Review

The Plethora of Microbes with Anti-inflammatory Activities

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The Plethora of Microbes with Anti-Inflammatory Activities

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Abstract: Inflammation which has important functions in human defense systems and in maintaining the dynamic homeostasis of the body has become a major risk factor for the progression of many chronic diseases. Although the applied medical products alleviate the general status, they still exert adverse effects in the long term. For this reason, the solution should be sought in more harmless and affordable agents. Microorganisms offer a wide range of active substances with anti-inflammatory properties. They propose important advantages such as renewable and inexhaustible nature. This review aims at the most recent updates on the microorganisms of different type and genera being carriers of anti-inflammatory activity.

Keywords: anti-inflammatory activity; microorganisms; lactic acid bacteria; fungi; marine bacteria

1. Introduction

In the last decades inflammation has turned into the main reason causing various diseases in human organism. Inflammation is an immunological defensive response to external stimuli such as tissue injury, microbial pathogen infection or chemical irritation and is the basis of a variety of physiological and pathological conditions [1]. This biological process includes the innate and adaptive immune system. Inflammation is initiated by migration of immune cells from blood vessels and the release of mediators, followed by inflammatory cells accumulation and secretion of reactive oxygen species (ROS), reactive nitrogen species (RNS), and pro-inflammatory cytokines for the inactivation of the pathogens and the repair of the injured tissue [2]. Various ROS and RNS like O_2^-, OH, H_2O_2, NO, and O_2 produced by the inflammatory cells damage cellular biomolecules (nucleic acids, proteins, lipids) which reflects in the augmentation in the state of inflammation [2]. The complex body response includes leukocyte cells, macrophages, neutrophils, and lymphocytes [3]. As a result of the inflammation, these cells release special substances, including amines and vasoactive peptides, eicosanoids, pro-inflammatory cytokines, and acute phase proteins which mediate the inflammatory process and prevent from additional tissue damage [4]. The activation of macrophage plays an important role in the initiation and distribution of the inflammation response through the production of cytokines such as interleukin 1β (IL 1β), NO, cyclooxygenase-2 (COX-2), tumor necrosis factor alpha (TNF-α), and other inflammation mediators [5]. Nuclear factor-kappa B (NF-kB), a nuclear transcription factor, takes part in the regulation of the expression of these cytokines [6].

In grave cases of inflammation excessive cytokines production results in a condition called "cytokine storm", which leads to damaging consequences, organ failure, and mortality [7]. During the cytokine storm, the level of IL-6 is three times higher than in normal conditions [8]. The cytokine storm is reported to be the major reason for patient death from COVID-19 [9].

Acute inflammation is a short-term self-limiting condition and the host's defenses can easily return the body to homeostasis. However, chronic inflammation provokes chronic disease development characterized by infiltration of inflammation cells, excessive production of cytokines, dysregulation of cellular signaling and loss of barrier function [10]. Chronic inflammation is a crucial component in multiple progressive diseases and conditions such as neurological disorders (Alzheimer's and Parkinson's diseases), chronic inflammation diseases (chronic obstructive

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pulmonary disease, psoriasis, pancreatitis, inflammatory bowel disease), hypertension, cancer, cardiovascular diseases (heart failure, atherosclerosis, cardiomyopathy, coronary diseases), type 2 diabetes, metabolic disorders (fatty liver disease, chronic kidney disease), rheumatoid arthritis, osteoporosis, etc. [2].

Diverse medicinal products are being developed worldwide as a counteraction to inflammation in the human body. These drugs can be divided into three groups – corticosteroids, non-steroidal anti-inflammatory medicines, and disease-modifying anti- rheumatoid drugs. Although these chemicals contribute to the reduction of inflammation symptoms, yet they exhibit side effects concerning the gastrointestinal tract, bleeding, platelet dysfunction, etc. [11]. Therefore, it is very important to employ natural products which on the one hand are not toxic to human organism, and on the other hand, are available, renewable and inexhaustible. Such opportunities are given to us by the plants and microorganisms that live in or around us. This review targets the microbes being carriers of anti-inflammatory activity.

2. Human Microbiota and Human-Friendly Microbes with Anti-Inflammatory Properties

Human microbiota refers to the trillions of commensal microorganisms that are colonizing our body. Microbes living in immediate relationship with humans (on different surfaces of the body) are very important for the protection against infections and diseases [12,13]. Normally, skin flora consist of representatives of bacteria (Propionibacterium, Staphylococcu,s and Corynebacterium species), fungi (Malassezia spp., Aspergillus spp., Cryptococcus spp., Rhodotorula spp., Epicoccum spp., etc.) and viruses [14]. Gut microbiome is an ecological entity characterized by thousands of microbes including bacteria, viruses, and some eykariotes. The most dominant phyla (comprising up to 90 % of gut microbiota) are Bacteroidetes and Firmicutes (including Lactobacillus sp.) followed by Proteobacteria, Fusobacteria, Tenericutes, Actinobacteria and Verrucomicrobia [15].

Human skin microbiota plays an important role in skin health maintenance and to potentially preventing from prematurely skin aging. Utilization of probiotics in skin therapeutic products is an attractive idea as it can provide interesting alternative possibilities for some skin disorders. In their study, the team of Khmaladze compare the employment of a live culture and lysate of Lactobacillus reuteri DSM 17938 aiming to investigate the anti-inflammatory and barrier functions of skin in ex vivo models and in vitro assays for antimicrobial activity. They induced inflammation through the application of ultraviolet B radiation in human epidermis and native skin models. The levels of IL-6 and IL-8 decreased in both assays – with live culture and lysate. It was established that live Lactobacillus reuteri increased the expression of aquaporin 3 gene while the lysate enhanced lamininA/B levels in a healthy reconstructed human epidermis which suggests a positive impact on the skin barrier. It can be concluded that Lactobacillus reuteri DSM 17938 could be used in skin products to avoid the UVB-R-mediated inflammation cascade and/or to prevent from photoaging, to enhance barrier function or for unhealthy skinprone to inflammation maintenance [16].

In a recent study Brandy et al. demonstrated that lactic acid bacteria (LAB) lysates stimulated the proliferation of keratinocytes and that L. plantarum SGL 07 and L. salivarius SGL 19 hasten the re-epitalization through the induction of keratinocyte migration. The secretion of specific pro-inflammatory mediators from keratinocytes was reduced, as well. In addition, it was shown that a specific proteome modulation of the exposed keratinocytes has been induced involving proteins dysregulation (interleukin enhancer-binding factor 2 and an ATP dependent RNA helicase) and pathways (such as cytokine, NF-kB, Hedgehog, and RUNX signaling) associated with the anti-inflammatory activity. These results indicate that these strains together could be used in therapies for skin relief [17].

