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# Native Brazilian Plants Against Nosocomial Infections: A Critical Review on their Potential and the Antimicrobial Methodology

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**Abstract:** The growing incidences of drug-resistant pathogens have increased the attention on several medicinal plants and their metabolites for antimicrobial properties. These pathogens are the main cause of nosocomial infections which led to an increasing mortality among hospitalized patients. Taking into consideration those factors, this paper reviews the state-of-the-art of the research on antibacterial agents from native Brazilian plant species related to nosocomial infections as well as the current methods used in the investigations of the antimicrobial activity and points out the differences in techniques employed by the authors. The antimicrobial assays most frequently used were broth microdilution, agar diffusion, agar dilution and bioautography. The broth microdilution method should be the method of choice for testing new antimicrobial agents from plant extracts or isolated compounds due to its advantages. At the moment, only a small part of the rich Brazilian flora has been investigated for antimicrobial activity, mostly with unfractionated extracts presenting a weak or moderate antibacterial activity. The combination of crude extract with conventional antibiotics represents a largely unexploited new form of chemotherapy with novel and multiple mechanisms of action that can overcome microbial resistance that needs to be further investigated. The antibacterial activity of essential oil vapours might also be an interesting alternative treatment of hospital environment due to their ability in preventing biofilm formation. However, in both alternatives more studies should be done on their mode of action and toxicological effects in order to optimize their use.

**Keywords:** Antimicrobial activity, antimicrobial agents, essential oils, native brazilian plants, plant extracts, nosocomial infections, therapy strategies.

## INTRODUCTION

Infectious diseases are caused by germs that kill more people worldwide than any other single death cause. Nosocomial infection, also known as hospital–acquired infection or healthcare-associated infections (HAIs), is one of the main transmissible diseases that are amongst the major causes of the increasing morbidity in hospitalized patients. The most frequent HAIs are surgical wounds, urinary tract and lower respiratory tract infections. According to the Council of the European Union, 8–12% of patients admitted to hospitals in European countries suffer from adverse events while receiving healthcare, being HAIs the most prominent of them [1]. This shows that HAIs are not only a problem for resource-poor regions but also affects economically developed countries [2].

Over the past few years in Europe, nosocomial infections affected 1 out of 10 patients admitted to hospitals and accounted for *ca*. of 5000 deaths/ year with a high cost for the public systems. On average, a patient with HAIs spent 2.5-times longer in hospital, incurring additional treatment costs, in comparison with uninfected patient. Intensive care units (ICU) have the highest prevalence of hospital-acquired infections in the hospital setting. The European Prevalence of Infection in Intensive Care Study (EPIC), involving over 4500 patients, demonstrated that the nosocomial infection prevalence rate in ICU was 20.6%. ICU patients are particularly at risk of hospital–acquired infections as a result of mechanical ventilation, invasive procedures and their immune deficiency [3]. According to WHO Program for the Control of Hospital Infections [4] a prevalence survey in 55 hospitals of 14 countries representing 4 WHO Regions (Europe, Eastern Mediterranean, South-Eastern Asia and Western Pacific) showed an average of 8.7% of hospital patients that contracted nosocomial infections. The infection prevalence was higher in Western Pacific, South-Eastern Asia, Eastern Mediterranean regions (9.0%, 10.0%, and 11.8% respectively) and the lowest in Europe (7.7%) [5].

Nosocomial infections are caused by bacteria, viruses, fungi and parasites which are acquired from another hospital (cross-contamination), may be caused by the patient's own flora (endogenous infection), from an inanimate object or substance newly infected, or from another human source (environmental infection). The bacteria are the most common causes of nosocomial infections being the predominant pathogens *Staphylococcus aureus*, *Pseudomonas aeruginosa*,

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*Enterococcus spp., Enterobacter spp.*, *Escherichia coli*, *Candida albicans*, and *Klebsiella pneumonia* [3, 6].

One of the factors that have influenced the development of nosocomial infections is antimicrobial resistance (AMR). The World Health Organization [7] defines this phenomenon as resistance of a microorganism to an antimicrobial drug for which it was originally sensitive. Though the evolution of resistant strains is a natural phenomenon, the misuse of antimicrobial drugs and inappropriate practices of infection control accelerate the AMR. Moreover, traces of resistance genes of nosocomial antibiotic resistance can be exchanged between certain types of bacteria spreading the resistance traits, particularly in hospitals, where various bacteria can come in close contact with one another [8]. That continuous development of various multi-resistant bacteria is a factor of concern and challenge because it limits the spectrum of effective antimicrobial. The methicillin-resistant *Staphylococcus aureus* (MRSA) have a particular facility for nosocomial transmission and is considered a major cause of bloodstream infections according to European Centre for Disease Prevention and Control/European Medicines Agency ECDC/EMEA [9-10]. The majority of MRSA strains are often resistant to several antibiotics including penicillins and cephalosporins, and occasionally are sensitive only to vancomycin and teicoplanin [7].

This scenario indicates potential antimicrobial therapy losses, making necessary to elaborate a strategy to combat the antibiotic resistance with the discovery and development of new active agents capable of circumventing the bacterial resistance mechanisms [11]. Traditionally, plants have been considered as a source of new drugs and clinical studies have demonstrated the therapeutic value of these biomolecules for the discovery of new therapeutic products. Regarding the RMAs, some studies show evidence that products derived from plants can be used to improve the efficacy of antibiotics [12]. Additionally, a special attention has been given to the scientific study of bioactive substances obtained from renewable sources, allowing sustainable activities. Some of the advantages expected by using natural antimicrobials include: reducing total dependence on antibiotics, diminishing development of antibiotic resistance by pathogenic microorganisms, controlling cross-contaminations by foodborne pathogens, and strengthening the human's immune system [13]. Therefore, plant extracts represent a considerable potential for the development of new effective agents against infections currently difficult to treat such as nosocomial infections [14-16]. Among several examples, Schelz and co-workers [17] proved the antiplasmid activity of peppermint oil and its main constituent, menthol, meaning that menthol-containing substances are potential agents that could eliminate the bacteria plasmids resistance. Therefore, plant-derived principles are a new area of chemotherapeutic infections treatment, coupled with different kinds of studies on the mechanisms of action, interactions with antibiotics or other medicinal plants or compounds, as well as the pharmacokinetic profile of the extracts [16].

Among the worldwide known plant species (estimated at 220,000–450,000 [18]) only a small fraction has been investigated for the presence of antimicrobial compounds [19-20]. Among 109 new antibacterial drugs approved in the period 1981–2006, 69% originated from natural products, and 21% antifungal drugs were natural derivatives or compounds mimicking natural products [21].

Brazil is considered to possess the richest flora in the world, with more than 43,000 recognized species —nearly 19% of the world's flora [22-23]. The broad climatic and geomorphologic variety found in the country is responsible for the presence of different biomes and ecosystems of which two, Atlantic Rain forest and Cerrado, were listed among the 25 biodiversity hotspots for conservation priorities based on the high endemism rate (2.5 and 1.5% of the world plant species) [24]. Therefore, it would be expected to find unique secondary compounds that could be useful for medicinal purposes within the Brazilian flora. This article presents an overview of the studies with native species from Brazilian flora with its implications in developing new strategies for the antimicrobial chemotherapy to circumvent AMR. The literature search was restricted to include native Brazilian plant species with properties against bacteria involved in nosocomial infections (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Mycobacterium tuberculosis*, *Clostridium difficile*, *Enterococcus faecium*, *Enterococcus faecalis*, *Legionella pneumophila* and *Escherichia coli*) within the databases SciFinder Scholar®, Scielo® and PubMed® over the last 15 years. In this review, we will focus on evaluating the potential of developing antimicrobials from plant extracts and essential oils from the Brazilian flora and to critically evaluate the methods currently employed to access their antimicrobial activity.

## ANTIMICROBIAL PLANT EXTRACTS AND ESSENTIAL OILS FROM THE NATIVE BRAZILIAN FLORA

### Plant Extracts

Despite having its immense biodiversity already recognized, nearly 18% of the priority areas for preservation in Brazil (Caatinga, Atlantic Forest, and the Southern Pampas) are still classified as "insufficiently known" in terms of inventories and biological surveys [22]. This lack of knowledge is also reflected in the few Public Policies for investments in research and product development from Brazilian plants. The literature survey for studies on Brazilian plants with antibacterial activity demonstrated that so far 112 papers were found, as shown in Table **1**. Despite the wide variety of native plants, the research included 240 angiosperms species that were evaluated for antimicrobial activity, which represent *ca.* 0.8 % of the recognized angiosperms species for Brazil [23]. With our search parameters, we did not find any papers dealing with antibacterial activity of native Brazilian ferns, bryophytes or algae, which together are responsible for 16% of the Brazilian flora [23]. These observations demonstrate the high potential of future target directed research to antimicrobial native plants

Nowadays Brazilian populations still have a large dependence on plants to treat various illnesses, among them microbial infections. Several species still used to date derive from the ancient Amerindian populations, especially along the Atlantic coast. Recently, an ethnobotanical survey identified 433 plant species that can be potentially useful for identification of new antimicrobial drugs from Brazilian plants [109]. The majority of the plants presented in Table **1** were

