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Inflammopharmacology

REVIEW

Advancement of nanomedicines in chronic inflammatory disorders

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Abstract

Chronic diseases, as stated by the WHO, are a threat to human health which kill 3 out of every 5 people worldwide. Therapeutics for such illnesses can be developed using traditional medicine. However, it is not an easy path from natural products to Western pharmacological and pharmaceutical methods. For several decades, chronic inflammatory disorders, especially in Westernized countries, have increased incidence and prevalence. Several NSAIDs are used to decrease inflammation and pain; however, there are numerous negative consequences of these anti-inflammatory medications, whereas plant-based natural products have anti-inflammatory therapeutic benefits that have little or no adverse effects. Nanoparticles are a new type of drug delivery device that may be designed to provide excellent target selectivity for certain cells and tissues while also having a high drug loading capacity, resulting in better pharmacokinetics, pharmacodynamics (PKPD), and therapeutic bioavailability. The size and polarity of phytochemical compounds make it hard to pass the blood–brain barrier (BBB), blood-vessel endothelial lining, gastrointestinal tract and mucosa. In addition, the gastrointestinal system is enzymatically destroyed. Therefore, nanoparticles or nanocrystals might also be used for encapsulation or conjugation of these chemicals as a method to improve their organic effectiveness through their gastrointestinal stability, absorption rate and dispersion. The therapy of numerous inflammatory illnesses, including arthritis, gastritis, Nephritis, Hepatitis (Type A, B &C), ulcerative colitis, Alzheimer's disease, atherosclerosis, allergic responses (asthma, eczema) or autoimmune disorders, is characterised by nanoparticles. This review paper provides information on the numerous nanosystem described with their probable mechanism to treat chronic inflammatory diseases.

Keywords Nanoparticles · Chronic inflammatory disorder · Severe acute respiratory syndrome · Interferon · Reactive oxygen species

Introduction

Inflammation is a complicated, stereotypic series of reactions, where the body protects against the invasion of foreign organisms (bacteria, viruses, funguses), such as thorn, irritating or microbial organisms and repairs wound cells to tissue. First time in history, it has been explained by Celsus in the first century AD and described four fundamental symbols in the form of "rubor et tumour cum calore et dolore" (redness, swelling, heat, and pain), while in 1858, another scientist Virchow introduced "functio laesa" (disturbance of function) as a fifth cardinal sign of inflammation (Brusini et al. 2020). It acts as a burden and affects the world population by 3–5% (Wang et al. 2015). Three out of five people globally die from chronic inflammatory illnesses, such as stroke, chronic respiratory illnesses, heart illnesses, obesity, and diabetes according to the World Trade Organization (WHO). While no inflammatory disorders appear to be connected with atherosclerosis, glomerulonephritis, hepatitis, diabetes, or different cardiovascular conditions it is possible to take part among illnesses caused by chronic inflammation (Pahwa et al. 2019).

The patient is affected not only by a specific area of the body, but also by a variety of physical responses triggered by the immune system (Nordqvist 2017) and inflammation

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manifested in the form of redness, rashes, tenderness, heat, long term soreness, swelling, pain, and mobility (loss of function) of a body part, etc. (Shukla et al. 2019). The most important features include oedema formation, fibrin deposition, and the presence of neutrophils in the injured tissue.

More than 100 different types of inflammatory disease are observed globally (Fig. 1) viz. rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), chronic obstructive pulmonary disease (COPD), asthma, psoriasis, idiopathic pulmonary fibrosis (IPF), type 1 diabetes (T1D) and multiple sclerosis (MS) (Zheng et al. 2021). Inflammation is initiated due to the production of chemical messengers including vasoactive amines or eicosanoids, products of multi-enzyme systems of blood plasma (complement, hemocoagulation, fibrinolytic, and kinin), various hormones, neurotransmitters, and neuropeptides (Malone 2016).

Figure 2 shows several chemical messengers are involved during the inflammation phenomena, such as lipid mediators—Eicosanoids (prostanoids, leukotrienes, thromboxanes, platelet-activating factors—(PAF) (Diegelmann 2016), vasodilators (NO, PGI2, PGE2, PGD2), vasoconstrictors (endothelins, TXA2, PGG2, PGH2), vascular endothelial products, chemotactic factors (C5a), Mast cells (histamine), bradykinins, and prostaglandins (Burini et al. 2020). Inflammatory mediators are solutions that release diffuses

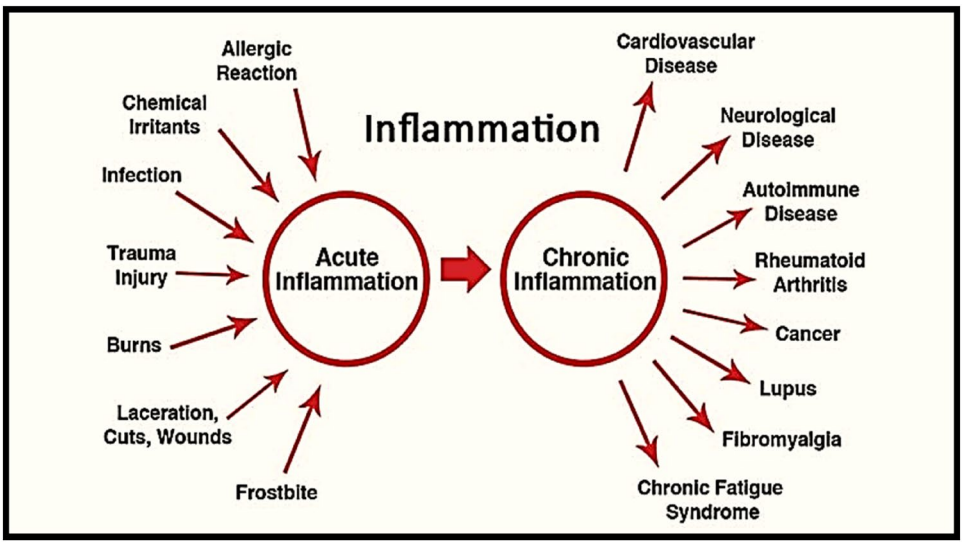


Fig. 1 Schematic representation of different types of acute and chronic inflammation

