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Microbial metabolites as promising anti-inflammatory resources in biomedicine

Faezeh Almasi[1], Fatemeh Salimi[2*], Fatemeh Mohammadipanah[1*]

[1] Department of Biology and Center of Excellence in Phylogeny of Living Organisms, Faculty of Science, University of Tehran, Tehran, Iran
[2] Department of Cellular and Molecular Biology, Faculty of Biology, Damghan University, Damghan, Iran

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Abstract

Numerous medical conditions, including cancers, rheumatoid arthritis, diabetes, autoimmune diseases, osteoporosis, cardiovascular disease, and more recently, COVID-19, show close linkage to inflammation as a complex pathophysiological process. In this review, we present a comprehensive outlook on microbial-derived anti-inflammatory compounds as remarkable biomedicine drugs, focusing on their efficiency, mode of action, and limitations. Various structures of microbial anti-inflammatory compounds are introduced, including Macrolactin, Lipopeptides, Pyrrol, Quinoline, Alkaloids, Carbazole derivatives, Bicyclic depsipeptides, Flavomannin, etc. The inhibitory effects on IL-5, IL-13, ICAM-1, and PTP1B expression, PGE2 release, and increasing TGF-b production are only reported for microbial-derived anti-inflammatory compounds. According to previous studies, some species of *Bifidobacterium*, *Streptococcus*, *Lactobacillus*, *Streptococcus*, *Bacillus*, *Streptomyces*, *Salinispora*, *Micromonospora*, *Talaromyces*, *and Faecalibacterium* are bacterial genera that can produce compounds with inhibitory effects on inflammation. Also, *Penicillium*, *Pleosporales*, *Aspergillus*, *Eurotium*, *Ascomycota*, *Eurotium*, *Lasiodiplodia*, and *Graphostroma* are fungal genera of fungal species with the ability to produce anti-inflammatory metabolites. Microbial-based approaches are among the main suggested natural resources that may be able to provide novel, applicable anti-inflammation drugs in the future. Furthermore, the efficiency of existing drugs could be modulated using these new microbial anti-inflammatory compounds. This will aid in the future development of novel bio-based medications to prevent and treat numerous debilitating inflammation-related diseases.

1. Introduction

Disrupted tissue homeostasis due to infection or physico-chemical tissue damage promotes inflammation as a pervasive form of host defense involving the innate and adaptive immune systems by rapidly destroying or isolating the source of the disturbance, usually resulting in restoring tissue homeostasis (Medzhitov 2008; Soehnlein et al. 2010). However, collateral damage to the tissues is unavoidable in inflammation due to the destructive characteristic of inflammation substances to both causing agents and hosts, e.g., inflammation creates granulomas to restrict access of pathogens and their products to healthy tissue. Extensive

*Corresponding author. Tel: *+982161113560/ 2335220223*
E-mail address: f.salimi@du.ac.ir
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granuloma formation can result in fibrosis (scarring), which hinders the natural functioning of host tissue and consequently cause organ failure (Wynn 2004).

The molecular patterns of pathogens are identified via the innate immune system, like the intracellular nucleotide-binding domain, Toll-like receptors (TLRs), and leucine-rich-repeat-containing receptors (NOD-like receptors (NLRs)). TLR activates common signaling pathways, leading to immediate activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). Activated NF-κB translocates to the nucleus and upregulates their expression by binding to target genes. In response to increasing numbers of molecular patterns, NLRs 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 disturbance site due to inflammatory cytokines. The activity of these immune cells leads to a cytotoxic environment following the release of harmful chemicals, including reactive nitrogen species (RNS), reactive oxygen species (ROS), 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 (Fig 1). Upon exposure to the antigens, native Th cells differentiate into several different cells, like Th1, Th2, and Treg cells. Th1 cells can act against intracellular pathogens by producing interferon-gamma (IFN-γ), IL-2, and TNF-α with antiviral and immunoregulatory characteristics and macrophage activation. Th2 cells can induce macrophage activation, IgE production, and eosinophil maturation by releasing IL-4, IL-5, and IL-13 (Graham 2002; Mosmann et al. 1989). The third group of Th cells (Treg) suppresses the activation, proliferation, and effector functions of immune cells, including NK cells, B cells, antigen-presenting cells (APCs), and T cells, by producing 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. However, the persistence of disturbance can lead to another form of inflammation, chronic inflammation, in which neutrophils are substituted with macrophages and T cells (Serhan et al. 2005).

