Research progress of local characteristic drugs for treatment of rheumatoid arthritis in Xinjiang

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Meng Y and Wang LR conceived the review and wrote the initial manuscript. Cong S proofread the manuscript. Luo L edited the manuscript.

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Abbreviations
RA, rheumatoid arthritis; IL, interleukin; ACPA, anti-citrullinated protein antibodies; RANKL, receptor activator of nuclear factor-κB ligand; LPS, lipopolysaccharide; NF-κB, nuclear factor kappa-B; CIA, collagen-induced arthritis; AIA, adjuvant-induced rheumatoid arthritis; TSGN5, Nigela glandulifera seeds.

Citation

Abstract
Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by synovitis. This disease tends to recur, persist, and is difficult to cure. The pathogenesis of RA is complex. Currently, the commonly used treatments for RA—non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, and immunosuppressants—have notable side effects with long-term use and may be ineffective for some patients. Therefore, it is crucial to find drugs with limited side effects and significant curative effects. Xinjiang's local characteristic drugs have a long history, abundant resources, and are known for their safety and effectiveness in treating RA. In recent years, many studies have reported on the mechanisms of action and therapeutic effects of Xinjiang's local characteristic drugs on RA. This article reviews the pathogenesis of RA, as well as the research progress and treatment characteristics of Xinjiang-featured drugs.

Keywords: local characteristic drugs in Xinjiang; rheumatoid arthritis
Background

Rheumatoid arthritis (RA) is a common systemic autoimmune disease characterized by synovial inflammatory hyperplasia, pannus formation, and the destruction of joint cartilage and bone. Clinically, RA manifests as the sudden onset of chronic, progressive joint swelling, pain, and deformity, which gradually lead to joint dysfunction and ultimately disability. The global incidence of RA is approximately 0.5–1%, and the prevalence in our country is about 0.42% [1, 2]. The pathogenesis of rheumatoid arthritis (RA) is intricate, involving genetic, environmental, and autoimmune factors, though the precise mechanisms remain uncertain. Presently, RA is typically managed with non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), glucocorticoids, and immunosuppressants. However, these treatments often come with substantial side effects when used long-term and may not be effective for all patients. Therefore, discovering medications that provide significant therapeutic benefits with minimal side effects is essential to alleviate pain and enhance the quality of life for RA patients [3]. Xinjiang's local characteristic drugs, known for their abundant resources, safety, and effectiveness, play an important role in the clinical treatment of RA. This review summarizes the therapeutic effects of Xinjiang's local characteristic drugs on RA and discusses their research progress in the treatment of this disease.

The pathogenesis of RA

The pathogenesis of RA is complex. RA joint inflammation arises from the intricate interaction between various immune cells, including dendritic cells, macrophages, T cells, B cells, and neutrophils, as well as fibroblasts and osteoclasts. Synovial dendritic cells present autoantigen-derived peptides, activating self-reactive T cells. These T cells then stimulate T helper (Th) 1 cells, Th17 cells, and follicular T helper cells. The pro-inflammatory mediators and chemokines secreted by these cells activate macrophages and fibroblasts [4]. Activated macrophages release large amounts of potent pro-inflammatory cytokines such as tumor necrosis factor (TNF-α), interleukin (IL)-1β, and IL-6, which drive synovial inflammation [5]. Fibroblast-like synoviocytes (FLS) proliferate and, under the influence of overexpressed cytokines, chemokines, and matrix metalloproteinases (MMPs), release vascular endothelial growth factor (VEGF), leading to pannus formation [6]. Additionally, activated T cells stimulate B cells to produce autoantibodies, such as anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF).