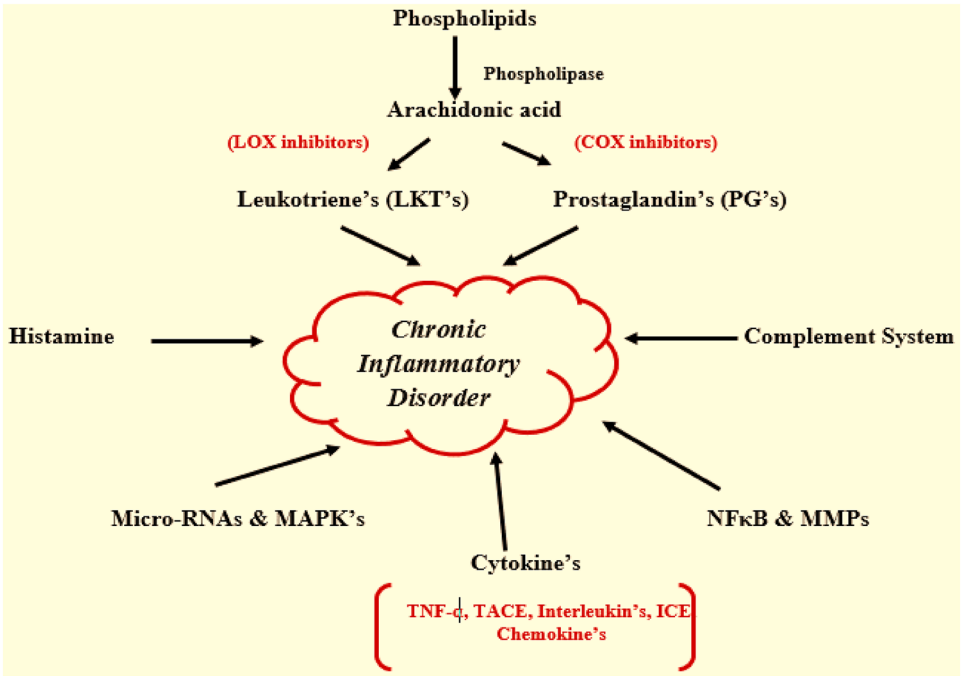


Fig. 2 Chemical messengers involved during the inflammation phenomena (Bhavya and Haridas, 2017)

chemicals from inflammatory or other cells. They operate both locally at tissue injury and infection sites and anatomically far away (Miyasaka and Takatsu 2016).

The mediators (Ley 2018) are divided into:

1. Exogenous: (bacterial products and toxic substances mainly (e.g., lipopolysack-like Gram-negative bacteria)
2. Endogenous (activity-like, complementary, hemocoagulatory, fibrinolytic, and kininetic systems, inflammation regulate and homeostasis)

Kinds of inflammation

Inflammation can be classified according to whether it is induced by an external substance or an endogenous aberrant reaction. Inflammation can be acute or chronic depending on how long it lasts (Xiao 2017).

Acute inflammation

Acute inflammation symptoms often last a few weeks, but sub-acute inflammation symptoms later 2–6 weeks. The body doubles the number of leukocytes while in an acute inflammatory reaction (i.e., White blood cells or granular cells) in the affected tissue site. These are the main cells involved in the acute inflammation process containing eosinophil's, mononuclear cells (monocytes and macrophages) and primary neutrophils, serum proteins (e.g., complement, C-reactive protein), cell receptors (e.g., Toll-like receptors activation), granulocyte–monocyte colony-stimulating factor (GM-CSF), interferon-gamma (IFN-g) from pathogen incursion (Wynn et al. 2013) and cells that discharge cytokines and inflammatory markers (i.e., macrophages, mast cells, natural killer cells) (Cronkite and Strutt 2018). White blood cells (leukocytes) are drawn to the location to help the elimination of wreckages (Shi et al. 2012). Thus, the objective of inflammation is to clean up the damage and begin the healing process, which is then followed by several phases that continue to involve the immune system until the injury or infection returns to equilibrium (Schauss 2013). Above mentioned symptoms and signs are sometimes not observed in the patient, such type of inflammation is known as "silent inflammation."

Chronic inflammation

Chronic inflammation is defined as chronic, low-level inflammation that might last for months, years, or even a lifetime. Constant tiredness, mouth sores, joint, chest, or stomach discomfort, rash, and fever are symptoms and indications of this kind of inflammation. On the other hand, the main cause of chronic inflammation is a longer period of perceptible of the harmful chemical or pathogen. Sometimes, defence mechanisms cannot be controlled easily and hence it damages utmost body parts viz. nervous and musculoskeletal systems, and blood vessels (Pahwa and Jilal 2018) and produces sepsis, asthma, obesity, type 2 diabetes, neurodegenerative diseases (Alzheimer's disease), cardiovascular diseases (e.g., atherosclerosis, cardiac ischemia/reperfusion), cancer, bowel disease, and few scientific journals also have reported Crohn disease, rheumatoid polyarthritis (Molinaro et al. 2016). It has been linked with certain other types of diseases, such as autoimmune diseases (e.g., allergies or hypersensitivity reactions, atopic dermatitis, psoriasis, asthma, chronic obstructive pulmonary disease(COPD), arthritis (osteoarthritis, rheumatoid arthritis), inflammatory bowel diseases (ulcerative colitis), celiac disease, auto inflammatory syndrome, or inflammation accompanying transplant rejection), diabetes, cardiovascular disease (CVD), etc. (Abdulkhaleq et al. 2018).

