IJP (2016), Vol. 3, Issue 2 **(Review Article)**

Received on 01 December, 2015; received in revised form, 21 January, 2016; accepted, 27 January, 2016; published 29 February, 2016

GARCINIA KOLA: THE PHYTOCHEMISTRY, PHARMACOLOGY AND THERAPEUTIC APPLICATIONS

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Keywords:

Garcinia kola, Phytochemistry, Pharmacological action

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ABSTRACT: Medicinal plants are bioresources harnessed by humans to combat diseases and maintain healthy life. Plants remain the basis for development of modern drugs for the preservation of health. *Garcinia kola* is considered a "wonder plant" because every part of it has been found to be of medicinal importance. *G. kola* seed is used as an antipyretic agent in indigenous system of medicine. Pharmacologic studies on the seed, leaf and root of this plant showed potent antimicrobial, antiviral, antiulcer, anti-inflammatory, antihepatotoxic, antidiabetic, antihypertensive, adaptogenic, aphrodisiac and antiasthma activities. This review highlights detailed pharmacological properties and phytochemistry of *G. kola* in an attempt to provide direction for further research toward drug discovery.

INTRODUCTION: Medicinal plants occupy an important place in the therapeutic arsenal of humans. According to the world health organization over 80% of the world's population, mostly in poor and less develop countries depend on traditional plant-based medicines for their primary health care needs [1]. Infectious diseases are the number one causes of death accounting for approximately one half of all deaths in tropical countries. Many infectious diseases are known to have been treated with herbal remedies throughout the history of mankind [2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.IJP.3(2).67-81

Article can be accessed online on: www.ijpjournal.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.3(2).67-81

Historically, plants have proved to be a source of inspiration for the discovery of novel drug compounds, as plant derived medicines have made large contributions to human health and well-being. Plants play a two-fold role in the development of new drugs, namely either as phytomedicine used for the treatment of disease or as sources of chemical scaffold for the development of new drug molecules [3]. For instance, in the last decades, there was increased pharmacological evaluation of medicinal plants that could be of benefit as contraceptive and fertility control agents as many plants were known to have promising contraceptive properties among others [4]. Globally, ethnopharmacology and drug discovery using plant-derived natural products remain an important issue [5]. *Garcinia kola* Heckel otherwise called bitter kola belongs to the family clusiaceae/guttiferae and is found mainly in the

tropical forest region of Central and West Africa [6]. It is predominant in the rainforest belt of southern Nigeria [7]. *Garcinia kola* is considered a wonder plant as every part of it has been found to be of medicinal importance. The plant is used in folklore remedies for the treatment of ailments such as liver disorder, diarrhoea, laryngitis, bronchitis and gonorrhea [8]. Extracts from the bark of the plant are used in traditional medicine for treatment of liver cirrhosis and hepatitis [9].

It produces brownish yellow gum resin called xanthone that is used commercially as pigment, and it also has some value in timber industry. The fruit has been used in Indian cuisines to flavor curries, preserve fish and as a condiment [10]. In view of the enormous relevance of *G. kola* in folkloric medicine, the present review focuses on the up-to-date experimental research covering the phytochemistry, pharmacology, and therapeutic studies on *G. kola* toward identification of further research gaps.

Pharmacologic Activity of the Plant *Garcinia Kola:*

G. kola has antipyretic activity due to the presence of certain phytoactive constituents [11]. Studies on the plant indicated it had antibacterial activity against caries causing microorganisms [12]. The plant is valuable in the treatment of cough and asthma [13]; it has purgative, antiparasitic, antiviral, anti-inflammatory activities; it is used as remedy for guinea-worm infection and for the treatment of gastroenteritis, rheumatism, menstrual cramps, bronchitis, throat infection, headache, colic, chest cold, liver disorder, as anti-diabetic, anti-oxidant, antihepatoxic [14], and anti-trichomonal [15]. It has also been reported to possess immunomodulatory activity [16], antimalarial activity [17], inhibition of certain drug metabolism, molluscicidal [18], anti-allergic effect and analgesic properties [19].

The seed have pharmacological potency in treating stomachache, gastritis [20], venereal diseases, nervous system disorder [21] and laryngitis [22]. The aim of the present review is to highlight the ethnomedicinal uses, phytochemical and pharmacological investigations reported on all parts of *Garcinia kola*, and to explain the multifaceted role of this medicinal plant.

The genus Garcinia includes more than 300 species and belongs to the family Clusiaceae. The genus is a native of Asia and Africa. They are evergreen polygamous trees, shrubs, and herbs. About 35 species are reported to exist in India, many of which are endemic and economically important with immense medicinal properties [23]. In Eastern part of West Africa, there are over fifty species of kola. In Nigeria, there are about twenty three species, out of which five are edible [24].

