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Ciências da Saúde

Nanoformulations for treatment of Rheumatoid Arthritis[1]

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Resumo

Artrite Reumatóide (AR) é uma doença crônica inflamatória autoimune que começa com danos nas articulações. A AR afeta 1% da população mundial e é caracterizada por inflamação da sinóvia, infiltração de células imunes e degradação da cartilagem e osso. O tratamento para esta doença inclui medicamentos anti-inflamatórios não esteróides (AINEs), glicocorticóides, medicamentos anti-reumáticos modificadores da doença (DMARDs) e muitos outros moduladores imunológicos. No entanto, esses tratamentos não tem conseguido curar a AR, e devido aos muitos efeitos colaterais que causam os pacientes não conseguem aderir ao tratamento. Outro método que tem sido aplicado para o tratamento da AR é o uso da Medicina Tradicional. Este ramo da terapia aplica extratos de plantas pelo seu efeito terapêutico conhecido. Geralmente, os compostos naturais de extratos vegetais, têm baixa solubilidade no corpo e grandes quantidades podem ser tóxicas para vários órgãos do corpo. O problema da seletividade tecidual para o tratamento, tem chamado a atenção para a Nanofarmacologia. Esta ciência formula medicamentos encapsulados em nanoescala que oferecem direcionamento específico para os tecidos, proteção dos medicamentos dentro da nanoestrutura, evitando a degradação do composto ativo e fornecendo atividade sustentada do medicamento. Além disso, a nanofarmacologia aumenta a seletividade do medicamento na nanoestrutura adicionando ligantes específicos direcionados às células inflamatórias. Todas essas vantagens oferecem uma possível solução para o tratamento da AR. Nesta mini-revisão, pretendemos fornecer alguns dos trabalhos mais recentes feitos com nanomateriais em modelo experimental de artrite. Unindo o uso da medicina ocidental e da medicina tradicional com a nanotecnologia.

Palavras-chaves: artrite reumatoide, modelo experimental, nanodrogas, nanofarmacologia, medicina natural.

Abstract

Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease that begins with damage to the joints. RA affects 1% of the world population and is characterized by inflammation of the synovium, immune cell infiltration, and degradation of the cartilage

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and bone. The treatment for this disease includes non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, disease-modifying antirheumatic drugs (DMARDs), and many more immune modulators. However, these treatments have not been successful in the cure of RA, and due to the many side effects, that they cause patients tend to drop-out of treatment. Another method applied for the treatment of RA is the use of Traditional medicine. This branch of therapy applies plant extracts for their known therapeutic effect. Generally, natural compounds of plant extracts have low solubility in the body and large amounts can be toxic to various organs of the body. The issue with tissue selectivity has brought attention to Nanopharmacology. This science formulates encapsulated nanoscale drugs that offer specific targeting for tissue, protection of the drugs inside the nanostructure, avoiding the degradation of the active compound, and providing sustained drug activity. Furthermore, nanopharmacology enhances the selectivity of the drug in the nanostructure by adding specific ligands addressed to inflammatory cells. All of these advantages offer a possible solution for the treatment of RA. In this mini-review, we aim to provide some of the latest works that have been made using nanomaterials on an experimental model of arthritis. Merging the use of western medicine and Traditional medicine with nanotechnology.

Keywords: Rheumatoid arthritis, experimental model, nanodrugs, nanopharmacology, natural medicine.

1. Introduction

Rheumatoid Arthritis (RA) is a synovial autoimmune disease, characterized by chronic inflammation of joints. This event leads to loss of function of the articulation and in consequence work disability, affecting 0.2 - 1% of the worldwide population (SMOLEN; ALETAHA; MCINNES, 2016; DINI et al., 2019). The degeneration of the affected joint starts with asymptomatic inflammation of the synovium and gradually progresses to deformity and destruction of the articular cartilage and bone (ALETAHA et al., 2010a).

RA is one of the most prevalent autoimmune diseases and its development is related to other comorbidities including cardiovascular disease, pulmonary, vascular, musculoskeletal, and psychological disorders; all of these increasing the mortality rate of patients with Rheumatoid Arthritis (MCINNES; SCHETT, 2011). The specific cause of Rheumatoid Arthritis is still unknown. Studies have linked the development of RA with the human leukocyte antigen HLA-DRB1 locus, which has demonstrated susceptibility in patients. The allele HLA-DR4 is expressed in 70% of RA patients, for this reason, scientists give it the name of "susceptibility epitope" (ALMEIDA et al., 2011).

Other explanations for the cause of RA are molecular mimicry by the proteins of pathogens, T-cell senescence induced by HLA molecules and proinflammatory signaling non-related in response to HLA and T cell activation (MCINNES, et al. 2011). Deciphering the specific cause of RA is key for treatment and prognosis. The main components of RA pathogenesis are the hyperplasia of the synovium,

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migration of immune cells that accumulate in the articular tissue and production of proinflammatory cytokines like TNF-a, IL-1β, IL-6 and IL-17 (SHARMA; BHAR; DEVI, 2017).

This cascade of cytokines induces the differentiation of B lymphocytes into plasma cells which then produce autoantibodies, known as anti-citrullinated protein antibody (ACPA) and rheumatoid factor (RF). The synthesis of ACPA, RF and proinflammatory cytokines lead to an autoreactive adaptive immune response and an ongoing cycle of destruction of the joint (SONG; KANG, 2009).

Not knowing the specific trigger of Rheumatoid Arthritis, makes it more difficult to find a cure. Current treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), like aspirin and Diclofenac, which inhibit the activity of cyclooxygenase (COX), a known enzyme that induces inflammation. These drugs are used to treat the pain sensation of the patients. (CHAN et al., 2010).

Other pharmaceuticals are glucocorticoids, like cortisone and prednisolone that inhibit the production of prostaglandins (PG) and tumor necrosis factor (TNF), helping on the reduction of inflammation of the joint tissue (FERREIRA; AHMED MOHAMED; EMERY, 2016). Finally, the disease-modifying antirheumatic drugs (DMARDs) and Biologic DMARDs, which include the anti-cancer drug Methotrexate, the immunosuppressant cyclosporin, anti-TNF-a monoclonal antibody adalimumab (LAMBERT, 2012).

