



Review

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



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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 heptaphyllum* 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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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 somniferum*) 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 Serturmer, 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 over 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.

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