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Metabolites from marine microorganisms in cancer, immunity, and inflammation: A critical review

[Metabolitos procedentes de microorganismos marinos en cáncer, inmunidad e inflamación: Una revisión crítica]

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Abstract

Context: Marine microorganisms represent a promising source of bioactive molecules for biomedical applications. Increasing scientific literature is describing novel metabolites isolated from marine microbes with attractive pharmacological properties, such as anti-inflammatory, immunomodulatory, and anticancer.

Aims: To reveal a background of the main marine microbial-derived products that have been isolated and characterized, including recent examples. The main mechanisms of action of these compounds in different models are also discussed.

Methods: This research was structured based on a four phases design. 1) the identification of research questions, 2) selection of relevant studies, 3) filtering of studies based on inclusion and exclusion criteria, and 4) collection and organization of the data. For the web search, were used PubMed, Web of Science, Science Direct and ProQuest. For the selection and classification of the papers was used PRISMA software.

Results: A wide variety of marine microbial metabolites with important pharmacological properties have been discovered and characterized so far. The main sources of these compounds are marine actinomycetes, bacilli, fungi from *Aspergillus* and *Penicillium* genus, microalgae, and some marine symbiotic bacteria and fungi. Most of these metabolites exhibit cytotoxic, pro-apoptotic, anticancer, anti-inflammatory, and immunomodulatory activities. Complex structural moieties, such as multiple aromatic rings and heteroatoms, seem to be related to these properties. The mechanisms of action of most of these molecules target apoptosis-related proteins, enzymes, transcription factors, DNA binding proteins and some cell surface receptors.

Conclusions: The marine environment offers an efficient and attractive way to obtain novel natural products. Marine microorganisms are a prolific source of new molecules and extracts with therapeutic potential in the treatment of chronic inflammatory diseases. They represent and ecofriendly and feasible option to obtain drug candidates with multiple mechanisms of action and important biomedical applications.

Keywords: bioactive compounds; biomedical applications; cancer; inflammation; immunity; marine microorganisms.

Resumen

Contexto: Los microorganismos marinos constituyen una fuente de moléculas bioactivas para aplicaciones biomédicas. En la literatura se han descrito metabolitos novedosos aislados de microbios marinos con propiedades farmacológicas atractivas como anti-inflamatoria, inmunomoduladora y anticancer.

Objetivos: Revelar estado del arte de los principales productos derivados de microbios marinos que han sido aislados y caracterizados, incluyendo ejemplos recientes. También se discuten los principales mecanismos de acción de estos compuestos en diferentes modelos.

Métodos: Esta investigación fue estructurada en un diseño de cuatro fases. 1) Identificación de las preguntas de investigación, 2) selección de los estudios relevantes, 3) filtrado de los estudios basado en los criterios de inclusión y exclusión, y 4) colección y organización de los datos. Para la búsqueda en la web se utilizaron PubMed, Web of Science, Science Direct and ProQuest. Para la selección y clasificación de los artículos se empleó el software PRISMA.

Resultados: Una amplia variedad de metabolitos derivados de microbios marinos con propiedades farmacológicas importantes han sido descubiertos y caracterizados hasta la fecha. Las principales fuentes de estos compuestos son los actinomicetos marinos, bacilos, hongos de los géneros *Aspergillus* y *Penicillium,* microalgas y algunas bacterias y hongos simbióticos. La mayoría de estos metabolitos exhiben actividad citotóxica, pro-apoptótica, anticancer, anti-inflamatoria e inmunomoduladora. Motivos estructurales complejos como múltiples anillos aromáticos y heteroátomos parecen estar relacionados con estas propiedades. Los mecanismos de acción de casi todas estas moléculas tienen como blanco proteínas relacionadas a la apoptosis, enzimas, factores de transcripción, proteínas de unión al ADN y algunos receptores de la superficie celular.

Conclusiones: El medioambiente marino ofrece una vía atractiva y eficiente de obtener novedosos productos naturales. Los microorganismos marinos son una fuente prolífica de nuevas moléculas y extractos con potencial terapéutico en el tratamiento de enfermedades inflamatorias crónicas. Ellos representan una opción ecológica y factible para obtener nuevos candidatos a fármacos con múltiples mecanismos de acción e importantes aplicaciones biomédicas.

Palabras Clave: aplicaciones biomédicas; cáncer; compuestos bioactivos; inflamación; inmunidad; microorganismos marinos.

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INTRODUCTION

Nowadays, the search for novel pharmacologically active compounds has been focused on natural products because they are an effective and less toxic alternative to synthetic drugs (Mouhid et al., 2017). Marine microorganisms, in particular, because of their abundance and diversity, are a promising source of bioactive substances for biomedical applications (Bhatnagar and Kim, 2010).

These species live in stressful conditions such as poor light, high pressure, and cold temperatures, which stimulate the production of many secondary metabolites that serve as a chemical defense against adverse environmental conditions (Bhatnagar and Kim, 2010). In addition, they produce toxins, pigments, and a variety of chemical compounds that possess a different degree of bioactivity against other microorganisms. It has been proven that these molecules have therapeutic applications and exhibit important pharmacological properties, including antimicrobial, cytotoxic, photo-protective, anti-inflammatory, and anticancer (Bhatnagar and Kim, 2010). They are able to modulate different cellular targets like enzymes, membrane receptors and transcription factors, covering a broad spectrum of action mechanisms (Stevenson et al., 2002; Toledo et al., 2014; Shin et al., 2016; Xu et al., 2016).

Among the main groups of microorganisms, there are bacteria, fungi, microalgae, and symbiotic microorganisms. More than 20 000 bioactive metabolites produced by marine microorganisms have been reported, and almost 10 000 are derived from actinomycetes, mainly of *Streptomyces* species (Berdy, 2005). Most of these metabolites are potent antibiotics; thus, streptomycetes have become a primary source of natural antibiotics for pharmaceutical and industrial applications (Berdy, 2005). A deeper exploration of actinomycetes from a genetic perspective and the use of high-throughput screenings have allowed the discovery of several novel compounds with different biological activities (Olano et al., 2009a;b). Other groups of marine microorganisms like fungi and cyanobacteria are also producers of complex and unique chemical structures with high pharmacological potential (Hasan et al., 2015; Vijayakumara and Muniraj, 2015). Moreover, microbes associated with macroorganisms, such as marine plants and animals, are emerging as an interesting source of new bioactive compounds (Penesyan et al., 2011; Mazard et al., 2016).

Terrestrial plants have been used for centuries in the treatment of human diseases, whereas the exploration of microorganisms as a source of therapeutical compounds has a relatively short history (Monciardini et al., 2014). In spite of that, more than 10% of the current natural bioactive products have a microbial origin (Hegazy et al., 2015). The huge biomedical potential of marine microorganisms remains mostly unexplored, and the wide chemical diversity of these microbial-derived products offers the possibility to modulate multiple molecular targets (Penesyan et al., 2013; Hasan et al., 2015). This review intends to highlight the pharmacological potentials of the main groups of marine microorganisms and their derived products/compounds in different pro-inflammatory and immunopathological conditions, including cancer.

METHODOLOGY

Study design

The present research was structured based on a four phases design, including the identification of research questions, selection of relevant studies, filtering of studies based on inclusion and exclusion criteria, and collection and organization of the data. The four phases were organized as follows (Fig. 1):

Phase 1 The research questions and objectives were established based on the critical review of crucial findings and experimental insights in the field of marine pharmacology for cancer, immunity, and inflammation.

Phase 2 The relevant papers were identified and collected by searching the keywords related to marine microbial pharmacology from various available databases such as Science Direct,

ProQuest, PubMed, WOS, IEEE, and search engines Google scholar. The queries that were used for the systematic search are presented in Table 1.

Phase 3 To select the articles, we use the PRISMA software. Using the questions represented in Table 1, 200 articles were identified in total. Then, we double-check the identified articles in terms of title, abstract, and content according to the inclusion and exclusion criteria (Table 2) using Endnote software. Finally, 122 articles were included in the study. The algorithm for the selection and filtering of articles is represented in Fig. 1.

Phase 4 The papers finally included were analyzed in detail to assess the most current and relevant information about the pharmacology of bioproducts derived from marine microorganisms in the area of cancer, immunity, and inflammation. The main structural moieties, mechanisms of action, and molecular targets of different products and compounds were discussed.