**Table 1. Highlights of Native Brazilian Plants with Antimicrobial Activity in Nosocomial Infections (Frac.: Fraction(s), MIC: Minimum Inhibitory Activity, ND: MIC Not Determined by Authors, NS: Data Not Specified by Authors, *: Plant Species Updated to the Correct Name [23], ** Not the Same Solvent Used in the Assay, *** Unless Otherwise Specified)**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Achyrocline satureiodes* DC. | flowers | ethanol | *Staphylococus aureus* (DFUB) | ND | [25] |
| | leaves | essential oil | *Escherichia coli (*EIEC 0461-4), (STEC 2781-8), (STEC 0157) | 900 | [26] |
| | | essential oil | *Escherichia coli serotype* (EIEC 240-1) | 1000 | |
| *Aegiphila verticillata* Vell.* | stems | ethanol | *Staphylococcus aureus (*resistant strains NorA, MsrA) | ND | [27] |
| | leaves | | | ND | |
| *Aloysia citriodora* Palau* | aerial parts | essential oil | *Staphylococcus aureus* (CCT2740*)* | 800 | [28] |
| | | | *Enterococcus faecium* (ATCC10541) | 50 | |
| | | | *Enterococcus faecium* (CCT 5079) | 2000 | |
| *Anacardium occidentale* L. | leaves | dried | *Staphylococcus aureus* (ATCC 15008) | ND | [29] |
| | | hexane | | | |
| | | dichloromethane | | | |
| *Anacardium occidentale* L. | leaves | ethyl acetate | *Staphylococcus aureus* (ATCC 15008) | ND | [29] |
| *Anacardium occidentale* L | leaves | ethanol (70%) | *Staphylococcus aureus* (NS) | ND | [30] |
| | barks | | *Enterococcus faecalis* (NS) | ND | |
| | leaves | | *Staphylococcus aureus* (NS) | >100 | |
| | barks | | | 25 | |
| *Annona coriacea* Mart. | leaves | cachaça (Brazilian rum) | *Bacillus subtilis* (ATCC 6623) *Staphylococcus aureus* (ATCC 25923) *Escherichia coli* (ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [31] |
| *Annona crassiflora* Mart. | leaves | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| | seeds | | *Staphylococcus aureus (*ATCC 25923) *Staphylococcus aureus* (resistant strains NorA, MsrA) | | |
| | fruit | | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Annona foetida* Mart. | leaves | essential oil | *Enterococcus faecium* (CCT 5079) | > 1000 | [32] |
| | | | *Escherichia coli* (ATCC 11775) | > 1000 | |
| | | | *Pseudomonas aeruginosa* (ATCC 13388) | > 1000 | |
| | | | *Staphylococus aureus* (ATCC 6538) | 200 | |
| *Annona salzmannii* A. DC. | fruit barks | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Aristolochia* sp. | leaves | hexane frac. | *Staphylococcus aureus* (ATCC 25923) | ND | [33] |
| | | methanol | | 5000 | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Aspidosperma ramiflorum* Mül. Arg | stems | ethanol | *Staphylococcus aureus subsp. aureus* (ATCC 25923) *Echerichia coli* (ATCC 25922) | ND | [34] |
| | leaves | | | | |
| *Avicennia schaueriana* Stapf & Leechm. ex Moldenke | barks | ethanol (70%) | *Staphylococcus aureus* (ATTC 6835) | 2500 | [35] |
| | roots | | | 620 | |
| *Baccharis articulata* (Lam.) Pers. | aerial parts | essential oil | *Staphylococcus aureus* (ATCC 65380) | 2500 | [36] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | 2500 | |
| | | | *Escherichia coli* (ATCC 11103) | 2500 | |
| *Baccharis crispa* Spreng.* | leaves | essential oil | *Escherichia coli* (ETEC 5041-1) | 600 | [26] |
| *Baccharis dracunculifolia* DC | leaves | methanol frac. | *Staphylococcus aureus* (ATCC 25923) | ND | [33] |
| | | methanol | | 2500 | |
| | NS | essential oil | *Escherichia coli* (ATCC 25922) | ND | [37] |
| *Baccharis dracunculifolia* DC | NS | essential oil | *Staphylococcus aureus* (ATCC 25923) | ND | [37] |
| *Baccharis dracunculifolia* DC | leaves | essential oil | *Staphylococcus aureus* (MRSA ATCC 43300) | ND | [38] |
| *Bixa orellana* L. | stem | ethanol | *Staphylococcus aureus* (ATCC 12228) | 34710 | [39] |
| | stem | | *Pseudomonas aeruginosa* (ATCC 27853) | 17770 | |
| | roots | | *Staphylococcus aureus* (ATCC 12228) | 14090 | |
| | roots | | *Pseudomonas aeruginosa* (ATCC 27854) | 75060 | |
| | leaves | | *Staphylococcus aureus* (ATCC 12228) | 18880 | |
| | leaves | | *Pseudomonas aeruginosa* (ATCC 27855) | 75540 | |
| | stem | | *Staphylococcus aureus* (ATCC 12228) | 1530 | |
| | stem | | *Pseudomonas aeruginosa* (ATCC 27856) | 4500 | |
| | roots | | *Staphylococcus aureus* (ATCC 12228) | 310 | |
| | roots | | *Pseudomonas aeruginosa* (ATCC 27857) | 250 | |
| | leaves | | *Staphylococcus aureus* (ATCC 12228) | 1880 | |
| *Bixa orellana* L. | leaves | ethanol | *Pseudomonas aeruginosa* (ATCC 27858) | 660 | [39] [39] |
| | | | *Mycobacterium tuberculosis* (NS) | 300 | |
| | roots | | *Mycobacterium tuberculosis* (NS) | 500 | |
| | stem | | | 200 | |
| *Buchenavia tetraphylla* (Aubl.) R. A. Howard | leaves | ethanol (70%) | *Staphylococcus aureus* (UFPEDA02) | 780 | [40] |
| | | cyclohexane frac. | *Staphylococcus aureus* (UFPEDA02) | 1560 | |
| | | ethyl acetate frac. | *Staphylococcus aureus* (UFPEDA02) | 3130 | |
| | | butanol soluble frac. | *Staphylococcus aureus* (UFPEDA02) | 3130 | |
| | | butanol non-soluble frac. | *Staphylococcus aureus* (UFPEDA02) | 6250 | |
| | | ethanol (70%) cyclohexane/ethyl acetate frac. | *Enterococcus faecalis* (UFPEDA138) | 25000 | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| | | butanol soluble frac. | *Enterococcus faecalis* (UFPEDA138) | 12500 | |
| | | butanol non-soluble frac. | *Enterococcus faecalis* (UFPEDA138) | 25000 | |
| | | ethanol (70%) | *Escherichia coli* (UFPEDA224) | 6250 | |
| *Buchenavia tetraphylla* (Aubl.) R. A. Howard | leaves | cyclohexane frac. | *Escherichia coli* (UFPEDA224) | 3130 | [40] |
| | | ethyl acetate frac. | *Escherichia coli (UFPEDA224)* | 6250 | |
| | | butanol soluble frac. | *Escherichia coli (UFPEDA224)* | 3130 | |
| | | butanol non-soluble frac. | *Escherichia coli* (UFPEDA224) | 12500 | |
| | | ethanol (70%) | *Pseudomonas aeruginosa* (UFPEDA416) | 200 | |
| | | cyclohexane frac. | *Pseudomonas aeruginosa* (UFPEDA416) | 200 | |
| | | ethyl acetate frac. | *Pseudomonas aeruginosa* (UFPEDA416) | 200 | |
| | | butanol soluble frac. | *Pseudomonas aeruginosa* (UFPEDA416) | 200 | |
| | | butanol non-soluble frac. | *Pseudomonas aeruginosa* (UFPEDA416) | 780 | |
| *Byrsonima crassifolia* (L.) Kunth* | leaves | methanol | *Staphylococcus aureus* (ATCC 25923) | 250 | [41] |
| *Byrsonima intermedia* A. Juss. | leaves | aqueous | *Staphylococcus aureus* (ATCC 25923) | ND | [42] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |
| | | methanol | *Escherichia coli* (ATCC 25922) | 500 | [43] |
| *Byrsonima intermedia* A. Juss | leaves | methanol | *Staphylococcus aureus* (ATCC 25923) | 250 | [43] |
| *Calea mediterranea* (Vell.) Pruski* | flowers | dichloromethane | *Staphylococcus aureus* (ATCC 25213) | ND | [44] |
| | leaves, flowers | | *Staphylococcus aureus* (field strain) | | |
| *Calophyllum brasiliense* Cambess. | stem barks | ethyl acetate | *Staphylococcus aureus* (ATCC 25923) | 1000 | [45] |
| *Campomanesia eugenioides* (Cambess.) D.Legrand ex Landrum | leaves | aqueous, water/alcohol (50%) | *Staphylococcus aureus* (ATCC 25923) | 250 | [46] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| *Caraipa grandifolia* Mart. | leaves | organic | *Staphylococcus aureus* (ATCC 29213) | 180 | [47] |
| | | | *Enterococcus faecalis* (ATCC 29212) | >200 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | >200 | |
| | | | *Escherichia coli* (ATCC 25922) | >200 | |
| *Chaptalia nutans* (L.) Polak | roots | ethyl acetate frac. | *Staphylococcus aureus* (ATCC 25923) | 250 | [48] |
| | roots | hexane, hexane/ethyl acetate, ethyl acetate/methanol, methanol frac. | | >1000 | |
| *Chromolaena laevigata* (Lam.) R. M. King & H. Rob. | capitula flowering stage | essential oil | *Staphylococcus aureus* (ATCC 29213) | 500 | [49] |
| *Chromolaena laevigata* (Lam.) R. M. King & H. Rob. | stems flowering stage | essential oil | *Staphylococcus aureus* (ATCC 29213) | 125 | [49] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| | leaves flowering stage | | | 62.5 | |
| | cypselas at fruiting stage | | | 125 | |
| | stems at fruiting stage | | | 62,5 | |
| | leaves at fruiting stage | | | 62,5 | |
| | capitula at flowering stage | | *Pseudomonas aeruginosa* (ATCC 9027) | 1500 | |
| | stems at flowering stage | | | 500 | |
| | leaves at flowering stage | | | 500 | |
| | cypselas at fruiting stage | | | 750 | |
| | stems at fruiting stage | | | 500 | |
| | leaves at fruiting stage | | | 500 | |
| | capitula at flowering stage | | *Escherichia coli* (ATCC 8739) | 1500 | |
| | stems at flowering stage | | | 500 | |
| *Chromolaena laevigata* (Lam.) R. M. King & H. Rob. | leaves at flowering stage | essential oils | *Escherichia coli* (ATCC 8739) | 500 | [49] |
| | cypselas at fruiting stage | | | 750 | |
| | stems at fruting stage | | | 500 | |
| | leaves at fruting stage | | | 750 | |
| *Clusia burle-marxii* Bittrich | leaves | ethanol | *Staphylococcus aureus* (ATCC 6538) | 62.5 | [50] |
| *Clusia columnaris* Engl. | stems | organic | *Staphylococcus aureus* (ATCC 29213) | >200 | [47] |
| *Clusia columnaris* Engl. | stems | organic | *Enterococcus faecalis* (ATCC 29212) | 180 | [47] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | 140 | |
| | | | *Escherichia coli* (ATCC 25922) | >200 | |
| *Comanthera suberosa* (Giul.) L.R.Parra & Giul.* | capitulae | methanol | *Staphylococcus aureus* (ATCC 6538p) *Escherichia coli* (ATCC 11103) *Pseudomonas aeruginosa* (ATCC 27853) | 2500 | [51] |
| *Combretaceae* (not determined) | stems | organic | *Staphylococcus aureus (ATCC 29213)* | 100 | [52] |
| *Condylocarpon isthmicum* (Vell.) A. DC. | leaves | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Copaifera duckei* Dwyer* | trunks | essential oil | *Staphylococcus aureuss* (ATCC 25923) | 250 | [53] |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | 125 | |
| | | | *Enterococcus faecalis* (ATCC 29212) | 500 | |
| *Copaifera langsdorfii* Desf. | leaves | methanol frac. | *Staphylococcus aureus* (ATCC 25923) | ND | [33] |
| | | methanol | | 5000 | |
| | trunks | essential oil | | > 1000 | [53] |
| *Copaifera langsdorfii* Desf. | trunks | essential oil | *Staphylococcus aureus* (MRSA ATCC 33591) | > 1000 | [53] |
| | | | *Enterococcus faecalis* (ATCC 29212) | | |
| *Copaifera lucens* Dwyer | trunks | essential oil | *Staphylococcus aureuss* (ATCC 25923) | 125 | [53] |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | > 1000 | |
| | | | *Enterococcus faecalis* (ATCC 29212) | 1000l | [53] |
| *Copaifera martii* Hayne | trunks | essential oil | *Staphylococcus aureuss* (ATCC 25923) | 62.5 | [53] |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | | |
| | | | *Enterococcus faecalis* (ATCC 29212) | | |
| *Copaifera multijuga* Hayne | trunks | essential oil | *Staphylococcus aureuss* (ATCC 25923) | 500 | [53] |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | 125 | |
| | | | *Enterococcus faecalis* (ATCC 29212) | 250 | |
| *Copaifera paupera* (Herzog) Dwyer | trunks | essential oil | *Staphylococcus aureuss* (ATCC 25923) | 250 | [53] |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | 250 | |
| | | | *Enterococcus faecalis* (ATCC 29212) | 62.5 | |
| *Copaifera reticulate* Ducke (Acre) | trunks | essential oil | *Staphylococcus aureuss* (ATCC 25923) | 62.5 | [53] |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | 125l | |
| | | | *Enterococcus faecalis* (ATCC 29212) | 62.5 | |
| *Copaifera reticulata* Ducke (Pará) | trunks | essential oil | *Staphylococcus aureuss* (ATCC 25923) | > 1000 | [53] |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | 1000 | |
| | | | *Enterococcus faecalis* (ATCC 29212) | 250 | |
| *Copaifera* spp. | NS | commercial oil | *Staphylococcus aureus* (ATCC 25923) | ND | [27] |
| *Cordia Americana* (L.) Gottschling & J.S.Mill. | barks | aqueous, water/alcohol (50%) | *Staphylococcus aureus* (ATCC 25923) *Pseudomonas aeruginosa (*ATCC 27853) | >1000 | [46] |
| | leaves | | | | |
| *Cordia oncocalyx* Allemão* | stems | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Croton antisyphiliticus* Mart. | roots | chloroform, hexane, hexane/ethyl acetate, ethyl acetate, methanol frac. | *Escherichia coli* (ATCC 25922)<br>*Staphylococcus aureus* (ATCC 6538)<br>*Escherichia coli (*clinical isolates)<br>*Staphylococcus aureus* (clinical isolates) | 2000 | [54] |
| *Croton cajucara* Benth | leaves | essential oil | *Mycobacterium tuberculosis* (ATCC 27294) | 4.8 | [55] |
| | | | *Staphylococcus aureus* (MRSA BMB9393) | 0.02 | |
| | | | *Mycobacterium tuberculosis* (ATCC 27294) | 0.02 | |
| | | | *Staphylococcus aureus* (MRSA BMB9393) | 0.02 | |
| | | | *Mycobacterium tuberculosis* (ATCC 27294) | 4.88 | |
| | | | *Staphylococcus aureus* (MRSA-BMB9393) | 0.004 | |
| | | | *Mycobacterium tuberculosis* (ATCC 27294) | 4.88 | |
| | | | *Staphylococcus aureus* (MRSA-BMB9393) | 0.001 | |
| | | | *Mycobacterium tuberculosis* (ATCC 27294) | 4.88 | |
| *Croton campestris* A.St.-Hil. | leaves | methanol, hexane | *Staphylococus aureus* (35 SA358) | ≥1024 | [56] |
| | | | *Staphylococcus aureus* (ATCC25923) | 512 | |
| *Croton Heterocalyx* Baill. | leaves | essential oil | *Staphylococcus aureus subsp. Aureus* (ATCC 25923) | ND | [57] |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | | |
| | | | *Escherichia coli* (ATCC 25922) | | |
| *Croton urucurana* Baillon | latex | NS | *Staphylococcus aureus* (ATCC 25924) | 100 | [45] |
| | | | *Enterococcus faecalis* (ATCC 29212) | 1000 | |
| | leaves | hexane | *Enterococcus faecalis* (ATTC 29212)<br>*Staphylococcus aureus* (ATTC 25923)<br>*Escherichia coli* (ATTC 25922)<br>*Pseudomonas aeruginosa* (ATTC 27853) | ND | [58] |
| | | dichloromethane | | | |
| | | ethyl acetate | | | |
| | | ethanol (75%) | | | |
| | barks | hexane | | | |
| *Croton urucurana* Baillon | barks | dichloromethane | *Enterococcus faecalis* (ATTC 29212)<br>*Staphylococcus aureus* (ATTC 25923)<br>*Escherichia coli* (ATTC 25922)<br>*Pseudomonas aeruginosa* (ATTC 27853) | ND | [58] |
| | | chloroform | | | |
| | | ethyl acetate | | | |
| | | ethanol (75%) | | | |
| | | ethanol | *Enterococcus faecalis* (ATCC 29212) | 500 | |
| | | chloroform | | | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| | | ethanol | *Staphylococcus aureus* (ATCC 25923) | 500 | |
| | | chloroform | | 100 | |
| | | ethanol | *Escherichia coli* (ATCC 25922) | 250 | |
| | | chloroform | | | |
| | | ethanol | *Pseudomonas aeruginosa* (ATCC 27855) | 250 | |
| *Croton urucurana* Baillon | barks | chloroform | *Pseudomonas aeruginosa* (ATCC 27855) | 250 | [58] |
| | NS | latex in nature | *Enterococcus faecalis* (ATCC 29212) | 250 | [58] |
| | | latex dried | | 125 | |
| | | latex in nature | *Staphylococcus aureus* (ATCC 25923) | 250 | |
| | | latex dried | | | |
| | | latex in nature | *Escherichia coli* (ATCC 25922) | 250 | |
| | | latex dried | | 125 | |
| | | latex in nature | *Pseudomonas aeruginosa* (ATCC 27855) | 125 | |
| *Croton urucurana* Baillon | NS | latex dried | *Pseudomonas aeruginosa* (ATCC 27855) | 125 | [58] |
| *Cupania oblongifolia* Mart. | stems | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| | leaves | | | | |
| *Cupania platycarpa* Radlk. | stems | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| | stem barks | | | | |
| *Curatella americana* Linn. | barks | cachaça (Brazilian rum) | *Staphylococcus aureus* (ATCC 25923) | 500 | [31] |
| | barks | cachaça (Brazilian rum) | *Escherichia coli* (ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | 1000 | [31] |
| | stem barks | ethanol | *Staphylococcus aureus* (ATCC 6538) | ND | [59] |
| *Cyperus articulatus* L. | roots | essential oil | *Escherichia coli* (ETEC TR 441), (EIEC 240-1) | 1000 | [26] |
| | | | *Escherichia coli* (EPEC 0031-2), (STEC 0157) | 800 | |
| | | | *Escherichia coli* (EPEC 0119) | 700 | |
| *Cyperus rotundus* L. | roots | essential oil | *Escherichia coli* (ETEC TR 441) | 1000 | [26] |
| *Ditassa crassifolia* Decne. | leaves | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Eclipta prostrata (L.)* L.* | aerial parts | ethanol | *Staphylococcus aureus* (ATCC 25985) | 1000 | [60] |
| *Elionurus muticus* (Spreng.) Kuntze | aerial parts (collection period: winter, spring, summer, autumn) | ethanol | *Escherichia coli* (ATCC 25922) | >2000 | [61] |
| | aerial parts (collection period: winter, spring, summer) | | *Pseudomonas aeruginosa* (ATCC 27853) | 2000 | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| | aerial parts (collection period: winter, summer) | | | 1000 | |
| | aerial parts (collection period: winter, summer) | | *Staphylococcus aureus* (ATCC 25923) | 2000 | |
| | aerial parts (collection period:autumn) | | | 1000 | |
| | aerial parts (collection period: spring) | | | 500 | |