Garcinia kola is a perennial crop growing in the forest, distributed throughout West and Central Africa [25]. *G. kola* is also found distributed in the forest zone of Sierra Leone, Ghana, Cameroon and other West African countries, particularly in Nigeria were it is common in the south western states and Edo state [26]. Amongst the African genera, Garcinia is characterized by the dioecism of its species and hence its unisexual flowers, the presence of a foveola at the base of the petiole, the peltate stigma, the ovary with a single apical ovule per locule and the berry-like fruit [27].

Scientific classification:

Kingdom: Plantae; Division: Magnoliophyta; Class: Magnoliopsida; Order: Theales; Family: Clusiaceae/ Guttiferae; Genus: Garcinia; Botanical name: *Garcinia kola* Heckel.

Vernacular name:

Botanically known as *Garcinia kola*, commonly called bitter kola and belongs to the family guttiferae/ clusiaceae. In Nigeria it is called oje in Bokyi; edun in Edo (Bini); adu in Edo (Esan); efiari in Efik; efrie in Ejagham-ekin; cida goro or namijin goro in Hausa; efiat in lbibio; emiale in Icheve; igoligo in Idoma; akaan in Ijo-izon; okain in Isekiri and orogbo in Yoruba. In Ibo it is called by many names such as aki-ilu, adu, agbuilu, akara-inu, ugugolu, aku ilu, akuruma, ugolo [28].

Taxonomy:

Garcinia kola has been recognized as an indigenous medicinal plant found in the rain forest of Central and Western Africa, especially Benin, Cameroon, Democratic Republic of Congo, Cote D'ivoire, Gabon, Ghana, Liberia, Nigeria, Senegal and Sierra Leone [29]. *Garcinia kola* is a medium sized tree, but sometimes growing up to 12 m tall

and 1.5 m wide. It is a spreading forest tree with dense and heavy crown; the bole is straight, the bark is greenish-brown, thick and smooth. It has broad leaves, 5-10 cm long, paired at the end of twigs, broadly elliptic, very shortly acuminate, cuneate, shiny above and leathery with very distinct resinous yellow canal. The leaf has ten pairs of lateral nerves with very obscure venation between; the midrib is prominent at the underside; petiole is much thickened; the stalk is stout, finely hairy in young leaves. It bears male and female flowers seperately, usually between December, March, and May-August. Female flower are yellow and fleshy, globose, 1.5 cm wide; male flower are smaller but with more prominent stamens (4 bundles), 4 sepals, 4 greenish-white petals. It fruits between July-October [29]. It produces characteristic large fruits (6 cm in diameter), reddish yellow, skin peach-like; containing 3-4 seed coated brown with branched line embedded in an orange-colored pulp; kernels are pale with resin pockets, seeds obtusely 3-sided, up to 3.8 cm by over 1.3 cm, showing a small resinous line when cut across [30].

FIG.1. FRUIT OF *G.KOLA*

FIG. 2: SEEDS OF *G. KOLA*

FIG.3: THE WHOLE TREE OF *G. KOLA*

Phytochemistry:

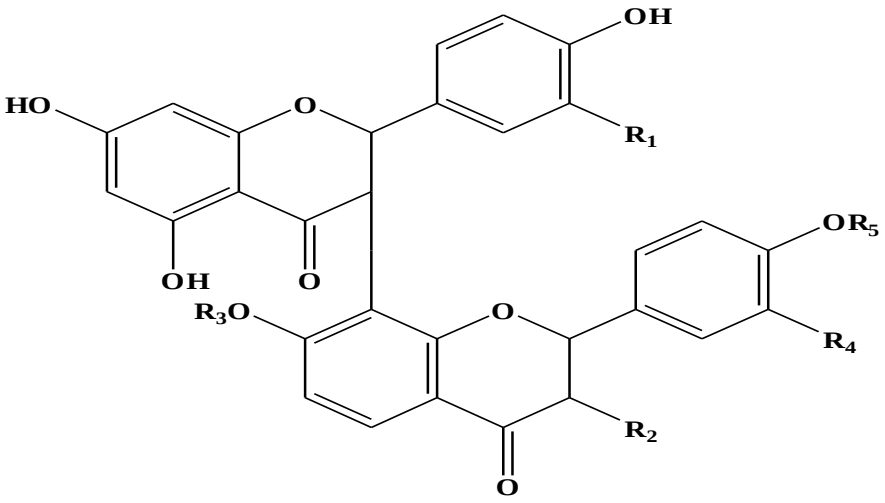
G. kola contains alkaloids, saponins, tannins, flavonoids, glycosides, sterols and phenols [31]. The major constituents of the plant are kolaviron, garcinia biflavonoid (GB)-1a-glucoside (1), GB-1a (2), GB-1 (3), GB-2 (4), kolaflavonone (5), benzophenone (6), xanthone (7), coumarin (8), apigenin (9), quercetin (10), garcinoic acid (11), Garcinianin (12).