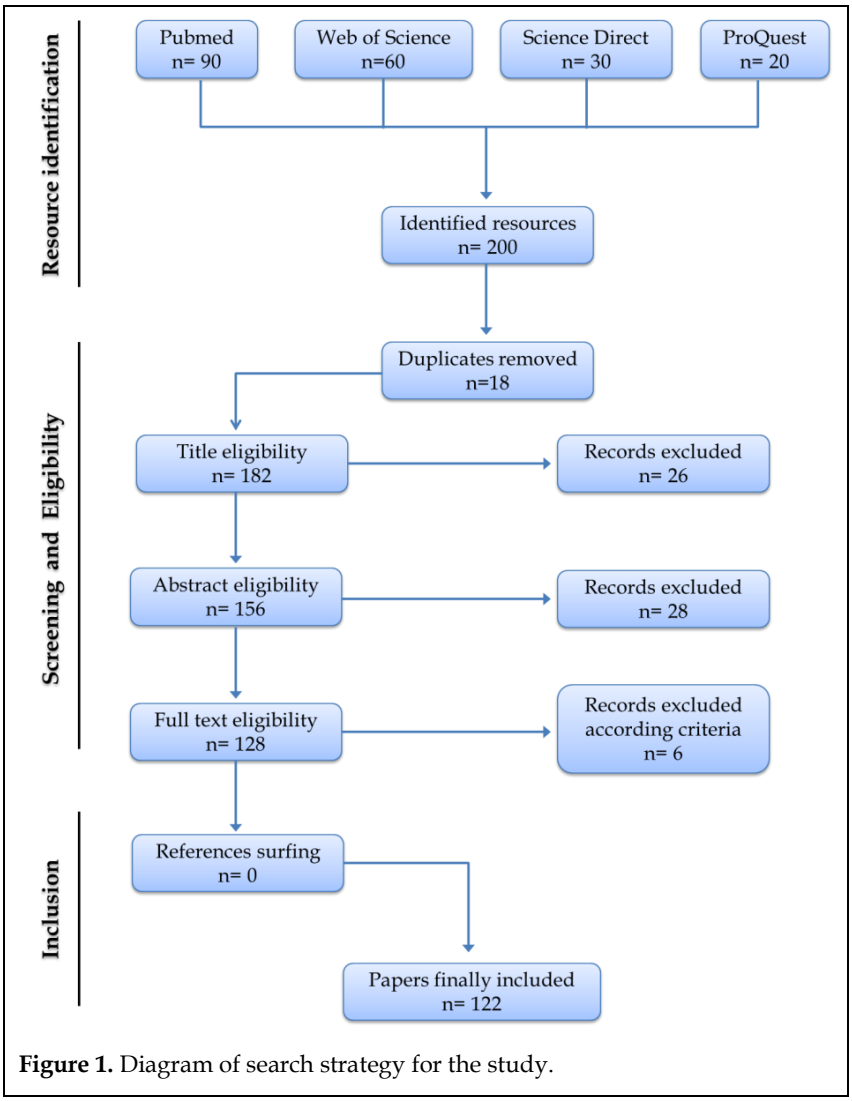

Figure 1. Diagram of search strategy for the study.

Table 1. Main search algorithm of the review.

Resources
Search engines and databases: PubMed, ISI web of science, Science Direct, ProQuest, Google Scholar
Limits: Language (only resources with at least an abstract in English)
Time: From 1976 to 2017
Search Algorithm
#1 AND #2 AND #3 AND #4 AND #5
#1 ("marine microbial" OR "microorganism") [TI]
#2 ("pharmacology" OR "drugs" OR "metabolites") [TI]
#3 ("cancer" OR "oncogenesis" OR "tumor" OR "cancer model") [TI-Abs-Key]
#4 ("immunity" OR "immune system" OR "immunological disease" OR "immunological model") [TI-Abs-Key]
#5 ("inflammation" OR "inflammatory condition" OR "inflammation model") [TI-Abs-Key]

Table 2. Inclusion and exclusion criteria for papers.

Inclusion criteria	**Exclusion criteria**
Journal articles, conference papers, and book chapters written between 1976 and 2017	Papers written in languages other than English
Papers published with title, abstract and full text	Papers with no available full text
Papers about marine microbial pharmacology in the area of cancer, immunity, and inflammation	Newspapers, posters, letters to the editors and workshops

RESULTS

After the selection, process 122 studies were chosen and critically analyzed. These include relevant research conducted between 1976 and 2017, which give us an overview of the development of marine microbial pharmacology in the areas of cancer, immunity, and inflammation. The papers are mainly from China, Japan and India, and the other number of studies were from Brazil, Spain, Italy, USA, and UK. The review is focused on the sources of microbial metabolites, the main chemical structures isolated from them, and the mechanisms of action of these molecules in different models of cancer, immunity, and inflammation (Table 3).

Molecular targets in disease

Cancer, immunity, and inflammation

It has been proven that oncogenesis, autoimmune diseases, and several inflammatory disorders have a common etiological basis, which is chronic and uncontrolled inflammation. The inflammatory process is involved in cancer progression and aggravates autoimmune syndromes (Franks and Slansky, 2012). At the same time, inflammation has a protective role during the immune response to pathogens and is an active process required for the efficient functioning of the immune system (reviewed in Xiao, 2017). Thus, the inflammatory response seems to be a double-edged sword that contributes to the immune response but could also lead to the development of an immunopathology.

Table 3. Summary of bioactive metabolites isolated from marine microorganisms.

Compound	Source	Activity	Reference
Fungi			
Penicillinolide A	*Penicillium sp.* SF-5292	Anti-inflammatory	Toledo et al., 2014
Pyrenocine A	*Penicillium paxilli* Ma (G) K	Anti-inflammatory	Toledo et al., 2014
Tanzawaic acid A, C, D, K and Q	*Penicillium steckii* 108YD142	Anti-inflammatory	Shin et al., 2016
Conidiogenone C	*Penicillium chrysogenum* QEN-24S	Antitumor, cytotoxic	Gao et al., 2010
c-Methylated hexaketide	*Penicillium citrinum*	Anticancer, cytotoxic	Hasan et al., 2015
Aspergiolide A	*Aspergillus glaucus*	Cytotoxic	Lin et al., 2008
Cephalimysin A	*Aspergillus fumigatus* OPUST106B- 5	Cytotoxic	Zhou et al., 2013
Zygosporamide	*Zygosporium masonii*	Antitumor, cytotoxic	Hasan et al., 2015
Austrocortirubin	*C. basirubescens* and *C. persplendidus*	Cytotoxic	Beattie et al., 2010
Anhydrofusarubin	*Fusarium spp.*	Cytotoxic	Beattie et al., 2010
Pyrrolidinone-A40	*Ascochyta salicorniae*	Anticancer, antimalarial	Querellou et al., 2010
Bacteria			
Thiochoraline	*Micromonospora*	Antiproliferative, cytotoxic	Schrempf, 2001
Lucentamycins A and B	*Nocardiopsis lucentensis*	Cytotoxic	Choi et al., 2007
Salinipyrones (A and B), pacificanones (A and B)	*Salinispora pacifica*	Cytotoxic, anti-inflammatory	Oh et al., 2008
Diazepinomicin (ECO-4601)	*Micromonospora*	Antitumor, antibacterial, anti-inflammatory	Charan et al., 2004
Salinosporamide A (NPI-0052)	*Salinispora tropica*	Anticancer	Fenical et al., 2009; Chen et al., 2011
Streptopyrrolidine	*Streptomyces spp.* KORDI-3973	Anti-angiogenic, cytotoxic	Shin et al., 2008b
Ammosamide A and B	*Streptomyces spp.* CNR-698	Cytotoxic	Hughes et al., 2009
Bohemamine and deoxybohemamine	*Streptomyces spp.* CNQ-583	Inhibition of cell adhesion	Zimmerman and Blanco, 2008; Cossío et al., 2007
6-Prenyltryptophol, aldoxime indole	*Streptomyces sp.*BL-49-58-005	Antitumor, antiproliferative	Sánchez et al., 2003
Streptochlorin	*Streptomyces spp.* 04DH110	Anti-angiogenic, anticancer	Choi et al., 2007; Shin et al., 2008a
Methylpyridine	*Streptomyces spp.* KORDI-3238	Cytotoxic	Jeong et al., 2006
Caboxamycin	*Streptomyces spp.* NTK 937	Antitumor, antiproliferative	Hohmann et al., 2009
Chandrananimycins A, B and C	*Streptomyces spp.* B6921	Cytotoxic	Olano et al., 2009a;b
Fridamycin D, himalomycin A and B	*Streptomyces spp.* B6921	Antitumor	Myhren et al., 2013
Chinikomycin A, B	*Streptomyces spp.* M045	Antitumor, cytotoxic	Li et al., 2005

Table 3. Summary of bioactive metabolites isolated from marine microorganisms (continued…)

