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GOLD NANOPARTICLES AS A CARRIER FOR METHOTREXATE IN RHEUMATOID ARTHRITIS TREATMENT: A REVIEW

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ABSTRACT
Rheumatoid arthritis (RA) is a chronic, systemic autoimmune and inflammatory disorder characterized by persistent synovitis, leading to the progressive destruction of articular cartilage and bone. While Methotrexate (MTX) remains the gold standard first line Disease Modifying Anti Rheumatic Drug (DMARD), its clinical utility is significantly limited by its narrow therapeutic index, poor pharmacokinetic profile, and severe systemic adverse effects, including hepatotoxicity and gastrointestinal distress. This study explores the potential of nanotechnology, specifically Gold Nanoparticles (GNPs), to enhance the targeted delivery of MTX. In this research, MTX coupled GNPs were synthesized and characterized to improve drug penetrability and bioavailability. The formulation was evaluated via both Intra-articular (direct joint injection) and Transdermal (nano gel) routes. In-vivo results demonstrate that MTX-GNPs significantly suppressed inflammatory markers including TNF-α, Anti-Cyclic Citrullinated Peptide (ACCP), and Cartilage Oligomeric Matrix Protein (COMP) much more effectively than free MTX. The study concludes that nano-formulations not only enhance therapeutic efficacy but also allow for dose reduction, thereby minimizing systemic toxicity and improving patient compliance in RA management.

KEYWORDS: Rheumatoid Arthritis (RA), Methotrexate (MTX), Gold Nanoparticles (GNPs), Targeted Drug Delivery, Nano-gel, Synovial Inflammation Pro Inflammatory Cytokines (TNF-α), Bioavailability, Bone Erosion prevention.

1. INTRODUCTION

Rheumatoid arthritis (RA) is defined as a chronic, systemic autoimmune and inflammatory disorder characterized by persistent high-grade inflammation. It primarily affects the joints, causing significant synovitis that leads to articular cartilage erosion. The disease is clinically evidenced by severe pain, morning stiffness, and markedly restricted physical mobility. Beyond joint damage, RA patients are at a significantly higher risk for developing complications such as osteoporosis, osteopenia, and cardiovascular diseases. Furthermore, serious extra-articular manifestations, such as interstitial lung disease (RA-ILD), contribute to increased mortality and morbidity among these patients.

Methotrexate (MTX) is currently the gold standard and first-line treatment among disease-modifying anti-rheumatic drugs (DMARDs) for RA. Despite its efficacy, traditional administration of MTX is hampered by a narrow safety margin and a poor pharmacokinetic profile. Common side effects include mucosal ulceration, gastric issues, bone marrow suppression, and hepatic fibrosis. Moreover, marketed topical formulations of MTX suffer from poor skin penetration due to the drug's hydrophilic nature. While intra-articular (IA) injections offer localized delivery, the drug often diffuses rapidly from the joint cavity into the bloodstream, necessitating frequent and painful injections.

This study aims to overcome the existing drawbacks of MTX by utilizing nanomedicine, specifically gold nanoparticles (GNPs), as an innovative drug delivery system. The primary objective was to fabricate and characterize MTX coupled GNPs to enhance the drug's penetrability, bioavailability, and therapeutic effectiveness while minimizing systemic toxicity. This

research explores whether intra-articular and transdermal (gel based) MTX-GNPs formulations provide superior anti-arthritic activity compared to free MTX. Furthermore, the study investigates the impact of this nano-formulation on specific inflammatory markers such as ACCP and COMP to provide a comprehensive evaluation of its protective effects on cartilage and joint health.[1]

