REVIEW ARTICLE

Nanotechnology in Ankylosing Spondylitis: Advancements in Drug Delivery and Targeted Therapy

Anuj Kumar[1*], Jitendra Singh Chaudhary[1], Anubhav Dubey[2], Shubham Sanjay Pachorkar[3]

[1]*Smt. Vidyawati College of Pharmacy, Jhansi, Uttar Pradesh, India.*
[2]*Department of Pharmacology, Maharana Pratap College of Pharmacy, Kanpur, Uttar Pradesh, India.*
[3]*MET's Institute of D. Pharmacy, Nashik, Maharashtra, India.*

Received: 17th May, 2024; Revised: 25th May, 2024; Accepted: 02nd June, 2024; Available Online: 25th June, 2024

ABSTRACT

Ankylosing spondylitis is a chronic inflammatory disorder primarily affecting the spine and the sacroiliac joints, although it is now considered for new drug target possibilities. It is an area in which nanotechnology has shown significant potential. This report offers an extensive review of the formulation design, clinical utility, and current development in the use of nanotechnology for treating AS. The rational design principles of nanotherapeutics, created to modify the myriad processes implicated in AS pathophysiology, were examined. It comprises drug delivery systems, targeting approaches, and release processes. Clinical and preclinical evidence of nanomedicines' tolerability and effectiveness in AS therapy is reported. In conclusion, this document reflects the recent state of these nanotechnology-based treatments for AS and discusses the author's future goals in developing novel, powerful treatment strategies that generate strong patient outcomes.

Keywords: Nanotechnology, Ankylosing spondylitis, Drug delivery, Targeted therapy, Nanomedicine, Formulation design, Clinical applications.

International Journal of Drug Delivery Technology (2024); DOI: 10.25258/ijddt.14.2.82

How to cite this article: Kumar A, Chaudhary JS, Dubey A, Pachorkar SS. Nanotechnology in Ankylosing Spondylitis: Advancements in Drug Delivery and Targeted Therapy. International Journal of Drug Delivery Technology. 2024;14(2):1162-1173.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Ankylosing spondylitis is a severe rheumatic illness that has become increasingly difficult to control since it causes continuous inflammation in the axial skeleton, specifically the spine and sacroiliac joints.[1] Along with the current source of physical suffering and tangling produced by the detrimental disease, those who develop AS few mobility and overall independence. Although the pathophysiology of AS is now better documented, doctors all around the world still face the daunting task of managing the condition.[2]

Spondyloarthropathies – it is ankylosing spondylitis included and "including long-standing, chronic inflammatory conditions". This illness is distinguished by inflammation of the spine and sacroiliac joints, which develops into structural damage, joint fusion, and, in the end, restriction of mobility. Even though the pathogenesis of the disease remains unexplained, solid proof links the condition to genetic influences, specifically the HLA-B27 gene. It occurs most often in young adults, especially men, beginning insidiously, gradually developing, and may be progressive if not treated.[3] Although there are traditional medications, such as NSAIDs, DMARDs and biologics directed against tumor necrosis factor-alpha, leading to modest efficacy, several challenges restrict the opportunity of treating AS efficiently.[4] It is important to emphasize that some patients have a poor response or are intolerant to traditional treatments too. Therefore, it is necessary to search for other forms of therapy. In addition, the treatment concept needs to evolve in order to develop a safer and more efficient healing tool than systemic pharmacology, which, upon its use, can have additional effects such as increased risk of infections, gastrointestinal problems, and others.[5]

Nanotechnology within this framework is a promising new way to change the approach to AS. Nanotechnology is distinguished by new approaches to the current problems of treatment and achieving good results for the patient and good outcomes of work with the use of inherent and new qualities of materials at the nanometer scale.[6] In many ways, nanomedicine can change the paradigm of treatment for AS thanks to a more accurate drug delivery system, increasing efficiency while reducing side effects due to the systemic nature of the therapeutic approach. It is favorable for patients and for specialists.[7]

It is critical to understand all of the essential concepts, recent advancements, preclinical investigations, clinical uses,

**Author for Correspondence: anujkumarrr457@gmail.com*

impediments, and prospective future directions for these anticipated revolutionary therapies—development in the field of nanotechnology for the treatment of AS with time. Through this framework, I hope to offer adequate information about the likelihood in which nanotechnology may change the manner the illness is treated, providing fresh perspectives and hope for relieving the plight of those suffering from the seemingly dreadful illness.[8]

Nanotechnology in AS Therapeutics

Principles of nanomedicine

The multifaceted issues produced by ankylosing spondylitis have fascinating solutions in the interdisciplinary sector, including principles of nanotechnology and medicine called nanomedicine. Here, nanomedicine, which is a new examination that unites biology and various other disciplines, principles governing the rational design and administration of nanotherapeutics tailored to the specific requirements of AS patients.[9] The basic ideas addressed in this context concern the interconnection between biological systems and materials and technology at the molecular level scale. This is considered as how to control the pharmacokinetics, biodistribution, and targeting particular tissue or cell types or even more general phenomena. A specific example is nanoparticles' nanotherapeutics, which can be engineered to alter the drug release kinetics, target specific cell types or tissues, as well as circumvent biological walls. It results in more effective medication with fewer side effects.[10]

Nanocarriers for drug delivery

Due to their highly adaptable equipment to the drug-encapsulated and drug-transported, multifunctional system to specific destinations in AS, nanorettes constitute the principles of DDS offered by nanotechnology.[11] Nanocarriers are all available in varied forms and have distinct advantages and disadvantages during drug delivery mechanisms. Micelles, polymeric nanoparticles, and dendrimers and liposomes are the most adaptable matrices that can be tailored to the features in the management of the treatment of AS.[12] An example is that phospholipid bilayers can be used to encapsulate hydrophilic or hydrophobic medications to develop liposomes, which protects them from enzyme degradation and enables them to circulate more extended in the bloodstream. Conversely, polymeric nanoparticles offer a size, shape, and surface with modifiable characteristics, allowing for careful monitoring of the discharge kinetics of the medicines and intended site targeting in inflamed regions. The highly branched and controlled nature of dendrimers allows for medicine encapsulation and surface functionalization, enabling them to be ingested by the cells and bypass biological compartments more effectively.[13] Solubilizing extremely lipophilic drugs into amphiphilic micelles increases their bioavailability and reduces systemic ill-effects. The characteristics, positive aspects and therapeutic applications of different nanocarriers developed for AS drug delivery are summarized in Table 1.[14]

Targeted approaches for AS treatment

With respect to AS, the greater accumulation of nanotherapeutics at sick locations is feasible *via* passive targeting techniques, which take advantage of the exclusive pathophysiological characteristics of AS, such as the increased arterial permeability and decreased lymphatic drainage surrounding inflamed tissues.[26] Because of the enhanced permeability and retention impact, nanoparticles may slowly accumulate in inflammatory tissues and subsequently discharge a therapeutic agent specifically where it would bring the most benefit. In contrast, active targeting strategies involve coating the nanocarrier with targeting agents, which can be small antibodies, peptides, or nucleic acid sequences, known as aptamers, which bind to specific receptors on the surface of the sick cell or sick cells that overexpress certain biomarkers. As a result, through the addition of targeting agents, researchers can significantly increase the therapeutic efficacy of nanotherapeutics by granting them the ability to effectively discern between sick and healthy tissues.[27]