The biflavanones GB1, GB2, GB1a, kolaflavanone and their glycosides, in addition to the seed, were also isolated from the stem bark. The ether soluble fraction of the alcoholic extract yielded apigenin-5,7,4‘-trimethyl ether, apigenin-4‘-methylether, fisetin, amento-flavone, kolaflavanone and GB1 [32], the following phytochemicals were isolated from the roots of *Garcinia kola*, garcinianin [33], phlobatannins, anthraquinones, glucosides [34], garcifuran-A, garcinifuran-B and two novel arylbenzofurans [35]. Alkaloids, flavonoids, anthraquinones, glycosides, tannins, terpenes, steroids and saponins were isolated from the mesocarp of *G. kola* [36].

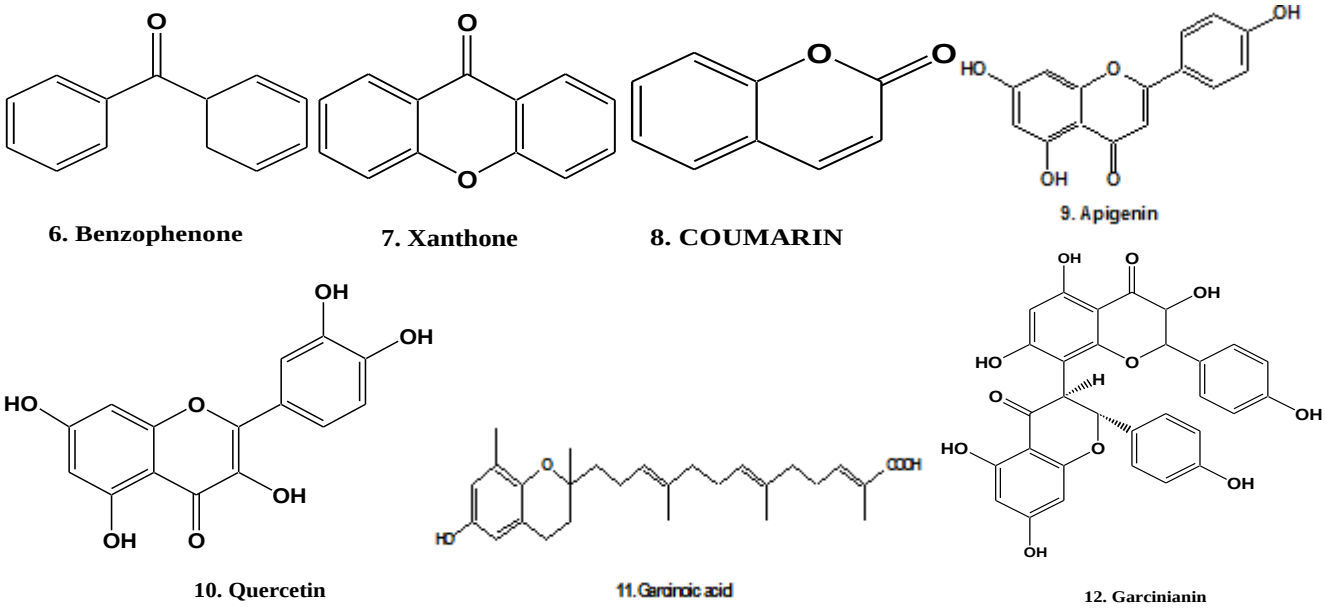
Haxadecanoic acid, 9-octadecanoic acid, methyl ester, linoleic acid, heptadecene-(8)-carbonic acid, formalaldehyde, *N*,*N*-Diethyl, n-tetradecanoic acid amide; 3,4,8-trimethyl-2-nonenal were isolated from the seed of *Garcinia kola* [37]. Carbohydrates were isolated from the seed [38]. The mineral composition of *G. kola* seeds and hulls has been reported, potassium and phosphorus were the most abundant in the seed, while phosphorus and

calcium were the most abundant in the hull. Other constituent include ash, crude protein, crude fiber, crude lipid, water soluble oxalate, terpenoids, and fat [39].

The chemical constituents of *G. kola* seed and hull had been studied by means of gas liquid chromatography and High Performance Liquid Chromatography. The seed oil composed of fatty acid and amino acid derivatives, namely meristic, pentadecanoic, margaric, trans-palmitoleic, cis-vaccenic, cis-oleic, cis-linoleic, α-linolenic, threonine, tyrosine, methionine, serine, histisdine and alanine. The hull yielded the following fatty acid and amino acid derivatives, pentadecanoic, margaric, pentadecanoic, myristoleic, cis-palmitoleic, cis-vaccenic and eicosadienoic, methionine, tyrosine, histidine, and arginine [40].