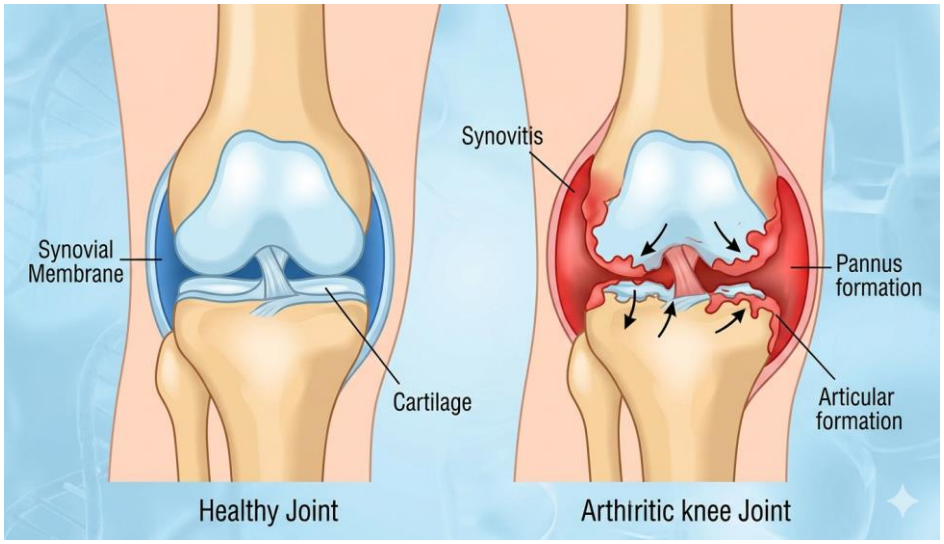

Figure 1: Disease State of Rheumatoid Arthritis.

2. ETIOLOGY

The exact etiology of rheumatoid arthritis remains unclear. It is believed to arise from an altered immune response in genetically predisposed individuals, possibly triggered by exposure to infectious agents. Potential contributors include microorganisms such as Mycoplasma, cytomegalovirus, Epstein–Barr virus, rubella virus, and parvovirus. However, the precise mechanism by which an infectious agent initiates and propagates chronic inflammatory arthritis has not yet been fully established.

The relevant factors influencing rheumatoid arthritis
a. Genetic and environmental factors
b. Smoking
c. Human microbiome.

a. Genetic and environmental factors

Genetic studies indicate that approximately 30–60% of the susceptibility to rheumatoid arthritis is influenced by hereditary factors. Among these, the most prominent genetic determinant is the "shared epitope," a specific sequence found in the DRB1 allele. The presence of this shared epitope has been associated with nearly a threefold higher risk of developing rheumatoid arthritis.

b. Smoking

Smoking is a major modifiable risk factor contributing to the onset of several chronic disorders, including rheumatoid arthritis. Evidence from cohort studies suggests that individuals who are ACPA-positive and consume high amounts of coffee may have an elevated risk of developing the disease, with a relative risk of about 2.06 in those drinking more than four cups per day. Occupational exposure also plays a role; for instance, studies from Sweden indicate that men exposed to mineral oils at the workplace have a higher likelihood of developing rheumatoid arthritis, with an observed increase of approximately 57%. Additionally, ACPA-positive individuals may be more prone to the disease when exposed to silica in occupational settings.

Dietary and lifestyle factors further influence risk, including low intake of vitamin D and antioxidants, along with excessive consumption of sugar, sodium, red meat, protein, and iron, all of which have been associated with a greater incidence of rheumatoid arthritis.

c. Human microbiome

A shift from a balanced, symbiotic microbiome to a dysbiosis state is considered a contributing factor in the development of rheumatoid arthritis. This imbalance is marked by the overgrowth of certain microbial populations along with a reduction in beneficial organisms. Such alterations in the microbial environment can disrupt immune homeostasis, leading to changes in both innate and adaptive immune responses.[14]

3. RISK FACTORS ASSOCIATED WITH RHEUMATOID ARTHRITIS

• Environmental influences such as hormonal exposure, frequent intake of decaffeinated coffee (more than three times daily), and tobacco use—including smoking—are associated with an increased risk of rheumatoid arthritis.

Hormonal exposure: In females, oestrogens generally exhibit pro-inflammatory effects, whereas androgens tend to have anti-inflammatory properties. The action of oestrogen varies across different immune cells, either stimulating or suppressing their activity depending on factors such as serum concentration, reproductive stage, ovarian aging, receptor expression, and intracellular

metabolism. Conditions such as hormone replacement therapy (HRT), use of oral contraceptives (OCs), polycystic ovary syndrome, and the post-partum phase are linked to altered hormonal influence on disease risk.

