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Anti-Inflammatory Potential of Withaniacoagulans in the Management of Arthritis: A Review

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Abstract

Arthritis, a chronic inflammatory disorder affecting millions worldwide, encompasses a group of musculoskeletal diseases primarily characterized by joint inflammation, stiffness, and pain. Among the various subtypes, rheumatoid arthritis and osteoarthritis are the most prevalent, leading to significant morbidity and compromised quality of life. Current therapeutic options, including non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, and disease-modifying antirheumatic drugs (DMARDs), are often associated with considerable side effects and limitations in long-term efficacy. This has intensified the search for safer, natural alternatives with anti-inflammatory and immunomodulatory properties.*Withaniacoagulans* (Dunal), commonly known as Indian rennet or Paneer dodi, is a lesser-known medicinal plant from the Solanaceae family, traditionally used in various systems of medicine for its anti-inflammatory, antioxidant, and adaptogenic properties. Recent pharmacological investigations have highlighted the plant's potential in modulating key inflammatory pathways implicated in arthritis. Bioactive constituents such as withanolides, alkaloids, and flavonoids have been shown to inhibit pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), suppress the NF-κBsignalling cascade, and attenuate oxidative stress, thereby exerting protective effects against joint degeneration.This review systematically compiles and analyses existing literature on the anti-inflammatory mechanisms of *Withaniacoagulans*, with a particular focus on its therapeutic relevance in arthritis management. It explores preclinical evidence from in vitro and in vivo studies, phytochemical composition, and possible synergistic effects with other herbs. The review also discusses formulation strategies, safety profiles, and current challenges in translating these findings into clinical practice. Overall, *Withaniacoagulans* emerges as a promising candidate for the development of complementary or integrative therapies for arthritis, warranting further exploration through rigorous clinical studies.

Keywords : Arthritis, Anti-inflammation, Withanolides, Mechanism of Action

Introduction

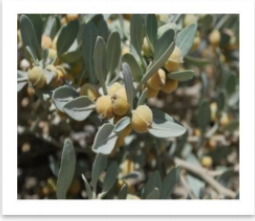
Arthritis represents a group of more than 100 inflammatory joint diseases that primarily affect the joints, connective tissues, and surrounding structures. The most common forms include rheumatoid arthritis (RA), an autoimmune disorder, and osteoarthritis (OA), a degenerative joint disease resulting from cartilage breakdown (Hunter & Bierma-Zeinstra, 2019). Globally, arthritis is one of the leading causes of disability, particularly among aging populations, with estimates suggesting that more than 350 million people are affected (Cross et al., 2014).The underlying pathophysiology of arthritis involves a complex interplay of inflammatory mediators, immune dysregulation, oxidative stress, and enzymatic degradation of joint cartilage and synovial tissues. In RA, the immune system erroneously attacks the synovial membrane, leading to chronic inflammation and joint destruction. Key inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) play a pivotal role in disease progression (McInnes &Schett, 2011). Similarly, in OA, inflammation is increasingly recognized as a contributing factor alongside mechanical stress, leading to the activation of matrix metalloproteinases (MMPs) and cartilage erosion (Bijlsma et al., 2011).

Conventional treatment options—such as NSAIDs, corticosteroids, and DMARDs—aim to alleviate symptoms and slow disease progression. However, their long-term use is associated with significant side effects, including gastrointestinal damage, cardiovascular risk, immunosuppression, and organ toxicity (Singh et al., 2016). Additionally, the high cost of biological therapies places a financial burden on healthcare systems, especially in low- and middle-income countries. This has led to growing interest in alternative and complementary therapies derived from medicinal plants, which are often perceived as safer, cost-effective, and more accessible. One such plant gaining attention is *Withaniacoagulans* (Dunal), a lesser-known member of the Solanaceae family, closely related to *Withaniasomnifera* (Ashwagandha). Traditionally used in Indian, Persian, and Middle Eastern medicine, *W. coagulans* has been employed to treat conditions such as diabetes, inflammation, liver disorders, and digestive issues (Kumar et al., 2021; Maurya et al., 2020).

