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Computational Investigation on Phytochemicals of *Coccinia grandis* as Potential Multi-Target Agents for Psoriatic Arthritis: Recent Developments and Future Prospects

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Abstract

Psoriatic arthritis (PsA) is an autoimmune inflammatory condition marked by synovitis, joint destruction, enthesitis, and psoriasis of the skin. While there are several biological agents and disease modifying antirheumatic drugs (DMARDs) available for treatment, prolonged treatment may lead to side effects, immunosuppression, and increased costs. Therefore, phytochemicals with multitarget properties have gained importance in the field of drug discovery. *Coccinia grandis (L.)* Voigt, also known as ivy gourd, is a medicinal plant extensively used in Ayurvedic and traditional medicine for treating inflammation, diabetes, infections, and oxidative stress diseases. Recent pharmacological and phytochemical studies have shown the presence of flavonoids, terpenoids, alkaloids, phenolics, cucurbitacins, and sterols having anti-inflammatory and antioxidant properties. The use of computational tools such as molecular docking, molecular dynamics simulation, network pharmacology, ADMET studies, and systems biology have helped in identifying bioactive phytochemicals targeting inflammatory molecules like TNF-α, IL-17, IL-23, NF-κB, COX-2, JAK/STAT, and MAPK involved in the pathology of PsA. The present article provides an overview of the phytochemistry, pharmacological activities, and computational studies on phytoconstituents of *Coccinia grandis* against psoriatic arthritis.

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Keywords: Autoimmune disorders; Phytopharmaceuticals; Ethnopharmacology; Drug discovery; TNF-α inhibitors; IL-17 pathway; Oxidative stress.

Introduction

Psoriatic Arthritis (PsA) is an autoimmune and inflammatory disease that is progressive in nature, characterized by the presence of psoriasis along with musculoskeletal involvement, including peripheral arthritis, enthesitis, dactylitis, and axial joint inflammation. PsA is a complicated combination of genetics, environment, and immune system dysfunction, which results in the development of persistent inflammation and joint destruction [1]. Worldwide, psoriatic arthritis is found in about 0.1-1% of the general population and affects nearly 20-30% of patients with psoriasis. PsA significantly impairs quality of life by causing chronic pain, joint deformities, reduced mobility, psychological stress, and cardiovascular comorbidities [2]. In recent decades, the development in immunology and molecular biology has provided new insights into the pathogenesis of psoriatic arthritis and identified various inflammatory molecules, including TNF-α, IL-17, IL-23, NF-κB, MAPK, and JAK/STAT pathway, as the main factors involved in disease progression [3]. The currently available treatment options for psoriatic arthritis include NSAIDs, corticosteroids, DMARDs, and biologic drugs targeting inflammatory cytokines. While current treatments can effectively manage symptoms and decrease disease progression, the prolonged use of such medications is commonly associated with numerous side effects, including liver toxicity, kidney toxicity, gastrointestinal side effects, opportunistic infections, cardiovascular side effects, and immunosuppression [4]. Moreover, biologics and targeted synthetic drugs are usually costly and not accessible to vast masses in developing nations. Another limitation related to conventional drug therapies is resistance against treatment and recurrence of disease upon stopping the medication. Such drawbacks have motivated scientists to find safer, affordable, and multitarget therapeutics using natural resources [5].

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 5, 2026

Many medicinal plants have been found to produce a range of bioactive compounds. Among all these, *Coccinia grandis (L.)* Voigt, which is commonly referred to as ivy gourd, scarlet gourd, kundru, or tindora, has gained much attention due to its numerous biological properties. This plant belongs to the Cucurbitaceae family and is native to tropical and subtropical regions of Asia, Africa, and Australia [6]. Ethnopharmacological research reveals that *Coccinia grandis* shows considerable anti-inflammatory, antioxidant, antimicrobial, antidiabetic, hepatoprotective, and immunomodulatory effects, which can be attributed to its rich phytochemistry. Chemical composition of this plant includes various compounds such as flavonoids, alkaloids, triterpenoids, cucurbitacins, glycosides, sterols, tannins, phenolic acids, and saponins. Bioactive substances like quercetin, rutin, kaempferol, β-sitosterol, cucurbitacin B, and gallic acid have shown impressive antioxidant and anti-inflammatory activities [7]. These molecules are known to have the ability to scavenge reactive oxygen species, inhibit inflammatory cytokines, block cyclooxygenase enzymes, and modulate immune responses, which implies that they could play a role in the treatment of autoimmune inflammatory conditions like psoriatic arthritis.

