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Bioengineered Bioactive Nanocarriers for Targeted Delivery and Improved Therapeutic Efficacy in Rheumatoid Arthritis

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Abstract: Rheumatoid Arthritis is one of the most widespread illnesses, which can affect millions of people and significantly limits their everyday activities. Patients who are suffering may exhibit a variety of clinical signs, from minor symptoms like mild discomfort, swelling, joint immobility, muscle atrophy. A person with severe arthritis is incapable of performing daily tasks, including walking and moving around. It may result in ligament deterioration and structural damage to joints over time. 180 million Indians, or about 15% of the population, suffer from rheumatoid arthritis. In rheumatoid arthritis, the immune system of the host attacks its own cells, causing joint swelling and immobility as well as widespread bone and damage cartilage in the joints. Due to formation of oxygen free radicals from O_2 metabolism leads increase in reactive oxygen species (ROS) which play significant roles in the pathophysiology of RA. The NF-kB pathway stimulation causes cells to release pro- inflammatory mediators as IL-1, TNF-α, and chemokines. Clinically, the major RA treatments are non-steroidal anti-inflammatory medicines (NSAIDs), disease modifying anti- rheumatic medications (DMARDs), and glucocorticoids they relieve RA patients' by reducing synovitis and systemic inflammation. Phytoconstituents have ability for treating rheumatoid arthritis by converting them into nanoparticles. Researchers are concentrating on natural compounds to generate novel anti-inflammatory medicines, despite the fact that numerous steroidal and NSAIDs have been created.

Keywords: NSAIDs, DMARDs, Phytoconstituents, Nanotechnology.

1. Introduction

In recent years, inflammation has grown to be a significant global health concern [1]. When subjected to any damaging stimuli, vascular tissues undergo a biological reaction called inflammation [2]. The elimination of injured tissue, the production of new tissue, and the weakening, destruction, or neutralization of dangerous chemicals is all protective responses that result in inflammation. A host defense reaction causes injury, tissue ischemia, autoimmune responses, or infectious pathogens which results inflammation. Signs and symptoms may last for several days or even a week. Chronic disorders including cancer, diabetes, asthma, heart attacks and arthritis can all be caused by uncontrolled inflammation. According to some definitions, inflammation is a reaction brought on by damaging stimuli and other unfavorable circumstances [3].

Arthritis is one of the most widespread illnesses, which can affect millions of people and significantly limits their everyday activities. It also causes musculoskeletal abnormalities. Patients who are suffering may exhibit a variety of clinical signs, from minor symptoms like mild discomfort, swelling, joint immobility, muscle atrophy. Arthritis symptoms include swelling and discomfort in one or more joints [4]. Arthritis could be developing any age, gender. Swelling, stiffness, joint pain and reduction in motion are some of the usual symptoms of arthritis. A person with severe arthritis is incapable of performing daily tasks, including walking and moving around. The two most common types of arthritis are osteoarthritis and rheumatoid arthritis [5]. Various plant-based herbal medicines are effective for the management of autoimmune disorders, and the most of the active constituents of the plant products are investigated for their immunosuppressive properties such as *Emblica officinalis, Tinosopra cordifolia, Curcuma longa, Tripterygium wilfordii, Withania somnifera, Glycyrrhiza glabra,* and baicalein, etc [6].

1.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) where “artho” means joint and “itis” means inflammation. The prevalence of rheumatoid arthritis increases with ageing, reaching its peak between the ages of 35 and 50 [7]. Rheumatoid arthritis (RA) is an autoimmune illness that induces arthritis. It is more frequent in women than in men and is observed in many different countries [8]. The symmetric polyarticular disease predominantly affects the small diarthrodial joints of feet and hands [9]. Clinically, the symptoms of RA significantly differ between early stages RA and insufficiently treated later stages of the disease. Early-stage RA is characterized by generalized disease symptoms such as fatigue, flu-like feeling, swollen and tender joints, and morning stiffness; and is paralleled by elevated levels of C-reactive protein (CRP) and an

increased erythrocyte sedimentation rate (ESR) [10]. In rheumatoid arthritis, the immune system of the host attacks its own cells, causing joint swelling and immobility as well as widespread bone and damage cartilage in the joints. Figure (1) shows the difference between a normal knee joint and a rheumatoid synovitis knee joint. It has a connection T-cells and more affects women than men. These triggers cause body's immune system to react improperly, which leads production of molecules i.e. attacks on joint, ultimately leading to the onset of rheumatoid arthritis [11]. Due to formation of oxygen free radicals from O_2 metabolism leads increase in reactive oxygen species (ROS) which play significant roles in the pathophysiology of RA. Damage to joint tissue in RA has been linked to oxygen-free radicals [3]. The extra-articular organ involvement, persistent synovitis, development of auto-antibodies and anti-citrulli-nated peptide protein antibodies are the key characteristics of RA. According to epidemiological data, 0.5–1.5% adults suffer from RA [14]. RA is a normal, defensive reaction to tissue injury brought on by abrasion, poisonous substances, infectious agents, or autoimmune disease [15]. Synovial macrophages release cytokines like tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6), which are associated with inflammatory processes, stimulation of fibroblast-like synoviocytes (FLS) and stimulation of osteoclasts activity [12]. Tumour necrosis factor-α, interleukins, prostaglandins, cytokines are mediators of RA [16]. Genetic markers of severity such as HLA-DRB1, TRAF1, PSORS1C1 and micro RNA 146a are differently associated with joint damage; other gene polymorphisms seem to be associated with response to biologic disease modifying anti-rheumatic drugs (DMARDs) [13]. A joint is the location at which two bones come into contact. Histologically and functionally, joints can be classified into three types fibrous, cartilaginous, and synovial joints [17].

