Nanoparticles and microbial metabolites as promising resources in anti-inflammatory nanomedicine and biomedicine

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Abstract

Inflammation is a complex pathophysiological process associated with atherosclerosis, cancers, diabetes, osteoporosis, rheumatoid arthritis, cardiovascular and autoimmune diseases. In this review, we represent an overview of microbial-derived compounds, and nanomaterial with anti-inflammatory activity and compare their efficiency, mode actions, and limitations. This paper aims to provide an insight on possible approaches to expand the chemical space of anti-inflammatory drugs. The micro-based approach through the discovery of new anti-inflammatory compounds from microorganisms and nano-based approach through the augmentation by nanomaterials are among the main suggested natural and chemical resources to provide new anti-inflammation drugs in the future. Furthermore, some nanomaterials by improving the anti-inflammatory properties of commercial drugs or microbial compounds through enhancing their solubility, decreasing unfavorable effects, donating excellent targeting, allowing a lower dosage, and providing substitute less-invasive delivery routes, have shown their indirect anti-inflammatory activity. Additionally, the efficiency of existing drugs can also be modulated by using new synergistic anti-inflammatory compounds from microorganisms or modification/augmentation by nanomaterials. This will aid in designing new nano and bio-based medications for the prevention and treatment of numerous inflammation related-debilitating diseases.

ABSTRACT

Inflammation is a complex pathophysiological process associated with atherosclerosis, cancers, diabetes, osteoporosis, rheumatoid arthritis, cardiovascular and autoimmune diseases. In this review, we represent an overview of microbial-derived compounds, and nanomaterial with anti-inflammatory activity and compare their efficiency, mode actions, and limitations. This paper aims to provide an insight on possible approaches to expand the chemical space of anti-inflammatory drugs. The micro-based approach through the discovery of new anti-inflammatory compounds from microorganisms and nano-based approach through the augmentation by nanomaterials are among the main suggested natural and chemical resources to provide new anti-inflammation drugs in the future. Furthermore, some nanomaterials by improving the anti-inflammatory properties of commercial drugs or microbial compounds through enhancing their solubility, decreasing unfavorable effects, donating excellent targeting, allowing a lower dosage, and providing substitute less-invasive delivery routes, have shown their indirect anti-inflammatory activity. Additionally, the efficiency of existing drugs can also be modulated by using new synergistic anti-inflammatory compounds from microorganisms or modification/augmentation by nanomaterials. This will aid in designing new nano and bio-based medications for the prevention and treatment of numerous inflammation related-debilitating diseases.

KEYWORDS: Inflammation; Anti-inflammation drugs; Microbial metabolites; Nanomaterial; Drug development; Green chemistry

INFLAMMATION PHENOMENON

Disrupted tissue homeostasis due to infection or physico-chemical tissue damage promotes inflammation as a pervasive form of host defense, which involves the innate and adaptive immune systems by rapidly destroying or isolating the source of the disturbance usually resulted in restoring tissue homeostasis (Medzhitov, 2008; Soehnlein & Lindbom, 2010). Collateral damage to the tissues is unavoidable in inflammation due to the destructive characteristic of inflammation substances to both causing agents and hosts (Wynn, 2004).

The molecular patterns of pathogens are identified via the innate immune system like intracellular nucleotide-binding domain, Toll-like receptors (TLRs), and leucine-rich-repeat containing receptors (NOD-like receptors (NLRs)). TLR activates common signaling pathways, which lead to immediate activation of NF-κB. Activated NF-κB translocates to the nucleus and, by binding to target genes upregulates their expression. NLRs in response to increasing numbers of molecular patterns activate the immune system through transcription and translation of target genes, which result in the inducible expression of pro-inflammatory cytokines like interleukin-1-beta (IL-1β), IL-6 and tumor necrosis factor (TNF)-α. Effector cells, including monocytes and neutrophils, are attracted to the site of the disturbance due to molecules. The activity of these immune cells led to a cytotoxic environment following the release of harmful chemicals, including reactive oxygen species (ROS) and reactive nitrogen species (RNS) and various proteinases from cytoplasmic granules.

The effector functions of inflammation are further arranged via the adaptive immune system, including T-helper (Th) cells, which modulate the inflammation process. Upon exposure of native Th cells to the antigens, they differentiate into several various cells, like Th1, Th2, and Treg cells. The first one, through producing interferon-gamma (IFN-γ), IL-2, and TNF-α with antiviral and immunoregulatory characteristics and activation of macrophage, can act against the intracellular pathogens. The second Th cells (Th2 cells) by releasing IL-4, IL-5, and IL-13 induce macrophage activation, and IgE production and eosinophil maturation (Graham, 2002; Mosmann & Coffman, 1989).

The third group of Th cells suppresses the activation, proliferation, and effector functions of immune cells including, NK cells, B cells, antigen-presenting cells, and T cells. This is derived by the production of IL-10 and TGF-β which lead to the resolution of acute inflammation as the last phase of this defense process once the disturbance is removed. The persistence of disturbance can lead to another form of inflammation, chronic inflammation, in which neutrophils are substituted with macrophages and T cells (Serhan & Savill, 2005).

Acute and chronic inflammation

Acute inflammation consists of the non-specific, urgent, and early responses to the adverse stimuli that are swiftly resolved. It is initiated by activation of the present immune cells in the affected tissue, including dendritic cells, macrophages, mast cells, which release mediators upon their activation. The inflammatory mediators have a short lifecycle and are degraded in tissue. Therefore, by removing the disturbance, selective pressure encourages termination of the inflammatory response and tissue repair starts restoring the functionality. The persist of the disturbance leads to chronic inflammation for years (Ashley, Weil, & Nelson, 2012).

