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TECHNOLOGICAL PROSPECTING OF LIPPIA WITH ANTI-HYPERTENSIVE ACTIVITY

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ABSTRACT

Cardiovascular diseases are evaluated as a public health problem. They are directly related to the development of chronic injuries such as systemic arterial hypertension (SAH). Some secondary metabolites of medicinal plants have antihypertensive properties. Thus, the aim of this work is to investigate the potential for technological prospecting of the genus *Lippia* as a possible anti-hypertensive agent. Patent applications were investigated in the main databases: National Institute of Industrial Property of Brazil (INPI), European Patent Institute (EPO), World Intellectual Property Organization (WIPO) and US Patents and Trademarks Office (USPTO), with publications between 1993 and 2014. The terms "vasorrelaxant", "hypotension" and "anti-hypertensive" were used in Portuguese and English, together with the Boolean operator "e". The collected data were organized considering: the year, the country of filing, the state and the International Patent Classification. 114,291 patents were identified. Of the 24 results found at the INPI, Sergipe stands out with a total of 6 patents, followed by Ceará (n=5) and São Paulo (n=5). United States (USA) is the largest holder with 233 deposit requests, followed by European countries (n=46). The filing of patents started in 2007 (n=34), with emphasis on the year 2016 (n=69). It is observed that the largest proportion of patent applications is in category A6 (health, life protection, medical or veterinary science and hygiene) (n=91). After a broad bibliographic review on the subject, it was possible to observe that the associated terms in patent searches showed scarce results, which reinforces the innovative character of research involving the use of *Lippia* as antihypertensive agents.

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INTRODUCTION

Systemic Arterial Hypertension (SAH) is a cardiac pathology triggered by the imbalance of blood pressure values and is evaluated as a public health problem due to its dimension, risk and difficulties in its control. It is a disease of high national and global prevalence, being characterized as a chronic, silent disease with multifactorial causes (Molina *et al.,* 2003; Kearney *et al.,* 2005; Boing, Boing, 2007; Gama *et al.,* 2013). It is one of the most important risk factors for the development of vascular lesions and for the appearance of dysfunctions in target organs (Nascimento *et al.,* 2013), being closely related to the high mortality rate from cardiovascular diseases (CVDs) (Mendieta *et al*., 2010; Pierin *et al.,* 2011; Gama *et al.,* 2013), such as: stroke, acute myocardial infarction and end-stage renal disease (Fonseca *et al*., 2009; Mendieta *et al.,* 2010). There is a wide therapeutic arsenal for the treatment of SAH with drugs that inhibit the renin-angiotensin system, antagonists of renal sodium reabsorption, vascular and myocardial L-type calcium channels, sympatholytic drugs, direct and indirect vasodilators. Clinical protocols are generally updated every 2-3 years, which increases the safety of the most efficient treatment. However, despite the current therapeutic possibilities, approximately 15% of patients present resistant hypertension, in addition to the variability of the final outcome of mortality and cardiovascular complications. Therefore, there is a need to obtain new treatment alternatives for CVDs, employing, for example, from industrial strategies such as drug repositioning or high throughput screening (HTS) to research on empirical knowledge of medicinal plants (Gama *et al*., 2013). Among the plants with the greatest empirical use in the treatment of various pathologies, including SAH, are those of the genus *Lippia* (Oliveira *et al.,* 2007; Pimenta *et al.,* 2007; Gomes, Nogueira, Moraes, 2011). In Brazil, there are approximately 120 species of the genus *Lippia*, with outstanding cardiovascular action for the species *L. origanoides*

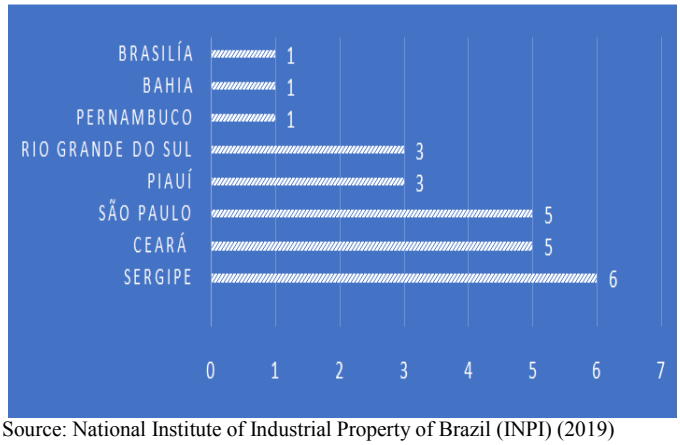
H.B.K. (Coelho *et al.,* 2015), *L. multiflora (*Lorenzo *et al.,* 2001; Bassole *et al.,* 2003) e *L.* alba (Guerrero *et al*., 2002; Oliveira *et al*., 2006; Maynard, 2011). The present study aims to investigate the potential for technological prospecting of the *Lippia* genus as a possible antihypertensive agent.

