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REVIEW

Bacterial Natural Compounds with Anti-Inflammatory and Immunomodulatory Properties (Mini Review)

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Abstract: Inflammation is part of the body's complex biological response to harmful stimuli such as damaged cells, pathogens, or irritants. It is a protective response involving blood cells, immune cells, and molecular mediators. The inflammation not only can eliminate the primary cause of cell injury but also clears out necrotic cells, tissue damaged from the original insults and inflammatory process. Furthermore, it can initiate tissue repair. Pro-inflammatory cytokines are produced predominantly by activated macrophages and are involved in the up-regulation of inflammatory reactions. They are involved in further regulating inflammatory reactions. There is ample evidence that some pro-inflammatory cytokines, such as interleukin 1β (IL-1β), IL-6, and tumor necrosis factor-α (TNF-α), are involved in the pathological pain process. Some of the natural compounds promote cytokines production and inhibit inflammatory responses. The natural compounds which are produced from microorganisms such as omega-3 fatty acid, cyclic peptide, antimicrobial peptide, oligosaccharides, and polysaccharides can reduce inflammation and could be easily incorporated into the diet without any adverse effects. For example, SCFA (short-chain fatty acids), peptide bacteriocin, and polycyclic peptide bacteriocin (nisin) could be used in the treatment of atherosclerosis, orthopedic postoperative infections, and *mycobacterium tuberculosis* infection, respectively. Also, fatty acids (saturated and unsaturated fatty acids) can be introduced as anti-inflammatory drugs. This review article summarizes bacterial natural compounds with modulating effects on cytokines that are surveyed which may have potential anti-inflammatory drug-like activity.

Keywords: bacterial natural materials, secondary metabolite, drug-like activity, anti-inflammatory activity, cytokine

Introduction

In nature, there are unlimited sources of pharmaceutical agents, and the origin of several modern medicines are found in natural products. The natural products include chemical compounds either as standardized extracts or as pure compounds produced by living organisms with biological effects on other organisms. Due to the availability of incomparable chemical diversity, natural product has interestingly enormous opportunities for new drugs.[1] Natural materials are found in multicellular origins such as plants, animals, marine sources, sponges, snails, and unicellular origins like bacteria and yeasts with pharmaceutical properties. For example, Borojó fruit with antihypertensive, diuretic, antitumor, healing, anti-inflammatory, aphrodisiac, and immunological effects,[2] *Austroeupatorium inulaefolium* (H.B.K.) essential oil with antimicrobial activity,[3] and

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the lavender essential oil with anti-inflammatory, antimicrobial and antioxidant activity were examined.[4]

In addition to temperature, the body maintains many factors of homeostasis. For example, the concentration of different ions in the blood must be constant, along with pH and glucose concentration. Maintaining homeostasis at any level is important for maintaining overall body function. The immune system is one of the most dynamic in the body. The mechanisms that keep immune homeostasis must be engaged in the continuous turnover of cell proliferation and apoptosis in many lineages in different locations. The mechanisms must also deal with challenges eg responses to a variety of pathogens, cancer or drug, and reset the status to the normal situations. The cell types involved in homeostasis in the immune system are immune cells such as B cell, dendritic cells, Natural killer cells (NK cells), and epithelial cells.[5]

Anti-inflammatory cytokines are a variety of immune regulatory molecules with the response to pro-inflammatory cytokines such as IL-1β, IL-6, IL-8, INF-γ, and TNF-α. Anti-inflammatory cytokines include antagonist IL-1 receptor, IL-4, IL-6, IL10, IL-11, and IL-13.[6]

Nitric oxide (NO) radicals and COX-2 are produced during inflammation. NO is produced by oxygen nitric oxide synthase (iNOS) from oxygen and L-arginine; this enzyme is regulated during the inflammatory process. Like iNOS, COX-2 is regulated precisely in response to infectious agents, atherosclerosis, and many malignancies. The up-regulation of iNOS and COX-2 during inflammation is controlled by the pro-inflammatory transcription factor NF-κB.[7] Some of the members of the toll-like receptor (TLR) family, especially TLR4, are now known as the main receptors for LPS. On the other hand, IκB is a suppressive protein that binds to the NFκB transcription factor in a normal condition. So, the degradation of IκB stimulated by LPS leads to the activation of this special transcription factor for COX-2 mRNA induction (Figure 1).[8]

Unicellular organisms like bacteria and yeasts include probiotics from the gastrointestinal tract (GIT) that could be useful for inflammatory bowel disease and treatment of infectious diarrhea.[2] Common commensal microbes such as Lactobacilli, *Bifidobacteria, Bacteroides fragilis, E.coli, Bacillus sp*, etc can produce the natural compounds with anti-inflammatory and immunomodulatory properties.

Culturable microbial varieties in the Hypersaline Lake belong to the various genera like *Halorubrum, Haloarcula, Salinibacter, Salicola, Rhodovibrio, Proteobacteria, Firmicutes*, and *Actinobacteria*. They could be useful in biotechnological applications, such as treatment of saline

