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(RESEARCH ARTICLE)

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Safe and natural oral solid tablets antihypertensive based on *Cassia occidentalis* (FABACEAE)

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Abstract

The roots of *Cassia occidentalis* Linn (CAESALPINIACEAE) are widely used in traditional Malagasy medicine to treat various conditions, including hypertension. This study aimed to scientifically investigate the acute oral toxicity in mice, assess the antihypertensive effects through *in vivo* assays in rabbits, screen for therapeutic phytochemical metabolites, and formulate an antihypertensive oral tablet based on aqueous root extract using direct compression and wet granulation methods. The pharmacological results showed reversible, dose-dependent antihypertensive and hypotensive actions in both normotensive and adrenaline-induced hypertensive models. The hypotensive effect of the extract (100 to 500 mg/kg b.w) is comparable to the effect of acetylcholine (25, 50 or 100 mg/kg b.w). Furthermore, the acute oral toxicity study revealed the extract to be safe up to a dose of 5,000 mg/kg. These results demonstrate the antihypertensive and safe potential of the plant root extract. Several beneficial chemical compounds that could contribute to these activities were also detected in the aqueous extract (EABCO), including tannins, steroids, polysaccharides, quinones, and saponins. Their presence could justify the traditional use of *C. occidentalis* roots against hypertension. The excipients used were compatible with the root extract's structure and enabled the production of stable, palatable tablets in accordance with good manufacturing practices. This study indicates the plant's potential as a natural ingredient in a safe, antihypertensive drug. Further in-depth studies are needed before this preparation can be made available.

Keywords: *Cassia occidentalis*; Antihypertensive; Hypotensive; Safety; Formulation; Tablets

1. Introduction

Hypertension is a primary risk factors for heart disease, kidney disease, stroke and other diseases. It affects over 1.4 billion people globally, with the highest prevalence (27 %) occurring in Africa [1]. In developing countries, including Madagascar, approximately 80 % of the population uses traditional medicine to treat various illnesses [2]. This practice is driven by affordability, cultural acceptance, perceived effectiveness and the irregular or limited availability of antihypertensive drugs [3,4]. Numerous plant families have been used on this Island based due to their potential antihypertensive benefits. However, without scientific validation, this practice carries risks such as toxicity and drug interactions. Therefore, there is a need for regulation and education to ensure safety, as well as ongoing exploration of these plants' potential for developing new medications [5].

According to studies, many Malagasy's medicinal species have shown promise in treating hypertension, but further scientific research is needed to confirm their efficacy and mechanisms of action. While, much research has been

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conducted on the antihypertensive properties of plants in the Malagasy pharmacopoeia, the therapeutic potential of some remains untapped.

An ethno-botanical survey conducted in the southwest of Madagascar, in the District of Betioky-Sud, found that *Cassia occidentalis* Linn is the one of the most frequently used plants for the treating hypertension. This flowering plant, widely distributed, belongs to the FABACEAE family and has various common names in Madagascar, including "Tsotsoronangatra", "Bemaimbo", "Voanembanalika", "Tsatsinangatra", "Famônoakoho" or "Sarongazany" [6]. Local communities in Salobe use a root decoction to treat hypertension. Despite this traditional use, detailed pharmacological data, especially regarding its blood pressure-lowering effect and toxicity, is limited, highlighting a gap in research. Previous, pharmacological studies of the *C. occidentalis* aqueous leaf extract have revealed relaxant effects in aortic rings [7,8]. This study investigates *Cassia occidentalis* roots for hypertension, aiming to confirm traditional use by testing its toxicity, blood pressure lowering effects (hypotensive/antihypertensive), and develop a safe, natural antihypertensive tablet containing the roots extract as an alternative for the treatment of hypertension.

2. Material and methods

2.1. Plant material

C. occidentalis roots were collect*ed in January 2021 in Salobe, in the Betioky-Sud district of Toliara, in southwestern Madagascar. The specimen was identified by the botanist of the National Center for Pharmaceutical Research Applications (CNARP) and a reference herbarium was deposited there (Fig.1).