Pharmacological investigations have identified a variety of bioactive compounds in *W. coagulans*, including withanolides, flavonoids, and alkaloids, that exhibit potent anti-inflammatory, antioxidant, and immunomodulatory properties (Aneja et al., 2020). Preclinical studies suggest that extracts of *W. coagulans* can downregulate pro-inflammatory cytokines, inhibit cyclooxygenase and lipoxygenase pathways, and modulate key signaling cascades such as NF-κB and MAPK—mechanisms highly relevant to the treatment of arthritis (Sharma et al., 2019).Given its traditional use and emerging scientific evidence, *Withaniacoagulans* has the potential to serve as an effective adjunct or alternative to conventional anti-arthritic therapies. This

review aims to critically examine the current state of knowledge regarding the anti-inflammatory and anti-arthritic potential of *Withaniacoagulans*, highlighting its mechanisms of action, phytochemical profile, preclinical and clinical findings, and future research directions.

Withaniacoagulans Botanical Description

Plant (fruits)	 
Feature	**Description**
Scientific Name	*Withania coagulans* (Stocks) Dunal
Family	Solanaceae
Common Names	Indian Rennet, Paneer Dodi, Vegetable Rennet, Dodi, Rishyagandha
Plant Type	Shrub or small bush
Leaves	Simple, ovate, alternate; pubescent on both surfaces
Flowers	Greenish-yellow; small; bell-shaped; axillary or terminal
Fruits	Berry, yellow-orange when mature; enclosed in a persistent calyx
Seeds	Small, kidney-shaped, light brown
Root	Thick, tuberous, fleshy, often used in medicinal preparations
Distribution	Native to India, Pakistan, Afghanistan, Iran; found in dry and sub-tropical regions
Habitat	Dry rocky slopes, scrublands, and cultivated fields
Fruit Bearing Season	October to January
Parts Used Medicinally	Whole plant (primarily berries and leaves); roots sometimes used
Traditional Systems Used	Ayurveda, Unani, Siddha, Folk medicine

Active Compounds of Withaniacoagulans

Active Compound	Class	Potential Therapeutic Effects
Withanolides	Steroidal Lactones	Anti-inflammatory, anticancer, neuroprotective, immunomodulatory
Alkaloids	Nitrogenous Organic Compounds	Analgesic, sedative, anti-anxiety, antimicrobial
Saponins	Glycosides (Triterpenoids)	Anti-inflammatory, immune system modulation, antimicrobial
Flavonoids	Polyphenolic Compounds	Antioxidant, anti-inflammatory, neuroprotective
Phenolic Acids	Aromatic Organic Acids	Antioxidant, anti-inflammatory, supports metabolic function
Coumarins	Organic Compounds	Antimicrobial, anti-inflammatory, neuroprotective
Tannins	Polyphenolic Compounds	Antioxidant, anti-inflammatory, antimicrobial

Mechanism of Action of Compounds for Anti-Inflammation Action

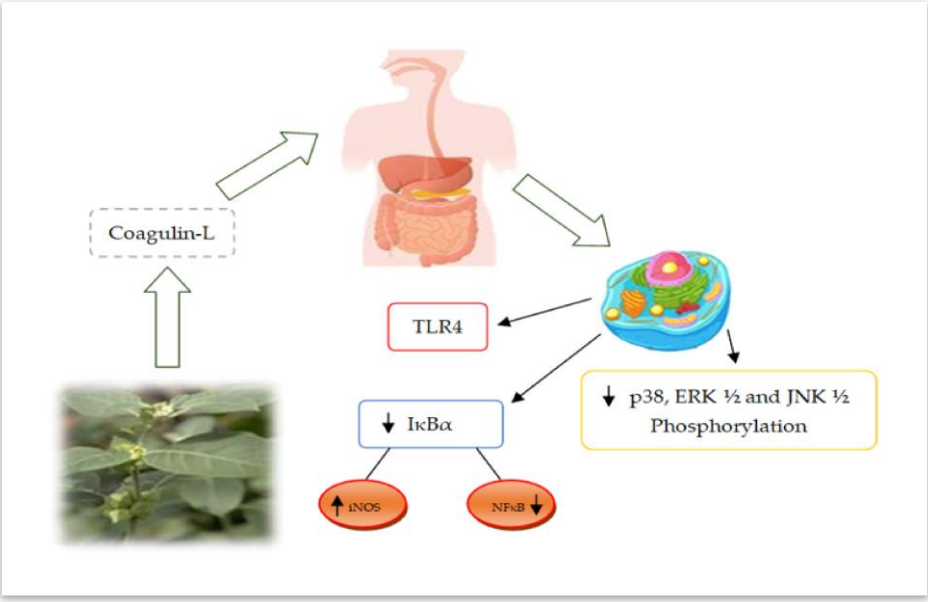


Fig:- Anti-inflammatory potential of *Withaniacoagulans*

Withaniacoagulans has emerged as a potential natural remedy for alleviating inflammation and promoting overall health.This herb's anti-inflammatory mechanism primarily involves the inhibition of pro-inflammatory cytokines, modulation of immune responses, and suppression of key enzymes involved in the inflammatory process. Additionally, *Withaniacoagulans* has been shown to act on cellular signaling pathways, such as the NF-κB pathway, which plays a central role in regulating inflammation. As a result, *Withaniacoagulans* is gaining attention not only as a traditional medicinal herb but also as a promising candidate for modern therapeutic applications in managing inflammatory diseases.

