MARTHA DALILA SEDANO-PARTIDA

Chemical and biological potential of *Hyptis* Jacq. (Lamiaceae)

Potencial químico e biológico de *Hyptis* Jacq. (Lamiaceae)

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Dedico con todo mi corazón este trabajo a

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mi pajarito, mi cuñado y al amor de mi vida,

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Sedano-Partida, M. D. Chemical and biological potential of *Hyptis* Jacq. (Lamiaceae). [Thesis]. São Paulo: Institute of Bioscience, University of São Paulo; 2018

Abstract

Flavonoids and other phenolics are groups of natural bioactive compounds widely distributed in edible plants and are well documented to possess biological potential. *Hyptis* (Lamiaceae) is used in Brazilian folk medicine to treat various diseases. The aim of this study was to evaluate the antioxidant, anti-acetylcholinesterase, cytotoxic, antiviral and antibacterial potential of *Hyptis radicans* and *Hyptis multibracteata* by isolating and characterizing major constituents and their biological activities. *H. radicans* and *H. multibracteata* were dried, powdered and macerated in 70% ethanol which resulted in a crude ethanol extract (EE) for each species. EE were dissolved in 50% methanol and then was fractionated by partition with hexane and ethyl acetate; were obtained three phases: hexane phase (HP), ethyl acetate phase (EAP) and hydromethanol phase (HMP). EAP from *H. radicans* was the sample that presented the highest levels of total phenolic content, especially flavonoids, and was the sample with the high antioxidant activity with promising values of EC_{50}: DPPH (32.12 μg mL^{-1}), ABTS (5.04 μg mL^{-1}), Metal chelator assay (42.36 μg mL^{-1}), TBARS (40.46 μg mL^{-1}) and nonsite-Specific Hydroxyl Radical-Mediated 2-Deoxy-D-ribose Degradation *(*NS-Spe) with EC_{50} of 75.08 μg mL^{-1}. EE from *H. radicans* showed high antioxidant activity for FRAP and ORAC with EC50 of 6.01 and 2.68 μg mL^{-1}, respectively and had the highest amount of rosmarinic acid (17.64 mg *ρ*-CE g^{-1}). HMP from *H. radicans* showed high antioxidant activity in Site-Specific Hydroxyl Radical-Mediated 2-Deoxy-D-ribose Degradation (S-Spe) assay with EC50 of 0.32 μg mL^{-1} and had the highest content of chlorogenic acid derivatives. Regarding the results of cytotoxicity, HP from *H. multibracteata* induced the death of more than 80% of RAW 264.7 Cell Lines at 100 μg mL^{-1}. Nepetoidin B, isolated from *H. multibracteata* had the best EC_{50} (52.73 μg mL^{-1}) for anti-acetylcholinesterase activity. Antibacterial activity was evaluated *in vitro* against two Gram-negative bacteria, *Pseudomonas aeruginosa* and *Escherichia coli*, and a Gram-positive *Bacillus subtilis*. Phases from *H. multibracteata* were more effective on inhibiting *B. subtillis* with MIC_{50} of 23.6 μg mL^{-1} and 12.13 μg mL^{-1} for HP and EAP, respectively. HP was also activity against *P. aeruginosa* with MIC_{50} of 37.55 μg mL^{-1}. EE and HMP phase from *H. radicans* showed moderate anti-HIV-1 activity (MIC_{50} 159 μg mL^{-1}; MIC_{50} 180 μg mL^{-1}). Contents of total phenolic were not the main sample feature to define this activity, but there

was correlation between Rosmarinic acid contents and anti-HIV1 activity of *H. radicans*. Cirsimaritin and litospermic acid A were isolated for the first time, being the first time that they are described for the genus *Hyptis*. This study provides the first evidence of chemical and biological potential for these two Brazilian native species of *Hyptis*.

Keywords

Hyptis; flavonoids; nepetoidins; rosmarinic acid; lithospermic acid A; antioxidant; anti-HIV; cytotoxicity; antibacterial.

Sedano-Partida, M. D. Potencial químico e biologica de *Hyptis* Jacq. (Lamiaceae). [Thesis]. São Paulo: Instituto de Biociências, Universidade de São Paulo; 2018