| *Elionurus muticus* (Spreng.) Kuntze | aerial parts (collection period: winter, spring, summer, autumn) | essential oils | *Escherichia coli* (ATCC 25922) | 2000 | [61] |
| | aerial parts (collection period: winter, summer, autumn) | | *Staphylococcus aureus* (ATCC 25923) | 2000 | |
| | aerial parts (collection period: spring) | | *Staphylococcus aureus* (ATCC 25923) | 500 | |
| *Eriocaulon ligulatum* (Vell.) L.B.Sm. | capitulae | methanol | *Staphylococcus aureus* (ATCC 6538p)<br>*Escherichia coli* (ATCC 11103)<br>*Pseudomonas aeruginosa* (ATCC 27853) | 2500 | [51] |
| *Erythrina speciosa* Andrews | stems | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | 500 | [62] |
| | | | *Pseudomonas aeruginosa* (ATCC 15443) | > 1000 | |
| | aerial parts | | *Staphylococcus aureus* (ATCC 25923) | 500 | [63] |
| | | | *Pseudomonas aeruginosa* (ATCC 15442) | >1000 | |
| *Erythrina verna* Vell.* | stem barks | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Erythroxylum suberosum* St. Hil. | stem barks | ethanol | *Enterococcus faecalis* (ATCC29218) | >1000 | [64] |
| *Erythroxylum suberosum* St. Hil.. | stem barks | hexane frac. | *Enterococcus faecalis* (ATCC29218) | >1000 | [64] |
| | | dichloromethane frac. | | >1000 | |
| | | ethyl acetate frac. | | >1000 | |
| | | methanol (90%) frac. | | >1000 | |
| | | ethanol | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | | hexane frac. | | >1000 | |
| | | dichloromethane frac. | | >1000 | |
| | | ethyl acetate frac. | | >1000 | |
| | | methanol (90%) frac. | | >1000 | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| | | ethanol | *Staphylococcus aureus* (ATCC 25923) | 250 | |
| | | hexane frac. | | >1000 | |
| | | dichloromethane frac. | | >1000 | |
| *Erythroxylum suberosum* St. Hil. | stem barks | ethyl acetate frac. | *Staphylococcus aureus* (ATCC 25923) | 250 | [64] |
| *Eugenia astringens* Cambess.* | leaves | essential oil | *Staphylococcus aureus* (ATCC 25923) | 119.2 | [65] |
| | | | *Escherichia coli* (ATCC 25922) | 477 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | 477 | |
| *Eugenia beaurepaireana* (Kiaersk.) D.Legrand | leaves | essential oil | *Staphylococcus aureus* (ATCC 25923) | 1110 | [65] |
| | | | *Escherichia coli* (ATCC 25922) | 556.6 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | 278.3 | |
| *Eugenia brasiliensis* Lam. | leaves | essential oil | *Staphylococcus aureus* (ATCC 25923) | 156.2 | [65] |
| | | | *Escherichia coli* (ATCC 25922) | 624.9 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | 624.9 | |
| *Eugenia mansoi* O.Berg* | leaves | acetone | *Mycobacterium tuberculosis* (H37Rv ATCC 27294) | 200 | [66] |
| | | chloroform | | 200 | |
| | | acetone | | 100 | |
| | | chloroform | | 100 | |
| *Eugenia uniflora* L. | leaves | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | 250 | [62] |
| | | | *Pseudomonas aeruginosa* (ATCC 15443) | > 1000 | |
| | aerial parts | | *Staphylococcus aureus* (ATCC 25923) | 250 | [63] |
| | | | *Pseudomonas aeruginosa* (ATCC 15442) | >1000 | |
| | leaves | ethanol | *Staphylococcus aureus* (ATCC 25928) | ND | [67] |
| | | | *Escherichia coli* (ATCC 25927) | | |
| | | | *Staphylococcus aureus* (ATCC 25927) | | |
| | NS | essential oil | *Staphylococcus aureus* (ATCC 27664) | | [68] |
| | | | *Eschiericia coli* | | |
| | | | *Pseudomonas aeruginosa* | | |
| *Gnetum leyboldii* Tul. | stems | dichloromethane/methanol, aqueous | *Staphylococcus aureus* (ATCC 29213) | 40 | [52] |
| *Guatteria elliptica* R.E. Fries (Caraguatatuba) | leaves | essential oil | *Staphylococcus aureus* (ATCC 25923) | ND | [69] |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | | |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | | |
| *Guatteria elliptica* R.E. Fries (Paranapiacaba) | leaves | essential oil | *Staphylococcus aureus* (ATCC 25923) | ND | [69] |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | ND | |
| *Guatteria riparia* R.E. Fries | leaves | dichloromethane/methanol, aqueous | *Staphylococcus aureus* (ATCC 29213) | 100 | [52] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Guatteria schomburgkiana* Mart. | stems | dichloromethane/methanol, aqueous | *Staphylococcus aureus* (ATCC 29213) | 80 | [52] |
| *Guatteriopsis friesiana* W.A.Rodrigues* | leaves | essential oil | *Escherichia coli* (ATCC 11775) | 900 | [70] |
| | | | *Pseudomonas aeruginosa (ATCC 13388)* | | |
| | | | *Staphylococcus aureus (ATCC 6538)* | 125 | |
| *Guazuma ulmifolia* Lam. | stem barks | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| | barks | methanol | *Staphylococcus aureus* (ATCC 25923) | | [41] |
| | stem barks | ethanol | *Enterococcus faecalis* (ATCC29218) | >1000 | [64] |
| | | hexane frac. | *Enterococcus faecalis* (ATCC29218) | | |
| *Guazuma ulmifolia* Lam. | stem barks | dichloromethane frac. | *Enterococcus faecalis* (ATCC29218) | >1000 | [64] |
| | | ethyl acetate frac. | | 250 | |
| | | water/methanol frac. | | >1000 | |
| | | ethanol | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | | hexane frac. | | | |
| | | dichloromethane frac. | | | |
| | | ethyl acetate frac. | | | |
| | | methanol (90%)frac. | | | |
| | | ethanol | *Staphylococcus aureus* (ATCC 25923) | 125 | |
| | | hexane frac. | | >1000 | |
| | | dichloromethane frac. | | >1000 | |
| | | ethyl acetate frac. | | 125 | |
| | | methanol (90%) frac. | | 62.5 | |
| *Gymnanthemum amygdalinum* (Delile) Sch.Bip. ex Walp.* | aerial parts | ethanol | *Staphylococcus aureus* (ATCC 25985) | 10000 | [60] |
| *Haploclathra paniculata* (Mart.) Benth. | seeds | organic | *Staphylococcus aureus (*ATCC 29213) | 140 | [47] |
| | | | *Enterococcus faecalis* (ATCC 29212) *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia coli* (ATCC 25922) | >200 | |
| *Hedyosmum brasiliense* Mart. ex Miq. | leaves | essential oil | *Escherichia coli* (ATCC 25922) | 2.5 % v/v | [71] |
| | | | *Pseudomonas. aeruginosa* (ATCC 27853) | | |
| | | | *Staphylococcus aureus* (ATCC 225923) | 0.312 % v/v | |
| *Heperozygis myrthoides* (A.St.-Hil. ex Benth.) Epling | leaves | essential oil | *Staphylococus aureus* (BMB 9394) | ND | [72] |
| | | | *Escherichia coli* (ATCC 25922) | | |
| *Himatanthus obovatus* (Müll.Arg.) Woodson | leaves | cachaça (Brazilian rum) | *Staphylococcus aureus* (ATCC 25923) | 1000 | [31] |
| | | | *Escherichia coli* (ATCC 25922) | | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Himatanthus sucuuba* (Spruce ex Müll.Arg.) Woodson | roots | chloroform frac. | *Staphylococcus aureus* (ATCC 6538p) | ND | [73] |
| | | | *Escherichia coli* (ATCC 25792) | | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |
| *Hyptis crenata* Pohl. ex Benth | whole plant | hexane | *Enterococcus faecalis* (ATCC29218) | >1000 | [64] |
| *Hyptis crenata* Pohl. ex Benth | whole plant | dichloromethane frac. | *Enterococcus faecalis* (ATCC29218) | 62.5 | [64] |
| | | ethyl acetate frac. | | 31.3 | |
| | | methanol (90%) frac. | | >1000 | |
| | | hexane frac. | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | | dichloromethane frac. | | >1000 | |
| | | ethyl acetate frac. | | >1000 | |
| | | methanol (90%) frac. | | >1000 | |
| | | hexane frac. | *Staphylococcus aureus* (ATCC 25923) | 125 | |
| | | dichloromethane frac. | | 62.5 | |
| | | ethyl acetate frac. | | 125 | |
| | | methanol (90%) frac. | | >1000 | |
| | | ethanol | *Enterococcus faecalis* (ATCC29218) | 500 | |
| | | ethanol | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | | ethanol | *Staphylococcus aureus* (ATCC 25923) | 250 | |
| *Jacaranda cuspidifolia* Mart. | barks | methanol | *Staphylococcus aureus* (ATCC 13709) | 9100 | [74] |
| | | chloroform frac. | | 9300 | |
| *Jatropha elliptica* (Pohl) Oken | rhizome | ethanol | *Staphylococcus aureus* (ATCC 25923) *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Kielmeyera lathrophyton* Saddi | barks | cachaça (Brazilian rum) | *Staphylococcus aureus* (ATCC 25923) | 250 | [31] |
| | | cachaça (Brazilian rum) | *Escherichia coli* (ATCC 25922) | >1000 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |
| *Kielmeyera neglecta* Saddi | leaves | hexane, ethyl acetate, ethanol | *Staphylococcus aureus* (ATCC 29213) | ND | [75] |
| | | ethanol | *Enterococcus faecalis* (ATCC 51299) | ND | |
| | | ethyl acetate, ethanol | *Staphylococcus aureus* (ATCC 43300) | ND | |
| *Kielmeyera variabilis* Mart. & Zucc. | stems | hexane | *Staphylococcus aureus* (ATCC 25923) | 62.5 | [76] |
| | | | *Escherichia coli* (ATCC 25922) | >100 | |
| | | | *Pseudomonas aeruginosa* (ATCC 15442) | | |
| | | methanol | *Staphylococcus aureus* (ATCC 25923) | >100 | |
| | | | *Escherichia coli* (ATCC 25922) | | |
| | | | *Pseudomonas aeruginosa* (ATCC 15442) | | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Lafoensia pacari* St. Hilaire | roots | ethanol | *Staphylococus aureus* (DFUB) | ND | [25] |
| *Lafoensia pacari* St. Hilaire | leaves | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| | stem barks | | | | |
| | stem barks | hexane frac. | *Staphylococcus aureus* (resistant strains NorA) | | |
| | | chloroform frac. | | | |
| | | methanol frac. | *Staphylococcus aureus* (ATCC 25923) *Staphylococcus aureus* (resistant strains NorA) | | |
| | | ethyl acetate frac. | | | |
| | leaves | methanol | *Staphylococcus aureus* (ATCC 25923) *Pseudomonas aeruginosa* (ATCC 27853) | | [42] |
| | | water/methanol (33%) | *Pseudomona aeruginosa* (ATCC 2785) | | [77] |
| | | | *Pseudomona aeruginosa* (ATCC 2785) | | |
| | | | *Staphylococcus aureus* (ATCC 25923) | | |
| | stem barks | water-methanol (33%) | *Pseudomona aeruginosa* (ATCC 2785) *Staphylococcus aureus* (ATCC 25923) | | |
| *Lantana camara* L. | leaves | hexane frac. | *Staphylococcus aureus* (ATCC 25923) | ND | [33] |
| | | ethyl acetate frac. | | ND | |
| *Lantana camara* L. | leaves | methanol frac. | *Staphylococcus aureus* (ATCC 25923) | ND | [33] |
| | | methanol | | 1250 | |
| | roots | dichloromethane | | ND | [41] |
| *Lantana fucata* Lindl.* | leaves | hexane frac. | *Staphylococcus aureus* (ATCC 25923) | ND | [33] |
| | leaves | methanol frac. | | | |
| | leaves, stems | methanol | | | |
| | leaves, stems | hexane frac. | | | |
| | leaves, stems | methanol frac. | | | |
| | leaves | methanol | | 625 | |
| | leaves, stems | methanol | *Staphylococcus aureus* (ATCC 25923) | 1250 | |
| *Leiothix spiralis* (Bong.) Ruhland | capitulae, leaves | methanol | *Staphylococcus aureus* (ATCC 6538p) | 2500 | [51] |
| | | | *Escherichia coli* (ATCC 11103) | | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |
| | leaves | hexane, methylene chloride, methanol | *Staphylococcus aureus* (ATCC 25923) | 1000 | [78] |
| | | | *Enterococcus faecalis* (ATCC 29212) | 500 | |
| *Leiothix spiralis* (Bong.) Ruhland | leaves | hexane, methylene chloride, methanol | *Escherichia coli* (ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [78] |
| | | methanol | *Staphylococcus aureus* (ATCC 25923) | 1000 | [79] |
| | | | *Enterococcus faecalis* (ATCC 29212) | 500 | |
| | | | *Escherichia coli* (ATCC 25922) | >1000 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Lippia alba* (Mill.) N.E.Br. | leaves | essential oil | *Escherichia coli* (ETEC TR 441), (EIEC 0461-4) | 1000 | [26] |
| | | | *Escherichia coli* (STEC 2781-8) | 800 | |
| | | | *Escherichia coli* (EIEC 240-1) | 500 | |
| | | | *Escherichia coli* (STEC 0157), (EPEC 0031-2) | 400 | |
| *Lippia alba* (Mill.) N.E.Br. | leaves | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | > 1000 | [62] |
| | | | *Pseudomonas aeruginosa* (ATCC 15443) | | |
| | aerial parts | | *Staphylococcus aureus* (ATCC 25923) | >1000 | [63] |
| | | | *Pseudomonas aeruginosa* (ATCC 15442) | | |
| | | essential oil | *Staphylococcus aureus* (ATCC 25923) | ND | [80] |
| | | | *Staphylococcus aureus* (MRSA BMB9393) | ND | [80] |
| *Luehea paniculata* Mart. & Zucc. | barks | aqueous, water-alcohol (50%) | *Staphylococcus aureus* (ATCC 25923) | 125-250 | [46] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| *Lygodium venustum* SW | leaves | ethyl acetate frac. | *Staphylococcus aureus* (multiresistant clinical isolates 358) *Escherichia coli* (27) | ≥1024 | [81] |
| *Marsdenia altissima* (Jacq.) Dugand | leaves | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Mikania glomerata* Spreng. | leaves | essential oil | *Escherichia coli* (all serothypes) | >1000 | [26] |
| | | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | 500 | [62] |
| | | ethanol (90%) | *Pseudomonas aeruginosa* (ATCC 15443) | > 1000 | |
| | aerial parts | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | 500 | [63] |
| | | ethanol (90%) | *Pseudomonas aeruginosa* (ATCC 15442) | >1000 | |
| *Mikania hirsutíssima* DC. | leaves | methanol | *Staphylococcus aureus* (ATCC 25923) | 2500 | [33] |
| | aerial parts | ethanol | *Staphylococcus aureus* (ATCC 25985) | 5000 | [60] |
| *Mikania laevigata* Sch. Bip. Ex Baker | leaves | essential oil | *Escherichia coli* (EIEC 1381-7) | 900 | [26] |
| | | | *Escherichia coli* (STEC 2781-8), (EIEC 240-1) | 600 | |
| *Mikania laevigata* Sch. Bip. Ex Baker | leaves | essential oil | *Escherichia coli* (ETEC 5041-1), (EPEC 0031-2) | 500 | [26] |
| | | | *Escherichia coli* (STEC 0157) | 300 | |
| *Mitracarpus frigidus* (Willd. ex Roem. & Schult.) K.Schum. | aerial parts | hexane frac. | *Enterococcus faecalis* | 313 | [82] |
| | | dichloromethane frac. | *Staphylococcus aureus* | 313 | |
| | | | *Escherichia coli* | 313 | |
| *Mora paraensis* (Ducke) Ducke | leaves, stems | dichloromethane/methanol, aqueous | *Staphylococcus aureus* (ATCC 29216) | ≥200 | [52] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Myrcia ovata* Cambess | leaves | essential oil | *Enterococcus faecalis* (ATCC 29212) | 0.031% | [83] |
| | | | *Escherichia coli* (ATCC 26992) | 1% | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | > 1% | |
| | | | *Staphylococcus aureus* (ATCC 25923) | 0.25 | |
| *Myrcianthes cisplatensis* (Cambess.) O.Berg. | leaves | chloroform | *Mycobacterium tuberculosis* (H37Rv ATCC 27294) | 100 | [66] |
| | | acetone | | 200 | |
| *Myrsine parvifolia* A.DC.* | aerial parts | dichloromethane/methanol, aqueous | *Enterococcus faecalis* (ATCC 29214) | 30 | [52] |
| *Ocimum carnosum* (Spreng.) Link & Otto ex Benth.* | aerial parts | essential oil | *Staphylococcus aureus* (ATCC 25923) | ND | [43] |
| *Ocimum carnosum* (Spreng.) Link & Otto ex Benth.* | aerial parts | essential oil | *Escherichia coli* (ATCC 25922) | ND | [44] |
| | leaves | | *Staphylococus aureus* (BMB 9393) | | [71] |
| | | | *Escherichia coli* | | [72] |
| *Ocotea* sp | aerial organs | organic | *Staphylococcus aureus* (ATCC 29213) | 180 | [52] |
| *Palicourea guianensis* Aubl. | aerial organs | organic | *Staphylococcus aureus* (ATCC 29213) | 40 | [52] |
| | | | *Enterococcus faecalis* (ATCC 29212) | | |
| | | dichloromethane/methanol, aqueous | *Enterococcus faecalis* (ATCC 29216) | | |
| *Paullinia elegans* Cambess. | leaves | ethanol (70%) | *Mycobacterium tuberculosis* H37Rv (ATCC 27294) | 200 | [66] |
| | | acetone | | | |
| | | chloroform | | | |
| *Petunia* sp. | aerial parts | acetone | *Mycobacterium tuberculosis* H37Rv (ATCC 27294) | 50 | [66] |
| *Petunia* sp. | aerial parts | chloroform | *Mycobacterium tuberculosis* H37Rv (ATCC 27294) | 50 | [66] |
| *Pffafia glomerata* (spreng.) Pedersen | Aerial parts | ethanol | *Staphylococcus aureus* (ATCC 25985) | 10000 | [60] |
| *Phyllanthus tenellus* Roxb. | leaves | methanol frac. | *Staphylococcus aureus* (ATCC 25923) | ND | [33] |
| | | methanol | | 625 | |
| *Pimenta pseudocaryophyllus* (Gomes) Landrum (Cardoso Island) | leaves | essential oil | *Escherichia coli* (ATCC 8739) | 48 µL/L | [84] |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | 48 µL/L | |
| | | | *Staphylococcus aureus* (ATCC 6538) | 0.047 µL/L | |
| *Pimenta pseudocaryophyllus* (Gomes) Landrum (Paranapiacaba) | leaves | essential oil | *Escherichia coli* (ATCC 8739) | 48 µL/L | [84] |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | 48 µL/L | |
| | | | *Staphylococcus aureus* (ATCC 6538) | 1.5 µL/L | |
| *Piper abutilodes* Kunth | leaves | essential oil | *Escherichia coli* (STEC 0157) | 700 | [26] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Piper aduncum* L. | leaves | essential oil | *Escherichia coli* (STEC 2781-8) | 1000 | [26] |
| | | essential oil | *Escherichia coli (*EPEC 0031-2), (EIEC 1381-7),( EIEC 0461-4), EIEC 240-1) | 900 | |
| *Piper aduncum* L. | leaves | essential oil | *Escherichia coli* (STEC 0157) | 500 | [26] |
| *Piper arboreum* Aubl. | aerial parts | dichloromethane/methanol, aqueous | *Staphylococcus aureus* (ATCC 29213) | 60 | [52] |
