IV isolated from Caralluma umbellate (Asclepiadaceae) [132]. Previous studies reported that some pregnane glycosides isolated from Hoya kerrii stems exhibited potent anti-inflammatory activity by suppressing the expression of iNOS and COX-2 mRNA [133]. Another explanation for the anti-inflammatory activity of pregnane glycosides [134] is the strong inhibition of 11β-hydroxylase and steroid 17-alpha-monooxygenase, and weak inhibition of cytochrome P450 side chain cleavage enzyme and 21β-hydroxylase [135].

Various *Clematis* species have been evaluated for their antiarthritic effects, such as Clematis henryi Oliv. against collagen-induced arthritis [136] and Clematis chinensis Osbeck against adjuvant-induced arthritis (AIA) [137]. Studies by Hasan et al [138] showed a significant inhibitory effect of the aqueous-ethanol extract and its fractions (especially the aqueous fraction) on the expression of proinflammatory cytokines. The aqueous-ethanol extract and fractions of Clematis orientalis significantly inhibited the expression of COX-2, TNF-α, IL-1β, IL-6, and NF-κβ. The aqueous-ethanol extract and its fractions prevented the development of the disease, reduced joint and periarticular tissue swelling, and bone resorption by suppressing the genes encoding proinflammatory cytokines and increasing the levels of anti-inflammatory cytokines (IL-4 and IL-10). *Clematis orientalis* extract along with its fractions reduced the levels of blood inflammatory biomarkers (ESR and RF) [139] in vivo. The results of antioxidant assays showed that the aqueous-ethanol extract and its fractions, preferably the aqueous fraction, exhibited significant antioxidant

activity, exerting a protective effect against tissue damage in arthritis [140]. In a study by Jin [141], various Clematis species containing saponins, flavonoids, anemonins, protoanemonins, ranunculins and essential oils were found to be responsible for their multiple anti-inflammatory and anti-arthritic effects by inhibiting the formation of ROS, COX-2, 5-lipoxygenases and various immunomodulatory molecules (cytokines and chemokines). Moreover, Han et al. [142] studied the anti-arthritic effect of clematichinoside, a triterpene saponin of the herbal formula Wei-Ling-Xian, obtained from *Clematis chinensis Osbeck, C. hexapetala Pall* or *C. manshurica Rupr.* (Ranunculaceae), which acted on the PI3 K/Akt and TNF-α signaling pathway associated with collagen-induced arthritis. It exerted immunomodulatory effects by suppressing the PI3 K/Akt–NF-κB pathway, resulting in a decrease in TNF-α levels. This prevented osteoclast formation. Preliminary phytochemical screening of the aqueous fraction revealed the presence of flavonoids and glycosides [143].

Commiphora muku is a commonly used medicinal plant (Guggul), commonly called Commiphora, which belongs to the Burseraceae family. It contains flavonoids, terpenes, and a phytosterol (guggulsterone), which have anti-inflammatory effects. An in vivo study of *C. muku* extract (as a therapy for arthritis in an animal model) demonstrated that the active component guggulsterone in *C. muku* acts as an anti-inflammatory agent by inhibiting MAPK and further inhibiting NF-κB, as well as suppressing inflammatory mediators (IFN-γ, IL-12, IL-1β, and NO) [144,145].

Coriander sativum (family Umbelliferae) contains linalool/coriandrol, geraniol, and borneol [146]. The therapeutic value of C. sativum, which contains cineole, has been demonstrated in the treatment of arthritis (at doses of 8, 16, and 32 mg/kg) due to a significant reduction in paw swelling and inhibition of TNF-α [147].

Costus speciosus (family Costaceae) contains active substances used in arthritis. Parts of this plant are used as a rich source of anti-inflammatory components (ascorbic acid, β-carotene, α-tocopherol, glutathione, phenols, flavonoids, alkaloids, terpenoids, steroids, tannins, phenolic and red sugar) [148]. *C. speciosus rhizome* extract inhibited the expression of proinflammatory mediators at different doses against FCA-induced arthritis (Freund's complete adjuvant) in rats and reduced arthritis symptoms by decreasing NO levels, m.

Ephedraceae extract (family Ephedraceae), including 45 species of the genus Ephedra [150], is used to treat joint pain [151]. In a study by Uttra et al [152], rats were administered *Ephedra gerardiana* extract and its fractions; serum levels of TNF-α and PGE-2 were increased in the adjuvant control group of lean rats compared to treated rats. The effect of *Ephedra gerardiana* was accompanied by a modulatory effect on proinflammatory mediators (TNF-α and PGE-2) [153]. A decrease in serum RF levels in arthritic rats administered the extract and its fractions demonstrates a protective effect against arthritis [154]. Significantly lower serum CRP levels in arthritic rats treated with the test substances and the reference drug, compared with adjuvant administration to control rats, indicate remission of inflammation [155].

ALT (alanine aminotransferase) activity in arthritis is an approximation of lysosomal integrity [156] and an indicator of bone destruction. Administration of *Ephedraceae* extract and its fractions decreased ALP (alkaline phosphatase), which may indicate increased lysosomal stability and reduced bone loss, as confirmed by radiographic data. *Ephedra gerardiana* extract does not exhibit hepatotoxicity, as indicated by decreased AST (aspartate aminotransferase) and ALT levels in all treatment groups [152]. IL-1β, TNF-α, and IL-6 levels found in control rats were significantly reduced in rats treated with *Ephedra gerardiana*. This suggests the extract's anti-inflammatory or anti-arthritic potential. COX-2 and PGE-2 levels were noted in control animals with arthritis, although a reduction in these inflammatory biomarkers was found in rats treated with *Ephedra gerardiana*. Thus, *Ephedra gerardiana* extract may partially limit prostaglandin synthesis due to the subdual

generation of COX-2. Inhibition of arachidonic acid metabolism may be another mechanism for the anti-inflammatory effect of *Ephedra gerardiana*. A significant decrease in IL-4 and IL-10 levels was shown in arthritic rats during arthritis treatment, and a significant increase in the levels of these anti-inflammatory cytokines was observed in each treatment group, indicating the anti-inflammatory/immunomodulatory role of *Ephedra gerardiana*. The antiradical and energy-reducing capacity of *Ephedra gerardiana* extract and fractions increased steadily with increasing concentration, and the results showed that the test substances clearly exhibited a strong antioxidant property compared to the standard (ascorbic acid) at the concentrations used. However, the plant extract and aqueous fraction exhibited greater antioxidant activity than the other fractions [152]. A wide variety of plants have therapeutic potential for the treatment of diseases containing ROS and free radicals [157] due to the presence of abundant free radical scavengers such as phenolic acids, terpenoids, lignans, flavonoids, stilbenes, coumarins, tannins, alkaloids, quinones and other metabolites [158] that scavenge free radicals and thus inhibit oxidative processes [159].

Eysenhardtia polystachya, commonly known as Palo Azul, belonging to the Leguminosae family, consists of major components such as (3S)-7-hydroxy-2',3',4',5',8-pentamethoxyisoflavan, (3S)3',7-dihydroxy-2',4',5',8-tetramethoxyisoflavan, stigmasterol, isodwartin, cuneatin, 7-hydroxy-2',4',5'-trimethoxyisoflavone and 3,4-dimethoxy-8,9-(methylenedioxy)pterocarpan has anti-inflammatory property and has been demonstrated in the therapy of arthritis[160,161,162]. The mechanism of therapeutic value of *E. polystachya* has been demonstrated to be due to the inhibition of secondary inflammatory responses and a decrease in serum concentrations of IL-6, TNF-α, and granulocyte colony-stimulating factor (GM-CSF) in rats with arthritis [163].

