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Formulation of Lippi alba (Verbenaceae) leaves capsules for the treatment of high blood pressure

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Abstract

High blood pressure is a real public health issue, affecting around 1.13 billion people worldwide. The World Health Organization (WHO) reports that less than 20% of people with high blood pressure are properly managed medically. The most common treatments are based on the use of diuretics, calcium channel blockers, beta blockers, and alpha blockers. However, due to the relatively high cost of antihypertensive drugs, the search for new alternatives is becoming a necessity. *Lippia alba* is known for its antispasmodic, analgesic, sedative, anxiolytic, and antihypertensive properties. These properties and the empirical use of the plant in the form of an infusion make it a potentially interesting herbal drug to develop. This study aimed to formulate capsules from *Lippia alba* leaves to improve the management of high blood pressure. To do this, the *Lippia alba* leaves were crushed and then infused in drinking water. The amount of extract needed to manage high blood pressure was determined in milligrams of gallic acid equivalent of total polyphenols per gram of extract. Several formulas were prepared by mixing the aqueous extract of *Lippia alba* leaves with suitable excipients. The capsules were also tested in accordance with the techniques described in the 11th edition of the European Pharmacopoeia. The extract was dark brown in color, very bitter, and had an aromatic odor; it was obtained with a yield of 18.60%. The polyphenol content was 175 mg gallic acid equivalent per gram of extract. The following excipients were used to formulate the capsules: colloidal anhydrous silica (Aerosol* 300), microcrystalline cellulose (Avicel*PH-102, PH-101), dicalcium phosphate (Fuji Calin*), ready-to-use lactose-polyvinylpyrrolidone K30-crospovidone (Ludi press*) LCE mixture. The chosen unit formula had good flow properties (3 seconds for 100g of powder), a Carr index of 14.80% and a Hausner index of 1.17. The powder was homogeneous and moderately fine (d50 < 300 am). Each size 0 capsule contains 364.5 mg of crude extract corresponding to 63.8 mg gallic acid equivalent of polyphenols, 73 mg of Ludi press* LCE, and 48.5 mg of Fuji Calin*. The daily dose determined for a 60 kg adult was 729 mg of extract, corresponding to 127.6 mg gallic acid equivalent of total polyphenols, which can be divided into 2 capsules for one day. The results of the physicochemical and pharmaceutical tests carried out on the capsules were found to comply with the specifications of the 11th edition of the European Pharmacopoeia. The characteristics of these capsules make them a good candidate for development into an improved traditional medicine (ITM).

Keywords: *Lippia alba*; Aqueous Extract; Leaves; Antihypertensive; Formulation; Capsule; ITM

1. Introduction

Hypertension is a major cause of disability and the leading risk factor for death worldwide. The WHO had predicted a total of 1.56 billion cases worldwide by 2025, 28.9% of which will be in sub-Saharan African countries [1]. In Cameroon, high blood pressure affects 35% of the 27.2 million inhabitants [2]. Currently, conventional treatment for high blood pressure aims to reduce the increased risks of cardiovascular and cerebrovascular morbidity and mortality associated with high blood pressure through the use of antihypertensive drugs such as diuretics, beta-blockers, calcium channel

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blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers [3]. High blood pressure imposes a huge economic burden on society in terms of direct healthcare costs and substantial productivity losses resulting from disability and premature mortality [4]. Although these drugs have brought about remarkable changes in the treatment of high blood pressure, there are still major concerns about their high cost, availability, side effects, and drug interactions during treatment [3]. *Lippia alba* (Mill.) N.E.Br. ex-Britton & P.Wilson, commonly known as bush mat herb, is one of the main plants commonly used in the management of hypertension. It is an aromatic tropical shrub whose aerial parts are used in infusions. Formulating its leaves into capsules could improve the acceptability and facilitate the use of this plant.

2. Materials

Lippia alba leaves were harvested from a farm in Banekané in western Cameroon and identified at the Cameroon National Herbarium. For extraction, formulation, and manufacturing, the equipment used included, among other things: a Mettler AM50 balance, a Buchi R200 rotary evaporator, a centrifuge, a spectrophotometer, a 100 semi-automatic capsule filler, an Erweka ZT6-1-D disintegration apparatus, an AS200 Basic sieve column, and a METTLER TOLEDO pH meter. Numerous reagents were also used: osmosis water, anhydrous colloidal silica (Aerosil* 200), dicalcium phosphate (Fujikalin*), microcrystalline cellulose (Avicel PH 101*, PH102), lactose-polyvinylpyrrolidone mixture, crospovidone (Ludipress* LCE), and numerous culture media.