	R1	R2	R3	R4	R5
1. GB-1a-glucoside	H	H	glc	H	H
2. GB-1a	H	H	H	H	H
3. GB-1	H	OH	H	H	H
4. GB-2	H	OH	H	OH	H
5. Kolaflavonone	H	OH	H	H	CH_3



6. Benzophenone **7. Xanthone** **8. COUMARIN** 9. Apigenin

10. Quercetin 11.Gardinoic acid 12. Garcinianin

FIG. 4: SOME CHEMICAL CONSTITUENTS OF *G. KOLA*

Medicinal value of the family Clusiaceae:
Clusiaceae plants are well known in traditional medicine to treat various illnesses such as cough, menstrual problem, dyspepsia, and renal disease among others [41].

Medicinal value of garcinia kola:
Almost all parts of *Garcinia kola* are used in traditional system of medicine for the treatment of various ailments in humans. The leaf, seed, bark stem, fruit and root of *G. kola* have significant medicinal properties as described below.

Traditional Uses:
Garcinia kola is cultivated throughout West Africa for it edible fruit and seeds which are used as rejuvenating agents. Traditionally, the seed of *Garcinia kola* is used as sialagogue to stimulate the flow of saliva. The seed coat is widely traded and eaten as stimulant. It is believe to clean the digestive system, without side effects such as abdominal problems, even when a lot of it is eaten. In traditional medicine, the dried seed is ground and mixed with honey to make a traditional cough mixture. The ground seed mixed with water is given to new born babies to relieve stomach cramps. *Garcinia kola* seed coat is used as hop substitutes in several indigenous alcoholic drinks as well as flavor enhancer in the beverage industry [29].

Garcinia kola is used as antidote for snake bites, remedy for cough, vomiting and as snake repellant. The seed is used in the treatment of diarrhoea, bronchitis, and throat infections, liver disorders and enjoys a folk reputation in Africa as poison antidote.

The seed of *Garcinia kola* have pharmacological uses in treating coughs, throat infection, bronchitis, hepatitis and liver disorders. The stem bark serves as purgative, the powdered bark is applied to malignant tumours, the sap is used for curing parasitic skin diseases and the latex or gum is used against gonorrhea infection and applied externally on fresh wounds to prevent bacteria contamination [29]. The twig of *G. kola* is used as tapers and the root yields chewing stick [25]. The leaf of *G. kola* is used in ethnomedicine for the treatment of tuberculosis [42] and also serves as remedy for typhoid fever [43].

Therapeutic Applications of Garcinia Kola:
Antimicrobial Activity:
Antimicrobial activities of crude extract of *Garcinia kola* against some bacterial isolates comprising of both Gram-positive and Gram-negative organisms had been reported [44] In another study, the antimicrobial interaction between *G. kola* seed and gatifloxacin, a fourth generation fluoroquinolone, was evaluated by a modification of the checkerboard technique [45]. The antimicrobial activity of five different solvent extracts of *Garcinia kola* seed had been investigated against 30 clinical strains of *Helicobacter pylori* and a standard control strain, NCTC 11638, using standard microbiological techniques [46]. Antibacterial activities of methanol and aqueous extracts of *G. kola* seeds against 50 Vibrio isolates obtained from wastewater final effluents had been reported [47]. The bioactivity of the seed was assessed on *Streptococcus pyogenes, Staphylococcus aureus, Plesiomonas shigelloides and Salmonella typhimurium* [37]. Extracts from the bark, stem and seed of *G. kola* have been reported to inhibit the growth of *plasmodium falciparum* by over 60% in vitro at a concentration of 6 mg/ml [48]. Leaves and stem bark of the plant showed anti-microbial activity [49]. A study to investigate the anti-bacterial activity of bitter kola and ginger (*zingiber officianale*) on four respiratory tract pathogens, namely *staphylococcus aureus, streptococcus pyogens, streptococcus pneumonia and Haemophilus influenza* revealed that the extracts from ginger and *Garcinia kola* exhibit anti-bacterial activities against the pathogens [50]. The effect of aqueous extracts of *Garcinia kola* seeds on membrane stability of human erythrocytes indicated possible use of the extract for the management of sickle cell. Antimicrobial activity of *G. kola* seed diethyl ether extract against *Pseudomonas aeruginosa; Bacillus subtilis; and Klebsiella pneumonia* had been reported. The strongly anti-bacterial and weakly anti- fungal actions of the extract may be due to activities of the triterpenoid and glycoside components of the extract [51].