MAIN DRUG TARGETS of THE INFLAMMATION PROCESS

The major anti-inflammatory targets are the enzymes, COX-1, COX-2, which catalyze the rate-determining process of arachidonic acid conversion to prostanoids. COX activation results in the formation of different prostanoids, including prostaglandins, prostacyclin, or thromboxane, which act as mediators of inflammatory and anaphylactic reactions, vasoconstriction (thromboxane), vasodilation (prostaglandin I2) and inhibition of platelet activation (prostacyclin). Activation of IκB kinase (IKK) complex through LPS or TNF-α leads to liberating cytosolic NF-κB from repression through IκBα ubiquitination and degradation. JNK-AP-1 pathway is activated by these stimuli. Inflammation is propagated by coordinated actions of NF-κB and AP-1 through enhancing transcription of cytokines, chemokines, and other pro-inflammatory genes (Figure 1).

Role of inflammation in the initiation of life-threatening diseases

The short term under control inflammation, acute inflammation, is considered to be beneficial to the detrimental agent while unresolved, persistent inflammation, chronic inflammation, is characterized by the simultaneous destruction and healing of the tissue. Therefore, this type of inflammation can lead to tissue damage, and consequently, several life-threatening diseases such as Alzheimer's disease (AD), rheumatoid arthritis, persistent asthma, atherosclerosis, cardiovascular disease, and cancer (Murakami & Hirano, 2012).

MICROBIAL DERIVED ANTI-INFLAMMATORY COMPOUNDS

The microorganisms derived natural products have been considered as one of the most prolific reservoirs of natural therapeutic compounds (F Salimi, Hamedi, Motevaseli, & Mohammadipanah, 2018). It has been estimated that the hit rate for natural products is 100-fold higher than the hit rate for synthetic compounds. Microbial natural compounds have unique properties including, structural diversity and complexity in the backbone, ring systems, and functional groups, occupying a unique chemical space (Lam, 2007). They mostly possess the expected pharmacokinetic characteristics which is necessary for clinical development. These natural compounds may target unknown pathological targets and contribute to revealing the detailed pathway of diseases. A large number of commercial drugs (more than 130 drugs) for the treatment of life-threatening diseases like cancers, diabetes, and infections have been originated from microorganisms. Also, more than 60 microbial-derived compounds with proved bioactivity against infections, inflammations, cancers, neurological, metabolic, cardiovascular and immunological disorders are currently in different steps of clinical trials. Microorganisms are the more readily reproducible source of bioactive compounds in comparison to the plants and animals. According to the statics of the microbial-derived commercial drugs, actinomycetes, fungi, and myxobacteria are the richest bioresources of structurally unique and medically important compounds (Harvey, 2008; Reichenbach, Gerth, Irschik, Kunze, & Höfle, 1988; Fatemeh Salimi, Hamedi, Motevaseli, & Mohammadipanah, 2019; F Salimi, Jafari-Nodooshan, Zohourian, Kolivand, & Hamedi, 2018; Schaberle, Lohr, Schmitz, & Konig, 2014; Vasundhara, Reddy, & Kumar, 2019; Watve, Tickoo, Jog, & Bhole, 2001). Many compounds with anti-inflammatory activity have been extracted from microorganisms and an overview of these prodrugs is summarized in Tables 1 and 2.

Limitations in anti-inflammatory drug discovery from microbial resources

Based on the survey in this paper, the most prevalent type of anti-inflammatory compounds produced by bacteria and fungi belongs to chemical groups of lactones, macrocyclic lactone, macrolactin 9 and 10 membered bis-lactones, lipopeptides, cyclic heptapeptides, bicyclic depsipeptides, norditerpens, merosesquiterpenoids, indole diterpenes, sesquiterpenoids, pyrrol, pyrone, oxopyran, alkaloids, dihydroisocoumarin, dichloroisocoumarins, carbazole, polyketides, and anthracene.

Despite the unprecedented value of natural compounds as an origin of pharmaceutically active compounds, the larger number of pharmaceutical companies have reduced or even ceased their research program on natural products. The dereplication approaches are generally not efficient enough to avoid the rediscovery of known compounds. Although new technologies could enhance the rate of drug discovery, they have not been greatly improved to meet the demands of the industry mainly due to the incompatibility of natural product libraries with the conditions of high-throughput screening. From an industrial point of view, discovering a natural drug with desirable therapeutic activity is a difficult, time, and cost-consuming process. Additionally, obtaining potent or compounds might need strains from marine or extreme habitats that demands a challenging and not always accessible sample collection step (Almasi, Mohammadipanah, Adhami, & Hamedi, 2018; Heidarian, Mohammadipanah, Maghsoudlou, Dashti, & Challis, 2019). Also, there are many compounds together with the compound of interest in the crude extracts. The low amount production of active compound another limitation that demand ether intensve purification procedures, production optimization or genetic manipulation. Besides, further quantities of active compounds are essential for preclinical development. Thus, large-scale fermentation is required which substantially affects the timeline of the development. Synthesis or modification of natural compounds via combinatorial chemistry is also not readily possible due to their large size, complexity, and a high number of functional groups.

