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Review Article

Hesperetin: A Potent Phytochemical Constituent for the Treatment of Rheumatoid Arthritis

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ABSTRACT

Hesperetin, a flavonoid abundant in citrus fruits and various vegetables, has emerged as a promising phytochemical for the treatment of rheumatoid arthritis (RA). With its strong anti-inflammatory and antioxidant properties, hesperidin offers a multifaceted approach to reducing the symptoms and progression of rheumatoid arthritis. The pathogenesis of RA involves a complex interplay between inflammatory cytokines, immune dysregulation, and oxidative stress. Hesperidin exerts its therapeutic effects by modulating these pathways. This drug prevents the production of pro-inflammatory cytokines such as tumor necrosis factor-α, interleukin-6, and interleukin-1β, thus reducing inflammation and joint damage. Hesperidin shows immunomodulatory effects by modulating the function of immune cells. It inhibits the activity of inflammatory cells such as macrophages and neutrophils, which play an important role in the development of rheumatoid arthritis. In addition, hesperetin inhibits the activation of nuclear factor κB, an important transcription factor involved in the expression of inflammatory genes, and exhibits broad anti-inflammatory effects. Hesperetin supplementation improves clinical symptoms and inflammatory markers in patients with rheumatoid arthritis. Hesperetin is a natural compound obtained from food sources and has fewer side effects than traditional rheumatoid arthritis drugs, making it an attractive alternative or complementary treatment. Hespertin is a promising approach for the treatment of rheumatoid arthritis. Its pleiotropic mechanisms of action, including anti-inflammatory, antioxidant and immunomodulatory effects, have great therapeutic potential to reduce the symptoms of rheumatoid arthritis, stop the progression of the disease and improve the quality of life of patients. This review article highlights the clinical trials needed to fully elucidate the therapeutic benefits of hesperetin and determine its role in the conventional treatment of rheumatoid arthritis.

INTRODUCTION

Rheumatoid arthritis (RA) is a long-lasting disease where the body's immune system causes swelling and pain in the joints. Rheumatoid arthritis is different from osteoarthritis. It happens when the body's immune system attacks healthy tissue, causing swelling in the joints. This is not because of wear and tear like osteoarthritis. Rheumatoid arthritis can cause mild to severe symptoms like joint pain, swelling, stiffness, and trouble moving our joints. It can affect many joints like the hands, wrists, knees, and feet, and can also cause symptoms like tiredness, fever, and losing weight [1]. The usual treatments involve exercises and Check grammar changing live, along with taking drugs to lessen swelling and pain. However, scientists are also considering other ways to help people with arthritis, such as using natural compounds like hesperetin, which help reduce swelling and relieve symptoms[2]. Figure number one shows the pharmacological properties of hesperetin.

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Highlight The Limitations of Current RA Treatments

There have been advances in the treatment of rheumatoid arthritis (RA), rephrase but some major problems remain [3]. Many medications used to treat rheumatoid arthritis have side effects. This is especially true for DMARDs and corticosteroids. These medications can cause stomach problems, increased illness, liver damage, bone loss, weight gain, and mood changes. Some medications used to treat arthritis can increase the chance of serious infections or certain types of cancer [4]. Biologic DMARDs are drugs used for moderate to severe rheumatoid arthritis. They may come with a high cost and prove challenging to reach for certain patients, particularly those lacking adequate insurance coverage [5]. rephrase Treatments for RA try to make the pain and swelling go away, but some people still feel pain and discomfort that makes it hard to do daily things, and just don't feel good overall [2]. We need to deal with these problems so that people with RA can have a better life and improve their future. rephrase We need to think about using different ways, like using plant chemicals gives us more good things and fewer bad side effects [6].

Introduce Hesperetin Source and Biological Activity

Hesperidin is a substance that is commonly found in citrus fruits like oranges and lemons. This is a type of flavonoid called flavanone. Hesperidin is good at reducing swelling in the body. Research has found that it stops the body from making and sending out molecules that make parts of the body swollen and hurt. This might help lower the swelling. This shows that hesperidin could be a good choice for treating inflammation, like rheumatoid arthritis [7]. Hesperidin has special properties what are those special properties that could be used to make new treatments for RA and other diseases that cause swelling. Table 1 shows how hesperetin can help treat rheumatoid arthritis using its healing powers and proof from studies with patients.

