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# Collaborative Development of Ghanaian Herbal Medicines for Malaria, BPH, Hypertension, and Diabetes: Case Studies from the Centre for Plant Medicine Research

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**Abstract:** ***This article reviews over 30 years of collaborative research at Ghana's Centre for Plant Medicine Research (CPMR) focused on developing herbal treatments for malaria, BPH, hypertension, and diabetes. Five herbal products- Mibima, URO 500, Diodia, Lippia Tea, and Bridelia- were derived from indigenous plants through ethnopharmacological research, preclinical studies, and limited clinical trials. The paper highlights the role of traditional knowledge integrated with modern scientific validation in achieving Universal Health Coverage (UHC). Emphasis is placed on collaborative frameworks, safety profiling, and policy support for the integration of herbal medicine into Ghana's public health system.***

**Keywords:** Herbal medicine, Ghana, traditional medicine, Mibima, URO 500

## 1. Introduction

The use of plants for medicinal purposes predates the oldest written history. Archaeologists have shown that humans began using medicinal plants for treating diseases as early as the Paleolithic era (1), which was about 60,000 years ago. Interestingly, animals such as dogs, cats, chimpanzees, and snakes are widely known to eat medicinal plants to treat illnesses (2). Long before the advent of allopathic medicine in the 19th century, humans relied on intuition, trial and error, observation of animal behavior, serendipity, and magico-religious beliefs to address basic health needs**,** using remedies mainly sourced from plants. Thus, before the introduction of allopathic medicine, herbal medicines, which involved the use of the whole or various plant parts (seeds, berries, roots, root barks, leaves, stem barks, or flowers) for medicinal purposes (3), served as the main sources of primary healthcare.

A systematic review of global healthcare systems brought to the fore a lack of equity in the treatment of many disease conditions worldwide. The World Health Organisation's (WHO) Commission on Social Determinants of Health (CSDH) in 2008, recognized that access to and utilization of healthcare were vital to good health. It therefore called for healthcare systems to be based on principles of disease prevention, equity, and health promotion with UHC, which could be achieved by focusing on primary healthcare, irrespective of individuals' ability to pay (4).

The concept of UHC was therefore developed to address the disparities in global healthcare delivery systems. It aims to ensure that people have access to appropriate health services whenever, wherever needed, and at affordable costs (5). Moreover, the WHO emphasized the important role of appropriate public health policies as a governmental responsibility in attaining UHC (5). UHC is grounded in the principles of the 1948 WHO Constitution (6), which affirms health as a fundamental human right and commits to ensuring the highest achievable standard of health for all (5). It is estimated that the majority of those residing in developing nations depend mainly upon traditional medicines for primary healthcare, with plant extracts or their active components constituting a substantial proportion. However, the onset of colonialism marked a significant shift in the history of this ancient culture, with the decline of traditional medical practices (7).

Given the extensive worldwide dependence on herbal medicines for primary healthcare, particularly in sub-Saharan African countries such as Ghana, their proper development could significantly advance the goals of UHC. The Ghanaian herbal medicine industry offers a wide range of products, many of which have demonstrated efficacy in managing both communicable and non-communicable diseases (8-10). However, a significant challenge arises from many products being marketed as panaceas, often based solely on traditional knowledge with little scientific evaluation of their safety, quality, and efficacy. To address this challenge, the Ghana Government established the Centre for Plant Medicine

Research (CPMR) situated in Mampong-Akuapem in 1975, to facilitate research and developmental efforts in herbal medicine.

In the past two decades, African countries have enjoyed an enabling political commitment to the promotion of traditional medicine. At the global level, the WHO developed the Traditional Medicine Strategy for 2014–2023, which aimed to support member states to develop effective policies as well as implementable activities that could facilitate the role of traditional medicine (TM) in promoting good health in the populations (11).

The African Summit of Heads of States and Governments at the continental level then agreed that the periods from 2001-2010 and 2011-2020 be designated as the 1st and 2nd decades of African traditional medicine, and they thus approved their corresponding plans of action for implementation during these periods (12).

At the Regional level, Africa developed the premier WHO Regional Strategy towards promoting the use of TM in the health systems of the Region for 2001-2010. The Strategy aimed to optimize the use of TM to improve healthcare in the African Region (13). In addition, the WHO also developed an Updated Strategy to enhance the Role of TM in Health Systems for the African Region for the period 2013-2023. This was also aimed to contribute to better health outcomes by consolidating and optimizing the role of TM in the prevailing healthcare systems (14). The WHO strategies on the implementation of the Decade of African traditional medicine also had Research and Development (R&D) as one of the priority intervention areas. In implementing this, the organization developed guidelines for conducting clinical studies of TM within the African Region with protocols for clinical trials for the treatment of malaria, diabetes, sickle-cell disease, HIV/AIDS, and high blood pressure (15), for whose treatment, R&D needed to be accelerated. Guidelines to aid registration of such TMs in this region was also developed (15). Also, during the COVID-19 pandemic, the WHO Regional Office developed a master and generic protocol for phase three multicenter clinical trials of herbal medicines for COVID-19 management, which was for adaptation to the various country situations (16).

At the country level, research institutes and national regulatory authorities, including Ghana, adapted the research and registration guidelines to their national situations. As of 2022, there were 34 research institutes dedicated to traditional medicines as compared to 18 in 2000. There were over 100 HMs that had been registered by the national regulators from 14 different countries as compared to 18 in the year 2000, and more than 45, which were by then included in the essential medicines lists of member countries (17).

Ghana has made giant strides in HMs' development. This article, therefore, highlights collaborative efforts between the CPMR and various research institutions and scientists in the development of five herbal preparations for managing malaria, diabetes, hypertension, and benign prostatic hyperplasia (BPH), namely Mibima decoction, Bridelia tea, Diodia decoction, Lippia tea, and URO 500 capsules, respectively. In addition, this shows the growing political commitment to the promotion and development of TM at global, continental, regional, and national levels (especially in Ghana) in the past two decades.

**Development of Herbal Medicines (HMs) in Ghana**

The rich history of HMs' utilization in Africa has been preserved by oral tradition for generations (18). In Ghana, plant-derived medicines contribute immensely to promoting good health and wellness. CPMR was therefore set up in 1975 by the Ghana Government. This was shortly after independence, to coordinate research activities on Ghanaian medicinal plants. A decade later, it became the first Centre for collaborative research in TM in Africa, accredited by WHO (19). This initiative was inspired by the vision of one Dr. Oku Ampofo, who was driven by personal experiences with the healing benefits of HMs, and familial reports also. He therefore became an advocate for herbalism from a young age (20).