Inula helenium L. (family Asteraceae) contains sesquiterpene lactones (mainly alantolactone and isoalantolactone), which have antiarthritic properties [164,165]. Oral administration of I. helenium L. root extract has shown efficacy in reducing arthritis symptoms by inhibiting inflammatory mediators (TNF-α-induced activation of NF-κB and MAPK pathways). The use of the extract in the treatment of IDD may be useful in suppressing the increased expression of inflammatory biomarkers, including TNF-α, MMP-3, IL-1, IL-6, MCP1 (monocyte chemoattractant protein 1), MCP2 in synovial fibroblasts [164,166].

Ipomoea batatas is a flowering plant with a diverse group of 500 species belonging to the Convolvulaceae family. It contains active phytocomponents (rutin, gallic acid, catechin, caffeic acid, apigenin, myricetin, quercetin, and kaempferol). These substances have anti-inflammatory properties, reducing the levels of pro-inflammatory interleukins (IL-1β and IL-6) and NO [167]. *Oenothera biennis*, commonly known as evening primrose, belongs to the Onagraceae family [168]. The plant is an excellent source of GLA as a major component that reduces inflammation by modulating NO, TNF-α, IL-1β and thromboxane B2 (TXB2) levels and suppressing the expression of the gene encoding COX-2 [169].

Paullinia pinnata L. (family Sapindaceae) contains phenols, flavonoids, triterpenes, saponins, tannins, steroids, and steroidal glycosides (cerebrosides and ceramides), which act as anti-inflammatory and antioxidant agents [170, 171, 172]. Methanol and aqueous extracts of *P. pinnata* leaves, when administered orally, inhibited the production of NO, TNF-α, and IL-1β [173].

Polystichum braunii (Spenn.) Fée is known as Holy Fern and belongs to the Dryopteridaceae family. It is popularly used to treat rheumatism [174]. A decoction of the plant's roots is used as an antipyretic and removes impurities and toxins from the body through vomiting. It is also used to treat gastrointestinal disorders and pneumonia. In addition, it is also applied topically to rheumatic joints [174]. Methanolic extracts of *P. braunii* and aqueous extracts of *P. braunii* roots demonstrated antiarthritic potential in a formaldehyde-induced arthritis model. Furthermore, the plant extracts showed the potential in

vitro to inhibit protein denaturation and stabilize the red blood cell membrane [175]. In a study by Saleem [176], the extracts improved the body weight of polyarthritic rats compared to the control group, the effect of which was closely related to the reduction in the expression of proinflammatory cytokines, which was also reported in previous studies [177]. The reduction in systemic inflammation due to the plant extracts was evident from the decrease in the levels of CRP and RF in polyarthritic rats [176]. In a study by Saleem [176], Polystichum braunii (Spenn.) restored COX-2 and PGE-2 levels in arthritic rats, improved polyarthritis symptoms, hematological parameters, and proinflammatory cytokine expression, which were comparable to previous studies [178,179]. In a study by Saleem [176], these extracts inhibited the production of CRP and IL-6 along with significant amelioration of articular and extra-articular symptoms [180,181]. The plant extracts (at a dose of 150–600 mg/kg) significantly suppressed the NF-κB signaling pathway either by blocking phosphorylation or by stimulating the expression of I-κB, and attenuated pathological changes in the ankle joints. They induced the production of anti-inflammatory cytokines IL-4 and IL-10, which prevents the progression of IDD [182].

Both extracts contain alkaloids, tannins, various phenols, and flavonoids (quercetin, kaempferol, gallic acid, and sinapic acid). Gallic acid, sinapic acid, coumaric acid, benzoic acid, kaempferol, and quercetin have previously been reported to possess significant antioxidant and anti-inflammatory properties [183, 184].

Punica granatum Linn—commonly known as pomegranate (family Lythraceae)—is used to treat arthritis and has potent anti-inflammatory and antioxidant properties due to its content of punicalagins, flavones, flavonones, and other flavanols. Punica granatum Linn extract significantly reduces the combined disease activity index in patients with rheumatoid arthritis [185]. *Punica granatum Linn* fruits (at doses of 13.6–34 mg/kg) inhibit NF-κB pathways in male Wistar rats [186], which play an important role in the development of IDD.

The currant and gooseberry *Genus Ribes (Grossulariaceae)* includes approximately 200 species of evergreen deciduous shrubs [187]. Ribes is used to treat joint pain [188]. The production of autoantigens in various rheumatic diseases may be associated with protein denaturation *in vivo.* The mechanism of denaturation possibly involves changes in electrostatic, hydrogen, hydrophobic, and disulfide bonds [111]. In the study by Uttra et al [123], *Ribes orientale* extract and its fractions significantly inhibited thermal denaturation of proteins, which could prevent protein denaturation and autoantigen formation, characterizing its antiarthritic effect. The plant extract and its fractions significantly prevented hypotonicity induced by hemolysis of the erythrocyte membrane. This suggests that *Ribes orientale* can prevent the rupture of the lysosomal membrane and prevent tissue damage caused by the release of hydrolytic enzymes from lysosomes. Oral administration of Ribes orientale extract and fractions in rats with arthritis significantly decreased the mRNA level, the expression of TNF-α, IL-1β, NF-κB and IL-6 and also decreased the levels of COX-2 and PGE-2. However, it increased the mRNA expression of IL-4 and IL-10. Treatment with Ribes orientale significantly reduced the expression of IL-6 and the production of inflammatory proteins. The plant extract/fractions suppressed the expression of IL1, IL6, and TNFA genes in arthritic rats and reduced joint inflammation [123]. Ribes extract and its fractions exhibited strong antioxidant activity. The free radical scavenging and reducing ability of Ribes orientale may be related to polyphenols, tannins, alkaloids, and flavonoids, [189, 190] Suppression of the production of proinflammatory mediators, inhibition of protein denaturation, stabilization of lysosomal membranes, and scavenging of redox potential/free radicals support the antiarthritic and immunomodulatory property of *Ribes orientale* [123]. PGE-2, COX-2, IL-1β, IL-6, NF-κB, and TNF-α levels were reduced, whereas IL-4 and IL-10 levels were not regulated compared to control FCA rats [191].

Schinus terebinthifolius, also known as Brazilian pepper (family Anacardiaceae), contains gallic acid, methyl gallate, and pentagalloylglucose. The extract reduces inflammation by inhibiting the production of synovial IL-6, IL-1β, CXCL-1, and TNF-α [192, 193].

Solenostemma argel (Del) Hayne (F. Asclepiadaceae) is a wild perennial shrub [194]. It is used to treat arthritis and other conditions [195, 196]. Several studies have shown that crude extracts of argel have anti-inflammatory activity in vitro [197]. Argel is rich in several secondary metabolites, especially pregnanes, among which 14, 15-secopregnan glycosides, namely argelosides, and 15-ketopregnan glycosides, namely stemmosides, have been isolated and characterized [198]. Other classes of secondary metabolites such as phenolic acids, flavonoids and their glycosides have also been reported. Solenostemma argel has been shown to have the highest inhibitory activity compared to standard celecoxib and exhibits the highest COX-2 selectivity index. Solenostemma argel has a specific inhibitory effect on the collagenase reaction and promising antidenaturant activity. Oral administration of Solenostemma argel significantly reduced the levels of RF, antibodies to cyclic citrullinated peptide (anti-CCP), CRP, proinflammatory cytokines, ROS, lysosomal enzymes (hyaluronidase, collagenase), and NF-κB. Myeloperoxidase (MPO) levels were restored to normal values after treatment with Solenostemma, achieving the effect of ibuprofen [199].