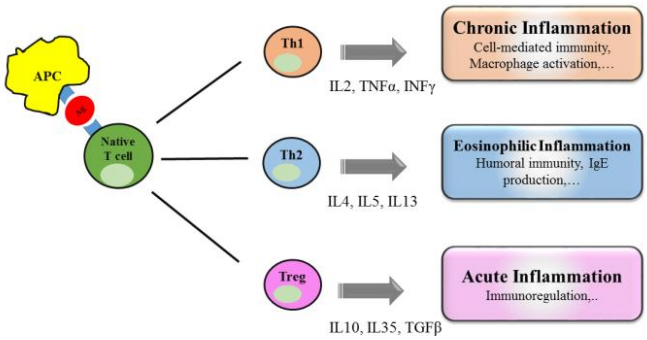

Figure 1. Modulation of T cells in the inflammation process. Upon exposure of Antigens (Ags) to native Th cells, various cells, including Th1, Th2, and Treg cells, are generated, producing different types of cytokines and causing inflammation.

2. Material and methods

The present comprehensive review is based on published articles on the antioxidant activity in the field of microbial metabolites during at least the last 20 years available in several databases, including Google Scholar, Web of Science, and Scopus citations.

3. Results and discussion

There are two types of inflammation, acute and chronic. Acute inflammation consists of non-specific, urgent, and early responses to adverse stimuli that are swiftly resolved. It is initiated by the activation of the present immune cells in the affected tissue, including dendritic cells, macrophages, and mast cells, which release mediators. 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. If the disturbance persists, it leads to chronic inflammation (Ashley et al. 2012). The initiation of chronic inflammation can be defined by the neutrophils replacement with macrophages and T cells (Medzhitov 2008).

3.1 Main drug targets of the inflammation process

The major anti-inflammatory targets are the enzymes COX-1 and COX-2, which catalyze the 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 the IκB kinase (IKK) complex through LPS or TNF-α liberates cytosolic NF-κB from repression through IκBα ubiquitination and degradation. The JNK-AP-1 pathway is activated by these stimuli. Inflammation is propagated by the coordinated actions of NF-κB and AP-1, which enhance the transcription of cytokines, chemokines, and other pro-inflammatory genes (Ye et al. 2022) (Fig 2).