It is most likely happens due to the continued production of inflammatory cytokines (i.e., interferon-gamma (IFN-γ), IL-2, IL-4, IL-6, IL-15, and IL-17) and fabrication of reactive oxygen species (ROS) forms oxidative stress and (hypoxia) metabolic stress (Schauss 2013). The pathophysiology of pain is influenced by pro-inflammatory cytokines such as IL-1, IL-6, and TNF. Interleukin (IL-6) is important in the neural response to microglial, astrocytic activation, nerve injury, and the regulation of a neuronal neuropeptides phase. TNFR1 and TNFR2 are two key cell surface receptors that regulate NF-β activation, inflammation, and the activation of stress-activated protein kinases (SAPKs) and apoptotic pathways. TNF-α, another inflammatory cytokine, is required for innate and adaptive immunity, proinflammatory characteristics, cell proliferation, and inflammatory and neuropathic hyperalgesia (Tanaka et al. 2014).

Comprising the pathophysiology of inflammation, proteins produced (Zarrin et al. 2021) by particular cells during inflammation may be identified (e.g., ICAM, VCAM, and selectins). Small compounds can influence three different types of protein targets (Durymanov et al. 2017).

(1) Inflammatory mediators' synthesis is regulated by enzyme kinases.
(2) In nucleic acid sensing pathways, receptors and critical signalling molecules.
(3) Soluble ligands (i.e., cytokines and receptors on the cell surface).

Therapeutic strategies for inflammation

High dosages of medicines that might sometimes generate adverse effects on healthy tissue are needed to accomplish the intended therapeutic effects on inflammatory cells. In addition, therapies are categorized in such a way (Whalen et al. 2019).

1) Non-drug (rehabilitation, physiatry, balneology)
2) Non-steroidal anti-inflammatory (Trevor et al. 2019) drugs, such as (indomethacin, diclofenac, ibuprofen, piroxicam, tenoxicam, meloxicam, nimesulide, celecoxib, parecoxib, lumiracoxib, aspirin, and naproxen etc.).
3) Glucocorticoids (hydrocortisone, prednisolone, methylprednisolone, triamcinolone, dexamethasone, betamethasone, etc.).
4) Immunosuppressant drugs, i.e., Cyclosporin A, Tacrolimus, Pimecrolimus (Ghasemian and Owlia 2015)

Nowadays, the treatment of acute and chronic inflammation has also been done using steroidal (betamethasone, prednisone, and dexamethasone). In the case of NSAIDs, lower doses are mostly accessible for treating inflammatory pain, but greater dosages of NSAIDs and steroidal drugs can be used as prescription drugs (Nordqvist 2017). Both are advantageous to treat chronic and acute inflammation through inhibition of cyclooxygenase (COX); however, excess use can produce some side effects in the tissue or cell. Furthermore, autoimmune diseases such as rheumatoid arthritis (RA) can be treated by anti-rheumatic agents (auranofin, aurothiomalate, D-penicillamine), aminosalicylates (sulfasalazine) (Mayoclinic 2020), and others are disease-modifying anti-rheumatic agents (DMARDs) such as methotrexate (MTX) are effective to slow down the RA development. A combined form of the drug (DMARDs with Glucocorticoids) may be helpful for the prevention and management of anti-inflammatory action and remove the complications that arise due to dose enhancement (Wailoo et al. 2014). In addition, asthmatic disorder and chronic obstructive pulmonary disorder (COPD) can be prevented or treated using combinational therapy (β2-mimetics, anticholinergic agent, phosphodiesterase-4 antagonist, and long-acting theophylline–methylxanthines) (Whalen et al. 2019).

Recently, two additional therapies were introduced in the market which may be breakthroughs in the helpful to indulgence chronic and acute inflammation for example the use of anti-leukotrienes (LTs) that constrain the necessity of inflammatory cells (anti-TNF-α or anti-IL-1 monoclonal antibodies) and proinflammatory cytokine inhibitors (Tabas 2013). However, sometimes treatment is not suitable to obtain up to the mark pharmacological activity and non-specific bio-distribution, poor bioavailability, and/or limited shelf life are the major demerits with the use of the drug.

The quest for novel anti-inflammatory drugs is becoming popular to minimize side impacts and pharmacological restrictions, to provide improved safety, effectiveness, and more economic treatment of inflammation.

Medicinal plant and their phytochemicals for anti-inflammation therapy

The utilization of natural ingredients as anti-inflammatory drugs has recently sparked increased interest in the pharmaceutical industry. The utilization of natural ingredients as anti-inflammatory and anticancer drugs has recently sparked increased interest in the pharmaceutical industry. The natural product has long been used for treating human diseases as inflammatory disorders, i.e., Crohn's disease, and ulcerative colitis. Inflammatory bowel disease (IBD) (chronic inflammation in the GIT zone or Intestinal tract). Secondary metabolites of the plants (Alkaloids, glycosides, flavonoids, phenolics and polyphenols, saponins, tannins, terpenes, anthraquinones, essential oils, and steroids) are only some of the bioactive molecules that may be employed to make pharmacological derivatives to fight inflammation (Salibay et al. 2021). The primary sources of natural agents that are potential bioactive natural chemicals in the pharmaceutical industry include plants, animals, microorganisms and aquatic animals. The phytoactive ingredients of medicinal plants are widely utilised for many therapeutic purposes and, owing to their accessibility and affordability, provide an appropriate alternative to conventional medicine.

