Pharmacological Research 112 (2016) 4–29

Contents lists available at ScienceDirect

Pharmacological Research

journal homepage: www.elsevier.com/locate/yphrs

Review

Medicinal plants in Brazil: Pharmacological studies, drug discovery, challenges and perspectives

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ARTICLE INFO

Article history:
Received 16 January 2016
Accepted 17 January 2016
Available online 23 January 2016

Keywords:
Biodiversity
Medicinal plants
Herbal drugs development
Phytomedicine
Cordia verbenacea
Euphorbia tirucalli
Mandevilla velutina
Euterpe oleracea
Vitis labrusca
Hypericum
Maytenus ilicifolia
Protium
Trichilia catigua

ABSTRACT

This review article focuses on pre-clinical and clinical studies with some selected Brazilian medicinal plants in different areas of interest, conducted by research groups in Brazil and abroad. It also highlights the Brazilian market of herbal products and the efforts of Brazilian scientists to develop new phytomedicines. This review is divided into three sections. The section I describes the Brazilian large biodiversity and some attempts of Brazilian scientists to assess the pharmacological profile of most plant extracts or isolated active principles. Of note, Brazilian scientists have made a great effort to study the Brazilian biodiversity, especially among the higher plants. In fact, more than 10,000 papers were published on plants in international scientific journals between 2011 and 2013. This first part also discussed the main efforts to develop new medicines from plants, highlighting the Brazilian phytomedicines market. Despite the large Brazilian biodiversity, notably with the higher plants, which comprise over 45,000 species (20–22% of the total worldwide), and the substantial number of scientific publications on medicinal plants, only one phytomedicine is found in the top 20 market products. Indeed, this market is still only worth about 261 million American dollars. This represents less than 5% of the global Brazilian medicine market. The section II of this review focus on the use of Brazilian plant extract and/or active principles for some selected diseases, namely: central nervous systems disorders, pain, immune response and inflammation, respiratory diseases, gastrointestinal tract and metabolic diseases. Finally, section III discusses in more details some selected Brazilian medicinal plants including: *Cordia verbenacea*, *Euphorbia tirucalli*, *Mandevilla velutina*, *Phyllanthus* spp., *Euterpe oleracea*, *Vitis labrusca*, *Hypericum caprifoliatum* and *Hypericum polyanthemum*, *Maytenus ilicifolia*, *Protium kleinii* and *Protium heptaphylium* and *Trichilia catigua*. Most of these publications are preliminary and only report the effects of crude extracts, both *in vitro* and *in vivo* studies. Only very few studies have been dedicated to investigate the mechanisms of action of isolated compounds. Likewise, studies on safety (toxicology), pharmacokinetic, and especially on well-conducted clinical trials are rare. In conclusion, in spite of the abundant Brazilian biodiversity and the thousands of academic publications on plants in international peer-reviewed scientific journals, few patents and medicines have been derived from such studies. Undoubtedly, great efforts must be made to improve the development of plant-derived medicine market in Brazil, especially by involving the partnership between academia and pharmaceutical companies.

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http://dx.doi.org/10.1016/j.phrs.2016.01.021
1043-6618/

Contents

1. Introduction

The use of medicinal plants by the population, as an alternative therapy to treat many diseases, has been a common practice since thousands of years before Christ. For example, the use of poppy (*Papaver somnniferum*) and marijuana (*Cannabis sativa*) has been described for as long as 4000 years. However, the search for the active constituents present in medicinal plants only began in the nineteenth century, thus leading to the conception of the first drug with the characteristics that we know today. Friedrich Serturner, in 1806, was a pioneer when he isolated the alkaloid morphine from poppy: an event that prompted a continuous search for other plant-derived medicines. In 1824, Pierre-Jean Robiquet isolated codeine, an antitussive agent also from poppy, and in 1848, George Merck Fraz isolated the anti-spasmodic alkaloid papaverine from this same plant. Other important examples of active constituents isolated from medicinal plants comprise atropine (muscarinic antagonist) isolated from *Atropa belladonna* by Mein in 1831; caffeine obtained by Runge in 1820 from *Coffea arabica*; digoxin (digitalis) isolated by Claude-Adolphe Nativelle in 1869 from *Digitalis lanata*; and curare (muscle relaxant) isolated by Winstersteiner and Dutcher in 1943 from *Chondrodendron tomentosum*, among many other examples.

The historical landmark in the global pharmaceutical industry development was the discovery of salicin (analgesic and antipyretic) by Rafaele Piria, in 1832, from *Salix alba*. In 1839, the first structural modification from salicin was performed, yielding salicylic acid to be used in the treatment of rheumatoid arthritis. From the salicylic acid, Felix Hoffman synthesized aspirin (acetylsalicylic acid) in 1897. Thus, the famous and powerful pharmaceutical industry Bayer in Germany was born, as well as the first patent in the area of drugs.

The interest in medicinal products derived from higher plants [also known as herbal remedies or herbal medicines (phytomedicines)] has increased significantly worldwide. This interest is especially seen in developed countries, mainly in some European countries and in the United States. It is estimated that the global market for this class of drugs has reached 20 billion dollars annually [1]. Notably, the plant-derived compounds are currently employed in modern therapy, in addition to playing an important role for the synthesis of some more complex molecules. It has been estimated that about 30% of the available therapeutic medications are derived from natural sources, notably from plants and microorganisms. In some therapeutic areas, such as oncology, the amount of plant-derived medicines achieves 60% [1–4].

Many classes of active principles have been isolated from Brazilian medicinal plants [5]. In fact, Brazil has the highest total of biodiversity in the world, comprising over 45,000 species of higher plants (20–22% of the total existing on the planet), 4680 algae, 32,715 angiosperms, 1519 of bryophytes, 5652 fungi, 30 gymnosperms and ferns, and 1239 lycophytes. Additionally, there are over 7000 species of known vertebrates, with 692 species of mammals, 1026 species of amphibians, 744 species of reptiles, 1901 species of birds, in addition to 3000 species of fishes. There is known to be 96,660 to 129,840 species of invertebrates. Beetles and butterflies are particularly abundant—each group with about 26,000 species (http://www.sibbr.gov.br/areas/?area=biodiversidade).

The Brazilian population has a long tradition in the use of medicinal plants for the treatment of different acute and chronic diseases. This has called the attention of Brazilian researchers and some Brazilian pharmaceutical companies to study native medicinal plants and their active principles. More recently, the use of new technologies, such as proteomic and genomic approaches, has led to a recurring interest in natural products both from academia and from pharmaceutical companies [6,7].

Keeping in mind the above data, this review article will focus on recent studies conducted to evaluate the pharmacological properties of extracts and active principles isolated from Brazilian medicinal plants. Special attention will be given to those medicinal plants that were the subject of pharmacological studies published in international peer-review journals, with attempts to discuss the mechanisms of action of the active constituents.

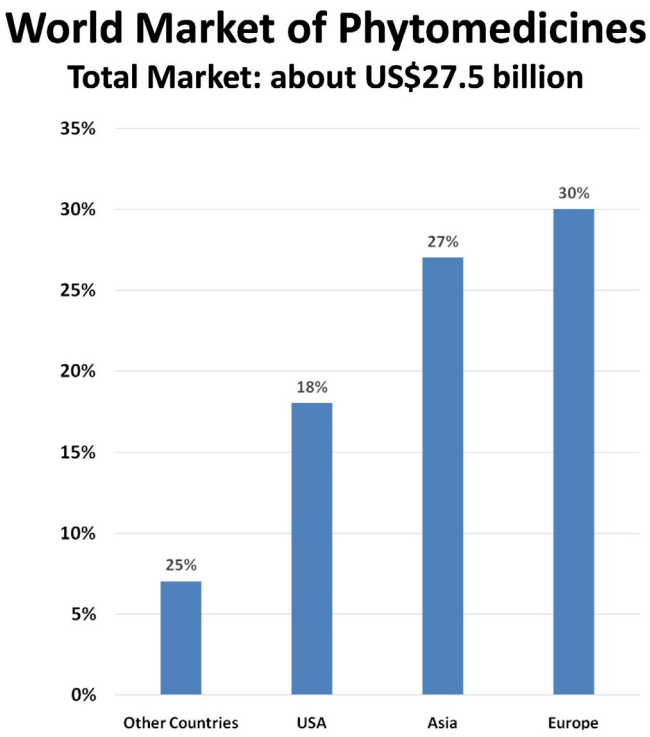

Fig. 1. World market of Phytomedicines.
This illustration shows that the world market of Phytotherapeutic agents earns about 27 billion American dollars and is mainly distributed in Europe, Asia and United States of America.
Source: Fitoscience Consultoria: www.fitoscience.com.br.

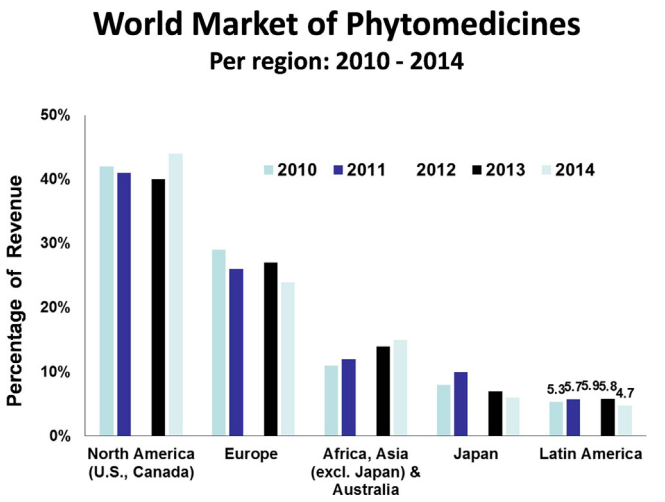

Fig. 2. World market of Phytomedicines per region between the years 2010 and 2014.
This graphic shows that the world market of Phytomedicines agents has been relatively stable during the last 5 years. Notwithstanding, the market for plant-derived drugs in Latin America, including Brazil is still very small, representing less than 5% of all marketed drugs.
Source: Fitoscience consultancy: www.coorpy.com.br/fitoscience-consultoria-ltda.

2. Section I

2.1. Brazilian market of herbal drugs (Phytotherapeutic agents)

In view of Brazil's large biodiversity and because of the great ethical influence of early colonization, Brazilians have a great interest in the use of herbal drugs to treat different illnesses [1]. It was in 1994 that the Brazilian Ministry of Health established the first directive to evaluate the safety, quality and efficacy of marketed herbal drugs. This proposed regulation was based mainly in the World Health Organization (WHO) guidelines and in the German and French directives that regulate the market of herbal drugs in such countries. The herbal drugs are considered medicines and their registration is based on scientific proof of safety, efficacy and quality. The Brazilian directives have been thoroughly improved, and new guidelines were launched and updated during the last two decades.

Despite the abundant Brazilian biodiversity and the great interest of the population in the use of traditional medicine, currently the Brazilian herbal medicine market is still very modest, representing about 261 million American dollars. This accounts for less than 5% of the global Brazilian medicine market, estimated to be about 28 billion American dollars in 2014. Fig. 1 shows that the world market of Phytotherapeutic agents is worth about 27 billion American dollars, mainly distributed in Europe, Asia and United States of America. Fig. 2 indicates that this market has been relatively stable during the last 5 years. As previously discussed [1], Brazilian scientists continue to publish a great amount of scientific papers on plants (Fig. 3). Despite this market and the great interest in herbal medicines in Brazil, Table 1 shows that only one Brazilian Phytotherapeutic agent (Acheflan® produced by the oil of the plant *Cordia verbenacea*) is found among the top 20 products marketed in Brazil. Plants imported from other countries, notably from Europe

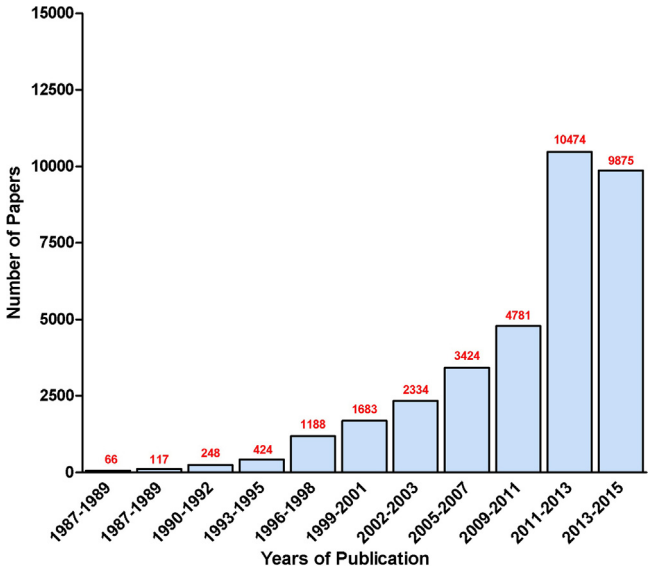

Fig. 3. Number of papers published by Brazilian scientists on plants in the last 28 years.
Brazilian scientists published a great amount of scientific papers about plants in the last 28 years (between the years 1987 and 2015). Surprisingly, between 2011 and 2013 Brazilian researchers published more than 10,000 scientific articles on this topic. Total number of manuscripts: 34,614 papers. Keywords used for searching were: plants (Title—Abstract—Keywords) in the Life Sciences or Health Sciences (Subject area). Document type—original article or review. Date: October 21st 2015.
Source: Scopus.

and Africa, take part of the other 19 products. Unfortunately, these data noticeably show a real dissociation among the great number of scientific publications on plants by Brazilian scientists, when compared to the low development of new innovative Phytotherapeutic agents, as well as the discreet innovation initiatives.

Table 1
Top 20 Brazilian Phytomedicines products by sales, 2013–2014 (millions of US dollars).