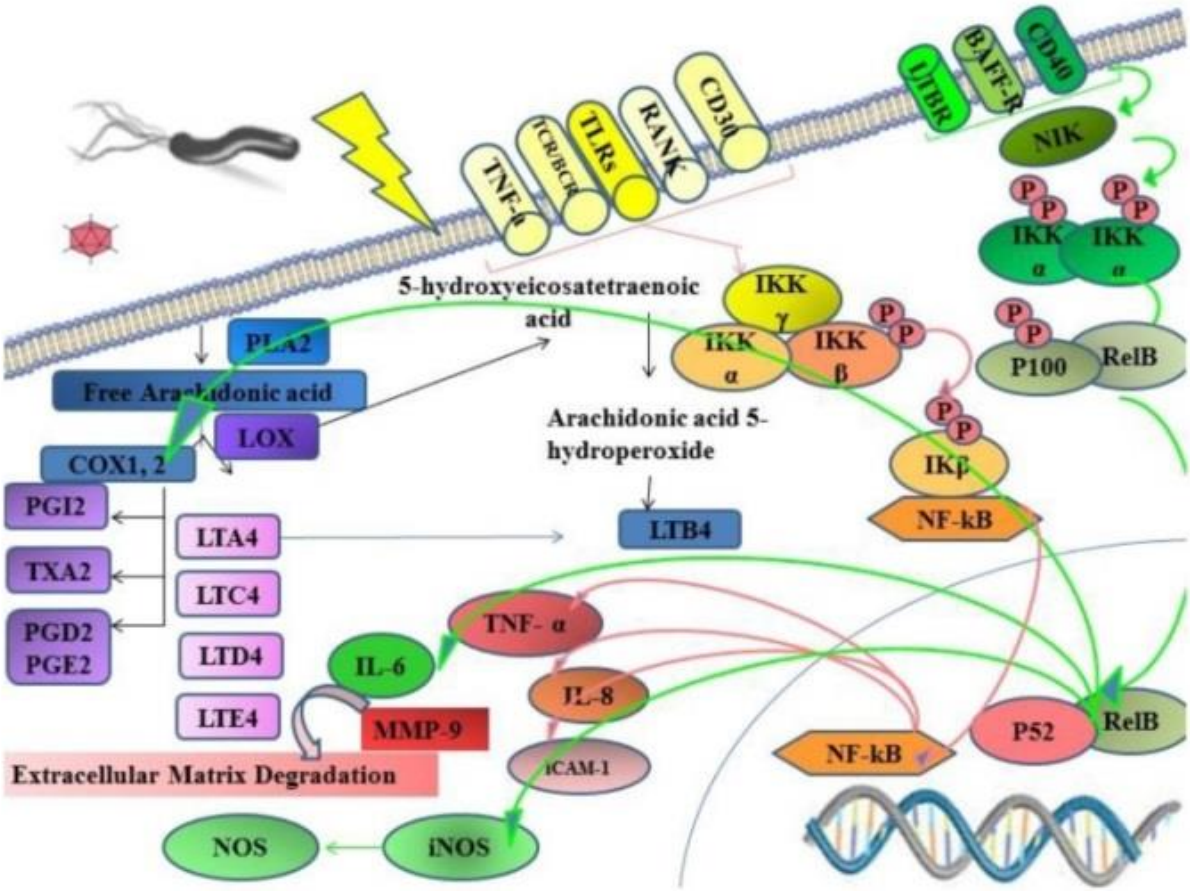

Figure 2. Inflammation cascade and involved pathological targets.

3.2 Role of inflammation in the initiation of life-threatening diseases

Acute inflammation is considered to be beneficial and necessary to remove the pathogenic agents; however, 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 et al. 2012). In addition, numerous recent studies support a link between the pathology of severe COVID-19 and the inflammation process (e Silva et al. 2022; Parthasarathy et al. 2022).

3.3 Anti-inflammatory compounds

3.3.1 Microbial-derived anti-inflammatory compounds

The pharmacological activities and low toxicity properties of natural anti-inflammatory agents have been of worldwide interest (Ge et al. 2022; Yuan et al. 2022). Although great attention has been paid to plant sources in the development of anti-inflammatory compounds, microorganisms are prolific producers of a wide variety of biologically active secondary metabolites with diverse activities (Salimi et al. 2018; Mohan et al. 2021; Maithani et al. 2022)

The microorganisms-derived natural products are considered one of the most prolific reservoirs of natural therapeutic compounds (Salimi et al. 2018). It has been estimated that the hit rate for natural products is 100-fold higher than 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). Most possess the expected pharmacokinetic characteristics necessary for clinical development. These natural compounds may target unknown pathological targets and contribute to revealing the detailed pathway of diseases. Many commercial drugs (more than 130) for treating life-threatening diseases like cancers, diabetes, and infections have originated from microorganisms. Also, more than 60 microbial-derived compounds with proven bioactivity against infections, inflammations, cancers, and neurological, metabolic, cardiovascular, and immunological disorders are currently in different steps of clinical trials. Microorganisms are the more readily reproducible source of bioactive compounds compared to plants and animals. According to microbial-derived commercial drugs statistics, actinomycetes, fungi, and myxobacteria are the richest bioresources of structurally unique and medically important compounds (Reichenbach et al. 1988; Watve et al. 2001; Harvey 2008; Schäberle et al. 2014; Salimi et al. 2018, 2019; Vasundhara et al. 2019). Many compounds with anti-inflammatory activity have been extracted from microorganisms; an overview of these prodrugs is summarized in (Tables 1 and 2). The structures of some bacterial and fungal anti-inflammatory compounds are presented in (Fig 3).

