Chapter 3
Antimicrobial Activity of Extracts and Essential Oils of Medicinal Plants Occurring in Amazonia: Nanotechnology as a Boon to Enhance Bioactivity

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Abstract The Brazilian Amazon is the largest biome in the country and encompasses about 40% of the forest remnants of the humid tropic. The use of homemade medicines from medicinal plants has been practiced since the dawn of human civilization. In prehistoric age, man sought to alleviate his pain or treat his illnesses through the action of bioactive compounds present in plants, although in an intuitive way based on random discoveries. Such secondary metabolites of medicinal plants

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have proven to have antimicrobial activity due to the action of their bioactive compounds. The extraction of bioactive compounds is an especially important step, not only for the separation of compounds, but also during the analysis of solid materials. There are several conventional and unconventional techniques for the extraction of bioactive compounds from plant matrices, those that use a solvent. Nanotechnology emerges as a potential technology to enhance the action of bioactive compounds present in plant matrices, as it can maintain its characteristics and stability, making these compounds used in several areas. As many of the biologically active compounds have insolubility and hydrophobicity, nanoencapsulation facilitates the delivery of these poorly bioavailable compounds when applied to functional products and drugs, which increases their absorption into cellular structures through properties of favorable particles of shape, size, and surface. Nanotechnology has proved to be a great tool to potentiate the action of such bioactive compounds.

Keywords Nanoencapsulation · Bioactive compounds · Antimicrobial activity · Ethnopharmacology · Brazilian Amazon

1 Introduction

The Amazon Forest is the largest humid tropical forest on Earth, being considered the region with the greatest biodiversity of animal and plant species. Regarding species of tree plants, it is estimated that approximately 16,000 occur along the Amazon basin (Oliveira Piva et al. 2020). The Brazilian Amazon constitutes the largest biome in the national territory and comprises around 40% of the remaining forests of the humid tropic having its relevance recognized in terms of maintaining biodiversity, regional hydrology, and climatic functions (Rodrigues et al. 2020).

The study carried out by Breitbach et al. (2013) showed that many medicinal plants in the Amazon have not been studied in more detail while some have not been studied at all. The collections of bibliographic and botanical samples that were collected by von Martius in the Amazon represent the abundance of high value materials for the development and conservation of this region. The work carried out by the same authors in 2013 was one of the additional incentives, to value the traditional knowledge of the people of the Amazon region and is also useful in protecting collective intellectual property rights.

The use of homemade medicine from medicinal plants has been practiced since the dawn of human civilization. In prehistory, man sought to alleviate his pain or treat his illnesses through the action of the active principles existing in plants. This conduct can also be observed among primitive, isolated people: for example, some indigenous tribes in South America (Rodrigues et al. 2020). The therapeutic effects of medicinal plants are due to their bioactive secondary metabolites, which act in the maintenance of tissues and prevention of a series of diseases.

Bioactive compounds can be found mainly in plant matrices as secondary metabolites; however, recently, some primary metabolites are already being considered as bioactive compounds. Such compounds have been used to prevent degenerative diseases and to even treat a wide range of other diseases. In plants, bioactive compounds act as a protector against biotic and abiotic stress and are present in different amounts. It is important to develop their production in order to obtain the largest amount possible and find viable techniques for their extraction (Azmir et al. 2013; Cvjetko Bubalo et al. 2015; Banožić et al. 2020).

There are many conventional techniques for the extraction of bioactive compounds from plants: those that use solvent (ethanol, methanol, ethyl acetate, acetone, methylene chloride, hexane, mixtures, and others) and those that use thermal extraction, heat reflux, and bioenzymatic extraction (Banožić et al. 2020). Emerging extraction techniques have also been studied to replace conventional ones, those that tend to cause negative impacts on health and the environment. Such techniques include the use of green solvents, ultrasound, subcritical water extraction, and pressurized liquid extraction among other techniques; however, these still need further studies and are better consolidated (Carvalho et al. 2018).

According to Bazana et al. (2019), nanotechnology has emerged as a potential tool to enhance the action of bioactive compounds present in plants, as it is able to maintain its characteristics and stability, making these compounds usable in a range of areas. As many of the biologically active compounds have insolubility and hydrophobicity, nanoencapsulation facilitates the delivery of these poorly bioavailable compounds when applied to functional products and drugs, which increases their absorption into cellular structures through favorable particle properties of shape, size, and surface. Such properties cause the nanoparticles to increase the solubilization potential; thus, by altering their absorption pathways and modifying the rate and location of the release, they influence gastrointestinal dispersion and prevent premature metabolic degradation of bioactive compounds.

In this context, this chapter aims to address the therapeutic properties of medicinal plants from the Brazilian Amazon region, mentioning the main herbs used and possible technologies that could be applied for their extraction (from conventional to emerging). Nanotechnology as an emerging technology to enhance the activity of bioactive compounds will also be addressed.

2 Medicinal Plants from Amazon: A Major Hot Spot of Biodiversity

The Portuguese colonized Brazil in the year 1500. The Jesuit priests were the first to establish contact with the native population of the Amazon, who passed on information from various medicinal plants in the region (Souza et al. 1938). However, Brazil was under a strong colonial regime, due to which the knowledge of medicinal plants from the Amazon until the end of the nineteenth century was hidden

(Breitbach et al. 2013). Over the years, many scientists and naturalists traveled around Brazil in search of registering animals and natural products. Among them, we highlight Carl Friedrich Philipp von Martius. He collected 22,267 species of Brazilian medicinal plants, with rich ethnobotanical and ethnopharmacological descriptions (Wuschek 1989; Riederer 2007). Until now, this collection is extremely important for research that seeks new drugs for the treatment of diseases.