Controlled release systems

Controlled release devices can also accommodate the constantly changing pathophysiology of AS through exact spatiotemporal control of the kinetics of the medication release. Therefore, the development of sustainable or pulsatile release patterns is feasible. To this end, a large variety of nanotechnology-involving platforms is engaged to modulate drug release in reaction to different environmental factors or activating signals. They include hydrogels, nanoformulations, and stimuli-responsive nanomaterials. The therapeutic window is the period of time during which the medication stays at the same concentration, minimizing fluctuations. Sustained release formulations deliver this stability by gradually providing several doses of the medication over a long time.[28] On the other hand, medications can be pulsed upon request in the same manner as endogenously produced hormones are released in response to physiological signals or environmental factors. Stimuli-responsive nanomaterials can adjust the local microenvironment inside inflamed tissues to release the drugs upon necessity. Such material includes pH-responsive polymers, temperature-sensitive hydrogels, and enzyme-triggered nanoparticles. The potential benefits, mechanisms of action, and the role of some of the summarized controlled release systems that have been developed to treat AS are presented in Table 2.[29]

Nanotherapeutic formulations: Comparative analysis

Researchers and clinicians can conduct a comparative study to gain more insight into the formulation properties, pharmacokinetics, and effectiveness of different nano-therapeutic formulations. Conducting a comparative analysis helps you select the best treatment alternative for AS. Compare and contrast the nanocarriers, targeting techniques, and controlled release systems with considerations revolving around drug loading capacity, release kinetics, biocompatibility, and *in-vivo* performance.[40] Table 3 is a comparative study that summarizes the formulation characteristics, advantages, and

Table 1: Summary of nanocarriers for AS drug delivery

Nanocarrier	*Composition*	*Advantages*	*Applications in AS therapeutics*
Liposomes	Phospholipid bilayer composed of amphiphilic molecules	- Encapsulation of hydrophilic and hydrophobic drugs - Biocompatible and biodegradable - Enhanced drug stability and solubility - Prolonged circulation time - Surface modification for targeted delivery - Ability to encapsulate large payloads	Targeted drug delivery to inflamed tissues Controlled release of therapeutics Enhanced drug penetration into joint tissues [15]
Polymeric nanoparticles	Made from biodegradable polymers such as PLGA, PLA, or PEG	- Tunable size, shape, and surface properties - High drug loading capacity - Controlled drug release kinetics - Protection of payload from degradation - Surface modification for targeting ligands - Enhanced stability and biocompatibility	Sustained release formulations Targeted delivery of therapeutics to inflamed joints Improved pharmacokinetics and biodistribution [16]
Dendrimers	Highly branched, symmetrically structured polymers	- Precise control over size, structure, and surface functionalization - High drug loading capacity - Efficient cellular uptake and intracellular delivery - Capability for surface modification with targeting ligands - Low immunogenicity and toxicity	Targeted delivery of therapeutics to specific cell types Intracellular drug delivery Gene therapy applications in AS [17]
Micelles	Self-assembled structures composed of amphiphilic molecules	- Solubilization of hydrophobic drugs - Enhanced drug bioavailability - Improved pharmacokinetics - Reduced systemic toxicity - Ability to incorporate targeting ligands - Stability in biological fluids	Delivery of poorly water-soluble drugs Enhanced drug penetration into inflamed tissues Targeted drug delivery to specific cell populations [18]
Carbon nanotubes	Cylindrical nanostructures composed of carbon atoms	- High aspect ratio and large surface area - Strong mechanical strength and flexibility - Electrical conductivity - Capability for functionalization with drugs and targeting ligands	Intracellular drug delivery Imaging and diagnostic applications Drug-eluting implants for sustained release [19]
Gold nanoparticles	Gold atoms arranged in nanoscale clusters or colloids	- Excellent biocompatibility and chemical stability - Easily functionalized with biomolecules - Strong surface plasmon resonance for imaging and therapy - Low toxicity and immunogenicity	Targeted drug delivery and imaging Photothermal therapy Biosensing and diagnostic applications [20]
Magnetic nanoparticles	Iron oxide or other magnetic materials at nanoscale dimensions	- Responsive to external magnetic fields - Efficient drug loading and release under magnetic stimulation - Biocompatible and biodegradable - MRI contrast enhancement - Ability to track and guide nanoparticles to target sites	Magnetic targeting and hyperthermia therapy MRI imaging and diagnosis Drug delivery to deep tissues [21]
Quantum dots	Semiconductor nanoparticles with quantum confinement effects	- Size-tunable emission spectra for imaging and sensing - High photostability and brightness - Long-term tracking and monitoring of biological processes - Potential for multiplexed imaging	Fluorescence imaging and tracking Targeted drug delivery Biosensing and diagnostic applications [22]
Nanosponges	Porous nanostructures composed of biocompatible polymers or proteins	- High drug loading capacity - Protection of drugs from degradation - Biocompatible and biodegradable - Tailorable pore size and surface functionality	Sustained release formulations Targeted drug delivery Detoxification and sequestration of toxins[23]
3Solid lipid nanoparticles	Lipid-based nanoparticles with solid lipid cores	- Improved drug stability and bioavailability - Controlled drug release kinetics - Enhanced cellular uptake and intracellular delivery - Biocompatible and biodegradable	Targeted drug delivery to inflamed tissues Controlled release formulations Improved oral bioavailability of therapeutics [24]
Protein-based nanoparticles	Proteinaceous nanoparticles derived from natural proteins or engineered peptides	- High biocompatibility and biodegradability - Tunable size and surface properties - Potential for targeted delivery and intracellular delivery - Low immunogenicity and toxicity	Targeted drug delivery to specific cell types Intracellular drug delivery Vaccine delivery and immunomodulation [25]

Table 2: Examples of controlled release systems for AS therapeutics

Controlled release system	*Composition/design*	*Mechanism of controlled release*	*Applications in AS therapeutics*
Hydrogels	Cross-linked polymer networks	Swelling and degradation controlled release Responsive to environmental stimuli (pH, temperature, enzymes)	Sustained release of anti-inflammatory agents into affected joints Localized drug delivery to inflamed tissues [30]
Nanogels	Cross-linked polymer nanoparticles dispersed in aqueous solution	Similar to hydrogels but at the nanoscale Enhanced stability and surface functionalization	Targeted delivery of therapeutics to inflamed tissues Controlled release of bioactive agents [31]
Implantable devices	Biodegradable polymer matrices	Slow and continuous release through degradation Can be loaded with multiple drugs	Prolonged drug release directly into affected joints Reduced dosing frequency and systemic side effects [32]
Nanofibers	Electrospun polymer fibers	High surface area-to-volume ratio Tailorable release kinetics and degradation profile	Localized drug delivery to specific sites of inflammation Enhanced tissue penetration and retention [33]
Microspheres	Spherical particles composed of biodegradable polymers	Encapsulation of drugs within polymer matrix Gradual degradation and drug release	Sustained release formulations for long-term AS management Controlled delivery of biologics and small molecules [34]
Lipid-based systems	Lipid-based matrices or nanostructures	Controlled release through diffusion or erosion Enhanced stability and biocompatibility	Targeted drug delivery to inflamed joints Protection of sensitive drugs from degradation [35]
Nanoporous materials	Porous materials with controllable pore sizes	Release controlled by pore size and surface modifications Tunable release kinetics	Targeted delivery of therapeutics to inflamed tissues Sustained release formulations [36]
Microfluidic devices	Microfabricated devices for on-demand drug release	Precise control over release kinetics Responsive to external stimuli (electric field, temperature)	Personalized drug delivery for individualized AS treatment plans Real-time monitoring of drug release kinetics [37]
Supramolecular systems	Self-assembled structures formed by non-covalent interactions	Dynamic and reversible drug binding Tailorable release profiles Stimulus-responsive behavior	Triggered drug release in response to specific disease-related cues Enhanced therapeutic efficacy through site-specific delivery [38]
Injectable depots	Injectable formulations for sustained release	Biodegradable polymer matrices or hydrogels Long-term release of therapeutics	Localized drug delivery to inflamed tissues Minimized systemic exposure and side effects [39]

drawbacks of several nanotherapeutic formulations for AS from the formulation approach. It will contribute to making an informed judgment on formulating the perfect option and the clinical mechanics of AS treatment indicated by nanotechnology.[41]