RKN	Products	Pharmaceutical companies	2013 (U$)	2014 (U$)
1°	TAMARINE	FARMASA	30.26	26.62
2°	ABRILAR	Farmoquímica	26.61	23.96
3°	SEAKALM	Natulab	17.55	19.28
4°	GINKOLAB	Multilab	15.93	15.41
5°	FORFIG	EUROFARMA	12.20	14.60
6°	EPAREMA	Takeda	16.46	14.35
7°	PASALIX	MARJAN FARMA	14.07	13.89
8°	NATURETTI	SANOFI-AVENTIS	14.09	12.70
9°	HAAR + HAIR INTEM	Vitamed	5.65	12.09
10°	CALMAN	Ativus	11.26	11.60
11°	PLANTABEN	Takeda	11.83	11.59
12°	ACHEFLAN	ACHÉ	11.35	11.06
13°	KALOBA	Takeda	10.72	10.46
14°	ARPADOL	APSEN FARMACÊUTICA	10.20	10.31
15°	ARLIVRY	Natulab	8.45	10.14
16°	TORANTE	EUROFARMA	10.61	9.86
17°	PHITOSS	Brasterápica	10.58	9.70
18°	GINKOMED	CIMED	7.73	8.24
19°	TEBONIN	Takeda	9.03	8.08
20°	LEGALON	Takeda	6.88	6.93

US dollar value in Reais (R$): 2013 1 U$ = R$ 2.173; 2014 1 U$ = R$ 2.259. RKN, ranking.

3. Section II

3.1. Medicinal plants and central nervous systems disorders

The central nervous system (CNS) is a complex and refined system that regulates and coordinates the body's main activities. It is vulnerable to a range of disorders, including: (i) vascular disorders (stroke and hemorrhage); (ii) infections (meningitis and encephalitis); (iii) structural disorders (brain or spinal cord injury, peripheral neuropathy and Guillain–Barré syndrome); (iv) functional disorders (headache and epilepsy); (v) neuromuscular diseases (motor neuron disease); (vi) degenerative diseases [Parkinson's disease, amyotrophic lateral sclerosis (ALS), and Alzheimer's disease]; (vii) autoimmune diseases [multiple sclerosis (MS) and myasthenia gravis] [8,9]. While most conditions in this group cannot be completely cured, the symptoms of CNS diseases can often be managed through a variety of therapies, from therapeutic to surgical treatment [10].

Pre-clinical studies showed that a small number of Brazilian researchers have focused their studies on the theme—medicinal plants and central nervous system disorders. From these, it is worth mentioning the studies for some disorders: stroke—Barbosa et al. [11], and de Lima et al. [12]; encephalitis—Chávez et al. [13]; peripheral neuropathy—Barreiros et al. [14], Nishijima et al. [15], Perez et al. [16], Klein-Júnior et al. [17], da Silva et al. [18], and Kassuya et al. [19]; epilepsy—Aragão et al. [20], Marques et al. [21], Nóbrega et al. [22], Branco et al. [23], Faggion et al. [24], Duarte et al. [25], and Viana et al. [26]; Parkinson's disease—Antunes et al. [27], Campos et al. [28], Moreira et al. [29] and Milioli et al. [30]; Alzheimer's disease—Bittencourt et al. [31], da Rocha et al. [32] and Figueiró et al. [33]; multiple sclerosis—Dias et al. [34] and Alberti et al. [35]. Nonetheless, only 28 processes describing the pharmacological effects of native medicinal plants for CNS disorders were found to have a registered patent in the Brazil patent database consulted—INPI. In Brazil, only methods or inventions are patentable—not species and their constituents, leading to many species being taken to other countries and studied in foreign laboratories. Together, these facts may explain the number of patents of Brazilian studies registered in international offices, as well as the absence of patents for Brazilian studies in the country. The fact that no records have been found of medications in Brazil for CNS disorders using native medicinal plants comes as no surprise. This could be explained, at least in part, by the lack of financial incentive from the government for the study of natural products and to the recent difficulties in Brazilian legislation concerning the study of medicinal plants. Thus, the incentive provided by university-business company partnerships to finance wide scale projects and train groups of professionals is of great importance to Brazil and is necessary to reverse these obstacles.

3.2. Use of medicinal plants during pain conditions

Pain is considered as a global health problem and the affected individuals can experience acute pain, chronic or intermittent pain, or a combination of them [36–39]. It is estimated that 20% of adults suffer from pain and that every year more than 10% of adults are diagnosed with chronic pain, worldwide [37,38]. Despite the painful processes affect the whole population, their markedly differ according to age, sex, incomes, race/ethnicity, and geography [38]. In addition, both acute and chronic pain conditions are a huge burden in the USA, costing 650 million lost workdays and about $65 billion a year [40]. The main causes of painful processes conditions are cancer, osteo- and rheumatoid arthritis, surgeries, injuries and spinal problems, making the etiology of pain complex. Moreover, pain induces multiple serious sequelae that cannot be underestimated, including inability to work, disrupted social relationships, depression and suicidal thoughts [37–39].

Of note, medicinal plants greatly contributed to the knowledge of the biological mechanisms related to generation, transmission, maintenance and control of pain. Notably, the main drugs currently used as analgesics were derived from plants or were synthesized based on natural products. However, the available analgesic drugs are not ideal for all patients and even for different types of pain. Therefore, they should be used carefully, taking into account patient-specific goals, disease states, and changes in pharmacokinetics and pharmacodynamics due to critical illness [39]. Thus, the developments of safe new analgesics with reduced side effects are urgently needed. In Brazil, the infusion of leaves, stems, and roots of different plants are widely used in popular medicine throughout the country for the treatment of various painful conditions. In this part of the review, we highlight the plants used to control pain.

According to the scientific evidence, the Brazilian National Agency of Sanitary Vigilance (Agência Nacional de Vigilância Sanitária, ANVISA) regulates the production and marketing of 66 plants, and establishes under which conditions each herbal medicine should be used (http://portal.anvisa.gov.br/). Among them, we highlight eight plants, which were referred for the treatment of various painful conditions, including the *Lippia alba* (Verbenaceae), *Arnica montana* (Asteraceae), *Calendula officinalis* (Asteraceae), *Harpagophytum procumbens* (Pedaliaceae), *Uncaria tomentosa* (Rubiaceae), *Vernonia condensata* (Asteraceae), *Casearia sylvestris* (Salicaceae), and *Zingiber officinale* (Zingiberaceae). Herein, we will describe other plants that also have potential for use in painful conditions.

Drymis winteri (Winteraceae) is a medicinal plant found in South America popularly known in Brazil as "casca-de-anta" and used in folk medicine as an anti-inflammatory. Pre-clinical studies have shown that hydroalcoholic extract, and the isolated sesquiterpenes polygodial and drimanial obtained from the barks of *D. winteri*, exhibit an analgesic effect on acute pain models in rodents [41–46]. The antinociceptive activity of polygodial depends on the interaction with the opioid receptors, mainly κ and δ subtypes, α_1-adrenoceptors, TRPV1 channels, and the serotonergic system [43,45,47]. The antinociceptive effect of drimanial seems to be associated with its ability to modulate metabotropic glutamate receptors and TRPV1 channels [44–47]. Collectively, these findings

suggest that polygodial and drimanial or their derivatives may be important for the development of new analgesic drugs in the future.

Other plants used in folk medicine for their antirheumatic, anti-inflammatory (sore throat) and analgesic activities, are those of genus *Pterodon* (Fabaceae) popularly known as "sucupira", "sucupira-branca", "faveira", among others. Trees of this genus are native and widely distributed in central Brazil and consist of 5 species, including *Pterodon abruptus Pterodon apparicioi* Pedersoli, *Pterodon polygalaeflorus*, *Pterodon pubescens* and *Pterodon emarginatus*. Alcoholic extracts from seeds of these plants are prepared and ingested by the population orally, in small quantities, at regular intervals due to their anti-inflammatory, analgesic, and anti-rheumatic properties [48,49]. Scientific studies have confirmed that the extract and terpenes (mainly sesquiterpenes and diterpenes) from *Pterodon* species seeds have antinociceptive effects in different animal models of acute and chronic pain without producing toxicity [50–59]. In addition, the hydroalcoholic extract of seeds of *P. pubescens* reduces the severity of collagen-induced arthritis in mice by inhibiting B-cell and CD4+ T-cell activation [60,61]. Further, the oleaginous extract of seeds *P. pubescens* inhibits the acute and chronic pain caused by plantar incision surgery (postoperative pain), hind paw ischemia and reperfusion (chronic post-ischemic pain), and partial sciatic nerve ligation (neuropathic pain) in mice [56,62]. However, the precise mechanism through of which extract of seeds of *P. pubescens* promotes its beneficial effects is still not completely known. It has been suggested that effects can be mediated, at least in part, by central blocking of ionotropic (NMDA and kainate) and metabotropic (mGluR1,5) glutamate receptors, as well as by inhibiting pro-inflammatory cytokines (TNF-α and IL-1β) signaling, cyclooxygenases, and by inhibiting both TRPV1 and TRPA1 channels located at the spinal cord dorsal horn [62,63].

Other plants used to treat pain are those belonging to the genus *Polygala*, including *Polygala cyparissias*, *Polygala paniculata* and *Polygala sabulosa*, are used in folk medicine as tonic remedies, topical anesthetics and expectorants. Pre-clinical studies have shown that the extract, fractions and some coumarins, xanthones, flavonoids and steroids obtained from *P. cyparissias*, *P. paniculata*, and *P. sabulosa* elicit antinociceptive effects in different animal models of acute and chronic pain, including cytokine-induced pain [17,64–67]. Pharmacological evidence indicates that the antinociceptive effect of the extract and constituents of *P. paniculata* and *P. sabulosa* depends on the interaction with ionotropic (NMDA and kainate) glutamate receptors and may involve the inhibition of pro-inflammatory cytokines pathways [66,67].

The native medicinal plant of Brazil, *Siphocampylus verticillatus* (Campanulaceae), popularly known as "coral" and "jarataca" is used in traditional medicine to treat asthma. However, pre-clinical studies have shown that the extract and alkaloid (*cis*-8,10-di-*N*-propyllobelidiol hydrochloride dehydrate, DPHD) obtained from the dried stems and leaves of *S. verticillatus* produces graded and long-lasting antinociception in several chemical models of pain in mice [68,69]. Moreover, the antinociceptive action of the extract and of the main alkaloid DPHD involves multiple sites of action, mainly the interaction with μ, δ and κ opioid receptors, serotonergic system and L-arginine-nitric oxide pathway [68,69]. Unlike morphine, the alkaloid DPHD does not cause tolerance or cross-tolerance with morphine [69]. A second alkaloid obtained from the plant, named oxysophoridine, causes antinociception in thermal and chemical behavioral models of pain in rodents [70,71]. Oxysophoridine-induced antinociception results from the activation of $GABA_A$ receptors in both central and peripheral nervous systems [70,71]. Also relevant are the findings demonstrating that the extract of *S. verticillatus*, administered orally, has an antidepressant-like effect in two models predictive of antidepressant activity, the forced swimming and tail suspension tests, in mice [72]. Interestingly, the extract of *S. verticillatus* inhibits the synaptosomal uptake of noradrenaline, serotonin and dopamine. Thus, both *in vivo* and *in vitro* data suggests that the antidepressant-like (and probably the antinociceptive) effect of *S. verticillatus* involves an interaction with adrenergic, dopaminergic, glutamatergic and serotonergic systems.

3.3. Immune response, inflammation and medicinal plants

Humans have evolved a highly complex immune system composed of specialized immune cells, which protects the host from infection and damage. However, during an uncontrolled immune response, such as chronic inflammation, genetic mutation, immunosuppression or molecular mimicry, individuals become more susceptible to diseases, for instance autoimmune diseases and other immune-mediated inflammatory disorders [73,74]. Inflammatory chronic diseases are the largest cause of death in the world. In 2015, the leading inflammatory chronic diseases—cardiovascular diseases, cancer, chronic respiratory diseases, autoimmune diseases, and diabetes—caused 300 million deaths worldwide (World Health Organization—WHO, 2015). Worldwide annual mortality due to inflammatory diseases is expected to increase in real numbers, as well as relative to deaths from injuries and diseases traditionally understood to be infectious such as polio, rubella, tuberculosis [75].

Over the past 25 years, the number of pre-clinical studies by Brazilian researchers related to anti-inflammatory effects and immunomodulatory medicinal plants is astonishing. Conversely, a limited number of clinical studies have emerged from these studies. This part of the review will focus on clinical studies using plant-derived products that are able to prevent the immune-mediated disorders. Initially, an open, randomized, controlled study with two parallel treatment groups was performed to evaluate the efficacy of *Lippia sidoides* essential oil (EO) 1% compared with chlorhexidine 0.12%, in the treatment of dental plaque and gingivitis. Interestingly, the clinical and microbiological parameters were significantly reduced by both treatments, associated with a significant reduction in the colony counts of *Streptococcus mutans* in both groups. Thus, the authors concluded that *L. sidoides* EO is clinically effective in reducing microbial plaque and gingival inflammation [76].

A publication by Colpo et al. [77] discussed the advantageous anti-inflammatory action of Brazilian nut consumption by healthy volunteers. The same study also demonstrated that a single intake of Brazil nuts (20 or 50 g) caused a significant decrease in serum IL-1, IL-6, TNF-α, and IFN-γ levels, whereas a serum level of IL-10 was significantly increased. This evidence has been further extended by studies showing that the supplementation of one unit of Brazil nut, *Bertholletia excelsa* popularly known as "castanha-do-brasil" (the richest known food source of selenium), once a day over 3 months effectively improves selenium status and increases glutathione peroxidase (GPx) levels in hemodialysis patients [78,79]. Recently, Viecili et al. demonstrated the anti-inflammatory and antihyperlipidemic effects of *Campomanesia xanthocarpa*, commonly known as "guavirova", in hypercholesterolemic (HL) individuals, when compared with the placebo group [80].

A clinical study showed the antihypertensive effect of chia supplementation (*Salvia hispanica* L.). The chia-group showed reduction in the: (i) mean clinical blood pressure (MBP); (ii) lipid peroxidation, and (iii) plasma nitrite levels compared with the placebo group [81]. Furthermore, *Pelargonium sidoides* extract up regulated the production of secretory IgA in saliva, as well as down regulated both IL-15 and IL-6 in serum, and IL-15 in the nasal mucosa of athletes after exhaustive exercise [82]. Finally, Bopp et al. demonstrated that aqueous leaf extract of *Syzygium cumini*, popularly known as "jamelão" inhibited adenosine deami-

nase activity and reduced glucose levels in hyperglycemic patients [83]. Thus, the scanty number of clinical studies evaluating the anti-inflammatory and immunomodulatory actions of herbal product conducted by Brazilian groups draws attention and especially alert to the quality and clinical relevance of research carried out in the country.

