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Role Of Irioid Glycoside For The Treatment Of Rheumatoid Arthritis

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Abstract

The study present examination of the therapeutic applications of iridoid glycosides in the management of rheumatoid arthritis (RA). The objective of this study was to assess the effectiveness of iridoid glycosides in mitigating symptoms of rheumatoid arthritis by conducting a comprehensive review of relevant literature and clinical trials. Mechanistic inquiries were undertaken to elucidate the mechanisms by which iridoid glycosides achieve their therapeutic effects in rheumatoid arthritis treatment. An examination of the safety profile of iridoid glycoside treatment for RA patients revealed that it has the potential to be a safe therapeutic option. The potential of iridoid glycosides as a supplementary treatment for rheumatoid arthritis in conjunction with conventional therapies was investigated in this study. In conclusion, of their multifaceted approach to symptom relief and enhanced patient outcomes, iridoid glycosides appear to be a viable and safe supplementary treatment option for rheumatoid arthritis, according to the findings of this study.

Key Words: Iridoid Glycosides, Rheumatoid Arthritis, Treatment, Mechanisms of Action, patients, etc.

Introduction

Introduction of rheumatoid arthritis (RA):

Rheumatoid arthritis (RA) is an autoimmune disease that has been recognized as a clinical entity for over two centuries. The most common presentation of Rheumatoid Arthritis is a symmetrical inflammatory polyarthritis, particularly of the hands and feet, although any synovial joint is at risk. Rheumatoid arthritis is also a systemic illness, with extra-articular manifestations occurring commonly, including subcutaneous nodules, pulmonary disease, vasculitis, and neuropathy. Rheumatoid Arthritis is the most common of the inflammatory arthritides and, combined with its multiple systemic effects and complications of therapy, causes significant morbidity. Some researchers believe that Rheumatoid Arthritis is a modem disease because there are few bony artifacts showing the characteristic bony changes of Rheumatoid Arthritis, compared to clear skeletal evidence of spondylitis. Skeletal remains in North America suggest that Rheumatoid Arthritis was present there in pre-Columbian times. Such discussions are potentially important in the continuing search for the cause of Rheumatoid Arthritis. As with many autoimmune diseases, women are at greater risk than men for the development of RA. Beyond gender differences in incidence rates, there is also a complex relationship among rheumatoid arthritis, female sex hormones, and reproductive status in modulating both the risks for disease and its clinical course in women. Genetic susceptibility also plays a role, with increased disease risk and severity in certain Human Leukocyte Antigen (HLA) haplotypes (see Section III, Immunogenetics). These factors make understanding the epidemiology of Rheumatoid Arthritis particularly relevant in discussion of women's health issues. The initiating event in Rheumatoid Arthritis is still unknown. It is now understood, however, that the time course of joint damage occurs early in the disease for many patients. Studies of morbidity and mortality in rheumatoid arthritis have demonstrated decreased life expectancy and lost wages that are comparable to other major illnesses such as stroke.

For this reason, early intervention with remittive therapies has become the standard of care for active, recent onset Rheumatoid Arthritis. Combinations of remittive drugs are often used for active disease. Improved surgical interventions, particularly in total joint replacement, offer pain relief and improved function to many patients. Studies also demonstrate the importance of psychosocial issues for Rheumatoid Arthritis patients. These include the issues associated with child-rearing and job performance for women with active disease. Additionally, studies of fatigue, depression, and self-efficacy in people with rheumatoid arthritis have shown the need for interventions to control or minimize these factors. A multidisciplinary approach, including an assessment of the psychosocial and economic impact, is important to manage Rheumatoid Arthritis optimally.

Iridoid Glycosides:

The iridoid glycosides C-1 are polyhydroxyl linked and polyglycoside formed, and most of them are β-d-glucoside. Among the isolated iridoid glycosides, some rare new structures have been found, such as asperuloside, which has a ketone functional group at C-6. This cyclopentane ring with ketoyl function, especially at C-6, is a rare compound in the plant kingdom. Besides, Iridoid glycosides with apiofuranosyl

moieties have been reported for the first time in Sambucus williamsii Hance. Based on the extensive spectroscopic analysis (NMR and HRESIMS) the structures were elucidated as williamsoside A and B.