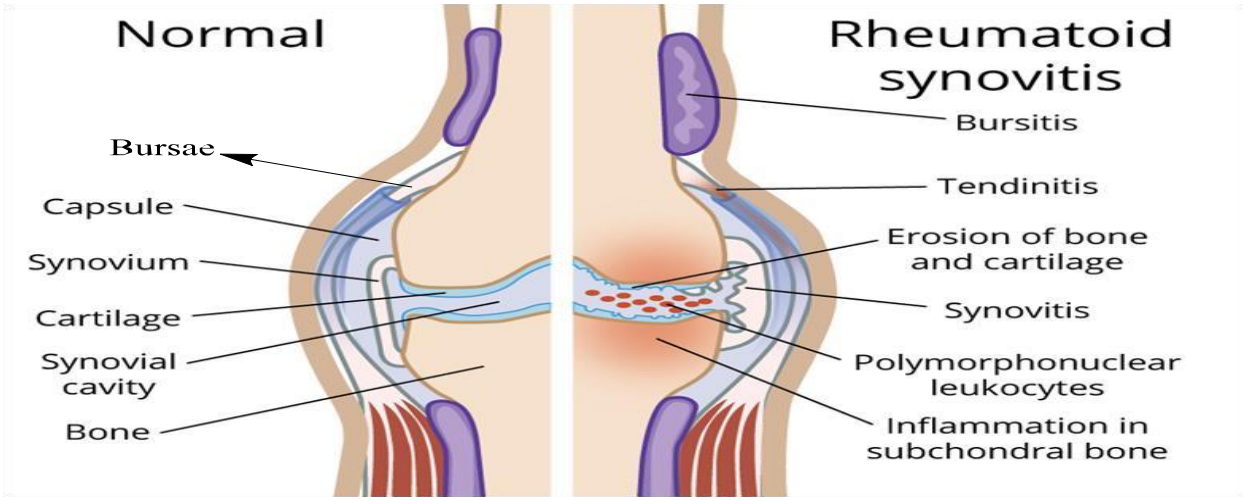

Figure 1. Rheumatoid Arthritis in knee joint [18].

1.2 Phyto-nanotechnology

Nanomedicine is an evolving area, using the application of nanoscience information and technology in remedial biology for treatment as well as disease prevention [19]. Nanodrug delivery systems are a novel but fast-emerging discipline in which very tiny materials are used as diagnostics or to administer therapeutic drugs to particular targeted locations in a controlled manner [20]. Nanotechnology has several advantages in the treatment of chronic human diseases through the site-specific and target-oriented delivery of precise medications [21]. A phyto-nanotechnology deals with the cost and safety efficient synthesis of biogenic nanomaterials by using different hearbs. Lower toxicity and simple scalability are benefits of producing nanoparticles using biological processes [22].

Nanotechnology is characterized by the examination and utilization of structures between 1 and 100 nm in size [23]. Among the various approaches for the development of advanced delivery systems nano sized drug delivery has grasped the foremost contemplation. The synthesis strategies embrace chemical, physical and biogenic technique of synthesis of nanoparticles. The field of nanotechnology is emerging day by day not solely having its impact on the pharmaceutical world however conjointly this new science for is being exploited within the field of physics, chemistry, and biological applications etc [24]. Nanoparticles aren't solely fabricated by single material but also by using organic and inorganic materials. Researchers round the world are currently exploiting this tool for developing differently coated nanoparticles that affects the pharmaceutical properties likewise as pharmacodynamics of the drug. Nanoparticles of various shapes and sizes can be produced by changing the synthesis pathways. The majority of noble metals are used to create metallic nanoparticles [25]. It has been documented that plants may produce nanoparticles of gold, silver, copper, silicon, zinc, titanium, magnetite, and palladium [26]. In order to create bioengineered nanoparticles with unusual compositions and functions, "green chemistry" is crucial. It is simple to scale up for large-scale synthesis, requires little high energy or high temperature, and is also reasonably priced to employ plants for the biosynthesis of nanoparticles [27].

When a substance is reduced down to the nanoscale, it behaves differently and exhibits some brand-new qualities that are not present in its macroscale version. Nanotechnology's recent advancement and application resulted in a new age known as the nano-revolution. Thus, "green nanotechnology" is becoming more and more in demand. Plant extract-based green synthesis nanoparticles provide an alternative strategy for solving issues. It was an easy, sustainable, and affordable green synthesis process. Plant extract contains functional groups

including phenolics and alkaloids that are responsible for stabilizing and capping nanoparticles [28]. Sol process, micelles, sol-gel process, chemical precipitation, hydrothermal method, pyrolysis chemical vapour deposition, bio-based protocols, etc. are some of the methods used to create nanoparticles [29].

Metal nanoparticles can be created using a variety of processes, such as physical, chemical, or biological ones. But when we take into account low toxicity, eco-friendliness, economic effectiveness, and low time consumption, physical and chemical procedures are not as ideal for the manufacture of silver nano-particles. Metal nanoparticles are being produced from various plant parts. Recent reports on the synthesis of nanoparticles from flower, leaf, fruit, fruit peel, root, bark, stem, and seed have been published. Plant extracts function as capping agents to stabilize and as reducing agents to convert silver ions into silver metal during the biosynthesis process. Generally speaking, the primary photochemical that are induced green synthesis of nanoparticles include alkaloids, tannins, steroids, phenols, saponins, and flavonoids components of plant extracts [30]. The reduction of ions, clustering, and subsequent nanoparticle growth are the major three steps in the mechanism of nanoparticle production. The plant extract's biomolecules serve as significant stabilizing and reducing agents [31].