3. Method

3.1. Preparation of the extract:

After harvesting, the leaves were cleaned, cut, and dried at room temperature (37°C), away from light to avoid impurities and contaminants. A 1kg portion was steeped for approximately 20 minutes in 10L of distilled water. The infusion was collected and filtered through Whatman No. 4 paper. A second infusion was made with the same residue, also followed by filtration under the same conditions. The filtrates were then mixed and concentrated in a rotary evaporator at 40°C for 48 hours. The residue was weighed and the yield (Y) determined using the formula

$$Y = = 100 \times \frac{\text{weight of extract}}{\text{Weight of dried leaves}}$$

3.2. Physicochemical characteristics of the extract

- **Organoleptic characteristics**. The organoleptic characteristics were determined by observing the appearance, texture, smell, and taste of the aqueous extract of dried leaves.
- **Residual water content**: A sample of approximately 2g (Mi) of extract was placed in an oven at 101 ± 2°C and weighed every hour until the mass became constant (Mf). The test was repeated three times and the water content (T) was calculated using the formula:

$$T = 100 \times \frac{Mi - Mf}{Mi}$$, and the average rate was retained.

- **Determination of ph.** A 10% aqueous dispersion of the extract was prepared and filtered using filter paper. The pH of the filtrate was measured using a pH meter after calibration with acid and base standard solutions. The test was repeated three times and the average value was recorded.
- **Determination of solubility**: Solubility was determined by gradually adding increasing volumes of water to 100 mg of the extract at room temperature in a beaker containing 10 mL of osmosis water. The mixture was stirred continuously using a magnetic stirrer for 10 minutes after each addition of water. The solubility of the mixture was checked visually. The result was the average of three measurements.

Table 1 Solubility of the extract in water

Approximative solubility in water							
Volume of water (ml)	0.1	0.5	1	2	10	100	> 100
Approximative Solubility (g/L)	>1000	1000 à 200	200 à 100	100 à 50	50 à 10	10 à 1	<1

3.3. Phytochemical screening.

Approximately ten grams (10g) of the extract were dissolved in 10mL of distilled water, and the resulting solution was used for standard qualitative phytochemical tests involving precipitation or coloration [5].

3.4. Polyphenol assay

The total polyphenols in the extract were evaluated using the well-known method described by Singleton and Rossi in 1965, using the Folin-Coalter reagent [6] and gallic acid as a standard or tracer; the result was expressed as gallic acid equivalent per gram of extract.

3.5. Formulation and manufacture of capsules

- **Specifications:** As shown in Table 2, the specifications for the formulation of Lippi capsules include sensory, taste, and formulation constraints.

Table 2 Specifications for the formulation of *Lippia alba* leaves capsules

Constraints	**Capsules**
Formulation Constraints	Size: adequate capsule size
Sensorial constraints	Medium size Mask the odor of the extract Mask the taste of the extract
Reglementary constraints	Up large to respect specifications stated in 'European pharmacopeia 11th edition'' compendium
Therapeutic function	Antihypertensive therapeutic properties
Cost	Lesser cost

- **Determination of the daily dose**. The dose to be administered was based on the dose obtained from in vivo studies in rats using the conversion factor to determine the equivalent human dose (EHD), in accordance with the Food and Drug Administration table in Table 3.

Table 3 Conversion factor for the determination of EHD [7]

Species	**EHD (mg/kg) = animal dose divided by**	**EHD (mg/kg) = Animal dose multiplied by**
Mouse	12.3	0.081
Hamster	7.4	0.135
Rat	6.2	0.162
Guinea Pig	4.6	0.216
Rabbit	3.1	0.324
Dog	1.8	0.541
Marmoset	6.2	0.162
Baboon	1.8	0.541

The value obtained from in vivo studies is multiplied by 0.612 to obtain the equivalent human dose, since the studies were conducted on rats.

- **Choice of excipients**. The choice was guided by the physical properties of the extract (it was hygroscopic), availability, and cost; however, the selection was made from among those that also had a monograph in the Handbook of Pharmaceutical Excipients, 6th edition [8].