Dr Oku Ampofo's journey began after graduating as a medical doctor from the Royal College in the United Kingdom in 1939. Following a short course at the Liverpool School of Tropical Medicine, he returned to his homeland, Ghana, then known as the Gold Coast, in 1940, where he sought employment with the Colonial Administration of Health. However, he was denied employment as a medical doctor due to the prevailing agitation for independence by the influential indigenes during that period. Driven by a strong desire to help in the health care of his compatriots, he established a private clinic in his hometown of Mampong-Akuapem under challenging circumstances. He named the clinic "Obikyere", an Akan language term meaning "someone teaches". This name was inspired by the adage, "obi nnim a, obi kyere", which translates to "if someone lacks knowledge, it takes another person to teach him" (21). Dr. Oku Ampofo embraced this belief wholeheartedly, recognizing that no individual has a monopoly over knowledge. Without access to allopathic medicines, Dr. Oku Ampofo decided to consult and collaborate with renowned traditional health practitioners to obtain herbal medicines for his patients. Through this collaboration, he documented over 300 plants, successfully treating diseases such as malaria, asthma, chickenpox, pneumonia, anaemia, arthritis, and others. Encouraged by these promising results, Dr. Oku Ampofo embarked on extensive journeys across Ghana to engage with traditional health practitioners, seeking to learn from their wealth of knowledge and, crucially, to document the useful medicinal plants they employed. Furthermore, he formed partnerships with numerous research institutions and universities in Ghana and abroad that shared interests in exploring the potential benefits of HMs. The culmination of Dr. Oku Ampofo's vision and dedication manifested into the establishment of the CPMR in the year 1975 at Mampong-Akuapem a few years after Ghana's independence (22). Through his efforts, the Centre has created a wealth of invaluable information on hundreds of medicinal plants, including their use and methods of preparation. Among these botanical treasures, *Cryptolepis sanguinolenta,* known as Mibima, emerged for its antimalarial properties, while *Croton membranaceus* formulated as URO 500, was found to be useful in managing benign prostatic hyperplasia (BPH).

With a mission to gain the highest recognition for research and development of herbal products that meet the exacting needs of both patients and industry, through innovative scientific research and productive partnerships (22), CPMR remains committed to strengthening existing scientific partnerships with both national and international organizations, while actively seeking avenues to establish new collaborations in advancing herbal medicine research.

## 2. Materials and Methods

This reviews well-known historical narratives, research articles, and data published by CPMR and other collaborators. It covers the origins of CPMR and the development of key medicines in response to prevalent public health challenges (malaria, benign prostatic hyperplasia, hypertension, and diabetes) in Ghana. The review outlines ethnobotanical data and phytochemical properties of the indigenous medicinal plants *Cryptolepis sanguinolenta*, *Croton membranaceus*, *Lippia multiflora*, *Hexasepalum scanden,* and *Bridelia ferruginea*. These plants were developed into five popular herbal products: Mibima, URO 500, Lippia tea, Diodia, and Bridelia tea. This article, therefore, summarizes the preclinical safety and efficacy assessments conducted to evaluate these herbal products for treating malaria, benign prostatic hyperplasia, hypertension, and diabetes. All reported studies at the CPMR were approved by the Ethical Committee of the Centre, while the animal studies were approved by the Department of Pharmacology and Toxicology Ethical Review Committee.

## 3. Results

### 3.1 Mibima, Herbal Preparation for the Treatment of Uncomplicated Malaria

#### 3.1.1 Malaria Prevalence, Mortality, and Treatment Options

Malaria is a result of a protozoan parasitic infection transmitted by bites from female anopheles mosquitoes harboring the *Plasmodium* parasite. The five *Plasmodium* parasite species that cause malaria in human beings are namely *P. falciparum, P. malariae, P. vivax, P. knowlesi*, and *P. ovale,* with *P. falciparum* accounting for more than 90 % of cases (23). *P. falciparum* is predominantly the cause of the severe and potentially fatal forms of most malaria cases (24). In 2023, the WHO reported that malaria represents Africa's leading public health challenge, posing a major barrier to socioeconomic development in endemic regions. Africa accounts for 94% of the global malaria burden, with 580,000 deaths attributed to malaria in 2022 (25). Malaria is hyper-endemic in Ghana (26). Despite efforts to combat malaria, it remains a pressing public health concern in Ghana. In 2021, an estimated 5.4 million cases were reported, resulting in 12,557 deaths. While Ghana had previously met targets set by the Global Technical Strategy for Malaria in 2015-2020, the incidence rate failed to decline sufficiently in 2021 (27).

In the face of the increasing burden of malaria on healthcare systems globally, which was compounded by increasing resistance of the parasite to existing anti-malarials, the WHO recommended artemisinin-based combination therapy (28). Having realized the high cost of procuring artemisinin-based therapies for malaria treatment, the CPMR intensified efforts to develop a potent herbal alternative that would be readily accessible and affordable. Drawing on collaborative efforts, the CPMR formulated Mibima, a decoction derived from the root of *C. sanguinolenta (LindL.)* Schltr. (Figure 1) for the treatment of malaria (29).

**Figure 1:** *C. sanguinolenta*

#### 3.1.2 Collaborative Efforts in Developing Mibima

##### *3.1.2.1 Ethnobotanical description of C. sanguinolenta*

Oku Ampofo, in his interaction with several traditional health practitioners, observed the common use of *C. sanguinolenta* among the people of the Akuapem area in Ghana for the treatment of fever. The plant is a climbing, twining, perennial with thin stems 6–7 m high over scrub vegetation of the Soudanian savanna, covering Senegal to the north and Nigeria to the south. It is also found in central, southern, and eastern Africa (30). The fresh sap is orange-red and resinous, which dries to form a red wax. The ethnomorphology of the plant has been extensively described by Appiah (2009) and Osafo *et. al.* (2017). *C. sanguinolenta* is widely used in traditional herbal medicine across West Africa (9, 31), particularly for treating jaundice and hepatitis. The root is commonly used in Ghana to treat malaria, and it is also believed to be effective in the treatment of upper respiratory and urinary tract infections (9). The plant is also utilized mainly to manage fever and urinary tract infections in Nigeria (32).

##### *3.1.2.2 Chemistry of C. sanguinolenta*

Studies carried out to characterize the chemical composition of *C. sanguinolenta* have consistently identified alkaloids as its primary constituents, particularly analogs of indole [3,2-b] quinoline (33). Cryptolepine is the major alkaloidal compound with 12 other related alkaloids that have been isolated and characterized (34). To corroborate these results,

researchers at the CPMR carried out several studies. For instance, studies conducted by Mills-Robertson *et al*. (2012) detected reducing sugars, anthocyanosides, alkaloids, and polyuronides in the ethanol extract, as well as the water and chloroform fractions. The aqueous fraction additionally contained triterpenes (35). In an earlier study, Ameyaw and Duker-Eshun (2009), also working at the CPMR, quantified the alkaloidal content of the plant (36).

#### *3.1.2.3 Pre-clinical Anti-malaria Studies of C. sanguinolenta*

Several pre-clinical studies proved that *C. sanguinolenta* had potent anti-malarial activity. Paulo *et. al.* (2000) demonstrated the antiplasmodial activities of the root as well as leaf extracts of *C. sanguinolenta* against multidrug-resistant KI strain and chloroquine-sensitive T996 clone of *P. falciparum* in *in vitro* studies. All the extracts inhibited at least 90% of the parasite's growth, at concentrations lower than 23$\mu$g/mL. The root extracts exhibited higher activity compared to that of the leaf (37). During a search for an herbal anti-malarial remedy, CPMR carried out studies on *C. sanguinolenta* extracts. This showed that the root extracts have potent antiplasmodial activity, with significant promise for further development into a drug (38).