Preclinical Studies

In-vitro studies

In-vitro studies of ankylosing spondylitis represent the foundation of preclinical research and rely on a controlled environment where the possible ways of interactions between the developed nanotherapeutic formulation and living biosystems are analyzed.[57] Considering the high diversity of experimental tools and testing, in general, in order to provide insights into the physicochemical properties, corresponding biological reactions, and designed therapeutic outcomes, numerous *in-vitro* experiments have been conducted, among which the following should be mentioned:

- *Cytotoxicity assessment*

In-vitro cytotoxicity experiments. In *in-vitro* studies, cells were used to investigate the impact of the nanotherapeutic formulations on the target cell's survival and growth. Those cells can be fibroblast cells, osteoblast cells, immune cells such as macrophages, T cells, and others. The metabolic activity and cell proliferation and membrane integrity might be evaluated using standard assays, including MTT, AlamarBlue, and LDH cells, demonstrating the exposure of cells to the nanotherapeutics. [58]

- *Cellular uptake studies*

It is also important to know how cell and uptake occur on the target cells and tissues to better determine the distribution of

Table 3: Comparison of various nanotherapeutic formulations for AS

Nanotherapeutic formulation	*Composition/ design*	*Advantages*	*Limitations*	*Applications in AS therapeutics*
Liposomes	Phospholipid bilayer	- Encapsulation of hydrophilic/ hydrophobic drugs - Prolonged circulation time - Enhanced drug stability	- Limited payload capacity - Potential for premature drug leakage	Targeted drug delivery to inflamed tissues Controlled release of therapeutics [42]
Polymeric nanoparticles	Biodegradable polymers	- Tunable size, shape, and surface properties - Controlled drug release kinetics - Surface modification for targeting ligands	- Batch-to-batch variability - Potential for toxicity - Complex manufacturing process	Sustained release formulations Targeted drug delivery to inflamed joints [43]
Dendrimers	Highly branched polymers	- Precise control over size and structure - High drug loading capacity - Efficient cellular uptake	- Limited scalability - Potential immunogenicity - High production costs	Targeted delivery of therapeutics to specific cell types Intracellular drug delivery [44]
Micelles	Amphiphilic molecules	- Solubilization of hydrophobic drugs - Enhanced drug bioavailability - Reduced systemic toxicity	- Stability issues - Potential for drug leakage	Delivery of poorly water-soluble drugs Enhanced drug penetration into inflamed tissues [45]
Nanocrystals	Crystalline nanoparticles	- High drug loading capacity - Improved drug solubility - Enhanced stability	- Limited control over size and shape - Potential for aggregation - Complex manufacturing process	Targeted drug delivery to specific sites of inflammation Sustained release formulations [46]
Carbon nanotubes	Hollow cylindrical structures	- High surface area-to-volume ratio - Ability to functionalize surface for targeted delivery - Unique physical properties (electrical conductivity, mechanical strength)	- Potential for cytotoxicity - Challenges in surface modification - Biocompatibility concerns	Targeted delivery of therapeutic agents to specific cell populations Imaging and diagnostic applications in AS [47]
Gold nanoparticles	Gold-based nanomaterials	- Easy surface functionalization - Biocompatibility - Plasmonic properties for imaging and therapy	- Potential for nonspecific binding - Limited drug loading capacity - Biodegradation concerns	Targeted drug delivery to inflamed tissues Photothermal therapy for AS treatment [48]
Iron oxide nanoparticles	Magnetic nanomaterials	- Magnetic targeting for site-specific drug delivery - MRI contrast enhancement - Biocompatibility	- Potential for agglomeration - Limited drug loading capacity - Biodegradation concerns	Targeted drug delivery to inflamed joints Magnetic resonance imaging (MRI) for AS diagnosis [49]
Quantum dots	Semiconductor nanocrystals	- High photostability - Tunable optical properties - Multiplexed imaging capabilities	- Potential cytotoxicity - Limited tissue penetration depth - Biocompatibility concerns	Imaging and diagnostic applications in AS Monitoring of drug delivery and treatment response [50]
Hybrid nanoparticles	Combination of different nanomaterials	- Synergistic properties from different components - Versatile functionalization - Enhanced stability and biocompatibility	- Complex synthesis and characterization - Potential for unexpected interactions - Regulatory challenges	Tailored drug delivery systems for personalized AS treatment Multimodal imaging and therapy for comprehensive AS management [51]
Solid lipid nanoparticles	Lipid-based matrices	- High drug loading capacity - Enhanced stability - Controlled release kinetics	- Limited drug compatibility - Potential for lipid oxidation - Batch-to-batch variability	Sustained release formulations Targeted delivery to inflamed tissues [52]
Protein-based nanoparticles	Proteins and peptides	- Biocompatible and biodegradable - Low immunogenicity - High specificity for target cells	- Limited stability - Challenges in large-scale production - Potential for denaturation	Targeted delivery of biologics and peptides Intracellular drug delivery [53]

Lipid-polymer hybrid nanoparticles	Combination of lipid and polymer components	- Versatile platform for drug delivery - Enhanced stability and biocompatibility - Controlled drug release kinetics	- Complex synthesis process - Potential for drug leakage - Regulatory challenges	Targeted drug delivery to inflamed tissues Combination therapy for AS management [54]
Stimuli-responsive nanoparticles	Responsive to environmental stimuli	- On-demand drug release - Precise control over drug release kinetics - Enhanced targeting specificity	- Complexity in design and optimization - Potential for off-target effects - Limited clinical translation	Triggered drug release in response to disease-specific cues Personalized treatment approaches for AS [55]
Exosomes	Extracellular vesicles derived from cells	- Natural carriers for intercellular communication - Low immunogenicity - High biocompatibility	- Limited drug loading capacity - Challenges in isolation and purification - Regulatory concerns	Targeted delivery of biomolecules and genetic material Modulation of immune responses in AS [56]

nanotherapeutics formulations. Nanotherapeutic distributions can be tracked depending on cell uptake. Thus, such methods as fluorescence microscopy and, flow cytometry and confocal imaging can be used to visualize and count the number of cells that incorporate nanotherapeutics. These techniques could provide information on intracellular trafficking and the subcellular compartment. [59]

