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Fruit extracts as a natural strategy against foodborne pathogens: antioxidant, antimicrobial, and cytotoxic evaluations

Lizeth Mercedes García Jaimes
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Dissertation submitted to the Food Science and Technology Graduate Program of the Universidade Federal de Viçosa in partial fulfillment of the requirements for the degree of *Magister Scientiae*.

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ABSTRACT

JAIMES, Lizeth Mercedes García, M.Sc., Universidade Federal de Viçosa, May, 2025. **Fruit extracts as a natural strategy against foodborne pathogens: antioxidant, antimicrobial, and cytotoxic evaluations**. Adviser: Pedro Henrique Campelo Felix. Co-advisers: Evandro Martins, Paulo Cesar Stringheta and Wilmer Edgard Luera Pena.

Waterborne and Foodborne Diseases (WFDs) remain a major concern for both the food industry and public health sectors. According to data from the Brazilian Ministry of Health, between 2020 and 2023, WFD outbreaks quadrupled, resulting in more than nineteen thousand reported cases in the most recent year. These outbreaks were primarily caused by the etiological agents Escherichia coli, Staphylococcus spp., and Salmonella spp.

Although pesticides, agrochemicals, chemical preservatives, and antibiotics are used to mitigate these problems, the indiscriminate application of such substances has led to new challenges, such as antimicrobial resistance.

One promising approach to counteracting this resistance involves the study of plant-derived compounds with antimicrobial potential, owing to the wide range of metabolites they contain and the extensive research on their bioactive components with diverse biological activities. These compounds include alkaloids, polyphenols, coumarins, terpenes, polysaccharides, and peptides.

Investigating compounds with antimicrobial potential present in plants is one possible strategy to counteract this multidrug resistance, given the variety of metabolites found and the extensive research on bioactive compounds with diverse biological activities. These compounds include alkaloids, polyphenols, coumarins, terpenes, polysaccharides, and peptides.

The objective of this study was to evaluate the antimicrobial potential of extracts from six red fruits—jabuticaba, strawberry, açaí, raspberry, blueberry, and juçara—against the pathogenic microorganisms Escherichia coli and Listeria monocytogenes. The extracts of jabuticaba and açaí exhibited the highest quantification of total phenolic compounds and antioxidant potential. However, the latter did not demonstrate strong antimicrobial activity. The extracts that stood out in inhibiting bacterial growth were jabuticaba, followed by raspberry and strawberry. The minimum inhibitory concentration (MIC) of jabuticaba extract for both bacteria was 1x, while the minimum bactericidal concentration (MBC) was determined only for L. monocytogenes, with the jabuticaba extract showing a value of 2x.

When isolated, anthocyanins and phenolic compounds displayed lower microbial inhibitory effects compared to the crude extract, suggesting that the antimicrobial potential may reside in organic acids or result from synergistic interactions among other constituents. No extract exhibited toxicity in live cells, thereby rendering them safe for applications within the food and pharmaceutical industries.

Keywords: red fruits; antimicrobial potential; phenolic compounds; anthocyanins

RESUMO

JAIMES, Lizeth Mercedes García, M.Sc., Universidade Federal de Viçosa, maio de 2025. **Extratos de frutas como estratégia natural contra patógenos de origem alimentar: avaliações antioxidante, antimicrobiana e citotóxica**. Orientador: Pedro Henrique Campelo Felix. Coorientadores: Evandro Martins, Paulo Cesar Stringheta e Wilmer Edgard Luera Pena.

As Doenças Transmitidas por água e alimentos (DTHA) continuam sendo uma preocupação das indústrias alimentícias e de saúde pública. De acordo com dados do Ministério da Saúde, entre os anos de 2020 e 2023, os surtos por DTHA quadruplicaram e resultaram em mais de dezenove mil doentes no último ano. Estes surtos foram ocasionados principalmente pelos agentes etiológicos Escherichia coli, Staphylococcus spp. e Salmonella spp.

Embora o uso de pesticidas, agrotóxicos, conservantes químicos e antibióticos são utilizados para minimizar esses problemas, o uso indiscriminado destes produtos, tem gerado novos desafios, como a multirresistência. O estudo de compostos com potencial antimicrobiano, presentes em plantas, é uma das possíveis formas de combater essa multirresistência, devido a variedade de metabólitos encontrados e extensos estudos de compostos bioativos com diferentes atividades biológicas. Estes compostos incluem alcaloides, polifenóis, cumarinas, terpenos, polissacarídeos e peptídeos.

O objetivo deste estudo foi avaliar o potencial antimicrobiano de extratos de seis frutas vermelhas, jabuticaba, morango, açaí, framboesa, mirtilo e juçara contra os microrganismos patogênicos Escherichia coli e Listeria monocytogenes. Os extratos de jabuticaba e açaí apresentaram a maior quantificação de compostos fenólicos totais e potencial antioxidante. Porém, este último, não apresentou um bom potencial antimicrobiano. Os extratos que se destacaram pelo potencial de inibição de crescimento das bactérias estudadas foi o extrato de jabuticaba, seguido pelo extrato de framboesa e morango. A concentração mínima inibitória (MIC) do extrato de jabuticaba para ambas as bactérias foi de 1x. Já a concentração mínima bactericida (MBC) foi determinada apenas para L. monocytogenes, com o extrato de jabuticaba apresentando um valor de 2x.

As antocianinas e fenólicos quando isolados apresentaram menor poder de inibição microbiano em relação ao extrato bruto, indicando que possivelmente os compostos com potencial antimicrobiano resultaram de possíveis sinergismo entre os componentes. Nenhum extrato apresentou toxicidade em células vivas, tornando-as seguras para aplicações na indústria alimentícia ou farmacêutica.

Palavras-chave: frutas vermelhas; potencial antimicrobiano; compostos fenólicos; antocianinas

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SUMARY

1. INTRODUCTION

One of the major concerns of the food industry is food safety, which may be compromised by physical, chemical, and biological hazards (Li et al., 2024). The industry mitigates biological hazards through the use of chemical preservatives, sanitizers, pesticides, and antibiotics.

However, the indiscriminate use of antibiotics in livestock has led to bacterial resistance via several defense mechanisms. These include biofilm formation, quorum sensing, reduced cell wall permeability impeding the entry of active antibiotic components, enzymatic modification leading to antibiotic degradation, and the efflux of these active components from the bacterial membrane (Li et al., 2024; Ruddaraju et al., 2020).

These multidrug-resistant bacteria and antibiotic residues may reach consumers through the ingestion of meat products, contamination of agricultural irrigation water, and soil contamination (Van Boeckel et al., 2019). Such exposure can alter the intestinal microbiota, trigger the onset of mild to severe diseases, and significantly contribute to the rise of drug-resistant bacteria (Sun et al., 2020).

According to Murray et al. (2022) the bacteria responsible for more than 300,000 deaths worldwide in 2019 due to drug resistance include *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Acinetobacter baumannii*, and *Pseudomonas aeruginosa*. In Brazil, during the same year, the Ministry of Health recorded approximately 800 cases of foodborne outbreaks and 10,000 patients, primarily associated with *E. coli*, *Salmonella* spp., *Staphylococcus* spp., and *Bacillus cereus* (Brasil, 2024).

The Ministry of Health has developed an action plan to prevent and control antibiotic resistance, emphasizing the importance of understanding the fundamental mechanisms of resistance, optimizing drug use in human and animal health, and promoting research into alternative approaches (Brasil, 2023). One such alternative involves investigating compounds with antimicrobial potential found in plants.

Brazil, with its rich biodiversity and six distinct biomes—the Amazon Rainforest, Cerrado, Pantanal, Caatinga, Atlantic Forest, and Pampas—is well positioned to explore these possibilities.

It is estimated that the Amazon Rainforest, the largest tropical forest in the world, harbors between 43,000 and 49,000 plant species, representing approximately 17% of all the world's plant species (Lewinsohn; Prado, 2005).

Several studies, including those by Hussain et al. 2024; Nayak et al. 2024; Silva Júnior et al. 2024; Tian et al. 2016; Weng et al. 2023, have highlighted the antimicrobial potential of extracts obtained from various parts of plants, such as roots, bark, and fruit pulps. Compounds including flavonoids, alkaloids, coumarins, terpenes, polysaccharides, and peptides have been identified in these extracts, all of which have demonstrated antimicrobial activity. These compounds may act by damaging the cell wall, disrupting the structure and function of the cell membrane, inducing oxidative stress, interrupting energy metabolism, and inhibiting biofilm formation, among other mechanisms (Chen; Lan; Xie, 2024).

This study is divided into two chapters, both written in article format. The first chapter presents a literature review on the bioactive compounds found in Amazonian fruits with antimicrobial potential. The second chapter comprises the experimental section, focusing on red fruits, in which antioxidant potential, antimicrobial activity, and cytotoxicity were evaluated.

2. OBJECTIVES

2.1. General objective

To evaluate the antimicrobial potential of fruit extracts from the Amazon region (açaí) and the Atlantic Forest (strawberry, jabuticaba, raspberry, blueberry and juçara).

2.2. Specific objective

- Prepare aqueous crude extracts of strawberry, jabuticaba, blueberry, raspberry, juçara, and açaí.
- Quantify the total phenolics in the extracts and evaluate the antioxidant capacity.
- Evaluate the antimicrobial activity of the extracts against the pathogenic microorganisms *Escherichia coli* ATCC 11229 and *Listeria monocytogenes* ATCC 19111.
- Find the Minimum Inhibitory Concentration (MIC) and Minimum Bactericidal Concentration (MBC) of the extracts that showed the greatest growth inhibition.

- Separate the phenolic and anthocyanin fractions of the crude extract and evaluate their antimicrobial potential individually.
- Perform cytotoxicity tests to determine the safety of the extracts.

3. CHAPTER 1:

This chapter presents a bibliographic review of compounds with antimicrobial potential found in Amazonian plants. The studied compounds include alkaloids, polyphenols, terpenes, coumarins, polysaccharides, and peptides. Their chemical structures are analyzed, along with the mechanisms by which they interact with pathogenic microorganisms, emphasizing their antimicrobial properties.

3.1. Introduction

The Amazon, the world's largest continuous humid tropical biome, spans approximately 6.7 million square kilometers across northern South America, covering portions of eight countries: Brazil, Bolivia, Peru, Ecuador, Colombia, Suriname, Venezuela, Guyana, and French Guiana (Porto-Gonçalves, 2015). In Brazil alone, it occupies around 60% of the national territory, totaling approximately 5 million square kilometers and encompassing 772 municipalities across nine states. The largest portion is found in the state of Amazonas, followed by Pará and Mato Grosso (Messias et al., 2021).

Amazonian ecosystems are characterized by remarkable biodiversity, hosting over 30,000 plant species, including approximately 6,700 tree species, 2,000 fish species, 60 reptile species, 35 mammal families, and around 1,800 bird species (Souza et al., 2023). At least 4,000 species have been utilized and managed for medicinal purposes, 700 for food, 2,000 for manufacturing applications, and 1,000 for construction (Clement, 2024). The Amazon is the center of domestication for several globally significant crops, including cassava—the world's second most important root crop—along with cocoa, pineapple, rubber, chili pepper, tobacco, coca, sweet potato, and many other lesser-known species (Clement, 2024).

The bioactive potential of Amazonian fruits is widely recognized for its various health benefits, often attributed to their rich composition of secondary metabolites. The scientific literature consistently associates these bioactive compounds with a range of biological activities, including anti-inflammatory, anticancer, antidiabetic, antimicrobial, antioxidant, and allelopathic effects (Fidelis et al., 2020; Franco et al., 2020; Kumar, 2024; Rezaul Islam et al., 2024; Rinaldi et al., 2017).

Additionally, these species exhibit high concentrations of antioxidants, vitamins, fibers, and other high-value compounds, making them applicable to diverse industrial sectors (Peixoto Araujo et al. 2021; Souza et al. 2023). Among the numerous Amazonian fruits recognized for their functional properties, açaí, buriti, guaraná, pitomba, tucumã, uxi, and cupuaçu stand out in the scientific community (Souza et al., 2023).

These natural resources hold particular significance in the face of global challenges such as antimicrobial resistance (AMR). Exploring natural products with antimicrobial properties is crucial for the development of alternative therapies or as natural preservatives against foodborne pathogens. For instance, studies have demonstrated that compounds present in Amazonian fruits such as copal, mari-mari, buriti, tucumã, taperebá, acerola, araçá seed, and taperebá exhibit activity against pathogens such as *Candida albicans*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Bacillus cereu*s, and *Listeria monocytogenes* (Jobim et al., 2014; Koolen et al., 2013; Souza et al., 2023; Valarezo et al., 2020).

However, despite the promising biotechnological potential of Amazonian resources, the sustainable exploitation of these fruits faces significant challenges. Unregulated exploitation, inadequate governance, and ongoing habitat loss due to deforestation pose severe threats. Between 2019 and 2021, deforestation in Brazil's Amazon biome increased by 56.6 % compared to the 2016–2018 period, with annual deforestation rates exceeding 10,000 km² (INPE, 2023).

The drivers of Amazonian deforestation include cattle ranching, agriculture, and logging (Rivero et al., 2009), as well as population growth, government policies favoring exports, and rural credit expansion (Young, 2001). Infrastructure development, such as road and pipeline construction, further accelerates this process (Das Neves et al., 2021) This scenario not only contributes to rising greenhouse gas emissions—aggravating climate change—but also profoundly affects biodiversity, hydrological cycles, and both regional and global climate stability.

Furthermore, the ongoing pressure on Amazonian ecosystems threatens the future of biotechnology that relies on natural resources, which are essential for sustainable development and the preservation of the ecosystem services the Amazon provides to the planet. Therefore, this article not only reviews the current state of knowledge on the antimicrobial potential of Amazonian fruits—focusing on bioactive compounds such as alkaloids, polyphenols, coumarins, terpenes, polysaccharides, and peptides, but also underscores the urgency of implementing conservation and sustainable management strategies to ensure the availability of these biotechnological resources for future generations.

3.2. Bioactive Compounds with Antimicrobial Potential in Amazonian Fruits

Amazonian fruits, including açaí, buriti, acerola, guaraná, taperebá, tucumã, camu-camu, and araçá, are recognized as rich sources of bioactive compounds with significant antimicrobial potential (Table 1). These compounds exhibit activity against a diverse range of pathogens, including Gram-positive and Gram-negative bacteria as well as fungal species (Albuquerque et al., 2023; Castro et al., 2020; Fidelis et al., 2020; Nonato et al., 2018).

Table 1. Amazonian fruits with antimicrobial potential.