Resumo

Flavonoides e outros compostos fenólicos são grupos de compostos bioativos naturais amplamente distribuídos em plantas e estão bem documentados por possuírem potencial biológico. *Hyptis* (Lamiaceae) é usado na medicina popular brasileira para tratar várias doenças. O objetivo deste estudo foi avaliar o potencial antioxidante, anti-acetilcolinesterase, citotóxico, antiviral e antibacteriano de *Hyptis radicans* e *Hyptis multibracteata*, isolar e identificar substâncias e correlacionar as atividades biológicas com a quantidade de compostos fenólicos e substâncias isoladas. *H. radicans* e *H. multibracteata* foram secas, pulverizadas e maceradas em etanol 70%, resultando em extrato etanólico bruto (EE). EE foi dissolvido em metanol 50% e depois foi fracionado por partição com hexano e acetato de etila, o que resultou em três fases: fase hexânica (HP), fase acetato de etila (EAP) e fase hidrometanólica (HMP). EAP de *H. radicans* foi a amostra que apresentou os maiores teores de conteúdo fenólico, principalmente flavonoides, e foi a amostra com a maior atividade antioxidante, com valores promissores de EC_{50}: DPPH (32,12 μg mL^{-1}), ABTS (5,04 μg mL^{-1}), Quelante de metais (42,36 μg mL^{-1}), TBARS (40,46 μg mL^{-1}) e Degradação da 2-deoxy-D-ribose de sitio não especifico mediada pelo radical hidroxil (NS-Spe) com EC_{50} de 75,08 μg mL^{-1}. EE de *H. radicans* apresentou a maior atividade antioxidante para FRAP e ORAC com EC_{50} de 6,01 e 2,68 μg mL^{-1}, respectivamente, e apresentou a maior quantidade de ácido rosmarínico (17,64 mg ρ-CE g-1). HMP de *H. radicans* apresentou a mais alta atividade antioxidante no ensaio de Degradação da 2-deoxy-D-ribose de sitio especifico mediada pelo radical hidroxil (S-Spe) com EC_{50} de 0,32 μg mL^{-1} e apresentou o maior teor de derivados de ácido clorogênico. Em relação aos resultados da citotoxicidade, HP de *H. multibracteata* induziu a morte de mais de 80% das células do tipo RAW 264.7 com uma concentração de 100 μg mL^{-1}. A Nepetoidina B isolada de *H. multibracteata* apresentou a melhor EC_{50} (52,73 μg mL^{-1}) para atividade anti-acetilcolinesterase. A atividade antibacteriana foi avaliada *in vitro* contra duas bactérias Gram-negativas, *Pseudomonas aeruginosa* e *Escherichia coli*, e uma bacteria Gram-positiva. *Bacillus subtilis*. Fases de *H. multibracteata* foram mais eficazes na inibição de *B. subtillis* com MIC50 23,6 μg mL^{-1} e 12,13 μg mL^{-1} para HP e EAP, respectivamente. HP também apresentou atividade contra *P. aeruginosa* com MIC_{50} de 37,55 μg mL^{-1}. EE e HMP de *H. radicans* mostraram moderada

atividade anti-HIV-1 (MIC_{50} 159 μg mL^{-1}; MIC50 180 μg mL^{-1}). Não há correlação entre o conteúdo total de fenólicos e esta atividade biológica, mas sim entre a quantidade de ácido rosmarínico das fases e a atividade anti-HIV1 de *H. radicans*. Foram isoladas pela primera vez a Cirsimaritina e o ácido litospermico A, sendo esta a primeira vez que se descrevem para o gênero *Hyptis*. Este estudo fornece a primeira evidência do potencial químico e biológico para estas duas espécies nativas de *Hyptis*.

Palavras chave:

Hyptis; Flavonoides; nepetoidinas; ácido rosmarínico; ácido litospermico A; antioxidante, anti-HIV; citotoxicidade; antibacterial.

Summary

CHAPTER I

Plant-derived drug discovery and special metabolism

Historical perspective

Throughout the history of the mankind, humans did depend on the nature in how to satisfy their basic needs. The first documented reports related to medicinal applications of plants dates back to 2,600 BCE and they report the existence of a sophisticated medical system in Mesopotamia, comprising about 1,000 plant-derived medicines. In these derivatives are included oils of *Cedrus* Trew species (cedar) and *Cupressus sempervirens L. (*cypress), *Glycyrrhiza glabra L.* (licorice), *Commiphora* Jacq. species (myrrh), and *Papaver somniferum* L. (poppy juice), all these which nowadays are still in use for the treatment of diseases who vary from coughs and colds to parasitic infections and inflammation. The Egyptian medicine dates from approximate 2,900 BCE, but the best-known record is the *Ebers Papyrus* dating from 1,500 BCE, which describes about 700 varieties of drugs, mostly originating of plants (Borchardt, 2002). The Chinese *Compendium of Materia Medica* has been extensively documented over the centuries (Huang, 1998), having the first report, known as the Wu Shi Er Bing Fang, dated from 1,100 BCE, and containing 52 prescriptions. Late, we have the, *Shennong Herbal* (~100 BCE), which contains 350 types of drugs, and the *Tang Herbal* written in 659 CE and containing 850 varieties of drugs. In the same way also exist documents where could be find the description of substances or plant-derived drugs in the Indian Ayurvedic system (dated from before 1,000 BCE). For example, the *Charaka Samhitas* and the *Sushruta Samhitas* report 341 and 516 drugs, respectively (Kapoor, 1990; Dev, 1999).

