Unlocking Nature's Treasure Trove: Exploring Microorganisms for Novel Bioactives

Tasbir Amin[1], Abu Bakar Karim[1], Israk Iram Oyshe[1], Amana Hossain[1], Tafsir karim[1], Jinath Sultana Jime[1], Nayeema Bulbul[1], Md. Asaduzzaman Shishir[2], Ashrafus Safa[3], Md. Fakruddin[1]*

Abstract

From the marine environment to plants and animals, microorganisms are everywhere. Microbes happen to be a very prominent resource of metabolites and bioactive compounds and in recent times, many therapeutic compounds have been discovered from microbial sources. This review provides an in-depth exploration into the world of microorganisms as a treasure trove of novel bioactives. Different groups of microbes contain unique metabolites and bioactive that might have the potential as therapeutic agents. So, it is very important to screen microbial metabolites to identify, isolate and characterize for potential therapeutic applications. Microbial metabolites are very advantageous in terms of large-scale production and purity of final products. Considering these advantages, research focusing on screening potential microbial bioactive is a very time demanding one. This comprehensive review aims to inspire researchers and stakeholders to further explore and unlock the vast potential of microorganisms for the discovery and development of innovative bioactive compounds.

Keywords: Microorganisms, Bacteria, Biologics, Therapeutics, Bioactives, Metabolites

Significance | The therapeutics benefit of natural compounds from microorganisms in cancer and other diseases.

*Correspondence: Md. Fakruddin, PhD, Assistant Professor, Department of Biochemistry & Microbiology, North South University, Dhaka, Bangladesh., Email- md.fakruddin@northsouth.edu

Editor Shamsuddin Sultan Khan. And accepted by the Editorial Board Oct 3, 2023 (received for review Aug 23, 2023)

Introduction

Microorganisms are living in almost all the conceivable places across the globe even with the environment being extreme. For more than thousand years, human beings have been using bacteria, molds, yeasts for the production of foods including vinegar, bread, cheese, wine, beer and yoghurt alongside fermented vegetable, meat and fish (Kharatyan, 1978; Xiang et al., 2019). Furthermore, Microorganisms not only cause diseases to living things, but they are also responsible for several positive aspects in the production of secondary metabolites (Bentley, 1997), industrially important compounds (Beshkova & Frengova, 2012), agriculture (Kalsoom et al., 2020) as well as nanotechnology (Bhattacharya & Gupta, 2005). With the usage of biotechnology, it has now become much more possible and easier to make use of the wide variety of microbes (Vitorino & Bessa, 2017). It includes different species of bacteria, fungi, and virus in the fields of food, pharmaceutical and several agriculture aspects (Kalsoom et al., 2020). It is needless to mention that the diversity of the microbes is very enormous. Among them, only a few proportions of fungi and bacteria have been cultured and effectively examined for secondary metabolites production of different type (Hawksworth, 2001).

Secondary metabolites can be described as the components that are only present in the restricted taxonomic groups alone (Bentley, 1997; Singh et al., 2019). Secondary metabolites mainly serve as one of the major competitive weapons which have been used to fight against bacteria, insects, fungi, plants, amoebae, and even other larger animals (Demain & Fang, 2000). Microbial secondary

Author Affiliation:
[1]Department of Biochemistry & Microbiology, North South University, Bashundhara, Dhaka, Bangladesh.
[2]Department of Microbiology, Primeasia University, Banani, Dhaka, Bangladesh.
[3]Department of Life Sciences, School of Environment and Life Sciences, Independent University, Bangladesh.