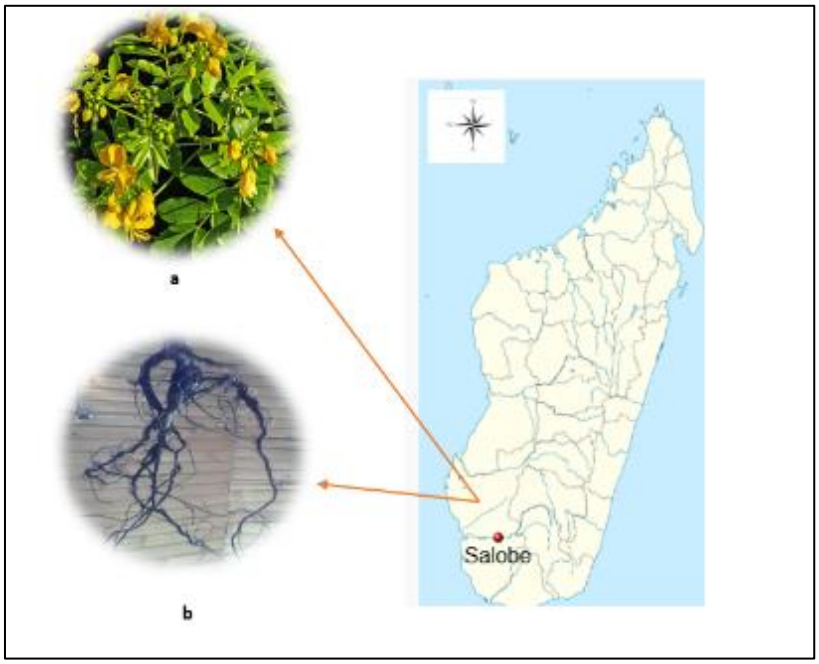


Figure 1 Location of Salobe (District of Betioky Sud) in Madagascar (Coordinates: 23°32'S 44°43'E) and photo of *Cassia occidentalis* Linn: aerial part (a), roots (b)

2.2. Animals

Normotensive rabbits (*Oryctolagus cuniculus*, LEPORIDAE) of either sex weighing between 1.7 and 2.5 kg were used for the antihypertensive pharmacological tests. They were obtanined from the Department of Animal Physiology and Pharmacology at the University of Antananarivo. Acute oral toxicity assays were carried out on SWISS mice weighing between 20 and 30 g, which were supplied by the animal house of the Department of IMVAVET (Institut Malgache des Vaccins Vétérinaires).

Animal tests were carried out according to the Organization for Economic Co-operation and Development (OECD) guidelines [9]. The 3Rs (Replacement, Reduction, and Refinement) principles were applied to implement this procedure [10,11]. All animal experimentation of was approved by the Pasteur Institute of Madagascar (IPM) Ethics Committee and aligned with the established standards.

2.3. Extraction method

According to the traditional methods, the plant extact was obtained by refluxing an aqueous decoction of the dried powdered roots at 100 ° C (1/10 (w/v)) for 30 min. After filtering through a Büchner funnel, evaporate the solvent using a rotary evaporator (Büchner type R-114, Switzerland) to obtain the final dry extract [12,13].

2.4. Qualitative phytochemical analysis

The detection reactions of the chemical groups were carried out using the standard methods developed by Fong *et al*. (1977) and Marini-Bettolo *et al*. (1981) [14,15,16].

2.5. Acute oral toxicity test

The acute oral toxicity study of the aqueous extract was carried out according to the OECD guidelines (423, 425) [17,18,19]. This test evaluates the adverse effects that occur when an organism is exposed to one or more doses of a test substance, administered orally within 24 hours [20]. The test was conducted using the method described by Enegide *et al*. (2013) with some modifications [21]. Swiss albino mice of both sexes were then selected and divided into ten groups of three animals in each. Doses ranging from 10 to 5, 000 mg/kg was administered orally in three steps for each group. The median lethal dose (LD_{50}) was calculated using the following formula:

$$Median\ Lethal\ Dose\ (LD50) = [M0+M1]\ /2$$

M0 is the highest dose of the test substance that produces no mortality and **M1**, is the lowest dose that produces mortality. The acute toxicity values were interpreted according to the classification rate, as shown in table 1 [22]. Lower numbers indicate higher toxicity (below 5 mg/kg), while higher numbers indicate lower toxicity (above 15,000 mg/kg). This test allows us to draw conclusions about the safety of the *C. occidentalis* extract.

Table 1 Classification of LD_{50} based on dose range

LD_{50} value	**Classification**
<5 mg/kg	Extremely toxic
5-50 mg/kg	Highly toxic
50-500 mg/kg	Moderately toxic
500-5,000 mg/kg	Slightly toxic
5, 000- 15, 000 mg/kg	Practically non-toxic
>15, 000 mg/kg	Relatively harmless

2.6. Pharmacological experiments

The method described by Léandre K. (2008) was used for the hypotensive test, with slight modifications [23]. The animals were anesthetized with an intraperitoneal injection of Thiopental (40 mg/kg body weight) and secured to a dissection table. A small midline incision was made in the trachea to expose it, the right jugular vein, and the carotid artery. The trachea was cannulated to maintain spontaneous respiration. The right jugular vein was cannulated to facilitate the intravenous administration of reference drugs and the test substances. The carotid artery was cannulated record blood pressure. Heparinized saline was used to prevent blood clotting. The animal's body temperature was maintained using a ceiling-mounted heater. After surgery, blood pressure was allowed to stabilize before the injecting the test substance: Acetylcholine (ACh: 1 to 20 µg/kg body weight) which was chosen as the drug standard curves for the hypotensive mechanism, and Adrenaline (ADR: 10, 20 and 30 µg/kg body weight) for the hypertensive mechanism [24].

