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ANALYSIS OF THE IMMUNOMODULATOR PROFILE OF SECONDARY METABOLITES DERIVED FROM *STREPTOMYCES SP.*

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ABSTRACT

Objective: To carry out a bibliographical survey, through a narrative literature review, on the use of secondary metabolites of *Streptomyces* sp. as an immunomodulatory agent.

Results and Discussion: Actinobacteria (phylum *Actinomycetota*) represent Gram-positive, filamentous, spore-forming bacteria that produce secondary metabolites, compounds that offer an advantage in the growth, reproduction and perpetuation of the microorganism, especially in environments in which there is ecological competition for nutrients and for territory between different species. These metabolites are notably known for their important antimicrobial action, having great utility in clinical, pharmaceutical and industrial settings. More than 10,000 bioactive compounds have already been obtained from actinobacteria, where approximately 75% of them come from the *Streptomyces* genus, currently responsible for the production of approximately 80% of antibiotics on the market, with great clinical importance. In addition to antimicrobial activity, several studies seek to identify the activity of secondary metabolites of *Streptomyces* sp. as immunomodulators of the immune response, positively or negatively regulating the chain of events that is established during an aggressive stimulatory process.

Conclusion: The genus *Streptomyces* is one of the focuses of studies in the biotechnology and pharmaceutical industry because its metabolite products present bioactivities of interest to different sectors. The metabolites produced by *Streptomyces* sp. They have the potential to act as an immunomodulatory booster against diseases, optimizing and regulating the work of the immune system.

Research Implications: The practical and theoretical implications of this research are discussed, providing insights into how the results can be applied or influence practices in the field of biotechnology. These implications may cover the areas of microbiology, pharmacy, medicines.

Originality/Value: This study contributes to the literature by addressing the importance of selecting microorganisms with biological activity. The relevance and value of this research are evidenced when it shows the capacity and versatility of microorganisms of industrial interest.

Keywords: Secondary Metabolism, *Streptomyces*¸Immunologic Factors, Anti-infective Agents.

ANÁLISE DO PERFIL IMUNOMODULADOR DE METABÓLITOS SECUNDÁRIOS DERIVADOS DE *STREPTOMYCES SP.*

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RESUMO

Objetivo: Realizar o levantamento bibliográfico, por meio de uma revisão narrativa de literatura, sobre o uso de metabólitos secundários de Streptomyces sp. como agente imunomodulador.

Resultados e Discussão: As actinobactérias (filo Actinomycetota) representam bactérias Gram-positivas, filamentosas, formadoras de esporos e produtoras de metabólitos secundários, compostos que oferecem vantagem no crescimento, na reprodução e na perpetuação do microrganismo, especialmente em ambientes nos quais há competição ecológica por nutrientes e por território entre diversas espécies. Estes metabólitos são notavelmente conhecidos pela sua importante ação antimicrobiana, possuindo grande utilidade no âmbito clínico, farmacêutico e industrial. Mais de 10 mil compostos bioativos já foram obtidos de actinobactérias, onde aproximadamente 75% deles advém do gênero Streptomyces, sendo responsáveis atualmente pela produção de aproximadamente 80% dos antibióticos presentes no mercado, com grande importância clínica. Além da atividade antimicrobiana, vários estudos buscam apontar a atividade de metabólitos secundários de Streptomyces sp. como imunomoduladores da resposta imunológica, regulando positiva ou negativamente a cadeia de eventos que se estabelece durante um processo agressivo estimulativo.

Conclusão: O gênero Streptomyces é um dos focos de estudos da indústria biotecnológica e farmacêutica devido seus produtos metabólitos apresentarem bioatividades de interesse para diferentes setores. Os metabólitos produzidos por Streptomyces sp. apresentam potencial para atuarem como reforço imunomodulador contra doenças, otimizando e regulando o trabalho do sistema imune.

Implicações da Pesquisa: As implicações práticas e teóricas desta pesquisa são discutidas, fornecendo insights sobre como os resultados podem ser aplicados ou influenciar práticas no campo de biotecnologia. Essas implicações podem abranger as áreas de microbiologia, farmácia, medicamentos.

Originalidade/Valor: Este estudo contribui para a literatura ao abordar a importancia de selecionar microrganismos com atividade biológica. A relevância e o valor desta pesquisa são evidenciados quando se mostra a capacidade e versatilidade dos microrganismos de interesse industrial.

Palavras-chave: Metabolismo Secundário, *Streptomyces*, Fatores Imunológicos, Anti-Infecciosos.

ANÁLISIS DEL PERFIL INMUNOMODULADOR DE METABOLITOS SECUNDARIOS DERIVADOS DE *STREPTOMYCES* SP.

RESUMEN

Objetivo: Realizar un levantamiento bibliográfico, a través de una revisión narrativa de la literatura, sobre el uso de metabolitos secundarios de Streptomyces sp. como agente inmunomodulador.

Resultados y Discusión: Las actinobacterias (filo *Actinomycetota*) representan bacterias Gram positivas, filamentosas, formadoras de esporas que producen metabolitos secundarios, compuestos que ofrecen una ventaja en el crecimiento, reproducción y perpetuación del microorganismo, especialmente en ambientes en los que existe competencia ecológica. de nutrientes y de territorio entre diferentes especies. Estos metabolitos son notablemente conocidos por su importante acción antimicrobiana, teniendo gran utilidad en entornos clínicos, farmacéuticos e industriales. Ya se han obtenido más de 10.000 compuestos bioactivos a partir de actinobacterias, de los cuales aproximadamente el 75% provienen del género *Streptomyces*, actualmente responsable de la producción de aproximadamente el 80% de los antibióticos del mercado, con gran importancia clínica. Además de la actividad antimicrobiana, varios estudios buscan identificar la actividad de metabolitos secundarios de *Streptomyces* sp. como inmunomoduladores de la respuesta inmune, regulando positiva o negativamente la cadena de eventos que se establece durante un proceso estimulador agresivo.

Conclusión: El género *Streptomyces* es uno de los focos de estudios en la industria biotecnológica y farmacéutica debido a que sus productos metabolitos presentan bioactividades de interés para diferentes sectores. Los metabolitos producidos por *Streptomyces* sp. Tienen el potencial de actuar como refuerzo inmunomodulador frente a enfermedades, optimizando y regulando el trabajo del sistema inmunológico.

Implicaciones de la investigación: Se discuten las implicaciones prácticas y teóricas de esta investigación, proporcionando información sobre cómo los resultados pueden aplicarse o influir en las prácticas en el campo de la biotecnología. Estas implicaciones pueden abarcar las áreas de microbiología, farmacia y medicamentos.

Originalidad/Valor: Este estudio contribuye a la literatura al abordar la importancia de seleccionar microorganismos con actividad biológica. La relevancia y valor de esta investigación se evidencia al mostrar la capacidad y versatilidad de microorganismos de interés industrial.

Palabras clave: Tratamiento Secundario, *Streptomyces*, Factores Inmunológicos, Antiinfecciosos.

