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Potential Role of *Parkia biglobosa* in the Management and Treatment of Cardiovascular Diseases

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1. Introduction

Non-communicable diseases (NCD), also known as chronic diseases represent one of the most serious health challenges of the 21st century. According to the World Health Organisation (WHO), global mortality due to NCD is projected to reach 55 million of deaths in the next 20 years, with 25 million of death caused by cardiovascular diseases (CVD) [1-3]. This is drawing a particular attention to the importance of intensifying research in the area aiming at fighting CVD through prevention and treatment. In a recent report of the WHO, CVD already accounted for 48% of NCD deaths [1]. Additionally, hypertension has been estimated to be the major risk factor for CVD morbidity and mortality, causing 51% of stroke deaths and 45% of coronary heart diseases deaths [1, 3]. Furthermore, CVD is increasing in the low- and middle-income with Sub-Saharan African countries recording the highest rate of hypertension [1-3]. It has been observed that these countries record an increase in the overall rate of hypertension mainly because of severe financial constraints for its management and control [1, 4].

With the prevalence of hypertension in the world's death rate, new approaches to investigate the treatment and management of this disease are highly in demand in order to reduce the overall rate of adult mortality from CVD. Quest for solutions has open doors to research in the field of alternative and complementary medicine as an effective, safe, simple and inexpensive strategy. Medicinal plants and fruits and vegetables are reputed for their excellent health-enhancing bioactive micronutrients, their cost-effectiveness and their widespread bioavailability [5-9]. While some medicinal plants have been investigated in hypertension research, many remain a mystery [5-9]. Therefore, the interest of this review is to summarize the findings of recent studies on the potential cardioprotective effect of *Parkia biglobosa*, a locally available medicinal West African plant that has been reported to display anti-inflammatory, antimicrobial, antioxidant, anti-cancer and hypotensive activities in its diverse parts [10-14]. In this

chapter, a brief explanatory overview of hypertension and its implication in CVD will be given followed by a summary of potential ability of *Parkia biglobosa* to modulate health, especially CVD.

2. Hypertension

Hypertension, also known as raised blood pressure (BP), is a chronic medical condition and a slow progressive disease defined by a mean systolic BP (SBP) of at least 140 mm Hg and/or a diastolic BP (DBP) of at least 90 mm Hg [4, 15- 16]. In the USA, the seventh report of the Joint National Committee (JNC 7) on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure has classified measured BP into different schemes and introduced a new classification referred to as "Prehypertension" [15]. Prehypertension was not defined as a disease-state but represented BP measurements of individuals at high risk of developing hypertension (Table 1). Hypertension has been classified into primary hypertension or essential hypertension (EH) and secondary hypertension (SH). They have respectively unknown and known aetiology.

JNC 7 category	Blood pressure (mm Hg)	
	SBP	DBP
Normal	lower than 120	lower than 80
Prehypertension	120 to 139	80 to 89
Hypertension	140 or higher	90 or higher
Stage 1	140 to 159	90 to 99
Stage 2	160 or higher	100 or higher

Table 1. JNC 7 Classification of blood pressure [4, 15]

Hypertension is a major public health problem responsible for 51% of stroke deaths and 45% of coronary heart diseases deaths [1, 3]. It represents the leading global risk factor of mortality, about 12.8% of global death [3] and is also reported to affects both man and woman [17]. Additionally, the prevalence of hypertension is reported to increase with body weight and advancing age [2, 15-16, 18]. Conversely, hypertension in children has been reported, especially, in overweight and obese children [19]. It has been observed that Black men and women have the highest prevalence of total hypertension [15-16]. Furthermore, while the large proportion of the population suffers from EH (90-95%), only 5-10% among the cases suffers from SH [20-24]. It has been reported that most individuals have an uncontrolled hypertension because the disease is predominantly a "silent" disease which is asymptomatic [17]. Epidemiological studies estimated that in the United States, one in five adult remains unaware of his diseased-state [16]. Nonetheless, with the rise of campaign aimed at increasing hypertension awareness and treatment, the prevalence of uncontrolled hypertension is declining in developed countries,

when compared to developing countries [16, 18]. Actually, the low- and middle-income countries, especially Sub-Saharan African countries record an increase in the overall rate of hypertension mostly because of the severe financial constraints, limited set of health services, low access to facilities and low level of awareness, control, treatment campaigns [4].