Please cite this article:
Tasbir Amin, Abu Bakar Karim, Israk Iram Oyshe, Amana Hossain et al., (2023), Unlocking Nature's Treasure Trove: Exploring Microorganisms for Novel Bioactives, Journal of Angiotherapy, 7(1), 1-8

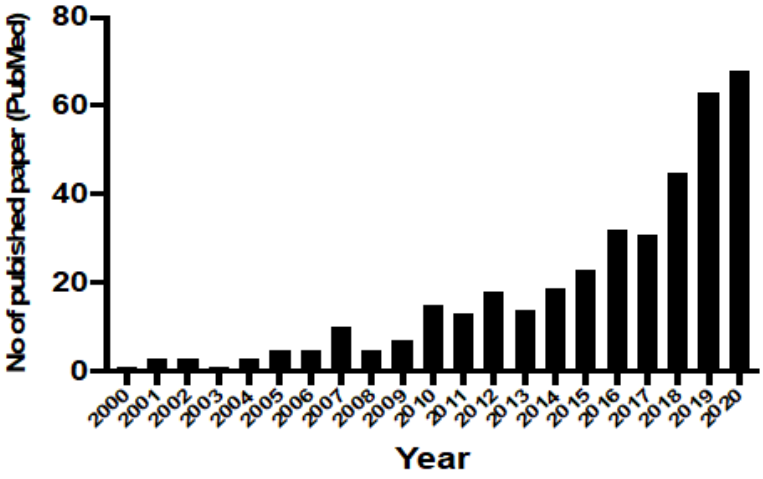

Figure 1. Trend of publication related to microbial derived bioactives

Table 1. Examples of some novel bioactives from microbial sources

Serial no.	Organisms	Bioactive	Biological Properties								Ref.
			Antibacterial	Antifungal	Cytotoxic	Immunosuppressive	Antitumor/Anticancer	Anti-Inflammatory	Anti-Oxidant	Immune Modulation	
1	*Streptomyces* spp.	Bagremycin A and B Bagremycins F and G Aranciamycin K Isotirandamycin B Mithramycin SK, Mithramycin SA, Demycarosyl-mithramycin SK, 3-methylcarbazoles Blanchaquinone Misamycin	√	√	√	-	√	√	-	-	Bertasso et al., 2001 Zhang et al., 2018 Cong et al., 2018 Núñez et al., 2012 Singh et al., 2017 Clark et al., 2004 Li et al., 2014
2	*Penicillium* spp.	Penicacids E–G Penisclerotiorin, Diaporthein C, Penidepsidone A Sesquiterpenoids and Isocoumarins	√	√	-	√	√	√	-	-	Chen et al., 2020 Zhao et al., 2020 Ma et al., 2020
3	*Bacillus* spp.	Bacillistatins Iso-C16 fengycin B, and anteiso-C17 fengycin B Bacillistatins 1 & 2 Lipopeptidolactone Mixirin A-C, Halobacillin	√	√	-	-	√	-	-	-	Komal, 2021 Ashu et al., 2019 Komal, 2021 Kai et al., 2013 Ashu et al., 2019
4	*Ascochyta* sp.	Ascochytatin	√	-	√	-	√	-	-	-	Kanoh et al., 2008
5	*Geitlerinema* sp.	Ankaraholide A	-	-	-	-	√	-	-	-	Ashu et al., 2019
6	*Amphidinium carterae*	Amphidinol 22	-	√	√	-	-	-	-	-	Ameen et al., 2021
7	*Decaisnella thyridioides*	Spirodioxynaphthalenes	√	√	-	-	√	-	-	-	Jiao et al., 2006
8	*Rhizopycnis vagum*	Dibenzo-α-pyrone	-	-	√	-	-	-	√	-	Lai et al., 2016
9	Lactic Acid Bacteria	Bioactive Peptides	-	-	-	-	-	-	√	√	Venegas-Ortega et al., 2019
10	*Aerococcus uriaeequi*	Exopolysaccharide	-	-	-	-	-	-	√	-	Ameen et al., 2021

metabolites including growth hormones, antibiotics, antitumor agents, and pigments are proven not to be essential in terms of the development and maintenance of the microorganism. Rather, these secondary metabolites have demonstrated a substantial potential for different aspects of both human and animal health (Ruiz et al., 2010).