DMARDs target specific molecules that intervene in the pathogenesis of RA, like proinflammatory cytokines and their receptors. The downside of these pharmaceuticals are the life-threatening adverse effects, like gastrointestinal and cardiovascular complications, impaired renal function, visual problems and increased risk of osteoporosis (BADER, 2012). All the adverse effects are due to the non-specific targeting for the inflamed tissue of these drugs leading to their systemic absorption.

This is where Nanopharmacology comes in discussion, offering medication in nanosized particles with specific target release, avoiding all the adverse effects, minimizing the dosage of the drug and providing sustained release throughout the treatment (BONIFÁCIO et al., 2014). With these advantages, Nanopharmacology seems to be a promising way of treatment for Rheumatoid Arthritis. The aim of this review is to describe the recent work made applying nanopharmacology in the study of an experimental model of arthritis. Comparing western medicine pharmaceuticals and traditional medicine compounds with nanotechnology. We will emphasize the advantages that nanomedicine brings to this issue.

2. Methodology

The references for this literature review were obtained from the following websites: *PubMed*, *ScienceDirect,* and Google Scholar. The timeline included the search of the articles was between the years 2000 and 2020. The keywords for searching were: "rheumatoid arthritis", "experimental model of arthritis", "nanoparticles", "nanotechnology", "nanocarriers", "herbal drug" and "traditional medicine", "nanoemulsion", "nanocapsules". The list of papers was analyzed and the works that did not relate to our objective were excluded.

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3. A background in nanopharmacology

Nanopharmacology develops nanoscale materials that have improved physical, chemical and biological properties (ASHAI et al, 2012). These nanomaterials have an increased surface size due to their nanoscale dimension, characteristics that give them an enhanced reactivity and strength in *vivo* experimentation. Nanopharmacology develops nanodrugs or nanomedicines that run on a size range generally from 1-1000 nm and have a spherical shape. These nanoparticles have improved solubility by an increased surface-to-volume ratio (AHMED et al., 2016).

Nanopharmaceuticals provide a sustained release of the encapsulated drug, they reach the targeted tissue and deliver the pharmaceutical (FISSELL, 2013). These nanomedicines enhance the selectivity and effectiveness of treatment alleviating drug toxicity. All of this is possible due to two different mechanisms: passive and active targeting (KOTHAMASU et al., 2012).

Passive targeting is due to the enhanced vascular permeability at sites of inflammation. The intercellular union of endothelial cells at inflammation areas have gaps where the nanoscale drugs can go through and reach the inflammation site (BERTRAND et al., 2014). Active targeting is possible thanks to adhesion of specific ligands for target cell receptors to the nanostructured pharmaceutical. Another advantage is the encapsulation of the drug, that protects it from excessive metabolism by enzymes, proteins, and other cells. Providing a major quantity of the drug to the specific tissue (CHUANG et al., 2018).

4. Types of nanoformulations according to their structural components

Polymeric Nanoparticles

Polymeric nanoparticles are generally made out of PGA (poly-γ-glutamic acid), polyethylene glycol (PEG), polyvinyl alcohol (PVA), poly-l-lactic acid (PLA), polycaprolactone (PCL), or chitosan (CH). They are biodegradable, biocompatible and minimally immunogenic. Polymeric nanoparticles can be synthesized as nanocapsules (polymeric shell) or nanospheres (porous shell) (DUDICS et al., 2018).

Metal-oxide Nanoparticles

Metallic nanoparticles are usually made out of silver (Ag) or gold (Au). They have a higher surface area and larger pore sizes which gives them the ability of better drug encapsulation. The metal gives the nanoparticle unique biodegradable characteristics, caused by the formation of labile bonds with the ligands (AHMED; ALJAEID, 2016).

Liposomes

Liposomes are vesicles with the nanoscale-sized and spherical shape made out of a bilayer of biological phospholipids. A lipophilic drug can be transported dissolved in the bilayer of the liposomes (ALLEN; CULLIS, 2013).

Nanoemulsions

Nanoemulsions are an isotropic system, a diffusion of two non-miscible liquids, generally water and oil. This diffusion is stabilized by a surfactant that helps decrease the tension between the water phase and the oil phase. Nanoemulsions have a high surface area and optical

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transparency (SINGH et al., 2017; JANA-KIRAMAN et al., 2018).

Solid Lipid Nanoparticles

Solid Lipid Nanoparticles (SLN), combine the characteristics of nanoemulsions and polymeric nanoparticles. They are made of phospholipids, fatty acids, monoglycerides, diglycerides, and triglycerides. As their name describes, these nanomaterials have a solid hydrophobic core surrounded by phospholipids. SLN have the capacity to carry lipophilic and hydrophilic drugs (KUMAR et al., 2018; GESZKE-MORITZ; MORITZ, 2016).

Nanomicelles

Nanomicelles are composed of a monolayer of phospholipids. They are an amphipathic particle, with a hydrophobic core, for the encapsulation of hydrophobic drugs, and a hydrophilic shell for better solubility. This junction of monomers ranges from 50-200 nm (VADLAPUDI; MITRA, 2013).

Nanocapsules

Nanocapsules have an internal core for the active materials and an external polymeric shell that protects the core from degradation. This is the reason why it is sometimes described as a polymeric nanoparticle. Nanocapsules can transport drugs in the form of liquid, solid or molecular dispersion (BALE et al., 2016; WANG et al., 2016).

Lipid-core Nanocapsules

Lipid core nanocapsules are made out of triglycerides and sorbitan monostearate covered by a polymeric wall. The core is formed by a liquid lipid and a solid lipid. Lipid-core nanocapsules derive from Nanocapsules (FRANK et al., 2015)

Biomimetic Nanoparticles

They imitate the natural characteristics of cell particles and cell membranes. These nanomaterials have the benefits of synthetic nanoparticles and natural nanomaterials. They mimic the natural mechanisms of the immune system to get to the inflammation area. Biomimetic nanoparticles can be: 1) Synthetic nanomaterials with a targeting ligand that imitates a cell membrane protein, 2) Nanoparticle coated with cell membrane or 3) Liposomes with cell membrane proteins. Whatever the structure, Biomimetic nanoparticles have enhanced selectivity for inflammatory areas making the delivery of the drug more accurate (JIN et al., 2018).