2.7. Pre-formulation studies

Pre-formulation studies, including pharmacotechnical characterizations, are essential for developing drug forms, especially tablets (Fig. 2). It is crucial to determine the fundamental physical and chemical properties of the plant extract and the drug powder. This information influences many subsequent events and approaches in formation development [25].

2.7.1. Organoleptic parameters

The organoleptic properties of the extract powder were inspected and assessed using the senses of touch, smell, and taste [26].

2.7.2. Powder extract solubility

Powder solubility is an important parameter for drug absorption. For this study, the flask method of OECD TG 105, as mentioned by Yoo *et al*. (2021) was used to evaluate the solubility test. Solubility was determined by gradually adding increasing volumes of water to approximately 100 mg of extract powder in a beaker containing 10 ml of reverse osmosis water at room temperature. After each addition, the mixture was stirred continuously for 10 minutes using a magnetic stirrer. The solubility of the powder was visually verified. If the powder was insoluble, the test continued in a 100-ml beaker for 24 to 96 hours [27]. The percentage of solubility was obtained using the following equation:

$$Solubility\ (\%) = \frac{(weight\ of\ initial\ powder) - (weight\ of\ dried\ residue)}{volume\ of\ solvent} x\ 100$$

2.7.3. Moisture Content

The moisture content (MC) of the powder extract (m_{wet}) was evaluated using the gravimetric method. A 2 g sample of the powder extract was finely ground and placed in an oven at 100-105° C for 3 hours. Its mass was then recorded (Fig.2). The sample was then returned to the oven at 105° C, and its mass was recorded hourly until the mass difference was less than 0.5 mg. The final mass obtained (m'_{dry}) is the last mass recorded mass. The MC value was then calculated using the following formula [28].

$$MC\ \% = (m_{wet}\text{-}m'_{dry}/m_{wet})\ x\ 100$$

2.7.4. Particle size analysis

The fineness of the powder was determined by sieve analysis (Fig. 2). A 10-gram sample was separated into fractions using a series of sieves (600, 300, 200, 100, and 50-µm) and shaken for 30 minutes. Then, the weight of the powder retained on each sieve was then measured to calculate the percentage by weight of each size fraction. This provides data on the powder's particle size distribution. The particle size and description were interpreted according to the 2013 British Pharmacopoeia [29].

2.7.5. Flowability

The angle of natural slope (α) is an important parameter for describing the fluidity of a powder. A specific apparatus was used to determine the angle of repose (Fig. 2). A 100-gram sample of *C. occidentalis* extract powder was introduced into a standardized funnel. The flow time of the powder was measured once the funnel was opened. The height (h) and radius (r) of cone that formed were also measured. The angle of the cone (α) was calculated using the following formula. The relationship between the angle of repose (α) and powder flow is shown in table 2 below [30,31].

$$Tan\ (\alpha) = \frac{h}{r}$$

Table 2 Interpretation of powder flowability

Angle of repose (α)	Type of flow	Angle of repose (α)	Type of flow
25	Excellent	30-40	Passable
25- 30	Good	> 40	Very poor

2.7.6. Tapped volume determination

A 100-gram sample of the roots extract powder was placed in a graduated cylinder and lightly tamped down. The initial volume (V_0) was recorded. Then, the sample was subjected to a series of tamping. Then, 10, 500, and 1250 tamping's were performed, corresponding to V_{10}, V_{500}, and V_{1250}, respectively. The final tapped volume (V_f) is determined by comparing V_{500} and V_{1250}.

If the difference between V_{500} and V_{1250} is less than 2 ml, then V_{1250} represents the final tamped volume. If the difference is greater than or equal to 2 ml, then additional tamping is performed until the difference between V_{500} and V_n is less than 2 ml. The final volume (V_n) is then designated as the final tapped volume V_f. The obtained values were used to calculate the Carr's index (CI) and the Hausner index (IH) according to formulas (a) and (b) respectively [32,33]:

$$IH = \frac{Vf}{V0}\ (a); \qquad IC\ \% = \frac{V0 - Vf}{V0} x\ 100\ (b)$$

2.7.7. Wettability measurement

To determine the minimum amount of reverse osmosis water required for full dispersion, a 2-gram sample of the powder is placed in a beaker, and reverse osmosis water is added incrementally with a pipette until the powder is fully dispersed. The wettability measurement is the total volume of water added at this point [34,35,36].

2.7.8. pH value

The pH value was measuring with a prepared and filtered aqueous dispersion containing 10 % of *C. occidentalis* extract powder, using a pH meter.

