International Journal of Multidisciplinary Research and Publications
ISSN (Online): 2581-6187

Formulation and Evaluation of an Antihypertensive Oral Solution Based on Sarongazany'Roots (CAESALPINIACEAE) from Madagascar

RAKOTOARISOA Mbolatiana Abigaila[1], TOHANDRAINY Mbola Adrien[2], RANDRIANASOLO Rivoarison[3]
[1]Department Of Galenic Pharmacy, National Center for Pharmaceutical Research Applications, Antananarivo, Madagascar
[2]Aromas Cosmetics Phytomedicines, Mention Chemistry-Faculty of Sciences, University of Antananarivo, Madagascar
[3]Analytical Chemistry and Formulation Laboratory, Faculty of Sciences, University of Antananarivo, Madagascar
Email address: abiartiana@yahoo.fr

***Abstract*—** *Cassia occidentalis Linn (CAESALPINIACEAE) is a plant commonly used in traditional medicine to treat various illnesses, especially hypertension, in the Salobe, Betioky-Sud, District of Toliara in southwest of Madagascar. High blood pressure is actully a major public health problem, affecting both adults and children. It is one of the leading causes of death, resulting in nearly 8 million deaths per year. This study aimed to scientifically validate the traditional use of this plant to treat hypertension. Then, formulate an antihypertensive oral solution with the aqueous root extract as the active ingredient. In vivo tests showed that the root extract (EBACO) had dose-dependant hypotensive potential in normotensive rabbits. Under the experimental conditions, 500 mg/kg of EBACO induced a greater drop in blood pressure than 1-20 µg of acetylcholine. According to OECD guidelines, EBACO is in the lowest toxicity (class 5). A prototype of an oral, multidose antihypertensive solution was formulated. This traditional remedy is safe, non- toxic, sterile, free of sugar and other endocrine-disrupting preservatives. All control parameters comply with Good Manufacturing Practices. This new herbal formulation offers several advantages in the treatment of hypertension in both adult and pediatric patients. However, further preclinical testing is needed to fully assess the plant's activity.*

Keywords*—Antihypertensive, Cassia occidentalis, formulation, oral solution, quality, toxicity*

I. Introduction

High blood pressure (hypertension) that has no clear cause, is a global health problem influenced by a combination of factors, including genetics, lifestyle, psychosocial stress, and environmental exposures. Significant contributors include dietary habits such as high sodium intake and weight gain, as well as psychosocial factors such as chronic stress and lack of physical activity. Environmental factors like noise and air quality, can also play a role [1]. Currently, exposure to chronic stress and social factors, urbanization and education level, as well as chronic social conflicts, are associated with higher blood pressure [2]. Several studies that high work demands and low work capacity, combined with coronary heart disease, are contributing factors to hypertension [3].

Based on statistics from 2000, estimates indicated that hypertension affected 972 million adults worldwide. Projections showed that this number would increase by 60 % to 1.56 billion by 2025 [4,5]. This augmentation was primarly due to a higher prevalence in developing countries, through high-income countries experienced a decline or stabilization during this period. Nearly two-thirds of people with hypertension live in low- or middle-income countries, which represent a considerable economic burden. Essential public health measures include raising awareness, preventing, treating, and controlling hypertension [4]. In the face of this alarming situation, the World Health Organization (WHO) has incorporated high blood pressure screening and treatment into its health programs for developing countries. The WHO supports these countries in strengthening their primary healthcare systems, implementing standardized protocols, and increasing access to affordable or free medication [6].

In Africa, the fight against hypertension is hindered by the by the high cost of clinical treatment. Medication prices are beyond the reach of more than 80 % of the population [7]. Faced with such poverty, traditional medicine is the only option for these populations to reduce the risk of death from hypertension. Thus, the use of local medicinal plants is seen as an alternative to conventional medicine [8].

For the Malagasy people, the use of traditional herbal medicines (THMs) is common in urban and rural areas for managing hypertension. Patients typically use decoctions or preparations of plant belonging to the ASTERACEAE, PIPERACEAE, RUTACEAE, or ZINGIBERACEAE families [9]. Many medicinal plants and traditional remedies are sold and used by the local population [10]. However, only a few of these plants have undergone clinical testing or chemical and biological studied to identify their active constituents or mechanisms of action [11]. Using traditional antihypertensive plants without rigorous scientific testing poses risks because the active compounds, dosages, and potential side effects have not been scientifically validated, unlike modern medications. This absence of evaluations means there is no scientific basis for specific dosages, which can lead to toxicity or uneffectiveness. In order to safely use these plants, research must first identify their active constituents and determine their mechanisms of action. Then, clinical trials must be conducted to establish their safety and effectiveness [12].