Phenolic compounds are the secondary metabolite and are structurally different from the hydroxyl group-containing cyclic aromatic rings (i.e., Tannin and lignin). They perform a strong antioxidant and anti-inflammatory activity at the broad spectrum level (Davatgaran-Taghipour et al. 2017). These derivatives are divided into main classes depending on the amount and arrangement of their carbon units: Flavonoids and Non-Flavonoids. More than 6000 phenolic constituents are renowned for their antioxidant activity. Flavonoids are further classified depending on chemical structure and number of hydroxyl sets and degree of alkylation or glycosylation. Subgroups of flavonoids are shown in Fig. 3: Flavones (i.e., apigenin and luteolin), flavanol (i.e., epigallocatechin-3-gallate—EGCG) (Singh et al. 2016), flavonols (i.e., QC & kaempferol) (Barreca et al. 2016), isoflavones (i.e., daidzein and genistein) (Aras et al. 2015), flavanones (i.e., naringenin & hesperetin) (Cirmi et al. 2016), and anthocyanins (i.e., cyanidin & delphinidin) (Strathearn et al. 2014) are the

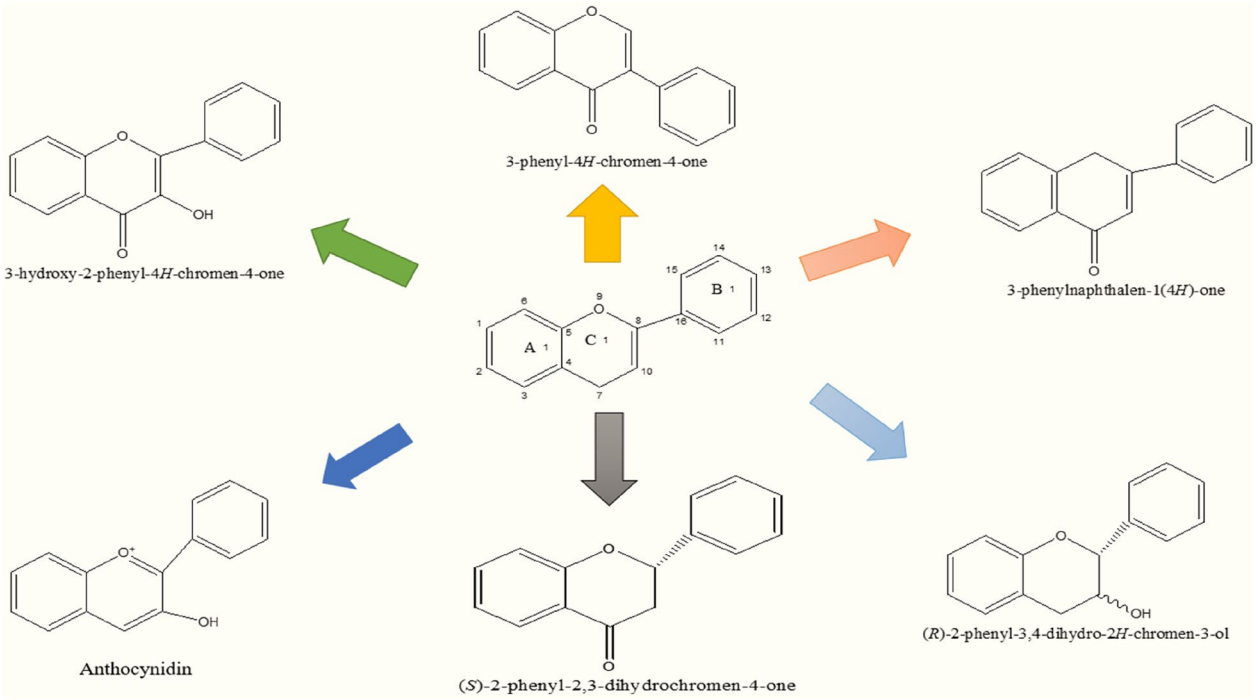


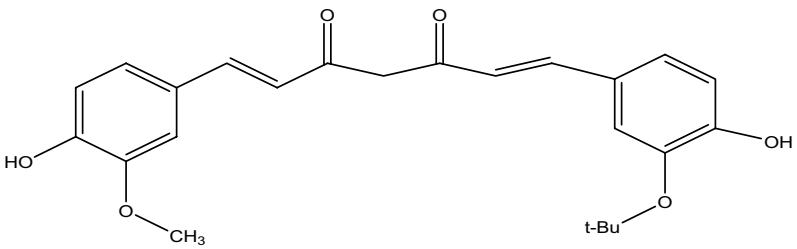
Fig. 3 Basic skeleton structure of flavonoids and their classes

best-known flavonoids which are helpful in various aliments (i.e., anti-inflammatory, neurological diseases, and cardiovascular disorder).

Bioactive compound Curcumin (1*E*, 6*E*)-1, 7-bis (4-hydroxy-methoxyphenyl)-1, 6 heptadiene-3, 5-dioneI) which is extracted from Curcuma longa roots and rhizome used in anti-inflammatory activity. Recent scientific reports suggest that nanoformulation of Nanocurcumin regulates the inflammatory response by inhibiting the activity of inducible nitric oxide synthase (iNOS), lipoxygenase (LOX), phospholipases A2 (PLA2s), and cyclooxygenase-2 (COX-2) enzyme pathway, which obstructs the synthesis of prostaglandin, pro-inflammatory leukotrienes an essential inflammatory response mediators (Farhood et al. 2019). Its inflammatory response is linked to an arachidonic acid production route for eicosanoid formation (Lee et al. 2020) (see Fig. 4).