3.4. Medicinal plants and respiratory diseases

There are a series of acute and chronic respiratory diseases affecting the population worldwide. Among the acute alterations, both lower respiratory tract infections and pneumonia represent life-threatening conditions commonly related to prolonged periods of hospitalization with an extensive use of antibiotics [84]. Alternatively, both environmental (air pollution and tobacco exposure) and genetic factors contribute to the high incidence of chronic airway diseases, including pulmonary fibrosis, chronic obstructive pulmonary disease (COPD), and asthma. In those circumstances, the affected individuals show exaggerated inflammatory responses compromising the bronchial and alveolar epithelium, which requires the continued use of diverse medications that present a series of collateral effects [84,85]. It has been suggested that traditional herbal-based therapies can represent valuable options for the treatment of cold, cough, fever, ear and throat infections, in addition to chest pain and asthma, in both developing and developed countries [86–91]. This supports the relevance of medicinal plants for respiratory diseases.

Of interest, the plants from genus *Mikania*, which are popularly known as “guaco” have long been used by the Brazilian Indians for their medicinal properties. In addition, the species *Mikania glomerata* and *Mikania laevigata* are widely used in folk medicine due to their beneficial effects on respiratory diseases, demonstrating anti-cough, expectorant and bronchodilator activities [92]. The literature data demonstrated that treatment with the aqueous or the hydroalcoholic extracts from *M. glomerata* and *M. laevigata*, along with the isolated compounds coumarin and *O*-coumaric acid, prevented the alterations observed in a mouse model of allergic inflammation [93]. Furthermore, the hydroalcoholic extracts from the aerial parts of *M. glomerata* and *M. laevigata* widely prevented the pulmonary inflammation and the generation of oxidative stress induced by the intratracheal exposure of rats to coal dust [92]. Another publication revealed the ability of the fraction MG1 obtained from the ethanolic extract from *M. glomerata*, to inhibit the allergic pleurisy in mice pre-sensitized to ovalbumin [94]. MG1 also reduced the neutrophil migration in the pleurisy model caused by the inflammatory mediator, platelet activating factor (PAF), although it failed to alter the pleurisy caused by histamine, serotonin (5-HT) or carrageenan [94]. Interestingly, a clinical study enrolling 86 patients demonstrated clear beneficial effects for the Brazilian phytomedicine product Melagrião® (composed by *M. glomerata* and associations) on the symptoms of acute bronchitis, with an efficacy similar to that observed for the mucolytic agent bromhexine (http://www.repositorio.ufc.br/handle/riufc/27350).

3.5. Medicinal plants and gastrointestinal tract pathology

Gastrointestinal disorders (GIDs), including peptic ulcer disease, inflammatory bowel disease (IBD), gastroesophageal reflux disease (GERD), colon cancer, and colonic diverticulitis affect millions of people worldwide and place a highly significant economic burden on the healthcare systems [95]. GIDs are currently treated with drugs and surgery, as well as psychological and behavioral therapy. Nonetheless, recently, alternative and complementary medicines, such as herbal/dietary therapies have become increasingly popular in persons with digestive disorders, especially when conventional therapies fail to improve their symptoms [96]. Earlier studies carried out by Brazilian scientists transformed plants and herbal remedies used as folk medicine into an important pharmacological tool aimed at improving the discovery of new therapeutic drugs for the GIDs. Herein, we focused our attention on the crucial and important species and/or molecules that have shown biological activity in the animal models of peptic ulcer and ulcerative colitis.

Initially, it was demonstrated that oral and intraperitoneal administration of the extract obtained from *Maytenus aquifolium* and *Maytenus ilicifolia* leaves inhibited the ulcer lesions induced by indomethacin and cold-restraint stress in rats [97]. This evidence was further extended by Vilegas et al., who demonstrated that quercetin 3-*O*-α-L-rhamnopyranosyl(1→6)-*O*-[β-D-glucopyranosyl(1→3)-*O*-α-L-rhamnopyranosyl(1→2)-*O*-β-D-galactopyranoside and kaempferol 3-*O*-α-L-rhamnopyranosyl(1→6)-*O*-[β-D-glucopyranosyl(1→3)-*O*-α-L-rhamnopyranosyl(1→2)-*O*-β-D-galactopyranoside isolated from *M. aquifolium* leaves showed antiulcer activity in rats [98]. Furthermore, an ethanolic fraction of the aerial parts of *Turnera ulmifolia* inhibited the cotton pellet granuloma and the increase of vascular permeability induced by histamine, 5-HT and PGE_2, but not that produced by bradykinin (BK), which may be related to an increase of mucosal defensive factors, such as prostaglandin and mucus [99,100]. Interestingly, resin obtained from *Copaifera langsdorffii* stem barks inhibited experimental gastric lesions in rodents [101].

Importantly, several pre-clinical studies conducted by Brazilian groups have been published in the last 25 years, which demonstrated the gastroprotective effect of miscellaneous plant species and/or isolated compounds such as: *Celtis iguanaea* (Jacq.) Sargent (esporão-de-galo) [102]; *Croton campestris* (velame do campo) [103]; *Citrus aurantium* (orange-bitter) [104]; *Hyptis martiusii* (Lamiaceae) (cidreira-do-mato) [105]; *Tabebuia avellanedae* (ipê-roxo) [106]; *Indigofera truxillensis* (anileira) [107]; *Hymenaea stigonocarpa* (jatobá-do-cerrado) [108]; *Byrsonima intermedia* (murici-pequeno) [109]; *Anacardium humile* (cajuzinho do cerrado) [110]; 1,3-*O*-dicaffeoylquinic acid isolated from *Arctium lappa* (greater burdock) [111]; β-myrcene [112] and β-pinene [113]; rhamnogalacturonan isolated from *Acmella oleracea* (jambu) [114]; carvacrol, a monoterpene present in the essential oil of oregano [115]; (−)-α-bisabolol [116]; ellagic acid [117]; barbatusin and 3-β-hydroxy-3-deoxibarbatusin isolated from *Plectranthus grandis* (boldo) [118]; centipedic acid from *Egletes viscosa* (macela) [119]; mangiferin, a glucosylxanthone from *Mangifera indica* (manga) [120]; nerolidol isolated from *Baccharis dracunculifolia* essential oil (alecrim-do-campo) [121]; nor-clerodane diterpene *trans*-crotonin isolated from the barks of *Croton cajucara* [122]; among others. Conversely, no toxicological and clinical study were conducted with these herbs and/or isolated compounds, as well as no new innovative drug have been launched in recent years to treat GIDs, justifying future clinical research.

Moreover, Rodrigues et al. showed the anti-colitis effect of *Myracrodruon urundeuva*, popularly known as ‘aroeira’ [123]. as well as administration of paepalantine, isolated from *Paepalanthus bromelioides*, inhibited 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced experimental colitis in rodents [124], which were associated to its antioxidant effects [125]. Other studies from our research group reported that different terpene compounds, such as β-caryophyllene, euphol and α,β-amyrin inhibited experimental acute colitis in mice [126–128].

Recently, a very interesting study conducted by Cazarin et al. showed that *Passiflora edulis* peel intake decreased colon damage scores, colon lipid peroxidation and number of aerobic bacteria and enterobacteria. It also improved the serum antioxidant status, acetic and butyric acid levels in the feces and number of bifidobacteria and lactobacilli, suggesting that *P. edulis* peel can

modulate microbiota during IBDs [129]. Likewise, the administration of grape juice concentrate (G8000™) supplied by Golden Juices in their drinking water reduced the noxious effects induced by colitis caused by TNBS [130] though down regulation in the expression of pro-inflammatory cytokines and reduction of genotoxicity in peripheral blood cells [131]. It was also reported that in mice orally treated with Hev b 13—an allergenic esterase obtained from the rubber tree *Hevea brasiliensis*—the clinical signs of diarrhea, rectal prolapse, body weight loss and histological damage of the distal colon, were reduced in comparison with TNBS-untreated mice [132].

3.6. Medicinal plants and metabolic diseases

The metabolic syndrome encompasses a group of metabolic and cardiovascular alterations, including abdominal obesity, hypertension, hyperglycemia, insulin resistance, and dyslipidemia, with a high risk of development of type-2 diabetes and myocardial infarction. This medical condition affects more than 40-million people only in the United States. Alarmingly, there has been a prominent increase in the rates of metabolic syndrome in developing countries, more specifically in Latin America and Asia during the last decade [133,134]. The core of the metabolic syndrome is a chronic inflammatory state, and most of the marketed therapeutic options for treating this syndrome are known to display anti-inflammatory effects, including the anti-hypertensive angiotensin-converting enzyme blockers or the lipid-lowering drugs statins [134]. Diet changes and alternative therapies (such as the use of medicinal herbs) also appear to be beneficial as adjuvants for the control of metabolic syndrome, partly due to their anti-oxidant and anti-inflammatory effects [135].

Besides the fish oil-derived omega-3 fatty acids from animal origin, there are various plant species including *Magnolia officinalis*, *Spirulina maxima*, *Cochlospermum vitifolium* that need to be mentioned, considering their common popular use to control the pathological changes associated to metabolic syndrome, especially for obesity control [136]. A publication by Pérez-Torres et al. [137] discussed the advantageous anti-oxidant, anti-inflammatory and anti-dyslipidemic actions of the aqueous extract of the popular medicinal plant *Hibiscus sabdariffa*, as well as the isolated active compounds, namely anthocyanins, protocatechuic acid and polyphenols. The same authors also presented a brief review on the benefits of the diet polyphenols curcumin and resveratrol, emphasizing their ability to interfere with relevant pathways involved in inflammation, including the PPARγ [137].

Graf et al. [138] published an interesting review article on several botanicals with recognized beneficial effects on the metabolic syndrome, which are widely used in the folk medicine. These included those from the genus *Cinnamomum* and *Crataegus* (popularly named cinnamon and hawthorn, respectively), as well as the plant species *Artemisia dracunculus* (Russian tarragon), *Momordica charantia* (bitter melon), *Trigonella foenum-graecum* (Fenugreek), *Vaccinium angustifolium* (lowbush blueberry), and *Vitis vinifera* (grape seed). Curiously, the authors highlighted the involvement of multiple biological targets in the mechanisms of action of such natural products.

To cite further examples of pre-clinical studies, the repeated administration of the aqueous leaf extract of *Clerodendron glandulosum* produced a reduction of plasma glucose, insulin resistance and dyslipidemia in a rat model of metabolic syndrome elicited by supplementation with 60% fructose in drinking water during 6 weeks [139]. Moreover, it was demonstrated that a single dose of the aqueous extract obtained from *Coriandrum sativum* was able to recover hyperglycemia, insulin resistance and dyslipidemia in obese-hyperglycemic-hyperlipidemic Meriones shawi rats [140]. Remarkably, the hydroalcoholic extract of the endemic Amazonian passion fruit species, *Passiflora nitida*, produced positive effects on oxidative stress and glycemic control, as shown by *in vitro* and *in vivo* models [141]. Confirming their popular use as antioxidants, both *Nigella sativa* (black seed; prepared as a powder) and *Allium sativum* (garlic, as a raw homogenate), administered alone or in combination, displayed favorable actions in a rat model of metabolic syndrome induced by the addition of 10% fructose in the drinking water [142,143]. In the light of literature data, it is rather clear that plant-derived products can be useful for preventing or treating the main alterations associated to the metabolic syndrome. However, most efforts should be engaged to integrate herbal formulations or phytotherapy products to the therapeutic arsenal for this intricate medical disorder.

4. Section III—special focus on selected Brazilian plants

4.1. Cordia verbenacea

C. verbenacea (Borraginaceae), popularly known as “erva-baleeira” or “maria-milagrosa”, is a perennial bush that grows throughout the Brazilian coast, within the Atlantic Forest. In folk medicine, their leaves have been used for their anti-inflammatory and cicatrizing effects. During the last 20 years, a few groups have investigated the potential effects of this plant and the related compounds, especially concerning its promising actions against inflammatory conditions. Accordingly, a Brazilian publication from 1990 demonstrated that oral administration of artemetin, a flavone isolated from *C. verbenacea*, produced a marked reduction of carrageenan-induced rat paw edema, with a similar grade of inhibition when compared to the non-steroidal anti-inflammatory drug phenylbutazone. In this study, the authors also showed the ability of this compound to reduce the granuloma formation, when administered in a protocol of repeated doses, showing low levels of toxicity [144]. The same group of research previously evaluated the crude extract from the leaves of *C. verbenacea*, and a similar anti-inflammatory effect with low toxicity was observed [145]. Another publication confirmed the anti-inflammatory effects of a lyophilized hydroalcoholic extract obtained from the leaves of *C. verbenacea* in an edema model induced by nystatin in rats, after the oral administration of the extract. Of interest, this extract displayed anti-inflammatory effects when applied topically, as evaluated in the ear edema formation evoked by croton oil in mice [146]. Moreover, both the oral and the topical administration of a crude lyophilized extract from leaves of *C. verbenacea* widely reduced the paw edema caused by nystatin in rats. This effect was similar to that obtained for naproxen [147]. The same crude extract, dosed orally, was also effective in preventing rat paw edema caused by miconazole, with superior anti-inflammatory effects in comparison to the non-steroidal or the steroidal anti-inflammatory drugs, nimesulide and dexamethasone, respectively [147]. In a protocol to assess possible fetal toxicity, the administration of the crude extract to male or pregnant female rats did not elicit any significant alteration of bone formation, development, sexual maturity or fertility of the progeny [147].

Almost one decade after the publication of the first Brazilian studies on *C. verbenacea*, our research group was engaged in a project involving collaboration between academia and industry, in order to identify the potential applicability of the essential oil extracted from the leaves of this plant as a novel anti-inflammatory strategy. This profitable collaboration resulted in the publication of scientific articles, but most importantly, it allowed the development of an innovative and highly effective analgesic and anti-inflammatory topical agent, named Acheflan®, which was first launched in the market as an ointment in 2005, and has been alternatively commercialized in a spray formulation since 2007.