RAKOTOARISOA Mbolatiana Abigaila, TOHANDRAINY Mbola Adrien, and Rivoarison Randrianasolo, "Formulation and Evaluation of an Antihypertensive Oral Solution Based on Sarongazany'Roots (CAESALPINIACEAE) from Madagascar," *International Journal of Multidisciplinary Research and Publications (IJMRAP)*, Volume 8, Issue 6, pp. 228-233, 2025.

The goal of this study's is to develop an Improved Traditional Remedy (ITR) effective and safe to help manage of high blood pressure in poor populations.

Cassia occidentalis Linn, belonging to the FABACEAE family and a subfamily of the CAESALPINIACEAE, is a plant with significant medicinal properties [13]. In Madagascar, this shrub is known by various names, including "Tsotsoronangatra," "Bemaimbo," "Voanembanalika," "Tsatsinangatra," "Famônoakoho," and "Sarongazany" [14]. It is an Ayurvedic plant used in traditional medicines to treat various ailments [15]. Ethnobotanical surveys of the people of Salobe, in the Betioky-Sud district (southwest of Madagascar), revealed that they use the roots of C. occidentalis to treat various diseases, in particularly hypertension.

This study was initiated because previous research has indicated that C. occidentalis has various medicinal properties (antibacterial, antifungal, antidiabetic, anticancer, and hepatoprotective) but there is a lack of data on its potential as an antihypertensive remedy [16,17]. The objective is to scientifically investigate the traditional use of root of this specific plant, confirm its antihypertensive capacity, and then use these findings to develop and control a new herbal remedy for hypertension.

II. Materials and Methods

A. Plant material

C. occidentalis roots were collected in January 2021 in Salobe, Betioky-Sud district of Toliara (southwest 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).

Fig. 1. Photo of Cassia occidentalis Linn : plant (a) and roots (b)

B. Animals

Male and female rabbits of the species *Oryctolagus cuniculus* (LEPORIDAE), weighing between 1.7 and 2.5 kg, were used for the pharmacological tests of the hypertension experiment. They were obtained from the Department of Animal Physiology and Pharmacology at the University of Antananarivo.

Oral acute toxicity assays were carried out on SWISS mice weighing between 20 g and 30 g, which were supplied by the animal house of the Department of IMVAVET (Institut Malgache des Vaccins Vétérinaires).

The animals were acclimated to room temperature for two to three days prior to use. They had free access to tap water and were fed a standard diet. The tests were carried out according to the Organization for Economic Co-operation and Development or OECD guidelines [18]. The 3Rs (Replacement, Reduction, and Refinement) principles were applied to this procedure. All animal experimentation was approved by the Pasteur Institute of Madagascar (IPM) Ethics Committee and aligned with the established standards.

C. Preparation of plant extract

To prepare the aqueous extract of dried *C. occidentalis* roots (EABCO), the process involves harvesting the roots, drying them in the shade for seven days, grinding them into a powder, and storing it in an airtight, light-protected container. Next, the powder is extracted by aqueous decoction at 100° C under reflux at a ratio of 1/10 (w/v) for 30 minutes. Then, it is filtered through a Büchner funnel, and the solvent is evaporated using a rotary evaporator (Büchner type R-114, Switzerland) to obtain the final dry extract [19]. This powder extract constitutes the aqueous extract of *C. occidentalis* roots (EABCO).

D. Acute oral toxicity test

The oral acute toxicity study of the aqueous extract (EABCO) was performed according to the method of the OECD guidelines (423, 425) as mentioned by Rakotoarisoa *et al.* (2025) [20]. Swiss albino mice of both sexes were selected and divided into ten groups of three animals. Each group received a dose ranging from 10 to 5,000 mg/kg orally. The median lethal dose (LD_{50}) was calculated as the geometric mean of the dose that did not produce mortality and the highest dose that produced mortality, assuming that the exposure was above the highest recorded dose if no mortality was observed [21].