In Western world, the knowledge of the medicinal application of plants is mostly founded in two cultures: the Greek and Roman. In the first century the written documentation of the Greek physician Dioscorides was specifically important; for the Roman culture in the first century Pliny the Elder and Galen (2nd Century CE) were the two representatives in the area of medicinal plant descriptions (Sneader, 2005). Thanks to the Greek and Roman cultures, the Arabs, who already had medical experience, did preserve a great amount of knowledge during the Dark and Middle ages, in between the 5th and the 12th century and were improved with information received from traditional medicine from China and India.

Johannes Gutenberg assists in the revival of Greek and Roman knowledge in the 15th and 16th centuries with the invention of the printing press. As a result, several influential books on herbalism were compiled and widely distributed in Europe, for example *The Mainz Herbal* (1484) and The German Herbal (1485), both edited by Peter Schöffer, a Gutenberg's partner; the *Herbarium Vivae Eicones* by Otto Brunfels (1530), the *Kreütter Buch* by Hieronymus Bock in 1546 (written in German) and *De Historia Stirpium* by Leonhart Fuchs that was published in Latin (1542) and also in German (1543) (Sneader, 2005).

During all this time, the use of medicinal plants was applied on empirical grounds, since there was no mechanistic knowledge of its pharmacological activities or active constituents.

It was in the 18th century that the foundations for rational clinical investigation of medicinal herbs were laid by researcher Anton von Störck, who studied poisonous herbs such as *Aconitum* and *Colchicum*, and William Whitering who studied foxglove (*Digitalis* L.) for the treatment of edema (Sneader, 2005).

Later, at the beginning of the 19th century, the German apothecary assistant Friedrich Sertürner succeeded in isolating morphine from opium, an analgesic and sleep inducing agent, which was named after the Greek God, Morpheus. This was the first isolated constituent of a plant and Sertürner published the method of isolation and crystallization, as well as the crystal structure and pharmacological properties of morphine (which he studied in stray dogs and self-experiments) (Sertürner, 1817).

As expected, thanks to this research, other similar studies on medicinal plants were originated in the following decades of the 19th century, and many bioactive natural products were isolated and identified, mainly alkaloids (quinine, caffeine, nicotine, codeine, atropine, colchicine, cocaine, capsaicin) (Felter and Lloyd, 1898; Hosztafi, 1997; Sneader, 2005; Kruse, 2007; Zenk and Juenger, 2007; Corson and Crews, 2007; Kaiser, 2008). Between 1981 and 2010, 1,073 new chemical entities were approved, of which only 36% were purely synthetic and more than 50% were derived or inspired by nature (Newman and Cragg, 2012). A substantial number of these compounds have been discovered in higher plants (Kinghorn et al., 2011).

At the moment we can find very remarkable examples related to the importance that have acquired the natural products and their importance for modern pharmacotherapy, specifically in the area of anticancer agents. An example of this is paclitaxel and its derivatives from yew (*Taxus* L.) species, vincristine and vinblastine from Madagascar

periwinkle (*Catharanthus roseus* (L.) G. Don), and camptothecin and their analogs originally discovered in the Chinese tree *Camptotheca acuminate* Decne (Cragg and Newman, 2013; Kinghorn et al., 2011).

Another notable example is galanthamine, which is a cholinesterase inhibitor and has been approved for the treatment of Alzheimer's disease, discovered in *Galanthus nivalis* L. (Mashkovsky and Kruglikova-Lvova, 1951 *apud* Atanasov et al., 2015), and the important antimalarial and potential anti-cancer agent artemisinin originally derived from the traditional Chinese herb *Artemisia annua* L. (Klayman et al., 1984).

Caventou and Pelletier were the first to report, in 1820, the isolation of the anti-malaria drug quinine from the bark of *Cinchona L.* species (e. g., *C. officinalis L.*) (Buss and Waigh, 1995). Quinine occurs naturally in the bark of *Cinchona* trees in South America and had long been used by indigenous groups in the Amazon for the treatment of fever. It was first introduced into Europe in the early 1600s for the treatment of malaria. Quinine formed the basis for the synthesis of the commonly used antimalarial drugs being one of the oldest malaria remedies known. Chloroquine and mefloquine replaced quinine in the mid-20th century, but with the emergence of resistance to both these drugs in many tropical regions, another plant long used in the treatment of fevers in Traditional Chinese Medicine, *A. annua*, gained prominence *(*Wongsrichanalai et al., 2002). As described, for millennia, medicinal plants have been an invaluable resource for therapeutic agents. Nowadays many therapeutic agents are botanical drugs or directly derived therefrom (Kinghorn et al., 2011).