(1: Moisture Content evaluation; 2: Particle size analysis; 3: Flowability testing)

Figure 2 Pre-formulation studies of the solid tablet

2.8. Galenic formulation

Solid tablets were chosen as the galenic form for this study. There are one of the most widely used pharmaceutical dosage forms due to their stability, ease of production, accurate dosing, and patient convenience. The *C. occidentalis* tablets are manufactured by wet granulation (Fig. 3). This common pharmaceutical technique involves agglomerating powders with a liquid binder, drying, sizing, blending them with lubricants, and compressing them to form free-flowing granules that produce better, more uniform tablets, and overcome issues like poor flow and dust [37]. The tablets were obtained by direct compression with a tablet press (ERWEKA), using excipients with low surface adsorption capacity (Fig. 4). This method has proven to be the most suitable for producing a solid form of a tablet that incorporates the dry extract EABCO as the active pharmaceutical ingredient (API) [38]. The galenic formulation process was conducted in strict accordance with the European Pharmacopoeia guidelines [39].

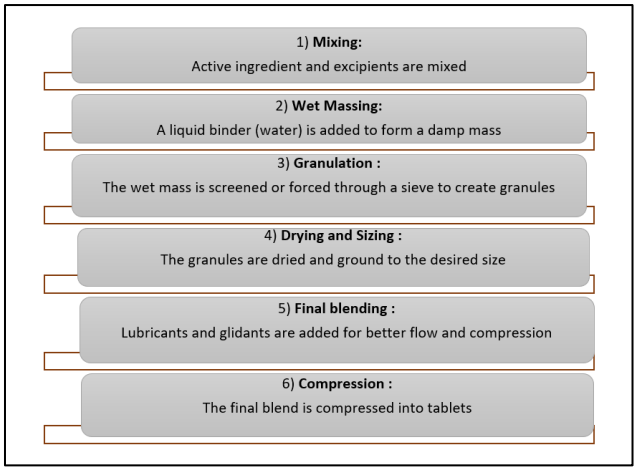
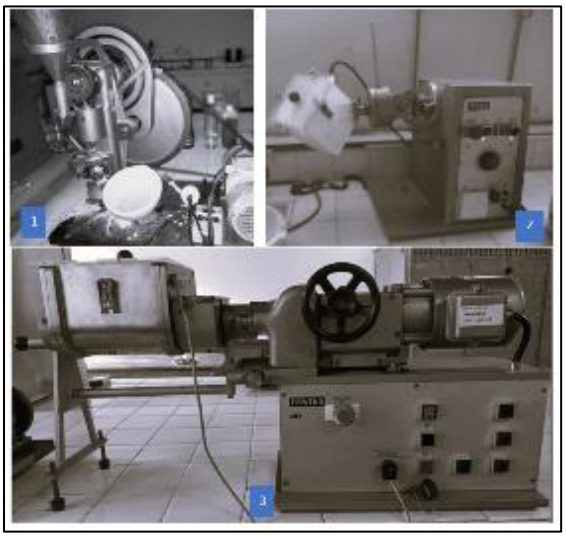


Figure 3 Galenic formulation processes for solid tablet



(1: Tablet press; 2: Powder mixer; 3: Powder blending machine)

Figure 4 Tablet manufacturing machines ERWEKA (CNARP)

2.9. Finished Product Quality Control (FPQC)

Quality control (QC) testing of tablets is a critical step in pharmaceutical manufacturing. This testing ensures that products are safe, effective, and consistent with pharmacopoeia standards [40]. Once the manufacturing process is complete, finished product quality control (FPQC) tests for tablets are performed in accordance with pharmacopoeia specifications to verify that the quality parameters are within acceptable limits [41]. According to these requirements, manufactured tablets must meet predefined quality criteria, such as uniformity, stability, good resistance, absence of flaking, creasing, and breakage, rapid disintegration time, and a good dissolution rate.

To ensure safety, efficacy, and uniformity, tablets must undergo various pharmacopeial tests during manufacturing and before batch release. In this step, were evaluate morphological parameters such as weight uniformity, hardness, friability, stability, and disintegration time in pharmacopeial acceptor fluids. Their specific surface area was also calculated. These tests detect defects, ensure compliance with regulatory standards, and prevent the marketing of substandard products.

2.9.1. Qualitative analysis

Quality testing specification were performed to confirm that the products are fit for their intended use. The developed tablet was then submitted for physicochemical parameters evaluation [42]. This evaluation is the first indicator of product quality and includes verification of appearance, pH, color, odor, and taste.

This information ensures that the tablets have the correct color, shape, markings, and a clean surface without cracks, chips, or contamination [43]. Additionally, pH variation can affect the medication's stability and effectiveness [44].

2.9.2. Quantitative analysis

Weight variation test: According to the United States Pharmacopeia (USP), the weight variation test involves weighing 20 tablets individually. The average weight is then calculated, and each tablet's weight is compared to the average. The result of the weight variation test is expressed as a percentage. The following formula is used:

$$Weight\ variation\ (\%) = \frac{Iw - Aw}{Aw}\ x100$$

Where, **Iw** : Individual weight of tablet ; **Aw** : Average weight of tablet. According to the USP, the tablet complies with the test if not more than 2 of the individual masses deviate from the average mass by more than the percentage deviation as shown in table 3, and no mass deviates by more than twice that percentage [45].