1 INTRODUCTION

The genus *Streptomyces* comprises gram-positive bacteria belonging to the phylum Actinobacteria, characterized by a high G+C content in their DNA, ranging from 50% to 70%. Morphologically, these microorganisms are spore-forming and produce hyphae that develop into an aerial mycelium, resulting in filamentous growth. This structure enhances their resistance and survival in various habitats, including terrestrial and marine environments (Kronheim *et al*., 2023; Luthe *et al*., 2023).

These bacteria are recognized for their prolific production of bioactive compounds derived from their secondary metabolism through the production of enzymatic systems and synthesis of substances, making them a group of high clinical and biotechnological relevance. They exhibit antioxidant, antiparasitic, anticancer, immunosuppressive, and antimicrobial activities (Ab Mutalib *et al*., 2020; Santos *et al*., 2024). Currently, they are responsible for the production of two-thirds of the antibiotics available on the market, with approximately 80% derived from the genus *Streptomyces*. Notable antibiotics of significant clinical and therapeutic importance include streptomycin, erythromycin, and tetracycline (Amorim *et al*., 2020; Lin *et al*., 2022).

Despite the variety of compounds already isolated, the emergence of multidrug-resistant microorganisms has increased dramatically. These pathogens seek mechanisms to evade and block the immune response. Once reaching their target, these microorganisms proliferate in the host, leading to infection and exhaustion. Included in this group of microorganisms are *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, among others (Alam *et al*., 2022; Pinto *et al*., 2021).

The immune system is responsible for defending and protecting the organism against agents recognized as foreign. After detection, it signals and recruits cells to achieve homeostasis and integrity (Ghosh *et al*., 2020). Immunomodulatory agents can assist the immune system by altering its function, potentially acting as immunostimulants or immunosuppressants (Targino *et al*., 2022; Zhao *et al*., 2020). Therefore, the search for biomolecules that beneficially modulate the immune system is crucial. The genus *Streptomyces* is a promising candidate due to its secretion of a variety of structurally diverse products.

Thus, this study aims to conduct a literature review on the use of secondary metabolites from *Streptomyces* sp. as immunomodulatory agents.

2 *STREPTOMYCES*: GENERAL CHARACTERISTICS

Actinobacteria (phylum Actinomycetota) represent gram-positive, filamentous, spore-forming bacteria that produce secondary metabolites. These compounds provide advantages in growth, reproduction, and the perpetuation of the microorganism, especially in environments where there is ecological competition for nutrients and territory among various species (Quinn *et al*., 2020). These metabolites are notably recognized for their significant antimicrobial activity, with great utility in clinical, pharmaceutical, and industrial contexts (Sivalingam *et al*., 2019).

Among all actinomycete genera, species of *Streptomyces* are particularly prominent for their metabolism of antimicrobial compounds, producing approximately 100,000 substances with some antibiotic activity, which represent about 70-80% of all bioactive natural products with pharmacological or agrochemical applications. *Streptomyces* constitutes about 95% of all actinomycete species present in terrestrial soil (Barka *et al*., 2016; Alam *et al*., 2022).

Decades after their discovery, metabolites from *Streptomyces* continue to be explored by researchers, who employ a range of strategies to stimulate the production of new metabolites by these species, including modification of culture conditions and genetic techniques such as heterologous expression and genomic mining (Lacey; Rutledge, 2022). The genome of *Streptomyces* spp. contains various regions known as biosynthetic gene clusters (BCGs), responsible for encoding multienzymatic complexes that act in the synthesis of bioactive metabolites (Lee *et al*., 2020).

The nomenclature *Streptomyces* was first proposed by Waksman and Henrici (1943) when they isolated a new aerobic, saprophytic, spore-forming actinomycete from soil. Since then, hundreds of species within this genus have been isolated from various habitats, including

soil, terrestrial and marine sediments, and extreme environments. These bacteria are also capable of colonizing symbiotically other organisms, such as plants, fungi, and animals (Law *et al*., 2019). Currently, more than 800 *Streptomyces* strains have been registered and validated, consolidating *Streptomyces* as the largest genus of secondary metabolite producers (Donald *et al*., 2022).

Actinomycetes also exhibit significant biochemical properties, including the production of enzymes that degrade high-complexity macromolecules, such as lipases, proteases, and cellulases. These enzymes also show excellent stability under temperature and pH variations, making them widely used in industrial applications (Moreira; Siqueira, 2006). Their presence is also crucial in soil biodegradation processes, as well as in the formation of humus and the production of volatile substances like geosmin, which is responsible for the characteristic "wet earth" odor of these microorganisms (Alam *et al*., 2022).

In this context, actinomycetes represent an extensive and diverse phylum of bacteria with a global distribution, notable for their production of secondary metabolites with biological activity. Bioactive substances derived from *Streptomyces* have the capability to act as antimicrobial, antiviral, antioxidant, pesticide, herbicide, antitumor, and immunosuppressive agents (Alam *et al*., 2022). The metabolites of these microorganisms, such as antibiotics, lectins, and peptides, have been described as immunomodulators in various experimental models (Fateh *et al*., 2015).

3 ANTIMICROBIAL ACTIVITY

Streptomyces é um gênero de bactérias pertencentes à classe das actinobactérias, que têm grande importância para o setor biotecnológico, uma vez que são amplamente reconhecidas como grandes produtoras de moléculas bioativas derivadas do seu metabolismo secundário, com diversas atividades já relatadas, especialmente sua atividade antimicrobiana para uso clínico e agrícola (Barka *et al*., 2016; Saldaña *et al*., 2020; Santos *et al*., 2020; Rios-Hernández *et al*., 2021).

A busca por novas biomoléculas com potencial para inibição e/ou destruição de agentes infecciosos começou após o advento da penicilina em 1928 por Alexander Fleming, o que levou à descoberta de novos antibióticos através da bioprospecção de produtos naturais microbianos (Goredema *et al*., 2020). Por exemplo, em 1944, Waksman e Schstz isolaram a estreptomicina a partir de Streptomyces griseus, sendo o primeiro medicamento eficaz no tratamento da tuberculose e apresentando grande potencial contra Mycobacterium tuberculosis.

De acordo com Pšeničnik *et al*. (2022), mais de 10 mil compostos bioativos já foram obtidos de actinobactérias, dos quais aproximadamente 75% advêm do gênero Streptomyces. Atualmente, essas bactérias são responsáveis pela produção de aproximadamente 80% dos antibióticos disponíveis no mercado, com grande importância clínica. Entre esses antimicrobianos estão as classes dos aminoglicosídeos, macrolídeos, β-lactâmicos, peptídeos, polienos, entre outros (Tomaseto *et al*., 2020; Evangelista-Martínez *et al*., 2022). A Tabela 1 lista alguns dos antibióticos promissores oriundos de Streptomyces sp.

Apesar das descobertas e avanços relacionados a essas classes de medicamentos, as doenças infecciosas continuam a figurar entre as principais causas de morte em todo o mundo, afetando principalmente indivíduos imunossuprimidos, crianças e idosos. A resistência aos antimicrobianos está se tornando cada vez mais um problema de saúde pública, uma vez que os agentes infecciosos buscam mecanismos através da formação de estruturas, como biofilmes, que conferem ao microrganismo uma resistência ampla a diversas substâncias (Neamah *et al*., 2020).