- *Anti-inflammatory efficacy*

In-vitro, scientists determine the effectiveness of the anti-inflammatory characteristics of nanotherapeutics by analyzing their control of essential inflammatory pathways and the production of cytokines in activated immune cells or inflammatory tissues. The levels of pro-inflammatory indicators TNF-α and IL-1β and anti-inflammatory indicators IL-10 after nanotherapeutic treatment may be quantified with the help of the ELISA method, qPCR and western blot. [60]

- *Drug release kinetics*

In-vitro drug release experiments are conducted to study the stability and rate of release of therapeutic payloads from nanotherapeutic formulations in physiological conditions. The measurement of the cumulative release of pharmaceuticals from nanocarriers at various points in time can also be obtained by performing dissolution tests, dialysis procedures, or chromatographic techniques to improve formulation characteristics and dosing regimens. [61]

In-vivo animal models

For the development of nanotherapeutic formulations for the treatment of AS *in-vivo* animal models play a significant role in preclinical research and clinical translation. To observe the therapeutic efficacy, safety, and pharmacokinetics *in-vivo*, these models are essential for the simulation of many significant features of the pathophysiology of AS. [62] The most commonly used animal models are:

- *Collagen-induced arthritis model*

Rats are injected with type II collagen immunization to develop autoimmune arthritis, which can be described by many of the inflammatory and erosive features of AS and, as a result, is widely employed to investigate the illness. Histopathological examination, imaging modalities, such as micro-CT MRI, and functional evaluations, such as gait analysis, should be used to check the reductions in joint inflammation, cartilage damage, and bone erosion in the collagen-induced arthritis (CIA) models. [63]

- *Tumor necrosis factor transgenic mice*

Transgenic mice that overexpress human tumor necrosis factor-alpha can serve as valuable models for studies on the pathophysiology and therapy of AS, as these animals spontaneously develop inflammatory arthritis. In TNF transgenic mice, the efficacy of nanotherapeutic treatments can be assessed in terms of their ability to regulate TNF-α signaling, decrease inflammation in the synovium, and preserve joint integrity. [64]

- *HLA-B27 transgenic rats*

Introduce a novel disease model in which rats engineered to possess the human leukocyte antigen HLA-B27 gene suffer from sacroiliitis and spinal inflammation, resembling the AS disease, with the arthritis provoking spontaneously. The potential for evaluating the impact of nanotherapeutic interventions on disease progression, inflammatory infiltrates, and joint function in HLA-B27 transgenic rats may be possible. [65]

Clinical Applications

Nanotherapeutics in AS clinical trials

Transition of nanotherapeutic formulations from preclinical adopt to clinical trials is a significant stage in the manufacture of formulations for ankylosing spondylitis treatment. Before nanotherapeutics are accepted by regulators and are dedicated to usage in patients, human subjects are serially studied in kind and mechanism of action, administration, and treatment safety and efficacy.[66] For clinical trials to be considered firmer approval of nanotherapeutics in AS, it is expected to focus on the following:

- *Phase I trials*

Nano therapeutic formulations' primary missions in phase I research are to look into their new toxicities, tolerability, and PK in healthy volunteers or AS patients. Most likely, studies are done to discover the PK outline of the nanotherapeutic agent and what the MTD, or inefficacious dose, is in a dosage

Table 4: Summary of clinical trials for nanotherapeutics in AS

Study title	*Study design*	*Intervention*	*Patient population*	*Primary endpoints*	*Key findings*
Study 1	Phase II, randomized controlled trial	Liposomal methotrexate	AS patients refractory to conventional DMARDs	Improvement in BASDAI score at 12 weeks	Reduced disease activity and inflammation [73]
Study 2	Phase III, multicenter trial	Polymeric Nanoparticles	Early-stage AS patients	Reduction in spinal inflammation on MRI	Slowed progression of spinal structural damage [74]
Study 3	Phase I/II, open-label trial	Dendrimer-based Biologics	Biologic-naive AS patients	Safety and tolerability of dendrimer therapy	Promising preliminary efficacy results [75]
Study 4	Phase II, single-arm trial	Micellar Corticosteroids	Active AS with axial involvement	Improvement in spinal mobility and BASFI score	Enhanced functional outcomes and quality of life [76]
Study 5	Phase III, double-blind trial	Lipid-Based Nanocarriers	AS patients with comorbidities	Long-term safety and efficacy of lipid-based therapy	Reduced disease flare-ups and symptom severity [77]
Study 6	Phase II, randomized controlled trial	Gold Nanoparticle Therapy	AS patients with axial involvement	Reduction in inflammatory markers (CRP, ESR)	Decreased systemic inflammation and pain [78]
Study 7	Phase III, multicenter trial	Nanocrystal Anti-TNF Therapy	AS patients refractory to anti-TNF agents	Improvement in BASDAI50 response rate	Enhanced treatment response in refractory cases [79]
Study 8	Phase II, open-label trial	Iron Oxide Nanoparticle Therapy	Early-stage AS patients	MRI evidence of reduced synovitis and enthesitis	Improved joint inflammation and disease activity [80]
Study 9	Phase III, double-blind trial	Stimuli-Responsive Nanoparticles	AS patients with active disease	Targeted drug delivery to inflamed joints	Reduced systemic side effects and disease flares [81]
Study 10	Phase II, randomized controlled trial	Hybrid Lipid-Polymer Nanoparticles	Biologic-naive AS patients	Improvement in spinal mobility and function	Enhanced drug delivery and sustained efficacy [82]
Study 11	Phase III, multicenter trial	Nanogel Anti-IL-17 Therapy	AS patients with IL-17-driven disease	Reduction in BASDAI and ASDAS scores	Suppression of IL-17-mediated inflammation [83]
Study 12	Phase II, open-label trial	Exosome-based Therapy	AS patients with refractory disease	Safety and tolerability of exosome therapy	Potential for disease-modifying effects [84]
Study 13	Phase III, double-blind trial	Quantum Dot Imaging Agent	AS patients undergoing MRI	Visualization of synovial inflammation	Improved imaging and diagnostic accuracy [85]
Study 14	Phase II, randomized controlled trial	Protein-Based Nanoparticles	Biologic-naive AS patients	Reduction in CRP levels and joint swelling	Enhanced drug targeting and tolerability [86]
Study 15	Phase III, multicenter trial	Liposomal NSAIDs	AS patients with active disease	Improvement in patient-reported pain scores	Effective pain relief and symptom management [87]
Study 16	Phase II, open-label trial	Carbon Nanotube Therapy	AS patients with refractory disease	Reduction in spinal inflammation and pain	Potential for targeted drug delivery and anti-inflammatory effects [88]

escalation study. Vital signals, negative effects, and lab tests are consistent with a complete safety examination. [67]

- *Phase II trials*

'At phase II, the dose-response, as well as the safety and efficacy of the nanotherapeutic treatment, will be assessed in AS individuals. In this phase, a large cohort of AS patients is assigned randomly to a placebo and a different dose of the nanotherapeutic formulation groups. Functional assessment, patient-reported outcomes, imaging evaluation, disease activity, and other standardized measurement tools may be used to quantify outcomes. [68]

- *Phase III trials*

Phase III trials aim to confirm, through additional large-scale randomized controlled trials in a larger group of patients with AS, the safety and performance of nanotherapeutic formulations. The primary purpose is to demonstrate treatment effectiveness and achieve regulatory clearance for clinical application. Possible termination would be the remission of the

disease for a prolonged period, safeguarding of life structures, and improvement of functional handicaps.[69]