Compound	Source	Activity	Reference
Marineosin A	*Streptomyces spp.*CNQ-617	Cytotoxic	Boonlarppradab et al., 2008
Phenazines, lavanducyanin	*Streptomyces sp.* CNS284	Chemopreventive, anti-inflammatory, antitumor	Kondratyuk et al., 2012
Pseudonocardians	*Pseudonocardia*	Antimicrobial, cytotoxic	Li et al., 2011
Prodigiosin and cycloprodigiosin	*Pseudoalteromonas rubra* and *Zooshikella rubidus*	Cytotoxic, anticancer, immunosuppressive	Williamson et al., 2007; Lee, et al., 2011; Wang, et al., 2012
Mixirins A, B and C	*Bacillus spp.*	Cytotoxic	Zhang et al., 2004
Phenazine	*Bacillus spp.*	Cytotoxic	Li et al., 2007
L-asparaginase	*Pseudomonas aureginosa* (AVP 17)	Anticancer	Cory and Cory, 2006; Verna 2007
Exopolysaccharide EPS-2	*Geobacillus thermodenitrificans*	Immunomodulatory, antiviral	Arena et al., 2009
Exopolymer	*Bacillus thuringiensis* S13	Cytotoxic	Parthiban et al., 2014
Violacein	*Chromobacterium violaceum*	Cytotoxic, antitumor	Sánchez et al., 2006; Choi et al.,2015
Microalgae			
Scytonemin	*Cyanobacteria*	Anti-angiogenic, anti-inflammatory	Malloy et al., 2012
Viridamides A and B	*Oscillatoria nigro-viridis*	Anti-trypanosomal, anti-leishmanial	Simmons et al., 2008
Ulithiacyclamide and patellamide A	*Cyanobacteria*	Antimalarial, antitumor	Sivonen et al., 2010
Symplocamide A	*Symploca spp.*	Antitumor	Talero et al., 2015
Apratoxin D, dragonamides C and D	*Lyngbya spp.*	Antitumor	Talero et al., 2015
C-phycocyanin	*Spirulina platensis*	Anti-inflammatory, cytoprotective, immunomodulatory	Pentón-Rol et al., 2011; Wu et al., 2016
Calothrixins A and B	*Cyanobacteria*	Cytotoxic, antiproliferative	Xu, et al., 2016
Violaxanthin	*Dunaliella tertiolecta*	Cytotoxic, antiproliferative	Pasquet et al., 2011
Violaxanthin	*Chlorella ellipsoidea* and *Chlorella vulgaris*	Anti-inflammatory, antiproliferative	Soontornchaiboon et al., 2012
Astaxanthin, lutein and zeaxanthin	*Chlorella sorokiniana, Chlorella zofigiensis*	Anti-inflammatory, cytoprotective, anticancer	Talero et al., 2015
Eicosapentaenoic acid (EPA)	*Phaeodactylum tricornutum*	Anti-inflammatory, immunomodulatory	Guzmán et al., 2003
Fucoxanthin	*Phaeodactylum tricornutum*	Antioxidant, anticancer, anti-diabetic, anti-photoaging	Peng et al., 2011

Table 3. Summary of bioactive metabolites isolated from marine microorganisms (continued…)

Compound	Source	Activity	Reference
Symbiotic microorganisms			
Kahalalide F (KF)	Microbes isolated from mollusk *Elysia rubefescens*	Cytotoxic, antitumor	Boopathy and Kathiresan, 2010
Metacycloprodigiosin and undecylprodigiosin	*Saccharopolyspora spp.* isolated from sponge *Mycale plumose*	Cytotoxic, antitumor	Olano et al., 2009a
Macrolactin-A	Marine bacteria isolated from microalga *Noctiluca scintillans*	Cytotoxic, antiviral	Boopathy and Kathiresan, 2010

The huge and fast progress in molecular medicine, biochemistry and molecular pharmacology has allowed the identification of several molecular targets involved in these processes. For example, different transcription factors like the nuclear factor κB (NF-κB), or some of its downstream genes such as the proinflammatory cytokines IL-1β, IL-6 or TNF are known to play a role in autoinflammation and cancer (Park and Hong, 2016; Shrihari 2017). Likewise, different membrane receptors, like growth factors receptors, adhesion molecules and cytokine receptors, are required for protective inflammation and immune response; but they are also deeply implicated in cancer and metastatic invasion, autoimmunity and chronic inflammation (Dorsam and Gutkind, 2007; Caspi, 2008; Shrihari, 2017). Other important targets for the three processes are the molecular system for DNA repair and replication, including polymerases, topoisomerases and DNA binding proteins; as well as cell death machinery, including caspases, kinases and mitochondrial permeability proteins (Pawlowski et al., 2001; Si et al., 2016). Last but not least, there are many pieces of research that identify different cellular mediators like prostaglandins, nitric oxide or histamine, and the molecular protein systems that produce them, as a valid pharmacological intervention to treat immunoinflammation and even cancer (Shrihari, 2017; Linus et al., 2017). In fact, some enzymes like nitric oxide synthase (NOS) and cyclooxygenase 2 (COX-2) are also important targets to attenuate chronic inflammation and its derived complications (Linus et al., 2017; Fernandes et al., 2015).

In line with this, several small molecules and chemical inhibitors of these receptors, transcription factors, DNA binding proteins and enzymes have demonstrated to be effective in different *in vitro* and *in vivo* models of inflammation, autoimmune disorders and cancer (Mandal et al., 2009; Linus et al., 2017; Mathur and Hoskins, 2017). However, the rational design of a drug to target a specific protein could be a difficult and high-cost process (Mathur and Hoskins, 2017). Additionally, synthetic libraries have a limited chemical diversity and, consequently, pure synthetic drugs have a limited range of biological targets (Stratton et al., 2015). In contrast, natural sources offer a wide range of metabolites with a huge chemical variety, which can be purified and isolated to screen their biological activity (Mathur and Hoskins, 2017). Particularly marine microbes, because of their distinct metabolism, have the capacity to produce many different compounds with complex structures and multiple biomedical applications (Bhatnagar and Kim, 2010). In next sections, we will discuss the main groups of marine microorganisms that are sources of novel structures with pharmacological potential, and the main biological targets that they are able to modulate.

Bioactive products

Marine fungi-derived metabolites

Marine fungi represent a valuable source of secondary metabolites with new biological activities. They have specific growth requirements for temperature, nutrients, competition, and salinity; this has stimulated the evolutionary development of distinct secondary metabolic pathways in comparison with terrestrial fungi (Hasan et al., 2015). The metabolic and productive capacities of facultative marine fungi have been extensively studied

since the 1990s. More than 690 fungal-derived natural products have been isolated from different species in distinct marine environments (Duarte et al., 2012).

Penicillium genus

Various bioactive compounds have been isolated from marine *Penicillium sp.* For example, various extracts obtained from marine fungus *Penicillium sp.* SF-5292 inhibit the production of nitric oxide (NO) in macrophages stimulated with LPS. In that study, a new 10-membered lactone-type metabolite, named penicillinolide A was isolated. Similarly, the pyrenocine A produced by marine fungus *P. paxilli* Ma (G) K has been identified and characterized, showing a potent anti-inflammatory activity. Pyrenocine A, in pre-treatment and post-treatment conditions, suppressed NO production and the synthesis of PGE_2 and pro-inflammatory cytokines in macrophages stimulated with LPS (Toledo et al., 2014). This compound also modulates the expression of Mac-1 receptor (directly involved in cell migration), the lymphocyte co-stimulatory molecule B7.1 and different NF-κB target genes (Toledo et al., 2014).

The chemical and functional analysis of other *Penicillium* species, like *P. steckii* 108YD142, led to the recent discovery of a new tanzawaic acid derivative: tanzawaic acid Q, along with other related acids previously identified in other species (tanzawaic acid A, C, D, and K) (Shin et al., 2016). These compounds showed a strong anti-inflammatory effect characterized by a significant inhibition of NO production. Additionally, tanzawaic acid Q was able to reduce the activity and expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS-stimulated RAW 264.7 cells (murine macrophages) (Shin et al., 2016). Not only anti-inflammatory, but also antitumor and cytotoxic compounds can be isolated from species of this fungal genus. For example, diterpene conidiogenone C, a potent cytotoxic compound to human leukemia (HL-60 cells), was identified in *Penicillium sp.* and various analogous of this compound have been obtained from culture extracts of *P. chrysogenum* QEN-24S (Gao et al., 2010). Likewise, different alkaloids with anticancer activity have been isolated from *P. citrinum* (Querellou et al., 2010), and more recently, C-methylated hexaketide (2E,4E)-1-(2,6-dihydroxy-3,5-dimethyl-phenyl)hexa-2,4-dien-1-one, present in *Penicillium sp.*, demonstrated a high cytotoxicity against HeLa (human cervical cancer) and SW-620 (human colorectal cancer) cells (Hasan et al., 2015).