2.1. Aetiology of essential hypertension

The aetiology of EH remains a mystery. Even though, EH is the commonest form of hyper‐tension (90% - 95% of all cases), the underlying defects triggering its onset are not known. This explains the difficulty in finding a definite cure. It has been theoretically proposed (Mosaic Theory of Dr Irvine Page) that the aetiology of EH is multifactorial with genetic, environmental, anatomical, adaptive, neural, endocrine, humoral, haemodynamic risk factors and that those different risk factors interlink together to cause hypertension [25-27]. Some of these risk factors are described below:

2.1.1. Environmental risk factors

Various dietary habits and unhealthy lifestyle have also been identified to play a major role in the pathogenesis of hypertension such as:

• Pollutants

• Use of tobacco,

• Chronic consumption of alcohol,

• Lack of weight maintenance (sport inactivity),

• Adoption of diets characterised by high intake of glucose, high intake of saturated fat and cholesterol, high intake of salt (exceeding 5.8 grams daily) [6, 28].

The consequences of this adopted lifestyle give the rise to metabolic and physiological alterations which mediate the pathogenesis of hypertension and promotes other deleterious conditions such as hyperglycaemia (principal characteristic of diabetes) and hyperlipidaemia (principal characteristic of obesity) [29].

2.1.2. Hereditary risk factors

Genetic factors are thought to play a prominent role in the development of essential hyper‐tension, especially genetic abnormalities of the baroreceptor system. However, the genes for hypertension have not yet been identified.

The baroreceptor system consists of nerves ending receptors sensitive to stretch, pulse rate and pressure changes of the blood vessels [30]. They are present on the wall of large arteries such as the aortic arch and the carotid sinus (Figure 1). They stand as the first line of neural control system over blood pressure fluctuation and constitute a short term regulation of BP [31-33]. With a significant change in BP, baroreceptors transmit impulses to central nervous system (CNS) to activate a "feedback" mechanism from autonomous nervous system called barorecep‐

tor reflex or baroreflex. The baroreceptor autonomous reflex restores the BP to normal values [30-33]. It has been reported that that lack of baroreflex sensitivity is associated with the presence of a family history of hypertension [32, 34]. This shows that hypertension could be initiated from specific hereditary genetic abnormalities involving baroreceptors sensitivity [32, 34].

In addition, hereditary genetic abnormalities of the neuroendocrine regulation of baroreceptors have similarly been recognised as predictors of EH. For instance, studies have related overexpression of Chromogranin A (Cg A) in plasma, adrenal medulla and sympathetic neurons to essential hypertension in both clinical and experimental models [25, 35]. Similarly, Cg A loci genetic polymorphism was related to hypertension [36]. Chromogranin A is a pro-hormone stored and released with catecholamine (epinephrine, norepinephrine and dopamine) by exocytosis [37-38]. It is believed that Cg A influence sympathetic tone since it is a pro-hormone for active peptides with regulatory properties, namely vasostatin, pancreastastin and catestatin [37, 39]. Catestatin exhibits catecholamine release-inhibitory function and may function as a vasodilator [40-41]. Decreased circulating level of catestatin has been related to EH because it increases adrenergic pressor response by no longer exerting antagonism to neuronal nicotinic acetylcholine receptor [40-41].