Streptococcus salivarius inhabits the oral cavity and the digestive tract. This strain becomes a normal inhabitant of the human body just a few hours after birth and remains predominant. It exerted anti-inflammatory activity in vitro as it inhibited the activation of the NF-kB pathway on intestinal epithelial cells. The performed mouse model experiments resulted in significantly reduced inflammation in severe and moderate colitis [18]. According to Kaci and collaborators, the in vitro anti-inflammatory effects could be a result of the intracellular signaling pathway and the innate

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immune responses of epithelial cells rather than by the immunocompetent cell-based host immunity [18]. Streptococcus salivarius has been used in New Zealand as a probiotic for prevention from streptococcal pharyngitis and halitosis [19].

Rothia mucilaginosa is one more normal human commensal of the oral cavity that exhibited anti-inflammatory activity. It is also found in the lower respiratory tract during chronic diseases. Two types of assays with this bacteria were performed – in vitro (three - dimensional cell culture model), and in vivo (mouse model) resulting in the conclusion that R. mucilaginosa expresses an inhibitory effect on the pathogen or lipopolysaccharide-induced pro-inflammatory responses. It was illuminated that R. mucilaginosa inhibited the production of pro-inflammatory cytokines by lung epithelial cells in vitro and induced high IL-8 production caused by the pathogen P. aeruginosa, and moderate or low IL-8 production in the case of exposure to S. aureus SP123, S. anginosus LMG14696, A. xylosoxidans LMG 26680, G. haemolysans LMG 18984. The anti-inflammatory effect of Rothia was confirmed in a 3D model of cystic fibrosis epithelial cells. LPS-induced pro-inflammatory response in an in vivo model was lowered. The supernatant of Rothia inhibited IL-8 production and NF-kB pathway activation in response to a pro-inflammatory stimuli [20]. The invention of anti-inflammatory activity in Rothia in the lung microbiota leads to the hypothesis that other nonpathogenic inhabitants in the respiratory tract, may possess immunomodulatory properties.

Inflammation bowel diseases (IBDs) are conditions associated with chronic abnormal inflammation of the gastrointestinal tract during which levels of IL-8 cytokine increase [21] and ROS are overproduced [22]. The two basic types of IBDs are Crohn's disease (CD) and ulcerative colitis (UC) with different physical symptoms displayed [23]. The core of these conditions is the disturbed balance between microorganisms in the gut [24]. In general, the studies with CD and UC patients reveal reduced presence of Firmicutes and Bacteroidetes phyla thus enhancing levels of Gammaproteobacteria [25,26]. The dysbiosis results in changes in short-chain fatty acids production which in turn can affect the inflammation pathways and immune system modulation [27]. Christensenella minuta DSM 22607 is a commensal bacteria usually found in the human gut and is believed to be maintaining the microbial balance there. C. minuta absence is related to IBD. Its anti-inflammatory effect was tested on human intestinal lines where reduced levels of pro-inflammatory IL-8 cytokines via the inhibition of the NF-kB signaling pathway were achieved. The bacteria was shown to protect intestinal epithelial integrity in vitro, as well. More in depth, the strain was proven to prevent from intestinal damage, reduce colonic inflammation, and promote mucosal healing in two distinct animal models of acute colitis. Both the supernatant and the bacterial culture were confirmed to possess anti-inflammatory properties. The supernatant decreased NF-kB pathway activation by 40 %, however, when the bacteria alone was used, no anti-inflammatory effects were monitored. Therefore, C. minuta probably secretes a potent anti-inflammatory effector into the supernatant [28]. Its anti-inflammatory capacity was also reported by the study of Relizani and co-workers where colonic inflammation was reduced through the inhibition of NF-κB signaling pathway and the secretion of proinflammatory cytokines IL-8 and IL-1β [29]. Moreover, a decrease in the concentration of LCN-2 (a non-invasive biological marker of intestinal inflammation) was registered in animal models where treatment with C. minuta was applied [30].

Deficiency of Faecalibacterium prausnitzii is also related to CD. Fecalibacterium can account for up to 6.5 % of the human microbiota [31]. The supernatant of this bacteria is known to exert anti-inflammatory effects both in vivo and in vitro. Quévrain et al. identified the nature of the peptide with anti-inflammatory properties produced by F. prausnitzii. This 15 kDa protein – MAM (microbial anti-inflammatory molecule) managed to inhibit the NF-kB pathway in intestinal epithelial cells and to prevent from colitis in an animal model. The work opens new lines for the prevention and treatment of IBD as MAM could represent a targeted biomarker to CD in terms of F. prausnitzii for predicting CD relapse [32]. Another representative, Faecalibacterium duncaniae, was observed to enhance the levels of a specific subset of IL-10-secreting Treg cells located in the lamina propria of the colon. These cells are missing in patients with IBD [33]. Lactobacilli have been demonstrated to impede inflammatory processes via different mechanisms, one of them, for example, is the maintenance of the balance of intestinal microbiota. Experiments with animal models of the IBD

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pathologies demonstrated the relationship between LAB administration with beneficial modulations of the intestinal microbiota, and more specifically with the normalization of lactobailli levels, and the reduction of Clostridium perfringens, enterococci, and coliforms [34]. This beneficial effect was also confirmed in human trials [35]. LAB can act by reducing the oxidative stress related to IBD, as well [36].

Bacteroides thetaiotaomicron is a gut commensal bacteria that produces extracellular vesicles responsible for its anti-inflammatory activity. These vesicles were administered to mice treated with colitis-inducing dextran sodium sulfate. Ameliorated symptoms of intestinal inflammation and improved survival rate were achieved. In addition, a high ratio of IL-10/TNF-α production was observed [37].

3. Bacteria and Yeasts with Anti-Inflammatory Properties in Food

Microbes are on one side responsible for food contamination and spoilage, and on the other – they are in the kernel of obtaining beneficial products that have a major contribution to the food industry. Yeast and bacteria are the most widely used microorganisms in the food industry. They produce different foods through fermentation, the main contributor among bacteria being lactic acid bacteria (LAB) [38].

LAB represent a heterogeneous group of microorganisms from different genera – Lactobacillus, Enterococcus, Carnobacterium, Lactococcus, Leuconostoc, Pediococcus, Oenococcus, Streptococcus, Vagococcus, Tetragenococcus, and Weissella. Some strains of LAB together with several strains from Bifidobacterium are concerned probiotics. Probiotics are defined as "live microorganisms that when administered in adequate amounts confer a health benefit to the host" [39]. They have been traditionally used as starter cultures for the preparation of fermented foods where lactic acid is the main product of carbohydrate metabolism. Lactic acid is known to inhibit the growth of many pathogens. LAB are included in functional foods as they provide multiple benefits for the host organism and possess GRAS status (Figure 1). LAB exert immunomodulating effects through the stimulation of IL-10 production and/or decreasing pro-inflammatory cytokines [40]. However, to manifest their beneficial qualities, they should be able to survive in the gastrointestinal tract and be in adequate quantity [41].