With about 80,000 plant species well distributed throughout the Amazon (Morales and Vinicius 2003), it is not surprising that the region has the largest collection of natural products capable of curing or preventing diseases that threaten life on Earth. About 25% of all modern drugs are derived directly or indirectly from medicinal plants, mainly through the application of modern technologies to traditional knowledge (Brasil 2012). However, only 1% of the species in the tropical forest were tested. This leads us to say that the more we learn about the biology and chemistry of the plants that surround the habitat of Amazon, the curative power that comes from plants increases exponentially, especially against different types of cancer.

According to the US National Cancer Institute, the plants identified with anticancer properties, 70% are found in the Amazon (data available at http://www.ars-grin.gov/duke/). Although we are just beginning to know the power behind the Amazon rainforest, indigenous people have used plants for many generations as an alternative form of cure (Lewis 1992). Unfortunately, we still do not understand scientifically the mechanism of action of these species, but the evidence continues to suggest an incredibly effective potential against several diseases. Among the thousands of species that make up the Amazonian flora, we present some of the most important medicinal plants that are used by the people of the forest to treat various prophylaxis (Table 3.1).

3 Antimicrobial Action of Medicinal Plants from the Amazon

Nowadays, an increasing number of infectious agents are becoming resistant to commercial antimicrobials (Hancock et al. 2012; Oliveira et al. 2013). The necessity to develop new drugs requires varied strategies; among them, the bioprospection of secondary metabolites produced by medicinal plants (Oliveira et al. 2013) is more important.

The use of plants for treating diseases is as old as the human species. Popular observations on the use and efficacy of medicinal plants significantly contribute to the disclosure of their therapeutic properties, so that they are frequently prescribed, even if their chemical constituents are not always completely known (Silva and Fernandes Júnior 2010).

Brazil has the world's largest biodiversity, accounting for over 20% of the total number of known species (Silva and Fernandes Júnior 2010). In the Amazon region,

Table 3.1 Medicinal species from the Brazilian Amazon

Botanical name	Vernacular name[a]	Occurrence state[a]	Traditional use[a]	Correlated studies
Manihot esculenta Crantz	Mandioca	Pará	Lymphatic system, fresh leaves are antidote	Antibacterial (Mustarichie et al. 2020); Antioxidant (Bahekar and Kale 2016)
Carapa guianensis Aubl.	Andiroba	Amazonas	Exanthema, especially that originating from bites of insects of the family Simullidae. Decoctions against Ascaris (internally), dermatophytosi	Antileishmanial (Oliveira et al. 2018); Antiplasmodial (Miranda Júnior et al. 2012)
Virola sebifera Aubl.	Ucuúba	Guyana, Pará	Colic, dyspepsia; rheumatic pain, arthritic tumors	Antioxidant (Rezende et al. 2005); Antiproliferative (Denny et al. 2007)
Paullinia pinnata L.	Timbó	Pará	Anorexia, nervous headache, dry skin. Aphrodisiac but decreases the fertility of Sperm. Poisonous to the brain and kidneys. Against hydrophobia, melancholia, and other types of mental illness	Antifungal (Ngandeu et al. 2019); Analgesic and anti-inflammatory (Ior et al. 2011)
Phyllanthus niruri L.	Quebra-pedra	Pará	Fight kidney and gallbladder stones. Diabetes mellitus	Anti-inflammatory and antinociceptive (Porto et al. 2013); Antimicrobial (Ibrahim et al. 2013)

Note: [a]Data adapted from Breitbach et al. (2013) with the permission of Journal of Ethnopharmacology

there is a large biodiversity of medicinal plants used empirically, but whose prescription has been consolidated through centuries of cultural interaction. Among many medicinal plants, some have been used specifically as anti-inflammatory and antimicrobial agents, including Andiroba (*Carapa guianense*), Alfavaca (*Ocimum micranthum*), Copaiba (*Copaifera multijuga*), Crajiru (*Arrabidaea chica*), Jambu (*Spilanthes acmella*), and Juca (*Libidibia ferrea*) (Carvalho et al. 1996; Conde et al. 2015). Conde et al. (2015) observed that extracts of Juca, Crajiru, Alfavaca, and Copaiba essential oils demonstrated antimicrobial activity against biofilm forming bacteria occurring in the mouth.

Machado et al. (2003) studied different plant species and plant fractions (*P. granatum, T. avellanedae, Cissampelos sympodialis, Croton salutaris, Piper nigrum, Zanthoxylum rhoifolia, Tibouchina granulosa, Alpinia zerumbet, Amburana cearensis, Lobelia thapsoides, Melissa officinalis, Spilanthes oleraceae, Schinus* sp., *Eugenia* sp.) against multiresistant hospital bacteria. *Staphylococcus aureus* strains are susceptible to extracts of *Punica granatum* and *Tabebuia avellanedae*. A mixture of ellagitannins isolated from *P. granatum* and two naphthoquinones isolated from *T. avellanedae* demonstrated antibacterial activity against all *S. aureus* strains tested. The results indicate that these natural products can be effective candidates for the development of new strategies to treat methicillin-resistant infections.

In another study, Suffredini et al. (2004) screened 705 organic and aqueous extracts of plants obtained from different Amazon Rainforest and Atlantic Forest plants for antibacterial activity at 100 μg/ml, using a microdilution broth assay against *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *Escherichia coli*. In another work, 1220 organic and aqueous extracts were screened against *Staphylococcus aureus*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, and *E. coli*. Seventeen organic and aqueous extracts obtained from 16 plants showed activity against both Gram-positive bacteria. None of the extracts showed relevant activity against the Gram-negative *E. coli* and *Pseudomonas aeruginosa* (Suffredini et al. 2006).

