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ADVANCEMENTS IN DRUG DELIVERY FOR CHRONIC INFLAMMATORY DISEASES: RECENT APPROACHES AND STRATEGIES

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Abstract
The inflammatory process constitutes one of the organism's most fundamental and obvious defense mechanisms. Inflammation is a physiological response of the immunity caused by pathogens, toxic compounds, and damaged cells capable of causing chronic and acute inflammation. This may cause tissue damage or disease. Several therapies are currently available to reduce symptoms and prevent disease progression. However, more efficient treatments are required due to the severe side effects of current therapies, particularly when used long-term. With several nano-formulations, the delivery of drug systems has proven clinically important. In the present paper, we have reviewed chronic inflammatory diseases based on their inflammatory response mechanism. Also focused on recent approaches and targets for treating rheumatoid arthritis is one example of a chronic inflammatory condition. Moreover, for the intervention of inflammation, the current scenario of nano-formulated anti-inflammatory agents from conventional drugs and phytochemical drugs is described in the paper.

Keywords: Chronic inflammation; Inflammatory disease; Drug delivery system; Anti-inflammatory drugs; Phytochemicals

Introduction

Inflammatory diseases are the world's most common cause of death. The World Health Organization considers chronic diseases to be the biggest risk to human health. In the coming 30 years, chronic inflammation-related disorders are expected to become more common in the USA. In 2000, approximately 125 million population had chronic diseases, with 61 million (21%) having multiple chronic conditions. According to the Rand Corporation, approximately 60% possessed one long-term disease in 2014, and 42% population possess more than one illness.(1–3). In India ranges from 0.28 to 0.7%, with rural populations experiencing higher rates than urban centers. The overall mortality rate for those with rheumatoid arthritis and atopic dermatitis is lower compared to that of the overall population, and the risk of developing the disease as an adult affects 3.6% (1 in 28) of women and 1.7% (1 in 59) of men and younger than older respectively (4). Inflammation is a natural defense response that may be triggered by several factors including infectious agents (viruses, bacteria), physical agents, reactive oxygen species (ROS), and metabolic stress (hypoxia) (5). Celsus was the first person in history to describe the clinical symptoms of inflammation. He identified four fundamental signs of inflammation: "rubor et tumour cum calore et dolore" (Heat and

pain are accompanied by redness and swelling).Virchow added a fifth fundamental sign in 1858: "functio laesa" (function disturbance). Inflammation can be acute or chronic, depending on its duration.

Acute inflammation is thought to be a defense of the natural immunity triggered by infection or injury, whereas chronic inflammation can occur in the absence of infection or injury. The chronic inflammatory condition can be described as a prolonged and persistent inflammatory state that is characterized in particular by the development of new connective tissue. This category includes a vast range of diseases, including cardiovascular disease (CVD), atopic dermatitis also autoimmune disease, metabolic syndromes, neurological diseases, chronic inflammatory bowel diseases, chronic obstructive lung diseases, and chronic venous disorders (6,7). Inflammatory diseases, both acute and chronic, can all be greatly improved by using anti-inflammation strategies. Drugs with small molecules have been used to manage various inflammatory conditions, including glucocorticoids, nonsteroidal anti-inflammatory medications, and antioxidants. Despite their effectiveness to varying degrees, these drugs show undesirable adverse effects as such a vascular necrosis, gastrointestinal bleeding, liver/kidney injury, cardiovascular risk, xerosis, puritness and rashes. Monoclonal antibodies against various pro-inflammatory cytokines and chemokines or other bio-macromolecules (nucleic acids and proteins) have been employed therapeutically or pre-clinically for RA management by controlling molecular mechanisms intimately connected with inflammatory responses, IBD, atherosclerotic disease, atopic dermatitis and asthma. However, due to these biological agents, the uses of small molecule drugs and biological therapies have been severely hampered due to their limitations and unwanted side effects, such as high cost, primary or secondary non response, and a higher risk of serious infections. Systemic distribution in non-target tissues and cells is primarily responsible for undesirable consequences. Furthermore, several newly developed medicines, such as specialized pro-resolving mediators that are extremely beneficial in the management of chronic conditions due to their powerful anti-inflammatory activity, rely on site-specific delivery and controlled release in inflammatory tissues/cells.