- **Stabilization of the extract.** By combining the extract, colloidal anhydrous silica (Aerosil 300), microcrystalline cellulose (Avicel PH 102, Avicel PH 101), dicalcium phosphate (Fujicalin) and the combination of lactose – polyvinylpyrrolidone K30 – crospovidone (Ludipress) combination, we prepared several formulas whose rheological properties were determined in order to find the most suitable powder for obtaining capsules. The texture of the different mixtures was monitored for 15 days at a temperature between 21°C and 33°C and a humidity level between 36% and 87%. The volume V0 was measured, followed by the volumes V10, V500, and V1250, corresponding successively to the volume after 10, 500, and 1250 compressions. Next, the Carr index and Hausner index were determined using the following formulas:

$$\text{Carr Index (\%)} = 100 \text{ X } \frac{V0-V1250}{V0}$$

$$\text{Hausner Index} = \frac{V0}{V1250}$$

The conclusion on the flowability of the powder was obtained by combining IC, IH, and the flow scale of the 11th edition of the European Pharmacopoeia (Table 4).

A V10–V500 value of less than 20 indicates a good tendency for the powder to reorganize.

Table 4 Flowability scale [6]

Carr Index (%)	Flow character	Hausner Ratio
1-10	Excellent	1,00-1,11
11-15	Good	1,12-1,18
16-20	Quite good	1,19-1,25
21-26	Fair	1,26-1,34
26-31	Poor	1,35-1,45
32-37	Very poor	1,46-1,59
> 38	Extremely poor	> 1,60

- **Particle size analysis**. The selected formula was subjected to particle size analysis (to verify its homogeneity) using a set of sieves with mesh sizes ranging from 1400 to 63 µm
- **Fluidity:** 100g of stabilized powder was placed in the conventional European Pharmacopoeia funnel with the opening closed. After opening the funnel, all the powder had to flow out in less than 10 seconds. The time taken was the average of three measurements.

In light of Table 5, the powder could be designated by the appropriate descriptive term.

Table 5 Classification of powders according to their fineness [6]

Descriptive Term	d50 (am)
Coarse	> 355
Moderately fine	180 – 355
Fine	125 – 180
Extremely fine	≤ 125

d50= median size.

3.6. Filling and inspection of capsules.

Encapsulation was carried out by pouring and leveling on a semi-automatic 100-capsule filling machine.

The usual pharmacopoeia checks [6] were carried out

- Organoleptic check: color, appearance, absence of cracks
- Uniformity of mass: determination of the maximum acceptable deviation from the average mass (m) of the contents of 20 capsules taken at random.
- If the average mass m is < 300 mg, the deviation e is 10% of m
- If the average mass m is ≥ 300 mg, the deviation e is 7.5% of m
- Disintegration time.

None of the capsules placed in the 6 tubes of the disintegration apparatus should show any solid residue after 30 minutes of operation of the apparatus at 37 ± 2°C

3.7. Microbiological quality

Microbiological quality control was carried out using the techniques recommended by the European Pharmacopoeia. A stock solution corresponding to 1 mg/ml was prepared by homogenizing the capsule powder in water for injectable preparations; then two 1/10th dilutions were seeded in 90mm Petri dishes. As shown in Table 5, the culture medium and incubation time depended on the type of microbe being sought.

Table 6 Conditions for microbe detection

	Culture Medium	**Incubation Time**	**Incubation Temperature**	**Observation at the end of incubation**
ETGA	Agar	24 H	33 °C	Colonies to count: ≤ 10^3 CFU/g
ETMY	Sabouraud	24 H	33 °C	Colonies to count ≤ 10^2 CFU/g
E. Coli	Hecktoen	24 H	33 to 37 °C	No red colony + light ring
Salmonella				No blue Colony
Shigella				No green colony
Staphylococcus aureus	Chapman	72 H	33 °C	No yellow or white colony
Enterococcus	Bile esculin	24 H	35 to 37 °C	No colonies

ETGA = Enumeration of Total Aerobic Germs ETMY= Enumeration of Total Moulds and Yeasts

4. Results

4.1. Characteristics of *Lippia alba* extract

The extraction yielded an aromatic, dark brown, hygroscopic powder that was very bitter and had a caramel flavor, with a yield of 18.60%. The pH was 8.53. The extract was hygroscopic and soluble in water.

The results of the phytochemical screening of the aqueous extract of *Lippia alba* leaves are presented in Table 7. It appears that this extract is rich in alkaloids, polyphenols, flavonoids, tannins, saponins, anthocyanins, and terpenoids.