Hesperetin and Its Properties

Chemical Structure and Classification of Hesperetin

Hesperidin is a type of flavonoid with the chemical name 3',5,7-trihydroxy-4'-methoxyflavanone. The chemical makeup of it is made repetition, this is already mentioned above from a type of molecule called a flavanone. It is a kind of flavonoid compound with a specific carbon structure. Flavonoids are a type of natural chemical found in plants. They are known for their ability to fight off harmful substances and reduce swelling in the body [8].

Pharmacological Properties Relevant to RA Treatment

Hesperetin can help with rheumatoid arthritis treatment repetition, this is already mentioned above because it has good properties [9]. Hesperetin helps to reduce swelling because it stops the body from making and releasing certain chemicals that cause swelling. Hesperidin can help reduce swelling and pain in the joints for people with rheumatoid arthritis [9]. Hesperidin helps the immune system by changing some immune cells' work, like macrophages and T-cells [10]. Hesperidin helps to reduce swelling, fight against harmful things in the body, boost the immune system, reduce pain, and treat arthritis. More research and testing are required to find out if this treatment works and is safe for rheumatoid arthritis [11]. repetition, this is already mentioned above

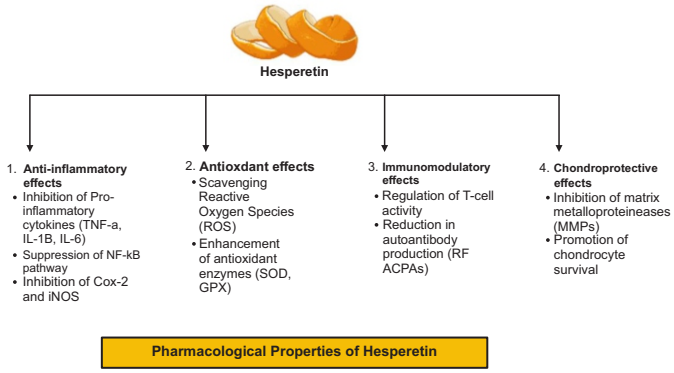

Figure 1: Show the Pharmacological Properties of Hesperetin

Mention Bioavailability and Absorption of Hesperetin

Hesperetin doesn't mix well with water, so it might not be absorbed well in the stomach. Making hesperetin easier to dissolve by using special techniques or mixing it with substances that help it dissolve better may help the body absorb and use it more easily [12]. After being taken into the body, hesperetin gets broken down a lot in the liver, mostly through processes called glucuronidation and sulfation. These ways the body processes things can affect well a substance can be used by the body [13]. Hesperetin moves from the intestines into the body with the help of different transporters, like P-glycoprotein. When these transporters are affected, it can change how hesperetin is taken in and spread throughout the body [14]. Enchanting hesperetin with food or certain nutrients could change body uses. For instance, some fats in food or parts of citrus fruits can help the body absorb hesperetin [15]. Address this properly Overall, hespertin shows promising pharmacological properties for the treatment of rheumatoid arthritis and other conditions, but optimization of its bioavailability and absorption is necessary to maximize its therapeutic efficacy. Further research is needed to elucidate the factors that influence hespertin absorption and metabolism and to develop strategies to increase the bioavailability of hespertin for clinical applications [16].

Table 1: The Potential of Hesperetin in the Treatment of Rheumatoid Arthritis Based on its Medicinal Properties and Clinical Evidence

Sr. No	Formulation	Pharmacological Activity	Doses	References
1	Pure Hesperetin	Improved stability, Sustained release, Enhanced therapeutic efficacy	Preclinical: 20-100 mg/kg (Animal Models)	[17]

