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Review Article

The Potentiality of Plant Species from the Lamiaceae Family for the Development of Herbal Medicine in the Control of Diseases Transmitted by *Aedes aegypti*

Lizandra Lima Santos*, Lethicia Barreto Brandão, Anderson Luiz Pena da Costa, Rosany Lopes Martins, Alex Bruno Lobato Rodrigues, Sheylla Susan Moreira da Silva de Almeida

ABSTRACT
The use of medicinal plants is an ancient practice used by man to treat various ailments and is expanding throughout the world. The so-called neglected diseases, such as dengue, yellow fever, Zika, and chikungunya transmitted by the *A. aegypti* mosquito, have affected and killed thousands of people. In this sense, the inclusion of herbal medicines in the public health system would help improve the quality of primary care provided for the population and serve as an alternative for vector control. In this context, as an alternative for chemical control of natural origin, herbal medicines that have insecticidal, larvicidal, and repellent action appear. Therefore, the present work aims to carry out a survey of some recent works related to the Lamiaceae family with potential for the development of herbal medicines for the control of diseases transmitted by *Aedes aegypti*, with an emphasis on promising technological innovations with a repellent, insecticide and larvicide action mechanism. The article was developed through surveys of scientific and ethnobotanical information, using information from works published in Portuguese, English, and Spanish. The results proved the potential for the development of herbal medicines with a larvicidal, insecticidal, and repellent action mechanism for species belonging to the Lamiaceae family, presenting significant toxicity against insects, but negligible toxicity for animals, being easy to obtain, manipulate and apply, also presenting economic viability and non-cumulative effect on man and animals. The researches listed contribute to the feasibility of new biological tests that help in determining the most appropriate concentrations of phytoconstituents from extracts or essential oils that may be suitable for the formulation of repellents and other products for vector control.
Key words: Herbal medicines, Lamiaceae, Vector control, Bioinseticidal, Repellent; Essential oil.

Lizandra Lima Santos*, Lethicia Barreto Brandão, Anderson Luiz Pena da Costa, Rosany Lopes Martins, Alex Bruno Lobato Rodrigues, Sheylla Susan Moreira Silva de Almeida

Laboratory of Pharmacognosy and Phytochemistry-Federal University of Amapa- 10 Highway JucelinoKubistichek, Garden Zero-CEP: Macapa-AP, BRAZIL.

Correspondence

Dr. Lizandra Lima Santos,

Laboratory of Pharmacognosy and Phytochemistry-Federal University of Amapa- 10 Highway Jucelino Kubistichek, Garden Zero-CEP: 68.902-280, Macapa-AP, BRAZIL.

E-mail: lizandralsantos@hotmail.com

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INTRODUCTION

The use of medicinal plants is an ancient practice used by man to cure various ailments and is expanding throughout the world. Medicinal plants are the only readily available resource found in fairs, popular markets, as well as backyards or areas of native vegetation. Brazil is a colossal source of natural chemical substances with therapeutic effects, due to its size and variety of ecosystems that offer rich possibilities that can meet the needs of different communities, especially those in need.[1]

Among this biodiversity of medicinal plants, the study of plant extracts, as well as their essential oils, arises as an expectation to find substances with repellent and insecticide activities that can be selected to be used in future formulations of a commercial product.

Plants with insecticidal activity have compounds originated from their secondary metabolism, which constitutes their chemical defense against herbivorous insects. The insecticidal active compounds can be derived from the whole plant or their parts, in most cases, they can be the plant material itself, usually ground until it is reduced to powder, or products derived by aqueous extraction or with organic solvents.[2]

The species of the Lamiaceae family have the potential to obtain essential oils (EO), which have several biological functions in folk medicine, used to treat burns, headache, colic, fever, as well as reports of anti-flu, insecticide, repellent activities, antibacterial and combating intestinal parasites.[3]

Given the need to combat so-called neglected diseases, such as dengue, yellow fever, Zika, and chikungunya, transmitted by the *A. aegypti* mosquito, which has victimized and caused the death of thousands of people, the insertion of herbal medicines in the public system of health would help in the quality of primary care provided tothe population and also as an alternative to vector control. Therefore, this review proposes to survey some recent works related to the Lamiaceae family with potential for the development of herbal medicines for control of diseases transmitted

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by *Aedes aegypti*, emphasizing the promising technological innovations with a repellent andinsecticide and larvicide action mechanism.