On one hand, ACPAs stimulate the inflammatory response by directly activating macrophages, initiating the complement cascade [5]. Conversely, ACPAs activate macrophages via immune complexes, leading to the secretion of TNF-α and receptor activator of nuclear factor-κB ligand (RANKL), which in turn promotes osteoclast differentiation. ACPAs can also directly stimulate osteoclast generation by binding to citrullinated proteins on osteoclast precursor cell surfaces, consequently resulting in bone destruction [7]. In recent years, the identification of novel immune cell subgroups has enhanced our understanding of pathogenesis. Peripheral helper T cells, situated in synovial B cell clusters and circulating in the bloodstream, can induce B cell production of IL-21 and facilitate B cell proliferation and differentiation into antibody-producing plasma cells. The immune barrier formed by CX3CR1+ tissue-resident macrophages on the synovial surface regulates the passage of proteins through the normal synovial membrane. ETS1 fibroblasts play a role in bone damage by generating RANKL and activating osteoclasts. Neutrophil extracellular traps in the synovial and pulmonary mucosa serve as platforms for citrullinated proteins, amplifying the immune response that produces ACPAs [8]. The aggregation of multiple inflammatory mediators, chemokines, and autoantibodies contributes to persistent synovial inflammatory hyperplasia, pannus formation, and destruction of articular cartilage and bone.

Research progress on treatment of RA with local characteristic drugs in Xinjiang

Saussurea involucrata

Saussurea involucrata belongs to the Compositaeae family and is known as "Saussurea involucrata (Kar.et Kir.) Sch-Bip" [9], in the Pharmacopoeia of the People's Republic of China and the Flora of China. In China, Saussurea involucrata is predominantly found in mountain slopes, valleys, and rock cracks at elevations ranging from 2400 to 4100 meters above sea level in Xinjiang. Its above-ground parts are commonly used as medicinal materials [10]. Chemical substances extracted from Saussurea involucrata include flavonoids, phenylacetone, coumarins, lignans, sesquiterpenoids, steroids, ceramides, and polysaccharides. These compounds exhibit various pharmacological activities such as anti-inflammatory, analgesic, anti-tumor, antioxidiant, anti-hypoxia, and immunomodulatory effects [10]. Rutin, a flavonoid, and chlorogenic acid, a phenylpropanoid, are identified as the main active compounds in Saussurea involucrata.

Rutin's metabolic product, 3, 4-2 hydroxy tolulene, demonstrates anti-inflammatory activity. In lipopolysaccharide (LPS)-induced macrophages, rutin possibly inhibits the expression of iNOS and COX-2 through the nuclear factor kappa-B (NF-κB) pathway, thereby reducing the transcription of upstream signals. Consequently, it decreases the production of pro-inflammatory factors such as TNF-α, IL-1β, and IL-6 [11]. Chlorogenic acid has been shown to alleviate joint inflammation in CIA mice. It also reduces the DNA-binding activity of NF-κB and the B cell activating factor (BAFF) promoters region in TNF-α-stimulated M17A fibroblast-like synoviocytes and inhibits BAFF expression through the NF-κB pathway [12].

Saussurea saussurea is widely used in the treatment of RA due to its anti-inflammatory and analgesic properties. Saussurea saussurea oral liquid, which consists of Saussurea saussurea, simple syrup, and citric acid, has shown promise in this regard. Wang Lingrui et al. found that Saussurea saussurea oral liquid may alleviate joint inflammation in CIA rats by inhibiting the activation of the autophagy pathway mediated by C-Jun N-terminal kinase (JNK)/B cell 2 (Bcl-2)/Bcl2-in the synovium [13]. Furthermore, Muzhi Chen et al. observed that the total effective rate of the Saussurea saussurea oral liquid group in treating RA patients was 10% higher compared to the oral rheumatic liquid group. It significantly improved clinical symptoms such as joint pain, swelling, tenderness, and morning stiffness [14]. Compound Saussurea saussurea capsules, composed of Saussurea saussurea, Qiangel, corydalis, Duhua, and other ingredients, have also shown efficacy. Yang Mengnan et al. found that these capsules were more effective than the control drug methotrexate in alleviating joint pain and other clinical symptoms, as well as in improving joint function and patients' quality of life [15]. Saussurea saussurea culture tablets, containing active ingredients such as flavonoids, polysaccharides, and chlorogenic acid, exhibit anti-inflammatory and analgesic effects.