Due to their numerous uses in photonics, optoelectronics, biological tagging catalysis, drug transport, and biomedical devices, metal nanoparticles (MNPs) are important. MNPs also have a high degree of surface reactivity, a big surface area, a powerful capacity for adsorption, and a high degree of catalytic efficiency. As a result, MNPs synthesis employing plants and herbs is receiving more and more attention today. Typically, a reaction starts and is finished in a few minutes at room temperature when an aqueous solution of a relevant salt is combined with an aqueous extract of the plant [33]. Environmental issues including solar energy conservation, agricultural production, catalysis, electronics, and biotechnology can all be resolved by biologically synthesizing nonmaterial’s. Herbal products today stand for safety in contrast of synthetics, which are viewed as being hazardous to both humans and the environment. Phytonanotechnology is a class of nanotechnology that deals with the low-cost and safe production of biogenic nanomaterials, as shown in figure (2). Nanoparticles are increasingly being used in different fields such as molecular biology, physics, organic and inorganic chemistry, medicine, and material science [34].

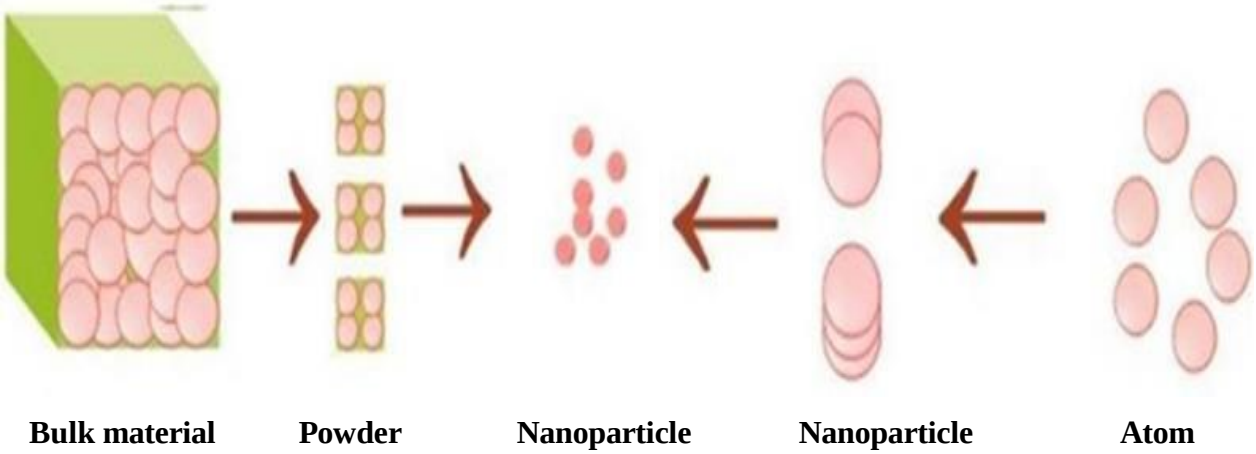

Figure 2. The schematic representation of top-down and bottom-up approach for synthesis of nanparticles.

2. Methodology of synthesized nanoparticles by using different metals and herbs

I. Silver nanoparticle synthesized using Cotyledon orbiculata Aqueous extract [22].
II. Iron nanoparticle synthesized using dried Ginger [23].
III. Silver nanoparticle synthesized using Cumin oil [25].
IV. Silver nanoparticles from *Tinospora cordifolia* [26].
V. Selenium nanoparticles synthesized using Thymus vulgaris [27].
VI. Copper Nanoparticles Using *Nyctanthes arbortristris* (Night jasmine) [28].
VII. Silver nanoparticles synthesized using Nutmeg oleoresin [29].
VIII. Silver nanoparticles synthesized using *Bixa olellana* seed extract [30].
IX. Silver, copper and iron nanoparticles from the leaf extract of *Catharanthus roseus* [31].
X. Biosynthesis of Silver nanoparticles of *Rhus Javanica, Rumex hastatus* and Callistemon [32].
XI. Silver nanoparticles *Nyctanthes Arbor-Tristis* Extract [34].
XII. Silver nanoparticles synthesized using *Cinnamomum cassia* and *Symplocos racemosa* [35].

Among the several metallic nanoparticles that are used in biomedical applications, silver nanoparticles (AgNPs) are one of the most significant and fascinating nanomaterials [35]. Due to the usage of silver nanoparticles in optoelectronics and their antibacterial properties, research on these particles has also become more important. The reduction of Ag+ to silver nanoparticles may be significantly influenced by the reducing ability of various plant

elements, such as geraniol. The size of the particles has an impact on the antibacterial and anti-inflammatory properties of colloidal silver [25]. The present research aims to provide a comprehensive overview of RA, centralizing updated information regarding recent advances in diagnosis and therapeutic approaches, to support specialists and patients to improve the management of RA.