Aspergillus genus

The fungal genus *Aspergillus* has also been identified as a prolific source of cytotoxic and other bioactive compounds (Hasan et al., 2015). The aspergiolide A, for example, represents a novel anthraquinone derivative isolated from marine filamentous fungus *A. glaucus*, which displays significant cytotoxicity against K562 (human myelogenous leukemia) and P388 (murine leukemia) cell lines (Lin et al., 2008). Similarly, different extracts from fungus *A. protuberus* demonstrate cytotoxic activity against HepG2 cells (Mathan et al., 2011). Cephalimysin A is another unique structure with biological activity that has been obtained from *Aspergillus* genus, in this case from the species *A. fumigatus* OPUST106B- 5. This compound exhibited significant cytotoxicity against murine and human leukemia cell lines (P-388 and HL-60, respectively) (Zhou et al., 2013).

Other fungal species of interest

Marine fungus *Zygosporium masonii* is another species that produces metabolites with antitumor activity. Seawater-based fermentation of this fungus have allowed the isolation of the cytotoxic depsipeptide zygosporamide, which has been tested against 60 cancer cell lines from NCI (Hasan et al., 2015).

Likewise, austrocortirubin, a metabolite produced by Australian *Cortinarius* toads (*C. basirubescens* and *C. persplendidus*), and naphtoquinone anhydrofusarubin from *Fusarium* spp. display a potent and selective cytotoxicity in human cancer cells (Beattie et al., 2010). Austrocortirubin is selectively cytotoxic to MCF-7 cells (human breast carcinoma); while anhydrofusarubin showed high cytotoxicity on human cancer cell lines such as HCT-8 (colon carcinoma), MDA-MB-435 (mela-

noma) and SF-295 (human multiform glioblastoma) (Beattie et al., 2010).

The species *Myceliophthora lutea Costantin* has also been highlighted to produce bioactive metabolites. Marine isolates of this fungal strain exhibit potent antibacterial and cytotoxic activities (Smetanina et al., 2011). Besides, different anticancer alkaloids have been isolated from *Fusarium sp.* and *Apiospora montagnei,* and the polyketide asco-sali pyrrolidinone-A40, a potential antimalarial agent, has been obtained from *Ascochyta salicorniae* (Querellou et al., 2010).

Bioactive products from marine bacteria

Bacteria have been used for food and industrial applications since the 1880s (Rishiram et al., 2016). In the last decade, the rapid development of microbiology as a science has allowed the exploitation of several bacterial strains as a source of antibiotics, antimycotics and other molecules of pharmacological interest, as well as in multiple biotechnological and biomedical applications (Nalwa, 2014). Marine bacteria, however, have been less explored, being actinobacteria, particularly actinomycetes, the marine microorganisms most employed to produce bioactive molecules, followed by the *bacillus* genus (Bindiya and Sarita G, 2016).

Actinomycetes

Actinobacteria have been considered microorganisms of biotechnological interest, due to their metabolic and secretory capacities, including the production of antibiotics, cytotoxic compounds, and extracellular enzymes (McCarthy and Williams, 1992; Schrempf, 2001). For example, *Micromonosporaceae* family is a potent source of anticancer agents that inhibit the function of the proteasome, among other cellular effects (Schrempf, 2001). Within this family, *Micromonospora marina* has been shown to produce thiocoraline, a bioactive depsipeptide that inhibits RNA synthesis. This compound is selectively cytotoxic against different cancer cell lines, such as melanoma, lung, and colon carcinomas (Schrempf, 2001). Another metabolite produced by *Micromonospora* genus is diazepinomicin (ECO-4601), an antibacterial, anti-inflammatory, and antitumor agent (Charan et al., 2004). This dibenzodiazepinone demonstrated antitumor activity *in vitro* and *in vivo*, in mouse models of glioma, breast and prostate cancer. Ecopia BioSciences Inc. completed the preclinical studies of ECO-4601 as an anticancer drug, allowing this compound to reach clinical trials in Canada on January 3rd, 2006 (Kin, 2006).

Lucentamycins A and B are also bioactive products isolated from a marine actinomycete, in this case from *Nocardiopsis lucentensis* (strain CNR-712) (Choi et al., 2007). These peptides exhibit significant cytotoxic effects in HCT-116 cells (human colon carcinoma) (Choi et al., 2007). Likewise, polyketides, salinipyrones A and B, and pacificanones A and B have been obtained from marine actinomycete *Salinispora pacifica* CNS-237 (Oh et al., 2008). This research proved that the mentioned compounds are not cytotoxic at least to HCT-116 cells, but salinipyrone A displayed a moderate inhibition of interleukin-5 production at 10 μg/mL in a mouse-derived splenocyte model of allergic inflammation (Oh et al., 2008). *Salinispora tropica* is another actinomycete of interest because of its capacity to produce bioactive compounds. For example, the β-lactone-γ-lactam, salinosporamide A (NPI-0052) has been obtained from this marine bacterium through fermentation processes (Fenical et al., 2009). This proteasome inhibitor induces apoptosis in multiple myeloma cells, but it displays particular mechanisms, different from other commercial proteasome inhibitors (Chen D. et al., 2011). Nereus Pharmaceuticals, Inc. is developing NPI-0052 as anticancer agent, a compound that is currently in phase I clinical trials for the treatment of multiple myeloma and other advanced malignancies (Harrison et al., 2016). In addition, actinobacteria are producers of many antitumor drugs of clinical use, including various anthracyclines, like aclarubicin, daunomycin and doxorubicin, the aureolic acid mithramycin, some peptides like bleomycin and actinomycin D, the antimetabolite pentostatin and other chemotherapeutic agents such as neocarzinostatin, carzinophilin and mitomycins (Newman and Cragg, 2007; Olano et al., 2009a).

Another marine bacterial-derived compound that has demonstrated relevant biological activity is benzyl tetrahydropyrrole-derivative streptopyrrolidine, purified from *Streptomyces sp.* KORDI-3973. Streptopyrrolidine has shown anti-angiogenic activity at 100 µg/mL, inhibiting the migration and capillary tube formation of human umbilical vein endothelial cells (Shin et al., 2008b). Ammosamides are also pyrrole-based structures (pyrroloiminoquinones) produced by the *Streptomyces* strain CNR-698. Ammosamide A and B are highly cytotoxic against HCT-116 cells with an IC_{50} of 320 nM for both compounds. These products have demonstrated selective cytotoxicity against a variety of cancer cell lines in a concentration range of 20 nM to 1 µM, and their specific cellular target has been identified as a member of the myosin protein family (Hughes et al., 2009).

Similarly, the *Streptomyces* strain CNQ-583 produces pyrrolizidine alkaloids like bohemamine and deoxybohemamine. These compounds inhibited cell adhesion in an LFA-1/ICAM-1 assay. Both alkaloids at IC_{50} values of 24.3 and 27.2 µg/mL, respectively, were able to inhibit adhesion of human pro-myelocytic leukemia (HL-60 cells) to Chinese hamster ovary (CHO) cells transfected with human ICAM-1 (Zhang et al., 2003). The interaction between LFA-1 and ICAM-1 promotes angiogenesis; it is implicated in chronic inflammation, autoimmune diseases, and cancer metastasis, suggesting both alkaloids as potential immunomodulatory and antitumor drugs (Cossío et al., 2007, Zimmerman and Blanco, 2008).

The 3,6-disubstituted indoles, 6-prenyltryptophol and aldoxime indole, obtained from *Streptomyces* strain BL-49-58-005 (collected in Mexico), are other examples of bacterial-derived bioactive substances (Sánchez et al., 2003). These compounds have been assayed against 14 different tumor cell lines, showing antiproliferative activity in human leukemia, prostate, colon, and pancreatic cancer cells. The 6-prenyltryptophol exhibited a GI_{50} value of 8.46 µM in K-562 cells; whereas aldoxime indole had GI_{50} values in the µM range and, without particular specificity, against HMEC1 (human endothelial cancer), LN-caP (human prostate cancer), PANC1 (human pancreatic adenocarcinoma) K-562 cells and LOVO and LOVO-DOX cells (human colon adenocarcinoma) (Sánchez et al., 2003).

Another indole-related compound with anticancer activity isolated from a marine actinomycete is streptochlorin, which is produced by *Streptomyces* strain 04DH110 (collected from the East Sea of Korea). Streptochlorin displays potent cytotoxic effects in K-562 cells with an IC_{50} of 1.05 µg/mL (Choi et al., 2007). The induction of apoptosis by streptochlorin has been evaluated in U937 (human leukemia) and Hep3B (hepatocarcinoma) cells, demonstrating a decrease in the mitochondrial membrane potential, caspase-3 activation, and down-regulation of antiapoptotic Bcl-2 protein (Park et al., 2008; Shin et al., 2008a). These effects are correlated with a production of reactive oxygen species (ROS) in Hep3B cells (Shin et al., 2008a); whereas in U937 cells it was reported the up-regulation of pro-apoptotic factors like Bax and FasL, and degradation of poly-(ADP-ribose) polymerase (PARP) and phospholipase C-γ1 (Park et al., 2008). In addition, streptochlorin possesses a potent antiangiogenic activity, inhibiting VEGF-stimulated endothelial cell migration and tube formation, possible through downregulation of NF-κB activation (Choi, 2007).

