

# Exploring the Role of Phytochemicals in Arthritic Disorders: A Review

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*Received: 08<sup>th</sup> September, 2023; Revised: 28<sup>th</sup> October, 2023; Accepted: 20<sup>th</sup> November, 2023; Available Online: 25<sup>th</sup> December, 2023*

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## ABSTRACT

Rheumatoid arthritis (RA) is a prevalent inflammatory condition exemplified by a prolonged course and diverse levels of complexity in symptoms involving joints, extra-articular organs and systemic manifestations, impacting a substantial number of people worldwide. The current treatment regimen of RA involves various synthetic drugs which cause severe side effects and occasionally infections also having high cost and impaired life quality. Plants and herbs contain abundant phytochemicals, which have demonstrated effectiveness in preventing, treating, or alleviating a range of health issues. Phytochemicals due to their low cost, safety and effectiveness in RA treatment and better patient acceptability are used as an alternative therapy. Currently, varied phytochemicals are isolated and evaluated for anti-arthritic drugs as they possess diverse chemical structures and specific biological actions. Phytochemicals are tested as a novel curative approach for arthritis management. In the present review, our intention is to present the role of different phytochemicals in reducing the progression of RA. We also aim to present a mechanism-based reduction of arthritic symptoms.

**Keywords:** Phytochemicals, Anti-arthritic, Flavonoids, Saponins, Alkaloids, Terpenoids, Interleukins, Tumour necrosis factor, Inflammation.

International Journal of Pharmaceutical Quality Assurance (2023); DOI: 10.25258/ijpqa.14.4.74

**How to cite this article:** Trivedi R, Hadia RB, Kardani S, Maheshwari RA. Exploring the Role of Phytochemicals in Arthritic Disorders: A Review. International Journal of Pharmaceutical Quality Assurance. 2023;14(4):1307-1311.

**Source of support:** Nil.

**Conflict of interest:** None

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## INTRODUCTION

Rheumatoid arthritis (RA) is known as a long-standing autoimmune disorder of unfamiliar etiology. Constant synovitis is the principal feature which is accompanied by multiple organ association and auto-antibodies such as rheumatoid factor (RF) and anti-citrullinated peptide protein antibodies (ACPAs) production. Joint dysfunction, particularly the hands, knees, and wrists occurs in RA. As the disorder progresses, it affects joints and various other parts of the body, which results in premature deaths and a number of troubles like disability as well as an inferior class of life in countries that are in the developing phase. Due to chronic inflammation, almost all patients complain about body imbalance and joint damage. According to the epidemiological data RA affects about 1.0% of adults. The disorder is susceptible to females and old age people. Near about 40 new cases in one lac population every year are affected by RA. According to the Centers for Disease Control and Prevention, factors like environmental for example obesity, adulthood, smoking, being feminine, and genetic factors are the chief hazard factors for developing RA.<sup>1-3</sup>

Presently the treatment of RA involves the use of non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs) and glucocorticoids, they mainly reduce inflammation of joints and

other systems and overcome the associated pain of arthritic patients. Though, the available treatment cannot produce sufficient outcomes on the promotion of the disease as well as associated adverse effects such as liver and kidney toxicity, also limit their medical application. In the later worse condition of RA, biological agents are applied but due to their high cost and severe infections, their use are also limited.<sup>4</sup> From the previous research findings it has documented that in the patients of RA, permeation and abnormal activation or repression of immune cells *viz* T and B cells and macrophages are plentiful in synovial fluids responsible for joint inflammation. Currently, the drugs are developed targeting these immune cells resulting in downstream of pro-inflammatory cells, rheumatoid factors and certain peptide proteins and C-reactive proteins as well in the blood and synovial fluid. On the other hand, more scientific investigations are required to prove the relationship between the pharmacological effects of developed drugs and decreased biomarkers of RA patients.<sup>5,6</sup>

India is recognized for the occurrence of an immense diversity of herbal drugs. In India, the traditionally used systems of medicine are very well known as Ayurveda, Unani and Siddha systems. The utilization of medicinal plants and their products, as food and medicines to treat and avoid diseases by humanity has been in practice since many years ago. It is