Popular name-scientific name	**Extraction**	**Class of compounds**	**Antimicrobial compound**	**Amount in fruit**	**Target microorganism**	**Reference**
Abiu (*Pouteria caimito*) (Peel)	Methanolic	organic acids	Palmitic acid* Linoleic acid*	34.38 ± 0.70 %* 22.14 ± 2.58 %*	*S.aureus** *S.epidermidis* * *E. coli* * *Klebsiella pneumonie* *	Abreu et al., 2019* Oliveira et al, 2025* Ivanova et al., 2017
Acerola (*Malpighia emarginata*) (Stem)	Hexanic	flavonoids fenolic acid	Taxifolin* Protocatechuic acid *	0.73 ± 0.01 mg/L* 0.56 ± 0.01 mg/L*	*C. albicans* * *S.aureus* * *S. typhimurium* * *E.coli* *	Pedro et al., 2020*

						Marafon et al., 2024* Yang et al., 2023
Açaí (*Euterpe oleraecea*) (pulp)	Methanolic	flavonoids, phenolic acid	Orientin Protocatechuic acid Cathequin	-	*S.aureus*	Dias - Souza et al, 2018 Khumbulani et al., 2022
Bacupari (*Gardneriana brasiliensis (*Mart) (peel)	Hexanic extract	alkaloids, flavonoids	Quinine* Formononetin *	111.00 ± 0.17 µg/g* 19.06 ± 0.46 µg/g*	*C.albicans* * *S.aureus* * *B.cereus* * *E.coli* *	Pedro et al., 2020* Melo et al, 2022* Antika et al., 2020 Das Neves et al., 2016
Biribá (*Annona hypoglauca* Mart.) (stem)	dichloromethane: methanol (1:1, v/v)	alkaloids	Actinodaphnine Isoboldine	-	*S.aureus* *Enterococcus faecalis* *E.coli*	Rinaldi et al, 2017
Buriti (*Mauritia flexuosa* L.f) (Oil)	methanolic	flavonoids polyphenols phenolic acid,	Quercetin Eugenol Vanillic acid	20.53 ± 0.37µ g/g 17.60 ± 0.16 µg/g	*Pseudomonas aeroginosa* *Klebsiella pneumonia* *Staphylococcus aureus*	Castro et al 2020 Osonga et al., 2019

				3.49 ± 0.04 µg/g		
Buriti (*Mauritia flexuosa* L.f) (Pulp - oil)	ethanolic	phenolic acid flavonoids	Caffeic acid Quercetin	3.96 ± 0.03 mg/g 3.87 ± 0.05 mg/g	*B.cereus* *Candida albicans* *Candida krusei* *Candida tropicalis*	Nonato et al, 2018 Kepa et al, 2018
Camu camu (*Myrciaria dubia*) (peel and seeds)	*n*-hexane	polyphenols	Myrciarone A Rhodomyrtone Isomyrtucommulone B Myrcianone B	-	*B.subtilis* *B.cereus* *M. luteus* *S.aureus* *S.epidermidis* *Streptoccus mutans*	Kaneshima et al., 2017
Camu-camu (*Myrciaria dubia*) Seeds	Hexanic extract	tannin phenolic acid	Castalagin Vescalagin Gallic acid	1036.00 ± 16 mg/100g 785.00 ± 7 mg/100g 10.87 ± 4 mg/100g	*Pseudomonas aeruginosa* *Salmonella Enteritidis* *Salmonella Typhimurium* *Escherichia coli* *Bacillus cereus* *Staphylococcus aureus* *Listeria monocytogenes* *Saccharomyces cerevisiae*	Fidelis et al 2020 Araujo et al, 2021
Graviola (*Annona muricata*) pulp	Hexanic extract	flavonoids	Gallic acid* Coumaric acid*	43.70 ± 0.25 µg/g* 27.66 ± 0.40 µg/g*	*S.aureus* * *S.typhimurium** *E.coli* *	Pedro et al., 2020* Domingues et al., 2024* Abdella et al., 2024
Mari-Mari (*Cassia*	Acetone extract	tanins	Engeletin	-	*S.aureus* *S.epidermidis* *E.coli*	De Souza et al., 2023

leiandra Benth.)						
Pindaíva-preta (*Unonopsis guatterioides* R.E.Fr. - Annonacae) Peels, Pulp	ethanolic extract	alkaloids	Asimilobine Anonaine Nornuciferine, Glaucine Norglaucine.	-	*Staphylococcus aureus* *Staphylococcus epidermidis*	Dos Santos et al, 2023 Rinaldi et al, 2017
Taperebá (*Spondias mombin* L.) (pulp, husks)	Hexanic extract	Phenolic acid	Ellagic acid* Chlorogenic acid *	19.40 mg/g* 12.00 mg/g *	*C.albicans* * *S.aureus* * *B.cereus* * *E.coli* *	Pedro et al., 2020* Cabral et al., 2016* Aljassim et al.,2022
Tucumã (*Astrocaryum vulgare*) Peel extract	ethanolic extract	Phenolic acid flavonoids	Quercetin + Caffeic acid Quercetin + Chlorogenic acid	-	*E. faecalis* *B. cereus* *L. monocytogenes*	Jobim et al, 2014
Tucumã (*Astrocaryum vulgare*) Pulp extract	ethanolic extract	Flavonoids	Quercetin + rutin	-	*Candida albicans*	Jobim et al, 2014
Uchi (Sacoglottis uchi Huber)pulp	ethanolic extract	Organic acid Phenolic acid	Citric acid Gallic acid	6.58 µg/g 0.36 µg/g	*S. aureus*	De Freitas et.al., 2018 Phasaludeen et al., 2025

Source: author

Among the major classes of antimicrobial compounds found in Amazonian fruits, the most notable include alkaloids, polyphenols, coumarins, terpenes, polysaccharides, and peptides, each possessing distinct chemical structures and biological activities (Table 1).

In the following sections, we will explore the primary bioactive compounds responsible for antimicrobial activity in Amazonian fruits in greater detail. The chemical structures of these compounds and their mechanisms of action, including their interactions with microbial cells, will also be analyzed to provide a comprehensive understanding of their potential applications in food preservation, pharmaceuticals, and biotechnology.

3.2.1. Alkaloids

Alkaloids are a diverse class of naturally occurring organic compounds characterized by the presence of one or more nitrogen atoms, typically incorporated within a heterocyclic ring system (Rezaul Islam et al., 2024) (Figure 1). The nitrogen atom can exist in different oxidation states, influencing the compound's reactivity, solubility, and interaction with biological targets (Hakimi et al., 2019). Most alkaloids possess heterocyclic cores such as pyridine, quinolilene, indole, isoquinoline, and purine, which contribute to their structural stability and functional diversity (Cordell; Quinn-Beattie; Farnsworth, 2001) (Figure 1). Additionally, alkaloids often contain various functional groups, including hydroxyl (-OH), methoxy (-OCH_3), carbonyl (-CO), amine (-NH_2), and ester moieties, further modulating their physicochemical properties and bioactivity (Figure 1) (Mohammed et al., 2020).

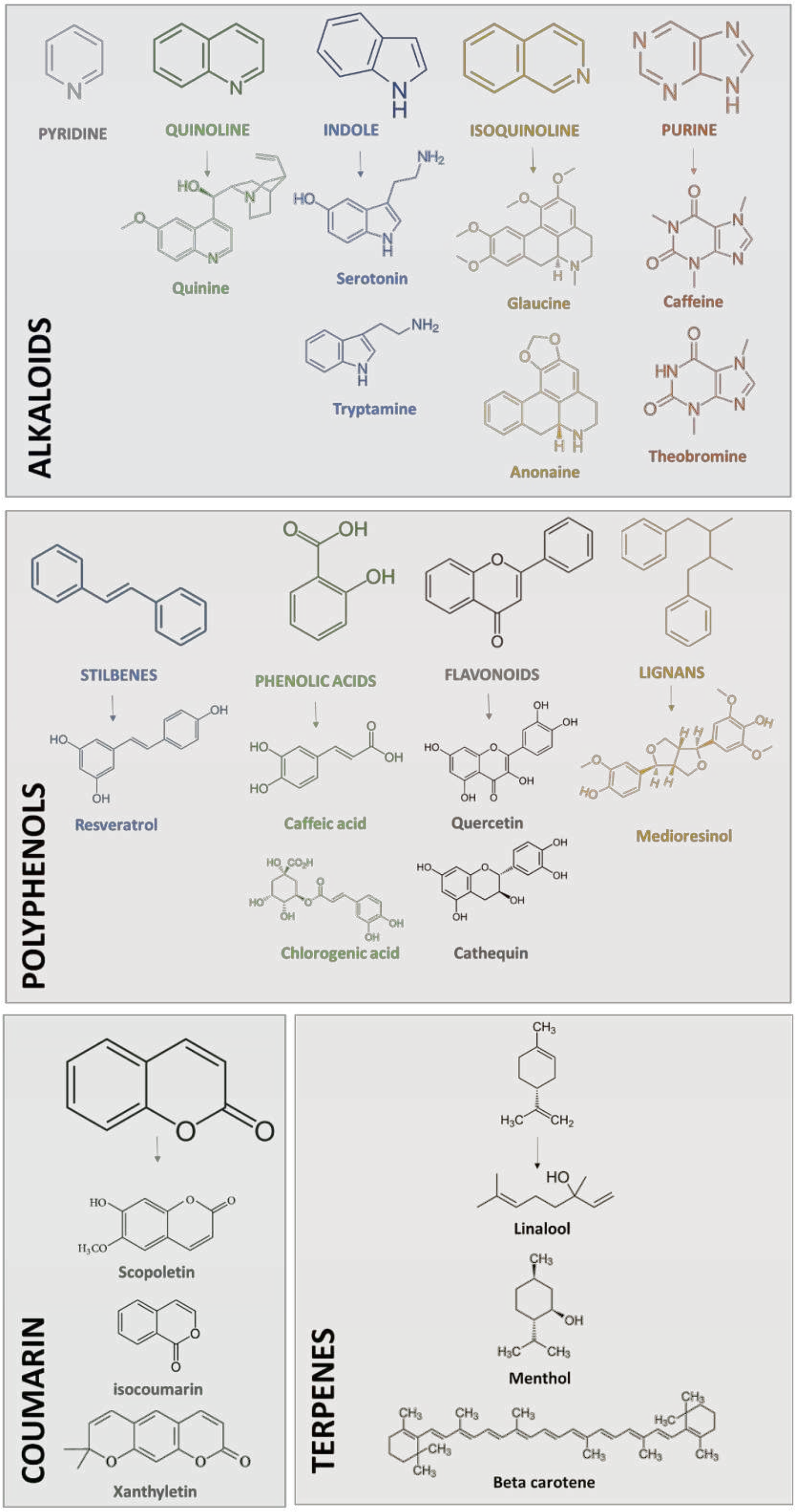

Figure 1 Chemical struture of antimicrobial compounds found in Amazonian fruits.
Source: author

The presence of nitrogen imparts basicity to the molecule, enabling alkaloids to form water-soluble salts in acidic environments, thereby enhancing their absorption and bioavailability in biological systems (Leitão et al., 2021). Despite this, many alkaloids exhibit lipophilic characteristics due to their cyclic structures and hydrophobic side chains, facilitating their solubility in organic solvents and their permeability across biological membranes (Tsuchiya, 2015).

Alkaloids are classified based on their heterocyclic backbone, with major subclasses including pyrrolidine, tropane, pyrrolizidine, indolizidine, quinolizidine, isoquinoline, and indole derivatives, among others (Cordell; Quinn-Beattie; Farnsworth, 2001). In Amazonian fruits, the predominant alkaloid classes include indole, purine, and isoquinoline alkaloids (Dey et al., 2020). Notably, indole alkaloids such as serotonin and tryptamine have been identified in Amazonian cocoa (Deus et al., 2021). Purine alkaloids, including caffeine and theobromine, are abundant in guarana and cocoa (Dos Santos Lima et al., 2024; Pereira-Caro et al., 2013). Moreover, isoquinoline alkaloids such as berberine, widely recognized for its antimicrobial, anticancer and anti-inflammatory properties, are present in *Berberis* spp. (Haque et al., 2025; Qin et al., 2024).

The antimicrobial activity of alkaloids arises from their ability to interact with microbial cellular structures and metabolic pathways, leading to growth inhibition or cell death (**Figure 2**) (Barati; Modarresi Chahardehi, 2024; Thawabteh et al., 2024). The mechanisms of action depend on the alkaloid's chemical structure, the target microorganism, and environmental factors.

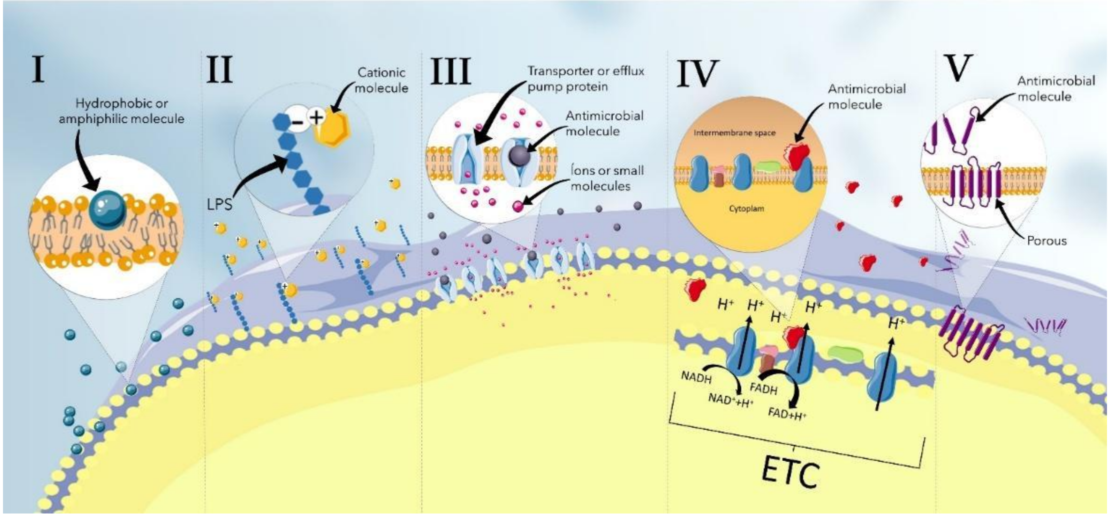

Figure 2 Main mechanism of antimicrobial action of bioactive compounds from Amazonian fruits. I - Integration into microbial membranes, disrupting their integrity and increasing permeability. Blue circles: Hydrophobic alkaloids such as quinoline and isoquinoline derivatives; amphiphilic alkaloids such as berberine; polyphenols or coumarins; II - Electrostatic interaction of cationic molecules (yellow hexagon: alkaloids such as caffeine or polysaccharides) with negatively charged lipopolysaccharides (LPS), resulting in depolarization, disruption of ion gradients, and leakage of intracellular components such as nucleotides, ions, and metabolic intermediates; III - Interaction of antimicrobial molecules (black circle) with transport or efflux pump proteins; IV - Interaction of antimicrobial molecule (Red form) with the electron transport chain (ETC) proteins. Terpenes such as carvacrol and thymol inhibit NADH dehydrogenase and cytochrome c oxidase, reducing ATP production and leading to energy depletion; V - Alkaloids such as sanguinarine or peptides (purple cylinder) form transmembrane pores that lead to uncontrolled ion flux and subsequent cell death. Source: author

Several alkaloids, particularly quinoline and isoquinoline derivatives, integrate into microbial membranes, disrupting their integrity and increasing permeability, ultimately leading to cell lysis (Figure 2) (Laumaillé et al., 2019). Many alkaloids, such as caffeine, are cationic at physiological pH, allowing them to interact with negatively charged components of bacterial and fungal membranes, including lipopolysaccharides (LPS) in Gram-negative bacteria and teichoic acids in Gram-positive bacteria (Figure 2) (Salas-Ambrosio et al., 2023). This electrostatic interaction facilitates membrane binding, resulting in depolarization, disruption of ion gradients essential for cell viability, and leakage of intracellular components such as nucleotides, ions, and metabolic intermediates (Figure 2) (Efimova; Zakharova; Ostroumova, 2020).

