



REVIEW

Mechanistic insights into anti-inflammatory and immunosuppressive effects of plant secondary metabolites and their therapeutic potential for rheumatoid arthritis

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Abstract

The anti-inflammatory and immunosuppressive activities of plant secondary metabolites are due to their diverse mechanisms of action against multifarious molecular targets such as modulation of the complex immune system associated with rheumatoid arthritis (RA). This review discussed and critically analyzed the potent anti-inflammatory and immunosuppressive effects of several phytochemicals and their underlying mechanisms in association with RA in experimental studies, including preliminary clinical studies of some of them. A wide range of phytochemicals including phenols, flavonoids, chalcones, xanthenes, terpenoids, alkaloids, and glycosides have shown significant immunosuppressive and anti-inflammatory activities in experimental RA models and a few have undergone clinical trials for their efficacy and safety in reducing RA symptoms and improve patient outcomes. These phytochemicals have potential as safer alternatives to the existing drugs in the management of RA, which possess a wide range of serious side effects. Sufficient preclinical studies on safety and efficacy of these phytochemicals must be performed prior to proper clinical

studies. Further studies are needed to address the barriers that have so far limited their human use before the therapeutic potential of these plant-based chemicals as anti-arthritic agents in the treatment of RA is fully realized.

KEYWORDS

anti-arthritic drugs, anti-inflammatory, immune system, immunosuppressants, phytochemicals, rheumatoid arthritis

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune illness that causes inflammation, stiffness, discomfort in the joints and characterized by swollen, red hands and feet. The disease can lead to severe pain, fluid buildup in the joints, shortness of breath, damage to internal organs (heart valves or lungs), diminished mobility and even death. The condition is characterized by synovial hyperplasia, an aggressive expansion of joint synovial tissue. This pathology degenerates articular joints, causing pain and edema (Merola et al., 2018). RA is associated with extensive degradation of cartilage and underlying bone that causes progressive disability, early death, and socioeconomic costs (Mueller et al., 2021). In addition to the systemic inflammation, patients with active RA also have higher mortality and morbidity rates than the general population due to a number of comorbidities, most notably cardiovascular diseases. The initiation and progression of RA are influenced by environmental and genetic factors (Fang et al., 2020). As a systemic disease, RA can still manifest even when joint damage is treated. Comorbidities, psychosocial deficiencies, and a reduction in well-being and quality of life that come along with RA's extra-articular symptoms must also be taken into account for a more thorough analysis of the burden of the disease (Raje et al., 2018).

There is no permanent cure for RA but early diagnosis and treatment with anti-inflammatory medications may help reduce symptoms over time. Different types of medications have been used to treat RA which include disease-modifying antirheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, biologic response modifiers, and Janus kinase (JAK) inhibitors. These drugs act on the target of pathogenesis that cause joint degeneration and inflammation by different mechanisms. However, it is difficult to select the appropriate treatment due to variable efficacy between patients with RA (Merola et al., 2018). The current therapeutic approach is starting intensive therapy as soon as a diagnosis is made and escalating the medication in the goal of clinical remission while being guided by an evaluation of the disease activity. Some of the conventional and biologic disease modifying therapies are ineffective or only yield partial results. It is difficult to obtain sustained remission, which necessitates continued pharmacologic therapy. Patients with RA have a greater death rate than people in general. In addition, cardiovascular and other systemic complications remain to be serious problems. Thus, improvements in the discovery and development of new therapies with better outcomes should be facilitated by developments in the understanding of the etiology of the disease (Ikebuchi et al., 2018).

Research continues to explore a variety of lead structures, which may be used as templates for the development of new drugs for RA. Natural products remain as safe and potential effective agents as alternative treatment for RA. Several plant-based compounds such as polyphenols, flavonoids, lignans, lactones, alkaloids, terpenoids, and glycosides have demonstrated strong immunosuppressive and anti-inflammatory properties (Hughes et al., 2017; Jantan et al., 2015). Several experimental studies have been conducted to evaluate the potency of natural-based compounds as anti-rheumatoid arthritis (anti-RA) agents. A number of reviews on the anti-inflammatory and immunosuppressive activities of medicinal plant extracts and plant-based compounds have been published recently (Jantan et al., 2015; Ghasemian et al., 2016; Hughes et al., 2017; Gandhi et al., 2021; Oliveira-Costa et al., 2022; Ali Reza et al., 2023; Habtemariam, 2023;). However, reviews on anti-inflammatory and immunosuppressive of plant secondary metabolites in relation to their potential use in the treatment of RA were scanty or even absent.

In this review, we gathered data on the anti-inflammatory and immunosuppressive effects of several phytochemicals and their underlying mechanisms in association with RA in *in vitro* and *in vivo* studies, including some preliminary clinical studies. This extensive review was conducted using scientific databases scanned from 2000 until now such as Google Scholar, Scopus, Science Direct, Elsevier, Springer, Pub Med, Taylor and Francis, and Wiley Online Library. The collected data underwent a rigorous analysis, and subsequent discussion focused on devising future strategies and adopting suitable viewpoints regarding the potential of plants as viable sources for developing new natural medicines to treat RA.

2 | THE PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

RA is an autoimmune disorder characterized by chronic inflammation of the joints, primarily affecting the synovial membranes. The pathogenesis of RA is not completely understood, but it is believed to involve a combination of environmental, genetic, and hormonal factors (Merola et al., 2018). The pathophysiology of RA involves immune dysregulation, synovial inflammation, synovial proliferation, pannus formation, joint destruction, and potential systemic effects. Understanding these processes helps in developing targeted treatment approaches for managing the disease. The etiology of this immunological dysregulation is hypothesized to be influenced by a confluence of