Table 1

Promising antimicrobials isolated from Streptomyces spp. with their mechanism of action

***Streptomyces* spp.**	**Antibiotic**	**Antibiotic**	**Insulations**	**Mechanism**
S. griseus	Estreptomicina	Aminoglicosídeo	1944	Inhibit protein synthesis - binds irreversibly to the 30S subunit of ribosomes
S. venezuelae	Cloranfenicol	Afenicol	1947	binds to the 30S subunit of the ribosome and appears to inhibit the movement of ribosomes along the mRNA
S. fradiae	Neomicinas A, B, C	Aminoglicosídeo	1949	Inhibit protein synthesis - binds irreversibly to the 30S subunit of ribosomes
S. noursei	Nistatina	Macrolideo polienos	1950	Binds to sterols present in the cell membrane, forming spores and causing the release of the contents
S. erythreus	Eritromicina	Macrolídeo	1952	Inhibit protein synthesis - acts by binding to the 23S ribosomal RNA of the 50S subunit
S. orientalis	Vancomicina	Glicopeptídeos	1956	Inhibition of bacterial cell wall biosynthesis
S. mediterranei	Rifampicina	Rifamicinas	1957	Inhibits RNA polymerase, binds to the β subunit of RNA polymerase, preventing the transcription of mRNA and consequent protein synthesis
S. nodosus	Anfotericina B	Polieno	1962	Binds to sterols present in the cell membrane, forming spores and causing the release of the contents
S. lincolnensis	Lincomicina	Lincosamida	1962	Binds reversibly to the 50S subunit
S. tenebrarius	Tobramicina	Aminoglicosídeo	1965	Inhibits protein synthesis – binds to the 30S subunit of ribosomes
S. clavuligerus	Ácido clavulânico	b-Lactâmicos	1974/75	Inhibits the action of the beta-lactamase enzyme
S. roseosporus	Daptomicina	Lipodepsipeptídeo	1986	Binds to bacterial cell membranes, causing rapid membrane depolarization by K efflux

Source: Adapted from Cartuche Flores (2021)

Studies report the resistance of *S. aureus* to various antibiotics, such as aminoglycosides, glycopeptides, and some quinolones. The increasing resistance of this pathogen to vancomycin is particularly concerning, as it is currently the drug of choice for treatment. In 2017, the WHO published a list of 12 bacterial species considered a priority due to antibiotic resistance. Asokan *et al*. (2019) analyzed the major pathogens reported as resistant, with methicillin-resistant *S. aureus* (MRSA) being the most frequently reported, followed by *Enterobacteriaceae* resistant to extended-spectrum beta-lactamases (ESBL) and *Enterococcus faecium* resistant to vancomycin.

Another promising substance is platensimycin, isolated from *S. platensis*. Currently in preclinical studies, it shows significant promise against MRSA and vancomycin-resistant

Enterococcus spp., acting on fatty acid biosynthesis and reducing pathogen resistance and toxicity (Cartuche Flores *et al*., 2021). Mu *et al*. (2020) conducted a study on actinomycin D isolated from *Streptomyces luteus*, demonstrating inhibition of biofilm formation by *Staphylococcus epidermidis*, making it a potentially valuable substance for reducing infections associated with this resistance structure.

The results and discussions of an article should be presented clearly and systematically, based on the data collected and analyses performed during the study. Initially, results should be presented objectively and concisely, using tables, graphs, and statistics if applicable, to highlight the main findings. Subsequently, in the discussion section, results are interpreted in light of existing literature, emphasizing similarities, differences, and implications for theory and practice.

Furthermore, the limitations of the study and possible directions for future research should be discussed. It is essential that both results and discussion are grounded in solid evidence and contribute significantly to advancing knowledge on the topic addressed.

4 IMMUNOMODULATION OF METABOLITES FROM STREPTOMYCES SP.

In addition to antimicrobial activity, several studies aim to highlight the immunomodulatory effects of secondary metabolites from *Streptomyces* spp., which regulate the immune response either positively or negatively during an aggressive stimulatory process. Below are some compounds derived from *Streptomyces* spp. that show promising results in immunomodulating various immunological processes (Table 2).

4.1 CYTOKINE MODULATION

Cytokines are soluble proteins of low molecular weight secreted by various cells, such as lymphocytes, macrophages, and natural killer cells, responsible for mediating and communicating all reactions seen in the immune response (Kulbe *et al*., 2012). They are classified into categories, including tumor necrosis factor (TNF-α), interleukins (ILs), lymphokines, monokines, interferons (IFNs), colony-stimulating factors (CSFs), and transforming growth factors (TGFs) (Sprague; Khalil, 2009). Depending on the stimulus, cytokines can be classified as pro-inflammatory (e.g., IL-1β, IL-6, IL-8, IL-12, TNF-α), which stimulate inflammatory reactions and immune-competent cells; or anti-inflammatory (e.g., IL-4, IL-6, IL-10, IL-11, IL-13, TGF-β), which mediate the immunosuppression of the

inflammatory response (Boshtam *et al*., 2017; Liu *et al*., 2021). As regulators of the immune response, cytokines are the primary target for the development of immunotherapeutics based on natural compounds such as those derived from *Streptomyces* spp.

TNF-α is a master cytokine that regulates inflammatory response and innate immunity. The main pathways activated by this cytokine include caspases, nuclear factor-kappa B (NF-κB), and mitogen-activated protein kinases (MAPK). Its regulation is crucial to prevent an excessive inflammatory response (Wong *et al*., 2008; Tiegs; Horst, 2022). NF-κB and MAPK are the primary pathways of pro-inflammatory cytokines and inducible nitric oxide synthase (iNOS) (Shabab *et al*., 2017). The NF-κB pathway consists of five transcription factors (p50/p105, p52/p100, p65 (RelA), c-Rel, and RelB), which are dispersed in the cytoplasm bound to inhibitory molecules of the IκB type (IκBα, IκBs, IκBβ, IκBγ, and IκBε). During an aggressive process, the immune system releases cytokines such as TNF-α and IL-1, which induce the phosphorylation of the NF-κB/IκB complex. Free NF-κB translocates to the nucleus and binds to DNA at specific sequences to regulate the expression of target genes, including the regulation of immune and inflammatory responses, such as the expression of pro-inflammatory cytokines (e.g., IL-6, IL-1β, and TNF-α), production of reactive oxygen species (ROS), and cellular apoptosis (Jimi *et al*., 2005; Hayden *et al*., 2014; Jimi *et al*., 2019). The MAPK pathway includes extracellular signal-regulated kinases (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, which are also activated by pro-inflammatory stimuli such as TNF-α production and cellular stress. MAPK shares a common structure composed of three sequential action proteins, including a MAPK kinase (MAPKK) and a MAPKK kinase (MAPKKK), along with some non-canonical exceptions (ERK3, ERK4, ERK7, and ERK8). This pathway mediates the activation of downstream substrate phosphorylation, including transcription factors, cytoskeletal proteins, mRNA translation, and other kinase proteins (Morrison; Davis, 2003; Kyriakis; Avruch, 2012; Sabio; Davis, 2015; Yang *et al*., 2020). The NF-κB and MAPK pathways have well-defined and elucidated mechanisms, making them the main targets for new therapeutic approaches, including immunomodulatory activity by *Streptomyces* spp. metabolites.