#### *3.1.2.4 Pre-clinical Toxicity Studies* of *C. sanguinolenta*

In 2002, Ansah, a collaborator of the CPMR, and his colleagues demonstrated that *C. sanguinolenta* extracts may have a deleterious effect on the marrow of the bone, shown by rise in granulocyte and platelet numbers, after 2 weeks of drug administration (39). This result contrasted with other published findings. For instance, a study done by Ajayi *et. al.* (2012) demonstrated that although administration of 2000 mg/kg extracts of *C. sanguinolenta* resulted in minimal enlargement of liver and kidney, biochemical and histological analyses largely remained unchanged, as no changes were detected in renal and hepatobiliary systems, and no evidence of toxicological insults to these organs upon histopathological examination was found (40).

The acute and sub-acute oral toxicological assessment of the aqueous root extract of *C. sanguinolenta* in Sprague Dawley rats administered at 250 – 3000 mg/kg, daily for three days and at 500 - 2000 mg/kg for fourteen days, respectively, produced no physiological as well as behavioral alterations. However, a dose-dependent rise in the platelet count was seen in animals treated in the subacute toxicity studies with 2000 mg/kg. Granulocyte number also increased with increase in dose from 0.77 ± 0.15 to 3.70 ± 0.20 in this same group, thus indicating possible induction of inflammation. Central nervous system (CNS) toxicity and marginal enlargement of the kidney and liver were evident with the 2000 mg/kg same-treated group. These outcomes did not correlate with the histopathological and biochemical studies since no pathological alterations were seen in the renal or hepato-biliary systems. This suggests that the aqueous root extract of at less than 500 mg/kg could be safe generally however, care must be taken with doses higher than 500 mg/kg since these could potentially induce inflammation, thrombocytosis, and CNS toxicity (41). Studies also conducted in the Department of Pharmacology and Toxicology at the CPMR proved that a single administration of *C. sanguinolenta* extracts orally at a dosage of 5000 mg/kg to mice and rats did not result in mortality. Moreover, observation of the animals over 14 d showed signs of no toxicity in terms of locomotion, pilo-erection, lachrymatory, or respiratory activities (CPMR, Mampong, Ghana).

#### *3.1.3 The Product: Mibima*

Drawing from the accrued body of research, including those mentioned above, the CPMR developed an anti-malarial named Mibima, which is a decoction from *C. sanguinolenta* roots (Figure 2). For treatment of malaria, 30 mL of Mibima is recommended to be taken three times a day (CPMR Mampong, Ghana, Product Literature on Mibima).

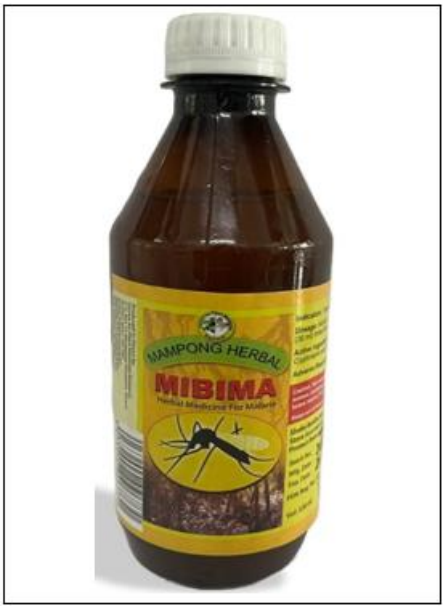


**Figure 2:** Mibima product manufactured by CPMR

#### *3.1.4 Clinical Data Collection*

In an open study on *C. sanguinolenta* root extract for clinical efficacy in the treatment of uncomplicated acute malaria caused by *P. falciparum* in a Ghanaian population, 50% of the recruited patients had their blood cleared of parasitemia within 72 hr, and complete clearance was observed in all patients by Day 7. This represented an average parasite clearance time of 82.3 hr and a fever clearance period of 24.5 hr. Symptoms of chills, pyrexia, vomiting, and nausea were resolved by Day 3 (38).

### 3.2 URO 500, Herbal Medicine for the Management of Benign Prostatic Hyperplasia (BPH)

#### *3.2.1 Etiology, Prevalence, and Racial Distribution of BPH*

An imbalance of androgen and estrogen levels biochemically, together with the overproduction of growth factors, all play a crucial role in the progression of BPH (42). Dihydrotestosterone (DHT), a testosterone metabolite that is also a crucial facilitator of prostate growth, is also synthesized in the prostate through the action of 5α-reductase. This enzyme is lipophilic and located on intracellular membranes (43). Oxidative stress is also a key factor in BPH development. It involves an imbalance in the production and elimination of free radicals, which can damage DNA, mRNA, and proteins, which are important components of tissues (44).

BPH typically affects older men, especially those after age 40, and arises from a gradual overgrowth of the prostate gland.

BPH is better defined as a non-cancerous enlargement of the prostate, marked by the excessive growth of the epithelial and stromal cells into nodules or distinct masses (45). Clinically, this leads to health challenges that range from mild to severe, thus impacting the quality of life in the affected (46).

Also, another condition that presents with similar risk factors and presentation is prostate cancer (47). Prostate cancer is a prevalent and expensive disease in Sub-Saharan Africa (48), with associated high prevalence and death rates. It is the most diagnosed solid tumor, second only to basal cell carcinoma. It was expected to claim about 34,700 lives in the United States of America in 2023 (49). Worldwide, an estimated 8 million new cases of BPH are added annually to the existing pool of sufferers. There is sufficient evidence to suggest that race is a risk factor in both the pathology and clinical manifestation of the condition. For instance, research shows that moderate to severe lower urinary tract symptoms (LUTS) are more prevalent in individuals of African descent compared to Caucasians, while the size of the prostate transitional zone tends to be greater in blacks than whites (50). However, there is ample evidence to suggest that differences in risk of LUTS are closely related to socioeconomic factors such as earnings and insurance rather than to race (51).

#### *3.2.2 Adverse Effects of Current BPH Treatment*

The 5α-reductase inhibitor, finasteride, prevents the growth of BPH by decreasing the release of DHT, a key factor in BPH development. Other medicines employed include α1-adrenergic receptor antagonists, which are preferable for the management of complications of BPH, such as LUTS. These medications work by relaxing smooth muscle both in the neck of the bladder and also the prostate (52). However, current recommended medications for BPH can elicit adverse effects, including severe myopathy, because of their similarities in structure to steroidal hormones. Other adverse effects of these drugs are erectile or ejaculatory dysfunctions and reduced sexual drive. As a result, herbal medicine has gained popularity as an alternative therapy for the management of BPH. Herbal remedies are often preferred due to the belief that they have fewer or no adverse effects (53).