With the rise of antibiotic resistance, alternatives of antibacterial compounds have been engineered. These alterative compounds (peptides) are called the Bacteriocin. These compounds are prepared from microbes and the majority of them are bacteria-derived (Delves-Broughton et al., 1996). Colicins is among the frequently researched bacteriocins which is produced by *E.coli* (Cramer et al., 1995). Furthermore, microorganisms have also proven their efficiency in producing both the water and the fat-soluble vitamins (Mahdinia et al., 2016).

Bioactives (Biologics & Therapeutics)

The term bioactive could be addressed as the alternative term for biologically active (Cammack et al., 2006). Plants, fungi, mammals, and microbes produce bioactive compounds through both primary and secondary metabolism (Demain & Sanchez, 2009). Apart from microbes and plants, bioactive compounds can also be found in mushrooms (Wang et al., 2020), marine sponges (Laport et al., 2009) as well as fishes of different species (Bougatef et al., 2010). Bioactive components include carotenoids, vitamins, organic acids, phytosterols, polyphenols etc. and have shown the ability to prevent chronic diseases (Kamiloglu et al., 2021). Many of these biologics have demonstrated antimicrobial potential (Wang et al., 2020; Bougatef et al., 2010), antioxidant activities (Bougatef et al., 2010), antiviral activities (Laport et al., 2009) as well as a potential therapeutic effect on hypertension, cancer, gastrointestinal diseases, and asthma (Bakal et al., 2017).

Back in 1928, Alexander Fleming's remarkable discovery of penicillin from *Penicillium notatum* was hailed as a potential shift from plants to microorganisms as a feasible source of useful bioactive (Gaynes, 2017). After identifying the antibacterial properties of penicillin, several antibiotics have been discovered mostly produced by the soil species of *Streptomyces* as well as molds (Běhal, 2000). Around 77% of the antibiotics that have given approval by the FDA since 2000 are proven to be derived from different natural products and bioactive of the microbes (Patridge et al., 2016). An extensive research is being carried out to on natural products, nature-inspired molecule, semi-synthetic natural products which have been showing thriving importance in health and medicine approved by the FDA (Cragg & Newman, 2013), food industry, agrochemicals as well as cosmetics (Guaadaoui et al., 2014).

More than 250,000 metabolites from different organisms were proven to have diverse bioactive properties (Bérdy, 2005). In the 21st century, rigorous studies have been conducted on bioactivity because of their potential application in a wide range of areas including modern pharmacology, geo-medicine, food industry, plant science, agrochemicals as well as cosmetics (Guaadaoui et al., 2014). Due to an increase in the frequency of many diseases such as neurological pathology, cancer, and the present antibiotics' decreasing efficacy, it has become important to identify new drugs (Romano et al., 2017). The below section would discuss in detail regarding different bioactives derived from microbes and their important roles.

Microbes as source of novel bioactives

In this review, we aim to summarize potential bioactives derived from microorganisms. To achieve the goal in a better systematic way, we have selected 50 (fifty) research article (keyword- microbe source bioactive therapeutics biologics) published between 2000-2020 (a list of all selected paper has been compiled in the supplementary file). We also analyzed the trend of paper published in this field in PubMed and we noticed a gradual increase in the number of papers published from 2000-2020 (Figure-1). This observation indicates growing attention of research communities towards microbial bioactives.

Microbes' antibiotic, antifungal, anticancer, immunosuppressive, anti-inflammatory, biofilm inhibitory, and other biological capabilities all have implications for human health. In the following section of this review, we are summarizing novel bioactives from microbial sources with different properties.