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hard to mark up the use of plants as medicines. In India, the written material medica of herbal drugs is available from 5000 years ago. Alternative medicines are used in a huge amounts worldwide in spite of the accessibility of allopathic drugs. Alternative medicines are collectively known as of herbals, mineral deposits, and macrobiotic matter in the conventional scheme of medication. Medicinal plants that occur naturally are the chief source of herbal drugs. In India a vast variety of medicinal plants are worn traditionally. Additionally, more than twenty thousand herbal plants and herbal formulations are utilized as conventional drugs. The use of herbal medicines augmented very rapidly in the 20<sup>th</sup> century. The description, such as pharmacology and use of selected remedial plants as herbal medicines are accessible, in diverse monographs of urban countries.<sup>7,8</sup>

Currently, a vast number of populace is using medicinal plants for holistic health. Medicinal plants and the constituent active phytochemicals are expertly employed to treat long-term disorders. The chief advantage of medicinal plants and phytochemicals is their affordable price and patient acceptance as compared to synthetic pharmaceuticals.<sup>9</sup>

Herbal medicines, phytochemicals and nutraceuticals are popularized in the present era, the key reasons behind this are, the competency of the current allopathic treatment and the public not being fond of it, owing to a variety of ill effects; the symptoms and disability of RA patients should be allayed in more effective manner; the stress produced due to chronic illness should be minimized efficiently; and patients perceive herbal remedies as safe and efficient seeing that the past of utilization of the same is extremely aged. The given factors boost the patient-driven investigation of complementary therapies in the management of RA.<sup>10</sup>

The chemical elements present in medicinal plants that propose medicinal properties as well as dietetic benefits to humans are termed as phytoconstituents/phytochemicals. These phytochemicals provide safety to plants from various diseases and other harms as well. In addition, they too augment the plant's color, fragrance, and taste. Usually, the chemicals that occur in plants that safeguard them from environmental hazards like contamination, stress, drought and microorganism threats are referred to as phytochemicals. Recent indication has markedly confirmed that these compounds also take part in the protection of human health, mostly when their utilization through the diet is ample.<sup>11,12</sup>

Conventionally, phytocompounds have been categorized as either primary or secondary metabolites based on their function in the metabolism of botanicals. Primary metabolites encompass common compounds like purines, pyrimidines, amino acids, sugars, and proteins. Conversely, secondary metabolites consist of residual plant chemicals such as phenolic compounds, saponins, alkaloids, terpenes, plant steroids, and glucosides.<sup>13</sup>

### Phenolic Compounds

Phenolic compounds form the largest category of plant-based chemicals and are widely distributed across various plants.

Acting as secondary metabolites, they serve as essential defense compounds. Phenolics exhibit diverse properties beneficial to humans, especially their antioxidant traits, which are vital in defining their function as safeguards against illnesses caused by free radicals. The main categories of phenolics found in diets include flavonoids, polyphenols and phenolic acids.

Flavonoids are a group of compounds created by linking two phenyl rings with phenolic hydroxyl groups *via* the central three carbon atoms. Flavonoids widely found and with minimal toxicity, can be safely included in diets, exhibiting strong anti-inflammatory and antioxidant effects. antioxidant properties of flavonoids are well known; though, they are capable of exhibiting anti-inflammatory properties. They hinder the generation of pro-inflammatory cytokines such as nitric oxide and eicosanoids as well, in addition, they also impede with the nuclear factor- $\kappa$ B transcription factor. Flavonoids alleviate RA symptoms by affecting various targets related to immune regulation, influencing the connection between the gut and joints, and suppressing inflammatory reactions.<sup>13-15</sup>

Examples of phenolic compounds having anti-arthritic activity are acacetin, quercetin, anthocyanin, narigenin, hesperidin, icariin, apigenin, bicalin, resveratrol, epigallocatechin-3-gallate, ferulic acid, catechin.<sup>2,3,13</sup>

### Saponins

A widely distributed secondary metabolite is found in almost all parts of the plants. As per literature findings, saponin molecules consist of a polar glycone structure segment, which comprises as many as four carbohydrate molecules connected by a glycosidic bond at C-3, attached to the nonpolar aglycone structure segment.<sup>16,17</sup> Saponins are varied in their structure and possess mechanisms like reduced generation of interleukins, interferons, tumor necrosis factors and decreased levels of nuclear factor  $\kappa$ -B, in addition, they possess anti-inflammatory and antioxidant potential.