Table 3 Unites States Pharmacopoeia limits for weight variation test for uncoated tablets interpretation of powder flowability

Average Weight (mg)	% deviation
130 mg or less	10 %
More than 130 mg and less than 324 mg	7.5 %
More than 324 mg	5 %

Thickness test: The thickness of a tablet is the only dimensional variable related to the process. Controlling it facilitates packaging. Figure 5 illustrates the process of measuring the thickness of each tablet using a digital caliper. This technique involved placing 10 tablets in a tray and measuring their total thickness. Tablet thickness (mm) must be controlled to within ± 5 % of a standard value [46].

Hardness Test: The apparatus used for this test is the tablet hardness tester illustrated in figure 5. Ten tablets were crushed and their hardness was measured. The breaking force is recorded in kilograms. The permissible range is 4 to 6 kg (40 to 60 N), unless otherwise specified (Tab.4) [47].

Table 4 Acceptance criteria for tablet hardness [48]

Tablet type	Crushing Strength
Oral tablets	4 – 10 N
Hypodermic & Chewable	3 N
Sustained release	10 – 20 N

Friability Test: The friability of a tablet was determined in the laboratory using a friability tester, as illustrated in figure 5. Twenty tablets were weighed and placed in the friability tester. The tester was spun at 25 rpm for 4 minutes. Then, the tablets were then dusted and weighed again. The difference between in weight is used to calculate the friability, which is expressed as a percentage. It is determined by the following formula:

$$Friability\ (\%) = \frac{Iw - Fw}{Iw} x\ 100$$

Where, **Iw**: Total Initial weight of tablets; **Fw**: Total Final weight of tablets. As indicated in the USP, conventional tablets that lose less than 0.5 % to 1 % (after 100 turns) of their weight are generally considered acceptable [45].

Disintegration Test: This test determines whether a solid dosage form breaks apart within a specified time when placed in a liquid medium under controlled conditions. The test is conducted using a disintegration apparatus (Fig. 5).

Six tablets are randomly selected and placed individually into tubes in the basket-rack assembly. The disintegration medium is reverse osmosis water at 37° C. The apparatus is then operated, and the time for each tablet to fully disintegrate (TD) is recorded. Complete disintegration is defined as a state in which the tablet residue, excluding shell fragments, forms a soft mass with no firm core [49]. A tablet passes the test if it disintegrates and all its particles pass through the 10-mesh sieve within the allotted time [50]. A tablet meets the USP test if all tablets have completely disintegrated [36]. The British Pharmacopoeia (BP) limits for tablet disintegration times are shown in table 5.

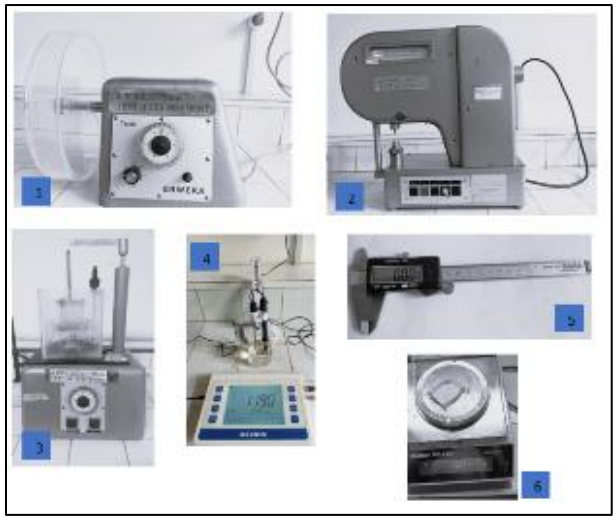
Table 5 British Pharmacopoeia limits for disintegration times of tablets

Categories of tablets	Disintegration times (min)
Uncoated tablets	15
Coated tablets	60
Effervescent tablets	5
Soluble tablets	3
Dispersible tablets	3
Orodispersible tablets	3
Gastro-resistant tablets	60
Oral lyophilizates	3

Moisture Content: This test measures the amount of water present in the finished tablet. Excess moisture can cause the tablet to soften, break, degrade, or become contaminated by microorganisms. Therefore, controlling the water content is important to ensure stability. The previously mentioned heating method was used.

Microbial limit test : Microbiological stability studies helps to confirm the sterility and stability of the manufactured product. According to the Good Manufacturing Practice (GMP), the agar plate inoculation method was used in Petri dish to check for microbial contamination levels [51]. Then, the tablet sample was dissolved and suspended in sterile diluent. After mixing and solidifying, the dishes were incubated at different temperatures: 30-35° C for bacterial during 3 days and 20-25° C during 5 days for fungi. Colony counts are performed on specific days to determine the results: days 1, 2, and 3 for bacteria, and days 1, 2, 3, 4, and 5 for fungi [52]. Each test was performed in duplicate.