Antibacterial Agents

Among the different therapeutic properties, most of the microbe derived bioactives reported is those with antibiotic properties. Researchers isolated antibacterial bioactive Bagremycin A and B; which have been derived from *Streptomyces* sp. Tii 4128 (Bertasso et al., 2001) and Bagremycins F and G from *Streptomyces* sp. ZZ745 (Zhang et al., 2018). SCSIO 41399, a marine-derived *Streptomyces* sp., produced Aranciamycin K and Isotirandamycin B with antibacterial activity (Cong et al., 2018). Many fungal species can also produce bioactives with antibacterial properties. *Penicillium parvum* HDN17-478 is one such fungus from which three mycophenolic acids (Penicacids E–G) derivate with antibacterial activity was isolated (Chen et al., 2020). Examples of such novel antibacterial bioactives include Andrimid and moiramide from Vibrio spp. (Silvers et al., 2016), Tauramamide from *Brevibacillus laterosporus* (Desjardine et al., 2007), Bacillistatins (novel cyclodepsipeptides) from *Bacillus silvestris* (Pettit et al., 2009), Thiopeptide TP-1161 from *Nocardiopsis* sp. (Engelhardt et al., 2010), Unnarmicins C and A from *Photobacterium sp.* strain MBIC06485, a marine bacterium (Oku et al., 2008), Holomycin from *Photobacterium halotolerans* (Komal, 2021), Ayamycin from *Nocardia sp.* (El-Gendy et al., 2008), Ascochytatin (a novel spirodioxynaphthalene metabolite) from a marine-derived fungus, Ascochyta sp. NGB4 (Kanoh et al.,

2008), misamycin (a novel anthracycline) from *Streptomyces* species (Li et al., 2014), Decaspirones A-E from *Decaisnella thyridioides*, a freshwater aquatic fungus species (Jiao et al., 2006). Antibacterial bioactives have also been identified from *Bacillus subtilis*, *Ralstonia solanacearum*, *Agrobacterium tumefaciens*, *Pseudomonas lachrymans*, *Staphylococcus hemolyticus,* and *Xanthomonas vesicatoria* (Ma et al., 2020).

Antifungal Agents

KB425796-A; a novel antifungal macrocyclic lipopeptidolactone had been isolated from *Paenibacillus* 530603 fermentation broth (Kai et al., 2013). From the fermentation broth of a fungal strain No. 14573, both FR220897 and FR220899 (antifungal lipopeptides) have been recovered. Based on physiological and morphological characteristics, this strain had been identified *as Coleophoma empetri* No. 14573. Antifungal activity of FR220897 and FR220899 against *Aspergillus fumigatus* and *Candida albicans* was related to suppression of 1,3-b-glucan production (Kanasaki et al., 2006). Bagremycin A and B; two novel secondary metabolites with antifungal activity, were discovered in the culture filtrate of Streptomyces sp. Tii 4128 (Bertasso et al., 2001). Decaspirones A–E, five novel components associated with palmarumycins, had been discovered from cultures of *Decaisnella thyridioides*. These compounds demonstrated potential antifungal activity against*Aspergillus flavus* and *Candida albicans* (Jiao et al., 2006).

Cytotoxic Agents

The endophytic fungus called *Rhizopycnis vagum* Nitaf22 had been isolated from *Nicotiana tabacum* produces novel dibenzo-α-pyrones (rhizopycnolides A and B, and rhizopycnins A and D, as well as eight recognized congeners) with antibacterial, antifungal as well as potent cytotoxic properties as assessed against human cancer cell lines (HepG2, HCT-116, NCI-H165, BGC-823) (Lai et al., 2016). Misamycin is a novel anthracycline discovered in endophytic *Streptomyces sp*. YIM66403. Misamycin demonstrated modest cytotoxicity against human promyelocytic leukemia HL-60, non-small cell lung cancer A-549, breast cancer MCF-7, human hepatoma SMMC-7721, and human colorectal carcinoma SW4801 cell lines as well (Li et al., 2014). A screening study centered on the bacterial two-component regulatory system discovered Ascochytatin, a novel spirodioxynaphthalene metabolite generated by the marine-derived fungus *Ascochyta sp.* NGB4. Ascochytatin's cytotoxicity was confirmed against mammalian cancer cells such as A549 and Jurkat cells (Kanoh et al., 2008). Aranciamycin K and isotirandamycin B, were obtained from a marine-derived Streptomyces sp. SCSIO 41399. Both of them showed moderate in vitro cytotoxic activity against the K562 cell lines (Cong et al., 2018).