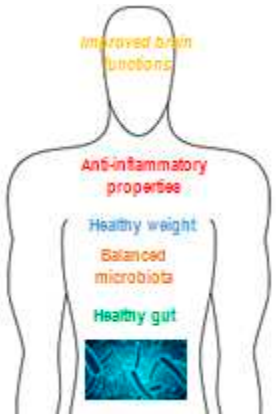

Figure 1. Main beneficial effects of probiotics.

Besides the production of lactic acid, LAB produce various beneficial substances including B-group vitamins (riboflavin, folates, cobalamin, thiamine), bacteriocins, bioactive peptides, biosurfactants, flavoring compounds, etc. Different strains of lactobacilli with anti-inflammatory activity are given in Table 1.

3.1. Vitamins Producing LAB

Riboflavin (vitamin B12) has a major role in cellular metabolism as it is a precursor of flavin mononucleotide and adenine flavin dinucleotide, coenzymes that protect cells from ROS.

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Unbalanced ROS secretion is usually associated with chronic intestinal inflammation in the initial stages of IBD. Several studies demonstrated the anti-inflammatory potential of riboflavin which plays the role of an antioxidant enzyme cofactor. For example, in the study of Al-Harbi and co-workers, vitamin B12 intake inhibited the production of TNF- α [42]. On the other hand, its short-term deficiency was found to affect the ability of macrophages to induce adequate immune response while its supplementation reduced the macrophage pro-inflammatory activation [43]. This vitamin was also demonstrated to decrease the inflammation caused by oxidative stress in diabetes [44]. Riboflavin-producing Lactobacillus plantarum CRL2130 was reported to reduce intestinal inflammation in a model of colitis in mice through the control of pro-inflammatory cytokines. For the aims of the experiment, the strain was wrapped in a food matrix (fermented soymilk), or administered as a bacterial suspension [45,46]. All these studies show that riboflavin could be an adequate prevention of inflammation.

Except for riboflavin, folates and folic acid (vitamin B9) take part in the reduction and prevention of inflammation, as well. A study of 2017 explores the relationship between arterial hypertension and the decrease in serum homocysteine concentrations, and indirectly with the decrease in other marks of inflammation [47]. Pan and collaborators reported that the reason for IBD may be associated with folate deficiency [48]. Moreover, folic acid supplementation could decrease the risk of colorectal cancer development in IBD-suffering individuals [49]. Lactobacillus reuteri ATCC PTA6475 indicated the ability to suppress the production of TNF - α in human monocytes and exerted anti-inflammatory activity in a murine model of acute colitis. This quality is determined by the folC2 gene involved in folate biosynthesis. [50].

A probiotic blend of LAB-producing vitamins was described by Levit et al. The strains Lactobacillus plantarum CRL2130, Streptococcus thermophilus CRL807, and Streptococcus thermophilus CRL808 with immunomodulatory properties were studied for anti-inflammatory activities. The results displayed even more emphasized anti-inflammatory effects than in the case of individual strains administered to rodents with induced intestinal mucositis [51]. Successful application of microbial mixtures regarding anti-inflammatory effects was reported for Lactobacillus casei, Lactobacillus plantarum, Lactobacillus acidophilus, Lactobacillus delbrueckii subsp. bulgaricus, Bifidobacterium longum, Bifidobacterium breve, Bifidobacterium infantis, and Streptococcus salivarius where the tumor development associated with intestinal inflammation in mice was prevented [52]. These conclusions designate that the employment of blends of microbes could enhance their individual anti-inflammatory properties.

In general, vitamin-producing LAB, especially those that secrete riboflavin and folate could find application in the treatment of various diseases. Additionally, the blends of vitamins-producing LAB would not only enhance the efficiency of the primary treatments but would also fill the shortages of essential vitamins provoked by the disease or the treatment [53]. According to Albuquerque et al., vitamins production can be initiated by prebiotic supplementation [54]. A very important invention accessed in murine models is that the vitamins produced by LAB are biologically active [55,56].

3.2. Anti-Inflammatory Exopolysaccharides (EPS)—Producing Bacteria

Another substance with proven anti-inflammatory properties secreted by LAB, especially by Lactobacillus kefiranofaciens, is the exopolysaccharide kefiran, which is a branched glucolactan. Kefiran is a constituent of the fermented beverage kefir. The consortium of microbes in kefir include the bacterial strains Lactobacillus, Lactococcus, Leuconostoc, Streptococcus, Acetobacter, and the yeasts Kluyveromyces, Torula, Candida, and Saccharomyces. According to Jenab et al., kefiran induced both CD4+ and CD8+ T-lymphocytes populations [57]. In another study, IL4 and IL5 levels were decreased to normal amounts after its administration in the ovalbumin-induced BALB/c mice asthma model. Therefore, kefiran has the potential to be used for pulmonary inflammation treatment [58]. It is believed to be a promising candidate for the treatment of bronchial asthma and lung inflammation [59].

Besides the kefir consortium, symbiotic microorganisms of the Tibetan mushroom were also revealed to possess anti-inflammatory properties. This symbiotic population consists of bacteria and

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yeast living in polysaccharide grains sectreted by them. Among the organisms of the consortia are Lactobacillus casei, Lactobacillus acidophilus, Lactococcus lactis, Leuconostoc citrovorum, Leuconostoc mesenteroides, Acetobacter aceti, Acetobacter rasens, Streptococcus thermophilus, Streptococcus lactis, Kluyveromuces sp., Sacharomyces sp. [60]. Tibetan mushroom suspension was tested on a cotton-induced granuloma and paw edema in rats resulting in a significant inhibition of 43 % on the formation of granuloma tissue [61].

Exopolysaccharide (EPS) isolated from the cell surface of the putative probiotic organism Lactobacillus paraplantarum BGCG11 was tested in a rat model induced by carrageenan injection in the hind paw. Reduced expression levels of pro-inflammatory mediators IL-1β, TNF-α,/and iNOS, and enhanced levels of pro-inflammatory cytokines IL-10 and IL-6 were reached. This suggests that the antihyperalgesic and antiedematous effects of EPS were associated with inflammatory response suppression [62]. EPS from Lactobacillus rhamnosus RW-9595M were detected to induce higher levels of TNF-α, IL-6, and IL-12 though inhibited IL-10 production [63].