Glycyrrhizin is a bioactive component of liquorice derived from the root of *Glycyrrhiza glabra* that contains pentacyclic triterpenoid and glycosidic saponin shows remarkable anti-inflammatory activity by inhibition of nuclear transcription factor (NF-kB) which play a vivacious role to regulate inflammation in human beings (Wang et al. 2020) and inhibiting TNF, MMPs, PGE2 and free radicals (Yang et al. 2017). Other plant-derived bioactive natural products resveratrol and stilbenes derivatives (Yuccaols A, B, C, D, and E) obtained from *Yucca schidigera* extract have shown potent anti-inflammatory activity through inhibition of the NF-kB, which stimulates the synthesis of NOS2 (Reinisalo et al. 2015) (see Fig. 5).

Fig. 4 Chemical structure of Curcumin



(1*E*,6*E*)-1-(3-*tert*-butoxy-4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione

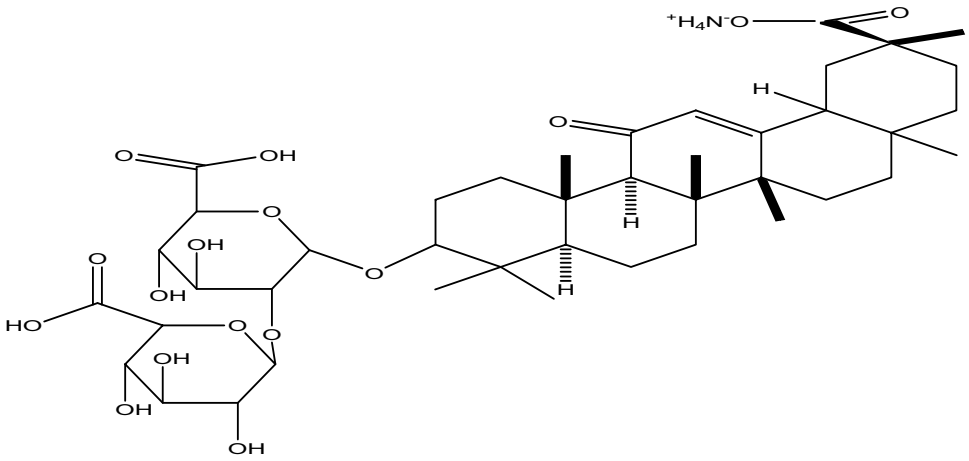


Fig. 5 Chemical structure of Glycyrrhizin

Nanoparticles

Nanoparticles (NPs) are the nanocarriers or natural colloids/synthetic colloids types of NPs which are available in different forms of colloids carriers, such as liposomes, micelles, dendrimers, inorganic or metallic nanoparticles, and solid–lipid nanoparticles (SLNs). Furthermore, Nanomedicine provides novel treatment possibilities for many drugs which cannot efficiently be employed as traditional formulations (Saraiva et al. 2016). In addition, other drug delivery system includes polymeric nanoparticles, carbon nanotubes, quantum dots, gold nanoparticles, magnetic nanoparticles, polymeric micelles, and viral vectors (Tekade et al. 2017). It is found in various shapes and sizes in the range (1×10^{-9}) have attached by covalent bonds or adsorbed to the surface of a particle or enclosed within a structure, such as liposomes and dendrimers (Landriscina et al. 2015). The desire for better treatments for inflammatory, developmental, viral, and degenerative nervous system diseases has driven its fast growth (Gendelman et al. 2015). In anti-inflammatory therapy, various hybrid NPs have recently been explored. According to current research, one or even more materials are formed into nanostructures, and the properties of every material are extensively used for enhanced biocompatibility and targeting ability. (Agrahari et al. 2019). Current literature shows that the size, shape, biocompatibility, and biodegradability of the component, the carrier and drug stability of many parameters impact the targeting of nanoparticles, the zeta and hydrophobic potential, and surface functionality in case of neurodegenerative illnesses. In this sense, poly (lactic-*co*-glycolic acid (PLGA) is the most promising hydrophobic synthetic polymer (Mir et al. 2017) utilized as the medication carrier to treat neurodegenerative illnesses (Alzheimer's disease, and Parkinson's disease) by the inhibition of galectin-3 and caspase-8 (cause of neuroinflammation). Therefore, several Nanomedicines were manufactured with cancer (Iqbal et al. 2018), cardiovascular pathology (Dormont and Couverur 2018), autoimmune diseases (Gharagozloo et al. 2015), metabolic syndrome (Veiseh et al. 2015), and neurodegenerative diseases (Goldsmith et al. 2014).