MATERIALS AND METHODS

This study is an analysis of the data concerning the potential of the Lamiaceae family in the control of diseases transmitted by the mosquito of the species *Aedes aegypti*, through a narrative review,[4] aimed to evaluate the published studies 2010 to 2021 (11 years).

In this sense, to contextualize this theme, searches were conducted in the electronic databases LILACS, SCIELO, Pubmed, and Scopus using the descriptors previously consulted in the DECs (Descriptors in Health Sciences) "*Aedes aegypti*", "*Lamiaceae*" AND "insecticide" and their correspondents in Portuguese and in Spanish.

After reading the titles and abstracts, it was included in this review articles that fit the proposed theme and addressed the development and validation of herbal medicines with plants belonging to the Lamiaceae family with applicability in disease control. Articles that did not present any aspect of the proposed theme or that were written in any other languages than those abovementioned, as well as thesis and dissertation results were adopted as exclusion criteria, due to the large amount publications.

RESULTS AND DICUSSION

The use of medicinal plants

The World Health Organization refers to medicinal plants as "plant species from which products of therapeutic interest can be obtained and used in the human species as medicine".[5] Therefore, they are plants that produce any chemical substances with pharmacological applicability for the human body and that, when administered, alleviate any harm.

The use of medicinal plants to treat diseases is a common practice in many communities. It is estimated that 80% of the world's population relies on medicinal plants to care for their health, whereas 25% of the medical prescriptions are formulations based on substances derived from plants or their synthetic analogs.[6]

According to Rocha *et al*.[7] the utilities of plants are products of a series of cultural influences, such as that of European, indigenous, and African colonizers. However, popular or traditional knowledge generally is developed by cultural groups that still live intimately with nature, closely observing their daily lives and exploring their potential, keeping this heritage alive and growing through systematic and constant experimentation.

In this sense, considering the popular or traditional knowledge and use over the years, a series of several plants and their respective functionalities can be listed. This knowledge is maintained through oral tradition without proof of benefits and harm, as it is a viable and accessible alternative for the treatment of diseases or health maintenance.

Popularly, a plant is considered medicinal if it is effective in preventing or treating a disease or its symptoms. It is not possible to know if the plant is sufficient to treat a disease or symptom and if its use will be better or more potent than a pharmaceutical drug, in addition to the safety of its administration. Thus, it is through the observation of the adverse effects that a plant produces on the organism, the population does not use it and considers it toxic. In addition, there is the idea that medicinal plants, as they are natural products, do not produce a toxic effect, however, it is necessary to know the identity of the plant before administering it, as well as it is also important to know its functionality, forms of preparation and the correct dosage to avoid the manifestation of the undesirable effects.[8]

In Brazil, the first record of the use of medicinal plants is attributed to Father Jose de Anchieta and other people from the religious order Jesuit who came to Brazil in colonial times. For the treatment of illnesses, they formulated recipes based on herbs called "Boticas dos colégios". The indigenous populations also made use of this resource, and even as the extinction of these peoples, they passed this information for generations that certainly reached European immigrants and African slaves.[9]

Medicinal plants have richly contributed to the development of new therapeutic strategies through their secondary metabolites. These substances act directly or indirectly in the body, helping to promote health and prevent diseases.[10]

SECONDARY METABOLITES

Metabolism is the set of chemical reactions (anabolic, catabolic, or biotransformation) that continuously occur inside cells. In the plant cells, metabolism is normally divided into primary and secondary. The primary metabolism has essential functions in the plant, such as photosynthesis, respiration, and transport of solutes; the compounds of this metabolism are distributed universally in plants. In contrast, the secondary metabolism occurs differently in each plant, and it usually does not occur universally distributed among the plant's parts; it has an important ecological function in plants, such as protection against herbivores and pathogens, competition between plants, attraction for pollinators, and seed dispersers, and symbiotic microorganisms.[11]

There are three major groups of secondary metabolites: terpenes, phenolic compounds, and alkaloids. Terpenoids have the most varied structures than other natural plant products, their name is because the first members of the class were isolated from turpentine (terpentin in German). They are formed through the successive juxtaposition of isopentenyl pyrophosphate (IPP-C5) from which the other terpenes (monoterpenes (C10), sesquiterpenes (C15), diterpenes (C20), triterpenes (C30), and tetraterpenes (C40)) originate.[12]