Examples of saponins having anti-arthritic activity are araloside a, asperosaponin vi, hecogenin, diosgenin, glycyrrhizin, ginsenoside, chlorogenic acid, oleanolic acid, and medecassoside.<sup>18</sup>

### Alkaloids

Alkaloids, as natural compounds, consist of nitrogen atoms within heterocyclic structures and consistently exhibit basic properties. The term "alkaloids" originates from their 'alkaline' characteristics and was coined to refer to any nitrogen-based compound. Alkaloids are varied in number and they are classified according to the heterocyclic ring present in the structure. Alkaloids are generated by various plants, bacteria, and fungi. Almost all alkaloids possess a bitter taste. The alkaloids isolated from medicinal plants possess antiarthritic activity as they trim down the level of generating interleukins and interferon. They too reduce the production of rheumatoid factors and tumor necrosis factors and reduce of rapid increase of chondrocytes.<sup>18,19</sup>

Examples of alkaloids having anti-arthritic activity are fangchinoline, montanine, sanguinarine, berberine, naloxone, 3-acetylaconitine, piperine, and capsaicin.<sup>19,20</sup>

### Terpenoids

This category encompasses natural substances that originate from five-carbon isoprene units. These particular types of natural lipids are present in all types of living organisms, building them the most widespread compilation of secondary metabolites set up in nature.<sup>21</sup> The pharmaceutical significance of terpenoids has been demonstrated and extensively recorded due to their abilities in reducing inflammation, fighting bacteria, viruses, and oxidative stress, and inhibiting carcinogenesis.<sup>22</sup> The terpene class of phytochemicals exerts their anti-arthritic action through decreasing levels of inflammatory mediators such as interleukin-1 $\beta$  and interleukin-6, suppressing the levels of tumor necrosis factors. Terpenes also reduce the levels of nuclear factor-B and cyclo-oxygenase enzyme for mitigating the inflammation process in RA.<sup>23</sup>

Examples of terpenoids having anti-arthritic activity are emodinol, geniposide, toriline, maslinic acid, madecassoside, celastrol, boswellic acid, eugenol, camphene, myrcene nimbolide.<sup>20,24</sup>

### Plant Steroids

Steroids possess a basic framework consisting of four carbon rings known as the steroid nucleus. Steroids constitute a collection of low-molecular-weight, lipophilic compounds derived from cholesterol, sourced from diverse marine,

terrestrial, and synthetic origins. Plant steroids are formed through the cyclization of 2,3-epoxysqualene into cycloartenol, which undergoes enzymatic conversion to generate biologically active steroids. Within plant steroids, phytosterols are widespread throughout the plant realm. It's notable that certain phytosterols have been documented to exhibit anti-inflammatory effects.<sup>25</sup> Phytosterols possess different activities like reduction of pro-inflammatory cytokines, interleukins and tumor necrosis factors; free radical scavenging, membrane stabilizing, etc which prove them to be a better anti-arthritic constituent contained from medicinal plants.

Examples of phytosterols having anti-arthritic activity are stigmasterol,  $\beta$ -sitosterol, brassicasterol, and ergosterol.<sup>26</sup>

### CONCLUSION

Arthritis stands as a highly misleading ailment on a global scale, affecting more than 300 million people presently. This condition results in the deterioration of the protective cartilage on adjacent joints. It triggers an inflammatory reaction alongside an increased growth of synovial cells. As a result, an excess buildup of synovial fluid in the joints forms mass in the synovial cells, leading to inflammation at the joint locations. The disease's progression often involves damage to the joint cartilage.<sup>27</sup> Herbal products hold considerable significance in traditional medication, with a range of plants and herbal remedies being employed since prehistoric eras. Various traditional systems like Ayurveda, Kampo, and Unani widely use herbal products that have been in practice globally since ancient times. Herbal products possess unmatched benefits, including widespread clinical histories and a distinct array of chemical compositions and biological functions. They have emerged as vital resources for creating novel lead compounds and frameworks, persistently utilized to address the pressing demand for effective medications. Herbal products are poised to take a forefront position in discovering drugs to treat various human diseases, particularly those of a critical nature.<sup>20,28</sup>