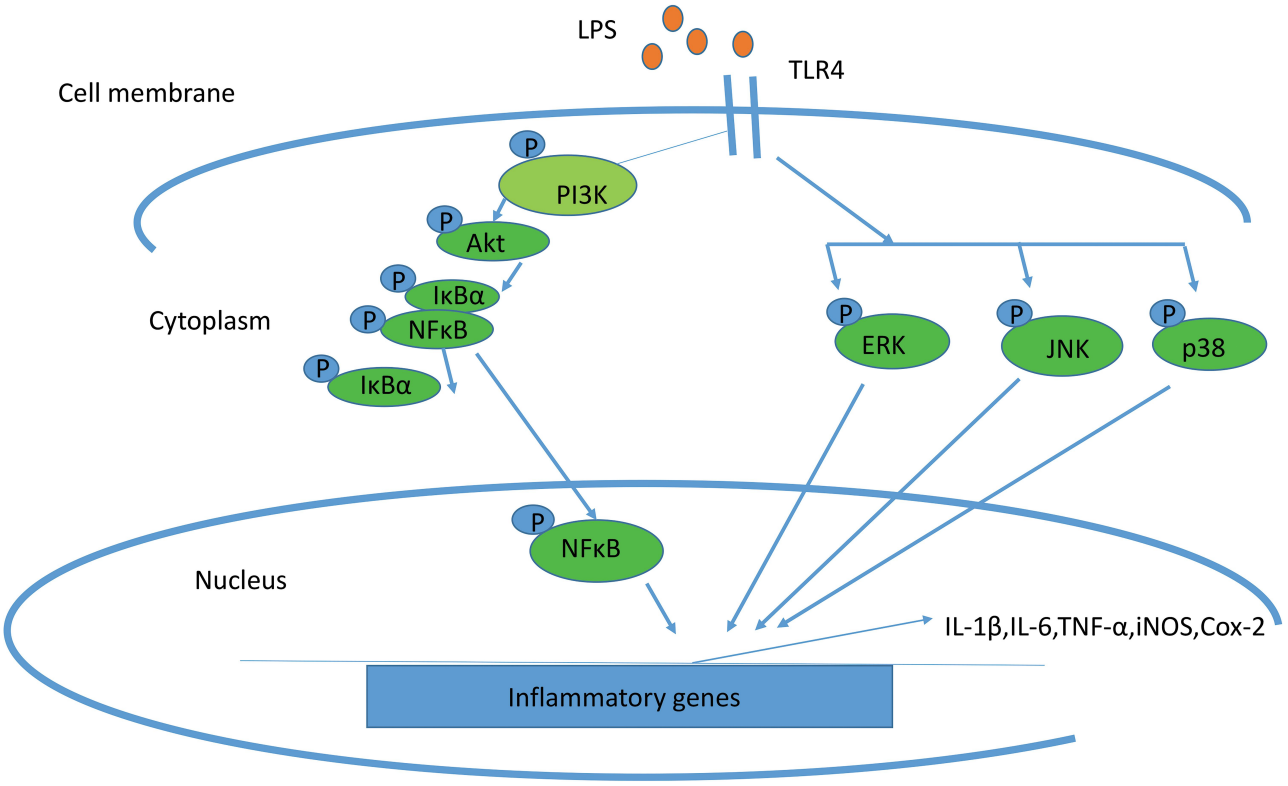


Figure 1 Schematic representation of the mechanisms in LPS-induced inflammation associated with iNOS and COX2.

wastewater and the production of salt-tolerant enzymes, β-carotene, compatible solutes, biofuels, and bioplastics.[9] Bacteria associated with marine algae produce natural compounds such as genus *Alteromona*. The genus *Alteromona* is found only in *Laurencia Pacifica*, generally isolated in the seawater and produced high molecular weight polysaccharide compounds used in the industries and medicines.[10] Also, several marine bacteria could be introduced as producers of secondary metabolites. *Chorommobacteria marinum* produces secondary metabolites with antibacterial activity against *Escherichia coli* (*E.coli*), *Pseudomonas aureginosa* (*P.aureginosa), Staphylococcus aureus* (*S.aureus*) and are useful for the treatment of pneumonitis, osteitis, arthritis, endocarditis, and localized abscesses. Also, *Flavobacterium uliginosum* (*F. uliginosum*) with anti-cancerous activity against sarcoma cells could be used in the treatment of viral tumors.[10] The cationic peptides with bacterial origin can prevent the secretion of pro-inflammatory cytokines (eg, TNF-α, IL- 1) by the host and are useful in acne vulgaris therapy.[11]

Natural microbial compounds have several advantages. The most important properties of the natural microbial compounds are their microbial origin, as their specific microbial producers; their unique chemical structures and their interaction with the environment, as various biological activities.[12,13] Natural compounds such as omega-3 fatty acid, cyclic peptide, antimicrobial peptide, acetyl derivatives, oligosaccharides, and polysaccharides can reduce inflammatory responses.

This review concentrates on the natural bacterial material with a modulating effect on cytokines and their application in anti-inflammatory drug-like activity (Tables 1–3) (Figure 2–3). The advantages of using bacteria as anti-inflammatory inhibitors are their faster and more natural growth than other microorganisms in large-scale. Additionally, bacterial cell mass could be used without enzyme purification.[14]

Bacterial Natural Compounds with Anti-Inflammatory Activities

Biosurfactants

Biosurfactants are natural products derived from bacteria, yeasts, or fungi. They are amphiphilic compounds, including a polar section (soluble in water) and a non-polar section

Table 1 Effects of Bacterial Bio-Active Materials Containing Peptide on Cytokine Production and Disease Therapy

Producer	Bacterial Bio-Active Compound	Active Factors	Disease Therapy	Type	References
Bacillus licheniformis VS16	Biosurfactant	Increasing:IL10,TGF, Decreasing of TNF-α and IL1β	Anti-inflammatory drugs, food industry	Lipopeptide surfactant	10
Yersinia pestis	YopM	Downregulating of TNF-α and interleukins 12, 15 and 18	Anti-inflammatory	Cell-Penetrating Peptides (CPPs)	46
Lactobacillus rhamnosus	Bacteriocin	Decreasing of CRP, IL_6	Treating or inhibitor of orthopedic postoperative infections	Peptides	45
B. subtilis	Surfactin	Inhibition of the inflammatory agent's production like IL-1β and iNOS. Decreasing of TNF-α and nitric oxide	Treating of septic shock	Cyclic lipopeptide	13
B.subtilis	Iturin Fengycin	Inhibition of inflammatory agents	Anti-inflammatory	Cyclic lipopeptide	14
LAB bacteria	Bacteriocin(nisin)	Down-regulating the lung Th2 response by increasing IFN-γ and reducing IL-4 &IL-13	Anti-mycobacterial *mycobacterium tuberculosis*)	Polycyclic antibacterial peptide	50
Escherichia coli (E.coli)	Microcin MccJ25 (bacteriocin)	Increasing IL-6 & IL-10 Modulating of TNF-α and NF-κB	Against enterotoxigenic *E. coli k88*	Few amino acids	53,54

Table 2 Effects of Bacterial Bio-Active Materials Containing Fatty Acids on Cytokine Production and Disease Therapy