| | | | *Enterococcus faecalis* (ATCC 29212) | 80 | |
| *Piper gaudichaudianum* Kunth. | leaves | aqueous | *Staphylococcus aureus* (ATCC 25923) *Escherichia coli* (ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [85] |
| | | crude | *Staphylococcus aureus* (ATCC 25923) | 250 | |
| | | crude | *Escherichia coli* (ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | | hexane frac. | *Staphylococcus aureus* (ATCC 25923) | 1000 | |
| *Piper gaudichaudianum* Kunth. | leaves | hexane, dichloromethane, ethyl acetate, dichloro-methane/ethyl acetate frac. | *Escherichia coli* (ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [85] |
| | | dichloromethane, ethyl acetate frac. | *Staphylococcus aureus* (ATCC 25923) | 62.5 | |
| | | Dichloromethane,ethyl acetate frac. | *Staphylococcus aureus* (ATCC 25923) | 125 | |
| | | ethyl acetate, methanol frac. | *Staphylococcus aureus* (ATCC 25923) *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia coli* (ATCC 25922) | >1000 | |
| *Piper marginatum* Jacq. | leaves | essential oil | *Escherichia coli* (EPEC 0031-2) | 900 | [26] |
| | | | *Escherichia coli* (STEC 0157) | 700 | |
| *Piper miquelianum* C.DC.* | roots, aerial parts | ethanol | *Enterococcus faecium* (ATCC 6569) | ND | [86] |
| | leaves, fruits, roots | essential oil | *Staphylococcus aureus* (ATCC 25923) | ND | |
| | leaves | essential oil | *Staphylococcus aureus* (ATCC 25923) | 9 | [87] |
| | | | *Pseudomonas aeruginosa* (27853) | ND | |
| | | | *Escherichia coli* (ATCC 25922) | | |
| *Piper miquelianum* C.DC.* | fruits | essential oil | *Staphylococcus aureus* (ATCC 25923) | 5 | [87] |
| | | | *Pseudomonas aeruginosa* (27853) | ND | |
| | | | *Escherichia coli* (ATCC 25922) | | |
| | roots | essential oil | *Staphylococcus aureus* (ATCC 25923) | 5 | |
| | | | *S. epidermides* (ATCC 12228) | 5 | |
| | | | *Pseudomonas aeruginosa* (27853) | ND | |
| | | | *Escherichia coli* (ATCC 25922) | | |
| *Piper mollicomum* Kunth. | leaves | essential oil | *Escherichia coli (STEC 0157)* | 1000 | [26] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Piper ovatum* Vahl. | leaves, root, barks | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia colli* (ATCC 25922) | >1000 | [88] |
| *Piper regnelli* (Miq.) C.DC. | leaves | essential oil | *Escherichia coli* (STEC 0157) | 1000 | [26] |
| | | | *Escherichia coli* (EPEC 0031-2) | 300 | |
| *Piper regnelli* (Miq.) C.DC. | leaves | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | 7.8 | [62] |
| | | | *Pseudomonas aeruginosa* (ATCC 15443) | 250 | |
| | aerial parts | | *Staphylococcus aureus* (ATCC 25923) | 7.8 | [63] |
| | | | *Pseudomonas aeruginosa* (ATCC 15442) | 250 | |
| *Piper regnellii (*Miq.) C. DC. var. *pallescens* (C. DC.) Yunck | leaves | aqueus | *Staphylococcus aureus* (MRSA ATCC 33591), (MRSA ATCC 4300) | 16 | [89] |
| | | ethyl acetate | *Staphylococcus aureus* (MSSA ATCC2921), (MSSA ATCC25923) | | |
| *Plathymenia reticulata* Benth. | barkss | cachaça (Brazilian rum) | *Staphylococcus aureus* (ATCC 25923) *Escherichia coli (*ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [31] |
| *Plenckia populnea* Reissek* | barks, heartwood | chloroform | *Staphylococcus aureus* (ATCC 21027) | ND | [90] |
| | branches barks | methanol | *Pseudomonas aeruginosa* (ATCC 15442) | 2000 | |
| | roots | methanol | | 1000 | |
| *Plenckia populnea* Reissek* | branches barks | methanol | *Staphylococcus aureus* (MARSA) | 2000 | [90] |
| | | butanol | *Staphylococcus aureus* (ATCC 21027) | 500 | |
| | | ethyl acetate | | | |
| | | methanol | | | |
| *Plinia cauliflora* (Mart.) Kausel | leaves | water-alcohol | *Staphylococcus aureus* (ATCC 25923) | 1250 | [91] |
| | | aqueous frac. | | | |
| *Plinia cauliflora* (Mart.) Kausel | leaves | ethyl acetate frac. | *Staphylococcus aureus* (ATCC 25923) | 1250 | [91] |
| *Poincianella* pyramidalis (Tul.) L.P.Queiroz* | leaves | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Poiretia bahiana* Müll. Hal. | aerial parts, fruits | essential oil | *Escherichia coli* (ATTC 25922) | 910 | [92] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | ND | |
| | | | *Staphylococcus aureus* (ATCC 25923) | 36300 | |
| | | | *Staphylococcus aureus* (MRSA ATCC 33591) | 36300 | |
| *Protium heptaphyllum* (Aubl.) March. | stem barks | ethanol | *Enterococcus faecalis* (ATCC29218) | >1000 | [64] |
| | | hexane frac. | | | |
| | | dichloromethane frac. | | | |
| | | ethyl acetate frac. | | | |
| | | methanol (90%) frac. | | | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| | | ethanol | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | | hexane frac. | | | |
| | | dichloromethane frac. | | | |
| *Protium heptaphyllum* (Aubl.) March. | stem barks | ethyl acetate frac. | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [64] |
| | | methanol (90%) frac. | | | |
| | | ethanol | *Staphylococcus aureus* (ATCC 25923) | 125 | |
| | | hexane frac. | | >1000 | |
| *Protium heptaphyllum* (Aubl.) March. | stem bark | ethyl acetate frac. | *Staphylococcus aureus (ATCC 25923)* | 125 | [64] |
| | | methanol (90%) frac. | | 62.5 | |
| *Psidium densicomum* Mart. Ex DC. | leaves, flowers | dichloromethane/methanol, aqueous | *Staphylococcus aureus* (ATCC 29213) | 40 | [52] |
| | | | *Enterococcus faecalis* (ATCC 29212) | 60 | |
| | aerial parts | | *Staphylococcus aureus* (ATCC 29213) | | |
| | | | *Enterococcus faecalis* (ATCC 29212) | | |
| | leaves, flowers | | *Staphylococcus aureus* (ATCC 29213) | 40 | |
| *Psidium densicomum* Mart. Ex DC. | leaves, flowers | dichloromethane/methanol, aqueous | *Enterococcus faecalis* (ATCC 29214) | 60 | [52] |
| | | | *Staphylococcus aureus* (ATCC 29213) | 40 | |
| | aerial parts | dichloromethane/methanol, aqueous | *Enterococcus faecalis* (ATCC 29215) | 60 | |
| | | | *Staphylococcus aureus* (ATCC 29214) | | |
| *Psidium guineense* Swartz | leaves | aqueou | *Staphylococcus aureus* (MRSA ATCC 25923) | 250 | [93] |
| *Pterodon emarginatus* Vogel | barks | cachaça (Brazilian rum) | *Staphylococcus aureus* (ATCC 25923), *Escherichia coli* (ATCC 25922) *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [31] |
| *Pterodon emarginatus* Vogel* | leaves | essential oil | *Staphylococcus aureus* (2592) | 50000 | [94] |
| | | | *Escherichia coli* (ATCC 8739) | >50000 | |
| | | | *Escherichia coli* (ATCC 11225) | | |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | | |
| | stem | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Qualea grandiflora* Mart. | leaves | cachaça (Brazilian rum) | *Staphylococcus aureus* (ATCC 25923) | >1000 | [31] |
| *Qualea grandiflora* Mart. | leaves | cachaça (Brazilian rum) | *Escherichia coli* (ATCC 25922) | >1000 | [31] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |
| | barks | methanol | *Staphylococcus aureus* (ATCC 25923) | ND | [42] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |
| | stem barks | ethanol | *Staphylococcus aureus* (ATCC 6538) | | [59] |
| | | | *Pseudomonas aeruginosa* (B 8) | | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Rollina sericea* (R.E.F.) R.E.Fr. | leaves | essential oil | *Staphylococcus aureus* (ATCC 6538) | ND | [95] |
| | | | *Escherichia coli* (ATCC 8739) | | |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | | |
| *Roupala montana* var. *brasil-iensis (*Klotzsch) K.S.Edwards* | stem barks | ethanol | *Enterococcus faecalis* (ATCC29218) | >1000 | [64] |
| | | hexane frac. | | | |
| | | dichloromethane frac. | | 62.5 | |
| | | ethyl acetate frac. | | >1000 | |
| *Roupala montana* var. *brasil-iensis* (Klotzsch) K.S.Edwards* | stem barks | methanol (90%) frac. | *Enterococcus faecalis* (ATCC29218) | | [64] |
| | | ethanol | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | | hexane frac. | | | |
| | | dichloromethane frac. | | | |
| | | ethyl acetate frac. | | | |
| | | methanol (90%) frac. | | | |
| | | ethanol | *Staphylococcus aureus* (ATCC 25923) | 125 | |
| | | hexane frac. | | 125 | |
| | | dichloromethane frac. | | 15.6 | |
| | | ethyl acetate frac. | | 125 | |
| | | methanol (90%) frac. | | 125 | |
| *Roupala* sp | stems | aqueous | *Staphylococcus aureus* (ATCC 29213) | 60 | [52] |
| | | organic | *Enterococcus faecalis* (ATCC 29212) | 100 | |
| *Ruizterania retusa* (Spruce ex Warm.) Marc.-Berti | wood | dichloromethane/methanol, aqueous | *Staphylococcus aureus* (ATCC 29213) | 140 | [52] |
| *Ruprechtia laxiflora* Meisn. | leaves | ethanol (70%) | *Mycobacterium tuberculosis* (H37Rv ATCC 27294) | 200 | [66] |
| *Sacoila lanceolata* (Aubl.) Garay* | aerial parts | ethanol | *Staphylococcus aureus* (ATCC 25985) | 10000 | [60] |
| *Sambucus canadensis* L. | leaves | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | > 1000 | [62] |
| | leaves | ethanol (90%) | *Pseudomonas aeruginosa* (ATCC 15443) | | |
| | aerial parts | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | | [63] |
| | aerial parts | ethanol (90%) | *Pseudomonas aeruginosa* (ATCC 15442) | | |
| *Schinus lentiscifolius* Marchand | aerial parts | aqueous | *Pseudomonas aeruginosa* (ATCC 17759) | 250 | [96] |
| | | | *Staphylococcus aureus* (ATCC 6538p) *Escherichia coli* (ATCC 25922) | 125 | |
| | | methanol | *Staphylococcus aureus* (ATCC 6538p) *Pseudomonas aeruginosa* (ATCC 17759) | 250 | |
| | | | *Staphylococcus epidermidis* (ATCC 12228) *Escherichia coli* (ATCC 25922) | 500 | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| | | hexane frac. | *Staphylococcus aureus* (ATCC 6538p) *Escherichia coli* (ATCC 25922) | >500 | |
| *Schinus lentiscifolius* Marchand | aerial parts | hexane frac. | *Pseudomonas aeruginosa* (ATCC 17759) | 500 | [96] |
| | | ethyl acetate frac. | *Staphylococcus aureus* (ATCC 6538p) | 125 | |
| | | | *Pseudomonas aeruginosa* (ATCC 17759) | 250 | |
| | | | *Escherichia coli* (ATCC 25922) | | |
| | | butanol frac. | *Staphylococcus aureus* (ATCC 6538p) | 250 | |
| | | | *Pseudomonas aeruginosa* (ATCC 17759) | | |
| | | | *Escherichia coli* (ATCC 25922) | | |
| *Schinus terebinthifolius* Raddi | wood barks | ethanol | *Staphylococus aureus* (DFUB) | ND | [25] |
| | stem barks | ethanol | *Staphylococcus aureus* (resistant strain Nor A) | | [27] |
| | | hexane frac. | *Staphylococcus aureus* (ATCC 25923), (resistant strains NorA, MsrA) | | |
| | | chloroform frac. | *Staphylococcus* aureus (resistant strains NorA, MsrA) | | |
| | | ethyl acetate frac. | *Staphylococcus aureus* (resistant strains NorA, MsrA) | | |
| | | water/methanol frac. | *Staphylococcus aureus* (resistant strains NorA, MsrA) | | |
| *Schinus terebinthifolius* Raddi | leaves | ethanol | *Staphylococcus aureus* (ATCC 25923) | ND | [27] |
| | barks | aqueous, water-alcohol (50%) | *Staphylococcus aureus* (ATCC 25923) | 250 | [46] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | |
| | NS | ethanol | *Enterococcus faecalis* (ATCC 29212) | ND | [96] [97] |
| *Scoparia* sp | aerial parts | ethanol | *Staphylococcus aureus* (ATCC 25985) | 2000 | [60] |
| *Scutia buxifolia* Reissek | leaves | dichloromethane/ethanol | *Mycobacterium tuberculosis* (H37Rv ATCC 25618) | 312.5 | [98] |
| | | | | 625.00 | |
| | | | | 156.25 | |
| | | | | 312.5 | |
| | | | | 312.5 | |
| | | | | 156.25 | |
| | | | | 625 | |
| *Serjania lethalis* A. St.-Hil | Stem | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Serjania lethalis* A. St.-Hil | stems | chloroform frac. | *Staphylococcus aureus* (ATCC 25923) *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| | | ethyl acetate frac. | | | |
| | | water/methanol frac. | | | |
| | leaves | ethanol | | | |
| | | hexane frac. | | | |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| | | chloroform frac. | | | |
| | | ethyl acetate frac. | | | |
| *Sideroxylon obtusifolium* (Roem. & Schult.) T.D.Penn.* | stem barks | ethyl acetate frac. | *Staphylococcus aureus* (MSSA ATCC 29213),( MRSA ATCC 33591) | 256-512 | [99] |
| *Simarouba amara* Aubl. | stems | ethanol | *Staphylococcus aureus* (MsrA RN4220) | ND | [27] |
| *Simarouba versicolor* A. St. Hil | stem barks | ethanol | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [64] |
| | | hexane frac. | | | |
| *Simarouba versicolor* A. St. Hil | stem barks | dichloromethane frac. | *Pseudomonas aeruginosa* (ATCC 27853) | >1000 | [64] |
| | | ethyl acetate frac. | | >1000 | |
| | | water/methanol frac. | | >1000 | |
| | | ethanol | *Staphylococcus aureus* (ATCC 25923) | 125 | |
| | | hexane frac. | | >1000 | |
| | | dichloromethane frac. | | >1000 | |
| | | ethyl acetate frac. | | 125 | |
| | | methanol (90%) frac. | | 62.5 | |
| | | ethanol | *Enterococcus faecalis* (ATCC29218) | >1000 | |
| | | hexane frac. | | | |
| | | dichloromethane frac. | | | |
| | | ethyl acetate frac. | | 250 | |
| | | methanol (90%) frac. | | >1000 | |
| *Smilax rufescens* Griseb. | aerial parts | organic | *Enterococcus faecalis* (ATCC 29212) | 80 | [52] |
| *Solanum palinacanthum* Dunal | aerial parts | methanol | *Staphylococcus aureus* (ATCC 25923) | 2500 | [100] |
| *Solidago chilensis* Meyen | NS | alcohol | *Pseudomonas aeriginosa* (ATCC 27853) | 400 | [101] |
| *Solidago chilens* Meyen* | aerial parts | essential oil | *Staphylococcus aureus* (ATCC 6538p) *Escherichia coli* (ATCC 25792) *Pseudomonas aeruginosa* (ATCC 27853) | 1250 | [102] |
| *Spilanthes acmella* (L.) Murr. | leaves | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | > 1000 | [62] |
| | | | *Pseudomonas aeruginosa* (ATCC 15443) | | |
| | aerial parts | | *Staphylococcus aureus* (ATCC 25923) | | [63] |
| | | | *Pseudomonas aeruginosa* (ATCC 15442) | | |
| *Stachytarpheta cayennensis* (Rich.) Vahl* | roots | butanol frac. | *Staphylococcus aureus* (ATCCC 25923) | ND | [103] |
| | | ethyl acetate frac. | *Staphylococcus aureus* (ATCCC 25923) | ND | |
| | leaves | essential oil | *Escherichia coli* (STEC 0157), (EIEC 1381-7), (EIEC 240-1) | 900 | [26] |
| | | | *Escherichia coli* (STEC 2781-8) | 700 | |
| | aerial parts | ethanol | *Staphylococcus aureus* (ATCC 25985) | 5000 | [60] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (µg/mL***) | Ref. |
|---|---|---|---|---|---|
| *Stryphnodendron pulcherrimum* (Willd.) Hochr. | stems | dichloromethane-methanol (50%), aqueous | *Enterococcus faecalis* (ATCC 29212) | 60 | [52] |
| *Tabernaemontana angulata* Mart. ex Müll. Arg. | stems | methanol/dichloromethane (50%) | *Staphylococcus aureus* (ATCC 6538) | 4000 | [104] |
| *Tachigali aurea* Tul.* | barkss | cachaça (Brazilian rum) | *Staphylococcus aureus* (ATCC 25923) | 1000 | [31] |
| | | | *Escherichia coli* (ATCC 25922) | >1000 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | | |
| | leaves | methanol | *Staphylococcus aureus* (ATCC 25923) | ND | [42] |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) | ND | |
| *Talisia esculenta* (Cambess.) Radlk. | Stem | ethanol | *Staphylococcus aureus* (resistant strains NorA, MsrA) | ND | [27] |
| *Tanacetum vulgare* L. | leaves | ethanol (90%) | *Staphylococcus aureus* (ATCC 25923) | > 1000 | [62] |
| | | | *Pseudomonas aeruginosa* (ATCC 15443) | 500 | |
| | aerial parts | | *Staphylococcus aureus* (ATCC 25923) | >1000 | [63] |
| | | | *Pseudomonas aeruginosa (ATCC 15442)* | 500 | |
| *Tillandsia streptocarpa* Baker | aerial parts | methanol | *Escherichia coli* (ATCC 25922) *Staphylococcus aureus* (ATCC 25923) *Pseudomonas aeruginosa* (ATCC15442) | 500 | [105] |
| *Tovomita aff. longifolia* (Rich.) Hochr. | leaves | organic | *Staphylococcus aureus* (ATCC 29213) | 100 | [47] |
| | | | *Enterococcus faecalis* (ATCC 29212) | 70 | |
| | | | *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia coli* (ATCC 25922) | >200 | |
| *Tovomita cf. brevistaminea* Engl. | leaves, fruits | aqueous | *Staphylococcus aureus* (ATCC 29213) *Enterococcus faecalis* (ATCC 29212) *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia coli* (ATCC 25922) | >200 | [47] |
| *Tovomita fructipendula* (Ruiz & Pav.)* | leaves | organic | *Enterococcus faecalis* (ATCC 29212) *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia coli* (ATCC 25922) | >200 | [47] |
| | | | *Staphylococcus aureus* (ATCC 29213) | 140 | |
| *Varronia curassavica* Jacq.* | leaves | carbon dioxide (10 MPa/50ºC) | *Staphylococcus aureus* (ATCC 25923) | 1000 | [106] |
| | | aqueous, ethanol (25%) | | 2000 | |
| | | carbon dioxide/ethyl acetate (5%) | | 500 | |
| *Varronia curassavica* Jacq.* | leaves | carbon dioxide (30 MPa/30ºC) | *Staphylococcus aureus* (ATCC 25923) | 375 ± 120 | [106] |
| | | carbon dioxide/ethyl acetate (5%), carbon dioxide/ethanol, ethyl acetate frac. | | 250 | |
| *Varronia curassavica* Jacq.* | leaves | ethanol (25%), aqueous, ethyl acetate, hexane | *Escherichia coli (*ATCC 25922) | 2000 | [106] |