Furthermore, 6-O-α-l-(2”-acetyl-4”-O-trans-isoferuloyl) rhamnopyranosyl catalpol is acylated and esterified at the C-2 and C-4 positions such compounds have never been separated from natural resources so far. Vestena et al. isolated and purified brasoside from both Verbena litoralis and Verbena montevidensis. In addition, asperuloside with a rare iridoid structure was isolated from the root and stem of Ronabea emetic.

Exploring the Potential of Iridoid Glycosides:

Iridoid glycosides are a group of natural compounds that have gained increasing attention in the fields of pharmacology, medicine, and plant biochemistry. These chemical compounds, often found in various plant species, have demonstrated remarkable potential for a wide range of applications. In this context, the exploration of the potential of iridoid glycosides has become a focal point of research and scientific inquiry.

Iridoid glycosides are known for their diverse biological activities, including anti-inflammatory, antioxidant, and antimicrobial properties. These attributes make them a subject of great interest for the development of new pharmaceuticals, dietary supplements, and functional foods. Moreover, their role in traditional medicine practices in different cultures has further spurred interest in studying their efficacy and safety.

In pharmaceutical research, iridoid glycosides have shown promise in the treatment of various ailments, such as inflammatory disorders, neurodegenerative diseases, and metabolic syndromes. Their anti-inflammatory properties, in particular, have piqued the curiosity of researchers seeking alternative treatments for chronic conditions. Additionally, their antioxidant capabilities make them potential candidates for combating oxidative stress-related diseases.

The study of iridoid glycosides extends to the realm of plant biochemistry. Researchers are exploring their biosynthesis, distribution in different plant species, and the ecological roles they play. Understanding the underlying mechanisms of iridoid glycoside production in plants can have implications for agriculture and conservation efforts.

Iridoid Glycoside in Rheumatoid Arthritis Treatment:

Rheumatoid arthritis (RA) is a persistent autoimmune condition distinguished by joint destruction and inflammation, which frequently culminate in excruciating pain and functional impairment. Although RA is incurable, numerous treatment modalities are designed to mitigate symptoms and impede the disease's progression. Recent interest has been drawn to iridoid glycosides, a class of naturally occurring compounds discovered in numerous plant species, due to their potential utility in the treatment of Rheumatoid Arthritis. In this discourse, we shall examine the potential utility of iridoid glycosides in the management of rheumatoid arthritis, emphasising five pivotal aspects:

Anti-Inflammatory Properties: Anthoid glycosides are notably anti-inflammatory in nature. They impede the synthesis of pro-inflammatory cytokines, including interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α), which are critical mediators of the inflammatory response in rheumatoid arthritis. In patients with rheumatoid arthritis, iridoid glycosides may ameliorate pain and rigidity by decreasing inflammation.

Immunomodulation: In rheumatoid arthritis, the joints in particular are targeted by the immune system in an erroneous attempt to destroy them. Regulatory of the immune response, irispodirid glycosides possess immunomodulatory properties. In order to mitigate joint injury associated with rheumatoid arthritis (RA), they regulate immune cells, including T cells and B cells, to inhibit their assault on healthy tissue.

Cartilage and Bone Protection: Rheumatoid Arthritis is characterised, in part, by cartilage and bone degeneration in the afflicted joints. Potential has been demonstrated for irisdoid glycosides to preserve cartilage and inhibit bone resorption. This may expedite joint structural deterioration and enhance the long-term prognosis for RA patients.

Antioxidant Activity: Rheumatoid Arthritis is associated with oxidative stress, which can exacerbate inflammation and tissue damage. Iridoid glycosides act as antioxidants, scavenging free radicals and reducing oxidative stress. By doing so, they can mitigate the overall impact of inflammation in the joints.

Symptomatic Relief: In addition to their disease-modifying effects, iridoid glycosides can provide symptomatic relief to Rheumatoid Arthritis patients. By reducing pain and inflammation, these compounds improve the overall quality of life for those suffering from the condition. This relief can be especially important for individuals with Rheumatoid Arthritis, as pain and discomfort can be debilitating.

Objective of the study:

- To evaluate the efficacy of iridoid glycosides in alleviating rheumatoid arthritis symptoms.
- To investigate the mechanism of action of iridoid glycosides in the management of rheumatoid arthritis.
- To assess the safety profile of iridoid glycoside treatment for rheumatoid arthritis patients.
- To explore the potential of iridoid glycosides as a complementary therapy for rheumatoid arthritis.