E. Hypotensive test

The method described by Léandre K. (2008), slightly modified, was used for the hypotensive test [22]. 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 the reference drugs and the test substances. The carotid artery was cannulated to 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 injecting the test substance : Acetylcholine (ACh : 1 to 20 µg/kg body weight), which was chosen as the drug standard curves for hypotensive mechanism [23,24].

F. Oral solution formulation

The oral solution was prepared using a cold process. This multidose liquid dosage form contains excipients that are suitable for a pediatric population and compatible with

RAKOTOARISOA Mbolatiana Abigaila, TOHANDRAINY Mbola Adrien, and Rivoarison Randrianasolo, "Formulation and Evaluation of an Antihypertensive Oral Solution Based on Sarongazany'Roots (CAESALPINIACEAE) from Madagascar," *International Journal of Multidisciplinary Research and Publications (IJMRAP)*, Volume 8, Issue 6, pp. 228-233, 2025.

metabolic disorders. First, the active ingredient (EABCO) was dissolved in purified water. Then the mixture was continuously stirred to ensure homogeneity. Next, the excipients and preservatives were added and thoroughly mixed. The solution was then filtered to obtain a stable and homogeneous finished product. The galenic formulation was conducted in strict accordance with the European Pharmacopoeia guidelines [25]. The finished product was transferred to an amber-colored bottle, tightly closed, and stored in a cool and dry place.

G. Quality control

Physicochemical parameters analysis

The developed product has undergone a physicochemical evaluation. This includes verification of pH, density, specific gravity, viscosity, color, odor, crystalization, sterility, and taste, all of which are essential to ensuring consistency and consumer acceptability [26]. The pH value was measured potentiometrically on three 3-ml batches using a pH meter. Organoleptic characteristics such as appearance (e.g., sedimentation and color), taste, odor, and texture, were monitored from day 0 to day 28. Color and the presence of particles were also assessed by visually on white and black backgrounds.

Accelerated stability testing

The goal of accelerated stability testing is to determine the storage conditions and expiration date that meet Good Manufacturing Practice (GMP) requirements [27]. The testing is conducted under varying environmental conditions to evaluate the product's resistance to degradation. Samples were stored at three different temperatures (+4° C, 20° C and 45° C) and observed for changes in color, odor, taste, and turbidity at at 24-, 48-, and 72-hour intervals over three months. Additionally, density, pH, homogeneity and the appearance of degradation products were measured over time [21,28].

Freeze-Thaw cycling testing

For the Freeze-Thaw cycling testing, the vials were alternately kept at 40° C and 4° C for 24 hours each, and shaken daily for five minutes on a vortex mixer. Two vials of the formulation were taken ; one was kept at 40° C, and the other was kept at 4° Con the first day.

Then, they underwent temperature cycling and shaking as described above. After 7-7 such cycles at 4° C and 40° C (alternately), the vials were observed to check for turbidity and precipitation, if any [21].

Sterility and microbiological stability testing

The selection of the preservative, its amount, and Good Manufacturing Practices are all supported by the microbiological stability and sterility studies. The agar plate inoculation method was used. This consisted of adding 1 ml of the sample to be examined to 19 ml of liquid agar in a Petri dish. This allows for the examination of a larger sample volume compared to surface inoculation.

After mixing and solidifying, the dishes were incubated at different temperatures: 30-35° C during 3 days for bacterial and 20-25° C during 5 days for fungi. Colony counts are then performed on specific days: days 1, 2, and 3 for bacteria and days 1, 2, 3, 4, and 5 for fungi. Each test was performed in duplicate [29,30].

Preservative Efficacy Test (PET)

Most multi-dose products depend on chemical preservatives to prevent microbial spoilage. As antimicrobial agents, preservatives are incorporated into formulations to inhibit microbial proliferation and ensure product integrity [31]. According to the European Pharmacopoeia's preservative efficacy test, a product's preservative effectiveness is assessed by challenging it with high microbial loads: 10^8 CFU for bacteria (*Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa*) and 10^6 CFU for yeast (*Candida albicans*) in 40 ml vials. The samples are stored at room temperature (20−25° C) protected from light and moisture. Inoculum testing is performed on day 0 to confirm the bacterial load. Then, to ensure the preservative prevents microbial growth, the microbial load is assessed at 14 and 28 days using the agar plate method, with the required dilutions for each microorganism. This PET, with its high inoculum and specific time points, helps validate the quantity and effectiveness of preservative to ensure product safety [32].