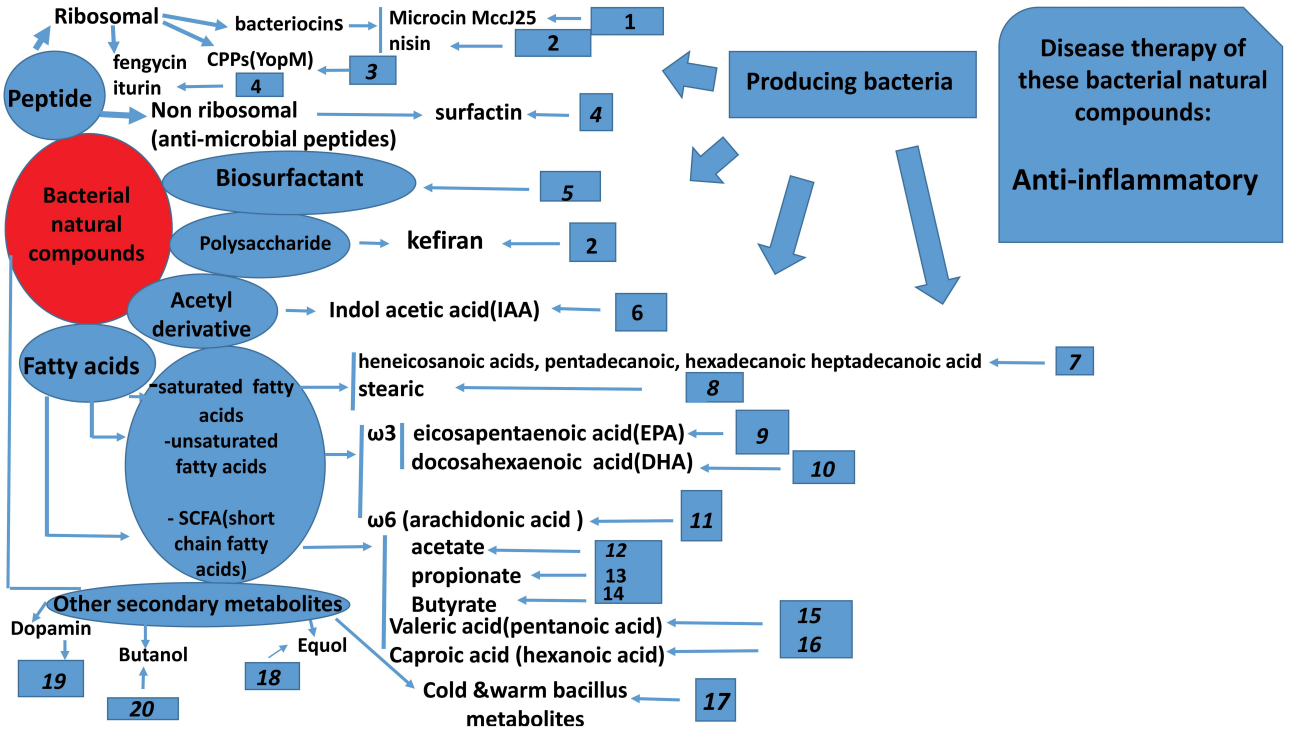
Producer	Bacterial Bio-Active Compound	Active Factors	Disease Therapy	Type	References
Cellulophaga *Pibocella* *Polaribacter* *Shewanella marinintestina* *Moritella marina* *Vibrio marinus*	EPA DHA Only DHA or only EPA EPA DHA DHA	Decreasing of inflammatory cytokine like (TNF)-α and IL-1β Inhibition from PGE-2 &LTB4(ω6 fatty acids derived eicosanoid)	Anti-inflammatory	Unsaturated fatty acids	26,28-30
Psychroflexus tarquis *Psychroflexus pacifica* *Krokinobacter eikastus* *Krokinobacter diaphorus* *Auriespira marina* gen.nov.sp. nov	Arachidonic acid	The inhibition of NO and TNF-α	Anti-inflammatory activity	Unsaturated fatty acids	31
Clostridium proteoclasticum 6BC	Stearic acid	The inhibition of NO and TNF α	Anti-inflammatory activity	Saturated fatty acids	32
Chlamydophila psittaci	(Heneicosanoic acid) Pentadecanoic acid Hexadecanoic acid Heptadecanoic acid)	The inhibition of NO and TNF α	Anti-inflammatory activity	Saturated fatty acids	5,33
Clostridium IV group (*Faecalibacterium prausnitzii*), *Clostridium* XIVa group (*Eubacterium rectale, E. halii, Roseburia sp.*) *Bacteroides* *Clostridium* XIVa group (*Blautia hydrogeotrophyca*)	Butyrate Propionate acetate	It is inhibiting gene expression of inflammatory cytokines through modulating of MAPK signaling pathway and activation of NF-κB via activation fatty acid (FFA) receptors type 2, 3 (FFA2 and FFA3 receptors) and G protein-coupled receptor 109A (GPR109A) or inhibition of histone deacetylases (HDACs).	Treatment of atherosclerosis and sepsis	SCFA (Short-chain fatty acids):	34,35
Megasphaera massiliensis MRX0029 RuminnococcaceaeCPB0	Valeric acid (pentanoic acid) Caproic acid (hexanoic acid)	Repression of IFN-γ, IL-10, IL-1β, TNF-α	Anti-inflammatory	SCFA(short-chain fatty acids)	36,37

(insoluble in water). The amphiphilic structure of biosurfactant is useful to reduce surface tension. This feature is used in various industries such as petroleum, petrochemical, pharmaceutical, cosmetics, medicine, agriculture, textiles, food industries, and many others.[15] Microorganisms use different types of organic compounds as a source of carbon and energy for their growth. When the source of carbon is an insoluble substrate such as hydrocarbons (CxHy), microorganisms facilitate their diffusion into the cell by producing different types of substances, the biosurfactants. They decrease surface tension in bacteria. A biosurfactant may have one of the following structures: glycolipids, a polysaccharide–lipid complex, phospholipid, mycolic acid, lipoprotein, or lipopeptide. Production of biosurfactant can be induced by

Table 3 Effects of Other Bacterial Bio-Active Materials on Cytokine Production and Disease Therapy

Producer	Bacterial Bio-Active Compound	Active Factors	Disease Therapy	Type	References
Bacteria isolated from soil samples in the beaches of Chennai, India(degrader chitin)	Chitosan:β(1–4) D-Glucosamine	No secretion of cytokine	None	Polysaccharide	[16]
Lactic acid bacteria	Kefiran (branched glucogalactan)	Reducing IL-4 and IL-5 to normal levels	Treatment of inflammation of lung tissue (maybe for allergic bronchial asthma in future)	Polysaccharide	[19]
Bacteroides cellulosilyticus *Bifidobacterium bifidum* *Bacteroides fragilis* *Bifidobacterium longum*	Acetamido-amino -2,4,6-trideoxygalactose (AATGal) amino sugar β-glucan/galactan Tetrasaccharide repeating unit Branched hexasaccharide repeating unit	Induces IL_10 decreases IFN-γ, IL-12, TNF-α, IL-17, IL-6 production	attenuates TNBS-induced colitis	Polysaccharide Capsules in the intestine	[25]
Rhizobium strains(symbiotic) *Paenibacillus* (non-symbiotic) *Pseudomonas fluorescens*	IAA(derivation of (Indol))	Anti-inflammatory possibility by its antioxidant activity	Mouse-ear edema	Acetyl derivatives	[22]
Enterococcus faecium	Dopamine(from the dietary substrate)	Modulating the immune system 1-Increasing IL-4 and IL-10(anti-inflammatory) 2-Modulating of IL-1β, IL-2. IL_6 and IFN-γ	Treating inflammatory diseases like IBD	An organic chemical of the catecholamine and phenethylamine families	[47,55]
Secondary metabolites of *Bacillus* sp isolated from Neogene permafrost	Cold Bacillus metabolite (isolated −5°C)	Secondary metabolites of *Bacillus* sp isolated from Neogene permafrost	Anti-inflammatory	Secondary metabolites of Bacillus sp isolated from Neogene permafrost	[56]
CS1,CS2,CS3 belonging to genus *pediococcus* and *lactobacillus*	Equol ((4′,7-isoflavandiol))	Reducing of IFNγ	Anti-inflammatory	isoflavandiol estrogen	[58,59]
Bifidobacterium adolescentis	Butanol extract	Boosting of TNF-α and NO	Anti- colon cancer	Four-carbon alcohol	[60,61]
strain *Streptomyces* sp. STA1	Camporidine A	suppressing nitric oxide production	Anti-inflammatory	Polyketide alkaloid	[70]

hydrocarbons or other water-insoluble substrates, the culture conditions, such as temperature, pH, agitation, the concentration of P, Fe, N, Mg, and Mn ions in the medium and dilution rate in continuous culture.[16] Microbial bio-surfactants have more advantages than chemical surfactants. They are higher foaming capability, less toxic,