Recent advancement of nanoparticles system for the treatment of inflammation

Nanocrystals are a new nanotechnology field that pertains to the BCS class II medications. According to Nanotechnology in Drug Delivery-Global Market Trajectory & Analytics, it is predicted at US$ 124.7 billion in 2027, with drug nano crystal forecast to reach US$ 83.1 billion by the conclusion of the analysis period, despite the coronavirus pandemic crisis and resulting economic slowdown (Research and Markets 2020). Reducing drug particle size improves the bioavailability of BCS class II medications and may help BCS class IV pharmaceuticals with low solubility and permeation, since increasing drug water solubility raises the concentration gradient and improves drug permeability (Peltonen and Hirvonen 2018). The nanocrystal approach, which is based on the diffusion of nanoparticles through an unstirred water layer, can be used to improve drug permeability (Wood et al. 2018). Furthermore, the mucus layer, which includes mucin glycoproteins, is thought to be a biological barrier to medication absorption; lipids, inorganic salts, and water were chosen based on quick diffusion (Liu et al. 2020). The main advantages of nanocrystals are: increased dissolving rate, increased saturation solubility, enhanced mucoadhesive, and reduced fed/fasted state variance. Furthermore, the increased bioavailability given by nanocrystal technology results in a faster beginning of the action, improving the quality of life in patients receiving anti-inflammatory medication therapy

for pain relief. These characteristics enhance the effectiveness and tolerability of anti-inflammatory medicines. They are an appealing method that leads to a significant change in the creation of novel items for various administration routes. The ability to target can reduce side effects and enhance efficacy in the treatment of inflammatory disorders. Bottom-up and top-down technologies, as well as mixtures of the two, are used in the manufacture of drug nanocrystals. The bottom-up process involves the formation of tiny particles from individual molecules. Because drug particles are precipitated from a supersaturated solution, this procedure is also known as nano-precipitation (Sinha et al. 2013). The driving force for crystal development is supersaturation, which is accomplished by cooling down or adding an anti-solvent (De Waard et al. 2011). The most significant industrial technique in micronization is the top-down method. These possible recommendations from the bottom-up in that it does not use organic solvents has better control over particle form and size and is easier to scale up (Salazar et al. 2012). It is a high-energy method in which micron-sized pharmaceuticals are suspended in an aqueous or non-aqueous dispersion media including stabilisers and reduced to the nanoscale by mechanical attrition (wet bead milling or high-pressure homogenization) (Tuomela et al. 2016b). In our findings, it is also the most commonly reported anti-inflammatory medication nano crystal technique. Various nanocrystals have recently been produced for usage in a variety of delivery routes, including oral, topical, parenteral, and ophthalmic. Table 1 shows anti-inflammatory medication nano crystals that can be made in a variety of ways and used in a variety of ways.

Nanoparticles (NP) may adsorb proteins from biological fluids and produce a protein layer known as a protein corona. The physicochemical features of NPs, such as size, shape, and surface chemistry, influence the protein corona composition (Schmid et al. 2017). Protein nanoparticles have various advantages as a drug delivery technology, including biodegradability, stability, particle surface modification, ease of particle size management, and fewer toxicity concerns, such as immunogenicity (Chu et al. 2017). When nanomaterial's are administered intravenously (i.v.), they are instantly coated by a layer of blood proteins known as the protein corona or bimolecular corona (Oh et al. 2018). The amount and kind of protein corona vary a lot depending on the physicochemical properties of nanoparticles, which consequently changes the nano-biological interfaces including targeting effectiveness, immunogenicity, and intracellular toxicity (Walkey et al. 2012). To reduce the problems produced by the protein corona and prevent clearance by the mononuclear phagocyte system (MPS), generally, pro coatings of nanoparticles such as poly (ethylene glycol) decorating were first utilised (Tenzer et al. 2013). According to recent research, the deliberate adsorption of specific types of proteins, particularly dysopsonins, can change the character of nanomaterial's (Dai et al. 2014).

For the treatment of inflammation, many kinds of nanoparticles (liposomes, polymer nanoparticles, micelles,

Table 1 Anti-inflammatory drug nano crystal using different preparation methods

Drug	Route of administration	Method of preparation	References
Indomethacin	Oral	Wet bead milling	Kuroiwa et al. (2018), Liu et al. 2013, 2015)
Meloxicam			Liu et al. (2018), Ochi et al. (2014)
Acelofenac			Narayan et al. (2017)
Naproxan			Kumar and Burgess (2014)
Nimesulide			Gulsun et al. (2013)
Dexibuprofen		Bottom-up technology	Ullah et al. (2018)
Hydrocortisone acetate		High-pressure homogenization	Moschwitzer (2013)
Ibuprofen			Fernandes et al. (2017)
Celecoxib			He et al. (2017)
Dexamethasone	Topical	Wet bead milling	Doge et al. (2016)
Sodium diclofenac acid			Pireddu et al. (2015)
Flurbiprofen		High-pressure homogenization	Oktay et al. (2018)
Beclomethasone dipropionate		Bottom-up technology	Assem et al., 2019
Meloxicam			Yu et al. (2018)
Methylprednisolone			Karabey-Akyurek et al. (2017)
Hyaluronic acid/chitosan	Parenteral		Negut and Grumezescu (2021)
Squalene–adenosine NPs			Flavio Dormont et al. (2020)
Etopozide		Solvent evaporation method	Yadav and Sawant (2010)

Table 2 Some examples of innovative pre-clinical nanomedicines system for chronic inflammatory diseases

Nanoparticles (Nps)	Main Compound	Inflammatory lesions	References
N-(2-hydroxypropyl) methacrylamide (HPMA) copolymer NPs	Dexamethasone	Arthritis	Jia et al. (2020)
Nanoemulsion formulation of cationic lipid DOTAP	TNF-α siRNA	Parkinson's disease	Yadav et al. (2019)
Omega-3 fatty acid-rich flaxseed oil-based nanoemulsion system	Cyclosporin A	neuroinflammation	
Pegylated liposomes	Prednisolone	Renal ischemia and reperfusion injury	Van Alem et al. (2018)
Hyaluronic acid/chitosan NPs	Cytokine response modifier A pDNA	Osteoarthritis	Zhou et al. (2018a, b)
Hyaluronic acid-coated solid–lipid NPs	Prednisolone	Arthritis	
Spherical polymeric Nano constructs	Dexamethasone		Lee et al. (2020)
Solid–lipid NPs	Dexamethasone and Butyrate		Dianzani et al. (2017)