METHODOLOGY

This is a prospective study, carried out through the investigation of patent deposits in the main databases: National Institute of Industrial Property of Brazil (INPI), *European Patent Office* (EPO), *World Intellectual Property Organization* (WIPO) e *United States Patent and Trademark Office* (USPTO), with publications between 1993 and 2014. The research was carried out in the period of March 2019, in which scientific articles and patent deposits were investigated from the first publication until the year 2018. Descriptors related to the mechanism involved in SAH and the use of the genus *Lippia* as a natural anti-hypertensive product were used, both were written alone or combined with the terms "vasorrelaxant", "hypotension" and "anti-hypertensive", in Portuguese and English, together with the Boolean operator "and". Documents that presented these terms in the abstract and/or title were considered valid. The collected data were organized considering: the year, the country of filing, the state (when Brazilian) and the International Patent Classification (CIP), for each database consulted. Data were analyzed using the Shapiro-Wilk homogeneity test. $\alpha \leq 0.05$ was set as the level for rejection of homogeneity between values. Statistical analysis used the*software Action* (EQUIPE ESTATCAMP, 2021).

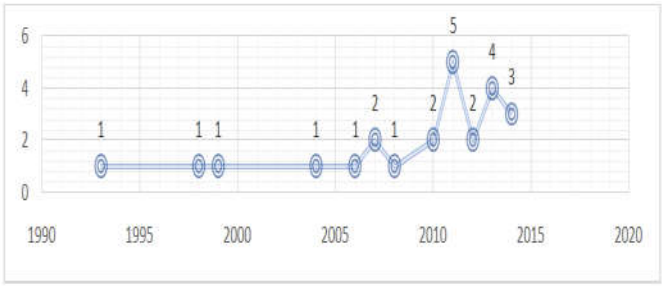
RESULTS AND DISCUSSION

114,291 patents were identified: 24 publications in the INPI database, 102,945 in the WIPO, 63 in the USPTO and 11,259 in the EPO. Brazil is a country of continental dimensions, with favorable soil and climates, which makes it a power to supply natural wealth (RUSSO, 2016). However, when analyzing the quantity at the INPI, there is a scarcity of works compared to the other databases. It is interesting to note that the genus *Lippia* is abundant in Brazil (Salimena, 2002, Pimenta *et al.,* 2009), which would facilitate the investigation of its pharmacological and industrial potential, however, as described by the United Nations Educational Organization, Science and Culture (UNESCO, 2010) for the development of the world economy, investments in science, technology and innovation are necessary, and these areas are still limited in Brazil, which would justify the lower number of patents filed with *Lippia* and others genres. When looking at the states of origin of patents with *Lippia*, of the 24 results found at the INPI, Sergipe stands out with a total of 6 patents, followed by Ceará (n=5) and São Paulo (n=5) (Figure 1).



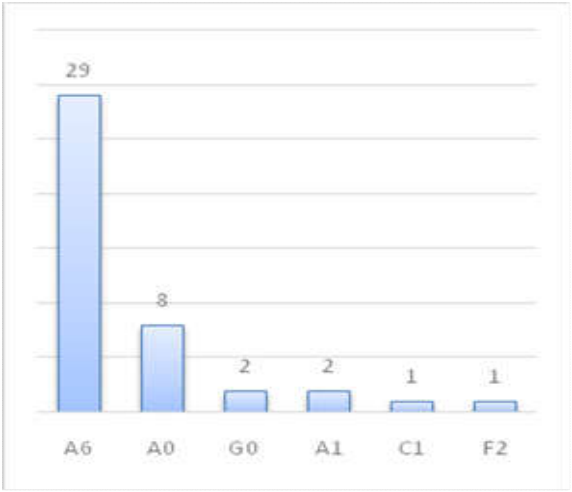
Source: National Institute of Industrial Property of Brazil (INPI) (2019)

Figure 1. States of origin of patents in the INPI database (INPI, 2019)