The phenolic compounds form a group that is very present in everyday life, even though it is not noticed. In this way, much of the flavor, odor, and color of several vegetables highlight the characteristics of this group. They are important substances for the protection of plants against adverse environmental and biotic factors, as well as the conquest of the terrestrial environment by plants. Chemically, they are formed by at least one aromatic ring in which at least one hydrogen is replaced by a hydroxyl group. There are two main routes for the biosynthesis of these compounds: the shikimic acid pathway and the mevalonic acid pathway, which is less significant.[13] Another important class of secondary metabolism is the alkaloids, which presents activity on the nervous system, many of which are widely used as poisons or hallucinogens. Chemically, they are formed by cyclic organic compounds with at least one nitrogen atom in their ring, most of which are alkaline due to the presence of the N atom representing a pair of unshared electrons.[12]

In this context, chemical analysis of secondary metabolites and botanical material, whether leaves, fruits, branches, and flowers, can provide essential information for the formulation of high-quality natural products through pharmacognostic research.

THE LAMIACEAE FAMILY

The plants of the Lamiaceae family (Labiatae) have agricultural importance and are widely used in cooking, traditional medicine, pharmaceutical, and cosmetic industries. Lamiaceae is one of the largest Angiosperm families, with a cosmopolitan distribution including approximately 300 genera and 7,500 species worldwide. In Brazil, there are about 350 species distributed in 26 genera.[14]

In the chemical and economic scope, the Lamiaceae family has the potential for the extraction of essential oils, which are produced from hairs and glandular trichomes, and their studies are aimed at evaluating

the constituentspresent in the oils. With the characterization and qualification of chemicals present in the OE, it is expected to establish a relationship between the possible application of a product of natural origin to problems that have accompanied humanity since ancient times, for example, crop infestation, bacterial control, fungicide, repellent,and insecticide, as long as they are tested through *in vivo* and *in vitro* assays, and that they have scientific proof.[15]

These species are herbaceous or shrubs with simple leaves, without stipules, with an entire leaf blade, jagged, serrated, lobed or split, with opposite crossed phyllotaxis, being less frequently verticillated or alternating and rarely composed.[16,17] They present tetrangular stems and branches, when young, strongly zygomorphic, bilabiate flowers, and a gynobasic stylet ovary.[18]

NEGLECTED DISEASES TRANSMITTED BY *AEDES AEGYPTI*

Neglected diseases are those caused by infectious agents or parasites and are considered endemic in low-income populations, contributing to the maintenance of inequality between countries. As examples of neglected diseases,we have dengue, yellow fever, Zika, and chikungunya, all transmitted by the *A. aegypti* mosquito.[19]

The occurrence of *A. aegypti* was first described in Egypt by Linnaeus, in 1762, which gave it its specific name (*Aedes aegypti*). It was recognized as a transmitter of yellow fever in 1881, by Carlos J. Finlay. In 1906, Brancroft published the first evidence that the mosquito was also the vector of dengue, a fact later confirmed by Agramonte, in 1906, and by Simmons, in 1931.[20] In Brazil, the entry of chikungunya and Zika viruses recently took place, in September 2014 and May 2015, respectively; both are also transmitted by *A. aegypti*.[21]

The *Aedes aegypti* mosquito measures less than 1 cm and has a harmless appearance, it is black in color with white stripes on the body and legs. Its sting doesn't hurt or itch. The life cycle of *A. aegypti* comprises four phases:egg, larva, pupa, and adult. The eggs of the transmitting mosquito are laid under suitable conditions, that is, in hot and humid places such as those close to the waterline.[22]

The ethology of *A. aegypti* influences its wide dispersion, favored in urban environments, preferably in the homeand peridomestic conditions offered by the way of life of man. Their breeding sites are preferably artificial containers, such as those abandoned in the open space, rainwater reservoir, or for storing water for domestic use. This vector prefers to reproduce in clean water reservoirs, although it can adapt to new situations imposed by anthropic activities, adapting to other types of breeding sites, such as bromeliads and open sewers found in variousurban centers. The presence of breeding sites in a human environment favors the rapid proliferation of the species, for two reasons: ideal conditions for reproduction and food sources.[19]

Given the challenges of vector control and a serious and worrying situation concerning arboviruses delineated by the expansion of these viruses throughout the world, it is essential to adopt specific strategies, with greater investments in suitable methods of control this mosquito species. Therefore, in the current scenario of outbreaksand epidemics of Zika, chikungunya, and dengue, such a study becomes relevant, as it provides a strategy to reduce mosquito contact with humans.