Additionally, certain alkaloids exhibit amphiphilic properties, such as berberine, which enables them to insert into the phospholipid bilayer, destabilizing membrane structure and function (Figure 2) (Shai, 1999; Zhang et al., 2020). Alkaloids like sanguinarine act analogously to antimicrobial peptides, forming transmembrane pores that lead to uncontrolled ion flux and subsequent cell death (Figure 2) (Sharma; Sahoo; Bhunia, 2015). Others interfere with lipid rafts or interact with membrane-bound enzymes and transport proteins, impairing membrane stability, signaling pathways, and essential enzymatic functions such as those associated with the respiratory chain and efflux pumps (Figure 2) (Anselmo et al., 2025; Marques-da-Silva; Lagoa, 2023). Inhibiting efflux pumps is particularly relevant in combating antimicrobial resistance (AMR), as it prevents the expulsion of antibiotics and other toxic compounds in pathogens such as *E. coli* and *Pseudomonas aeruginosa* (Dashtbani-Roozbehani; Brown, 2021; Lorusso et al., 2022).

Beyond membrane interactions, alkaloids also exert antimicrobial effects by targeting intracellular processes. Quinoline and purine alkaloids interfere with DNA and RNA synthesis through intercalation or inhibition of key enzymes (Figure 3) (Avendaño; Menéndez, 2015; Zhou et al., 2024). For instance, berberine and harmane intercalate into DNA, disrupting replication and transcription, ultimately inhibiting bacterial growth (Jin et al., 2011). Indole alkaloids have been reported to bind ribosomal subunits, inhibiting protein synthesis, inhibition of efflux pumps and impairing bacterial and fungal proliferation (**Figure 3**) (Cushnie; Cushnie; Lamb, 2014; Liu et al., 2020). Furthermore, some alkaloids interfere with microbial metabolic pathways, particularly those involved in ATP production, thereby disrupting energy homeostasis and cellular viability (Langlois et al., 2020).

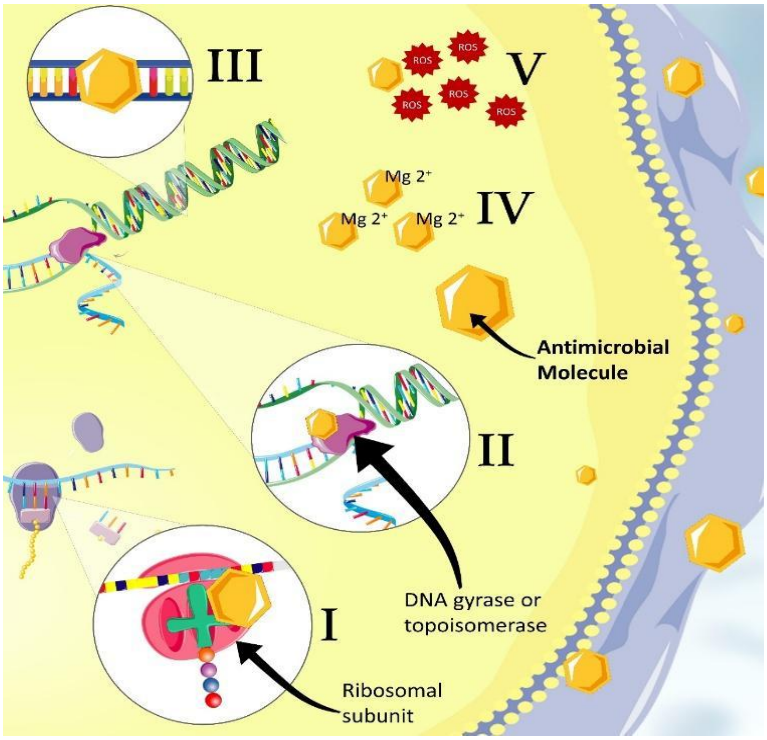

Figure 3 Main antimicrobial action mechanisms of bioactive compounds from Amazonian fruits on enzymes, ribosomes, and DNA. I - Binding of antimicrobial molecules (e.g., indole alkaloids or coumarins) to ribosomal subunits, inhibiting protein synthesis; II - Binding of antimicrobial molecules (e.g., phenolic acids) to DNA gyrase and topoisomerases; III - Interaction of antimicrobial molecules (e.g., phenolic acids or coumarins with planar aromatic structures) with DNA bases within the enzyme-DNA complex, leading to DNA fragmentation; IV - Chelation of Mg^{2+}*by phenolic acids, disrupting enzyme function; V- Induction of ROS accumulation, promoting oxidative damage to proteins, lipids, and DNA, ultimately triggering microbial apoptosis. Source: author*

Alkaloids exhibit broad-spectrum antimicrobial activity against various bacterial and fungal pathogens, including *S. aureus, B. cereus, E. coli, P. aeruginosa, Salmonella spp., C. albicans, and Aspergillus spp.* (Table 1) (Rinaldi et al, 2017; Monosalva et al., 2016; Yan at al., 2021; Mabhiza et al., 2016). Notably, berberine has demonstrated potent antimicrobial activity against both Gram-positive and Gram-negative bacteria, while harmane and harmine have exhibited antifungal properties, particularly against *Candida* spp. (Zhang et al., 2024). The antimicrobial activity of alkaloids underscores their potential as natural alternatives to synthetic antibiotics, particularly in the context of rising antimicrobial resistance. Their ability to target multiple cellular processes, disrupt microbial metabolism, and act synergistically with conventional drugs highlights their relevance in food preservation, pharmaceuticals, and biotechnological applications.

3.2.2. Polyphenols

Polyphenols constitute a diverse class of naturally occurring secondary metabolites characterized by the presence of multiple hydroxyl (-OH) groups attached to aromatic rings (Figure 1) (Watson, 2014). These compounds are classified as phenolic compounds and exhibit structural complexity ranging from simple monomers to highly polymerized forms.

Structurally, polyphenols are composed of one or more benzene rings with hydroxyl substituents, which confer their antioxidant properties (Figure 1). Based on their structural backbone, they are categorized into flavonoids, phenolic acids, stilbenes, and lignans (Figure 1) (Wei et al., 2025). Flavonoids, characterized by a C6-C3-C6 skeleton, consist of two phenyl rings (A and B) connected by a three-carbon bridge forming a heterocyclic pyran or pyrone (C-ring) (Bhat et al., 2017). Phenolic acids encompass hydroxybenzoic and hydroxycinnamic acids, which feature a C6-C1 (benzoic acid derivatives) or C6-C3 (cinnamic acid derivatives) backbone (Gaur; Gänzle, 2023) . Stilbenes contain a C6-C2-C6 backbone with a central ethylene (-C=C-) bridge, while lignans are derived from the coupling of two phenylpropanoid (C6-C3) units (Gaur; Gänzle, 2023).

Chemically, the hydroxyl groups on the aromatic rings of polyphenols enable electron donation, facilitating free radical scavenging and metal ion chelation (Vuolo et al., 2019). Additionally, polyphenols can undergo oxidation to form quinones, leading to polymerization reactions, as observed in tannins (Liu et al., 2022; Vera; Urbano, 2021). Moreover, they can function as weak acids, forming phenolate anions in alkaline conditions due to their hydroxyl constituents (Lone et al., 2024).

Amazonian fruits are recognized as rich sources of polyphenols, particularly flavonoids, phenolic acids, and tannins (Table 1, pg. 17). These bioactive compounds are predominantly localized in the peel, pulp, seeds, and leaves, with concentrations influenced by species, ripeness, and environmental conditions (Barboza et al., 2022; Bezerra et al., 2024). In Açaí and Bacaba, anthocyanins (cyanidin-3-glucoside, cyanidin-3-rutinoside), flavonoids, and phenolic acids predominate, whereas Camu-Camu contains substantial amounts of ellagic acid, flavonols (quercetin, myricetin), and anthocyanins (Table 1).

Polyphenols exhibit broad-spectrum antimicrobial activity against bacteria and fungi through multiple biochemical and structural mechanisms (Cruz et al., 2024). These mechanisms include disruption of cell membranes, inhibition of essential enzymes, interference with quorum sensing (QS), and metal ion chelation, ultimately leading to microbial cell death or inhibition (Figures 2, 3 and 4) (Ivanov et al., 2022; Santos et al., 2021; Wang et al., 2022, 2024).

In bacterial cells, polyphenols disrupt the bilayer membrane through mechanisms analogous to those described for alkaloids (Figure 2) (Chen; Lan; Xie, 2024; Cushnie; Lamb, 2005). In brief, polyphenols interact with membrane lipids and proteins or alter the electron transport chain, leading to changes in membrane fluidity and permeability (Li et al., 2024). This results in intracellular leakage, lipid peroxidation, and compromised ATP synthesis (Mandal; Domb, 2024; Wang et al., 2022). Such mechanisms have been described for compounds including epicatechin, catechins, anthocyanins, proanthocyanidins, and gallic acid (Mandal; Domb, 2024).

Ikigai et al. (1993) demonstrated that catechins exhibit greater efficacy against Gram-negative bacteria, likely due to their interaction with negatively charged lipopolysaccharides. The same study found that epigallocatechin gallate induces leakage of intraliposomal content by interacting with liposomal membranes. Wei et al. (2024) further reported that natural flavonoids with lipophilic groups exhibit enhanced antibacterial activity, owing to their ability to penetrate the bacterial phospholipid bilayer.

A study on beetroot (*Beta vulgaris*) extract with a high polyphenol content (~28%) against *B. cereus* provided evidence that polyphenols contribute to antimicrobial activity through ATP depletion and apoptosis-like cell death (Gong et al., 2023). The extract induced membrane depolarization (observed via increased fluorescence intensity), activation of caspase-like proteins, phosphatidylserine translocation, DNA fragmentation, and a reduction in reactive oxygen species, ultimately disrupting redox homeostasis and leading to cell death (Gong et al., 2023).

In fungal cells, polyphenols target β-glucans, chitin, and ergosterol in the cell membrane (Figure 2) (Dhawale et al., 2023; Janeczko, 2018; Nazzaro et al., 2019; Simonetti et al., 2020). Catechins and proanthocyanidins bind to ergosterol, disrupting membrane integrity (Mekoue Nguela et al., 2015; Tóth Hervay et al., 2024). Furthermore, polyphenols inhibit β-glucan synthase, chitin synthase, and oxidoreductases, impairing cell wall synthesis and energy production (Davidova et al., 2024). Studies have shown that certain polyphenols can inhibit the activity of β-(1,3)-glucan synthase, compromising the integrity of the fungal cell wall and leading to cell death. For example, phenolic compounds isolated from *Turnera diffusa*, such as apigenin and luteolin, demonstrated the ability to inhibit fungal endo-1,3-β-glucanase activity by 90% and 60%, respectively, resulting in the inhibition of *Botrytis cinerea* spore germination (Tapia-Quirós et al., 2020).

At the intracellular level, phenolic acids bind to and inhibit bacterial DNA gyrase and topoisomerases, thereby disrupting DNA replication (Davidova et al., 2024). DNA gyrase, an ATP-dependent enzyme responsible for relieving supercoiling during replication, consists of two subunits: GyrA (catalytic core) and GyrB (ATPase domain) (Figure 3) (Germe et al., 2024). Flavonoids such as quercetin, myricetin, and catechins contain multiple hydroxyl (-OH) groups that form hydrogen bonds with the catalytic residues of DNA gyrase (Verma et al., 2021). Additionally, polyphenols possess planar benzene rings capable of stacking with DNA bases within the enzyme-DNA complex, leading to DNA fragmentation (Figure 3) (Li et al., 2012). Phenolic acids such as gallic acid, ellagic acid, and caffeic acid also chelate Mg^{2+}, disrupting enzyme function (Figure 3) (Keyvani-Ghamsari et al., 2023).

Polyphenols further inhibit topoisomerases, enzymes that regulate DNA supercoiling by introducing transient breaks (Figure 3) (Sitarek et al., 2024). Certain polyphenols, such as catechins, structurally mimic ATP, competing for the ATPase binding site and thereby inhibiting ATP hydrolysis essential for enzymatic activity (Gradišar et al., 2007). Moreover, anthocyanins and flavonols undergo oxidation to quinones, forming covalent adducts with cysteine residues in topoisomerases, resulting in irreversible inhibition (Joyner, 2021).

Mori et al. (1987) investigated the inhibition of nucleic acid synthesis by plant-derived flavonoids against *P. vulgaris* and *S. aureus*. Their findings indicated that free hydroxyl groups on the aromatic A and B rings of flavonoids are critical for antimicrobial activity. Robinetin, myricetin, and (-)-epigallocatechin exhibited the highest inhibition of DNA synthesis in *P. vulgaris*, followed by RNA synthesis. In S. *aureus*, myricetin, (-)-epigallocatechin, and 7,8-dihydroxyflavone were most effective against RNA synthesis.

Polyphenols have also been shown to disrupt QS signaling pathways, including acyl-homoserine lactones (AHLs) in Gram-negative bacteria and autoinducing peptides (AIPs) in Gram-positive bacteria, reducing bacterial virulence and biofilm formation (Davidova et al., 2024). Phenolic hydroxyl (-OH) and carboxyl (-COOH) groups enable hydrogen bonding with AHL lactone rings, while polyphenols such as ellagic acid and catechins oxidize these rings, leading to hydrolysis and inactivation of signaling molecules (Figure 4) (Sarabhai et al., 2013). Additionally, polyphenols can mimic AHL structures, binding to LuxR-type QS receptors and blocking QS signaling (Nazzaro et al., 2019). In Gram-positive bacteria, polyphenols react with cysteine residues in AIPs, forming covalent adducts that prevent recognition by the AgrC QS sensor kinase (Yftah at al., 2013).

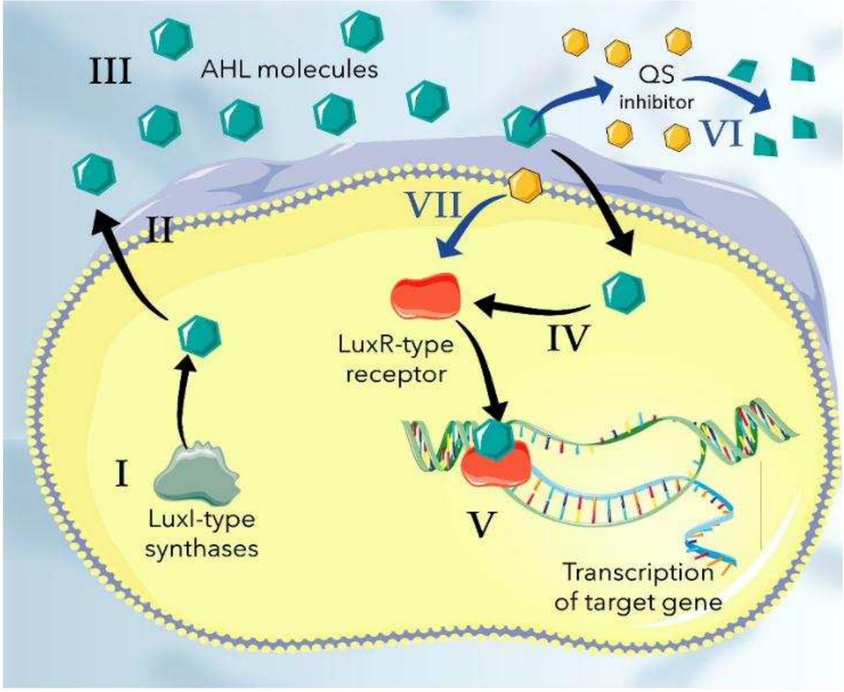

Figure 4 Mechanism of quorum sensing in Gram-negative bacteria using acyl-homoserine lactones (AHLs). (I) AHLs (Green hexagon) are synthesized by LuxI-type enzymes; (II) AHLs diffuse passively or actively across the bacterial membrane. (III) As bacterial density increases, AHLs accumulate in the extracellular environment, reaching a threshold concentration. (IV) Once internalized, AHLs bind to LuxR-type transcriptional regulators, inducing conformational changes that stabilize the LuxR-AHL complex that binds to quorum sensing (QS) box sequences in DNA, regulating the expression of genes involved in biofilm formation, virulence factor production, motility, antibiotic resistance, and bioluminescence. (VI) Polyphenols such as ellagic acid and catechins (yellow hexagon) oxidize the lactone rings e AHL molecule, leading to it hydrolysis. (VII) Additionally, polyphenols can mimic AHL structures, binding to LuxR-type QS receptors and blocking QS signaling. Source: author

Several studies have investigated the antimicrobial potential of Amazonian fruit polyphenols (Table 1). Nonato et al. (2018) evaluated buriti pulp oil fractions and observed antifungal activity against *Candida* spp., as well as synergistic effects with antibiotics against *B. cereus* and *S. choleraesuis*. Dias-Souza et al. (2018) reported that açaí pulp extract exhibited activity against *S. aureus*, eradicating biofilms and enhancing antibiotic efficacy. Similarly, Albuquerque et al. (2023) demonstrated that rambutan (*Nephelium lappaceum*) bark extract exhibited antimicrobial efficacy superior to chemical preservatives.