The initial pre-clinical studies carried out with the essential oil from *C. verbenacea* showed its ability to reduce the edema formation elicited by a series of phlogistic agents, including carrageenan, bee venom, bradykinin (BK), substance P, histamine, and platelet activating factor (PAF), when given orally to rats. The administration of the essential oil also displayed marked anti-inflammatory effects in the neutrophil migration in the rat paw tissue, the pleural cavity or in the air-pouch model after the stimulation with carrageenan. Extending this evidence, the essential oil markedly inhibited both the allergic edema and the pleurisy caused by ovalbumin, in previously sensitized rats. Biochemical and molecular biology studies suggested that a modulation of TNF-α level is likely related to the anti-inflammatory actions of *C. verbenacea* essential oil, although the inhibition of COX-1 and COX-2 activity, or even changes in the production of IL-1β, do not seem to account for its effects. Two sesquiterpene compounds, namely α-humulene and *trans*-caryophyllene, appear to be responsible for the main anti-inflammatory effects of *C. verbenacea* essential oil. Of note, the administration of both compounds by gavage produced a great inhibition of carrageenan-induced paw edema in mice [148]. The oral administration of α-humulene and *trans*-caryophyllene also reduced the edema formation, the leucocyte migration, the production of cytokines, as well as the activation of mitogen-activated kinases (MAP-kinases) and NF-κB, finally preventing the up-regulation of the kinin inducible B_1 receptor in the rat paw tissue [149]. Additionally, both compounds reduced the production of TNF, whereas only α-humulene diminished the IL-1β levels, in carrageenan-injected rat paws. Notably, there was a marked reduction in the expression of inducible nitric oxide synthase and COX-2, as well as in the PGE_2 levels, in the experimental model of paw inflammation induced by carrageenan, in animals that had been treated with α-humulene and *trans*-caryophyllene [150]. The administration of α-humulene by oral or aerosol routes displayed marked anti-inflammatory effects in a mouse model of pulmonary inflammation evoked by ovalbumin re-exposure, whereas *trans*-caryophyllene failed to alter any inflammatory parameter in this experimental paradigm [151].

A series of previous publications revealed favorable actions for β-caryophyllene on experimental models of Alzheimer's disease, anxiety, depression and pain, probably by mechanisms dependent on μ-opioid and mainly cannabinoid type 2 receptors [152–154]. In this regard, a publication by our group showed marked inhibitory effects for beta-caryophyllene in the experimental models of colitis induced by DSS or oxazolone, via mechanisms involving the activation of cannabinoid 2 receptors and the proliferator-activated receptor-γ (PPARγ) [126]. The pharmacokinetic evaluation of the active compound α-humulene revealed a rapid onset and a satisfactory absorption following both oral and topical administration, supporting the clinical data on the marketed phytotherapy product Acheflan® [155].

Other Brazilian researchers extended reports on the anti-inflammatory effects of *C. verbenacea* and active compounds. Interestingly, the methanolic extract from *C. verbenacea* and the active isolated compound rosmarinic acid showed promising antiophidian properties in pre-clinical assays. This conclusion is based on experiments showing that treatment of animals with either the extract or the isolated compound significantly prevented the paw edema induced by the venom of the snake *Bothrops jararacussu* or its basic PLA_2 homologs in rats. Furthermore, *C. verbenacea*-derived rosmarinic acid improved the effects of a commercial polyvalent anti-venomous serum, in a model of myotoxicity induced by the intramuscular injection of *Bothrops* venoms or toxins into the right gastrocnemius muscle of mice [156]. As well, the ethanol extract from the leaves of *C. verbenacea* was able to lessen the release of histamine from mast cells of guinea pigs and hamsters, further showing the anti-allergic potential of this plant [157]. Of clinical relevance, the topical application of essential oil from *C. verbenacea* markedly prevented bone loss in a rat model of ligature-induced periodontitis, by mechanisms involving a decrease of the pro-inflammatory cytokine IL-1α, allied to an increase of the anti-inflammatory cytokine IL-10 [158]. More recently, an independent group published an article showing that the topical application of the phytomedicine Acheflan® led to an improvement of wound healing in rats, with a complete remodeling of epidermis, via modulation of metalloproteinase-9 (MMP-9) and vascular endothelial growth factor (VEGF) expression [159].

Toxicological pre-clinical studies (with both rodents and non-rodents) revealed a very satisfactory safety profile for the essential oil from *C. verbenacea*, containing both α-humulene and *trans*-caryophyllene, and the subsequent phase I, II and III clinical trials confirmed the efficacy of this product as anti-inflammatory and analgesic when used topically (unpublished results). This finally resulted in the approval of the phytotherapy product Acheflan® for human use by the Brazilian regulatory agency ANVISA in 2005. There is no doubt that development of Acheflan® was a real case of success in Brazilian history regarding medicinal plants. As shown in Table 1 Acheflan® is one the most prescribed phytomedicine in Brazil. We hope that this is going to occur more frequently, especially when considering the great potential of several research groups and the great Brazilian biodiversity. However, this will not be possible without radical changes in the culture of scientists, Brazilian pharmaceutical companies and in the governmental policies around drug development. Meanwhile, major efforts must be devoted to consolidating the culture of interaction between researchers in the Universities and in the productive sector.

4.2. *Euphorbia tirucalli*

Euphorbia tirucalli, commonly referred in Brazilian traditional medicine as "aveloz or espinho-italiano", is used in folk medicine for the treatment of syphilis, asthma, rheumatism, cancer and skin tumors [160]. On the other hand, the exposure to *E. tirucalli* has been suggested to be an important environmental risk factor for Burkitt's lymphoma (BI), considering a coincidence between endemic Bl and human exposure to *E. tirucalli*, particularly observed in Africa [161]. which draws attention to the toxic effects of this specie. This plant displays a diverse range of bioactive constituents, especially terpenes and sterols, including the alcohol euphol, α-euphorbol, taraxasterol and tirucallol [162]. The main constituents of the latex obtained from *E. tirucalli* are: (1) water (50–80%); (2) tigliane (phorbol esters) and (3) ingenane (ingenol esters). Moreover, fresh latex contains terpenic alcohol, taraxasterol and tirucallol [162].

Initially, a cooperative study was developed between the Center of Reproductive Biology of Juiz de Fora Federal University and the Antibiotic Department of Pernambuco Federal University (UFPE) to investigate the acute, chronic and reproductive toxicity of the latex from *E. tirucalli*. Interestingly, no clinical signs of maternal toxicity, such as alterations in locomotion, stereotypy, and presence of piloerection, diarrhea and deaths were observed after treatment with the latex of *E. tirucalli*. Additionally, maternal body, liver, kidney and ovary weights were similar in all groups. Moreover, the mean of embryos/mother, the proportion of blastocysts, late blastocysts and external malformation of face and limbs did not differ between the groups [162]. Another study addressed the anti-tumor effect of *E. tirucalli* after Ehrlich ascites tumor (EAT) model. Therapeutic treatment with ethanolic extract obtained from the aerial parts of *E. tirucalli* (125, 250 and 500 mg/kg, p.o.) stimulated marrow myelopoiesis, reduced spleen colony formation and tumor growth in the peritoneal cavity and enhanced survival, through inhibition of PGE_2 levels induced by the tumor [163].

Another study conducted by Bani et al. demonstrated the immunomodulatory effect of biopolymer fraction (BET) from the aerial parts of *E. tirucalli* in an experimental arthritic model through inhibition of T cells proliferation and pro-inflammatory mediators levels [164]. Four years later, our research group reported that preventive and therapeutic oral administration of euphol, a tetracyclic triterpene obtained from the sap of *E. tirucalli*, inhibited both DSS- and TNBS-induced acute colitis in mice, through inhibition of colon tissue levels and expression of IL-1β, CXCL1/KC, MCP-1, MIP-2, TNF-α, IL-6, NOS2, VEGF, Ki67, adhesion molecules, associated with the inhibition of NF-κB. Furthermore, euphol blocked LPS-induced release of pro-inflammatory mediators and up-regulated pro-resolution cytokine, like IL-10, from bone marrow-derived macrophages *in vitro* [127]. Supporting the above results, another study has reported that euphol significantly attenuates neurological signs of multiple sclerosis model through inhibition of pro-inflammatory mediators and adhesion molecules in the CNS [165]. This evidence has been further extended by a study showing that the topical application of euphol markedly blocked 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced ear edema and leukocytes influx through the inhibition of CXCL1, MIP-2, ERK, COX-2 expression and PKCα/PKCδ isozymes in the ear tissue [166]. Together, these data suggest that euphol, the main active constituent isolated from *E. tirucalli*, represents a promising agent for the management of peripheral and central inflammatory disorders with or without an autoimmune component. This notion has been extended by Abreu et al. (2014), who demonstrated that novel ingenol synthetic similar to those isolated from the sap of *E. tirucalli*, inhibited the HIV replication through modulation of LTR-driven transcription and surface proteins [167].

More recently, our group demonstrated that oral treatment with euphol elicited pronounced and long-lasting antinociception when assessed in different rodent behavior models of inflammatory and neuropathic persistent pain. These effects are associated with the ability of euphol to inhibit TNF-α, IL-1β levels, PKCε and COX-2 expression, as well as by inhibiting both transcription factors NF-κB and cyclic AMP response element binding protein (CREB) through modulation of both CB1 and CB2 cannabinoids receptor. The euphol effects occur both in the spinal cord and dorsal root ganglia levels [168,169]. In fact, King et al. demonstrated that euphol is able to inhibit the monoacylglycerol lipase (MGL) activity, which is a serine hydrolase, essential to the modulation of endocannabinoid system [170].

Relevantly, euphol, a triterpene alcohol isolated from the sap *E. tirucalli*, inhibited human gastric cancer cell growth through the modulation of ERK1/2-mediated apoptosis and cyclin D1 [171,172]. Thus, the Brazilian company "Amazonia Fitomedicamentos" decided to investigate the standardized extract of the sap of *E. tirucalli*, through non-clinical and clinical studies. The extract of *E. tirucalli* containing 64% euphol was effective in inhibiting *in vitro* a large panel of human cancer cells, and was safe when assessed orally in three-month toxicology assay, in both rats and dogs (non-published data). A Phase I clinical study conducted with the standardized extract of *E. tirucalli* revealed that it was safe for patients with cancer. However, a phase II clinical trial conducted in patients suffering from breast cancer failed to demonstrate the clinical efficacy of the standardized extract of *E. tirucalli* (data not published).

Additional relevant evidence indicates that other species from genus *Euphorbia* have important biological properties, as shown in Table 2. Recently, the FDA and the European, Australian and Brazilian regulatory agencies approved the ingenol mebulate (bland name Picato) isolated from *E. peplus* in the treatment of actinic keratosis—a pre-malignant lesion for sun-related squamous-cell carcinoma [173–175].

4.3. *Mandevilla velutina*

The genus *Mandevilla* belongs to the Apocynaceae family, and grows in the Brazilian savanna. *Mandevilla* species are popularly known as "Jalapa", and their rhizomes are used in folk medicine for treating inflammatory complications, as well as for the management of snakebites. This part of the review aims to describe some pharmacological studies on the endemic species *Mandevilla velutina*.

The history of *M. velutina* in Brazilian Pharmacology is quite interesting, as this plant and some of its isolated pregnane glycoside compounds had been described as the first idea of non-peptide antagonists for the peptide bradykinin receptors [182,183]. As it is well known, bradykinin was discovered in Brazil by Professor Rocha e Silva and his group in 1949, and many Brazilian researchers had been involved in the pharmacological characterization of bradykinin and their receptors over the last 65 years. Moreover, the study of medicinal plants had been one of the most relevant subjects of preclinical pharmacology research in Brazil. Relevantly, the study of bradykinin and plants from the *Mandevilla* genus contributed in a significant manner to the scientific formation of several researchers in Brazil, in both pharmacology and in chemistry of natural products. Some pieces of this history are presented therein.

Most literary evidence on the effects of *M. velutina* were obtained by testing this plant and its related compounds in a series of isolated *in vitro* preparations, in addition to *in vivo* models of pain and inflammation [182]. For instance, a study carried out in 1991 demonstrated that oral treatment with the crude extract of *M. velutina* markedly inhibited the edema formation elicited by arachidonic acid (AA) in the mouse ear. The edema caused by AA was also reduced by the topical application of the pregnane glycosides, denoted MV8608 and MV8612 [184]. For clarification, the compounds were labelled considering the name of the species (MV, for *M. velutina*), the year of the chemical isolation (86, for 1986), and the sequence number in which the compound was obtained (08 or 12; there are others).

To gain insights on the mechanisms underlying the effects of MV8608 and MV8612 in the AA-induced ear edema model, both compounds were tested on the contractile responses evoked by AA or PGE_2 in an isolated rat stomach preparation. Neither of them affected the contractile responses in this model, indicating that MV8608 and MV8612 act by alternative mechanisms, without interfering with COX or PGE_2 [184]. Otherwise, a separate *in vivo* study revealed a potent action for both compounds on the pro-inflammatory actions of phospholipase A_2 (PLA_2), by testing them in a rat model of paw edema caused by PLA_2 from *Naja naja* [185]. Consistent with the anti-PLA_2 actions of MV compounds, treatment with the crude extract from *M. velutina* abolished the phospholipase activity of the snake *Crotalus durissus*, showing a partial inhibition of *Bothrops* venoms. Of note, the extract from *M. velutina* also reduced, with distinct grades of inhibition, the myotoxic effects and the hemorrhage caused by the venom of snakes from the genus *Crotalus* and *Bothrops*, in addition to extending the survival of mice injected with lethal doses of the venoms [186]. Additionally, the oral administration of the crude extract of *M. velutina* caused a marked reduction of the inflammatory alterations induced by a series of phlogistic agents, in rodent models of paw edema and pleurisy. In this case, the authors highlighted a preferential effect in the inflammation models relying on the release of kinins [187]. The compounds MV8608 and MV8612 isolated from this plant also displayed inhibitory effects against BK-induced contraction of epithelium-denuded trachea strips from guinea pigs, while those compounds failed to alter the contractility caused by $PGF_{2\alpha}$, carbachol and

Table 2
Some species from genus *Euphorbia*. Includes the plant parts used, the biological property, the model used, and references.