**(Table 1) contd….**

| Plant species | Plant part | Extract type or Extraction solvent** | Microorganism | MIC (μg/mL***) | Ref. |
|---|---|---|---|---|---|
| | | carbon dioxide (10 MPa/50ºC, 30 MPa/30ºC), carbon dioxide/ethyl acetate, hexane | *Pseudomonas aeruginosa* (ATCC 27853) | >4000 | |
| | | ethyl acetate frac. | | 1500 ± 500 | |
| | | ethanol (25%), aqueous, carbon dioxide/ethanol (5%) | | 1000 | |
| | | essential oil | *Escherichia coli* (STEC 0157), (EIEC 1381-7), (EIEC 240-1) (STEC 2781-8) | >1000 | [26] |
| *Virola sebifera* Aubl.* | leavs | dichloromethane/methanol, aqueous | *Enterococcus faecalis* (ATCC 29213) | 40 | [52] |
| *Vismia guianensis* (Aubl.) Choisy | aerial parts | organic | *Staphylococcus aureus* (ATCC 29213) *Enterococcus faecalis* (ATCC 29212) *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia coli* (ATCC 25922) | >200 | [47] |
| | | aqueous | | | |
| *Vismia schultesii* N.Robson | aerial parts | aqueous | *Staphylococcus aureus (ATCC 29213), Enterococcus faecalis (ATCC 29212), Pseudomonas aeruginosa (ATCC 27853), Escherichia coli (ATCC 25922)* | >200 | [47] |
| *Vismia schultesii* N.Robson | stems | aqueous | *Staphylococcus aureus* (ATCC 29213) *Enterococcus faecalis* (ATCC 29212) *Pseudomonas aeruginosa* (ATCC 27853) *Escherichia coli* (ATCC 25922) | >200 | [47] |
| *Xylosma ciliatifolia* (Clos) Eichler | root barks | hexane, chloroform frac. | *Staphylococcus aureus* (ATCC 6538) | 250 | [107] |
| *Zanthoxylum* sp. | stems | dichloromethane/methanol (50%), aqueous | *Staphylococcus aureus* (ATCC 29213) | 60 | [52] |
| *Ziziphus joazeiro* Mart. | barks | triterpenoid frac. | *Staphylococcus aureus* (ATCC 29213), (MRSA ATCC 33591) | 128 | [108] |

selected for the studies based on their medicinal properties, which represents about half of the potential species. From the 2871 angiosperm genera accepted for Brazil [23], six were the most studied for antimicrobial activities: *Copaifera* L. (9 species), *Piper* L. (9 species), *Eugenia* L. (7 species) and *Hypericum* L. (6 species).