Table 7 Phytochemical composition of the aqueous extract of *Lippi alba* leaves

Secondary metabolites	Reactive	Results
Alkaloids	Dragonwort	+
Polyphenols	$FeCl_3$	+
Flavonoids	Magnesium turnings	+
Gallic Tannins	$FeCl_3$	+
Catechisation's	Hot HCl	-
Saponins	Foaming index	+
Terpenoids	Acetic anhydride chloroform / H_2SO_4	+
Sterols		-
Anthraquinones	NH_4OH	-
Anthocyanins	HCl /NH_4OH	+

the sign (+) indicates the presence of secondary metabolites and the sign (-) indicates its absence

4.2. Formulation and manufacture of capsules

- **Polyphenol dosage**. The total polyphenols in *Lippi alba* leaves were evaluated using the method described by Singleton and Rossi in 1965, using the Folin-Coalter reagent. Ref This is a spectrophotometric method with a reading at 725 nm. The gallic acid calibration range (Figure 1) allowed the results to be expressed in milliequivalents of gallic acid (EGA) per gram of extract. Thus, the crude extract had an average polyphenol content of 175 mg EGA per gram.

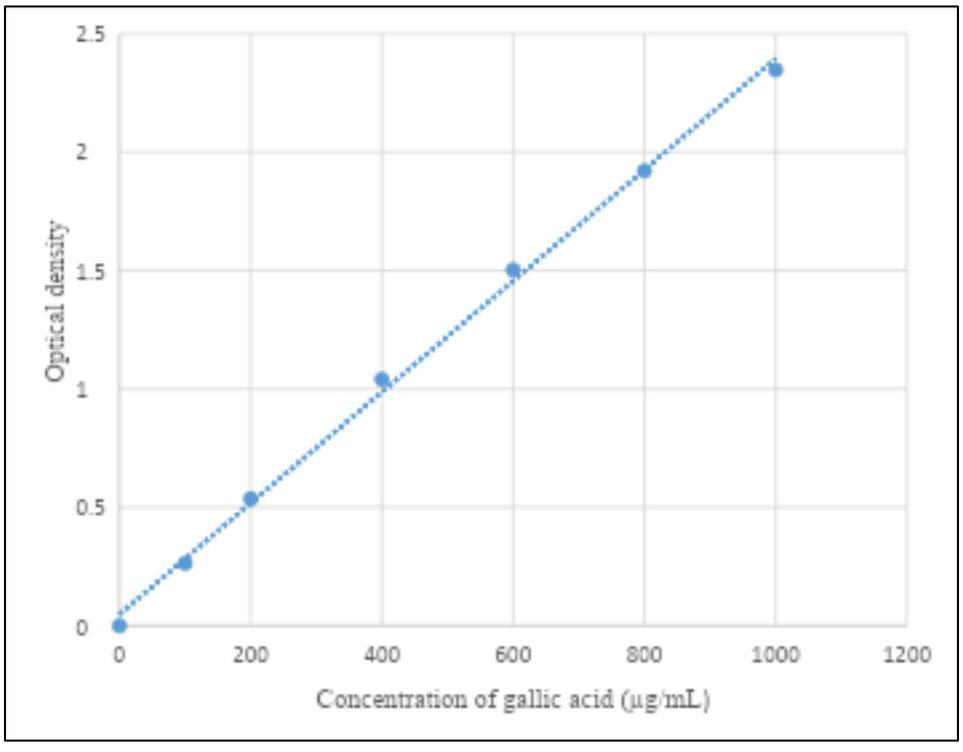

Figure 1 Calibration curve of gallic acid

- **Determination of the daily dose**. According to the literature, preclinical studies conducted on rats concluded that the daily dose was 75 mg/kg of extract [8]. Under these conditions, the ADI factor is 0.162, which leads to an equivalent human dose (EHD) of 75 x 0.162 = 12.5 mg of extract/kg/day.

For a 60 kg human, the daily dose is therefore 12.5 mg x 60 = 729 mg of extract. As the extract is titrated to 175 mg EAG/gram, the daily 729 mg of extract corresponds to 729 x 175/1000 = 127.5 mg EAG per day.

4.3. Formulas tested

The formulas tested and their characteristics are presented on table 8.