Anhydroesfoliamycin is a compound produced by *Streptomyces* spp. that can inhibit the activation of microglial cells in the pro-inflammatory M1 phenotype, which are responsible for the release of pro-inflammatory cytokines, including pro-inflammatory interleukins (IL) and TNF-α (Norden; Godbout, 2013; Tang; Le, 2016), as well as nitric oxide (NO) and ROS (Cherry *et al*., 2014). This pro-inflammatory activation, if exacerbated and chronic, can lead to neurodegenerative damage, such as Alzheimer's and Parkinson's diseases (Zusso *et al*., 2019).

Anhydroesfoliamycin is identified as a potential neuroprotective agent against neurodegenerative diseases due to its modulation of the NF-κB and MAPK pathways, reducing the expression of pro-inflammatory cytokines and compounds (Alvarino *et al*., 2019; Gegunde *et al*., 2021).

A similar effect was observed with ebosine, a new exopolysaccharide (EPS) isolated from *Streptomyces* sp. 139. The metabolite was found to decrease the mRNA expression levels of genes encoding pro-inflammatory cytokines IL-23, IL-22, IL-17α, IL-6, IL-1β, and TNF-α, providing a mitigating effect on inflammatory activity at both transcriptional and post-transcriptional levels. Additionally, the compound inhibited the genes tnfaip3, tnip1, and IκBα, key genes that regulate the pro-inflammatory NF-κB signaling pathway, interrupting the binding of NF-κB and DNA, which leads to reduced cytokine expression. Ebosine also showed activity in the negative regulation of p38 MAPK and JNK phosphorylation induced by TNF-α (Zhang *et al*., 2013; Guo *et al*., 2021; Zhang *et al*., 2022).

The gene expression of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) was suppressed by the action of streptinone, a new indanone derivative from *Streptomyces massiliensis* of marine origin, resulting in reduced inflammatory activities caused by particulate matter. Additionally, the compounds were responsible for decreased phosphorylation and nuclear translocation of IκB-α, p65, and p50, suppressing pro-inflammatory pathways, such as NF-κB pathway mediated by TLR (Lee *et al*., 2023).

The marine isolate *Streptomyces specialis* 208DD-067 produces different compounds of the streptoglyceride family (A-H), with confirmed anti-inflammatory activity. The streptoglyceride compounds showed inhibitory effects on inflammatory mediators, particularly IL-6, due to reduced mRNA expression. A decrease in ERK, JNK, and p38 MAPK phosphorylation was also observed, interfering with the establishment of the inflammatory response (Choi *et al*., 2019; Shin *et al*., 2022).

The mutant strain *Streptomyces somaliensis* SCSIO ZH66 showed significant changes in the production of biotechnologically relevant secondary metabolites. Compounds derived from α-pyrone, somalimycin, and two known analogs (UFS-19A and urauchimycin D) were capable of inhibiting the production of IL-5 in in vitro tests (Huang *et al*., 2016; Li *et al*., 2017; Huayue *et al*., 2017). This activity may be attributed to substitutions in the bis-lactone ring chains of antimicrobial-type compounds from the depsipeptide class, which likely adjust the physicochemical properties of the compound and alter its biological activity, demonstrating anti-inflammatory activity (Strangman *et al*., 2009; Li *et al*., 2017).

The polyketide antibiotic manumycin A, derived from *Streptomyces parvulus*, inhibits the production of IL-1β, IL-6, and IL-8 in THP-1 cells and monocytes by downregulating pro-inflammatory genes that regulate the expression of these cytokines (Cecrdlova *et al*., 2016). Additionally, manumycin-derived compounds, named ManA, ManB, Asu, and Col, were able to suppress the expression of pro-inflammatory genes, including Il1b and Tnfa, limiting the production of IL-1β and TNF-α, respectively, and enhancing the anti-inflammatory effect (Hrdý *et al*., 2020).

The compound ASK2 was isolated from *Streptomyces* sp. ASK from the rhizosphere of a medicinal plant. ASK2 exhibited various modulatory effects on the immune response associated with antimicrobial activity. One of these effects was the induction of gene expression responsible for IL-12, IFN-γ, and TNF-α in stimulated macrophages, improving phagocytic activity (Lalith *et al*., 2017).

Streptomyces gramineus strains, associated with the lichen *Leptogium trichophorum*, produce actinofuranones D-I with anti-inflammatory effects. The actinofuranones produced are derived from rare polyketides, consisting of a skeleton of 2-hydroxy-2-(1-hydroxyethyl)-2,3-dihydro-3(2H)-furanone. These metabolites were able to inhibit the release of IL-6 and TNF-α, with the anti-inflammatory effects associated with the positioning of the hydroxyl substituent on the unsaturated alkyl chains, which possibly adjusts the physicochemical properties of drugs and their biological activities (Ma *et al*., 2018).

4.2 ANTIOXIDANT ACTIVITY

Some neurodegenerative diseases, such as Alzheimer's and Parkinson's, are characterized by mitochondrial dysfunction and a consequent increase in the production of reactive oxygen species (ROS), which accumulate and generate oxidative stress (Gandi; Abramov, 2012). The main free radicals formed from the metabolism of O_2 are superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH) (Melo *et al*., 2011), and their increase can cause mitochondrial damage, lipid peroxidation, and genomic damage (Gandi; Abramov, 2012; Leirós *et al*., 2014).

Antioxidant activity is essential for the natural control of free radical formation (Leirós *et al*., 2014). The antioxidant effect is regulated by nuclear factor erythroid 2-related factor 2 (NRF-2), which translocates to the nucleus when oxidative imbalance occurs, binding to the Maf protein, and regulating the activation of genes responsible for producing antioxidant

enzymes (e.g., superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT)), and anti-apoptotic proteins (Kaspar *et al*., 2009).

Various studies evaluate the use of compounds isolated from *Streptomyces* spp. with antioxidant activity, such as anhydroesfoliamycin, naftopiranomycin, 3-epi-5-deoxyenterocine, 5-deoxyentocine, nocardamine, undecylprodigiosin, and metacycloprodigiosin. These compounds exhibit antioxidant activity primarily through the activation of the NRF-2 pathway, which induces the release of an antioxidant response, such as increased production of antioxidant enzymes, reduced formation of ROS, and inhibition of cytosolic Ca^{2+} uncoupling. Thus, these metabolites allow for a reduction in mitochondrial damage and lipid peroxidation of the membrane, stabilization of mitochondrial membrane potential, improvement of cellular viability, control of cytosolic Ca^{2+}, as well as inhibition of cytochrome C release and caspases, which are responsible for apoptotic responses (Leirós *et al*., 2014).

NO is produced by macrophages as a mechanism of inflammation mediation, being increased during the inflammatory process and associated diseases (Bourgou *et al*., 2010). Its function involves inhibition of the pro-inflammatory NF-κB pathway, suppression of inflammatory mediators, regulation of blood flow, among others (Hattori *et al*., 2004; Naseem *et al*., 2005; Wallace *et al*., 2009). Different nitric isoforms are involved in NO production by catalyzing the oxidation of L-arginine to L-citrulline: neuronal (nNOS), endothelial (eNOS), and inducible (iNOS). The iNOS isoform is characterized by being calcium-independent, induced by inflammatory cytokines, oxidative stress, and hypoxia (Kashfi, 2018), and its exacerbated expression leads to increased NO production, which, under pathological conditions, becomes a toxic free radical for cells and tissues, leading to oxidative stress and apoptosis (Murakami; Ohigashi, 2007; Bao *et al*., 2018). Inhibition of its production is a strategy for treating inflammatory diseases.