By a similar approach, (Jeong et al., 2006) tested the methylpyridine compound streptokordin, produced by *Streptomyces sp.* KORDI-3238, against various human tumor cell lines. This research showed that streptokordin is cytotoxic to (breast cancer) MDA-MB-231, (colon cancer) HCT 15, (prostate cancer) PC-3, (lung cancer) NCI-H23, (renal cancer) ACHN, (skin cancer) LOX-IMVI and (leukemia) K-562 cells with IC_{50} values ranging from 3.2 to 8.6 µg/mL (Jeong et al., 2006). Other authors have reported that caboxamycin, a benzoxazole compound isolated from *Streptomyces sp.* NTK 937, demonstrates a growth inhibitory activity in human breast carcinoma MCF7, hepatocellular carcinoma HepG2 and gastric adenocarcimona AGS with GI_{50} values of 7.5, 7.4 and 7.3 µg/mL, respectively (Hohmann et al., 2009).

Butenolides are another class of actinomycete-derived compounds that have shown biological activity. Marine actinomycete S*treptomyces luteover-*

ticillatum 11014 has been reported to produce four butenolides: (4S)-4,10-dihydroxy-10-methyl-undec-2-en-1,4-olide, (4S)-4,10-dihydroxy-10-methyl-dodec-2-en-1,4-olide (Mukku et al., 2000; Cho et al., 2001), and the diastereomeric mixture of (4S)-4,11-dihydroxy-10-methyl-dodec-2-en-1,4-olides (Li et al., 2006). All compounds are cytotoxic against K562 cells with IC_{50} values of 8.73, 6.29, and 1.05 µmol/mL and P388 cells with IC_{50} values of 0.34, 0.19, and 0.18 µmol/mL, respectively. Butenolides 3 and 4, tested as a mixture, resulted the most active, but it remains to be defined if both diastereisomers are equally active or not (Li et al., 2006).

Some active metabolites derived from marine actinomycetes have been discovered as antibiotics; however, they exhibit additional properties of biomedical interest. That is the case of the phenoxazin-3-one antibiotics chandrananimycins A, B and C (Olano et al., 2009a). These compounds have cytotoxic activity against human melanoma (MEXF 514L), colon carcinoma (CCL HT29), breast carcinoma (CNCL SF268, LCL H460 and MACL MCF-7), lung carcinoma (LXFA 526L and LXFL 529L), and prostate (PRCL PC3M) and renal cancer (RXF 631L) cells with IC_{70} values of 1.4 µg/mL. Likewise, the known antibiotics iodinin and 1,6-phenazinediol display antitumor activity in human melanoma (MEXF 462NL), lung carcinoma (LXFA 629L and LXFL 529L) and breast (MAXF 401NL), renal (RXF 944L) and uterus (UXF 1138L) cancer cell lines with IC_{50} values of 3.6 and 3.2 µg/mL, respectively (Myhren et al., 2013). Fridamycin D and himalomycin A and B, isolated from *Streptomyces sp.* B6921 strain, are additional examples. These glycosylated pigmented anthracycline antibiotics possess strong antibacterial activity against *Escherichia coli*., *Bacillus subtilis*, *Streptomyces viridochromogenes* and *Staphylococcus aureus* (Maskey et al., 2003). Similarly, chinikomycin A and B, two pigmented antitumor antibiotics with chlorine containing moieties, were isolated from a marine *Streptomyces sp.* strain M045 (Li et al., 2005). These quinone derivatives exhibited cytotoxic effects in different human cancer cell lines. Chinikomycin A was selective toward melanoma, breast cancer and renal cancer cell lines; while chinikomycin B was active against mammary cancer cell lines (Li et al., 2005).

Another *Streptomyces* strain of interest is CNQ-617 (from marine sediment offshore La Jolla, California), which produces the red pigments marineosins. This spiroaminal pyrrolic compounds have displayed significant cytotoxicity in HCT-116 cells with IC_{50} values of 0.5 µM and 46 µM for marineosin A and B, respectively (Boonlarppradab et al., 2008). Additionally, marineosin A has demonstrated selective anti-proliferative activity against melanoma and leukemia cells (Boonlarppradab et al., 2008).

Recent studies have also shown the potential of actinomycetes as producers of pharmacologically active molecules. Consistent with this idea, (Rajan et al., 2012) identified and characterized marine actinomycete *Streptomyces chida* for the capacity to secrete cytotoxic compounds. Ethyl acetate extracts from this microorganism displayed antioxidant capacity in the DPPH scavenging assay, and anti-proliferative activity to human cervical cancer cells (HeLa) (Rajan et al., 2012).

Kondratyuk et al. (2012) also screened chemical extracts derived from a streptomycete (*Streptomyces sp.* strain CNS284) for anti-inflammatory and chemopreventive properties. This study led to the identification of two novel brominated, terpenoid phenazines and the known N-monoterpenoid lavanducyanin. The three compounds were able to inhibit TNF-α-induced NF-κB activity and decrease NO production stimulated with LPS in RAW murine macrophages. They also suppress the PGE_2 production (a well-recognized mediator of inflammation) and decrease the expression of iNOS and COX-2 enzymes, suggesting phenazines as potent anti-inflammatory agents (Kondratyuk et al., 2012). Additional cell cycle analysis and TUNEL assay demonstrated that these brominated compounds also induce apoptosis in HL-60 cells, revealing their potential as antitumor products (Kondratyuk et al., 2012).

Furthermore, Li et al. (2011) found the novel compounds pseudonocardians, diazaanthraquinone derivatives structurally related to rebeccamycin and staurosporine, which were isolated

from marine *Pseudonocardia* and has demonstrated antimicrobial activity and cytotxic potential in human cancer cell lines (Li et al. 2011). Other bacterial strains of *Pseudonocardia* sp. from marine sediments also produce compounds with cytotoxic and antimicrobial activity such as the gamma-butyrolactones called pseudonocardides (Zhang et al. 2016) or the curvuralin macrolide antiobiotics (Ye et al. 2016).

Bacilli

It has been demonstrated that probiotic bacteria, such as lactobacilli, stimulate and modulate the mucosal immune system, by reducing the production of proinflammatory cytokines, and have chemopreventive effects against colorectal cancer (McCarthy and Williams, 1992; Stach and Bull, 2005). Marine bacilli have also been explored to obtain bioactive molecules with antimicrobial, anticancer and immunomodulatory properties. In this sense, *Pseudoalteromonas denitrificans* (Gauthier et al., 1995) has been reported to produce the immunosuppressive, antimalarial, and apoptosis-inducing agent cycloprodigiosin (Kawauchi et al., 1997; Kim et al., 1999; Yamamoto et al., 1999).

Pseudoalteromonas rubra isolated from Mediterranean coastal waters (Gauthier et al., 1995) and Pacific Coast of Japan (Wang et al., 2012) has also been identified as a producer of cycloprodigiosin and prodigiosins (Gerber and Gauthier, 1979; Feher et al., 2008; Wang et al., 2012). This kind of compounds belonging to prodiginin family have demonstrated immunosuppressive and anticancer activities (Williamson et al., 2007). Lately, prodigiosin and its analogues 2-methyl-3-butyl-prodiginine, 2-methyl-3-pentyl-prodiginine, 2-methyl-3-hexyl-prodiginine, and 2-methyl-3-heptyl-prodiginine have been evaluated for their cytotoxicity in U937 leukemia cells, being 2-methyl-3-butyl-prodiginine the most potent cytotoxic compound among them. A deeper molecular research into the cytotoxic mechanisms of these prodiginine derivatives has revealed cellular effects like caspase-3 activation and DNA fragmentation, indicating an apoptosis-inducing capacity in leukemia cells (Wang et al., 2012).