Bacillus licheniformis BioE-BL11 and Leuconostoc mesenteroides BioE-LMD 18 isolated from the Korean fermented kimchi were found to inhibit the secretion of pro-inflammatory cytokine IL-6 in LPS-stimulated RAW 264.7 mouse macrophage. In addition, the secretion of the anti-inflammatory cytokine IL-10 was increased and it was established that the extent of the inhibition was dose-dependent. These results suggest that EPS produced by B. licheniformis and L. mesenteroides could be proper ingredients for application in pharmacy, cosmetics, and in the food industry [64]. In another study, L. plantarum LM17, L. plantarum LM19, and L. rhamnosus LM07 with probiotic characteristics were isolated from the agave fermentation stage in mezcal production [65]. The strains were shown to exert anti-inflammatory properties in TNF-α-stimulated HT-29 cells. These species were tested in vivo in a mouse model with dinitrobenzene sulfonic acid (DNBS)-induced chronic colitis. The inflammation indicators were weight loss, intestinal permeability, and cytokine profiles. L. plantarum improved mice health as observed by reduced weight loss and significantly decreased intestinal permeability. These results confirm the capability of LAB isolated from the agave fermentation to be used as probiotic supplements for IBD treatment [65]. The study of Hsieh and Allen manifested that the exopolysaccharide from the probiotic strain Bacillus subtilis protected mice from acute colitis caused by the pathogen Citrobacter rodentium. The polysaccharide inhibited the activation of T-cells and therefore controlled T-cells-mediated immune responses in multiple inflammatory diseases [66].

3.3. Biosurfactants with Anti-Inflammatory Properties—Producing Bacteria

Biosurfactants are natural products derived from bacteria, yeasts or fungi, and represent amphiphilic compounds that contain polar-(water soluble) and non-polar-(insoluble in water) sections. The amphiphilic structure of biosurfactants is important for surface tension reduction. This property is applied in various industries such as pharmaceutical, cosmetics, food, petroleum, etc. [67]. Biosurfactants are produced when the carbon source is an unsoluble substrate, thus microorganisms facilitate their diffusion into the cell by the production of different substances. They reduce surface tension in bacteria. Glycolipids, a polysaccharide–lipid complex, phospholipid, mycolic acid, lipoprotein, or lipopeptide are the possible structures of biosurfactants. Besides the availability of insoluble carbon sources, biosurfactant production may be induced by the culture conditions such as temperature, pH, agitation, and concentration of P, Fe, N, Mg, and Mn ions in the media [68]. Among biosurfactants-producing bacteria are Bacillus, Rhodococcus, Mycobacterium, Pseudomonas, Arthrobacter, etc. [69]. Bacillus subtilis produce the cyclic lipopeptide surfactin. Surfactin possesses several biological activities among which is the anti-inflammatory. Its mechanism of action in the lipopolysaccharides (LPS)-stimulated macrophages displayed prevention on the secretion of anti-inflammatory agents (such as IL-1β and iNOs), reduction of TNF-α and NO levels in response to septic shock [70]. The central LPS receptor is TLR4. It is a signal transduction pathway mediating LPS-induced inflammation. The studies showed that surfactin downregulated the LPS-induced TLR4 protein expression of macrophages. Surfactin was also demonstrated to express anti-inflammatory activity by reducing the activation of nuclear factor-kB which plays a role in NF-κB cell

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signaling pathways [70,71]. Zhao et al. reported a Bacillus subtilis with anti-inflammatory properties owing to the possession of the cyclic lipopeptides fengycin and iturin [71].

In conclusion, microbial biosurfactants possess various advantages over chemical ones, for example, they are less toxic, have higher foamer capability, have higher biodegradability, specific activity at extreme pH and temperature [69].

3.4. Bacteriocins with Anti-Inflammatory Properties—Producing Lactobacilli

Lactobacilli produce bacteriocins, extracellular compounds with peptide structures synthesized by ribosomes. Their function is the defense against other microorganisms [72]. One example of bacteriocin produced by lactobacilli is nisin which enhances the bacterial activity of mononuclear phagocytes. This action occurs through the increase of autophagy-inducing cytokine-like IFN-γ levels and decreasing IL-4 and IL-13 which is followed to down-regulate the lung Th2 response, which is known to restrict autophagy. Therefore, therapy with probiotics could modulate immune responses in the lung which augments the regulatory T-cell response in the therapy of peripheral blood mononuclear cells (PBMCs) and macrophages with combined M. tuberculosis and LAB [73]. Bacteriocins produced by Lactobacillus rhamnosus successfully reduced IL-6 and C-reactive protein levels in the serum accumulated after infectious diseases. Therefore, these biochemicals could be used as the prevention of postoperative infections [74].

3.5. Other Substances with Anti-Inflammatory Effects Produced by Lactobacilli

LAB are known to produce γ-aminobutyric acid (GABA). GABA is a non-protein amino acid that regulates neuronal activity by nerve transmission inhibition. Its defiiency is associated with various neurological diseases such as epilepsy, anxiety, depression, Alzheimer's and Parkinson's diseases, Huntington's chorea, and schizophrenia [75]. According to several studies, GABA enhances plasma growth, the brain's protein synthesis, hormone level, cognitive ability and memory, relaxes nerves and lowers blood pressure [76,77]. The advantage of microbially produced GABA over chemical synthesized one is that it is economically safe and friendly [78]. Soltani et al. reported that GABA increased the production of the anti-inflammatory mediator TGF-β1 and decreased the production of inflammatory mediators such as IL-β1, TNF-α, interferon-γ, and IL-12 in streptozotocin-treated mice [79]. Kim et al. isolated GABA-producing LAB from several fermented Korean foods and evaluated the anti-inflammatory effects of these strains on macrophages to determine their potential utilization as probiotics. The strains with pronounced GABA-producing ability were from the species L. brevis. The analysis revealed that almost all of the strains inhibited NO and iNOs production, and NF-kB activity, thus exhibiting anti-inflammatory activity [78].

Kombucha, a fermentative drink, and the consortium involved in its production were subject to an anti-inflammatory assay [80]. Kombucha which is a beverage of Manchurian origin, is the fermentation product of various bacterial (Lactobacillus sp., Acetobacter xylinoides, Gluconobacter oxydans, Komagataeibacter xylinum, Gluconacetobacter hansenii, Oenococcus oeni, Komagataeibacter europaeus) and yeast strains (Schizosaccharomyces pombe, Zygosaccharomyces kombuchaensis, Torulaspora delbrueckii, Saccharomyces sp., Brettanomyces sp., etc.). In kombucha fermentation the black tea leaves turn into valuable metabolites such as vitamins (C, B1, B2, B12), glucuronic and acetic acids, and ethanol [81]. The fermented drink was analyzed for different biological activities. The anti-inflammatory capacity against the enzyme lipoxigenase (LOX) was measured and it was defined as the percentage of inhibition of 5-LOX enzyme. The control was nordihydroguaiaretic acid. The authors reported an improvement in the anti-inflammatory activity after the fermentation with kombucha consortium (87-91 %) while the non-fermented tea obtained 66 % or even 0 % of inhibition. It was also registered an IC50 value of 9.0±0.0 μg/mL which is close to the maximal inhibitory concentration of 7.0±0.2 μg/mL for the natural LOX inhibitor nordihydroguaiaretic acid. An optimization of the operational parameters was conducted, as well. According to the obtained results, the higher surface/height ratio of the fermentation vessel accelerated the fermentation kinetics and the anti-inflammatory properties. The observation reached in the aforementioned research indicates that kombucha extracts could be effective candidates for the