In summary, polyphenols exhibit antimicrobial activity against pathogens of significance in both food safety and clinical settings. They can act as potential of antibiotic activity, enhancing the efficacy of conventional antimicrobial treatments by disrupting microbial resistance mechanisms. Additionally, polyphenols can be employed as natural preservatives in food products, extending shelf life by inhibiting spoilage microorganisms and pathogenic bacteria through various biochemical and structural mechanisms, such as membrane disruption, enzyme inhibition, and quorum sensing interference. Their broad-spectrum activity and natural origin make them promising candidates for applications in food preservation and alternative antimicrobial strategies in medicine.

3.2.3. Coumarins

Coumarins are a class of organic compounds belonging to the benzopyrone family, characterized by a fused bicyclic system comprising a benzene ring (C_6H_6) and a pyrone ring (C_3O), with the molecular formula $C_9H_6O_2$ (Chaudhary et al., 2022). Their core structure consists of a six-membered benzene ring fused to a five-membered pyrone ring, where the oxygen atom is an integral part of the lactone system (Figure 1).

The pyrone ring in coumarins functions as a lactone, containing an ester (C=O) linked to a hydroxyl group (–OH). The oxygen in the pyrone ring forms a single bond with a carbon atom in the benzene ring, creating a planar, conjugated, and aromatic system. This conjugation significantly influences the chemical reactivity of coumarins, particularly their ability to absorb light in the ultraviolet-visible spectrum (Ellis, 1987).

Coumarins exhibit structural diversity due to possible substitutions at various positions on both the benzene and pyrone rings, affecting their chemical and biological properties. These substitutions typically occur at positions 6, 7, or 8 on the benzene ring, as well as on the pyrone ring, leading to distinct subclasses such as simple coumarins, O-substituted coumarins (with hydroxyl, methoxy, or ester groups), and C-substituted coumarins (with halogens or alkyl groups attached to the pyrone ring (Galkin et al., 2009; Kornicka et al., 2023). The simplest coumarin structure consists of an unmodified benzopyrone system, where the oxygen in the pyrone ring is bonded to the benzene ring at position 7 (Figure 1). This configuration forms the characteristic fused bicyclic system observed in all coumarin derivatives (Chaudhary et al., 2022).

Coumarins are naturally occurring compounds found in various plant species, including those native to the Amazon rainforest. These compounds are recognized for their distinct fragrance and possess a wide range of biological activities, including antimicrobial, anti-inflammatory, and antioxidant properties (Venugopala et al., 2013).

Coumarins exhibit antimicrobial activity through multiple mechanisms, affecting cell membranes, metabolic enzymes, DNA replication, inhibiting the detection of quorum and biofilm formation (Figures 2 and 3) (El-Sawy et al., 2024). Coumarins act similarly to alkaloids and polyphenols, compromising microbial cell membranes and leading to structural damage (Wang et al., 2024). By inserting into lipid bilayers, coumarins alter membrane fluidity and permeability, resulting in leakage of essential intracellular components, depolarization, and cell death (Figure 2) (Galkin et al., 2009).

Specific coumarins, such as scopoletin, can undergo photochemical or redox reactions, generating reactive oxygen species (ROS) (Zaynab et al., 2024). These ROS induce oxidative damage in microbial cells by targeting lipids, proteins, and DNA, causing lipid peroxidation, enzyme inactivation, and genetic mutations that lead to apoptosis or necrosis (Figure 3) (Maslovska et al., 2023).

Coumarins can inhibit enzymes involved in bacterial peptidoglycan synthesis, weakening the cell wall and increasing bacterial susceptibility to lysis (Figure 2) (Chate et al., 2019). This effect is particularly pronounced in Gram-positive bacteria, which rely on their thick peptidoglycan layer for structural integrity (Souza et al., 2005). Coumarins with planar aromatic structures can intercalate into microbial DNA, disrupting the double-helix structure and inhibiting transcription and replication (Figure 3) (Citarella et al., 2024). Additionally, these compounds act on bacterial DNA gyrase and topoisomerase IV, enzymes essential for DNA supercoiling and topology maintenance, leading to impaired cell division and bacterial death (Hooper, 1998).

Certain coumarins, particularly those bearing hydroxyl and methoxy groups, interact with microbial ribosomal subunits, inducing conformational changes that inhibit translation (Figure 3) (Reen et al., 2018). This mechanism impairs the production of vital bacterial proteins, ultimately affecting cell viability (Reen et al., 2018).

Coumarins can inhibit key metabolic enzymes in microbial cells. For instance, Raja et al. (2011) demonstrated that imperatorin inhibited copper and zinc superoxide dismutase in *Shigella dysenteriae*, increasing oxidative stress and leading to bacterial toxicity. Among various coumarins studied for antimicrobial activity, amicoumacin A, a nitrogen-substituted isocoumarin, has been shown to target Gram-positive bacteria, including *Salmonella* sp., *Shigella* sp., and methicillin-resistant *S. aureus* (MRSA). Recent studies have highlighted the role of coumarins in biofilm disruption. Tian et al. (2016) tested novel coumarin glycosides against *P. aeruginosa* clinical isolates. The (3*S*)-6-*O*-(4′-*O*-methyl-6′-acetyl-β-D-glucopyranoside)-7-*O*-methyl-8-hydroxyl-3-[(3*E*)-penta-3-enyl]-3,4-dihydroisocoumarin significantly reduced biofilm formation by interfering with QS regulatory systems.

Although studies on the antimicrobial activity of coumarins from Amazonian plants remain limited, their presence has been documented in several native species. *Randia formosa* (Jacq.) K. Schum, known as northern star or blackberry jelly fruit, contains two coumarins: 8-hydroxy-5-*O*-β-D-glucopyranosylpsoralen and 7,8-dimethoxycoumarin (De Mello e Silva et al., 2022). The genus *Brosimum* (Moraceae) predominantly contains pyranocoumarins and furocoumarins, as well as prenylated derivatives such as brosiparin and brosiprenin (Gottlieb, Da Silva, & Maia, 1972). *Brosimum gaudichaudii* roots contain several coumarins, including xanthyletin, luvangetin, psoralen, bergapten, and multiple glycosylated derivatives (Monteiro et al., 2002).

Coumarins exhibit broad-spectrum antimicrobial activity and their ability to target various aspects of microbial physiology makes them promising candidates for developing novel antimicrobial agents. Further research into coumarins from Amazonian plant species may reveal new bioactive compounds with potential food and biotechnological applications.

3.2.4. Terpenes

Terpenes are a diverse class of naturally occurring organic compounds derived from isoprene (C_5H_8) units, forming the structural basis for various hydrocarbons and oxygenated derivatives (Figure 1) (Bakkali et al., 2008). Their chemical properties are influenced by molecular structure, functional groups, and degree of unsaturation. They are classified based on the number of isoprene units they contain: monoterpenes ($C_{10}H_{16}$), composed of two isoprene units, found in essential oils (e.g., limonene, pinene, and linalool); sesquiterpenes ($C_{15}H_{24}$), formed by three isoprene units, often contributing to plant defense mechanisms (e.g., farnesene, caryophyllene); diterpenes ($C_{20}H_{32}$), built from four isoprene units, commonly found in plant resins (e.g., retinol, taxadiene);

triterpenes ($C_{30}H_{48}$), comprising six isoprene units and serving as precursors to steroids and saponins (e.g., squalene, lupeol); and tetraterpenes ($C_{40}H_{64}$), containing eight isoprene units and including carotenoids, which are crucial for pigmentation and antioxidant activity (e.g., β-carotene, lycopene) (Masyita et al., 2022). Terpenes may be acyclic, monocyclic, or polycyclic, with functional groups that significantly impact their chemical behavior and biological activity (Figure 1). Hydrocarbon terpenes consist solely of carbon and hydrogen (Bakkali et al., 2008; Rathod et al., 2021). Oxygenated terpenes, such as camphor, linalool, menthol, contain hydroxyl (−OH), carbonyl (C=O), carboxyl (−COOH), or ether (−O−) groups, which enhance solubility and reactivity (Paduch et al., 2007). Phenolic terpenes feature hydroxyl groups attached to aromatic rings, contributing to antioxidant and antimicrobial properties as found in thymol and carvacrol (Konuk; Ergüden, 2020). Terpenes exhibit stereoisomerism due to multiple chiral centers, influencing their interaction with biological targets. For example, (+) limonene has a citrus scent, whereas (–) limonene has a pine-like aroma, despite having the same molecular formula (Zhu et al., 2021).

Most terpenes are highly lipophilic, allowing them to integrate into cell membranes and modulate permeability. Their low molecular weight and volatility make them key components of essential oils, influencing fragrance and evaporation rates. Terpenes are susceptible to oxidation, polymerization, and rearrangement reactions, which can alter their biological activity (Bakkali et al., 2008).

Terpenes are found in various Amazonian fruits, contributing to their unique aromas, flavors, and potential health benefits. Amazonian fruits are recognized for their complex profile of phytochemicals, including vitamins, fatty acids, and secondary metabolites, predominantly led by terpenes (Corrêa et al., 2023). Carotenoids, a class of tetraterpenoid pigments (C_{40}), are widely distributed in nature and are responsible for the red, orange, and yellow tones in many Amazonian fruits (Amorim et al., 2022). They possess an extensive system of conjugated double bonds, known as a chromophore, which is responsible for their characteristic colors and properties (Chandrika, 2023). The distribution and concentration of terpenes in Amazonian fruits can vary significantly among species and even among different parts of the same fruit. Factors such as ripeness, environmental conditions, and genetic variations influence terpene profiles. These compounds not only contribute to the sensory qualities of the fruits but also offer potential health benefits, including antioxidant, anti-inflammatory, and antimicrobial effects (Masyita et al., 2022; Sharma; Khare; Rai, 2024).

Terpenes exhibit broad-spectrum antimicrobial activity against bacteria and fungi. Their antimicrobial mechanisms involve multiple targets within microbial cells, affecting membrane integrity, enzyme function, genetic material, and metabolic pathways (Kumar, 2024; Rathod et al., 2021). One of the primary antimicrobial mechanisms of terpenes involves their interaction with microbial cell membranes, leading to increased permeability and eventual cell lysis (Figure 1). Terpenes, particularly monoterpenes (e.g., thymol and carvacrol), have a high affinity for lipid membranes due to their hydrophobic nature (Pezzola et al., 2024). They integrate into the phospholipid bilayer, disrupting the structural organization of the membrane and destabilize the lipid bilayer, increasing membrane fluidity and permeability (Cristani et al., 2007; Rathod et al., 2021). This causes leakage of vital intracellular components such as ions (K^+, Ca^{2+}) leading to loss of membrane potential and cellular homeostasis (Griffin et al., 2005).

Bai et al. (2022) demonstrated that eugenol a phenolic compound structurally related to terpineols exerts significant antibacterial activity against *Shigella flexneri*. Their study revealed that eugenol treatment disrupts the integrity of the bacterial cell membrane, induces membrane depolarization, causes intracellular ATP leakage, and leads to marked morphological alterations in the bacterial cells. Guimarães et al. (2019) evaluated the antibacterial activity of 33 free terpenes found in essential oils and, among these, non-oxygenated monoterpenes (*m* - cymene, R - (+) - limonene), oxygenated monoterpenes ((-) -borneol, (+) - borneol, (±) - camphor, ʟ-carveol, ʟ-carvone, citral , (±) - citronellal, β-citronellol, *trans*-geraniol, (±) - linalool, terpineol) and phenolic monoterpenes (carvacrol, eugenol and thymol) showed antimicrobial activity on *S. typhimurium*, *S. aureus* and *E.coli*. In the presence of terpenes, the authors observed irregular cell sizes in *S. aureus*, along with the presence of cellular debris and morphological changes, including disruptions in the characteristic “grape-like” clustering due to altered cell adhesion or membrane destruction. Similar morphological changes were also observed in *B. subtilis*, *K. pneumoniae* and *S. enterica* treated with essential oils (De Souza et al., 2022). These results were attributed to the presence of oxygenated monoterpenes (citronellal and citronellol) in the essential oil.

In the presence of terpenes (thymol, carvacrol, limonene and eugenol), Di Pasqua et al. (2006) verified an increase in the amount of unsaturated fatty acids in strains of *E. coli* and *S. typhimurium*. The authors believe that this behavior is a response to the stress that bacteria undergo in the presence of antimicrobial compounds to maintain membrane structure and function. Some terpenes, such as farnesol and α-humulene, inhibit key enzymes involved in bacterial peptidoglycan synthesis, including penicillin-binding proteins (PBPs) and transglycosylases (Ibáñez et al., 2022). This weakens the bacterial cell wall, making it more susceptible to osmotic stress and lysis. In fungi, terpenes like limonene and β-caryophyllene inhibit chitin synthase and β-glucan synthase, key enzymes involved in fungal cell wall biosynthesis (Zeng et al., 2024). This results in defective cell walls, leading to increased sensitivity to osmotic pressure and cell death. Terpenes can act as enzyme inhibitors, disrupting essential microbial metabolic pathways.

For instance, carvacrol and thymol inhibit NADH dehydrogenase and cytochrome c oxidase, reducing ATP production and leading to energy depletion (Figure 2) (Meeran et al., 2016; Lim et al., 2018). Terpenes like farnesol and α-pinene block autoinducer signaling molecules (AHLs, AI-2) preventing coordinated microbial behaviors as pathogenicity and resistance (Figure 4) (Naga; Shaaban, 2023; Roy; Adhikari; Tiwary, 2023). Some terpenes such as β-caryophyllene and humulene stimulate the production of ROS, such as superoxide anions (O_2^-) and hydrogen peroxide (H_2O_2) (Staton Laws Iii & Smid, 2024). ROS accumulation leads to oxidative damage of proteins, lipids, and DNA, ultimately triggering microbial apoptosis (Figure 3).

An increase in intracellular ROS causing oxidative stress with the formation of apoptotic bodies was observed for an essential oil obtained containing terpenes such as *trans*-sesquisabinene hydrate, *trans*-caryophyllene, β-pinene, *trans*-β-farnesene, 14-hydroxycaryophyllene, limonene and p-cymene (Henrique Fontoura et al., 2024). In addition, the essential oil showed bacteriostatic and bactericidal activity against *B. subtilis*, *E. coli*, *L. monocytogenes* and *S. Typhimurium* (Henrique Fontoura et al., 2024).