3. Treatment of RA

In this study we see that inflammatory disease model systems, *in-vitro & in-vivo* studies gives idea that, phytochemicals have anti-rheumatoid arthritis properties. Reactive oxygen species (ROS) and nitric oxide (NO), besides pro-inflammatory cytokines together with interleukin-1, IL-6, and tumour necrosis factor-alpha (TNF-α), are released as part of the rheumatoid arthritis response [36]. The primary threat to public health is the inflammatory process and the illnesses. Inflammation is a normal, defensive reaction to tissue injury brought on by abrasion, poisonous substances, infectious agents, or autoimmune diseases. In reaction to injury, leukocytes, in particular neutrophils are drawn to the inflammatory centre. Nuclear factor-kappa B (NF-KB) pathway stimulation causes these cells to release pro-inflammatory moderator such as interleukin (IL)-1, tumour necrosis factor (TNF-α), and chemokines. Prostaglandins are powerful vasodilators that also cause inflammation and fever. Endogenous pyrogens known as cytokines can raise fever and have a deleterious impact on the development of metabolic dysfunction [15].

Clinically, the major RA treatments are non-steroidal anti-inflammatory medicines (NSAIDs), disease modifying anti-rheumatic medications (DMARDs), and glucocorticoids they relieve RA patients' by reducing synovitis and systemic inflammation, as tabulated in table 1. However, these medications can't adequately alleviate the disease, and they come with substantial adverse effects include hepatorenal toxicity and toxic consequences when used with DMARDs. Corticosteroids are a more potent anti-inflammatory medication than NSAIDs, but they come with greater side effects. For this reason, they are only indicated for a short period of time at low doses, during exacerbations or flares of RA. Intra-articular injections of corticosteroids can be used for the local symptoms of inflammation [37]. List of phytochemicals which can be used as alternative therapeutic agents against RA were tabulated in table 2. In adjuvant-induced arthritis (AIA) and collagen-induced arthritis (CIA), herbs and foods can reduce RA via regulating T cells.

It is generally recognised that joint degeneration from chronic inflammation in the joints is one of the key signs of RA. T lymphocytes, B cells, and macrophages are prevalent in RA patients' inflamed synovial membranes and have been linked to the pathophysiology of the disease. Inflammatory mediators produced by genetic expression and immune cells' secretion, such as chemokines, histamine, cytokines, proteases and integrins are what cause bone erosion, inflammation at synovial sites, and the progression of RA. Balance and resolution of inflammation are now thought to be effective treatments for RA. Inflammation and synovial hyperplasia are thought to be the

pathogenic characteristics of RA. In the case of RA, fibroblast-like synovial (FLS) cells have the capacity to generate a large number of inflammatory cytokines and to stimulate FLS cells continually, leading to unchecked proliferation. The PI3K/Akt signalling pathway is thought to be a link between FLS cell growth and apoptosis. PI3K and Akt are abundantly expressed in RA-FLS cells and affect FLS cells' excessive motility. In addition, many inflammatory cytokines, including IL-17 and IL-21, can induce and activate PI3K, which in turn can enhance the inflammatory proliferation of FLS cells [14].

By interfering with inflammatory pathways, compounds made from plants have evolved into secure substitutes for anti-inflammatory medications [1]. Ayurveda describes inflammation as a vascular and cellular response, just as modern medicine [2]. The tissue necrosis factor (TNF), prostaglandins (PGs), cytokines, interleukins (ILs), etc. Inflammatory conditions like rheumatoid arthritis could be successfully treated by inhibition [16]. While negatively signaling regulators are transcribed in order to preserve innate immune homeostasis and avoid long-lasting inflammatory immune responses, positive inflammatory transducers and regulators are produced by the innate immune response for combating pathogens. Several epigenetic modifications control the expression of these regulators. The most important cellular components of the innate immune system are neutrophils and macrophages, which are effective phagocytes that act as an initial line of protection against outside substances. These cells are known as "antigen-presenting cells" (APCs), and they frequently recognise infections by binding to molecular patterns presented on the surfaces of invading bacteria via surface-expressed receptors described as "pattern recognition receptors" (PRRs) [38]. Oligomerization receptor activates PRR subunits, resulting in the activation of mediators that attract leukocytes to the site of infection or damage. Leukocytes, which include macrophages, neutrophils, and dendritic cells, phagocytose microbial elements and release more proinflammatory cytokines, such as TNF-α, IL-6, IL-12, and type I and II interferons (IFNs), preserving the pathogen till highly specific, activated cells of the adaptive immune response become involved to totally eliminate the infection [39].

The production of histamine, nitric oxide and prostaglandins promotes vasodilation, which leads to a rise in the flow of blood and buildup of circulating leukocytes. This is the main cause of inflammatory reactions. Furthermore, proinflammatory cytokines released by activated immune cells, such as tumour necrosis factor-alpha, interleukin-1as well as interleukin-6 , they increase the quantity of leukocyte adhesion molecules on endothelial cells, increasing leukocyte vascular permeability [40].

Today, most of the drugs available for the treatment of RA, including disease-modifying antirheumatic drugs (DMARDs), act by targeting cytokines, nonspecific immune suppression

or T-cell and B-cell activation [41]. NSAIDs are used to control RA in the short term. Members of this class of medications include naproxen, indomethacin, ibuprofen, aspirin, and aspirin. The cellular mechanism of these drugs is anti-arthritic and anti-inflammatory effect is COX-1 and COX-2 suppression, which prevents only production of prostaglandins linked to inflammatory arthritis. Although they have analgesic and anti-inflammatory properties, they do not stop RA from progressing. Various antirheumatic medications, including both biologic and traditional disease-modifying antirheumatic medicines (DMARDs), are being utilised to treat RA. However, the majority of these medications are known to have side effects. It is well known that traditional DMARDs (methotrexate and sulfasalazine) cause frequent adverse effects, such as nausea and diarrhoea. Methotrexates in particular are known to produce serious adverse effects such lung fibrosis [36]. Today's treatments include corticosteroids, NSAIDs, and DMARDs; however, they are mostly employed to address clinical issues rather than the underlying causes, such as membrane stabilisation, protein denaturation, hepatic damage, gastric bleeding [42], gastrointestinal distress and ulcers are two side effects of NSAIDS. However, the use of NSAIDS and DMARDS is constrained by their negative side effects, possible toxicity, and high cost [43].