5. Nanopharmacology in experimental model of Arthritis

Many studies have been made regarding nanomedicine and the treatment of Rheumatoid Arthritis. Prabhu et al. demonstrated the anti-rheumatic effect of lipid nanovesicles loaded with methotrexate on adjuvant-induced arthritis induced rats. The novel treatment was compared with free solution of methotrexate (MTX). The authors observed a significant diminution of edema volume in the hind paws of rats treated with the PEGylated MTX liposomal formulation, in comparison with the arthritis control group that did not receive any treatment. The strongest anti-rheumatic effect was observed in the PEGylated MTX nanoformulation, followed by the chitosan-coated lipid vesicles and at last the conventional treatment with a free solution of MTX. When analyzing the serum levels of hepatic proteins of each treatment group, SGOT and SGPT levels

of the nanoformulations were significantly lower in comparison with the treatment of MTX solution. With these results, the authors demonstrate the effectiveness that nanoencapsulation with lipid vesicles have over conventional treatment of MTX (PRABHU et al., 2012).

Following the lipid nanostructure particles, a lipid nanoemulsion of methotrexate (LDE-MTX) was tested in rabbits to measure its anti-inflammatory activity on experimental arthritis. Mello et al. induced arthritis on New Zeland white rabbits with CFA. Their results showed a significant reduction of leukocytes count on the synovial fluid of the rabbits treated with LDE-MTX, in comparison with the untreated group. The authors tested the following doses for the nanoemulsions 0.25 and 0.5µmol/kg. Furthermore, the lipid nanoemulsion showed a better reduction of cytokine levels of IL-17 and IFN-y when compared with commercial MTX that did not alter cytokine levels of the synovial fluids (MELLO et al., 2013).

A few years later, studying the same drug (MTX), Boechat et al. compared the anti-inflammatory effects of a lipid-core nanocapsules loaded with methotrexate (MTX-LNC), on a chronic animal model of arthritis in rats, and in vitro cells obtained from synovial fluid of RA patients. Analyzing the edema volume of the hind paws, they observed similar results when comparing MTX-LNC with MTX, taking in consideration that the dose of MTX inside the nanocapsule was 75% lower than the solution of MTX. The animal group treated with the loaded nanocapsules presented significantly lower levels of proinflammatory cytokines TNFa and IL-1a. Also, the CRP levels of the MTX-LNC group were lower in comparison with the solution of MTX. Evaluating the *in vitro* experiments with the human synovial cells, the group that received loaded nanocapsules showed a reduction of the proinflammatory cytokines TNFa and IL-6 and lower levels of IFN-y and IL-17A. Demonstrating a better anti-inflammatory activity of methotrexate when administered in nanocapsules (BOECHAT et al., 2015).

In 2017 Zhao et al., published their work on polymeric lipid nanoparticles loaded with methotrexate (PPLNP/MTX) marked with folic acid (FA) ligand. The FA ligand was produced with the purpose to interact with the folate receptor (FRβ) of activated macrophages of the inflamed areas. The authors observed the lowest clinical score (0.6) on the group treated with FA-PPLNPs/MTX. The nanoparticle with the folic acid ligand showed a significantly reduced paws thickness in comparison with the PPLNP/MTX and with the solution of MTX. The biochemical analysis showed a significant reduction of serum levels of TNF-a and IL-6 in comparison with MTX. Furthermore, the authors analyzed the cellular uptake of the nanoparticle by RAW246.7 cells. On the fluorescent test, they observed that the activated macrophages that were treated with FA-PPLNPs/MTX showed higher intensity of rhodamine B, suggesting a better uptake of the nanoparticle due to the ligation of the FA ligand with the FRβ receptor. Their results demonstrate that targeting specific receptors enhances the selectivity of the nanoparticle (ZHAO et al., 2017).

Also targeting the folate receptor, Duan et al., fabricated a liposome loaded with siRNA and MTX with a pegylated coating and folate ligand (F-siRML). The authors used siRNA to silence the gene of NF-kB and enhance the anti-inflammatory activity of the MTX nano-

particle. They observed a significant reduction of paw thickness and arthritic score on the mice treated with F-siRML, in comparison with siRML and free MTX. Also they observed a larger diminution of the inflammatory cytokines TNF-a and IL-1β. The team measured the lymphocyte count of the treated mice and observed no diminution of lymphocytes on the mice that received the F-siRML. On the in vitro test, they activated RAW246.7 cells with LPS and measured through fluorescence the uptake of the FA nanoparticle in comparison with another nanoparticle that did not contain the FA ligand. They observed a sustained uptake of the FA loaded liposome by higher fluorescence. The results show the efficacy and selectivity that nanoformulations can offer for treatment, without causing side effects (DUAN; LI, 2018).

Targeting the folic acid receptor, Shi et al., tested the anti-inflammatory capacity of chitosan (CH) nanocarrier with folic acid ligands (FA), formulated with polyethylene glycol (PEG) and carrying siRNA (folate-PEG-CH-DEAE15/siRNA) to silence TNF-a gene. Their results presented a significant decrease of arthritic score and hind paw edema in the group of animals treated with folate-PEG-CH-DEAE15/siRNA, when compared with the control group and CH-DEAE15/siRNA-TNFa. Via immunohistochemistry they observed a diminution of the concentrations of TNF-a in the synovium of mice. To analyze the degradation of cartilage and bone, they used the bone density test and serum levels of CTX-II (C-terminal telopeptide type II collagen), ALP (Alkaline phosphatase) and OC (osteocalcin). The group that received the folate chitosan nanoparticle showed better conservation of the cartilage and bone structures with lower levels of serum CTX-II (SHI et al., 2018).

