Journal of Traditional Medicine & Clinical Naturopathy

Review Article Open Access

Targeted Delivery of Natural Products for Autoimmune Arthritis: Enhancing Efficacy and Minimizing Side Effects

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Abstract

Rheumatoid arthritis (RA) is a chronic, debilitating illness characterized by painful swelling of the joints, inflammation of the synovial lining of the joints, and damage to cartilage and bone. Several anti-inflammatory and disease-modifying drugs are available for RA therapy. However, the prolonged use of these drugs is associated with severe side effects. Furthermore, these drugs are effective only in a proportion of RA patients. Hence, there is a need to search for new therapeutic agents that are effective yet safe. Interestingly, a variety of herbs and other natural products offer a vast resource for such anti-arthritic agents. The application of nanoparticles for efficient delivery of such products; and the interplay between dietary products and the host micro biome for maintenance of health and disease induction. We believe that with several advances in the past decade in the characterization and functional studies of natural products, the stage is set for widespread clinical testing and/or use of these products for the treatment of RA and other diseases.

Introduction

Rheumatoid arthritis (RA) is a multifactorial disease that involves both genetic predisposition and environmental components. RA is prevalent worldwide with approximately 1.3 million people affected by RA in the United States alone. Moreover, women are more likely to develop RA than men. It is anticipated that with people living longer, the incidence of RA is likely to increase. RA is typically characterized by chronic inflammation of the synovial membrane that lines the joints, damage to the cartilage, and erosion of the bone [1]. Swelling and redness of the hands and feet is the most common sign of RA along with pain in the afflicted areas. Ulnar deviation, Swan neck deformity, and subcutaneous nodules are among the clinical manifestations of untreated severe RA. The most common serum biomarkers for RA are rheumatoid factor and anti-citrullinated protein. Furthermore, ACPA can also be used as prognostic markers for RA similarly to RF, as they are present a median of 4.5 years prior to clinical onset of the disease. A relatively new potential biomarker for RA is the on protein surviving, which is already a known biomarker for cancer. In one study, surviving was detected in 50.7% of RA patients but only 5.6% in controls, which indicates its high specificity [2].

Herbal CAM for the Treatment of Inflammatory Autoimmune Arthritis Conventional anti-inflammatory drugs are the mainstay of treatment for a variety of immune disorders, including rheumatoid arthritis (RA). The nonsteroidal anti-inflammatory drugs (NSAIDs) and biologics represent a prominent group of such drugs. However, the usage of these drugs is associated with severe adverse effects, including gastrointestinal bleeding and cardiovascular complications [3]. Owing to the side effects and the high cost of conventionally used anti-inflammatory drugs, patients with arthritis are increasingly using complementary and alternative medicine (CAM) modalities of treatment. Over 36% Americans used CAM products annually for different disorders and the trend is on the rise Traditional Chinese medicine, Ayurvedic medicine, Kampo, and Homeopathy are among the major contributors to the natural products consumed by patient populations. However, despite the increasing usage and popularity of CAM products in the western world .one of the main limitations of their use is the meager information about their mechanisms of action and objectivity in evaluating efficacy. This also is one of the main reasons for skepticism about CAM in the minds of both the lay public and the professionals. Thus, there is a need for continued studies on the mechanistic aspects of action of CAM products [4].

The cellular and soluble mediators of arthritic inflammation

Under normal conditions, the mature T cells encounter self-antigens in the periphery all the time; however, their activation is kept under control via diverse mechanisms, including unresponsiveness due to lack of adequate interaction between the peptide. Major histocompatibility complex complex and the T cell receptor, induction of energy in the absence of co-stimulation, or suppression by T regulator cells. The initiation of RA involves interplay among components of the innate and adaptive immune responses leading to unintended activation of auto reactive T cells specific for potentially arthritogenic self-antigens in the peripheral lymphoid organs. Antigen-presenting cells, including dendritic cells [5], macrophages as well as activated B cells, present arthritogenic auto antigens to T cells that have specific TCRs. That can recognize these autoantigens. At the same time, upregulation of co-stimulatory molecules expressed by the APCs under inflammatory conditions facilitates activation of these potentially arthritogenic T cells.