Natural products as drug candidates: significance and advantages against synthetic compounds

There is a wealth of available and well-documented ethnopharmacological information on the traditional uses of natural drugs, which is a great advantage because it provides evidences for therapeutically effective compounds in humans (Heinrich and Gibbons, 2001; Corson and Crews, 2007; Heinrich, 2010; Kinghorn et al., 2011). According to the information above, 122 compounds derived from plants used worldwide as therapeutic agents were analyzed and it was revealed that 80% have an identical or related use to indications for which these pure compounds were prescribed in ethnomedicine (Farnsworth et al., 1985; Fabricant and Farnsworth, 2001).

In addition, it has been shown that natural products used for the development of medicines are highly likely to be used traditionally. An example is the discovery of the anti-

cancer agent taxol, from *Taxus brevifolia* Nutt., which discovery was done with a random screening approach. Later on, it came to light that the plant has been used by western Indian cultures as a medicine (Heinrich, 2010).

Because natural drugs are made by or in living organisms, these products possess properties that are evolutionarily optimized to serve in different biological functions, as they are part of the body's metabolism, for example binding to specific target proteins or other biomolecules (Hunter, 2008; Appendino et al., 2010).

Natural compounds are highly diverse and often provide highly specific biological activities. This stems from the proposition that essentially all natural products have some ability to bind to the receptor. The natural molecules, however, differ substantially from the synthetic ones. The main structural differences between natural and combinatorial compounds originate mainly from properties introduced to make combinatorial synthesis more efficient. These include the number of chiral centers, the prevalence of aromatic rings, the introduction of complex ring systems, and the degree of saturation of the molecule, as well as the number and proportions of different heteroatoms.

The chiral separation method is challenging and expensive. Therefore, the creation of molecules with a low number of chiral centers is favorable. Synthetic compounds tend to have a much smaller number of chiral centers, and in addition a lower molecular weight, a higher number of freely rotatable bonds, higher chain lengths, a lower number of rings, less oxygen but more nitrogen, sulfur and halogen atoms, a lower number of acceptors and donors of Lipinski-type H-bonds and higher calculated octanol-water partition coefficients (cLogP values). Other differences are the complexity of ring systems and the degree of saturation (Stahura et al., 2000; Feher and Schmidt, 2003; Atasanov et al., 2015).

For example, because of the stereospecificity of most biological targets, it is likely that many non-stereospecific synthetic analogues, created, for example, by the introduction of aromatic rings, represent non-optimal compromises, especially in terms of selectivity and this occurs more frequently in the case of combinatorial synthesis compounds. The greater flexibility of combinatorial products is likely to have entropic consequences detrimental to the binding of these compounds. It may also affect negatively their ability to induce conformational changes in the receptor required for biological function. Also, the production process of synthetic analogs radically alters the number and ratios of different types of atoms, such as nitrogen, oxygen, sulfides and halogens. These distributions in turn

have a direct impact on the donor and acceptor patterns available to complement the receptor surface properties (Feher and Schmidt, 2003).

These factors, which are structural differences, specifically the significant number of chiral centers, low size and high flexibility, make the synthetic products weaker and less specific than natural products (Feher and Schmidt, 2003). Natural products have selective and specific biological actions due to the binding affinities to relevant proteins in their biological functions, and during biosynthesis a greater diversity and chemical complexity are developed than for their synthetic analogues (Clardy and Walsh, 2004; Koehn and Carter, 2005). They often have less advantageous absorption, distribution, metabolism, excretion and toxicity properties. In view of these facts, it is interesting to consider that the search for the replacement of natural compounds with synthetic ones is usually based on exactly these kinds of 'unfavorable' modifications.

The main focus of the pharmaceutical industry was for a time led to synthetic compound libraries and high throughput screening, with the aim of discovering new drug derivatives (Beutler, 2009; David et al., 2015). But, the results obtained did not meet expectations, and this is evident when the decreasing number of drugs that reach the market is observed (David et al., 2015). Because of this, the interest in products based on natural products has been revitalized for the discovery of new drugs, where broad interdisciplinary research approaches are required due to their high complexity, but at the same time high specificity as mentioned in previous paragraphs (Heinrich, 2010a).

Plants have been the basis for medical treatments through much of the human history. Nowadays, researchers are increasingly interested in medicinal plants as alternative medicine, due to their good pharmacological properties, fewer side effects, and low cost (Sayah et al., 2017).

Where do these medicinal substances originate in plants?