Aldayel et al., synthesized acid-sensitive sheddable PEGylated solid-lipid nanoparticle formulation of TNF-a-siRNA (ASTNF-a-siRNA-SLNs). The team tested the nanoparticle on three different experimental models of arthritis: LPS induced, Collagen Induced (CIA) and Collagen Antibody Induced Arthritis (CAIA). With the LPS and CIA model, they evaluated the accumulation and distribution of ASTNF-a-siRNA-SLNs on the inflamed tissue and organs. Through fluorescent and spectrum image they observed that fluorescence intensity was significantly higher in the inflamed feet of mice that received tha acid sensitive nanoparticle (AS-siRNA-SLNs) in comparison with the mice that received the acid insensitive nanoparticle (AI-siRNA-SLNs). The distribution of the nanoparticles on the paws of CIA model, was compared with free siRNA. The results showed that fluorescent signals in the inflamed joints in mice injected with the AS-siRNA-SLNs were significantly higher than that in mice injected with free siRNA. Furthermore, evaluating the therapeutic effect of ASTNF-a-siRNA-SLNs on inflamed joints of CAIA mice, the authors observed that treatment with AS-TNF-a-siRNA-SLNs significantly reduced the paw thickness and diminished the inflammation when compared with Methotrexate and AS-siRNA-SLNs. Demonstrating the potential of the novel nanoparticle on treating arthritis (ALDAYEL et al., 2018).

Using NSAIDs therapeutics, one group studied the anti-inflammatory capacity of indomethacin loaded nanocapsules (IndOH-NC) on experimental model of arthritis. On the acute

protocol of arthritis, they observed a major reduction of paw edema in the rats that received IndOH-NC compared with the solution of IndOH. With the chronic protocol of edema, the indomethacin nanocapsule also presented a marked reduction of paw edema. Analazing the biochemical analysis, the treatment with IndOH-NC showed a significant reduction of the serum levels of TNF-a, IL-6 and a significant increase of the anti-inflammatory cytokine IL-10. Finally the reserchers evaluated the gastrointestinal lesional index (LI) of the arthritis group and observed the lowest LI on the group treated with IndOH-NC. Demonstrating the efficacy of the anti-inflammatory activity of the encapsulated drug and avoidance of adverse effects (BERNARDI et al., 2009).

Also applying NSAIDs, Nguyen et al, tested the transdermal drug delivery (TDD) capacity of a Diclofenac loaded lipid nanocarrier (DFC-LNC). They observed that particle size and composition of lipids of the nanoparticles have major impacts on transdermal drug delivery. The amount of permeated drug after 24hrs of the application was higher with the nanocarrier that had a smaller size. Furthermore, these same small nanocarriers presented a more efficient reduction of paw edema, when compared with the solution of Diclofenac. Since nanoparticles have instant access to the skin with a better absorption rate, they obtained the strongest diminution on paw edema with these nanomedicines (NGUYEN et al., 2017).

Lornoxicam (Lx) is another NSAID used for the treatment of RA, preferred by many because of its protective effect (TAYAL, 2012). In 2017, Helmy et al., published their work on lornoxicam loaded nanomicellar (Lx-NM) formulas on the experimental model of RA. Analyzing the paw edema of the rats, they observed that the higher doses of Lx-NM produced a significant reduction of the edema volume in comparison with the low dose of Lx-NM. Furthermore, they observed that the nanomicellar formulation produced more reduction of the edema than the free solution of Lx. Also, the use of Lx-NM significantly reduced the serum levels of TNF-a, IL-1β, PGE2, and NF-kβ. The treatment with the nanomicellar formula showed a significant decrease in levels of malondialdehyde and nitric oxide. Demonstrating a better efficacy of the drug in the nanoparticle presentation (HELMY et al., 2017).

Using polymeric nanoparticles, Shao et al., tested the capacity of rapamycin to regulate the immune response in the RA mice model and in vitro tests. The in vitro test with the rapamycin/NP showed a downregulation on the activation markers CD80+ and CD40+ of dendritic cells. Also, the production of proinflammatory cytokines by macrophages was reduced when treated with rapamycin/NP. All IL-6, TNF-a and IL-1β cytokines had a significant reduction compared with the empty nanoparticle. The results of the in vivo experiment showed that rapamycin/NP caused a marked reduction in clinical score and diminution of serum levels of TNF-a and IL-6. Demonstrating an enhanced immune regulation by the drug presented on the nanoformulation (SHAO et al., 2017).

Studying glucocorticoid therapy, Zhou et al., tested the efficacy of solid lipid nanoparticles (SLN) loaded with Prednisolone (PD), with hyaluronic acid (HA) as ligand to enhance specificity (HA-SLNs/PD). The authors observed that the arthritic score of mice treated with

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the coated nanoparticle was the lowest (mean score 1) in comparison with free prednisolone (mean score 2.9) and the uncoated nanoparticle (mean score 2). Also, the HA coated nanoparticle reduced joint swelling and erosion of the bone of the mice. Furthermore, the serum levels of proinflammatory cytokines (TNF-α, IL-1β, IL-6) were reduced on the mice treated with HA-SLN-PD. These results demonstrate efficacy and selectivity of the drug, when presented as a nanoparticle (ZHOU et al., 2018).

Merging the use of glucocorticoids and polymeric nanoparticles, Yu et al., formulated a lipid-polymer hybrid nanoparticle loaded with Dexamethasone (Dex). Using PCADK; Poly (cyclohexane-1,4-diyl acetone dimethylene ketal); egg phosphatidylcholine (egg PC) and polyethylenimine (PEI) with a coating of Hyaluronic acid (HA) for the structure of the nanoparticle. Testing cellular uptake, the rhodamine B test showed strong fluorescence in the cells that received HAP-NPs/Dex nanoparticles in comparison with the nanoparticles that did not have HA. In the *in vivo* experiment, the authors observed a decrease in the clinical score of the rats treated with the hybrid nanoparticle (HAPNPs/Dex). The paw thickness of the rats treated with HAPNPs/Dex, was considerably lower compared with the other treatments. Also, the rats treated with HAPNPs/Dex showed better conservation of bone and cartilage structure with a reduced cell infiltration (YU et al., 2019).