Croton pullei (Euphorbiaceae) also showed moderate antibacterial and antifungal activity. The chemical composition of essential oils from the leaves and stems of this Amazonian plant showed linalool as the main compound, followed by α-pinene and β-pinene (Peixoto et al., 2013). The plant extracts showed antimicrobial activity against *E.*

coli, *P. aeruginosa*, *Salmonella* sp., *S. aureus*, *B. cereus*, *C. albicans* and *C. parapsilosis* (Peixoto et al., 2013). The ability of terpenes to target various microbial structures and pathways makes them promising candidates for novel antimicrobial agents. Further research on terpene derivatives and their synergistic effects with conventional antibiotics could enhance their application in clinical and industrial settings.

3.2.5. Polyssacharides

Polysaccharides found in Amazonian plants exhibit diverse chemical structures and biological functions, playing crucial roles in both the structural integrity and bioactivity of these plants. Composed of monosaccharide units linked by glycosidic bonds, these macromolecules can form linear or branched structures. Their composition, degree of branching, and functional groups significantly influence their physicochemical properties and bioactivity (Yang et al. 2022).

These polysaccharides serve multiple purposes, including providing mechanical support and protection to plant cell walls. Cellulose, the most abundant polysaccharide in Amazonian plants, is a linear polymer of β-D-glucose units connected by β(1→4) glycosidic bonds (Shamsabadi et al., 2025). Through extensive hydrogen bonding, cellulose forms microfibrils, which contribute to the rigidity of plant cell walls. Hemicelluloses, a group of heterogeneous branched polysaccharides, include xylans, mannans, and arabinogalactans (Teli et al., 2024). Their backbones are primarily β (1→4)-linked, with side chains containing arabinose, xylose, galactose, and glucuronic acid, providing flexibility to the cell wall (He et al., 2024). Pectins, highly branched polysaccharides rich in galacturonic acid, include homogalacturonan, rhamnogalacturonan I, and rhamnogalacturonan II regions (Moore et al., 2008).

In addition to structural roles, some polysaccharides also act as energy reserves in Amazonian plants. Starch, composed of amylose and amylopectin, is abundant in Amazonian tubers and fruits, including *Inga edulis* (ice cream bean) and pupunha (Do Rosário et al., 2025; Pireda et al. 2017; Felisberto et al. 2020). Amylose is a linear chain of α (1→4)-linked glucose, while amylopectin is highly branched with α (1→6) linkages (Sissons et al., 2023). As fruits ripen, starch is converted into simpler sugars, contributing to their sweetness. Fructans, found in some Amazonian species, consist of β (2→1) or β (2→6)-linked fructose units, often with terminal glucose residues (Sjöö & Nilsson, 2018).

The structural diversity of Amazonian plant polysaccharides contributes to their wide range of functional properties, making them valuable for food, pharmaceutical, and cosmetic applications. These polysaccharides are also abundant in Amazonian fruits, where they influence the fruit's texture, metabolism, and bioactivity. In particular, these macromolecules contribute to fruit texture, water retention, and nutritional value, while offering health benefits such as antioxidant, immunomodulatory, and prebiotic effects (Chen; Lan; Xie, 2024; Gong et al., 2022).

Polysaccharides also exhibit significant antimicrobial activity through a range of mechanisms, such as disrupting microbial membranes, inhibiting microbial adhesion, interfering with metabolism, and modulating immune responses (Liang et al., 2024). The antimicrobial potential of polysaccharides varies based on their chemical composition, molecular weight, branching degree, and functional groups, including sulfate, carboxyl, and amino groups (Ferreira et al. 2014). Cationic and sulfated polysaccharides can disrupt bacterial membranes, leading to cell lysis through electrostatic interactions, pore formation, and alterations in membrane fluidity (Figure 2) (Mu et al., 2022; Liu et al. 2020).

Mucilages found in camu-camu and cupuaçu are highly hydrated polysaccharides composed of galactose, arabinose, rhamnose, and uronic acids (Viana et al. 2020; Vriesmann and Petkowicz 2009). These polysaccharides form gel-like structures and exhibit antimicrobial activity, possibly by interacting with microbial membranes, disrupting their integrity, and inhibiting microbial adhesion (Messing et al., 2024; Chokri et al., 2024). Arabinogalactans present in buriti have their antimicrobial activity linked to their ability to modulate immune responses and inhibit microbial growth, although more specific mechanisms remain an area of study Silva et al. (2023). Fucoidans and Sulfated Polysaccharides may inhibit bacterial and fungal growth by interfering with microbial membrane integrity or by inhibiting biofilm formation. These polysaccharides have shown promise in inhibiting the adhesion and colonization of pathogens (Jeong et al. 2024). Finally, the pectins, which can be found in cupuaçu and graviola, are rich in galacturonic acid and potentially disrupt microbial adhesion and act as barriers against pathogen invasion (Rincón et al. 2023; Jimenez et al. 2020).

Overall, these polysaccharides hold great potential for various applications in the food, pharmaceutical, and cosmetic industries, and further research into their extraction, characterization, and applications could expand their utility across different sectors.

3.2.6. Peptides

Peptides in Amazonian fruits primary structure consists of a specific sequence of amino acids, which determines their biological activity. Many of these peptides contain hydrophobic amino acids (e.g., leucine, valine, and phenylalanine), contributing to their interaction with cell membranes (Seo et al., 2012). The side chains (R-groups) of amino acids in Amazonian fruit peptides help to determine their bioactivity. Sulfhydryl (−SH) groups present in cysteine-containing peptides, enable the formation of disulfide bonds, which stabilize the peptide's three-dimensional structure (A. Sharma & Singh, 2024). On the other hand, basic groups ($-NH_2$), found in lysine and arginine residues, influence the peptide charge and interaction with microbial membranes (Nonato Da Silva Júnior et al., 2023).

Some peptides may undergo modifications such as glycosylation, phosphorylation, or cyclization, which enhance their stability, solubility, or biological activity. For instance, cyclic peptides often display greater resistance to enzymatic degradation (Martian et al., 2025). The defensins, found in seeds and pulp of Amazonian fruits such as *Theobroma cacao* (cacao), are cysteine-rich peptides with multiple disulfide bonds (Lopes et al., 2008). These peptides can bind to microbial membranes, increasing permeability and leading to cell lysis (Figure 2). Also, exhibit antifungal activity by interfering with fungal cell wall integrity (Freitas et al., 2020; Silva et al., 2014).

The cyclotides present in Rubiaceae and Violaceae families, are cyclic peptides stabilized by a cysteine-knot structure, which disrupt bacterial and fungal membranes by forming pores, leading to leakage of intracellular contents (Grover et al., 2021). Once, Lipid Transfer Proteins (LTPs), found in *Anacardium occidentale* (cashew fruit) and *Carica papaya* (papaya), are small peptides rich in cysteine residues that interact with microbial membranes, leading to disruption of lipid organization and inhibition of fungal growth (Amador et al., 2021; Helmy & Parang, 2023). Cationic peptides (positively charged) interact with negatively charged bacterial membranes by electrostatic interactions, weakening membrane integrity (Figure 1) (Ciumac et al., 2019). In another way, molecules, such as defensins and peptaibols, insert into microbial membranes, forming pores that allow leakage of essential ions and intracellular metabolites, leading to cell death (Brogden, 2005; Hou et al., 2022).

In addition, some peptides prevent cross-linking of peptidoglycan in bacterial cell walls or interfere with ergosterol synthesis, destabilizing fungal membranes (Figure 1) (Mohid et al., 2022). It is also described that some peptides interfere with QS signaling molecules and inhibit metabolic enzymes, preventing the biofilm formation and impairing respiration and energy production, respectively (Figure 4) (K R et al., 2024; Yasir et al., 2018).

Some studies also report that the peptides, as that found in Amazonian fruits, interact with bacterial DNA or ribosomes preventing replication and protein synthesis or causing oxidative damage to microbial proteins, lipids, and DNA by stimulating the production of ROS (K R; Balenahalli Narasingappa; Vishnu Vyas, 2024). However, the chemical interaction of these peptides with the cellular structures remains unclear.

3.3. Conclusion

Amazonian fruits represent a rich source of bioactive compounds with significant antimicrobial properties. These compounds primarily act by disrupting microbial membranes, leading to increased permeability and cell lysis. However, some exhibit intracellular mechanisms, such as enzyme inhibition or direct interaction with DNA, further impairing microbial survival. Among these bioactive molecules, certain peptides and secondary metabolites have demonstrated the ability to reduce microbial resistance to antibiotics. For example, defensins and cyclotides can enhance bacterial membrane permeability, facilitating antibiotic penetration, while flavonoids and alkaloids have been reported to inhibit efflux pumps, thereby increasing the effectiveness of conventional antibiotics. Such findings suggest that compounds derived from Amazonian fruits could be used to potentiate antimicrobial therapies and combat drug-resistant pathogens. Beyond their medical applications, these antimicrobial compounds have potential applications in food preservation. By inhibiting microbial growth, they can serve as natural alternatives to synthetic preservatives, either through direct incorporation into food formulations or as bioactive coatings for perishable products. This could significantly reduce the reliance on artificial preservatives, addressing consumer demand for cleaner-label foods while enhancing food safety and shelf life. Despite this promising potential, research on antimicrobial compounds from Amazonian fruits remains limited. The Amazon biome harbors an unparalleled diversity of plant species, many of which remain unexplored in terms of their biochemical composition and bioactivity. The discovery of new antimicrobial molecules could lead to groundbreaking advancements in pharmaceuticals, biotechnology, and food science. Expanding studies in this field is not only essential for scientific innovation but also for fostering conservation efforts. By demonstrating the economic and medicinal value of Amazonian biodiversity, such research can provide incentives for sustainable forest management and discourage deforestation for short-term economic gains. In conclusion, Amazonian fruits offer a vast, largely untapped reservoir of antimicrobial compounds with potential applications in medicine, food science, and biotechnology. Further studies are crucial to fully exploring their benefits, optimizing their use, and support conservation strategies that emphasize the sustainable utilization of natural resources. Investing in this research not only enhances scientific knowledge but also contributes to preserving one of the world's most important ecosystems.

3.4. References

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4. CHAPTER 2

This chapter presents the physicochemical, microbiological, and cytotoxicity analyses performed on hydroethanolic extracts of red fruits. Figure 5 displays a flowchart of the analyses that were conducted.

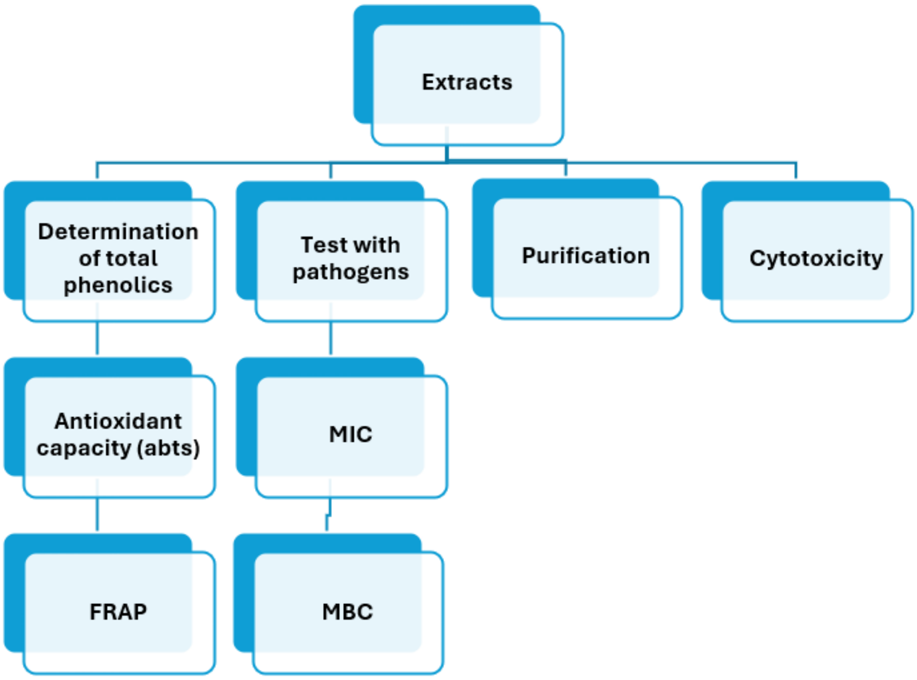

Figure 5 Flowchart of the analyses performed on red fruit extracts. Source: author

4.1. Introduction

Research on the use of plant-based matrices, either alone or in combination with antibiotics, has been gaining prominence as an alternative to address resistance and combat pathogenic microorganisms. Studies such as those by G. C. Da Silva et al., 2024; Weng et al., 2023; Silva Júnior et al., 2024; Hussain et al., 2024; Nayak et al., 2024; Nonato et al., 2018; Dias-Souza et al., 2018 have highlighted the antimicrobial potential of extracts from various plant parts, including roots, bark, and fruit pulp. These studies have demonstrated that the use of plant-based matrices in combination with antibiotics exhibits synergistic effects, reducing dosage, mutation rates, and resistance.

These extracts contain compounds such as flavonoids, alkaloids, coumarins, terpenes, polysaccharides, and peptides, all of which have demonstrated antimicrobial activity.

These compounds can act by damaging the cell wall, disrupting the structure and function of the cell membrane, inducing oxidative stress, interfering with energy metabolism, and inhibiting biofilm formation, among other mechanisms (Chen, Lan, & Xie, 2024).

Red fruits form a group of fruits distinguished by their rich content of anthocyanins, which are responsible for their vibrant coloration, typically in shades of red, purple, or blue (Nazzaro et al., 2019). These fruits have a high concentration of bioactive compounds, such as flavonoids and polyphenols (Bortolini et al., 2022), which contribute to cardiovascular health, protection against inflammatory diseases, and the strengthening of the immune system.

The primary varieties belong to the families Rosaceae (strawberry, raspberry, and blackberry), Ericaceae (blueberry), Myrtaceae (jabuticaba), and Arecaceae (açaí) (Bortolini et al., 2022). These fruits are appreciated not only for their sweet and slightly acidic flavor but also for their nutritional benefits, as they are rich in antioxidants, vitamins, and fiber.

Among the health benefits associated with red fruits, they have demonstrated antioxidant, anti-glycemic, immunomodulatory, antitumor, anti-obesity, and antimicrobial activity (Yang et al., 2024; Bortolini et al., 2022).

Studies on the antimicrobial potential of red fruits conducted by (Köpsel et al., 2025; Stafussa et al., 2021; Hacke et al., 2016) have demonstrated significant antimicrobial activity against pathogenic bacteria such as *Escherichia coli, Salmonella enterica, Bacillus cereus, Staphylococcus aureus,* and *Listeria monocytogenes* (Fleck et al., 2023).

This antimicrobial potential has been attributed to the quantity of phenolic compounds found in red fruits. However, none of the reviewed studies describe the mechanism of action by which these phenolic compounds inhibit the growth of the evaluated microorganisms (Bortolini et al., 2022).

Therefore, the objective of this study is to evaluate the antioxidant, antimicrobial, and cytotoxic potential of extracts from strawberries, raspberries, blueberries, jabuticaba, açai, and jussara. In addition, the study aims to quantify the total phenolics, assess the antimicrobial effect of the phenolic and anthocyanin fractions of each fruit, and correlate possible mechanisms of action with the scientific literature.