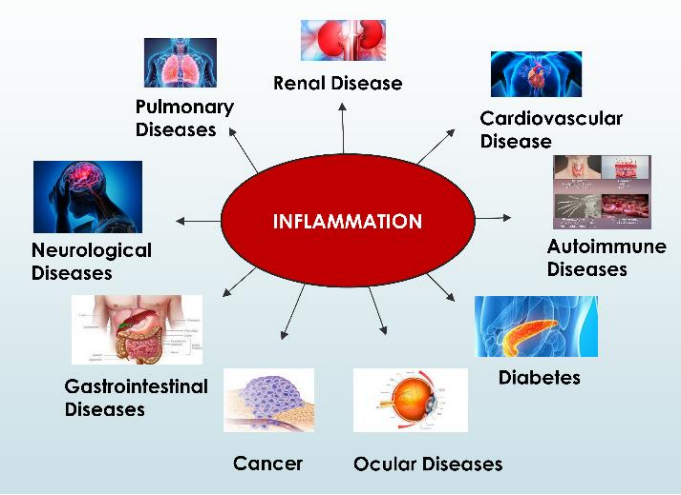

Fig. 1: Various inflammatory diseases

Approaches for the inflammation management

Growing interest has emerged in using nanoparticles (NPs), which have a size range of nanometers, to get around some of these limitations. Today, biocompatible nanoformulation (i.e, NPs containing active principles) are attainable with finely regulated surface charges, shapes, and sizes (8–11). Furthermore, passively exploiting this unique leaky vasculature has improved nanoformulation transport and accumulation through sub-endothelial space. Moreover, trying to target conjugates on nanoparticle surfaces may enable active accumulation and regulated drug release into affected tissues and cells thereby minimizing toxicity and adverse side effects (12–14) There are numerous

types of nanoparticles that have been produced for inflammation management either they already exist or have reached the pre-clinical stage. Examples include hydrogel formulations, liposomes, micelles, dendrimers, and polymer nanoparticles which may also be lipid base such as nanostructured lipid carrier gel (NLC). The functionalization of these nanoparticles with particular moieties, such as coating groups, antibodies, or affinity ligands, is an option as well as leaving the nanoparticles unmodified. Through the leaky vasculature, they can actively or passively target primary inflammatory actors such as macrophages, endothelial cells, membrane receptors on inflammatory cells, anti-inflammatory genes, and cytokines. The development of well-designed nanocarriers has led to some new approaches in inflammation therapy Evidently, Nanoparticles (NPs) can be specially designed to preferentially continue moving to the targeted site from the site of application, resolving problems with conventional medicines including systemic toxicity and off-target organ adverse effects, which are aggravated by repeated and prolonged dosing. Whereas NLC have a good retention time and produce the drug's prolonged effect. There is a lot of potential for the degenerative processes in the formation of nanoparticles that phagocytose inflammatory sensors or macrophages and regulate the formation of pro-inflammatory and anti-inflammatory molecules. Moreover, because of their modulability, which allows them to either passively (by improving the size and/or surface charge of nanoparticles) or actively (by coating nanoparticles with specific antibodies), target specialized cells, especially monoclonal antibodies, may have a significant role in enhancing cellular immunity or response (15).