Oliveira et al. (2013) evaluated the antimicrobial activity of medicinal plants of family Fabaceae collected from the Amapa state (members of Caesalpiniaceae subfamily), Rubiaceae, Ochnaceae, Apocynaceae, and Clusiaceae families. *Hymenelobium petraeum* showed inhibitory activity against *Staphylococcus aureus*, *Enterococcus faecalis*, *Salmonella enterica* serovar Typhi, and *Candida albicans*. Aqueous extracts of *Vatairea guianensis* and *Symphonia globulifera* presented inhibitory activity exclusively for *Staphylococcus aureus*. Also, the aqueous extract of *Ptychopetalum olacoides* and *Pentaclethra macroloba* inhibited the growth of *Klebsiella ozaenae* and *Acinetobacter baumannii* (Oliveira et al. 2013).

In another study, the antimycobacterial activity of various plants' extracts was tested against three strains of *Mycobacterium tuberculosis*. The extracts of *Duroia macrophylla*, *Ferdinandusa rudgeoides*, *Ferdinadunsa* sp., and *Palicourea guianensis* (Rubiaceae) were active against *M. tuberculosis* RMPr strain. The activity of these extracts may be associated with the possible presence of flavonoids, since this substance is present in these species, which is commonly found in Rubiaceae family species, whose antimicrobial activity against *Escherichia coli* has been demonstrated (Carrion et al. 2013).

The antimicrobial activity of essential oils from leaves of *G. blepharophylla, Guatteriopsis friesiana*, and *Guatteriopsis hispida*, three species of Amazon Brazilian plants, were evaluated against 11 species of microorganisms. The oil of *G. friesiana* exhibited significant antimicrobial activity against all microorganisms tested, whereas *G. hispida* and *G. blepharophyla* showed potent activity against *Rhodococcus equi*. The major constituents of each oil were also tested separately, which showed lower activity compared to the oils (Costa et al. 2008).

Santos et al. (2012) studied *in vitro* antimicrobial activity of Andiroba and Copaíba essential oils against *Paenibacillus* species, including *P. larvae*. The results showed for the first time that these oils presented a high activity against *Paenibacillus* species, showing that Copaíba oil may be a candidate for the treatment or prevention of American foulbrood disease.

Studies of antimicrobial activity and inhibition of the enzyme acetylcholinesterase of fixed oils and hexane extracts of the fruits, abiu (*Pouteria caimito*), acerola (*Malpighia emarginata*), araçá (*Psidium cattleianum*), bacupari (*Rheedia gardneriana*), biribá (*Rollinia mucosa*), camu-camu (Myrciaria dubia), fruta-do-conde (*Annona squamosa*), graviola (*Annona muricata*), and taperebá (*Spondias mombin L.*), were carried out against *Candida albicans ATCC 18804, Staphylococcus aureus ATCC* 29212, *Bacillus cereus* ATCC 11778, *Escherichia coli* ATCC 25922, and *Salmonella typhimurium* ATCC 14028 (Fernández et al. 2020). Of these microorganisms, the best inhibition results were obtained for yeast *C. albicans* with inhibition of 94.46% by taperebá barks extracts, acerola barks (87.12%), araçá seeds (85.23%), and taperebá pulp (85.22%). The % inhibition of bacteria tested was low as compared to antifungal activity (Fernández et al. 2020).

In another work, the antioxidant, cytotoxic, antimicrobial, and schistosomicidal activities of the methanolic extract of *Cassia grandis* L. (Fabaceae), a native tree from Amazon Forest, was evaluated. The ethyl acetate fraction exhibited both antibacterial activity against multidrug-resistant *S. aureus*, and schistosomicidal activities, which could be attributed to the presence of flavonoids, such as catechin derivatives, quercetin, and luteolin (Magalhães et al. 2020).

Antimicrobial and phytotoxicity activities of aqueous crude extract from the Amazonian ethnomedicinal plant *Bellucia grossularioides* (L.) Triana (popularly known as Muúba or Angry-Jambo) were tested against four human pathogenic microorganisms. The results showed no antimicrobial potential against *Staphylococcus aureus*, *Candida albicans*, and *Candida krusei*, which cause furunculosis and leukorrhea, respectively. Additionally, growth inhibition of the toxigenic fungus *Aspergillus parasiticus* was assayed *in vitro* and the results showed no inhibitory activity for any of the tested concentrations. These findings contradict the traditional knowledge and may assist in the targeting of future therapeutics practices (Martins et al. 2016).

Rodrigues et al. (2014) reported the antifungal activity of twenty-eight species of plants extracts of Amazon forest belonging to twenty botanical families. The minimum inhibitory concentrations of the one hundred fourteen crude extracts of dichloromethane, methanol, and water were evaluated against three *Candida* species: *Candida albicans*, *Candida glabrata*, and *Candida parapsilosis*. Seventy-four extracts showed activity, with minimum inhibitory concentration between (0.06 and 1) mg/mL, against the three species evaluated. The results observed in this study, mainly about the families Arecaceae, Apocynaceae, Salicaceae, and Urticaceae, showed that these extracts are promising for the development of new drugs that can be used in the treatment against opportunistic fungal infections (Rodrigues et al. 2014).

Pires et al. (2016) analyzed and compiled information regarding the species *Bauhinia variegata*, *Cecropia obtusa*, *Cecropia palmata*, *Connarus perrottetii* var. *angustifolius*, *Chrysobalanus icaco*, and *Mansoa alliacea*. These common species of the Brazilian Amazon region, widely used in folk medicine, show antioxidant, antibacterial, cytotoxic, hypoglycemic, antifungal, antiangiogenic, antitumor, anti-inflammatory, and antiallergic activities (Pires et al. 2016).

