



Amazonian fruits as reservoirs of antimicrobial bioactive compounds: mechanisms of action and biotechnological perspectives

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Abstract

Amazonian ecosystems are globally recognized for their extraordinary biodiversity, encompassing thousands of plant, animal, and microbial species. Among the vast array of botanical resources, Amazonian fruits are distinguished by their rich composition of bioactive compounds, which contribute to a wide range of health benefits and industrial applications. This review highlights the broad-spectrum antimicrobial potential of Amazonian fruits, describing the key bioactive compounds and their mechanisms of action against bacterial and fungal pathogens, with potential applications in food preservation, medicine, and biotechnology. Notably, fruits such as açaí (*Euterpe oleracea* Mart.), buriti (*Mauritia flexuosa* L.f.), cupuaçu (*Theobroma grandiflorum* (Willd. ex Spreng.) K.Schum.), guaraná (*Paullinia cupana* Kunth), taperebá (*Spondias mombin* L.), tucumã (*Astrocaryum aculeatum* G.Mey.), camu-camu (*Myrciaria dubia* (Kunth) McVaugh), and araçá (*Eugenia stipitata* McVaugh) have demonstrated antimicrobial properties against Gram-positive and Gram-negative bacteria as well as fungal species. Future investigations of the biofunctionality of Amazonian fruits highlight the existence of a vast and still underexplored biodiversity with strong potential for scientific discovery and biotechnological innovation. Advances in the characterization of bioactive compounds, together with biotechnological approaches such as metabolic engineering, synthetic biology, and microbial fermentation, may enable the development of novel ingredients, functional products, and industrial applications derived from Amazonian resources. In this context, the Amazon region represents a promising reservoir of bioactive compounds that can be systematically studied and translated into future biotechnological products.

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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, and this ecosystem hosts over 30,000 plant species, including approximately 6,700 tree species (Messias et al. 2021; De Souza et al. 2023a, b). 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 Brazilian Amazon harbors approximately 163 edible fruits species, of which only about 20 are regularly used for human consumption (do Nascimento & Guimarães, 2020; Rebello et al. 2022). The limited national consumption of these fruits is mainly associated with logistical challenges, cultural factors, and, above all, the lack of scientific and technological knowledge regarding many of these species.

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 (Rinaldi et al. 2017; Fidelis et al. 2020; Franco et al. 2020; Kumar 2024; Rezaul Islam et al. 2024).

Additionally, these species exhibit high concentrations of antioxidants, vitamins, fibers, and other high-value compounds, making them applicable to diverse industrial sectors (Curimbaba et al. 2020; Peixoto Araujo et al. 2021; Souza et al. 2023a, b). Among the numerous Amazonian fruits recognized for their functional properties, açai (*Euterpe oleracea* Mart.), buriti (*Mauritia flexuosa* L.f.), guarana (*Paullinia cupana* Kunth), pitomba (*Talisia esculenta* (A.St.-Hil.) Radlk.), tucumã (*Astrocaryum aculeatum* G.Mey.), uxi (*Endopleura uchi* (Huber) Cuatrec.), and cupuaçu (*Theobroma grandiflorum* (Willd. ex Spreng.) K.Schum.) stand out in the scientific community (Souza et al. 2023a, b).

These natural resources hold particular significance in the face of global challenges such as antimicrobial resistance (AMR). Exploring microbial natural products with antimicrobial properties could open new avenues for the development of alternative therapies or as natural preservatives against a wide range of microbial pathogens. For instance, studies have demonstrated that compounds present in Amazonian fruits such as copal (*Hymenaea courbaril*), mari-mari (*Cassia leiandra*), buriti, tucumã, taperebá, acerola (*Malpighia emarginata*), and araçá (*Eugenia stipitata*) seed exhibit activity against fungal and bacterial pathogens such as *Candida albicans*, *Pseudomonas aeruginosa*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Escherichia coli*, *Enterococcus faecalis*, *Bacillus cereus*, and *Listeria monocyto-*

genes (Koolen et al. 2013; Jobim et al. 2014; Valarezo et al. 2020; Albuquerque et al. 2023; Souza et al. 2023a, b).

Considering the importance of exploring the biotechnological potential of Amazonian fruits, this article reviews the current state of knowledge on their antimicrobial potential, focusing on bioactive compounds such as alkaloids, polyphenols, coumarins, terpenes, polysaccharides, and peptides. From this perspective, understanding the antimicrobial activity of these compounds could support the development of pharmaceuticals, cosmetics, and food preservatives.

Materials and methods

This narrative review was conducted through a systematic search and analysis of the scientific literature to identify, evaluate, and synthesize studies on the antimicrobial potential of bioactive compounds from Amazonian fruits. The methodological approach was designed to ensure comprehensiveness, reproducibility, and validity of the findings presented.

Search strategy and databases

A comprehensive literature search was performed using the electronic databases PubMed, Scopus, Web of Science, and SciELO. To ensure the inclusion of regionally relevant studies, databases specializing in Brazilian and Latin American research (e.g., CAPES Periodicals, LILACS) were also consulted.

Identification of fruit species from search terms: the search employed combinations of keywords structured to capture both broad and specific results. Broad terms included “Amazonian fruits,” “Brazilian Amazon fruits,” and “native Amazonian species.” These were combined with specific bioactive compound classes (“alkaloids,” “polyphenols,” “terpenes,” “coumarins,” “polysaccharides,” “peptides”) and antimicrobial activity descriptors (“antimicrobial activity,” “antibacterial,” “antifungal,” “mechanism of action”). Boolean operators (AND, OR) were used to refine the search.

To systematically identify fruit species, the initial search results were screened for any mention of Amazonian fruit species names (both common and scientific names). From these initial results, a list of fruit species was compiled. Subsequently, targeted searches were performed using the scientific names of these identified species combined with the antimicrobial and bioactive compound keywords (e.g., “*Euterpe oleracea* AND antimicrobial,” “*Mauritia flexuosa* AND polyphenols”). This iterative approach, where initial broad searches informed specific species-level searches, ensured comprehensive coverage of the literature. Additionally, backward citation tracking (reviewing references of included articles) and forward citation tracking (identifying articles that cited key papers) were conducted to identify additional fruit species and relevant studies that may have been missed in the initial database searches.

Timeframe and inclusion criteria

The search encompassed publications from January 1993 to December 2025. This timeframe was selected to include seminal early studies on plant-based antimicrobials (e.g.,

Ikigai et al. 1993) and the most recent advances in the field. Studies were included if they met the following criteria:

- (i) Focused on fruits native to the Amazon biome OR exotic fruit species that are widely cultivated, naturalized, and commercially relevant in the Amazon region;
- (ii) Reported original experimental data (in vitro or in vivo) on antimicrobial activity against bacterial or fungal pathogens;
- (iii) Identified or characterized the specific bioactive compound(s) responsible for the observed effects;
- (iv) Were published as full-text articles in peer-reviewed journals in English, Portuguese, or Spanish.

Exclusion criteria

Studies were excluded from the analysis if they:

- (i) Did not specifically investigate fruits of Amazonian origin;
- (ii) Were theoretical studies without original experimental data;
- (iii) Presented incomplete methodological details or insufficient data for evaluation;
- (iv) Were not accessible in full text after exhaustive attempts.

Data extraction and synthesis

Data from the selected studies were systematically extracted and organized using a standardized template. The extracted information included: fruit species (common and scientific name), plant part used (pulp, peel, seed), type of extract or compound isolated, target microorganisms, quantitative measures of activity (e.g., Minimum Inhibitory Concentration - MIC), proposed mechanisms of action, and key reference details. The collected data were qualitatively synthesized to identify patterns, consensus findings, knowledge gaps, and future research directions.

Quality and reliability assessment

To ensure the inclusion of high-quality evidence, only studies published in peer-reviewed, indexed journals were considered. The methodological rigor of each included study, particularly regarding compound identification, antimicrobial assays, and statistical analysis, was critically evaluated.

This structured and transparent methodological framework ensures the reproducibility of the literature search and analysis, thereby strengthening the validity and reliability of the conclusions drawn in this review.