Chen Ying et al. observed significant improvement in joint pain, swelling, and morning stiffness of RA patients following a 4-week treatment with Saussurea-sulphate culture tablets [16]. Tan Li et al. demonstrated that Saussurea saussurea injection restored the dynamic balance of Th1/Th2 cytokines by suppressing the levels of IL-2, IL-6, and IL-21 secreted by Th1 cells in the serum and synovium of rats with CIA [17]. Furthermore, Gu Yun et al. suggested that combining acupuncture and moxibustion at acupoints with Saussurea saussurea injection at acupoints could enhance the absorption and therapeutic effect of Saussurea saussurea injection in RA patients, thereby improving overall therapeutic efficiency [18]. Saussurea exhibits potential in alleviating RA symptoms by relieving pain, improving blood circulation, and modulating immunity. However, existing clinical studies suffer from limitations such as small sample sizes, poor follow-up effects, and low overall quality grades. Hence, further research is warranted to expand sample sizes, refine methodologies, and prolong follow-up periods to establish its positive clinical value.

Aconitum leucostomum Worosch
Aconitum leucostomum Worochs, a perennial herb of the Ranunculaceae family, is widely distributed in the Yili and Altay regions of Xinjiang [19]. According to Kazak Medicine records, Aconitum leucostomum Worochs is frequently employed as a medicinal material among the Kazak nationality, with its roots being utilized for medicinal purposes. It possesses a hot and bitter taste and is known to be toxic. Its medicinal properties include dispelling wind, cold, reducing swelling, relieving pain, and activating meridians. It is primarily used in the treatment of wind-cold-dampness impediment, rheumatoid arthritis, and other related ailments [20]. The main active ingredient in Aconitum leucostomum Worochs is alkaloid, which exhibits analgesic, anti-inflammatory, and anti-tumor effects [21]. Wang Fang et al. isolated five monomer compounds from Aconitum leucostomum, namely Delvestidine (I), lappaconitine (II), N-deacetylappaconitine (III), antranhydrilycocotone (IV), and leucostine (V) [22]. Delvestidine, identified for the first time from Aconitum leucostomum, is a white powder with a positive reaction to bismuth potassium iodide and a molecular weight of 600, with a chemical formula of C33H48N2O8 [21]. Lappaconitine constitutes a significant portion of the total alkaloid content, accounting for about 40%. Its hydrobrome is used in China as a non-addictive analgesic. Leucosticine possesses a structure of 8-β-hydroxy-leucosticine [23]. Delvestidine may regulate Ebi3, Calcr, Fzd10, and Eps8 gene signaling by influencing miRNA expression, thereby inhibiting the maturation of bone marrow-derived dendritic cells [24].

Zhang Yong et al. demonstrated that the combined use of low-dose hyperaconitine hydrobrome tablets (primarily lappaconitine) and methotrexate tablets can effectively improve the pain symptoms of RA patients and reduce the incidence of adverse reactions [25]. Yang et al. investigated the effects of raw Aconitum diptheriae, processed products (boiled, autoclaved, and co-cooked with excipients), and monomeric components (delvestidine, antranhydrilycocotone) on human fibroblast-like synovial cell rheumatoid arthritis (HFLS-RA) cells. They found down-regulation of hypoxia-inducing factor-1α and Toll-like receptor 4 expression in HFLS-RA cells, along with decreased levels of pro-inflammatory cytokines IL-6, IL-1β, and TNF-α. These effects contributed to its anti-rheumatic properties and delayed arthritis development [26].