The emergence of computational biology and bioinformatics in pharmaceutical studies has significantly transformed the approach used in the discovery of drugs based on natural products. Molecular docking, molecular dynamics simulations, QSAR modeling, pharmacophore modeling, network pharmacology, and ADMET predictions are some of the computational methods used to identify and optimize active bio-molecules [8]. Such computational methods allow the quick screening of phytochemicals against a target molecule, ligand-protein interaction prediction, determination of binding affinity, and pharmacokinetics and toxicity assessments without the need for experimental methods. Compared to traditional experimental studies, the use of computational approaches is less expensive, less time-consuming, and allows for screening of multiple compounds simultaneously

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 5, 2026

[9]. With regard to psoriatic arthritis, the in-silico analysis can offer important information about the interaction between phytochemicals and inflammatory mediators including TNF-α, IL-17, IL-23, COX-2, NF-κB, and JAK/STAT proteins. Thus, computational analysis has become an important method in studying the multitarget mechanism of action of phytochemicals [10].

Although there is an increased interest in natural product-based therapies, very few comprehensive reviews are available that discuss the computational analysis of the phytochemicals from *Coccinia grandis* used to treat psoriatic arthritis. In this regard, the objective of the current review is to present a detailed review on the phytochemical profile, pharmacological properties, and in-silico analysis of *Coccinia grandis* in treating psoriatic arthritis [11]. In this review, the pathology of PsA, the molecular targets associated with the progression of PsA, anti-inflammatory mechanism of action of phytochemicals, molecular docking analysis, network pharmacology, and ADMET properties of phytochemicals will be discussed. Also, the review will present current problems, gaps in research, and future directions in the development of phytopharmaceuticals using computational tools [12].