Table 1 Bioactive compounds from Amazonian fruits exhibiting demonstrated antimicrobial potential

Antimicrobial class	Popular name (scientific name)	Antimicrobial compound/extract	Target microorganism	MIC/effective concentration	Comparative potency	Reference
Alkaloids	Cupuaçu (<i>Theobroma grandiflorum</i>)	Purified caffeine	<i>S. aureus</i>	0.01544 mmol/mL (≈ 3 mg/mL)	-	Beulah et al. (2025)
	Various	Purified caffeine	<i>E. coli</i> , <i>L. monocytogenes</i> (biofilm)	MIC (<i>E. coli</i>): 9.37 mM (~ 1.82 mg/mL) MIC (<i>L. monocytogenes</i>): 37.5 mM (~ 7.28 mg/mL)	Strong antibiofilm activity in fruit juice matrices. Inhibits biofilm formation by 98.1–99.0% in both co-treatment and post-treatment assays. Disrupts biofilm architecture and bacterial cell integrity.	Dos Santos et al. (2025)
	Cacao (<i>Theobroma cacao</i> L.)	Theobromine (Class: methylxanthine alkaloid)	<i>S. mutans</i> (biofilm)	Biofilm inhibition: ≥ 6.25 mg/mL Complete eradication: ≥ 25 mg/mL	Biphasic effect: promotes biofilm at 3.125 mg/mL; inhibits at higher concentrations.	Almoabid et al. (2025)
	Bacupari (<i>Garcinia brasiliensis</i> - Mart)	Seed oil	<i>C. albicans</i> , <i>S. aureus</i>	Inhibition zone: ~ 10 mm (Quantitative MIC data not reported)	Weak activity (by diffusion assay).	Pedro et al. 2020; Melo et al. (2022)
Polyphenols	Biribá (<i>Annona hypoglauca</i> - Mart.)	Total alkaloids (fraction)	<i>S. aureus</i> , <i>E. faecalis</i>	MIC: 60 μ g/mL (<i>S. aureus</i>) MIC: 50 μ g/mL (<i>E. faecalis</i>) MBC: 70 μ g/mL (<i>S. aureus</i>) MBC: 50 μ g/mL (<i>E. faecalis</i>)	Selective bactericidal activity against Gram-positive bacteria. MBC equal or close to MIC indicates bactericidal action. Inactive (MIC > 100 μ g/mL) against <i>E. coli</i> . Activity resides in the alkaloid fraction.	Rinaldi et al. (2017)
	Cacao (<i>Theobroma cacao</i> L.)	Polyphenol-rich fraction (Class: polyphenols)	<i>S. mutans</i> (biofilm)	Biofilm inhibition: 0.78–200 mg/mL Complete eradication: ≥ 25 mg/mL	Most potent and consistent antibiofilm activity. Active across all tested concentrations.	Almoabid et al. (2025)
		Flavonoid fraction (Class: flavonoids)		Biofilm reduction: 5- to 33-fold (6.25–25 mg/mL) Complete eradication: ≥ 50 mg/mL	Potent, dose-dependent antibiofilm effect.	Almoabid et al. (2025)

Table 1 (continued)

Antimicrobial class	Popular name (scientific name)	Antimicrobial compound/extract	Target microorganism	MIC/effective concentration	Comparative potency	Reference
	Camu-camu (<i>Myrciaria dubia</i> (Kunth) McVaugh)	Cocoa extract (Class: polyphenol-rich plant extract)		22-fold reduction: 12.5 mg/mL Complete eradication: 200 mg/mL	Strong antibiofilm activity at higher concentrations.	Almoabid et al. (2025)
		Peel aqueous extract	<i>S. aureus</i>	256 µg/mL	Moderate activity	Kaneshima et al. (2017)
			<i>E. coli</i>	512 µg/mL	Weak activity	Kaneshima et al. (2017)
		Myrciarone A, Castalagin, etc.	Multiple pathogens	Quantitative MIC data not reported	Broad-spectrum, bacteriostatic/fungistatic activity by diffusion assay. Most potent against Gram-positive bacteria (<i>S. aureus</i> , 9.7 mm).	Fidelis et al. (2020)
	Açaí (<i>Euterpe oleracea</i>)	Pulp extract	<i>S. aureus</i>	MIC (planktonic): 512 µg/mL Biofilm formation inhibited at: 256 µg/mL	~2x more potent against biofilm initiation than against planktonic growth	Dias-Souza et al. (2018)
		Chloroform, ethyl acetate and ethanol fractions (fruit pulp)	<i>Candida</i> spp.	MIC: 512 µg/mL (for all fractions and all species)	Consistent, moderate fungistatic activity. Suggests a broad-spectrum anti- <i>Candida</i> principle present across different polarity fractions.	Nonato et al. (2018)
		Ethyl acetate and ethanol fractions (fruit pulp)	<i>B. cereus</i>	MIC: 426.66 µg/mL	Selective, moderate activity against <i>B. cereus</i> only. Inactive (MIC ≥ 1024 µg/mL) against other tested bacteria (<i>S. aureus</i> , <i>E. coli</i> , <i>Salmonella</i>).	Nonato et al. (2018)
	Buriti (<i>Mauritia flexuosa</i>)	Buriti oil nano-encapsulated in porcine gelatin	<i>P. aeruginosa</i> , <i>K. pneumoniae</i> , <i>S. aureus</i>	Growth inhibition at 5 mg/mL: • <i>P. aeruginosa</i> : 62% • <i>K. pneumoniae</i> : 69% • <i>S. aureus</i> : 67% (Crude oil inhibition: 16–42%)	Nanoencapsulation potentiates activity. Gelatin nanoparticles increase antimicrobial effect by 43–62% compared to crude oil, enabling water dispersibility.	Castro et al. (2020)

Table 1 (continued)

Antimicrobial class	Popular name (scientific name)	Antimicrobial compound/extract	Target microorganism	MIC/effective concentration	Comparative potency	Reference
	Tucumã (<i>Astrocaryum aculeatum</i> G.Mey.)	Hydroalcoholic extract (Peel and pulp) Rich in: quercetin, rutin, phenolic acids (gallic, caffeic, chlorogenic)	<i>B. cereus</i> , <i>L. monocytogenes</i> , <i>E. faecalis</i> , <i>C. albicans</i>	MIC range: 16.6–46.5 mg/mL • <i>B. cereus</i> : 16.6 mg/mL (both extracts) • <i>L. monocytogenes</i> : 16.6 (pulp)–46.5 (peel) mg/mL • Others: 46.5 mg/mL	Selective activity against Gram-positives and <i>C. albicans</i> . Most potent against <i>B. cereus</i> . Quercetin (bacteria) and rutin (<i>C. albicans</i>) are key contributors.	Jobim et al. (2014)
	Uchi (<i>Endopleura uchi</i> (Huber) Cuatrec.)	Pulp extract	<i>S. aureus</i>	MIC: 250 µg/mL	Moderate antibacterial activity. Less potent than tetracycline (MIC = 1.25 µg/mL). No activity reported against <i>C. albicans</i> , <i>B. cereus</i> , <i>E. coli</i> , or <i>S. mutans</i> .	De Freitas et al. (2018)
		Bergenin (isolated compound)		MIC: 250 µg/mL	Moderate antibacterial activity. Major constituent of uchi pulp. Activity equivalent to crude extract.	De Freitas et al. (2018)
	Mari-mari (<i>Cassia leiandra</i> Benth.)	5,7-Dibenzoyloxy-bergenin (semi-synthetic derivative)		MIC: 125 µg/mL	Enhanced activity compared to bergenin. Derivative is 2-fold more potent than the natural compound.	De Freitas et al. (2018)
		Peel (methanol extract)	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>Staphylococcus saprophyticus</i> , <i>E. coli</i> , <i>Klebsiella oxytoca</i> , <i>P. aeruginosa</i>	MIC (µg/mL): <i>S. aureus</i> : 25 <i>S. epidermidis</i> : 25 <i>S. saprophyticus</i> : 20 <i>E. coli</i> : 30 <i>K. oxytoca</i> : 25 <i>P. aeruginosa</i> : 35	Potent, broad-spectrum antibacterial activity. Active against both Gram-positive and Gram-negative bacteria. Most potent against <i>S. saprophyticus</i> (MIC = 20 µg/mL). Less potent than chloramphenicol (MIC = 3.2–12.2 µg/mL) and rifampicin (MIC = 0.8–10 µg/mL), but among the most potent Amazonian fruit extracts reported.	De Souza et al. (2023a), Souza et al. (2023b)

Table 1 (continued)

Antimicrobial class	Popular name (scientific name)	Antimicrobial compound/extract	Target microorganism	MIC/effective concentration	Comparative potency	Reference
Coumarins	<i>Dipteryx odorata/punctata</i> Synthetic derivatives	Peel (acetone extract)	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>S. saprophyticus</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>P. aeruginosa</i>	MIC: > 40 µg/mL (all strains)	Weak activity. Less potent than methanol extract.	De Souza et al. (2023a), Souza et al. (2023b)
		Engelitin (flavonoid isolated from peel)	<i>S. aureus</i> , <i>S. epidermidis</i> , <i>E. coli</i>	MIC range: 10–100 µM (exact numerical MIC in µM not specified; demonstrated relevant antimicrobial effect)	Active compound responsible for peel activity. Also exhibits antioxidant and antiproliferative properties.	De Souza et al. (2023a), Souza et al. (2023b)
		Ethanollic extracts	<i>E. coli</i> , <i>S. aureus</i>	Activity only at high concentrations	Limited/bacteriostatic	Sousa et al. (2022)
		7-Hydroxy-6-methoxycoumarin (Esculetin 6-methyl ether/Scoparone)	<i>S. aureus</i> , <i>B. cereus</i>	64 µg/mL (for both)	Potent, broad-spectrum Gram-positive activity. Inactive (> 512 µg/mL) against tested Gram-negative bacteria (<i>E. coli</i> , <i>Salmonella</i>).	Yang et al. (2017)
		6,7-Dimethoxycoumarin (Esculetin dimethyl ether/Escoparone)	<i>S. aureus</i> , <i>B. cereus</i> , <i>L. monocytogenes</i>	64 µg/mL (for all)	One of the most active in the study. Consistently potent across key Gram-positive foodborne pathogens.	Yang et al. (2017)

