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MINI-REVIEW

Therapeutic applications and biological activities of bacterial bioactive extracts

Zainab Abdelghani[1] · Nancy Hourani[2] · Zahraa Zaidan[1] · Ghassan Dbaibo[2,3] · Marguerite Mrad[2,3] · Rouba Hage-Sleiman[1]

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Abstract

Bacteria are rich in a wide variety of secondary metabolites, such as pigments, alkaloids, antibiotics, and others. These bioactive microbial products serve a great application in human and animal health. Their molecular diversity allows these natural products to possess several therapeutic attributes and biological functions. That's why the current natural drug industry focuses on uncovering all the possible ailments and diseases that could be combated by bacterial extracts and their secondary metabolites. In this paper, we review the major utilizations of bacterial natural products for the treatment of cancer, inflammatory diseases, allergies, autoimmune diseases, infections and other diseases that threaten public health. We also elaborate on the identified biological activities of bacterial secondary metabolites including antibacterial, antifungal, antiviral and antioxidant activities all of which are essential nowadays with the emergence of drug-resistant microbial pathogens. Throughout this review, we discuss the possible mechanisms of actions in which bacterial-derived biologically active molecular entities could possess healing properties to inspire the development of new therapeutic agents in academia and industry.

Keywords Secondary metabolites · Bacterial extracts · Anti-cancer · Immunomodulation · Antibacterial · Antifungal · Antiviral · Antioxidant

Introduction

Secondary metabolites originate as natural products from a variety of sources, including terrestrial plants, animals, marine organisms, terrestrial vertebrates and invertebrates, and microorganisms (Chin et al. 2006). These molecules are structurally and chemically diverse and act as a remarkable class of therapeutics to heal a myriad of diseases. The earliest natural products found to improve human health were first described in ancient Mesopotamia from 2900 to 2600 BCE (Siddiqui et al. 2014). Given the historical successes of natural products, large pharmaceutical companies invested in this traditional domain (Maher 2020) and approximately 60% of small-molecule approved drugs are related to natural products (Patridge et al. 2016).

In 1928, Alexander Fleming discovered penicillin from *Penicillium chrysogenum* previously known as *Penicillium notatum* which marked the significant shift from plants to microorganisms as a source of natural products (Gaynes 2017). Since then, the utilization of microorganism-derived compounds has spread in medicine, agriculture, the food industry and scientific research (Choi and Oh 2015). Nowadays, the chemical and biological tools allowed scientists to uncover the biological effects of natural compounds on the human body, as well as to apply possible synergies, which help in developing new therapies (Ji et al. 2009). Natural compounds have been investigated for their pharmacological potency, safety and ability to alleviate the symptoms of many diseases by modulating immune system effector cells and

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✉ Marguerite Mrad
mm220@aub.edu.lb

✉ Rouba Hage-Sleiman
rouba.hagesleiman@ul.edu.lb

[1] Department of Biology, Faculty of Sciences, Lebanese University, Hadath, Lebanon

[2] Department of Biochemistry and Molecular Genetics, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

[3] Department of Pediatrics and Adolescent Medicine, Center for Infectious Diseases Research, Faculty of Medicine, American University of Beirut, Beirut, Lebanon

molecules (Mok et al. 2020). Since many anti-cancer drugs showed nonspecific toxicity against normal cells (Yingchoncharoen et al. 2016), ongoing researches aim to discover selective anti-cancer treatments with minimal undesired side effects (Cragg et al. 2009; Pucci et al. 2019).

Herein, we summarize the biological activities and applications of a variety of bacterial extracts and their secondary metabolites and review the mechanisms of action behind their therapeutic effects. We cover past and current studies that describe the use of these biological products in treating cancer, inflammatory diseases, allergies, autoimmune diseases, infections and others. In addition, we discuss the antibacterial, antifungal, antiviral and antioxidant activities of some natural products. Our aim is to highlight the role of bacterial extracts and their identified secondary metabolites in the modern drug industry and their importance as potential therapeutic agents.

Anti-cancer activity of bacterial extracts

Cancer is the most significant cause of death worldwide (Siegel et al. 2020). In 2018, 9.6 million people were estimated to have died from different types of cancer (Dube et al. 2019). This number is expected to continue rising to 13.1 million deaths in 2030 (Lichtman 2013). Cancer is characterized by an uncontrolled and deregulated cell growth, immortalization, invasion, angiogenesis and metastasis (Chang et al. 2011). Cancer can be treated with surgery, traditional chemotherapy, radiation therapy and immunotherapy. Since many cancers cells, not particularly tumors developed resistance to apoptosis-inducing treatments (Lalitha et al. 2016), the search for natural products from plants, animals and microorganisms have been investigated over the past decades for cancer prevention, therapy and minimization of cancer prevalence (Tan et al. 2019). Microorganisms, especially those living under harsh conditions, were found to be potent and valuable reservoirs of natural anti-cancer metabolites due to their novel and distinctive compounds (Safarpour et al. 2019). A total of 70% of microbial secondary compounds are produced by Actinomycetes, 7% by Bacillus and 1–2% by other bacteria (Khalifa et al. 2019). The anti-cancer compounds derived from microorganisms are summarized in Table 1.

Actinomycetes

Actinomycetes are filamentous gram-positive bacteria that belong to the phylum Actinobacteria known for its high genomic and metabolic diversity (Sudha and Masilamani 2012). Actinomycetes are the most promising source of anti-cancer chemotherapeutics and they account for approximately 45% of all secondary metabolites, 80% of which are produced by the largest known genus of Actinobacteria, Streptomyces (Dhaneesha et al. 2017). Actinomycetes-derived anti-cancer drugs include anthracyclines (aclarubicin, daunomycin and doxorubicin), peptides (bleomycin and actinomycin D), aureolic acids (mithramycin), enediynes (neocarzinostatin), antimetabolites (pentostatin), carzinophilin, mitomycins and others (Krishnan et al. 2014).

Bleomycin produced by *Streptoalloteichus hindustanus* has been used for its potential therapeutic activity against different types of cancer including testicular cancer, ovarian cancer, Hodgkin's lymphoma (Demain and Vaishnav 2011). It acts by inducing DNA strand breaks, and some studies suggest that bleomycin also inhibits the incorporation of thymidine into DNA strands (Hecht 2000). Moreover, a diterpenoid derivative was extracted from Actinobacteria isolated from Chinese mangrove soil of Zhangzhou, *Micromonospora zhangzhouensis* HM134 and showed in vitro anti-proliferative activity against liver cancer HepG2, colon cancer HCT-116 and lung cancer A549 cells (Fu et al. 2020). A cyclic peptide antibiotic, urukthapelstatin A, isolated from *Merchercharimyces asporophorigenes* YM11-542 was found to inhibit the growth of A549 cells and exert cytotoxicity against multiple cancer cell lines (Matsuo et al. 2007). In addition, thiocoraline, a depsipeptide derived from *Micromonospora marina*, inhibited the synthesis of RNA in murine leukemia P388, lung cancer A549 and murine erythroleukemia MEL cell lines (Romero et al. 1997) and induced cell cycle arrest at G1 phase in LOVO and SW620 colon cancer cell lines (Erba et al. 1999).

Several studies have focused on the therapeutic activity of trehalose, a disaccharide isolated from a variety of organisms, in cancer and neurodegenerative diseases. In fact, trehalose was found to induce autophagy in primary keratinocytes and in HaCaT human keratinocyte cell line independently of mTOR inhibition (Chen et al. 2016)**.** It also interfered with the assembly of the dysregulated RNA-binding protein complex (stress granules) through enhancing the phosphorylation of the α subunit of eukaryotic initiation factor 2 (eIF2), which prevents abnormal protein translation and aggregation in neurodegenerative diseases like amyotrophic lateral sclerosis (ALS) (Mazroui et al. 2006). On the other hand, trehalose enhanced post-stress p-eIF2α dephosphorylation and restoration of the polysome translation allowing stress recovery (Dimasi et al. 2017). Enzyme-stable trehalose analogs lentztrehaloses A, B and C were isolated from the Actinomycete strain *Lentzea* sp. ML457-mF8 and demonstrated an autophagic activity in human melanoma and ovarian cancer cells with an improved bioavailability compared to trehalose. They also showed potential activity against neurodegenerative diseases and other autophagy-related diseases, such as diabetes, arteriosclerosis and heart diseases (Wada et al. 2015).