### *3.2.3* Collaborative Efforts in Developing URO 500

#### *3.2.3.1 Ethnobotanical description of C. membranaceus* Mull. Arg.

*C. membranaceus* (Figure 3) is a tropical plant native to West Africa, particularly Ghana, Nigeria, and Niger (54). It grows sparsely around hilly areas along large rivers, reaching 1-2 m tall (55). Its ethnomorphology has been well documented by several publications, and it includes use in the treatment of BPH (9, 10, 55, 56).

**Figure 3:** *C. membranaceus*

Oku Ampofo, the originator of CPMR, observed that the ethanolic extract of *C. membranaceus* roots was effective in relieving BPH-associated urine difficulties. Since its inception, formulations of the roots have been given to patients suffering from BPH at the CPMR for over 30 years (9, 10). In a case study conducted at the CPMR, Dogbatsey in 2006 observed significant improvement from the administration of *C. membranaceus* preparation to a BPH patient aged 60 years. Within 30 days of treatment, the patient experienced improved urine flow, and over a period of three months, the weight of the patient's prostate gland decreased from 230g to 115g, representing a 50% reduction (10, 57).

#### *3.2.3.2 Chemistry of C. membranaceus*

In a collaborative study with CPMR, julocrotine was isolated from the root parts of *C. membranaceus* (58). The team further isolated N[N-(2-methyl butanoyl) glutaminoyl]-2-phenylethylamide and cis-terpene from the same part (10). In other studies, involving the CPMR and its partners, various other compounds were isolated from this same plant part, including coumarins, alkaloids, phytosterols, and diterpenoids. Furthermore, larixol, phytosterols (campesterol, stigmasterol, and β-sitosterol), and fatty acids were isolated from the stem, and the leaf extract yielded phytosterols (10, 55, 58).

#### *3.2.3.3 Pharmacological Activities of C. membranaceus*

In a study to establish the 5α-reductase inhibitory activity of the plant (55), naive male rats were allowed to ingest testosterone and subsequently orally administered with the aqueous extract of *C. membranaceus* (root, leaf, or stem separately), or with finasteride as the treated control for six days. Upon termination, the animals were sacrificed, and the prostates excised and weighed. The roots and stems extract significantly inhibited the testosterone-induced enlargement of the prostate by 19%, which was comparable to the results of the positive control, while the leaf extract did not affect prostate growth. In the same study, julocrotine, a compound known to inhibit 5α-reductase, was extracted from the root (55). In another study led by Aboagye *et. al.,* 2000, it was also confirmed that the ethanolic extract of *C. membranaceus* and its isolate julocrotine demonstrated 5α-reductase inhibitory activities (58).

Investigations on the cytotoxic potential of the plant revealed that an isolate of the methanol root extract of *C.*

*membranaceus* root had cytotoxic effects on DLD1 and also MCF-7 cells (59). The effect on these cancerous cells indicates possible usefulness in prostate cancer also (60). Similarly, a novel furano-clerodane diterpenoid named crotomembranafuran, which was obtained from the roots, moderately inhibited human prostate cancer (PC-3) cells, but was inactive against MCF-7 and DLD-1. Several studies have also shown that scopoletin, a constituent of *C. membranaceus,* inhibits the proliferation of HL-60 and PC-3 (prostate cancer) cells by inducing apoptosis (61-63).

#### *3.2.3.4 Antioxidant Activity of C. membranaceus*

In a study carried out at the CPMR, the methanolic crude extracts of *C. membranaceus* root, leaf, and stem were shown to possess DPPH radical scavenging activity, which was concentration-dependent and significant (10). Scopoletin, an isolate of *C. membranaceus*, also scavenged for superoxide anion concentration-dependently in a xanthine/xanthine oxidase system (64). Scopoletin is also known to prevent hepatic lipid peroxidation and enhance catalase and superoxide dismutase activity *in vivo* (65). The findings suggest that scopoletin has the potential for preventing superoxide anion-induced damage, as reported by some studies (66) thus could be useful as a prevention against BPH.

#### *3.2.3.5 Pre-clinical Toxicity Studies of C. membranaceus*

Pre-clinical studies showed that the $LD_{50}$ of the aqueous and ethanolic freeze-dried extracts of all roots, stems, and leaves of *C. membranaceus* was higher than 5000 mg/Kg body weight of rats and mice(67).

When root extracts of *C. membranaceous* were prepared by 96% ethanol extraction, lyophilized, re-extracted with deionized water, freeze-dried, and finally administered one time to male Sprague–Dawley rats of weights 180–200 g at a low dose, and high dose of 1500 and 3000 mg/kg body weight respectively for 14 d, the conclusions reached after considering all the parameters was that oral intake of *C. membranaceous* did not produce general acute toxicity. However, there was a reduction in creatinine kinase levels, which needs further investigation (68). This went a long way to support results from studies by CPMR that claimed that *C. membranaceous* was non-toxic at the dose administered for BPH.

Acute oral toxicological investigations of *C. membranaceus* aqueous stem extract was also reported not to cause mortality or induce clinical indications of toxicity during 14 days up to a maximum dose of 5000 mg/kg of the extract in rats. The study concluded that the extract was relatively safe, having an $LD_{50}$ greater than 5000 mg/kg. However, the leaves must be used with caution when substituting them for the roots (56).

### *3.2.4 The Product URO 500*

From the research described above, which was conducted for nearly two decades, the CPMR developed URO 500 (Figure 4), a capsule derived from the ethanol extracts of the roots and stems of the plant. Two capsules of URO 500 are prescribed three times daily (CPMR Mampong, Ghana, Product Literature on URO 500).

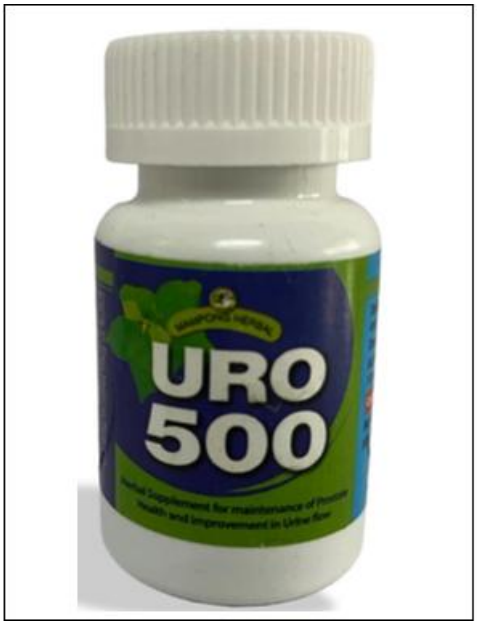


**Figure 4:** URO 500 capsules manufactured by CPMR

#### *3.2.4.1 Clinical Study and Possible Mechanism of Action of URO 500*

In a study that utilized the freeze-dried ethanolic root extract of *C. membranaceus* for BPH management in 33 patients for a period of 3 months at 20 mg three times daily orally, it was shown that the product significantly reduces prostate volume, PSA concentrations, and also enhances the quality of patients' lives with BPH (69).