Although it seems that screening of natural products is being improved through the emergence of new tech-

nologies including various high-throughput screening methods, genome mining, and innovative approaches in analytical chemistry such as the high-resolution separation technique and efficient detection systems which make it possible to trace compounds and determine the structures at the nanomole scale. In addition, combined or tandem technologies can accelerate the dereplication, isolation and structure elucidation of the effective natural compounds which exist in the crude extracts. Nevertheless, the risk of the rediscovery of known drugs can be minimized by novel sampling methodologies from unusual or extreme habitats or marine environments and screening the new microbial taxa (Exarchou, Fiamegos, van Beek, Nanos, & Vervoort, 2006; Exarchou et al., 2005; Lam, 2007; Tatsis et al., 2007).

NANOMATERIAL AS ANTI-INFLAMMATORY AGENTS

Understanding the significance of nanoparticle properties like size, shape and surface characteristics to optimize biological interactions, are creating new dimensions to develop nanoparticles as healing agents. Ultra-small size of nanomaterials, which lead to an exponential enhancement in the surface region, effective stiffness, and high reactivity donate altered physiochemical properties, which cannot be observed in the bulk material with the same composition. Recently, some therapeutic nanomaterials, including nanoparticles, nanopatterned surfaces, nanofibers, nanoporous, scaffolds, and nanotubes have been developed to treat life-threatening diseases like cancer, diabetes, pain, asthma, allergy, infections (Petros & DeSimone, 2010; Zhang et al., 2008). The promising therapeutic activity of nanomaterials in the suppression of inflammation has also been reported, and some of the nanomaterial derivatives has presented with anti-inflammation activity in Table 3 and 4.

Mechanism of action of nanomaterial with anti-inflammatory activities

Anti-inflammatory activities of nanomaterials can be divided into indirect and direct mechanisms (Ilinskaya & Dobrovolskaia, 2014). Among the indirect anti-inflammatory activities of nanomaterials can be their ability to carry anti-inflammatory drugs to provide targeted delivery and controlled release (Cooper & Harirforoosh, 2014). Nanomaterials including liposomes, dendrimers, polymeric nanoparticle (NP), lipid NP, chitosan NP, dendrimer-like polymers are reported as successful carriers of agents with anti-inflammatory activities like corticosteroids, indomethacin, methotrexate, receptor's antagonists, siRNA against cytokines and signaling molecules, siRNA against C-C chemokine receptor type 2 (CCR2) and selectins' antagonists. In addition, these delivery agents can increase the solubility and half-life of imperfectly water-soluble drugs, extend the half-life of systemic drug circulation via minimizing immunogenicity and the frequency of administration through releasing drugs at a sustained rate or in an environmentally responsible procedure and alleviate systemic side effects through drug delivery in a targeted manner. Nanomaterials via reducing particle size up to nanosize and encapsulating the drug in to water-soluble polymer enhance solubility and bioavailability of drugs. Nanomaterials also can simultaneously deliver more than one drug (Ilinskaya & Dobrovolskaia, 2014).

In addition to indirect anti-inflammatory activities of nanomaterials, they can directly reduce the inflammation process when they act as anti-cytokines. They can exhibit anti-cytokines either through the reduction of cytokine gene expression or preventing interaction among cytokine and its receptor-like gold NP. Nanomaterial can also illustrate the anti-selectin activity which blocks extravasation of leukocytes across the endothelial barrier affected regions such as dendritic polyglycerol sulfates or antioxidants like cerium oxide NP, gold NP, fullerene derivate. The nanomaterial structures that their anti-inflammatory activity is revealed so far are presented in Tables 3 and 4, respectively.

Limitation in applications of nanomaterial derived anti-inflammatory agents

Development of nanomaterials with anti-inflammatory effects to drugs is currently confronting their production by their probable systematic toxic effect because of their very high reactivity, going through blood-brain barrier, generating reactive oxygen species, imposing adverse effects on cell organelles, accumulating or disintegrating in the body as the major existing challenges. Different types of nanoparticles can be synthesized using various physical, chemical, and biological approaches (De Jong & Borm, 2008; Shubhika, 2013). Due to the ability of physical and chemical methods to produce high quantities of nanoparticles with a unified

size and shape in a relatively short time, these methods are more prevalent than the biological methods. Nevertheless, physically and chemically synthesis of nanoparticles are complicated and lead to the production of hazardous toxic wastes which are harmful to human and ecosystems (Gan, Ng, Huang, & Li, 2012). Such disadvantages of physical and chemical methods confine the application of physically and chemically synthesized nanoparticles, especially in their biomedical applications.

Consequently, biological or hybrid strategies can be considered as green, nontoxic, cost-effective and eco-friendly alternatives owning to the elimination of consuming toxic chemicals and reduction of energy consumption (Parveen, Banse, & Ledwani, 2016). Metallic nanoparticles with specific properties like higher catalytic reactivity and a greater specific surface area can be biosynthesized in a biogenic enzymatic process using metal resistant microorganisms such as bacteria (e.g., actinomycetes), fungi and yeasts which are readily cultivable in labs and possess various intracellular and extracellular enzymes (Li, Xu, Chen, & Chen, 2011). Despite considerable advantages of bio-based synthesis of nanoparticles, limited control on the size, shape and distribution of nanoparticles, time-consuming process of production and cost-intensive down streaming processing are major challenges of nanoparticle biosynthesis, which should be addressed to evolve it as an economically profitable method for large-scale production of nanoparticles.