Antitumor/Anticancer agents

Endophytes generate a variety of bioactive compounds that have been discovered as potential anti-cancer drugs (Firáková et al. 2007). EML-CAP3, an endophytic bacterial strain derived from the leaves of *C. annuum* L, can produce lipophilic peptides with significant anti-angiogenic action (Jung et al. 2014). *Bacillus* provides the first anti-tumor EPS, a natural substance with significant therapeutic efficacy for treating cancer (Chen et al. 2013). Endophytic *B. licheniformis*, *B. pseudomycoides*, and *Paenibacillus denitriformis* showed the ability to produce L-asparaginase, which catalyzes the conversion of L-asparagine, required for several cancer cells, such as lymphoblasts, to function (Joshi & Kulkarni 2016). *Streptomyces argillaceus* was found to produce novel bioactives including Mithramycin SK, Mithramycin SA, Demycarosyl-mithramycin SK which showed anti-tumor activity against colon carcinoma (CCL HT29), melanoma (MEXF 514L), Lung carcinoma (LXFA 526L), breast carcinoma (MACL, MCF-7), kidney tumor (PRCL PC3M, and RXF 631L) cell lines (Maskey et al., 2003). Many other anti-cancer & anti-tumor bioactives from microbial sources had been reported such as Chandrananimycin A-C produced by *Actinomadura sp.,* Iso-C16 fengycin B and anteiso-C17 fengycin B produced by *Bacillus mojavensis*, Mixirin A-C produced by *Bacillus* spp., Halobacillin produced by marine *Bacillus* (Trischman et al., 1994), Dermacozine F and G produced by *Dermacoccus abyssi*, Ankaraholide A produced by Geitlerinema *sp.*, Nisin A produced by *Lactococcus lactis* (Ashu et al., 2019).

The marine fungus *Hansfordia sinuosae* produces a polysaccharide with anti-tumoral activity on human cervical cancer (HeLa cells) as well as breast cancer (MCF-7) cells (Li et al. 2018). Asperphenin A, derived from *Aspergillus sp.* demonstrated anti-tumoral action in human colon cancer cells (Bae et al. 2020).

Anti-inflammatory Agents

Endophytic *Streptomyces species* LJK109 that has been isolated from the root of Alpinia galangal is reported to produce 3-methylcarbazoles, exhibiting a significant anti-inflammatory property while inhibiting the production of different inflammatory mediators including IL-1b, TNF-a IL-6, PGE2 and IL-10 by macrophages (Taechowisan et al. 2012). The fungus *Penicillium sclerotiorum* GZU-XW03–2 produced two new components including penisclerotiorin A and diaporthein C, alongside a novel natural product called penidepsidone A with anti-inflammatory properties demonstrated against lipopolysaccharide-induced microglial cells (Zhao et al., 2020).

Antioxidant Agents

An exopolysaccharide with antioxidant property was discovered from *Aerococcus uriaeequi* (marine bacterium) and according to a study on mouse models, it was proven to be safe for both the oral and topical use (Ameen et al., 2021). Methanolic extract derived from *Novosphingobium sp.* PP1Y has also showed

potent antioxidant activities in both human cells and in vivo (Petruk et al., 2018). Furthermore, different bioactive peptides derived from a wide variety of lactic acid bacteria have also showed antioxidant activity along with opioids, immune modulators, angiotensin-converting enzyme inhibitors, antithrombotic, mineral binding, antimicrobial, and cyto-modulatory activities (Hayes et al., 2007; Aluko, 2012).