The methanol extract and fractions of *Garcinia kola* seed has potential as a new source of antibacterial compounds [37]. An antimicrobially active compound was isolated from the active

fraction and purified by recrystallization in 50%v/v aqueous ethyl acetate. Spectroscopic analysis revealed the isolate to be II-3-4'-I-4'-5-II-5-I-7-II-7-heptahydroxy-3,8-biflavan one (GB1) previously isolated from the bark and fruits of *G. kola* [52]. Cycloartenol, 24-methylenecycloartanol and garcinianin isolated from the seeds of *G. kola* exhibited antimicrobial activity against caries-causing organisms [12]. Polyisoprenyl benzophenone, kolanone from the petroleum ether and hydroxyl biflavanols from the ethyl acetate fraction of *G. kola* seed showed activity against gram positive and gram negative bacteria and against *Candida albicans and Aspergillus flavus* [53]. Also, GB1 was active against *streptococcus mutans* and other oral bacteria with MIC values of 32-64µg/ml [54].

Crude ethanol extracts of *G. kola* seed demonstrated inhibitory effects on some pathogenic organisms of medical importance. The inhibitory effects shown by the ethanol extracts may be due to the presence of some phytochemical components [55]. The antimicrobial properties of ethanol extracts of *G. kola* seed was attributed to the presence of benzophenone. Research involving the bioassay of fractions of the seed showed mixtures of triterpenes, phenolic compounds, benzophenones, kolanone with potent antimicrobial properties [56, 57].

Kolaviron isolated from *G. kola* demonstrated inhibitory effects against *methicilin-resistant, Staphylococcus aureus (MRSA) and vancomycin-resistant Enteroccoci* (VRE) [58]. Lack of activities in hexane and ethyl acetate fractions was an indication that the bioactive constituents may be polar in nature, more so as the aqueous fraction of methanol extract showed the best activity. The chloroform fraction had relatively good activity. The anti-trichomonal activity had been reported as a potentially useful therapeutic agent in the control of trichomoniasis [14].

Antiviral Activity:

Kolaviron has been identified as the specific antiviral bioflavonoid in bitter kola as suggested by both *in vitro* and *in vivo* studies [59].

The biflavonoids constituents of the seeds of *G. kola* have shown remarkable broad spectrum antiviral activity against a variety of viruses including *puntatoro, pichinde, sandfly fever, influenza A, Venezuelan Equine Encephalomyelitis*, HIV-1 and Ebola, with IC50 values of 7.2-32 µg/ml and TMC of more than 320 µg/ml [60]. Biflavonoids from *G. kola* seed have antiviral activity, remarkable immune boosting and antioxidant property, coupled with its ability to inhibit kinases and several signalling pathways [30, 59].

Anti-Inflammatory Activities:

The anti-inflammatory activities of flavonoids is complemented by their ability to activate NF-E2 related factor 2 (Nrf2), thus increasing anti-oxidant defenses [61]. The analgesic and anti-inflammatory properties of kolaviron, a defatted seed extract of *Garcinia kola*, was investigated in mice and found to exhibit a weak analgesic but very strong anti-inflammatory activity when compared to a standard reference drug, acetyl salicylic acid. The activity of Kolaviron may not be unrelated to the presence of the biflavonoid group. The biflavanones of *G. kola* are pharmacologically active with several pharmacokinetic advantages over simple monomeric flavonoids. The traditional use of *G. kola* in the management of inflammatory conditions is justified. [62] Kolaviron from seed of *G. kola* had been shown to interfere with LPS signaling by reducing the activation of several inflammatory transcription factors and signaling pathways [63].

Anti-Diabetic Activity:

The hypoglycaemic and hypolipidaemic effects of fractions from kolaviron were investigated in normal and streptozotocin (STZ)-induced diabetic rats [64]. *G. kola* seed powder had also been shown to have antidiabetic, antilipidemic and anti-atherogenic properties with a tremendous potential to protect against coronary heart disease [22]. Significant hypoglycaemic and hypolipidemic activity of *Garcinia kola* in alloxan-induced diabetic rats had been reported [65]. Kolaviron inhibited rat lens aldose reductase activity with an IC_{50} value of 5.4×10^{-6} M [66]. Kolaviron reduced blood sugar levels in STZ-induced diabetic rats within 4 h of oral administration and showed favorable effect on the plasma lipid profile of diabetic animals [64]. In addition to its antidiabetic property, kolaviron showed remarkable protective

effects on cardiac, renal and hepatic tissues of STZ-induced-diabetic rats. Many antidiabetic drugs do not offer significant tissue-protective effect in diabetic animals as kolaviron [67]. Kolaviron treatment of diabetic rats restored the activities of antioxidant enzymes, reduced lipid peroxidation and increased oxygen radical scavenging capacity and glutathione concentration in renal tissues. *Garcinia kola* seed powder dose dependently reduced blood glucose level and improved lipid profile; showed indication of an antidiabetic agent with potent cardioprotective effect [22].