Lorscheider et al., developed a Dexamethasone nanoparticle to analyze the anti-inflammatory activity of the pegylated nanocarrier of Dexamethasone palmitate (DXP-NPs). The nanoparticles presented a size of 130nm. The dose of DXP-NPs (100 µg/mL) wass compared with a free solution of Dexamethasone. The treatment was tested *invitro* with a culture of RAW 264.7 cells stimulated with LPS. The researchers measured pro-inflammatory cytokines like TNF-a and MCP-1, and observed a significant decrease of MCP-1 in the presence of DXP-NPs when compared with the control. DXP-NPs was also tested on DBA/1OlaHsd mice with Collagen Induced Arthritis (CIA) model. The authors tested two doses of DXP-NPs the first one was 0.1 mg/kg and the second was 1mg/kg and compared this treatment with a free solution of Dexamethasone. The authors observed a significant reduction of the inflammation on the mice's paws, compared to free drug at the dose of 0.1mg/kg of DXP-NPs. At the dose of 1mg/kg of DXP-NPs, they observed significant reduction of the arthritis score compared to free dexamethasone. Histological findings showed that DXP-NPs caused a remarkable reduction of inflammation of the tissue, compared with the control group. Moreover, Hepatic enzymes and renal function showed no signs of toxicity for DXP-NPs. The authors concluded that the encapsulation of Dexamethasone demonstrated to be efficient for the reduction of inflammation with the absence of side effects. Making it a possible way of treatment for RA (LORSCHEIDER et al., 2019).

These studies (**Table 1**) showed that the common drugs used for treating rheumatoid arthritis, have a better capacity of action when presented in any form of nanoparticle drug delivery system. Avoiding toxicity and adverse effects. The use of nanoparticles can also enhance the activity of other types of pharmaceuticals.

6. Traditional Medicine meets Nanotechnology

Natural plant extracts are the basis of many pharmaceutical drugs and can have their therapeutic effects enhanced when applied with nanomaterials (STROHL, 2000). Usually, these plant extracts have low bioavailability because they are easily degraded. Nanoformulations provide the structure to keep the active principle from being degraded by enzymes. This is why both therapeutic branches, traditional medicine and nanopharmacology, have merged to provide enhanced natural medications (DEVI; JAIN; VALLI, 2010).

Traditional medicine applies the use of plant extracts to treat diseases. Many plants have been attributed with the capacity to treat Rheumatoid Arthritis (CAMERON et al., 2009). In Chinese traditional medicine is well known the use of Tripterygium wilfordii. This plant is use to treat inflammatory and autoimmune diseases (MATTA et al., 2009). Triptolide (TP), is a diterpenoid epoxide, present in this Chinese plant. The chemical compound has proven to have the immunosuppressive capacity and protective activity towards inflamed joints in RA. But the serious side effects that Triptolide (TP) causes, restrain its use (LI et al., 2017).

To prove the medicinal capacity of TP, Zhang et al. made a polymeric nanocarrier system containing Triptolide (PAT) and tested it on arthritic transgenic mice (TNF-a transgenic). Evaluating through near-infrared range with ICG, the authors observed that 24hrs after the administration, PAT tended to accumulate more at the inflamed joints and was completely cleared after 80hrs. For cytotoxicity the authors made kidney and liver function tests. Treatment with PAT presented lower damage to the liver and kidneys (ALT: 81.58±14.12 mmol/L; AST: 38.58±18.38 mmol/L; CRE: 175.36±35.76 mmol/L; BUN: 7.84±1.30 mmol/L). In addition, the TP loaded nanoparticle showed a reduction of inflammation on synovium, less cartilage loss and reduced bone erosion on the knees and ankles of the treated mice. These results demonstrate the efficacy and reduced toxicity that the implementation of nanoparticles offer (ZHANG et al., 2018).

More recently, Gu et al.made a study evaluating the transdermal drug delivery (TDD) of Triptolide lipid nanocarriers (TPL-NLCs), on the inflamed joints of CFA's arthritic rats. The authors made in vitro analysis to evaluate drug permeation with Franz diffusion cells method, using excised rat skin. The penetration rate of TPL-NLC was 73.51 ± 17.29 μg/cm2 and for the nanoemulsion 23.94 ± 0.78 μg/cm2. In the in vivo experiment, the team analyzed the concentration of the Triptolide loaded lipid nanocarrier in the skin and plasma of the rats with a synchronous microdialysis system. The scientists observed a high mean residence time (MRT) on the plasma of the nanocarrier (20.06h) and a longer half-life in the blood (12.2-fold). Their results demonstrated a diminution in joint edema of the knees of the animals treated with TPL-NLC. Also, the nanocarrier showed reduction on the expression of proinflammatory cytokines TNF-α, IL-1β and IL-6 of the joint fluids. Presenting a promising treatment for inflammation-related to rheumatoid arthritis (GU et al., 2019).

Another plant extract known for its medicinal properties is *Curcuma longa* L. (Zingiberaceae) or Curcumin. Curcumin is found in Turmeric, an ancient Asian spice. One of its active components is

curcuminoid, recognized for anti-inflammatory, antibacterial, antiviral and antifungal effects (JURENKA, 2009). The anti-inflammatory properties of curcumin come from its ability to modulate some pro-inflammatory compounds like TNF-a, IL-1β, IL-6, NF-kB, COX-2 and others (MOGHADAMTOUSI et al., 2014).

In 2018, Fan et al., made a study using curcumin as a treatment for arthritic rats. They formulated a nanomicelle composed of Hyaluronic acid (HA) and Curcumin (Cur), and tested the anti-inflammatory and joint lubrication capacity of this nanomaterial. The in vitro tests showed elevated proliferation of chondrocytes for all the concentrations of nanomicelles tested. The authors analyzed the edema of the ankle with the CT energy spectrum and observed that the group of rats treated with the nanomicelle had a major diminution of edema (30%) in comparison with the other treatments. When evaluating the ankle joint with Multiple planar reconstruction photographs of CT, the HA/Cur nanomicelle group presented the less blurred articular surfaces with no swelling of the soft tissues. The histological analysis of the ankle joints revealed no evidence of inflammation or cartilage damage in the group treated with the nanomicelle. Finally, the authors tested the lubrication status of the joints with a UMT-2MT tribometer in a ball-on-plate contact configuration. Here the HA/Cu group presented the lowest friction coefficient (~0.03) in comparison with the other treatments. Suggesting a better function of the knee articulation (FAN et al., 2018).

Another component known for its antioxidant and anti-inflammatory properties, is Resveratrol, a polyphenol found in grape seed and red wine (SHAKIBAEI; HARIKUMAR; AGGARWAL, 2009). Resveratrol has shown the capacity to modulate the levels of insulin growth factor I (IGF-1) (BROWN et al., 2010) and diminished the proliferation of colorectal epithelial cells in cancer tissue (PATEL et al., 2010). The anti-inflammatory action of Resveratrol is associated with the inhibition of the transcription factor NF-kappa B (BISHT; WAGNER; BULMER, 2010).