Table 1 List of microbial-derived natural products with anti-cancer activities

Anti-cancer compound	Origin	Activity/mechanism	Cancer types or cell lines	References
Actinomycin D	*Streptomyces* sp. ZZ338	Targeting glycolysis, glutaminolysis and lipogenesis	Glioma cell lines	Zhang et al. (2016)
BAEPS exopolysaccharide	*Bacillus amyloliquefaciens* 3MS 2017	Inhibition of COX-2, aromatase, Na^+/K^+ ATPase, and estrogen production	MCF-7 cells	Ibrahim et al. (2020)
Bleomycin	*Streptoalloteichus hindustanus*	Induction of DNA strand breaks	Testicular cancer Ovarian cancer Hodgkin's lymphoma	Demain and Vaishnav (2011)
Brartemicin	*Nonomuraea* sp.	Reduction of invasion	26-L5 cells	Igarashi et al. (2009)
Butanol extract	*Bifidobacterium adolescentis* SPM0212	Anti-proliferative activity	Caco-2, HT-29 and SW480 cells	Lee et al. (2008)
Butyrate and propionate	*Firmicutes* phylum	Apoptotic, anti-proliferative and epigenetic activity	Colon, lung and prostate cancer cells	Górska et al. (2019), Kim et al. 2019)
Diethyl ether extract	*Streptomyces levis* ABRIINW111	Apoptosis	ALL cells	Valipour et al. (2018)
Diterpenoid derivative	*Micromonospora zhangzhouensis* HM134	Anti-proliferative activity	HepG2, HCT-116 and A549 cells	Fu et al. (2020)
Ether extract	*Streptomyces levis* ABRIINW111	Cell cycle arrest and apoptosis	SW480 cells	Faramarzian et al. (2018)
Ethyl acetate extract	*Streptomyces artemisiae* MCCB 248	Induction of nucleus shrinkage, DNA fragmentation and chromatin condensation	H460 cells	Dhaneesha et al. (2017)
Ethyl acetate fraction	*Streptomyces* sp. OA293	Apoptosis	HPV-16-positive SiHa and Caski cells	Dan et al. (2018)
Ethyl acetate fraction	*Streptomyces* sp. MUM256	Cell cycle arrest and apoptosis	HCT-116 cells	Tan et al. (2019)
Galvaquinone B	*Streptomyces spinoverrucosus*	Cytotoxicity and epigenetic activity	NSCLC, Calu-3 and H2887 cells	Hu et al. (2012)
Geldanamycin	*Streptomyces hygroscopicus* var. *geldanus*	HSP90 inhibition-mediated cytotoxicity	Myeloma, breast, prostate and cervical cancer	Gorska et al. (2012)
Iturin A	*Bacillus megaterium*	Cell cycle arrest and apoptosis	Breast cancer cell lines	Dey et al. (2015)
Jadomycins	*Streptomyces venezuelae*	ROS generation	Breast cancer cells	Hall et al. (2015)
Komodoquinone A	*Streptomyces* sp. K53	Induction of cell differentiation	Neuro2A cells	Itoh et al. (2003)
Kosinostatin	*Streptomyces violaceusniger* HAL64	Apoptosis	MCF-7 cells	Rambabu et al. (2015)
Lentztrehaloses A, B and C	*Lentzea* sp. ML457-mF8	Autophagy	Human melanoma Ovarian cancer	Wada et al. (2015)
Lipophilic peptides	EML-CAP3 bacterial strain	Anti-angiogenic activity by suppressing HIF-1α and VEGF	HepG2 cells	Jung et al. (2015)
Mensacarcin	*Streptomyces bottropensis*	Apoptosis	Melanoma cell lines	Plitzko et al. (2017)
Neoantimycin F (NAT-F)	*Streptomyces conglobatus*	Apoptosis	NSCLC cells	(Liu et al. 2019)
Novobiocin	*Streptomyces* strain	Anti-proliferative activity	Breast cancer cell lines	Donnelly and Blagg (2008)

Table 1 (continued)

Anti-cancer compound	Origin	Activity/mechanism	Cancer types or cell lines	References
N-acetyl-deformylantimycin	*Streptomyces* sp. strain THS-55	Induction of ROS-mediated ubiquitin–proteasome system, degradation and inhibition of ERK1/2, STAT3	HPV-infected cervical cells	Zhang et al. (2017)
Organic extracts	*Pseudomonas* spp. AS 8, 106 and 70	Cytotoxicity	MCF-7 cells	Anas et al. (2016)
p8	*Lactobacillus rhamnosus* (LR)	Slowing cell cycle progression	CRC cells	An et al. (2019)
Prodigiosin (PG)	*Serratia marcescens*	Apoptotic and anti-metastatic activities	Mouse melanoma model	Chang et al. (2011)
Proteinase K-activated parasporin-2Aa 1 protein	*Bacillus thuringiensis* strain A1547	Apoptosis	HepG2, PC-3 and MCF-7 cells	Brasseur et al. (2015)
Pyrrolo (1,2-a) pyrazine-1,4-dione, hexahydro-3-(phenylmethyl)	*Streptomyces* MUM256 and MUSC137	Apoptosis	HT-29 cells	Ser et al. (2017)
Pyrrolo (1,2-a) pyrazine-1,4-dione, hexahydro 3-(2-methyl propyl)	*Staphylococcus* sp. strain MB30	Cell cycle arrest and apoptosis	A549 and HPV18 positive HeLa cells	Lalitha et al. (2016)
Proteinase K-activated parasporin-2Aa 1 protein	*Bacillus thuringiensis* strain A1547	Apoptosis	HepG2, PC-3 and MCF-7 cells	Brasseur et al. (2015)
Quercetin-3-O-b-L-rhamnopyranosyl- (1 to 6)-b-D-glucopyranoside	*Streptomyces* sp. ERINLG-4	Apoptosis	A549 cells	Balachandran et al. (2014)
Romidepsin	*Chromobacterium violaceum*	Inhibition of HDAC	CTCL and PTCL	Furumai et al. (2002)
Salinomycin	*Streptomyces albus*	Inhibition of VEGF-VEGFR2-Akt/FAK signaling pathway	Glioma cell lines	Bi et al. (2017)
Trichostatin A	*Streptomyces hygroscopicus*	Inhibition of HDAC and anti-proliferative activity	MCF-7, T-47D, ZR-75-1, BT-474, MDA-MB-231, MDAMB-453, CAL 51, SK-BR-3 cells	Vigushin et al. (2001)
		Cell cycle arrest and apoptosis	T24 cells	Qu et al. (2010)
Urukthapelstatin A	*Merchercharimyces asporophorigenes* YM11-542	Cytotoxicity	A549 cells	Matsuo et al. (2007)
Valinomycins and compounds 1 and 2	Crude extract of *Streptomyces* sp. ZZ406	Anti-proliferative activity	U87 MG cells	Chen et al. (2018a, b, c)
Violacein	*Chromobacterium, Janthinobacterium, Alteromonas, Duganella, Massilia, Pseudoalteromonas and Collimonas*	Anti-proliferative activity	HeLa cells	Alem et al. (2020)
	Chromobacterium violaceum	Chemosensitization to 5-Fluorouracil	CACO-2, DLD-1, SW480 and HCT-116 cells	Kodach et al. (2006)

Streptomyces

Streptomyces are filamentous, mainly gram-positive bacteria that belong to the order Actinomycetales (Strobel et al. 2005). Streptomyces is the largest genus of Actinobacteria that comprises about 780 species that colonize marine and terrestrial habitats (Law et al. 2017). More than 50% of the discovered antibiotics have been isolated from Streptomyces species (Hu et al. 2017). In fact, Streptomyces produce angiogenesis inhibitors, antifungal, anti-parasitic, antiviral, antioxidant, anti-inflammatory, immunosuppressive, cytotoxic and cytostatic compounds (Law et al. 2017). Natural products derived from these species have great potential for the discovery of anti-cancer drugs (Valipour et al. 2018) such as saptomycins, bleomycin, cremeomycin, clecarmycins, moromycins A and B, mitomycin C, pentostatin, saquayamycin B and aclarubicin (Krishnan et al. 2014). These compounds act by either inducing apoptosis, inhibiting enzymes involved in oncogenic signal transduction pathways, causing mitochondrial membrane permeabilization (MMP), inhibiting angiogenesis, cellular differentiation, or serving as DNA intercalating agents (Aftab et al. 2015). Furthermore, elaiophylin, isolated from *Streptomyces melanosporus*, blocked angiogenesis both in vitro and in vivo by downregulating VEGFR2 pathway in endothelial cells and hypoxia-inducible factor-1α (HIF-1α) levels in tumor cells leading to tumor growth reduction (Lim et al. 2018).

Brain cancer

Actinomycin D from *Streptomyces parvulus* is the first antibiotic to clinically treat Wilms' tumor, childhood rhabdomyosarcoma, Ewing's sarcoma and metastatic non-seminomatous testicular cancer (Pham et al. 2019). It was found that actinomycin D produced by *Streptomyces* sp. ZZ338 inhibits the enzymes involved in the regulation of the metabolism of glioma cell lines (Zhang et al. 2016). In addition, valinomycins and new compounds 1 and 2 isolated from the crude extract of *Streptomyces* sp. ZZ406 cultured in soluble starch and casein liquid medium were found to inhibit the proliferation of glioma U87 MG cells by downregulating glioma metabolic regulators (Chen et al. 2018a, b, c). Moreover, compound 1 also significantly downregulated the expression of tumor glycolytic enzymes such as hexokinase 2 (HK2), 6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3 (PFKFB3), pyruvate kinase M2 (PKM2) and lactate dehydrogenase 5 (LDH5) (M. Chen et al. 2018a, b, c). Salinomycin, a polyether antibiotic derived from *Streptomyces albus*, has an anti-cancer activity against human glioma growth by inhibiting the VEGF-VEGFR2-Akt/FAK signaling pathway involved in angiogenesis (Bi et al. 2017). Another study has shown that the anthracycline compound, komodoquinone A from *Streptomyces* sp. K53 has the ability to induce differentiation of Neuro2A neuroblastoma cell line (Itoh et al. 2003).