Several genetic factors can affect the renin-angiotensin-aldosterone system and indirectly result in hereditary hypertension. For instance, deficient formation of kinin components (proteins that act locally to induce vasodilatation) in the body may also lead to hypertension and development of CVD. Renal kinin-kallikrein system helps to excrete excess sodium from the biological system [42]. Therefore, a reduction in renal expression of kinin-kalllikrein system can also be identified as a genetic factor for hypertension as a result of accumulation of sodium in the body. Consequently, diminished urinary kallikrein (sub-group of serine protease) excretion could represent a genetic marker of hereditary hypertension [42-43].

2.1.3. Haemodynamic, endocrine, neural, anatomical risk factors

The cardiovascular system ensures the supply of blood to all organs and tissues via distensible blood vessels such as arteries, veins and capillaries of the circulatory system (peripheral and pulmonary). Blood pressure represents the force with which the blood pushes against the wall of the arteries. At physiological level, factors such as blood volume, cardiac output, diameter of artery lumen, and elasticity of artery determine BP [44-45]. In addition, different systems contribute to the short-term and long-term regulation of BP such as:

- The nervous system baroreceptor reflex [46].

- The humoral secretion of vasoconstrictors and vasodilators substances such as acetylcholine, atropine [47].

- The kidneys regulation of BP via renal body fluid feedback, namely the renin-angiotensin-aldosterone system and the pressure natriuresis [31, 43].

Therefore, any molecular and physiological dysfunction affecting the regulation of BP can be associated with the pathogenesis of hypertension such as dysfunctions of the renin angiotensin system (RAS), dysfunctions in electrolytes homeostasis, dysfunctions of the endocrine system

and increased arterial resistance [25, 48]. For example, the renin angiotensin system (RAS) is a central system involved in the regulation of BP and electrolytes homeostasis. Briefly, with a decrease in BP, kidneys prorenin are converted into active renin. Active renin cleaves the hepatic precursor protein angiotensinogen into the inactive angiotensin I (Ang I) [43, 49]. Then, the angiotensin converting enzyme (ACE) hydrolyses two principal molecules. Firstly, ACE cleaves the inactive Ang I to give active vasoconstrictor hormone Angiotensin II (Ang II). Angiotensin II, not only increases BP by constricting blood vessels but also causes the adrenal gland to release aldosterone, a hormone which increase BP through renal retention of sodium and water (increase of blood volume) and decrease excretion of potassium [42-43, 49]. Secondly, ACE which is a kininase II interact with the kinin-kalllikrein system and inactivate the vasodilator bradikinin by releasing pentapeptide Arg-Pro-Pro-gly-Pheo and tripeptide Ser-Pro-Phe fragments [42]. Therefore, failure to regulate the activated RAS at different level could lead to hypertension. Another example of system dysfunction involved the failure to regulate the increased activity of norepinephrine [48].

2.2. Aetiology of secondary hypertension

The aetiology of SH has been often identified with an underlying illness which indirectly increases BP. It has also been demonstrated that SH can emerge from drugs intake and health conditions such as pregnancy [15, 20, 50-52] (Table 2). Therefore, the treatment of SH is associated along with the treatment of the identified underlying factors.

Causes	Examples	
Renal diseases	RENAL PARENCHYMAL DISEASES:	RENOVASCULAR DISEASES/RENAL ARTERY STENOSIS
	•Glomerulonephritis	
	•Polycystic kidney diseases	•Atherosclerotic renal artery diseases
	•Diabetic nephropathy	•Fibromuscular dysplasia
	•Hydronephrosis	•Renal artery embolism
	•Chronic kidney disease (CKD)	•Arteriovenous malformation of the renal artery
Vascular diseases	•Coarctation of aorta	
	•Aortoarteritis	
Endocrinal and metabolic diseases	•Primary aldosteronism (Conn Syndrome),	
	•Primary sodium retention (Liddle's Syndrome)	
	•Cushing syndrome	
	•Pheochromocytoma	
Neurological diseases	•Brain tumours	
	•Encephalitis	
Drugs	•Oral contraceptive pills	
	•Non-steroidal anti-inflammatory medications	
	•Drug Abuse (Cocaine, Alcohol)	