Moreover, Zhang et al. (2004) isolated three novel cytotoxic cyclic acylpeptides from *Bacillus sp.* These peptides, known as mixirins A, B and C, restricted the growth of HCT-116 cells with an IC_{50} of 0.68, 1.6 and 1.3 mg/mL, respectively (Zhang et al., 2004). Other cytotoxic compounds derived from marine bacilli are phenazine or its derivatives, which have been isolated from a deep-sea bacterium *Bacillus sp.* (Li et al., 2007). Likewise, some novel antibiotics, like macrolactin S, were obtained from marine *Bacillus sp.* (Lu, 2010). On the other hand, Rudrapati and Audipudi (2014) identified *Pseudomonas aureginosa* AVP 17 strain as a high producer of anticancer enzyme L-asparaginase. This enzyme degrades L-asparagine that is an essential metabolite to cancer cells, particularly to hematopoietic cancers, representing an effective biotechnological product against lymphocyte sarcoma and lymphoblastic leukemia that has been clinically evaluated (Cory and Cory, 2006; Verna, 2007).

Exopolysaccharides (EPS) and exopolymers (EP) are also interesting molecules secreted by marine bacteria as an adaptation to their environmental conditions (Annarita et al., 2010). This kind of compounds, due to their glycosidic nature, have found multiple biotechnological and industrial applications (Leal et al., 2015). Nevertheless, marine glycosides are getting attention as bioactive molecules with therapeutic potential. In 2009, the exopolysaccharide EPS-2 was isolated from *Geobacillus thermodenitrificans* collected from a shallow marine vent of Volcano Island, Italy. This compound demonstrated immunomodulatory and antiviral effects on immunocompetent cells (Arena et al., 2009). More recently, an exopolymer, obtained from *Bacillus thuringiensis* S13, was reported to exhibit cytotoxicity against human lung cancer cells (A549) with an IC_{50} of 100 µg/mL (Parthiban et al., 2014). The authors suggest that the cytotoxic potential of this exopolymer is related to the brominated compound 1,1,3,1-terphenyl 3,3,5,5-tetrabromo-5-(3,5-dibromo-phenyl), which was identified as part of the glycosylated structure.

Other bacterial species of interest

Chromobacterium violaceum is another bacterial species that has been extensively studied due to its capacity to produce the indole-related violet pigment violacein (Rettori and Durán, 1998; Sánchez et al., 2006). This compound exhibits potent cytotoxic effects against U937 and HL-60 cells, with IC_{50} values ranging from 0.5 to 1 μM (Choi et al., 2015). This bioactive pigment induces various apoptosis-related events, including caspase activation, chromatin condensation, and DNA fragmentation. It also targets protein kinases, which are involved in signal transduction and cancer (Choi et al., 2015). In addition, *Zooshikella rubidus* S1-1 has been identified as a major source of prodigiosin and cycloprodigiosin, with immunosuppressive and anticancer activities through the regulation of NF-κB pathway (Lee et al., 2011).

The genera *Halomonas* and *Sulfitobacter* have also demonstrated to produce metabolites with antitumor activity. Sagar et al. (2013) identified bacterial strains from these genera with potent cytotoxic and apoptosis-inducing capacities, in a screening of 12 isolates from deep sea brines in the Red Sea. Ethanolic and chloroformic extracts obtained from these strains are highly cytotoxic and stimulate apoptosis in MCF-7, HeLa and DU145 (prostate carcinoma) cells (Sagar et al., 2013).

Bioactive compounds from microalgae

Microalgae comprise a variety of unicellular prokaryotic and eukaryotic organisms mainly autotrophic, except for *Polytoma sp.*, *Polytomella sp.*, or *Prototheca wickerhamii*, which have been described as heterotrophical with degenerated chloroplasts (Ueno et al., 2003). This group of microorganisms includes chlorophytes, diatoms, prasinophytes, haptophytes, rhodophytes, dinoflagellates, and cyanobacteria among others, and is the most distributed in both marine and terrestrial waters (Irigoien et al., 2004). This interesting group of photosynthetic microorganisms produces complex secondary metabolites, as a chemical defense against the adverse conditions of its habitats and other opportunistic microbes (de Carvalho and Fernandes, 2010). In addition, microalgae can produce distinct and novel molecular structures due to the high levels of halogen atoms in the composition of their surrounding seawater (Raff et al., 2009). A huge variety of compounds including carotenoids, lipids, polysaccharides, and proteins have been obtained from different microalgae species, demonstrating biomedical potential as anti-inflammatory and anticancer agents (Talero et al., 2015).

Cyanobacteria

There is a special interest in marine cyanobacteria-derived compounds, due to their unique structural features and their pharmacological and biotechnological potential (Malloy et al., 2012). For instance, scytonemin, a yellowgreen pigment that protects cyanobacteria from UV-radiation during sunlight exposure, has shown a selective inhibition of protein kinase Cβ (PKCβ), a recognized mediator of inflammation, and polo-like protein kinase 1 (PLK1), a protein that regulates cell cycle progression. Furthermore, scytonemin exhibits anti-inflammatory effects in mouse model of phorbol-induced ear edema, and antiangiogenic capacity measured as the inhibition in the proliferation of human umbilical vein endothelial cells (Stevenson et al., 2002).

Marine cyanobacteria are also a potential source of antimicrobial and cytotoxic compounds. Two new bioactive linear lipopeptides, viridamides A and B, were isolated from the filamentous cyanobacterium *Oscillatoria nigro-viridis* (Simmons et al., 2008). Both peptides display antimicrobial activity, but particularly viridamide A showed remarkable anti-trypanosomal activity with an IC_{50} of 1.1 μM, and anti-leishmanial activity with an IC_{50} of 1.5 μM. Likewise, polar and non-polar extracts of two cyanobacteria (*Anabaena oryzae* and *Nodularias spumigena*) were tested *in vitro* for their antibacterial activity against *Salmonella typhi*, *Bacillus cereus*, *Klebsiella aerogenes*, *Micrococcus luteus*, and *Staphylococcus aureus*. The acetone extract of *Anabaena oryzae* showed preferential antimicrobial activity against *Salmonella typhi,* whereas *Nodularia spumigena* exhibited a major antibacterial activity against *Bacillus cereus* (Digamber, 2015).

Using a similar approach, a recent study reported different chemical extracts of cyanobacterial mats from hypersaline lakes in northern western desert, Egypt, which exhibit antimicrobial activity against *Vibrio cholerae, Candida tropicalis*, *Staphylococcus lentus*, *Escherichia coli*, *Flavobacterium sp.* and *Shigella sp.* at 1 mg/mL (Abd M., 2016). All extracts contained short-chain fatty acids, amino acids, alcohols, esters, and benzene derivatives. A previous phytochemical screening of cyanobacterial mats had revealed the presence of terpenoids, alkaloids, saponins and glycosides (Raaman, 2006). Similarly, certain anticancer compounds, initially obtained from marine sources, are truly produced by cyanobacteria (Luesch et al., 2002). Ulithiacyclamide and patellamide A, currently classified as cyanobactins, have potent antimalarial, antitumor, and multidrug reversing activities (Sivonen et al., 2010). On the other hand, several cyanobacterial peptides with antitumor activity have been characterized, including somocystinamide A from *Lyngbya majuscula,* apratoxin D from *L. majuscula* and *L. sordida,* symplocamide A from *Symploca sp.*, dragonamides C and D from *L. polychroa* and mitsoamide from *Geitlerinema sp.* (Talero et al., 2015).

Among cyanobacteria, the species *Spirulina platensis* and *Spirulina maxima* have been extensively recognized to produce anti-inflammatory, immunomodulatory and anticancer metabolites (Wu et al., 2016). Particularly *S. platensis* exhibits potent anti-inflammatory, cytoprotective and immunomodulatory properties, due to its high content of the antioxidant deep-blue pigment C-phycocyanin (Wu et al., 2016). This phycobiliprotein has demonstrated protective effects in a mouse model of experimental autoimmune encephalitis (EAE), decreasing the oxidative and inflammatory damage in the central nervous system, and improving myelin and axonal damage (Pentón-Rol et al., 2011). C-phycocyanin also triggers a regulatory T-cell response in peripheral blood mononuclear cells from patients with multiple sclerosis (MS), suggesting the immunomodulation of T-cell populations as a possible mechanism underlying its neuroprotective effects (Pentón-Rol et al., 2011). In addition, this compound significantly reduces LDH release, and expression of iNOS, COX-2, TNF-α, and IL-6 in LPS-stimulated BV-2 microglial cells (Chen et al., 2012). Another interesting molecule isolated from this cyanobacterial specie is the polysaccharide immulina, which have shown stimulating effects on immune function of THP-1 human monocytic cells (Pugh et al., 2001). Dietary consumption of immulina-enriched extracts from *S. platensis* has demonstrated an enhancing on innate immunity in mice and humans (Hayashi et al., 2004). A recent study has also revealed the cytotoxic potential of *S. platensis* extracts in Kasumi-1 (human acute leukemia) and K-562 cells (Hernandez et al., 2017).