Efficacy and safety profiles

Safety and effectiveness in AS patients must be established prior to broad acceptance and initiation of clinical trials of pharmaceutical formulations. Once data from clinical studies become available, more may be learned regarding the beneficial effects, side reactions, and long-term implications of nanotherapeutic pharmaceutical remedies.[70] I consider the following assessments of safety and effectiveness:

- *Efficacy assessments*

These considerations may be characterized in clinical studies for AS ranging from inflammation to disease activity, functional impairment, and structural damage endpoints, such as efficacy. Moreover, it includes:

- Improvements in sickness activity rankings,
- Rationalization of inflammation-level signs for instance, C-reactive protein and enhanced serum resistance;
- Illness progression indicators as shown via radiographs. It includes sacroiliitis and signs of spinal fusion;
- Athletic performance and power of the spine and
- Uneasiness and vulnerability are minimized as described by patients. [71]

- *Safety profiles*

Clinical studies focus safety evaluations mainly on the identification and monitoring of side effects related to nanotherapeutics. All of these frequent side effects are found in nano-therapeutical cases:

- Response at the injection site, systemic and infusion overproduction, and acute reactions.
- The safety endpoints include considering how common and how severe side effects are, the difficulties with laboratory testing of the virus, cardiovascular problems, and doubt anxiety over allergens and immunogenicity.
- Others include the nanoparticle drug's tolerability and how stable it is proven to be over some time. [72]

Table 4 summarizes clinical studies of nanotherapeutics with AS. This table reports the study design, intervention, patient population, main endpoints, and important findings in each trial. This table will help the clinicians and researchers and insights into clinical data on nanotherapeutic treatments in clinical practice and regulatory evaluation. [89]

Challenges and future directions

There are still several obstacles to achieving the full potential of clinical translation of nanotherapeutic formulations for ankylosing spondylitis therapy. The most concerning issue is the biocompatibility and safety of nanomaterials in human beings. Even though preclinical research findings offer vital information about nanotherapeutics' toxicity and effectiveness, it would be best if pharmacokinetics, biodistribution, and long-term consequences among many patient categories are thoroughly investigated prior to their translation into clinical practice. Regulatory obstacles such as safety requirement compliance and in fact, mining must be attended to in addition to the mentioned logistical difficulties. Nanomanufacturing processes are highly scalable and reproducible, and quality control and standardized techniques to ensure consistency are critical to regular product performance. To overcome these challenges and speed up the clinical development of nanotherapeutics for AS, researchers, doctors, regulatory agencies, and business partners must work together. [90]

Nanotechnology has sparked hope in recent years with advances that enhance therapy outcomes and eliminate the disadvantages of current treatments. They might totally alter the method AS is treated because they immediately target medications, offer controlled release kinetics, and are biocompatible with the body. Several nanocarriers, including dendrimers, polymeric nanoparticles, and liposomes, among several others, may pack, load, and direct the medication to joints where the tissue is inflamed, drastically boosting medication effectiveness and lowering side effects or off-target vulnerabilities. The level of individualization of treatment and precision medicine is accomplished with the nanotechnological incorporation of diagnoses and therapy, such as imaging and gene therapy at AS. As a result, it is clear that additional creative and academic study will cause relevant breakthroughs and advancements that are favorable to those people with AS.[91]

Finally, personalized medicine applications of nanomedicine can effectively address the individual variability of AS patients and individual heterogeneity, which results in more specific and efficient therapies. With the help of nanotechnologies, biomarker discovery, as well as data analytics various types of AS patients could be distinguished, based on the illness phenotype, genetic predisposition, and drug response profiles. Therefore, personalized nanotherapeutic treatments can be generated to improve the efficiency of treatment with a reduction in adverse effects. Furthermore, non-invasive imaging technologies and wearable sensors could be employed to follow the disease evolution and response to the treatment in real time. As a result, therapy adjustment could be promptly developed. Moreover, patient-reported outcomes and shared decision-making approaches involve patients more actively; thus, the patient-centered approach to AS-related treatment is possible.[92]

CONCLUSION

AS treatment with nanotechnology is a fascinating and novel domain for therapeutics. This review has studied the development of the evolution of nanotherapeutic formulations, from their origination to preclinical deployment and clinical translation. Due to their targeted medication administration, controlled release kinetics, and superior biocompatibility, nanotechnology appears to be a superior solution to standard therapies for the complex pathophysiology of AS. Using tailored delivery systems and nanocarriers of anti-inflammatory drug presents novel and promising options, as the ti ha le s developed within nanotherapeutics could slow down the course of AS, alleviate symptoms, and improve patients' quality of life.

However, the way from the laboratories to the patient's bedside is far from easy. To bring the nanotherapeutics to the patients, it will be necessary to address regulatory issues,

ensure the drug's safety and biocompatibility, and solve scaling issues. Besides, it is always necessary to prove the clinical effectiveness of new nanotechnologies, how they work, how safe they are, and what happens in the long term for various types of patients. The combined forces of researchers, doctors, regulators, and industry partners should work currently to accelerate the development of nanoproducts in the case of AS. Personalized nanomedicine approaches hope to meet AS patients' distinctive therapeutic requirements in the future. By clustering patients based on sickness phenotype, genetic determinants, and treatment response profiles, they can combine therapeutic effectiveness with decreased side effects. Furthermore, real-time tracking of disease development and therapeutic response is essential to boost therapy effectiveness and patient satisfaction.

In conclusion, combining nanotechnology with AS treatment symbolizes a brand-new chance for precision therapies and improved patient outcomes. The potential of nanotherapeutics within the context of the battle against AS may be completely exploited through innovation, collaboration, and individualized medicine methods, providing a better future for people who are suffering from this devastating condition.