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development of non-steroidal drugs for inflammation treatment [80]. The relationship between the anti-inflammatory activity and the culturing conditions was also demonstrated by another group of scientists [82]. Culturing conditions were found to affect the anti-inflammatory effect of Lactobacillus plantarum OLL 2712 (with confirmed anti-inflammatory properties) in murine model cells where the levels of IL-10 and IL-12 were measured with OLL 2712 cells prepared under various culture conditions. The IL-10-inducing activities of OLL 2712 cells differed seriously between the groups at different culture phases, different medium, temperature, and pH. The cells in their exponential phase of growth exhibited higher IL-10-inducing activity than those in their stationary phase [82].

Metabolites of LAB isolated from equid milk were reported to exhibit anti-inflammatory activity. Kostelac and co-workers isolated two strains of Lactobacillus species, namely L. plantarum M2 and L. 0020plantarum K09 from donkey and mare milk, respectively. They determined the TNF-α suppression associated to their extracellular metabolites in lipopolisaccharide-(LPS)-stimulated human peripheral blood mononuclear cells (PBMCs). The extracellular metabolites with molecular mass under 2000 Da were found to suppress TNF-α production up to 67 % in LPS-stimulated PBMCs. The latter finding confirmed the anti-inflammatory properties of the two lactobacilli strains. Moreover, no cyto/genotoxic effects toward PBMCs were ascertained as a result of the extracellular metabolite activity. Hence, the production of TNF-α in immune cells can be initialized in the presence of lipopolysaccharides which are a building block of the outer membrane of G - bacteria [83].

Table 1. LAB with anti-inflammatory activity.

Strain	Activity	Reference
L. reuteri DSM 17938 (lysate)	decreased levels of IL-6 and IL-8	[16]
L. reuteri ATCC PTA6475	synthesizes folate; suppression of TNF- α production in human monocytes	[50]
L. reuteri MG9012	Reduced NO production	[84]
L. paracasei CBA L74		
L. brevis	GABA production; inhibition of NO and iNOs production, and NF-kB activity	[78]
L. fermentum MG9014	reduced NO production	[84]
L. plantarum CRL2130	produces riboflavin; intestinal inflammation reduction via pro-inflammatory cytokines control	[45]
L. plantarum OLL 2712	induced activity of IL-10	[82]
L.plantarum M2, *L.plantarum* K09	*TNF-α suppression*	[83]
L. paraplantarum BGCG11	EPS production; decreased levels IL-1β, TNF-α,/and iNOS, and enhanced levels IL-10 and IL-6	[62]
L. rhamnosus RW-9595M	EPS production; IL-10 production inhibition	[63]
Lactobacillus rhamnosus	reduced levels of IL-6 and C Reactive Protein	[74]
L. intestinalis LE1 *and L. johnsonii* LE2	reduces in vitro mercury toxicity on the intestinal mucosa	[85]
L. plantarum SGL 07, *L. salivarius* SGL 19 (lysates)	stimulation of keratinocytes proliferation	[17]
L. plantarum CRL2130, *Streptococcus thermophilus* CRL807, *and Streptococcus thermophilus* CRL808 (blend)	riboflavin, folate production, immune-modulatory properties; decreased levels of IL-6, increase in TNF-α	[51]
L. casei, L. plantarum, L. acidophilus, L. delbrueckii subsp. *bulgaricus, Bifidobacterium (B.) longum, B. breve, B. infantis*, and *S. salivarius*	decreased levels of TNF-α and IL-6 in colon tissue	[52]

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(blend)		
Lactobacillus, Lactococcus, Leuconostoc, Streptococcus, Acetobacter, Kluyveromyces, Torula, Candida, Saccharomyces (kefir consortium)	kefiran production; induced CD^{4+} and CD^{8+} T-lymphocytes popoulations	[57]
	kefiran production; normalized levels of IL4 and IL5 levels	[58]
L. casei, L. acidophilus, Lactococcus lactis, Leuconostoc citrovorum, L. mesenteroides, Acetobacter aceti, A. rasens, Streptococcus thermophilus, S. lactis, Kluyveromuces sp, *Sacharomyces* sp (Tibetan mushroom consortia)	granuloma formation inhibition	[61]
Lactobacillus sp., Acetobacter xylinoides, Gluconobacter oxydans, Komagataeibacter xylinum, Gluconacetobacter hansenii, Oenococcus oeni, Komagataeibacter europaeus, Schizosaccharomyces pombe, Zygosaccharomyces kombuchaensis, Torulaspora delbrueckii, Saccharomyces sp., Brettanomyces sp. (kombucha consortia)	riboflavin production; 87-91 % improved anti-inflammatory activity; IC_{50} value close to the maximal inhibitory concentration of nordihydroguaiaretic acid	[80]
Leuconostoc mesenteroides BioE-LMD, *Bacillus licheniformis* BioE-BL11 (isolated from Korean kimchi)	EPS production; inhibited secretion of IL-6; increased secretion of IL-10	[64]
L. plantarum LM17 and LM19, *L. rhamnosus* LM07 (agave fermentation stage)	decreased intestinal permeability	[65]
L. casei EMRO 002, *L. casei* EMRO 213, *L. plantarum* EMRO 009, *L. fermentum* EMRO 211, *L. rhamnosus* EMRO 014, *L. bulgaricus* EMRO 212, *Rhodopseudomonas palustris* EMRO 201 (multistrain extract)	Inhibition of migration inhibitory factor tautomerase activity	[86]
L.mucosae AN1, *L. fermentum* SNR1 (encapsulated)	anti-inflammatory cytokines upregulation and pro-inflammatory cytokines downregulation	[41]

In 2021, a team of scientists reported that the membrane vesicles (MV) from lactobacilli exert anti-inflammatory therapeutic effects [87]. MV are extracellular spherical particles shed from the cell surface. They are released in the extracellular space and carry parental cell cargo such as enzymes or nuclear acids responsible for the cell's communication [88]. Additionally, the authors optimized the culture conditions with L. casei DSMZ 20011 and L. plantarum NCIMB 8826 to obtain an even more emphasized anti-inflammatory effect. MV from L. casei cultured at a pH of 6.5 with agitation resulted in the strongest interleukin-10 release and tumor necrosis factor-α reduction. Concerning the MV from L. plantarum, pH = 5 had the most visible effect on the anti-inflammatory activity [87].