The compounds streptinone, cyclo-(D)-Pro-(D)-Phe, actinofuranones D-I, and anhydroesfoliamycin, derived from *Streptomyces* spp., exhibit antioxidant properties by reducing iNOS expression and consequently reducing NO release (Leiros *et al*., 2014; Ma *et al*., 2018; Hassan *et al*., 2020; Gegunde *et al*., 2021; Lee *et al*., 2023). Another *Streptomyces* compound with similar activity is streptoglycerides, which demonstrated inhibitory effects on NO mediators by inhibiting nitrite production, important for NO composition, and by inhibiting iNOS expression (Shin *et al*., 2022). In contrast to these findings, the compound ASK2 exhibited stimulating activity of NO production by antigen-stimulated macrophages, contributing to the microbicidal activity of NO during phagocytosis (Lalith *et al*., 2017).

4.3 CELLULAR IMMUNOSUPPRESSION

The goal of immunosuppression is to reduce the innate and adaptive immune response, either naturally or induced, to avoid interference with immunity in certain contexts, such as organ transplantation and autoimmune diseases. Well-established immunosuppressive agents in clinical practice include calcineurin inhibitors (CNI) such as cyclosporine (CsA) and tacrolimus (Tac), which were introduced in the 1980s (Yu *et al*., 2018; Farouk *et al*., 2020; Job *et al*., 2023). However, these inhibitors are associated with severe toxic effects when used long-term, such as nephrotoxicity, neurotoxicity, cancer, and susceptibility to infections (Farouk; Rein, 2020; Pallet, 2021), leading to the search for compounds with fewer adverse effects.

Streptomyces hygroscopicus is responsible for producing over 180 bioactive metabolites, including rapamycin (Li *et al*., 2014; Salwan; Sharma, 2020). In addition to its antimicrobial properties, rapamycin has been observed and approved for its immunosuppressive activity due to its ability to interact with mTOR (mammalian target of rapamycin) signaling, binding to the FKBP12 protein and inhibiting the proliferation of key cytokines and T cells (Schreiber *et al*., 2019; Ganesh; Devi, 2023). Rapamycin is indicated for clinical use in post-transplant patients (Sehgal *et al*., 1975), presenting fewer side effects, such as neurotoxicity and nephrotoxicity, compared to other calcineurin inhibitors (Dang *et al*., 2017).

(-)-Citoxazone is a rare type of oxazolidinone-2-one isolated from cultures of a *Streptomyces* sp. strain RK95-31 (Kakeya *et al*., 1999). Studies indicate that (-)-citoxazone and its derivatives exhibit modulatory effects on cytokines through selective signaling of Th2-type TC4 lymphocytes, specific for human allergens, but not Th1, making it a potent immunotherapeutic agent (Kakeya *et al*., 1999; Zappia *et al*., 2007; Miranda *et al*., 2016).

The enzyme L-asparaginase is an aminohydrolase used in the treatment of Acute Lymphoblastic Leukemia (ALL) and other lymphomas (Balasubramanian *et al*., 2012). Its mechanism of action involves the hydrolysis of asparagine into aspartic acid and ammonia, inducing nutritional stress and disrupting the cell cycle and proliferation of cancer cells in ALL (Yang *et al*., 2014). Studies are investigating the production of L-asparaginase by *Streptomyces* species for commercial use in treating cancer cells, demonstrating its capacity to induce Th1 cytokine production in lymphocytes and activation of cytotoxic T cell subsets, which are effective in immune responses against cancer (Eyileten *et al*., 2016; Lacerda *et al*., 2018). A similar effect was observed with ebosina, which also exhibits cellular immunomodulation of CD3 and CD8 T cells, associated with autoimmune diseases such as psoriasis. Reduction in cellular expression was noted with high and medium doses of ebosina, in addition to aiding in

the increase of Treg cell expression in the immune response (Zhang *et al*., 2013; Guo *et al*., 2021).

4.4 MODULATION OF PHAGOCYTOSIS

Macrophages are the primary phagocytes involved in the immune response, playing roles in homeostasis, defense, and repair throughout all body tissues (Gessain *et al*., 2020; Gonzales *et al*., 2023). Prior to activation, they are known as resident tissue macrophages in a stationary state. During phagocytosis, macrophages are responsible for engulfing and metabolizing extracellular material, both "self" and "non-self," such as pathogens, apoptotic bodies, and neoplastic cells, present in the interstitial medium of healthy or diseased tissues (Watanabe *et al*., 2019; Gessain *et al*., 2020). Depending on the stimuli, macrophages can manifest different phenotypes, particularly the pro-inflammatory/anti-tumoral (M1) profile dependent on glycolytic metabolism, or the anti-inflammatory/pro-tumoral (M2) profile dependent on glycolytic metabolism or mitochondrial oxidative phosphorylation (Viola *et al*., 2019).

Macrophage activation is crucial for increased phagocytic activity, making it a suitable target for the immunomodulatory bioactivity of *Streptomyces* sp. (Vergadi *et al*., 2017). The compound ASK2 was able to enhance the phagocytic activity of non-activated macrophages, acting as an opsonin against microbial antigens that stimulate immune responses (Lalith *et al*., 2017). Conagenin also influenced the increase in phagocytic response due to the increased expression of the Fc receptor on the membrane of alveolar macrophages, stimulating phagocytosis (Hamada *et al*., 1999).

Thiolholgamide A (thioA) is a peptide produced by *Streptomyces lividans* ΔYA8. This metabolite exhibited activity against mitochondrial morphology, reducing and inhibiting ATP synthase action in cancer cells. Additionally, thioA was effective in inducing increased proliferation of M1-type macrophages, which are antagonistic in cancer processes. Thus, the compound has emerged as a strong candidate as an anti-tumor antiproliferative agent and macrophage modulator (Dahlem *et al*., 2020).