Uncaria tomentosa, also known as cat's claw (family Rubiaceae), is rich in polyphenols, flavonoids, proanthocyanidins, tannins and sterols, as well as alkaloids (pentacyclic oxindole) [200]. The use of U. tomentosa extract relieves joint pain, swelling and morning stiffness by inhibiting the release of proinflammatory interleukins (IL-1α, IL-1β, IL-4 and IL-17, TNF-α) [201,202,203].

3. THE USE OF INDIVIDUAL BIOACTIVE COMPONENTS OF HERBAL PREPARATIONS TO CORRECT CYTOKINE IMBALANCE IN INTERVERTEBRAL DISK DEGENERATION

Acacetin (4'-O-methylated flavone of the parent compound apigenin, found in *Robinia pseudoacacia* (black locust), *Turnera diffusa* (damiana), *Betula pendula* (silver birch), and the fern *Asplenium normale*) has potential use in the treatment of IDD. In a study by Wang et al [204] using an in vitro rat model of IDD, acacetin attenuated TBHP (tert-butyl hydroperoxide)-induced ROS generation and increased the expression of antioxidant proteins, including HO-1, NQO1, and SOD. Furthermore, acacetin attenuated TBHP-induced generation of inflammatory mediators (COX-2, iNOS) and degradation of the extracellular matrix (aggrecan, collagen II, MMP-13, MMP-9, and MMP-3). Acacetin exerted its effects by activating the Nrf2 pathway and inhibiting the phosphorylation of p38, JNK, and ERK1/2. In vivo, acacetin reduced IVD puncture-induced degeneration in a rat tail model [204].

Alantolactone and isoalantolactone, sesquiterpene lactones found in the roots of I. helenium L., have antiarthritic properties [164,165]. Alantolactone and isoalantolactone have been shown to reduce arthritis symptoms by inhibiting inflammatory mediators such as TNF-α-induced activation of the NF-κB and MAPK pathways. It inhibits the production of TNF-α, MMP-3, IL-1, IL-6, MCP1 (monocyte chemoattractant protein 1), MCP2 in synovial fibroblasts [164,166].

Andrographolide, a diterpenoid from Andrographis paniculata, inhibits the activation of the transcription factor NF-κB and plays an important role in the regulation of proinflammatory genes studied using an animal model [22,23]. Andrographolide exhibits good anti-inflammatory pharmacological activity in an animal model of inflammation,

which attenuates the expression of MPO and neutrophil-derived protease in mice [205]. It can scavenge ROS and inhibit the activation of NF-κB and NLRP-3, inflammatory proteins [206], and can regulate the activity of an antioxidant enzyme to prevent oxidative damage induced by CCL-4 [207]. Andrographolide exerts a protective effect on autoimmune arthritis by reducing the levels of TNF-α, IL-1β, and IL-6 in vitro and in vivo and inhibiting the MAPK pathway [208]. Oral administration of andrographolide to rats dose-dependently reduced the levels of TNF-α and IL-6 in the blood [22]. Andrographolide can attenuate lipid peroxidation and NO activity, enhance the activity of antioxidant defense enzymes, and suppress oxidative stress [209].

Anthraquinone, an alkaloid found in aloe vera, exhibits anti-inflammatory activity by inhibiting PGE-2 and iNOS. It can be used to modulate the inflammatory response [105, 106] in patients with IDD.

Aucubin, an iridoid glycoside found in asterides [210], suppresses MMP-1, -3, and -13 and activates IVD regeneration factors [78].

Baicalein is a natural bioactive compound found in several species of the *Genus scutellaria.* It is also present in *Oroxylum indicum* bark isolate. This substance exhibits anti-inflammatory activity, inhibits inflammatory responses in chondrocytes, and improves morphology and avascular supply of NP cells. Baicalein may have therapeutic effects on IDD. In an in vitro study by Jin et al [211], NP cells were pretreated with baicalein for 2 h and then incubated with IL-1β for 24 h. Baicalein not only inhibited the overexpression of proinflammatory mediators (NO, PGE-2, TNF-α, and IL-6) but also suppressed the expression of COX-2 and iNOS. IL-1β-induced overexpression of MMP-13 and ADAMTS-5, as well as the degradation of aggrecan and type II collagen, were inhibited by baicalein in a dose-dependent manner. Baicalein suppressed IL-1β-induced activation of NF-κB and MAPK pathways. Moreover, in vivo, baicalein treatment was demonstrated to improve the course of IDD in a puncture-induced rat model.

Berberine, an isoquinoline alkaloid isolated from *Phellodendri Chinensis* cortex, suppresses the overexpression of proinflammatory cytokines and other inflammatory mediators, including NO, PGE-2, TNF-α, and IL-6. Berberine attenuates oxidative stress-induced endoplasmic reticulum stress and autophagy via the inositol-requiring kinase 1 (IRE1)/c-Jun N-terminal kinase (JNK) pathway. Berberine suppresses the expression of MMP-1, -3, -13 and activates the expression of COL2, proteoglycans [78]. Berberine has potential therapeutic value in the treatment of rheumatoid arthritis due to its antiproliferative effect on rheumatoid arthritis fibroblast-like synoviocytes (RAFLS) [212]. In addition, berberine has been reported to inhibit chronic inflammatory responses [113,114] and exhibit immunosuppressive effects [213] by suppressing the expression of TNF-α, IL-1β, IL-6, PGE-2, COX-2, NF-κβ, repression of Th17 dendritic cell responses and other signaling pathways [113,114]. Moreover, berbamine suppresses the appearance of STAT-4 and the assembly of IFN-γ [213]. Berberine and berbamine, as the main constituents of Berberis sp., are antioxidants and prevent the formation of ROS [214].

Brucine and brucine N-oxide, isolated from S. nux-vomica seeds, exhibit potent anti-inflammatory activity [49]. Preclinical studies have demonstrated the anti-arthritic activity of brucine and brucine N-oxide by suppressing PGE-2 and reducing vascular permeability, which is a key factor in the sensation of arthritic joint pain in carrageenan-induced paw edema in rats [50,51].

Cardamomin, a chalcone extracted from Alpinia katsumadai and other plants, exhibits anti-inflammatory activity in many diseases. Xie et al. [215] examined the protective effect of cardamomin on rat NP cells stimulated by IL-1β in vitro and in a rat puncture-induced IDD model in vivo. Cardamomin treatment was shown to inhibit the expression of proinflammatory factors such as COX-2, iNOS, PGE2, NO, TNF-α, and IL-6 in rat NP

cells. Furthermore, the activation of MMP-13 and ADAMTS-5 and the degradation of aggrecan and collagen II induced by IL-1β were reversed by cardamomin. This herbal preparation inhibits NF-κB signaling by activating Nrf2 in IL-1β-induced rat NP cells. Furthermore, the protective effect of cardamomin was shown in the IDD model with persistent intragastric administration [215].

Celastrol (thunder god vine and regel's threewingnut extract) shows therapeutic potential in proinflammatory diseases including asthma, Crohn's disease, arthritis and neurodegenerative disorders by inhibiting the NF-κB inflammasome pathway [216,217,218]. The results of Chen et al [219] showed that celastrol reduced the expression of catabolic genes (MMP3, 9, 13, ADAMTS4, 5), oxidative stress factors (COX-2, iNOS) and proinflammatory cytokines (IL-6, TNF-a) induced by IL-1β in nucleus pulposus cells, and the phosphorylation of IκBα and p65 was attenuated by celastrol, indicating that the NF-κB pathway was inhibited by celastrol in NP cells. An in vivo study showed that celastrol-treated rats had a stronger T2-weighted signal than vehicle-treated rats at 2 and 6 weeks, suggesting that celastrol may attenuate IDD in vivo.