4.2. Materials and methods

4.2.1. Fruits

The fruits selected for the study include strawberry (*Fragaria* x *ananassa* Duch), raspberry (*Rubus idaeus*), blueberry (*Vaccinium myrtillus*), juçara (*Euterpe edulis* M.), jabuticaba (*Plinia cauliflora*) and açai (*Euterpe precatoria*). The strawberries used in this research were produced and packaged by JMRM Frutas, obtained from Sitio Capoeira Bonita, Tanque Zona Rural, Alfredo Vasconcellos, MG (21°08'45.2"S 43°46'30.9"W). The raspberries and blueberries were produced and packaged by EMPALI in Barbacena, MG (latitude 21°13′33′′ S, longitude 43º46′25" W). The juçara was collected in the rural area of Viçosa, MG (20º47`28.082" S 42º52`45.120" W). The Sabará jabuticaba fruits were collected in the Fruit Growing Sector of the Federal University of Viçosa, MG (latitude 20º 45'14" S, longitude 42º 52' 55" W). The frozen açaí pulp was obtained from the city of Cametá, PA (latitude: 2°14′21.8″ S and longitude: 49°29′54.3″ W). All fruits were stored in a freezer until they were used in the Natural Dyes Laboratory and Bioactive Compounds (LaCbio) and Laboratory of Industrial Hygiene and Food Microbiology (LHMA).

4.2.2. Preparation of raw extracts

The preparation of the raw extracts of the fruits will be carried out at the Laboratory of Natural Dyes and Bioactive Compounds (LaCbio). The extraction of bioactive compounds from the samples will be carried out according to the methodology described by (Rocha et al., 2017), with modifications. The jabuticaba, blueberry, açaí, strawberry and raspberry fruits will be weighed (10 g) in an amber Erlenmeyer flask with a capacity of 125 mL. The fruits will be macerated with the aid of a glass rod and 100 mL of 80% (v/v) ethanol will be added. Then, the Erlenmeyer flasks will be subjected to an ultrasonic bath (model TRANSSONIC TI-H-10, ELMA brand), for 50 minutes at a frequency of 45 kHz, 50% power and a temperature of 40 °C. After ultrasound, the solid material will be discarded, and the aqueous phase will be transferred to 50 mL Falcon tubes and centrifuged at 5000 rpm for 22 minutes. The supernatant will be concentrated by rotary evaporation (BRAND, MODEL) until reducing 80% of the initial volume. Then, the final volume will be adjusted to 25 mL with distilled water using a graduated cylinder. After standardizing the volume, the extracts will be sterilized by membrane filtration (0.45 µM), stored in sterile microtubes and kept in a freezer (-18°C) until use.

4.2.3. Determination of total phenolic compounds in extracts by spectrophotometry

The analysis of total phenolic compounds by spectrophotometry will be performed according to the methodology proposed by Singleton; Rossi (1965), with modifications. 200 µL of each extract will be transferred to a 10 mL flask and the volume will be completed with distilled water. The Folin Ciocalteau reagent will be prepared at a concentration of 1:10, and the gallic acid solution will be prepared at a concentration of 200 mg/L.

The standard curve will be constructed by performing the following dilutions:

Table 2 Quantities used to construct the gallic acid standard curve

Gallic acid standard solution (mL)	Water volume (mL)	Concentration (mg/L)
1,25	8,75	25
2,5	7,5	50
3,75	6,25	75
5,0	5,0	100
6,25	3,75	125
7,5	2,5	150
8,75	1,25	175
10	0	200

Source: author

The curve points will be performed in triplicate, mixing 30 µL of each prepared solution (25, 50, 75, 100, 125, 150, 175 and 200 mg/L) and 150 µL of Folin-Ciocalteau reagent. After letting the mixture rest for 3 minutes, 120 µL of sodium carbonate solution (7.5% m/v) will be added, homogenized and left to rest for 1 hour in the absence of light.

After the resting period, readings will be performed on the spectrophotometer at 760 nm (UV/VIS-1601 PC - Shimadzu). The same procedure will be performed for the samples and for the control. The total phenolic values will be expressed as gallic acid equivalents in 100 grams of fruit (EAG/100g).

4.2.4. ABTS Free Radical Scavenging Assay

The ABTS radical was prepared by the reaction of the ABTS stock solution (7.0 mM) and potassium persulfate (2.45 mM) in a 1:1 ratio in a water bath at 50 ºC for 15 minutes in the dark (Re et al., 1999, modified). This solution was diluted with 80 % alcohol until an absorbance of 0.700 ± 0.05 at 734 nm was obtained. The sample curve was constructed from four dilutions in 80% alcohol, using the Trolox standard curve (200 µM) as a reference. Then, 38 µL of each dilution was transferred to an ELISA plate with 266 µL of ABTS and, after 6 minutes of reaction, readings were performed in an ELISA reader and Multiskan Skyhigh microplate photometer – Termo Fisher Scientific. The results were expressed in µmol of Trolox/mL of extract.

4.2.5. Iron Reducing Antioxidant Power (FRAP)

The FRAP reagent was prepared by mixing 0.3 M acetate buffer, 10 mM TPTZ and 20 mM ferric chloride in a 10:1:1 ratio, respectively. Several dilutions of the 2 mM ferrous sulfate solution were performed to construct the standard curve. To construct the sample curve, it was necessary to perform 4 different dilutions with distilled water. In a 96-well Elisa plate, an aliquot of 9 µL of each dilution was placed for reaction with 27 µL of distilled water and 270 µL of the FRAP reagent, kept in a water bath at 37 ºC for 30 minutes and the readings were performed at 595 nm. The results were expressed in µmol of ferrous sulfate/mL of extract.

4.2.6. Determination of antimicrobial activity

The pathogenic microorganisms used to evaluate the antimicrobial potential of the extracts were: *Escherichia coli* ATCC 11229 and *Listeria monocytogenes* ATCC 19111. These microorganisms were stored in Brain Heart Infusion (BHI) broth with 30% glycerol (1:1) and stored at -80 °C in microtubes. The microdilution technique was chosen and the test was performed following the recommendations of the Clinical and Laboratory Standards Institute Manual (CLSI, 2012 with modifications).

The strains were reactivated and incubated in BHI broth at 37 °C for 24 hours and diluted in BHI broth until a concentration of 10^3 CFU/mL was obtained. Then, pathogenic cultures (100 μL), fruit extracts (100 μL) and double-concentration BHI broth (100 μL) were added to a 96-well ELISA plate. The plate was incubated for 24 hours at 37 ºC in an ELISA reader and Multiskan Skyhigh microplate photometer – Termo Fisher Scientific. Absorbance readings were performed every 2 hours at 600 nm, without shaking. The same procedure was performed for the positive controls (pathogenic cultures (100 μL), single-concentration BHI (100 μL) and double-concentration BHI broth (100 μL) and blank (fruit extracts (100 μL), single-concentration BHI (100 μL) and double-concentration BHI broth (100 μL).

4.2.7. Determination of minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC)

The extracts that showed potential for reducing bacterial growth were tested in a 96-well microplate. The pathogenic cultures were combined with the extracts at different concentrations (2x, 1x, 0.5x e 0.25x) and the procedure previously described was performed (section 4.2.6).

To determine the Minimum Inhibitory Concentration and Minimum Bactericidal Concentration, the suspension that did not show turbidity was plated. Basically, a 10 μL aliquot of each dilution was deposited on the surface of BHI agar and incubated at 37 ºC for 24 hours. The CMB was identified as the lowest concentration of the extract in which there was no formation of visible colonies and the MIC, the concentration that did not show turbidity, but there was colony growth in agar medium (CLSI, 2012 with modifications).

4.2.8. Obtaining phenolic fraction and anthocyanins

The separation of bioactive compounds (phenolic fraction and anthocyanins) from the raw extracts was performed following the methodology of Rodriguez-Saona and

Wrolstad (2001). A C18 column (Sep-Pak Vac 35 cc, Waters) was soaked with 50 mL of methanol, 50 mL of acidified water (0.01% HCl) and 25 mL of raw extract. The addition of 50 mL of acidified water removed the sugars and organic acids. To obtain the phenolic fraction, observed by the change in the color of the eluate from clear to yellow, 50 mL of ethyl acetate was added. Finally, 50 mL of acidified methanol (0.01% HCl) was added to obtain anthocyanins. These fractions were rotary evaporated to remove the solvents and resuspended in 10 mL of distilled water. After sterilization using membrane filters, the fractions were stored in eppendorf and kept in the freezer until use (Rodriguez-Saona; Wrolstad, 2001).

4.2.9. Cytotoxicity

Vero (ATCC® CCL-81™) and HEK-293 (ATCC® CRL-1573™) cell cultures were maintained in continuous culture in 75 cm² culture flasks, incubated in an atmosphere with 5% CO_2 at 37 °C. Dulbecco's Modified Eagle's Medium (DMEM; Vitrocell Embriolife) containing penicillin (100 IU/mL) and streptomycin (100 μg/mL) was used, supplemented with fetal bovine serum (FBS; Vitrocell Embriolife) at 10-20% (v/v), according to the needs of the cell line, with regular medium changes. When the cells reached approximately 80% confluence in the culture flask, they were detached with the addition of 0.025% (m/v) trypsin-EDTA solution. After checking cell detachment, the cells were resuspended in DMEM supplemented with 10% FBS and centrifuged at 1300 rpm for 6 minutes. The cell pellet formed was resuspended in complete DMEM, and the cell concentration (number of cells/mL) was determined by counting in a Neubauer chamber. From the cell suspension, 96-well plates were prepared with 1×10^4 cells/well, which were used in experiments after reaching a confluence greater than or equal to 80% (International Organization for standardization, 2009).

Each extract was diluted to concentrations of 100 and 10 μg/mL. The dilutions were applied in triplicate to the plates with confluence greater than 80%, together with the DMEM control containing 0.5% DMSO, and the plates were returned to the incubator. After 24 hours of incubation, cell viability was assessed by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, which converts the yellow tetrazolium salt into insoluble purple formazan in viable cells (RISS et al., 2004). For this, a 0.5 mg/mL MTT solution was prepared by dissolving MTT in incomplete

DMEM (without FBS). Then, all the medium from the 96-well plate was removed and replaced with the MTT solution. The plate was returned to the oven for incubation for 3 hours. After this period, the medium was replaced by DMSO (100 µL per well) to solubilize the formazan crystals, and finally, the absorbance was measured at 540 nm (Adapted from International Organization for standardization, 2009)

4.3. Results and discussions

The choice of extraction method directly influences the production of bioactive compounds. Ethyl alcohol was used to extract these compounds from fruits such as jabuticaba, açaí, juçara, raspberry, strawberry and blueberry, due to its organic solvent nature and the lower associated environmental impact. Studies by Krzepilko et al. (2021) highlighted the high efficiency of ethanolic solvents in the extraction of bioactive compounds. In addition, the application of heat treatments and technologies such as ultrasound in a water bath were used to enhance extraction.

4.3.1. Total phenolics and antioxidant capacity

The quantification of total phenolics and the determination of the antioxidant capacity of strawberry, jabuticaba, raspberry, açaí, blueberry and juçara extracts can be seen in Table 3.

Table 3. Quantification of total phenolic compounds (TPC) and antioxidant capacity by the free radical (ABTS) and iron reduction (FRAP) methods of fruit extracts.

	TPC (mg of gallic acid equivalent/100g of fruit)	**ABTS (µmol Trolox/ mL extract)**	**FRAP (µmol ferrous sulfate/mL extract**
Acai	504.58 ± 17.19^{b}	117.34 ± 0.68^{b}	91.19 ± 1.35^{b}
Raspberry	252.02 ± 15.28^{d}	56.91 ± 0.41^{d}	20.48 ± 0.35^{d}
Jabuticaba	1058.32 ± 13.37^{a}	1565.95 ± 33.10^{a}	966.83 ± 31.23^{a}
Jucara	401.94 ± 9.55^{bc}	51.97 ± 0.02^{e}	32.19 ± 1.34^{cd}
Blueberry	427.60 ± 19.10^{bc}	42.11 ± 0.54^{f}	41.46 ± 0.69^{c}
Strawberry	365.47 ± 19.10^{c}	78.27 ± 1.28^{c}	34.31 ± 0.40^{cd}

Triplicate results expressed as mean ± standard deviation. Values in the same column accompanied by different letters show a significant difference between them using the Tukey test ($P \leq 0.05$). Source: author

Phenolic compounds are secondary metabolites, produced by plants as a defense mechanism against different types of stress (Lone; Khan; Mohammed Al-Sadi, 2024) the study of these compounds is important due to their biological potential and health promotion as anti-allergic, anti-inflammatory, anticancer, anti-obesity, antioxidant and antimicrobial (Daglia, 2012; Lang et al., 2024; Li et al., 2014).

According to Vasco; Ruales; Kamal-Eldin (2008), fruits can be classified according to the concentration of phenolic compounds into three categories: low, medium and high. Among the extracts analyzed, raspberry, blueberry, juçara and strawberry extracts presented medium concentrations of phenolics (100–500 mg GAE/100 g). Only jabuticaba and açaí extracts were classified as having a high concentration of total phenolics (> 500 mg GAE/100 g of fresh mass).

These results corroborate the data of Bortoline et al. (2022), who reported total phenolic concentrations ranging from 626.57–1201.05 mg GAE/100 g in jabuticaba, 607–708.22 mg GAE/100 g in açaí, and 100.77–324 mg GAE/100 g in blueberry.

Studies carried out by Santos et al. (2021) and Bittencourt et al. (2018), on the total phenolic content in aqueous extract and blueberry pomace extract (502 and 420 GAE mg/100g, respectively), showed that these were close to those obtained in this study (427.60 ± 19.10 GAE mg/100g).

However, higher values were found by Rigolon et al., (2024) in jabuticaba and blueberry extracts (2094.98 ± 72.19 and 665.35 ± 16.66 mg AGE/100 mL respectively)

In a study carried out by Stafussa et al. (2021), jabuticaba and açaí extracts presented values of 5794.54 ± 61.81 mg GAE/100 g and 6166.36 ± 6.36 mg GAE/100 g dry weight, respectively. Total phenolic compound contents of raspberry extract from different cultivars ranged from 43.64 to 83.13 mg/g dry extract (Bobinaitė et al., 2013).

On the other hand, blueberry, raspberry and strawberry extracts presented lower TPC values (100.77 ± 0.97; 135.03 ± 3.22 and 221.29 ± 5.63, respectively) than those found in this study. Similarly, Giampiere et al. (2014) and Hussain et al (2024) found lower values for strawberry extracts (219 mg GAE/100g and 37.93 mg GAE/100g respectively).

This variation in the results is understandable, due to the genotype of the plant (Krzepilko et al., 2021), several environmental factors, such as climate, soil, cultivation methods, ripening state and, mainly, the use of different solvents for extraction of bioactive compounds, can influence the observed concentrations (Manganaris et al. 2014).

Table 3 shows that jabuticaba and açai presented a significant difference at the 5% level by the Tukey test, however the phenolic values of açai, juçara and blueberry did not present a significant difference. In addition to jabuticaba and açaí extracts exhibiting the highest total phenolic values, these extracts demonstrated the greatest antioxidant capacity among the analyzed fruits when evaluated using the ABTS and FRAP methods. By the ABTS method, all samples showed a significant difference at the 5% significance level according to the Tukey test**.** In the FRAP test, only the jabuticaba and açaí differed statistically from the other samples (Table 3). These results can be attributed to the presence of phenolic compounds with hydroxyl groups bound to aromatic rings, which facilitate electron donation, allowing for the neutralization of free radicals and the chelation of metal ions. (Watson, 2014; Vuolo et al., 2019).

Previous studies have identified a positive correlation between phenolic compounds and antioxidant capacity (Krzepilko et al., 2021; Rigolon et al., 2024). Different concentrations of raspberry extracts were evaluated by the DPPH assay to measure their antioxidant potential, revealing that as the concentrations were reduced, the potential was also reduced (Gomathi et al., 2024). Furthermore, specifically glycosylated anthocyanins also showed a significant relationship with antioxidant activity, as demonstrated by the DPPH, ABTS and FRAP assays (Tian et al., 2018).