Yang Junling et al. explored various processing methods of Aconitum diptheriae, including boiling, high-pressure steaming, and co-cooking with auxiliary materials based on pharmacopoeia references and traditional Kazak folk methods. They observed improvements in joint swelling, inflammatory changes in synovial tissue, and serum levels of C-reactive protein, RF, and cortisol in adjuvant-induced rheumatoid arthritis (AIA) rats treated with Aconitum diptheriae and its processed products [27]. Currently, there is limited research on the chemical components, pharmacological effects, and other aspects of Aconitum diptheriae. It is imperative to enhance research on the active, effective, and toxic components of Aconitum diptheriae, elucidate the mechanism of action or relevant targets of specific bioactive substances in RA treatment, and further explore the clinical utility of Aconitum diptheriae.

Nigella glandulifera

Nigella glandulifera, belonging to the Ranunculaceae family, is widely distributed in the Xinjiang Uyghur Autonomous Region. Its dried and ripe seeds are commonly utilized in Uyghur medicine. Nigella glandulifera has been incorporated into the Pharmacopoeia of the People’s Republic of China under the name Nigella Glandulifera. The seeds of Nigella glandulifera (TSNGS) are abundant in alkaloids, saponins, flavonoids, volatile oils, fats, esters, and primary metabolites such as sucrose, amino acids, and phospholipids, among other bioactive substances, which confer antibacterial, anti-inflammatory, anti-tumor, and immunomodulatory properties [28]. Alkaloids inhibit the activity of dihydrosorcinol dehydrogenase, reduce LPS-induced nitric oxide production, and possess anti-inflammatory properties. Total saponins enhance the activity of plasma superoxide dismutase and glutathione peroxidase while reducing malondialdehyde levels. Water extracts of TSNGS improve antioxidant enzyme activity, enhance free radical scavenging, and decrease lipid peroxide production, thereby exhibiting anti-inflammatory, analgesic, antioxidant, and immunomodulatory effects [29–32]. TSNGS finds extensive use in treating inflammatory conditions like arthritis and bronchitis, exhibiting comparable efficacy with minimal side effects [33]. Research indicates that TSNGS diminishes clinical scores, paw swelling, and histological alterations in AIA and CIA rats. It also down-regulates pro-inflammatory factors TNF-α, IL-1β, IL-4, and IL-10A in serum and synovial tissue while up-regulating anti-inflammatory factors IL-4 and IFN-γ. Moreover, it increases the proportion of CD4/CD8 T cells in peripheral blood and enhances the expression of transcription factor Foxp3 in knee joints. Additionally, TSNGS demonstrates a protective effect on bones by up-regulating the OPG/RANKL pathway [28, 34]. Wang Linlin et al. affirmed that TSNGS total saponins exhibit notable anti-inflammatory and therapeutic effects on both primary and secondary damage in AA and CIA models [35]. Currently, the variances in chemical components across different parts of TSNGS and their medicinal value remain unexplored. Moreover, there is a scarcity of studies investigating the chemical composition of TSNGS and its corresponding pharmacological effects in treating RA. It is imperative to bolster such research endeavors to furnish insights into its therapeutic mechanisms, further medicinal advancements, and comprehensive utilization.

Juniperus sabina L.