Cineole, a monocyclic terpene found in essential oils from the leaves of eucalyptus globulus, from all parts of marina root, from flower baskets and leaves of wormwood, from fragrant rue [220], has been shown to be effective in the treatment of arthritis at varying doses of 8, 16, and 32 mg/kg by significantly reducing paw swelling by inhibiting proinflammatory cytokines such as TNF-α [147].

Cinnamic acid has a powerful antioxidant and anti-inflammatory effect, inhibiting the activation of the NF-κB inflammatory signaling pathway and reducing the expression of the pro-inflammatory cytokine TNF-α [221].

Clemathichinoside is a triterpene saponin with the Chinese herbal formula Wei-Ling-Xian, obtained from Clematis chinensis Osbeck, C. hexapetala Pall, or C. manshurica Rupr. (Ranunculaceae). Han et al. [142] studied the antiarthritic effect of clemathichinoside on the activation of the PI3K/Akt signaling pathway and the proinflammatory cytokine TNF-α in a collagen-induced arthritis model. This resulted in the suppression of the PI3K/Akt–NF-κB pathway and TNF-α levels, thereby preventing osteoclast formation.

Crocin, a carotenoid compound found in crocus and gardenia flowers, may be used for IDD. In an *in vitro* study by Li et al [222] (using an IDD rat model), crocin significantly inhibited LPS-induced overexpression of catabolic enzymes (MMP-1, MMP-3, MMP-13, ADAMTS-1, ADAMTS-4, and ADAMTS-5), proinflammatory factors (IL-1β, TNF-α, IL-6, and iNOS), and Toll-like receptor (TLR)-2 in a concentration-dependent manner. Crocin partially prevented the downregulation of aggrecan and type II collagen. Furthermore, crocin suppressed LPS-induced activation of the MAPK pathway by inhibiting JNK phosphorylation. Ex vivo experiments showed that crocin protected IVD rats from LPS-induced depletion of extracellular matrix components, including proteoglycan and type II collagen [222].

Curcuminoid isolated from C. longa suppresses activation of the NF-κB signaling pathway, which plays a role in inflammation, thereby preventing the acute and chronic phases of arthritis [36,37].

Ferulic acid, hydroxycinnamic acid, is an organic compound found in several plant species. Ferulic acid has anti-inflammatory and anti-arthritic properties. Molecular docking of ferulic acid showed promising inhibition of JAK-2 with a docking score of -6.7, which is comparable to that of ruxolitinib, a standard inhibitor. However, an in vitro JAK-2 inhibition assay revealed a half-maximal inhibitory concentration (IC50) of 6.67 ± 0.88 μg/mL Both doses of ferulic acid (25 and 50 mg/kg) significantly attenuated primary (paw edema volume) and secondary lesions in the induced arthritis model. Ferulic acid also reversed changes in biochemical parameters and inflammatory markers, such as CRP and RF. Ferulic acid reduced JAK-2 levels and TGF-β levels in tissue homogenate. Thus, ferulic

acid has antiarthritic activity, which is mediated by inhibition of the JAK/STAT pathway [223].

Phenolic compounds (phenols) are a class of secondary metabolites with potential antioxidant and anti-inflammatory activities [224]. Compounds belonging to different chemical classes, such as steroids, terpenoids, polyphenols, phenylpropanoids, fatty acids and lipids, and pregnanes are considered to be highly effective anti-inflammatory natural products [225]. The anti-inflammatory activity of plants is highly correlated with their phenolic acid and flavonoid content, as established in previous studies [196,226,227]. Phenolic compounds have been reported to exhibit anti-inflammatory activity by inhibiting the production or action of proinflammatory mediators, including cytokines [228]. The flavonoids kaempferol, quercetin, and isorhamnetin have been shown to exert anti-inflammatory effects by inhibiting lipopolysaccharide-induced iNOS expression, NF-κB activation, and NO production [198]. Caffeoylquinic acid derivatives exhibit in vivo anti-inflammatory activity mediated by a decrease in the levels of proinflammatory cytokines (TNF-α and IL-1β) in rats using the carrageenan-induced rat paw edema model [229]. Similarly, feruloylquinic acids have been shown to play an essential role in the control of inflammatory stress conditions [230]. Phenolic glycosides, vanilla glucoside, an aglycone, and vanillin exhibit anti-inflammatory activity, which was assessed using the carrageenan-induced rat paw edema assay [231]. Pregnane glycosides have also been reported to have anti-inflammatory activity [232]. Flavonoids, especially those derived from kaempferol, were more active than pregnane glycosides [233]. Interestingly, secopregnane glycosides, especially argelosides isolated from S. argel leaves, exhibited anti-inflammatory activity in lipopolysaccharide-stimulated mouse RAW 264.7 cells by inhibiting TNF-α release, only at very high concentration (100 μM), while other argelosides showed no inhibitory activity at all [234].

Ginsenoside Rg1, found in *Panax* plants, can promote the regeneration of extracellular matrix structures in degenerating IVDs by activating collagen and proteoglycan synthesis and inhibiting the Wnt/β-catenin inflammatory pathway [78]. In addition, ginsenosides can promote the regeneration of IVDs extracellular matrix structures, NP cells, and inhibit IVD cell apoptosis by inhibiting the Wnt(Wingless and Int-1)/β-catenin inflammatory pathway [78].

Glycyrrhizic acid, or glycyrrhizin, is a pentacyclic triterpenoid with anti-inflammatory properties [38]. Glycyrrhizin has been shown to inhibit the production of IL-6, TNF-α, NO, and PGE-2, which may be useful in IDD [38].

Guggulsterone in *C. muku* acts as an anti-inflammatory agent by limiting the activation of the MAPK signaling pathway and further inhibiting the NF-κB signaling pathway, as well as suppressing proinflammatory cytokines (IFN-γ, IL-12, IL-1β) and NO [144].

Icariin is a flavonoid extract from several Epimedium species and prevents neuroinflammation, attenuates oxidative stress-induced damage [235], demonstrating its bone and muscle strengthening properties, it enhances its mesenchymal activity on bone marrow, osteogenesis, and stem cell (BMSC) proliferation [236, 237]. Icariin regulates gene expression to promote the proliferation of human neural stem cells, demonstrating a potential neuroprotective effect on nerves [238]. Icariin also enhances the function and viability of NP-derived human mesenchymal stem cells [239]. Icariin exerts a protective function on human NP cells in IDD through nuclear factor erythroid 2-related factor 2 (Nrf-2) signaling [240]. Icariin attenuates the inflammatory response of human NP cells induced by IL-1β [241]. Furthermore, icariin can increase the expression of TGF-β in BMSCs [242] and IGF-1 in mouse dermal papillary cells [243]. Icariin can also reverse the protein and mRNA expression levels of IGF-1(insulin-like growth factor 1), TGF-β, SDF-1(stromal cell-derived factor 1), and CCL-5 in IDD tissues and increase the expression levels of stem cells [244].

Ligustilide, a bioactive phthalide from angelica roots essential oil, appears to have anti-inflammatory and antiapoptotic effects in IDD [245,246]. The protective effect of ligustilide on degenerating IVDs and its potential mechanism have been studied. In a study by Wang et al [247], ligustilide inhibited apoptosis, suppressed the expression of related inflammatory mediators (iNOS and COX-2), and reduced the expression of proinflammatory cytokines (TNF-a and IL-6) in NP cells. At the same time, IL-1β-induced degradation of the NP extracellular matrix was suppressed. Furthermore, ligustilide inhibited the inflammatory response by inhibiting the NF-κB signaling pathway. Moreover, TUNEL (terminal deoxynucleotidyl transferase dUTP nick end labeling) assay and histological analysis showed that ligustilide could inhibit NP cell apoptosis and improve the progression of IDD in a rat IVD puncture model. Ligustilide, isolated from Chuanxiong Rhizoma, exerts anti-inflammatory and anti-apoptotic effects on IL-1β-stimulated NP cells by inhibiting the NF-κB inflammasome signaling pathway [78].