1-*E.coli*
2-*Lactic acid bacteria*
3-*Yersinia pestis*
4-*Bacillus subtilis*
5-*Bacillus licheniformis*
6-*Rhizobium strains(*symbiotic*), Paenibacillus(*non symbiotic*), Pseudomonas fluorescences*
7-*Chlamydia psittaci*
8-*Clostridium proteoclasticum68C*
9-*Cellulophaga,Polaribacter,Shewanella,Marinintestina*
10-*Pibocella,Polaribacter,Moritella marina,Vibrio marinus*
11-*Psychroflexus tarquis,Psychroflexus pacifica,Krokinobacter eikastus,Krokinobacter diaphorus ,Auriespira marina gen.nov.sp. nov*
12-*Bacteroides XIVa group (Blautia hydrogeotrophyca)*
13-*Clostridium XIVa group (Eubacterium rectale, E. halii, Roseburia sp.)*
14-*ClostridiumIV group (Faecalibacterium prausnitzii)*
15-*Megasphaera massiliensis* MRX0029
16-*Ruminnococcaceae CPB0*
17-*Bacillus sp*
18-*Pediococcus, lactobacillus*
19-*Enterococcus faecium*
20-*Bifidobacterium adolescenctis*

Figure 2 Summary of the bacterial bio-active compounds, active components, their producing bacteria, and potential mechanism of their actions (anti-inflammatory).

environmentally compatible, higher biodegradability, specific activity at extreme pH, temperatures, high selectivity. Also, it can be obtained from renewable food sources.[15] Bacteria such as *Bacillus, Pseudomonas, Rhodococcus, Arthrobacter, Mycobacterium*, etc. can make biosurfactants. Bio-surfactant produced from *Bacillus mojavensis* showed antibacterial activities. So, it could be used as a natural product with potential medicinal usages. It needs more studies about the mechanisms of the treatment related to this bio-surfactant.[17] Some lipopeptides like N-palmitoyl-S-(2,3-bis(palmitoyloxy)-(2RS)-propyl)-(R)-cysteinyl-a and alanyl-glycine (Pam3Cys-Ala-Gly), are a synthetic analog of the N-terminal part of bacterial lipoprotein and capable of activating macrophages and B cells in vitro. After injecting the lipopeptide to mice, low levels of IL-6 and no levels of TNF-α were detected in the serum.[16] In contrast, bacterial LPS induced pro-inflammatory cytokines such as IL-6, IL-11, and TNF-α, indicating the lack of immune cell response to lipopeptide While, bacterial LPS induces very high amounts of IL-6, IL-1, and TNF-α.[18] *Labeo rohita* fingerlings were injected intraperitoneally with purified biosurfactant from *Bacillus licheniformis* VS16 at various concentrations. It was shown that bio-surfactant produced by *Bacillus licheniformis* VS16 cause to down-regulates of pro-inflammatory cytokines TNF-α and IL-1β. But the expression of anti-inflammatory cytokines IL-10 and TGF-β were up-

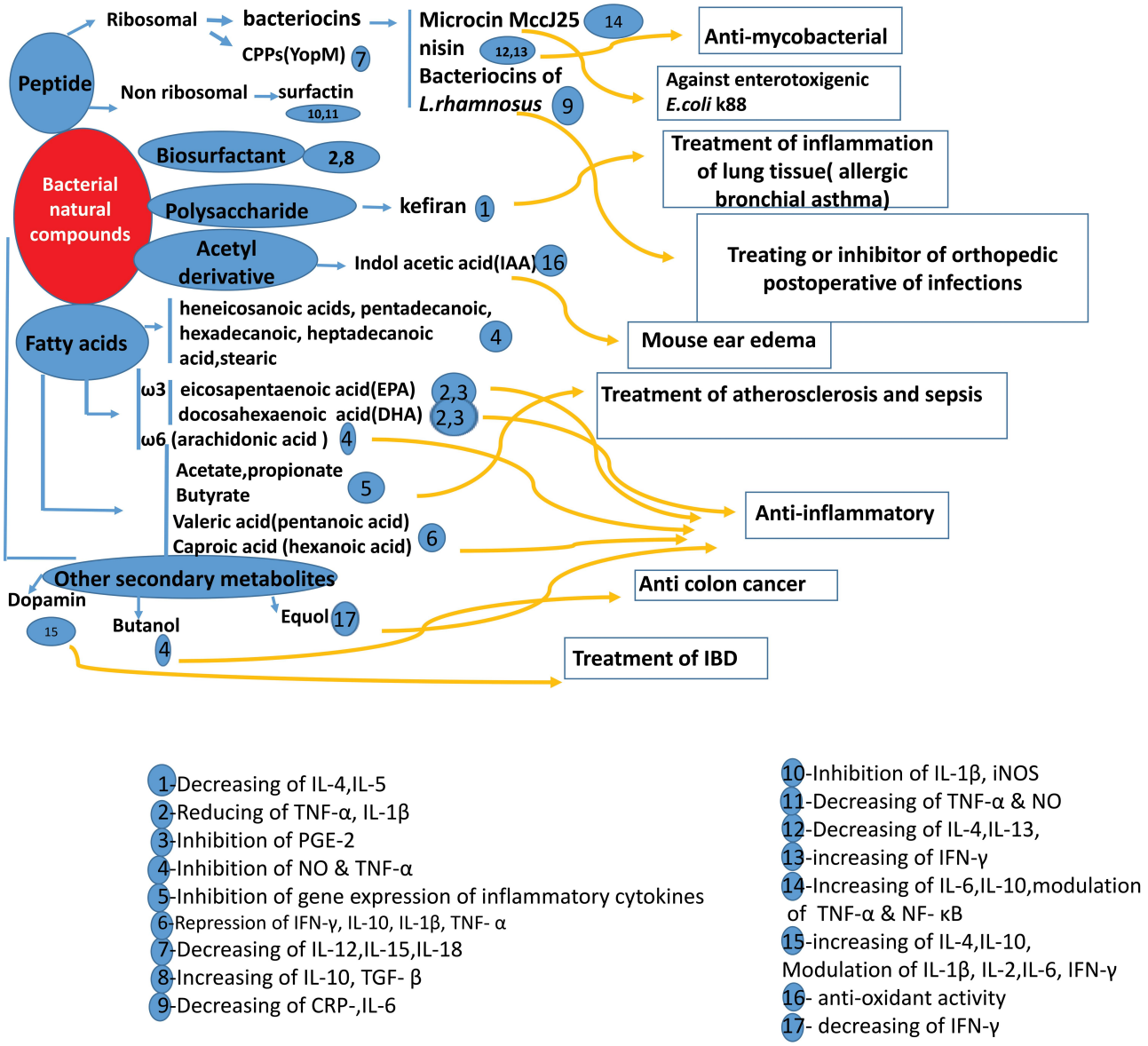


Figure 3 Summary of the bacterial bio-active compounds, active components, the potential mechanism of their actions, and treatment of different diseases.