Juniperus sabina L. is an evergreen creeping shrub belonging to the Cupreace family, extensively found in Altai Mountain, Tianshan Mountain, and the western regions of Junggar in Xinjiang. Thriving on sandy terrain and barren mountains at elevated altitudes, Juniperus Sabina L. boasts a rich composition of essential oils, terpenes, lignans, flavonoids, phenolic acids, and other bioactive constituents, with flavonoids predominating as the principal components [36–38]. In a study utilizing silica gel and Sephadex LH-20, flavonoids extracted from the leaves of Cypress chinensis yielded Cypress flavone and Cypress flavone 4’, among others, totaling nine flavonoids, including 4-dimethyl ether, spirotaxus flavone, Podocarpodendron A flavone, catechin, quercetin, isohomoBaicalin 7-O-β-D-Malxoside, myricetin 3O-β-D-glucoside, and rutin [39]. Previous research has documented the pharmacological efficacy of Juniperus sabina L. extracts, citing antibacterial, antioxidant, anti-tumor, and anti-inflammatory properties [40]. In traditional Chinese Uyghur medicine, Juniperus sabina L. is frequently employed to alleviate RA, joint pain, and wind-cold headaches, attributed to its wind-dispersing, calming, blood-activating and pain-relieving [36, 41]. Zhao et al. verified that total flavonoids extracted from Juniperus sabina (JSTF) effectively mitigate foot swelling, reduce arthritis scores, and lower serum levels of pro-inflammatory cytokines TNF-α and IL-1β in AIA rats, thereby ameliorating inflammation and synovial hyperplasia in knee joints. Additionally, JSTF exhibits anti-inflammatory properties by inhibiting the activities of cyclooxygenase-2 and 5-lipoxygenase, while also exerting analgesic effects through the inhibition of prostaglandin and histamine mediator release [41, 42]. Despite the evident anti-inflammatory effects of Juniperus sabina L., the precise substance basis and specific mechanisms of its anti-inflammatory action remain elusive. The pursuit of compounds demonstrating notable anti-inflammatory activities is therefore crucial, offering promising leads for novel drug development.

Capparis spinosus L.

Capparis spinosa L. belongs to the Chinese cabbage family and is primarily distributed in Xinjiang, Tibet, Gansu, and other regions. In Xinjiang, Capparis spinosa L. predominantly thrives in desert, arid, sandy, and other extreme environments [43]. Its principal chemical constituents encompass alkaloids, flavonoids, phenolic acids, vitamin components, and more [44]. The diverse array of active ingredients endows capers with significant pharmacological effects, including anti-inflammatory, analgesic, antioxidant, and anti-tumor properties.
Research indicates that ethyl acetate extracts of capers exhibit notable anti-inflammatory and analgesic effects, while caper fruit extract displays potential immunosuppressive properties. It is hypothesized that the extract may hinder LPS-induced dendritic cell maturation and proinflammatory cytokine expression by impeding the phosphorylation of mitogen-activated protein kinase and related proteins within the NF-κB signaling pathway. Additionally, the extract enhances the expression of anti-inflammatory cytokine IL-10 and augments antigen phagocytosis capabilities [45]. Due to their ability to dispel wind, cold, dampness, and alleviate swelling, capers are frequently employed topically to treat conditions such as RA, scapulohumeral periarthritis, and gout [43].

Numerous studies have explored the utilization of caper in formulations such as caper fruit rheumatism pain relief patches, caper gel, and refined caper fruit extracts for anti-inflammatory and anti-RA investigations. Several studies have demonstrated that caper rheumatic pain relief patches possess anti-inflammatory and analgesic properties, effectively treating RA by downregulating serum levels of TNF-α and IL-1β, as well as MMP-9 and VEGF in synovium tissue, while inhibiting soluble intercellular adhesion molecule-1 and autophagy-related protein microtubule-associated protein light chain 3-II in rats [46, 47]. Moreover, they upregulate the expression of Beclin protein complex-1 (BCLEIN-1) in synovial tissue, thereby alleviating joint inflammation in RA rats [46, 49]. Kalimanjiang Gelinman et al. administered caper gel to the hind foot and ankle of AIA rats, observing an improvement in the histopathological inflammatory condition of the rats’ ankle joints. They noted a decrease in serum levels of pro-inflammatory factors TNF-α, IL-1β, and IL-17, along with an increase in the expression level of the anti-inflammatory factor IL-10 [50]. Haifeng Zhou et al. investigated the anti-rheumatic effect of refined caper fruit extract, observing its capacity to inhibit RA-related inflammation in AIA and CIA rats, and to ameliorate secondary lesions in AIA rats [51]. Xinhui Hu et al. discovered that a mixture comprising caper powder, 45% liquor, and egg white, when applied to the ankles of RA rats, could rectify the Th17/Treg cell imbalance, decrease the secretion of pro-inflammatory factors IL-17 and IL-6, and elevate the level of anti-inflammatory factor IL-10, thereby effectively treating arthritis in RA rats [52]. Presently, caper research predominantly concentrates on effective part extraction, isolation, and the pharmacological actions of these constituents. With the ongoing advancement of modern analytical technologies, future studies can delve into molecular biology, metabolomics, network pharmacology, and other methodologies to systematically explore the in vivo and in vitro pharmacodynamic properties, pharmacological mechanisms, and modern preparation techniques of capers. Such endeavors will lay a robust groundwork for their comprehensive development, particularly in anti-inflammatory, analgesic, and immunosuppressive applications.