Table 1 (continued)

Antimicrobial class	Popular name (scientific name)	Antimicrobial compound/extract	Target microorganism	MIC/effective concentration	Comparative potency	Reference
		7,8-Dihydroxy-6-methoxycoumarin (Fraxitin)	<i>S. aureus</i>	128 µg/mL	Active against <i>S. aureus</i> and <i>B. cereus</i> (128 µg/mL). Slightly less potent than the hydroxy/methoxy analogues above.	Yang et al. (2017)
	Rambutã (<i>Nephelium lappaceum</i> L.)*	Peel extract (Rich in ellagitannins, geranin, delphinidin derivatives)	<i>S. aureus</i> , <i>B. cereus</i> , <i>L. monocytogenes</i> , <i>E. coli</i> , <i>S. Typhimurium</i> , <i>Enterobacter cloacae</i> , <i>Aspergillus</i> spp., <i>Penicillium</i> spp., <i>T. viride</i>	MIC range: 0.25–1.0 mg/mL MBC/MFC: 0.5–2.0 mg/mL • Best MIC: 0.25 mg/mL vs. <i>A. versicolor</i> • Most MICs: 0.5–1.0 mg/mL	Consistent broad-spectrum bactericidal and fungicidal activity. More efficient than chemical preservatives	Albuquerque et al. (2023)

Notes: This table includes MIC (Minimum Inhibitory Concentration) values only when explicitly reported in the cited studies. The absence of MIC values for several entries reflects a common methodological limitation in the literature: many studies report antimicrobial activity only qualitatively (presence/absence of inhibition zones) without determining quantitative MIC values, which hinders direct potency comparisons. To strengthen future evidence, we recommend that all antimicrobial activity studies report MIC values obtained through standardized methods (e.g., broth microdilution according to CLSI guidelines)

**Nephelium lappaceum* is native to Southeast Asia but is widely cultivated and naturalized in the Amazon region, where it has adapted to local conditions and gained commercial relevance as an exotic fruit

Bioactive compounds with antimicrobial potential in Amazonian fruits

Alkaloids and polyphenols extracted from Amazonian fruits are by far the most extensively studied classes of compounds in terms of demonstrated antimicrobial activity (Table 1). The antimicrobial effects of other classes, such as organic acids and fatty acids, have also been reported in Amazonian fruits, although to a much lesser extent (Table 1).

Despite the limited number of studies focused on other metabolite classes, compounds such as terpenes, coumarins, polysaccharides, and peptides are known to be present in the chemical composition of several Amazonian fruits, and their antimicrobial activity has been widely demonstrated in studies involving fruits and plant matrices from other geographical origins.

In the following sections, we present the primary bioactive compounds responsible for antimicrobial activity. The chemical structures of these compounds, as well as their mechanisms of action, including interactions with microbial cells, will also be discussed.

Alkaloids

Alkaloids are characterized by the presence of one or more nitrogen atoms, typically incorporated within a heterocyclic ring system such as pyridine, quinoline, indole, isoquinoline, and purine (Cordell et al. 2001) (Fig. 1).

The presence of nitrogen in the molecule gives alkaloids basic properties, allowing them to form water-soluble salts in acidic conditions, which facilitates their absorption and availability in biological systems (Leitão et al. 2021). Despite this, many alkaloids contain nitrogen atoms incorporated into aromatic or heterocyclic rings, which contribute to lipophilic characteristics, facilitating their solubility in organic solvents and permeability across biological membranes (Tsuchiya 2015).

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 (Pereira-Caro et al. 2013; Santos et al. 2024). Moreover, isoquinoline alkaloids such as berberine, widely recognized for its antimicrobial, anticancer and anti-inflammatory properties, are present in *Berberis* spp. (Qin et al. 2024; Haque et al. 2025).

Aqueous and hydroalcoholic extracts obtained from the pulp of *Ambelania acida* Aubl. (Apocynaceae) fruits contain monoterpene indole alkaloids (Silva et al. 2024). Among the major compounds detected are tabersonine, pseudocopsinine, ajmalicine, and strictosidine, which are biosynthetically derived from the condensation of tryptophan and monoterpene precursors. On the other hand, cupuaçu contains alkaloids predominantly belonging to the methylxanthine class. The main alkaloids identified in the seeds are caffeine, theobromine, theophylline, and theacrine, with concentrations ranging from approximately 0.25 to 2.33 mg g⁻¹ on a dry weight basis (Da Silva et al. 2024). Among these compounds, caffeine and theobromine are the most characteristic alkaloids of the *Theobroma* genus (Da Silva et al. 2024).

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) (Mabhiza et al. 2016; Manosalva et al. 2016; Yan

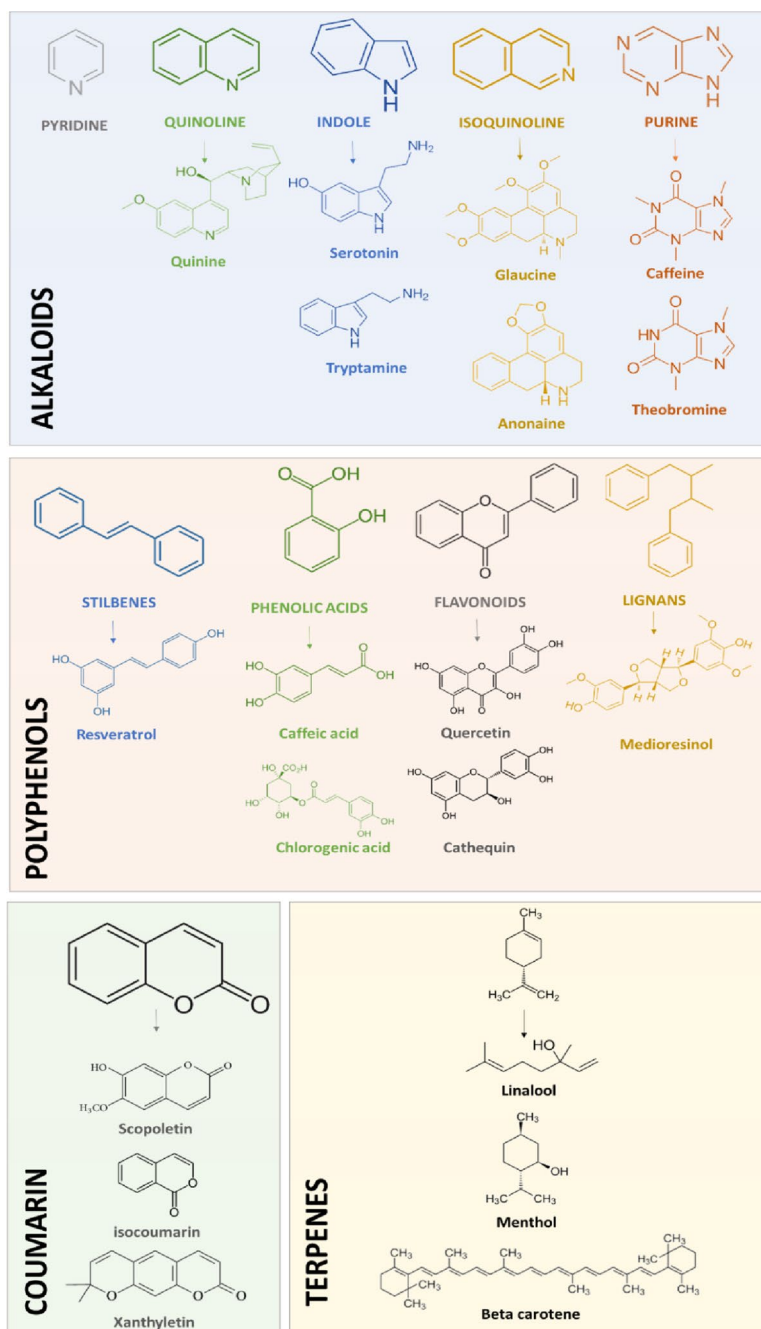


Fig. 1 Chemical structure of antimicrobial compounds found in Amazonian fruits

et al. 2021). For instance, berberine has demonstrated potent antimicrobial activity against both Gram-positive and Gram-negative bacteria, while harmaline and harmine have exhibited antifungal properties, particularly against *Candida* spp. (Zhang et al. 2024).