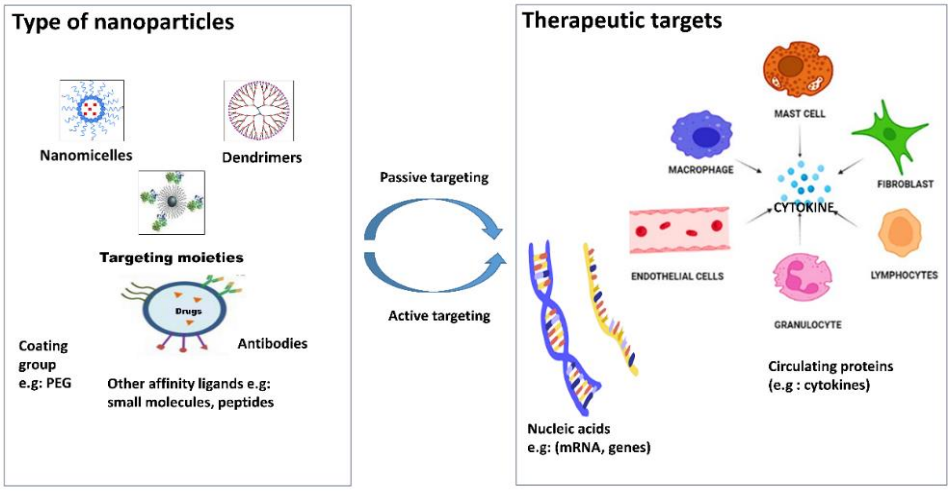

Fig. 2: Strategy and targets for inflammation management

Nanotechnology-based novel drug delivery systems

Numerous improved delivery of drug systems has been researched over the years to overcome the drawbacks of anti-inflammatory medicines. Dendrimers, lipid-based nanoparticles, polymeric molecules, micelles, nanocrystals, nanoemulsions, nanofibers, nanostructured lipid carriers and hydrogels were studied as delivery mechanisms for molecular or therapeutic cells for inflammatory therapies. Exosomes, cell membrane-based nano-vehicles, and cellular carriers are examples of biomimetic particles developed for anti-inflammatory therapy delivery, in addition to completely synthesized vehicles over several length scales (16).

Small-molecule drug delivery

One of the therapeutic strategies is the use of steroidal or non-steroidal anti-inflammatory drugs can also be used to treat extracellular or cell-surface targets for inflammation. (Table 1). However, two new therapeutic modalities have recently emerged: the use of anti-leukotrienes, which inhibit the recruitment of inflammatory cells, and pro-inflammatory cytokine inhibitors, such as anti-TNF alpha or anti-IL-1 monoclonal antibodies. However, these treatments are insufficient to achieve

optimal pharmacological activity. Some drug constraints include low bioavailability, non-specific biodistribution, and/or a relatively short half-life in the body. Furthermore, patients receive high doses that have unwanted side effects and are ineffective in managing the symptoms of inflammatory diseases (17). On cancer therapy, there have been excellent reviews. So we have excluded nanoformulations used during cancer therapy where inflammatory processes take place. (18–20).

Table 1: Therapeutics available for inflammatory disease management

Therapeutic Classification	Category	Drugs/therapeutic agents	Mechanism of action	Side Effect	Reference
NSAIDs	-	Aspirin, celecoxib, indomethacin, ibuprofen	COXs inhibitors, Immunomodulation	Gastrointestinal reaction, failure of the kidney,etc	(21)
Glucocorticoids	-	Dexamethasone, hydrocortisone, prednisone, and methylprednisolone	Immunosuppression	Hyperadrenocorticism, Infection, high blood pressure, atherosclerosis, osteoporosis, and osteonecrosis, among other conditions	(22)
DMARDs	-	Methotrexate, hydroxychloroquine, sulfasalazine, clodronate and leflunomide	Immunosuppression, Disease-modifying activity	Myelosuppression, digestive reaction, liver and kidney dysfunction, etc.	(23)
Biological agents	Anti-cytokines	Anakinra, Sarilumab, tocilizumab	IL-1 receptor	Infection	(24)
		Sarilumab, tocilizumab	Interleukin-6R inhibitor	Infection, gastrointestinal perforation	
		Sirukumab, olokizumab, siltuximab	Interleukin-6 inhibitor	Infection, gastrointestinal perforation	
		Etanercept, adalimumab, ifliximab, certolizumab pegol, golimumab	TNF-α inhibitor	Infection, tuberculosis	
	Anti-T cell	Abatacept	Co-stimulation inhibitors	Infection, malignancy	
	Anti-B cell	Rituximab	B-cell depletion (anti-CD20)	Infection, hypertension	
	Kinase inhibitors	Baricitinib, tofacitinib	Janus kinase(JAK)1 and 2 inhibitor	Infection	
Natural product	-	Curcumin, Resveratrol, Guggulsterone, Withanolid	IL-6, COX-2, TNF-α	-	(25)