Table 2

Compounds isolated from Streptomyces sp. with immunomodulatory bioactivity

Compound	Isolated	Immunomodulatory Activity	Reference
Anidroesfoliamicina	*Streptomyces* spp.	Cytokine modulator, antioxidant	Norden; Godbout, 2013; Tang; Le, 2016; Alvarino *et al*., 2019; Gegunde *et al*., 2021
Ebosina	*Streptomyces* sp. 139	Cytokine modulator, immunosuppression	Zhang *et al*., 2013; Guo *et al*., 2021; Zhang *et al*., 2022
Estreptinone	*Streptomyces massiliensis*	Cytokine modulator, antioxidant	Lee *et al*., 2023
Estreptoglicerídeos (A-H)	*Streptomyces specialis* 208DD-067	Cytokine modulator, antioxidant	Choi *et al*., 2019; Shin *et al*., 2022
α-pirona	*Streptomyces somaliensis* SCSIO ZH66	Cytokine modulator	Huang *et al*., 2016; Li *et al*, 2017; Huayue *et al*., 2017
Somalimicina	*Streptomyces somaliensis* SCSIO ZH66	Cytokine modulator	Huang *et al*., 2016; Li *et al*, 2017; Huayue *et al*., 2017
UFS-19[a]	*Streptomyces somaliensis* SCSIO ZH66	Cytokine modulator	Huang *et al*., 2016; Li *et al*, 2017; Huayue *et al*., 2017
Urauchimycin D	*Streptomyces somaliensis* SCSIO ZH66	Cytokine modulator	Huang *et al*., 2016; Li *et al*, 2017; Huayue *et al*., 2017
Manumicina A	*Streptomyces parvulus*	Cytokine modulator	Cecrdlova *et al*., 2016; Hrdý *et al*., 2020
ASK2	*Streptomyces* sp. ASK	Cytokine modulator	Lalith *et al*., 2017
Actinofuranonas (D-I)	*Streptomyces gramineus*	Cytokine modulator, antioxidant, phagocytosis	Ma *et al*., 2018
Ciclo-(D)-Pro-(D)-Phe	*Streptomyces* sp. SH-1327	Cytokine modulator, antioxidant	Hassan *et al*., 2020
Naftopiranomicina	*Streptomyces* sp.	Cytokine modulator, antioxidant;	Leiros *et al*., 2014
3-epi-5-desoxienterocina	*Streptomyces* sp.	Antioxidant	Leiros *et al*., 2014
5-desoxientocina	*Streptomyces* sp.	Antioxidant	Leiros *et al*., 2014
Nocardamina	*Streptomyces* sp.	Antioxidant	Leiros *et al*., 2014
Undecilprodigiosina	*Streptomyces* sp.	Antioxidant	Leiros *et al*., 2014
Metacicloprodigiosina	*Streptomyces* sp.	Antioxidant	Leiros *et al*., 2014
Rapamicina	*Streptomyces hygroscopicus*	Immunosuppression	Li *et al*., 2014; Schreiber *et al*., 2019; Salwan; Sharma, 2020; Ganesh; Devi, 2023
(-)-Citoxazona	*Streptomyces* sp. RK95-31	Immunosuppression	Kakeya *et al*., 1999; Zappia *et al*., 2007; Miranda *et al*., 2016
L-asparaginase	*Streptomyces* sp.	Immunosuppression	Eyileten *et al*., 2016; Lacerda *et al*., 2018
Conagenina	*Streptomyces* sp.	Phagocytosis	Hamada *et al*., 1999
Tioholgamida A	*Streptomyces lividans* ΔYA8	Phagocytosis	Dahlem *et al*., 2020

5 CONCLUSION

The genus *Streptomyces* is a major focus of research in the biotechnology and pharmaceutical industries due to the bioactivities of its metabolic products, which are of interest across various sectors. It has been observed that this genus has enabled the development of a range of clinically used antimicrobials, which are now employed in the therapeutic management of various infections. Additionally, the metabolites produced by *Streptomyces* sp. have the potential to act as immunomodulatory enhancers against diseases, optimizing and regulating the immune system's function.

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REFERENCES

Ab Mutalib, N. S. *et al*. Progress in microbes and molecular biology bioprospecting of microbes for valuable compounds to mankind. Journal Article, 2020.

Alam, K. *et al*. *Streptomyces*: The biofactory of secondary metabolites. Frontiers in Microbiology. Frontiers Media S.A., 29 set. 2022.

Alvarino, R. *et al*. Caniferolide A, a macrolide from *Streptomyces caniferus*, attenuates neuroinflammation, oxidative stress, amyloid-beta, and tau pathology *in vitro*. Molecular pharmaceutics, v. 16, n. 4, p. 1456-1466, 2019.

Amorim, E. A. F. *et al*. Antimicrobial potential of *Streptomyces ansochromogenes* (PB3) isolated from a plant native to the Amazon against *Pseudomonas aeruginosa*. Frontiers in Microbiology, v. 11, 9 out. 2020.

Asokan, G. V. *et al*. WHO global priority pathogens list: A bibliometric analysis of medline-pubmed for knowledge mobilization to infection prevention and control practices in Bahrain. Oman Medical Journal. Oman Medical Specialty Board, 2019.

Balasubramanian, K. *et al*. Production, isolation, and purification of L-asparaginase from *Aspergillus terreus* using submerged fermentation. Int J Adv Pharm Res 3, 778–783, 2012.

Bao, Y. *et al*. Protective effects of osthole against inflammation induced by lipopolysaccharide in BV2 cells. Molecular medicine reports, v. 17, n. 3, p. 4561-4566, 2018.

Barka, E. A. *et al*. Taxonomy, physiology, and natural products of actinobacteria. microbiology and molecular biology. Reviews, v. 80, n. 1, p. 1–43, mar. 2016.

Bostham, M. *et al*. Aptamers Against Pro- and Anti-Inflammatory Cytokines: A Review. Inflammation. 2017 Feb;40(1):340-349.

Bourgo, S. *et al*. Bioactivities of black cumin essential oil and its main terpenes from Tunisia. South African J Bot. 2010; 76(2): 210-216.

Cartuche, L. Metabolitos secundarios con actividad antiparasitaria de actionobacterias de manglar de la la costa ecuatoriana. 2021.

Cecrdlova E. *et al*. Manumycin A downregulates release of proinflammatory cytokines from TNF alpha stimulated human monocytes. Immunol Lett. 2016 Jan;169:8-14.

Cherry, J. D. *et al*. Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. Journal of neuroinflammation, v. 11, p. 1-15, 2014.

Choi, B. K. *et al*. Correction to "Streptoglycerides A-D with a Rare 6/5/5 Tricyclic Ring Skeleton from a Marine Actinomycete Streptomyces species". Org Lett. 2019 Oct 4;21(19):8144.

Dahlem, C. *et al*. Thioholgamide A, a New Anti-Proliferative Anti-Tumor Agent, Modulates Macrophage Polarization and Metabolism. Cancers (Basel). 2020 May 19;12(5):1288.

Dang, L. *et al*. Enhancement of rapamycin production by metabolic engineering in Streptomyces hygroscopicus based on genome-scale metabolic model. Journal of Industrial Microbiology and Biotechnology, v. 44, n. 2, p. 259-270, 2017.

Evangelista-Martinez, Z. *et al*. Actividad antimicrobiana de *Streptomyces* sp. Y15 contra bacterias patógenas y evaluación de medios de cultivo para la producción de antibióticos. TIP Revista Especializada en Ciencias Químico-Biológicas, v. 25, 15 fev. 2022.

Eyileten, C. *et al*. (2016) Immune cells in cancer therapy and drug delivery. Mediators of Inflamm 2016, 5230219.

Farouk, S. S. *et al*. The Many Faces of Calcineurin Inhibitor Toxicity-What the FK? Adv Chronic Kidney Dis. 2020 Jan;27(1):56-66.

Gandhi S, Abramov AY. Mechanism of oxidative stress in neurodegeneration. Oxid Med Cell Longev. 2012;2012:428010.