COMPARING ANTI-INFLAMMATORY MODE ACTION OF MICROBIAL AND NANO-MATERIAL DERIVED COMPOUNDS

The current commercial anti-inflammatory drugs are the steroidal and the non-steroidal agents with their side effects such as the increased risk of liver cancer, cardiomyopathy, blood pressure, heart attack, stroke, gastrointestinal complications, and infertility. Therefore, development of novel anti-inflammatory drugs is vital to ensure the prevention of some systemic and metabolic disease which are associated or triggered with the chronic inflammation. Accordingly, the secondary metabolites from microorganisms from diverse chemical classes, including alkaloids, steroids, terpenoids, polyphenolics, phenylpropanoids, fatty acids, and lipids have been screened for the development of drugs with anti-inflammatory effects through various mechanisms such as reduction of TNF-α levels, attenuation of cyclooxygenase (COX)-2 activity, inhibition of TNF-α and nitric oxide synthase (NOS), interleukins formation and NF-ϰB translocation to the nucleus. In addition, the anti-inflammatory activity of various nano-materials with various mode actions, including anti-cytokine, antiadhesive, antioxidant activities and inhibiting COX has also been revealed. These nanomaterials are likely to become nanotechnology-derived pharmaceuticals in the future.

Overall, the chemical diversity of the anti-inflammatory compounds described from microbial sources so far is observed higher than nanomaterials. The common mechanism of action between microbial and nanomaterial sources includes anti-TNF-α and INF-γ activity, inhibitory effect on IL-1, IL-6 and nitric oxide synthase expression and NF-ϰB, Cox-2 and T-helper activities. Some anti-inflammatory activities like inhibitory effect on IL-5, IL-13, ICAM-1 and PTP1B expression, PGE2 release, and increasing TGF-β production are just reported from microbial derived compounds with anti-inflammatory activities.

On the other hand, some anti-inflammatory mode action including inhibiting expression of IL-8 and generation of anaphylatoxin C5a, blocking P and L selectins on leukocytes and endothelial cells, preventing degranulation of mast cells, decreasing the infiltration of neutrophils and macrophages as well as increasing expression of anti-inflammatory products such as mannose receptor C-type 1. Although these reported mode actions extensively depend on the applied bioassays in corresponding studies and extensive investigations are needed to achieve comprehensive comparison among microbial and nanomaterial derived compounds.

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FIGURE LEGEND

FIGURE 1 Inflammation cascade and involved pathological targets (Murakami & Hirano, 2012; Sahlmann & Strobel, 2016)

TABLE 1 The structure and mechanism of anti-inflammatory compounds reported from bacterial sources

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Other Activities	Other Activities	Other Activities	Reference	Reference	Reference	R
Unknown non-protein molecules	—	*Bifidobacterium breve* *Streptococcus thermophiles* *Lactobacillus rhamnosus* Non-pathogenic *Salmonella*, *Ruminococcus gnavus,* and *Bifidobacterium bifidum*	Anti-TNF-α effect Inhibit activation of NFkβ pathway by preventing IkB ubiquitination and therefore the release of proinflammatory cytokines	LPS induced TNF-a secretion by immune cells	—	—	—	—	(Menard et al., 2004)	(Menard et al., 2004)	(Menard et al., 2004)	(e 2
Unknown molecules	—	*Streptococcus salivarius*	Inhibits the activation of the NF-kB pathway in intestinal epithelial cells	Human intestinal epithelial cells, peripheral blood mononuclear and colitis mouse models	—	—	—	—	(Cosseau et al., 2008)	(Cosseau et al., 2008)	(Cosseau et al., 2008)	(e a 2

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Other Activities	Other Activities	Other Activities	Reference	Reference	Reference	R
7,13-epoxyl-macrolactin A	Macrolactin	*Bacillus subtilis* B5	Exhibits an inhibitory effect on the expression of inducible nitric oxide synthase and cytokine (IL1 and IL6)	LPS-stimulated RAW 264.7 macrophages	—	—	—	—	(Abd-Elnaby, Abo-Elala, Abdel-Raouf, Abd-elwahab, & Hamed, 2016)	(Abd-Elnaby, Abo-Elala, Abdel-Raouf, Abd-elwahab, & Hamed, 2016)	(Abd-Elnaby, Abo-Elala, Abdel-Raouf, Abd-elwahab, & Hamed, 2016)	(A e & H 2
Surfactin C	Lipopeptides	*Bacillus subtilis*	Inhibit the production of nitric oxide and suppress the expression of pro-inflammatory cytokine	LPS-stimulated RAW264.7 macrophages	—	—	—	—	(S.-D. Kim et al., 2006)	(S.-D. Kim et al., 2006)	(S.-D. Kim et al., 2006)	(K e a 2