regulated.[15] Bio-surfactant can inhibit biofilm formation, and it removes cadmium (Cd) from tested vegetables such as radish, ginger, potato, and carrot so that it could be useful for food industries.[15]

Surfactin is a bacterial cyclic lipopeptide produced by *B. subtilis*. Because of its multifunctional interactions with biological systems, it has several physiological and biochemical activities. The anti-inflammatory mechanism of surfactin in lipopolysaccharide (LPS)-stimulated macrophages showed that surfactin prevents the formation of inflammatory agents like IL-1β and iNOS; also, it decreases TNF-α and nitric oxide levels in response to septic shock.[19,20] TLR4 is the central receptor for LPS; thus, the TLR4 signal transduction pathway is the major pathway that mediates LPS-induced inflammation. The results show that surfactin down-regulated the LPS-induced TLR4 protein expression of macrophages. It was also shown that surfactin has an anti-inflammatory property by reducing the activation of nuclear factor-κB (NF-κB), which is involved in the nuclear factor-κB (NF-κB) cell signaling pathways.[20,21] The anti-inflammatory activity of surfactin was demonstrated in the interaction of LPS with macrophage cells. The proposed mechanism of the anti-inflammatory activity includes interaction with cytosolic phospholipase A2 (PLA2), inhibition of lipoteichoic acid (LTA)-induced NF-κB, activation of signal transducer

and activator of transcription-1 (STAT-1), modulation of the TLR4 and the nuclear factor-κB (NF-κB) cell signaling pathways, and increased phosphorylation of STAT-3.[21] There are few reports of clinical trials. Significant efforts are needed to develop and use these materials as therapeutic drugs.[21]

Other cyclic lipopeptides like fengycin, and iturin lipopeptides, which are produced by *B. subtilis* have a variety of capabilities in biological activities, containing interactions with biofilms, anti-fungal, anti-tumor, anti-virus, anti-platelet, and anti-inflammatory properties.[21]

Polysaccharide

Polysaccharides are long chains of carbohydrate molecules, specifically polymeric carbohydrates that are composed of monosaccharide units joined together by glycosidic bonds. Polysaccharides contain more than ten monosaccharide units, whereas oligosaccharides contain three to ten monosaccharide units. They are classified according to their biological functions into intracellular storage polysaccharides (glycogen), capsular polysaccharides that are close to the cell surface, and extracellular bacterial polysaccharides. Extracellular bacterial polysaccharide such as xanthan, alginate, cellulose, and levan is produced by *Xanthomonas campestris, Pseudomonas* and *Azotobacter, Acetobacter xylinum, Leuconostoc mesenteroides* respectively with different applications.[22] Also, exopolysaccharide (EPS) producing lactic acid bacteria strains have a variety of health benefits for their hosts such as anti-inflammatory, antioxidant, antitumor, and stress-tolerant effects.[23]

2-1-Kefiran is a polysaccharide (Branched glucogalactan) produced by lactic acid bacteria of Kefir. Due to the antimicrobial activity of kefiran against isolated *Pseudomonas, Rhizoctonia*, and *S. aureus*, kefiran nanofiber was introduced as a biocontrol agent for food packaging and food preservation.[24] Also, Jenab et al examined the amount of the entrapped platelets in kefiran and the released platelets from kefiran by coulter counter. Results showed that, in the beginning, platelets are decreased, and then the platelets are released from kefiran. So, Kefiran may have the potential to be used for surface bleeding. The presence of nisin in kefiran with lantibiotics properties is an advantage of kefiran. It induces both $CD4^+$ and $CD8^+$ T-lymphocytes populations.[25] Interleukin-4 (IL-4) and interleukin-5 (IL-5) were decreased to the normal levels after administration of kefiran in BALB/c mice stimulated with ovalbumin.[26] So, Kefiran could be used to treat pulmonary inflammation in a murine model.[26] Kefiran is not only an excellent promising of allergic bronchial asthma therapy and food packaging but also is an accurate candidate as a drug for the treatment of inflammatory, bacterial infection, tumor cells, surface bleeding. On the other hand, kefiran extraction is easily done at a low cost by ethanol.[24,25] Also, Jenab et al confirmed that no significant changes were measured for the level of IL-6 in PAN/kefiran 5% nanofiber treated PBMC cell cultures compared to the control ($p \geq 0.05$), while PAN nanofiber revealed the enhancement level of IL-6. So, the kefiran-PAN nanofiber may be promising for the neural stem cell culture, especially for repairing the injured spinal cord. So, kefiran is safer and user-friendly to humans and animals with no side effects, which may have potential anti-inflammatory drug-like activity.[27]

2-2-Exopolysaccharide (EPS) from the probiotic spore-forming bacterium *Bacillus subtilis* Protects Mice from acute colitis induced by the enteric pathogen *Citrobacter rodentium*. It can broadly inhibit T cell activation and thus control T cell-mediated immune responses in various inflammatory diseases.[28]

2-3-Polysaccharide capsules in the intestine. The capsular polysaccharide of *Bacteroides cellulosilyticus* and *Bifidobacterium bifidum* induces IL-10. Due to that 2,4,6-trinitrobenzene sulfonic acid (TNBS) induces chemical colitis, this polysaccharide can attenuate TNBS-induced colitis.[29] Also, Capsular polysaccharide of *Bacteroides fragilis* induces IL-10. It protects against TNBS-induced colitis and *Helicobacter hepaticus*-induced colitis. *Bifidobacterium longum* decreases IFN-γ, IL-12, TNF-α, IL-17, and IL-6 production and protects against the T cell transfer model of colitis.[28] EPS from *Streptococcus thermophilous* in the intestine decreases IL-6, IFN-γ, and TNF-α production. EPS from *Pediococcus parvulus*, the commensal bacterium in the intestine, decreases TNF-α and IL-8 production. EPS from *Faecalibacterium prausnitzii* the commensal bacterium in the intestine, decreases IL-12 and IFN- γ and increases IL-10 secretion through TLR-2 signaling by *Lactobacillus plantarum* attenuates DSS-colitis. *Bifidobacterium longum* decreases.[28]

2-4- Exopolysaccharide produced by probiotic strain *Lactobacillus paraplantarum* BGCG11 was examined in the rat model. It decreases expression levels of pro-inflammatory mediators IL-1β, TNF-α,/and iNOS, and increases the level of anti-inflammatory cytokines such

as IL-10 and IL-6, while neutrophil infiltration was not changed. The EPS CG11 was examined as antihyperalgesic and anti-edematous agents. Intraperitoneal administration of EPS CG11 was used in a model of inflammatory rats induced by carrageenan injection in the hind paw. EPS CG11 decreased the hind paw swelling and pain sensations (mechanical hyperalgesia) in a dose-dependent manner.