Lung cancer

Nucleus shrinkage, DNA fragmentation, and chromatin condensation were detected in H460 human lung cancer cell line treated with the ethyl acetate extract of *Streptomyces artemisiae* MCCB 248 (Dhaneesha et al. 2017). In addition, neoantimycin F (NAT-F) from *Streptomyces conglobatus* induced apoptosis in non-small cell lung cancer (NSCLC) cells by triggering loss of the mitochondrial membrane potential (MMP), upregulating pro-apoptotic protein BAX, downregulating anti-apoptotic proteins Bcl-2, Bcl-XL, and Mcl-1, releasing cytochrome c and activating caspases-9 and -3 (Liu et al. 2019). It also induced reactive oxygen species (ROS) generation, enhanced the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun N-terminal kinase (JNK) and inhibited extracellular signal-regulated kinase (ERK1/2) phosphorylation resulting in MAPK-dependent mitochondria-mediated apoptosis in NSCLC cells (Liu et al. 2019). Anthraquinones are the largest group of naturally occurring quinones isolated mainly from fungal sources, they exhibit a wide range of activities including anti-inflammatory, antimicrobial, antioxidant, antiviral, and antitumor properties. In this concept, several anthraquinone analogs have been isolated from the bacterial source *Streptomyces spinoverrucosus*, out of which, galvaquinone B exerted moderate cytotoxicity against different types of cell lung cancer NSCLC, Calu-3 and H2887, and demonstrated epigenetic modulatory properties (Hu et al. 2012). The isolated compound quercetin-3-O-b-L-rhamnopyranosyl-(1 to 6)-b-D-glucopyranoside from soil-derived *Streptomyces* sp. ERINLG-4 was tested on colorectal and kidney cells but the potent cytotoxic effect was selective to lung cancer by inducing both intrinsic and extrinsic apoptosis via caspase-dependent cytochrome c release in A549 lung cancer cells (Balachandran et al. 2014).

Cervical cancer

Cervical cancer, specifically HPV-induced cervical cancer, is characterized by changes in PI3K/AKT/mTOR and ERK1/2 signaling pathways that lead to a poor response to cervical cancer treatments. Thus, drugs targeting PI3K/AKT/mTOR pathway are ideal to achieve a better efficacy (Bahrami et al. 2017). A natural product, n-acetyl-deformylantimycin (NADA) isolated from a crude extract of *Streptomyces* sp. strain THS-55 was shown to enhance ROS-mediated ubiquitin–proteasome system (UPS) degradation of oncoproteins E6/E7 in HPV-infected cervical cells resulting in S-phase cell cycle arrest and apoptosis, and inhibiting ERK1/2, STAT3 and PI3K/AKT/mTOR pathway (Zhang et al. 2017).

One study explained how bioactive compound(s) from ethyl acetate fraction of *Streptomyces* sp. OA293 induced BAX-mediated intrinsic apoptosis with complete inhibition of mTOR signaling pathway in cervical cancer cell lines (HPV-16-positive SiHa and Caski) (Dan et al. 2018). Another compound is Geldanamycin (GDA), a benzoquinone ansamycin compound isolated from *Streptomyces hygroscopicus* var. *geldanus*, has an anti-cancer activity in multiple myeloma, breast, and prostate cancer (Gorska et al. 2012). It also acts as an inhibitor of the heat shock protein HSP90 and causes cytotoxicity in HPV-18-positive HeLa cells (Khalifa et al. 2019).

Colon cancer

Ether extract of *Streptomyces levis* ABRIINW111 showed an increase in p53 expression, cell cycle arrest in G1 and G2/M phases and apoptosis in SW480 colon cancer cell line (Faramarzian et al. 2018). Metabolites from this extract decreased anti-apoptotic K-RAS and Bcl-2 proteins expression and increased pro-apoptotic p53 protein expression (Fatourachi et al. 2018). Similarly, ethyl acetate fraction of *Streptomyces* sp. MUM256 filtrate caused G1 and G2/M arrest, p21 and p53 upregulation, cyclin B1, CDK2, CDK4, cdc25A phosphatase downregulation, and intrinsic apoptosis in HCT-116 colon cancer cells (Tan et al. 2019). Pyrrolo (1,2-a) pyrazine-1,4-dione, hexahydro-3-(phenylmethyl)-, a cyclic dipeptide found in extracts of *Streptomyces* MUM256 and MUSC137 induced PARP cleavage and increased caspase-3 activity resulting in apoptosis in HT-29 colon cancer cells (Ser et al. 2017). Another study reported that the latter cyclic dipeptides have the ability to induce the collapse of mitochondrial membrane potential MMP, DNA fragmentation and cell cycle arrest in the subG1 phase in Caco-2 colon cancer cells (Teng Hern et al. 2019).

Blood cancer

Metabolites derived from *Streptomyces* sp. SY-103 have been shown to induce apoptosis in human leukemic cells upon treatment; through activating caspase-3 and inactivating AKT (Faramarzian et al. 2018). Some of these metabolites are pure cytotoxic compound (PCC), spicamycin and its derivative KRN5500, which were found to induce apoptosis by decreasing expression of Bcl-2 and modulating the normal localization pattern of promyelocytic leukemia protein (PML) from speckled pattern to microspeckled pattern in myeloid and lymphoid leukemic cells (Jeong et al. 2010; Zhang et al. 2000). Similarly, diethyl ether extract of *Streptomyces levis* ABRIINW111 upregulated BAX and downregulated Bcl-2 resulting in the induction of p53-dependent apoptosis in acute lymphoblastic leukemia (ALL) cells (Valipour et al. 2018).

Actinomycetes-derived anthracyclines are antitumor antibiotics that mainly perform their anti-cancer activity via topoisomerase II inhibition (Khalifa et al. 2019). For instance, daunorubicin and doxorubicin are two FDA approved drugs from the anthracyclines family used to treat acute lymphoblastic or myeloblastic lymphoma (Di Marco et al. 1981) by acting as DNA/RNA intercalating agents, generating reactive free radicals, and causing DNA double-strand breaks by the expulsion of histones from chromatin (Pang et al. 2015).

Other types of cancer

Mensacarcin isolated from *Streptomyces bottropensis* was shown to induce caspase-3/7-dependent apoptosis and mitochondrial dysfunction with selective cytotoxicity against melanoma cell lines that hold a BRAFV600E mutation associated with drug resistance (Plitzko et al. 2017). Moreover, Streptochlorin from *Streptomyces* sp. induced apoptosis in human hepatocarcinoma cells via the mitochondrial pathway (Valipour et al. 2018). Kosinostatin, a quinocycline antibiotic derived from *Streptomyces violaceusniger* HAL64, was shown to induce p53-dependent apoptosis in MCF-7 mammary carcinoma cell line (Rambabu et al. 2015). Several studies identified Salinomycin as a strong anti-cancer agent against breast, colorectal, lung, gastric, pancreatic and osteosarcoma (Safarpour et al. 2019) by inducing DNA damage, autophagy, mitophagy, upregulation of death receptors and hyperpolarization of mitochondria (Li et al. 2016). Novobiocin isolated from a *Streptomyces* strain, in anti-proliferative assays against breast cancer cell lines, showed the ability to bind to the C-terminus of Hsp90 resulting in the release and destruction of Hsp90-dependent client proteins responsible for the hallmarks of cancer such as ErbB2, mutant p53, Raf-1, HDAC6, AKT and c-Met receptor tyrosine kinase (Donnelly and Blagg 2008).

Endophytic actinobacteria and other bacterial species

Endophytic microorganisms are endosymbiotic organisms, mainly fungi and bacteria that colonize plant tissues (Ek-Ramos et al. 2019). Some of the endophyte-derived secondary metabolites include alkaloids, benzopyranones, chinones, flavonoids, phenolic acids, quinones, steroids, terpenoids, teralones and xanthones (Pimentel et al. 2011). These bioactive metabolites can act as antibiotics, antimycotics, immunosuppressants and anti-cancer treatments (Strobel et al. 2005).

Bacillus and *Streptomyces* species are the most abundant metabolite-producing gram-positive bacterial endophytes (Ek-Ramos et al. 2019). Exopolysaccharides isolated from *Bacillus amyloliquefaciens* sp., an endophytic

microorganism hosted in *Ophiopogon japonicas* plant, demonstrated antitumor activity against gastric carcinoma cell lines (Abdalla & Matasyoh, 2014). BAEPS, an acidic exopolysaccharide produced from Marine *Bacillus amyloliquefaciens* 3MS 2017, demonstrated both prophylactic and curative potential against 7,12-dimethylebenz-(a)-anthracene (DMBA)-induced breast cancer in female rats through inhibition of COX-2, aromatase, Na^+/K^+ ATPase, and estrogen production (Ibrahim et al. 2020). Crude extracts from *Acinetobacter guillouiae,* an endophytic organism isolated from *Crinum macowanii* Baker bulbs, were shown to reduce the growth of U87MG glioblastoma cell line by half (Sebola et al. 2019b). Moreover, lipophilic peptides derived from the endophytic EML-CAP3 bacterial strain isolated from *Capsicum annum L.* exerted an anti-angiogenic activity by suppressing hypoxia-inducible factor-1α (HIF-1α) and its target gene vascular endothelial growth factor (VEGF) in human hepatocellular carcinoma cell line HepG2 and inhibiting the proliferation of human umbilical vein endothelial cells (HUVECs) (Jung et al. 2015). Brartemicin, a trehalose-derived compound isolated from endophytic *Nonomuraea* sp. associated with *Artemisia vulgaris*, limited the invasion of murine colon carcinoma 26-L5 cells (Igarashi et al. 2009). Other chemotherapeutic anti-cancer compounds include Paclitaxel (Taxol), a drug produced by endophytic actinomycete strains BPSAC77, BPSAC101, and BPSAC121 as well as from *Kitasatospora* sp., an endophytic actinomycete associated with the *Taxus baccata* plant, Kaempferol, a phenolic compound present in the endophytic actinomycete strains BPSAC77, BPSAC101, and Tc052, and L-asparaginase produced by endophytic *Bacillus licheniformis, Bacillus pseudomycoides* and *Paenibacillus denitriformis* (Passari et al. 2017; Singh et al. 2017). Jadomycins, isolated from *Streptomyces venezuelae*, showed a cytotoxicity against multidrug-resistant MCF7 breast cancer cells that overexpress ATP-binding cassette (ABC) drug efflux transporters ABCB1, ABCC1, and ABCG2. Thus, this suggests their potential use as chemosensitizing agents (Issa et al. 2014). Another study demonstrated that jadomycin cytotoxicity in both drug-sensitive and taxol-resistant MCF-7 cells is ROS-mediated and requires the presence of copper (Hall et al. 2015).