Caffeine has demonstrated potent antibacterial and antibiofilm effects against major foodborne pathogens through multiple complementary mechanisms. In *S. aureus*, in vitro assays revealed a minimum inhibitory concentration (MIC) of 0.01544 mmol mL⁻¹, while treatment at 2×MIC induced nucleotide leakage and potassium efflux, confirming its membrane-active mode of action (Beulah et al. 2025). Whole-genome sequencing of caffeine-treated cells revealed extensive genomic instability, characterized by a drastic reduction in read mapping (from 99.96% to 23.68%) and GC content (from 30.69% to 6.93%), driven by tens of thousands of single nucleotide polymorphisms and insertions/deletions affecting genes involved in membrane organization, virulence, and DNA repair (Beulah et al. 2025). Still in the same study, in silico docking and molecular dynamics simulations further supported these findings, revealing strong and stable interactions between caffeine and key cell wall-associated proteins, including LtaA and LtaS (proteins involved in the biosynthesis of lipoteichoic acid).

Beyond planktonic cells, caffeine has also exhibited strong antibiofilm activity against *S. Enteritidis*, *S. Typhimurium*, *E. coli*, and *L. monocytogenes*, with MIC values ranging from 9.37 to 37.5 mM depending on the species (dos Santos et al. 2025). In these systems, caffeine significantly inhibited biofilm formation and extracellular polymeric substance production, reduced bacterial motility at sub-inhibitory concentrations, and caused pronounced structural disruption of established biofilms.

Still regarding biofilm control, theobromine at a concentration of 6.25 mg mL⁻¹ significantly inhibited *Streptococcus mutans* biofilm formation, resulting in a 3.35-fold reduction compared with the control (Almoabid et al. 2025). This pathogen is strongly associated with dental caries and other oral health disorders.

The quantitative analysis of alkaloids reveals considerable variation in potency. Purified caffeine demonstrates a relatively low MIC against *S. aureus* (0.01544 mmol/mL ≈ 3 mg/mL; Beulah et al. 2025), while theobromine requires higher concentrations to inhibit *S. mutans* biofilms (6.25 mg/mL; Almoabid et al. 2025). It is crucial to contextualize these values: the natural caffeine concentration in cupuaçu seeds is only 0.25–2.33 mg/g (Da Silva et al. 2024), suggesting that direct fruit consumption may not achieve effective antimicrobial concentrations. Therefore, the reported activity of purified alkaloids does not directly translate to the whole fruit, emphasizing the need for extraction and concentration for practical applications. Furthermore, while caffeine shows promising antibiofilm activity against *E. coli* and *L. monocytogenes* (9.37 and 37.5 mM, respectively; Dos Santos et al. 2025), these concentrations exceed typical physiological levels, highlighting formulation challenges.

Polyphenols

Polyphenols are composed of one or more benzene rings with hydroxyl substituents, which confers their antioxidant properties (Fig. 1). Based on their structural backbone, they are categorized into flavonoids, phenolic acids, stilbenes, and lignans (Wei et al. 2025). From a chemical perspective, the hydroxyl groups on the aromatic rings of polyphenols enable electron donation, facilitating free radical scavenging and metal ion chelation (Vuolo et al. 2019).

Amazonian fruits are recognized as rich sources of polyphenols, particularly flavonoids, phenolic acids, and tannins (Table 1). 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).

Ikigai et al. (1993) and Wei et al. (2024) demonstrated that natural flavonoids exhibit notable activity against *E. coli*, *Salmonella enterica*, *P. aeruginosa*, MRSA (methicillin-resistant *S. aureus*), and VRE (vancomycin-resistant *Enterococcus*). Both studies suggest that these compounds can interact with the phospholipid bilayer, compromising bacterial cell structures.

Other studies also demonstrate that flavonoids such as quercetin and epicatechin reduce biofilm formation by interfering with the synthesis of extracellular polymeric substances that stabilize microbial communities (Vazquez-Armenta et al. 2018; Mu et al. 2021). Moreover, polyphenols have been reported to inhibit critical resistance-related enzymes, including β -lactamases and sortase A, impairing bacterial adhesion and virulence (Teng et al. 2025).

Gong et al. (2023) provided evidence that polyphenols contribute to antimicrobial activity against *B. cereus* through ATP depletion and apoptosis-like cell death. According to the authors, polyphenols are associated with membrane depolarization, 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.

According to Almoabid et al. (2025), polyphenols consistently inhibited *S. mutans* biofilm formation across all tested concentrations, producing effects ranging from an almost tenfold reduction to complete biofilm eradication compared with the control. The authors highlighted polyphenols as the most effective compounds at lower concentrations, suggesting strong potential for the development of strategies aimed at controlling *S. mutans* biofilms and, consequently, improving dental health management.

In fungal cells, polyphenols target β -glucans, chitin, and ergosterol in the membrane (Janeczko 2018; Simonetti et al. 2020; Dhawale et al. 2023). Catechins and proanthocyanidins bind to ergosterol, disrupting membrane integrity (Mekoue Nguela et al. 2015). Furthermore, polyphenols inhibit β -glucan synthase, chitin synthase, and oxidoreductases, impairing cell wall synthesis and energy production (Davidova et al. 2024).

Nonato et al. (2018) evaluated buriti pulp oil fractions and observed antifungal activity against *Candida* spp., related to polyphenols as well as synergistic effects with antibiotics against *B. cereus* and *Salmonella choleraesuis*. Dias-Souza et al. (2018) reported that açaí pulp extract exhibited polyphenol-based activity against *S. aureus*, eradicating biofilms and enhancing antibiotic efficacy. Similarly, Albuquerque et al. (2023) demonstrated that rambutan (*Nephelium lappaceum*) bark extract exhibited a polyphenol antimicrobial more efficient than that obtained with chemical preservatives. Although *N. lappaceum* is native to Southeast Asia, it has been widely cultivated and naturalized in the Brazilian Amazon for decades, particularly in the states of Pará and Amazonas, where it has adapted well to local conditions and become commercially relevant as an exotic fruit. Its inclusion in this review reflects its importance in the current Amazonian agricultural landscape and its potential for valorization of locally generated fruit residues.

The reported MIC values for polyphenolic extracts from Amazonian fruits range from 256 to 512 $\mu\text{g/mL}$ (e.g., camu-camu peel extract; Kaneshima et al. 2017), indicating moderate to weak activity compared to standard antibiotics (e.g., ampicillin typically has $\text{MIC} < 1 \mu\text{g/mL}$ for susceptible *S. aureus*). This limited potency may be compensated by synergistic effects among multiple polyphenols in crude extracts, a phenomenon that remains under-explored. Additionally, most studies do not report MBC (Minimum Bactericidal Concentration) or time-kill kinetics, limiting our understanding of whether these compounds are merely bacteriostatic or truly bactericidal, a crucial distinction for food preservation or therapeutic applications. The study on açai pulp extract illustrates this gap: while it exhibited a MIC of 512 $\mu\text{g/mL}$ against planktonic *S. aureus*, its bactericidal and biofilm eradication profiles were not conclusively determined. However, its ability to inhibit biofilm formation at a sub-MIC concentration (256 $\mu\text{g/mL}$) (Dias-Souza et al. 2018) suggests its potential lies primarily in preventing initial contamination or biofilm development on surfaces, rather than in treating existing biofilms.

Coumarins

Coumarins belong to the class of organic compounds of 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 $\text{C}_9\text{H}_6\text{O}_2$ (Chaudhary et al. 2022) (Fig. 1). Modifications to the chemical structure, such as hydroxylation, methoxylation, or glycosylation at different positions on the benzene or pyrone rings, can modulate their biological activity. For example, 7-hydroxycoumarin (umbelliferone) and 7,8-dihydroxycoumarins exhibit enhanced antioxidant activity (Todorov et al. 2023), while methoxylated derivatives, such as 7-methoxycoumarin and 6,7-dimethoxycoumarin, display improved antimicrobial properties against *E. coli*, *B. cereus*, *Staphylococcus intermedius*, *L. monocytogenes* and *C. albicans* (Kabeya et al. 2013; Yang et al. 2017).

These compounds affect microbial metabolism by inhibiting key enzymes, as demonstrated by imperatorin, which suppresses copper and zinc superoxide dismutase activity in *Shigella dysenteriae*, thereby increasing oxidative stress and bacterial toxicity (Raja et al. 2011). Specific coumarin derivatives, such as amicoumacin A, exhibit activity against clinically relevant pathogens, including *Salmonella* spp., *Shigella* spp., and MRSA. Additionally, certain coumarin glycosides disrupt biofilm formation in *P. aeruginosa* by interfering with quorum sensing regulatory systems (Tian et al. 2016).