Coffee consumption: High coffee intake has been associated with increased production of rheumatoid factor, thereby contributing to disease development. This association may be influenced by variables such as age, serum LDL cholesterol levels, and smoking habits. The likelihood of rheumatoid arthritis appears to rise with the number of cups consumed, and the combined effect of smoking and coffee intake further elevates the risk.

Tobacco use: Smoking, particularly due to nicotine exposure, enhances oxidative stress within the body, which may initiate inflammatory pathways leading to rheumatoid arthritis. It also promotes the upregulation of matrix metalloproteinase-12 (MMP-12), produced by macrophages and dendritic cells. Elevated levels of MMP-12 contribute to pannus formation, synovial thickening, macrophage infiltration, and progressive cartilage destruction in advanced stages of the disease.

• Genetic determinants include female gender, a positive family history, increasing age, and specific HLA genotypes, all of which contribute to susceptibility.

• Certain protective factors may lower the risk of rheumatoid arthritis, including higher intake of vitamin D, regular tea consumption, use of oral contraceptives, and breastfeeding.[14]

4. SIGNS AND SYMPTOMS

Rheumatoid arthritis affects nearly 1% of the global population, although its prevalence varies across different regions and ethnic groups. Higher incidence rates have been reported among Native American populations, such as the Chippewa Indians (around 6%), while comparatively lower rates are observed in Japanese, Chinese, and Saharan African populations.

The disease primarily involves synovial joints, commonly affecting the wrists, fingers, feet, elbows, ankles, and knees, and may also extend to the shoulders, hips, and cervical spine. Typical clinical features include pain during movement, joint swelling, warmth, and morning stiffness lasting longer than one hour. A characteristic deformity known as spindle-shaped fingers may also develop. For diagnosis, these symptoms generally persist for more than six weeks.

Rheumatoid arthritis is frequently associated with the formation of rheumatoid nodules, which are extra-articular manifestations. These nodules consist of a central necrotic core surrounded by inflammatory cells and a palisading layer of connective tissue, usually located in the subcutaneous tissue over pressure areas such as the fingers and elbows. They may also appear in other regions including the scalp, back, feet, hands, buttocks, knees, as well as internal sites like heart valves, pericardium, lungs, and spleen.

Vascular complications may arise due to peripheral blood vessel thrombosis, leading to conditions such as myocardial infarction, stroke, Raynaud's phenomenon, and, in rare cases, skin ulcers. Systemic manifestations include fatigue, weight loss, depression, lymphadenopathy, splenomegaly, muscle weakness, pallor (white nails), tachycardia, and fever of unknown origin.

Ocular involvement may also occur, presenting as scleritis. Anterior scleritis is typically painful and may show a bluish discoloration, while posterior scleritis can be associated with more severe complications such as choroidal effusion and vision impairment, sometimes linked with underlying conditions like hyperthyroidism.[14]

5. CLINICAL COMPLICATIONS

1. Depression: Around 40% of patients receiving corticosteroid therapy may experience depressive symptoms. This condition is influenced by multiple factors, including socioeconomic conditions (income, education, occupation, race, and living environment), patient-related aspects (age, gender, ethnicity, comorbidities, and level of social support), as well as disease-specific factors such as severity, pain intensity, physical disability, and reduced functional capacity.
2. Infections: Individuals with rheumatoid arthritis are at an increased risk of infections, which may result from the disease itself or from the use of immunosuppressive therapies. Treatments such as biologics, corticosteroids, and DMARDs can further predispose patients to serious infections.
3. Malignancies: The likelihood of certain cancers is elevated in rheumatoid arthritis patients. Notably, the risk of lymphoma is approximately doubled. Lung cancer risk is also higher, particularly in individuals with a history of smoking or interstitial lung disease. Additionally, prolonged use of immunosuppressive agents may increase the incidence of skin cancers.
4. Cardiovascular diseases: Rheumatoid arthritis is associated with a higher risk of cardiovascular complications, including heart failure, ischemic heart disease, myocardial infarction, and the need for coronary revascularization procedures. [14]

6. DIAGNOSIS

Typical clinical examination findings include joint swelling, a boggy or fluid-filled (waterlogged) consistency, tenderness on palpation, increased local temperature, and wasting of the muscles surrounding the affected joints.