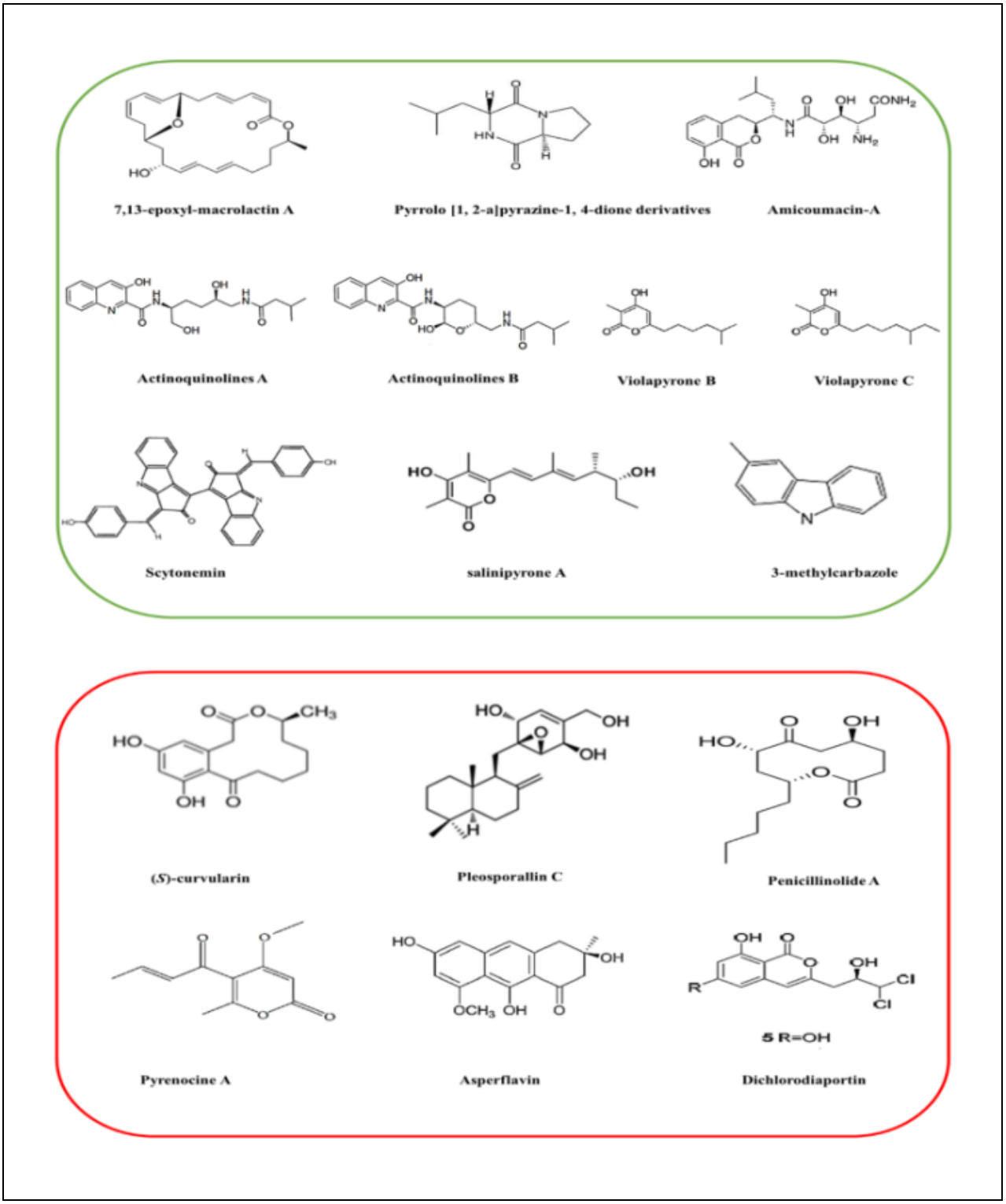

Figure 3. The structure of some bacterial (upper box) and fungal (lower box) anti-inflammatory compounds.