A. Inhibition of Pro-inflammatory Cytokines :

Cytokines are small signalling proteins secreted by cells, especially immune cells, that regulate immunity and inflammation. Pro-inflammatory cytokines promote inflammation and include:

- TNF-α (Tumour Necrosis Factor-alpha)
- IL-1β (Interleukin-1 beta)
- IL-6 (Interleukin-6)
- IFN-γ (Interferon-gamma)

These cytokines:

- Trigger fever
- Promote swelling, redness, and pain
- Recruit immune cells to the site of infection or injury

Pathway –

1. Downregulation of Cytokine Gene Expression

- Withaniacoagulans contains bioactive compounds (e.g., withanolides) that interfere with signaling pathways (especially NF-κB) that control cytokine gene transcription.
- By inhibiting NF-κB, it prevents the expression of TNF-α, IL-1β, and IL-6 at the gene level—meaning these cytokines are not even produced in the first place.

2. Blocking the Activation of Immune Cells

- Macrophages and T cells are major producers of pro-inflammatory cytokines.
- Extracts of *W. coagulans* suppress the activation of these immune cells, thus reducing the cytokine release.

3. Modulation of Signaling Molecules

- The plant compounds interfere with intracellular signaling molecules like:
    - MAPKs (Mitogen-Activated Protein Kinases)
    - JAK/STAT pathway
- These pathways are required for cytokine production. Inhibition of these signals leads to reduced cytokine synthesis.

B. Suppression of NF-κBPathway :

The NF-κB pathway is a key signaling pathway in the immune system. It controls the expression of many pro-inflammatory genes, including:

- Cytokines (like TNF-α, IL-6, IL-1β)
- Enzymes (like COX-2 and iNOS)
- Adhesion molecules (ICAM-1, VCAM-1)

Normally, NF-κB is inactive in the cell's cytoplasm, bound to an inhibitor called IκB.

Pathway –

1. Inhibition of IKK Activation

- Bioactive compounds in *W. coagulans* (e.g., withanolides) inhibit the activation of IKK enzymes.
- This prevents phosphorylation and degradation of IκB, so NF-κB stays inactive in the cytoplasm.

2. Blocking NF-κB Nuclear Translocation

- Even if IκB is degraded, *W. coagulans* compounds can prevent NF-κB from entering the nucleus, further stopping it from activating inflammatory genes.

3. Downregulation of NF-κB Target Genes

- Studies show that *W. coagulans* reduces the expression of NF-κB-dependent genes:
    - TNF-α
    - IL-6
    - COX-2
    - iNOS (inducible nitric oxide synthase)

C. Inhibition of COX and LOX Enzymes :

These enzymes are involved in the arachidonic acid pathway, which produces pro-inflammatory mediators:

1. COX (Cyclooxygenase) Enzymes

- There are two main forms:
    - COX-1: Constitutively active; protects stomach lining, regulates blood flow.
    - COX-2: Inducible; highly expressed during inflammation.
- COX enzymes convert arachidonic acid into prostaglandins:
    - Prostaglandin E2 (PGE2) causes pain, swelling, redness, and fever.

2. LOX (Lipoxygenase) Enzymes

- Convert arachidonic acid into leukotrienes, especially:
    - Leukotriene B4 (LTB4) – promotes white blood cell recruitment, edema, and chronic inflammation.
    - LOX is heavily involved in asthma, arthritis, and allergic responses.

Pathway –

1. Direct Enzyme Inhibition

- Phytochemicals such as withanolides, alkaloids, and flavonoids in *W. coagulans* have been shown to directly bind and inhibit the active sites of:
    - COX-2 (more than COX-1, making it safer on the stomach)
    - 5-LOX (5-lipoxygenase)

This reduces the production of:

- Prostaglandins (via COX)
- Leukotrienes (via LOX)

Result: Reduced pain, swelling, inflammatory cell migration, and fever.

2. Downregulation of COX-2 and LOX Gene Expression

- *W. coagulans* also inhibits upstream inflammatory signals (like NF-κB), which reduces the gene expression of COX-2 and LOX enzymes.
- This leads to long-term suppression of inflammatory responses.