Ganesh, S. K., Molecular and therapeutic insights of rapamycin: a multi-faceted drug from Streptomyces hygroscopicus. Mol Biol Rep. 2023 Apr;50(4):3815-3833.

Gegundes S, *et al*. Anhydroexfoliamycin, a Streptomyces Secondary Metabolite, Mitigates Microglia-Driven Inflammation. ACS Chem Neurosci. 2021 Jul 7;12(13):2336-2346.

Gessain G, *et al*. Non-genetic Heterogeneity of Macrophages in Diseases-A Medical Perspective. Front Cell Dev Biol. 2020 Dec 14;8:613116.

Ghosh, R.; *et al*. *Panax quinquefolius* (North American Ginseng) polysaccharides as immunomodulators: current research status and future directions. Molecules MDPI, 1 dez. 2020.

Gonzalez, M. A. *et al*. A fagocitose aumenta a assinatura oxidativa, metabólica e imunossupressora em macrófagos tumorais. J Exp Med 2023 5 jun; 220(6):e20221472.

Goredema, N. *et al*. In vitro suppression of pathogenic fungi by *Streptomyces* spp. African Crop Science Journal, v. 28, n. 2, p. 141–149, 27 jul. 2020.

Guo W. *et al*. Ebosin Ameliorates Psoriasis-Like Inflammation of Mice via miR-155 Targeting tnfaip3 on IL-17 Pathway. Front Immunol. 2021 Apr 26;12:662362.

Hamada, M. *et al*. Conagenina derivada de *Streptomyces roseosporus* aumenta as funções de macrófagos. J Antibiot (Tóquio). Junho de 1999; 52(6):548-51.

Hassan, S. S. U. *et al*. Metals-triggered compound CDPDP exhibits anti-arthritic behavior by downregulating the inflammatory cytokines, and modulating the oxidative storm in mice models with extensive ADMET, docking and simulation studies. Front Pharmacol. 2022 Nov 23;13:1053744.ori

Hattori, Y. NO suppresses while peroxynitrite sustains NF-κB: a paradigm to rationalize cytoprotective and cytotoxic actions attributed to NO. Cardiovascular Research, v. 63, n. 1, p. 31-40, 2004.

Hayden, M.S. Regulation of NF-κB by TNF family cytokines. Semin. Immunol. 2014;26:253–266.

Hrdy, J. *et al*. Inhibition of Pro-Inflammatory Cytokines by Metabolites of Streptomycetes-A Potential Alternative to Current Anti-Inflammatory Drugs? Microorganisms. 2020 Apr 25;8(5):621.

Huang, H. *et al*. Activation of a plasmid-situated type III PKS gene cluster by deletion of a wbl gene in deepsea-derived Streptomyces somaliensis SCSIO ZH66. Microb. Cell Fact. 15:116 10.1186/s12934-016-0515-6, 2016.

Jimi, E. *et al*. The Role of NF-κB in Physiological Bone Development and Inflammatory Bone Diseases: Is NF-κB Inhibition "Killing Two Birds with One Stone"? Cells. 2019 Dec 14;8(12):1636.

Jimi, E.; GHOSH, S. Role of nuclear factor-κB in the immune system and bone. Immunol. Rev. 2005;208:80–87.

Job, K. M. *et al*. Treatment optimization of maintenance immunosuppressive agents in pediatric renal transplant recipients. Expert Opin Drug Metab Toxicol. 2021 Jul;17(7):747-765.

Kakeya, H. *et al*. Cytoxazone: A novel Cytokine modulator containing a 2-Oxazolidinone ring produced by Streptomyces sp. The Journal of Organic Chemistry, v. 64, n. 3, p. 1052-1053, 1999.

Kashifi K. The dichotomous role of H2S in cancer cell biology? Déjà vu all over again. Biochem Pharmacol. 2018 Mar;149:205-223.

Kaspar, J. W. *et al*. Nrf2:INrf2 (Keap1) signaling in oxidative stress. Free Radic Biol Med. 2009 Nov 1;47(9):1304-9.

Kronheim, S. *et al*. Complete genomes and comparative analyses of *Streptomyces* phages that influence secondary metabolism and sporulation. Scientific Reports, v. 13, n. 1, 1 dez. 2023.

Kulbe, H. *et al*. A dynamic inflammatory cytokine nettargk in the human ovarian cancer microenvironment. Cancer Res. 2012 Jan 1;72(1):66-75.

Kyriakis, J. M. Mammalian MAPK signal transduction pathways activated by stress and inflammation: a 10-year update. Physiol Rev. 2012;92:689–737.

Lacerda, G. R. S. *et al*. L-asparaginase isolated from Streptomyces ansochromogenes promotes Th1 profile and activates CD8+ T cells in human PBMC: an in vitro investigation. J Appl Microbiol. 2018 May;124(5):1122-1130.

Lalitha, C. *et al*. ASK2 Bioactive Compound Inhibits MDR Klebsiella pneumoniae by Antibiofilm Activity, Modulating Macrophage Cytokines and Opsonophagocytosis. Front Cell Infect Microbiol. 2017 Aug 4;7:346.

Lee, HS, *et al*. Streptinone, a New Indanone Derivative from a Marine-Derived Streptomyces massiliensis, Inhibits Particulate Matter-Induced Inflammation. Mar Drugs. 2023 Dec 14;21(12):640.

Leiros, M. *et al*. Mitigation of ROS insults by Streptomyces secondary metabolites in primary cortical neurons. ACS Chem Neurosci. 2014 Jan 15;5(1):71-80.

Li, H. *et al*. Discovery of Antimycin-Type Depsipeptides from a wbl Gene Mutant Strain of Deepsea-Derived Streptomyces somaliensis SCSIO ZH66 and Their Effects on Pro-inflammatory Cytokine Production. Front Microbiol. 2017 Apr 19;8:678.

Li, Jing, *et al*. Rapamycin: one drug, many effects. Cell metabolism, v. 19, n. 3, p. 373-379, 2014.

Lin, P. *et al*. Isolation, biosynthesis, and biological activity of rubromycins derived from actinomycetes. Engineering Microbiology Elsevier Inc., 1 set. 2022.

Liu, C. Cytokines: From Clinical Significance to Quantification. Adv Sci (Weinh). 2021 Aug;8(15):e2004433.

Luthe, T. *et al*. *Streptomyces* development is involved in the efficient containment of viral infections. MicroLife, v. 4, 4 jan. 2023.

Ma, J. *et al*. Actinofuranones D-I from a Lichen-Associated Actinomycetes, Streptomyces gramineus, and Their Anti-Inflammatory Effects. Molecules. 2018 Sep 18;23(9):2393.

Melo, A. *et al*. Oxidative stress in neurodegenerative diseases: mechanisms and therapeutic perspectives. Oxid Med Cell Longev. 2011;2011:467180.

Miranda I. L. *et al*. Synthesis Approaches to (-)-Cytoxazone, a Novel Cytokine Modulator, and Related Structures. Molecules. 2016 Sep 6;21(9):1176.

Morrison DK. Regulation of MAP kinase signaling modules by scaffold proteins in mammals. Annu Rev Cell Dev Biol. 2003;19:91–118.