A review of the chemical constituents, pre-clinical studies, as well as clinical observation studies following URO 500 treatment suggests that the mechanism of action could be by various means: 5α-reductase inhibition, α-adrenergic receptor antagonism, antioxidant, and anti-atherogenic activity. The 5α-reductase inhibition could be through the phytoconstituent julocrotine (55). The action of 5α-reductase inhibition is to decrease tissue and blood DHT levels with eventual reduction in prostate dimensions (70).

Adrenergic receptor antagonists (alpha blockers) could also alleviate symptoms of BPH within 2 weeks in comparison to 5α-reductase inhibitors, which may require longer than 3 months to manifest effects. Alpha blockers also function by inhibiting the noradrenaline transmission, thus relaxing the smooth muscles of both the bladder neck and the prostate capsule. This helps to relieve dysuria and rapidly improves BPH symptoms. They are also reported to significantly enhance spontaneous urination in patients suffering from acute urine retention (71). Scopoletin, a phytochemical constituent of URO 500, is known to have smooth muscle relaxant activity and blocks peripheral adrenergic transmissions (72, 73). Thus, the swift effect of URO 500 in alleviating urinary blockade in patients with BPH may likely be a result of its potential effect as a smooth muscle relaxant.

#### *3.2.4.2 Antioxidant and Anti-atherogenic Actions of URO 500*

Oxidative stress is also a major factor responsible for the progression of BPH (74). The nucleoside, 8-OH dG, which is an indication of oxidative stress, is markedly raised during BPH, and notably correlates with prostate weight (75). URO

500, and its constituent scopoletin (54) are known to have significant antioxidant activities (64). Preclinical studies have shown that URO 500 has anti-atherosclerotic effects, effectively preventing the accumulation of fatty acid deposits within the arteries (76). Asare *et. al*, 2015 established that *C. membranaceous* also has beneficial effects on cardiovascular markers in animal models by causing hypotriglyceridaemic effects with high-density lipoproteins and low-density lipoproteins showing significant rises ($p = 0.013$) and declines ($p = 0.003$), respectively. Basal glucose level was also decreased in metformin ($p = 0.000$), and *C. membranaceous* ($p = 0.006$) groups significantly after 3 h (77).

### 3.3 Lippia Tea and Diodia, Herbal Medicines for the Management of Hypertension

#### 3.3.1 Etiology and prevalence of hypertension

The WHO defines arterial hypertension, or elevated blood pressure (BP), as a disease in which blood vessels have persistently elevated pressure. Blood pressure comprises two components: systolic pressure (the peak when the heart contracts) and diastolic pressure (the lowest when the heart rests) (78). High BP is a multifactorial, insidious and chronic syndrome characterized by persistent systolic arterial pressure (SAP), which is consistently higher than 140 mmHg alone or together with a diastolic blood pressure (DBP) also persistently higher than 90 mmHg (79). Hypertension is also a hemodynamic disorder as a result of a systemic increase in peripheral vascular resistance, which, if not detected and treated early, results in renal failure, myocardial infarction, strokes, and finally death (80). Elevated BP is an escalating global health challenge that is associated with many underlying pathophysiological factors, such as endothelial dysfunction, metabolic syndrome, oxidative stress, ventricular hypertrophy, a procoagulant state, inflammation, and a hereditary predisposition to cardiovascular accidents (81). The renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system play a crucial role in the regulation of arterial BP. Three main factors determine the BP, namely, vascular tone, kidney sodium excretion, and its impact on plasma and total body volume, and cardiac function (82).

Hypertension is a global epidemic affecting nearly a billion individuals, with two-thirds of these living in developing countries. It is a primary cause of premature mortality worldwide and presents a growing health challenge (83). WHO predicts that cardiovascular diseases will claim 23.6 million lives by 2030, with hypertension being one of the leading causes of disability and death, particularly through stroke, heart attack, and kidney failure in the United States (84). Hypertension is becoming an increasingly prevalent health challenge because of increasing life expectancy and the increase of contributing factors such as physical inactivity, obesity, and unhealthy diets (85).

#### 3.3.2 Current Pharmacological Management and Associated Challenges of Hypertension

Management of hypertension involves both pharmacological and non-pharmacological interventions (8). Despite the current existence of various groups of BP drugs, the disease is generally inadequately controlled. The recommended anti-hypertensive drugs are associated with significant adverse effects. For instance, certain diuretics may induce hypokalemia and hypercalcemia (86). Atenolol, a commonly prescribed medication, has been linked with depression and impotence, while combination therapy involving vasodilators and beta-blockers has been linked to heart blockade, severe bradycardia, or pump dysfunction (86). The adverse effects of some conventional BP drugs, coupled with factors such as affordability and accessibility, have necessitated the need for more suitable treatment options, which include herbal medicines (8).

#### 3.3.3 Collaborative Efforts in Developing Lippia tea and Diodia

The CPMR, through collaborative research, developed two herbal products: Diodia decoction, a diuretic, and Lippia Tea, an anti-hypertensive from *Diodia scandens* (currently *Hexasepalum scandens),* and *Lippia multiflora,* respectively (Figures 5 and 6).

##### 3.3.3.1 *Ethnobotanical description of Lippia multiflora*

*L. multiflora* is a perennial shrub that is a woody, stout, and aromatic plant mostly found in tropical Africa, Central, and South American nations. It grows across varying ecological ranges within West Africa, and to a height of about 2.7 to about 4.0 m, having big oblong to lanceolate bluish-green coloured leaves (36, 87). Ameyaw (2009) (88) and Folashade and Omoregie (2012)(89) have comprehensively described the ethno-morphology of the plant. Rural dwellers in West African communities drink the boiled leaves as tea in the evening, especially after a strenuous day's work for relaxation and to improve sleep (90). Conversely, in the urban centers, the tea is often taken in the mornings to reduce stress and promote relaxation for the day (91). *L. multiflora* is used traditionally as a tea substitute and mouth disinfectant (90). Across West Africa, tea-like infusions of *L. multiflora* are used as traditional home remedies for various ailments, including malaria fever, hypertension, stress, venereal diseases, constipation, and conjunctivitis (92-94). The leaves that have been dried in the sun are taken as an infused tea sweetened with honey or sugar for managing stomach disorders in Ghana. (92-94).