Table 1. The structure and mechanism of anti-inflammatory compounds reported from bacterial

Compound name	Structural type	Microbial source	Mode of action	*In vitro* & *In vivo* models	Other Activities	Reference
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)
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)
7,13-epoxyl-macrolactin A	Macrolactin	*Bacillus subtilis* B5	Exhibits an inhibitory effect on the expression of inducible nitric oxide and cytokine (IL1 and IL6)	LPS-stimulated RAW 264.7 macrophages	---	(Abd-Elnaby et al. 2016)
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)
	Pyrrol	*Bacillus baekryungensis*	Inhibits denaturation of the proteins	Albumin denaturation technique	---	(Manal M. El-Naggar 2016)
Amicoumacin-A	Dihydroiso coumarin	*B. subtilis*, *B. pumilus*	Inhibits the edema	Carrageenan induced paw edema	Antibacterial, antifungal, and anticancer	(Itoh et al. 1981)
Surfactin	Acidic lipopeptide	*Bacillus subtilis*	Inhibits expression of IFN-γ, IL-6, iNOS and NO	LPS-stimulated RAW264.7 macrophages	antibacterial, antiviral, antitumour, and antimycoplasma	(Carrillo et al. 2003)

Table 1: Continued

Microbial Anti-inflammatory Molecule	Protein	*Faecalibacterium prausnitzii*	Inhibit the NF-kB, reduce Th1,Th2, and Th17 immune response, and increase the TGFb	DNBS and DSS-induced Colitis model in mice	---	(Breyner et al. 2017; Munukka et al. 2017)
Actinoquinolines A and B	Quinoline Alkaloids	*Streptomyces* sp. CNP975	Inhibit arachidonic acid inflammatory pathway enzymes (cyclooxygenases-1 and -2)	Not reported	---	(Hassan et al. 2016)
Violapyrone 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 antitumor activities	(H.-S. Lee et al. 2015)
Dianemycin	Polyether compound	*Streptomyces* sp. MT 2705-4	Reducing edema	Mouse ear edema using croton-oil or arachidonic acid	Antimicrobial	(S. J. Lee et al. 1997)
3-methylcarbazole	Carbazole derivative	*Streptomyces* sp. LJK109	Suppresses the release of NO, PGE2, TNF-α and IL-1β, IL-6	LPS and pam3CSK (synthetic triacylated lipopeptide) –induced RAW 264.7 macrophages	Antifungal activity	(Taechowisan et al. 2012)

Table 1: Continued

Cyclomarin A-C	Cyclic heptapeptides	*Streptomyces* sp.	Inhibit the edema	Phorbol ester-induced mouse ear edema assay	Antimicrobial	(Renner et al. 1999)
Salinamides A and B	Bicyclic depsipeptides	*Streptomyces* sp. CNB-	Inhibit the edema	Phorbol ester-induced mouse ear edema assay	Antimicrobial	(Moore et al. 1999)
salinipyrone A	Polyketides	*Salinispora pacifica*	Inhibits production of	Mouse splenocyte model of	Not reported	(Oh et al.

			interleukin-5	allergic inflammation		2008)
Arenamide A and B	Polyketides	*Salinispora arenicola*	Inhibit NF-κB, NO, and PGE(2)	LPS-induced RAW 264.7 macrophages	Not reported	(Jensen et al. 2015)
	Polysaccharide	Cyanobacterial strains including including *Nostoc*, *Scytonema*, *Calothrix*, *Lyngbya*, *Rivularia*, *Chlorogloeopsis*, *Hyella*	Not reported	LPS/IFNγ-stimulated RAW264 Cells	Antiproliferative	(Stevenson et al. 2002)
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	Not reported	(Strangman et al. 2009)
Marinenes A and B	Norditerpenes	*Micromonospora* sp.	Inhibit the production of IL-5	Mouse splenocyte assay	Not reported	(Strangman 2007)
Unknown compound (Compound C)	Flavomannin	*Talaromyces wortmannii*	Inhibits TNF-a-induced ICAM-1 expression	*Propionibacterium acnes* mediated inflammation in keratinocytes (HaCaT cells)	Antibacterial	(Pretsch et al. 2014)
---	Unknown compound	Mangrove-derived Streptomyces rochei	Suppresses the expression of TNF-α and IL-6	lipopolysaccharide-induced inflammation in RAW264.7 macrophages	Not reported	(Gomathi et al. 2019)