Ethanollic extracts of *Dipteryx odorata* and *Dipteryx punctata* revealed the presence of coumarins, particularly 2 H-1-benzopyran-2-one (coumarin) and 3,4-dihydrocoumarin, with seeds being the main source in both species (Sousa et al. 2022). Antimicrobial assays demonstrated limited antibacterial activity, with inhibition of *E. coli* observed only at high concentrations and *D. punctata* extracts showing bacteriostatic activity against *S. aureus* (Sousa et al. 2022). In contrast, the extracts exhibited promising antifungal effects against phytopathogens, especially *Colletotrichum gloeosporioides* and *Fusarium* spp., with reductions in mycelial growth exceeding 50%, depending on the extract type and concentration.

Quantitative data for coumarins from Amazonian sources are scarce. While synthetic coumarin derivatives demonstrated promising MICs (64–128 $\mu\text{g/mL}$; Yang et al. 2017), natural extracts from *Dipteryx* spp. showed activity only at high concentrations (Sousa et al. 2022). This discrepancy suggests that coumarins may be present at sub-inhibitory concen-

trations in native fruits, or that current extraction methods are inefficient. The lack of standardized MIC values for coumarins isolated from Amazonian fruits represents a significant knowledge gap that needs addressing to assess their potential. Notably, coumarins showed stronger antifungal than antibacterial effects (> 50% mycelial growth reduction), indicating they may be more promising as antifungal agents despite their limited antibacterial potency.

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 (Bakkali et al. 2008). They may be acyclic, monocyclic, or polycyclic, with functional groups that significantly impact their chemical behavior and biological activity (Fig. 1). 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 (Bakkali et al. 2008).

Terpenes are found in various Amazonian fruits, contributing to their unique aromas, flavors, and potential health benefits (Corrêa et al. 2023). Carotenoids, a class of tetraterpenoid pigments, are widely distributed in nature and are responsible for the red, orange, and yellow tones in many Amazonian fruits (Amorim et al. 2022; 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. 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 et al. 2024).

In a study conducted by Franco and Shibamoto (2000), 30 compounds were detected in araçá-boi samples, whereas in camu-camu the most abundant compounds were α -pinene and d-limonene. In araçá-boi, sesquiterpenes were the predominant class, with germacrene D showing the highest relative abundance (Franco and Shibamoto 2000). In addition to volatile compounds, several tropical fruits, such as peach palm, tucumã, mango taperebá, murici (*Byrsonima crassifolia*), and guava, exhibit high carotenoid contents (dos Santos et al. 2024).

In another study, the volatile composition of *Myrtaceae* fruit pulps revealed a high chemical diversity dominated by compounds derived from secondary metabolism (Barroso et al. 2024). Monoterpenes and sesquiterpenes were the main constituents including α -pinene, limonene, β -ocimene, terpineol, curzerene, germacrene, and caryophyllene derivatives.

Guimarães et al. (2019) evaluated the antibacterial activity of 33 free terpenes commonly found in essential oils and demonstrated that several chemical classes, including non-oxygenated monoterpenes (m-cymene and R-(+)-limonene), oxygenated monoterpenes ((-)-borneol, (+)-borneol, ($\pm$)-camphor, carveol, carvone, citral, ($\pm$)-citronellal, β -citronellol, trans-geraniol, ($\pm$)-linalool, and terpineol), and phenolic monoterpenes (carvacrol and thymol), exhibited antimicrobial activity against *S. Typhimurium*, *S. aureus*, and *E. coli*. Exposure to these compounds induced pronounced morphological alterations, particularly in *S. aureus*, including irregular cell sizes, cellular debris, and disruption of the characteristic “grape-like” clustering pattern, suggesting impaired cell adhesion and membrane integrity. Comparable structural damage was also reported for *Bacillus subtilis*, *Klebsiella pneumoniae*, and *S. enterica* treated with terpene-rich essential oils, an effect attributed mainly to oxygenated monoterpenes such as citronellal and citronellol (De Souza et al. 2022).

At the membrane level, bacterial exposure to terpenes such as thymol, carvacrol, and limonene promoted an increase in the proportion of unsaturated fatty acids in *E. coli* and *S. Typhimurium*, a response interpreted as an adaptive mechanism to preserve membrane fluidity and functionality under antimicrobial stress (Di Pasqua et al. 2006). In addition, certain terpenes, including farnesol and α -humulene, interfere with cell wall biosynthesis by inhibiting enzymes involved in peptidoglycan assembly, such as penicillin-binding proteins and transglycosylases, further compromising bacterial structural integrity (Ibáñez et al. 2022).

Fontoura et al. (2024) showed that an essential oil rich in terpene constituents induced intracellular accumulation of reactive oxygen species, triggering oxidative imbalance and the formation of apoptotic bodies. These effects were associated with both bacteriostatic and bactericidal activities against *B. subtilis*, *E. coli*, *L. monocytogenes*, and *S. Typhimurium*, highlighting the broad-spectrum antimicrobial potential of terpene-rich matrices.

In fungal systems, terpenes have similarly been shown to interfere with enzymes involved in cell wall biosynthesis, such as chitin synthase and β -glucan synthase, resulting in structurally weakened cell walls, increased susceptibility to osmotic stress, and ultimately cell death (Zeng et al. 2024).

Despite the frequent occurrence of terpenes in Amazonian fruits and their well-established antimicrobial mechanisms, the quantitative bioactivity of terpenes specifically isolated from these fruits against clinically relevant pathogens remains an underexplored field. While foundational studies provide crucial quantitative MIC data for pure, commercially available terpenes (e.g., Guimarães et al. 2019; who tested 33 compounds) and for complex essential oils from Amazonian foliage (e.g., De Souza et al. 2022), a significant gap persists. There is a lack of systematic studies that isolate terpenes directly from Amazonian fruits, determine their MICs using standardized protocols, and benchmark their potency against clinical antibiotics or other natural agents. Consequently, although the membrane-disruptive mechanism of terpenes is known, the applied potential of Amazonian fruit-derived terpenes cannot be accurately gauged or compared, hindering the rational development of new antimicrobials from this unique biota.

Polysaccharides

Polysaccharides from Amazonian fruits display structural diversity and play important roles in fruit texture, metabolism, and bioactivity. These macromolecules contribute to cell wall integrity and energy storage, while also being associated with biological functions such as antioxidant, antimicrobial, and prebiotic effects (Yang et al. 2022; Gong et al. 2022; Chen et al. 2024). Major polysaccharides found in Amazonian fruits include cellulose, hemicelluloses, pectins, and starch, which influence firmness, water retention, sweetness, and nutritional value.

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. 2015). Cationic and sulfated polysaccharides can disrupt bacterial membranes, leading to cell lysis through electrostatic interactions, pore formation, and alterations in membrane fluidity (Liu et al. 2020; Liang et al. 2024).

Mucilages found in camu-camu and cupuaçu are highly hydrated polysaccharides composed of galactose, arabinose, rhamnose, and uronic acids (Vriesmann and De Oliveira Petkowicz 2009; Viana et al. 2024). 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. 2014; Chokri et al. 2024). Arabinogalactans present in buriti have their antimicrobial activity linked to their ability to modulate immune responses and inhibit microbial growth (Da 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 (Jimenez et al. 2019; Díaz-Rincón et al. 2023).

Polysaccharides from Amazonian fruits represent promising biopolymers for food technology, contributing to texture enhancement, stability, and overall product performance; however, their antimicrobial properties remain comparatively underexplored relative to other bioactive classes such as terpenes, phenolics, and alkaloids. The available evidence is largely indirect rather than quantitative: studies report potential mechanisms including microbial membrane interactions and biofilm inhibition (Jeong et al. 2024), yet MIC values for purified polysaccharides from specific Amazonian fruits are rarely documented. This lack of quantitative potency data constitutes a major limitation for assessing their practical antimicrobial relevance. Although mucilages, arabinogalactans, and pectins from fruits such as camu-camu, buriti, and cupuaçu exhibit notable functional properties, their direct antimicrobial efficacy remains insufficiently characterized, underscoring the need for standardized bioactivity evaluation to transition from theoretical promise to evidence-based application.

Peptides

Peptides in Amazonian fruits are composed of specific sequences of amino acids that determine their biological activity. Many contain hydrophobic residues, such as leucine, valine, and phenylalanine, which facilitate interactions with cell membranes (Seo et al. 2012). Functional groups in the amino acids, such as sulfhydryl ($-SH$) in cysteine, enable disulfide bond formation and stabilize the three-dimensional structure of the peptide (Sharma and Singh 2020), while basic groups ($-NH_2$) in lysine and arginine influence peptide charge and membrane interactions (Da Silva Júnior et al. 2023). Some peptides undergo modifications, including glycosylation, phosphorylation, or cyclization, enhancing stability, solubility, and biological activity, with cyclic peptides showing increased resistance to enzymatic degradation (Martian et al. 2025). Notably, defensins from seeds and pulp of Amazonian fruits such as *Theobroma cacao* are cysteine-rich peptides with multiple disulfide bonds that bind microbial membranes, increase permeability, and induce cell lysis, while also exhibiting antifungal activity by compromising fungal cell wall integrity (Lopes et al. 2008; Freitas et al. 2020).