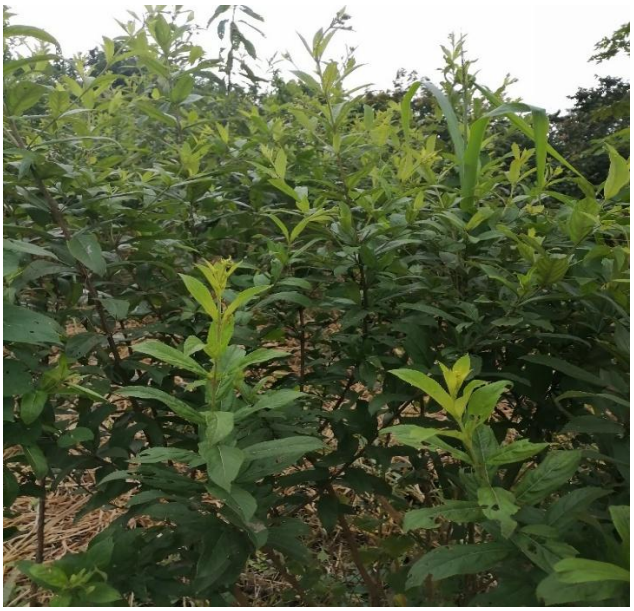

**Figure 5:** *L. Multiflora*

#### 3.3.3.2 Chemistry of *L. multiflora*

This plant contains polyuronides, phenolic compounds, reducing sugars, flavonoids, anthracenosides, saponins, phytosterols, and alkaloids (95). The main phytoconstituents of the leaves are their essential oils, which have been reported to be more than 2% of the weight of dried material (96). The main compounds of the infusion of *L. multiflora* herbal were also identified as phenylethanoid glycosides (PhGs), isoverbascoside, verbascoside, isonuomioside A, nuomioside A, and luteolin-7-O-glucuronide, with verbascoside being identified as the major PhG (97). In studies of the essential oils of this plant in Burkina Faso and the Ivory Coast, it is mainly composed of germacrene D, caryophyllene, humulene, γ-terpinene, and P-cymene (98). In Ghana, the essential oils of the plant exhibit remarkable diversity in both color and chemical composition, with more than 35 varieties of chemotypes identified. Monoterpenoid-rich chemotypes, containing high levels of thymol and thymol derivatives, carvacrol, ρ-cymene, as well as sesquiterpenoid-rich chemotypes, ocimenone isomers, and ipsdienone were among the most dominant (89).

#### 3.3.3.3 Pharmacology *L. multiflora*

Kanco *et al* (2004) found that the leaves of *L. multiflora* possessed potent hypotensive, fatigue-relieving, and diuretic activities. Many studies have corroborated the folkloric use of *L. multiflora* as an anti-hypertensive and muscle relaxer (99-104). In studying the effects of the leaf extracts on TXA2 biosynthesis, it was found that the extracts prevented the synthesis of TXA2 in a dose-dependent manner. The team concluded that the observed anti-thromboxane synthetase activity may serve as a major contributor to its anti-hypertensive mechanism of action (104).

#### 3.3.3.4 Pre-clinical Toxicity Studies of *L. multiflora*

Very few studies have documented the toxicity of *L. multiflora*; however, Folashade and Omoregie (2012) reported a high level of safety, with an $LD_{50}$ of 3000 mg/kg body weight for the leaf extract (89). Researchers at CPMR also showed that a one-time dose administration of 5000 mg/kg of the leaf extract to rats and mice did not result in mortality. In chronic toxicity studies, daily administration of aqueous leaf extracts (100-400 mg/kg) for six months did not induce any adverse effects upon biochemical, hematological, and histopathological (lungs, liver, kidney, and heart) analyses (CPMR, Mampong, Ghana).

### 3.3.4 *Ethnobotanical description of Hexasepalum scandens*

*Hexasepalum scandens* (previously *Diodia scandens*) (Sw.) J.H. Kirkbr. & Delprete, belonging to the family Rubiaceae, is known as “apraprayam” in the Akan language. It is a straggling herb with slender stems that grows from 1-2 m with scabrid leaves, and whitish flowers (105). It grows in the wet tropical biomes and is common in thickets. It is distributed natively in the Dominican Republic and Haiti, but was introduced to Africa specifically through Benin, Cameroon, Ghana, Gabon, and Togo (106). Traditionally, it has antifungal, anti-inflammatory, cough, hypertension, convulsion, oedema, asthma, anthelmintic, diuretic, hemostatic, and wound healing (105, 106). It is used to treat hypertension, malaria, diabetes mellitus, and dermatological infections (107).

**Figure 6:** *H. scandens*

### 3.3.5 Chemistry of *H. scandens*

Qualitatively, the phytochemicals identified in *H. scandens* are ethereal oils, polyphenols (flavonoids), phenols, phytate, cardiac glycosides, phytin phosphorus, steroidals, and oxalates (108-112). The presence of alkaloids at 10.53%, tannin at 2.27 mg/100 g, saponin at 6.58%, and phytin phosphorus at 1.80 mg/g, was revealed in a quantitative analysis (113). Upon spectroscopic analysis, the n-hexane-ethyl acetate fraction contained *cis,* cis-9,12-octadecadienoic acid, and *cis,cis*-9,12-octadecadienoate (109).

### 3.3.6 Pharmacology of *H. scandens*

The water extract of the leaves of *H. scandens* exhibited both anti-inflammatory and analgesic activities in the paw edema test in rats, and the extract inhibited some inflammatory mediators (114). The petroleum extract of the plant exhibited anti-ulcerative activity in several studies (108, 115, 116). Both ethanolic and aqueous leaf extracts showed potent anti-oxidative and anti-microbial activities (111, 117). The methanolic leaf extract is reported to have anti-plasmodial activity at IC50 below 5 µg/mL (118). The n-hexane leaf extract of the plant reportedly exhibited potential anti-diabetic activity in alloxan-induced diabetic murine model (119).

### 3.3.7 Preclinical toxicity studies *H. scandens*

A study led by Asiedu-Larbi *et. al*. 2020 to examine the pre-clinical toxicity of the product Diodia, which is an aqueous extract of the leaves. The study was performed in accordance with guidelines from OECD with minor modifications, using adult Sprague-Dawley rats. After observation of the test animals for 14 days, the $LD_{50}$ was higher than 5000 mg/kg (110). Extract doses at 40, 400, and 800 mg/kg administered 24-hourly over 6 months, with periodic observation, did not result in mortality, nor were there any toxicity in the locomotion, pilo-erection, lachrymatory, and respiratory activities of the subjects. Safety parameters (biochemical and

hematological) as well as histopathological (lungs, liver, kidney and heart) analyses were normal (110).

### 3.3.8 The Products Lippia Tea and Diodia

Based on the above-mentioned studies, the CPMR developed Lippia Tea from the dried foliage of *L. multiflora* for the management of high BP and as a stress relief. For the management of BP, Lippia Tea is jointly administered with a decoction of Diodia, a diuretic prepared from *H. scandens* (Figures 7 and 8). Two bags of Lippia tea are placed in 250 mL of hot boiled water and allowed to cool, and taken twice daily, while 30 mL of Mist Diodia is recommended to be taken three times a day (CPMR Mampong, Ghana, Product Literature on Lippia and Diodia).