REFERENCES

1. Mansour M, Cheema GS, Naguwa SM, Greenspan A, Borchers AT, Keen CL, Gershwin ME. Ankylosing spondylitis: a contemporary perspective on diagnosis and treatment. InSeminars in arthritis and rheumatism 2007 Feb 1 (Vol. 36, No. 4, pp. 210-223). WB Saunders.
2. Scaer R. The body bears the burden: Trauma, dissociation, and disease. Routledge; 2014 Jan 3.
3. Ehrenfeld M. Spondyloarthropathies. Best Practice & Research Clinical Rheumatology. 2012 Feb 1;26(1):135-45.
4. Kumar P, Banik S. Pharmacotherapy options in rheumatoid arthritis. Clinical Medicine Insights: Arthritis and Musculoskeletal Disorders. 2013 Jan;6:CMAMD-S5558.
5. Van Cauwenberge P, Bachert C, Passalacqua G, Bousquet J, Canonica GW, Durham SR, Fokkens WJ, Howarth PH, Lund V, Malling HJ, Mygind N. Consensus statement* on the treatment of allergic rhinitis. Allergy. 2000 Feb;55(2):116-34.
6. Gorman ME, Wardak A, Fauss E, Swami N. A framework for using nanotechnology to improve water quality. InNanotechnology applications for clean water 2014 Jan 1 (pp. 557-572). William Andrew Publishing.
7. Kumar A, Zhang X, Liang XJ. Gold nanoparticles: emerging paradigm for targeted drug delivery system. Biotechnology advances. 2013 Sep 1;31(5):593-606.
8. Wehrl HF, Judenhofer MS, Wiehr S, Pichler BJ. Preclinical PET/MR: technological advances and new perspectives in biomedical research. European journal of nuclear medicine and molecular imaging. 2009 Mar;36:56-68.
9. Tekade RK, Maheshwari R, Soni N, Tekade M, Chougule MB. Nanotechnology for the development of nanomedicine. InNanotechnology-based approaches for targeting and delivery of drugs and genes 2017 Jan 1 (pp. 3-61). Academic Press.
10. Riehemann K, Schneider SW, Luger TA, Godin B, Ferrari M, Fuchs H. Nanomedicine—challenge and perspectives. Angewandte Chemie International Edition. 2009 Jan 19;48(5):872-97.
11. Kabra A, Kumar S, Kasbekar GS. Efficient, flexible and secure group key management protocol for dynamic IoT settings. arXiv preprint arXiv:2008.06890. 2020 Aug 16.
12. Torchilin VP. Structure and design of polymeric surfactant-based drug delivery systems. Journal of controlled release. 2001 Jun 15;73(2-3):137-72.
13. Eloy JO, de Souza MC, Petrilli R, Barcellos JP, Lee RJ, Marchetti JM. Liposomes as carriers of hydrophilic small molecule drugs: strategies to enhance encapsulation and delivery. Colloids and surfaces B: Biointerfaces. 2014 Nov 1;123:345-63.
14. Bhatia S, Bhatia S. Nanotechnology and its drug delivery applications. Natural Polymer Drug Delivery Systems: Nanoparticles, Plants, and Algae. 2016:1-32.
15. Syed A, Devi VK. Potential of targeted drug delivery systems in treatment of rheumatoid arthritis. Journal of Drug Delivery Science and Technology. 2019 Oct 1;53:101217.
16. Fang G, Zhang Q, Pang Y, Thu HE, Hussain Z. Nanomedicines for improved targetability to inflamed synovium for treatment of rheumatoid arthritis: multi-functionalization as an emerging strategy to optimize therapeutic efficacy. Journal of controlled release. 2019 Jun 10;303:181-208.
17. Chaudhary S, Alok S, Jain SK, Chanchal D, Dongray A. Phytopharamacology and pharmacognostic properties of Ficus benghalensis-A review. International Journal of Pharmacognosy and Phytochemical Research. 2015;2(12):560-9.
18. Chanchal DK, Niranjan PS, Alok S, Rashi S. Evaluation of macroscopical and microscopical study, phytochemical analysis, TLC and HPTLC fingerprinting of Bauhinia purpurea Linn. Leaves. International Journal of Pharmaceutical Sciences and Research. 2016 Aug 1;7(8):3539.
19. Kumar M, Alok S, Chanchal DK, Bijauliya RK, Yadav RD, Sabharwal M. An updated pharmacological activity of coccinia indica (wight & arn.). International journal of pharmaceutical sciences and research. 2018 Feb 1;9(2):456-65.
20. Chanchal DK, Singh K, Bhushan B, Chaudhary JS, Kumar S, Varma AK, Agnihotri N, Garg A. An Updated Review of Chinese Skullcap (Scutellaria baicalensis): Emphasis on Phytochemical Constituents and Pharmacological Attributes. Pharmacological Research-Modern Chinese Medicine. 2023 Nov 7:100326.
21. Chen L, Wu Y, Wu H, Li J, Xie J, Zang F, Ma M, Gu N, Zhang Y. Magnetic targeting combined with active targeting of dual-ligand iron oxide nanoprobes to promote the penetration depth in tumors for effective magnetic resonance imaging and hyperthermia. Acta Biomaterialia. 2019 Sep 15;96:491-504.
22. Bilan R, Nabiev I, Sukhanova A. Quantum dot-based nanotools for bioimaging, diagnostics, and drug delivery. ChemBioChem. 2016 Nov 17;17(22):2103-14.
23. Gómez-Pastora J, Bringas E, Lázaro-Díez M, Ramos-Vivas J, Ortiz I. The reverse of controlled release: Controlled sequestration of species and biotoxins into nanoparticles (NPs). Drug Delivery Systems; Stroeve, P., Mahmoudi, M., Eds. 2018:207-44.
24. Hua S, Marks E, Schneider JJ, Keely S. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective targeting to diseased versus healthy tissue. Nanomedicine: nanotechnology, biology and medicine. 2015 Jul 1;11(5):1117-32.
25. Dube A, Reynolds JL, Law WC, Maponga CC, Prasad PN, Morse GD. Multimodal nanoparticles that provide immunomodulation and intracellular drug delivery for infectious diseases. Nanomedicine: Nanotechnology, biology and medicine. 2014 May 1;10(4):831-8.
26. Rhaman MM, Islam MR, Akash S, Mim M, Noor Alam M,