Peganum harmala L

Peganum harmala L is a perennial herb belonging to the Tribulus family, extensively found in Xinjiang, Gansu, Ningxia, and Inner Mongolia. Its seeds and whole plant have been traditionally employed in treating rheumatic joint pain, with Uygur practitioners favoring the use of dried, mature seeds for medicinal purposes. These seeds are reputed for their ability to fortify the semen pulse, invigorate and warm the Yang, and dispel cold and dampness. In Kazakh medicine, the dried aerial parts of Peganum harmala L. are commonly used and are known for their wind-dispelling, pain-relieving, blood-promoting, and menstrual-regulating effects [36]. The principal chemical constituents of Peganum harmala L. encompass alkaloids, flavonoids, sterols, anthraquinones, amino acids, fatty acids, vitamins, and sugars, among others. Alkaloids, notably the most abundant, serve as the primary active components contributing to its pharmacological effects. Pharmacological investigations have revealed that Peganum harmala L. exhibits immune regulation, tumor inhibition, anti-inflammatory and analgesic effects [53]. Dehydroharponine, for instance, does not affect the mononuclear macrophage system but can suppress the production of sensitized β-cells and antibody formation during humoral immunity [54]. Additionally, the alkaloid of harbourine can alleviate the inflammatory pain sensitivity reaction induced by formalin in mice, with harboring identified as the principal active component [55].

Mahajna et al. discovered that in 1 μg/mL LPS-activated human macrophages, a concentration of 64 μg/mL LPS-activated extract exerts an anti-inflammatory effect by enhancing the release of the anti-inflammatory factor IL-10 and suppressing the expression of pro-inflammatory factors IL-1, IL-6, and TNF-α [56]. Wang Zhenglin et al. verified that Peganum harmala L. can impede neovascularization formation, thus halting the progression of synovial inflammation, consequently alleviating the joint swelling, pain and dysfunction of RA patients [57]. Tian Xinwei et al. demonstrated that topical application of Peganum harmala L. reduces serum levels of cytokines IL-1β and TNF-α in CIA rats, thereby inhibiting synovial tissue proliferation, diminishing pannus formation and inflammatory cell infiltration within joints, and forestalling the degeneration of bone and cartilage in CIA rats [58]. The rich alkaloid content in Peganum harmala L. holds promise for identifying effective ingredients for RA treatment and developing them into novel therapeutics. Moreover, there is a pressing need to intensify pharmaceutical investigations of Peganum harmala L. to enhance its bioavailability. Additionally, research on the toxicological mechanisms and toxicity correlations of Peganum harmala L. must be expanded to improve drug safety and guide its clinical application.

Prospect

This review presents a comprehensive overview of the research advancements in treating RA with locally distinctive drugs in Xinjiang. As longstanding fixtures in folk medicine, these indigenous remedies have abundant resources and notable therapeutic efficacy, warranting further in-depth investigation, development, and utilization. Nevertheless, current research on locally distinctive drugs in Xinjiang primarily emphasizes alleviating clinical symptoms in RA patients and ameliorating joint inflammation in RA animal models, with limited exploration into their biological active ingredients and specific mechanisms of action in treating RA. Hence, there is a pressing need to delve into molecular mechanisms to enhance the safety and efficacy of clinical treatments, thereby providing valuable insights for the innovative development and clinical application of Xinjiang-specific medications.

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