In 2015, Coradini et al., published their work on resveratrol and curcumin co-encapsulated lipid-core nanocapsules (RC-LNC). They compared the treatment with a free solution of resveratrol and curcumin. The team evaluated the anti-inflammatory activity of the nanocapsules in CFA experimental model of arthritis. Researchers observed a significant reduction in paw edema (37-55%) with the treatment of RC-LNC. On the biochemical analysis they observed, that the co-encapsulation of the polyphenols did not alter the hepatic enzymes (ALP, ALT, AST) demonstrating the absence of side effects. Furthermore, on the histopathological evaluation, the paws treated with RC-LNC showed lower levels of fibrosis on the cartilage and synovial membrane, and reduction of bone loss. Demonstrating the benefits of the nanocapsules (CORADINI et al., 2015).

In Pakistan, traditional medicine recognizes the anti-inflammatory and antioxidative capacity of the cactus Opuntia dillen (MAHMOOD, MAHMOOD, TABASSUM, 2018). This plant has been used to treat asthma, gastric ulcers and diabetes. Its therapeutic effects are conferred by the two major compounds a-pyrones opuntiol and opuntioside. These two bioactive compounds have demonstrated anti-inflammatory and antinociceptive effects (SIDDIQUI et al., 2016).

Roome et al. studied the antirheumatic capacity of opuntiol (OP) and

opuntioside (OPG) in silver and gold nanoparticle formulations (OP-AgNPs/ OP-AuNPs). They tested the metallic nanoparticles in an experimental model of arthritis with Wistar rats. Also, the authors target mRNA expression of TLR-2, TLR-4, IL-1β and TNF-a. The results demonstrated a marked diminution of the arthritic score (score 1), in the groups receiving the metallic nanoparticles at a dose of 1 and 3 mg/kg. Furthermore, OP-AgNPs and OP-AuNPs reduced paw inflammation on >40% compared to the non-treated rats. Radiographic analysis showed minor edema of the soft tissue and mild erosion of the bone in the presence of opuntioside nanoparticles. On the histological analysis, the gold and silver nanoparticles showed better conservation of the joint tissue with a diminution of inflammatory cell infiltration. Furthermore, in rat spleen tissue the expression of TLRs was diminished from 65-80% in the presence of metallic nanoparticles. (ROOME et al., 2019).

Recently, Barros Silva et al. conducted a study analysing the anti-inflammatory activity of a nano-capsule loaded with nerolidol (NN) in a Zymosan induced arthritis model. Norelidol is a sesquiterpene found on more than 30 species of plants, one of them being *Ginkgo biloba L.*(TAO; WANG; KONG, 2013). To test the toxicity of the nanoparticcels, the researchers made *in vitro* tests with a culture of J774 cells. The cell viability essays using reduction of resazurin and MTT tests, demonstrated that the cultured cells remained viable and the formulation may not presente toxicity, MTT reduction percentage varied from 90 to 95%. To test the anti-inflammatory activity of the nerolidol nanoparticles (NN) the authors analyzed the joint neutrophil migration, histological analysis of the joint and quantification of interleukins of the joint of Zymosan arthritic mice. The neutrophil migration assay showed that NN reduced neutrophil migration in 26.7%, similar with Indomethacin 26.6% and free nerolidol at 10 mg/kg 27.4%. The histological evaluation demonstrated that the synovial membrane of the groups treated with NN and free nerolidol had reduced inflammation and edema, compared with the control. Furthermore, the authors measured the effects of nerolidol and NN on intra-articular interleukins like TNF-a, IL-1β and IL-10. The authors observed that the treatments elevated the concentrations of all the cytokines, specially NN elevated the levels of anti-inflammatory IL-10. The results show that nanoencapsulation of nerolidol improves its anti-inflammatory activity (BARROS SILVA SOARES DE SOUZA et al., 2020). These studies are summarized in Table 2

7. Conclusion

As the number of patients diagnosed with Rheumatoid Arthritis grows, the need for an effective treatment turns urgent. Many pharmaceuticals have been created for this purpose, but their poor specificity for tissue makes them prominent to serious side effects. Studies with nanopharmaceuticals are demonstrating a better range of action on treating diseases. With their high specificity for inflamed tissue, they provide target delivery and sustained release of the drug. Encapsulating the pharmaceuticals or plant extracts, in nanomaterials avoids the dissemination of the drugs through the whole system, minimizing the side

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effects that these could cause. Nanopharmacology is a promising field for the treatment of Rheumatoid Arthritis. Even though the results presented with these nanomaterials seemed to be nonharmful for *in vivo* and *in vitro* experiments, these scenarios could not represent the systemic reactions that nanoformulations could have on humans. For this reason, more studies need to be conducted.

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Table 1. List of pharmaceuticals and their nanoformulations on experimental model of Arthritis.