H. Statistical analysis

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

III. Resultats

A. Extraction result

The yield of the aqueous extract (EBACO) obtained from *C.occidentalis* root powder is 11.3 %.

B. Acute oral toxicity

Doses ranging from 10 mg/kg to 5,000 mg/kg did not result in the death of any within 72 hours of observation. Since no mortality was observed at theses doses, the median lethal dose of EBACO is therefore greater than 5,000 mg/kg by oral route. According to OECD's 2008 guidance, the aqueous extract of C. occidentalis root may be classifed as having the lowest toxicity, class 5 (LD50 > 2000 mg/Kg) [33]. The animals did exhibed any signs of acute toxicity or any major behavioral changes. Signs such as changes in locomotion and piloerection were found to be primarly traditional indicators of illness. The absence of the traditional signs of toxicity in the tested animals led to the conclusion that the EBACO aqueous extract was safe in cases of acute exposure because severe poisoning would have produced such effects. These results indicate that the drug concentrations were non-toxic and safe for use [34].

C. EBACO and ACh effects on the blood pressure of rabbits

Figure 2, curves (B) and (D), show typical recordings of dose-dependent hypotension induced by EBACO and ACh, respectively, in rabbits. Under the experimental conditions, acetylcholine (ACh) caused an increase in hypotension when injected in doses between 1 µg and 20 µg. EBACO doses between 100 and 500 mg/kg b.w also induced reversible, dose-

RAKOTOARISOA Mbolatiana Abigaila, TOHANDRAINY Mbola Adrien, and Rivoarison Randrianasolo, "Formulation and Evaluation of an Antihypertensive Oral Solution Based on Sarongazany'Roots (CAESALPINIACEAE) from Madagascar," *International Journal of Multidisciplinary Research and Publications (IJMRAP)*, Volume 8, Issue 6, pp. 228-233, 2025.

dependent hypotension. An aqueous EBACO extract at a dose of 500 mg/kg of body weight was able to induce a drop in blood pressure (BP).

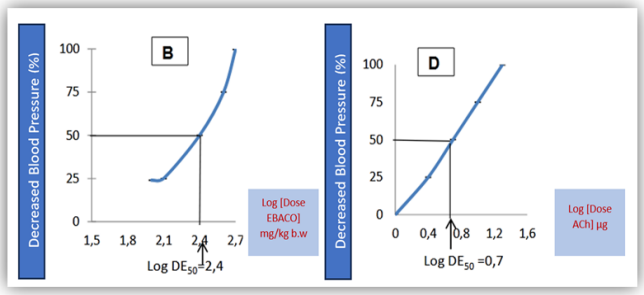

Fig. 2. Effect of the aqueous extract (EBACO) and acethylcholine (ACh) on blood pressure in rabbits in a dose-dependant hypotension manner

D. Formulation results

The prepared pharmaceutical form was a multidose oral solution. More than tests were carried out to determine the most suitable formula, as presented in table 1 and figure 3. Potassium sorbate was chosen as the preservative due to its good tolerability and lack of side effects.

TABLE I. Antihypertensive oral solution formula

Denomination	Composition (125 ml)	Proportion
Antihypertensive multidose oral solution of *C. occidentalis*	Plant extract (EBACO)	1.85 %
	Potassium sorbate	Qs
	Excipients	Qs

Fig. 3. Manufacturing process of the antihypertensive oral solution based on *C. occidentalis root extract*
(1 : Homogenization ; 2 : Filtration ; 3 : Addition of excipients and preservatives ; 4 : Quality controls)

E. Physicochemical and organoleptic parameters of the manufactured oral solution

Table 2 summarizes the quality controls results on the finished product.