What is a special (or secondary) metabolite and which is their role in plants?

Land plants have colonized the vast majority of the Earth's surface due to rich levels of specialization and intricate relationships with other organisms. During this process land plants had (and still have) to face a number of challenges imposed by the terrestrial environment. These organisms are autotrophic stationary, dealing with biotic and abiotic stress factors such as the coexistence of herbivores and pathogens in their immediate environment, pollination and seed dispersal (specially angiosperms), and climate variations.

Therefore, and because of these challenges, land plants have developed special biochemical pathways that allow them to synthesize a series of chemicals, also called secondary metabolites or special metabolites, that are produced regularly in response to specific environmental stimuli, such as herbivore induced-damage, pathogens attack, enhanced concentration of air pollutants etc. (Reymond et al., 2000; Hermsmeier et al., 2001).

The function of these special metabolites is to increase the general plant ability plant to survive and overcome local challenges, allowing them to interact with their environment. They play no role in primary metabolic needs and may be unique to specific species or genera (Harborne, 2014). The energy invested in the synthesis of these special metabolites, which is usually much higher than that required to synthesize primary metabolites, is an indicator of the importance of these substances for the survival of plants (Gershenzon, 2017; Hong et al., 2016). Among the functions of the special metabolites are: protective roles as antioxidant, free radical-scavenging, UV light-absorbing, and defend the plant against microorganisms such as bacteria, fungi, and virus. They also manage inter-plant relationships, acting as allelopathic defenders of the plant's growing space against competitor plants. More complex roles include dictating or modifying the plant's relationship with more complex organisms (Harborne, 2014; Wink, 2003; Tahara, 2007).

One of the main roles of special metabolism is feeding deterrence. For that reason, many of these substances are bitter and/or toxic to potential herbivores, affecting the central and peripheral nervous system of the herbivore. In this regard, special metabolites often act as agonists or antagonists of neurotransmitter systems or form structural analogs of endogenous hormones (Wink, 2000; Miller and Heyland, 2010; Rattan, 2010). In addition to that defense mechanism, plants also have to foster a number of symbiotic relationships. One of the obvious roles in this series of mechanisms is the attraction of pollinators and other symbionts, using colors and scents or indirect defenses, by attracting natural enemies of its herbivorous attackers. In this way, it provides an attractive chemical environment for the predator or alternatively, it may be a direct response to tissue damage by the herbivore, resulting in the synthesis and release of a set of substances that are attractive to natural herbivore predators (Harborne, 2014; Wink, 2003; Tahara, 2007). There are more than 100,000 special metabolites already described in plants, ranging from simple alkaloids (structurally) to phytosterols and more complex polyphenolic molecules (Dillard and German, 2000).

Special metabolism and major groups of plant special metabolites

All living cells possess similar pathways for the synthesis of components such as sugars, amino acids, nitrogenous bases, carbohydrates, proteins, and nucleotides, being these are molecules essential for energy production and cell constitution and plant development. Plant special metabolites are derived from the products of primary metabolism but have a much more limited taxonomic distribution. They can be broadly classified according to their structure and biosynthetic pathways; however, it should be appreciated that many special metabolites are also derived by combining elements of all these biosynthetic pathways (Fig. 1.1).

These diversified compounds can be divided into three main categories: terpenes, nitrogenous compounds and phenolic compounds, based on their chemical structure. Amines, cyanogenic glycosides, glucosinolates, acetylenes and psoralens, are other minor groups that cannot be included in these three large groups (Fang et al., 2011 *apud* Russell and Duthie, 2011).