Silva et al. (2018) compiled information of the antileishmanial activity of extracts, isolated compounds, and essential oils commonly used by the local population in the Brazilian Amazonian region to treat several illnesses. Scientific research widely involved natural products in the form of extracts, essential oils, and purified compounds. Moreover, it is important to emphasize that medicinal plants in the Brazilian Amazonian region are used in the form of teas and infusions based on limited access to highly purified compounds due to their high production cost (Silva et al. 2018).

The antimicrobial activity of plants was proven by various examples, in the form of both essential oils and extracts. Thus, this property can be a promising ally in the development of medicine necessary to combat the increasing number of bacterial strains that become resistant to conventional antibiotics (Silva and Fernandes Júnior 2010).

Brazil is the country with the greatest potential for plant research. Recent data show that the Brazilian Amazon region has at least 45,000 different species of plants and many of them are rich in active ingredients (Pires et al. 2016). However, the genetic resources of this vast biodiversity are still poorly explored (Pires et al. 2016). This should be changed using incentives to follow up promising findings: with more investment, especially in the Amazonian region (Silva et al. 2018).

4 Medicinal Plants to Combat Antibiotic-Resistant Human Pathogens

As previously mentioned, many studies with medicinal plants are being developed to combat human pathogens, either due to their natural resistance to control methods, or by developing resistance against commercially used antibiotics, a great concern in the health field.

In 2017, a list of pathogenic microorganisms highly resistant to antibiotics was published, such microorganisms were related to 12 families of bacteria that were among those that caused the greatest threats to the health of the population. These groups were divided into following categories: the first category (critical): *Acinetobacter baumannii*, resistant to carbapenem; *Pseudomonas aeruginosa*, resistant to carbapenem; *Enterobacteriaceae*, resistant to carbapenem, producing ESBL. Second category (high): *Enterococcus faecium*, resistant to vancomycin; *Staphylococcus aureus*, resistant to methicillin, intermediate to vancomycin, and *Helicobacter pylori* resistant, resistant to clarithromycin; *Campylobacter* spp., *Salmonella* resistant to fluoroquinolone, resistant to fluoroquinolone*; Neisseria gonorrhoeae*, resistant to cephalosporin, resistant to fluoroquinolone. Third category (medium): *Streptococcus pneumoniae*, not sensitive to penicillin; *Haemophilus influenzae*, resistant to ampicillin; *Shigella* spp., Resistant to fluoroquinolones. These data were obtained from the World Health Organization (WHO 2017).

In CDC's landmark report (CDC 2019), a similar list is published, but now with 18 microbial groups divided into the following: **Urgent Threats:** Carbapenem-resistant *Acinetobacter*, *Candida auris, Clostridioides difficile*, Carbapenem-resistant *Enterobacteriaceae*, Drug-resistant *Neisseria gonorrhoeae*. **Serious Threats:** Drug-resistant *Campylobacter*, Drug-resistant *Candida*, ESBL-producing *Enterobacteriaceae*, Vancomycin-resistant *Enterococci*, Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant nontyphoidal *Salmonella*, Drug-resistant *Salmonella* serotype Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus*, Drug-resistant *Streptococcus pneumoniae*, Drug-resistant *Mycobacterium tuberculosis*. **Concerning Threats:** Erythromycin-resistant group A *Streptococcus*, Clindamycin-resistant group B *Streptococcus*.

According to the report, more than 2.8 million antibiotic-resistant infections occur in the United States each year, and more than 35,000 people die as a result. In addition, nearly 223,900 people in the United States required hospital care for *C. difficile* and at least 12,800 people died in 2017 (CDC 2019).

Staph bacteria, including methicillin-resistant (MRSA), are also one of the most common causes of healthcare-associated infections. In 2017, CDC estimated 323,700 cases of hospitalized patients and 10,600 estimated deaths.

Therefore, many studies aim at alternatives to combat infections originating from these microbial groups, and natural plant molecules are very promising. Recently, Reis et al. (2020) evaluated antibiofilm, antibacterial, and antioxidant activities of *Brosimum acutifolium* flavonoids, with highly promising results in control preformed *S. aureus* biofilms of importance in the medical field.

Recent studies using plants from other Brazilian region have also shown satisfactory results in the fight against bacterial resistance. Among them, Matias et al. (2016) evaluated the antibacterial activity of *Cordia verbenacea* extracts and found a moderate antibacterial activity against *S. aureus*, *Escherichia coli*, and *P. aeruginosa.* However, they observed a synergistic effect between the fractions of plants with antibiotics, and this could be an alternative to these treatments.

Freitas et al. (2020) reported the antibacterial and antibiotic-modulating activity of *Baccharis coridifolia* essential oil against *P. aeruginosa* and *S. aureus,* where they also found a synergism between the combinations of subinhibitory doses of the oil with conventional antibiotics, indicating potentiation of the antibacterial effect.

Gomes et al. (2020) investigated extracts and residues from the Brazilian pepper tree against multidrug-resistant strains of hospital origin (*S. aureus, Enterococcus faecium, E. faecalis, P. aeruginosa*, and *Acinetobacter baumannii*) and found promising results, where the methanolic fraction and the hydroethanolic extract were the most active mainly against *S. aureus*, *E. faecium*, and *E. faecalis.* In another study, Cruz et al. (2020) isolated a flavonoid from *Croton piauhiensis* leaves to evaluate the antimicrobial action against *E. coli*, *P. aeruginosa*, and *S. aureus.* The results revealed that the compound had no antibacterial activity at concentrations <1024 μg/mL, but the combination of 128 mg/mL of flavonoid with gentamicin presented synergistic effects against *S. aureus* and *E. coli,* as Amikacin also showed synergistic effects against both organisms.