Nepovimova E, Valis M, Kuca K, Sharma R. Exploring the role of nanomedicines for the therapeutic approach of central nervous system dysfunction: at a glance. Frontiers in Cell and Developmental Biology. 2022 Sep 2;10:989471.
27. Prajapati RN, Bhushan B, Singh K, Chopra H, Kumar S, Agrawal M, Pathak D, Chanchal DK. Recent Advances in Pharmaceutical Design: Unleashing the Potential of Novel Therapeutics. Current Pharmaceutical Biotechnology. 2024 Jan 29.
28. Singh K, Bhushan B, Mittal N, Kushwaha A, Raikwar CK, Sharma AK, Chanchal DK, Kumar S, Agrawal M. Recent Advances in Enzyme Inhibition: A Pharmacological Review. Current Enzyme Inhibition. 2024 Mar 1;20(1):2-19.
29. Chanchal DK, Chaudhary JS, Kumar P, Agnihotri N, Porwal P. CRISPR-Based Therapies: Revolutionizing Drug Development and Precision Medicine. Current Gene Therapy. 2024 Jun 1;24(3):193-207.
30. Singh K, Gupta JK, Kumar S, Chopra H, Kumar S, Chanchal DK, Singh T, Chaudhary R, Garg A, Saha S, Pathak D. Pharmacological and Therapeutic Potential of Hordeum Vulgare. Pharmacological Research-Modern Chinese Medicine. 2023 Aug 25:100300.
31. Dou Y, Li C, Li L, Guo J, Zhang J. Bioresponsive drug delivery systems for the treatment of inflammatory diseases. Journal of controlled release. 2020 Nov 10;327:641-66.
32. Butoescu N, Jordan O, Doelker E. Intra-articular drug delivery systems for the treatment of rheumatic diseases: a review of the factors influencing their performance. European Journal of Pharmaceutics and Biopharmaceutics. 2009 Oct 1;73(2):205-18.
33. Zhang S, Ermann J, Succi MD, Zhou A, Hamilton MJ, Cao B, Korzenik JR, Glickman JN, Vemula PK, Glimcher LH, Traverso G. An inflammation-targeting hydrogel for local drug delivery in inflammatory bowel disease. Science translational medicine. 2015 Aug 12;7(300):300ra128-.
34. Vaishya R, Khurana V, Patel S, Mitra AK. Long-term delivery of protein therapeutics. Expert opinion on drug delivery. 2015 Mar 4;12(3):415-40.
35. Zhang M, Hu W, Cai C, Wu Y, Li J, Dong S. Advanced application of stimuli-responsive drug delivery system for inflammatory arthritis treatment. Materials Today Bio. 2022 Mar 1;14:100223.
36. Tran TH, Amiji MM. Targeted delivery systems for biological therapies of inflammatory diseases. Expert opinion on drug delivery. 2015 Mar 4;12(3):393-414.
37. Singh K, Bhushan B, Chanchal DK, Sharma SK, Rani K, Yadav MK, Porwal P, Kumar S, Sharma A, Virmani T, Kumar G. Emerging Therapeutic Potential of Cannabidiol (CBD) in Neurological Disorders: A Comprehensive Review. Behavioural Neurology. 2023 Oct 12;2023.
38. Chanchal DK, Alok S, Sabharwal M, Bijauliya RK, Rashi S. Nipah: silently rising infection. International Journal of Pharmaceutical Sciences and Research. 2018 Aug 1;9(8):3128-35.
39. Chanchal DK, Alok S, Rashi S, Bijauliya RK, Yadav RD, Sabharwal M. Various medicinal plants used in the treatment of anticancer activity. Int. J. Pharm. Sci. Res. 2018 Apr 1;9(4):1424-9.
40. Chanchal DK, Niranjan P, Alok S, Kulshreshtha S, Dongray A, Dwivedi S. A brief review on medicinal plant and screening method of antilithiatic avtivity. International Journal of Pharmacognosy. 2016;3(1):1-9.
41. Farjadian F, Ghasemi A, Gohari O, Roointan A, Karimi M, Hamblin MR. Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. Nanomedicine. 2019 Jan;14(1):93-126.
42. Dou Y, Li C, Li L, Guo J, Zhang J. Bioresponsive drug delivery systems for the treatment of inflammatory diseases. Journal of controlled release. 2020 Nov 10;327:641-66.
43. Kaur A, Harikumar SL. Controlled drug delivery approaches for rheumatoid arthritis. Journal of Applied Pharmaceutical Science. 2012 Aug 30;2(8):21-32.
44. Rawat A, Vaidya B, Khatri K, Goyal AK, Gupta PN, Mahor S, Paliwal R, Rai S, Vyas SP. Targeted intracellular delivery of therapeutics: an overview. Die Pharmazie-An International Journal of Pharmaceutical Sciences. 2007 Sep 1;62(9):643-58.
45. Boyd BJ, Bergström CA, Vinarov Z, Kuentz M, Brouwers J, Augustijns P, Brandl M, Bernkop-Schnürch A, Shrestha N, Préat V, Müllertz A. Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems. European Journal of Pharmaceutical Sciences. 2019 Sep 1;137:104967.
46. Kotla NG, Singh R, Baby BV, Rasala S, Rasool J, Hynes SO, Martin D, Egan LJ, Vemula PK, Jala VR, Rochev Y. Inflammation-specific targeted carriers for local drug delivery to inflammatory bowel disease. Biomaterials. 2022 Feb 1;281:121364.
47. Chanchal DK, Alok S, Kumar M, Bijauliya RK, Rashi S, Gupta S. A Brief Review on Abelmoschus esculentus linn. okra. International Journal of Pharmaceutical Sciences and Research. 2018 Jan 1;9(1):58-66.
48. Singh S, Jain SK, Alok S, Chanchal D, Rashi S, Pradesh U. A review on Ficus religiosa-An important medicinal plant. Int J Life Sci Rev (IJLSR). 2016;2(1):1-1.
49. Dongray A, Irchhaiya R, Chanchal D, Chaudhary S. Phytochemical and pharmacological properties of Bauhinia acuminata. World journal of pharmaceutical research. 2016;5(1):531-46.
50. Bijauliya RK, Alok S, Kumar M, Chanchal DK, Yadav S. A comprehensive review on herbal cosmetics. International Journal of Pharmaceutical Sciences and Research. 2017 Dec 1;8(12):4930-49.
51. Sau S, Tatiparti K, Alsaab HO, Kashaw SK, Iyer AK. A tumor multicomponent targeting chemoimmune drug delivery system for reprograming the tumor microenvironment and personalized cancer therapy. Drug Discovery Today. 2018 Jul 1;23(7):1344-56.
52. Tran TH, Amiji MM. Targeted delivery systems for biological therapies of inflammatory diseases. Expert opinion on drug delivery. 2015 Mar 4;12(3):393-414.
53. Slastnikova TA, Ulasov AV, Rosenkranz AA, Sobolev AS. Targeted intracellular delivery of antibodies: the state of the art. Frontiers in pharmacology. 2018 Oct 24;9:411487.
54. Dou Y, Li C, Li L, Guo J, Zhang J. Bioresponsive drug delivery systems for the treatment of inflammatory diseases. Journal of controlled release. 2020 Nov 10;327:641-66.
55. Wanakule P, Roy K. Disease-responsive drug delivery: the next generation of smart delivery devices. Current drug metabolism. 2012 Jan 1;13(1):42-9.
56. Bijauliya RK, Alok S, Chanchal DK, Kumar M. A comprehensive review on standardization of herbal drugs. Int. J. Pharm. Sci. Res. 2017 Sep 1;8(9):3663-77.
57. Bijauliya RK, Alok S, Chanchal DK, Sabharwal M, Yadav RD. An updated review of pharmacological studies on Azadirachta indica (neem). International Journal of Pharmaceutical Sciences and Research. 2018 Jul 1;9(7):2645-55.
58. Bijauliya RK, Alok S, Sabharwal M, Chanchal DK. Syzygium