Epothilone, from myxobacterium *Sorangium cellulosum* prevented microtubule depolymerization resulting in cell cycle arrest at G2/M interphase in P-glycoprotein-expressing multiple-drug-resistant tumor cell lines (Molnár et al. 2000). Pyrrolo (1,2-a) pyrazine-1,4-dione, hexahydro 3-(2-methyl propyl) (PPDHMP) derived from the marine bacterium *Staphylococcus* sp. strain MB30, isolated from the deep-sea sediment of Bay of Bengal, India, was shown to cause G1 cell cycle arrest, apoptotic morphological changes, caspase-9 and 3 activation, PARP cleavage and anti-apoptotic proteins downregulation in lung cancer A549 and HPV18 positive human cervix cancer HeLa cells (Lalitha et al. 2016). Induction of apoptosis was also obtained upon the treatment of U-87MG glioblastoma cells with *Bacillus*-derived cyclo (L-Pro-L-Phe), via AKT1 inactivation (Hong et al. 2008; Teng Hern et al. 2019). Similarly, proteinase K-activated parasporin-2Aa 1 protein isolated from *Bacillus thuringiensis* strain A1547 induced apoptosis in human liver HepG2, human prostate PC-3 and mammary carcinoma MCF-7 cancer cells via caspases-3/7 and poly (ADP-ribose) polymerase (PARP) cleavage, and inhibited the survival pathways through downregulation of AKT and ERK1/2 (Brasseur et al. 2015). Iturin A, a lipopeptide molecule extracted from *Bacillus megaterium*, was shown to upregulate BAX, downregulate Bcl-2, Bcl-xl, and Mcl-1 and inhibit the phosphorylation of AKT and its downstream proteins FoxO3a and GSK3B leading to cell cycle arrest and apoptosis in breast cancer cell lines (Dey et al. 2015). Anionic exopolysaccharide derived from *Nitratireductor* sp. strain PRIM-31 was shown to bind the epidermal growth factor (EGF) released by the brain tumor, prevent EGF receptor phosphorylation, and halt the AKT/PI3K pathway, thus acting as a potential brain anti-tumor drug (Abdelnasser et al. 2017).

Prodigiosin (PG), the red pigment produced by *Serratia marcescens* and other gram-negative bacteria, possesses a p53-independent apoptotic activity on malignant cells as well as anti-metastatic activity in a mouse melanoma model via matrix RhoA and metalloproteinase-2 inhibition (Chang et al. 2011). In addition, this compound prevented metastasis in C57BL6 mice inoculated with the syngeneic B16BL6 melanoma cells and limited the migration/invasion of the highly metastatic lung carcinoma 95-D cells through down-regulation of cell invasion promoters RhoA and matrix metalloproteinase-2 (MMP-2) (Zhang et al. 2005). Interestingly, PG induced identical cytotoxicity in cell lines overexpressing multidrug-resistant pumps when compared to their parental counterparts; and unlike classical chemotherapies (daunorubicin or mitoxantrone), ABC transporters were unable to efflux PG out of gastric carcinoma and epithelial ovarian cells thus circumventing the problem of drug resistance (Elahian et al. 2013). The organic extracts from *Pseudomonas* spp. AS 8, 106 and 70 retrieved from sediments of the Arabian Sea exhibited cytotoxicity against MCF-7 cells with 41, 50, and 45% mortality, respectively (Anas et al. 2016). Moreover, several bacterial extracts (lipophilic and hydrophilic) were obtained from the brine-seawater interface of the Red Sea and were tested for cytotoxicity. Among twelve extracts with demonstrated cytotoxicity at 24 h, P1-37B and P1-37A isolated from *Halomonas* and P1-17B from *Sulfitobacter* exhibited the most potent effect against mammary carcinoma MCF-7, HPV18 positive human cervix HeLa and human prostate DU145 cancer cells (Sagar et al. 2013).

Recently, violacein, a secondary metabolite pigment produced by many bacterial strains including *Chromobacterium, Janthinobacterium, Alteromonas, Duganella, Massilia, Pseudoalteromonas* and *Collimonas,* has been evaluated for its anti-cancer effect on HeLa cells and showed an antiproliferative activity. Moreover, it sensitized HeLa cells to chemotherapeutic agent cisplatin (Alem et al. 2020). In addition to its effect on cervical cancer, violacein has been shown to sensitize CACO-2, DLD-1, SW480 and HCT-116 colorectal cancer cell lines to 5-fluorouracil (5-FU), a commonly used chemotherapeutic agent (Kodach et al. 2006).

Romidepsin (FK228, depsipeptide) is an anti-tumor antibiotic originally derived from *Chromobacterium violaceum*. It received FDA approval for the treatment of cutaneous T cell lymphoma (CTCL) and peripheral T cell lymphoma (PTCL) (Moskowitz and Horwitz 2017). FK228 was later reported to have a histone deacetylase (HDAC) inhibitory activity. In fact, FK228 is converted to its reduced active form, exposing its sulfhydryl group which binds to the zinc ion of the HDAC active site and inhibits it (Furumai et al. 2002). Another HDAC inhibitor is trichostatin A (TSA), a hydroxamic acid that was first isolated from *Streptomyces hygroscopicus* in 1976 and described as antifungal and antibacterial agent (Singh et al. 2010). Later, TSA was found to significantly inhibit the activity of class I, II, and IV HDACs and the proliferation of eight breast cancer cell lines (MCF-7, T-47D, ZR-75–1, BT-474, MDA-MB-231, MDAMB-453, CAL 51, and SK-BR-3) (Vigushin et al. 2001). Moreover, TSA was able to induce cell cycle arrest of bladder cancer T24 cells in the G0/G1 phase and cause apoptosis of cancer cells (Qu et al. 2010). In A549 cells, the combination of TSA and cisplatin produced an enhanced synergistic anti-cancer effect compared to using either of them alone (Zhang et al. 2015). However, its application in clinical trials remains hindered due to its toxicity (Vanhaecke et al. 2004).

Human microbiota metabolites

The gastro-intestinal tract (GI) is the organ most colonized with microorganisms in the human body, dominated by bacteria most of which (90%) belong to the phyla *Bacteroidetes* and *Firmicutes*, with the colon demonstrating the highest bacterial count (10^{11} bacteria/ml) (Coleman and Haller 2018). GI tract microbiota plays a protective role where alterations in their structure and abundance (dysbiosis) have been related to pathogenic cases including inflammation and carcinogenesis, mainly colorectal cancer (CRC) (Coleman and Haller 2018). The mechanisms of action of microbiota include the modulation of anti-inflammatory cytokines, the alteration in prostaglandin secretion and the activation of phagocytes that in turn eliminate cancer cells at the early stages of the disease (Górska et al. 2019). Bacteria in the GI tract metabolize certain dietary components, such as dietary fibers, to produce tumor-suppressive metabolites (Bhatt et al. 2017). These metabolites either act locally or enter the systemic circulation to act on distant targets in the host to protect from inflammation and carcinogenesis.

Tryptophan metabolites, released by colonic bacteria, target and activate aryl hydrocarbon receptor and pregnane/xenobiotic responsive receptor driving anti-inflammatory response and preventing colon carcinogenesis (Bhutia et al. 2017). Gut microbiota is a source of short-chain fatty acids (SCFAs) including acetate, propionate and butyrate that were described to maintain epithelial integrity (Górska et al. 2019). One function of SCFAs is the epigenetic regulation of gene expression via HDAC inhibition. Butyrate and propionate have been known as inhibitors of both class I and class II HDACs (Cousens et al. 1979; Thangaraju et al. 2006). In colon cancer, both butyrate and propionate showed the ability to inhibit proliferation, invasion and migration. They induced apoptosis in lung cancer cells and suppressed proliferation by upregulating p21 (Kim et al. 2019). Butyrate produced by members of *Firmicutes* phylum induced apoptosis and suppressed in vitro proliferation of colon, lung and prostate cancer cells (Górska et al. 2019; Kim et al. 2019). Butyric acid was shown to suppress the activation of the nuclear transcription factor kappa B, inhibit histone deacetylation and cyclooxygenase (COX)–2, and control the activity Bcl–2, Bak, caspase-3 and -7 leading to apoptosis in colorectal cancer (Molska and Reguła 2019).

Cadaverine is a bacterial metabolite produced as a product of decarboxylation of lysine catalyzed by lysine decarboxylase (LDC) expressed in the human bacterial microbiome. Treating Balb/c female mice grafted with 4T1 breast cancer cells with cadaverine results in smaller primary tumors, less metastasis and lower grade tumors. Carried out through trace amino acid receptors (TAARs), cadaverine treatment of breast cancer cell lines provoked mesenchymal-to-epithelial transition, restrained invasion, and reduced mitochondrial oxidation, which in turn reduced the stemness of breast cancer stem cells (Kovács et al. 2019).