Species	Plant parts used	Biological property	Model	Reference
Euphorbia hyssopifolia	Ethanolic extract—aerial parts	Cytotoxic and genotoxic effects	HepG2 cells	[176]
Euphorbia splendens var. *hislopii*	Latex	Selective control of schistosomiasis transmission	*Biomphalaria glabrata* infected with *Schistosoma mansoni*	[177]
Euphorbia milii, var. *milii*	Euphorbin, isolated from the latex	Induction of migration and aggregation of neutrophils	Male Wistar rats and human neutrophils cells	[178]
	Latex	Absence of tumor promoting activity	Male and female DBA/2 mice	[179]
	Eumiliin, isolated from the latex	Analgesic and anti-inflammatory effects	Swiss male mice	[180]
Euphorbia peplus	Ingenol-3-angelate from the sap	Chemotherapeutic effects	Clinical fundings	[181]

histamine [188], further suggesting a possible selectivity for kinin-mediated effects. Additionally, MV8608 and MV8612 presented anti-inflammatory and antinociceptive effects in a rat model of hemorrhagic cystitis caused by the chemotherapy agent cyclophosphamide, which has been demonstrated to be sensitive to kinin antagonists [189,190].

Another pregnane compound isolated from the roots of *M. velutina*, named velutinol A, was found to be effective in reducing the inflammatory pain evoked by phorbol myristate acetate (PMA), capsaicin, and carrageenan in mice. Remarkably, the treatment with velutinol A markedly inhibited the nociceptive responses caused by the selective agonist of the kinin B_1 receptor des-Arg^9-BK, without altering the nociception elicited by either bradykinin or PGE_2 [191]. Moreover, the topical application of velutinol A failed to significantly affect the rat paw edema induced by histamine, PAF, substance P (SP) or BK, whereas it consistently reduced the edema formation caused by des-Arg^9-BK in rats that had been primed with bacterial endotoxin (LPS) or PAF [192]. These pieces of evidence suggest a selective effect for velutinol A on kinin B_1 receptor-mediated responses.

The experimental evidence described in this section confirms the folk use of *M. velutina* as anti-inflammatory and antiophidian, and revealed a preferential effect for the isolated pregnane compounds against kinin-mediated responses. In spite of the interesting data and the great efforts devoted to chemical and pharmacological characterization of this plant, there is no related product in advanced phases of development, even as a phytomedicine or nutritional supplement. This might be partly attributed to the challenging processes for the isolation of compounds and to the advances of agriculture in savanna areas, with a reduction of *M. velutina* occurrence in Brazil. However, considering the relevance of previous studies discussed in this review, it is tempting to propose novel studies with this plant, hoping to get advances towards the market and to the benefit of the population.

4.4. *Phyllanthus spp.*

The genus *Phyllanthus* belongs to Euphorbiaceae family, comprehending 550 to 750 species of plants distributed throughout tropical and subtropical countries. Approximately 200 species of *Phyllanthus* are found in the Americas, mainly in Caribe and Brazil [193]. In Brazil, *Phyllanthus* spp. plants are popularly known as “quebra-pedra”, “erva-pombinha” or “arrebenta-pedra”. The infusion of leaves, stems, and roots of the *Phyllanthus* spp. have been used in Brazilian folk medicine and other countries for the treatment of kidney and urinary bladder disorders, intestinal infections, diabetes and against the hepatitis B virus [193]. A series of phytochemical and pharmacological studies have been conducted with the *Phyllanthus* spp. and many molecules were isolated and identified, primarily alkaloids, flavonoids, steroids and terpenes. Among all the studied species, *Phyllanthus niruri*, *Phyllanthus urinaria*, *Phyllanthus emblica*, *Phyllanthus flexuosus*, *Phyllanthus amarus*, and *Phyllanthus sellowianus* have received much great attention [193].

Of note, our research group proposed 30 years ago that the beneficial effects of *Phyllanthus* spp. infusions against disturbances of the kidney and urinary bladder might be associated to their diuretic and/or spasmolytic activities [193]. Indeed, we confirmed that the hydroalcoholic extract and alkaloid phyllanthimide from the leaves, stems, and roots of *P. sellowianus* display pronounced and reversible antispasmodic activity, similar to that observed for papaverine, in the smooth muscle isolated from guinea-pig ileum, rat uterus and aorta *in vitro* [194]. The hydroalcoholic extract of *P. urinaria* also causes contractions in the guinea-pig urinary bladder, likely by a direct action on smooth muscle. This effect appears to rely on the mobilization of extracellular calcium, unrelated to the activation of L- and N-type calcium channels, vanilloid receptors or PKC activation [195,196]. The endothelium is also implicated in the actions of the extract and compound, and the effects are likely dependent on the activation of NK_1 and NK_2 tachykinin receptors, as well on the release of COX metabolites. Moreover, the extract of *P. urinaria* promoted relaxation in the guinea-pig trachea pre-contracted by carbachol, via the stimulation of ATP-activated potassium channels [197]. *Phyllanthus acidus*, *P. niruri* and *P. urinaria* promoted relaxation in vascular and non-vascular preparations, and showed significant hypotensive effects *in vivo* [194,198–200]. Interestingly, it was demonstrated that *P. emblica* extract produced a decrease of mean percent change in the indices of arterial stiffness in a double-blinded, placebo-controlled, crossover study conducted with 12 volunteers. The patients enrolled in this trial received two capsules of standardized *P. emblica* extract 250 mg or two capsules of placebo twice daily, during 14 days. An increase of the sub-endocardial viability ratio was also observed in individuals allocated in the treatment arm of the study [201]. Both treatments were well-tolerated and no serious adverse events were reported [201].

Of interest, a preliminary clinical study carried out by Santos showed that patients receiving the infusion of the leaves, stems, and roots of *P. niruri* reported a significant relief of the pain responses, which are very common in kidney and bladder disturbances [202]. This fact prompted us to investigate the possible analgesic properties of the plant *Phyllanthus* spp. Indeed, our research group demonstrated, for the first time, that hydroalcoholic extract of *Phyllanthus corcovadensis* promoted significant antinociceptive effect in various chemical models of acute pain in mice [203]. Our research group and others confirmed this initial observation, demonstrating that the extracts and some steroids (stigmasterol and β-sitosterol), polyphenols (gallic acid ethyl ester, phyllanthin, hypophyllanthin, niranthin), and ellagitannins (geraniin and furosin) obtained from various species of *Phyllanthus* used in Brazil have significant antinociceptive effects

in mice and rats [193,203–213]. Importantly, the extract and lignan-rich fraction obtained from *P. amarus* were also effective in reducing chronic pain in experimental rodent models of musculoskeletal inflammatory and neuropathic pain [19,204]. Moreover, the hydroalcoholic extract of *P. niruri* and its isolated compounds rutin, quercetin and gallic acid, markedly attenuated the nociception, edema, and hemorrhage evoked by cyclophosphamide in mice, similar to Mesna—a positive control drug used in clinics [214]. In contrast, the hexanic extract of *P. amarus*, containing the lignans phyllanthin, 5-demethoxyniranthin, and niranthin, was not effective in reducing the persistent pain in the experimental autoimmune encephalomyelitis in mice, a model of multiple sclerosis [215]. Some studies indicated that plants of the genus *Phyllanthus* and its derivatives can directly or indirectly inhibit the production of different inflammatory mediators and intracellular signaling molecules, such as cytokines (IL-1β, IL-10, and TNF-α), autacoids (bradykinin, serotonin, prostanoids, platelet activating factor) and enzymes among others [204,208,216–222].

In a randomized, double-blind, placebo-controlled study, Dirjomuljono et al. showed that capsule extracts containing 360 mg *N. sativa* and 50 mg *P. niruri*, administered orally for 7 days to 186 patients, markedly alleviated swallowing pain and difficulty caused by tonsillo-pharyngitis. Furthermore, it was demonstrated that subjects in treatment arm needed significantly less analgesic therapy (paracetamol tablets) and had their sore throat completely relieved at the end of treatment, when compared to the placebo group. In this study, the capsule extracts were also found to be safe and well tolerated [223].

Pre-clinical studies also revealed that extracts and purified compounds from *Phyllanthus* spp. possess an anti-inflammatory effect. According to de Melo et al., a spray-dried extract of *P. niruri* significantly reduced acetic acid-induced colitis in rats by reducing TNF-α, IFN-γ, p53 protein, leukocyte infiltration and myeloperoxidase activity. This is likely related to the antioxidant properties of the extract [224]. In another study, Pradit et al. demonstrated that *P. amarus* extract and their major compounds, phyllanthin and hypophyllanthin, presented chondroprotective effect in a cartilage explant model, suggesting its therapeutic potential as an antiarthritic agent [225]. Sousa et al. demonstrated that the *P. acidus* extract and its compounds adenosine, kaempferol, and hypogallic increases the intracellular levels of cAMP and Ca^{2+}, thereby activating Ca^{2+}-dependent Cl^- channels and basolateral K^+ channels, and inhibiting epithelial Na^+ channel (EnaC) in cystic fibrosis airway cells. The authors suggest that these combinatorial effects of the *P. acidus* on epithelial transport may provide a novel complementary treatment for cystic fibrosis lung disease [226]. The *P. urinaria* extract and their compound corilagin inhibited the NF-κB/DNA interactions and affected IL-8 gene expression in TNF-α treated IB3-1 cells. Moreover, corilagin also inhibited TNF-α induced secretion of MCP-1 and RANTES in cystic fibrosis IB3-1 cells [227]. In addition, pre-clinical *in vivo* and *in vitro* studies have shown that the extract and constituents of *Phyllanthus* spp. have a hepatoprotective effect against liver injury induced by Hepatitis B virus and chemical agents [221,228–233].

The extracts of *P. amarus* and *P. emblica* have a gastroprotective effect against gastric lesions induced by ethanol and indomethacin in rats. Again, this was correlated with the anti-oxidant activity of the extracts *in vivo* [234,235]. In addition, *P. urinaria* extracts showed antimicrobial activity against *Helicobacter pylori*, inhibition of bacterial adhesion and invasion of human gastric epithelial AGS cells. Furthermore, *H. pylori*-induced NF-κB activation, and the subsequent release of interleukin (IL)-8 in AGS cells was also inhibited by the *P. urinaria* extracts [236]. The antimicrobial activity of this extract and its constituents obtained from several species of *Phyllanthus* against *Escherichia coli*, *Enterococcus faecium*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Clostridium sporogenes*, and *Mycobacterium smegmatis* has also been reported [237–240].

Regarding the antineoplastic activity, there are several preclinical studies showing the therapeutic potential of various extracts and constituents of *Phyllanthus* spp., including *P. niruri*, *P. amarus*, *P. urinaria*, *Phyllanthus polyphyllus*, *P. emblica* [241–249]. For instance, it was reported that the mechanism of action of the *Phyllanthus* spp. depends on DNA fragmentation, down-regulation of Bcl-2, cyclin B1, Myt1, p-cdc2, pan-Ras, c-Raf, RSK, phospho-Elk1, c-myc, Akt, HIF-1α, Bcl-2, VEGF and p-Weel, up-regulation of the Fas protein, Bax, p-JNK-1/2 and p-GSK3β, increased caspase-3/7 and caspase-8 activities, and inhibition of matrix metalloproteinase (MMP) −2, −7, −9, and −26 activities [245,250–253].

4.5. *Euterpe oleracea*

Euterpe oleracea, popularly known as "açaí", is a fruit bearing palm being easily found throughout the northern region of Brazil, as well as in other countries in South and Central America [254]. The phytochemical composition of the "açaí" fruit has been well characterized and includes: phenolic acids, anthocyanins—especially cyanidin-3-*O*-rutinoside, cyanidin-*O*-glucoside—proanthocyanidins, lignans—such as aryltetrahydronaphthalene, dihydrobenzofuran, furofuran, 8-*O*-4′-neolignan, tetrahydrofuran—and polyphenolic constituents—such as epicatechine, catechine homoorientin, orientin, isovitexin, taxifolin deoxyhexose [254–257].

In Brazil, pharmacological studies conducted with *E. oleracea* were initiated only in 2006, when Matheus et al. evaluated the effects of *E. oleracea* flowers, fruits and spike fractions on: nitric oxide (NO) production, NO scavenger capacity, and expression of iNOS. The authors reported that the fractions obtained from fruits were the most potent in inhibiting NO production, followed by those from flowers and spikes, which were accompanied by inhibition of iNOS expression. Moreover, these effects were also observed in the fractions in which the concentration of cyanidin-3-*O*-glucoside and cyanidin-3-*O*-rhamnoside were higher [258]. These findings were confirmed and extended substantially by Rocha et al., who demonstrated the vasodilator effect of "açaí" extracts, which were dependent on the activation of NO-cGMP pathway and endothelium-derived hyperpolarizing factor (EDHF) release, suggesting that *E. oleracea* could be useful in the treatment of cardiovascular diseases [259]. Likewise, Spada et al. demonstrated that "açaí" inhibited H_2O_2-induced damage of both lipids and proteins, as well as re-established the activities of the antioxidant enzymes in the CNS, suggesting neuroprotective effects [260]. A particularly interesting study conducted by de Souza et al. suggested that the consumption of "açaí" reduced total and non-high-density lipoprotein cholesterol, carbonyl proteins and total, free and protein sulfhydryl groups in an animal model of dietary-induced hypercholesterolemia [261]. Likewise, oral chronic treatment with "açaí" seed extract inhibited the increase of plasma malondialdehyde levels, body weight, plasma triglyceride, total cholesterol, glucose levels, glucose intolerance and insulin resistance in high-fat (HF) diet-induced metabolic syndrome (MS) in C57BL/6J mice [262]. Furthermore, the same study reported that the "açaí" seed extract was able to block the atherosclerotic plaque area in the aorta after a cholesterol-enriched diet (0.5%) for 12 weeks, associated with a better balance in the synthesis and absorption of sterols [263]. Of note, these effects were correlated to an increase in the expression of LDL-receptors, ABCG5 and ABCG8 transporters—two representatives of the ATP-binding cassette subfamily G [264].

Moreover, "açaí" treatment also inhibited doxorubicin (DXR)-induced DNA damage [265]. Also of interest are the results from the de Moura group demonstrating that cigarettes enriched with

"açaí" (100 mg of hydroalcoholic extract of *E. oleracea*) inhibited emphysema in mice. Chronic inhalation (60 days) of smoke this cigarettes blocked: (i) enlargement of alveolar space; (ii) increase in leukocytes; (iii) oxidative damage and (iv) macrophage and neutrophil elastase levels in the lungs tissue. Such results led the authors to conclude that the addition of "açaí" extract to normal cigarettes could reduce their harmful effects and resulted in a patent application (PCT/BR2009/000274) related to the insertion of the "açaí" stone extract inside the cigarette [266,267]. It was also reported that dietary supplements with 5% spray-dried "açaí" pulp reduced transitional cell carcinoma incidence, multiplicity, tumor cell proliferation and p63 expression, as well as elicited a significant reduction in DNA damage induced by H_2O_2 [268]. In addition, da Silva Santos et al., demonstrated that anthocyanin-rich "açaí" extract protect astrocytes against manganese-induced neurotoxicity [269].