TABLE II. Physicochemical and organoleptic parameters of *C. occidentalis* oral solution

Parameters	Results	Parameters	Results
Color	Dark brown	**Crystallization**	Absence
Odor	Good	**Clarity**	Clear
Taste	Slightly sweet	**pH**	4.67
Form	Liquid	**Density**	1.29
Precipitation	Absence	**Viscosity**	Non-viscous
Appearance	Homogeneous solution	**Temperature (°C)**	21.8° C

F. Oral solution stability

No differences or changes in color, odor, taste, or turbidity were observed when the bottle was stored at room temperature (20-25° C) for up to three months. The physicochemical parameter values showed no significant difference compared to the initial formulation. However, when the solution was stored at 35-40° C, changes in color, turbidity, and taste occured within 48 hours. These changes indicate that higher temperatures accelerate chemical degradation, impacting solution stability and possibly efficacy.

G. Oral solution sterility

The oral solution is safe for consumers as it is free from bacterial and yeast contamination, with a total germ count of zero Colony-Forming Units (CFUs) after a five-day incubation period. These results indicate that the product is sterile and meets the standards of the European pharmacopoeia and Good Manufacturing Practices for oral medications.

H. Preservative efficacy of the formulated oral solution

The results of the preservative efficacy test are summarized in table 3.

TABLE III. Results of preservative test on formulated oral solution

Colony count (CFU)	Day-0	Day-14	Day-28
S. aureus	-	0 ± 0	0 ± 0
Innocuous control (dilution $1/10^6$)	90	>500	>500
E. coli	-	0 ± 0	0 ± 0
Innocuous control (dilution $1/10^6$)	40	>500	>500
P. aeruginosa	-	0 ± 0	0 ± 0
Innocuous control (dilution $1/10^6$)	70	>500	>500
C. albicans	-	0 ± 0	0 ± 0
Innocuous control (dilution $1/10^4$)	25	>500	>500
Negative control	0 ± 0	0 ± 0	0 ± 0

According to these findings, the oral preparation meets the European Pharmacopoeia's criteria for antimicrobial preservation. No bacterial growth was observed for 28 days at a temperature between 20 to 25° C. This result is similar to that of the negative control, and the preparation's organoleptic characteristics remained unchanged. These results indicate that the preservative in this preparation has sufficient antimicrobial activity to prevent microbial growth. Therefore, the addition of another preservative is unnecessary under these conditions. These findings also confirm the stability of the preparation formulated according to Good Manufacturing Practices.

I. Packaging and labeling

The solutions were packaged in 125-ml amber glass bottles (Fig. 4). These bottles are inert to the contents and effectively protect against air, light and other potential contaminants. Amber glass absorbs most UV radiation, which protects the filling material from possible changes.

RAKOTOARISOA Mbolatiana Abigaila, TOHANDRAINY Mbola Adrien, and Rivoarison Randrianasolo, "Formulation and Evaluation of an Antihypertensive Oral Solution Based on Sarongazany'Roots (CAESALPINIACEAE) from Madagascar," *International Journal of Multidisciplinary Research and Publications (IJMRAP)*, Volume 8, Issue 6, pp. 228-233, 2025.

Fig. 4. Labeling of the *C. occidentalis* antihypertensive oral solution

Fig. 4. Packaging of the *C. occidentalis* antihypertensive oral solution

IV. Discussions

The aim of this study is to develop an oral antihypertensive solution based on a roots extract. To achieve this objective, a multidose liquid was chosen as the pharmaceutical form due to its ease of oral administration. C. occidentalis was selected for its traditional use in ethnomedicine. During an ethnobotanical survey in southern Madagascar, a decoction of its roots was found to be used for treating hypertension.

Experimental results on normotensive rabbits demonstrated its dose-dependent hypotensive effect. Thus, following the injection of EABCO at higher doses, the duration of the hypotensive effect increaded, as evidenced by the lower, sustained blood pressure level. At lower doses, however, EABCO produced only temporary hypotension. The hypotension induced by EABCO appeared comparable to that induced by acetylcholine. Various antihypertensive mechanisms have been reported in the literature, and numerous studies have shown that plant extracts exert antihypertensive effects through the combined activities of their bioactive components [35]. Previous phytochemical studies on the plant have revealed its richness in active constituents [36]. These results suggests that the hypotensive effect of the roots extract of C. occidentalis on hypertension is probably linked to the presence of antihypertensive and hypotensive metabolites.

In light of these results, and after demonstrating its safety in animal models, the aqueous extract (EBACO) was used as the active ingredient in the oral solution formulation.