Polysaccharide A produced by the commensal *Bacteroides fragilis* was shown to suppress the development of colitis-associated colon cancer (Lee et al. 2018). Butanol extract of the probiotic *Bifidobacterium adolescentis* SPM0212 exhibited an anti-proliferative effect on Caco-2, HT-29 and SW480 colon cancer cells and activated RAW264.7 macrophages by inducing TNF-α and nitric oxide expression (Lee et al. 2008). Lactic acid bacteria have proved advantageous effects in colorectal cancer (CRC) by eliminating carcinogens, synthesizing anti-tumorigenic and anti-mutagenic metabolites, and strengthening the host immunity (An et al. 2019). For example, p8, a protein derived from *Lactobacillus rhamnosus* (LR), halts the cell cycle progression in CRC cells by downregulating the expression of cyclin B1 and Cdk1 (An et al. 2019). On the

other hand, the biotransformation of cranberry proanthocyanidins by this bacterium resulted in higher cytotoxicity against HepG2 hepatocellular cell line compared to the parent extract, by Apaf-1 activation and mitochondria-dependent apoptotic mechanism via ATP depletion (Rupasinghe et al. 2019). Moreover, metabolites derived from *Lactobacillus plantarum* (LDMs) sensitized 5-FU-resistant HCT-116 cells to chemotherapy through downregulating the expression of claudin-1 (CLDN-1), a tight junction transmembrane protein (An & Ha, 2020). Baicalein, a byproduct of the transformation of an anti-inflammatory component of herb *Scutellaria baicalensis* by the intestinal microbiota, inhibited gut inflammation by reducing the levels of inflammatory cytokines (IL-2, IL-6) and induced cellular death of cancer cells (Wang et al. 2020).

Ellagic acid, a component of pomegranates, berries, and nuts can be transformed into urolithin A by enteric gut bacteria (García-Mantrana et al. 2019). Urolithin A can halt the expression and activity of Ras-related C3 botulinum toxin substrate 1 (Rac1) and p21 protein-activated kinase 1 (PAK1), thus modulating cellular cytoskeleton by inducing the depolymerization of actin filaments and inhibiting proliferation and migration of cancer cells (Alauddin et al. 2020). Moreover, urolithin A showed the ability to stabilize p53 and upregulate p21 thus inhibiting proliferation and causing G2/M arrest in colon cancer cells. The anti-proliferative effect of urolithin A is also mediated by TIGAR, a p53-dependent glycolytic inhibitor that results in low ATP production and limited cellular growth of colon cancer cells (Norden and Heiss 2019). Urolithin A exerts an anti-cancer activity via the downregulation of both wnt and IGF-1 signaling pathways in colon and pancreatic cancers. It downregulates components of PI3K/AKT/mTOR signaling pathway, decreases the infiltration of immunosuppressive cells such as Tregs and induces apoptosis in pancreatic cancer (Totiger et al. 2019).

Immunomodulatory activity of bacterial extracts

Immune system deregulations entail many diseases including inflammatory diseases, allergies, autoimmune and infectious diseases (Matsushita and Kawaguchi 2018). Several bacterial extracts have been shown to modulate the immune system to fight such diseases and alleviate their symptoms.

Inflammatory diseases

Inflammation is a normal and healthy response to stimuli such as injury, pathogens, damaged cells and irritants. In some cases, the immune system attacks the body's own cells or tissues and results in abnormal inflammation, which leads to chronic pain, redness, swelling, stiffness, and damage to normal tissues. Activated immune cells play a significant role in the pathogenesis of many inflammatory diseases (Chen et al. 2018a, b, c). Chronic inflammatory diseases contribute to 50% of all deaths worldwide being attributable to diseases such as cancer, diabetes mellitus, chronic kidney disease, ischemic heart disease, stroke, non-alcoholic fatty liver disease, and autoimmune and neurodegenerative conditions (Gregory et al. 2018). Several studies have been conducted to find alternative anti-inflammatory immunomodulators to regulate the function and activation of the adaptive and innate immune response. N11, a secondary metabolite from marine microorganisms *Pseudomonas* sp. was shown to possess anti-inflammatory properties mediated by multiple mechanisms including inhibition of intracellular calcium level and reduction in phosphorylation of p38 MAPK and JNK in human neutrophils (Yang et al. 2014). In fact, inhibitors of the p38 MAPK pathway prevent the progression of collagen-induced arthritis, inflammatory bowel disease and chronic obstructive pulmonary disease (Lomas et al. 2012).

Necrotizing enterocolitis (NEC) is an inflammatory disease that affects premature infants and is characterized by necrosis of the distal small intestine and colon (Meyer et al. 2020). Short-chain fatty acids produced by *Bifidobacterium infantis* demonstrated anti-inflammatory activities in mature enterocytes and immunocytes (Zheng et al. 2020) which suggests the symbiotic action of breast milk and probiotics in preventing necrotizing enterocolitis (Repa et al. 2015). SCFAs (acetate, propionate and butyrate) were anti-inflammatory in a fetal cell line in a mouse intestine after an inflammatory stimulus with IL-1β. Their mechanism of action involved the G-protein coupled receptor (GPR 109A) and the inhibition of histone deacetylase 4 and 5 (Zheng et al. 2020). Seven peptides isolated from *Faecalibacterium prausnitzii* supernatant were found to inhibit NF-κB pathway in vitro and showed anti-inflammatory properties in vivo in a dinitrobenzene sulfate-induced colitis model (Breyner et al. 2017).

ADR-159, composed of heat-treated fermentates of *Lactobacillus fermentum* and *Lactobacillus delbrueckii* along with the microbial biomass generated by them, has been shown to have a therapeutic effect on inflammation induced by *117r* (Warda et al. 2019). ADR-159 diet in murine models reduced *Citrobacter*-induced inflammatory damage without preventing *Citrobacter rodentium* infection in female mice (Warda et al. 2020). This effect was accompanied by an increase in the expression of IL-12 subunit beta, IFN-γ, and IL-22 (Jeffrey et al. 2018). *Lactobacillus rhamnosus* and *Lactobacillus helveticus* have also been shown to secrete bioactive molecules possessing immunomodulatory activity. They modulate host intestinal epithelial cells response to innate immune stimulants through the secretion of bioactive molecules. These bioactive molecules are able to

down-regulate IL-8 production by human intestinal epithelial cells (IECs) induced by various innate immune stimuli (Jeffrey et al. 2018).

It is significant to note that some ether extracts of the metabolites of *ß-streptococcus, Staphylococcus albus, Staphylococcus aureus, Salmonella enterica* serovar Typhi, *Salmonella enterica* serovar Paratyphi, *Escherichia coli, Haemophilus influenza, Moraxella cattarhalis* and *Diptheroid bacilli* showed pro-inflammatory properties. They contain different collagenases which when purified, can stimulate the production of pro-inflammatory cytokines TNF-α and IFN-γ *in-vitro* and *in-vivo* without inducing noticeable stress and toxicity (Singh and Bhattacharyya 2014).

Allergies and autoimmune diseases

An allergy is an immune system response to a foreign substance that does not usually cause any harm to the body. Allergy symptoms can range from mild tolerable reactions to a serious life-threatening anaphylaxis (Eller et al. 2018). Allergic rhinitis and asthma are chronic and reversible allergic airway diseases considered significant global public health concerns (Cho et al. 2014). Broncho-Vaxom (OM-85 BV) is an extract from *Haemophilus influenzae, Diplococcus pneumoniae, Klebsiella pneumonia, Klebsiella ozaenae, S. aureus, Streptococcus pyogenes*, *Streptococcus viridans* and *Neisseria catarrhalis* responsible for respiratory infections (Bitar and Saade 2013). A study showed that short- and long-term pretreatment with OM-85 BV leads to the protection from the majority of allergy-specific symptoms in mice. OM-85 BV alleviated nasal symptoms, suppressed eosinophil infiltration in the nose and reduced inflammatory infiltrates. It also reduced the Th2 cytokine response by lowering IL-4, IL-5, IL-13, IgE and IgG1 levels (Han et al. 2014). The level of INF-γ was markedly elevated in the OM-85 BV group, which caused a significant reduction in the ratio IL-4/INF-γ. Thus, OM-85 BV acts by improving the overall mucosal immunity via the maintenance of an optimal Th1/Th2 cytokine balance (Meng et al. 2019).

A recent study showed that treatment with *Helicobacter pylori* extracts inhibited inflammatory features in murine models sensitized to allergens that induce allergic airway inflammation. Treatment with the extract decreased allergen-specific IgE and increased IL-10 and IL-17 in cells isolated from the mediastinal lymph node of mice (van Wijck et al. 2019). Moreover, *Helicobacter pylori* extract has been shown to be a potential therapeutic agent against food allergies. In fact, *H. pylori* extract and its purified immunomodulator VacA conferred detectable protection against anaphylactic symptoms in mice models exposed to ovalbumin and peanut extract. Treatments conferred detectable protection against anaphylactic symptoms of food allergy in the examined models and decreased Th2 cytokine production, mast cell protease secretion, and allergen-specific serum IgG1 levels. The same treatments were shown to affect the epigenome of T cells, thereby promoting stable Treg differentiation and functionality through the demethylation of the Treg specific demethylated region (TSDR) in FoxP3 + Tregs, promoting their lineage commitment and suppressive activity (Kyburz et al. 2017).