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2	Hesperetin Nanoparticles	Increased absorption, Enhanced antioxidant activity, Better clinical outcomes	Preclinical: 10-50 mg/kg (Animal Models)	[18]
3	Hesperetin-Loaded Liposomes	Synergistic effects with other anti-inflammatory agents , Reduced doses of conventional drugs	Preclinical: 5-25 mg/kg (Animal Models)	[19]
4	Hesperetin Phytosomes	Enhanced solubility, Improved bioavailability, Rapid absorption	Preclinical: 10-30 mg/kg (Animal Models)	[13]
5	Hesperetin in Combination Therapy	Controlled release, Enhanced stability, Improved bioavailability	Varies; typically 50-100 mg/day of hesperetin with standard drugs	[20]
6	Hesperetin Microemulsions	Improved solubility, Enhanced dissolution rate, Increased bioavailability	Preclinical: 15-60 mg/kg (Animal Models)	[21]
7	Hesperetin Solid Lipid Nanoparticles	Targeted delivery, Enhanced solubility, Prolonged circulation time	Preclinical: 10-40 mg/kg (Animal Models)	[13]
8	Hesperetin Nanosuspensions	Improved solubility, Enhanced stability, Increased bioavailability	Preclinical: 20-80 mg/kg (animal models)	[13]
9	Hesperetin Polymer Micelles	Controlled release, Enhanced bioavailability, Targeted delivery	Preclinical: 5-20 mg/kg (Animal Models)	[22]
10	Hesperetin Cyclodextrin Complexes	Convenient administration, Standardized dosing, Improved patient compliance	Preclinical: 10-50 mg/kg (Animal Models)	[23]
11	Hesperetin-Encapsulated Hydrogels	Enhanced bioavailability, Easy to administer, Rapid absorption	Preclinical: 5-25 mg/kg (Animal Models)	[24]
12	Hesperetin Tablets/ Capsules	Localized anti-inflammatory effects, Reduced systemic side effects	Suggested human dose: 50-500 mg/day	[25]
13	Hesperetin Oral Suspensions	Direct delivery to lungs, Rapid absorption, Potential for treating inflammatory lung conditions	Preclinical: 1-5 mg/kg (Animal Models)	[26]
14	Hesperetin Topical Formulations	Localized anti-inflammatory effects, Reduced systemic side effects	Preclinical: 10-40 mg/kg (Animal Models)	[27]
15	Hesperetin Inhalable Formulations	Direct delivery to lungs, Rapid absorption, Potential for treating inflammatory lung conditions	Suggested human dose: 100-400 mg/day	[28]
16	Hesperetin Platelets Membrane-Coated PLGA Nanoparticles	Prolonged circulation , Targeted delivery, Enhanced bioavailability, Reduced immunogenicity	Preclinical: 0.1-1% concentration	[29-32]

Mechanisms of Action of Hesperetin in RA

Explanation of Hesperetin Reduces Inflammation

Hespertin helps reduce inflammation in rheumatoid arthritis by changing the way certain proteins work, stopping the body's response to inflammation, and controlling the immune system [33].

Modulation of Cytokines

Heparin can stop the body from making and releasing certain substances that cause inflammation. These cytokines are important in starting and continuing swelling and joint damage in rheumatoid arthritis. They do this by causing inflammation in the joint lining, breaking down cartilage, and eroding bone. Heparin can help reduce the symptoms of rheumatoid arthritis by stopping the body from making certain cytokines that cause inflammation [34, 35].

Inhibition of NF-κB Pathway

Heparin stops the body from making and releasing certain substances that cause inflammation. These cytokines are important in starting and continuing the inflammation process in rheumatoid arthritis by making the joints swollen, damaging the cartilage, and wearing away the bone. Heparin can reduce symptoms of rheumatoid arthritis by stopping the body from making certain proteins that cause inflammation [36].

Suppression of MAPK Pathway

Heperetin also controls cells respond to inflammation by regulating the MAPK signaling pathway. MAPKs, such as ERK, JNK, and p38, are turned on in RA synoviocytes. This makes them produce substances that cause inflammation

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and break down the tissue. Heperetin stops a process that causes inflammation in RA [37].

Antioxidant Activity

Hesperetin has antioxidants that help reduce inflammation by getting rid of harmful molecules and lowering stress in inflamed tissues. Oxidative stress is important in causing rheumatoid arthritis, inflammation, and tissue damage. Hesperetin might help reduce inflammation and slow down the progression of RA by protecting cells from damage caused by ROS [9].

Regulation of Immune Responses

Heperetin helps control immune responses in rheumatoid arthritis by changing the activity of certain immune cells. Heparin stops immune cells from getting activated and turning into different kinds of cells. It also stops activated immune cells from releasing chemicals that cause inflammation, which reduces problems with the immune system and swelling in rheumatoid arthritis [38].

Anti-Inflammatory and Antioxidant Effects

Hesperetin helps reduce inflammation and damage to cartilage and bone in people with rheumatoid arthritis because of its anti-inflammatory and antioxidant benefits. Long-term swelling and the body's struggle against harmful substances are the main reasons for the breakdown of cartilage and bones in joints affected by rheumatoid arthritis [39]. Hesperetin can help reduce swelling and stress in the joint, which can make it less damaged. It also supports keeping the cartilage and bone strong. This can help stop joints from getting worse and make bones less damaged in rheumatoid arthritis [9][40]. In simple words, we need more research to understand hesperetin affects cartilage damage and bone erosion in rheumatoid arthritis. Hesperetin may help by stopping enzymes that break down cartilage, slowing down bone damage, and reducing inflammation. We need more research to understand how different effects are connected. Research has found that hesperetin can help protect joints and keep them working well for people with rheumatoid arthritis [41-43]