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 5, 2026

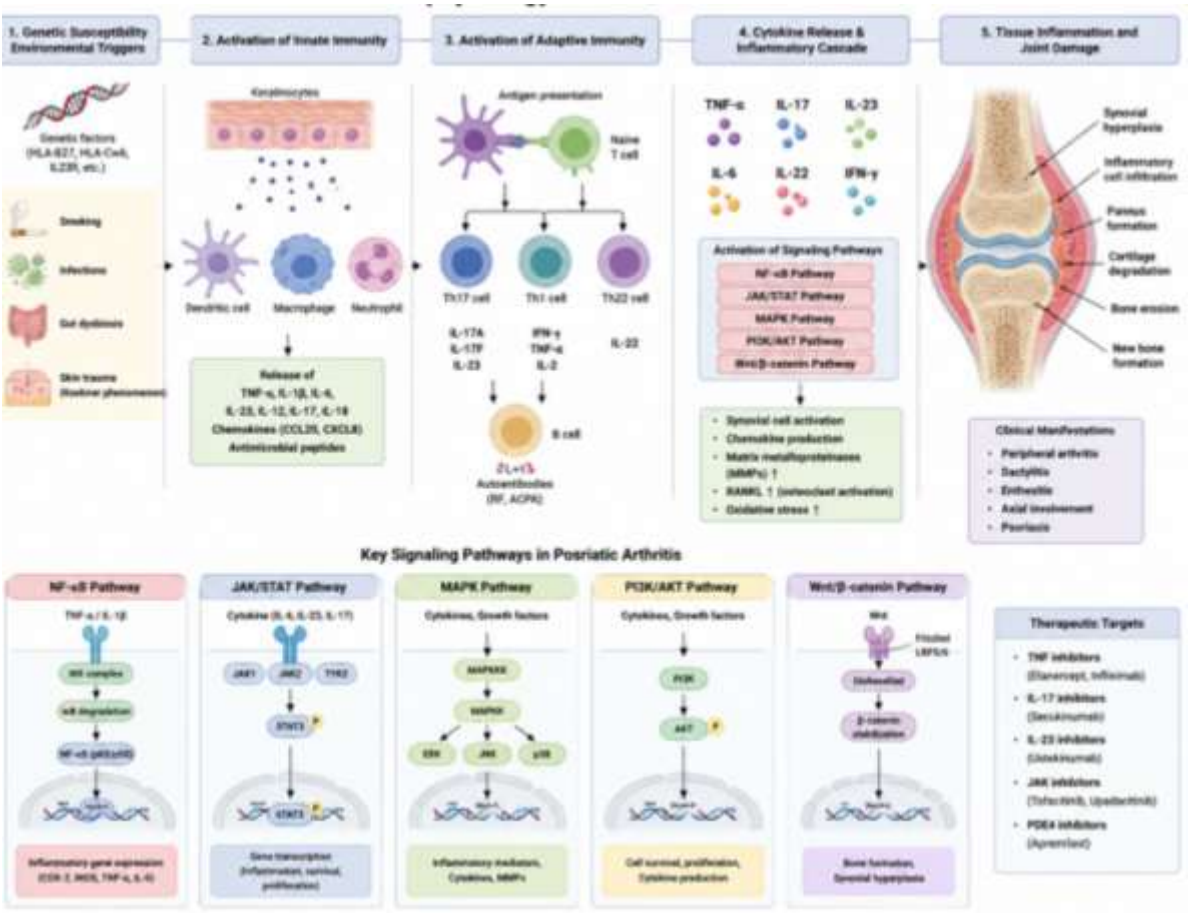

Figure 1. Pathophysiology and Major Signaling Pathways Associated with Psoriatic Arthritis

Diagrammatic representation showing the intricate pathophysiological process of psoriatic arthritis (PsA) along with the important inflammatory signaling pathways associated with the development of this condition. The diagram shows the sequential steps starting from genetic predisposition to external factors, leading to initiation of innate and adaptive immunity. Activation of various immune cells including dendritic cells, macrophages, neutrophils, and T-helper cells (Th1, Th17, and Th22) causes production of various pro-inflammatory cytokines like TNF-α, IL-17, IL-23, IL-6, and IFN-γ, which, in turn, activate the NF-κB, JAK/STAT, MAPK, PI3K/AKT, and Wnt/β-catenin pathways. Continuous activation of these pathways leads to synovitis, oxidative stress, cartilage destruction, pannus formation, bone erosion, and abnormal bone remodeling. The diagram also shows the major sites of therapeutic intervention [13].

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 5, 2026

2. Computation-based Study of *Coccinia grandis* Phytochemicals

Molecular docking and network pharmacology are computational techniques that can be used to identify phytochemicals with possible therapeutic effect against PsA [14]. This technique aids in determining how bioactive compounds interact with inflammation-related targets such as TNF-α, NF-κB, COX-2, IL-17, and JAK/STAT signaling molecules. *Coccinia grandis* phytochemicals such as flavonoids, sterols, and cucurbitacins have been proven to exhibit promising anti-inflammatory and antioxidant effects through computational analysis [15].

2.1. Docking Studies Targeted at Inflammatory Molecules

Results of molecular docking studies reveal that there are some plant-based molecules that exhibit high binding affinities towards inflammatory molecules responsible for inducing PsA. This could be helpful in the inhibition of cytokine production, oxidative stress, and synovial inflammation [16].

One of the important flavonoids found in *Coccinia grandis* is quercetin. This molecule shows high hydrogen bonding interaction with inflammatory molecules like NF-κB and TNF-α. This molecule has anti-inflammatory and antioxidant activities due to the inhibition of NF-κB and oxidative stress [17].

The triterpenoids of *Coccinia grandis* known as cucurbitacins have been reported to exert significant inhibition of the JAK/STAT signaling pathway. This effect of the compound may involve the suppression of inflammatory cytokines and regulation of abnormal immune response linked to psoriatic arthritis. Moreover, the anti-proliferative effects of cucurbitacins may inhibit the growth of synovial cells [18].