THE PHYTOTHERAPIC POTENTIAL OF THE LAMIACEAE FAMILY AS AN ALTERNATIVE FOR VECTOR CONTROL

Controlling *Aedes* is a major challenge, especially in developing countries. There are financial resources for vector control through program implementation, however, success has often not been achieved. Aspects related to the lack of garbage collection and intermittence in the water supply are factors that directly influence the traditional control methods.[19]

As an alternative for chemical control of natural origin, herbal remedies that have insecticidal, larvicidal, and repellent action mechanisms appear. The use of insecticides to control adult mosquito populations (adulticides) and in their larval form (larvicides) can be done through focal and perifocal treatment and aerospace spraying of insecticides in an ultra-low volume (ULV). Repellents can be applied to the individual's skin to repel mosquitoes and prevent bites.[23]

Plants have defense mechanisms against insects, being able to synthesize, from different metabolic pathways, compounds as secondary metabolites and proteins that act as insecticidal toxins. These substances of plant origin that have recognized entomotoxic potential that awakes the interest of several researchers in the search for alternative strategies for the chemical control of *Aedes aegypti*.[3]

Generally, chemical compounds are extracted from essential oils and plant extracts with repellent and insecticidal potential and studied for the formulation of products that are effective in controlling *Aedes* spp. Natural products of plant origin do not have environmental toxicity because they are biodegradable, avoiding environmental contamination. Unlike synthetic products, to which insects become increasingly resistant, making such products toxic and polluting.[24]

With the operational and economic difficulties generated by the growing resistance of mosquitoes to synthetic insecticides, alternative methods gained new prominence and gained greater attention for being more efficient and cheaper, as they are obtained from renewable resources, rapidly degradable, and contain several substances that act simultaneously, causing the development of insect resistance to these substances to occur very slowly.[23] The study for the development of herbal medicines with larvicidal, insecticidal, and repellent action against *Aedes aegypti* is recent, beginning in the 1980s, aiming to isolate and characterize these bioactive substances. Most studies are performed using crude extracts and essential oils, and in most of these cases, the compound responsible for the activity presented is not known. Many herbal products have active compounds, which act synergistically or in isolation, having characteristics that can be efficient for the control and monitoring of mosquito population.[25]

Many studies prove the activity of essential oils and plant extracts in the control of different mosquito species[26-28] including *A. aegypti*.[29,30] The study of larvicide, insecticide, and repellent activities of compounds extracted from plants has been an alternative to synthetic products for vector control since there is no vaccine against dengue, which is treated only with medications that alleviate symptoms.

The research applied to vector control has identified the presence of several chemical compounds, that in general are monoterpenes, as well as sesquiterpenes, which have significant toxicity against insects, but negligible toxicity for animals.[23,31,32] The mixture of these compounds provides the plants with their characteristic odor, protection against herbivores and pathogens, competition between plants, attraction for pollinators and seed dispersers, and symbiotic micro-organisms.[25]

According to Silva,[33] substances with LC_{50} values (lethal death concentration of 50%) lower than 100ppm are considered good larvicidal agents. Ramos[3] in his studies found that the plants *Ocimum gratissimum*, *Ocimum basilicum*, *Pogostemon heyneanus*, and *Hyptis crenata* showed significant larvicidal potential with LC_{50} values (ppm) of 76.6, 67.2, 69.9, and 89.4 respectively. Nasir *et al*.[30] showed that the *Mentha piperita* species is highly toxic to *A. aegypti* mosquito larvae, reaching approximately 90% of larval mortality.