Future prospect of microbial bioactives

Research related to drug discovery has got substantial attention due to several factors such as greater insight associated with the underlying factors related to the development and progression of a disease, emergence of resistant strains or cell types, molecular understanding of the physiology of infectious agents or cells, etc. Among the different sources of potential novel drugs and therapeutics, microorganisms outcompete other sources in terms of diversity of bioactive and therapeutics, ease of characterization, and industrial production. Out of 12,000 antibiotics discovered within the 1950s, around 22% were filamentous fungi (Strohl, 1997). Apart from that, around 90% of the antibiotics used practically have been derived from actinomycetes being the major natural producers of antibiotics (Hamaki et al., 2005). These data indicate the contribution of microorganisms in drug discovery and their potential to produce much more bioactive in the future.

Apart from the primary source of antibiotics, microorganisms are acknowledged to be a promising source of many therapeutics with exciting potential to treat many other human diseases such as cancer (Kanoh et al., 2008), leukemia (Singh et al., 2017), gut repair (Shanahan, 2000), neurologic disorders (De Silva et al., 2013), etc. One classic example of such microbial biologic is Lovastatin (previously named Mevacor), produced by *Aspergillus terreus*. In 1987, Lovastatin got its approval by the FDA as a drug to reduce total cholesterol levels in the blood (Demain, 2013). Many other such microbe-derived biologics have already entered clinical trials worldwide. Potential anticancer agents derived from marine bacteria such as Synthadontin (ILX-651) and Tasidontin entered phase II, whereas Sobidontin (TZF 1027) entered Phase III clinical trial (Mayer & Hamann, 2002). Another anticancer agent named thiocoraline (isolated from *Micromonospora marina*, an Actinomycete) is undergoing preclinical evaluation as of now (Newman & Cragg, 2004). Salinosporamide A, an irreversible proteasome inhibitor from Marine actinomycetes, *Salinospora tropica*, showed the substantial cytotoxic property and entered phase I clinical trial (Feling et al., 2003). One of the secondary metabolites from *Aspergillus fumigatus*, known as Fumagillin, has anti-angiogenesis properties, one of the four ways to treat cancer, and soon will enter clinical trial (Demain, 2014). Preclinical evaluation is undergoing Tubulysin, isolated from Myxobacteria (Kaur et al., 2006), demonstrating anticancer properties.

Such microbe-derived biologics targeting many other communicable and non-communicable diseases are in a clinical trial currently or will enter the clinical trial soon. It is expected that some of these potential therapeutics will soon be approved by regulatory bodies and will bring a paradigm shift in the treatment of difficult to treat diseases and will contribute immensely to the improvement of quality of life globally.

Conclusion

In this review paper, we dove into another world of microbes and uncover how fascinating their abilities are. The discussion was focused on bioactive compounds produced by different microorganisms. In the 21st century, with countless medical complications, health complexities, and lack of food production, the study on microbial properties has been taken to the next step, unveiling jaw-dropping discovery of how these tiny organisms can contribute to health pharmacy, agriculture, food production, and industry. Sir Alexander Fleming's discovery of penicillin was aided by microbial bioactive molecules, which sped up the entire drug discovery process. However, the mesmerizing story of microbes does not end here. They have been successfully administered in lieu of ineffective antibiotics increasing the possibility to cure any bacterial infection. Countless antibiotics have been derived from natural products and microbial bioactive. Others have demonstrated antimicrobial, antitumor, anticancer, and antioxidant properties and stand their ground in preventing chronic diseases in humans. Many of these bioactive is already in several phages of the clinical trials giving hope to the life scientists in an effective discovery of drugs and therapeutics. Even drugs having the bioactive components in its composition have proven to be effective in treating any particular disease where traditional methods are not effective. The ongoing and future research on microbial bioactive and their potential impact could bring a revolutionary change in healthcare.

Author Contributions

MF conceived the idea and prepared the outline of the review. TA, ABK, IIO, AH, JSJ, NB, MA and AS performed the literature search and data extraction, analysis of extracted data and manuscript preparation. MF supervised the manuscript preparation and prepared the final draft. All authors read and accepted the final version of the manuscript.

Acknowledgment

None declared

Competing financial interests

The authors have no conflict of interest.

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