Moracin M, a phenolic component derived from Mori Cortex, could inhibit LPS-induced inflammatory response in NP in vivo by regulating PI3K/Akt/mTOR phosphorylation [78].

Naringin, a flavonoid extracted from citrus fruits, can inhibit the inflammatory response by regulating PI3K/Akt/mTOR phosphorylation [78]. In a study by Gao et al [248], it was found that naringin could significantly downregulate the expression of MMP-3, MMP-13, ADAMTS-4, and ADAMTS-5 and proinflammatory cytokines in IL-1β-stimulated human NP cells, while collagen type II and aggrecan were increased at the mRNA and protein levels. Immunofluorescence showed that pretreatment with naringin decreased the expression of p65 protein in the nucleus and suppressed the phosphorylation of IκBα and p65.

Piperine is an analogue of the active phenolic component of black pepper. In the study by Li et al [249], piperine significantly inhibited the expression of various proinflammatory mediators associated with oxidative stress (IL-1β, TNF-α, IL-6, iNOS), MMP (MMP-3, MMP-13), ADAMTS mRNA (ADAMTS-4, ADAMTS-5), and NO production in a concentration-dependent manner in the NP IVD rat cell culture model. Moreover, piperine can reverse the lipopolysaccharide-induced inhibition of aggrecan and type II collagen gene expression. Piperine inhibits lipopolysaccharide-mediated JNK phosphorylation and NF-κB activation [249]. Screening of a piperine-containing P. nigrum extract in arthritic rats showed that administration of 20–100 mg/kg to the plant resulted in a decrease in enzymes responsible for leukotriene and prostaglandin biosynthesis [45,46].

Polydatin, resveratrol-3-O-β-mono-D-glucoside, also known as piceid, is a natural compound isolated from Polygonum cuspidatum plants and widely used in folk medicine for its numerous medicinal properties [250]. Previous studies have demonstrated the immunomodulatory effect of polydatin through the inhibition of proinflammatory cytokines (IL-6 [251] and IL-17 [252]). Polydatin suppresses IL-6 expression, which may be useful in rheumatoid arthritis [253]. Polydatin suppresses IL-6, STAT-3, VEGF, IL-17, and NF-κB through inhibition of IL-6. Furthermore, the observed reduction in IL-6 may be secondary to the reported property of polyphenols to suppress stimulated proliferative fibroblast-like synoviocytes [45]. Polydatin-induced suppression of IL-6 indirectly suppresses STAT-3, as the latter is activated by IL-6 [254]. The anti-inflammatory effect of polydatin was further emphasized by the significant suppression of the pro-inflammatory cytokine IL-17. This was also attributed to the impaired expression of STAT-3 in Th17 lymphocytes [255]. Polydatin was previously shown to reduce IL-17 production and Th17 differentiation in a dose-dependent manner in vitro [252]. Jiang et al. [251] claimed that polydatin exerts anti-inflammatory effects in lipopolysaccharide-induced acute lung injury by modulating the NF-κB signaling pathway in vivo and in vitro. Polydatin-induced NF-κB suppression improved the levels of downstream inflammatory mediators, as confirmed

by the reduction in TNF-α homogenate levels. Polydatin was verified to alleviate non-alcoholic fatty liver disease by inhibiting TNF-α expression [256]. Inhibition of VEGF (vascular endothelial growth factor) by polydatin, in addition to its antioxidant potential, may reduce the process of angiogenesis. In support, polydatin was noted to be an effective suppressor of VEGF in ovarian cancer cell lines [257]. Also, administration of polydatin resulted in a significant decrease in MMP-3 levels and RANKL (receptor activator of nuclear factor kappa-B ligand) expression [258]. In a study by Li et al. [259], the anti-inflammatory and antioxidant effects of polydatin were established. However, the authors reported an increase in MMP-9 levels, which may lead to further worsening of cartilage damage. In contrast, Zhang et al. [256] reported that polydatin was able to reduce MMP-9 expression in the aortas of apolipoprotein double knockout mice.

Protodioscin, a furostanol saponin extracted from the rhizome of the Chinese herb Dioscorea collettii var. Hypoglauca (Dioscoreaceae), is widely used to treat various diseases in traditional Chinese and Indian medicine systems [260,261]. The protective effect of protodioscin or methylprotodioscin against inflammation is mediated by inhibiting the production of proinflammatory cytokines (IL-6, IL-1β, IL-17, TNF-α, IL-12, and IFNγ[262,263,264]). Arthritic rats administered protodioscin showed relative remission of arthritis and a decrease in CFA-induced expression of IL-6, IL-1β, TNF-α, COX-2, and PGE-2 production [265]. Protodioscin also improves CFA-induced neutrophil infiltration in rat joints, reduces elevated lipid peroxidation, and increases NO, GSH (γ-glutamylcysteinylglycine reduced), SOD, and catalase levels in rats with CFA-induced arthritis [265].

P-coumaric acid inhibits the production of inflammatory mediators (iNOS, COX-2, IL-1β, TNF-α) by inhibiting the activation of NF-κB and MAPK signaling pathways, reducing circulatory immune complex levels, and exerting antiperoxidant and lysosomal membrane stabilizing effects [266].

Quercetin, a flavonoid, reduces clinical symptoms of arthritis in adjuvant-induced chronic arthritis. Inhibits the production of COX-2, PGE-2, NO, TNF-α and iNOS expression with inhibition of NF-κB stimulation. In addition, it reduces the intensity of CRP production in inflamed tissues [267]. It also has antiproliferative and antioxidant effects [143]. Quercetin suppressed lipopolysaccharide-induced mRNA expression of TNF-α, IL-1α, COX-2 and LOX by inhibiting various signaling pathways in the RAW 264.7 cell line [268].

Russeolyside B, the major pregnane glycoside found in C. quadrangula, significantly suppresses inflammation by reducing paw volume, paw edema, and arthritic index at a high dose (50 mg/kg) compared to the control group [131]. This effect was consistent with the results obtained for carumbelloside-II and -IV isolated from Caralluma umbellate (Asclepiadaceae) [132]. Treatment with russelioside B significantly suppressed RF and anti-CCP levels compared to CFA arthritic rats, with no significant difference between normal and ibuprofen-treated groups [269]. Russeolyside B significantly reduced the serum levels of NF-κB, TNF-α, IL-6, and IL-1β ($p < 0.01$) [131]. Russeolyside B supplementation effectively suppresses MPO, protecting cartilage and bone degeneration by reducing elevated levels of cartilage-degrading enzymes such as hyaluronidase and the activity of degenerative lysosomal enzymes such as β-glucuronidase [135].

Sesamin, a bioactive component extracted from sesame, has anti-arthritic potential. In a study by Li et al [270], sesamin significantly inhibited lipopolysaccharide-induced expression of MMP-1, MMP-3, MMP-13, ADAMTS-4, ADAMTS-5, and inflammatory factors (IL-1β, TNF-α, iNOS, NO, COX-2, PGE-2) in a dose-dependent manner in vitro (in a rat IVD model). Lipopolysaccharide-induced macrophage migration is inhibited by sesamin treatment. Organ culture experiments demonstrated that sesamin protects IVD from LPS-induced extracellular matrix depletion ex vivo. Furthermore, sesamin suppresses

LPS-induced MAPK pathway activation by inhibiting the phosphorylation of JNK, a common downstream signaling pathway of LPS and IL-1β, which may be a potential mechanism of action of sesamin [270].