Literature review:

Priyanka Pandey et.al (2018) Studied the main aim of the treatment of RA is to eliminate the symptoms of the disease or to slowdowns the development of the disease. Presently many types of drugs are used for the treatment of this disease like disease modifying antirheumatic drugs (DMARDs), glucocorticoids and non-steroidal anti-inflammatory drugs (NSAIDs). Long term usage of these drugs causes many adverse effects. Use of plants for the treatment of the disease causes no side-effects. India has blessed with enormous wealth of medicinal plants. Since ancient time, herbal drugs are used for the treatment of various disorders in India. In the present review many plants having antirheumatic property are mentioned.

Rahul Bodkhe et.al (2019) presents Rheumatoid arthritis (RA) is an autoimmune disorder with multifactorial etiology; both genetic and environmental factors are known to be involved in pathogenesis. Treatment with disease-modifying antirheumatic drugs (DMARDs) plays an essential role in controlling disease progression and symptoms. DMARDs have immunomodulatory properties and suppress immune response by interfering in various pro-inflammatory pathways. Recent evidence has shown that the gut microbiota directly and indirectly modulates the host immune system. RA has been associated with dysbiosis of the gut microbiota. Patients with RA treated with DMARDs show partial restoration of eubiotic gut microbiome.

Shancai Tan et.al (2017) determined the in vitro antioxidant ability of the IGF through radical scavenging assays and assessed the in vivo hepatoprotective potential in an acetaminophen- (APAP-) induced acute liver injury murine model. The IGF was separated by HSCCC and three major iridoid glycosides (verproside, catalposide, and amphicoside) were identified as potent antioxidants and hepatoprotective compounds. Treatment with the IGF significantly suppressed the APAP-induced elevation in serum alanine aminotransferase, aspartate aminotransferase, and tumor necrosis factor-alpha (TNF-α); improved serum total antioxidant capacity; decreased malondialdehyde formation; elevated superoxide dismutase and glutathione activity; and decreased expression of proinflammatory factors (TNF-α, nuclear factor kappa B) in the liver.

Yi Shen et.al (2020) evaluate the ameliorating effect of MOIG on joint swelling and bone destruction and the protective effect against MTX toxicities. The anti-arthritic activity of MOIG was investigated by clinical arthritis scoring, paw swelling inspection, as well as histological analysis in CIA rats. The anti-bone loss activity of MOIG was evaluated by bone mineral density (BMD) and bone morphometric analysis assessed by Micro-CT and biochemical parameters in serum related with bone metabolism. The serum metabolomics and NF-κB signaling pathway were used to explore and clarify the action mechanism.

Qin Ma et.al (2016) studied Rheumatoid arthritis (RA) is a chronic systemic disorder characterized by persistent synovitis and systemic inflammation. Currently, the widely used drugs for the treatment of RA are disease-modifying antirheumatic drugs, biological agents and glucocorticoids. But their clinical use has been limited because of their adverse effects with a high frequency and high cost of treatment. It is essential to find novel candidate agents. Traditional Chinese medicine (TCM) has been used for RA treatment for a long period of time. In recent years, significant amounts of studies have shown that some TCMs and their active ingredients have obvious therapeutic effects on RA. In this review, the compounds in TCMs that have an effect in clinic or animal experiments of RA are critically reviewed and summarized.

Chenzhe Gao et.al (2021) studied Iridoid glycosides (IG) as the major active fraction of Syringa oblata Lindl. has a proven anti-inflammatory effect for ulcerative colitis (UC). However, its current commercial formulations are hampered by low bioavailability and unable to reach inflamed colon. To overcome the limitation, dual functional IG-loaded nanoparticles (DFNPs) were prepared to increase the residence time of IG in colon. The protective mechanism of DFNPs on DSSinduced colonic injury was evaluated in rats. We prepared DFNPs

using the oil-in-water emulsion method. PLGA was selected as sustained-release polymer, and ES100 and EL30D-55 as pH responsive polymers. The morphology and size distribution of NPs were measured by SEM and DLS technique. To evaluate colon targeting of DFNPs, DiR, was encapsulated as a fluorescent probe into NPs. Fluorescent distribution of NPs was investigated. The therapeutic potential and in vivo transportation of NPs in gastrointestinal tract were evaluated in a colitis model.