Successful determination of biologically active compounds from plant material is largely dependent on the type of solvent used in the extraction procedure. Good solvent properties in plant extractions include low toxicity, easy evaporation at low heat, and promotion of rapid physiologic absorption of the extract, preservative action and inability to cause the extract to complex or dissociate [110]. Eloff [111] examined several solvents for their ability to solubilise antimicrobials from plants, considering several of the factors mentioned earlier, and acetone received the highest overall rating, presenting the lowest minimum inhibitory concentration for Gram positive organisms tested and the largest number of different components and inhibitors from two plants tested. However, the author also remarks that different results may be obtained if other plants are used and a generalization cannot be made on the usefulness of acetone as the solvent of choice. The most commonly used solvents for antimicrobial activity screenings in plants are methanol and ethanol, pure or mixed with different proportions of water, considering their properties and the fact that most of the plant secondary metabolites are soluble in both solvents [110, 112]. For these reasons, the preferable extraction solvents for most of plant species (127) were ethanol or methanol.

The ideal method for screening plants for a variety of compounds is a successive exhaustive extraction with solvents of increasing polarity from a non-polar (hexane) to a more polar (methanol), or the classical method of bio-guided fractionation. In this method as soon as an activity is observed in the crude extract, it is subjected to fractionation by solvents of increasing polarity affording fractions containing mixtures of different classes of secondary metabolites [110, 113]. The fractionation also can separate compounds with selectivity for determined microorganism, as can be seen in

the case of *B. tetraphylla* where the crude hydroalcoholic presented a minimum inhibitory concentration (MIC) of 25 mg/mL against *E. faecalis* and in its *n*-butanol fraction the MIC decreased for 12.5 mg/mL [91].

The best way to compare the *in vitro* antibacterial activity of plant extracts is by their MIC values. The survey of publications shows that most of the studies with Brazilian plants used unfractionated extracts of various plant parts, and still a considerable number do not present MIC values for the crude extracts (Table **1**). Plant extracts generally present a weak antibacterial activity, with MIC values for crude extracts exceeding 100 µg/mL, and often in the mg/mL range, against nosocomial pathogens such as *S. aureus* and *P. aeruginosa* [114]. Normally, in screening studies where MIC values are lower than 100 µg/mL, the extracts are considered with a good antimicrobial activity for further studies [69, 52, 115]. Considering these values, some native species could be considered targets for the development of new antibiotics such as *P. regnelli,* with MIC of 7.8 µg/mL against *S. aureus*, *M. parvifolia* and *Virola sebifera*, with respective MIC´s of 30 and 40 µg/mL for *E. faecalis*, and *P. densicomum* and *G. leyboldii*, both with MIC's of 40 µg/mL against *S. aureus* [47, 52, 63, 62].

Although some of the studies presented interesting results, the authors usually concluded that further *in vitro* studies are still need, but in most cases no complimentary research is found. Few articles describe the identification of the main components and test them for antimicrobial activity. Pretto *et al.* [115] tested the antimicrobial activity in the extracts and fractions of different parts of *C. brasiliense* as well as of some compounds that already had been isolated from the leaves of this plant. The results suggested a synergistic effect of these compounds once some of the extracts and fractions presented lower MIC values than any of the isolated compounds.

Although several metabolite classes, including phenolic acids and polyphenols [116], phenanthrenes [117], flavonoids [118], terpenoids, [119] present in plant extracts have been described as antibacterial products, to date, none has been approved as a systemic antibacterial drug. This is in part, because the narrow spectrum of activity or their mode of action is often very specific or it can also be completely non-specific. For these reasons, the concept of antimicrobial synergy may enhance efficacy, reduce toxicity, decrease adverse side effects, increase bioavailability, lower the dose and reduce the advance of antimicrobial resistance. This approach of combining antibacterial drugs with natural product has recently become a research priority, since few articles are found dealing with this subject. In the extracts from native Brazilian plants, only the *S. rotundifolium* crude extract was evaluated in combination with conventional aminoglycoside antibiotics (gentamicin, kanamycin, amikacin and neomycin) against multidrug resistant strains of *S. aureus* and *E. coli*. The crude hydroalcoholic extract showed a low antibacterial activity with MIC value of 512 µg/mL. However, when combining the antibiotics with sub-inhibitory concentration of the extract (64 µg/mL) the MIC's from the antibiotics decreased from a range of 2500-39 µg/mL to a range of 312.5-2.4 µg/mL [91].

Several studies proposed that natural compounds in combination with antibiotics are a new strategy for developing therapies for infections caused by bacterial species and that natural plant products can potentiate the activity of antibiotics in combination [120, 121; 122; 123]. Resistant strains of *S. aureus* and *P. aeruginosa* to aminoglycosides are involved in nosocomial infections. The main resistance mechanisms to aminoglycosides are active efflux and enzymatic inactivation [122, 124]. Some plant secondary metabolites can effectively inhibit the efflux pumps involved in antibiotic resistance mechanisms [122, 125]. Understanding the synergy molecular mechanisms between plant metabolites and antibiotics is fundamental for the development of a new strategy for the treatment of infectious diseases, overcome drug-resistant pathogens, and decrease the use of antibiotics and their side effects.

Many native plants have been used in the folk medicine because of their antimicrobial traits and the properties of some of them have been investigated, as it could be seen in Table **1**. However, in most cases the investigations stop after assessing the antimicrobial activity of the crude extract [27, 39] or after a first fractionation step with solvents of different polarity [29, 40]. The majority of the studies do not present a characterization of the major components present in the extracts or fractions, not even using metabolite profiling technologies. In the survey was found only 42 isolated compounds that were evaluated for their antimicrobial activity against relevant bacteria in nosocomial infections (Table **2**). These compounds were distributed among several classes, like terpenes, neolignans, iridoid lactones, flavonoids, with no major predominance of one single class.

In the literature, different groups of plant-derived compounds, such as alkaloids, flavonoids, phenylpropanoids, coumarins and terpenes, are described as antimicrobials. On average, these metabolites have shown to possess moderate-to-weak activity against rapidly growing mycobacteria and staphylococci. [114, 116-119]. The compounds isolated from native Brazilian plants were no different, the activities ranged from a MIC of 1.56 µg/mL for the naphtoquinone plumbagin against *S. aureus* [127] to 2000 µg/mL for the diterpene *ent*-kaur-16-en-18-oic acid against *E.coli* and *S. aureus* [54]. Plumbagin was the most active compound found in the literature survey, no other isolated compound showed such an activity. The second most active compound was another diterpene, kaurenic acid, with MIC of 6-8 µg/mL against *S. aureus* [126]. The rest of the compounds were in the same activity range found for the crude extracts.

These findings suggest that the use of plant extracts over isolated compounds can be of great significance in therapeutic treatments of multi-drug resistant organisms. Moreover, the synergistic effects of antimicrobial extracts in association with antibiotics can provide an effective therapy against drug resistant bacteria. These synergistic combinations represent a largely unexploited new form of chemotherapy with novel and multiple mechanisms of action that can overcome microbial resistance.

## Essential Oils

Aromatic plants and their essential oils were always applied for their antimicrobial effects in traditional medicine all

**Table 2. Isolated Compounds from Native Brazilian Plant Species Tested for Antimicrobial Activity. (NA: Not Active; ND: MIC Not Determined by Authors)**

| Plants species | Plant part | Isolated compound | Microorganism | MIC (μg/mL) | Ref. |
|---|---|---|---|---|---|
| *Chromolaena laevigata* | leaves | laevigatin | *Candida albicans* (ATCC 10231) | 500 | [49] |
| | | | *Staphylococcus aureus* (ATCC 2913) | 125 | |
| | | | *Pseudomonas aeruginosa* (ATCC 9027) | 1500 | |
| | | | *Escherichia.coli* (ATCC 8739) | 1500 | |
| *Clusia burlemarxii* Bittrich | leaves | 2,2-dimethyl-3,5-dihydroxy-7-(4- hydroxyphenyl) chro-mane | *Staphylococcus aureus* (ATCC 6538) | 50 | [50] |
| | | lyoniresinol and 3-O-α-L-rhamnopyranosylkaempferol | *Staphylococcus aureus* (ATCC 6538) | 25 | |
| | | 3-O-α-L- rhamnopyrano-sylquercetin | *Staphylococcus aureus* (ATCC 6538) | 100 | |
| *Copaifera paupera* (Herzog) Dwyer | trunk oil | (-)-copalic acid , | *Staphylococcus aureus* (ATCC 6538) | 10 - 8 | [126] |
| | | (-)-polyalthic acid , | *Staphylococcus aureus* (ATCC 6538) | 50 - 40 | |
| | | (-)-methyl-18-hydroxy-copaiferolate | *Staphylococcus aureus* (ATCC 6538) | >50 | |
| | | (-)-kaurenic acid | *Staphylococcus aureus* (ATCC 6538) | 8- 6 | |
| *Croton antisyphiliticus* Mart. | roots | *ent*-kaur-16-en-18-oic acid | *Escherichia coli* (ATCC 25922), *Escherichia coli; Staphylococcus aureus* from clinical isolates | 2000 | [54] |
| | | *ent*-kaur-16-en-18-oic acid | *Staphylococcus aureus* (ATCC 6538) | 250 | |
| *Croton cajucara* Benth. | leaves | 7-hydroxy-calamenene | *Staphylococcus aureus* MRSA (ATCC 9394) | 39.06 | [55] |
| | | 7-hydroxy-calamenene | *Mycobacterium tuberculosis* (ATCC 27295) | 312.5 | |
| | | 7-hydroxy-calamenene | *Candida albicans* (ATCC 24434) | 78.12 | |
| *Guatteriopsis friesiana* (W. A. rodrigues) Erkens e Maas. | leaves | α - eudesmol | *Candida albicans* (ATCC 10231) | 125 | [70] |
| | | β-eudesmol | *Candida albicans* (ATCC 10231) | 125 | |
| | | φ-eudesmol | *Candida albicans* (ATCC 10231) | 500 | |
| | | α - eudesmol | *Staphylococcus aureus* (ATCC 6538) | 250 | |
| | | β-eudesmol | *Staphylococcus aureus* (ATCC 6538) | >1000 | |
| | | φ-eudesmol | *Staphylococcus aureus* (ATCC 6538) | 600 | |
| *Guatteriopsis friesiana* (W. A. rodrigues) Erkens e Maas. | leaves | α - eudesmol | *Pseudomonas aeruginosa* (ATCC 13388) | 200 | [70] |
| | | β-eudesmol | *Pseudomonas aeruginosa* (ATCC 13388) | >100 | |
| | | φ-eudesmol | *Pseudomonas aeruginosa* (ATCC 13388) | 300 | |
| | | α - eudesmol | *Escherichia coli* (ATCC 11775) | ND | |

**(Table 2) contd….**

| Plants species | Plant part | Isolated compound | Microorganism | MIC (µg/mL) | Ref. |
|---|---|---|---|---|---|
| | | β-eudesmol | *Escherichia coli* (ATCC 11775) | >1000 | |
| | | φ-eudesmol | *Escherichia coli* (ATCC 11775) | >1000 | |
| *Himatanthus sucuuba* (Spruce ex Müll.Arg.) Woodson | roots | allamandin | *Staphylococcus aureus* (ATCC 6538p)<br>*Escherichia coli* (ATCC 25792) | 10 | [73] |
| | | allamandin | *Pseudomonas aeruginosa* (ATCC 27853) | 20 | |
| | | plumericine | *Staphylococcus aureus* (ATCC 6538p)<br>*Pseudomonas aeruginosa* (ATCC 27853) | 10 | |
| | | plumericine | *Escherichia coli* (ATCC 25792) | 40 | |
| *Kielmeyera variabilis* Mart. & Zucc. | stems | assiguxanthone-B | *Staphylococcus aureus* (ATCC 25923) | 100 | [76] |
| | | 2,5-dihydroxy benzoic acid | *Staphylococcus aureus* (ATCC 25923) | >100 | |
| | | kielcorin | *Staphylococcus aureus* (ATCC 25923) | >100 | |
| | | assiguxanthone-B | *Bacillus subtilis* (ATCC 6623) | 25 | |
| | | 2,5-dihydroxy benzoic acid | | >100 | |
| | | kielcorin | | >100 | |
| *Leiothix spiralis* (Bong.) Ruhland | leaves | luteolin-6-C-β-D-glucopyranoside | *Escherichia coli* (ATCC 25922)<br>*Pseudomonas aeruginosa* (ATCC 27853)<br>*Enterococcus faecalis* (ATCC 29212)<br>*Staphylococcus aureus* (ATCC 25923) | >500 | [78] |
| *Leiothix spiralis* (Bong.) Ruhland | leaves | 4′-methoxyluteolin-6-C-β-D-glucopyranoside | *Escherichia coli* (ATCC 25922)<br>*Pseudomonas aeruginosa* (ATCC 27853)<br>*Enterococcus faecalis* (ATCC 29212)<br>*Staphylococcus aureus* (ATCC 25923) | >500 | [78] |
| | | 8-carboxymethyl-1,3,5,6-tetrahydroxyxanthone | *Enterococcus faecalis* (ATCC 29212)<br>*Escherichia coli* (ATCC 2592) | >500 | |
| | | 8-carboxymethyl-1,3,5,6-tetrahydroxyxanthone | *Staphylococcus aureus* (ATCC 25923) | 125 | |
| | | 8-carboxymethyl-1,3,5,6-tetrahydroxyxanthone | *Pseudomonas aeruginosa* (ATCC 27853) | 125 | |
| *Plumbago scandens* | roots | plumbagin | *Staphylococcus aureus* (ATCC 6538) | 1.56 | [127] |
| *Praxelis clematidea* R.M. King & Robinson | aerial parts | apigenine | *Staphylococcus aureus* (AS 1199 B – NorA) | 256 | [128] |
| | | genknanine | | 256 | |