dendrimers, and hydrogel-based formulations) have been created or are presently in pre-clinical research. The first closed system for bilayer phospholipids was the liposomes originally provided as nanomedicines and is used for different types of cancer in clinical studies. Liposomal nanoparticles that have anti-inflammatory properties are currently being investigated (Chang et al. 2020). Furthermore, the use of nanocarriers to the specific target effector cells particularly antigen-presenting cells can be of great benefit in supporting cell response because of their module capacity, which allows them passively to optimise the size and/or surface load of nanoparticles or activate the nanoparticles for antimicrobial studies (Dacoba et al. 2017).To avoid the adverse effects found in traditional treatment, much emphasis has been given to developing more effective anti-inflammatory nanomedicines. Table 2 includes many examples of new revolutionary nanomedicines systems for pre-clinical treatment for inflammatory diseases. To present, FDA has authorized just a few tenths of the nanomedicines and several hundred new clinical trials. Three additional Patisiran/ONPATTRO, VYXEOS, and NBTXR3/Hensify nanomedicines have recently been authorized. However, few anti-inflammatory nanoparticles were able to carry out clinical investigations to our knowledge. Table 3 provides instances of nanomedicines in clinical trials.

Herbal medicines and natural products nanocarriers explored so far for chronic inflammatory diseases

Herbal medicine is a great source for inflammatory disease prevention and therapy. The current era has included the creation of nanoformulations using numerous natural or phtyocompounds.

The derivatives of phenolic and terpene are removed from the plan and are not stable for a long time owing to environmental conditions so that nanoformulations can be kept. It displays a harsh taste when taken orally, therefore, a high derivative or dose concentration was needed for therapy. Furthermore, to overcome the drawbacks of administering natural products through the use of supramolecular nanotherapeutics, which improve biopharmaceutical characteristics following injection via an oral, local, and systematic route.

For the prevention of inflammation, a variety of synthetic or organic compounds are increasingly being utilized. Organic nanoparticles (NPs) have higher biocompatibility than inorganic nanoparticles, and most carriers are made of biomaterials or polymers (Mir et al. 2017). In comparison, when using PLGA as a carrier, the organic nanoparticles form numerous structures with greater stability. When exosome is produced, they produce enough source and organic targeting impact (Wu et al. 2020). For liposomes, the nature of liposomes is simple, extremely stable, and biodegradable.

Table 3 Nanomedicines under clinical trials

Nanocarrier/Nanoparticles (NPs)	Principle compound	Disorder	References
Nanoemulsion (oil in water emulsion)	Tretinoin	Acne vulgaris	Sabouri et al. (2018)
Liposome	Cyclosporine (lipogel or cream)	Psoriasis	Kumar et al. (2016)
PEGylated liposomes	Prednisolone	Ulcerative colitis	Enceladus Pharmaceuticals. (2016)

When silver and gold (Ag/Au) are applied as a transport in the case of inorganic nanoparticles, they are employed to act antibacterial or bacterial. Carbon nanotube (Jia and Wei 2017) utilized as an organic nano parts carrier provides excellent biocompatibility, whereas quantum dot (Kalangi et al. 2018) has the best targeting and the capacity to imagine bio-carbon. Although the advantages for both organic and inorganic nanoparticles may be many, some disadvantages have been discovered. With organic nanoparticles, the structurally homogeneous character of pure exosomes is difficult to produce. They are very unstable when dissolved in water molecules; therefore, the product's shelf life is quite short. Inorganic nanoparticles are very unstable, have significant biological toxicity, and have a poor targeting impact (Yan et al. 2020).

Drug delivery methods based on organic nanoparticles are now commercially available in a variety of forms, such as Lutetium-177-1,4,7,10-tetraazacyclododecane–1,4,7,10-tetraacetic acid–hyaluronic acid–poly (lactic-co-glycolic acid) (Trujillo Nolasco et al. 2019), Dexamethasone (Yan et al. 2020) for Rheumatic arthritis. Among the commercially available inorganic nanoparticle-based drug delivery systems are Monocycte (Shi et al. 2020a) for osteomyelitis, Celecoxib (Kalangi et al. 2018) for oedema, and SAM