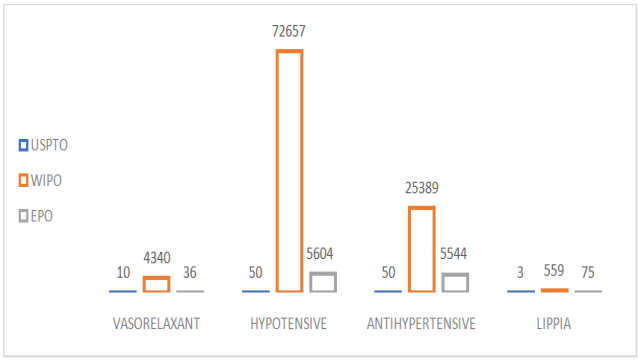
Source: National Institute of Industrial Property of Brazil (INPI) (2019). Data showed heterogeneity according to the Shapiro-Wilk test (α=0.005)

Figure 2. Search for the term *Lippia* regarding the years of filing of applications as a function of the number of patents (INPI, 2019)



Source: National Institute of Industrial Property of Brazil (INPI) (2019). Data showed heterogeneity according to the Shapiro-Wilk test (α=0.0021).

Figure 3. Search for the term *Lippia* according to the CIP codes, dependingon the

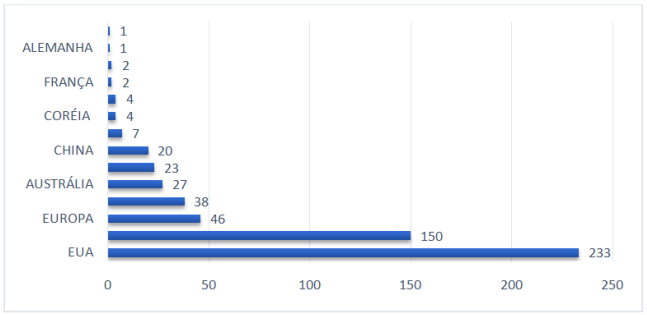


Source: USPTO, WIPO and EPO databases (2019). Data showed heterogeneity according to the Shapiro-Wilk test ($\alpha \geq 0,05$) between and between categories.

Figure 4. Search for the individual *Lippia* term or associated with the descriptors "vasorrelaxant", "hypotensive" and "antihypertensive", in the USPTO, WIPO and EPO databases, 2019

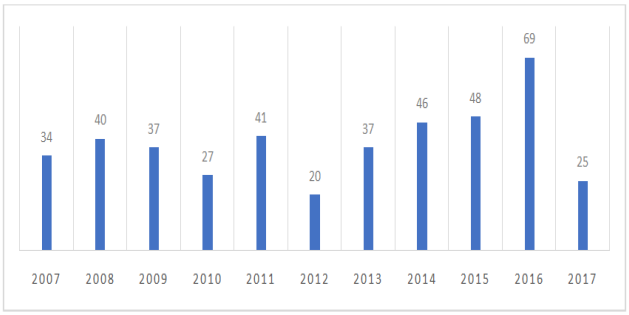
As for the distribution of patents, there was an increase in the number of filings from the year 2010, demonstrating a possible advance in studies on the subject in relation to previous years, especially research using the species of *L. alba, L. gracilis* and *L. origanoides*, as shown in Figure 2. Based on the CIP (Figure 3), it can be seen that the largest proportion of patent filing applications is found in categories A6, A0, G0, A1, C1 and F2, respectively.