Table 2. The structure and mechanism of anti-inflammatory compounds reported from fungal

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)
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-□ and IL-1 production	LPS-induced RAW 264.7 macrophages	Not reported	(D.-S. LeeJang 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. LeeKo 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 NO 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)
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)

Table 2: Continued

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 et al. 1999)
Desmethyldichlorodiaportintone Desmethyldichlorodiaportin Dichlorodiaportin	Dichloroisocoumarins	Endophytic fungus *Ascomycota* sp. CYSK-4	Inhibit NO production	LPS-stimulated RAW264.7 macrophages	Antibacterial	(Y. Chen et al. 2018)
Questinol	Anthraquinone derivative	Marine-derived fungus *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)
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)

3.3.1.1 Limitations in anti-inflammatory drug discovery from microbial resources

Based on this paper's survey, the most prevalent type of anti-inflammatory compounds produced by bacteria and fungi belongs to the 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, a 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 and time- and cost-consuming process. Additionally, obtaining potent compounds might need strains from marine or extreme habitats that demands a challenging and not always accessible sample collection step (Almasi et al. 2018; Heidarian et al. 2019). Also, there are many compounds together with the compound of interest in the crude extracts. The low production amount of active compounds is another limitation that demands either intensive purification procedures, production optimization, or genetic manipulation, and increased quantities of active compounds are essential for preclinical development. Thus, large-scale fermentation, which substantially affects the development timeline, is required. 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 the screening of natural products is being improved through the emergence of new technologies, 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 effective natural compounds that exist in 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 et al. 2005; Exarchou et al. 2006; Lam 2007; Tatsis et al. 2007).

4. Conclusion

Current commercial anti-inflammatory drugs, steroidal and non-steroidal agents, come with side effects such as the increased risk of liver cancer, cardiomyopathy, blood pressure, heart attack, stroke, gastrointestinal complications, and infertility. Therefore, developing novel anti-inflammatory drugs is vital to prevent certain systemic and metabolic diseases associated with or triggered by chronic inflammation. Accordingly, the secondary metabolites of bacterial and fungal from diverse chemical classes, including alkaloids, steroids, terpenoids, polyphenolics, phenylpropanoids, fatty acids, and lipids have been screened by various mechanisms, such as reduction of TNF-α levels,

attenuation of cyclooxygenase (COX)-2 activity, inhibition of TNF-α and nitric oxide (NO), interleukins formation and NF-kB translocation to the nucleus, for the development of drugs with anti-inflammatory effects. The anti-TNF-α and INF-γ activity, inhibitory effect on IL-1, IL-6 and nitric oxide expression and NF-kB, Cox-2 and T-helper activities are common mechanisms in other sources. Some anti-inflammatory activities like the inhibitory effect on IL-5, IL-13, ICAM-1 and PTP1B expression, PGE2 release, and increasing TGF-b production are only reported from microbial derived compounds with anti-inflammatory activities.

On the other hand, some anti-inflammatory mode action includes 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, and level of CD64 and CD13 as well as increasing expression of anti-inflammatory products such as mannose receptor C-type 1. Although these reported mode actions largely depend on the applied bioassays in corresponding studies, extensive investigations are needed to comprehensively compare microbial and nanomaterial derived compounds. It seems that new therapeutic drugs can be developed by discovering novel microbial compounds with significant inhibitory effects on pathological targets in inflammation. Furthermore, these new drugs will be more effective without side effect.

Conflict of Interest

The authors declare that they have no conflict of the interest for the content of the paper.

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Ethical approval

This article does/does not contain any studies with human participants or animals performed by any of the authors. This article does/does not contain any studies with human participants or animals performed by any of the authors.

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