Cyclotides from the *Rubiaceae* and *Violaceae* families are cyclic peptides stabilized by a cysteine-knot structure, capable of disrupting bacterial and fungal membranes by forming pores that cause leakage of intracellular contents (Grover et al. 2021).

Knowledge regarding the occurrence of bioactive peptides in Amazonian fruits remains extremely limited, despite the well-established antimicrobial potency of peptide classes such as defensins and cyclotides reported in other plant systems (Freitas et al. 2020; Grover et al. 2021). This scarcity of compositional and quantitative bioactivity data, including the

absence of MIC values for peptides specifically isolated from Amazonian fruits, represents a major knowledge gap and a high-priority research frontier. Given the potent membrane-disruptive mechanisms documented for peptides in other biological contexts, the targeted exploration and molecular characterization of antimicrobial peptides in Amazonian fruits, particularly in seeds and peels, may reveal novel lead compounds that are chemically distinct from the more extensively studied polyphenols and alkaloids, provided that future studies incorporate rigorous quantitative antimicrobial assessment.

Antimicrobial mechanisms of bioactive compounds from Amazonian fruits

Bioactive compounds present in Amazonian fruits exhibit a wide diversity of antimicrobial mechanisms of action, reflecting the chemical complexity of these natural matrices. In general, these metabolites interfere with multiple cellular targets that are essential for microbial survival, including the cytoplasmic membrane, the cell wall, and genetic material. In addition, many compounds act on regulatory processes such as quorum sensing-mediated cell communication, thereby impairing the coordination of virulence factors, biofilm formation, and antimicrobial resistance.

At the cell wall and cytoplasmic membrane (Fig. 2) level, several classes of bioactive compounds compromise microbial viability by disrupting membrane integrity. Terpenes, especially monoterpenes such as thymol and carvacrol, integrate into lipid bilayers, increasing membrane fluidity and permeability and causing leakage of ions and metabolites, which

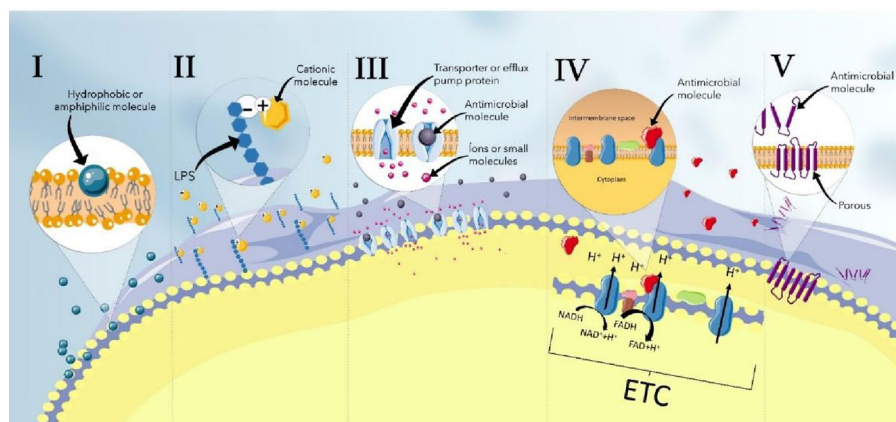


Fig. 2 Main mechanisms of antimicrobial action of bioactive compounds from Amazonian fruits. I – Integration of compounds into microbial membranes, disrupting integrity and increasing permeability. Blue circles: Hydrophobic alkaloids such as quinoline and isoquinoline derivatives; amphiphilic alkaloids 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), leading to depolarization, disruption of ion gradients, and leakage of intracellular metabolites. 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 – Pore formation by compounds such as sanguinarine or antimicrobial peptides (purple cylinder), resulting in uncontrolled ion flux and cell death

ultimately impairs cellular homeostasis (Griffin et al. 2005; Rathod et al. 2021; Pezzola et al. 2024). Coumarins similarly interact with microbial membranes, altering permeability and inducing membrane depolarization, structural damage, and cell death; in addition, they inhibit enzymes involved in peptidoglycan biosynthesis, weakening the bacterial cell wall, particularly in Gram-positive bacteria (Souza et al. 2005; Galkin et al. 2009; Chate et al. 2019; Wang et al. 2024).

Alkaloids exert antimicrobial effects through combined membrane and intracellular actions. Quinoline and isoquinoline derivatives increase membrane permeability and promote lysis, while cationic alkaloids such as caffeine interact electrostatically with negatively charged membrane components, leading to depolarization and leakage of intracellular contents (Efimova et al. 2020; Laumailé et al. 2019; Salas-Ambrosio et al. 2023). Amphiphilic alkaloids, including berberine, destabilize phospholipid bilayers, and others, such as sanguinarine, form transmembrane pores analogous to antimicrobial peptides. Many alkaloids also inhibit efflux pumps and respiratory enzymes, disrupting energy metabolism and contributing to the mitigation of antimicrobial resistance (Shai 1999; Sharma et al. 2015; Dashtbani-Roozbehani and Brown 2021; Lorusso et al. 2022).

Polyphenols display broad-spectrum antimicrobial activity by interacting with membrane lipids and proteins, impairing membrane fluidity, electron transport, and ATP synthesis, which leads to cellular leakage and oxidative damage (Wang et al. 2022; Mandal and Domb 2024; Li et al. 2024). Finally, peptides, including cationic peptides, defensins, and peptaibols, disrupt microbial membranes through electrostatic interactions and pore formation, and may also inhibit peptidoglycan cross-linking or interfere with ergosterol synthesis in fungi (Brogden 2005; Ciumac et al. 2019; Hou et al. 2022; Mohid et al. 2022).

In cytoplasmic, genetic, and transcriptional levels (Fig. 3), terpenes affect enzyme function, genetic material, and metabolic pathways, notably by inhibiting key enzymes of respiratory chains, reducing ATP production, and inducing energy depletion (Rathod et al. 2021; Kumar 2024; Nagoor Meeran et al. 2016; Lim et al. 2019). Coumarins disrupt metabolic enzyme activity and, in some cases, promote reactive oxygen species (ROS) generation through redox or photochemical reactions, leading to oxidative stress, DNA damage, and apoptosis- or necrosis-like cell death (El-Sawy et al. 2024; Maslovska et al. 2023; Zaynab et al. 2024). Planar coumarins intercalate into DNA and inhibit DNA gyrase and topoisomerase IV, while substituted coumarins interact with ribosomal subunits, impairing replication, transcription, and protein synthesis (Citarella et al. 2024; Reen et al. 2018). Alkaloids exert antimicrobial activity by targeting metabolic enzymes and interfering with DNA and RNA synthesis, ultimately inhibiting growth or inducing cell death (Barati and Modarresi Chahardehi 2024; Thawabteh et al. 2024). Polyphenols act through enzyme inhibition, metal ion chelation, and interference with DNA replication and transcription, with compounds such as catechins, anthocyanins, and gallic acid inhibiting DNA gyrase and topoisomerases and disrupting cell division (Santos et al. 2021; Ivanov et al. 2022; Davidova et al. 2024). In addition, terpenes such as thymol and carvacrol induce oxidative stress and apoptosis by inhibiting metabolic enzymes and promoting ROS formation (Nagoor Meeran et al. 2016; Lim et al. 2019; Laws III and Smid 2024). Peptides further contribute by impairing metabolic enzymes, interacting with DNA or ribosomes, and inducing ROS-mediated damage, although their precise molecular interactions remain to be fully elucidated (Mohid et al. 2022; Gagandeep et al. 2024).