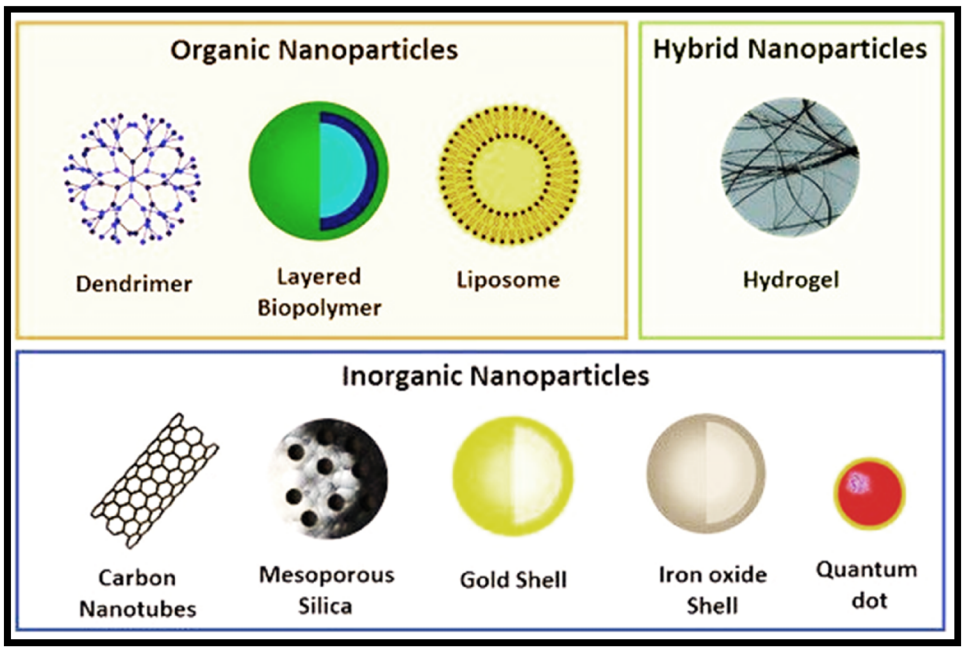


Fig. 6 Schematic representation of different types of nanoparticles (NPs) divided into organic, hybrid, and inorganic categories (Silva et al. 2019)

Table 4 Natural compound-based nanoparticle formulations

Nano formulation	Main Compound	Plant name	References
Liposome	Berberine (BBR)	*Berberis thunbergii*	Duong et al. (2021)
Ethosome	Alpha Phellandrene	*Moringa oleifera*	Valsalan Soba et al. (2021)
Niosomes	Monoammonium Glycyrrhizinate	*Glycyrrhiza glabra*	Maione et al. (2019)
Solid–Lipid Nanoparticles (SLNs)	Curcumin	*Curcuma domestica*	Ganesan et al. (2019)
Nanostructured lipid (NLCs)	Capsaicinoids (Capsaicin-8-methyl-N-vanillyl-6-nonenamide	*Capsicum annuum*	Nava-Ochoa et al. (2021)
Dendrimers	Sinomenine (7,8-didehydro-4-hydroxy3,7-dimethoxy-17-methyl9α, 13α,14α-morphinan-6-one; Sino)	*Sinomenium acutum*	Sharma et al. (2020)
Nanoemulsion	Cordycepin (3′-Deoxyadenosine)	*Cordyceps militaris*	Rupa et al. (2020)
Polymeric Nanogels and Nanosuspensions	Aloe-emodin (1, 8-Dihydroxy-3-(hydroxymethyl)-9, 10-anthraquinone)	*Aloe vera*	Divya et al. (2016)
Carbon Nanotubes (CNTs) and Nanofibers	Bis-demethoxy curcumin	*Curcuma longa*	Francis et al. (2018)
Polymeric Nanomicelles	Sesamol	*Sesamum indicum*	Ning et al. (2021)
Polymeric Nanoliposomes	Curcumin	*Curcuma longa*	Sogut et al. (2020)
Phospholipid–nanoparticles (PLN)	Thymoquinone (TQ)	*Nigella sativa*	Rathore et al. (2019)

(sodium 10-amino-2-methoxyundecanoate) (Kumar et al. 2016).

Figure 6 depicts several types of nanoparticles (NPs). Nanoparticles (NCs) or nanoparticles (NPs) can be made from a variety of organic and inorganic constituents (Metallic/metallic oxide NPs, Metallic NPs, and Metallic oxide NPs) including biodegradable and nondegradable polymers (polymeric nanoparticles (PNPs), polymeric conjugates), lipids (solid–lipid nanoparticles (SLNs), liposomes, and Nanoemulsions), dendrimers, micelles, nanocrystals, nanofibers, quantum dots, Nanodiamonds, etc. The natural compound-based nanoparticle formulations reported in Table 4 have aided in the treatment of different inflammatory disorders.

Polymer-based on nanoparticles can efficiently carry medicines, proteins, macromolecules, natural chemicals, hydrophobic and hydrophilic products, enhance their pharmaceutical and biopharmaceuticals characteristics and minimize the adverse effects. Poly (lacticco-glycolic acid) is a synthetic hydrophobic polymer that has been identified as the most effective polymer employed as a vehicle in the transport of medicines and has tremendous potential to target and treat drug incorporation into PLGA and is well researched in the formation of complexes. The polymers are also authorized for pharmaceutical usage by the FDA and the EMA (Anderson and Shive 1997). The polymers based on nanoparticles have two primary structures which rely on raw material collection (Di Marzio et al. 2016): (a) nanospherescore structure: the polymer matrix is distributed and or adsorbed by the Bioactive Compound(s). (b) Nanocapsules: displays water or oil loading medication and a polymer shell.

If NPs reach the outer membrane of a cell, they can interact with plasma or extracellular membrane components and enter the cell mostly by endocytosis. It leads to the absorption and squeezing in membrane invaginations of NPs into endocytic vesicles, which are ultimately transported into specific intracellular trial and trafficking compartments. Endocytosis may be categorized into various kinds, depending on the cell type, proteins, lipids, and other process molecules (Behzadi et al. 2017). Phagocytosis, Clathrin-mediated endocytosis pathway (≤200 nm) Caveolae-dependent pathway (≥ 500 nm) Clathrin/Caveolae-independent endocytosis and macro pinocytosis (0.2–5 µm).

Conclusions

Most inflammatory disorders are chronic thus therapies are needed for their treatment with an adequate therapeutic index. Alongside the advancement in sophisticated nanoscience and significant insights into nanomedicine technology, which helps build translational trust for effective use, the toolkit for clinical efficacy is enriched by innovations in chemical biology and medicinal chemistry.

In short, drug delivery systems based on nanomedicines for the prevention, diagnosis and treatment of chronic inflammatory diseases are offering good possibilities for clinical application which should be a new paradigm in chronic inflammatory pharmacotherapy.

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Declarations

Conflict of interest All authors declare no conflict of interest.

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