Drug/Agent	*Nanoformulation*	*Nanoparticle size*	*Compared treatment*	*Experimental model*	*in vitro Test*	*Effect on arthritic joint*	*Effect on blood, tissue and fluids*	*References*
Methotrexate	Lipid Nano vesicles 1)DSPC:MPEGDSE: CH (0.13 mg/kg) 2) DSPC: CH (0.13 g/kg)	1)210 nm 2) 253 nm	Mtx solution 0.13 mg/kg	AIA	Dialysis membrane in Franz diffusion cell.	Diminution of paw edema volume (*P<0.01*) by the DSPC:MPEGDSE: CH	Decrease on serum levels of hepatic proteins SGOT and SGPT (*P<0.01*).	(PRABHU et al., 2012)
	Lipid Nanoemulsion LDE-MTX (0.0625, 0.125, 0.25 and 0.5 µmol/kg)	60 nm	Mtx solution 0.5 µmol/kg	AIA	--	Decline of cell infiltrate on the synovial membrane.	Reduction of leukocytes count on the synovial fluid (*P=0.004*) and diminution of cytokines levels of IL-17 (*P = 0.05*) and IFN-y (*P = 0.05*)	(MELLO et al., 2013)
	Lipid-core Nanocapsule MTX-LNC (0.375 mg·kg-1)	175±17 nm	Mtx solution 1.5 mg·kg-1	AIA	Human mononuclear synovial cells	Diminution of paw edema similar to Mtx solution (P=0.951).	Lower levels of proinflammatory cytokines TNFα (*P=0.0114*), IL-1α (*P=0.778*) and CRP (*P=0.011*). *In vitro:* reduction of the proinflammatory cytokines TNFα and IL-6 (P=0.046 and P=0.033), IFN-y (P=0.046) and IL-17A (P=0.006).	(BOECHAT et al., 2015)
	Polymeric lipid nanoparticle with Folic Acid ligand 1)PPLNP/MTX (257 µg/kg) 2)FA-PPLNPs/MTX (257 µg/kg)	1) 148.8 nm 2) 133.6 nm	MTX solution 0.5 mL	AIA	Activated RAW246.7 cells	FA-PPLNPs/MTX showed decrease of clinical score (score 0.6) and paw thickness *(P < 0.01*). Lower bone and cartilage erosion of the joint.	Reduction of serum levels of TNF-α (P< 0.001) and IL-6 (P< 0.01) *In vitro:* Higher uptake of the nanoparticle by better interaction of the FRβ receptor	(ZHAO et al., 2017)
	Calcium phosphate/liposome-based hybrid nanocarrier loaded with siRNA and Folic Acid ligand (F-siRML) 0.4 mg/kg	170 nm	MTX solution 0.6 mg/kg	CIA	Activated RAW246.7 cells	Reduction of paw thickness and arthritic score (*P< 0.001*)	Diminution of the inflammatory cytokines TNF-α (< 15 pg/mL) and IL-1β (< 10 pg/mL) *In vitro*: Increase internalization of the nanoparticle with better interplay of ligand and receptor activity.	(DUAN; LI, 2018)
siRNA-TNF- α	Polymeric nanocarrier of Chitosan with Folic Acid ligands	233±21 nm	Naocarrier without folic acid ligands (CH-DEAE15/siRNA-	CAIA	Hela cells (cell viability)	Decrease of inflammation and arthritic score (*P<0.05*)	Diminution on the concentrations of TNF-α in the synovium (*P<0.05*), low serum levels of CTX-II (P<0.05).	(SHI et al., 2018)

	(folate-PEG-CH-DEAE15/siRNA, 50 µg siRNA)		TNFa, size 259±3 nm)				*In vitro*: 89-97% cell viability with both nanoparticles.	
siRNA-TNF- α	Acid-sensitive sheddable PEGylated solid-lipid nanoparticle of TNF-α-siRNA (ASTNF-α-siRNA-SLNs) 2 mg/kg	120 nm	free siRNA (0.5 mg siRNA/kg) Methotrexate (5 mg/kg)	1)LPS 2) CIA 3) CAIA	J774A.1 cells	Reduction fo joint inflammation and clinical score ($p < 0.05$)	Accumulation of the nanoparticle on the inflamed tissue with release of the therapeutic on the inflamed area. Lower cartilage damage and less roughness of the articulation bone ($p \leq 0.05$)	(ALDAYEL et al., 2018)
Indomethacin	Nanocapsule (IndOH-NC, 1 mg·kg-1 i.p.)	240 nm	Indomethacin (IndOH) solution (1 mg·kg-1)	1)Carrageenan 2)AIA	--	1)Carrageenan: reduction of paw edema (44±7%, $P < 0.05$) 2)AIA: reduction of paw edema (33 ±4%, $P<0.05$)	2) AIA: Reduction of serum levels of TNF-**α** ($P<0.05$), IL-6 ($P<0.01$) and increase of IL-10 ($P<0.001$). Low gastrointestinal lesional index (LI) (*P<0.001*)	(BERNARDI et at., 2009)
Diclofenac	Nanostructure Lipid Carrier (DFC-NLC) NLC1: 0.5% DFC NLC2: 0.4% DFC NLC3: 0.2% DFC Equivalento to 4mg of Diclofenac	NLC1: 54.38 ± 1.54 nm, NLC2: 126.67 ± 1.21 nm, NLC3: 92.75 ± 0.82 nm (all transdermal)	Voltaren Emulgel; Vol)	Carrageenan	Cellulose acetate synthetic membrane	Reduction of edema with all nanocarries (*P<0.01*). NLC1 presented 72.2% inhibition of inflammation	Better transdermal drug permeation with NLC1 (153.3%).	(NGUYEN et al., 2017)
Lornoxicam	Nanomicelle (Lx-NM) 1)Doses 0.325, 0.65 and 1.3 mg/kg 2)Dose 0.325 mg/kg	169.45 nm	1)Lornoxicam (Lx) solution (1.3 mg/kg) 2)Lx solution (0.325 mg/kg)	1)Carrageenan 2)AIA	--	Carrageenan: higher doses of Lx-NM cause reduction of paw edema (*p <0.001*) AIA: reduction of paw edema (*p<0.001*)	AIA: reduced the serum levels of TNF-*α*, IL-1β, PGE2 and NF-kβ ($p<0.001$)	(HELMY et al., 2017)
Rapamycin	Polymeric nanoparticle (rapamycin/NP, 135 µg)	165±35 nm	Empty nanoparticle (NP, 1 mg)	CIA	1)Mice spleen DC 2)Mice bone marrow macrophages	Reduction on the clinical score (mean score 7)	Diminution of serum levels of TNF-*α* and IL-6 ($P<0.05$). *In vitro*: DC: downregulation on the activation markers CD80+ and CD40+ ($P<0.05$). Macrophages: reduction on cytokine production IL-6, TNF-*α* and IL-1β ($P<0.05$)	(SHAO et al., 2017)