The yield obtained during the decoction extraction of the root was 11.13 %. This value is high compared to the decoction extraction results obtained with other plant species [37]. The roots of *C. occidentalis* appears to contain numerous active compounds that can be extracted with water. This finding could facilitate its use in the pharmaceutical industry to produce and market a new, affordable, accessible antihypertensive solution. Furthermore, it is a plant that grows worldwide and multiplies easily [13].

Studies on the galenic formulation of the aqueous root extract have yielded promising results. The manufactured product complies with the physicochemical standards of the European Pharmacopoeia and Good Manufacturing Practices for oral liquid dosage forms [38].

This multidose formulation offers several advantages for treating hypertension. First, it is ready to use, unlike the single-dose powder form, which requires dissolution in water and increases the risk of handling errors or underdosing. Second, an oral solution allows for larger doses to be administered at once than solid forms, such as capsules or tablets, can. Thus, the oral formulation is preferred for pediatric patients or those with swallowing difficulties. It allows for easy adjustment based on weight changes in consultation with a physician without needing to prepare a new formulation. However, drawbacks were observed during product quality control of the oral solution form. Compared to solid forms, liquid preparations appear to have a short shelf life despite the addition of effective preservatives.

In summary, this new antihypertensive formula fulfills all the conditions necessary to be considered an improved traditional remedy. It is accessible to all and has no harmful side effects when managing high blood pressure in both adult and pediatric patients.

V. Conclusion

The aim of this study is to address the needs of both adult and pediatric patients, primarily in developing countries. The objective is achieved by the formulation of an oral antihypertensive solution based on an aqueous extract of C. occidentalis roots, which has demonstrated hypotensive effects in vivo. This improved, non-toxic traditional remedy is supported by scientific evidence, complies with Good Manufacturing Practices, and is free of sugar and other endocrine-disrupting preservatives. Further, in-depth studies are necessary to identify the active compounds in the extract, investigate its mechanism of action, and conduct clinical trials.

Acknowledgment

We are grateful to the National Center for Pharmaceutical Research Applications (CNARP) and the Analytical Chemistry and Formulation Laboratory (LCAF) Antananarivo, Madagascar for their help in this study.

References

[1] Pickering, T.G. The effects of environmental and lifestyle factors on blood pressure and the intermediary role of the sympathetic nervous system. *Journal of Human Hypertension*, 11 Suppl 1: S9-18, PMID: 9321735, 1997.

[2] Beilin, L.J. Stress, coping, lifestyle and hypertension: a paradigm for research, prevention and non-pharmacological management of