The development of inflammatory arthritis in the joints involves the migration of activated pathogenic T cells from the peripheral lymphoid tissues into the joint tissue (synovial tissue), which is mediated primarily by a chemotactic process. These T cells initiate joint-destructive activities by secreting cytokines and other mediators described below. This creates an inflammatory environment which attracts other cell types such as neutrophils, macrophages and fibroblasts to the local site. Collectively, these cells together with various effector molecules induce joint inflammation and cartilage and bone damage [6]. The B cells contribute to the pathogenesis of RA, not

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Received: 1-May-2023, Manuscript No: jham-23-99123, **Editor assigned:** 3-May-2023, Pre QC No: jham-23-99123 (PQ), **Reviewed:** 17-May-2023, QC No: jham-23-99123, **Revised:** 23-May-2023, Manuscript No: jham-23-99123 (R), **Published:** 29-May-2023, DOI: 10.4172/2573-4555.1000378

Citation: Nightingale J (2023) Targeted Delivery of Natural Products for Autoimmune Arthritis: Enhancing Efficacy and Minimizing Side Effects. J Tradit Med Clin Natur, 12: 378.

only through antigen presentation to the T cells, but also through the production of cytokines and autoantibodies, such as RF and ACPA, which can further reinforce the inflammation induced by the T cells . Similarly, the Th17 cells produce receptor activator of nuclear factor kappa-B ligand, which along with other soluble mediators produced by myeloid cells, facilitates osteoclastogenesis. These osteoclasts can cause bone damage via secreting matrix-degrading enzymes such as matrix metalloproteinases and cathepsin K.

Liposomes

Liposomes are spherical-shaped nanovesicles that are extensively used as carriers for the delivery of therapeutic drugs. Liposomes can encapsulate both hydrophobic and hydrophilic drugs and can release the entrapped drug at designated targets . A study using triptolide-entrapped liposomes in a rat model of CIA showed slower release and a longer half-life in plasma as well as decreased hepatic and digestive tract toxicity when compared to free triptolide. Furthermore, there was a decrease in IL-1β and IL-6 levels in serum as well as reduced expression of Flk-1, Flt-4, and HIF-1α in synovia of liposome-triptolide group when compared to arthritic control group [7]. In a recent study, we have shown that liposomes encapsulating an immunomodulatory cytokine IL-27 and displaying a joint-homing peptide on their surface are more effective in suppressing AA in rats compared with liposomes containing IL-27 but lacking the peptide on the cell surface as well as free IL-27. We propose that IL-27 combined with a natural product such as celastrol might have an additive or synergistic protective effect against AA, and we plan to test this in the near future [8].

Nano emulsions

Nanoemulsions result from the dispersion of two immiscible liquids, typically water and oil, and are stabilized using an appropriate surfactant. In a study on AA, free curcumin was administrated i.v., whereas the curcumin-nanoemulsion formulation was administrated orally. The plasma concentration of curcumin was increased three-fold, whereas the levels of TNF-α and IL-1β in both synovial fluid and serum were reduced two-fold in the curcumin-Nano emulsion-treated group compared to free curcumin-treated group [9].

Nanomicelles

Nano micelles are self-assembling colloidal constructs composed of amphiphilic monomers. Their hydrophobic core can encapsulate hydrophobic drugs/natural products, whereas the hydrophilic shell helps enhance the solubility of the drug. The surface of the Nano micelles is suitable for conjugation with cell/tissue-targeting ligands . Nano micelles were shown to improve the therapeutic efficacy of curcumin in CIA . Curcumin-nanomicelles caused a significant reduction in paw edema, whereas free curcumin failed to reduce the paw swelling. Moreover, serum levels of IL-1β and vascular endothelial growth factor (VEGF) were significantly decreased in curcumin-nanomicelles-treated rats compared to free curcumin-treated rats [10].

Conclusion

It is clear that natural products can be effective forms of therapy for RA. We described in detail four such natural products and their bioactive components, but there are many more that have been shown to possess anti-inflammatory and anti-arthritic properties. One of the major hurdles of using natural products for therapy is their poor bioavailability. In order to combat this issue, researchers are turning to nanoparticle delivery of such products, and have reported successful application of these approaches. Nanoparticles are designed for the delivery of drugs/biologics to improve their pharmacological and therapeutic properties. They can protect the drug against degradation and deliver the drug to a specific target. In consequence, lower dose of the drug is required to achieve the desired efficacy. Thus, nanoparticles can ensure controlled release of drugs and reduce their toxicity. Furthermore, natural products might also contain prebiotic components, whose interaction with the host microbiome can have a significant impact on health and disease. This is a new area of research that would further help optimize the selection of natural products for therapy and define their mechanisms of action. Taken together, in the past couple decades; there has been a gradual increase in the use of natural products for the maintenance of health and treatment of arthritis and other diseases all over the world.

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