Sinapinic acid is a cinnamic acid derivative with 3,5-dimethoxy and 4-hydroxyl substitutions at the phenyl group of cinnamic acid (found in rye, some fruits, and vegetables). In a study by Yun et al. [271], immunoblot and RT-PCR (reverse transcription polymerase chain reaction) showed that sinapinic acid effectively blocked the induction of both inducible nitric oxide synthase (iNOS) and COX-2 and their mRNA levels. In parallel, sinapinic acid inhibited lipopolysaccharide-induced NO and PGE-2 production in a dose-dependent manner. Sinapinic acid significantly inhibited lipopolysaccharide-induced TNF-Re and IL-1 production, as well as the expression of their mRNA in vitro. Sinapinic acid effectively prevents lipopolysaccharide-induced NF-κB activation and the DNA-binding activity of p65. Degradation and phosphorylation of IκB-R (the inhibitory subunit of NF-κB) were also inhibited by sinapinic acid in a concentration-dependent manner. Sinapinic acid significantly inhibits IκB kinase precipitated from lipopolysaccharide-induced cell lysate [271].

Taracasterol, a pentacyclic triterpene isolated from Taraxacum officinale, also possesses significant anti-inflammatory and antioxidant activity [56,57]. Taraxasterol can reduce the levels of proinflammatory cytokines and other inflammatory mediators in LPS-induced murine arthritis RAW 264.7 in vitro, FLSs-RA (fibroblast-like rheumatoid arthritis) and collagen-induced arthritis by suppressing the levels of TNF-α and IL-6. The secretion of MMPs was reduced in FLSs-RA [58]. Taraxasterol inhibits the NF-κB pathway in LPS-stimulated mouse peritoneal macrophages [56,57,58,59]. It has been found that taraxasterol can alter the activation of TAK-1 (a central regulator of cell death) by inhibiting the activation of NF-κB through modulating the TAK1/IκB/IKK pathway [272,273]. Taraxasterol can block the expression of NLRP-3 inflammasomes as well as its modulators including TXNIP (thioredoxin-interacting protein) and ASC (apoptosis-associated speck-like protein) in HFLS-RA and collagen-induced arthritis (CIA) mouse models [58].

Trans-cinnamaldehyde: animals treated with trans-cinnamaldehyde showed a marked reduction in NF-κB, COX-2, and TNF-α translocation, accompanied by a significant decrease in NF-κB, TNF-α, and COX-2 levels in inflamed joints. Trans-cinnamaldehyde exhibits anti-inflammatory activity, as confirmed by many studies, which stated that trans-cinnamaldehyde inhibits inflammation in in vivo and in vitro models by suppressing NF-κB in rats with osteoarthritis [274]. In addition, the cinnamon metabolite attenuated NF-κB activation in mice with autoimmune encephalomyelitis [275]. In a study by El-Tanbouly et al [276], trans-cinnamaldehyde was shown to counteract joint inflammation in mice with collagen-induced arthritis, as evidenced by the reversal of all elevated levels of inflammatory cytokines IL-1β, IL-6, IL-23, and IL-17. Meanwhile, cinnamaldehyde significantly suppressed the expression of proinflammatory cytokines (IL-1β, IL-6, and TNF-α) in the synovium of rats with adjuvant arthritis [277] and in collagen-induced arthritis rats [278]. Cinnamaldehyde and cinnamon inhibited the proliferation of Th-17 cells [275] in mice, respectively. Withanolides and withaferin A isolated from *W. somnifera* [63,64] dose-dependently reduced inflammation by inhibiting the activation of the NF-κB signaling pathway and its regulated expression of genes involved in inflammation [65].

Wogonin (a natural monoflavonoid found in Scutellaria bai-calensis) may have anti-arthritic potential in the treatment of IDD. In a study by Fang et al [279], wogonin suppressed IL-1β-induced inflammatory mediators (iNOS, IL-6, and COX2) and extracellular matrix-degrading proteinases (MMP-1, MMP-3, MMP-13, and ADAMTS-4). Wogonin also activated some key extracellular matrix components, such as type II collagen. Furthermore, wogonin was found to exert anti-inflammatory effects by activating the

Nrf2/HO-1-SOD2-NQO1-GCLC signaling axis. IL-1β-induced stimulation of the MAPK signaling pathway was reversed by wogonin treatment.

5-chlorogenic acid actively suppresses the production of IL-1β, TNFα, IL-6, NO, COX-2, and NF-κβ, preventing inflammation and IDD [229].

γ-linolenic acid is a precursor of anti-inflammatory prostaglandins (arachidonic acid) and modulators of inflammatory responses, including eicosanoids (prostaglandins and leukotrienes) and cytokines (interleukins). γ-linolenic acid also inhibits NF-κB, ERK1/2, and JNK1, which play roles in the pathogenesis of arthritis. Borage oil contains γ-linolenic acid, which exhibits antiarthritic activity [126] by modulating the levels of nitric oxide NO, TNF-α, IL-1β and thromboxane B2 (TXB2) and by suppressing COX-2 expression [169].

4. DISCUSSION

Chronic inflammation, as one of the key mechanisms in the development and progression of IDD, continues to be actively studied, which in turn affects approaches to the use of both drug [9] and non-drug treatment methods. Among non-drug methods, rapidly developing high-tech methods [280] for correcting cytokine imbalance and chronic inflammation in degenerating human IVDs are relevant, while possible ways of correcting these pathological processes using well-known methods of traditional medicine, primarily herbal preparations, are being reviewed and studied. Paradoxically, the use of herbal preparations for IDD remains relevant in modern medical science and practice. The production, composition, and active components of herbal preparations vary depending on the plants and their parts (leaves, flowers, stems, rhizomes) used, as well as the region of their growth. At the same time, plants native to various regions of the world may contain active ingredients that have demonstrated clinical effects on cytokine imbalance in patients with IDD. These active ingredients include flavonoids, phenols, terpenes, phenylpropanoids, phytosteroids, organic acids, etc. (Table 1, Appendix 1). The advantages and disadvantages of herbal therapy for IDD are shown in Figure 3.

Herbal remedies traditionally used in various regions of the world are conventionally divided into two groups: traditional, predominantly Eastern herbal remedies; and traditional, predominantly Western herbal remedies. However, we recognize that this classification is conditional in the context of the modern world, when the exchange of medical information on the development of herbal remedies and their use is carried out most actively, and the delivery of plant raw materials for the production of herbal remedies is rapid, unlike in past centuries, when this required many years and even centuries. Developments in pharmacology, pharmaceuticals, and medical biochemistry help us understand which bioactive substances or their combinations have advantages in certain herbal remedies for the correction of chronic inflammation in IDD. There is an increase in preclinical studies of herbal remedies using animal models of IDD and arthritis (including arthritis of the facet joints of the spine), which increases the level of evidence for the efficacy and safety of herbal remedies (Tables 2 and 3).

However, randomized, placebo-controlled clinical trials, if any, are few and far between. Most clinical studies have a Class D evidence rating (animal model studies). The advantages and limitations of herbal medicine research for IDD are presented in Figure 4. Furthermore, we may have analyzed only a subset of the pool of herbal medicines that can be used to correct cytokine imbalance in IDD. The number of promising herbal medicines may be higher, as the results of some studies were unavailable to us, especially if they were published in regional and national journals or in languages other than English.

Table 1. Mechanisms of action of bioactive phytocomponents on cytokine balance in degeneration of intervertebral discs (short version).