Since ancient times herbal drugs have been used as medicines worldwide. Specific pharmacological activity, molecular properties, and wide chemical diversity are the key features of herbal drugs that make them a potential aspirant for lead molecule identification. Several isolated phytoconstituents that belongs to the flavonoids, saponins, alkaloids, tannins, terpenoids, and steroid category are previously reported as anti-arthritic agents having lesser side effect, better availability, low cost as well as better patient acceptability, and improving quality of life.<sup>29,30</sup> These factors compose the phytochemicals as prospective anti-arthritic agents. Phytochemicals possess a definite chemical structure that is responsible for producing precise biological action and they are available in pure forms which are isolated from herbal plant extracts.

Previously the isolation of phytochemicals from medicinal plants was too costly and tiresome. At, present the availability of precise and sophisticated instruments like advanced spectroscopic devices and chromatography techniques as well as nuclear magnetic resonance etc has reduced the time spent and the results obtained will be more accurate.

**Table 1:** Example of phytochemicals and their role in mitigating RA progression

S.No.	Phytochemical name	Role in mitigating RA progression
1	Luteolin	Reduced generation of TNF- $\alpha$ , interleukin-6 (IL-6), IL-2. Decreased Reactive Oxygen Species (ROS).
2	Quercetin	Declined expression of IL-17A in addition IL-21, and Reduced generation of TNF- $\alpha$ .
3	Hesperidin	Reduced expression of TNF- $\alpha$ . Decreased osteoclastogenesis
4	Berberine	IL-6 as well as IL-17 generation is suppressed.
5	Ellipticine	Decreased synovial cell differentiation.
6	Platycodin D	Reduced generation of IL-6 and TNF- $\alpha$ .
7	Madecassoside	Reduced level of IL-6, TNF- $\alpha$ , Cyclo-oxygenase (COX)-2, increased IL-10.
8	Swertiamarin	Decrease level of IL-6, TNF- $\alpha$ and Cyclo-oxygenase (COX)-2,
9	Cholorogenic acid	Reduce the level of TNF- $\alpha$ and IL-6 as well.
10	Ferulic acid	Suppress the production of IL-6 and TNF- $\alpha$

The isolated phytochemicals from medicinal plants possess free radical scavenging, reduction of inflammation, immune system modulation, and enzymatic effects, these factors can delay arthritis progression or improve arthritic symptoms. In addition, the phytochemicals are specifically acting on the pathways responsible for the progression of RA like increased level of cytokines, interferons and tumor necrosis factors, increased osteoclastogenesis, cyclo-oxygenase enzyme and reactive oxygen species, overactive immune functions as well as increased in proinflammatory mediators. Thus, phytochemicals can be a potential alternative for the development of anti-arthritic drugs which are competent of improving the eminence of life of arthritic patients.<sup>31</sup>

In Table 1, a few examples of isolated phytoconstituent and their role of mitigating RA progression are given.<sup>14,18,20</sup>

Over the last 15 years, use of isolated phytoconstituents as therapeutic agents is increased efficiently. The controlled and targeted drug delivery system using phytochemicals are also developed to treat various disorders. Various nanoformulations are also prepared for the treatment of several disorders. Some examples are; Solid lipid nanoparticles of piperine and  $\beta$ -sitosterol, nanoemulsion of curcumin and quercetin, liposomes of rosmarinic acid, gold nanoparticles of chlorogenic acid, etc. In the present study, we conclude that the isolated phytoconstituents from herbal drugs would be a gold mine for the treatment of arthritic disorders as they are specific in action, easily available and have lesser cost and side effects as compared to conventional drugs. The in-depth study and preclinical and clinical evaluation of phytochemicals are warranted to discover potential lead compounds and to overcome pharmacokinetic-related gaps.

#### ACKNOWLEDGMENT

The authors acknowledge the Department of Pharmacy, Sumandeep Vidyapeeth deemed to be University, Vadodra, Gujarat.

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