Beta-sitosterol has been identified as an anti-inflammatory compound capable of inhibiting COX-2 and oxidative stress. It is also possible that the compound helps

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to protect the cellular membrane and tissues from inflammatory damage, which can contribute to its antiarthritic effect [19].

The flavonoids rutin and kaempferol have high binding affinities towards the protein components of IL-17 and MAPK signaling pathways. These compounds can reduce the formation of inflammatory cytokines and synovial inflammation, as well as the destruction of cartilage. Their antioxidant and immunomodulatory properties further confirm their therapeutic significance [20].

3. Drug-Likeness and ADMET Evaluation

Drug-likeness and ADMET analysis are important in identifying therapeutic targets from *Coccinia grandis*. The *in-silico* drug-likeness analysis of any compound is usually done using the Lipinski's rule of five, which involves assessing the oral bioavailability of compounds in terms of molecular weight less than 500 Da, no more than five hydrogen bond donors, no more than ten hydrogen bond acceptors, and LogP less than five [21]. Various phytochemicals from *Coccinia grandis*, such as flavonoids and sterols, have been found to satisfy the above conditions, thus showing good pharmacokinetics and oral bioavailability. Besides, in silico ADMET and toxicity predictions can be used to assess the safety of phytoconstituents through the prediction of possible adverse effects like hepatotoxicity, carcinogenicity, mutagenicity, and cardiotoxicity. Phytochemicals that demonstrate good drug-likeness properties and low toxicity are regarded as promising lead molecules for safer multitarget therapeutics against psoriatic arthritis [22].

4. Problems Associated with Translation of Research

Despite the promising results obtained by both computational and pharmacological research, there are certain problems associated with the successful translation of phytochemicals derived from *Coccinia grandis* into therapeutic agents for the treatment of psoriatic arthritis. Firstly, there is a lack of

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 5, 2026

adequate clinical trials and experimental evidence to prove the efficacy and safety of these bioactive compounds in humans [23]. The other problem related to these bioactive compounds is that they have poor bioavailability and low absorption rate along with rapid metabolism and poor pharmacokinetic properties. There could be variations in the phytochemicals based on geographical location, environmental conditions, harvesting period, and extraction process [24]. Molecular dynamics simulations and pharmacokinetic data would help in making predictions about the long-term behavior of these phytochemicals as therapeutic agents. Standardization of extraction processes, dosage determination, and isolation of active components are important tasks to develop effective phytopharmaceuticals from *Coccinia grandis*.

5. Future Perspectives

Future research on *Coccinia grandis* phytochemicals must concentrate on the application of state-of-the-art computational and experimental tools for the rapid identification of potent multitarget drugs for the treatment of psoriatic arthritis. Modern technologies like artificial intelligence-driven drug discovery, QSAR modeling using machine learning techniques, and multi-omics data integration can help improve the identification and optimization of phytochemicals with higher therapeutic efficacy [26]. Experimental studies involving cytokine inhibition assays, animal models of psoriatic arthritis, and well-conducted clinical trials will be essential in validating the results obtained using computational approaches and in assessing safety and efficacy. The use of nanotechnology methods, including nanoformulations and targeted drug delivery systems, can enhance the bioavailability, stability, and selective targeting of phytochemicals [27]. In addition, the application of systems pharmacology and multi-target pathway analysis can enable the development of personalized phytomedicine treatment approaches, which will be able to target multiple pathways responsible for psoriatic arthritis development simultaneously [28].

ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 5, 2026

Conclusion

Coccinia grandis is an effective medicinal plant with immense potential in the treatment of psoriatic arthritis owing to its high content of phytochemicals and various pharmacological properties. Based on computer-based analysis, phytochemicals like quercetin, rutin, kaempferol, cucurbitacins, and β-sitosterol demonstrate significant binding affinity towards inflammatory targets such as TNF-α, NF-κB, COX-2, IL-17, and JAK/STAT signaling pathway. They have anti-inflammatory, antioxidant, and immunomodulatory properties that may be helpful in slowing down the progress of the disease. Despite the promising results obtained from computational studies, more research needs to be conducted through experimental and clinical studies to validate their effectiveness.

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ISSN: 0975-3583,0976-2833 VOL 17, ISSUE 5, 2026

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