Other studies have addressed the pharmacological effects of "açaí", including: (i) antitumor activity in the MCF-7 cell line—a breast cancer cell line [270]; (ii) inhibition of cardiac dysfunction in rats subjected to myocardial infarction [271]; (iii) analgesic effects during acute and neuropathic pain models [272] and (iv) anticonvulsant properties in mice [273]. Finally, a recent clinical finding showed that consumption of "açaí" reduces muscle stress and improves effort tolerance in elite athletes [274]. Thus, considering the diverse pharmacological activities of "açaí" as described above, the Brazilian pharmaceutical industries should effort on developing a new phytotherapy product obtained from *E. oleracea*.

4.6. Vitis labrusca

Grape has pronounced concentration of phenolic compounds, especially flavonoids, which have been associated to important human health benefits [275]. Concord and Isabel are the most cultivated varieties of grapes within Brazil [276]. The polyphenols found in the Bordo grape are mainly flavonoids, particularly anthocyanins, some monomers and dimers of the group of flavan-3-ols, and non-flavonoids—like hydroxycinnamic acids and stilbenes, particularly resveratrol [276]. The consumption of polyphenol-rich diets by the population is associated with a reduced risk of developing chronic diseases such as atherosclerosis, heart disease, cancer and diabetes. Epidemiological studies have shown that these compounds exert a protective effect on oxidative damage induced by free radicals present in cells and tissues [277].

In Brazil, Soares de Moura et al. reported the antihypertensive, vasodilator and antioxidant effects of *Vitis labrusca* grape skin extract [278]. Madeira et al. extended this notion, by showing that alcohol-free grape-skin extract (GSE) induced a significant vasodilation in the isolated mesenteric vascular bed of the rat, via NO release and hyperpolarization of the mesenteric vascular smooth muscle, and the activation of soluble guanylate cyclase and Ca^{2+}-dependent K^+ channels ($K_{Ca^{2+}}$), respectively. Moreover, the vasodilator effect of GSE does not involve receptors activated by acetylcholine, bradykinin, histamine, and adrenaline or opening of voltage-dependent K^+ channels [279]. Another interesting study has shown that a non-alcoholic ethyl acetate fraction (EAF) obtained from *V. labrusca* grapes inhibited total cholesterol, triglycerides, and low-density lipoprotein (LDL) plus very low-density lipoprotein levels in LDL receptor knockout (LDLR−/−) mice [280]. The same authors have also reported that administration of EAF preserved the vasodilatation induced by acetylcholine on isolated thoracic aorta from LDLR−/− mice, associated with a decrease of lipid deposits on arteries, suggesting an anti-atherogenic effect of *V. labrusca* grapes [280]. Additionally, previous results demonstrated that both organic and conventional grape leaf extracts of *V. labrusca* inhibited neuronal damage induced by damage induced by H_2O_2 by re-establishing the antioxidant properties of the grape [281]. Extending this idea, Andrade et al. demonstrated that *ad libitum* and voluntarily drunk black grape juice supplementation (*V. labrusca*) inhibited liver oxidative damage in whole-body acute X-irradiated rats [282].

Additionally, no mutagenicity activity was detected in alcohol extract obtained from skins of *V. labrusca* using the *Salmonella*/microsome assay [283]. More recently, Scola et al. demonstrated that *V. labrusca* seed extract (VLE) induced DNA damage on liver (HepG2) and breast cancers (MCF-7) cells, accompanied by high NO production, up-regulation of p53, Bax and AIF, and suppression of Her-2 expression in HepG2 cells [284]. Importantly, acute and long lasting toxicological studies (90-days of repeated doses assay) carried out in both rodents and dogs, revealed that the standardized extract obtained from *V. labrusca* was well-tolerated and failed to show toxic actions (unpublished data). Finally, Aché Laboratory from Brazil is currently conducting a clinical study to evaluate the safety and efficacy of this standardized extract.

4.7. Hypericum caprifoliatum and Hypericum polyanthemum

Due to the wide use of *Hypericum perforatum* for the treatment of minor depressive disorders [285], other *Hypericum* species such as *Hypericum caprifoliatum* and *Hypericum polyanthemum* (Guttiferae), commonly growing in the south of Brazil, have called the attention of Brazilian researchers. The pharmacological studies with these two plants are mostly related to the investigation of their analgesic, antidepressant, anti-infective, and anti-tumor effects. The methanol and the cyclohexane extracts of both *H. caprifoliatum* and *H. polyanthemum* displayed antinociceptive effects in the hot plate model in mice, when dosed by both intraperitoneal and oral routes. This action was completely reverted by the pretreatment with naloxone, indicating an opioid-mediated mechanism in the thermal analgesic actions of these botanicals. However, acetic acid-induced visceral pain was prevented only by the cyclohexane extract of both plants, dosed orally, whereas the methanol extract was ineffective in this model [286]. Furthering the evidence on the analgesic actions of *H. polyanthemum*, the isolated benzopyran compound HP1 promoted a dose-related antinociceptive effect in both the hot plate and the acetic acid models, by activating the opioid system [287].

The phloroglucinol compound uliginosin B isolated from *H. caprifoliatum* and *H. polyanthemum* was effective in reducing the nociceptive behavior in the hot plate and acetic acid models without altering motor coordination, when given low dose (15 mg/kg) intraperitoneally. However, an elevated dose of this compound (90 mg/kg) triggered ataxia in the rotarod paradigm. Based on pharmacological and biochemical approaches, the authors concluded that uliginosin B actions are dependent on monoamine uptake, with the subsequent activation of dopamine and opioid receptors [288]. An additional publication demonstrated that antinociceptive effects of uliginosin B were augmented by the α_1 and the α_2 receptor antagonists, prazosin and yohimbine, respectively. Otherwise, the inhibitor of serotonin (5-HT) synthesis (ρCPA) or the glutamate antagonist (MK801) prevented the ataxia caused by uliginosin B [289], suggesting different mechanisms for analgesic and ataxic effects.

From a screening study conducted with the crude methanol extract from three *Hypericum* species, only that obtained from *H. caprifoliatum* displayed antidepressant effects by reducing the immobility time in the rodent model of forced swimming test. Some fractions were obtained from this plant species by using solvents with increasing polarities, but only the petroleum ether fraction showed antidepressant actions. These favorable effects on depression were probably dependent on the high contents of phenolic compounds in this fraction, mainly the phloroglucinol type [290]. Extending this notion, crude and a purified extract, in addi-

tion to the phloroglucinol-enriched derivative (named HC1) from *H. caprifoliatum* were able to produce a concentration-dependent inhibition of the uptake of dopamine (DA), serotonin (5-HT) and noradrenaline (NA) in rat synaptosomal preparations [291,292]. The long-term treatment with HC1 caused a significant increase in Na^+, K^+ ATPase activity in the mouse cortex and hippocampus, which might further support the antidepressant-like effects of this product [293]. Another compound isolated from *H. caprifoliatum*, namely hyperoside, produced antidepressant effects in rats and mice, an action that was prevented by pre-treating animals with the dopamine D_2 receptor antagonist sulpiride. Otherwise, no analgesic effect was observed after treating animals with this compound, whereas it increased the pentobarbital sleeping time in mice [294]. Interestingly, the combination of low doses of the cyclohexane extract of *H. polyanthemum* or uliginosin B, with sub-effective doses of the classical antidepressant drugs imipramine, bupropion and fluoxetine led to an increased antidepressant action in the forced swimming test [295]. The acute toxicological assay with the cyclohexane extract from *H. polyanthemum* defined this botanical as safe in category 5 of OECD. However, the repeated treatment for 28 days with this extract was associated with liver toxicity, which could compromise its use over long periods, as it is recognized as critical for treating depression in clinics [296].

Regarding the anti-cancer potential, a study evaluating the crude methanol extract of 6 Brazilian *Hypericum* species identified *H. caprifoliatum* as one of the most active plants, according to the evaluation in three human tumor cell lines, namely HT-29 colon carcinoma cells, H-460 non-small cell lung carcinoma, and U-373 glioma cells [297]. Similarly, the proliferation activity of these three cell lines was significantly reduced by a series of benzopyran compounds isolated from *H. polyanthemum*, via an arrest of the cell cycle at G2/M phase, followed by apoptosis [298,299]. The analysis of the genotoxicity of these benzopyrans revealed a low level of DNA damage, as demonstrated in the micronuclei and the comet assays, which is an advantage for a potential anti-tumor compound [300].

Of high interest, the dried and powered materials from the aerial parts of several plants from the genus *Hypericum*, especially those derived from *H. polyanthemum*, produced a notable anti-leishmanial activity, without affecting the viability of mammalian macrophages [301]. This same plant and its active benzopyran compound HP1 presented promising effects against *Trichomonas vaginalis*, with a superior profile when compared to the reference anti-protozoal drug metronidazole [302]. Importantly, no data was found regarding phytomedicine registered in Brazil and developed as from these species.

4.8. *Maytenus ilicifolia*

Maytenus ilicifolia Mart. ex Reissek is popularly known as “espinheira-santa”, “cancerosa”, “cancorosa-de-sete-espinhos” and “maiteno”, among others. This plant belongs to the Celastraceae family, which comprises approximately 55 genus and 850 species spread on Atlantic forest [303]. Its leaves are popularly used to treat dyspepsia and gastric ulcers [97]. In southwestern Brazil, the roots of *M. ilicifolia*, known as “cancorosa”, are added to alcoholic drinks and terere, a common local beverage with a bitter taste. Phytochemical studies have shown that the *M. ilicifolia* leaves present many classes of compounds, including tannins (e.g., epicatechin, epigallocatechin and epigallocatechin-3-gallate), flavonoids, glycolipids (mono-, di-, tri-, tetragalactosildiacilglicerol, and sulfoquinovosildiacilglicerol), alkaloids (maitein, maitanprin e maitensin), terpenes (maytenin, tringenona, isotenginona II, A and B congorosinas, and maitenoic acid, friedelol, friedelin, friedelan-3-β-ol, A, B and C maytefolin, and uvaol-3-cafeato) [303–305]. According to Dr. Carlini, an important researcher of *M. ilicifolia*, the first studies on the therapeutic efficacy of this plant were performed by Dr. Aluizio France, professor at Paraná Medical School (Brazil) in 1922, who tested *M. ilicifolia* in patients with gastric ulcers, with successful outcomes. Since then, many studies have been conducted to demonstrate the pharmacological actions and to confirm the popular use of this plant.

The first pre-clinical studies conducted by Souza-Formigoni et al. proved the protective action of the tea prepared with fresh or dried leaves (“abafado”) of *M. ilicifolia* and *M. aquifolium* against gastric lesions induced by indomethacin and cold-restraint stress in rats. After application of a lyophilized extract, there was a reduction in the number of ulcers, associated to an increase in volume and pH of the gastric secretion [97]. According to the authors of that study, the protective effect of ‘espinheira-santa’ was comparable to that of cimetidine, a well-known histamine H_2-receptor antagonist [97]. Of note, these previous results were confirmed by Murakami et al., who also showed that tannin epigalocatequin-3-gallate could be responsible for the antiulcerogenic effect of *M. ilicifolia* [306]. Moreover, Ferreira et al. demonstrated that the ethanolic extract of *M. ilicifolia* exhibits similar activity compared to cimetidine, inhibiting the production of HCl induced by histamine in the isolated frog gastric mucosa by antagonizing histamine H_2 receptors [307]. Further studies have confirmed these early observations and demonstrated that polysaccharides (Type II arabinogalactan), but not triterpenes (friedelan-3β-ol 1 and friedelin 2) from *M. ilicifolia* are responsible, at least in part, for the significant gastroprotective effects of this plant [305,308,309]. In addition, the flavonoid-rich fraction of *M. ilicifolia* also reduced gastric lesions caused by ethanol and indomethacin in rats, and this result *in vivo* was correlated with the *in vitro* inhibition of rabbit gastric H^+,K^+-ATPase activity [310]. Of interest, there are pre-clinical studies showing that other species of *Maytenus*, including *Maytenus robusta*, *Maytenus senegalensis*, and *M. aquifolium* also have gastroprotective effects, thereby confirming the potential of plants of this genus as gastroprotective [98,311–315]. Another interesting finding by Baggio et al. is that the flavonoid-rich fraction of *M. ilicifolia* inhibits gastric emptying and intestinal motility, suggesting an interaction of the flavonoid-rich fraction of *M. ilicifolia* with the cholinergic system [316]. In line with this view, Jorge et al. showed that the hexane and the ethylacetate extracts of *M. ilicifolia* inhibit gastric lesions induced by cold-restraint stress in rats to the same extent that decrease nociception and paw edema in rats [303].

A particularly important study conducted by Oliveira et al. showed that the tea prepared by pouring boiling water on fresh or dried leaves of *M. ilicifolia* and *M. aquifolium*, both acutely administrated by p.o. or i.p. routes in rats and mice does not induce any apparent toxicity [317]. Furthermore, the chronic administration of these species does not alter overall behavior or weight gain in mice. Several biochemical and hematological parameters, as well as pathological examinations of different organs did not show any significant alterations after three months of treatment. A search for the potential effects of the extract on the fertility of female and male rats and on the course of pregnancy, such as a search for potential teratogenic effects, did not reveal any significant differences from the controls [317]. In addition, it was shown that the aqueous extract of *M. ilicifolia* was not able to induce mutagenic activity in the Ames test (*Salmonella*/microsome) [318]. In line with this view, the ethanolic extract of *M. ilicifolia* leaves does not cause visible alteration in sperm production in mice, suggesting no effect on spermatogenesis [319]. Accordingly, the lyophilized hydroalcoholic extract of *ilicifolia* leaves does not cause any morphological alteration in the reproductive system or embryotoxic effects in rodents [320]. However, since the extract has an uterotrophic effect, a putative estrogenic activity that may interfere with the uterine receptivity to the embryo has been proposed [320]. More recently, it was demonstrated that the extract obtained from the acetone-

water (70:30) mixture of *M. ilicifolia*, administered by gavage, at a dose of 15.11 mg/kg/day, to pregnant rats does not produce any toxic effect on pregnant rats and does not interfere with the progress of embryonic and fetal development [321].