Table 2. Causes of secondary hypertension [52]

2.3. Molecular mechanisms involved in the pathogenesis of hypertension

Previous studies have shown the involvement of excessive reactive oxygen species (ROS) in the pathophysiology of CVD [53-56]. At a molecular level, oxidative stress (Oxs) has been identified to have major implication in the development of clinical and experimental hypertension [57-59]. It was demonstrated that chronic glutathione depletion induced severe elevation of arterial BP [60]. The lack of endogenous antioxidant enzymes worsens oxidative stress and can indirectly promote the risk of hypertension. For example, a recent research supports the influence of genetic polymorphism of antioxidant enzymes in increasing the risk of hypertension [61]. Likewise, [62] in Taiwan demonstrated that manganese superoxide dismutase (MnSOD) polymorphism significantly increased the risk of hypertension.

Inflammation and lipid peroxidation are central to the development of multiple CVD and are mediated by a variety of cell types including macrophages, lymphocytes, endothelial cells and vascular smooth muscles cells [63-65]. The multiple cell types which participate in vascular inflammation produce various pro- and anti-inflammatory cytokines and specific membrane receptors allowing them to transmit their effects to the cells. Studies place a strong emphasis on the role of oxidative stress in the pathophysiology of hypertension through promotion of chronic inflammation [66]. In fact, the rise of Oxs in the vasculature decreased bioavailability of nitric oxide (NO). This leads to endothelial dysfunction due to the loss of vasodilation of blood vessels [58, 67-69]. In addition, oxidative stress coupled with hyperlipidaemia and hypercholesterolemia in the vasculature gives rise to atherosclerosis by oxidation of lipids in the vessels. Atherosclerosis is an inflammatory disease leading to increased arteriolar resistance and increased large artery stiffness and obstruction of blood vessels and subsequent ischemia [70].

2.4. Consequences of hypertension

The continuous high pressure exerted on the arteries wall causes long term damages to both blood vessels and organs. In fact, when hypertension is not timely acknowledged and controlled, damages to organs can become severe and fatal [15, 51-52]. Numerous complications resulting from hypertension are illustrated in Table 3.

2.5. Orthodox therapeutic approaches to managing/treating hypertension

Although, no definite cure has been found to treat essential hypertension, many approaches have been used to manage and control its incidence; in particular lifestyle changes and the use of medications. Lowering salt and alcohol intake, lowering consumption of saturated fats and cholesterol rich food and practising regular exercise are important steps taken towards control of BP [17]. However, these steps are often associated with prescription of anti-hypertensive medication. Many types of anti-hypertensive drugs have been developed over the years such as diuretics, ACE inhibitors, angiotensin II receptor-blocker, calcium channel blockers, alpha and beta blockers [71-73]. Even though a wide variety of anti-hypertensive drugs are effective to control and manage hypertension, they are not without considerable side effects [74-75]. Additionally, the cost of medication is not

End Organ	CVD Damages	Complications/ Consequences
Heart	•Acute coronary syndrome, •Ischaemic heart diseases •Myocardial infarction, •Atrial fibrillation, •Arrhythmias, •Coronary artery disease, •Left ventricular hypertrophy leading to chronic heart failure	Sudden death
Brain	•Constant headaches •Stroke •Neurological damages (memory loss, dementia) •Disability (paralysis)	Sudden death
Kidney	•Renovascular dysfunction, •Chronic kidney failure, •End stage renal diseases (ESDR)	Death
Eyes	Hypertensive retinopathy	Blindness
Vascular system	•Atherosclerosis •Arterial resistance •Aneurysm •Embolus and thrombo-embolus •All the above	Brain, heart, kidney, eyes damages Death

Table 3. End organs damages related to hypertension

always affordable for the majority of the population, especially in developing countries, since managing hypertension represents a lifelong financial investment. Henceforth, research is now turning to alternative and complementary medicine. Many reports support the concept that natural or dietary supplementation can be used to develop effective, safe, simple and inexpensive antihypertensive treatment [6, 28]. As a result, many researches are currently directed towards a search for useful bioactive compounds in medicinal plants as a new strategy for the treatment and management of hypertension [5, 8, 49, 76].