Autoimmune diseases are conditions that are triggered by the immune system attacking healthy cells in the body. OM-89 (Uro-Vaxom®), a bacterial extract prepared from 18 uropathogenic *Escherichia coli* strains, has been shown to modulate immunity in rheumatoid arthritis patients. OM-89 induced a strong production of IL-10, accompanied by a significant decrease in IL-4 production as well as TNF-α and IFN-γ (Toussirot et al. 2006). It contains HSP60 and HSP70 and is used for oral administration in the treatment of rheumatoid arthritis models (Nakai, 2016).

Infectious diseases

Resistance outcomes to anti-infective treatments raised alerts among health authorities to find new antimicrobial treatments like bacterial extracts as alternative drugs for infectious diseases (Esposito 2016). For instance, OM-89 (Uro-Vaxom®) is used to prevent recurrent urinary tract infections (UTI). Typically, it is administered orally as a daily dose for 3 months and is recommended by the European Association of Urology for women with recurrent uncomplicated UTI (Wade et al. 2019). OM-89 acts as an immunostimulator increasing both the innate and adaptive response, and also as an immunoregulator acting on dendritic cells and promoting Treg cells differentiation (Wade et al. 2019). OM-85 BV has been used for nearly 30 years in several countries in both adults and children for the treatment and prevention of recurrent respiratory infections (Triantafillou et al. 2019). This bacterial lysate increases immunoprotection, boosts immunity, reduces the number of respiratory tract infection recurrence and incidence rates in adults and children alike, reduces the intensity of airway-related symptoms, shortens the duration of infection-associated pyrexia, and reduces the number of infections requiring antibiotic treatment (Jurkiewicz and Zielnik-Jurkiewicz 2018). In mice, OM-89 activated macrophages and induced a TH1-type immune response that was observed by increased IgG2a in the serum and IFN-γ in spleen cell supernatant. Moreover, OM-89 increased IL-6 and IFN-γ levels and decreased inflammation in the mouse bladder (O'Brien et al. 2016).

For influenza virus, OM-85 BV treatment in mice enhanced both innate and adaptive immunity, led to a dose-dependent increase in the surface expression of MHC II, CD40, and CD86 on both CD11b + and CD11b − dendritic cell populations, and enhanced B cell activation and release of broadly protective antibodies (Pasquali et al.

2014). OM-85 reduced rhinovirus infection and cell death in lung epithelial cells. It induced an increase in C1q-R and β-defensin expression important for antigen presentation and phagocytosis, which highlights its modulatory activity on rhinovirus docking proteins on the epithelial cells (Sánchez-Ramón et al. 2018). Acquired immunodeficiency syndrome (AIDS) is a disease of the immune system due to the infection with an enveloped human immunodeficiency virus (HIV). Some studies have focused on the role of the extracellular vesicles (EVs) released by *Lactobacillus* spp. in preventing HIV-1 transmission. Two *Lactobacillus* stains, *L. gasseri* BC12 and *L. crispatus* BC3-derived EV, were found associated with high amounts of metabolites such as methionine, glycine, hypoxanthine, and glutamate. The EVs derived from these strains reduced the infection of MT-4 cells with HIV-1 LAI.04 at the late stage of infection and inhibited the replication of this retrovirus by decreasing the viral entry (Nahui Palomino et al. 2019).

Neuro- and cardioprotective effects of bacterial extracts

Alzheimer's disease is the most common cause of brain disorders in old adults and it leads to a progressive neurodegeneration of memory and thinking skills. New studies established the neuroprotective effect created by secondary metabolites of marine bacteria (Zhu et al. 2020). Acetylcholinesterase (AChE) inhibitors protect brain cells from neurodegeneration and ROS generation in Alzheimer's disease. *Streptomyces* sp. UTMC 1334 also known as *Streptomyces lateritius* was shown to produce pyrroles and other metabolites with AChE inhibitory activity (Almasi et al. 2018). Astrocytes protect the nervous system from oxidative damages caused by ROS generation (Drukarch et al. 1998). Myxobacterial extracts were found to protect the human primary astrocytes from oxidative stress. In fact, pre-treatment of astrocytes with myxobacterial extracts from *Archangium sp.* UTMC 4070 and *Cystobacter* sp. UTMC 4073 increased the level of glutathione, an abundant antioxidant molecule in the brain (Dehhaghi et al. 2019).

The relationship between gut microbial metabolism and mental health is one of the most important mechanisms regulating many aspects of host physiology, including immune system maturation and neurodevelopment. This communication has been explored in animal models specifically the bacterivore nematode *Caenorhabditis elegans* (Sekirov et al. 2010; Valles-Colomer et al. 2019). A recent study has shown that *E. coli* HT115 strain produces a neuroprotective compound that generates the neurotransmitter γ-aminobutyric acid (GABA) and thus protects *Caenorhabditis elegans* neurons from degenerating (Urrutia et al. 2020).

In many pathological conditions, lactic acid bacteria, responsible for the fermentation of milk, are a rich source of metabolites such as peptides that have a cardioprotective effect. Thus, the fermentation of milk with specific strains of *Lactococcus lactis* has antithrombotic and hypocholesterolemic activities before and after exposure to a simulated gastrointestinal digestion (SGD) model. Two strains of lactic acid bacteria (LAB) Lc-572 and Lc-571 were shown to release bioactive peptides that inhibit thrombine activity before and after gastrointestinal digestion (Rendon-Rosales et al. 2019).

Biological activities of bacterial secondary metabolites

Bioactive microbial products such as pigments, alkaloids, toxins, antibiotics, gibberellins, carotenoids and biosurfactants, known as secondary metabolites are produced by several bacterial species, fungi and plants, and serve fundamental biological activities such as antibacterial, antifungal, antiviral and antioxidant activities (Table 2).

Antibacterial activity

Antibiotics are synthesized during the stationary phase of the bacterial division after depletion of one nutrient source such as carbon, nitrogen, or phosphate (Fedorenko et al. 2015). Both gram-positive and gram-negative bacteria have shown resistance to antibacterial therapy, which became the biggest public health challenge of our time. All this led to the discovery of new bioactive molecules secreted by microbial communities in terrestrial niches, endophytes and marine environments (Marinelli et al. 2015).

Positively charged peptides isolated from genus *Bacillus* were described as antibiotic treatments that can bind to the outer bacterial envelopes, permeabilize the bacterial membranes and translocate into the cytoplasm (Abriouel et al. 2011). Certain strains of *Serratia marcescens* produce prodigiosin, an antibacterial red pigment (Clements et al. 2019) that exerts an inhibitory effect against gram-positive bacteria *S. aureus*, *Staphylococcus saprophyticus*, *Enterococcus avium* and *Streptococcus pyogenes* (Darshan and Manonmani 2015) and a bacteriostatic effect on *Escherichia coli* (Danevcic et al. 2016a, b). Moreover, prodigiosin can cause cell lysis and death in *Bacillus subtilis* by interacting with the cytoplasmic membrane, increasing the membrane permeability and disrupting the metabolic activity (Danevcic et al. 2016a, b). *Serratia marcescens* was also shown to produce two classes of biosurfactants, namely lipopeptides and glycolipids. Lipopeptides include three molecular species serrawettin W1, W2, and W3 (Ganley et al. 2018). Serrawettin displayed antimicrobial activity against *Pseudomonas aeruginosa, S aureus* and *Cryptococcus neoformans* (Clements

Table 2 List of microbial-derived natural products with antibacterial, antifungal, antiviral and antioxidant activities

Name	Origin	Activity	References
Prodigiosin	*Serratia marcescens*	Antibacterial	Clements et al. (2019), Danevcic, et al. (2016a, b), Darshan and Manonmani (2015)
Serrawettin	*Serratia marcescens*		Clements et al. (2019)
Germicidins, c-Actinorhodin	*Streptomyces lanatus*		Nass et al. (2017); Čihák et al. (2017)
Methanolic pigment extract	*Micrococcus* sp.		Karbalaei-Heidari et al. (2020)
Aminoglycosides (S-137-R)	*Bacillus velezensis*		Kudo and Eguchi (2016), Pournejati et al. (2019)
Ethyl acetate extract	*Pseudoalteromonas rubra*, *Virgibacillus salaries*		Kristiana et al. (2020)
Daptomycin	*Streptomyces roseospours*		Canepari et al. (1990), Richter et al. (2003), Sader et al. (2004)
Acyl depsipeptide (ADEP)	*Streptomyces hawaiiensis*		Goodreid et al. (2014)
Lipopeptide lipid 430	*Algibacter* sp. M09B557 and M09B04		Schneider et al. (2019)
3-Benzyl-hexahydropyrrolo[1,2-a] pyrazine-1,4-dione	*Exiguobacterium indicum* SJ16		Singh et al. (2019)
Juglomycin A	*Streptomyces achromogenes* E91CS4		Ahmad et al. (2020)
Kribellosides	*Actinobacteria, Kribella* MI481-42F6	Antifungal	Igarashi et al. (2017)
Mohangamides A and B	*Streptomyces* sp. SNM55		Bae et al. (2015)
Iturine A	*Bacillus amyloliquefaciens*		Dang et al. (2019)
Methanolic extract	*S. aureus*		Hameed (2016)
Antimycin A	*Streptomyces kaviengensis*	Antiviral	Raveh et al. (2013)
Xiamycins D	*Streptomyces* sp. *#HK18*		Kim et al. (2016)
4862F Ahmpatinin iBu	*Streptomyces albosporus I03A-04862 and Streptomyces* sp. CPCC 202,950		Chen et al. (2018a, b, c), Liu et al. (2012)
Nostoflan	*Nostoc flagelliforme*		Kanekiyo et al. (2007)
Thiangazole, phenalamide A1, phenoxan	*Polyangium sp.* and *Myxococcus stipitatus* strain		Jurkiewicz et al. (1992)
Ratjadon A	*Sorangium cellulosum*		Fleta-Soriano et al. (2014)
Valinomycin	*Streptomyces tsusimaensis*		Cheng (2006), Midhun and Jyothis 2021)
Glutathione, Butyrate, Folate	*Bifidobacteria, Lactobacillus fermentum* E-3 and E-18, *Clostridium butyricum* MIYAIRI 588	Antioxidant	Wang et al. (2017)
Intracellular Glutathione	*Streptococcus thermophilus* YIT 2001 (ST-1)		Kusuhara et al. (2018)

et al. 2019). Another lipopeptide, Daptomycin, derived as a fermentation product from *Streptomyces roseosporus* has an excellent bactericidal activity against vancomycin-resistant enterococci, coagulase-negative staphylococci, penicillin-resistant *Streptococcus pneumoniae* (Sader et al. 2004), methicillin-resistant and glycopeptide-intermediate *S. aureus* (Richter et al. 2003). Cell fractionation experiments revealed that daptomycin binds to cell walls and blocks different enzymes or inhibits the synthesis of cell wall macromolecules leading to the permeabilization of the bacterial membrane (Canepari et al. 1990).