Silva *et al*.[34] sought to evaluate the larvicidal potential in dragonfly larvae, in which the results were considered to be highly potent oils of the species *Hesperozygis ringens* (Bentham) Epling and *Ocimum gratissimum* with LC_{50} of 62.92; 75.05 µl respectively. Veloso *et al*.[35] found in their study efficient larvicidal action of the species *Ocimum basilicum* L. (basil) against *A. aegypti* larvae, noting that the rates of 5.0, 7.5, and 10 .0 µL of the essential oil were more efficient, showing 100% of dead larvae from the second evaluation period. These results corroborate the potential use of the species for larvicidal and repellent activity in future work to elucidate the mechanism of biological action.

The toxicity of a chemical substance is not necessarily associated with the death of insects, because other aspects may be linked to this action, such as repellency, deterrence, and antibiosis (adverse effect on their biology). To be considered a good insecticide or 'ideal insecticide', several factors must be taken into account, such as efficacy at low concentrations, absence of toxicity against higher mammals and animals, absence of phytotoxicity, easy obtainment, manipulation and application, economic viability and it does not have a cumulative effect on man and animals.[25]

Several studies prove the insecticidal activity of essential oils and plant extracts in the control of different species.[27,36,37] Savaris *et al*.[38] in their study that evaluated the insecticidal activity of *Cunila angustifolia* found that all doses of essential oil of the species were 100% efficient in the mortality of adults of *A. obtectus*, 24 hr after exposure to insects. The species *Foeniculum vulgare*, also from the Lamiaceae family, showed 93% mortality compared to *Tribolium castaneum* H., a result found by Brito.[39]

According to the bibliographic survey carried out by Lima *et al*.[32] several plants of the Lamiaceae family produce essential oil with insecticidal activity, such as mint, oregano, thyme, and sage. Among the compounds with insecticidal activity, we can mention the terpenoid menthol, found in plants of the *Mentha* genus, which is a potent insecticide with inhibitory activity to the larval growth. In addition to the phenolic monoterpenoids, thymol, and carvacrol have antioxidant and insecticidal activity.

The essential oil of *Ocimum selloi* also showed efficient insecticidal (repellent) activity and did not present mutagenic and irritant risk in human skin[40] Several compounds present in essential oils of other genera of this family, such as *Origum*, *Teucrium* and *Hyptis*, have been proven as insecticides, with compounds such as γ- terpinene, α-terpinene, linalool, methyl-eugenol, eugenol, β-pinene, α -pinene, 1,8-cineole, and citronellol.[41-43] Essential oils extracted from different plants have been reported to have larvicidal and repellent properties against *A. aegypti*.[44,45]

The study by Oliveira *et al*.[46] verified the repellent activity of two species of the Lamiaceae family. The essential oil of *O. vulgare* showed moderate repellent action with values of 8.9% to 37.8% of escape, with the highest percentage of escape (37.8%) observed for two different concentrations (0.5% and 1 .0%), which may indicate the knockdown effect that prevents the mosquito from escaping. The escape rates for *T. vulgaris* oil were higher, ranging from 4.4% to 68.9%. Concentrations of 0.1% and 0.5% are the most active, with an escape percentage of 66.7% and 68.9%, respectively. The values observed are based on the number of mosquitoes that escaped during the 30 min of the test, which was checked every 1 min.

In the repellency test against *A. aegypti* performed by Govindarajan *et al*.[47] it can be seen that at concentrations of 1.0, 2.5 and 5.0 mg/cm^2 of *Origanum scabrum* provided 100% protection up to 210, 180, 150, and 120 min, respectively. These experimental data emphasizes the potential of the essential oil of the Lamiaceae family against *A. aegypti*.

CONCLUSION

This review was able to verify the larvicidal, insecticidal, and repellent potential of essential oils and plant extractsof the species of the Lamiaceae family, in the control of several species, including *A. aegypti*. The diversity of the chemical composition of these species is the most relevant factor associated with biological actions, proven by research that directs and supports the action of the major compounds in isolation or together (synergy).

The compounds found demonstrated the absence of toxicity against mammals and higher animals, the absence ofphytotoxicity, in addition to the fact that the species of the Lamiaceae family are easy to obtain, manipulate and adapt, and their cultivation is economical and without cumulative effect for man and animals.

In this context, this review presents perspectives that encourage the execution of new tests using samples with lower concentrations to verify which may be suitable for the formulation of herbal medicines, such as repellents that can serve as a natural alternative for the control and reduction of diseases transmitted by *A. aegypti*.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest

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