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Other Activities	Other Activities	Other Activities	Reference	Reference	Reference	R
Pyrrolo [1, 2-a]pyrazine-1, 4-dione derivatives	Pyrrol	*Bacillus baekryungensis*	Inhibits denaturation of the proteins	Albumin denaturation technique	—	—	—	—	(Manal M. El-Naggar, 2016)	(Manal M. El-Naggar, 2016)	(Manal M. El-Naggar, 2016)	(M El N 2
Amicoumacin A	Dihydroisocoumarin	*B. subtilis, B. pumilus*	Inhibits the edema	Carrageenan induced paw edema	Antibacterial, anti-fungal, and anticancer	Antibacterial, anti-fungal, and anticancer	Antibacterial, anti-fungal, and anticancer	Antibacterial, anti-fungal, and anticancer	(Itoh et al., 1981)	(Itoh et al., 1981)	(Itoh et al., 1981)	(e 1
Surfactin	Acidic lipopeptides	*Bacillus subtilis*	Inhibits expression of IFN-γ, IL-6, iNOS and NO	LPS-stimulated RAW264.7 macrophages	antibacterial, antiviral, anti-tumour, and antimycoplasma	antibacterial, antiviral, anti-tumour, and antimycoplasma	antibacterial, antiviral, anti-tumour, and antimycoplasma	antibacterial, antiviral, anti-tumour, and antimycoplasma	(Carrillo, Teruel, Aranda, & Ortiz, 2003)	(Carrillo, Teruel, Aranda, & Ortiz, 2003)	(Carrillo, Teruel, Aranda, & Ortiz, 2003)	(T A & O t 2
Microbial Anti-inflammatory Molecule	Protein	*Faecalibacterium prausnitzii*	Inhibit the NF-κB, reduce Th1,Th2, and Th17 immune response, and increase the TGFβ	DNBS and DSS-induced Colitis model in mice	—	—	—	—	(Breyner et al., 2017; Munukka et al., 2017)	(Breyner et al., 2017; Munukka et al., 2017)	(Breyner et al., 2017; Munukka et al., 2017)	(e a 2 M e a 2

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Other Activities	Other Activities	Other Activities	Reference	Reference	Reference	R
Actinoquinolines A and B	Quinoline Alkaloids	*Streptomyces* sp. CNP975	Inhibit arachidonic acid inflammatory pathway enzymes (cyclooxygenases-1 and -2)	Not reported	—	—	—	—	(Hassan, Boonlarppradab, & Fenical, 2016)	(Hassan, Boonlarppradab, & Fenical, 2016)	(Hassan, Boonlarppradab, & Fenical, 2016)	(H l p & c 2
Violapyrones B and C	3, 4, 6-trisubstituted α-pyrone derivatives	Marine *Streptomyces* sp. 112CH148	Inhibit NO production, down-regulate iNOS expression	LPS-stimulated RAW264.7 macrophages	Antibacterial and anti-tumor activities	Antibacterial and anti-tumor activities	Antibacterial and anti-tumor activities	(H.-S. Lee et al., 2015)	(H.-S. Lee et al., 2015)	(H.-S. Lee et al., 2015)	(H.-S. Lee et al., 2015)	(S I e a 2
Dianemycin	Polyether compounds	*Streptomyces* sp. MT 2705-4	Reducing edema	Mouse ear edema using croton-oil or arachidonic acid	Mouse ear edema using croton-oil or arachidonic acid	Antimicrobial	Antimicrobial	(S. J. Lee et al., 1997)	(S. J. Lee et al., 1997)	(S. J. Lee et al., 1997)	(S. J. Lee et al., 1997)	(I e a 1

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Other Activities	Other Activities	Other Activities	Reference	Reference	Reference	R
3-methylcarbazole	Carbazole derivative	*Streptomyces* sp. LJK109	Suppresses the release of NO, PGE2, TNF-α and IL-1β, IL-6	LPS and pam3CSK (synthetic tricylated lipopeptide) – induced RAW 264.7 macrophages	LPS and pam3CSK (synthetic tricylated lipopeptide) – induced RAW 264.7 macrophages	Antifungal activity	Antifungal activity	(Taechowisan, Chanaphat, Ruensamran, & Phutdhawong, 2012)	(Taechowisan, Chanaphat, Ruensamran, & Phutdhawong, 2012)	(Taechowisan, Chanaphat, Ruensamran, & Phutdhawong, 2012)	(Taechowisan, Chanaphat, Ruensamran, & Phutdhawong, 2012)	(e s r & P d w 2
Cyclomarin A-C	Cyclic heptapeptides	*Streptomyces* sp.	Inhibit the edema	Phorbol ester-induced mouse ear edema assay	Phorbol ester-induced mouse ear edema assay	Antimicrobial	Antimicrobial	Antimicrobial	Antimicrobial	Antimicrobial	Antimicrobial	(e a 1
Salinamides A and B	Bicyclic depsipeptides	*Streptomyces* sp. CNB-	Inhibit the edema	Phorbol ester-induced mouse ear edema assay	Phorbol ester-induced mouse ear edema assay	Antimicrobial	Antimicrobial	Antimicrobial	Antimicrobial	Antimicrobial	Antimicrobial	A
Salinipyrone A	Polyketides	*Salinispora pacifica*	Inhibits production of interleukin-5	Mouse splenocyte model of allergic inflammation	Mouse splenocyte model of allergic inflammation	Mouse splenocyte model of allergic inflammation	Not reported	Not reported	Not reported	(Oh, Gontang, Kauffman, Jensen, & Fenical, 2008)	(Oh, Gontang, Kauffman, Jensen, & Fenical, 2008)	(G P n J & P c 2

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Other Activities	Other Activities	Other Activities	Reference	Reference	Reference	R
Arenamide A and B	Polyketides	*Salinisporaarenicola*	Inhibit NF-κB, NO, and PGE(2)	LPS-induced RAW 264.7 macrophages	LPS-induced RAW 264.7 macrophages	LPS-induced RAW 264.7 macrophages	Not reported	Not reported	Not reported	(Jensen, Moore, & Fenical, 2015)	(Jensen, Moore, & Fenical, 2015)	(M & F c 2
Scytonemin	Polysaccharide	Cyanobacterial strains including including *Nostoc*, *Scytonema*, *Calothrix*, *Lyngbya*, *Rivularia*, *Chlorogloeopsis*, *Hyella*	Not reported	LPS/IFN-γ-stimulated RAW264 Cells	LPS/IFN-γ-stimulated RAW264 Cells	LPS/IFN-γ-stimulated RAW264 Cells	Antiproliferative	Antiproliferative	Antiproliferative	Antiproliferative	(Stevenson et al., 2002)	(e 2
Splenocins A-J	9-membered *bis*-lactones	*Streptomyces* sp. CNQ431	Suppress the cytokine production (IL-5 and IL-13) and inhibit the production of IL-1and TNF-α	*Ovalbumin* (OVA)-stimulated splenocytes	*Ovalbumin* (OVA)-stimulated splenocytes	*Ovalbumin* (OVA)-stimulated splenocytes	Not reported	Not reported	Not reported	Not reported	(Strangman Kwon, Broide, Jensen, & Fenical, 2009)	(F J & F c 2