Macrophage migration inhibitory factor (MIF) is a homotrimeric protein, a key cytokine responsible for the inflammation progression. This cytokine binds to the CD74 receptor promoting immune response's cascade through the activation of macrophages and T-cells. This way it triggers multiple cytokines production like TNF, IFN- γ, IL-1β, IL-2, IL-6, IL-8, NO, COX-2, PGE2 [89,90]. Nyotohadi and Kok aimed to evaluate the anti-inflammatory capacity of a multi strain extract of LAB, specifically – MIF. The multi-strain extract consisted of Lactobacillus casei EMRO 002, L. casei EMRO 213, L. plantarum EMRO 009, L. fermentum EMRO 211, L. rhamnosus EMRO 014, L. bulgaricus EMRO 212, and Rhodopseudomonas palustris EMRO 201. The team intended to study the potential

 doi:10.20944/preprints202402.0053.v1

inhibitory effect of the bacterial consortium on the MIF tautomerase activity, the reversibility, and the mechanism of inhibition. MIF tautomerase activity was inhibited with an IC50 value of 7.80 ± 1.96 mg/L. It was confirmed that the reaction is reversible [86]. MIF was also reported to inhibit glucocorticoid production which is a basic factor for the anti-inflammatory effects [91]. Therefore, MIF activity inhibition may relieve the inflammation.

Ayyanna et al. tested two probiotic strains (Lactobacillus mucosae AN1 and Lactobacillus fermentum SNR1) for anti-inflammatory capacity. Two types of experiments were conducted - with encapsulated and unencapsulated strain in rat paw tissues. The strains were in small capsules which released the contents after a prolonged period. They were administered orally. The first group revealed 85±13 % of inhibition while the latter - 77±25 %. The strains exhibited anti-inflammatory cytokines upregulation and pro-inflammatory cytokines downregulation [41].

Five strains of animal origin including Lactobacillus reuteri MG9012(YH9012), Lactobacillus fermentum MG9014(YH9014), Pediococcus pentosaceus MG9015 (YH9015), Enterococcus faecium MG9003(YH9003), Enterococcus faecium MG9007(YH9007), were evaluated for potential utilization as probiotics and anti-inflammatory effects. The investigation demonstrated that the strains exerted inhibition of NO and inhibited the expression of inducible nitric oxide synthase and cyclooxygenase [84].

In a study with milk for infant formula, it was confirmed that the anti-inflammatory properties are not related to the inactivated bacteria but to their fermentation products. In vitro and ex-vivo experiments with L. paracasei CBA L74 were carried out and it was determined that the fermentation products inhibit the pro-inflammatory cytokine secretion leaving anti-inflammatory cytokines either unaffected or even enhanced in response to Salmonella typhimurium [92].

The anti-inflammatory properties of whey fermented by Enterococcus faecalis M157 against oral cavity pathogens were estimated [93]. Bacterial pathogens cause chronic inflammation leading to periodontitis in the oral cavity, Porphyromonas gingivalis being the main causative. Lipopolysaccharides from its cell wall represent the basic virulence factor for chronic periodontitis as it was displayed to induce the production of the inflammatory mediators IL-1β, IL-6, and NO [94]. M157 strain successfully inhibited IL-1β, IL-6, and induced NO of Porphyromonas gingivalis in RAW 264.7 cells. IL-6 and IL-8 in human periodontal ligament cells were inhibited, as well [93].

4. Fungi with Anti-Inflammatory Potential

As an origin of valuable substances and biological activities, fungi are a promising bioresource employed both in functional foods production as well as in the pharmaceutical industry [95]. *Talaromyces wortmanii* is an endophytic fungi that was tested for anti-inflammatory activity against the causative of acne vulgaris – *Propionibacterium acnes*. Acne vulgaris is the most common skin complaint leading to serious psychosocial problems such as anxiety and depression. The anaerobic microbe *P. acnes* plays a role in the inflammatory phase of this condition through the activation of the pro-inflammatory mediators IL-8 via the NF-kB and mitogen–activated phosphokinase (MAPK) pathways. As known, *T. wortmanii* is a producer of bioactive compounds, thus its crude extract was studied to have the capacity to inhibit the TNF-α-induced ICAM-1 expression and *P. acnes*-induced IL-8 release. Compound C from *T. wortmanii* inhibited *P. acnes* mediated activation of NF-kB and AP-1 by means of inhibition 1 kB degradation and the phosphorylation of ERK and JNK MAP kinases, and IL- secretion in a dose-dependent manner. Two compounds were found to be anti-inflammatory substances - BB and C, with an inhibitory activity of 46 and 55 %, respectively. However, the mechanism of inhibition remains unclear [96].

A compound named Physcion (C1) was recently isolated from another endophytic fungus, Aspergillus versicolor SB5 [97]. This substance exhibited inhibitory activity against COX-2 and LOX-1 with IC_{50} values of 43.10 and 17.54 μg/mL, respectively, making it a potential anti-inflammatory agent [97]. New polyketides from Aspergillus rugulosa demonstrated anti-inflammatory activity. Asperulosin A and aspertetronin A significantly inhibited NO production with IC_{50} values of 1.49 ± 0.31 and 3.41 ± 0.85 μM, respectively. In addition, the secretion of anti-inflammatory cytokine IL10

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was evidently enhanced while the secretion of the pro-inflammatory cytokines IL6, TNF-α, IFN-γ, MCP-1, and IL12 was suppressed [98].

Several substances with anti-inflammatory properties were isolated from the endophytic fungus Colletotrichum gloeosprioides JS0419. Colletogloeopyrone A, monocillin II, and monocillin II glycoside effectively reduced NO production without cytotoxicity and inhibited the secretion of IL-6 and TNF-α. Monocillin II, and monocillin II glycoside inhibited the protein expression of NF-κB pathway, inducible NO synthase, and COX-2 while colletogloeopyrone A only inhibited COX-2 expression [99].

Phellinbaumins A and D from the fungus Phellinus baumii were found to display moderate inhibitory activity on NO production in a murine model, with IC_{50} values of 31.7 and 24.3 μM, respectively [100].

Two new ergosterol derivatives (chlamydosterols A and B) and three known with anti-inflammatory activity were isolated from another endophytic fungus - Fusarium chlamydosporum. Chlamydosterol A showed a moderate 5-LOX inhibitory capacity with IC_{50} values of 3.06 and 3.57 μM, respectively (compared to indomethacin with IC_{50} 1.13 μM) [101].

β-glucans in fungi are believed to be one of the sources of anti-inflammatory properties. β-glucans are polysaccharides, glucose polymers differing based on their length and branching structure. Several studies have demonstrated their beneficial effects towards IBD [102].