2.6. Alternative therapeutic approach to hypertension

Deeper exploration of phytochemicals found in medicinal plants is used as an approach to discover potential prophylactic and therapeutic agents in cardio protection [7-9]. Medicinal plants can be used to develop effective, safe, simple and inexpensive antihypertensive treatment since they are reputed for their excellent health-enhancing bioactive micronutrients, their cost-effectiveness and their widespread bioavailability [7, 77-78]. As a result, research is currently directed towards discovering useful bioactive compounds in medicinal plants that could be used as new strategies for treatment and management of hypertension [5, 8, 49, 76].

3. *Parkia biglobosa*

3.1. Brief description

Parkia biglobosa, also called the African Locust Bean tree is a multipurpose tree indigenous to the tropical regions of West Africa. *Parkia biglobosa* belongs to the family Mimosaceae (Leguminosae - Mimosoideae) [79-evidences. Therefore, studies of the]. *Parkia biglobosa* is a widespread savannah tree used for nutritional and medicinal purposes [7, 81, 71]. The matured tree can grow up to 30 m in height with a crown large of low branches. The bark is thick and fissured with a grey to brown colour. The leaves are alternate, dark green and bipinnate. The leaves are about 8-30 mm x 1.5-8 mm in size with 13-60 pairs of leaflets held on a long rachis [82].
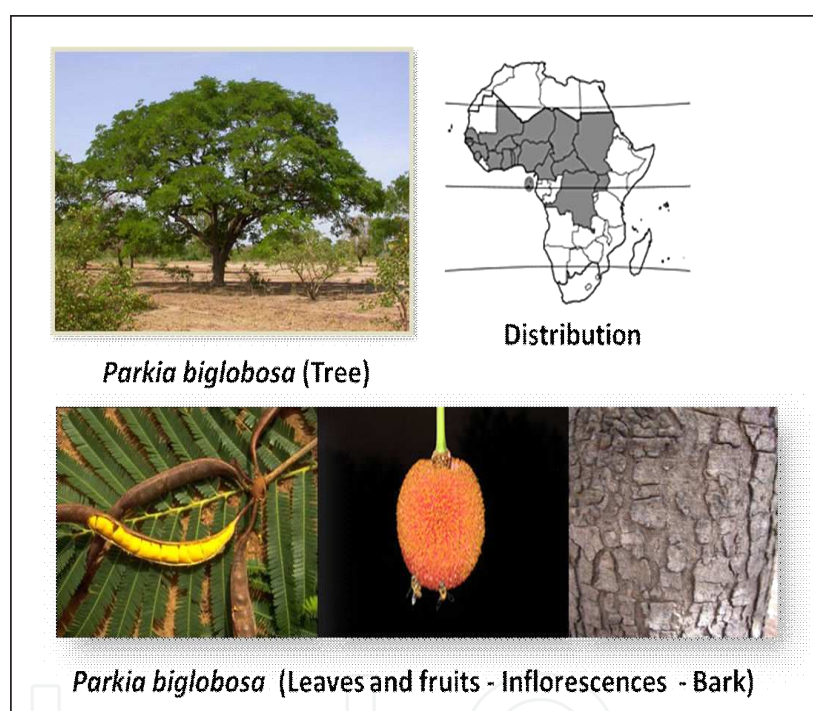

Figure 1. *Parkia biglobosa* [83]

The analysis of the phytochemicals present in *Parkia biglobosa* revealed the presence of alkaloid, flavonoids, tannins, saponins, cardiac glycosides, sterols, resins and terpenes (Table 4) [80, 84-85].