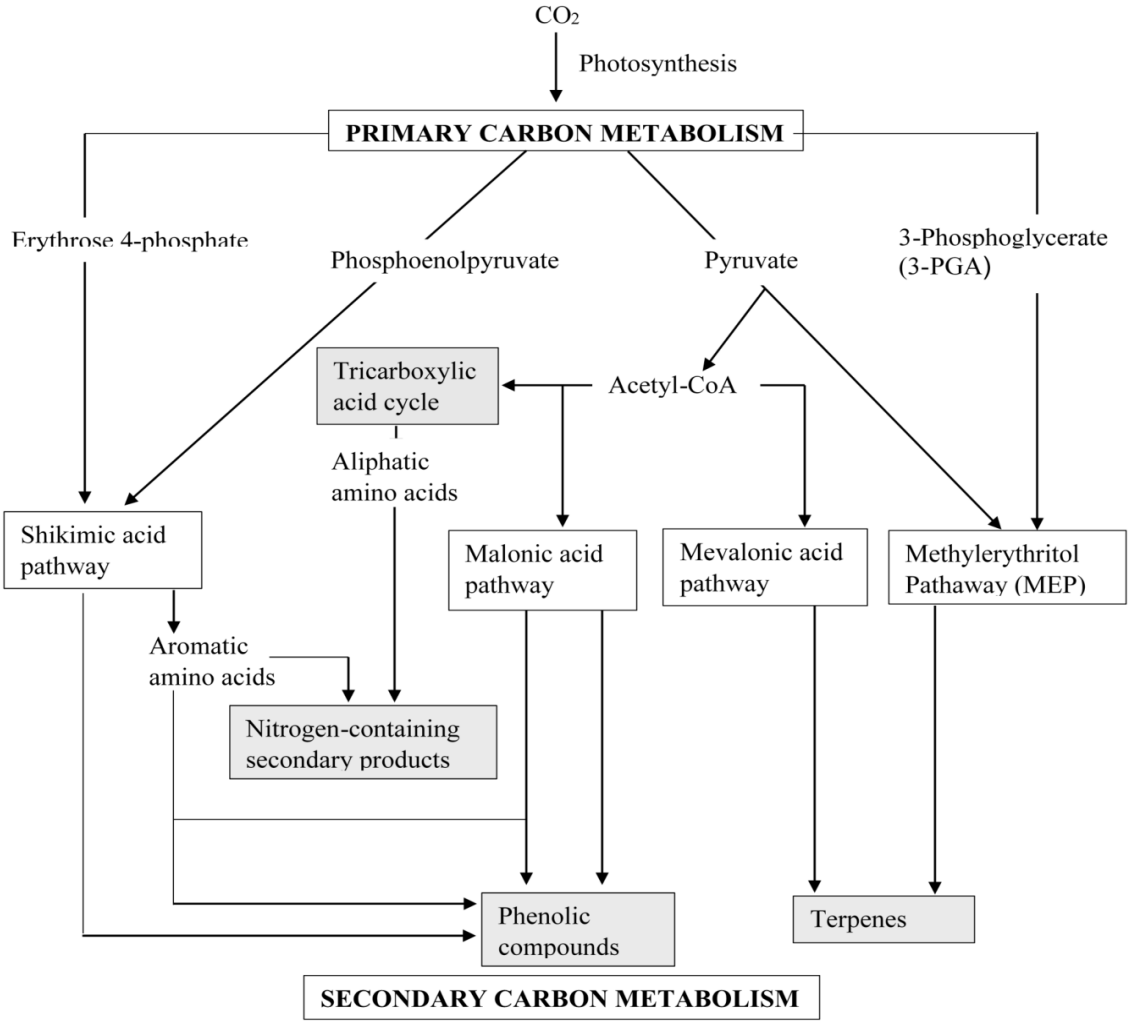

Figure 1.1. A simple schematic representation of the major secondary metabolites in plants (Ncube and Van Staden, 2015)

Terpenes

Terpenes represent the most abundant and structurally diverse group of plant special metabolites, in which more than 36,000 structures have been identified. They are a structurally diverse group of hydrocarbons derived from the five-carbon precursors: isopentyl diphosphate (IPP) or dimethylallyl diphosphate (DMPP), synthesized, in photosynthetic organisms, by mevalonate and methylerythritol phosphate pathways.

Terpenes are classified according to the degree of isoprene incorporation as follow: hemiterpenes (C_5), monoterpenes $(C_5)_2$, sesquiterpenes $(C_5)_3$, diterpenes $(C_5)_4$, sesterpenes $(C_5)_5$, triterpenes $(C_5)_6$, tetraterpenes (or carotenoids) $(C_5)_8$, and through to higher polymers such as rubber $(C_5)_{>100}$. Isoprene units are often joined in a head-to-tail and head-to-head linkage and a few terpene structures are formed by irregular head-to-middle linkage. After the basic terpene skeletons are formed, subsequent modifications occur which give rise to different structures such as steroids like cholesterol, ergosterol, sitosterol and stigmasterol, which are synthesized from a triterpene precursor. Among the modifications that the basic terpene skeleton receives are: reduction, isomerization, oxidation, conjugation and degradation (Grayson, 2000; Croteau et al., 2000; Maimone and Baran, 2007).

Pharmacological active molecules derived from terpenes include, for example, the herbal tranquilizer valtrate, the major component of valerian (*Valeriana officinalis* L.) and the anti-cancer drug taxol, extracted originally from the Pacific Yew (*Taxus brevifolia*) (Hayes et al., 2008).