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Other Activities	Other Activities	Other Activities	Reference	Reference	Reference
Marinenes A and B	Norditerpenes	*Micromonospora* sp.	Inhibit the production of IL-5	Mouse splenocyte assay	Mouse splenocyte assay	Mouse splenocyte assay	Not reported	Not reported	Not reported	Not reported	(Strangman 2007)
Unknown compound (Compound C)	Flavomannin	*Talaromyces wortmannii*	Inhibits TNF-α-induced ICAM-1 expression	*Propionibacterium acnes* mediated inflammation in keratinocytes (HaCaT cells)	*Propionibacterium acnes* mediated inflammation in keratinocytes (HaCaT cells)	*Propionibacterium acnes* mediated inflammation in keratinocytes (HaCaT cells)	Antibacterial	Antibacterial	Antibacterial	(Pretsch et al., 2014)	(Pretsch et al., 2014)
—	Unknown compound	**Mangrove-derived *Streptomyces rochei***	Suppresses the expression of iNOS and IL-6	lipopolysaccharide-induced inflammation in RAW264.7 macrophages	lipopolysaccharide-induced inflammation in RAW264.7 macrophages	lipopolysaccharide-induced inflammation in RAW264.7 macrophages	Not reported	Not reported	Not reported	(Gomathi & Gothandam 2019)	(Gomathi & Gothandam 2019)

TABLE 2 The structure and mechanism of anti-inflammatory compounds reported from the fungal sources

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Reference
(*S*)-curvularin	Macrocyclic lactone	*Penicillium* sp. IBWF3-93	Reduces the expression of proinflammatory cytokines and chemokines	Collagen-induced arthritis in mice	Not reported	(Schmidt et al., 2012)

Compound name	**Structural type**	**Microbial source**	**Mode of action**	*In vitro* **&** ***In vivo*** **models**	**Other Activities**	**Reference**
Pleosporallin A-C	Merosesquiterpenoids	*Pleosporales* sp.	Inhibits IL-6 production	LPS-induced RAW 264.7 macrophages	Not reported	(C. J. Chen et al., 2015)
Penstyrylpyrone	Styrylpyrone-type metabolite	*Penicillium* sp.	Inhibits PTP1B activity and reduces NO, PGE2, TNF-α and IL-1 production	LPS-induced RAW 264.7 macrophages	Not reported	(D.-S. Lee, Jang, et al., 2013)
Penicillinolide A	10-membered lactone	*Penicillium* sp.	Suppresses production of pro-inflammatory mediators	LPS-induced RAW 264.7 macrophages	Not reported	(D.-S. Lee, Ko, et al., 2013)
Pyrenocine A	Oxopyran	*Penicillium paxilli* Ma(G)K	Exhibits anti-inflammatory effects on the expression of receptors directly related to cell migration	LPS-induced RAW 264.7 macrophages	Antiantimalarial and anticancer	(Toledo et al., 2014)
Tanzawaic acid Q	Tazawaic acid derivative	*Penicillium steckii* 108YD142	Inhibits NOS and PGE2 production	LPS-induced RAW 264.7 macrophages	Not reported	(Shin et al., 2016)
Neoechinulin A	Alkaloid	*Eurotium amstelodami*	Suppresses production of pro-inflammatory mediators, and cytokines	LPS-induced RAW264.7 macrophages	Not reported	(K.-S. Kim et al., 2013)

Compound name	**Structural type**	**Microbial source**	**Mode of action**	*In vitro* **&** ***In vivo*** **models**	**Other Activities**	**Reference**
Asperflavin	Anthracene	*Eurotium* spp. and *Aspergillus flavus*	Inhibits NO, PGE2 and pro-inflammatory cytokines, TNF-α, IL-1 and IL-6 production	LPS-stimulated RAW264.7 macrophages	Not reported	(Yang et al., 2017)
Lolitrem B and 31-epilolitrem B	Indole diterpenes	Endophytic fungus	Inhibit IL-6 and TNF-a production	LPS-stimulated RAW264.7 macrophages	Not reported	(McLeay, Smith, & Munday-Finch, 1999)
Lolitrem B Desmethyldichlorodiaportin Desmethyldichloro-diaportin Dichlorodiaportin	Lolitrem B Dichlorodiaportin	Lolitrem B Endophytic fungus *Ascomycota* sp. CYSK-4	Lolitrem B Inhibit NO production	Lolitrem B LPS-stimulated RAW264.7 macrophages	Lolitrem B Antibacterial	Lolitrem B (Y. Chen et al., 2018)
Questinol	Anthraquinone derivative	Marine-yerived *Eurotium amstelodami*	Inhibits production of NO, PGE2, COX and proinflammatory cytokines including TNF-α, IL-1β, and IL-6	LPS-stimulated RAW264.7 macrophages	Not reported	(Yang et al., 2014)
Dihydroisocoumarin Derivatives (1-6)	Lactones	*Aspergillus* sp. SF-5974 *Aspergillus* sp. SF-5976	Inhibit NO and PGE2 production by suppressing the expression of iNOS and COX-2	LPS-stimulated RAW264.7 macrophages	Not reported	(D.-C. Kim et al., 2015)
Lasiodiplactone A	Lactone	*Lasiodiplodia theobromae* ZJ-HQ1	Inhibits NO production	LPS-stimulated RAW264.7 macrophages	Not reported	(S. Chen et al., 2017)