Mention Other Mechanisms Potentially Beneficial for RA

Hesperetin can help with rheumatoid arthritis by reducing swelling and working as an antioxidant [44]. Hesperetin helps stop cells from dying naturally in different types of cells. In RA, when cells die in a disorganized way, it leads to more immune cells that continue to cause swelling and harm to the body's tissues. Hesperetin can help the body by causing inflammatory cells to die and stopping healthy cells from dying. This can help decrease swelling and harm in joints affected by rheumatoid arthritis [45]. Synovial fibroblasts are important cells that play a part in rheumatoid arthritis. This condition can cause arthritis, break down cartilage, and wear away bones. Hesperetin can make synovial fibroblasts work differently, stopping them from growing, moving, and making chemicals that cause inflammation. Hesperetin may help reduce damage in arthritis and rheumatoid arthritis by targeting certain cells in the joints [46, 47]. People with rheumatoid arthritis often feel pain and have problems with their nerves because of swelling and damage in their joints. Hesperetin helps protect the brain by reducing damage caused by harmful substances, swelling, and brain cell death. Hesperetin could help RA patients feel better by reducing pain and protecting their nerve function [48].

Clinical Studies on Hesperetin for RA

Clinical Trials on Hesperetin for RA Treatment

Hesperetin has shown promise in early studies for reducing inflammation and acting as an antioxidant. However, there aren't many studies to see how well it works for treating rheumatoid arthritis in people. Most of the information we have is from studies done in test tubes, on animals, and a few small studies on people [49].

Preclinical and in Vitro Studies

Animal Models

Studies in animal models of arthritis have shown that hespertin reduces joint inflammation, lowers cytokine levels, and protects cartilage from deterioration. For example, in a collagen-induced arthritis (CIA) model, administration of hespertin significantly improved clinical arthritis scores and reduced histopathological signs of inflammation and joint damage [50].

In Vitro Studies

Experiments using human cell lines and primary cells derived from RA patients have shown that hesperetin inhibits synovial fibroblast proliferation, reduces the production of pro-inflammatory cytokines, and reduces markers of oxidative stress [51]. There are many clinical trials on hesperetin for RA, but there are studies on hesperetin affects inflammation and oxidative stress in humans [49].

Efficacy and Safety Outcomes

Efficacy

Reduction of inflammation and anti-inflammatory effects observed in preclinical models and small human studies suggest that hesperetin may be effective in reducing joint and systemic inflammation in patients with rheumatoid arthritis. Joint protection: Animal studies have shown that hesperetin can protect against cartilage damage and bone erosion, which are major concerns in rheumatoid arthritis. This protective effect may improve joint function and slow disease progression in humans [13].

Safety

General Safety Hespertin is considered safe due to its presence in common food sources such as citrus fruits. Clinical trials of hespertin supplements have shown that they are well tolerated and no serious side effects have been reported [20][52]. Safety and efficacy results in clinical practice highlight the importance of determining

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optimal doses. Higher doses may be required to achieve a therapeutic effect, but this must be balanced against the risk of potential side effects [13][53]. Variability in hesperetin's bioavailability among individuals can affect its clinical efficacy. Studies addressing bioavailability enhancements are necessary to ensure consistent therapeutic effects. while preclinical data and limited human studies suggest that hesperetin has potential as a treatment for RA, more rigorous and large-scale clinical trials are needed to establish its efficacy and safety definitively[20].

Efficacy Comparison of Hesperetin Conventional RA Medications

Nonsteroidal Anti-Inflammatory Drugs

Efficacy is Effective in reducing pain and inflammation but does not alter disease progression.

Side Effects of the Gastrointestinal issues (ulcers, bleeding), cardiovascular risks, and kidney damage[41]. Efficacy, Potent anti-inflammatory effects, and rapid relief of symptoms. Side Effects include weight gain, osteoporosis, diabetes, and increased infection risk with long-term use[54]. Efficacy, Slow disease progression and improve long-term outcomes. Side Effects include liver toxicity, bone marrow suppression, lung issues, and gastrointestinal disturbances [55]. Efficacy is highly effective in reducing inflammation and halting disease progression by targeting specific components of the immune system. Side Effects an increased risk of infections, the potential for allergic reactions, and high cost [56, 57]. Efficacy, preclinical studies, and limited human trials suggest that hesperidin may reduce inflammation, protect cartilage, and reduce oxidative stress. However, more robust clinical data are needed to confirm its efficacy in RA patients. Potential benefits, similar anti-inflammatory effects seen in preclinical models and additional antioxidant properties that help reduce oxidative stress[58].