Stability and degradation studies: Degradation studies are essential during formulation to quickly assess the stability of the active ingredient. According to the International Conference on Harmonization (ICH) guidelines and the GMP requirements, an accelerate stability testing method was used to determine the appropriate storage conditions and expiration date of the formulated tablet [53,54]. The test was conducted under varying environmental conditions to evaluate the product's resistance to degradation. When samples were stored at three different temperatures (+4° C, 20° C, 45° C), changes in color, odor, taste, pH and appearance were observed at 2-weeks, 4-weeks, and over six months [55,56].



(1: Friability tester; 2: Hardness tester; 3: Disintegration tester; 4: pH-meter; 5: Digital caliper; 5: Precision scale)

Figure 5 Instruments for tablet quality control (CNARP)

2.10. Statistical analysis

All experiments were repeated three times, and the results are expressed as the mean ± standard error of the mean (SEM). A Student's t-test was performed using Microsoft Excel 2013 software for statistical analysis. Differences were considered significant at $p < 0.05$.

3. Results and Discussion

3.1. Extraction result

The resulting extract, named EABCO, had a good yield of 11.3 %, which highlighting the effectiveness of the decoction method for extracting water-soluble compounds from resistant plant material such as roots. This high yield indicates efficient extraction of water-soluble compounds similar to those found in *C. occidentalis* from fibrous roots [57]. Additionally, aqueous extraction is preferable because it reduces the environmental damages caused by organic solvents. Decoction is the most widely described method for extracting active compounds from medicinal plant materials.

3.2. Phytoconstituents of EABCO

The major secondary metabolites detected in the aqueous extracts of *C. occidentalis*' roots are tannins, steroids (sterols/triterpenes), polysaccharides, quinones, and saponins, all of which are frequently identified in aqueous extracts. These compounds are crucial for the plant's defense and its various traditional uses in medicine uses, making this species a significant in herbal remedies. To the best of our knowledge, these compounds were first detected in the roots of *C. occidentalis* aqueous extract. A study of Janaky Ranjithkumar *et al*. (2010) have identified many diverse groups of secondary metabolites with pharmacological activities in the plant but this was in methanolic leaf extract [58]. Based on these phytochemical results, *C. occidentalis* may have more beneficial effects due to the presence of many active secondary metabolites that could combat diseases such as cancer and cardio-vascular disease and boost the immune system.

3.3. Acute oral toxicity

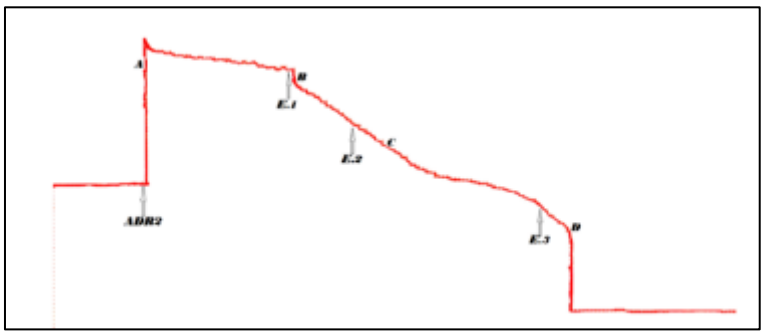
The acute oral toxicity test is the first phase of a toxicological and safety evaluations in drug development. The results obtained with EABCO demonstrated that no mortality was observed in any of the treatments, with the doses ranging from 10 to 5,000 mg/kg over 24- hour observation period. The median lethal dose (LD_{50}) of EABCO in mice is greater than 5,000 mg/kg via oral route [59]. According to the 2008 OECD guidance, EBACO is relatively non-toxic and may be classified as the lowest toxicity (class 5) for a single exposure (LD_{50} > 2,000mg/kg) [60]. However, the LD_{50} value may vary depending on the species of animal tested, the tester's skill level, and the testing method [61]. Therefore, the absence of signs of toxicity led to the conclusion that EABCO, is safe to use as an active ingredient. Hence, evaluation of sub-chronic, chronic, carcinogenic and reproductive effects is crucial when considering its use for public health protection, as exposure to chemicals can result in adverse effects in humans [62].

3.4. Antihypertensive and hypotensive effects of EABCO on rabbits

Figures 6 and 7 present curves showing the results of typical experiments. The baseline blood pressure was 90 ± 6.70 mmHg in anesthetized normotensive rabbits (n = 2).

After an intravenous injection of adrenaline at a dose of 20 µg/kg, transient hypertension was observed, with a maximum blood pressure of 126.00 ± 6.27 mmHg (approximately 36 mmHg above baseline). After the second injection of EABCO at a dose of 50 mg/kg, blood pressure rapidly returned to its lowest level, below 90 mmHg (Fig. 6). These results suggest that EABCO exhibits antihypertensive activity against adrenaline-induced hypertension.