hypertension. *Clinical and Experimental Hypertension*, 19(5-6), 739-752,1997.
[3] Stamler, J., Elliott, P., Appel, L., Chan, Q., Buzzard, M., Dennis, B., Dyer, A.R., Elmer, P., Greenland, P., Jones, D., Kesteloot, H., Kuller, L., Labarthe, D., Liu, K., Moag-Stahlberg, A., Nichaman, M., Okayama, A., Okuda, N., Robertson, C., Rodriguez, B., Stevens, M., Ueshima, H., Horn, L.V., Zhou, B. Higher blood pressure in middle-aged American adults with less education-role of multiple dietary factors : the INTERMAP study. *Journal of Human Hypertension*, 17(9):655-775, 2003.
[4] Kearney, P.M., Whelton, M., Reynolds, K., Muntner, P., Whelton, P.K. & He, J. Global burden of hypertension: analysis of worldwide data. *Lancet*, 365(9455), 217-23, 2005.
[5] Chockalingam, A., Campbell, N.R., Fodor, J.G. Worldwide epidemic of hypertension. *Canadian Journal of Cardiology*, 15 ;22(7):553-5, 2006.
[6] World Health Organization, traditional medicine strategy 2014-2023, (2013) 2 – 4, 2013.
[7] Latifah, E., Kristina, S.A., Suryawati, S. Overview of drug availability and influencing factors in several low, lower and upper- middle countries: a systematic review search results. *Rev Artic*, 10 :67–72, 2019.
[8] Mounkaila, S., Soukaradji, B., Morou, B., Karim, S., Issoufou, H. B. A., Mahamane, A., Ikhiri, K. and Saadou, M. Inventaire et gestion des plantes médicinales dans quatre localités du Niger. *European Scientific Journal*, 13 (24): 498 – 521, 2017.
[9] Neamsuvan, O., Komonhiran, P., Boonming, K. Medicinal plants used for hypertension treatment by folk healers in Songkhla province, Thailand. *Journal of Ethnopharmacology*,214 :58-70,2018.
[10] Randriamiharisoa, M.N., Kuhlman, A.R., Jeannoda, V., Rabarison, H., Rakotoarivelo, N., Randrianarivony, T., Raktoarivony, F., Randrianasolo, A., Bussmann, R.W. Medicinal plants sold in the markets of Antananarivo, Madagascar. *Journal of Ethnobiology and Ethnomedicine*, 11 :60, 2015.
[11] Lahadson, S.F., Randrianjatovo, M., Rabemandroso, F.L., Toghueo, K.R.M., Rakotoarison, O., Ravelomanantsoa, G., Randrianasolo, R., Nkengfack, E.A., and Rasoanaivo, H.L. Biological activity of leaves extracts and active ent-kaurane from *Erythroxylum ferrugineum* cav. (ERYTHROXYLACEAE). *American Journal of Innovative Research and Applied Sciences*, 11(3):131-136, 2020.
[12] Vaou, N., Voidarou, C., Rozos, G., Saldari, C., Stavropoulou, E., Vrioni, G. et Tsakris, A. Dévoiler les secrets de la nature: transformer les plantes médicinales en agents thérapeutiques modernes. *Pharmaceutics*, 17 (6), 754, 2025.
[13] Badock, E.A., Ndiaye, A.Y., Drame, A., Drame, M., Ayessou, N.C., & Cisse, M. Enquête ethnobotanique d'une plante médicinale *Cassia occidentalis* Linn au Sénégal. *Afrique Science*, 22(4), 79-87, 2023.
[14] Descheemacker, A. RAVIMAITSO, 5ème édition, Ambositra, 1979.
[15] Ethnopharmacoligia. Quelques plantes médicinales issues des enquêtes ethnobotaniques à Madagascar, *Ethnopharmacologia*, n°36, 2005.
[16] Verma L., Yadav J.P., Vedpriya A., Sanjay Y., Manju P., Sandeep K., Seema D., *Cassia occidentalis* L. A review on its ethnobotany, phytochemical and pharmacological profile. *Fitoterapia*, 81(4): 223-230, ISSN 0367-326X, 2010.
[17] Hatano, T., Mizuta, S., Ito, H., & Yoshida, T. C-Glycosidic flavonoids from Cassia occidentalis. *Phytochemistry*, 52, 1379-1383, 1999.
[18] OECD. Guidance Document on Acute Oral Toxicity. Environmental Health and Safety Monograph Series on Testing and Assessment No 423. 2000.
[19] Rakotoarisoa, M. A. Development and evaluation of topical antifungal products based on leaf extract of *Cassia alata* Linn (FABACEAE). *World Journal of Advanced Research and Reviews*, 27(03), 1127-1139, 2025.
[20] Rakotoarisoa, M. A. Gastroprotective and antiulcer potential of aerial part extract of *Gaertnera phanerophlebia* Baker (RUBIACEAE). *International Journal of Innovative Science and Research Technology*, 10(10), 2524-2533, 2025.
[21] Rakotoarisoa, M.A., Randrianomenjanahary, A.R. & Randrianasolo, R. Herbal syrup expectorant from *Allium cepa* L. (LILIACEAE) and *Eriobotrya japonica* Lindl. (ROSACEAE). *International Research Journal of Modernization In Engineering Technology and Sciences*, 7(7), ISSN: 2582-5208, 2025.