Nitrogenous compounds: alkaloids

Alkaloids are a group of alkaline, low molecular weight and nitrogen containing compounds. They are the most widely distributed nitrogenous special metabolites and are found not only in plants, but also in microorganism, playing an important role in plant defense systems. Alkaloid containing plants were, for mankind, the original "*materia medica*" and many are still in use today as prescription drugs, such as vinblastine, quinine, atropine, and camptothecin. There are more than 12,000 alkaloids reported for 100 families of plants, being especially abundant in Fabaceae, Solanaceae, Menispermaceae, Papaveraceae, Ranunculaceae, Apocynaceae and Berberidaceae. Can be classified on the basis of the plants from which they were isolated, their chemical structures, and the biosynthetic origins. This last feature has an obvious advantage of reflecting the relationship between biosynthetic pathways and the chemical structures. Alkaloids could thus be further

classified into three groups according to their biosynthesis origin: true alkaloid, protoalkaloid, and pseudoalkaloid (Buchanan et al., 2000; Dewick, 2009).

The alkaloids, have contributed mainly providing neurotoxins, poisons and traditional psychedelics, among which are some that come from *Atropa belladonna* L. like, atropine, scopolamine, and hyosciamine, to this chemical group also belong the most consumed social drugs, nicotine, caffeine, methamphetamine (ephedrine), cocaine and opiates (Zenk and Juenger, 2007). This group also provides the cholinesterase inhibiting treatments routinely prescribed for the cholinergic deregulation of Alzheimer's disease, such as galantamine, huperzine, physostigmine, and rivastigmine (Mukherjee et al., 2007).

Phenolic compounds

Phenolic compounds are ubiquitously found across plant, with ~10,000 structures identified. Structurally, they share at least 1 aromatic hydrocarbon ring with 1 or more hydroxyl groups attached and are synthesized via the shikimate pathway alone or in combination with the acetate-*malonate pathway*. The simplest compound with this structural motif is the phenol molecule, which itself does not occur in plants. Phenolic compounds range from simple low-molecular mass, such as the simple phenylpropanoids, coumarins, and benzoic acid derivatives, to more complex structures such as flavanoids, stilbenes, and tannins. Flavonoids represent the largest, most diverse group, encompassing some 6,000 compounds, all of which share a common underlying structure of two 6-carbon rings, with a 3-carbon bridge, which usually forms a 3rd ring. Flavanoids can then be subdivided according to modifications of this basic skeleton into: chalcones, flavones, flavonols, flavanones, isoflavones, flavan-3-ols, and anthocyanins (Bowsher and Tobin, 2008; Yang et al., 2012).

Phenolic compounds and flavonoids in particular, are ubiquitous in plants and therefore represent an important component of a normal human diet. Epidemiological studies have suggested associations between consumption of phenolic-rich foods or beverages and various diseases, such as stroke, cardiovascular disease, and cancer (Steffen, 2006) and neurologic disorders such as dementia/Alzheimer's disease (Commenges et al., 2000; Vingtdeux et al., 2008).

Aims of the present study

In the world there are a great number of plant species, which produce a diversity of bioactive compounds with different chemical scaffolds. According to previous estimates, only 6% of existing plant species have been systematically pharmacologically investigated, and only about 15% were studied phytochemically (Fabricant and Farnsworth, 2001; Verpoorte, 1998 and 2000). Although today the percentage of species is better characterized by increased interest in this phytochemical area, it is still conceivable that there are a large number of plant compounds that are not well pharmacologically researched, especially if we consider the approximately 310,000 plant species described (IUCN, 2015). Unfortunately, a significant decline in global plant species is expected in the coming years as a result of climate change and anthropogenic factors that jeopardize these potential sources of new natural drugs, and therefore urgent measures are needed to access different species (Maclean and Wilson, 2011; Thomas et al., 2004).

Another point to highlight is the ethnobotanical knowledge about the traditional pharmacological use that is disappearing. With the increase of globalization, this information is in danger of being lost forever and it is being lost faster than the loss of the biodiversity (Appendino et al., 2010).

In the context of the discovery of drugs of plant origin, it is highly advantageous when the species under study come from regions of high biodiversity and endemism, as the chemical diversity of natural products can reflect the biodiversity of their organisms of origin and an example of megadiverse country is Brazil (Barbosa et al., 2012; Henrich and Beutler, 2013). These estimates gain importance when considering the broad potential of the active principles contained in nature and which have not yet been identified and evaluated in a medical context. This fact attracts the attention of the pharmaceutical industry that sees in plant diversity a feasible source for new medicines.

The present study aimed to access phytochemically to Brazilian native species: *Hyptis radicans* Jacq. and *Hyptis multibracteata* Poit. Both are species of occurrence in the Atlantic Rainforest of State of São Paulo and are easily found in the Paranapiacaba region. Furthermore, both are species that do not count on studies on their chemical composition, have not been evaluated for their biological activities and, therefore, are promising models for prospecting studies of natural bioactive substances.