The high antioxidant capacity demonstrated is reinforced when we analyze the main chemical compounds of these extracts. For example, in jabuticaba, the main phenolic acids found are hydroxybenzoic acid derivatives, hydroxycinnamic acid derivatives, flavonoids such as myricitrin, quercitrin, globularicitrine, myricetin and quercetin and glycosylated anthocyanins such as cyanidin-3-o-glucoside and delphinidin-3-glucoside (Benvenutti; Zielinski; Ferreira, 2021).

Similarly, in açaí, Vasconcelos et al., (2019) identified cyanidin 3-glucoside and cyanidin 3-rutinoside as the main anthocyanins, quercetin, orientin and their derivatives as proanthocyanidins among the main flavonoids and organic acids such as citric acid, caffeic acid, ferulic acid and quinic acid (Stafussa et al., 2021).

As seen in chapter 1, these compounds (derived from phenolic acids and anthocyanins) found in jabuticaba and açaí have several free hydroxyls, thus contributing to the antioxidant potential.

4.3.2. Antimicrobial activity, MIC and MBC

The antimicrobial activity of extracts from açaí, raspberry, jabuticaba, juçara, blueberry, and strawberry was tested against the pathogenic microorganisms *E. coli* and *Listeria monocytogenes* (Figure 6) using the microdilution technique. This technique allows the use of smaller aliquots of extracts and reagents, has high reproducibility, is more sensitive than other methods, and can be used on a large number of samples (Ostrosky et al. 2008).

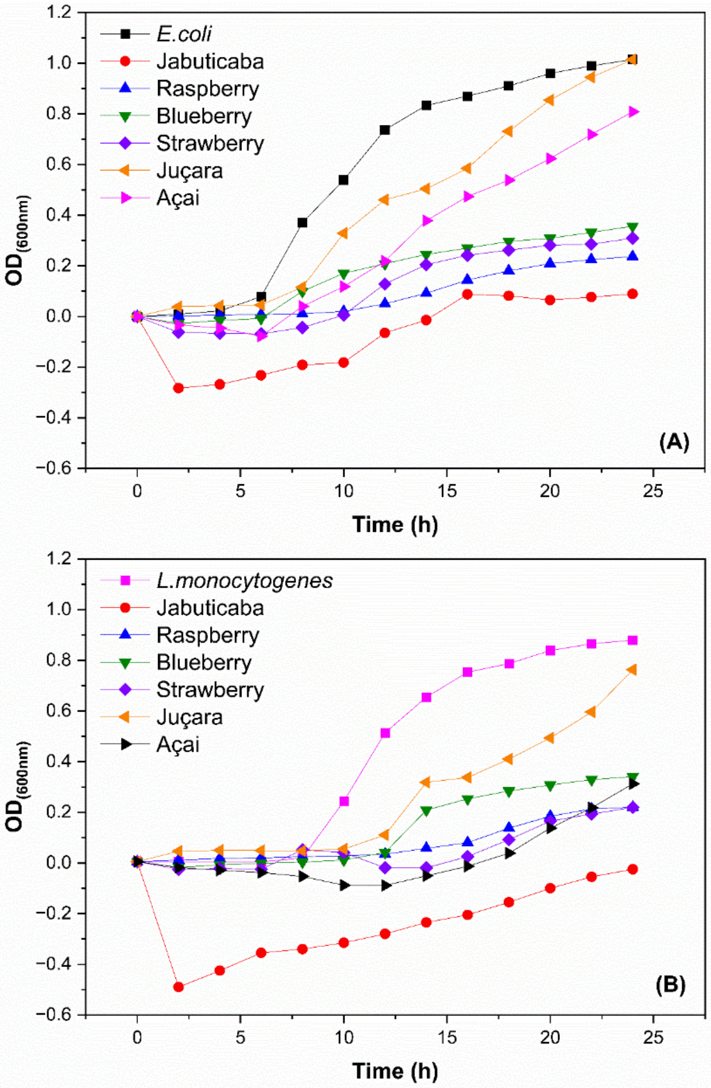

Figure 6 Antimicrobial activity of jabuticaba, raspberry, blueberry, strawberry, juçara and açai extracts against E.coli (A) and L.monocytogenes (B). Source: author

We observed that among the extracts studied, the jabuticaba, strawberry and raspberry extracts were able to significantly reduce the growth of both bacteria when compared to the control for a period of 24 hours (Figure 5).

As previously seen, jabuticaba extract stood out from other fruits due to the amount of phenolic compounds and high antioxidant activity, which may have reflected its high antimicrobial activity.

A similar behavior was observed in pomegranate juice, which presented high amounts of phenolic compounds, high antioxidant capacity and good antimicrobial potential against strains such as *E.coli*, *S.aureus*, *S.enterica* and *L.monocytogenes* (Köpsel et al., 2025).

However, raspberry and strawberry extracts were the extracts with the lowest TPC (Table 2) and were able to reduce the growth of pathogens, while chokeberry juice showed low TPC levels, low antimicrobial potential against Gram-negative bacteria, but a relatively good effect for Gram-positive bacterial strains (Köpsel et al., 2025), which suggests that results on the quantification of phenolic compounds alone are not sufficient to predict antimicrobial potential.

Tian et al. (2018), for example, found no correlation between total phenolics and antimicrobial potential in *E. coli* strains. However, a relationship was observed with Gram-positive bacteria such as *S. aureus*, *B. cereus*, and *L. monocytogenes*.

After observing a significant reduction in the growth of these bacteria, only the jabuticaba, strawberry and raspberry extracts were tested at different concentrations to find the Minimum Inhibitory and Minimum Bactericidal Concentration (Figure 7).

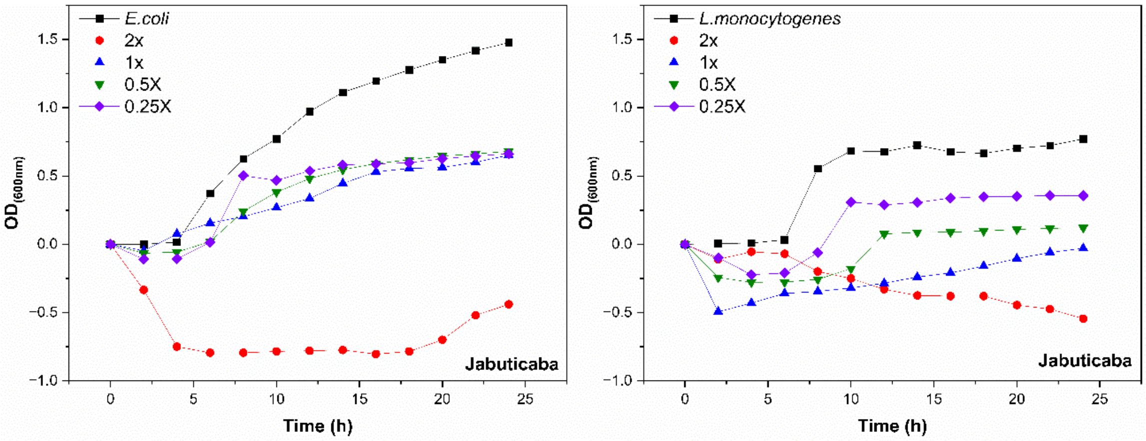

Figure 7 MIC and MBC of jaboticaba extract in E.coli and Listeria monocytogenes. Source: author

Figure 7 shows that the jaboticaba extract presented a Minimum Bactericidal Concentration of 2x for *Listeria monocytogenes* and a Minimum Inhibitory Concentration (MIC) of 1x among the concentrations tested. In the case of *E. coli*, only the MIC was found at the concentration of 2x. The concentration of 2.5x when tested did not present absorbance readings in a spectrophotometer at 600 nm due to the intense dark coloration of the jaboticaba.

The greater resistance of gram-negative bacteria to bioactive compounds from plant extracts was also evidenced by (Köpsel et al., 2025; Martins et al., 2020; Stafussa et al., 2021). These authors studied several fruits such as cranberry, chokeberry, elderberry, pomegranate, red grape, blackcurrant, sour cherry, açaí seeds, acerola, araçá, cambuci, murici, panã, pitanga, starfruit and strawberry, all these extracts showed greater antimicrobial activity in gram-positive bacteria.

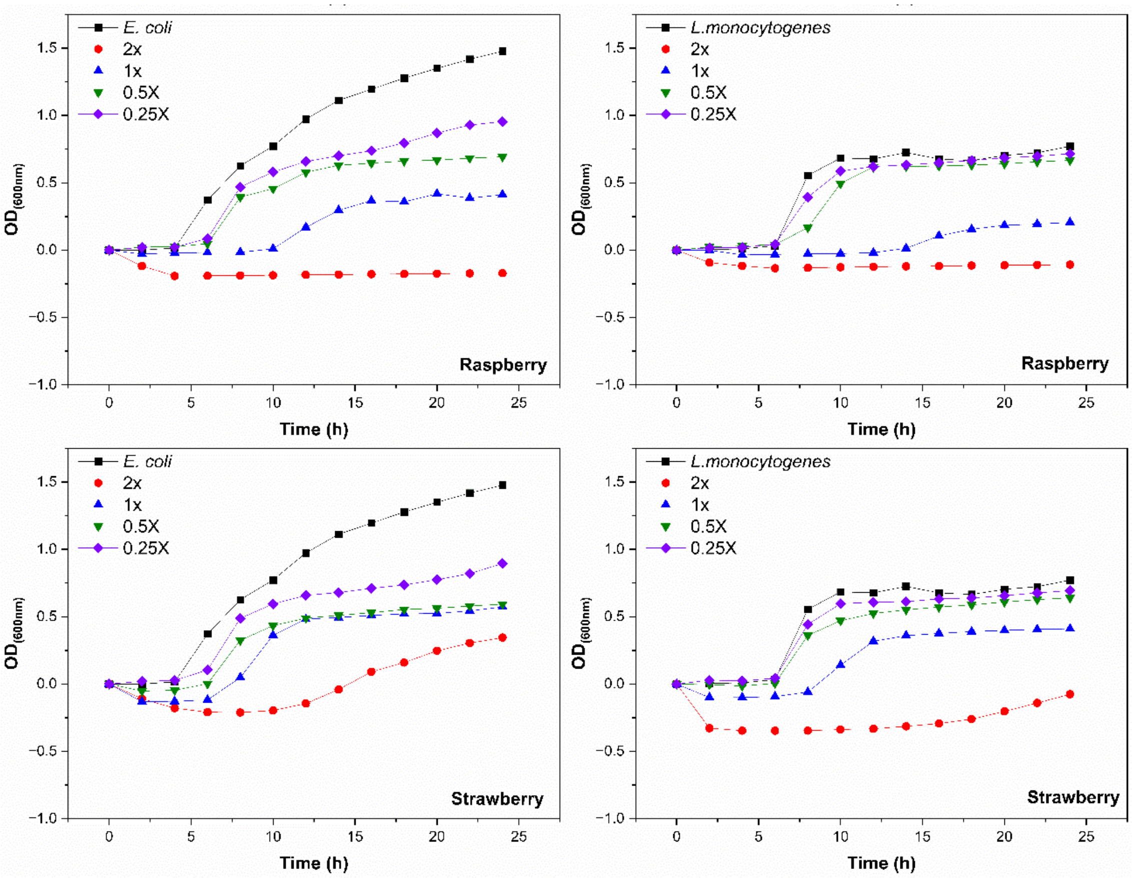

Figure 8 MIC and MBC of raspberry and strawberry extracts on E.coli and L.monocytogenes. Source:author

Figure 8 shows the results found for the MIC of raspberry (top side) and strawberry (bottom side) extracts for the bacteria *E.coli* and *Listeria monocytogenes*. These extracts, unlike jaboticaba, only showed a bacteriostatic effect at a concentration of 1x mg/mL for the two bacteria studied.

In addition, it is possible to observe that, as the concentration of the extract decreases, the antimicrobial potential is also reduced, corroborating what was observed by Gomathi et al. (2024).

Studies on the antimicrobial potential of raspberry extracts have already been studied by Demirbas et al. (2017) in bacteria such as *E.coli, S.enterica, S.aureus* and *B. cereus*. In addition, a reduction in the growth of *Streptococcus mutans*, *Candida albicans* (Gomathi et al., 2024), *B. subtilis* and *E. faecalis* (Bobinaite et al., 2013) was observed.

Krisch et al. (2009) observed antimicrobial activity of methanolic strawberry extracts against Gram-positive bacteria such as *B. subtilis* and *B. cereus*. These same authors demonstrated the bactericidal potential of raspberry extract against *C. jejuni*.

Raspberry and strawberry extracts, when associated with silver nanoparticles, showed significant inhibition when compared to raw extracts (Demirbas et al., 2017). Similarly, raspberry leaf extracts with silver nanoparticles reduced the growth of Pseudomonas aeruginosa, *Staphylococcus aureus* and *Escherichia coli* (Pradeepa et al., 2014).

These effects were associated with the ability of nanoparticles to adhere to the bacterial wall through the interaction and inactivation of essential enzymes, causing permeability disturbances and consequently cell death (Pradeepa et al., 2014).

Changes in the permeability or structure of the cell wall of *Listeria monocytogenes* and *E. coli* were identified by Fleck et al. (2023), who observed cell agglomeration induced by phenolic compounds. In particular, weak phenolic acids have been shown to cause acidification of the cytoplasm, resulting in membrane changes and consequently cell death (Bobinaite et al., 2013).

On the other hand, Gram-negative bacteria are more resistant because, in addition to a thin cell wall, they have an outer membrane rich in lipopolysaccharides that prevent bioactive compounds from penetrating the cell membrane.

4.3.3. Separation of phenolic compounds and anthocyanins from raw extracts

To understand which fraction was responsible for the antimicrobial action, the jabuticaba, strawberry and raspberry extracts underwent a purification process, removing sugars and organic acids (ascorbic acid, amino acids). In this process, the phenolic fraction and anthocyanins of each extract were obtained. Each fraction was standardized according to the concentration of total phenolics and tested with pathogenic microorganisms.

Although the results of chemical identification and quantification of each fraction are not available, the scientific literature already describes the compounds generally present in each type of fruit extract.

Delphinidin-3-glucoside and cyanidin-3-glucoside are highlighted as the main anthocyanins present in jabuticaba (Da Silva et al., 2025; Rigolon et al., 2024). The predominant phenolic compounds include gallic acid and ellagic acid, while the organic acids include citric, malic, succinic and quinic acids (Borges et al., 2024; Das Neves et al., 2021; Stafussa et al., 2021).

In the case of strawberries, the most relevant anthocyanins are pelargonidin-3-glucoside, cyanidin-3-arabinoside, pelargonidin-3-acetylglucoside and pelargonidin-3-malonylglucoside (Gianpieri et al., 2014). Ellagic acid is the major phenolic compound in this fruit (Bortoline et al., 2022), while the predominant organic acids include quinic acid and citric acid (Wang and Gao, 2013).

Raspberries, on the other hand, have chlorogenic acid, gallic acid, epicatechin gallate, procyanidin B2 and rutin among their phenolic compounds. The main anthocyanins include delphinidin-3-glucoside, cyanidin-3-*O*-sophoroside and cyanidin-3-glucoside (Bortoline et al., 2022).

Table 4 shows the quantification of total phenolics for each fraction obtained from the jabuticaba, strawberry and raspberry extracts.