Mu, Y. Q. *et al*. *Streptomyces*-derived actinomycin D inhibits biofilm formation via downregulating ica locus and decreasing production of PIA in *Staphylococcus epidermidis.* Journal of Applied Microbiology, v. 128, n. 4, p. 1201–1207, 1 abr. 2020.

Murakami, A. *et al*. Targeting NOX, INOS and COX-2 in inflammatory cells: chemoprevention using food phytochemicals. International journal of cancer, v. 121, n. 11, p. 2357-2363, 2007.

Naseem, K. M. The role of nitric oxide in cardiovascular diseases. Molecular aspects of medicine, v. 26, n. 1-2, p. 33-65, 2005.

Neamah, A. J. *et al*. Inhibition of *Escherichia coli* biofilm formation by *Streptomyces* sdli crude extract. Iraqi Journal of Veterinary Sciences, v. 34, n. 2, p. 305–310, 1 jun. 2020.

Nordem, D. M. Microglia of the aged brain: primed to be activated and resistant to regulation. Neuropathology and applied neurobiology, v. 39, n. 1, p. 19-34, 2013.

Pallet, N. Calcineurin inhibitors nephrotoxicity revisited. Am J Transplant. 2021 Sep;21(9):2929-2930.

Pinto, J. S. *et al*. Manual de imunomoduladores com ação antineoplásica: aspetos práticos relacionados com o tratamento Experiência profissionalizante na vertente de Investigação e Farmácia Comunitária. 2021.

Psenicnik, A. *et al*. Simple and reliable in situ CRISPR-Cas9 nuclease visualization tool is ensuring efficient editing in *Streptomyces* species. Journal of Microbiological Methods, v. 200, 1 set. 2022.

Rios-Hernandez, T. A. *et al*. Biological control of *Fusarium oxysporum* causal agent of gladiolus corm rot by *Streptomycetes*. Revista Mexicana de Fitopatología, Mexican Journal of Phytopathology, v. 39, n. 3, 19 ago. 2021.

Sabio, G. TNF and MAP kinase signalling pathways. Semin Immunol. 2014 Jun;26(3):237-45.

Salwan, R. Bioactive compounds of Streptomyces: biosynthesis to applications. Studies in natural products chemistry, v. 64, p. 467-491, 2020.

Santos, D. C. P. *et al*. Potencial antimicrobiano de metabólitos secundários de *Streptomyces* sp. isolados de solo impactado. Peer Review, v. 6, n. 5, p. 233–245, 9 mar. 2024.

Schreiber, Katherine H. *et al*. A novel rapamycin analog is highly selective for mTORC1 in vivo. Nature communications, v. 10, n. 1, p. 3194, 2019.

Sehgal, S. N. *et al*. Rapamycin (AY-22, 989), a new antifungal antibiotic II. Fermentation, isolation and characterization. The Journal of antibiotics, v. 28, n. 10, p. 727-732, 1975.

Shabab, T. *et al*. Neuroinflammation pathways: a general review. International Journal of Neuroscience, v. 127, n. 7, p. 624-633, 2017.

Shin, H. J. *et al*. Streptoglycerides E-H, Unsaturated Polyketides from the Marine-Derived Bacterium Streptomyces specialis and Their Anti-Inflammatory Activity. Mar Drugs. 2022 Jan 1;20(1):44.

Sprague, A. Inflammatory cytokines in vascular dysfunction and vascular disease. Biochem Pharmacol. 2009 Sep 15;78(6):539-52.

Stngman W. K. *et al*. Potent inhibitors of pro-inflammatory cytokine production produced by a marine-derived bacterium. Journal of medicinal chemistry, v. 52, n. 8, p. 2317-2327, 2009.

Tang, Y; LE, W. Differential roles of M1 and M2 microglia in neurodegenerative diseases. Molecular neurobiology, v. 53, p. 1181-1194, 2016.

Targino, A. B. DA C. *et al*. Imunomodulação com cogumelos: Cordyceps sinensis, Ganoderma lucidum e Grifola frondosa. Brazilian Journal of Development, v. 8, n. 10, p. 66097–66112, 6 out. 2022.

Vergani, E. *et al*. Akt signaling pathway in macrophage activation and M1/M2 polarization. The Journal of Immunology, v. 198, n. 3, p. 1006-1014, 2017.

Viola, A. *et al*. 2019. The metabolic signature of macrophage responses. Front. Immunol. 10:1462. 10.3389/fimmu.2019.01462

Wallace, J. L.; *et al*. Cyclooxyagenase-inhibiting nitric oxide donators for osteoarthritis. Trends in pharmacological sciences, v. 30, n. 3, p. 112-117, 2009.

Watanabe, S., *et al*. The role of macrophages in the resolution of inflammation. J. Clin. Invest. 129:2619–2628. 10.1172/JCI124615

Wong, M. *et al*. TNFalpha blockade in human diseases: mechanisms and future directions. Clin Immunol. 2008;126:121–36.

Yang, H. *et al*. (2014) Down-regulation of asparagine synthetase induces cell cycle arrest and inhibits cell proliferation of breast cancer. Chen Biol Drug Des 84, 578–584.

Yang, L-X. *et al*. Poncirin suppresses lipopolysaccharide (LPS)-induced microglial inflammation and ameliorates brain ischemic injury in experimental stroke in mice. Annals of Translational Medicine, v. 8, n. 21, 2020.

Yu M. *et al*. Pharmacokinetics, Pharmacodynamics and Pharmacogenetics of Tacrolimus in Kidney Transplantation. Curr Drug Metab. 2018;19(6):513-522.

Zappia, G. *et al*. Oxazolidin-2-one ring, a popular framework in synthetic organic chemistry: Part 1. The construction of the oxazolidin-2-one ring. Current Organic Synthesis, v. 4, n. 1, p. 81-135, 2007.

Zhang, Y. *et al*. Anti-inflammatory effect of ebosin on rat collagen-induced arthritis through suppressing production of interleukin-1β, interleukin-6 and tumor necrosis factor-α. Journal of Inflammation . 2013;11(3):697–708.

Zhang, Y. *et al*. Anti-inflammatory effect of ebosin on rat collagen-induced arthritis through suppressing production of interleukin-1β, interleukin-6 and tumor necrosis factor-α. Journal of Inflammation . 2013;11(3):697–708.

Zhan, Y. *et al*. Ebosin Attenuates the Inflammatory Responses Induced by TNF-α through Inhibiting NF-κB and MAPK Pathways in Rat Fibroblast-Like Synoviocytes. J Immunol Res. 2022 Mar 17;2022:9166370.

Zhang, Y. *et al*. Ebosin Attenuates the Inflammatory Responses Induced by TNF-α through Inhibiting NF-κB and MAPK Pathways in Rat Fibroblast-Like Synoviocytes. J Immunol Res. 2022 Mar 17;2022:9166370.

Zhao, J. *et al*. *Streptomyces paludis* sp. Nov., isolated from an alpine wetland soil. International Journal of Systematic and Evolutionary Microbiology, v. 70, n. 2, p. 773–778, 2020.

Zusso, M. *et al*. Ciprofloxacin and levofloxacin attenuate microglia inflammatory response via TLR4/NF-kB pathway. Journal of neuroinflammation, v. 16, p. 1-12, 2019.