Table 1. Allopathic treatment of rheumatoid arthritis.

Drug	**Mechanism of action**
Etanercept, Infliximab, Certolizumab pegol	Tumor necrosis factor (TNF) inhibitors
Abatacept	T-cell Costimulatory blockade
Rituximab	B-Cell Depletion
Tocilizumab	Interleukin-6 (IL-6) inhibitors
Anakinra	Interleukin-1 (IL-1) antagonist
Cyclophosphamide, azathioprine	Immunosuppressive agent
Methotrexate	Inhibition of adenosine deaminase

Table 2. List of phytochemicals which can be used as alternative therapeutic agents against RA

Phytochemicals	**Mechanism of action**
Curcumin	Decrease the IL-1B, NF-kB, TNF-α
Resveratrol	Decrease the C-reactive protein(CRP),TNF-α, Myeloperoxidase(MPO), increase the IL-10 in serum
Epigallocatechin-3-gallate(EGCG) Green Tea	Decrease Cytokinase(IFN-γ,IL-6,TFN-α, IL-1β), increase Treg cells in indoleamine-2-3-dioxygenase
Mangiferin	Decreases the IL-β, TNF-α, IL-6, supress NF-kB ligand
P-Coumaric Acid	Decrease TNF-α in synovial Tissue
Genistrin	Decrease IFN-γ secreation & increase IL-4 secreation in spleen lymphocytes
B-cryptoxanthin	Reduce polyarthritis
Chlorogenic acid	Antigout activity
Triptolide	Decrease the number of CD4+ T cells, decrease IL-18 recptor and increase CD8+ T cells
Ursolic acid	Inhibit cytokines TNF-α, IF-2, IFN- γ
Clerodendrum serratum	Inhibit COX-2 and TNF-α
Aloe barbadenis	Inhibits the cyclooxygenase pathway and reduces prostaglandin fromarachidonic acid
Withania somnifera	increase the antioxidant potential and decrease oxidative stress in seminal plasma, decrease in testosterone level
Zingiber officinate	Decrease NF-kB, which results decrease in cytokine gene expression

3.1 Medicinal plants and their parts used for anti-rheumatoid arthritis activity

Phyto-nanotechnology is a branch of nanotechnology that involves the manufacture of biogenic nanomaterials utilising environmentally friendly, safe, and cost-effective technologies. Various medicinal plant parts are used as anti-rheumatoid arthritis activity were tabulated in table 3. Nanoparticles aren't solely fabricated by single material but also by using organic and in organic materials [22]. Researchers round the world are currently exploiting this tool for developing differently coated nanoparticles that affects the pharmaceutical properties likewise as pharmacodynamics of the drug. The surface plasmon resonance is depends on their physicals properties of particle likes size, shape & dielectric

properties. If we will change the preparation methods then different shape and size nanoparticles would be prepared from noble metal [25]. MNPs have high surface reactivity, large surface area, strong adsorption capacity, and high catalytic efficiency [32]. List of MNPs with their biological activity were tabulated in table 4. Nanoscience and nanotechnology is the new source to diagnose and treat the plethora diseases in human being [35]. Nanomedicines could be made from polymers, lipids and inorganic nanostructures. In general, drug delivery systems fall into two categories: polymer–drug conjugates and nanoparticle systems [44].

Table 3. Plants with anti-rheumatoid arthritis activity.

Plant Names	**Part used**	**Extract**	**References**
Aquilaria	Leaves	Ethanol Aqueous	[1]
Tratodashang Gugglu	Powder	Aqueous	[2]
Blighia Sapida	Steam Bark	Ethanol Aqueous	[3]
Clerodendrum Serratum	Root	Ethanol Aqueous	[4]
Martynia annua L	Leaves	Ethanol Aqueous	[7]
Echinops gracilis	Root	Methanol Aqueous	[33]
Cleistophalis	Root	Ethanol Aqueous	[43]
Bauhina	Steam Bark	Ethanol Aqueous	[45]
Datura metel	Leaves	Methanol Aqueous	[46]
Ruellia Prostrata Poir	Aerial part	Ethylacetate extract	[47]
Biophytum Veldkampii	Whole plant	Methanol Aqueous	[48]
Thymus Algesiensis	Aerial part	Methanol Aqueous	[49]

Capsella Burra-postosis	Aerial part	Methanol Aqueous	[50]

Table 4. List of MNPs with their biological activity

Plant Name	**Metal Used**	**Observation**	**Biological Activity**	**Reference**
Cotyledon orbiculata	Silver	SPR-420nm PDI-0.2(Monodispersed Size- 106 nm Zeta potential - -19	Antimicrobial and anti- inflammatory	[22]
Ginger	Iron	SPR-360 nm	Anti inflammatory	[23]
Cumin oil	Silver	SPA – 400nm	Anti inflammatory	[25]
Thymus vulgaris	Selenium	SPR-420 nm	Antioxidant and Anti inflammatory	[27]
Nyctanthes arbor-tristris	copper	SPR-301 nm, 300.50 nm, 300 nm	Anti inflammatory	[28]
Nutmeg oleoresin	Silver	SPR-430 nm	Anti inflammatory	[29]
Bixa orellana seed	Silver	SPR- 420 nm FTIR- 2930, 1615, 1383 cm^{-1}	Antioxidant, antibacterial and antioriliferative	[30]
Catharanthus roseus	Silver, Copper, Iron	SPR- 415 nm,300nm, 400nm	Anti inflammatory	[31]
Rhus javanica, Rumex hastatus, Callistemon viminakis	Silver	SPR- 430 nm, 427 nm, 431 nm SEM-67 nm,	Antioxidant and Antibacterial	[32]