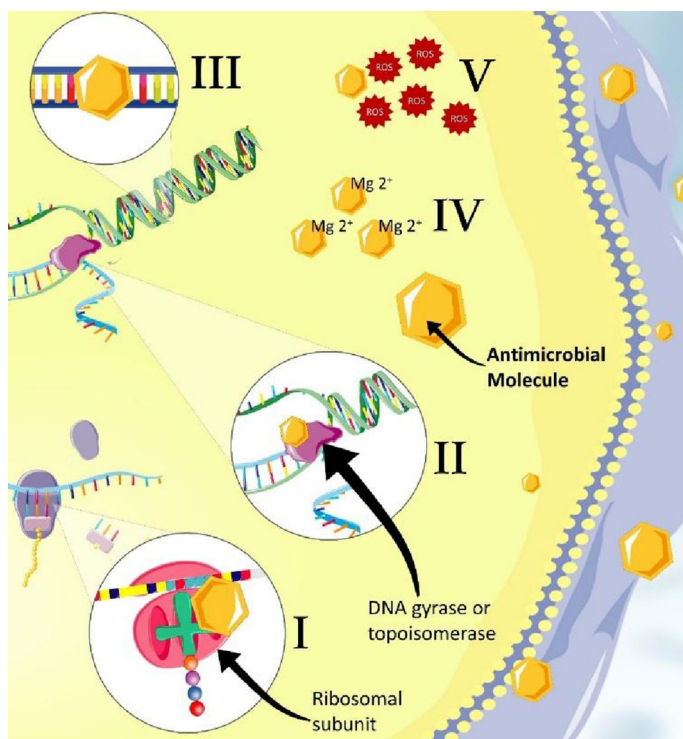


Fig. 3 Main antimicrobial mechanisms of Amazonian fruit bioactive compounds targeting enzymes, ribosomes, and DNA. I – Binding of molecules (e.g., indole derivatives, coumarins) to ribosomal subunits, inhibiting protein synthesis. II – Binding of antimicrobial molecules (e.g., phenolic acids) to DNA 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, impairing enzyme activity. V – Induction of reactive oxygen species (ROS) accumulation, causing oxidative damage to proteins, lipids, and DNA, ultimately leading to microbial apoptosis

In terms of cell communication via quorum sensing (Fig. 4), several bioactive compounds from Amazonian fruits disrupt microbial signaling networks, thereby impairing coordinated behaviors essential for pathogenicity. Terpenes inhibit quorum sensing molecules such as acyl-homoserine lactones (AHLs) and AI-2, suppressing virulence, biofilm formation, and antimicrobial resistance, with monoterpenes like thymol and carvacrol being particularly effective (Nagoor Meeran et al. 2016; Lim et al. 2019; Naga and Shaaban 2023; Roy et al. 2023; Laws III and Smid 2024). Similarly, peptides and coumarins also interfere with quorum sensing and biofilm development, further compromising microbial viability (Mohid et al. 2022; Gagandeep et al. 2024; El-Sawy et al. 2024). Polyphenols modulate quorum sensing by disrupting signaling molecules, including AHLs and autoinducing peptides (AIPs), leading to reduced virulence and biofilm formation (Sarabhai et al. 2013; Ivanov et al. 2022; Wang et al. 2022, 2024).

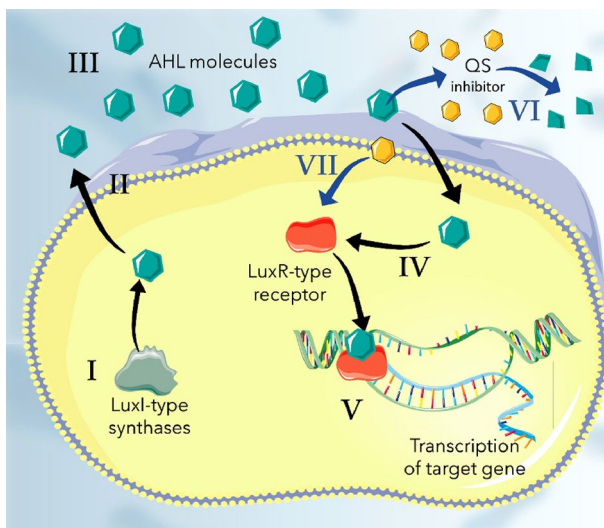


Fig. 4 Mechanism of quorum sensing (QS) in Gram-negative bacteria using acyl-homoserine lactones (AHLs). (I) AHLs (green hexagons) are synthesized by LuxI-type enzymes (II) AHLs diffuse passively or actively across the bacterial membrane (III) As bacterial density increases, AHLs accumulate in the extracellular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

Critical analysis, research gaps, and evidence assessment

Critical analysis of current research landscape

While the antimicrobial potential of Amazonian fruits is increasingly recognized, the current research landscape reveals several critical limitations. Most studies to date have adopted a reductionist approach, focusing on isolated compounds rather than synergistic interactions within complex fruit matrices. This overlooks the potential entourage effect, where the combined action of multiple bioactive compounds may yield superior antimicrobial efficacy compared to purified constituents. Furthermore, the predominance of *in vitro* studies (approximately 85% of cited references) presents a significant translational gap, as these models often fail to replicate the complex physiological conditions of *in vivo* systems or real food matrices.

Methodologically, there is considerable heterogeneity in extraction protocols, antimicrobial testing methods, and compound characterization techniques across studies, complicating direct comparisons and meta-analysis. A critical assessment of evidence strength reveals that approximately 70% of the cited studies do not report quantitative MIC values, relying instead on qualitative disc diffusion assays or simple growth inhibition observations. This quantitative data deficiency severely limits cross-study comparisons and potency assessments. Standardization of these protocols is urgently needed to enable robust cross-

study comparisons and establish reliable structure-activity relationships for Amazonian fruit bioactives.

Methodological limitations

The evidence bases for reported antimicrobial activity exhibits substantial heterogeneity in methodological rigor, which must be considered to avoid overinterpretation of efficacy claims. The most robust studies are those that integrate multiple quantitative approaches, as exemplified by Beulah et al. (2025), who substantiate caffeine's activity through minimum inhibitory concentration determination (0.01544 mmol/mL), membrane integrity assays based on potassium efflux, genomic analyses, and molecular docking, whereas a considerable portion of the literature remains limited to preliminary screening assays lacking MIC values or validation.

Comparability across studies is further undermined by poor methodological standardization, including wide variation in extraction solvents, tested concentrations, microbial strains (reference strains versus clinical isolates), and assay conditions such as culture media and incubation parameters, thereby complicating data synthesis and precluding reliable meta-analytical integration.

An additional constraint is the concentration disconnect observed for several bioactive classes, particularly alkaloids and polyphenols, in which the effective concentrations of purified compounds greatly exceed their natural abundance in fruit matrices - for example, caffeine's MIC of approximately 3 mg/mL contrasted with its native levels in cupuaçu seeds (0.25–2.33 mg/g), raising questions regarding ecological relevance and practical feasibility without downstream extraction and concentration steps.

Finally, the limited assessment of host-cell cytotoxicity and the frequent absence of selectivity index calculations (cytotoxic concentration/MIC) represent a critical gap, as these parameters are essential to distinguish therapeutic potential from nonspecific toxicity.

Identified research gaps

Our analysis highlights several critical research gaps that must be addressed to ensure more robust advancement in this field. Although general mechanisms such as membrane disruption and enzyme inhibition are commonly described for broad classes of compounds, the precise molecular targets and signaling pathways modulated by most bioactive compounds from Amazonian fruits remain poorly characterized; for example, it is still largely unknown how specific polyphenols from açai regulate bacterial virulence gene expression beyond interference with quorum sensing. Another underexplored area is synergy, as potential synergistic or antagonistic interactions among different classes of bioactives within a single fruit, as well as between fruit extracts and conventional antimicrobials, remain severely understudied despite their clear implications for biological efficacy.

A further major omission involves resistance development studies, since the literature rarely evaluates whether prolonged exposure to sublethal concentrations of these bioactives could promote microbial adaptation or resistance, a central consideration for their development as sustainable alternatives. In addition, pharmacokinetic and toxicity profiles are virtually absent for purified compounds in the context of pharmaceutical applications, with limited data on absorption, distribution, metabolism, excretion, and toxicological

thresholds, while for food-related uses there is a lack of assessment of impacts on sensory properties, nutrient bioavailability, and potential allergenicity. Finally, ecological and seasonal variability is widely underestimated, as most studies treat fruits as uniform raw materials, even though the concentration and profile of antimicrobial compounds can vary substantially with soil characteristics, rainfall patterns, ripening stage, and post-harvest handling, factors that are rarely quantified but are essential for standardization and commercial implementation.

Understudied and overlooked species

The research focus has been disproportionately concentrated on a few commercially promising species. Açaí (*Euterpe oleracea*), cupuaçu (*Theobroma grandiflorum*), and camu-camu (*Myrciaria dubia*) collectively account for over 60% of the studies reviewed. In contrast, numerous species with high traditional use and preliminary bioactivity reports remain severely understudied, representing a lost opportunity for discovery.

High-priority yet understudied species include pajurá (*Couepia bracteosa*), which is cited in ethnobotanical literature for treating infections but lacks modern phytochemical and antimicrobial investigations; mari-mari (*Cassia leiandra*), which, although mentioned by De Souza et al. (2023a, b), still has an unexplored antimicrobial compound profile beyond initial reports; abiu (*Pouteria caimito*), for which preliminary studies exist (Abreu et al. 2019; Oliveira et al. 2025), but whose antimicrobial spectrum and active principles remain incompletely characterized; bacuri (*Platonia insignis*), recognized for anti-inflammatory properties, yet lacking dedicated antimicrobial screening of its diverse seed and peel constituents; and uxi (*Endopleura uchi*), whose antimicrobial potential remains largely uncharacterized beyond the report of gallic acid by De Freitas et al. (2018). Additionally, research shows a strong bias toward fruit pulp, neglecting other plant tissues that often contain higher concentrations of defensive metabolites. Seeds, peels, leaves, and bark from Amazonian fruit species represent vastly underexplored reservoirs of antimicrobial compounds, as illustrated by the potent activity identified in rambutan peel (Albuquerque et al. 2023) - an example of a naturalized exotic species in the Amazon that highlights the relevance of adopting similar waste-to-value strategies for both native and naturalized biodiversity in the region.