Drug delivery for Steroid-based drugs

Corticosteroids are a collection of steroid hormones that have a role in a variety of physiological functions, such as the immune system, the stress response, and the control of inflammation. Glucocorticoids in particular are potent anti-inflammatory corticosteroids that work primarily through a lipocortin-1 synthesis mechanism, regardless of the inflammatory source (26,27). Prednisolone, dexamethasone, hydrocortisone, and budesonide are a few examples of using the wide glucocorticoids used to treat inflammation. The autoimmune disease (RA) is characterized by the

body's immune misidentifying the joints and attacking them. This leads to inflammation, which thickens the tissue lining joints, causing swelling and pain in and around the joints. According to several studies the abundance and decreasing macrophages count in the synovium correlate directly with disease severity, making macrophages a potential biomarker in RA (28). Since encapsulated medications that remove macrophages from the liver and spleen significantly affect RES functioning, it is possible to administer glucocorticoids in liposomes consistently without eliminating macrophages but with a suppressing effect on pro-inflammatory functions. Currently, the treatment of Atopic Dermatitis disease is based on a "reactive management" strategy that includes a combative response to acute flare-up episodes as well as anti-inflammatory topical medicines. However, acanthosis and perivascular lymphatic infiltration can be observed histologically or as a subclinical inflammatory alteration in normal-appearing skin. As a result, normal-appearing skin is still a target for anti-inflammatory drugs. This treatment is supplemented with additional therapeutic treatment and the occasional use of anti-inflammatory medicines, which is referred to as "proactive treatment." However, these therapies may not be helpful in all people.

Drug delivery for Nonsteroidal Anti-Inflammatory Drug (NSAIDs)

NSAIDs act by inhibiting cyclooxygenase proteins, from which prostaglandins are produced by converting arachidonic acid. Because of their short half-life and a high percentage of protein binding, NSAIDs require high doses to be effective, which results in undesirable adverse effects such as a higher probability of gastric problems and cardiovascular complications (29,30). To try and combat these side effects, some nanomaterials have been developed, but they are currently only being studied in vitro at the pre-clinical stage. Diclofenac, an NSAID that inhibits prostaglandin synthesis by reducing cyclooxygenase-1 and cyclooxygenase-2 with relative equivalence, was loaded into chitosan poly(glutamic acid) NPs (31). This method had no cytotoxicity for human macrophages. Prostaglandin E2 and IL-6 synthesis was similarly inhibited as NPs rapidly phagocytosed and activated these cells (32). Formulations incorporating carbopol-based gels were made, and evaluations of their ex vivo permeation, purity, pH, and rheological stability were carried out. For comparison, celecoxib-containing niosomes and gels that include noisomes were created. The in vivo activity was determined by using a preclinical disease model. Many inflammatory indicators, such as Paw tissue was examined before and after therapy for TNF-α, NF-κB, and COX-2 levels (33).

Drug delivery for nano-encapsulated anti-inflammatory mediators

Anti-inflammatory mediators are another treatment option for inflammatory diseases such as rheumatoid arthritis and atopic dermatitis. The anti-inflammatory cytokine IL-10, for example, has several effects on inflammation and immune modulation (34). Other anti-inflammatory or pro-inflammatory substances cytokines are primarily down regulated, as are immune B cell survival, proliferation, and antibody production. Furthermore, it is thought that IL-10 inhibits NF-B activity and regulates the JAK-STAT signaling pathway (35). To overcome these shortcomings, new IL-10 anti-inflammatory preparation was developed.

Drug delivery for biomimetic nanoparticles

The majority of intravenously administered nanomedicines are quickly seized and removed by the innate system if they are not PEGylated. Biomimetic nanoparticles are hybrid nanocarriers with a top layer that mimics the membrane of a cell (for example, platelets, immune cells, erythrocytes, and cancer cells). Nanoparticles with cell membrane coating and liposomes engineered with cell membrane proteins are included in this category (36, 37). This strategy incorporates the biological characteristics of the source cells, resulting in a prolonged circulation of the nanoparticles and an active targeting capability; additionally, these biomimetic nanoparticles are less likely to be identified by the immune due to the membrane coating's inherent mother cell characteristics. Current rheumatoid arthritis and atopic dermatitis treatment focuses on the inflammatory reaction by using anti-cytokine biologics such as those that inhibit tumor necrosis factor-alpha (TNF-α) and