Kolaviron at 100 mg/kg significantly ameliorated hyperglycemia and liver dysfunction. It also prevented diabetes induced increase in the hepatic levels of proinflammatory cytokines, interleukin (IL)-1beta, IL-6, tumour necrosis factor (TNF-α) and monocyte chemotactic protein (MCP-1) [68]. Quercetin, one of the chemical constituents of *Garcinia kola* seed protected against high glucose-induced damage in bone marrow-derived endothelial progenitor cells [69].

Antioxidant Activities:

Antioxidants are known to terminate chain reactions in lipid peroxidation, by removing free radical intermediates, and inhibit other oxidation reactions. The body's internal production of antioxidants is not sufficient to neutralize all the free radicals, hence there is need for supplementary dietary intake of antioxidants to maintain health and prevent diseases associated with free radicals [70]. Reactive Oxygen species (ROS) generated endogenously or exogenously are associated with the pathogenesis of various diseases such as atherosclerosis, diabetes, cancer, arthritis and aging process. Thus antioxidants which can scavenge ROS are expected to improve these disorders. Saponin extract from the root of *Garcinia kola* exhibit significant inhibition of MDA production and cause a significant elevation of free radical scavenging enzyme activities such as SOD and Catalase [71].

The leaf extract of *Garcinia kola* produced antioxidant effect and protective response against the destructive effects of free radicals on both brain and liver [72]. The phytochemical contents of the seed extracts of *G. kola* shows that it is rich in phenolic acids, flavonoids and vitamin C. Antioxidant potentials of plants are assessed by their ability to scavenge DPPH (1,1-diphenyl–2-picrylhydrazyl) radicals. Moreover, antioxidants can act by chelating transition metals. Antioxidants could reduce and deactivate transition metals. Besides, sodium nitroprusside elicits its cytotoxic effect through the release of cyanide and/or nitric oxide (NO) both of which have been implicated in the pathophysiology of strokes, traumas, seizures and Alzheimer's, and Parkinson's diseases. Comparatively, ethanol extract of *G. kola* exhibited higher antioxidant properties than the aqueous extract [73].

Antioxidant property of *G. kola* is attributed to its very high content of ascorbic acid [74]. Antioxidant potential of five fractions (ME1–ME5) of methanolic extract of *G. kola* seeds was studied. ME4 fraction possessed the greatest activities. Fraction ME4 strongly inhibited nitric oxide production in lipopolysaccharide activated macrophage U937 cells. Chromatographic and spectroscopic analysis of ME4 revealed the presences of biflavonoid GB1 and GB2, garcinal and garcinoic acid [75]. Polyphenolic compounds, flavonoids and their derivatives are known to have antioxidant activities. Also some anthraquinones have been reported to possess antioxidant activity [76]. Ethanolic extract of *Garcinia kola* leaf had been reported to inhibit Fe^{2+} induced lipid peroxidation thus providing justification for its medicinal use in the treatment of different diseases. Hence, *Garcinia kola* leaf is a source of natural antioxidants [70]

Hepatoprotective Activity:

G. kola has protective effect against a variety of experimental hepatotoxins. Anti-hepatoxic efficacy of this plant seed was due to it kolaviron content [77]. Garcinia biflavonoids protected against hepatotoxicity induced by phalloidin, amanita, 2-acetylaminofluorene, carbon tetrachloride, paracetamol, aflatoxin, dimethyl nitrosamine in rodents [32]. Even at 500 mg/kg *G. kola* did not cause significant degenerative or trophic changes in liver cells. Hepatic lobules which are polyhedral three dimensional in shape were preserved [77]. *G. kola* seed boosts the antioxidant status and did not cause adverse effect on liver, testes, and spermatozoa of rats [78].

G. kola seed alleviated the hepatic degenerative changes associated with ciprofloxin. The hepatoprotection exhibited by *G. kola* seed as an adoptagen is generally ascribed to the presence of constituents with antioxidant properties [79]. *G. kola* extract at 60 mg/kg significantly protected against damages caused by exposure to hepatotoxic antitubercular drug [80].

Kolaviron protected against carcinogen-induced hepatotoxicity by free radical scavenging, metal chelation, upregulation of the detoxification system, down regulation of NF-KB [81]. Saponin extract from the root of *Garcinia kola* protected the structural integrity of hepatocytic cell membrane and enhanced regeneration of the damaged liver cells. It exhibited reasonable hepatoprotective ability against paracetamol induced hepatotoxicity [82]. The ability of *G. kola* seed extract to attenuate the raised serum levels of liver marker enzymes is an indication of its hepatoprotective potential [83]. Glycogen granulation is a function of the liver which can be inhibited as a result of hepatotoxicity. Hepatoprotective effects of *Garcinia kola* seed against paracetamol-induced oxidative damage and glycogen degranulation in hepatocytes of rats had been reported [84]. *G. kola* seeds had been reported as a potent preventive agent for coronary heart diseases [85].