		61 nm, 55 nm		
Nyctanthes Arbor-Tristis	Silver	SPR-700nm	Anti inflammatory and Antioxidant	[34]
Lodhra and Cinnamon Bark	Silver	SPR- 660 nm	Anti inflammatory	[35]
Tinospora cardifolia	Silver	SPR- 421 nm SEM- 30 to 40 nm Shape- Spherical	Anti inflammatory	[51]

4. Conclusion

Phytochemicals can be employed as alternative medicinal agents to treat rheumatoid arthritis, according to experimental research. Adults and seniors are affected by arthritis which is a chronic illness To prevent and treat a variety of immunological illnesses depend on the inhibition of pro-inflammatory cytokines like interleukin-1, IL-6, and tumour necrosis factor-alpha (TNF- α), non-cytokine mediators like reactive oxygen species (ROS) and nitric oxide (NO) inflammatory responses. The natural substance has a significant influence on the treatment of rheumatoid arthritis while having fewer adverse effects. A variety of bio-chemical mediators used in the treatment of rheumatoid arthritis. In both traditional and certain modern medications, phytoactive substances are known to have significant anti Rheumatoid arthritis properties. The usage of medicinal herbal plants offers yet another different strategy in the treatment of RA & some of these plants are now being researched for the development of new medications. The medicinal plants offer cutting-edge and superior therapy options with few adverse effects. The phytochemical components may have an anti-arthritic impact. They have the potential to be used as a herbal remedy in the treatment of rheumatoid arthritis. Herbal medicines have several benefits for treating a variety of illnesses. Phytoconstitents are utilised to create the silver nanoparticles, which have strong anti-rheumatoid properties is synthesized. In addition to having anti-rehumatoid effects, AgNPs also prevented macrophages from producing the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α. Researchers are concentrating on natural compounds to generate novel anti-inflammatory medicines, despite the fact that numerous steroidal and NSAIDs have been created.

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References

[1] Eissa MA, Hashim YZ, Abdul Azziz SS, Salleh HM, Isa ML, Abd Warif NM, Abdullah F, Ramadan E, El-Kersh DM. Phytochemical Constituents of Aquilaria malaccensis leaf extract and their anti-inflammatory activity against LPS/IFN-γ-stimulated RAW 264.7 cell line. ACS omega. 2022 Apr 26;7(18):15637-46.

[2] Gupta S, Dey YN, Kannojia P, Halder AK, Sharma D, Wanjari MM, Chougule S, Pawar S, Kaushik A, Gaidhani SN, Gurav S. Analgesic and Anti-inflammatory Activities of Trayodashang Guggulu, an Ayurvedic Formulation. Phytomedicine Plus. 2022 Aug 1;2(3):100281.

[3] Adekola MB, Areola JO, Fagbohun OF, Asaolu FT, Ogundepo GE, Fajobi AO, Babalola OO. In-vitro antioxidant and anti-inflammatory activities of ethanol stem-bark extract of Blighia sapida KD Koenig. Journal of Pharmaceutical Analysis. 2022 Apr 1;12(2):350-4.

[4] Tiwari RK, Chanda S, Singh M, Agarwal S. Anti-inflammatory and anti-arthritic potential of standardized extract of Clerodendrum serratum (L.) Moon. Frontiers in pharmacology. 2021 Apr 12;12:629607.

[5] Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020 Apr 3;9(4):880.

[6] Saharan A, Dhanawat M, Parkash Dora C, Sindhu RK, Verma I. Natural Products Used in the Treatment of Autoimmune Disorder. InBioprospecting of Tropical Medicinal Plants 2023 Aug 31 (pp. 1247-1263). Cham: Springer Nature Switzerland.

[7] Kaushik S, Jain P, Satapathy T, Purabiya P, Roy A. Evaluation of anti-arthritic and anti-inflammatory activities of Martynia annua L. Ethanolic extract. Clinical Phytoscience. 2021 Dec;7:1-11.

[8] Goyal S, Thirumal D, Rana J, Gupta AK, Kumar A, Babu MA, Kumar P, Sindhu RK. Chitosan based nanocarriers as a promising tool in treatment and management of inflammatory diseases. Carbohydrate Polymer Technologies and Applications. 2024 Jun 1;7:100442.

[9] Sultana F, Arora B, Arora S, Sindhu RK. Comprehensive review on ayurvedic formulations and herbal medicines for treatment of rheumatoid arthritis. Journal of University of Shanghai for Science and Technology. 2021;23:771-90.

[10] Lin YJ, Anzaghe M, Schülke S. Update on the pathomechanism, diagnosis, and treatment options for rheumatoid arthritis. Cells. 2020 Apr 3;9(4):880.

[11] Maeda K, Yoshida K, Nishizawa T, Otani K, Yamashita Y, Okabe H, Hadano Y, Kayama T, Kurosaka D, Saito M. Inflammation and bone metabolism in rheumatoid arthritis: molecular mechanisms of joint destruction and pharmacological treatments. International Journal of Molecular Sciences. 2022 Mar 6;23(5):2871.