interleukin (IL-1). And NF-Kbeta and MAPK Pathway. However, the response rate remains inadequate. Neutrophils are important in resolving inflammation and repairing tissue damage (38, 39). Recently, lipidoid-polymer hybrid nanoparticles (NPs) were created to provide activated macrophages with siRNA against IL-1to prevent the pathogenesis of RA caused by collagen antibodies (40, 41). The delivery of combined therapy is also made easier by such DDS. For example, calcium phosphate/liposome-based hybrid nanoparticles (hybrid-NPs) were developed to deliver methotrexate and NF-B-specific siRNA to the diseased site's lipopolysaccharide (LPS)-activated macrophages (42, 43).

Additional uses of nanoparticles for immune system modulation

Potential methods of reducing inflammation include techniques to either activate or inhibit the receptors taking part in the immune response (Table 1). One such is the triggering of the hepatic X receptors (LXRs), which is atheroprotective and reduces inflammation in macrophages (44, 45). As a result, recent studies have focused on the preparation of LXR analogs have been found in macrophage-targeted nanomaterials such as mannose dendrimeric nanoparticles (46-48) and biodegradable diblock PLGA-b-PEG copolymer NPs (49, 50). Cyclosporine A was incorporated in a liposomal nano-formulations as well. For instance, intravenous administration of lipid-based cyclosporine A could mitigate the effects of cerebral ischemia and reperfusion damage such as neuro-inflammation by decreasing inflammatory responses such as MPO activity and TNF-α level (51). Cyclosporine- A which has anti-inflammatory efficacy intranasally was also demonstrated using a nanoemulsion. in a subsequent investigation on neuroinflammation in a model for preclinical studies (52).

Delivery system for anti-inflammatory phytochemicals

An in vivo model system was used to study phytoconstituents and their effects on a variety of chronic inflammatory conditions that are summarized using structure-based classification (53, 54). Furthermore, when compared to current drugs used in each chronic inflammatory disease, in animal model systems, some of these phytochemicals are in the clinical phase, and effective dosages of them are equally relevant. Mannosylation of naringenin-loaded transfersomes (MA-NgTfs), showed in vitro release studies, and marketed formulation diffusion was found to be 69.31%, 62.03%, 58.71%, and 65.02%, respectively. The observations provided convincing evidence for vesicular delivery by mannose-directed carriers via phagocytes via mannose receptors (55). Withaferin-A, a steroidal lactone loaded with mannosylated liposomes (ML-WA), an effective strategy for the rheumatoid arthritis treatment (RA), was administered to adjuvant-induced arthritic rats to target synovial macrophages. IL-10, an anti-inflammatory cytokine, was discovered to be abundantly removed as well as for atopic dermatitis (56).

Conclusion

This review covers chronic inflammation and the inflammatory response mechanism. Over the last few decades, various drug delivery systems have been explored to overcome the drawbacks of anti-inflammatory medicines based on traditional formulations such as glucocorticoids, corticosteroids, and other nonsteroidal drugs, many biological agents, such as antibodies and nucleic acids, are developed for cytokine inhibition and to reduce immune cell extravasation into inflamed tissues. Exosomes, cell membrane-based nano-vehicles, and cellular carriers are examples of biomimetic particles developed for anti-inflammatory therapy delivery. Anti-leukotrienes, and pro-inflammatory cytokine inhibitors, either alone or in combination, are two therapeutic modalities that have recently emerged. Current research on advanced drug-delivery systems and targeted approaches has demonstrated improved therapeutic efficacy, reduced systemic side effects, and site-specific delivery with prolonged drug release in experimental animal models. At present, therapies using targeted nanomedicine and new phytochemicals have showed great promise in combating inflammatory disease. In coming years, phytochemicals have been predicted to lead to the discovery of new drugs for symptomatic relief of inflammation, because they are highly effective, considered

safe, and without any side effects. Further clinical studies are required to develop more efficient and safer plant-based molecules and bring them to market as anti-inflammatory drugs, either alone or in combination.

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