Antiarthritis Activity:

Garcinia kola seed acts as antioxidant to either inhibit or slow down the progression of symptomatic knee osteoarthritis. It also acts as scavenger to remove the particles on the surface of human articular cartilage following trauma and osteoarthritis. The particles contained calcium and phosphorus which were identified only in structurally abnormal cartilage. Bitter kola has been shown to protect against the oxidation of lipoprotein, presumably through the mechanisms involving metal chelating and antioxidant activity. The relief of pain experienced by arthritis patients on *Garcinia kola* could be associated with either removal of free radicals and or revascularization of subchondria bone through the anti-atherogenic effect. It may be due to the cytokines selective inhibition of inducible nitric oxide synthase which has been shown to reduce the progression of experimental osteoarthritis in *vivo* [86].

Kolaflavanone and apigenin which are major phytoconstituents of *Garcinia kola* had been reported to exhibit antiarthritis activity [87]. Reduction of intraosseous/subchondria pressures could by other pathways for reduction of knee pain experienced by patients on *Garcinia kola*. The ability to lower intraocular pressure was observed in glaucoma patients and confirmed scientifically in animals and human glaucoma. *G. kola* induces vasodilatation which could improve the subchondria blood circulation in knee osteoarthritis. *G. kola* had been shown to have antithrombotic activities. *G. kola* is a potential osteoarthritis disease modifier [86].

Anti-Ulcer Activity:

The antiulcer effect of petroleum ether extract of *G. kola* had been reported [88]. *G. kola* contains tannins which are known to have antiulcer properties [89]. Flavonoids have been implicated as possible bioactive agents responsible for antiulcerogenic effects [90, 91, 92]. *Garcinia kola* extract produced significant decrease in the ulcerogenic indices, morphological damage score, ulcer score, and gastric wall thickness which are indications of ulcerogenic potentials [93, 94]. It has been documented that gastritis and gastric ulcers are associated with stress. *G. kola* extract prevented lipid peroxidation by increasing the enzymatic anti-oxidants, catalase and superoxide dismutase levels and reducing malondialdehyde, lipid peroxidation index. *G. kola* extract had previously been shown to improve oxidative status [94, 95a, 95b, 96]. Flavonoids have been reported to inhibit isoforms of inducible nitric oxide synthase (iNOS) and of cyclooxygenase (COX-2) which are responsible for the synthesis of prostaglandins and nitric oxide, as well as reactive C-protein and adhesion molecules, mediators of inflammation [61].

The flavonoids present in the methanolic extract of *Garcinia kola* might be responsible in enhancing the oxidative defense mechanisms which led to significant reduction in the ulcerogenic and inflammatory indices. Kolaviron from *Garcinia kola* at 200 mg/kg reduced the incidence of ulcers. Kolaviron inhibited the H^+, K^+-ATPase activity with IC_{50} of 43.8 mg /ml compared with omeprazole with IC_{50} of 32.3 mg/ml. Kolaviron showed both cytoprotective and anti-secretory

potentials against peptic ulcer models, and pump inhibitory activity [97].

Anti-hepatotoxic activity:
G. Kola protected the liver from heavy metal toxicity in rats [98]. Kolaviron inhibited dimethyl nitrosamine-induced hepatotoxicity by suppressing COX-2 and iNOS expression [99]. Antihepatotoxic properties have been evaluated using four experimental toxins, namely carbon tetrachloride, galactosamine, alpha-amanitan and phalloidin. Kolaviron, a fraction of the defatted ethanol extract and two biflavononoids of *G. Kola* seed (GB1 and GB2) significantly modified the action of all these heptatotoxins [100].

Anti-asthma activity:
Xanthone have anti-asthmatic activity by dependently inhibiting the Ca^{2+} influx induced by either norepinephrine or high K^{+}, suggesting that xanthone might act as a blocker of both receptor operated and voltage dependent Ca^{2+} channels. Furthermore, xanthone causes increase in the level of intracellular cyclic adenosine 3',5'-monophosphate (cAMP) but not cyclic guanosine 3',5'-monophosphate (cGMP) content. Xanthone showed inhibitory effects of cAMP phosophodiesterase. Intracellular levels of cAMP can be increased by β-adrenoceptor agonists, which increase the rate of its synthesis by adenyl cyclase (AC) inhibitors such as xanthone, which slow the rate of its degradation.