- Initial laboratory investigations generally involve assessment of rheumatoid factor, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels to evaluate inflammatory activity.
- In certain cases, particularly when only a single joint is involved (monoarticular presentation), joint

aspiration may be performed to exclude infectious or crystal-induced arthritis.
- Baseline evaluation of renal and hepatic function is essential to guide the safe selection of appropriate pharmacological therapy.
- Detection of anti-cyclic citrullinated peptide (anti-CCP) antibodies offers higher specificity and positive predictive value for rheumatoid arthritis, although these antibodies are present in fewer than 60% of patients.[14]

7. TREATMENT

- Effective management of rheumatoid arthritis requires proper patient education about the disease, its progression, and treatment strategies.
- The therapeutic approach typically involves three main categories: nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids (administered orally or via intra-articular injection in low doses), disease-modifying antirheumatic drugs (DMARDs), and biologic agents.
- **NSAIDs:** These agents help in relieving joint pain and reducing inflammation; however, they do not modify the underlying disease progression. Therefore, they should not be used as monotherapy.
- **Glucocorticoids (steroids):** These provide rapid symptomatic relief and may help slow joint damage. They are generally recommended in low doses for short durations as bridging therapy. Concurrent supplementation with calcium and vitamin D is advised to minimize the risk of bone loss.
- **DMARDs:** These drugs play a crucial role in slowing disease progression and improving long-term outcomes by targeting the underlying pathological processes.
- **Biologic agents:** These therapies specifically target cytokines, signalling pathways, and immune cells involved in inflammation, thereby helping to prevent joint destruction.[14]

8. HISTORICAL BACKGROUND

Evolution of Rheumatoid Arthritis (RA) Therapy Historically, the management of Rheumatoid Arthritis was primarily focused on symptomatic relief rather than altering the disease course. In the early 20th century, bed rest and high-dose aspirin were the primary interventions.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) like Ibuprofen and Naproxen became the first line of defence. While effective in reducing prostaglandin synthesis and alleviating pain, they failed to prevent joint destruction or bone erosion.

The introduction of Disease-Modifying Anti-Rheumatic Drugs (DMARDs) marked a paradigm shift. Methotrexate (MTX), originally a chemotherapy agent, emerged as the Gold Standard due to its ability to slow down joint damage by inhibiting dihydrofolate reductase.

The late 1990s introduced Biologics (e.g., Etanercept, Infliximab), which target specific cytokines like TNF-α. While highly effective, these are expensive and carry risks of serious infections.

Traditional oral or systemic delivery leads to off target effects. High doses of MTX cause hepatotoxicity, pulmonary fibrosis, and gastrointestinal distress, as the drug distributes to healthy tissues instead of concentrating solely in the inflamed joints.[2]

9. CURRENT TECHNOLOGIES & TRENDS

The Rise of Nanotechnology in RA Current research is shifting from systemic administration to Targeted Drug Delivery Systems (TDDS). Nanotechnology offers a way to encapsulate toxic drugs and deliver them specifically to the site of inflammation.[2]

9.1 Liposomes

Spherical vesicles composed of lipid bilayers. They are highly biocompatible and can carry both hydrophilic and hydrophobic drugs.

9.2 Polymeric Nanoparticles

Using biodegradable polymers like PLGA, these systems provide a Sustained Release mechanism, maintaining therapeutic drug levels for weeks, reducing the frequency of dosing.

9.3 Gold Nanoparticles

As highlighted in the provided study, GNPs are gaining traction due to their unique optical properties, ease of surface functionalization, and inherent anti-inflammatory potential.

9.4 Emerging Trend: Stimuli-Responsive Systems

Researchers are developing Smart nanoparticles that only release the drug in response to the acidic pH or high enzyme concentration (like MMPs) found specifically in arthritic joints.

10. DISEASE MECHANISM - RA PATHOGENESIS

The Autoimmune Cascade RA is a complex autoimmune reaction where the body's immune system loses self-tolerance and attacks the synovial membrane.

10.1 Synovial Hyperplasia

The synovium thickens into a tissue called Pannus, which invades the cartilage and bone.