It was measured by the plethysmometer and von Frey anesthesiometer, respectively. So, this bacterial EPS has the antihyperalgesic effect as the novel property of bacterial EPSs.[30]

2-5- The EPS derived from *Bacillus licheniformis* BioE-BL11 and *Leuconostoc mesenteroides* BioE-LMD18, isolated from Korean fermented kimchi inhibited secretion of the pro-inflammatory cytokine IL-6 in lipopolysaccharide-stimulated RAW264.7 mouse macrophage. Also, it enhanced the secretion of the anti-inflammatory cytokine IL-10 in a dose-dependent manner.[31]

2-6- The mucous variant of *Lactobacillus rhamnosus* RW-9595M induced low or no TNF-α and IL-6 and decreased the inflammatory cytokine. Also, the EPS of *Lactobacillus rhamnosus* RW-9595M increased the IL-10 produced by macrophages. Whereas, conditioned media were produced by macrophages treated with parental *Lactobacillus rhamnosus* induced higher levels of TNF-α, IL-6, and IL-12 but inhibited IL-10 production. So, the EPS from *Lact. rhamnosus* RW-9595M may be useful as a new immunosuppressive product in dairy food.[32]

Acetyl Derivatives

Indol-3 acetic acid (IAA) is a derivative of indole, containing a carboxymethyl residue. It is the most important and the most abundant auxin hormone that stimulates the growth of plants.[33,34] It is produced by *Rhizobium* strains, symbiotic, *Paenibacillus* non-symbiotic bacteria and *Pseudomonas fluorescens*.[35] IAA with antioxidant effect shows anti-inflammatory activity against croton oil- and arachidonic acid-induced mouse ear edema.[36] The indole-3-acetic acid produced by *Burkholderia heleia* plays a role as a phenylacetic acid antagonist to inhibit tropolone biosynthesis in *Burkholderia plantarii*.[37] *Burkholderia heleia* PAK1-2 is a potential biocontrol agent that can suppress *B. plantarii* virulence.

Fatty Acids

Fatty acids have long and linear aliphatic chains. They are classified according to the link between the carbon including saturated fatty acids and unsaturated fatty acids and the other based on the length of the chain including SCFA (short-chain fatty acids), MCFA (medium-chain fatty acids), LCFA (long-chain fatty acids) and VLCFA (very-long-chain fatty acids). Due to the limited sources of ω_3 and ω_6 fatty acids from animal and plant sources, attention has been focused on microbial production like marine bacteria (*Shewanella* sp. strain SCRC-2738).[38] The amounts and relative ratio of acetate, glycerol, carbohydrate, lipid, and nitrogenous substances available in the medium; oxygen supply; pH; and the age of the culture influence the fatty acid content of the bacteria. It should be mentioned that the extraction of bacterial fatty acids is difficult. Prevention of NO and TNF-α production in LPS stimulated macrophages were related to the higher level of Saturated Fatty Acids (SFAs) and Poly Unsaturated Fatty Acids (PUFA), and a lower concentration of Mono Unsaturated Fatty Acids (MUFAs). The composition of the fatty acids can influence anti-inflammatory activities.[39]

Unsaturated Fatty Acids (ω_3 and ω_6)

Fatty acid chains have at least one double bond. Unsaturated Fatty acids (ω_3 and ω_6) are precursors of lipid intermediates. Marine bacteria like *Vibrio cyclitrophicus* were identified as EPA producer.[38] Each strain of *Cellulophaga* and *Pibocella* could produce EPA and DHA, respectively. While *Polaribacter* could produce only DHA or only EPA.[40] *Shewanella marinintestina* contains a significant amount of EPA. Their functions in inflammatory regulation are very important. ω_6 fatty acids like arachidonic acid increase inflammation, while ω_3 Fatty acids like eicosapentaenoic acid and docosahexaenoic play a role as anti-inflammatory agents. Production of inflammatory cytokines like TNF-α and IL-1β was inhibited. ω_3 fatty acids inhibit the formation of ω_6 fatty acids-derived pro-inflammatory eicosanoids (eg, PGE2 and LTB4).[41] Also, the bacterium *Moritella marina* produces high levels of DHA. The membranes of *Vibrio marinus* strain MP-1 contain substantial amounts of DHA.[42] Also, arachidonic acid-producing bacteria from marine have been isolated, including; *Psychroflexus torquis, Psychroflexus pacifica, Krokinobacter eikastus*, and *Krokinobacter diaphorus Aureispira marina* (a gliding bacterium). They produce the most significant amounts of arachidonic acid (about 40%) that show anti-inflammatory activities.[43]

Saturated Fatty Acids

Saturated fatty acids are long-chain carboxylic acids, including 12 and 14 carbon atoms like stearic acid without

double bonds. They play critical roles in immune responses. It forms from linoleic acid produced by *Clostridium proteoclasticum* with anti-inflammatory activity.[44] Fatty acid analyses revealed the presence of the heneicosanoic acids, pentadecanoic, hexadecanoic, and heptadecanoic acid as primary ester-bound fatty acids in LPS from *Chlamydophila psittaci* 6BC.[45] These fatty acids can influence the anti-inflammatory activity through the inhibition of NO and TNF-α.[39]

Short-Chain Fatty Acids

Short-chain fatty acids (SCFAs) are fatty acids, including 1–6 carbon atoms. Studies in both animals and humans showed that SCFA reduced cholesterol levels, and they play a significant role in colon health. SCFAs, mainly acetate, propionate, and butyrate, can inhibit from MAPK (mitogen-activated protein kinase) signaling pathway and activation of NF-κB (nuclear factor-κ light-chain) enhancer of activated B cells via activation fatty acid (FFA) receptors type 2, 3 (FFA2 and FFA3 receptors) and GPR109A (G protein-coupled receptor 109A) or inhibition of HDACs (histone deacetylases) (Figure 4). It inhibits gene expression, including inflammatory cytokines, chemokines, and adhesion molecules, which play essential roles in the improvement of atherosclerosis and sepsis.[46] The main butyrate producers are *Clostridium* IV group (*Faecalibacterium prausnitzii*), and *Clostridium* XIVa group (*Eubacterium rectale, E. halii, Roseburia*). Also, the main propionate producers are *Bacteroides*, and the main acetate producer are *Clostridium* XIVa group (*Blautia hydrogeotrophyca*).[47]

The overexpression of several isoforms of HDACs has been identified in different types of cancerous cells, inflammatory diseases, and neurological diseases. A role for HDAC inhibitors is the suppression of IFN-γ, IL-10, IL-1β, and TNF-α.[48] Valeric acid (pentanoic acid) and caproic acid (hexanoic acid) were identified as histone deacetylase enzymes (HDAC) inhibitors, produced with high concentration by *Ruminococcaceae* bacterium CPB6[48] and *Megasphaera massiliensis* MRx0029.[49]