Table 8 Tested formulas

Composition	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Leaves of *Lippia*	90%	85.8%	80%	80%	77%	75%	85%	84%	80%
Ludi press* LCE	10%	14.2%	20%	15%	15%	15%	14%	14%	14%
Fuji Calin*				5%	8%	10%			
Avicel* PH-200								1%	5%
Flow time (seconds)	5	5	4	4	3	3	5	5	3
Hausner Ratio	1.23	1.17	1.18	1.20	1.18	1.17	1.22	1.21	1.19
Carr Index (%)	18.5	14.3	15.2	16.7	15.2	14.8	18.6	18.0	16.3
Interpretation	Quite good	Good	Good	Quite good	Good	Good	Quite good	Quite good	Quite good

Formula F6 had the best characteristics for production; the 15-day stability study also showed it to be advantageous.

Figure 2 shows that 57% of the powder from formula F6 is collected in the 355 µm mesh sieve. This powder can be considered homogeneous and suitable for encapsulation.

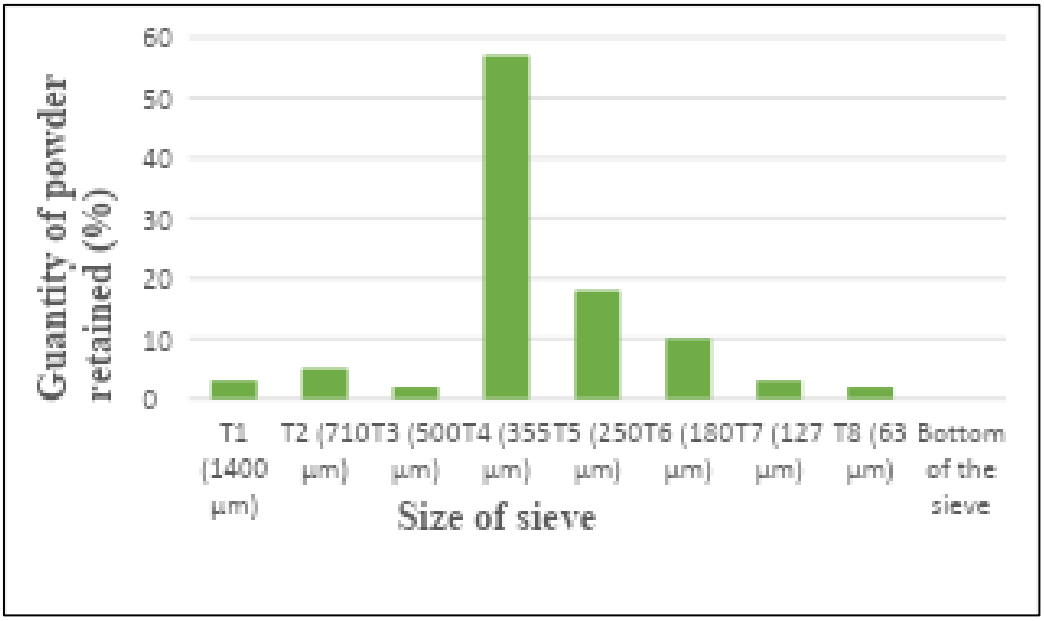

Figure 2 Particle size analysis of the final formulation (F6)

4.4. Final formulation and unit formulation

Table 8 shows the composition of the daily dose and unit dose.

Table 9 Composition of the daily dose and unit dose

	Daily Dose	**Unit Dose (capsule)**
Extract of *Lippia alba*'s leaves	75% = 729 mg	364,5 mg
Ludi press LCE	15% = 145mg	72.5mg
Fuji Calin	10% = 97.2mg	48.6mg
Total	100% = 971.2mg	For 1 capsule N°0

An encapsulation test showed that to contain 971.2 mg, either one size 000 capsule or two size 0 capsules are required (i.e., two capsules each containing 486 mg of powder). As compliance with the treatment is a priori easier with smaller capsules, the daily option of two size 0 capsules (i.e., 486 mg x 2) was adopted.

4.5. Inspection of the capsules obtained

- Macroscopic appearance: As shown in Figure 3, the obtained capsules are red and white, size 0, and have no visible imperfections.

Figure 3 *Lippia alba* capsules

Mass uniformity. The average mass of the contents of the 20 capsules taken at random was 584.9 mg, with extreme values of 575 mg and 592 mg. According to the requirements of the European Pharmacopoeia, this average allows for a tolerance of e = 7.5% of the average, i.e., 584.9 x 0.075 = 44.21 mg; the lower limit was therefore 575 mg - 44.2 mg = 530.8 mg and the upper limit was 575 mg + 44.2 mg = 619.2 mg. All the capsules sampled for the test had a content within these acceptable limits.

4.6. Disintegration time.

After three trials, the average disintegration time for the six capsules was 7 minutes, which complies with the requirements of the 11th edition of the European Pharmacopoeia.