5. Marine Bacteria and Fungi with Anti-Inflammatory Properties

Ocean represents a rich source of still not fully investigated biological and chemical diversities with potential health benefits. As born in the ocean, these microorganisms are an important part of marine ecosystems. They are capable to survive and reproduce constantly in extreme conditions of low/high pressure, low temperatures, high salinity, oxygen deficiency, and darkness. Besides their ability to survive harsh conditions, marine microorganisms can form symbiotic relationships with another marine organism, adapt and evolve at the genetic level. They possess unique metabolic pathways for coping with the extreme environmental conditions. Therefore, compared to terrestrial microorganisms, marine ones are more likely to produce secondary metabolites with novel structures and high activities. They are the frontier of new drugs discovery and a large number of bioactives have been derived from them [1,103]. Marine bacteria and fungi are known to produce anti-inflammatory peptides, polyketides, and phenol-derivatives [1]. Summarize of the different strains with anti-inflammatory activities is demonstrated in Table 2.

According to the bibliography, most of the marine species with anti-inflammatory activity belong to the Aspergillus (41.4 %) and Penicillium (27.1 %) genus. These marine genera produce anti-inflammatory agents of various structure types – alkaloids, terpenoids, polyketides, peptides, etc. [104]. Preussins from Aspergillus flocculosus 16D-1, isolated from a marine sponge displayed even stronger inhibition of IL-6 expression than those of the positive control [105]. A. terreus was reported to inhibit NO due to the content of alkaloids, terpenoids, peptides, and polyketides. [106]. A. versicolor was shown to possess alkaloids which act against iNOs [107]. A. terreus CFCC 81836 and Aspergillus sp. SCSIOW2 exerted anti-inflammatory activity through NO inhibition thanks to the terpenoids (brasilanones and dihydrobipolaroxins, dihydrobipolaroxin, respectively) content [108,109]. Polyketides from A. niger SCSIO Jcsw6F30 and Aspergillus sp. SCSIO Ind09F01 acted against the COX-2 [110,111]. The peptides violaceotide A and Diketopiperazine dimer from A. violaceofuscus were found to act against the IL-10 expression with rate of inhibition 84.3% and 78.1% at 10 μM in LPS-activated THP-1 cells [112].

The alkaloids viridicaol, brevicompanines E and H, methylpenicinoline from several *Penicillium* species were the reason for NO inhibition [113–115]. Thomimarine E from *P. thomii* had activity against NO with 22.5 % inhibition rate at 10.0 μM in LPS-activated RAW264.7 cells [116]. Özkaya and co-authors reported for anti-neuroinflammatory activity of *Penicillium atrovenetum* with citreohybridonol being the active substance [117].

Several compounds with anti-inflammatory activity were illuminated in the marine-derived fungi *Penicillium glabrum* (SF-7123), namely neuchromenin, myxotrichin C, and deoxyfunicone. These

 doi:10.20944/preprints202402.0053.v1

metabolites demonstrated inhibitory activity against the overproduction of NO in LPS-stimulated BV2 microglial cells with IC_{50} values of 2.7 μM, 28.1 μM, and 10.6 μM, respectively. The excessive production of NO in LPS-stimulated RAW 264.7 macrophage cells with IC_{50} values of 4.7 μM, 41,5 μM, and 40.1 μM, respectively was inhibited, as well. Moreover, these compounds inhibited LPS-induced overproduction of prostaglandin E_2. The most active metabolite (neuchromenin) passed through a further investigation which revealed that the anti-inflammatory activity was related to the suppressive effect on the overproduction of inducible NO synthase and COX-2 enzymes. It was also established that these effects were mediated through the downregulation of inflammation-associated pathways such as those dependent on NF-kB and p38 mitogen-activated protein kinase in LPS-stimulated BV2 and RAW 264.7 cells [118].

Bacillus liquefaciens M116 was recently isolated from sediments of the south coasts of the Cuban platform. The extract obtained from its fermented broth proved to contain anti-inflammatory compounds. It inhibited acute inflammation in a Croton oil-induced atrial edema in mice. Croton oil induces the typical phases of acute inflammation. The single oral dose of M116 extract for acute inflammation reduction was 50÷200 mg/kg. Inhibition of chronic inflammation in cotton pellet-induced granuloma in Balb/c mice was achieved, as well [119]. In a study by Abdel-Wahab et al., it was suggested that the anti-inflammatory properties of other Bacillus strains are owing to the ability to inhibit the activities of the enzymes LOX and COX [120].

Melanin from marine Bacillus spp. BTCZ31 was reported to exert anti-inflammatory properties [121]. Melanins are brown complex pigments that are produced via the amino acid tyrosine and are responsible for various biological functions, such as thermoregulation, cation chelators, photoprotection, free radicals sinks, and antibiotics. In humans, besides the determination of skin color, melanin protects against UV radiation. In microorganisms, this pigment prevents from the environmental stresses. Melanins are known to possess antioxidant properties as they reduce ROS generation [122]. The reduction of ROS minimizes inflammation, as well. Kurian and co-authors established that melanin from Bacillus spp. BTCZ31 inhibited COX and LOX enzymes effectively at increasing concentrations. LOX enzyme was inhibited with an IC_{50} value of 104.34 μg/mL, while in contrast, LOX enzyme was inhibited with an IC_{50} value of 10.5 μg/mL. It was calculated that 100 μg/mL of BTCZ31 melanin inhibited COX and LOX enzymes at 47.92 and 69.48 %, respectively. Moreover, cellular nitrite levels, an NO indicator produced during inflammation reduced with the increase in melanin concentration. These results altogether prove the potential of melanin as an anti-inflammatory agent [121].

Yellow-pigmented Micrococcus sp. was demonstrated to exhibit anti-inflammatory activity. The pigment was extracted with methanol from the bacterial pellet. The conducted in vivo assays with rats resulted in higher collagen content, granulation tissue formation, and increased migration of macrophages and fibroblasts cells on the site of the wound. The anti-inflammatory properties of the extracted pigment were developed using the carrageenan-induced rat paw edema. Carrageenan-induced edema is biphasic: in the first phase serotonin and histamine are released, and in the second phase are mediated by prostaglandins, and cyclooxygenase products. The application of 10 % pigment resulted in reduced wound closure time. The results of this study show that the yellow pigment from Micrococcus is a promising option for wound healing treatment [123]. The team of Srilekha tested another marine bright yellow-pigmented bacteria identified as Brevibacterium sp. [124]. They conducted analysis of the pigment extract in vivo and it was revealed that it possesses effective anti-inflammatory properties. Microbial pigments are a scientific target as they are natural, safe, they are characterized by medicinal properties, vitamin composition, production independent of the season and geographical conditions, controllable and predictable yield. Furthermore, natural colorants are believed to be non-toxic, non-carcinogenic, and biodegradable [125].