[12] Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. Cells. 2021 Oct 23;10(11):2857.

[13] Conigliaro P, Triggianese P, De Martino E, Fonti GL, Chimenti MS, Sunzini F, Viola A, Canofari C, Perricone R. Challenges in the treatment of rheumatoid arthritis. Autoimmunity reviews. 2019 Jul 1;18(7):706-13.

[14] Miao Z, Zhao Y, Chen M, He C. Using flavonoids as a therapeutic intervention against rheumatoid arthritis: The known and unknown. Pharmacological Research-Modern chinese Medicine. 2022 Jun 1;3:100014.

[15] Tabassum S, Ahmad S, Ali B, Usman F, Jabeen Q, Sajid-ur-Rehman M, Ahmed M, Zubair HM, Alkazmi L, Batiha GE, Basit A. Chemical profiling and evaluation of toxicological, antioxidant, anti-inflammatory, anti-nociceptive and Tyrosinase inhibitory potential of Portulacaria afra using in-vitro, in-vivo and in-silico studies. Arabian Journal of Chemistry. 2023 Jun 1;16(6):104784.

[16] Arora S, Rushiya P, Tirpude K, Sapkal N, Yende S, Ittadwar A, Shah S. Exploring the phytoconstituents targeting TNF-α as potential lead compounds to treat inflammatory diseases: an in-silico approach. Digital Chinese Medicine. 2022 Sep 1;5(3):264-75.

[17] Juneja P, Munjal A, Hubbard JB. Anatomy, joints.

[18] Shukla S, Jadaun A, Arora V, Sinha RK, Biyani N, Jain VK. In vitro toxicity assessment of chitosan oligosaccharide coated iron oxide nanoparticles. Toxicology reports. 2015 Jan 1;2:27-39.

[19] Kumari S, Goyal A, Sönmez Gürer E, Algın Yapar E, Garg M, Sood M, Sindhu RK. Bioactive loaded novel nano-formulations for targeted drug delivery and their therapeutic potential. Pharmaceutics. 2022 May 19;14(5):1091.

[20] Nasrollahzadeh M, Sajadi SM, Sajjadi M, Issaabadi Z. An introduction to nanotechnology. InInterface science and technology 2019 Jan 1 (Vol. 28, pp. 1-27).

[21] Sindhu RK, Rani K, Singh V, Singh Y, Hans B, Babu MA, Goyal A. Basics of Nanotechnology and Drug Delivery Systems. InNanotechnology and Drug Delivery 2024 (pp. 1-59). Jenny Stanford Publishing.

[22] Tyavambiza C, Elbagory AM, Madiehe AM, Meyer M, Meyer S. The antimicrobial and anti-inflammatory effects of silver nanoparticles synthesised from Cotyledon orbiculata aqueous extract. Nanomaterials. 2021 May 20;11(5):1343.

[23] Ganta SS, Jeevitha M, Preetha S, Rajeshkumar S. Anti-inflammatory activity of dried ginger mediated iron nanoparticles. Journal of Pharmaceutical Research International. 2020;32(28):14-19.

[24] Tiwari H, Gupta P, Verma A, Singh S, Kumar R, Gautam HK, Gautam V. Advancing Era and Rising Concerns in Nanotechnology-Based Cancer Treatment. ACS Chemical Health & Safety. 2024 Mar 13;31(2):153-61.

[25] Jain A, Anitha R, Rajeshkumar SJ. Anti inflammatory activity of Silver nanoparticles synthesised using Cumin oil. Research Journal of Pharmacy and Technology. 2019;12(6):2790-3.

[26] Begum HJ, Ramamurthy V, Kumar SS. Study of synthesis and characterization of silver nanoparticles from Tinospora cordifolia. The Pharma Innovation Journal. 2019;8(1):612-5.

[27] Pandiyan I, Sri SD, Indiran MA, Rathinavelu PK, Prabakar J, Rajeshkumar S. Antioxidant, anti-inflammatory activity of Thymus vulgaris-mediated selenium nanoparticles: An: in vitro: study. Journal of Conservative Dentistry and Endodontics. 2022 May 1;25(3):241-5.

[28] Saikia S, Saikia M, Khanam SA, Lee S, Park YB, Saikia L, Gogoi G, Bania KK. Cobalt oxide decked with inorganic-sulfur containing vanadium oxide for chromium (vi) reduction and UV-light-assisted methyl orange degradation. Materials Advances. 2023;4(23):6244-58.

[29] Narendra S, Roy A, Shanmugam R, Thangavelu L. Anti-inflammatory activity of nutmeg oleoresin mediated silver nanoparticles-An In-vitro study. Biomedicine. 2019;39(2):234-8.

[30] Maitra B, Khatun MH, Ahmed F, Ahmed N, Kadri HJ, Rasel MZ, Saha BK, Hakim M, Kabir SR, Habib MR, Rabbi MA. Biosynthesis of Bixa orellana seed extract mediated silver nanoparticles with moderate antioxidant, antibacterial and antiproliferative activity. Arabian Journal of Chemistry. 2023 May 1;16(5):104675.

[31] Sultana MJ, Nibir AI, Ahmed FR. Biosensing and anti-inflammatory effects of silver, copper and iron nanoparticles from the leaf extract of Catharanthus roseus. Beni-Suef University Journal of Basic and Applied Sciences. 2023 Feb 27;12(1):26.

[32] Khan W, Khan N, Jamila N, Masood R, Minhaz A, Amin F, Atlas A, Nishan U. Antioxidant, antibacterial, and catalytic performance of biosynthesized silver nanoparticles of Rhus javanica, Rumex hastatus, and Callistemon viminalis. Saudi Journal of Biological Sciences. 2022 Feb 1;29(2):894-904.