Spirulina maxima also shows antioxidant and anti-inflammatory effects. The administration of this extract ameliorates 6-hydroxydopamine-dependent oxidative stress and neurotoxic effects in rats, reducing the levels of NO, ROS, and lipid peroxides in brain tissue of treated animals (Tobón-Velasco et al., 2013). Likewise, Sin et al. (2014) demonstrated DPPH scavenging properties and a strong inhibition of NO production in human skin fibroblasts CCD-986sk, for an *S. maxima* extract obtained by ultrasonication.

In addition, a latest study has identified calothrixins A and B, as two cyanobacterial metabolites structurally like quinoline, quinone, and indole pharmacophores, which show a high potential as cytotoxic and antitumor compounds through the selective inhibition of topoisomerase I. They are also able to interfere with RNA synthesis in bacteria targeting different steps of the process. Further investigation is still required to define the precise action mechanism for many of its analogs (Xu et al., 2016).

Chlorophytes

Another major group within microalgae, the chlorophytes, has been studied because of its active production of pigmented metabolites with strong antioxidant and anticancer properties. For example, *Dunaliella* genus has generated attention due to its capacity to produce β-carotene-related molecules. In line with this, β-carotenoids with antiproliferative and cytotoxic activity, like violax-

anthin, have been isolated from some species such as *Dunaliella tertiolecta* (Pasquet et al., 2011). Likewise, *D. bardawil* has been identified as the major source of β-carotenoids among microalgae (Davidi et al., 2014).

Some chlorophytes of genus *Chlorella,* like *C. ellipsoidea* and *C. vulgaris,* also produce violaxanthin and other bioactive compounds. Extracts from these microorganisms show anti-proliferative effects on HCT-116 cells with induction of apoptosis (Cha et al., 2008). Violaxanthin derived from *C. ellipsoidea* also demonstrates anti-inflammatory activity through the selective inhibition of NF-κB activity, NO production and PGE_2 synthesis in RAW cells (Soontornchaiboon et al., 2012). Other species like *C. sorokiniana*, *C. zofigiensis*, *C. prothecoides* and *C. saccharophila* produce anticancer, cytoprotective and anti-inflammatory β-carotenoids, such as astaxanthin, lutein and zeaxanthin (Talero et al., 2015). In addition, different sulphated polysaccharides isolated from *Chlorella stigmatophora* have shown significant anti-inflammatory and immunomodulatory effects (Guzmán et al., 2003).

Other microalgae of interest

Among microalgae, diatoms have demonstrated to be a reliable source to obtain new marine bioactives. According to this, Desbois et al. (2009) isolated the eicosapentaenoic acid (EPA), with antibacterial activity, from marine diatom *Phaeodactylum tricornutum*. This polyunsaturated fatty acid showed activity against both Gram-positive and Gram-negative bacteria, including methicillin-resistant *Staphylococcus aureus* (Desbois et al., 2009). On the other hand, *P. tricornutum* has been studied to produce exopolysaccharides with anti-inflammatory and immunomodulatory effects (Guzmán et al., 2003).

Xanthophyll fucoxanthin is another bioactive molecule, produced by diatoms and other microalgae, which has shown antioxidant activity, anticancer, anti-diabetic and anti-photoaging properties (Peng et al., 2011). Besides, some prasinophytes, such as *Tetraselmis sp.* and *Nannochloropsis oculata,* are also species with pharmacological potential, because they are rich in polyunsaturated omega-3 fatty acids, with anti-angiogenic and anti-tumor capacities (Spencer et al., 2009; Lee and Han, 2015).

Symbiotic marine microorganisms

The surfaces of all marine eukaryotes are rich in colonic microbes, which exist in symbiosis with the host, generally in communities and attached as biofilms (Penesyan et al., 2010). This associated microbiota has common aspects and differences in comparison to microorganisms of the surrounding seawater, and even to symbiotic communities of other hosts, as a result of specific adaptations to a particular macroorganisms (Penesyan et al., 2010). Consequently, it can produce distinct molecules with pharmacological potential, due to its symbiotic interactions, or can be considered as an alternative source of known bioactive compounds.

Various marine-derived natural products have been identified as metabolites of macroorganisms such as algae or invertebrates; however, the real producer is, in many cases, a symbiont microorganism. For example, the tricyclic diterpene glycosides pseudopterosins, with demonstrated anti-inflammatory and analgesic activities, were initially isolated from the Caribbean Sea whip *Pseudopterogorgia elisabethae* (Look et al., 1986). Later, it was reported that these glycosides are produced by symbiont dinoflagellate *Sympoidinium* sp. found within the tissues of the sea whip (Mydlarz et al., 2003). In the same way, kahalalide F (KF) is a depsipeptide isolated from Hawaiian mollusk *Elysia rubefescens*; this compound is believed to be synthesized by associated microbes (Boopathy and Kathiresan, 2010). KF induces cytotoxicity and cell cycle arrest in G1 phase in a p53-independent manner. *In vitro*, KF displays selectivity for prostate cancer cell lines; it has also been evaluated *in vivo*, demonstrating activity against breast cancer.

Likewise, symbiotic microorganisms have also been reported to produce prodigiosins. Heptyl prodigiosin has been obtained from α-proteobacteria isolated from a marine tunicate collected in Zamboanga, Philippines. This compound exhibits its selective *in vitro* antimalarial activity against *Plasmodium falciparum* (Lazaro et al., 2002). In addi-

tion, two previously identified compounds of prodigiosin family have been obtained from cultures of *Saccharopolyspora* sp., a symbiotic actinomycete isolated from sponge *Mycale plumose* (coast of Qingdao, China) (Olano et al., 2009a). Metacycloprodigiosin and undecylprodigiosin exhibited an important cytotoxic activity against P388 and HL-60 cells, A549 and SPCA4 cells (lung carcinomas) and hepatic carcinoma BEL-7402, with IC_{50} values between 0.007 and 7.52 μM for metacycloprodigiosin and 0.013 to 0.11 μM for undecylprodigiosin (Olano et al., 2009a).

Other metabolites with antimicrobial, antitumor and immunomodulatory properties have been isolated from symbiotic microbes. That is the case of topoisomerase I inhibitors cyclopropane and 14-methylhexadecanoic acid (14-MHDA) produced by *Streptomyces sp.* strain KM86-913, isolated from a marine sponge collected from the seashore of Keomun Island, Korea (Lee, 1998). Similarly, marine bacteria associated with *Noctiluca scintillans* produce macrolactin-A, which is cytotoxic to B16-F10 murine melanoma cells, restrict the replication of mammalian herpes simplex virus (HSV) (type I and II), and protects T lymphocytes against human immunodeficiency virus (Boopathy and Kathiresan , 2010).

Marine alkaloids like tambjamines represent another group of compounds synthetized by colonic bacteria from higher organisms (Burke et al., 2007). These pigments have demonstrated antimicrobial, immunosuppressive, antitumorigenic and anti-proliferative activities (Bhatnagar and Kim, 2010). In a similar line, another study reported antibacterial and antilarval compounds from marine bacterium *Bacillus amyloliquefaciens* SCSIO 00856, isolated from gorgonian *Junceella juncea* (South China Sea) (Gao et al., 2010).

DISCUSSION

Marine microorganisms have demonstrated to be a promising source to obtain new molecules with different properties of biomedical interest. Due to the adverse environmental conditions of marine habitats and the presence of diverse pathogens and opportunistic microbes, marine microorganisms have developed a variety of secondary metabolites with different bioactivities. In addition, the chemical composition of seawater is rich in uncommon atoms, such as sulfur and halogens, thus allowing microorganisms to produce distinct compounds like sulfated polysaccharides and brominated derivatives, with important pharmacological properties.

The existence of a particular metabolic pathways in marine microbes has allowed them to synthetize complex chemical structures different from marine macroorganisms, as well as from terrestrial microorganisms. As it has been discussed throughout this review, novel compounds with aromatic and polypirrolic moieties can be obtained from marine microbial sources, including actinomycetes, cyanobacteria, symbiotic microorganisms, and some selected fungi. Furthermore, terpenoids, long-chain fatty acids, polysaccharides, carotenoids, alkaloids and some bioactive peptides and proteins have also been isolated from marine fungi, bacilli, and microalgae. Due to their huge chemical variety, marine microbe-derived products have the capacity to display multiple action mechanisms (Fig. 2). The connection between a particular structure and a specific mechanism is not clear, but the presence of more than one aromatic ring and polyunsaturated bonds seems to be a common and special feature for many of these metabolites. They can inhibit angiogenesis and modulate the activity of different apoptosis-related factors (Bcl2, Bax, FasL, PARP, caspase-3), phospholipases and kinases involved in multiple signal transduction pathways and oncogenesis (C-γ1, PLK1, PKCβ), as well as topoisomerases which contribute with tumor proliferation. Not surprisingly, most of these compounds are selectively cytotoxic and anticancer. Additionally, they have demonstrated important anti-inflammatory effects through inhibition of iNOS and COX-2 enzymes, modulation of PGE_2 synthesis and reduction of proinflammatory cytokines such as TNF-α and IL-6.