5 Techniques for Extraction

5.1 Conventional Techniques

Medicinal plants have a multitude of compounds of interest, which can have the most diverse technological applications with emphasis on the medical and cosmetic areas. Countless antioxidant compounds of interest can be found in fruits and vegetables, including phenolics, carotenoids, anthocyanins, and tocopherols (Jakubowski and Bartosz 1997). These have various applications, ranging from a simple treatment of skin blemishes to cancer treatment. As a result, there are countless studies aimed at the components found in plants with possibilities of technological application.

However, to obtain these chemical components, extraction is necessary. Extraction can be defined as the separation of medically active portions of the plant using selective solvents through standard procedures (Handa et al. 2008).

There are many methodologies for preparing plant extracts and for isolating their chemical constituents. However, hydroalcoholic extraction (ethanol/water 50/50, v/v), is usually initially applied, for chemical-pharmacological analysis. In the case of possible biological effects of interest, a systematic study method should be used. In this case, the most suitable solvent for obtaining the crude extract is methanol, as it allows the extraction of a greater number of compounds (Cechinel Filho and Yunes 1998).

For many years, conventional methods, such as maceration, boiling, immersion, hydrodistillation, and Soxhlet, were used with great success. There are more and more chemical and pharmacological studies involving medicinal plants that aim to obtain new compounds with different therapeutic properties, which have driven a great scientific advance in this area.

There are multitudes of methods that can be used to extract these compounds, but from an industrial point of view, there is still a strong focus on conventional extraction methods. The extraction of very useful products is an issue of great interest and importance from the point of view of their exploitation. However, the content of these compounds can differ between cultivars and extraction methods. In this way, several extraction methods have been studied to maximize both the quality and quantity of the components obtained.

Among the conventional extraction methods, we can highlight those that use water, with or without heating, and a mixture of solvents such as ethanol, methanol, and organic acids. The different combinations and conditions applied with these solvents include most of the conventional extraction methods for chemical components of plants with an emphasis on phenolic compounds.

The extraction of phenolics can be carried out using organic, or inorganic, solvents. According to Wong and Kitts (2006), highly polar solvents, such as methanol, are highly effective in obtaining antioxidant compounds. Many parameters can influence the performance of phenolic, among which the extraction time, temperature, solvent/sample ratio, number of repeated extractions of the sample, and type of solvent are important. Another important factor is the recovery of the phenolic compounds obtained, which is different from one sample to the next and depends on the type of plant and its active compounds of interest. The yields of the extracted phenolic compounds are influenced by the solvents used such as water, acetone, ethyl acetate, alcohols (methanol, ethanol, and propanol), and their mixtures (Garcia-Salas et al. 2010).

It is important to note that the various solvents used will behave differently according to the material from which the compound of interest is being extracted: for example, an investigation into the effect of different solvents on the extraction of phenolics from aerial parts of *Potentilla atrosanguinea* showed that 50% aqueous ethanol was more efficient than pure aqueous forms or 50% methanol and acetone (Kalpana et al. 2008). That is, although there is evidence that methanol would be more efficient for most of the extraction processes, this behavior may vary depending on the material used. It was observed observed that the highest levels of phenolics extracted from *Vitis vinifera* and sunflower with the use of pure methanol and 80% aqueous acetone (Casazza et al. 2010; Taha et al. 2011).

It is verified that for the extraction, for example, of flavonoids, methanol was better than heptane, which was observed as a poor solvent, while ethanol and acetone are moderate solvents for the extraction (Sathishkumar et al. 2012). Sathishkumar et al. (2012) further reported that maximum amount of flavonoids can be extracted with 75% ethanol, and further increase in the concentration of ethanol was not helpful when it came to increased extraction of flavonoids. The addition of a liquid modifier can enhance the extraction efficiency by reducing the extraction time and improving the recovery of different types of natural products from plant materials (Liu et al. 2008).

One of the benefits of choosing ethanol in extraction processes is because it has a benign character from an environmental point of view, it is relatively safe for human health and it interacts with the flavonoid probably through noncovalent interactions, leading to a rapid diffusion in the solution (Shi et al. 2003). The choice of the solvent used in the extraction of compounds of interest is based on the polarity of the solute of interest. A solvent of polarity similar to the solute dissolves the solute more efficiently. Many solvents can be used sequentially to limit the number of analogous compounds in the desired yield. It is possible to use several solvents sequentially or simultaneously; in the first situation, this can be done to limit the number of analogous compounds in the desired yield. According to Altemimi et al. (2017), the polarity of some common solvents from less polar to more polar is as follows: Hexane < Chloroform < Ethylacetate < Acetone < Methanol < Water.

The extraction of medicinal compounds from plants through the Soxhlet apparatus is the most commonly used, mainly to extract phenolic compounds, due to its lower processing cost, simplicity of operation, good recovery of extracts, and less consumption of time and solvent compared to other conventional methods, such as maceration or percolation (Seidel 2012).

The Soxhlet method generally uses solvents such as ethanol and methanol, which usually present good yields, with methanol being more efficient according to Scherer and Godoy (2014). This high yield of bioactive compounds by the Soxhlet method can be explained using the high temperature that increases the intensity of solution. The content of phenolic compounds obtained from medicinal plants is generally affected by the solvent used, with methanol being the best when compared to ethanol and ethyl acetate (Scherer and Godoy 2014). It is a well-established technique that has an excellent performance when compared to other conventional extraction methods (Luque de Castro and García-Ayuso 1998).

The ethyl acetate solvent and the chloroform/dichloromethane solvent showed lower yields when compared to methanol (Moure et al. 2000). A decreasing yield is observed in the literature for phenolic compounds extracted with the solvent methanol, ethanol, and ethyl acetate, with maceration with methanol, in general, being the one that provides the highest yield of phenolic compounds.