Xueling Liu et.al (2022) investigate Rheumatoid arthritis (RA) is an autoimmune disease involving joints, with clinical manifestations of joint inflammation, bone damage and cartilage destruction, joint dysfunction and deformity, and extra-articular organ damage. As an important source of new drug molecules, natural medicines have many advantages, such as a wide range of biological effects and small toxic and side effects. They have become a hot spot for the vast number of researchers to study various diseases and develop therapeutic drugs. In recent years, the research of natural medicines in the treatment of RA has made remarkable achievements. These natural medicines mainly include flavonoids, polyphenols, alkaloids, glycosides and terpenes. Among them, resveratrol, icariin, epigallocatechin-3-gallate, ginsenoside, sinomenine, paeoniflorin, triptolide and paeoniflorin are star natural medicines for the treatment of RA. Its mechanism of treating RA mainly involves these aspects: anti-inflammation, anti-oxidation, immune regulation, pro-apoptosis, inhibition of angiogenesis, inhibition of osteoclastogenesis, inhibition of fibroblast-like synovial cell proliferation, migration and invasion.

Hidayat Hussain et.al (2019) examine Iridoids belong to a family of monoterpenoids comprising the cyclopentan[c]-pyran system; this class of compounds offers a wide range of biological effects, namely antileishmanial, anticancer, antiplasmodial, and anti-inflammatory potency. To date, a large number of biologically active iridoid derivatives have been reported from various plant families, including Rubiaceae, Plantaginaceae, Scrophulariaceae, and Verbenaceae. Furthermore, iridoids have the potential to form conjugates with other anticancer, antidiabetic, antileishmanial, and antimalarial drugs which synergistically have the potential to increase their effects.

Na Jia et.al (2016) the flowers of Gentiana macrophylla have been usually applied to cure the joint in flammation and rheumatoid arthritis in Traditional Chinese Medicine. Hypothesis/purpose: This work aimed to investigate the anti-rheumatoid arthritis effect and possible mechanism of iridoid glycosides from G. macrophylla (GMI) using an animal model of collagen-induced rheumatoid arthritis (CIA) in rats. All rats were randomly divided into five groups: normal control, CIA, dexamethasone, 15 mg/kg and 30 mg/kg GMI. Methods: CIA was induced (day 0) in male Sprague-Dawley rats by intradermal injection of complete Bovine CII at the base of the tail. Dexamethasone was chosen as the positive drug. The administration of different drugs started from day 1 and continued for 28 days. Paw swelling, arthritis score and histopathological changes were examined to assess the severity of arthritis.

Xiaohui Zhao et.al (2021) evaluate the anti-rheumatoid arthritis (RA) activities and underlying mechanisms of the total iridoid glucosides (TIG) from Lamiophlomisrotata (Benth.) Kudo. The chemical constituents of TIG were analyzed by high-performance liquid chromatography (HPLC) with seven reference compounds (penstemonoside, chlorotuberside, shanzhiside methyl ester, phloyoside, 7- epliamalbide, phlorigidoside C and lamalbide). The anti-rheumatoid arthritis effects of TIG were investigated by arthritis indexes and paw swelling degrees, as well as histopathological and Micro-CT analysis in adjuvantinduced arthritis (AIA) rats. The impacts of TIG on the level of inflammatory cytokines (IL-1β, TNF-α, IL-6, IFN-γ, IL-17 and IL-10), and the regulation of OPG/RANKL/NF-κB pathways were determined by the ELISA and western blot, respectively.

Linlin Yin et.al (2014) investigated the therapeutic benefit of cornel iridoid glycoside (CIG), the main component extracted from Cornus officinalis, in experimental autoimmune encephalomyelitis (EAE) rats. CIG was intragastrically administered daily after EAE initiation for 20 days and reduced disease severity, incidence, disease onset and ongoing paralysis. Histopathological staining showed that CIG could reduce T cell entry to the central nervous system and microglia activation, increased brain-derived neurotrophic factor (BDNF) expression and mature oligodendrocytes, and decreased oligodendrocyte progenitor cells (OPCs).