[22] Léandre, K.K., Kouakou, J-C. ABO, T.F. and Ehouan, E.E. Effet antihypertensif de BpF2, une fraction d'extrait aqueux de feuilles de *Bidens pilosa* L. (ASTERACEAE) chez le lapin. *The Science of Nature*, 5(1): 29-37,2008.
[23] Dimo, T., Nguelefack, T.B., Kamtchouing, P., Dongo, E., Rakotonirina, A., & Rakotonirina, S. V. Hypotensive effects of a methanol extract of *Bidens pilosa* Linn on hypertensive rats. *Comptes Rendus de L'academie des sciences*. Serie III, Sciences de la vie, 322(4), 323-329, 1999.
[24] Abo, K.J.C., Ehile, E.E., Guédé-Guina, F. & Traore F. Effets cholinergiques d'un extrait aqueux de *Mareya micranttha* (EUPHORBIACEAE) sur la pression artérielle et l'activité cardiaque. *Afrique biomédicale*, 5 (3): 11-20,2000.
[25] Le Hir, A., Chaumeil, J.C., Brossard, D.M., Issy-les-Moulineaux. Pharmacie Galénique- *Bonne Pratique de fabrication des médicaments*. 382 pp. ISBN: 978-2-294-61204-6, 2009.
[26] Jadhao, A.G., Sanap, M.J., & Patil, P.A. Formulation and evaluation of herbal syrup. *Asian Journal of Pharmaceutical Research and Development*, 9 (3),16-22, 2021.
[27] Cundell, T. The role of microbiological testing in drug product stability testing Program,2004.
[28] Parrenne, L., Ribier, Z., Abisror, J., Ahil, S., Figueiredo, C., Marchadour, P., Benoit, G., Bordenave, J. Formulation d'une solution buvable de phénobarbital à usage pédiatrique, *European Society of Hospital Pharmaceutical Technologies*, 2021.
[29] Nalesso-Leao, C.C.F., Milani, P.G., Formigoni, M., Zorzenon, M.R.T., Dacome, A.S., Monteiro, ARG et COSTA, S.C.D. Substitution du sucralose par le rébaudioside A dans les aliments à base de soja: équivalent en goût sucré, analyse physico-chimique, évaluation microbiologique et test d'acceptabilité. *Food Science and Technology*, 40(2), 410-414,2020.
[30] Terrones-Fernandez, I., Casino, P., López, A., Peiró, S., Ríos, S., Nardi-Ricart, A., García-Montoya, E., Asensio, D., Marqués, A.M., Castilla, R., Gamez-Montero, P.J., Piqué, N. Improvement of the pour plate method by separate sterilization of agar and other medium components and reduction of the agar concentration. *Microbiology Spectrum Journal*,11(1): e0316122,2023.
[31] Asnaashari, S., Heshmati -Afshar, F., Amin -Aghdam, N., Asgharian, P., Hallaj-Nezhadi, S. Evaluation of antimicrobial activities of different extracts from *Phlomis tuberosa*, *Abutilon fruticosum*, and *Nepeta transcaucasica*. *Acta Microbiologica Bulgarica*. 182-8, 2023.
[32] Mousavi G., Seyed, S., Zarei, Z., Hamidian, K., Nikrou, S., Seidi, M-R., Jamalifar, H., Samadi, N. Preservative efficacy testing of refrigerated pharmaceuticals: choice of challenging isolate and storage temperature. PDA *Journal of Pharmaceutical Science and Technology*. 003021, 2024.
[33] OECD Guidelines for the testing of chemicals. Test no. 425, Acute oral toxicity: Up-and down procedure. *OECD Publishing*, 1-12, 2008.
[34] Akwongo, B., Kakudidi, E.K., Nsubuga, A.M., Andama, M., Namaganda, M., Tugume, P., Asiimwe, S., Anywar, G., Katuura, E. Acute and sub-acute toxicity assessment of methanolic stem bark extract of *Khaya anthotheca* (MELIACEAE) in Wistar rats. *Tropical Medicine and Health*. 29 ;53(1) :120, 2025.
[35] Boudendouna A. Méthodologie de la formulation d'une forme libération prolongée. Thèse de doctorat. Science Génie Matériaux, Université de Toulouse. 2010, 246 p.
[36] Ravalison, A., E., Rakotosaona, R., Andrianaivoravelona, O.J., Andrianarison, R.J., Handrinirina, J.E., & Andrianary, P.A. Screening phytochimique et isolement par voie bioguidée de substances à activité antibactérienne d'extraits de *Cassia occidentalis* Sond récoltée à Maevatanàna, *MADA-HARY*, 2015.
[37] Rakotoarisoa M.A. New Anti-inflammatory Balm Based on a POACEAE Weed: *Eleusine indica* (L) Gaertn. *International Journal of Multidisciplinary Research and Publications*, 8(2), 54-57, ISSN: 2581-6187, 2025.
[38] Le Hir A. Comprimés. In: Abrégés de pharmacie galénique, *Bonnes pratiques de fabrication des médicaments*, 8ème édition. Masson, 251-77, 2001.