Peptides

Antimicrobial peptides (AMP) are groups of various antimicrobial compounds. They are of interest due to the importance of pathogenic resistance to conventional antibiotics.[50] These compounds include two groups of bacteriocins and antibacterial peptides as based on their biosynthesis mechanism. Bacteriocins are synthesized compounds by ribosomes that are produced in some bacteria and against the others. While antibiotic peptides are not synthesized by ribosomes. They are produced by

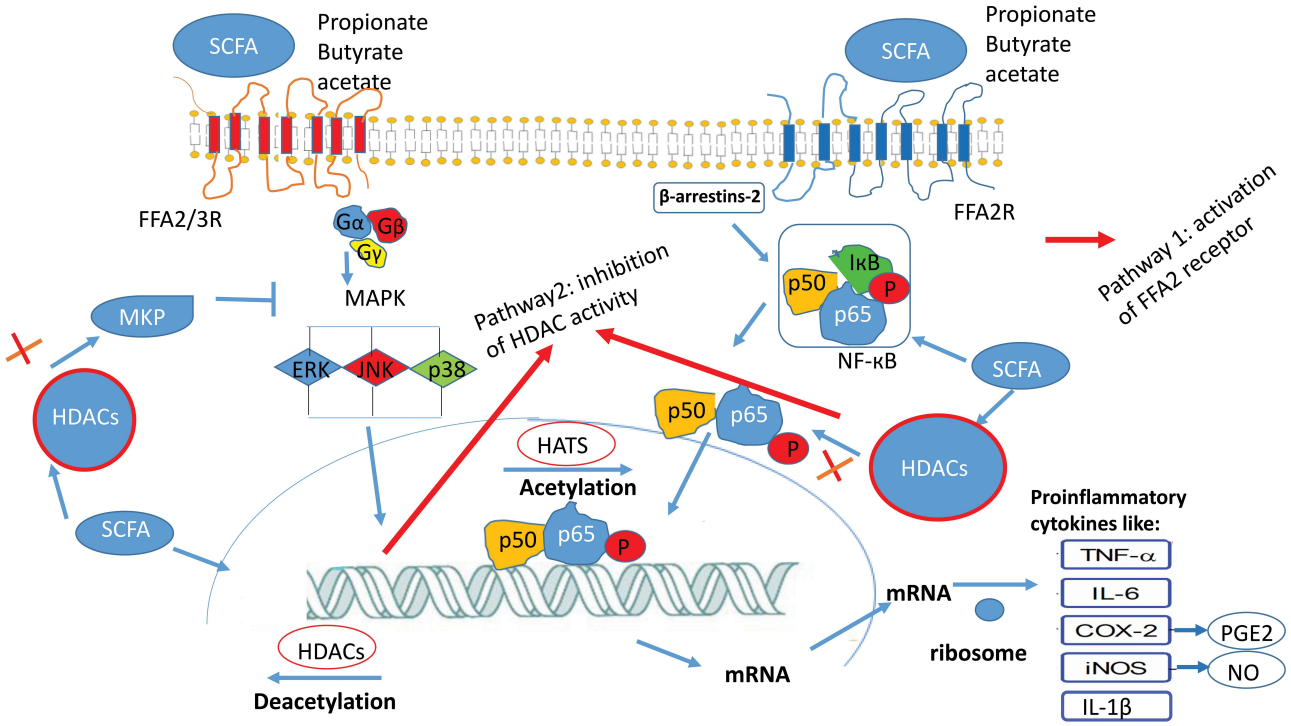


Figure 4 The downstream effect of short-chain fatty acids (SCFA) occurs with the regulation of MAPK signaling pathway and activation of NF-κB through two pathways: 1- activation of receptor FFA2, FFA3 receptors 2- inhibition of HDAC (histone deacetylase).[46]

compression reactions and complex stages using large non-ribosome peptide syntheses (NRPS) enzyme.[51,52] Bacteriocins produced by *lactobacilli* are based on the building and biochemical specifications.[51] Bacteriocins are extracellularly released peptides, which are produced by Gram-positive (+) and Gram-negative (-) bacterial species. Gram-negative bacteriocins are typically classified by size. Microcins are less than 20 kDa in size, colicin-like bacteriocins are 20 to 90 kDa in size and tailocins or so-called high molecular weight bacteriocins. Also, bacteriocins are divided into four groups based on their structure.

1. 1-Lanthia antibiotics: Active and small peptides against bacteria, containing unusual amino acids of lantinum.
2. 2-Small peptides (< 10 kDa), resist heating without lanthionine, and active against membranes.
3. Proteins are unstable against heat and large (>10kDa).
4. Complex bacteriocins containing lipid or carbohydrate moieties.[51]

Some antimicrobial peptides are useful as bio-control, such as bacteriocins produced by *Bacillus pumilus* ZED17, and DFAR strains. These bacteriocins have the antifungal effect against *Rhizoctonia solani* (agent of the fungal diseases in plants) and inhibitory activity for seed germination.[53] Peptide antibiotics such as Actinomycin, Gramisidine, Surfactin are useful in the industry and medical drugs.[54,55] Some bacteriocins not only used for antimicrobial activity but also have the potential for usage in high blood pressure treatment like ancovenin. Its mechanism of action in antibacterial activity is that they target the bacterial cell membranes, deplete the transmembrane potential and/or the pH gradient and form membrane pores, resulting in membrane disruption and cellular leakage.[56] To be applied as drug agents, they have some obstacles, such as their toxicities and high cost of construction.[52] Today, there is a high potential for the usage of antimicrobial peptides, and it needs more studies to be done in this field.

Several bacteriocins have been produced by lactic acid bacteria. Nine lactic acid bacteria with anti-listeria activity were identified and used in food additives.[57]

LAB is used in anti-mycobacterial (*Mycobacterium tuberculosis)* therapy. Nisin is the bacteriocin produced by LAB. It increases the bactericidal activity of mononuclear phagocytes. This activity occurs through increasing autophagy-inducing cytokine-like IFN-γ levels and reducing IL-4 and IL-13 that is followed to down-regulate the lung Th2 response, which is known to restrict autophagy. The treatment with probiotics can modulate the immune responses in the lung, which increases the regulatory T cell response in the treatment of PBMCs and macrophages with combined *M. tuberculosis* and LAB.[58,59]

Microcins are bacteriocins produced by *E.coli* in the ribosomal pathway. Microcins with the Bactericide effect have smart mechanisms to cross from the outer and inner membrane of gram-negative bacteria. Microcins use trojan horse strategies and destroy their competitors. It could be used for novel, efficient antibiotics. Pro-inflammatory cytokines levels were determined in intestinal porcine cells line (IPEC-J2 cells) after treatment with biogenic Microcin j25 (MccJ25) and challenge with (*enterotoxigenic Escherichia coli K88*) *ETEC K88*. MccJ25 increases the level of IL-6 and IL-10 anti-inflammatory cytokines and modulates the level of tumor necrosis factor-α through inhibition of MAPK and NFκB activation. MccJ25 can be used to protect against *ETEC K88*, which induce intestinal damage.[60,61]