3.2. Potential health benefits of *Parkia biglobosa*

For a long time, native populations of West Africa have been using different parts of *Parkia biglobosa* to meet their nutritional and basic health care needs. In different countries, *Parkia biglobosa* has been used as a multipurpose plant in the therapy of a variety of diseases including

	Plant	*Parkia biglobosa*			REFERENCES
	Extracts (W,P,C,M)	Leaf extracts	Bark extracts	Root extracts	
Bioactive components	Saponins	+	+	+	[85, 86, 87]
	Cardiac Glycosides	+	+	+	[85, 87]
	Tannins	+	+	+	[85, 86, 87]
	Flavonoids (Anthocyanins, flavonones, coumarins, catechins)	+	+	+	[85, 86, 87]
	Alkaloids	-	+	+	[85, 87]
	Resins	+	+	+	[85]
	Carbohydrates	+	+	+	[85]
	Sterols and Terpenoids	+	+	+	[86, 87, 88]

Abbreviations: W: water, P: petroleum ester, C: Chloroform, M: Methanol, +: Present, - : Absent.

Table 4. Brief summary of the bioactive components in *Parkia biglobosa*

hypertension. A summary of traditional medicine practices from different West African countries is illustrated in Table 5.

The fact that repetitive information was obtained from traditional healers and population from diverse regions and countries indicated the need to scientifically authenticate these folkloric evidence. Therefore, studies of the extracts of *Parkia biglobosa* have been conducted and experimental and clinical data are now recognizing the health benefits attributed to *Parkia biglobosa* in its diverse parts. *Parkia biglobosa* bark extracts have been identified to have significant anti-inflammatory, analgesic, antibacterial and anti-helminthic activities. For example, the analgesic and anti-inflammatory property of *Parkia biglobosa* bark extract in the management of toothache has been demonstrated [102]. The anti-venom activity of the bark extract against snake bites has also been reported [103]. In 2007, some clinical investigations described the antibacterial properties of *Parkia biglobosa* bark and root extracts against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli*, *Shigella dysenteriae* responsible for urinary tract and digestive system infections [84, 86, 104]. Additionally, *Parkia biglobosa* stem bark has been attributed anti-microbial effects against *Bacillus subtilitis* and was recommended as a natural preservative against pharmacological contaminations [85]. *Parkia biglobosa* leaf extract were described to exhibit anti-plasmodial activity against malaria [105]. Recently, antioxidant, anti-carcinogenic and anti-trypanosomic activities of the plant have been acknowledged [78, 97, 106-107].

3.3. Potential benefits of *Parkia biglobosa* in the treatment of hypertension and CVD

Previous investigations have indicated the hypotensive potential of *Parkia biglobosa* extracts. For example, it was reported that a methanolic seed extract decreased blood pressure in the

Countries	Used Parts	Traditional medicine practice	References
Benin	All parts	Treatment of digestive system diseases (diarrhoea, dysentery, abdominal pain) Treatment of diseases of the cardiovascular system Treatment of injuries and burns Treatment of infectious diseases (shingles, malaria, abscesses, yellow fever, scabies, measles, chicken-pox, oedema, jaundice) Treatment of paediatric pathologies Treatment of symptoms and syndromes: malaise, tiredness, headaches, hip pain, ache, rheumatism, elephantiasis, onset of paralysis	[89]
Burkina Faso	Fermented seeds, leaves, stem bark	Treatment of oral infections: Gingivitis, toothache, sores (tongues and lips)	[90]
Ghana	Leaves, stem bark, raw fruit, fermented seed	Treatment of malaria, stomach ache	[77]
Ivory coast	Stem bark	Treatment of malaria	[91]
Mali	Leaves	Wound healing	[92]
	Leaves, stem bark	Treatment of malaria, urinary tract infection and internal wounds of pregnant women	[93]
	Stem bark	Personal health, insect management	[94]
Nigeria (North)	Leaves	Treatment of inflammations	[95]
	Stem bark	Treatment of diarrhoea	[96]
Nigeria (South West)	Stem bark	Treatment of trypanosomiasis, fever, ulcer, wound healing	[78, 97]
	Roots	Treatment of hypertension, infertility, stomach ache, sore eye, anti-poison	[98, 99]
	Leaves	Treatment of stroke, leprosy, skin lesion, eye infections	[99]
Nigeria (South East)	Stem bark	Treatment of hypertension	[7]
Togo	Roots	Treatment of haemorrhoids, Diarrhoea	[100]
	Stem bark	Cardioprotection	[101]