Phytocomponents	**Effect on cytokine balance**
Alkaloids (piperine, berberine, berbamin, brucin, anthraquinone)	Reduction of ROS levels (antioxidant effect); inhibition of inflammatory signaling pathways (JNK, NF-κB, Th17) Suppression of high levels of proinflammatory mediators (IL-1β, TNF-α, IL-6, iNOS, MMPs, ADAMTS, NO, PGE-2, COX-2) Activation of type II collagen and proteoglycan production
Glycosides (russeolyside B, argeloside, aucubin)	Inhibition of the NF-κB inflammatory signaling pathway Suppression of high levels of proinflammatory mediators (TNF-α, IL-6, IL-1β, iNOS, COX-2, MMPs) Activation of type II collagen and proteoglycan production
Organic acids (cinnamic acid, sinapic acid, ferulic acid, P-coumaric acid, 5-chlorogenic acid, caffeoylquinic acid, γ-linoleic acid	Inhibition of inflammatory signaling pathways (NF-κB, JNK, ERKs, JAK/STAT, MAPK) Suppression of expression of proinflammatory mediators (TNF-α, PGE-2, IL-8, TNF-α, IL-6, IL-1, iNOS, COX-2, NO) Inhibition of inflammatory signaling pathways (NF-κB, JNK, ERKs, JAK/STAT, MAPK) Suppression of expression of proinflammatory mediators (TNF-α, PGE-2, IL-8, TNF-α, IL-6, IL-1, iNOS, COX-2, NO)
Saponins (clematichinoside, glycyrrhizin, protodioscin)	Inhibition of the PI3K/Akt–NF-κB inflammatory signaling pathway Reduction of ROS levels (antioxidant effect) Suppression of the expression of proinflammatory mediators (IL-6, TNF-α, NO, PGE-2, COX-2, IL-1β, IL-17, IL-12, IFNγ). Inhibition of the Wnt/β-catenin apoptotic pathway
Terpenes (alantolactone, taraxasterol, andrographolide, cineole)	Inhibition of inflammatory signaling pathways (NF-κB, MAPK, NLRP3) Suppression of expression of proinflammatory mediators (TNF-α, MMPs, IL-1, IL-6, NO) Reduction of ROS levels (antioxidant effect)
Phenols (moracin M, cardamonin, curcuminoid)	Inhibition of the NF-κB inflammatory signaling pathway Suppression of the expression of proinflammatory mediators (COX-2, iNOS, PGE-2, NO, TNF-α, IL-6, MMP-13, ADAMTS)
Phytosteroids (guggulsterone, β-sitosterol, withanolides)	Inhibition of inflammatory signaling pathways (MAPK, NF-κB) Suppression of expression of proinflammatory mediators (IFN-γ, IL-12, IL-1β, NO)
Flavonoids (naringin, icariin, baicalein, wogonin, acacetin)	Reduced ROS synthesis (antioxidant effect). Inhibition of inflammatory signaling pathways (NF-κB, MAPK, JNK, ERK1/2) Suppression of expression of proinflammatory mediators (MMPs, ADAMTS, TGF-β, NO, PGE-2, TNF-α, IL-6, IL-1, TNF-α, COX-2, iNOS) Activation of production of type II collagen, aggrecan, and proteoglycans

Note: NF-κB - Nuclear factor kappa-light-chain-enhancer of activated B cells; IL - Interleukin; STAT - Signal transducer and activator of transcription; MMPs - Matrix metalloproteinase; RF - Rheumatoid factor; TNF - Tumor necrosis factor; iNOS – Inducible Nitric oxide synthases; COX-2 - Cyclooxygenase-2; ROS - Reactive oxygen species; Wnt - Wingless and Int-1; PI3K - Phosphatidylinositol 3-kinase; Akt - Protein kinase B; PGE - Prostaglandin E; IFN – Interferon; NO - Nitric oxide; MAPK - Mitogen-activated protein kinase; NLRP3 - Nucleotide-binding oligomerization domain (NOD)-like receptor family pyrin domain containing 3; ADAMTS - Disintegrin and Metalloproteinase with Thrombospondin Motifs; TGF - Transforming growth factor; ERKs - Extracellular Signal-regulated Kinases; TH17 - T helper 17 cells; JNKs - c-Jun N-terminal kinases; JAK - Janus kinase.

Table 2. Mechanisms of action of oriental herbal remedies on cytokine balance in intervertebral disc degeneration (short version).

Whole herbs	**Effect on cytokine balance**	**Evidence class**
Cortex A. membranaceus	Reduction in the level of the proinflammatory cytokine IL-6	D
Allium sativum	Decreased levels of proinflammatory cytokines (IL-1β, IL-6, TNF, IL-8) Increased levels of the anti-inflammatory cytokine IL-10	C, D
Andrographis paniculata	Inhibition of activation of the NF-κB inflammatory signaling pathway	D
Boswellia serrata Linn	Inhibition of activation of the NF-κB inflammatory signaling pathway	D
Cannabis sativum	Inhibition of the release of proinflammatory cytokines (TNF-α, GM-CSF, IFN-γ, TNF-α, IL-6, IL-8) Increase in the level of the anti-inflammatory cytokine IL-10	C, D
Citrus limon	Reduction in levels of proinflammatory cytokines (IL-6, IL-1β, TNF-α)	D
Curcuma longa	Inhibition of activation of the NF-κB inflammatory signaling pathway	D
Moringa oleifera	Reduction in levels of proinflammatory cytokines (IL-6, IL-1β, TNF-α)	D
Piper nigrum	Reduction in levels of proinflammatory mediators (leukotrienes and prostaglandins)	D
Taraxacum officinale	Inhibition of activation of the NF-κB inflammatory signaling pathway Reduction in levels of proinflammatory cytokines (IL-6, TNF-α)	D
Terminalia chebula	Reduction in levels of proinflammatory cytokines (IL-6, IL-1β, TNF-α)	D
Mixtures/Charges	**Effect on cytokine balance**	**Evidence class**
Bushen Huoxue	Suppression of proinflammatory cytokine production (IL-1β, TNF-α) Inhibition of the expression of MAPK inflammatory signaling proteins	B, D
Duhuo Jisheng	Inhibition of activation of inflammatory signaling pathways (NF-κB, Th17)	B, D
Кампо: - Hochuekkito (HET) - Juzentaihoto (JTT), - Ninjin'yoeito (NYT)	Inhibition of the expression of proinflammatory cytokines (IL-6, IL-17A, IFN-γ, TNF-α) and the anti-inflammatory cytokine IL-10	B, D
Herbal remedies	**Effect on cytokine balance**	**Evidence class**
Liuwei Dihuang	Regulation of the expression of inflammatory signaling pathways (JNK, MAPK) Suppression of the expression of oxidation enzymes (MMP-1, -3, -13)	B, D
Fufang Qishe	Inhibition of activation of the NF-κB inflammatory signaling pathway	B, D
Combined herbal therapy	**Effect on cytokine balance**	**Evidence class**
Cyclophosphamide, prednisolone and Qing Shen Fang	Reduction in the level of proinflammatory cytokine IFN-γ and anti-inflammatory cytokine IL-4	C, D
Campo and prednisolone	Restructuring of the immune cell composition towards Th-2 dominance	C, D
Pharmacopuncture	**Effect on cytokine balance**	**Evidence class**
Shinbaro	Inhibition of inflammatory signaling pathways (NF-κB, Akt) Reduction in levels of proinflammatory mediators (PGE-2, COX-2, NO) by suppressing their mRNA expression, iNOS Reduction in high levels of proinflammatory cytokines (IL-1β, TNF-α, IFN-β) Reduction in the activity of oxidative enzymes (ADAMTS-5, MMPs)	B, C

Note: IL - Interleukin; TNF - Tumor necrosis factor; COX – Cyclooxygenase; Akt - Protein kinase B; PGE - Prostaglandin E; NO - Nitric oxide; iNOS – Inducible Nitric oxide synthases; NF-κB - Nuclear factor kappa-light-chain-enhancer of activated B cells; MMP - Matrix metalloproteinase; MAPK - Mitogen-activated protein kinase; IFN – Interferon; GM-CSF - Granulocyte-macrophage colony-stimulating factor; JNKs - c-Jun N-terminal kinases; Th - T helper cells; ADAMTS - Disintegrin and Metalloproteinase with Thrombospondin Motifs.