**(Table 2) contd….**

| Plants species | Plant part | Isolated compound | Microorganism | MIC (µg/mL) | Ref. |
|---|---|---|---|---|---|
| | | 7,4-dimethylapigenine | | 256 | |
| | | trimethylapigenin | | 256 | |
| | | cirsimaritin | | 256 | |
| | | tetramethyl cutellarein | | 256 | |
| *Schinus lentiscifolius* Marchand | aerial parts | morolic acid | *Bacillus subtilis* (ATCC 6633) *Staphylococcus epidermidis* (ATCC 12228) *Escherichia coli* (ATCC25922) *Pseudomonas aeruginosa* (ATCC 17759) *Shigella sonnei* (ATCC15305) | 100 | [96] |
| | | | *Streptococcus pyogenes* (ATCC 19615) *Staphylococcus saprophyticus* (ATCC15305) | 50 | |
| | | | *Staphylococcus aureus* (ATCC 6538p) | 200 | |
| | | moronic acid | *Bacillus subtilis* (ATCC 6633) *Staphylococcus aureus* (ATCC 6538p) *Staphylococcussaprophyticus* (ATCC15305) *Escherichia coli* (ATCC25922) | 200 | |
| | | | *Pseudomonas aeruginosa* (ATCC 17759) | 100 | |
| *Schinus lentiscifolius* Marchand | aerial parts | acridocarpusic acid | *Bacillus subtilis* (ATCC 663) *Staphylococcus aureus* (ATCC 6538) *Streptococcus pyogenes* (ATCC 19615) *Staphylococcus saprophyticus* (ATCC15305) *Shigella sonnei* (ATCC15305) *Staphylococcus epidermidis* (ATCC 12228) *Pseudomonas aeruginosa* (ATCC 17759) *Escherichia coli* (ATCC 25922) | 100 | [96] |
| | | quercetin | *Bacillus subtilis* (ATCC 6633) *Staphylococcus aureus* (ATCC 6538p) *Streptococcus pyogenes* (ATCC 19615) *Staphylococcus saprophyticus* (ATCC15305) *Shigella sonnei* (ATCC15305) *Staphylococcus epidermidis* (ATCC 12228) | 100 | |

**(Table 2) contd….**

| Plants species | Plant part | Isolated compound | Microorganism | MIC (µg/mL) | Ref. |
|---|---|---|---|---|---|
| | | | *Pseudomonas aeruginosa* (ATCC 17759) *Escherichia coli* (ATCC 25922) | | |
| *Schinus lentiscifolius* Marchand | aerial parts | quercitrin | *Bacillus subtilis* (ATCC 663) *Staphylococcus aureus* (ATCC 6538) *Streptococcus pyogenes* (ATCC 19615) *Staphylococcus saprophyticus* (ATCC15305) *Staphylococcus epidermidis* (ATCC 12228) *Pseudomonas aeruginosa* (ATCC 17759) *Escherichia coli* (ATCC 25922) | 200 | [96] |
| | | | *Shigella sonnei* (ATCC15305) | 100 | |
| | | gallic acid | *Bacillus subtilis* (ATCC 663) *Staphylococcus aureus* (ATCC 6538) *Streptococcus pyogenes* (ATCC 19615) *Staphylococcus saprophyticus* (ATCC15305) *Shigella sonnei* (ATCC15305) *Staphylococcus epidermidis* (ATCC 12228) *Pseudomonas aeruginosa* (ATCC 17759) *Escherichia coli* (ATCC 25922) | 100 | |
| *Schinus lentiscifolius* Marchand | aerial parts | gallic acid methyl ester | *Bacillus subtilis* (ATCC 663) *Staphylococcus aureus* (ATCC 6538) *Streptococcus pyogenes* (ATCC 19615) *Staphylococcus saprophyticus* (ATCC15305) *Shigella sonnei* (ATCC15305) *Staphylococcus epidermidis* (ATCC 12228) *Pseudomonas aeruginosa* (ATCC 17759) *Escherichia coli* (ATCC 25922) | >200 | [96] |
| *Scutia buxifolia* Reissek | leaves | quercetin | *Mycobacterium tuberculosis* H37Rv (ATCC 25618) | 312.50 | [98] |
| | | | | 625.00 | |
| *Solanum palinacanthum* Dunal | aerial parts | rutin | *Staphylococcus aureus* (ATCC 25923) | >1000 | [100] |
| | | 3,5-dicaffeoylquinic acid | | 1000 | |
| *Xylosma ciliatifolia (*Clos) Eichler | root barks | ugandensidial (6-acetoxy-9-α-hydroxy-drim-7-en-11,12-dial) | *Staphylococcus aureus* (ATCC 6538) | 10 | [107] |
| | | | | 62.5 | |

**(Table 2) contd….**

| Plants species | Plant part | Isolated compound | Microorganism | MIC (µg/mL) | Ref. |
|---|---|---|---|---|---|
| *Ziziphus joazeiro* Mart. | barks | methylbetulinato | *Staphylococcus aureus* (ATCC 29213) | NA | [108] |
| | | betulinic acid | | 128 | |
| | | alphitolic acid | | 32 | |
| | | methylcenothate | | 16 | |
| | | epigoianic acid | | NA | |
| | | methylbetulinato | *Staphylococcus aureus MRSA* (ATCC 3359) | NA | |
| | | betulinic acid | | >128 | |
| | | alphitolic acid | | 32 | |
| | | methylcenothate | | 16 | |
| | | epigoianic acid | | NA | |
| *Ziziphus joazeiro* Mart. | barks | methylbetulinate | *Staphylococcus aureus* (ATCC 12228) | ND | [108] |
| | | betulinic acid | | NA | |
| | | alphitolic acid | | 32 | |
| | | methylcenothate | | 16 | |
| | | epigoianic acid | | NA | |

over the world since ancient times [129]. When the aim is to screen the aromatic plants for antimicrobial activity, the interest is directed to their essential oils, and then the method of choice for extraction would be steam distillation, volatile solvent extraction or supercritical fluid extraction [130]. In our survey we found studies for 27 essential oils obtained by steam distillation and only one obtained by extraction with supercritical $CO_2$ (Table **1**). The MIC's values for the essential oils ranged from 36300 µg/mL for *P. bahiana* oil against *S. aureus* [92] to 0.001 µg/mL for *C. cajucara* oil against a methicillin-resistant strain of *S. aureus* (MRSA) [55]. In general, essential oils are known to have a higher antibacterial effect against Gram-positive bacteria [27, 131, 130]. The outer cell membrane of Gram-negative bacteria possesses hydrophilic properties that impede the contact of the hydrophobic essential oil constituents with the bacterial cell [131]. These reasons made MRSA a popular test microorganism in nosocomial infections due to the increasing resistance of this pathogen against current drugs.

Most of the essential oils antimicrobial activity is found in the oxygenated terpenoids (e.g., alcohols and phenolic terpenes), while some hydrocarbons also exhibit antimicrobial effects [131, 119]. As the oils are composed of a complex mixture of compounds, interactions between these components may lead to antagonistic, additive or synergistic effects. Some studies have demonstrated that crude essential oils normally have higher antibacterial activity than the mixtures of their major components, suggesting that the minor components are critical to the synergistic activity, though antagonistic and additive effects have also been observed [132, 133, 134]. This kind of effect was observed for the oils of *C. cajucara* containing different amounts of 7-hydroxycalamenene against MRSA, the MIC for the isolated compound was 39.06 µg/mL and those from the crude oils varied from 0.001 to 0.019 µg/mL [55].

The synergistic effects of antibiotics and essential oils have also been evaluated in antibiotic-resistant pathogens. This is one strategy employed to counter the resistance mechanisms developed in multidrug resistant pathogens across the years. Many studies have shown positive correlations and the essential oils were active against antibiotic resistant bacteria under minimal concentration, hence minimizing potential toxic effects [135]. Besides this, essential oils can interfere with the expected result of antibiotics through alteration of the susceptibility of microbes to these drugs [123].

Essential oils from some native Brazilian plants demonstrated synergistic effects with antibiotics against resistant bacterial strains, such as *C. zehntneri* [136], *L. camara* and *L. montevidensis* [137], *R. leptopetala* [138] using direct contact methods, as it has been described for several other essential oils [139]. However, the vapours from *L. microphylla* essential oils were able to enhance the activity of gentamicin against *P. aerugionosa* and norfloxacin against a resistant strain of *S. aureus* in 47% and 225%, respectively [140]. Essential oils in the vapour phase could be highly effective against surface pathogens and food spoilage bacteria at relatively lower concentrations than the liquid phase [141], including MRSA and *Pseudomonas fluorescens* [142, 143]. Due to its environmentally friendly characteristics, the antibacterial activity of essential oils in the vapour phase might be an interesting treatment in a hospital environment due to their ability in preventing biofilm formation or revomoving it, since the microbial biofilms are an important route for cross-contamination [141]. Essential oils vapours might also be used as inhalation therapy against bacterial respiratory tract pathogens [144]. However, before the vapour therapy of essential oil is applied in clinical practice further studies are required to determine the range of the possibilities- important factors such as the minimal exposure

time for efficacy, applicability and the possibility of toxicity needs to be further evaluated.

Another drawback of essential oils is their chemical composition. Since they consist of multiple components their antimicrobial activity cannot be assigned to one particular component. In most cases their activity is a result of the additive, synergistic or antagonistic effects of the individual constituents, as was observed in the *C. cajucara* oil [55]. Therefore, the main compound generally exerts the strongest activity, but can be influenced by the other molecules. Several aromatic plant species are well known for their high intraspecific variation in terpene composition. These variations in yield and composition of volatiles may be caused by geographic differences or the existence of distinct chemotypes/chemical races [145].

As Brazil is a country of continental dimensions, a diversified range of ecosystems is found forming distinct biomes, also with a wide range of transitional regions and specific ecosystems and niches [22]. Therefore, it is not surprising that a plant species occurring along these environments formed different chemical traces. The identification of chemotypes from the Brazilian aromatic flora is far from over. Some of these varieties were already described and evaluated for their antibacterial activity as mentioned above for *C. cajucara* [55, 84]. Also analyses of the essential oil from two *P. pseudocaryophyllus* populations collected at two different ecosystems found in the Atlantic forest (a Restinga forest at sea level and an upper montane forest, *ca.* 1000 m height), indicated that the essential oils had a distinct composition. The first population presented eugenol (72%) as main component while in the second population the oil was composed almost entirely of methyl-eugenol (95%). This difference in the chemical composition also changed the activity against *S. aureus*. The oil with eugenol presented a MIC of 0.0047 μL/L while that with methyl-eugenol showed less activity (MIC of 1.5 μL/L). However, no difference was noticed in the activity against *E. coli*.

Another factor influencing the essential oils antimicrobial activities is that their chemical composition can also be affected by seasonal changes. Apart from climatologically fluctuations, particularly in the rainfall months, these variations might also be associated with the vegetative or flowering period of the plant [145]. There are not many examples of the antibacterial activity analysis along the seasonal variations in the essential oils composition. In most cases, the seasonal effects are evaluated through a year, but the antimicrobial activity is analysed in one sample only. This was the case for *M. myrtifolia* that showed a variation in the α-pinene concentration along a year of study from 61.5 to 90.9%, but the antimicrobial activity was evaluated only for the sample of a specific month [146]. However, the *C. laevigata* essential oils from the leaves, stems, capitula, and cypselas were evaluated at two different phenological stages (flowering and fruiting), regarding their chemical compositions and antimicrobial activities. The *C. laevigata* essential oils showed a more complex composition during the fruiting stage compared with the flowering period, but in both periods no significant changes were observed in the amounts of the major components (laevigatin and spathulenol). These changes in the oil composition increased the activity of the stem oils against *S. aureus* from a MIC of 125 μg/mL, during the flowering stage, to 62.5 μg/mL in the fruiting stage. These results might be associated with the higher levels of monoterpene hydrocarbons, mainly α-thujene, α-pinene, sabinene, β-pinene, and myrcene, present in the oil during fruiting [49].

Several studies have been carried out concerning the antimicrobial activity of essential oils from Brazilian aromatic plants. Some of these oils presented outstanding effect against a wide spectrum of microorganisms, including multidrug resistant strains, as was the case from the *C. cajucara* oil. Nevertheless, for Gram negative bacteria strains most of the essential oils when tested isolated still did not demonstrate a satisfactory effect. In addition, the majority of the screenings do not include other nosocomial infection related bacteria such as *Acinetobacter baumannii*, *Stenotrophomonas maltophilia*, *Mycobacterium tuberculosis*, *Clostridium difficile*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Legionella pneumophila*.

Although many of the essential oils found in this review possess strong antimicrobial activity against various microorganisms, some disadvantages have to be considered such as; limited stability and high volatility represent drawbacks that complicate the *in vitro* tests as well as the storage and application. Moreover, there are reports of microbial resistance of essential oils due to natural resistance or emerging tolerance by habituation [147]. In addition, it is very difficult to ascribe the antimicrobial activity to one particular component because the complexity of the essential oils composition. Further tests are needed to understand the interactions between the individual compounds in the mixtures, as well as modelling studies for chemical modification of essential oil constituents to increase their antimicrobial activity.