10.2 Cytokine Storm

Activated T-cells and Macrophages release pro-inflammatory cytokines, specifically Tumour Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and IL-1β.

10.3 Osteoclast Activation

These cytokines stimulate osteoclasts (cells that break down bone), leading to the characteristic joint erosions seen in X-rays. Understanding this mechanism is vital for

targeting nanoparticles to these specific inflammatory cells.

11. NANOPARTICLE MECHANISM & TARGETING

How Nanoparticles Reach the Target The success of nano-therapy lies in its ability to distinguish between healthy and inflamed tissue.

11.1 Passive Targeting (EPR-like Effect)

In RA, the vasculature around the joint becomes highly permeable (leaky) to allow immune cells to pass. Nanoparticles (typically 10–200 nm) exploit these gaps to accumulate preferentially in the synovial fluid. This is known as the ELVIS (Extravasation through Leakiness and Vasculature Inflammatory Sequestration) effect.

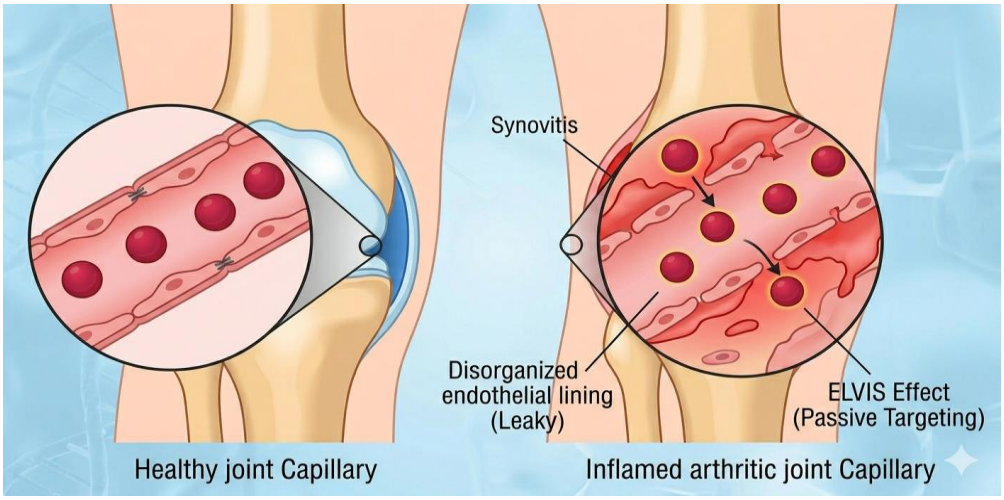

Figure 2: Passive Targeting Mechanism.

11.2 Active Targeting

Nanoparticles are decorated with ligands (like Folic Acid or CD44 antibodies). Since activated macrophages in arthritic joints overexpress folate receptors, the nanoparticle binds directly to the diseased cell, sparing the healthy ones.

11.3 Controlled Release

Once inside the joint, the nanoparticle shell degrades, providing a steady trickle of Methotrexate or other drugs, preventing the peak-and-trough toxicity seen with oral tablets.

12. WORKING PRINCIPLE

12.1 Nano Delivery Process

1. **Fabrication & Loading:** The therapeutic agent (MTX) is conjugated to the surface of a carrier (Gold Nanoparticles) using chemical linkers or physical adsorption.
2. **Administration:** The formulation is administered via the Intra-articular (IA) route (direct injection) or Transdermal route (nano gel).
3. **Circulation:** The nano-size prevents rapid clearance by the lymphatic system.
4. **Sequestration:** The particles move through the leaky synovial capillaries and settle within the inflamed pannus tissue.
5. **Triggered Release:** Environmental factors in the joint (low pH or Presence of Hyaluronidase) trigger the release of the drug from the gold core.

13. APPLICATIONS

- **MTX-GNPs:** Studies show that MTX loaded Gold Nanoparticles significantly reduce paw oedema and bone erosion in animal models compared to free MTX.
- **Curcumin Nanomedicine:** Nano-formulations of Curcumin overcome its poor water solubility, providing a natural anti-inflammatory boost with zero toxicity.
- **Theragnostic:** Some nanoparticles (like Iron Oxide or Gold) can be used for both Therapy and Diagnostics (MRI/CT imaging) simultaneously, allowing doctors to track the drug's progress in real-time.