Zhao Qu et.al (2019) found the effect of cornel iridoid glycoside (CIG), main component extracted from Cornus officinalis, on microglia activation has not been elucidated so far. We induced a mouse model of multiple sclerosis (MS), namely, the experimental autoimmune encephalomyelitis (EAE) model by immunization subcutaneously with the MOG35–55 peptide, which causes neuroinflammation and microglia activation. Our data demonstrated that CIG delayed the onset of the EAE, ameliorated the severity of the symptoms and inhibited the activation of microglia in different brain regions. In addition, we also found that CIG has therapeutic potential by modulating microglia polarization by reducing the expression and release of

proinflammatory cytokines, chemokines and inhibiting phosphorylation in the JAK/STAT cell signalling pathway. Based on our findings, CIG might be a promising candidate for the prevention of neurological disorders such as multiple sclerosis (MS).

Yaya Hu et. al (2018) Discovering novel compounds with higher activities is a key aim of natural prod ucts research. Gardenia jasminoides Ellis is a herb with anti-inflammatory properties. Iridoid glycosides (mainly geniposide) and crocetin derivatives (crocins) are the two majors active co nstituents in this herb and are considered its active ingredients. However, which component s are responsible for the anti-inflammatory properties of gardenia have remained to be inve stigated. Purpose: Here, we prepared total iridoid glycocides (TIG) and total crocins (TC) from Gardeni a jasminoides Ellis, determined their main chemical constituents, and performed animal stu dies to evaluate their anti-adjuvant arthritis activities, thus, proposing a reasonable mecheni sm to explain the anti-inflammatory activities of the active components in this herbal remedy.

Shareen Singh et.al (2020) investigate Rheumatoid arthritis is a chronic autoimmune disease manifested clinically by polyarthralgia associated with joint dysfunction triggering the antibodies targeting against the self-neoepitopes determined by autoimmune responses associated with chronic arthritic attacks. The activation of macrophages and other defence cells in response to self-epitopes as biomarkers in RA provides a better understanding of pathogenesis of disease and has led to the development of novel therapeutic approaches acting as potent inhibitors of these cells. Key findings the current review retrieved the various medicinal plants possessing an active phytoconstituents with anti-inflammatory and antioxidant properties, which tends to be effective alternative approach over the synthetic drugs concerned with high toxic effects.

Cho-Won Kim et.al (2021) determine Iridoids are glycosides found in plants, having inherent roles in defending them against infection by viruses and microorganisms, and in the rapid repair of damaged areas. The emerging roles of iridoid glycosides on pharmacological properties have aroused the curiosity of many researchers, and studies undertaken indicate that iridoid glycosides exert inhibitory effects in numerous cancers. This review focuses on the roles and the potential mechanism of iridoid glycosides at each stage of cancer development such as proliferation, epithelial mesenchymal transition (EMT), migration, invasion and angiogenesis. Overall, the reviewed literature indicates that iridoid glycosides inhibit cancer growth by inducing cell cycle arrest or by regulating apoptosis-related signaling pathways. In addition, iridoid glycosides suppress the expression and activity of matrix metalloproteinases (MMPs), resulting in reduced cancer cell migration and invasiveness.

WANG Dong-Mei et.al (2015) present a rapid and validated UPLC-MS method was developed for investigating the absorbed components of Paederia scandens (Lour.) Merrill (P. scandens) in rat plasma. The bioactive constituents in plasma samples from rats administrated orally with P. scandens extract were analyzed by Ultra-performance liquid chromatography quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF-MS). Four prototype compounds were identified in rat serum as potential bioactive components of P. scandens by comparing their retention times and mass spectrometry data or by mass spectrometry analysis and retrieving the reference literatures. Glucuronidation after deglycosylation was the major metabolic pathway for the iridoid glycosides in P. scandens. These results showed that the methods had high sensitivity and resolution and were suitable for identifying the bioactive constituents in plasma after oral administration of P. scandens. providing helpful chemical information for further pharmacological and mechanistic researched on the P. scandens.