## CRITICAL ANALYSIS OF THE METHODOLOGY USED FOR ASSESSING THE ANTIMICROBIAL ACTIVITY

Currently there are several techniques to determine whether a plant extract or a particular compound isolated from it has the same antimicrobial activity. The screening methods available for the detection of antimicrobial activity of natural products are divided into three groups, including bioautography, diffusion and dilution methods [67]. There are few studies reporting on the best screening method to be used according to the type of extract or isolated compounds to be tested, the most commonly used methods are agar diffusion and broth dilution [148] In the literature database search, we found about 112 references dealing with the screening of native Brazilian plants for antibacterial activity that can be useful in the search of new drugs for nosocomial infections using different methodologies (Fig. **1**).

The bioautography is a simple, fast, reliable and convenient method to test the antimicrobial effects of plant extracts and pure substances, which can direct the isolation of bioactive constituents [149]. The disadvantage of this method is that only not volatile compounds can be tested [150]. Additionally, too acidic and too alkaline solvents remain on TLC plate even after long drying times, possibly inhibiting bacterial growth [67]. In the screening of Brazilian plants, this method was not used frequently to test antimicrobial activity [28, 48, 54, 57, 62, 63, 85-87, 101, 151].

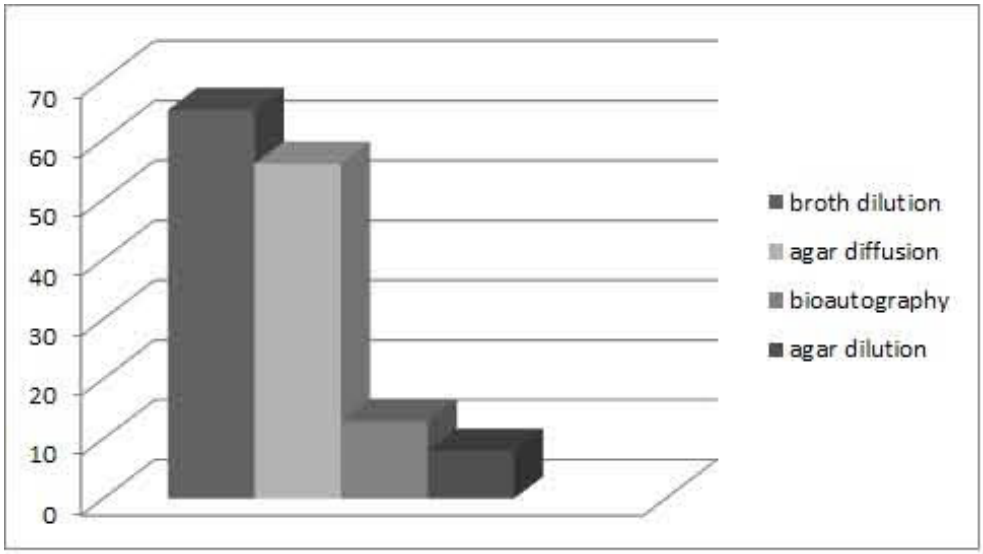


**Fig. (1).** Overview of the most common methods for determining the antimicrobial activity found in the researched literature.

Agar diffusion method, based on the diffusion process consisting on transferring matter from one position to another, involves filling Petri dishes with agar broth and microorganism inoculation. Later, suspensions turbidity of tested microorganism cultures is adjusted, antimicrobial agent is applied in different concentration and plates are incubated. The antimicrobial agent is diffused into the agar and prevents microbial growth, resulting in inhibition zones indicating positive results. The size of the inhibition zones is proportional to the antimicrobial activity and is compared to positive (antibiotic) and negative control (solvent) [150, 152]. According to the diameter of the inhibition zone, microorganism can be classified as sensitive, moderate or resistant [152]. When one uses a diffusion method, several factors can become errors sources such as culture medium composition, incorrect inoculum density, use of excess broth in the swab for plate inoculation, temperature and incubation time inadequate, interactions between the antimicrobial to be tested and the culture medium, misuse of $CO_2$ in atmosphere, premature reading error of the inhibition zone measurements, or the use of contaminated or mixed cultures [153]. This method is often used as a preliminary qualitative test due to its limitation for compounds with low diffusibility in the culture medium [86]. The method can be performed through the diffusion techniques in discs, wells, templates [154], or by using the agar drop diffusion technique [80].

The disc diffusion technique consists in the application of a certain volume of an antimicrobial agent solution in various concentrations to be tested in filter paper discs with 6 mm diameter [152], originally described by Bauer *et al.* [155] and standardized by the CLSI (NCCLS document M2-A8, 2003 [156] NCCLS document M2-A7 [157], NCCLS document M31-T, 1997 [158], NCCLS M100-S12, 2002 [159]. This was the second most commonly used methodology among the antimicrobial activity tests found in the literature [29, 37, 40, 58, 74, 151, 102, 160-168]. One of the disc variant disadvantages is the precipitation of water-insoluble substances in the disc which prevents diffusion of the antimicrobial agent into the agar. Additionally, this variant is more time consuming and expensive [67].

The well diffusion technique involves partially removing the semi-solid culture medium with the help of 6-8 mm diameter cylinders forming wells in which it is possible to apply the substances to be analysed [152]. Valgas *et al.* [67] showed that the well variant is more sensible than the disc. In the well variant, the presence of suspended particulate matter in the sample is much less likely to interfere with the diffusion of the antimicrobial agent into the agar than in the filter paper disc. Even though the well variant is more satisfactory then the disc, there are evidences that sometimes the inhibition zones are not proportional to the antimicrobial agent concentration, indicating diffusion issues [169]. This technique still is very popular in the screening articles [34, 42, 97, 170-175] and it is even used to determine the MIC [44, 173].

The template technique involves the application of stainless steel cylinders on the surface of the already solidified and inoculated culture medium followed by the addition of the test solution into the cylinders [152]. Nowadays, this technique is not that frequently used for testing Brazilian plants [91, 176-178]. The drop test consists in adding 1-10 µl of each sample directly on the surface of the culture medium previously inoculated with the test microorganism [179], and it was used to determine the antimicrobial activity of essential oils [55,80].

A study compared three agar diffusion techniques (discs, wells and templates) [169]. On this research, the well technique was performed according to Grove and Randall [180] which uses double-layer plates (base layer and seed layer with adequate medium for the test microorganism), the disc technique was performed according to CLSI updates M2-A8 [156], and the template technique as a modified version of that found in the Brazilian Pharmacopoeia 4th edition [181]. The conclusions were that among the three groups studied the templates promoted the smallest number of inhibition zones, considering that this technique had the larger amount of extract applied to the plate. The well diffusion technique was more suitable for the detection of antibacterial activity in the samples by easily providing a greater contact between the samples and microorganisms.

Currently, the dilution method is used to determine the minimum concentration of an agent needed to inhibit or to kill a microorganism and can be performed either by means of broth or agar dilution [182]. The test is set up with the preparation of various test tubes or plates, containing broth or agar medium, to which are added various concentrations of antimicrobial agents. Subsequently, the tubes or plates are inoculated with a standard suspension of the organism to be tested. After overnight incubation at 35 °C, the tests are examined to determine the MIC, which can be done visually or by means of photometric detection. The agar dilution method is still not frequently used in the researched literature to test antimicrobial activity [74, 94,183]. However, this technique is standardised by NCCLS (document M7-A8, 2008) [184], and the broth macrodilution method is standardised by NCCLS (document M7-A3, 1993) [185]. The main disadvantage of the latter is that the technique is time consuming, requires lots of space and amounts of tested substances and reagents. As a result, it generates large amounts of waste, allows small number of replicates [152].

The broth macrodilution technique should be substituted by broth microdilution method that involves several two-fold antimicrobial agent dilution made in a polystyrene tray containing 80, 96 or more wells with a volume between 0.1 and 0.2 mL. The bacteria inoculum density is standardized with 0.5 McFarland turbidity scale and the final inoculum is adjusted. Changes in the growth rate and the MIC are assessed by changes in the bacterial suspension turbidity against positive controls (antibiotics) or by adding viability indicators and the measurement is carried out visually or by photometric analysis at 620 nm [186, 187, 188]. Although the method is standardised by the NCCLS for aerobic bacteria (NCCLS document M7-A6, 2003) [189], filamentous fungi (NCCLS document M38-A, 2002) [190] and yeasts (NCCLS document M27-A2, 2002) [191], the researched literature revealed differences in the antimicrobial agent concentration, final inoculum, incubation time and temperature, among others. Hence, more effort should be made to follow standard procedure, allowing direct comparison of the antibacterial activity tested for a pure compound or extract, as the broth microdilution gives the most accurate and consistent results [192, 152, 169]. Furthermore, the method is considered as quantitative and the results are not affected by the growth rate of the different microorganisms. Moreover, the method is inexpensive and has a high rate of reproducibility. According to the researched literature, it is 30 times more sensitive than other methods. Importantly, small amount of sample is required, allowing large numbers of replicates. The disadvantages of this method are the difficulty in detecting contamination, inoculum viability and solvent inhibitory effect [91,152]. These limitations could be avoided by reserving a number of wells in each plate to check sterility (without inoculum), inoculum viability (without extract) and solvent inhibitory effect [91]. Both macrodilution and microdilution techniques respond to the same influences when determining the MIC, that means primary factors as the sensitivity of the organism, the diluents used, and the rate of bacteria growth stage [193].

Macro- and microdilution techniques were compared in kill time studies, and the microplate method has been found to be more efficient, economical and easier to perform than the macrodilution variation. Although the two methods showed similar results, the microplate method has several positive aspects, one of those is the significantly smaller amount of the sample required; for the same sample concentration the volume needed by the microplate method is reduced by 50 or even 100 times than that required by macrodilution method. The operation procedure is more convenient with the microplates; we can directly read the turbidity of bacterial culture at 620 nm, showing good reproducibility in parallel experiments. The antibacterial analysis on 96-well is suitable for the high-throughput screening of new antibiotics [194].

The researched literature used a variety of screening methods for the detection of antimicrobial activity from natural products, as well as the use of non-standardized methodologies, without detailed description of the experimental procedures, often associated with a lack of essential information for reproducing the work (culture medium, microorganism serotype, incubation parameters, sample amount, etc.), thus making the results neither comparable nor reproducible.

The methodology used for each experiment must be chosen carefully and taking into account their advantages and disadvantages. In this sense, the broth microdilution method should be the method of choice for testing new antimicrobial agents from plant extracts or isolated compounds, since it uses small sample size, a relevant factor for natural products research laboratories, where the total amount of the extract or the isolated compounds is reduced. Moreover, this method presents the best cost/benefit relationship, and it is the best method to expresses consistent accurate and comparable results, with a good reproducibility in parallel experiments.

## FINAL CONSIDERATIONS

In the past decades, there were enormous expectations that the exploitation of genomics, *in silico* drug design and target-based high-throughput screening of combinatorial compound libraries would yield a new generation of novel antibacterial drugs addressing new molecular targets which have not been realized despite the massive investments [195; 196]. For these reasons, the interest is growing in the untapped potential of plant metabolites as a source of novel molecules for a new generation of antibacterial drugs [197, 198]. Worldwide only a very limited number of herbal medicines for the treatment of infections have been subjected to evidence-based evaluation, this is also the case of Brazil, even though the use of medicinal plants is very common among the population. Considering the available biodiversity in the country, the present evaluation shows that there is still little systematic work done.

Although there are countless number of papers claiming the extraordinary antimicrobial activity of plant secondary metabolites, most often in the form of crude extracts or essential oils, no single plant-derived antibacterial has been yet commercialized [199]. One of the reasons that might explain this fact is that in almost all cases no single isolated compound was more active than the crude extract. Moreover, most authors overestimated the degree of activity achieved having MIC values higher than 1 mg/mL for extracts and over 0.1 mg/mL for pure compounds, and in most cases only

against normal strains of *S. aureus* or *P. aeruginosa* not the multi-drug resistant ones. In these conditions, it is difficult to envisage how such materials could be developed as potential sources of therapies for nosocomial infections.

The discrepancies in results cause difficulties in making a firm conclusion of the antimicrobial activity from plant extracts or essential oils, and most of the current research rely on postulations and past reports to explain their results. However, it is unlikely to standardize a single method for all research since studies often have different aims and objectives that require different experimental designs. It is fundamental, at least, during screenings efforts to use comparable methods to quantify the antimicrobial activity of the plant extracts or isolated compounds by their MIC. Standardization is particularly relevant to methods that are sensitive enough to detect small amounts of biologically active substances such as broth microdilution method, which is considered promising for the small amounts of sample required and affords comparable and reproducible results.

On the other hand, several studies have proposed that natural compounds in combination with antibiotics are a new strategy for developing therapies for infections caused by bacterial species and that natural plant products can potentiate the activity of antibiotics in combination. There are already some examples describing that isolated natural products or extracts are also active against clinically-relevant pathogens and their use as "antibiotic potentiators" or "virulence attenuators" for the control of infectious diseases in humans is promising. Furthermore, the mechanisms for the antimicrobial activity of natural products with allopathic antimicrobials has been extensively reviewed indicating different targets such as, receptor site modification, enzymatic degradation, reduced accumulation of the drug within the bacterial cell, decreased membrane permeability, and efflux pumps [121; 200]. Perhaps the reductionist approach, considering only one isolated compound, limits the complexity and variability of the effects obtained with the plant extract in which major and minor compounds may contribute to the overall activity [125]. Thus, innovative scientific methods for the discovery, validation and to determine the safety of multicomponent botanical therapeutics are needed for the development of such new medicines. As most of these studies are in the initial stages, both the standardization of extracts and the identification of the biologically active compounds are also needed. Therefore, emphasis must be placed on the preservation of plant populations to guarantee pharmacologically active sources of material for herbal medicine. [201].

Essential oils present an additional advantage over plant extracts for their application in the preventive treatment for nosocomial infections that is their volatility. There is growing evidence that essential oils in vapour phase are effective antimicrobial systems. Essential oils in vapour phase have the advantage that they can treat large areas without requiring direct contact with surfaces. This can make them suitable for use as disinfectant of rooms and as air decontaminants [141]. However, there is no standardized method available for assessing the antimicrobial activity in the vapour phase. Investigations should be carried out on their mode of action and their probable toxicological effects in order to optimize their use.

## CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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