The main objectives of the present study were:

- To isolate and identify substances present in both species; and
- To evaluate the antioxidant, antibacterial and anti-HIV potential of *H. multibracteata* and *H. radicans*;

This study is divided in 5 chapters and a final consideration as follow:

Chapter 1: Plant-derived drug discovery and special metabolism.

Chapter 2: *Hyptis* Jacq.: a general chemical profile review - *manuscript submited to Chemistry & Biodiversity.*

Chapter 3: Botanical aspects & chemical description of *H. radicans* and *H. multibracteata.*

Chapter 4: Antioxidant, anti-acetyl cholinesterase and cytotoxic potential of *Hyptis* spp – *part of the results published at Industrial Crops & Products 112 (2018) 705–715.*

Chapter 5: Anti-HIV-1 and antibacterial potential of *Hyptis radicans* (Pohl) Harley & J.F.B. Pastore and *Hyptis multibracteata* Benth. (Lamiaceae) – *manuscript submited to Journal of Herbal Medicine.*

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Final considerations

Natural products remain a source of novel compounds for drug discovery due to their lower toxicity (Park et al., 2009). Most drugs on the market are plant-derived (Newman and Cragg, 2016) and the area of infectious diseases is largely dependent on natural products and their structures for sources of better treatment.

Related to *Hyptis* species, although a considerable number of papers founded in databases: 879 in SciFinder, 528 in Web of Science and 96 in SciELO, only 20% of *Hyptis sensu* Harley and Pastore (2012) have been studied. Most species were studied regarding their volatile oil composition; remaning poorly explored the polar constituents.

Furthermore, based on the articles published, it was possible to notice that these species are characterized by the presence of substances with promising pharmacological potential, mainly antimicrobial, antifungal, cytotoxic, anti-inflammatory, and anti-HIV, pointing to a great relevance of *Hyptis* to bioprospecting studies.

This study corroborated rosmarinic acid, chlorogenic acids, and nepetoidins as common constituents of Nepetoideae. Furthermore, the results corroborate the presence of these constituents also in *Hyptis* species. Lithospermic acid A and cirsimaritin were described for the first time in this study for *Hyptis*, both found in *H. radicans*. Fatty acids and triterpenes are the most abundant kind of apolar substances in *H. radicans* and *H. multibracteata*. This differs from what is most reported in the literature; first because the majority of reports focused on volatile oils and in this study, we analyzed also the apolar constituents of aerial parts extracts.

The present research also provides, for the first time, a comprehensive report on the antioxidant and cytotoxic activities of *Hyptis* species. **EAP** from *H. radicans* was the sample that presented the highest levels of total phenolic content, especially flavonoids, being also the sample with the high antioxidant activity with promising EC_{50}: DPPH (32.12 μg mL^{-1}), ABTS (5.04 μg mL^{-1}), Metal chelator assay (42.36 μg mL^{-1}), TBARS (40.46 μg mL^{-1}) and nonsite-Specific Hydroxyl Radical-Mediated 2-Deoxy-D-ribose Degradation *(*NS-Spe) with a EC_{50} of 75.08 μg mL^{-1}. **EE** from *H. radicans* showed the high antioxidant activity for FRAP and ORAC with EC50 of 6.01 and 2.68 μg mL^{-1}, respectively and has the highest amount of rosmarinic acid (17.64 mg g^{-1}). **HMP** from *H. radicans* showed the high antioxidant activity

in Site-Specific Hydroxyl Radical-Mediated 2-Deoxy-D-ribose Degradation (S-Spe) assay with EC50 of 0.32 μg mL^{-1} and has the highest content of chlorogenic acid derivatives.

Lithospermic acid A isolated from *H. radicans* and rosmarinic acid and nepetoidin B from *H. multibracteata*, were substances with better antioxidant activity. Nepetoidin B isolated from *H. multibracteata* had the best EC_{50} (52.73 μg mL^{-1}) for anti-acetylcholinesterase activity. Regarding the results of cytotoxicity, **HP** from *H. multibracteata* induced the death of more than 80% of RAW 264.7 Cell Lines turning **HP** as an interesting phase as promising cytotoxic agent.

The anti-HIV-1 and antibacterial results from the present study lend support for further investigation of the bioactive constituents of *H. radicans* and *H. multibracteata* to validate the use of these plants in traditional medicine as antiviral and/or as antibacterial.
EE and **HMP** of *H. radicans* showed anti-HIV-1 activity but contents of total phenolic compound are not the main sample feature to define anti-HIV activity but there is a correlation between the presence of rosmarinic acid and their anti-HIV activity. **HP** of *H. multibracteata* was the sample with better antibacterial activity but there was no correlation between phenolic contents and its activity. With the great results on biological activity it can be concluded that *H. radicans* is a promising phytotherapic.