Many of these bioactive molecules also have immunomodulatory properties. Some of them can act as immunosuppressants, decreasing immune cell activation, interfering with cell migration and

LFA-1/ICAM-1 interaction, and even inducing a regulatory T-cell response. In contrast, other compounds stimulate innate immunity and antiviral status in immunocompetent cells. Moreover, several marine microbial-derived metabolites are potent antiviral, antimicrobial and antiparasitic agents, biological activities that contribute to immunological defense and immune surveillance. Remarkably, a common mechanism displayed by many of these products is the inhibition of NF-κB, which has a pivotal role in immunity, inflammation, and cancer.

Natural products from marine microorganisms are promising therapeutic alternatives in the treatment of immunopathologies, inflammatory diseases and cancer. This review has addressed only representative examples of bioactive molecules and their action mechanisms, but the huge pharmacological and biomedical potential of marine microorganisms is yet to be explored. Thousands of bioactive molecules have been isolated from marine microbial sources; however, just a few have reached clinical trials. A deeper characterization of these compounds to elucidate their action mechanisms, as well as more rigorous preclinical assessments in different animal models, are required for the successful development of novel drugs from natural products of marine microbial origin. Additionally, previously characterized compounds have to be re-examined in various models under different experimental conditions, to reveal new bioactivities and mechanisms.

Marine microorganisms also represent an ecologically sustainable source of new bioactive drugs, which is the main issue of natural products at present. Unlike multicellular organisms such as plants, algae or marine invertebrates, microorganisms have the advantage of producing high amounts of specific metabolites through fermentation processes. Besides, microorganisms can be more easily collected and maintained under laboratory conditions to ensure a continuous production, without massive and periodical collections that could affect marine ecosystems. An optimization of fermentation processes to increase the production of a particular metabolite, and the development of new ways to successfully isolate and culture symbiotic microorganisms, are among the biggest challenges. More efforts should be dedicated to the development of novel anti-inflammatory, immunomodulatory and anticancer drugs from marine microbial strains. They offer a feasible option for the pharmacological intervention of complex diseases, which currently lack an effective treatment and represent a huge health problem worldwide.

CONCLUSIONS

The marine microbial pharmacology has experienced a rapid growth in the past 40 years, particularly in the last decade. Several compounds of different and complex structures have been isolated from multiple microbial sources including marine fungi, bacteria, microalgae, and symbiotic microorganisms. Beyond the classical antibiotics isolated from marine fungi an some selected bacterial strains, new glycosidic, polypirrolic and halogenated structures has been obtained and purified from these two groups of microorganisms as well as from some symbiotic microbial species, demonstrating novel and potent pharmacological properties in various models of cancer, immunity and inflammation, including *in vitro* cell culture and animal models. In addition, some strains of microalgae are source of carotenoids, natural pigments and fatty acids with antioxidant, immunomodulatory and anticancer activities. All these compounds have multiple modes of action and are able to modulate different pathways within the cell. Most of them can act on NF-κB and caspase signaling, modulate the activity of DNA binding enzymes, regulate apoptosis, inhibit the production of proinflammatory mediators including PGE_2 and NO and interfere with activity/expression of cell surface receptors. Due to the high pharmacological potential of the marine microbial derived products and the feasibility of their production in an ecofriendly way, these compounds have played an important role in the therapeutical intervention of many complex diseases and still today represent a crucial alternative to treat different immunological, inflammatory and malignant conditions.

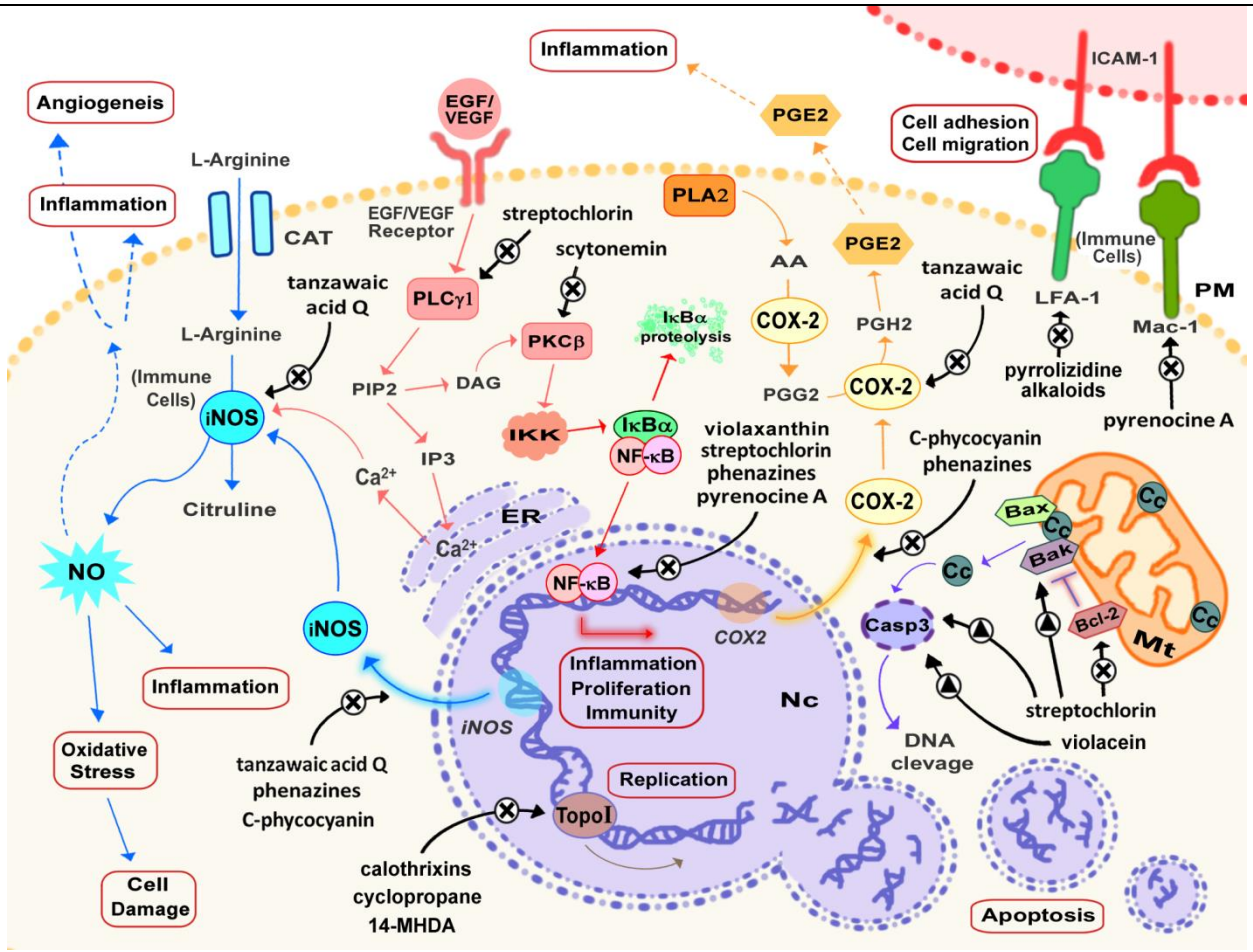

Figure 2. Overview of the main molecular targets and cellular pathways modulated by microbe-derived compounds**.**

Most of the bioactive metabolites isolated from marine microorganisms have demonstrated to modulate the activity and/or expression of inducible nitric oxide synthase (iNOS), cyclooxygenase-2 (COX-2), topoisomerase I (TopoI), kinases and phosphatases like phospholipase Cγ1 (PLCγ1) and protein kinase Cβ (PKCβ), membrane receptors involved in cell adhesion and migration like lymphocyte function-associated antigen 1 (LFA-1) and macrophage-1 antigen (Mac-1), and some apoptosis-related factors such as BAX, BAK, BcL-2 and Caspase 3. Representative examples are shown. Black arrows with triangles represent activation/upregulation, and black arrows with X symbols represent inhibition/downregulation. PM: plasma membrane, Nc: nucleus, ER: endoplasmic reticulum, Mt: mitochondria.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTION:

Contribution	Riera-Romo M	Wilson-Savón L	Hernandez-Balmaseda I
Concepts or ideas	x	x	x
Design	x		
Definition of intellectual content	x		x
Literature search	x	x	x
Experimental studies			
Data acquisition	x	x	x
Data analysis	x	x	
Statistical analysis		x	x
Manuscript preparation	x	x	
Manuscript editing			x
Manuscript review	x	x	x

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