[33] Nguyen LN, Kaushik N, Lamichhane P, Mumtaz S, Paneru R, Bhartiya P, Kwon JS, Mishra YK, Nguyen LQ, Kaushik NK, Choi EH. In situ plasma-assisted synthesis of polydopamine-functionalized gold nanoparticles for biomedical applications. Green Chemistry. 2020;22(19):6588-99.

[34] Dhinakaran DI, Sakthivel G. Antioxidant and anti-inflammatory activities of Nyctanthes arbor-tristis extracts. Journal of Advanced Botany and Zoology. 2016;4(1):1-5.

[35] Yazhlini P, Cecil A, Rajeshkumar S. Anti-Inflammatory Activity Of Symplocos Racemosa (Lodhra) And Cinnamomum Cassia (Cinnamon Bark) Assisted Silver Nanoparticles. Journal of Pharmaceutical Negative Results. 2022 Dec 21:2864-70.

[36] Shin SA, Joo BJ, Lee JS, Ryu G, Han M, Kim WY, Park HH, Lee JH, Lee CS. Phytochemicals as anti-inflammatory agents in animal models of prevalent inflammatory diseases. Molecules. 2020 Dec 15;25(24):5932.

[37] Bullock J, Rizvi SA, Saleh AM, Ahmed SS, Do DP, Ansari RA, Ahmed J. Rheumatoid arthritis: a brief overview of the treatment. Medical Principles and Practice. 2019 Mar 1;27(6):501-7.

[38] Tobón GJ, Youinou P, Saraux A. The environment, geo-epidemiology, and autoimmune disease: Rheumatoid arthritis. Autoimmunity reviews. 2010 Mar 1;9(5):A288-92.

[39] Mueller AL, Payandeh Z, Mohammadkhani N, Mubarak SM, Zakeri A, Alagheband Bahrami A, Brockmueller A, Shakibaei M. Recent advances in understanding the pathogenesis of rheumatoid arthritis: new treatment strategies. Cells. 2021 Nov 4;10(11):3017.

[40] Saleh HA, Yousef MH, Abdelnaser A. The anti-inflammatory properties of phytochemicals and their effects on epigenetic mechanisms involved in TLR4/NF-κB-mediated inflammation. Frontiers in immunology. 2021 Mar 26;12:606069.

[41] Bodkhe R, Balakrishnan B, Taneja V. The role of microbiome in rheumatoid arthritis treatment. Therapeutic advances in musculoskeletal disease. 2019 Jul;11:1759720X19844632.

[42] Craig E, Cappelli LC. Gastrointestinal and hepatic disease in rheumatoid arthritis. Rheumatic Disease Clinics. 2018 Feb 1;44(1):89-111.

[43] Aloke C, Ibiam UA, Orji OU, Ugwuja EI, Ezeani NN, Aja PM, Obasi NA. Anti-arthritic potential of ethanol and aqueous extracts of stem bark of Cleistopholis patens on complete Freund's adjuvant-induced rheumatoid arthritis in rats. Journal of Ayurveda and integrative medicine. 2021 Jan 1;12(1):28-34.

[44] Wang Q, Sun X. Recent advances in nanomedicines for the treatment of rheumatoid arthritis. Biomaterials science. 2017;5(8):1407-20.

[45] Prabhu S, Vijayakumar S, Ramasubbu R, Praseetha PK, Karthikeyan K, Thiyagarajan G, Sureshkumar J, Prakash N. Traditional uses, phytochemistry and pharmacology of Bauhinia racemosa Lam.: a comprehensive review. Future Journal of Pharmaceutical Sciences. 2021 May 12;7(1):101.28

[46] Prasad KS, Patel H, Patel T, Patel K, Selvaraj K. Biosynthesis of Se nanoparticles and its effect on UV-induced DNA damage. Colloids and Surfaces B: Biointerfaces. 2013 Mar 1;103:261-6.

[47] Chen F, Aqeel M, Maqsood MF, Khalid N, Irshad MK, Ibrahim M, Akhter N, Afzaal M, Ma J, Hashem M, Alamri S. Mitigation of lead toxicity in Vigna radiata genotypes by silver nanoparticles. Environmental Pollution. 2022 Sep 1;308:119606.

[48] Bandaru N, Prasanth DS, Reddy AR, Rao GK, Nemmani KV, Rao AN. In-silico Molecular Docking Studies of some Isolated Phytochemicals from Biophytum Veldkampii against Cyclooxygenase-II Enzyme and in vivo Anti-inflammatory Activity. Pharmacognosy Research. 2021;13(4).

[49] Nezhad-Mokhtari P, Akrami-Hasan-Kohal M, Ghorbani M. An injectable chitosan-based hydrogel scaffold containing gold nanoparticles for tissue engineering applications. International journal of biological macromolecules. 2020 Jul 1;154:198-205.

[50] Kharaghani D, Jo YK, Khan MQ, Jeong Y, Cha HJ, Kim IS. Electrospun antibacterial polyacrylonitrile nanofiber membranes functionalized with silver nanoparticles by a facile wetting method. European Polymer Journal. 2018 Nov 1;108:69-75.

[51] Naseem K, Begum R, Wu W, Irfan A, Al-Sehemi AG, Farooqi ZH. Catalytic reduction of toxic dyes in the presence of silver nanoparticles impregnated core-shell composite microgels. Journal of cleaner production. 2019 Feb 20;211:855-64.