Gram-positive bacteria such as Actinomycetes extracted from marine *Erylus* spp. sponges produce important bioactive metabolites. *Microbacterium* sp. Berg02-79 showed antibacterial activity against the methicillin-resistant *S. aureus* (Santos et al. 2019). Germicidins and c-actinorhodin isolated from *Streptomyces lanatus* have a selective bactericidal effect on *Bacillus subtilis* and *S. aureus* (Nass et al. 2017; Čihák et al. 2017). A methanolic pigment extract from *Micrococcus* sp. MP76 was described to inhibit the growth of *S. aureus*, *P. aeruginosa* and *E. coli* (Karbalaei-Heidari et al. 2020). Aminoglycosides produced by the *Bacillus velezensis* strain RP137 were found to target bacterial ribosomes including the inhibition of protein synthesis and S-137-R had a moderate antibacterial effect on *S. aureus* and *P. aeruginosa* (Kudo and Eguchi 2016; Pournejati et al. 2019). Moreover, a study has shown that the ethyl acetate extracts of the supernatant of *Pseudoalteromonas rubra* and *Virgibacillus salaries* inhibit

the growth of resistant *S. aureus* (Kristiana et al. 2020). Acyl depsipeptide antibiotics derived from *Streptomyces hawaiiensis* protect against resistant *Streptococcus pneumoniae*, *S. aureus* and *Enterococcus faecalis* bacteria by binding to ceramide-1-phosphate phosphatase (C1pP) and causing the degradation of cell division-specific proteins (Goodreid et al. 2014).

Two bacterial strains belonging to the genus *Algibacter*, M09B557 isolated from *Alcyonidium gelatinosum* and M09B04 isolated from a soft coral, were described to inhibit the growth of *Streptococcus agalactiae* by secreting lipid 430, a bioactive lipopeptide (Schneider et al. 2019). Gram-positive and gram-negative bacteria use cell-to-cell communication systems such as quorum sensing circuits to regulate gene expression in response to cell density. N-acyl-homoserine lactones are a class of signaling molecules involved in bacterial quorum sensing. *Rhodococcus erythropolis* strain R138 showed an anti-virulence effect against the human pathogen *P. aeruginosa* PA14 by catabolizing N-acyl-homoserine lactones (Barbey et al. 2018). Moreover, a study has shown that *Bacillus sp.* QSI-1 disrupts the virulence of *A. hydrophila* YJ-1 by decreasing significantly the expression of virulence factors such as hemolysin, protease and N-Acyl homoserine lactones (Zhou et al. 2019). Additional studies have demonstrated that the active compound 3-Benzyl-hexahydropyrrolo[1,2-a]pyrazine-1,4-dione extracted from *Exiguobacterium indicum* SJ16 inhibits the biofilm formation of two *P. aeruginosa* strains, PAO1 and PAH by decreasing their motility and the production of virulence factors, and quorum sensing regulatory mediators such as pyocyanin, rhamnolipid, elastase and protease (Singh et al. 2019).

Endophytes are rich sources of bioactive compounds and secondary metabolites used as antibacterial agents (Afzal et al. 2019). *Pseudomonas sp.* crude extract isolated from *Crinum macowanii* Baker inhibits the growth of *Bacillus cereus, Staphylococcus epidermidis,* and *Mycobacterium marinum* (Sebola et al. 2019a). Endophytes *Pantoea eucalypti, Pantoea vagans* and *Pantoea ananatis* isolated from *Solanum mauritianum* have an antibacterial activity against *S. aureus, Bacillus cereus, Staphylococcus epidermidis* and *Bacillus subtilis* (Uche-Okereafor et al. 2019). A recent study showed that the biological compound Juglomycin A produced by *Streptomyces achromogenes* E91CS4, an endophyte of *C. sativus,* reduces the biofilm formation in *Escherichia coli* by inhibiting its motility and down-regulating its adhesion mediator fimH gene. Juglomycin A also inhibits the growth of several bacteria such as *Shigella dysenteriae, Pseudomonas fluorescens, Streptococcus pyogenes, S. aureus, Staphylococcus warneri, Clostridium pasteurianum* and *Candida albicans* (Ahmad et al. 2020).

Antifungal activity

The need for antifungal secondary metabolites increased with the expanding number of fungal infections (De Lucca and Walsh 1999). Actinobacteria *Kribella* MI481-42F6 was shown to produce kribellosides that inhibit the activity of RNA 5'-triphosphatase in *Saccharomyces cerevisiae* (Igarashi et al. 2017). Mohangamides A and B, purified from *Streptomyces* sp. SNM55, inhibited the growth of *Candida albicans* by decreasing the expression of its isocitrate lyase (Bae et al. 2015). Moreover, it was recently shown that *Bacillus velezensis* DTU001 reduces the growth of *C. albicans* under planktonic conditions and during biofilm development (Devi et al. 2019). Further reports are required to define the role of iturin, an amphiphilic antifungal metabolite, composed from a peptide and a fatty acyl moiety (Chae Gun et al. 1990; Verschuere et al. 2000). These compounds form a cyclic structure through the linkage of the hydrophobic long alkyl chain to a hydrophilic polypeptide which has the ability to accumulate between fluid phases reducing surface and interfacial tension. Consequently, this moiety leads to the deformation of the rough cell surface and the cytoplasmic material leakage of the bacterial cell (Rautela et al. 2014).

Among the gene clusters, the operons *itu* D*, itu* A, *itu* B and *itu* C are responsible for iturin A biosynthesis. The strong constitutive promoter C2up enhances the transcription of the *itu* operons. The substitution of C2up for the native iturin synthetase promoter enhanced the production of Iturine A by *B. amyloliquefaciens* LL3. Currently, more efforts are still needed for the elucidation of the industrial production of iturin A by the strain (Dang et al. 2019). Iturine A produced by *Bacillus amyloliquefaciens* C2LP inhibited the growth of *Alternaria alternate, Botrytis cinerea, Colletotrichum gloeosporioides, Fusariumoxysporum* and *Rhizoctoniasolani* (Dang et al. 2019). Furthermore, previous studies showed that thirty-five bioactive chemical constituents identified in the methanolic extract of *S. aureus* suppress the growth of *Aspergillus terreus* (Hameed 2016). In addition, the secondary metabolites produced by *Pseudomonas stutzeri* ST1302 and *Klebsiella pneumonia* ST250 have a promising effect against 11 strains of fungus-like *Pythium insidiosum* isolated from human pythiosis in Thailand (Wittayapipath et al. 2020).

Antiviral activity

Pathogenic viral infections not only cause morbidity and mortality of the host but are also associated with a considerable economic damage necessitating immediate intervention strategies ranging from prevention, treatment discovery and establishment of effective vaccines. Secondary metabolites produced by bacteria hold a great antiviral therapeutic

potential. Antimycin A1a isolated from *Streptomyces kaviengensis* disrupted the mitochondrial electron transport and the biosynthesis of pyrimidine in Western Equine Encephalitis virus (WEEV) and its commercial form reduced viral titers in mice infected with WEEV and improved their overall survival (Raveh et al. 2013). Xiamycins D produced by *Streptomyces sp*. #HK18 inhibited the expression of structural proteins GP6 nucleocapsid, GP2 spike, and GP5 membrane of porcine epidemic diarrhea virus (PEDV) (Kim et al. 2016). 4862F and Ahmpatinin iBu isolated from *Streptomyces albosporus* I03A-04862 and *Streptomyces* sp. CPCC 202,950 respectively, targeted HIV-1 protease which perturbates the life cycle of this virus (Chen et al. 2018a, b, c; Liu et al. 2012). Moreover, thiangazole, phenalamide A1 and phenoxan isolated from two strains of *Polyangium sp*. and *Myxococcus stipitatus* strain Mx s40 inhibited HIV-1 reverse transcriptase activity and prevented cell death in virus-infected MT-4 cells (Jurkiewicz et al. 1992). Another study showed that the Rev/CRM1-mediated nuclear export pathway in HIV virus was blocked by Ratjadon A isolated from *Sorangium cellulosum* (Fleta-Soriano et al. 2014). Nostoflan produced by *Nostoc flagelliforme* restrained the binding of enveloped viruses such as HSV, HCMV, and influenza A virus to the host cells (Kanekiyo et al. 2007). Interestingly, valinomycin extracted from the endophytes *Streptomyces tsusimaensis* was studied for its antiviral activity against coronaviruses such as SARS-CoV, MERS-CoV, and human coronavirus OC43 (HCoV-OC43), which highlights its future potential use as an antiviral agent against SARS-CoV-2 (Cheng 2006; Midhun and Jyothis 2021).