D. Antioxidant Activity :

Antioxidants are molecules that neutralize free radicals—unstable and highly reactive molecules known as reactive oxygen species (ROS) and reactive nitrogen species (RNS).

- Examples of ROS: superoxide anion (O_2^-), hydroxyl radical (•OH), hydrogen peroxide (H_2O_2)
- When present in excess, these free radicals cause oxidative stress, which:
    - Damages DNA, proteins, lipids
    - Triggers inflammatory signaling pathways
    - Contributes to chronic diseases like arthritis, diabetes, cancer, and neurodegeneration

Pathway -

1. Free Radical Scavenging

- *Withaniacoagulans* contains phytochemicals that directly neutralize free radicals by donating electrons.
- Common assays that prove this include:
    - DPPH radical scavenging
    - ABTS radical cation decolorization
    - Superoxide and hydroxyl radical scavenging assays

2. Enhancing Endogenous Antioxidant Enzymes

- *W. coagulans* boosts the body's own antioxidant defense system by increasing the activity of:
    - Superoxide dismutase (SOD)
    - Catalase (CAT)
    - Glutathione peroxidase (GPx)
    - Reduced glutathione (GSH)

This enhances the body's ability to neutralize ROS and detoxify harmful substances.

3. Inhibition of Lipid Peroxidation

- ROS attack lipids in cell membranes, leading to lipid peroxidation, which damages cells.
- Extracts of *W. coagulans* inhibit this process, preserving cell membrane integrity.
- This is often measured by reduced levels of malondialdehyde (MDA) in tissues.

4. Metal Chelation

- Transition metals like iron (Fe^{2+}) and copper (Cu^{2+}) catalyze ROS formation.
- *Withaniacoagulans* shows metal-chelating activity, reducing metal-induced oxidative stress.

Phytochemicals Responsible

The antioxidant effect is mainly due to:

- Withanolides (steroidal lactones)
- Flavonoids
- Tannins
- Phenolic acids
- Alkaloids

These compounds have strong redox properties, enabling them to absorb and neutralize free radicals.

Connection Between Antioxidant & Anti-inflammatory Activity :

Oxidative stress activates inflammatory signaling pathways like:

- NF-κB
- MAPK
- JAK/STAT

By reducing oxidative stress, *W. coagulans*:

- Prevents activation of these pathways

- Reduces the release of pro-inflammatory cytokines
- Protects tissues from inflammatory damage

This makes antioxidant activity a key part of its overall anti-inflammatory mechanism.

Mechanism of Action	Description	Effect on Arthritis
Inhibition of Pro-inflammatory Cytokines	Reduces the production of pro-inflammatory cytokines like TNF-α, IL-6, and IL-1β.	Reduces joint inflammation and pain.
Suppression of NF-κB Pathway	Inhibits activation and nuclear translocation of NF-κB, a key regulator of inflammation.	Prevents inflammatory gene expression, reducing inflammation.
Inhibition of COX and LOX Enzymes	Blocks COX-2 and LOX enzymes, reducing the production of inflammatory mediators (prostaglandins and leukotrienes).	Decreases pain, swelling, and chronic inflammation.
Antioxidant Activity	Neutralizes free radicals and enhances the body's own antioxidant defenses (SOD, CAT, GSH).	Protects joints from oxidative stress and tissue damage.

CONCLUSION

Withaniacoagulans demonstrates significant potential as a natural therapeutic agent in the management of arthritis due to its multifaceted anti-inflammatory mechanisms. The plant's rich phytochemical profilecomprising withanolides, flavonoids, alkaloids, and phenolic compoundscontributes to its ability to modulate key inflammatory pathways.This review highlights that *W. coagulans* exerts its anti-inflammatory effects primarily through the inhibition of pro-inflammatory cytokines, suppression of the NF-κBsignaling pathway, inhibition of COX and LOX enzymes, and strong antioxidant activity. These mechanisms collectively contribute to the reduction of joint inflammation, oxidative stressand tissue degeneration typically seen in arthritic conditions.Preclinical studies have consistently demonstrated the efficacy of *W. coagulans* in reducing edema, inflammatory markers and oxidative damage, making it a promising adjunct or alternative to conventional non-steroidal anti-inflammatory drugs (NSAIDs), which often carry long-term side effects.In conclusion, *Withaniacoagulans* represents a promising candidate for plant-based, multi-targeted therapy in the long-term management of arthritis and other chronic inflammatory disorders.

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