Figure 7 shows typical recordings of dose-dependent hypotension induced by EABCO and acetylcholine (ACh), respectively, in rabbits. Curves (B) and (D) illustrate this phenomenon. Under these experimental conditions, ACh injections between 1 and 20 µg cause an increase in hypotension. EABCO doses between 100 and 500 mg/kg b.w also induced reversible, dose-dependent hypotension. EABCO at a dose of 500 mg/kg of b. w induced a drop in blood pressure (BP).



(ADR2: adrenaline at the dose of 20 µg/kg, E.1: EABCO at the dose of 25 mg/kg, E.2: EABCO at 50 mg/kg, E.3: EABCO at the dose of 100 mg/kg)

Figure 6 Antihypertensive effect of EABCO on the hypertension induced by intravenous injection of Adrenaline on anesthetized rabbits

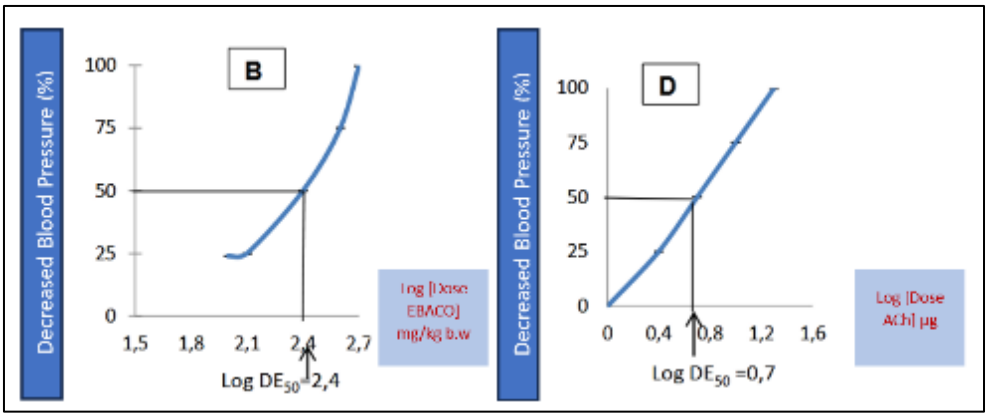


Figure 7 Effect of the aqueous extract (EABCO) and Acethylcholine (ACh) on blood pressure in rabbits in a dose-dependent hypotension manner

These results demonstrate that the root extract of *C. occidentalis* can lower the blood pressure of anesthetized, normotensive rabbits. The effects appear to be dose-dependent. Thus, after the injection of high doses of EABCO, the hypotensive effect is prolonged, as evidenced by lower blood pressure over a long period of time. At lower doses, however, EABCO only produces transient hypotension. The hypotension induced by EABCO appears comparable to those observed with acetylcholine.

Furthermore, the antihypertensive activity of EABCO was evaluated *in vivo* using hypertension models with adrenaline as the agonist that produced the hypertensive effect. The results showed that EABCO reduced adrenaline-induced hypertension. These results suggests that adrenoceptors may play a role in the hypotensive mechanism of this extract.

Various antihypertensive mechanisms have been reported in the literature, and numerous studies have demonstrated that plant extracts exert antihypertensive effects through the combined activities of their bioactive components.

The results imply that *C. occidentalis* extract's therapeutic effect on hypertension is likely associated with the presence of recently detected antihypertensive and hypotensive metabolites, thus validating its empirical use in hypertension treatment.

3.5. Pre-formulation characterizations

The pre-formulation is an important step in developing a new drug. It influences the drug's safety, effectiveness, controllability, stability, and compliance. Physical and chemical properties are part of pre-formulation studies [63, 64]. The objective of the pre-formulation testing is to generate information useful for developing a stable, bioavailable dosage form [65]. The physicochemical and organoleptic characteristics of the aqueous extract (EABCO) powder are summarized in table 6.

Table 6 Pharmacotechnical characteristics of the aqueous extract of *C. occidentalis* roots

Characteristics	**Aqueous extract (EABCO)**
Physical appearance	Uniform fine powder; pH= 5.2 ± 0.1
Organoleptic	Dark green colored powder, characteristic odor, bitter taste
Solubility (g/ml)	1 /10 of water
Moisture Content (%)	4
Flowability (angle of repose°)	26.9
Hausner index	1.18 ± 0.12
Carr's Index (%)	13.3 ± 0.6
Wettability (ml)	2.3 ± 0.6

As shown in the above table, the aqueous extract of *C. occidentalis* roots is a fine, free-flowing, dark green powder that has a distinctive odor and bitter taste. It is completely soluble in water. Based on the compressibility index and Hausner's ratio values obtained for the powder extract, the extract was found to have good flow properties. According to British Pharmacopoeia standards, the powder's particle size is medium-fine, giving it excellent free-flowing properties and making it ideal for tablet manufacturing.