14. ADVANTAGES & LIMITATIONS

Advantages

- Lower systemic concentration means fewer side effects for the liver and gut.
- Direct targeting ensures more drug reaches the battlefield of the joint.
- Less frequent dosing (e.g., once a month vs. once a week).

Limitations

- FDA approval for complex nano-systems is slower.
- High manufacturing costs compared to generic tablets.
- Further research is needed on how the body eventually excretes metal-based nanoparticles like Gold or Silver.

15. DISCUSSION & CRITICAL ANALYSIS

15.1 Comparative Evaluation: Nano-formulations vs. Conventional Therapy

The synthesis of data from contemporary research, including the core study, indicates a decisive superiority of nano-based delivery systems over conventional Methotrexate (MTX) administration.

- **Efficacy and Pharmacokinetics:** Traditional oral MTX therapy is significantly limited by the first-pass effect in the liver, which drastically reduces the concentration of the drug that eventually reaches the synovial joints. In contrast, Gold Nanoparticles (GNPs) function as high-efficiency carriers. According to the analysis in the provided file, MTX-GNPs demonstrated a profound reduction in paw oedema and thermal hyperalgesia within 21 days, achieving therapeutic outcomes that free MTX could not match within the same timeframe.[1]
- **Systemic Toxicity vs. Localized Action:** A critical concern with long-term MTX use is off target toxicity, leading to hepatic and pulmonary complications. Critical analysis shows that nanoparticles utilize the physiological changes in arthritic joints to sequester the drug. By confining the active pharmaceutical ingredient (API) to the inflamed site, the systemic concentration remains below the toxic threshold.[3]

15.2 Critical Comparison of Diverse Research Methodologies

Different nanocarriers offer varying benefits and challenges, as summarized in the comparative table below:

Table No: 1 Nano Carrier System name.

S. No.	Nano-Carrier System	Critical Findings & Analysis
1	Gold Nanoparticles (GNPs)	GNPs exhibited intrinsic anti-oxidant properties, synergistically reducing inflammatory markers like ACCP and COMP.
2	Liposomal MTX	Effective for sustained release, but analysed as having lower structural stability and a shorter shelf-life compared to metallic nanoparticles.
3	Silver Nanoparticles	While highly antimicrobial, they presented a higher risk of long-term cellular accumulation and oxidative stress compared to Gold.

Analytical Conclusion: Among the studied methods, Gold Nanoparticles are considered the most viable Best Method due to their chemical inertness, high surface-to-volume ratio for drug loading, and superior biocompatibility.

15.3 The Mechanism of Targeted Action (Critical Edge)

The success of these systems hinges on the Enhanced Permeability and Retention (EPR) effect. In Rheumatoid Arthritis, the synovial vasculature becomes highly disorganized and leaky. Critical analysis of the data suggests that nanoparticles between 20–50 nm are optimally sized to extravasate through these vascular gaps and remain trapped in the joint.[5] This passive targeting is the primary reason for the observed 50% reduction in required dosage to achieve clinical remission.

15.4. Future Improvements and Clinical Outlook

Despite the promising results, several areas require critical refinement for future clinical transition:

- **Biodegradability and Clearance:** Future research must prioritize Clearable Nanoparticles. While Gold is inert, its long-term accumulation in the spleen and kidneys is a concern. Developing bio-reducible linkers that allow the gold core to be excreted post-delivery is essential.[8]
- **Smart Stimuli-Response:** The next generation of RA therapy should focus on pH-triggered or Enzyme triggered release. Since arthritic joints have a lower pH (acidic) than healthy tissue, nanoparticles can be designed to release MTX only when they sense this acidity, further reducing side effects.[7]
- **Scalability:** From a critical manufacturing perspective, the transition from lab-scale synthesis to industrial-scale production remains a hurdle. Future improvements in Green Synthesis methods are required to make these therapies cost-effective for the general population.