Table 3. Mechanisms of action of Western herbal remedies on cytokine balance in intervertebral disc degeneration (short version).

Whole herbs	Effect on cytokine balance	Evidence class
Aloe barbadensis	Inhibition of inflammatory signaling pathway activation (NF-κB, JNK, ERK, and p38 kinases) Suppression of proinflammatory mediators (IL-8, TNF-α, IL-6, IL-1, PGE-2)	D
Berberis orthobotrys	Inhibition of activation of inflammatory signaling pathways (NF-κβ, Th17) Suppression of proinflammatory mediators (IFN-α, IL-1, IL-6 and TNF-α, PGE-2, COX-2)	D
Borago officinalis L	Inhibition of activation of inflammatory signaling pathways (NF-κB, ERK1/2, and JNK1) Suppression of TNF-α and other proinflammatory cytokines	D
Caragana pruinosa	Decreased production of proinflammatory cytokines (IL-1β, IL-6) and anti-inflammatory cytokine IL-10	D
Clematis	Inhibition of NF-κβ inflammatory signaling pathway activation Suppression of proinflammatory mediators (TNF-α, COX-2, TNF-α, IL-1β, IL-6) Increased levels of anti-inflammatory cytokines (IL-4 and IL-10)	D
Ephedraceae	Suppression of proinflammatory mediators (IL-1β, IL-6, TNF-α, PGE-2) Increased levels of anti-inflammatory cytokines (IL-4, IL-10)	D
Inula helenium L	Inhibition of activation of inflammatory signaling pathways (NF-κB, MAPK) Suppression of proinflammatory mediators and oxidative enzymes (TNF-α, MMP-3, IL-1, IL-6).	D
Paullinia pinnata L	Inhibition of the production of proinflammatory cytokines (TNF-α, IL-1β)	D
Polystichum braunii (Spenn.)	Inhibition of NF-κB inflammatory signaling pathway activation Suppression of proinflammatory mediator production (IL-6, TNF-α, COX2, PGE-2) Increased levels of anti-inflammatory cytokines (IL-4, IL-10)	D
Punica granatum Linn	Inhibition of activation of the NF-κB inflammatory signaling pathway	D
Ribes	Inhibition of NF-κB inflammatory signaling pathway activation Suppression of proinflammatory mediators (PGE-2, TNF-α, IL-1β, IL-6, COX-2) Increased levels of anti-inflammatory cytokines (IL-4, IL-10)	D
Schinus terebinthifolius	Inhibition of proinflammatory mediators (IL-6, IL-1β, CXCL1, TNF-α)	D
Solenostemma argel (Del) Hayne	Inhibition of NF-κB inflammatory signaling pathway activation Suppression of proinflammatory mediators (COX-2, IL-1β)	D
Uncaria tomentosa	Inhibition of NF-κB inflammatory signaling pathway activation Suppression of proinflammatory cytokines (IL-1α, IL-1β, IL-17, TNF-α)	A,D

Note: IL - Interleukin; TNF - Tumor necrosis factor; COX – Cyclooxygenase; PGE - Prostaglandin E; NF-κB - Nuclear factor kappa-light-chain-enhancer of activated B cells; MMP - Matrix metalloproteinase; MAPK - Mitogen-activated protein kinase; IFN – Interferon; JNKs - c-Jun N-terminal kinases; Th - T helper cells; ERKs - Extracellular Signal-regulated Kinases; CXCL - Chemokine (C-X-C motif) ligand.

Figure 3: Advantages and disadvantages of herbal therapy for intervertebral disc degeneration

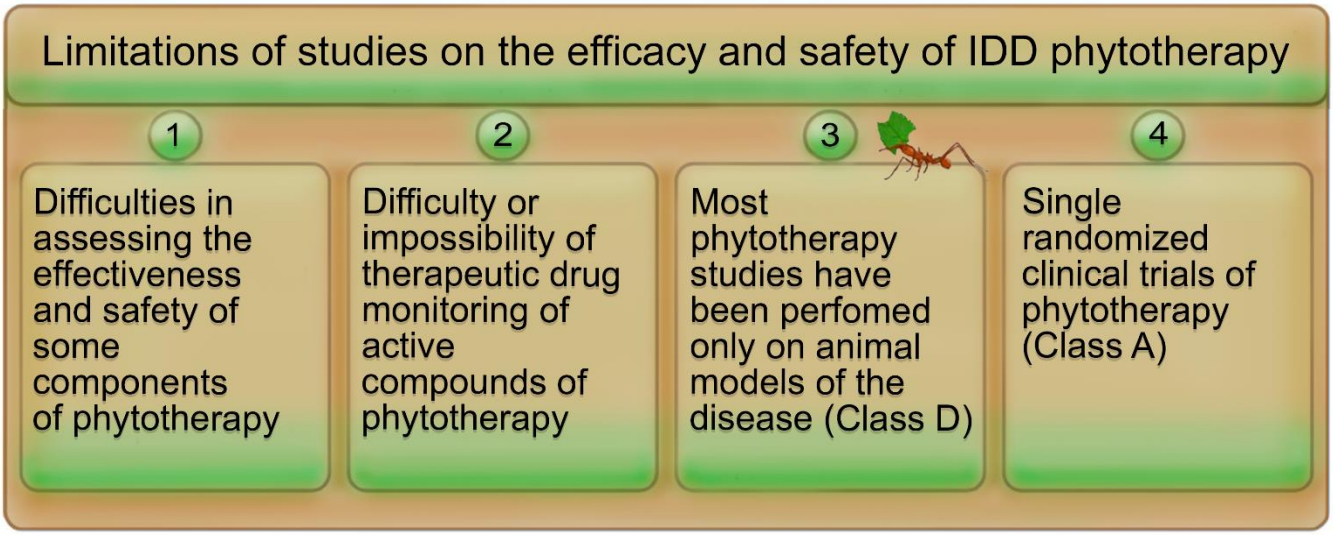

Figure 4. Benefits and limitations of herbal medicine research in intervertebral disc degeneration.
Note: Class A – double-blind, placebo-controlled studies; Class D – studies in animal models

Thus, this narrative review is of clinical and scientific interest, as it updates the knowledge of both practicing physicians (neurologists, orthopedists, and pharmacologists) regarding the potential use of traditional herbal medicine to correct chronic inflammation and cytokine imbalance as its main mechanism in patients with IDD. Unlike previously published reviews, we have attempted to summarize and systematize the accumulated knowledge, taking into account the results of preclinical and clinical studies of the last decade. However, this review also includes several earlier studies that are of undoubted historical interest and help understand traditional approaches to the use of these herbal remedies in Eastern and Western medicine.

In this review, herbal medicine was examined from the perspective of a hormetic approach: the good is the long-forgotten old.

5. CONCLUSIONS

This review demonstrated that traditional herbal medicine has not lost its clinical significance and can be used as a component of disease-modifying therapy for IDD in humans. Planning and conducting new preclinical and clinical trials of herbal remedies for this disease are necessary to increase the level of evidence for their use in real-world good clinical practice in line with modern requirements.

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