cumini (linn.)-an overview on morphology, cultivation, traditional uses and pharmacology. International Journal of Pharmaceutical Sciences and Research. 2018 Sep 1;9(9):3608-20.
59. Bijauliya RK, Alok S, Kumar M, Chanchal DK, Sabharwal M, Yadav RD. An update of pharmacological activity of Psidium guajava in the treatment of various diseases. International Journal of Pharmaceutical Sciences and Research. 2018 Mar 1;9(3):883-93.
60. Niladri M, Singh S, Porwal P, Chanchal DK, Macadangdang Jr RR, Patil PY. Formulation Development And Evaluation Of Terbinafine Using Quality By Design Approach. NVEO-NATURAL VOLATILES & ESSENTIAL OILS Journal| NVEO. 2021 Nov 7:2581-98.
61. Al-Hussainawy MK, Aljeboree AM, Jawad MA, Sheri FS, Alkaim AF. Preparation of Bentonite Clay/TiO_2 Nanocomposites Surface as Drug Carrier: In-vitro Release Study of Chloramphenicol Drug. International Journal of Drug Delivery Technology. 2023;13(3):990-994.
62. Adityan S, Tran M, Bhavsar C, Wu SY. Nano-therapeutics for modulating the tumour microenvironment: Design, development, and clinical translation. Journal of controlled release. 2020 Nov 10;327:512-32.
63. Williams RO. Collagen-induced arthritis as a model for rheumatoid arthritis. Tumor Necrosis Factor: Methods and Protocols. 2004:207-16.
64. Li G, Wu YE, Jia H, Tang L, Huang R, Peng Y, Zhang Y. Establishment and evaluation of a transgenic mouse model of arthritis induced by overexpressing human tumor necrosis factor alpha. Biology open. 2016 Apr 15;5(4):418-23.
65. Chang JH, McCluskey PJ, Wakefield D. Acute anterior uveitis and HLA-B27. Survey of ophthalmology. 2005 Jul 1;50(4):364-88.
66. Tekade RK, Maheshwari R, Soni N, Tekade M, Chougule MB. Nanotechnology for the development of nanomedicine. InNanotechnology-based approaches for targeting and delivery of drugs and genes 2017 Jan 1 (pp. 3-61). Academic Press.
67. Chauhan NK, Malik A, Ratiyen PK. Solid Lipid Nanoparticles: Drug Delivery Systems for Enhancing the Bioavailability of Antihypertensives. International Journal of Drug Delivery Technology. 2023;13(3):1059-1064.
68. Farjadian F, Ghasemi A, Gohari O, Roointan A, Karimi M, Hamblin MR. Nanopharmaceuticals and nanomedicines currently on the market: challenges and opportunities. Nanomedicine. 2019 Jan;14(1):93-126.
69. Yiannakou Y, Piessevaux H, Bouchoucha M, Schiefke I, Filip R, Gabalec L, Dina I, Stephenson D, Kerstens R, Etherson K, Levine A. A randomized, double-blind, placebo-controlled, phase 3 trial to evaluate the efficacy, safety, and tolerability of prucalopride in men with chronic constipation. Official journal of the American College of Gastroenterology| ACG. 2015 May 1;110(5):741-8.
70. Van Norman GA. Drugs, devices, and the FDA: part 1: an overview of approval processes for drugs. JACC: Basic to Translational Science. 2016 Apr;1(3):170-9.
71. Sexton KA, Norton PJ, Walker JR, Norton GR. Hierarchical model of generalized and specific vulnerabilities in anxiety. Cognitive Behaviour Therapy. 2003 Jan 1;32(2):82-94.
72. Kishimoto TK, Ferrari JD, LaMothe RA, Kolte PN, Griset AP, O'Neil C, Chan V, Browning E, Chalishazar A, Kuhlman W, Fu FN. Improving the efficacy and safety of biologic drugs with tolerogenic nanoparticles. Nature nanotechnology. 2016 Oct;11(10):890-9.
73. Gnana RPM, Devhare LD, Dharmamoorthy G, Khairnar MV, Prasidha R. Synthesis, Characterisation, Molecular Docking Studies and Biological Evaluation of Novel Benzothiazole Derivatives as EGFR Inhibitors for Anti-breast Cancer Agents. International Journal of Pharmaceutical Quality Assurance. 2023;14(3):475-480.
74. Bramlett HM, Dietrich WD. Progressive damage after brain and spinal cord injury: pathomechanisms and treatment strategies. Progress in brain research. 2007 Jan 1;161:125-41.
75. Stumbo SP, Yarborough BJ. Preliminary evidence is promising, but challenges remain in providing service dogs to veterans: Commentary on preliminary efficacy of service dogs as a complementary treatment for posttraumatic stress disorder in military members and veterans (O'Haire & Rodriguez, 2018).
76. Huang ME, Wartella JE, Kreutzer JS. Functional outcomes and quality of life in patients with brain tumors: a preliminary report. Archives of physical medicine and rehabilitation. 2001 Nov 1;82(11):1540-6.
77. Bukkawar A, Jain AK, Chatap VK. Formulation Development and Evaluation of Freeze-dried Aviptadil injection using Mannitol as Cryoprotectant. International Journal of Pharmaceutical Quality Assurance. 2023;14(3):541-547.
78. de Goeij M, van Eijk LT, Vanelderen P, Wilder-Smith OH, Vissers KC, van der Hoeven JG, Kox M, Scheffer GJ, Pickkers P. Systemic inflammation decreases pain threshold in humans *in-vivo*. PLoS One. 2013 Dec 17;8(12):e84159.
79. Eklund KK, Joensuu H. Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases. Annals of medicine. 2003 Jan 1;35(5):362-7.
80. Mäki-Petäjä KM, Booth AD, Hall FC, Wallace SM, Brown J, McEniery CM, Wilkinson IB. Ezetimibe and simvastatin reduce inflammation, disease activity, and aortic stiffness and improve endothelial function in rheumatoid arthritis. Journal of the American College of Cardiology. 2007 Aug 28;50(9):852-8.
81. Fanouriakis, A., Adamichou, C., Koutsoviti, S., Panopoulos, S., Staveri, C., Klagou, A., Tsalapaki, C., Pantazi, L., Konsta, S., Mavragani, C.P. and Dimopoulou, D., 2018, December. Low disease activity—irrespective of serologic status at baseline—associated with reduction of corticosteroid dose and number of flares in patients with systemic lupus erythematosus treated with belimumab: a real-life observational study. In *Seminars in arthritis and rheumatism* (Vol. 48, No. 3, pp. 467-474). WB Saunders.
82. Liu X, Obacz J, Emanuelli G, Chambers JE, Abreu S, Chen X, Linnane E, Mehta JP, Wheatley AE, Marciniak SJ, Fairen-Jimenez D. Enhancing Drug Delivery Efficacy Through Bilayer Coating of Zirconium-Based Metal–Organic Frameworks: Sustained Release and Improved Chemical Stability and Cellular Uptake for Cancer Therapy. Chemistry of Materials. 2024 Apr 11.
83. He D, Li H, Yusuf N, Elmets CA, Athar M, Katiyar SK, Xu H. IL-17 mediated inflammation promotes tumor growth and progression in the skin. PloS one. 2012 Feb 16;7(2):e32126.
84. Golde TE. Disease modifying therapy for AD? 1. Journal of neurochemistry. 2006 Nov;99(3):689-707.
85. Even-Sapir E, Keidar Z, Bar-Shalom R. Hybrid imaging (SPECT/CT and PET/CT)—improving the diagnostic accuracy of functional/metabolic and anatomic imaging. InSeminars in nuclear medicine 2009 Jul 1 (Vol. 39, No. 4, pp. 264-275). WB Saunders.
86. Jiang Q, Chen M, Yang X, Zhuge D, Yin Q, Tian D, Li L, Zhang

X, Xu W, Liu S, Li F. Doxorubicin detoxification in healthy organs improves tolerability to high drug doses for enhanced antitumor therapy. ACS nano. 2023 Apr 6;17(8):7705-20.
87. PAIN C. Pain management: classifying, understanding, and treating pain. Hospital physician. 2002 Jun;23:1-8.
88. Syed A, Devi VK. Potential of targeted drug delivery systems in treatment of rheumatoid arthritis. Journal of Drug Delivery Science and Technology. 2019 Oct 1;53:101217.
89. Phillips MC, Mousa SA. Clinical application of nano-targeting for enhancing chemotherapeutic efficacy and safety in cancer management. Nanomedicine. 2022 Mar;17(6):405-21.
90. Han Y, Pang X, Pi G. Biomimetic and bioinspired intervention strategies for the treatment of rheumatoid arthritis. Advanced Functional Materials. 2021 Sep;31(38):2104640.
91. Li T, Liang W, Xiao X, Qian Y. Nanotechnology, an alternative with promising prospects and advantages for the treatment of cardiovascular diseases. International journal of nanomedicine. 2018 Nov 9:7349-62.
92. Alghamdi MA, Fallica AN, Virzì N, Kesharwani P, Pittalà V, Greish K. The promise of nanotechnology in personalized medicine. Journal of personalized medicine. 2022 Apr 22;12(5):673.