Despite the predominance of patents for the application of *Lippia* in the health area, none of them were used for the cardiovascular system, as shown in Figure 4. Previous studies carried out by Guerrero et al., (2002), Oliveira et al., (2006), Maynard (2011) and Coelho et al., (2015), in which they used different species, such as *L. alba, L. Moldenke multiflora* and *L. origanoides*, respectively, show that *Lippia* has an effect on the cardiovascular system, triggering hypotensive and vasorelaxant activity. In this sense, the research sought for the direct and isolated association of *Lippia* with the descriptors "vasorrelaxant", "hypotensive" and "anti-hypertensive", not obtaining any results, which shows the scarcity of national studies with applicability of *Lippia* on the system cardiovascular. By expanding the searches to international databases (WIPO, USPTO and EPO), there is a better exploration of *Lippia*, however, with pharmacological activities aimed at antimicrobial, analgesic and pesticide action, and, similarly to the Brazilian database, none The result was identified when *Lippia*was associated with the descriptors of the cardiovascular system (Figure 4), and its pharmacological action was predominantly explored for the antiparasitic, analgesic and antibacterial action, as described by Oliveira et al., (2007), Sivira (2011) and Betancourt et al., (2012) in their studies. However, despite the absence of patents correlating *Lippia's* gender with the cardiovascular system, the literature presents several articles that describe its vasodilating and hypotensive activity, as shown in the work by Maynard (2011), in which he analyzed the activity of the essential oil of *L. Alba* geranial chemotype, showing that it has hypotensive activity, followed by dose-dependent bradycardic action, suggesting the participation of the autonomic nervous system, since there was attenuation of the response in animals pretreated with atropine (2 mg/kg) and hexamethonium (20 mg/kg). Carvalho (2015) analyzed the vascular reactivity of *L. origanoides* H.B.K. in normotensive *Wistar* rats, showing vasorelaxant activity, dependent and independent of the endothelium, and hypotensive, followed by reflex tachycardia. As for international patent publications with *Lippia*, the United States (USA) is the largest holder with 233 filing requests, followed by PCT with 150, countries in Europe (n=46), Canada (n=38), Australia (n =27), Japan (n=23), China (n=20), United Kingdom (n=7), Korea (n=4), Mexico (n=4), France (n=2) and South Africa (n=2), plus a request of deposit in Germany, Spain, Israel and Russia, respectively (Figure 5), a result that concerns the above, since the USA is the greatest economic power, it implies greater investments in science, research and innovation. Figure 6 shows the chronological analysis for patents with *Lippia*, starting in 2007, with a significant number of patent filings (n=34), which remained in the last decade, with emphasis on the year 2016, where there was agreater number of deposits, with 69 works, in which they cover pharmaceutical formulations, extracts and application of EO, formulation for agriculture with antimicrobial value, fungicide and larvicide. In a search guided by the CIP (Figure 7), it is observed that the largest proportion of patent applications on this basis is distributed among the following categories: A6 (health, life safety, medical or veterinary science and hygiene) and A2 (food or foodstuffs and their treatment), followed by A0, C1 and C0. *Lippia* is an extensive genus known as "oregano-del-monte", popularly used in cooking as a seasoning, as well as, as it contains aromatic species and rich in monoterpenes, its pharmacological potential is widely explored (STASHENKO et al, 2010, SIVIRA et al, 2011), which applies to the predominance of categories A6 and A2. The search generated in the USPTO database generated 3 patents with *Lippia* and no results for its association with the other descriptors for the cardiovascular system. In the search for patent applications at the USPTO with *Lippia* based on the requesting country, Japan (2016), Brazil (2013) and India (2002) follow chronologically with the highest number of requests, respectively (Figure 8). However, the USPTO database shows scarcity in studies aimed at the use of *Lippia* applied to the fundamentals of treatment of pathophysiological disorders in humans, the 3 studies found are focused on the plant's adaptation properties, its effectiveness as a potent antimicrobial in the control of bovine mastitis and the presence of linolol in the species *L. alba*, a monoterpene prevalent in essencial oils.



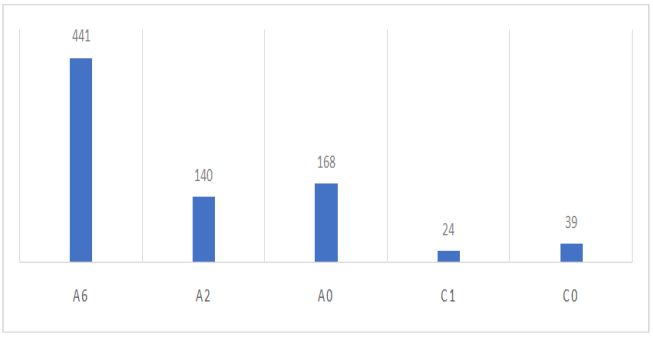
Source: WIPO, 2019. Data showed heterogeneity, according to the Shapiro-Wilk test (α=0.0001).

Figure 5. Search for the term *Lippia* regarding the countries of filing of the requests according to the number of patents (WIPO, 2019)



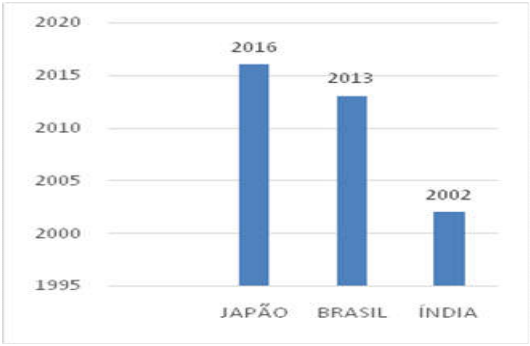
Source: WIPO, 2019. Data showed heterogeneity, according to the Shapiro-Wilk test (α=0,43).

Figure 6. Search for the term *Lippia* regarding the years of filing of applications as a function of the number of patents (WIPO, 2019).