Compound name	**Structural type**	**Microbial source**	**Mode of action**	*In vitro* **&** ***In vivo*** **models**	**Other Activities**	**Reference**
Graphostromanes F	Sesquiterpenoids	*Graphostroma* sp. MCCC 3A00421	Inhibits NO production	LPS-stimulated RAW264.7 macrophages	Antioxidant, antimalarial, antinociceptive, antiemetic, antitumor, anti-inflammatory, and antibacterial	(Niu et al., 2018)

TABLE 3 Nanomaterial with reported direct anti-inflammatory activities

Nanomaterial	**Structural type**	**Anti-inflammatory mechanisms**	*In vivo* **or** ***In vitro*** **assay**	**Reference**
1,2-diaminoethane-cored generation 4.5 generation poly (amidoamine) (PAMAM) skeleton with 64 carboxylic acid surface groups which nine of them have been amido-conjugated to glucosamine and glucosamine-6-sulfate (Glyco-Conjugated PAMAM Dendrimers)	Dendrimers	Inhibit chemokines (macrophage inhibitory protein [MIP]-1α and IL-8) and cytokines (TNF-α, IL-1β, and IL-6) release by peripheral blood mononuclear cells	*Salmonella minnesota* LPS-stimulated immune cells like monocyte-derived macrophages and immature monocyte-derived dendritic cells	(Hayder, Fruchon, Fournié, Poupot, & Poupot, 2011; Shaunak et al., 2004)
PAMAM dendrimers with terminal-NH_2 (G4-NH2), -OH (G4-OH) and –COOH (G4.5-CO_2H)		Inhibits nitric oxide synthase and COX- 2	LPS-induced peritoneal macrophages	(Shaunak et al., 2004)

Nanomaterial	**Structural type**	**Anti-inflammatory mechanisms**	*In vivo* **or** ***In vitro*** **assay**	**Reference**
Aminoethylethanolamine-capped dendrimers (G4-AEEA) and hydroxyl terminated dendrimers (G4-OH)		Inhibitory activity on COX-2	LPS-induced peritoneal macrophages	(Chauhan, Diwan, Jain, & Tomalia, 2009)
Azabisphosphonate which is capped by amino-bisphosphonate groups) dendrimers (phosphorus-based dendrimers)		Increase the expression of anti-inflammatory products such as mannose receptor MRC1 with reduced levels of CD64 and CD13	*In vitro* cell culture of human peripheral blood mononuclear cells	(Poupot et al., 2006)
3- and 4-arm Polyethylene Oxide 'stars' and second-generation dendrimer on the N3P3 core (Polyethylene Oxide (PEO) Dendrimers)		Blocking P-and L-selectins via sulfate-dependent interactions and reduce infiltration of neutrophils and macrophages	Mice models of acute inflammation which is generated by intraperitoneal injection of thioglycollate	(Rele et al., 2005)
Dendritic polyglycerol sulfates (dPGS)		Targets both L-selectin and P-selectin on leukocytes and endothelial cells, respectively and inhibit anaphylatoxin C5a generation	Acute allergic contact dermatitis mice model	(Dernedde et al., 2010)
Dendrimers with terminated acetylene (DG0-A, DG1-A and, DG2- A) and hydroxyl groups (OH) (DG1-OH)		Inhibit nitric oxide synthase, and COX-2 in N9 microglia cells	LPS-induced peritoneal macrophages	(Neibert et al., 2013)
Cerium oxide nanoparticles	Metal oxide nanoparticle	Reduce inducible NOS amounts at both mRNA and protein levels by the 'reactive sites' quenching free radicals		(Hirst et al., 2009)

Nanomaterial	**Structural type**	**Anti-inflammatory mechanisms**	***In vivo* or *In vitro* assay**	**Reference**
Gold nanoparticles	Metal nanoparticle	Anti-cytokine activity, anti-TNF-α, interfere with NF-ϰB, decrease IϰB-α degradation and p-Akt	LPS-induced peritoneal macrophages	(Ilinskaya & Dobrovolskaia, 2014)
Iron oxide	Metal oxide nanoparticle	Block activity of T_{helper} cells and macrophages, inhibit pathways involved in cytokine processing, reduce expression of interferon-γ, IL-6, and TNF-α,	Stimulated J774A.1 murine macrophages	(Shen, Liang, Wang, Liao, & Jan, 2012)
Non-modified fullerene C60 (N7)	Fullerene	Limit inflammation of damaged limb and promote the reduction of leukocyte level	Adjuvant arthritis in rats	(Shen et al., 2012)
The water-soluble form of fullerene C60		Significantly suppresses production of IgE and Th2, Inhibit IgE-mediated histamine release from peripheral blood basophils, suppresses anaphylaxis	Mouse models of atopic dermatitis using subcutaneous and epicutaneous applications during 50 days period Ovalbumin administrated mice model	(Shershakova et al., 2016)
Fullerenol (C60(OH)n) and amino-fullerene (C60(NHCH2CH3)n)		Inhibit IgE-dependent degranulation of mast cells and secretion of cytokines and prostaglandins	*In vitro* culture of human Mast cells and peripheral blood basophils	(Ryan et al., 2007)