Table 4 Quantification of total phenolics in each fraction obtained after purification of the raw extract of jabuticaba, strawberry and raspberry.

Quantification of total phenolics (mg EAG/100g)	**Phenolic fraction**	**Anthocyanin fraction**	**Raw extract**
Jabuticaba	523.44 ± 14.17^a	220.84 ± 0.00^b	897.25 ± 17.00^a

Strawberry	417.40 ± 4.59^b	260.45 ± 2.75^a	737.52 ± 11.01^b
Raspberry	298.93 ± 30.54^c	185.22 ± 0.90^c	544.49 ± 14.37^c

Source: author

Figures 9, 10 and 11 show the results of the antimicrobial potential of each fraction obtained from the raw extract of jaboticaba, raspberry and strawberry respectively against the pathogenic bacteria *E.coli* and *Listeria monocytogenes*.

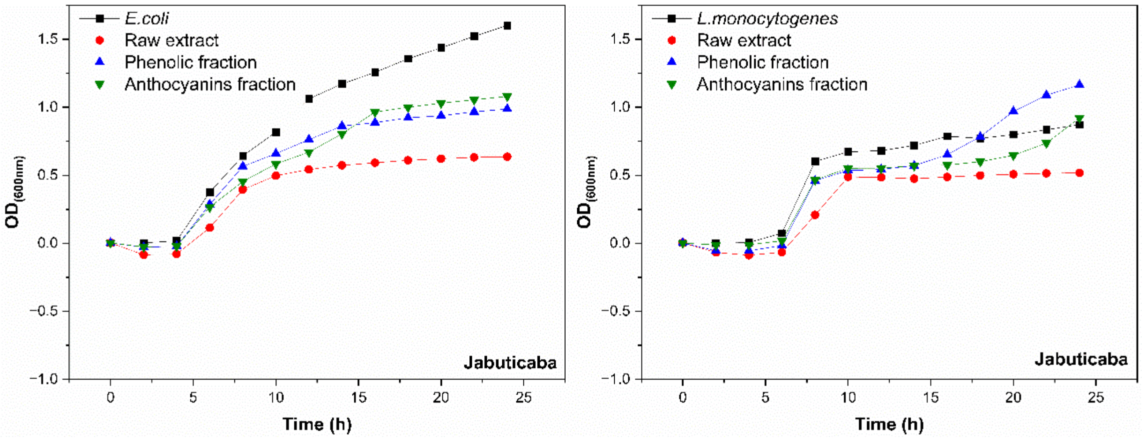

Figure 9 Microbial growth of E.coli and L.monocytogenes in phenolic fraction, anthocyanin and raw extract of jabuticaba. Source: author

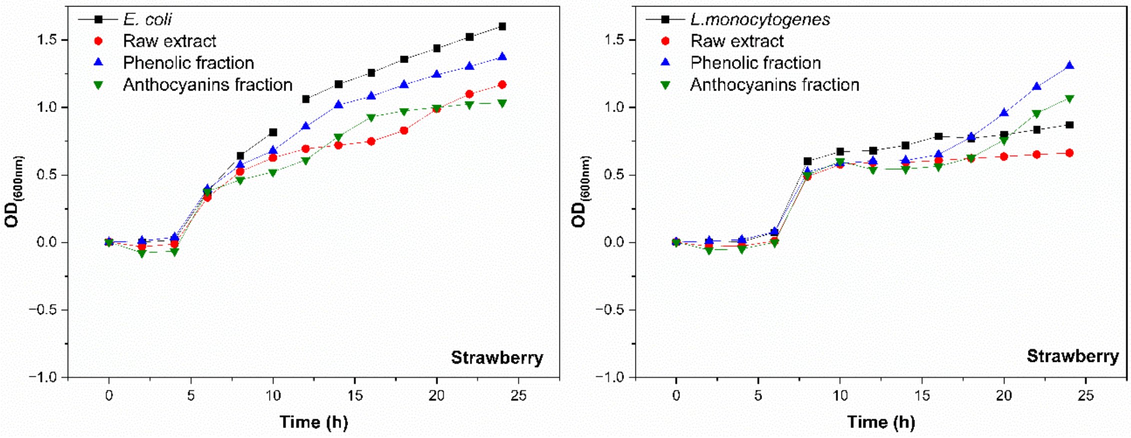

Figure 10 Microbial growth of E. coli and L. monocytogenes in phenolic fraction, anthocyanin, and raw extract of strawberry. Source: author

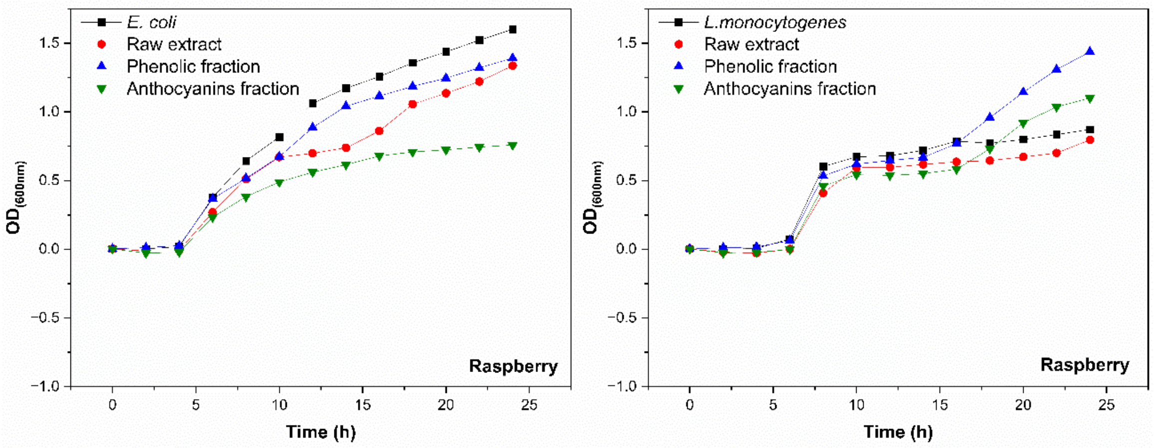

Figure 11 Microbial growth of E. coli and L. monocytogenes in phenolic fraction, anthocyanin, and raw extract of raspberry. Source: author

Tests of the phenolic and anthocyanin fractions of fruit extracts (jabuticaba, raspberry and strawberry) with pathogenic microorganisms indicated that these two fractions, when tested individually, do not contribute significantly to the reduction in bacterial growth. Furthermore, it was observed that these fractions can contribute to growth above the control curve (jabuticaba, raspberry and strawberry extracts in *L. monocytogenes*).

On the other hand, it is possible to observe that the crude extract obtained good results in comparison to the purified fractions. Similar behavior was observed in blackcurrant concentrates and their purified anthocyanins. While the concentrates achieved a reduction in the growth of *Staphylococcus aureus* and *Enterococcus faecium*, their anthocyanins caused no antimicrobial effect (Werlein et al., 2005).

As in other studies, Da Silva et al. (2025) did not observe a reduction in bacterial growth when they evaluated anthocyanins isolated from jabuticaba and strawberry. This leads us to believe that the antimicrobial potential would be linked to the organic acids present in the crude extract or possible synergisms between the phenolic fractions and anthocyanins.

Although the purified fractions present more specific compounds, their antimicrobial capacity is not sufficient in their isolated form, needing to interact with other substances to enhance their action. Anthocyanins, for example, have a unique copigmentation characteristic, this characteristic provides greater stability and color intensity when associated with compounds such as flavonoids, alkaloids, amino acids, organic acids, nucleotides, polysaccharides or metals (Rigolon, Oliveira and Stringheta, 2021).

A study on anthocyanins and copigments of cranberry and pomegranate shows that these fruits presented higher percentages of copigments in relation to the amounts of anthocyanins and showed great antimicrobial potential in *S. enterica*, *L. monocytogenes*, *S. aureus* and *E. coli* (Köpsel et al., 2025). In this same study, blackcurrant also showed antimicrobial potential, although with lower concentrations of copigments. Concluding that the antimicrobial potential is linked to the interactions between anthocyanins and phenolic compounds, regardless of the concentrations presented.

Studies on isolated phenolic compounds such as caffeic acid, ellagic acid and chlorogenic acid and their antimicrobial potential were evidenced (Table 1). These same compounds are present in the fruit extracts studied. Regarding the mechanisms of interaction of these compounds in bacterial cells, we can include the rupture of cell membranes, the inhibition of essential enzymes, the interference in quorum sensing (QS) and the chelation of metal ions, leading to the death or inhibition of the microbial cell (Figures 2, 3 and 4).

4.3.4. Cytotoxicity

All fruit extracts studied were subjected to cytotoxicity tests with the aim of identifying possible adverse effects on living cells, in addition to ensuring their safety for use in food, cosmetic or pharmaceutical applications. These tests evaluate cell viability after exposure to different concentrations of extract (Eliasen; Kristiansen; Kohlmeier, 2025; Lopes-Corona et al., 2022) and for this purpose HEK and VERO cells were used.

HEK cells are embryonic cells originating from human kidneys and are commonly used due to their rapid proliferation, high transfection efficiency and growth stability (Eliasen; Kristiansen; Kohlmeier, 2025).

On the other hand, VERO cells are derived from the kidney of African green monkeys and are sensitive to bioactive compounds and allow the evaluation of their effects on cells (Muniz-Filho et al., 2017).

Figure 12 shows the cytotoxicity results of extracts of jabuticaba, raspberry, blueberry, strawberry, juçara and açaí at concentrations of 10 µg/mL and 100 µg/mL for HEK and VERO cells.

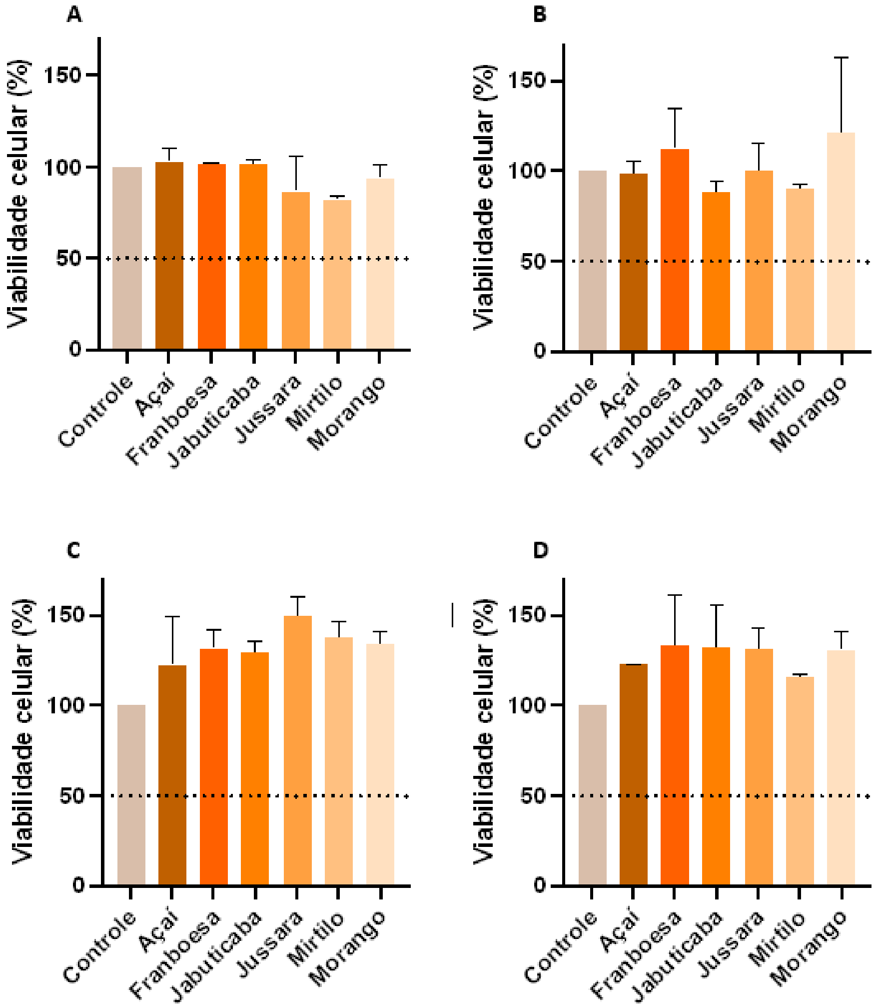

Figure 12 Cell viability after treatment with different red fruit extracts: Vero cell lines (ATCC® CCL-81™) treated with 10 µg/ml (A) and 100 µg/ml (B) of the extracts. HEK cells (ATCC® CRL-1573™) treated with 10 µg/ml (C) and 100 µg/ml (D) of the extracts. All data are the means of three replicates, and error bars indicate the standard deviation.

Figure 12-A indicates that the extracts of açaí, raspberry and jabuticaba maintained the viability of VERO cells at a concentration of 10 µg/mL, presenting results similar to the control. Only the extracts of jussara and blueberry caused a slight reduction in cell viability. With the increase in concentration (Figure 12-B), there was no significant

decrease in cell viability; on the contrary, the extracts of strawberry and raspberry demonstrated a stimulating effect, increasing the number of cells, suggesting that these extracts do not present relevant toxicity to VERO cells.

Similarly, figures 12-C and 12-D show the results of the cytotoxicity of the extracts in HEK cells at concentrations of 10 µg/mL and 100 µg/mL respectively. It can be observed that all extracts presented cell viability percentages higher than the control, which indicates that the extracts did not cause a cytotoxic effect on the cells.

Borges et al. (2024) evaluated the cytotoxicity of the fermented jabuticaba peel beverage and observed that this sample presented cytotoxicity only in cancer cells, however, in HEK cells, no significant cytotoxicity was observed.

Similarly, different açaí fermentates studied by Nascimento et al. (2023) did not present cytotoxicity in lung adenocarcinoma epithelial cells (A549), in human ileocecal adenocarcinoma cells (HCT8) and normal human lung fibroblast (IMR90). Furthermore, there was no reduction in the viability of colorectal adenocarcinoma cell lines CACO-2 and HT-29 and breast cancer cell line MDA-MB-468 when exposed to açaí extracts (Silva et al., 2014).

On the other hand, chokeberry, pomegrate, and blueberry showed toxicity in liver (Hep-G2) and colon (CACO-2) cancer cells (Kopsel et al., 2025)

4.4. Conclusion

All extracts showed a reduction in the microbial growth of *E. coli* and *L. monocytogenes*. This potential is possibly associated with phenolic compounds and anthocyanins, as evidenced in extraction purification tests. The presence of these phenolic compounds and anthocyanins is directly related to their antioxidant potential, but mere quantification of these compounds is not sufficient to predict antimicrobial potential. Among the mechanisms of action of fruit extracts related to phenolic compounds is the modification of bacterial membrane permeability. No extract showed toxicity in human cells, indicating that the extracts can be safely applied.

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5. CONCLUSION

The two chapters of this dissertation demonstrated the great potential of Amazonian and red fruits as natural sources of bioactive compounds with antimicrobial activity. The literature review showed that Amazonian fruits contain a significant diversity of molecules, such as flavonoids, anthocyanins, peptides, and alkaloids, which act mainly on the integrity of the bacterial membrane, intracellular mechanisms, enzyme inhibition, and direct interaction with DNA. The experimental study reinforces the efficacy of red fruit extracts, with a significant reduction in the growth of *Escherichia coli* and *Listeria monocytogenes*. The observed activity was associated with the presence of phenolic compounds and anthocyanins. The absence of cellular toxicity in the tests supports the viability of using these extracts in human and food applications, further highlighting their relevance as functional and sustainable ingredients.

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