Synthesis: from descriptive cataloguing to translational science

Moving forward, the field must transition from descriptive cataloguing of activity to hypothesis-driven research. This requires: (1) prioritizing understudied species with ethnobotanical leads while employing standardized quantitative assays; (2) employing omics technologies (genomics, metabolomics) to comprehensively characterize bioactive profiles; (3) developing standardized bioassays that include biofilm and persistence cell models with MIC/MBC determination; (4) assessing compound stability and activity in relevant matrices (food, physiological conditions); (5) investigating synergistic combinations; and (6) evaluating efficacy against multidrug-resistant clinical isolates rather than only reference strains.

To advance the field, future research should prioritize standardized methodologies that generate comparable quantitative data. Research should advance beyond simple activity confirmation to include validation, safety assessment, and evaluation in relevant application matrices. By addressing these gaps, research on Amazonian fruits can evolve from

confirming traditional knowledge to driving innovative solutions for global antimicrobial challenges.

Future perspectives

Biotechnological approaches, including metabolic engineering, synthetic biology, and microbial fermentation, offer viable pathways to produce these valuable compounds without compromising biodiversity. Importantly, these technologies contribute to conservation by reducing the need for large-scale harvesting of wild fruits, thereby alleviating pressure on natural populations and supporting in situ biodiversity preservation.

Metabolic engineering encompasses the strategic modification of microbial metabolic pathways to optimize the synthesis of target compounds. Recent advances have demonstrated that engineered microorganisms can serve as efficient biofactories for producing bioactive metabolites originally found in Amazonian fruits. Carotenoids, which are abundant in fruits such as açai and camu-camu, represent a class of bioactives with strong antioxidant and antimicrobial properties. Through metabolic engineering, microbial hosts - particularly yeast and bacterial strains - can be optimized to overproduce specific carotenoids, enhancing yield, stability, and bioactivity while reducing dependence on wild-harvested fruit (Dos Santos et al. 2024; Fonseca et al. 2025).

Synthetic biology goes beyond conventional metabolic engineering by enabling the construction of novel biosynthetic pathways for the production of rare, unstable, or low-abundance compounds that are difficult to obtain directly from natural sources. Through the modular assembly of biosynthetic routes and precise optimization of enzyme expression, this approach allows the scalable production of bioactive molecules with improved stability and efficacy, thereby expanding the portfolio of compounds available for industrial applications (Qin et al. 2025; Simpson 2025).

In this context, synthetic biology has become a robust platform for the sustainable production of fruit-derived bioactive compounds, particularly polyphenols, using engineered microbial systems. The reconstruction of plant biosynthetic pathways in yeast hosts such as *Saccharomyces cerevisiae* and *Yarrowia lipolytica* has enabled the efficient production of flavonoids, phenolic acids, stilbenes, and coumarins naturally present in fruits (Gomes et al. 2022). These strategies combine heterologous expression of key enzymes from the phenylpropanoid and flavonoid pathways with metabolic rewiring to improve precursor supply, redox balance, and carbon flux toward target metabolites. Although production levels vary according to pathway complexity, host strain, and degree of genetic optimization, substantial titers have already been achieved for compounds such as resveratrol, naringenin, kaempferol, quercetin, and p-coumaric acid (Gomes et al. 2022). Collectively, these advances demonstrate that synthetic biology decouples bioactive compound production from agricultural limitations, offering a scalable, controllable, and biodiversity-friendly alternative to fruit extraction while enabling access to high-value metabolites for pharmaceutical, food, and biotechnological applications.

Complementing these strategies, microbial fermentation harnesses the metabolic capabilities of microorganisms to convert Amazonian fruit residues or pulp into value-added products. Fermentation can increase the bioavailability and stability of antimicrobial compounds while enhancing functional properties. For example, the fermentation of bacaba

pulp with probiotic strains has been shown to improve both antioxidant and antimicrobial activities of the final product (De Assis et al. 2025). Microbial fermentation of Amazonian fruit residues also represents a circular bioeconomy strategy, converting waste into high-value antimicrobial compounds (De Assis et al. 2025). These tools would reduce pressure on natural resources while ensuring a consistent supply of bioactives for industrial use (Fidelis et al. 2020).

Although substantial *in vitro* evidence has demonstrated the antimicrobial activity of phytochemicals such as alkaloids, polyphenols, terpenes, polysaccharides, and peptides, the transition toward clinical and industrial applications remains limited. Most studies have been restricted to *in vitro* or small-scale *in vivo* experiments, with a lack of standardized protocols, controls, and translational studies. Rigorous preclinical studies and well-designed randomized clinical trials are urgently required to confirm the efficacy, pharmacokinetics, bioavailability, and safety of these natural antimicrobials in humans (Cushnie and Lamb 2005; Oliveira et al. 2013). Moreover, the exploration of synergistic combinations of Amazonian fruit extracts with conventional antibiotics, antifungals, or other natural bioactives should be prioritized, as these may reduce the required dose of synthetic drugs and slow the development of antimicrobial resistance (Dias-Souza et al. 2018).

Techniques such as nanocarriers, liposomes, and biodegradable polymers can enhance the solubility, stability, and targeted delivery of plant-derived compounds, particularly those with poor pharmacokinetic profiles. Emerging stimuli-responsive systems, microemulsions, and co-encapsulation with probiotics or enzymes could further improve bioactivity and facilitate controlled release in gastrointestinal or dermal applications. These technologies may also enhance penetration into microbial biofilms, where pathogens often show increased resistance (Amador et al. 2021; Kothapalli and Vasanthan 2024).

Beyond pharmaceutical applications, the integration of Amazonian fruit extracts into functional foods, nutraceutical beverages, and active packaging films could simultaneously extend shelf life, provide health benefits, and reduce dependence on synthetic preservatives. Extracts from fruits such as açai, buriti, and cupuaçu could be incorporated into edible coatings, active packaging, or functional beverages to achieve these effects (Costa et al. 2022; Gupta et al. 2024).

Conclusion

Amazonian fruits represent an exceptional reservoir of antimicrobial compounds, holding significant promise for addressing the dual challenges of antimicrobial resistance and the demand for natural preservatives. This review confirms that polyphenols and alkaloids are the most extensively studied and potent classes of bioactive compounds in these fruits, with well-characterized mechanisms including membrane disruption, enzyme inhibition, and interference with quorum sensing. Terpenes, coumarins, polysaccharides, and peptides also contribute to the antimicrobial potential, although they remain critically understudied.

Despite this promising bioactivity, the field faces three major translational barriers: (i) methodological heterogeneity and lack of standardized quantitative assays (e.g., MIC/MBC), which prevent cross-study comparisons; (ii) a predominance of *in vitro* studies, with scarce validation in food matrices, *in vivo* models, or clinical settings; and (iii) sustain-

ability and scalability concerns, as the effective concentrations of purified compounds often exceed their natural abundance in fruits, necessitating extraction or synthesis.

To overcome these challenges, the biotechnological approaches outlined in this review—particularly metabolic engineering, synthetic biology, and microbial fermentation—emerge as the most promising solutions. These strategies decouple bioactive production from wild harvesting, enable the scalable synthesis of rare or unstable compounds (e.g., specific flavonoids and coumarins), and allow the valorization of fruit residues through circular bioeconomy models. When combined with advanced formulation technologies (e.g., nano-encapsulation), these tools can enhance stability, bioavailability, and targeted delivery.

Furthermore, our critical analysis underscores a pronounced research bias toward commercial species (açaí, cupuaçu, camu-camu) and fruit pulps, while numerous ethnobotanically relevant species (e.g., pajurá, mari-mari, bacuri) and underutilized plant parts (seeds, peels) remain virtually unexplored. Addressing this gap through hypothesis-driven bio-prospecting is a high-priority frontier.

Realizing the full potential of Amazonian antimicrobials therefore requires a paradigm shift from descriptive cataloguing to application-oriented science. This transition must be guided by methodological standardization, rigorous safety and toxicity assessment, and ethical frameworks that ensure fair benefit-sharing with traditional communities and active biodiversity conservation. By confronting these challenges with scientific rigor and social responsibility, Amazonian fruits can evolve from subjects of academic interest into sustainable, high-impact solutions for global health and food security.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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