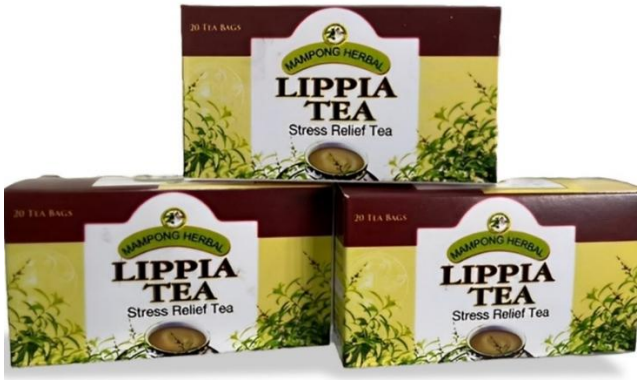


**Figure 7:** Lippia Tea manufactured by CPMR

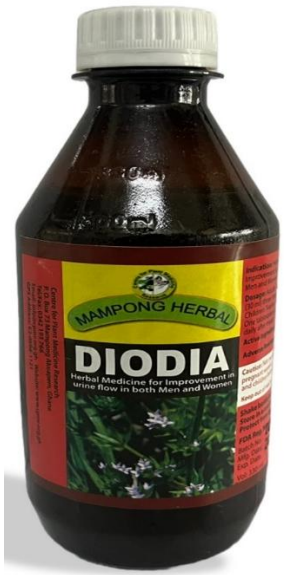


**Figure 8:** Diodia manufactured by CPMR

### 3.3.9 Clinical Data on Lippia Tea

In an observational clinical study on Lippia tea conducted by CPMR to assess the safety as well as the efficacy of the tea in managing hypertension, 28 hypertensive patients visiting the outpatient clinic of CPMR were taught on how to prepare tea by boiling 30 g of the plant material in 250 mL of water for 4 minutes. The tea was filtered and drunk twice daily for 4 weeks. The BP showed a significant drop in both systolic and diastolic blood pressure over the period, with a difference of 11.6 mmHg in mean SBP, while the mean DBP also decreased by 6.43 mmHg. It was then concluded that aqueous extract of the leaves of the plant held promise as an anti-hypertensive (120). These findings thus supported the folkloric use of *L. multiflora* as an antihypertensive (122).

### 3.3.10 Pre-Clinical Data Collection on Diodia

When the anti-hypertensive property of Diodia was assessed in two murine models, results indicated the preparation had significant anti-hypertensive activities ($p < 0.05$). The preparation increased urine output in all the animal models and significantly inhibited tissue chymase enzyme activity *in vitro* with $p < 0.05$. The antioxidative status and serum lipid profiles were also enhanced significantly ($p < 0.05$). The concentrations of potassium and sodium in the serum were markedly reduced ($p < 0.05$) with an associated corresponding increase in urine concentrations of these two ions. This study concluded that Mist Diodia had anti-hypertensive properties which could be mediated by the RAAS and diuresis. This system is responsible for regulating vascular resistance, electrolyte imbalance, and blood volume (121). Additionally, improvement in lipid levels of the serum could also be a possible mechanism for its action.

### 3.3.11 Clinical Data Collection on Mist Diodia

In a clinical study on Diodia (8), data obtained from folders of 265 patients who were diagnosed with hypertension and treated at the CPMR outpatient clinic from January to December 2015 were examined. Following the retrospective analysis, the results showed a drop in both systolic and diastolic blood pressures. Specifically, the average systolic pressure decreased to 163.9 mmHg from a baseline of 174 mmHg, while the average diastolic pressure decreased to 96.1 mmHg from 99.5 mmHg. Based on these findings, it was concluded that Diodia might be efficacious in managing hypertension (8).

## 3.4 Bridelia Tea, Herbal Medicines for the Management of Diabetes

### 3.4.1 Etiology and Epidemiology of Diabetes

Diabetes mellitus (DM) encompasses a variety of conditions marked by impaired insulin function; impaired insulin action or secretion, or both, resulting in hyperglycemia in affected individuals (123). Diabetes mellitus (DM) is classified into type I, type II, gestational, and other rarer forms (124). The development of DM arises as a complex interplay between environmental factors, genetics, and lifestyle choices (123, 125). For instance, type I diabetes involves the self-destruction of beta pancreatic cells (126). Type II diabetes, on the other hand, essentially emanates from insulin resistance and is usually accompanied by progressive beta cell dysfunction (125, 127). Type II diabetes is the most prevalent form of diabetes, and is responsible for 85 to 95% of cases in developed nations and an even higher number in developing countries (128). Gestational diabetes occurs only in pregnancy and disappears after delivery. It involves placental hormones (estrogen, cortisol, and human placental lactogen), produced during pregnancy, blocking the effect of insulin in peripheral tissues, leading to hyperglycemia. Clinically, diabetes manifests classic symptoms of elevated blood sugar, resulting in polyuria, polyphagia, and polydipsia, as well as chronic complications that affect several organs in the body. The effects include retinopathy, microvascular complications involving nephropathy and neuropathy, while macrovascular complications involve cardiovascular disease and peripheral

vascular disease (129). Current data also underscores the effect of oxidative stress, chronic inflammation, and dysfunction of adipose tissue in the onset of insulin resistance and beta cell impairment (123, 130).

Using data from 138 countries, it was estimated that the worldwide incidence of diabetes in the year 2019 was 9.3% and was to rise up to 10.2% by 2030 and to 10.9% by the year 2045. It was found that the prevalence of diabetes was higher in urban areas, with 10.8%, than in rural areas, with 7.2%. It was also higher in high-income countries (10.4%) than in lower-income countries (4.0%). They further estimated that 50.1% of people with diabetes were unaware of their status. They also found that the worldwide incidence of impaired glucose tolerance stood at 7.5% (accounting for 374 million people) in 2019. This was projected to reach 8.0% (representing 454 million people) by 2030 and 8.6% ( representing 548 million people) by the year 2045 (124).

### 3.4.2 Adverse Effects of Current Antidiabetics

The major groups of anti-diabetic medications are seven, these include: peroxisome proliferator-activated receptor (PPAR) agonist, aldose reductase inhibitors, protein tyrosine phosphatase 1B (PTP1B) inhibitors, α-glucosidase inhibitors, dipeptidyl peptidase IV (DPP-4) inhibitors, sodium-glucose co-transporter (SGLT) inhibitors (131), and G protein-coupled receptor (GPCR) agonists. Though these new agents have dramatically increased the number of options available to healthcare providers and patients, there are still problems with management, accessibility, affordability, and the rampant reported adverse effects. As a result, there is a need for safer, cheaper, and readily accessible alternative management options (132).

### 3.4.3 Collaborative Efforts in Developing Bridelia

#### 3.4.3.1 *Ethnobotanical Description of Bridelia ferruginea*

*B. ferruginea* Benth is a non-latex-producing, small scaly shrub or tree that grows up to about 15 m. It belongs to the family Euphorbiaceae (133). The plant bears spines and leaves that are simple, alternate, distichous or spiral, elliptic, and covered with fine hairs. The stem bark decoction is employed in the management of oedema, epilepsy, infant irritability, gastralgias, dysentery, anaemia, rheumatisms, diabetes, arthritis, intestinal and bladder disorders, boils, etc. (133).