TABLE 4 Nanomaterial with indirect anti-inflammatory activities

Structural type	**Nanomaterial**	**Anti-inflammatory mechanisms**	*In vivo* **or** ***In vitro*** **assay**	**Reference**
Dendrimers	G5 Poly (propylene imine) loaded by Indomethacin	Improved solubility of Indomethacin	HPLC analysis	(Gupta, Agashe, & Jain, 2007)
	PAMAM loaded by Ketoprofen	Improvement of drug permeation through the skin	*In vitro* permeation studies with excised rat skins	(Yiyun et al., 2007)
	Diflunisal loaded by PAMAM			
	G0 PAMAM loaded by Naproxen	High permeability across Caco-2 monolayers	Analysis of transepithelial electrical resistance using a voltohmmeter	(Najlah, Freeman, Attwood, & D'emanuele, 2007)
Liposomes	Liposomes containing cortisol palmitate	Decreases the joint temperature of an acute inflammatory on an underlying chronic arthritis	Acute arthritis in the rabbit knee by measuring joint temperature and diameter	(Phillips, Thomas, Knight, & Dingle, 1979)
	Liposomal prednisolone	Inhibits vascular inflammation, reduces lymphocytes and granulocytes in the vascular wall	Murine arteriovenous fistula model and LPS-induced peritoneal macrophages	(Wong et al., 2016)
	Glucocorticosteroids encapsulated in large oligolamellar liposomes	Prolongs the anti-inflammatory effect produced by glucocorticoids	induction of arthritis in rabbits by an intra-articular administration into the knee joint of poly-D-lysine and hyaluronic acid	(Rosenberg, Seiliev, Shulga, Zhuikov, & Volchkov, 2017)
Micelles	Dexamethasone-loaded E-selectin-targeting sialic acid-polyethylene glycol-dexamethasone conjugate micelles	Ameliorate LPS-induced production of pro-inflammatory cytokines	LPS-activated human umbilical vein endothelial cells	(Hu et al., 2017)

Structural type	**Nanomaterial**	**Anti-inflammatory mechanisms**	*In vivo* **or** ***In vitro*** **assay**	**Reference**
	Cholesterol-conjugated polyamidoamine micelles loaded by Resveratrol micelles	Inhibits the nuclear translocation of NF-ϰB and reduced pro-inflammatory cytokines in the lungs A carrier for combined delivery of anti-inflammatory gene and drug into the lungs by inhalation	LPS-activated macrophage cells Acute lung injury (ALI) animal model	(G. Kim, Piao, Oh, & Lee, 2018)
	Poly(ethylene oxide)-b-poly(n-butyl acrylate)-b-poly(acrylic acid) (PEO-PnBA-PAA) polymeric micelles loaded by prednisolone and budesonide	Exhibit high colloidal stability, show a significant protective effect against the cytotoxic damage	Polymeric micelles as carriers for anti-inflammatory drugs	(Yoncheva, Petrov, Pencheva, & Konstantinov, 2015)
	N-benzyl-N,O-succinyl chitosan polymeric micelles	Improves solubility	Determination of polymeric micelles diameter and surface charge using Zetasizer Nano ZS	(Woraphatphadung et al., 2017)
Solid lipid nanoparticles	Solid lipid nanoparticles loaded by ibuprofen, ketoprofen, nabumetone	Controls delivery of poorly water-soluble non-steroidal anti-inflammatory drugs with slow and sustained drug release Exhibit significant efficiency in drug entrapment	Microprocessor dissolution test apparatus	(Kumar, Singh, Garg, & Siril, 2018)
Polymeric Nanoparticle	Dexamethasone loaded polylactic-co-glycolic acid nanoparticles were combined with siRNA targeting COX-2	Co-delivery of anti-inflammatory agents suppress inflammatory responses	Measuring the COX-2 and iNOS in C28/I2 cells induced by TNF-α pre-tto provoke the expression of arthritis-related molecules i	(Park et al., 2012)

Structural type	Nanomaterial	Anti-inflammatory mechanisms	*In vivo* or *In vitro* assay	Reference
Nanoparticles	Chitosan nanoparticles and cationic liposomes loaded by siRNA inhibiting TNF-α	Decreases the TNF-α secretion	Mouse model of collagen-induced arthritis	(Howard et al., 2009)
Nanoparticles	Arginine-glycine aspartic acid-coated polylactic-co-glycolic acid nanoparticles	Targets improved siRNA uptake in the paw tissue of arthritic mice and increased delivery of nanoparticles into lungs Protects STAT1 siRNA from degradation by serum nucleases	Rheumatoid arthritis in a mouse model	(Scheinman, Trivedi, Vermillion, & Kompella, 2011)
Lipid nanoparticles	Encapsulated chemokine receptor CCR2-specific siRNA	Prolongs the normoglycemic period	Pancreatic islet transplantation in mice with streptozotocin-induced diabetes	(Leuschner et al., 2011)
Solid lipid nanoparticles	Cholesteryl butyrate solid lipid nanoparticles	inhibits the adhesion of neutrophil endothelial cells	Adhesion analysis by quantified microimaging fluorescence analysis	(Brioschi, Zara, Calderoni, Gasco, & Mauro, 2008; Dianzani et al., 2006)