Antioxidant activity

Reactive oxygen species (ROS) including superoxide anion radicals, hydroxyl radicals and hydrogen peroxide trigger an oxidative stress that leads to many human diseases such as diabetes, atherosclerosis, Alzheimer's disease and cancer (Lobo et al. 2010). Probiotics that contain enzymes like superoxide dismutase, glutathione peroxidase and glutathione reductase as well as antioxidants such as glutathione, thioredoxin, vitamins C and E, help reducing damages caused by oxidation (Stecchini et al. 2001). Glutathione, butyrate, and folate from *Bifidobacteria*, *Lactobacillus fermentum* E-3 and E-18 and *Clostridium butyricum* MIYAIRI 588 demonstrated an antioxidant effect (Wang et al. 2017).

Moreover, *Lactobacillus plantarum, Alteromonas australica, Bacillus niacini, Lysinibacillus fusiformis* and *Vibrio harveyi* produce bioactive compounds that exhibit antioxidant activity (Baker et al. 2019). AR2 crude extract from *Streptomyces lanatus* attenuates oxidative stress (Riahi et al. 2019) and 18 *Streptomyces* strains isolated from rhizosphere soils exhibit significant antioxidant activity (Law et al. 2019). A lactic acid bacterial strain, *Streptococcus thermophilus* YIT 2001 (ST-1), was found to contain intracellular glutathione that provides an antioxidant activity against low-density oxidation (Kusuhara et al. 2018).

Conclusion

The discovery of natural remedies is expanding through the efforts done to find alternative therapies using microbial species. Research on microbes has always played an essential role in the improvement of biotechnological and biomedical areas. As discussed in this review, bacteria remain a potent factory for natural products with vast therapeutic effectiveness. The important biological functions of these products along with their anti-cancer mechanisms of action are illustrated in Fig. 1. Bacterial secondary metabolites continue to broaden their diverse and integral role in modern medicine and their involvement in human health still expects further global work and research.

Combination of secondary metabolites with chemotherapies is one of the most promising pathways in the battle against cancer. Several clinical trials are conducted to find therapeutic candidates. For instance, in a phase II study on 49 cervical cancer patients, the treatment with a combination of ifosfamide, bleomycin, and cisplatin (BIP) for a median duration of 8 months showed that 69% of patients presented an objective response while 20% showed a complete response (Buxton et al. 1989). 75% of patients treated with BIP followed by radiotherapy showed a complete response compared to 56% with radiotherapy only (Tobias et al. 1990). Epigenetic regulation through HDAC inhibitors (HDACi) is a widely studied anti-cancer mechanism. HDACi romidepsin isolated from *Chromobacterium violaceum* was found to inhibit the growth of T cell lymphoma in phase I and II clinical trials (Nakajima et al. 1998). 35% of patients with cutaneous T cell lymphoma (CTCL) responded to romidepsin after durations of 11.1 months (Piekarz et al. 2009). However, phase I/ II trials showed concerns about few side effects such as a reduction in the number of blood cells (Maruyama et al. 2017). Future phase II trial using Romidepsin after Gemcitabine, Dexamethasone, and Cisplatin will be tested in Japan against peripheral T cell lymphoma with short-term effects (Yamasaki et al. 2019). Since 2003, the first geldanamycin derivative 17-AAG (17-N-allylamino17-dimethoxygeldanamycin) has been used in a total of 35 phase I clinical trials in cancer patients. Despite its pharmacological potency, 17-AAG showed low water solubility and high hepatotoxicity that restricted its clinical use and 23% of the phase I trials were not progressed past phase II (Sanchez et al. 2020). Nowadays, the use of advanced technology and nanomaterials-based drug delivery carriers and the understanding of the mechanisms of

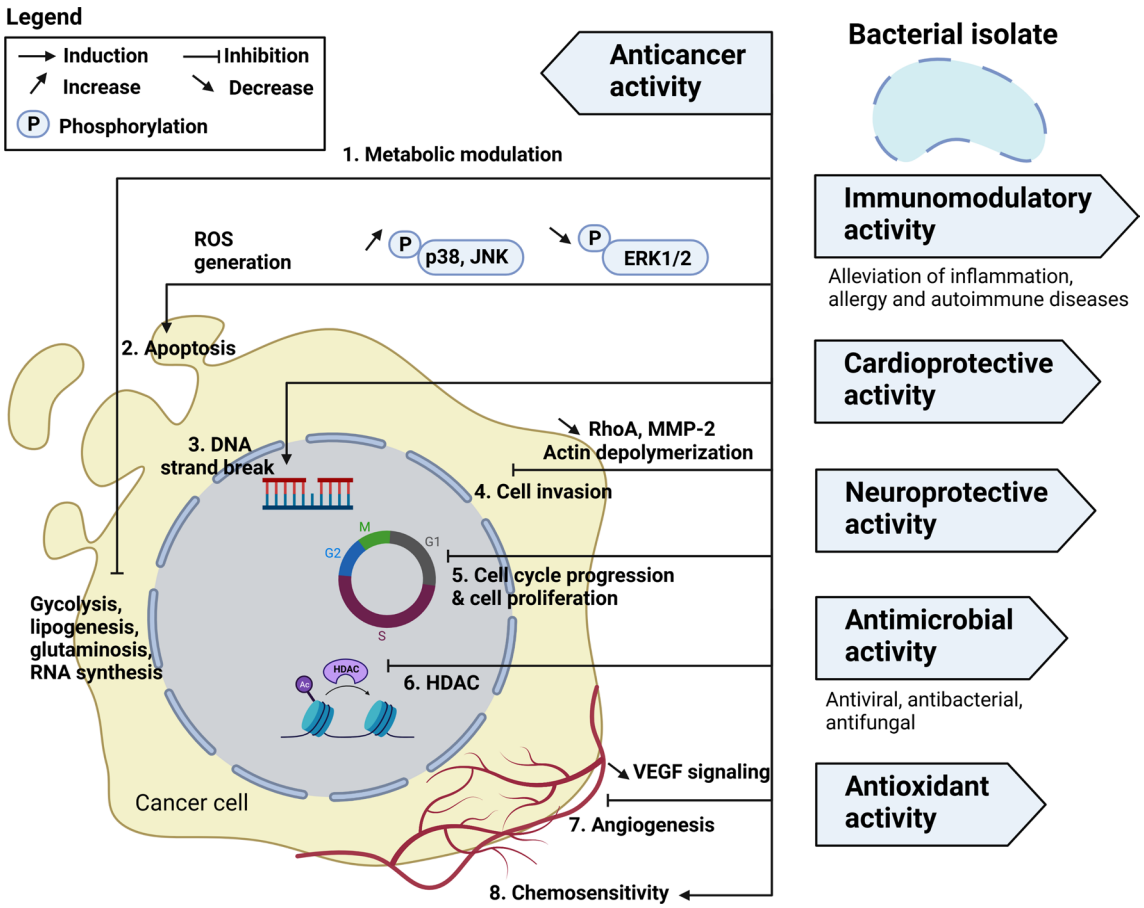

Fig. 1 Biological activities and applications of bacterial-derived compounds. Bacterial isolates can modulate the immune system and alleviate inflammation, allergies and autoimmune diseases. They can exert biological activities such as antibacterial, antifungal, antiviral and antioxidant activities, as well as neuro- and cardioprotective effects. Bacterial-derived compounds can have anti-cancer properties and their mechanisms of action include (**1**) the modulation of the metabolism in cancer cells by inhibiting glycolysis, lipogenesis, glutaminosis and RNA synthesis; (**2**) the induction of apoptosis via ROS generation, upregulation of phosphorylated p38 mitogen-activated protein kinase (p38 MAPK) and c-Jun N-terminal kinase (JNK), and downregulation of phosphorylated extracellular signal-regulated kinase (ERK1/2); (**3**) the induction of DNA strand break; (**4**) the inhibition of cancer cell invasion by downregulating Ras homolog family member A (RhoA) and matrix metalloproteinase (MMP) and inducing actin depolymerization; (**5**) the inhibition of cell proliferation and progression through the cell cycle; (**6**) the inhibition of histone deacetylase (HDAC); (**7**) the inhibition of angiogenesis by downregulating vascular endothelial growth factor (VEGF); (**8**) the stimulation of chemosensitivity in drug-resistant cancer cells "Created with BioRender.com"

action of the metabolites will allow more controlled and efficient clinical trials. An ongoing phase III trial is evaluating the efficacy and safety of oral Paclitaxel in recurrent and metastatic breast cancer as first-line therapy. A clinical study was launched to evaluate the role of OM-85 BV on children with Wheezing Lower Respiratory Tract Illness (WLRI) and is expected to be completed in 2025. Thus, as discussed, whether in clinical testing, FDA approval or the mechanisms behind their therapeutic activity, the applications of bacterial secondary metabolites and extracts still hold vast openings for exploration and investigation.

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Declarations

Conflict of interest The authors Zainab Abdelghani, Nancy Hourani, Zahraa Zaidan, Ghassan Dbaibo, Marguerite Mrad and Rouba Hage-Sleiman declare that they have no conflict of interest.

Ethical approval The work is completely within the professional code of ethics.

Consent to participate All authors consent to participate in this work.

Consent for publication Informed consent was obtained from all individual participants included in the study.

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