Qi Zhang et.al (2020) determine how MOIG exerted anti-inflammatory and anti-arthritic effects in vivo and in RAW 264.7 macrophages. MOIG were enriched by XDA-1 macroporous resin. The maximum feasible dose method was adopted to evaluate its acute toxicity. The analgesic effect of MOIG was evaluated by acetic acid writhing test and the antiinflammatory effect was evaluated by cotton-pellet granuloma test in rats and air pouch granuloma test in mice. The anti-arthritic effect was evaluated by establishing an adjuvant arthritis model induced by Complete Freund's Adjuvant (CFA). The viability of the cultured RAW 264.7 macrophages was assessed by 3-(4, 5-dimethylthiazol-2-yl)-2, 5-diphenyl tetrazolium bromide (MTT) assay. The anti-inflammatory activity was evaluated by measuring NO, IL-1β, IL-6 and TNF-α levels in LPS-stimulated RAW 264.7 cells. The protein level of inflammatory responsive genes was evaluated by Western blot analysis.

Ting Wang et.al (2022) aims to clarify the chemical components and molecular mechanism of iridoid glycosides of Eucommia ulmoides Oliver in the treatment of osteoporosis by integrating network pharmacology and molecular simulations. The active iridoid glycosides and their potential targets were retrieved from text mining as well as Swiss Target Prediction, TargetNet database, and STITCH databases. At the same time, DisGeNET, GeneCards, and Therapeutic Target Database were used to search for the targets associated with osteoporosis. A protein–protein interaction network was built to analyze the interactions between targets. Then, DAVID

bioinformatics resources and R 3.6.3 project were used to carry out Gene Ontology enrichment analysis and Kyoto Encyclopedia of Genes and Genomes pathway analysis. Moreover, interactions between active compounds and potential targets were investigated through molecular docking, molecular dynamic simulation, and binding free energy analysis.

Jyoti B. Wadekar et.al (2015) showed Rheumatoid Arthritis (RA) is a chronic autoimmune disease of unknown aetiology that affects 0.5% of the population and can result in disability owing to joint destruction, characterized by joint synovial inflammation and progressive cartilage and bone destruction resulting in gradual immobility. The greatest disadvantage in the presently available potent synthetic drugs lies in their toxicity and reappearance of symptoms after discontinuation. With limitations of existing drug molecules herbal drugs are gaining interest among RA patients.

Ahmed Jafar Talukdar et.al (2023) investigate Rheumatoid arthritis (RA) is a debilitating, persistent autoimmune condition that affects by a variety of endogenous and external causes. It is distinguished by cartilage and bone deterioration. The present traditional allopathic treatment is costly and has negative side effects. Recently, some ethnopharmacological research on RA was published, including anti-RA properties and therapeutic targets of various dosage forms of Traditional Herbal Treatments (THMs). Given the increased herbalists' interest medicines among people suffers from rheumatoid arthritis, further research into their safety and efficacy is needed. The goal of this research was to carry out a comprehensive assessment of the evidence based on the use of herbal medications in the treatment of RA Randomised Clinical Trials (RCTs).

Research gap:

Iridoid glycosides have attracted considerable interest in the treatment of rheumatoid arthritis because of their possible immunomodulatory and anti-inflammatory properties. Although preclinical and in vitro investigations have yielded encouraging outcomes, the literature is research gap of complete clinical trials and translational research that assess the safety, effectiveness, and mechanisms of action of iridoid glycosides in human subjects afflicted with rheumatoid arthritis. The optimal dosing regimens, potential adverse effects, and long-term outcomes of iridoid glycoside treatment remain poorly understood. Therefore, it is imperative that future research fills this knowledge gap and contributes to the development of innovative therapeutic approaches for this incapacitating autoimmune disorder.

Conclusion:

In summary, iridoid glycosides have demonstrated potential as therapeutic agents for rheumatoid arthritis, presenting a viable approach to the management of this incapacitating autoimmune disorder. Their immunomodulatory, anti-inflammatory, and antioxidant properties, which may aid in the mitigation of symptoms and progression of the condition, have been the subject of extensive research. Although further clinical research is required to validate their safety and effectiveness, the available evidence indicates that iridoid glycosides have considerable promise as a supplementary or substitute treatment for rheumatoid arthritis. Patients interested in complementary treatments may find them appealing due to their natural origin and comparatively low adverse effect profile. However, it is critical that patients and healthcare professionals collaborate when incorporating iridoid glycosides into a comprehensive management plan for rheumatoid arthritis, taking into account individual needs and the entire range of available treatments.

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