Several studies have evidenced the antimicrobial activity of selected compounds from *M. ilicifolia.* Of interest, Annuk et al. demonstrated that the Gallic tannins inhibit bacteria growth by changing the permeability of the cell wall [322]. Moreover, Mabe et al. have demonstrated that catechin (tannin) presents *in vivo* and *in vitro* activity against *H. pylori* in Mongolian gerbils [323]. Further, Singh and Dubey demonstrated that friedelin and friedelan-3-β-ol inhibits *in vitro* growth of bacteria *S. aureus*, *E. coli* and the fungus *Aspergillus niger* [324]. Moreover, Portillo et al. showed that stem extracts of *M. ilicifolia* presented activity against *Microsporum gypseum* and *Trichophyton mentagrophytes* fungus, but the leaves did not show this effect [325]. Dos Santos et al. described *in vitro* leishmanicidal and trypanocidal activities of two quinonemethide triterpenes, maytenin and pristimerin, isolated from *M. ilicifolia* root barks [326].

The first studies on antineoplasic activity of compounds derived from *M. ilicifolia* were performed at the Antibiotics Institute of the Federal University of Pernambuco (Brazil), which showed that the isolated triterpenoidic compounds have cytotoxic activity against tumor cells *in vitro*. According to Zeng other triperpenes found in *M. ilicifolia* also exhibit cytotoxic activity against tumor cell lines *in vitro*, such as friedelin and friedelol. The tannins epigallocatechin and epigallocatechin-3-gallate inhibit the incorporation of marked thymidine in gastric tumor cells, which indicates interference in their growth capacity [327]. These substances also inhibit the release of TGF-β, whose activity can induce the emergence of malignant cells and inhibit the transcription of NF-κB—a transcriptional factor related to carcinogenesis [328]. In another study, Yamane et al. showed that epigallocatechin-3-gallate inhibits *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine-induced stomach cancer in rats by partially inhibiting ornithine decarboxylase, which inhibition causes cell cycle arrest [329]. Horn and Vargas evidenced that the aqueous extract of *M. ilicifolia* has antimutagenic effect *in vitro* [330]. In addition, the triterpenoid pristimerin from *M. ilicifolia* inhibits the growth of different cancer cell lines: lung (A-549), breast (MCF-7), hepatocarcinoma (HepG2) and liver (Hep3B). However, the pristimerin is cytotoxic to human peripheral blood mononuclear cells. Moreover, the authors also demonstrated that pristimerin has antiproliferative effect on HL-60 by inhibiting DNA synthesis and triggering cell death, apparently by apoptosis [331]. Dry extract of *M. ilicifolia* also inhibits the growth of human hepatocellular cells (HepG2) and colorectal carcinoma cells (HT-29), but does not alter the growth of normal keratinocytes (HaCaT). Therefore, it has been suggested that the *M. ilicifolia* dry extract induces apoptosis through down-regulation of Bcl-2 and involvement of caspase-3 in human carcinoma cells, without altering normal cell growth [332].

Much research has been conducted in order to assess whether *M. ilicifolia* presents an antioxidant profile, since it has about 19% of polyphenols in the form of tannins not derived from catechin condensate. Vellosa et al., using ethanolic extract of *M. Maytenus*, confirmed that the root bark presents an antioxidant action through its ability to scavenge free radicals [333]. Melo et al. showed that *M. ilicifolia* extract exhibits high antioxidant activity against stannous sulfate—a *Salmonella* mutation model—and heavy metal chelating ability [334]. Accordingly, catechin, a component of the extract, is a known antioxidant (more potent than vitamin C or E to inhibit oxidation *in vitro*) [335]. Experimental evidence suggests that the antioxidant activity of catechin and its derivatives is more prominent in the gut mucosa because they inhibit the cell damage induced by free radicals that are generated during digestion. This effect also relates to an antimutagenic action because these compounds protect against genotoxic agents such as MeIQX (3,8-dimethyl-3H-imidazo[4,5-f]quinoxalin-2-amine), which may induce malignant transformation in mucosal gut cells [336]. According to Dos Santos et al., the antioxidant properties of the crude extract and individual components of *M. ilicifolia* involve a possible synergistic association of phenolic substances and quinone-methide triterpenes [337].

The extract from the leaves of *M. ilicifolia*, which is particularly rich catechin, epicatechin, and tannins, relaxes intact aorta rings of rats by mechanisms that presumably involve the production of nitric oxide, guanylate cyclase activation and the opening of potassium channels [338]. In fact, Crestani et al. extended previous observations and confirmed that the extract and semipurified fraction from leaves of *M. ilicifolia* decrease blood pressure in rats and that NOS inhibitors block this effect [339]. Recently, Leme et al. demonstrated that a purified fraction from *M. ilicifolia* causes diuresis, natriuresis and hypotension by mechanisms that involve the prostaglandin/cAMP pathway, with no sign of toxicity in markers of renal function [340].

4.9. *Protium kleinii and Protium heptaphylium*

Protium (the principal genus of the family Burseraceae) is widely distributed in South America and is particularly represented in the flora of the Amazon region [341]. The main classic species of the genus *Protium* are *Protium kleinii* and *Protium heptaphyllum*, which are known for the production of oleoresin exudates that occur as a result of insect stings, broken branches, or other acts injurious to their barks [342,343]. Moreover, *P. kleinii* and *P. heptaphyllum* can be found in the southwest states of Brazil, where they are popularly known as “almécega”, “almíscar”, “pau-de-breu”, “pau-de-incenso”, “guapoí”, among others. The resinous exudates collected from the trunk wood of this plant in its natural form is a reputed folk remedy with anti-inflammatory, analgesic, insect repellant, expectorant and wound healing actions [344,345].

In addition, pre-clinical studies carried out by Siani et al. showed that the essential oils from *P. heptaphyllum*, *Protium strumosum* and *Protium lewellyni* inhibit the protein extravasation caused by zymosan in the mouse pleural cavity. Furthermore, the oils from *Protium grandifolium*, *P. lewellyni* and *P. heptaphyllum* inhibit the neutrophil accumulation, whereas *P. heptaphyllum* and *P. lewellyni* inhibited LPS-induced eosinophil accumulation in mouse pleural cavity, and *P. heptaphyllum* and *P. strumosum* inhibit LPS-induced NO production and proliferation of Neuro-2a (mouse neuroblastoma), SP2/0 (mouse plasmocytoma) and J774 (mouse monocytic cell line) neoplasic cell lines. Moreover, the resin oil is mainly constituted by monoterpenes and phenylpropanoids (α-terpinolene, *p*-cymene, *p*-cimen-8-ol, limonene and dillapiol), whereas sesquiterpenes predominate as the volatile constituents of the leaves [344]. On the other hand, it was demonstrated that the resin, consisting mainly of triterpenoid α- and β-amyrin of *P. heptaphyllum*, effectively reduces the formation of cotton pellet-induced granuloma in rats, but not the hind-paw edema induced by carrageenan, suggesting it has an inhibitory effect on collagen formation but not on acute edema. Furthermore, the resin does not induce overt toxicity in mice when tested in doses up to 5 g/kg, whereas it significantly reduces the vascular permeability increase induced by acetic acid in mice [346]. Okuti et al. (2005) demonstrated that topical application of the ether extract or the main active constituent from *P. kleinii* α-amyrin inhibits ear edema and cell influx in response to the topical application of 12-O-tetradecanoylphorbol-acetate (TPA) in the mouse ear, in a manner similar to the glucocorticoid dexamethasone. Both the ether extract and α-amyrin, given topically, dose-dependently prevent the increase of pro-inflammatory cytokine levels in response to the topical application of TPA. Medeiros et al. (2007) showed that top-

ical application of α-amyrin inhibits TPA-induced increase of PGE_2 levels, but fails to alter either COX-1 or COX-2 activities *in vitro*. However, α-amyrin dose-dependently inhibits TPA-induced COX-2 expression and prevents IκBα degradation, p65/RelA phosphorylation and NF-κB activation in the mouse skin. Furthermore, topical α-amyrin inhibits the activation of upstream protein kinases, namely extracellular signal-regulated protein kinase (ERK), p38 mitogen-activated protein kinase (MAPK) and PKC-α, following topical TPA treatment [347]. Together, these findings suggest that the active constituents present in the ether extract of *P. kleinii*, including the triterpene α-amyrin, are good candidates to develop a skin permeable anti-inflammatory drug.

More recently, Melo et al. demonstrated that α- and β-amyrin from *P. heptaphyllum* attenuates the cerulein-induced increase of TNF-α, IL-6, lipase, amylase, MPO and TBARS, in a manner similar to thalidomide. Moreover, α- and β-amyrin suppress the cerulein-induced pancreatic edema, inflammatory cell infiltration, cell necrosis, and TNF-α and inducible nitric oxide synthase (iNOS) expression, suggesting that α- and β-amyrin ameliorates acute pancreatitis by acting as an anti-inflammatory and antioxidant agent [348]. Oliveira et al. showed that the resin of *P. heptaphyllum*, which presents high levels of the triterpenoids α- and β-amyrin, attenuates the gastric lesion induced by ethanol or acidified ethanol (HCl/ethanol), in a manner similar to *N*-acetyl-l-cysteine (NAC). However, in contrast to NAC, the resin does not restore the non-protein sulfhydryl content. Moreover, the resin reduces the total acidity without changing gastric secretory volume in pylorus-ligated rats [346]. Additional studies confirmed the gastroprotective effects of the mixture of α- and β-amyrin from *P. heptaphyllum* resin and demonstrated that its effect depends, at least in part, on the activation of capsaicin-sensitive primary afferent neurons [349].

In addition, Vitor et al. demonstrated that α- and β-amyrin from *P. kleinii*, like dexamethasone, reverse the macroscopic and microscopic outcomes of trinitrobenzene sulphonic acid-induced colitis in mice. Moreover, α- and β-amyrin decreases interleukin (IL)-1β levels, vascular endothelial growth factor (VEGF) expression and partially restores IL-10 levels in colon tissue after colitis induction. Further, both α- and β-amyrin and dexamethasone inhibit colonic expression of COX-2 and of phospho-NF-κB and phospho-CREB after colitis induction [128]. Additional studies confirmed the anti-inflammatory effects of α- and β-amyrin in the dextran sulfate sodium (DSS)-induced colitis in mice [350]. Accordingly, oral preventive or therapeutic treatment with α- and β-amyrin reduces disease activity, body weight loss, colonic damage, as well as colonic myeloperoxidase and N-acetylglucosaminidase activity increases. Moreover, α- and β-amyrin decrease the colonic pro-inflammatory mediators TNF-α, IL-1β and keratinocyte-derived chemokine and up-regulates IL-4 levels. Additionally, α- and β-amyrin significantly reduce mRNA expression for intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), platelet cell adhesion molecule 1 (PCAM-1), β(2)-integrin and protein expression for proliferation marker Ki67, the macrophage molecule CD68 and for adhesion molecule P-selectin. Interestingly, the anti-inflammatory effects of α- and β-amyrin on DSS-induced colitis is dependent on the activation of cannabinoid 1 (CB1), but not CB2 receptors. Further supporting a role for endocannabinoids in the effect of these compounds, α- and β-amyrin-treated mice show reduced mRNA expression of both monoglyceride lipase 1 (MGL1) and fatty acid amide hydrolase (FAAH) in the colon. These studies suggest that α- and β-amyrin might have potential therapeutic application for the treatment of inflammatory bowel disease, by a mechanism that depends on the activation of cannabinoid CB1 receptors [350].

Of interest, Oliveira et al. reported that the resin from *P. heptaphyllum* (which is rich in α- and β-amyrin) attenuated the acute liver injury and completely suppressed the mortality associated with acetaminophen and potentiated the pentobarbital sleeping time in mice [351]. Furthermore, α- and β-amyrin also suppressed the nociceptive responses evoked by sub-plantar or intracolonic application of capsaicin in mice. However, the antinociception produced by α- and β-amyrin against capsaicin-induced pain behavior was abolished in animals pre-treated with naloxone, suggesting an opioid mechanism [342].

Aragao et al. reported that α- and β-amyrin of *P. heptaphyllum* inhibit acetic acid-induced writhing and licking behavior in the inflammatory phase of the formalin test, as well as an antiedematogenic effect in the carrageenan-induced paw edema, in addition to increasing the reaction time to thermal stimulus [352]. Also relevant are the findings demonstrating that the ether fraction and the triterpene identified as urs-12-ene-3β-16β-diol, known as Brein, isolated from *P. kleinii*, reduces pain behavior caused by chemical stimuli (e.g., acetic acid, formalin, capsaicin and glutamate), but not by thermal stimuli (heat), in rodents. The same authors also showed that the antinociception caused by the ether fraction, in contrast to that of morphine, was not reversed by naloxone and is not dependent on changes in motor coordination or the core body temperature in mice [343]. These findings are in agreement with that described above for the α- and β-amyrin of *P. heptaphyllum* [352]. Of interest, Otuki et al. extended these earlier data and demonstrated that systemic (i.p. and p.o.) or central [intracerebroventricular (i.c.v.), or intrathecal (i.t.)] administration of α- and β-amyrin caused a dose-related and significant antinociception against acetic acid, formalin, and capsaicin in mice. Moreover, i.p. treatment with α- and β-amyrin reduces the nociception produced by 8-bromo-cAMP (8-Br-cAMP) and by TPA, as well as the hyperalgesia caused by glutamate. In contrast to morphine, α- and β-amyrin fail to cause analgesia in thermal models of pain. It has been suggested that α- and β-amyrin-induced antinociception does not involve the opioid, α-adrenergic, serotonergic, and nitrergic system, since it is not affected by naloxone, prazosin, yohimbine, DL-pchlorophenylalanine methyl ester, or L-arginine. Interestingly, the i.p. administration of α- and β-amyrin reduces the mechanical hyperalgesia produced by carrageenan, capsaicin, bradykinin, substance P, PGE_2, 8-BrcAMP, and TPA in rats. However, α- and β-amyrin did not alter the binding sites of [^{3}H]bradykinin, [^{3}H]resiniferatoxin, or [^{3}H]glutamate *in vitro*. According to the authors of that study, α- and β-amyrin produces consistent peripheral and central antinociception in rodents, especially when assessed in inflammatory models of pain, and when its mechanism of action involved the inhibition of PKA- and PKC-sensitive pathways [353]. In addition, Lima-Júnior et al. (2006) demonstrated that α- and β-amyrin of *P. heptaphyllum* suppresses pain-related behavioral responses to intraperitoneal cyclophosphamide and to intracolonic mustard oil in mice. The authors suggest that the blockade of TRPV1 is involved in the antinociceptive property of α- and β-amyrin, and it does not significantly alter the pentobarbital sleeping time, nor impair the ambulation or motor coordination, indicating the absence of sedative or motor abnormalities that could account for its antinociception [354]. In another study da Silva et al. showed that α- and β-amyrin significantly reduces mechanical and thermal hyperalgesia and inflammation induced by complete Freund's adjuvant and by partial sciatic nerve ligation in mice [355]. Moreover, α- and β-amyrin largely decreases IL-1β, TNF-α, keratinocyte-derived chemokine and IL-6 levels, and myeloperoxidase activity. Further, α- and β-amyrin prevents the activation of NF-κB and the cyclic adenosine monophosphate response element binding (CREB) and the expression of COX-2 in the mouse paw skin and spinal cords. In addition, the authors demonstrated that the analgesic effect of α- and β-amyrin occurs by the interaction of CB1 and CB2 cannabinoid receptors [355]. Since β-amyrin inhibits the degradation of the

endocannabinoid 2-AG without directly interacting with CB receptors, indirect cannabimimetic mechanisms have been implicated in the analgesic and anti-inflammatory effects of this compound [356].