In Soxhlet extraction, the extraction time is essential in reducing energy and cost of the extraction process, being one of the most important factors, which alter the recovery of phenolic compounds from the plant matrix, since if the sample is in an overexposure situation, phenolic compounds tend to degrade, so it is necessary to determine a time considered appropriate for a greater recovery of the compounds (Mojzer et al. 2016).

According to Alara et al. (2018) in the extraction with Soxhlet and ethanol, it is possible to find maximum yields after 2 hours of extraction, with additional times promoting a reduction in the recovery yields of the compounds (total phenolic content and total flavonoid content). This can be explained by the degradation of phenolic compounds, due to the excessive heating of the plant samples (Dahmoune et al. 2014). For this type of observation, it is possible to apply Fick's second law of diffusion, in which the final balance between the extraction solvent and the plant sample will be achieved at a certain time of the extraction.

Most of the modifications carried out to date in the conventional Soxhlet extraction method developed in recent years aimed to make its performance more similar to that of recent techniques for the treatment of solid samples: with reducing the time of the leaching step, energy and automation (Luque de Castro and García-Ayuso 1998).

There are many divergences between the different methods used; however, it is of great importance that each material used is evaluated for different extraction methods, which will include different solvents. For example, according to Anokwuru et al. (2011) acetone and N, N dimethylformamide (DMF) are highly effective in extracting antioxidants. Koffi et al. (2010) found that methanol was more effective in a large amount of phenolic content of nut fruits when compared to ethanol.

Ethanol extracts from plants in Côte d'Ivoire were reported to extract higher concentrations of phenolics compared to acetone, water, and methanol (Koffi et al. 2010) Multiple solvents were commonly used to extract phytochemicals, and scientists often use dry powder from plants to extract bioactive compounds and eliminate water interference at the same time.

Another widely used method for extracting medicinal compounds from plants is maceration. According to Vongsak et al. (2013), one of the more useful methods would be, convenient, and relatively cheaper for small- and medium-sized companies when compared to other modern extraction methods; however, there is a wastage of chemicals during the application of the technique. The isolation and purification of extracts are quite complex and time consuming. This method, which is commonly used in wine production, was adopted for application in medicinal plants. According to Handa et al. (2008), this method is characterized by immersing the material, in whole or powder form, in containers, together with the solvent, for a minimum period of 3 days, after which the content is pressed or filtered. This method is generally used at room temperature. They further reported that the method of infusion and decoction uses the same principle of maceration, because in both, the material is immersed in cold or boiled water. Rathi et al. (2006) stated that the decoction is more suitable for the extraction of heat-stable compounds (hard parts of the plant: root and bark) and generally results in compounds with greater oil solubility. It is also important to remember the percolation process, which is usually applied to coffee, in this process the samples in the form of dry powder, encounter boiling water, using a strainer, and the compound of interest is extracted at a moderate rate.

5.2 Nonconventional Technologies for Obtaining Extracts

In the literature, the comparison between conventional and nonconventional methods of extraction is quite common; for example, de Oliveira et al. (2020) obtained yields of superior phenolic compounds by enzymatic extraction compared to a conventional extraction performed with the association of methanol: water: acetic acid (5:4:1), which demonstrates that it is necessary to evaluate different extraction methods for the same plant matrix when maximum extraction efficiency is being sought.

There is a tendency to reduce the use of conventional organic solvents, since such solvents are harmful to health and the environment. However, researchers have been looking for new extraction alternatives such as green extraction techniques, which work using lower temperatures, shorter residence times, more accessible separation and purification, higher yield, and better efficiency during extraction. In general, these techniques have better environmental, health, and safety properties. However, it is still impossible to use a totally solvent-free technique, because they have an irreplaceable impact on mass transfer during extraction. Thus, new extraction techniques have great potential to replace conventional techniques, but their application and optimization still needs further studies (Banožić et al. 2020).

A nonconventional method of extracting bioactive compounds is that of ultrasound waves. In this process, cavitation bubbles will be generated within the medium; following a cellular collapse, millions of these microscopic bubbles are capable of releasing energy and can create localized areas of high pressure and temperature. Such a mechanism is known as the cavitation effect (Panja 2018) (Fig. 3.1).

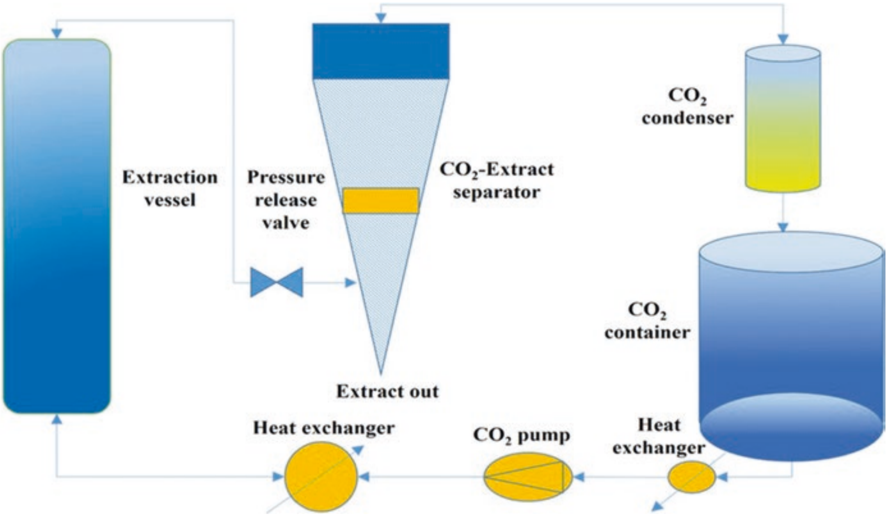

Fig. 3.1 Sketch of the mechanism of release of bioactive compounds from plant cells using ultrasound waves taken from Panja (2018) with permission from *Current Opinion in Food Science*

6 Nanotechnology as an Emerging Tool to Enhance Bioactivity

6.1 Nanoencapsulation of Bioactive Compounds

Nanotechnology is well known for production and application of structures, devices, and systems that have a scale size of 10^{-9} m. This technology has many applications in various areas and has been developing at an accelerated rate in recent years, with its wide applications, sectors such as medicine, pharmacy, and food especially in the stages of processing, packaging, storage, transportation, functionality, and others. Thus, industry and academic researchers have carried out many studies for the application of nanotechnology to encapsulate, protect, and release biologically active compounds from plants (fruits, leaves, roots, and seeds, among others) (Rai et al. 2017; Bazana et al. 2019).