Table 5. West African folkloric use of *Parkia biglobosa* for the treatment of diseases

rat [10], an aqueous bark extract decreased blood pressure in rabbits [12] a hydroalcoholic bark extract of *Parkia biglobosa* caused vasorelaxation [13] and a methanolic leaf extract demonstrated hypotensive activities [14]. Hypercholesterolemia and hypertriglyceridemia are known risk

factors associated with hypertension and CVD. The anti-hyperlipidaemia effect of the aqueous and methanolic extracts of *Parkia biglobosa* has been described to reduce hypercholesterolemia and hypertriglyceridemia in diabetic rats [11]. Therefore, *Parkia biglobosa* could offer protection against the development of coronary heart diseases in diabetics [11]. Recently, another study on the methanolic leaf extract of Parkia biglobosa also confirmed protection against doxorubicin-induced cardiotoxicity in rats [87]. In this study, scientists proposed that protection was offered through the antioxidant content and anti-inflammatory properties of the plant extract. Alternatively, it was proposed that protection against cardiotoxicity might have originated from the potential synergistic interactions among the plant phytochemicals. In fact, *Parkia biglobosa* has a rich composition of secondary metabolites which have been individually reported to possess excellent cardiovascular properties, namely:

- saponins (a vast group of glycosides) recently known for providing cardioprotective effects in experimental model [108],

- cardiac glycosides (group of steroidal glycosides) reported to act as cardiotonic agent [109],

- tannic acid (typical product containing hydrolysable tannins) known for its ability to reduce serum cholesterol and triglycerides [110-111],

- triterpenoids such as lupeol known to display antioxidant, anti-hypercholesterolemic and cardioprotective activities [112-113],

- catechins (flavan-3-ol compounds) reported to reduce atherosclerotic plaques formation in animal models [114],

- epicatechins known to reduce the risk of stroke and heart failure [115-116].

Furthermore, it was also reported that a leaf extract of *Parkia biglobosa* is a strong inducer of endothelium-dependent relaxations involving both NO and EDHF via a redox-sensitive mechanism [117]. Moreover, it was suggested that procyanidins fraction of the leaf extract exerted beneficial effects on the endothelial function by decreasing vascular tone and are the major inducers of the vasorelaxation [117].

In conclusion, many experimental and ethnopharmacological studies gave credence to the health enhancing-potential of *Parkia biglobosa* extracts in the treatment of disease conditions such as high blood pressure and CVD. However, there is still an important shortage of scientific evidence elucidating the exact mechanisms through which *Parkia biglobosa* extracts offer protection against hypertension. Therefore, further studies are warranted in CVD diseased-model in order to identify the main phytoconstituents involved in the hypotensive response. The mechanisms of action through which the plant extract offer protection against cardiotoxicity and hypertension should also be investigated. Furthermore, the indigenous population have not adopted standardised methods (the population continue to use uncontrolled dosages and in most instances, preparations of *Parkia biglobosa* extracts are stored in inappropriate conditions) on the medicinal use of the plant. Therefore, caution and care are still needed to be applied on the folkloric use of *Parkia biglobosa*.

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