3.6. Formulation result

The tablets were manufactured using wet granulation. The plant extract was mixed with the appropriate excipients, compressed into tablets, and weight at 500 mg [66]. Each tablet contains the following in its final composition, each: the active ingredient (EABCO), a diluent, a binder, a disintegrant, a lubricant and a flavoring agent. This single-dose pharmaceutical preparation is free of sugar and other endocrine-disrupting preservatives (Fig. 8). Multiples tests were carried out to determine the most suitable formula. Any changes in the physicochemical constitution of the active ingredient were detected after combining EABCO with the excipients. The advantage of the solid tablet form is that it improves the stability and delivery of plant extracts. This overcomes the problems of traditional teas, such as poor absorption, degradation by gastric acids and inconsistent dosing. This leads to better bioavailability and a better therapeutic effect because it protects the compounds until they reach the intestine. Tablets also offer precise, consistent amounts of the extract, unlike teas, whose potency varies with brewing time and plant material. For many patients, it is more practical and more pleasant to taste that drinking tea, especially for those who dislike the taste or have difficulty swallowing liquids.

Figure 8 Antihypertensive oral solid tablets made from *C. occidentalis* root extract

3.7. Finished product quality parameters

Table 7 summarizes the FPQC results for the manufactured antihypertensive tablet based on *C. occidentalis* root extract.

Table 7 FPCS results of tablet based on EABCO

Qualitative Parameters	**Results**	**Quantitative Parameters**	**Results**
Color	Brown	Weight individual (mg)	502,5 - 507,2
Odor	Good	Thickness (mm)	4.51 ± 0.02
Taste	Slightly sweet	Hardness (N)	10,20 ± 0.6
Form	Solid, round	Friability (%)	0.15
pH	4.67	Disintegration Time (mn)	11
Appearance	Homogeneous	Moisture Content (°C)	21.8
Microbiological stability/ Sterility			
No bacterial and yeast growth was observed for 28 days at a temperature between 20 to 25° C			
Stability and Storage conditions T (25° C, 30° C, 45° C); RH (70 %)			
No change until 6 months			

As shown in the table above,

- Macroscopically and overall, the tablets observed during the post-formulation control exhibited uniform appearance (color, shape and texture) and reveal no anomalies, such as manufacturing defects, holes, cavities, and swelling or moisture [67].
- The 20 tested tablets ranged from 502.5 (minimum mass) to 507.2 mg (maximum mass). Within these ranges, no value deviated by more than ± 5 % from the average tablet mass (480.0 mg to 530.6 mg). Consequently, mass uniformity is observed, and the *C. occidentalis* tablets are conform to the specifications when these values are compared to the USP standards.
- The manufactured tablets have an average hardness of 10.20 N ± 0.6 meeting the acceptance criteria for tablet hardness.
- The mass loss of the 20 tablets tested is 0.15 %, which is less than 1 %. According to the USP, this value is considered acceptable.
- Disintegration time is an important parameter for tablets. An ideal tablet should disintegrate within 15 min. These tablets produced in this study disintegrated in 11 minutes 48 seconds, leaving no residue on the grid. These results comply with pharmacopeial requirements (BP).
- The qualitative and quantitative physicochemical characteristics of the finished product confirm that the solid tablets based on *C. occidentalis* root extract are acceptable for their intended use. No change in these characteristics was observed during 6 months of storage under various conditions. This strongly suggests that good manufacturing practices were followed during the formulation stage.

- The solid tablet formulated is safe for consumers as it is free from contamination. This indicates that the preservative in the preparation has sufficient antimicrobial activity to prevent microbial growth and ensure stability.

4. Conclusion

This study focuses on formulating and evaluating tablets based on aqueous extract of *C. occidentalis* roots for antihypertensive treatment. The antihypertensive and hypotensive efficacy of the aqueous extract has been validated and found to be comparable to acetylcholine. The aqueous extract (EABCO) was screened for various pharmacological active phytoconstituents and used as an active ingredient. Furthermore, the extract was formulated into tablets using direct compression. Formulating the solid tablet is advantageous because it reduces manufacturing steps, minimizes exposure to moisture, and thus preserves the stability of the phytochemicals, while adhering to Good Manufacturing Practices. The developed product meets the pharmacopoeia requirements in terms of physical quality (disintegration, hardness, friability) as well as acute toxicological safety. To obtain marketing authorization for an Improved Traditional Medicine (ITM), precise identification of chemical markers is necessary to ensure standardization of each batch. Studies on bioaccessibility, bioavailability, and the mechanism of action studies would provide a thorough understanding of this new product before its market launch.

Compliance with ethical standards

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Disclosure of Conflict of interest

The authors declare no conflict of interest.

Statement of ethical approval

All the tests on animals were approved and in line with the standard established by Ethics Committee of the Pasteur Institute of Madagascar (IPM).

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