The emergence of different diseases such as diabetes, cancer, obesity, and Alzheimer's has increased severely in recent years and this has led people to think better about having healthier habits (such as a diet rich in healthy plant foods). The plants contain bioactive compounds that act as antioxidants and help prevent these diseases. Nanotechnology came as a technology that increased health promotion through the manufacturing of functional products (such as drugs, supplements, etc.). In the process of using nanotechnology, some of the main physicochemical properties of the particles are changed, reducing their size to nanodimension. European Food Safety Authority (EFSA) claims that particles below 100 nm are nanoparticles. However, in general, particles smaller than 1000 nm can be considered as nanoparticles (Esfanjani and Jafari 2017).

Much work has been carried out concerning the use of nanotechnology in the line of research on nanoencapsulation of bioactive compounds. Although these compounds promote disease prevention, as well as improvements in human health, they are poorly absorbed. Interestingly, these nanostructures can improve many characteristics of these elements. In addition, they can also promote protection against degradation, solubility, stability, and bioavailability, among others. However, the development of nanostructure has many challenges, ranging from choosing the best method for obtaining it to identifying the ideal type of nanomaterial for a bioactive compound of interest. In addition, the characterization of toxicological effects is sought through specific regulations for safety in human consumption and the environment, such as the use of green synthesis (Bazana et al. 2019).

Bioactive compounds are particularly important for the maintenance of human health; they are mostly hydrophobic and/or poorly soluble in water. The most known compounds are phenolics, carotenoids, essential oils, essential fatty acids, and insoluble vitamins. One of the biggest bottlenecks in the industry is the application of these compounds in the pharmaceutical and food industries due to their low bioavailability and stability. By incorporating functional elements in food, its bioavailability can be increased. Thus, nanotechnology has become a useful tool for this purpose, with nanoemulsions and nanocomposites in development (Hamad et al. 2018; Rezaei et al. 2019).

Nanoencapsulation is an emerging and interesting alternative for application in the preservation and protection of bioactive compounds (against inappropriate environmental circumstances) and with this increase in their bioavailability and stability, the bioactive compounds could be applied in food and pharmaceutical products (Rezaei et al. 2019). The encapsulation can decrease volatility and increase chemical and thermal stability; it can also protect these compounds from factors such as oxygen, light, pH, moisture, and gastric digestion; another interesting fact is that nanoencapsulation can also disguise the unpleasant taste and aroma of the compounds. It can also promote controlled release and improve the solubility of lipophilic compounds in aqueous media, allowing prolonged absorption of nutrients. Such advantages are possible by reducing the size of the nanoparticles, thus increasing the area per unit volume (Rezaei et al. 2019; Bazana et al. 2019).

Nanoencapsulation is the action of involving a substance using nanocarriers by absorption, incorporation, chemical interaction, or dispersion. There are several nanoencapsulation techniques to produce bioactive and nutraceutical compounds. Bazana et al. (2019) developed different nanocarriers, such as nanoemulsions; they can be nanostructured lipid transporters, nanosuspensions, solid lipid nanoparticles, nanometric liposomes and phytosomes, solid biopolymer lipid nanoparticles, and micelles made of proteins, polysaccharides, or their complete conjugates (Bazana et al. 2019).

The literature also discusses other nanotransporters, such as inclusion complexes by means of cyclodextrins, amylose and yeast cells, nanogels, nanofibers, nanosponges, or nanoparticles made of lipids and biopolymers. Some nanoencapsulation techniques require specialized equipment, such as electrospinning, electrospray, nanospray dryers, and microfluidic devices. Various natural and synthetic polymers are used for nanoencapsulation. Natural encapsulating materials include polymers such as chitosan, alginates, cyclodextrins, and phospholipids, among others. Synthetic polymers include biodegradable esters, such as lactic-co-glycolic polyacid, poly-and-caprolactone polymers, and methacrylate. Few studies have compared various methods or materials for a specific bioactive compound or ingredient, making this difficult (Bazana et al. 2019).

6.2 Nanoencapsulation Process of Phenolic Compounds and Antioxidants

The study on the nanoencapsulation of phenolic compounds and antioxidants is very promising, because this technique can increase surface area, causing an orientable release, protection against different stresses during the processes, and storage of biomolecules when compared to microencapsulation. In addition, it causes an improvement in the bioavailability of such molecules, in relation to combating free radicals, diseases, and enhancing antimicrobial activity. The bioavailability of phenolic and antioxidant compounds can be increased with greater solubility, absorption, and permeation of such substances in the body and in food and medication formulations through the nanoencapsulation process (Fig. 3.2).

When humans consume nanoencapsulated products, many physical and chemical changes occur during their passage through the digestive system from the mouth-stomach to the intestine, which can affect their digestion and/or absorption capacity. Phenolic and nanoencapsulated antioxidants are more stable in stomach conditions, as the pH and enzymes are low, compared to their unencapsulated form. Nanoencapsulation can allow phenolics and antioxidants to be passively absorbed from the lumen of the intestine into the blood and lymphatic circulatory system; therefore, its bioavailability can increase considerably (Esfanjani and Jafari 2017).