Side Effect Profile Comparison and Conventional RA Medications

NSAIDs, Long-term use is associated with gastrointestinal bleeding, ulcers, kidney damage, and cardiovascular issues. Corticosteroids, Chronic use leads to serious side effects such as osteoporosis, diabetes, weight gain, and increased susceptibility to infections. DMARDs, Side effects include liver toxicity, suppression of the immune system, lung problems, and gastrointestinal discomfort. Biologics, while effective, these drugs can increase the risk of serious infections, and allergic reactions, and are often expensive[46].

Safety Profile

Hesperetin is generally considered safe, as it is found in common dietary sources such as citrus fruits. Studies on hesperetin supplements have not reported significant adverse effects, suggesting good tolerability. Side Effects, Hesperetin's side effect profile appears to be mild, with minimal reports of adverse effects in clinical trials. However, comprehensive safety data specifically in RA patients are still needed[13].

Potential Advantages of Hesperetin and Reduced Side Effects

Hespertin has a favorable safety profile compared to traditional rheumatoid arthritis drugs, and fewer and mild side effects have been observed in previous studies [59]. Because hespertin is a natural compound found in citrus fruits, it may be more acceptable to patients seeking natural or dietary treatments[48][60].

Future Directions

Need for Further Research on Hesperetin for RA Treatment

Despite promising preclinical findings and limited clinical evidence, much research is needed to fully understand the potential of hesperetin in the treatment of rheumatoid arthritis(RA)[44]. Detailed clinical trials with larger sample sizes and diverse populations are needed to confirm the efficacy and safety of hesperetin in patients with RA [61]. Longitudinal studies are needed to evaluate the long-term safety and possible side effects of hesperetin, especially in the treatment of chronic diseases such as rheumatoid arthritis[62].

Mechanistic Studies and Molecular Mechanisms

We need to study the way HES works in our body to understand how it helps with inflammation, oxidative stress, and immune system function. This will help us fully understand how HES can be used as a treatment [63]. Finding biomarkers that change with hesperetin treatment can help track the treatment and customize treatment plans. Hesperetin looks like it could be a good extra or different way to treat rheumatoid arthritis. It might be safer, come from nature, and have multiple health benefits [64]. New evidence shows that it might help with swelling, keep joints healthy, and change how the body's immune system works. But we need to do bigger and better studies to be sure it helps with arthritis and to figure out the best way to use it. More studies are needed, but hesperetin could be helpful for people with rheumatoid arthritis. It could make their lives better and be a safer, more natural option than regular medicines[56][65].

Adverse Effects

Mild gastrointestinal symptoms may occur with high doses. There is limited data on the adverse effects at therapeutic doses required for RA treatment [66]. Long-term safety studies are necessary to rule out potential cumulative or delayed side effects, particularly in chronic conditions like RA [67]. Rheumatoid arthritis is a heterogeneous disease with variations in clinical presentation, response to treatment, and progression. Personalized medicine

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approaches are crucial for optimizing treatment [56][68]. Genetic, metabolic, and lifestyle factors can affect how a person responds to hespertin. A personalized approach can help adjust our dosage and treatment plan to maximize effectiveness and minimize side effects [69]. Personalized medicine helps find the best ways to use hesperetin with other treatments, to make treatment better and individualized for each person. Hesperetin seems like it could be a good treatment for rheumatoid arthritis because it helps reduce inflammation and has antioxidants. However, we need more research to make sure it is safe for long-term use with other medications [16].

CONCLUSIONS

Hesperidin, a flavonoid found in citrus, shows promising potential in the treatment of rheumatoid arthritis due to its anti-inflammatory and antioxidant properties. Although current evidence highlights its effectiveness and favorable safety profile, more research is needed to confirm its benefits and understand potential drug interactions. Personalized medicine approaches allow us to tailor treatments to the needs of specific patients and optimize their use. With larger clinical trials and safety studies, hesperidin may become a valuable complementary or alternative therapy, a natural and effective option to treat rheumatoid arthritis and improve patients' quality of life.

Authors Contribution

Conceptualization: SA
Methodology: TI, MRS
Formal analysis: TI, QA, MRS, A
Writing-review and editing: SA, IB, MAN, SH, US

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

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