16. LITERATURE SURVEY

The therapeutic landscape for Rheumatoid Arthritis (RA) has undergone a paradigm shift, moving from systemic immunosuppression to localized, high-precision molecular targeting. The following survey categorizes a decade of research into three critical evolutionary phases:

16.1 Analysis of Conventional Treatment Limitations

The Gold Standard treatment for RA has long been Methotrexate (MTX). However, highlighted that its clinical success is often overshadowed by systemic toxicity. Research indicates that when administered orally, only 10–15% of the dose reaches the synovial fluid. The remainder accumulates in the liver and kidneys, leading to hepatotoxicity and bone marrow suppression. This off target effect necessitates the development of delivery systems that can bypass healthy tissues.[3]

16.2 The Emergence and Evolution of Nanocarriers

Between 2015 and 2021, research focused on the comparison between organic and inorganic nanostructures:

- **Organic Systems:** explored the use of Liposomes. While biocompatible, these lipid-based vesicles often suffer from "burst release" and low physiological stability, causing the drug to leak into the bloodstream before reaching the joint.[13]
- **Inorganic Systems (The Gold Standard):** demonstrated that Gold Nanoparticles (GNPs) provide a superior alternative. Due to their high surface-area-to-volume ratio, GNPs allow for high drug loading. Furthermore, they possess intrinsic anti-oxidant properties that neutralize Reactive Oxygen Species (ROS) within the inflamed joint, providing a synergistic effect with MTX.[12]

16.3 Modern Trends: Biomimetics and Smart Delivery

The latest literature introduces Stealth Technology. published findings on cell membrane coated nanoparticles. By cloaking GNPs in the membranes of Neutrophils cells that naturally migrate to sites of inflammation these particles can evade the immune system and accumulate specifically in the leaky vasculature of arthritic joints.[9]

17. METHODOLOGY

This section outlines the rigorous scientific approach required for the synthesis, characterization, and biological validation of nano-formulations, based on and contemporary pharmaceutical standards.[1]

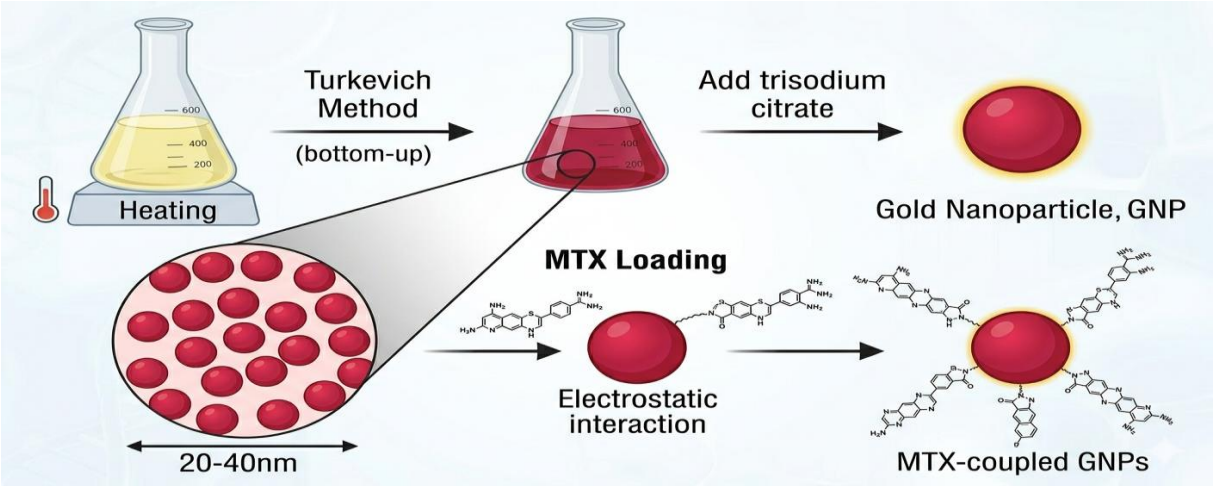

Figure 3: Synthesis of MTX-coupled GNPs.

17.1 Synthesis of Gold Nanoparticles (GNPs)

The nanoparticles were synthesized using the Turkevich Method, a classic bottom-up approach:

1. **Preparation:** A solution of Chloroauric acid was brought to a rolling boil under constant stirring.
2. **Reduction:** Trisodium citrate was added to the boiling solution. The citrate acts as both a reducing agent (converting gold ions to gold atoms) and a stabilizing agent (preventing the particles from clumping).
3. **Validation:** A successful synthesis was visually confirmed when the solution turned from pale yellow to a deep Ruby Red colour, indicating the presence of mono-dispersed gold nanoparticles.