According to Esfanjani and Jafari (2017), nanoencapsulation of phenolic and antioxidant compounds can provide the following main benefits:

1. Provide a larger surface area for interaction with biological substrates.
2. Delivers greater encapsulation efficiency compared to the microencapsulation process.
3. Increase the solubility of antioxidants and phenolics that are poorly soluble in water: this can occur in nanoparticles based on biopolymers. In fact, poorly soluble compounds are trapped within the nanoparticles and are coated by polar groups on the surface of the particles.
4. Increase the absorption of phenolics and antioxidants by interrupting hermetic junctions and / or direct uptake by epithelial cells through endocytosis.
5. Protect phenolics and antioxidants against oxidation / degradation in the gastrointestinal tract.

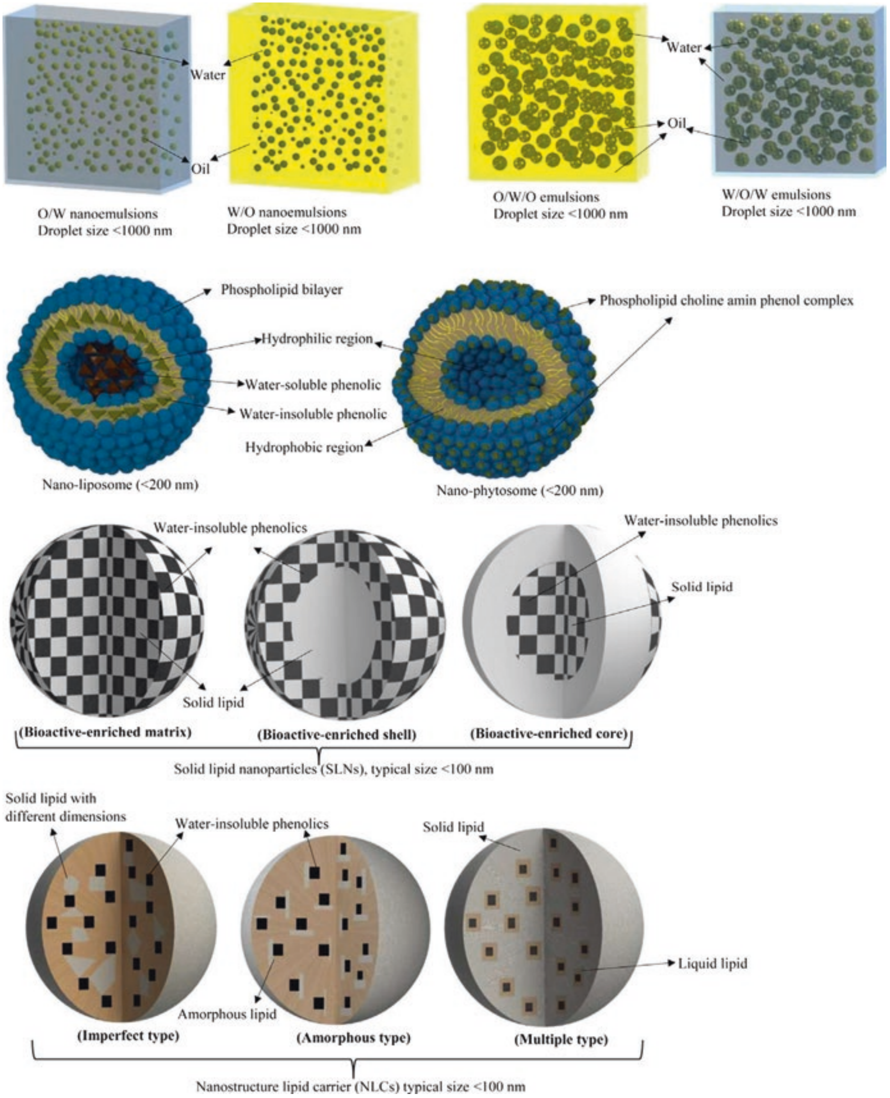

Fig. 3.2 Presents a schematic of a nanoencapsulation of phenolics by lipid-based formulation method. (Reproduced from Esfanjani and Jafari (2017) with permission of *Nanoencapsulation of food bioactive ingredients*)

6. Temperature, pH, oxygen, light, mixing, enzymes, proteins, and metal ions are among environmental and process stresses that phenolics and antioxidants must withstand. This can help it last longer in storage and processing.
7. Multilayer nanoencapsulation technologies, for example, can release and target phenolic chemicals in food formulations for a longer period of time.

8. It can mask the bitter taste of phenolics and antioxidants, limiting its use in food compositions such beverages and chewing gums.
9. Commercialization of transparent drinks enriched with phenolics and antioxidants; these goods can be made using nanoemulsions (100 nm) in which other taste constituents are disrupted in the emulsion's oil or water phase.
10. Nanoencapsulated powders produced using drying nanoprojection, electrospray, and electrospinning devices provide easy handling and packaging of phenolic and nanoencapsulated antioxidants.

7 Conclusion

The importance of ethnobotanical information on medicinal plants in the Amazon is extremely important for the identification of bioactive compounds and the production of possible drugs from these raw materials. The available literature shows that these bioactive compounds have already been tested on a wide range of microorganisms. Amazon has a great biodiversity and within that diversity, it represents several potential herbs that are utilized in the maintenance of health. Several techniques for the extraction of bioactive compounds from plants have already been reported; however, greater attention is now being paid to unconventional techniques. Nanotechnology has emerged as a great tool to help potentiate the action of bioactive compounds; however, the toxicity and safety of nanomaterials should also be evaluated before its use.

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