Prednisolone	Solid Lipid Nanoparticle coated with Hyaluronic Acid 1)HA-SLNs/PD (15 mg PD/kg) 2)SLNs/PD (15 mg PD/kg)	1) 166.86 ± 1.25 nm 2) 147.8 ± 1.46 nm	Prednisolone (PD) solution (15 mg PD/kg)	CIA	RAW264.7 cells	Low arthritic score (mean score 1)	HA-SLNs/PD presented longer periods on plasma (29 μg/mL) and the joints. Serum levels of proinflammatory cytokines (TNF-α, IL-1β, IL-6) were reduced ($p < 0.05$) *In vitro:* higher uptake of HA-SLNs/PD than SLN/PD ($p<0.05$)	(ZHOU et al., 2018)
Dexamethasone	Acid sensitive Polymeric Nanoparticle 1)HAPNPs/Dex 2)HANPs/Dex 3)PNPs/Dex	150 nm	Dexamethasone (Dex) solution (5 mg/kg)	AIA	RAW 264.7 cells	Low clinical score presented by the HAPNP/Dex ($p<0.001$) and reduced paw thickness ($p<0.001$)	Conservation of bone and cartilage structure with a reduced cell infiltration. Low levels of serum TNF-α ($p<0.01$) and IL-6 ($p<0.001$) *In vitro:* higher uptake of HAPNPs/Dex	(YU et al., 2019)
Dexamethasone	Pegylated nanocarrier of Dexamethasone palmitate (DXP-NPs) At 0.1,m/kg And 1 mg/kg	310nm	Dexamethasone solution (DSP) At 0.1,m/kg And 1 mg/kg	CIA	RAW 264.7 cells	Reduction of joint edema and diminution of arthritic score ($p<0.001$)	Conservation of the joint. Increse of white blood cells count ($p < 0.005$) and lymphoctes ($p < 0.01$). No significant difference on the concentraton of hepatic ALAT. Increase on serum level of Creatinine ($p < 0.01$)	(LORSCHEIDER et al., 2019)

The *in vitro* release tests of the papers were not taken in consideration for this table. **Abbreviations**: AIA, adjuvant induced arthritis; CIA, collagen induced arthritis; CAIA, collagen antibody induced arthritis; SGOT, aspartate aminotransferase; SGPT, serum glutamic pyruvic transaminase; INF-y, interferon gamma; TNF- a, tumor necrosis factor alpha; PGE2 prostaglandin e two; NF-Kb, nuclear factor kappa b; CRP, c-reactive protein; IL-1β, interleukin 1 beta; IL-1 interleukin 1; IL-6, interleukin 6; IL-10, interleukin 10; IL-17 interleukin 17.

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Table 2. List of Nanoformulations loaded with natural compounds in the use of experimental model of Arthritis.

Plant Name	*Bioactive Compound*	*Nanoformulation*	*Size (nm)*	*Compared treatment*	*Experimental Model*	*In vitro test*	*Effect on arthritic articulation*	*Effect on blood, fluids and tissue*	*References*
Tripterygium wilfordii	Triptolide	Polymeric Nanoparticle (PAT) (0.15 mg/kg)	79±18	Triptolide (TP) solution (0.15 mg/kg)	TNF- a Transgenic mice	RAW246.7 cells	Higher absorption of the nanoparticle on inflamed joints. Conservation of bone and cartilage of the joint.	Low damage to the liver and kidneys. *In vitro*: high cellular viability (*P<0.05*) and low apoptosis rate 7.2%	(ZHANG et al., 2018)
		Lipid Nanocarrier (TPL-NLCs) (90 mg/kg)	179.0 ± 0.286	Diclofenac sodium gel (25 mg/kg)	AIA	Franz diffusion cells method with excised rat skin	Diminution in joint edema of the knees (*P<0.05*)	Elevated penetration rate 73.51 ± 17.29 µg/cm2. High MRT on plasma 20.06h and longer half life in blood (12.2 fold). Reduced levels TNF-a, IL-1β and IL-6 (*P<0.05*)	(GU et al., 2019)
Curcumalonga L. (Curcumin)	Curcuminoid	Nanomicelle (HA/Cur) (336 µg/mL)	164	Curcuminoid solution (Cur, 100 µL)	AIA	Bovine chondrocytes	Diminution of edema (30%, p<0.05), conservation of bone and cartilage of the joint.	Diminution of TNF-a , IL-1 (p<0.05) and liver proteins (AST,ALT, ALP). Friction coefficient (~0.03) *In vitro*: elevated proliferation of chondrocytes with ~3.7 absorbance	(FAN et al., 2018)

Vitis Vinifera and Curcumalonga L. (Curcumin)	Resveratrol and Curcuminoid	Lipid-core nanocapsules 1)B-LNC (Blank nanocapsule) 2)R-LNC (Resveratrol nanocapsule) 3)C-LNC (Curcumin nanocapsule) 3)RC-LNC (Resveratrol and Curcumin nanocapsule) Common dose: 1.75mg/kg	1)197±5 2)192±5 3)200±3 4)196±7	1)Resveratrol solution 1.75 mg/kg 2)Curcumin solution 1.75 mg/kg	AIA	--	Diminution of paw edema ($p < 0.05$), attenuation of fibrosis in the synovial membrane, cartilage and bone loss ($p < 0.05$).	No alteration on the levels of hepatic enzymes (ALT, AST, ALP).	(CORADINI et al., 2015).
Opuntia dilleni	Opuntiol Opuntioside	Metallic Nanoparticles (OP-AgNPs/ OP-AuNPs) (10 mg/kg)	5-7	1)Opuntiol (OP) and opuntioside (OPG) solution (100 mg/kg) 2) Dexa 0.5 mg/kg) 3)Indo 5 mg/kg)	AIA	Rat splenocytes	Diminution of arthritic score (score 1) and reduced paw inflammation on >40%.	Conservation of the joint tissue with diminution of inflammatory cell infiltration. Reduction on the expretion of TLRs 65-80%. In vitro: low levels of IL-1**β** and TNF-**α** (*p<0.001*)	(ROOME et al., 2019)
--	nerolidol	Nanocapsule NN 3mg/kg	219 ± 8.4	Nerolidol solution 1)300 mg/kg 2)3mg/kg - Indomethacim 5mg/kg	Zymosan	J774 cells	Diminuition of inflammation and edema	Reduction of neutrophil migration to the inflamed tissue. Increase of anti-inflammatory cytokine IL-10	(BARROS SILVA SOARES DE SOUZA et al., 2020)

Abbreviations: AIA, adjuvant induced arthritis; TNF- a, tumor necrosis factor alpha; TLR2, toll like receptor 2, TLR4, toll like receptor 4; IL-1β, interleukin 1 beta; IL-1 interleukin 1; IL-6, interleukin.