Microbiological quality: The ETGA gave 35 CFU/g and the ETMY 0 CFU/g; there were no coliforms, Staphylococcus aureus, or Pseudomonas; therefore, from a microbiological standpoint, the capsules also complied with the recommendations of the 11th edition of the European Pharmacopoeia

4.7. Packaging and labeling

The finished capsules were packaged in pill boxes containing 60 units (Figure 4). Each box bears the proposed trade name (NORMAPRESS) as well as the regulatory information relating to identification and traceability.

Figure 4 Secondary package

5. Discussion

The extract obtained was dark brown, with an aromatic odor and a very bitter taste. This unpleasant taste could negatively influence treatment compliance. The chosen dosage form (capsules) was welcome as it significantly improved this drawback. Phytochemical screening of the aqueous extract of *Lippia alba* leaves showed the presence of several classes of secondary metabolites, including alkaloids, polyphenols, flavonoids, tannins, saponins, anthocyanins, and terpenoids, while sterols and anthraquinones were absent. This result confirms that of Anapa et *al* [10]. The involvement of compounds belonging to this chemical class in antihypertensive, antioxidant, and antispasmodic activities [10,11,12] has already been demonstrated. Indeed, numerous studies have shown the efficacy of *Lippia alba* leaves in vivo [13]. The total polyphenol content in the extract was high (175 mg EAG), which explains its antihypertensive activity. The pH (8.53) and good solubility of the extract indicate that it will not be aggressive to the digestive tract.

Although dry, the aqueous extract of *Lippia alba* leaves was hygroscopic, thick, and unsuitable for encapsulation. It was therefore important to stabilize it. Several mixtures were made, but the one with Aerosil* 200 was not selected because obtaining a homogeneous mixture is laborious and not reproducible on an industrial scale. The mixture of lactose-polyvinylpyrrolidone K30-crospovidone (Ludipress* LCE) and dicalcium phosphate (Fujicalin*), which is easily miscible with the aqueous extract, has the advantage of making the powder more stable and helping to lubricate it, and has no notable effects, as reported by Autamshih et al [12] using the same combination of excipients in other stability studies. The proportions used are in accordance with those authorized in the “Handbook of Pharmaceuticals Excipients” [8].

The particle size analysis of the powder yielded a median diameter (d50) of less than 355 µm. This is therefore a moderately fine powder with a homogeneous distribution, which could explain the good flow time (3s) and good filling of the capsules.

The selected unit formula doses each capsule with 364.5 mg of aqueous extract of *Lippia alba* leaves, corresponding to 63.8 mg EAG/g of total polyphenols, 73 mg of Ludipress* LCE, and 48.5 mg of Fujicalin*. The dosage for an individual weighing approximately 60 kg is 2 capsules in a single dose once a day for the treatment of high blood pressure. The content of the capsules was expressed as total polyphenol mass. Thus, during subsequent manufacturing, the total polyphenols in the extract batch will be measured to determine the amount of extract corresponding to 63.8 mg of total polyphenols to be introduced into each capsule; this makes it possible to manage the problem of variations in polyphenol concentrations depending on the season and place of harvest.

The capsules obtained successfully passed not only the pharmaceutical and physicochemical tests but also the microbiological requirements of the European Pharmacopoeia. It is therefore important to note the seriousness with which the handling was carried out: effective disinfection of the premises and equipment, absence of contaminants in the raw materials, and strict compliance with good manufacturing practices.

6. Conclusion

The objective of this study was to formulate capsules based on aqueous extract of *Lippia alba* leaves for the treatment of high blood pressure. Thanks to the use of Fuji Calin* and Ludi press* LCE to stabilize the extract, the formula developed showed excellent physicochemical and pharmaceutical properties, with good fluidity and compaction, as well as a homogeneous particle size distribution. Each size 0 capsule contains 364.5 mg of crude Lippi alba extract, providing a standardized dose of 127.6 mg EAG/g of total polyphenols. These capsules can be offered for the treatment of high blood pressure at a dose of two units once a day for adults. The capsules have been rigorously tested and have met the quality control standards described in the “European Pharmacopoeia 11th edition,” ensuring their safety and efficacy. The encapsulation process also masked the bitter taste of the extract, making it more acceptable and convenient for patients to use.

This study confirms the potential of *Lippi alba* as a viable alternative in traditional medicine for the management of high blood pressure.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclsoed.

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