Source: WIPO, 2019. Data showed heterogeneity, according to the Shapiro-Wilk test (α=0,09)

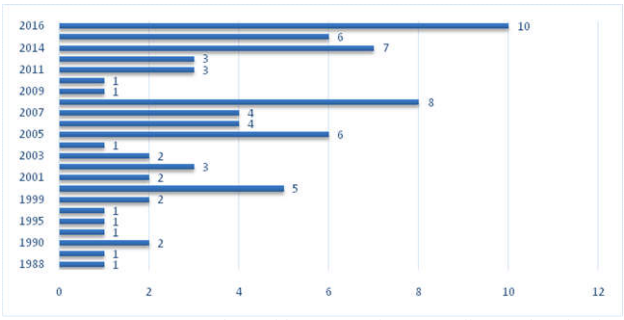
Figure 7. Search for the term *Lippia* according to the CIP codes, depending on the number of patents (WIPO, 2019)



Source: USPTO, 2019. Data showed heterogeneity, according to the Shapiro-Wilk test (α=0,19)

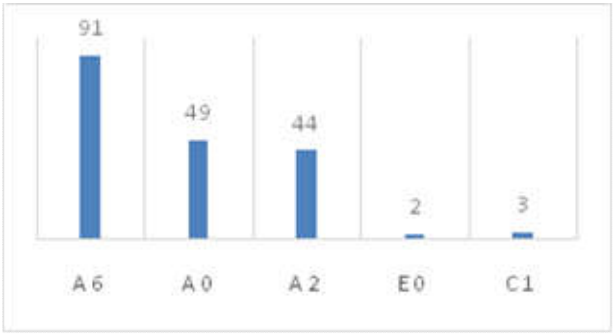
Figure 8. Search for the term *Lippia*regarding the countries of filing the applications depending on the number of patents and the time of publication (USPTO, 2019)

As for the descriptors with cardiovascular association "hypotensive" and "antihypertensive", they were found for every 50 publications, followed by the term "vasorelaxant", where 10 publications were found, in which they are focused on the action of peptides, published predominantly in the 90s, with 1 work published in 2014. In the EPO database, 75 patent documents with *Lippia* were found, without any results for their association with the descriptors of the cardiovascular system, however, when analyzed separately, 36 works for the term "vasorrelaxant" published between the years of 1983 were identified. to 2015, 5,604 for "hypotensive" and 5,544 for "antihypertensive", both without any correlation to the genus *Lippia.*



Source: EPO, 2019. Data showed heterogeneity, according to the Shapiro-Wilk test (α=0, 0016)

Figure 9. Search for the term *Lippia* regarding the years of filing of applications as a function of the number of patents (EPO, 2019)



Source: EPO, 2019. Data showed heterogeneity, according to the Shapiro-Wilk test (α=0,08)

Figure 10. Search for the term *Lippia* according to the CIP codes (EPO, 2019)

In the EPO database, 75 patent documents with *Lippia* were found, without any results for their association with the descriptors of the cardiovascular system, however, when analyzed separately, 36 works for the term "vasorrelaxant" published between the years of 1983 were identified. to 2015, 5,604 for "hypotensive" and 5,544 for "antihypertensive", both without any correlation to the genus *Lippia.* Regarding the annual distribution of patent applications with *Lippia*in the EPO database (Figure 9), it is observed that the studies were discreetly started in the year 2000, followed by few publications until 2005, with a total of 13 publications. From 2005 to 2008 there was an increase with 22 works, followed by a notable drop to 8 works between the period 2009 to 2012, highlighting the last 3 years, with a total of 23 publications, 10 of which were published only in 2016. When analyzing the data according to the CIP, it was found that most of the deposit requests were included in the categories: A6, A0, A2, followed by two publications in E0 and C1, and 1 publication in C1 (Figure 10), similar to the one presented at WIPO.

CONCLUSION

Such data represent the technological advance achieved in the last decade, however, the associated terms in patent searches showed scarce results, which reinforces the innovative character of research involving the use of *Lippia* as antihypertensive agents. Regarding the approach contents, it was observed that the focus of studies involving *Lippia* is mainly linked to health treatments aimed at agriculture, antimicrobial, antifungal and larvicide, with a shortage of studies on human applicability, especially on the cardiovascular system. It is believed that research involving *Lippia's* antihypertensive, vasorelaxant and/or hypotensive activity is still restricted to research centers, which reflects the scarcity of patents found. However, studies have advanced in the investigation of different species of this genus on blood pressure control through the modulation of vascular and cardiac tone, aiming at the therapeutic formulation and the mechanisms involved, suggesting a future rise of the panorama in the scientific bases with *Lippia*.

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