#### 3.4.3.2 Chemistry of *Bridelia ferruginea*

Several compounds have been isolated from *B. ferruginea* roots, including lignans ([beta]-peltatin, [beta]-peltatin-5-O[beta]-D-glucopyranoside, deoxypodophyllotoxin, and 5'demethoxy-[beta]-peltatin-5O-[beta]-D-glucopyranoside (134). Flavonoids, including rutin, quercetin, quercetrin, myricitrin, myricetin-3-O-[beta]-glucoside, ferrugin (135), gallocatechin-(4'-O-7)-epigallocatechin gallocatechin-[4-O-7]-epigallocatechin, have been found in the bark. Rutin and quercetin are present in the leaves (136, 137).

#### 3.4.3.3 Pharmacology and Toxicity Studies of *Bridelia ferruginea*

The leaf extract of *B. ferruginea* has anti-diabetic activity in rats (133, 138). The plant is also recorded to have antimicrobial, anti-infective, anti-inflammatory, analgesic, antipyretic, natriuretic, diuretic, and antioxidant activities (133, 139). There are several reports on the safety of various extracts of *B. ferruginea*. The stem bark water extract, administered at 250 to 4000 mg/mL both intraperitoneally as well as orally in acute toxicity studies, demonstrated no marked signs of toxicity and no associated mortality, with the $LD_{50}$ estimated to be greater than 4000 mg/kg. The changes observed in animal weights and organ, hematological, and biological parameters were insignificant ($p \geq 0.05$). Levels of lipid peroxidation, however, increased markedly ($p < 0.05$) while sperm counts also reduced for the treated group (133).

The herbal-drug interaction during coadministration of the aqueous extract of *B. ferruginea* leaves was also investigated on the pharmacokinetic parameters of metformin (one of the first-line antihypertensives in Ghana), which was also reported to markedly affect ($p < 0.05$) all the parameters of metformin apart from the duration to reach the maximum concentration, which increased but insignificantly. The blood concentration, area under the curve, and half-life of metformin significantly decreased with coadministration of *B. ferruginea*, the clearance, absorption rate constant, volume of distribution, and elimination rate constant of metformin, however, rose markedly. Consequently, it was recommended in clinical practice that patients be advised on the implications of taking metformin concurrently with *B. ferruginea* (140).

### 3.4.4 The Product Bridelia Tea

Based on the above studies, the CPMR formulated Bridelia Tea from the leaves of *Bridelia ferruginea* for the management of diabetes (Figure 10). One cup of tea is prepared by putting four teaspoonfuls of Bridelia in 300 mL of boiling water, and left to boil for a further 3 minutes, and the mixture is cooled and decanted. The recommended dosage is one prepared cup of tea two times a day, thirty minutes before a meal (CPMR Mampong, Ghana, Product Literature on Bridelia Tea).

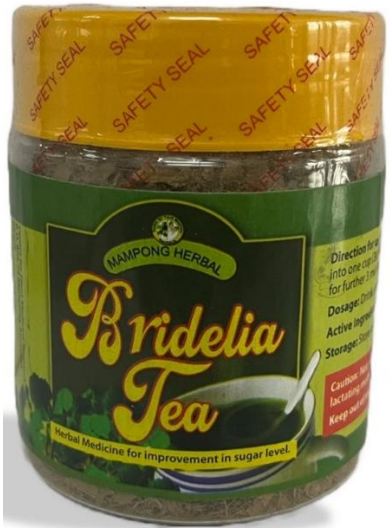


**Figure 10:** Bridelia Tea manufactured by CPMR

### 3.4.5 Clinical Data of *B. ferruginea*

In a retrospective clinical study conducted by CPMR, data were collected on the clinical efficacy of Bridelia. The study analyzed data from patients visiting the CPMR Outpatient Clinic over one year (May 2012 and May 2013). Twenty-two (22) patient records that met the criteria were selected and analysed. The tea caused an average reduction in Fasting

Blood Sugar (FBS) of 1.886 from a baseline of 13.55 (±4.79) units (141).

**Preclinical Studies of *B. ferruginea***

It is also reported in other spheres that *B. ferruginea* aqueous extract can decrease the diabetogenic effect of gestational diabetes in albino rats through a decrease in blood sugar level and enhanced glucose metabolism (142).

## 4. Conclusion

The article highlights the potential of herbal medicines as a viable option for managing serious prevailing illnesses, especially in resource-constrained countries such as Ghana. Consistent with efforts to advance UHC, there has been a growing political commitment to the development of traditional medicine at the continental, regional, and national levels in the past two decades. This political commitment has provided an enabling environment for countries in the African Region and Ghana to advance in the research and development of herbal medicines. This study shows the importance of involving traditional healthcare practitioners in local community engagement initiatives to develop their remedies into acceptable quality products, bearing in mind the safety and efficacy. The need to address the issues of intellectual property rights and equitable benefit sharing during such collaborations is important. Furthermore, the article summarizes the ethnopharmacological, phytochemical, safety, and clinical studies of the five herbal products derived from indigenous plants and offers valuable insights into Ghana's rich herbal medicine history and opportunities for advancing herbal medicine research and development in the country.

Moreover, ensuring the quality of these products, from identity and content to efficacy, is essential. Standardizing herbal formulations is important for maintaining consistency and reliability, and thereby ensuring patient safety. This is therefore under development. Above all, establishing partnerships for such research and development initiatives is emphasized to promote knowledge exchange and the adoption of best practices across borders.

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**Authors' Contributions**

KD, AA, OMJK: Conceptualized the study and co-wrote the manuscript. EOB, MB: Conducted the literature review and co-wrote the manuscript. KB: Critically reviewed the manuscript. KD, EOB: Edited the final manuscript, and all authors reviewed and approved the final version for publication.

**Competing Interests**

Authors of this manuscript confirm that the use of data generated at CPMR in this review does not influence the integrity or objectivity of the reviews presented herein.

**Abbreviations**

Blood Pressure (BP), Centre for Plant Medicine Research (CPMR), Commission on Social Determinants of Health (CSDH), Central Nervous System (CNS), Diastolic blood pressure (DBP), Dihydrotestosterone (DHT), Diabetes mellitus (DM), Deoxyribonucleic acid (DNA), Benign Prostatic Hyperplasia (BPH), Dipeptidyl peptidase IV (DPP-4), 2,2-Diphenyl-1-picrylhydrazyl (DPPH), G protein-coupled receptor (GPCR), High-performance liquid chromatography (HPLC), Lethal dose 50 (LD50), Lower urinary track symptoms (LUTS), Messenger RNA (mRNA), Organization for Economic Cooperation and Development (OECD), Peroxisome proliferator-activated receptor (PPAR), Protein tyrosine phosphatase 1B (PTP1B), Renin-angiotensin-aldosterone system (RAAS), Ribonucleic Acid (RNA), Systolic arterial pressure (SAP), Sodium-glucose co-transporter (SGLT), Traditional Medicine (TM), Thromboxane A2 (TXA2), Universal Health Coverage (UHC), World Health Organization (WHO)

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