Eurotium amstelodami was isolated from marine materials. The anti-inflammatory assays with its broth and its mycelium extracts resulted in an inhibition of NO production in LPS-stimulated RAW 264.7 cells without cytotoxicity. Further, several components were extracted including asperflavin, neoechinulin A and preechinulin. Asperflavin markedly inhibited LPS-induced NO and

 doi:10.20944/preprints202402.0053.v1

PGE2 production in a dose-dependent manner. Asperflavin inhibited the production of TNF-α, IL-1β, and IL-6 as well [126].

Various marine microorganisms synthesize fatty acids. Fatty acids can be separated into two major groups – saturated and unsaturated. Unsaturated fatty acids can be mono-, di- and polyunsaturated fatty acids (PUFA). Omega 3 (n-3) and omega 6 (n-6) are examples of PUFA with pronounced anti-inflammatory activity [127]. However, the human organism is incapable of synthesizing them. Their function to regulate inflammation is very important. The polyunsaturated fatty acids (PUFA) omrga 6 like arachidonic acid (ARA) promote inflammation while omega 3 fatty acids like eicosapentaenoic (EPA) and docosahexaenoic (DHA) acid exhibit anti-inflammatory properties. Omega 3 fatty acids suppress inflammation through different pathways. On one side, they inhibit omega-6 fatty acids-derived pro-inflammatory eicosanoids (prostaglandin E, leucotriene B4) formation. On the other side, omega 3 can create diverse potent anti-inflammatory lipid mediators (such as resolvins and protectins) [127]. EPA is associated with important physiological functions including the cardiovascular system and blood pressure, it cleanses the arteries, diabetes, treats atherosclerosis, and suppresses the inflammatory systems. ARA is the most important PUFA for normal brain function. Both EPA and ARA were reported to be produced by the red marine microalgae Porphyridium sp. Porphyridium possess GRAS status. [128]. In a recent paper high amounts of ARA from Porphyridium cruentum were reported [129]. Microalgae are an important constituent of the human diet for their nutritional value and the rich protein content which is higher than the protein content of some vegetables [130].

Table 2. Marine microbes with anti-inflammatory properties.

Strain	Activity	Reference
A. flocculosus 16D-1	inhibition of IL-6 expression	[105]
A.terreus	NO inhibition	[106]
A. terreus CFCC 81836	NO inhibition	[108]
A.versicolor	possession of alkaloids which act against iNOs	[107]
Aspergillus sp. SCSIOW2	NO inhibition	[109]
A. niger SCSIO Jcsw6F30	act against the COX-2	[110]
Aspergillus sp. SCSIO Ind09F01	act against the COX-2	[111]
A. violaceofuscus	act against the IL-10 expression	[112]
P.thomii	NO inhibition	[116]
Penicillium atrovenetum	possession of anti-neuroinflammatory meroterpenoid citreohybridonol	[117]
Penicillium glabrum (SF-7123)	NO inhibition	[118]
Bacillus liquefaciens M116	granuloma reduction	[119]
Bacillus sp.	inhibition the activities of LOX and COX enzymes	[120]
Bacillus spp. BTCZ31	melanin production; COX and LOX inhibition	[121]
Micrococcus sp.	produces yellow pigment reducing the wound closure period	[123]
Brevibacterium sp.	anti-inflammatory activity comparable to diclofenac	[124]
Eurotium amstelodami	produces asperflavin; inhibition of LPS-induced NO, PGE2, TNF-α, IL-1β, and IL-6 production;	[126]
Vibrio cyclitrophicus	EPA production	[131]
Cellulophaga	EPA and DHA production	[132]
Pibocella	EPA and DHA production	[132]
Porphyridium sp.	ARA production	[128]
Streptomyces specialis	inhibition of mRNA expression of iNOs and IL-6	[133]

EPA was shown to be produced by the marine bacteria Vibrio cyclitrophicus [131]. Producers of EPA and DHA are reported among the strains of Cellulophaga and Pibocella [132].

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Marine actinomycete Streptomyces are known to produce a wide range of secondary metabolites with potent biological activities [133]. The team of Shin isolated from Streptomyces specialis four new streptoglycerides E-H (1-4) with a rare 6/5/5/-membered ring system. All of the compounds displayed moderate anti-inflammatory effect with IC_{50} values in the range of 3.5 – 10.9 μM. The analysis showed that compound 2 inhibited the mRNA expression of iNOs and IL-6 in RAW 264.7 cells without cytotoxicity observed. NO_2^- accumulation was used as a criterion for NO production in media [134]. These streptoglycerides are promising bioactives with good anti-inflammatory activity with potential for further studies for their therapeutic use.

6. Conclusions

Inflammation is responsible for a broad spectrum of pathophysiological dispositions ranging from acute and chronic infections and cancer to autoimmune-based conditions such as those in the gastrointestinal tract. Targeting the reduction of chronic inflammation to normal levels is key to striving with associated diseases. Although the medicines that are applied in these cases (steroidal and non-steroidal drugs) suppress inflammation, they are not a good alternative in the long term due to the side effects associated with their use (liver and kidney dysfunction, intestinal problems, disorders in the cardiovascular and endocrine systems, etc.).

Nature provides unlimited sources of pharmaceutical agents. The employment of beneficial microorganisms has repeatedly proven its merits in various socially significant diseases. A plethora of microbes with anti-inflammatory effects between bacteria, yeast, and fungi living in different habitats have been reported in recent years. These microorganisms produce specific metabolites which suppress cytokines over-production and/or continuous secretion of pro-inflammatory cytokines, thus providing anti-inflammatory effect. Most of them are found in the lactobacilli family or consortia with them. As a form of adjuvant therapy, probiotic microorganisms are used to alleviate patients' symptoms, and promising effects in the case of inflammatory diseases have been shown. The probiotics are characterized by a limited number of side effects which is contributed by their pleiotropic immune modulatory behavior. They are commonly included in functional foods due to their GRAS status and diverse benefits for human health.

On the other hand, marine microorganisms are another valuable renewable resource with proven bioactive characteristics including anti-inflammatory properties. Given their ability to survive under extreme conditions, they are expected to synthesize a wide variety of substances with incomparable chemical diversity and drug-like effects. Among the marine microbes with reported anti-inflammatory properties, the greatest contribution was made by members of the *Aspergillus* and *Penicillium* fungus.

Counteracting chronic inflammation through natural drug sources is characterized by multiple advantages, including their renewable and inexhaustible nature, the fact that they are non- or low-toxic, and the lack of side effects. The production of metabolites with anti-inflammatory properties could be enhanced by varying the culture conditions. Although a significant body of knowledge has been accumulated, regarding the unexpendable variety of microorganisms in nature, still a large number of representatives with anti-inflammatory properties has not been fully recognized and appreciated. The opportunity to discover and utilize new drug sources and to optimize their isolation and purification still lies in front of researchers.

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