According to Santos et al. α- and β-amyrin from *P. heptaphyllum* significantly reduces streptozotocin-induced increase of blood glucose, total cholesterol and serum triglycerides. Unlike glibenclamide, α- and β-amyrin does not decrease normal blood sugar levels, but at 100 mg/kg, they caused a hypolipidemic effect. In addition, α- and β-amyrin effectively reduce the elevated plasma glucose levels during the oral glucose tolerance test. Accordingly, the plasma insulin levels and the histopathological analysis of the pancreas revealed the beneficial effects of α- and β-amyrin in the preservation of β-cell integrity. α- and β-amyrin or fenofibrate also decrease the high-fat diet-associated increase of serum cholesterol and triglycerides. The hypocholesterolemic effect of α- and β-amyrin appeared more prominent at 100 mg/kg with significant decreases in VLDL and LDL cholesterol and an elevation of HDL cholesterol. Additionally, the atherogenic index was significantly reduced by α- and β-amyrin. Thus, it has been also suggested that α- and β-amyrin have potential anti-hyperglycemic and hypolipidemic effects [357]. In another recent study, Carvalho et al. demonstrated that the resin of *P. heptaphyllum* prevents high-fat diet-induced obesity in mice by its modulatory effects on various hormonal and enzymatic secretions related to fat and carbohydrate metabolism. Additionally, resin significantly elevated the plasma levels of ghrelin and decreased the levels of insulin, leptin, and resistin. Moreover, the increased plasma levels of the pro-inflammatory mediators TNF-α, IL-6, and MCP-1 in an obesity model induced by a high-fat diet were significantly lowered by *P. heptaphyllum*. Furthermore, *in vitro* studies revealed that *P. heptaphyllum* could significantly inhibit the lipid accumulation in 3T3-L1 adipocytes [358]. Despite the fact that several pre-clinical studies have shown that α- and β-amyrin exhibited several pharmacological actions when given systemically to rodents, so far, no pre-clinical assays for safety assessment or clinical trials have been conducted with this compound.

4.10. *Trichilia catigua*

Trichilia catigua, popularly known as “catuaba” or “catigua”, is a native plant from Brazil, commonly used as neurostimulant and aphrodisiac [359]. Chemical studies on *T. catigua* have shown the presence of alkaloid compounds, lactones, β-sitosterol, stigmasterol and flavalignans [360,361].

Initially, Calixto and Cabrini demonstrated that Catuama®—a Brazilian herbal medicine constituted by *Paullinia cupana*, *T. catigua*, *Zingiber officinalis* and *Ptychopetalum olacoides*—showed vasorelaxant actions dependent on the NO pathways [362]. In addition, it was demonstrated that Catuama® exerts antinociceptive actions when administered orally in several models of chemical and thermal nociception [363], via an interaction with the NO pathway and the opioid system. These results were confirmed and estended by Antunes et al., who demonstrated long-term relaxation of the corpus cavernosum through cAMP levels [364], without the occurrence of adverse reactions in healthy volunteers [365]. Moreover, Catuama® caused a marked reduction of the immobility time when assessed in rodent models of depression. The same study also demonstrated that Catuama® inhibited the synaptosomal uptake of noradrenaline, serotonin and dopamine in the rat brain after long-term oral treatment. Additionally, it augmented the release of serotonin and dopamine in rat brain synaptosomal membranes. The authors concluded that Catuama® might be useful for the clinical management of moderate and mild depressive states, alone or in association with current antidepressant drugs [366]. Pontieri et al. demonstrated Catuama® and *T. catigua* extract reverted ventricular fibrillation in the isolated rabbit heart, prevented re-induction, and prolonged intraventricular conduction, in addition to prolonged monophasic action in the potential second phase [367].

More recently, our group demonstrated that oral treatment with Catuama®, in both acute and chronic schedules of treatment, inhibited the mechanical allodynia induced by the intraplantar (i.pl.) injection of complete Freund’s adjuvant (CFA), although it failed to modify the mechanical allodynia or hyperalgesia observed following the partial ligation of the sciatic nerve or the diabetic polyneuropathy, respectively. Surprisingly, the antinociceptive effects of Catuama® in the inflammatory model were reversed by the non-selective dopamine antagonist haloperidol, but not by the serotonin methysergide or the adrenergic yohimbine receptor antagonists, suggesting that the mechanisms underlying Catuama® analgesia are associated with the modulation of dopaminergic pathways [368]. Then, a randomized, double-blinded, placebo-controlled clinical study showed that systemic administration of Catuama® (2 capsules/day, before lunch and dinner, for 8 weeks after the first evaluation) reduced the symptoms of burning mouth syndrome [369].

In addition, Barbosa et al. demonstrated that hydroalcoholic extract of *T. catigua* abolished the phospholipase A_2 (PLA_2) activity in human platelets, suggesting anti-inflammatory properties [370]. Campos et al. showed that oral treatment with the hydroalcoholic extract obtained from *T. catigua* produced antidepressant-like effects in rodents through inhibiting the uptake and increasing the release of serotonin and dopamine, when evaluated on rat brain synaptosomal preparations [371]. Chassot et al. [372] confirmed this hypothesis. Supporting this data, Bonassoli et al. showed that *T. catigua* showed antidepressant-like effects and increased the hippocampal cell proliferation in mice [373]. Extending this idea, Viana et al. (2011) demonstrated that *T. catigua* extract caused significant analgesic effects, which was reversed by selective dopamine D_1 receptor antagonist treatment [374]. Other authors demonstrated that *T. catigua*: (i) showed antioxidant activity, and may be considered for future investigations on anti-aging formulations for the skin [375,376]; (ii) promoted functional recovery, decreased the delayed hippocampal cell loss, and mitigated the ongoing neurodegenerative processes induced by bilateral common carotid occlusion (BCCAO)—a experimental model of cerebral ischemia [377]; (iii) interfered with in exposed mothers during the initial phases of pregnancy, but did not induce changes in maternal behavior or in male offspring’s reproductive and behavioral parameters [378]; and (iv) showed antiviral activity of Herpesvirus and Poliovirus in HEp-2 cell culture [379].

Three months of toxicological pre-clinical studies (conducted in both rodents and non-rodents) revealed that the standardized extract obtained from the barks of *T. catigua* was well-tolerated and failed to show toxic actions (unpublished data). The phase I clinical trial conducted by Federal University of Ceará (UFC) from Brazil confirmed the safety of this extract. Finally, the phase II and III clinical study, conducted by Catarinense Laboratory SA, to evaluate the efficacy of Catuama® (LABCAT TCJUSS) in patients with depressive episodes was expected to start in December 2015 (https://clinicaltrials.gov/*T. catigua*).

5. Concluding remarks

In this review article, we highlighted the recent efforts made by Brazilian researchers to study, in pre-clinical and clinical aspects, some medicinal plants widely used in folk medicine. Brazil has the greatest amount of biodiversity in the world, representing approximately 20–22% of all known plant species. Certainly, the area of plants is one of the most relevant fields of investigation in Brazil, as echoed by the great number of scientific articles published in peer-

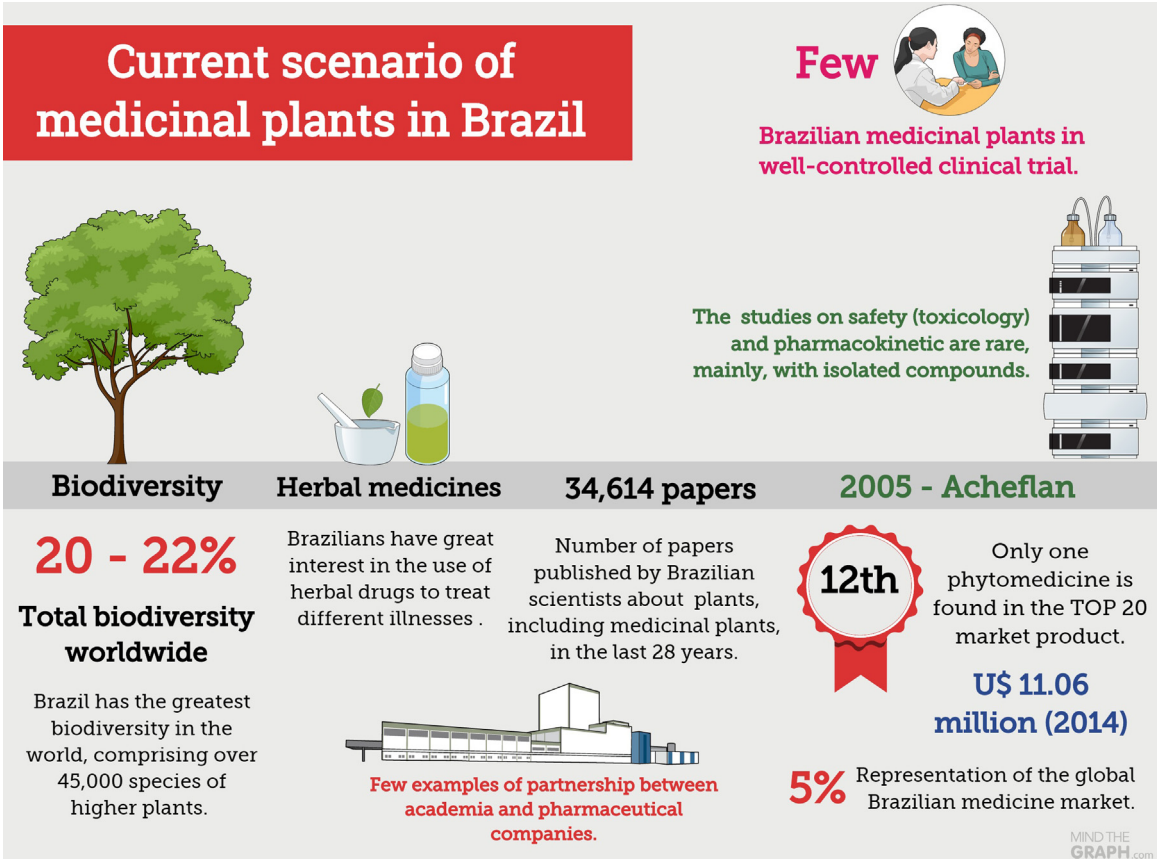

Fig. 4. Current scenario of medicinal plants in Brazil.
Brazil has the highest total of biodiversity in the world (20–22% of the total existing on the planet), which justifies the great interest in the use of herbal drugs to treat different illnesses. Brazilian scientists have published a great amount of scientific papers about plants, including medicinal plants, over the last 28 years. Notwithstanding, the studies conducted with plant-derived active ingredients bring some notions about the mechanisms of action and are commonly published in the best quality scientific journals, although safety (toxicology), pharmacokinetics studies, and clinical trials are lacking, mainly, with isolated compounds. Moreover, only one phytotherapy product, named Acheflan®, obtained from *C. verbenacea* is among the 20 most sold phytomedicines in Brazil (U$ 11.06 million—2014), confirming that research in medicinal plants in Brazil remains restricted to the academy, with few examples of partnership with pharmaceutical industries. Finally, the market for plant-derived drugs in Brazil (phytomedicines) is still very small, representing less than 5% of all marketed drugs.

reviewed scientific journals. A search carried out between 2011 and 2013 revealed that Brazilian researchers published more than 10,000 scientific articles in this topic (Fig. 3). Notwithstanding, the market for plant-derived drugs in Brazil (phytomedicines) is still very small, representing less than 5% of all marketed drugs (Fig. 2). A careful analysis of recent pharmacological publications on plants reveals that in general, the studies were conducted with crude extracts, and only a few articles investigated the safety (toxicology) and the underlying mechanisms of action. In contrast, the studies conducted with plant-derived active ingredients bring some notions about the mechanism of action and they are commonly published in the best quality scientific journals, although safety studies (toxicology) and pharmacokinetics are lacking. For clinical research, the situation is even worse. Very few Brazilian medicinal plants (either extracts or their active principles) have been evaluated in well-controlled clinical trials. Consequently, few herbal medicines were developed and approved by the Brazilian regulatory agency ANVISA. As shown in Table 1, only one phytotherapy product named Acheflan®, obtained from *C. verbenacea*, is among the 20 most sold phytomedicines in Brazil (see Table 1 and the scheme proposed in Fig. 4). It is feasible to conclude that research in medicinal plants in Brazil remains restricted to the academy, with few examples of successful partnerships with pharmaceutical industries. Indeed, a great effort will be necessary to stimulate the partnership between academia and pharmaceutical companies and to improve the scientific level of publications, seeking to explore mechanistic aspects, safety, pharmacokinetics and clinical aspects to make it possible to develop new drugs from our vast biodiversity in the future.

Conflict of interest

The authors declare that there are no conflict of interest.

Acknowledgements

This review article and cited papers from our group were supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Fundação de Amparo à Pesquisa e Inovação do Estado de Santa Catarina (FAPESC), all from Brazil.

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