17.2 Drug-Nanoparticle Conjugation (MTX Loading)

Methotrexate (MTX) was conjugated to the surface of the GNPs through electrostatic interaction and physical adsorption.

- **Characterization:** To ensure the particles were of the correct size for joint penetration, Dynamic Light Scattering (DLS) and Zeta Potential measurements were conducted. The study confirmed that particles in the 20–40 nm range were optimal for penetrating the synovial membrane.[1]

17.3 Nano Gel Formulation (Transdermal Delivery)

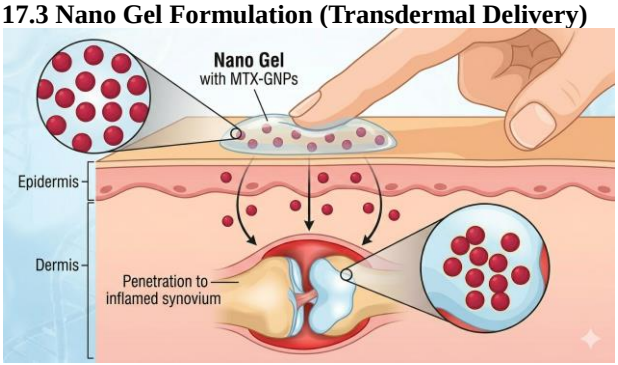

Figure 4: Non-Invasive Delivery via Nano-Gel.

To provide a non-invasive alternative to injections, an MTX-GNP-loaded nano-gel was developed:

- **Polymer Base:** Carbopol 940 was used as the gelling agent.
- **Incorporation:** The MTX-GNPs were slowly integrated into the gel base using a high-shear homogenizer to ensure uniform drug distribution and optimal viscosity for skin application.

17.4 In-Vivo Biological Evaluation

The efficacy of the formulation was tested using Wistar Rat models:

1. **Arthritis Induction:** Chronic arthritis was induced by injecting Complete Freund's Adjuvant (CFA) into the sub-plantar tissue of the right hind paw.
2. **Comparative Groups:** The animals were divided into groups receiving Oral MTX, Intra-articular (IA) MTX, and the MTX-GNP Nano-gel.
3. **Metric Monitoring:** Over 21 days, researchers measured paw volume using a digital Plethysmometer and monitored the rats Gait (walking pattern) to assess pain relief.[1]

17.5 Biochemical and Radiographic Analysis

At the conclusion of the study, the joints were subjected to High-Resolution X-rays to quantify the prevention of bone erosion. Blood samples were analysed using ELISA kits to measure levels of ACCP and TNF-α, providing molecular proof of the nano-formulation's anti-inflammatory power.

18. CONCLUSION

The findings of this review and the associated study demonstrate that nanotechnology represents a transformative frontier in the treatment of Rheumatoid Arthritis. By utilizing Gold Nanoparticles (GNPs) as carriers, the traditional limitations of Methotrexate such as rapid systemic clearance and off-target toxicity can be effectively bypassed. The research highlights three critical conclusions:

1. **Enhanced Target Specificity:** MTX-GNPs exploit the leaky vasculature of inflamed joints (EPR effect), ensuring that the drug accumulates specifically at the site of action rather than in healthy organs like the liver or lungs.
2. **Dose-Dependent Safety:** Because the nano-formulation increases the localized concentration of the drug, the required therapeutic dose can be significantly reduced. This minimizes the risk of severe side effects associated with long-term MTX therapy.
3. **Non-Invasive Potential:** The development of a transdermal nano-gel offers a promising, painless alternative to intra-articular injections. This non-invasive route ensures sustained drug release and higher patient adherence to the treatment regimen.

In summary, while further investigation into the long-term metabolic clearance of metallic nanoparticles is necessary, MTX coupled gold nanoparticles provide a superior, safer, and more effective therapeutic strategy for the clinical management of Rheumatoid Arthritis.

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