Bacteriocin produced by *Enterococcus faecium* has anti-listerial activity in the sterile milk that might be useful as a natural preservative.[62] On the other hand, *E. faecium* can produce the neurochemical dopamine from the dietary substrate. Both dopamine and *E. faecium* can modulate the immune system and increase the production of anti-inflammatory IL-4 and are useful in the treatment of inflammatory diseases. *E. faecium* probiotics are good enough in IBD therapy. After the per oral administration of *E. faecium* strain NCIMB 11181 in broiler chickens, the serum levels of IL-4, IL-10, IL-1β, IL-2, IL-6, and IFN-γ are changed.[62] Bacteriocins produced by *Lactobacillus rhamnosus* with antibacterial effect showed significant inhibitory effects on *S.aureus* biofilm formation. Also, it decreases the level of C Reactive Protein (CRP) and IL-6 in the serum following surgery and infectious diseases. So, bacteriocins could be used in the prevention of postoperative orthopedic infections.[63]

Lipopeptides, such as amphomycins, polymyxins, teicoplanins, and bacitracin are well-known for immunomodulatory activity. For example, daptomycin was shown to be an immunomodulator. It suppresses the cytokine expression after host immune response stimulation by methicillin-resistant *S. aureus*. Also, it is a membrane permeabilizing lipopeptide.[64]

The synthetic bacterial lipopeptide Pam3Cys-Ala-Gly, which is capable of activating macrophages and B cells in vitro, was injected into the mice. After injection, a little increase of IL-6 was detected in the serum without affecting the level of TNF-α.[18]

Cell-penetrating peptides (CPPs) can pass the cellular membrane. This process can be done alone or in association with bio-active cargo. YopM can down-regulate the transcription of TNF-α, and interleukins 12, 15, and 18 (pro-inflammatory cytokines) without affection on anti-inflammatory cytokines in infected mice with *Yersinia pestis* (*Y.pestis*). YopM cell uptake, mediated by the N-terminal -helical domain, is essential to counteract the pro-inflammatory response induced by LPS. It was analyzed in HL60-derived macrophages with either recombinant YopM or the short YopM87-C derivatives, followed by stimulation with LPS (1 g/mL). So, just YopM (without infection with *Yersinia*) could be suggested as a tool for protein delivery.[65,66]

Lactobacillus delbrueckii and *Streptococcus thermophilus* are lactic acid bacteria (LAB), which can inhibit localized inflammatory diseases. Beside conventional therapy, they could be used as an additional treatment. Their usage causes down-regulation of the inflammatory cytokines such as IL-17 and IL-12.[67]

Other Bacterial Natural Compounds

Secondary Metabolites

Bacillus sp isolated from Neogene permafrost has secondary metabolites, which increases the secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-8, IL-2, and IFNγ) and anti-inflammatory cytokines (IL-4 and IL-10) by human peripheral blood mononuclear cells (PBMC). The activity of these metabolites depends on the incubation temperature. Cold isolated *Bacillus* metabolites at −5° C increase the secretion of Th1-dependent cytokines such as IFN γ. Warm isolated *Bacillus* metabolites at 37°C increase the secretion of Th2-dependent cytokines such as IL-4. So, metabolites of *Bacillus* spare materials for evolution and progressing immunomodulating drugs.[68]

Equol

Isolated new intestinal bacteria, CS1, CS2, and CS3, showed that belonging to the genus *Pediococcus* and *Lactobacillus* can produce equol or its related intermediates.[69]

Pretreatment of PBMC with equol reduces the production of interferon-gamma) IFN- γ).[70]

Butanol

Bifidobacterium adolescentis (*B. adolescentis*), which is one of the LAB strains, produces the butanol extract. The butanol extract significantly causes to boost the production of NO and TNF-α, which are cytotoxic for tumor cells.[71,72] It was shown that the butanol extract of *B. adolescentis* SPM0212 dose-dependently prevented the growth of Caco-2, HT-29, and SW480 cells by 70%, 30%, and 40%, respectively, at 200 μg/mL. It was shown that the LAB by-product has anti-tumor immune effects.[71] Therefore, this extract has anti-proliferative activity against human colon cancer.[73]

Polyketide

Camporidine A, polyketide alkaloid, from a gut bacterium of carpenter ant *Camponotus kiusiuensis* (*Streptomyces* sp. STA1) displayed an anti-inflammatory activity by suppressing nitric oxide production induced by lipopolysaccharide after treatment of mouse macrophages with these compounds in the iNOS assay.[74]

Conclusion

In this review, the bacterial natural compounds with modulating effect on cytokines are surveyed, which may have an anti-inflammatory drug like activity. The primary mechanism of the impact of natural products is through modulating cytokines. Cytokines can down-regulate and, or up-regulate different genes. It can affect their associated transcription factors to reduce the signs and symptoms of diseases or disease therapy. The main bacterial natural components are fatty acids, peptide, antimicrobial peptide, secondary metabolite, polysaccharide, and oligosaccharide. The effects of these natural products are mediated mainly by cytokines like TNF-α, IL-1β, IL-6, which are the main pro-inflammatory cytokines and IL-10 that are anti-inflammatory cytokine. Some of these bacterial natural compounds have been used as anti-inflammatory drugs such as biosurfactant of *B. licheniformis* and Fatty acids (saturated and unsaturated fatty acids). Other bacterial natural compounds could be used as treating drugs such as SCFA (butyrate, propionate, and acetate) in the treatment of atherosclerosis and sepsis, cyclic lipopeptide (surfactin) in treating of septic shock, and peptide bacteriocin in treating and inhibiting of orthopedic postoperative infections. Also, bacteriocin (nisin) is a polycyclic peptide

with anti-mycobacterium tuberculosis activity and microcin with anti enterotoxigenic *E.coli* k88 properties. Among all, kefiran as a polysaccharide natural compound is cheap and user-friendly with easy extraction. Kefiran could be promising as a drug for the treatment of inflammatory especially in repairing injured spinal cord by using kefiran-PAN nanofiber. Because it is confirmed that no significant changes were measured for the level of IL-6 in PAN/kefiran nanofiber treated cells compared to the control ($p \geq 0.05$). Also, It is confirmed that morphological changes (differentiation) of PC12 cells were shown in PAN-kefiran 10% nanofiber.[27] On the other hand, new unknown bacteria are discovered taxonomically. The new metabolites produced by these new unknown bacteria could be useful in various sections.[11,75] They may have significant influences on the treatment of different diseases. This theory requires further studies to be done.

Disclosure

The authors report no conflicts of interest in this work.

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