Flavonoids exhibits anti-asthmatic activity by inhibiting platelet-activating factor (PAF), phospholipase A_2, (PLA_2) and phosphodiesterase (PDE). Flavonoids exhibit a predilection to inhibit histamine release stimulated by IgE-dependent ligands. Copper, a metal transition, most effectively block the inhibitory activity of flavonoids, possibly through a chelation mechanism.

Flavonoids inhibit phospholipids metabolism and 5-lipoxygenase (5-LO). These 5-LO products mediate constriction of air way smooth muscle, leukocyte chemotaxis and vascular permeability. *G. kola* appears to be very promising in the treatment and management of asthma [13].

Anti-hypertensive activity:
G. kola reduced glutation concentration, and also inhibits prostaglandin synthesis. *G. kola* has spasmolytic effect on gastrointestinal smooth muscle. It relaxes the smooth muscles of the uterus and gastrointestinal tract. It has been reported to stimulate histamine dependent gastric acid secretion. Antithrombotic activity of *G. kola* has also been reported. Aqueous extract of the plant stabilized the membranes of HbAA, HbAS and HbSS human erythrocytes and reduced blood viscosity [101].

The effect of *G. kola* on blood pressure has been traced to its ability to reduce total peripheral resistance either by direct or indirect action on the vascular smooth muscle. It has been observed that Raynodine lowered mean arterial pressure and suppressed basal heart rate. This may be via a calcium chelating mechanism as it is know that most flavonoids are antinutrients, removing cholesterol, calcium and glutathione from the blood. Also the removal of glutathione from the blood could help the vasodilatation of resistant vessel as it has been observed that reduced glutathione level improved coronary endothelial vasomotor function by potentiating the vasodilator function of Nitroglycerine. Membrane stabilization and reduction of blood viscosity is another possible way by which *G. kola* may reduce blood pressure. It also contains a vasoactive ingredient, which is capable of lowering blood pressure [101].

Anti-cancer activity:
Tannins had been observed to have remarkable activity in cancer prevention. [89] Cardiac glycosides had been reported as novel cancer therapeutic agents [102]. A dietary pattern rich in lignin, quercetin and resveratrol such as *G. kola* decrease the risk of oesphageal cancer [103]. *G. kola* contains allicin which had been reported to inhibit TNF-α-mediated induction of VCAM-1 through blocking ERK1/2 and NF-kB signaling pathways and enhancing interaction between ER-α and p65, leading to the suppression of invasion and metastasis of MCF-7 cells. Therefore, allicin could be useful for preventing the advancement of breast cancer [104]. Apigenin also present in *G. kola* seed is useful for cancer prevention [105].

Apigenin promotes apoptosis, inhibits invasion and induces cell cycle arrest of T24 human bladder cancer cells [106]. Kolaviron effectively suppressed dimethyl hydrazine induced colon cancer in rats [107]. Caffeine and caffeic acid both of which are constituents of *G. kola* seed inhibit growth and modify estrogen receptor and insulin-like growth factor receptor levels in human breast cancer [108]. Also lycopene and beta-carotene induce cell-cycle arrest and apoptosis in human breast cancer line [109].

Other activities:

G. kola extracts showed anti-fungal activity [110]. *G. kola* seed possesses anti-conceptive and weak estrogenic properties [111]. *G. kola* seed had been shown to have numerous pharmacological properties including antifertility effect, haematological effect [112] and antiemetic effect [113]. Kolaviron protects against ischemia/reperfusion injury [114]. *G. kola* seed had been reported for the management of sickle cell anemia [115]. The bark of *G. kola* tree has been documented to possess aphrodisiac activity [116]. *G. kola* seed have anti-progestational, anti-implantation and anti-ovulatory effects in female rats. Methanolic extract of *G. kola* seed exhibited anti-contraceptive and weak estrogenic properties. [117] *G. kola* seed meal fed to rabbit increased the white blood cell count of rabbit bucks; especially the lymphocytes, thereby increasing their immunity [118].

CONCLUSION: The therapeutic efficacy of *G. kola* has been established through modern testing and evaluation in different disease conditions. These studies placed this indigenous drug plant as a novel candidate for bio-prospecting and drug development for the treatment of diseases, such as diabetic, asthma, ulcer, infectious diseases, cancer and inflammatory conditions. The medicinal applications of this plant and the countless possibilities for further investigation are enormous. The plant is rich in phytochemicals with numerous therapeutic applications.

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How to cite this article:
Buba CI, Okhale SE and Muazzam I: *Garcinia Kola*: The Phytochemistry, Pharmacology and Therapeutic Applications. *Int J Pharmacognosy* 2016; 3(2): 67-81:.doi link: http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.3(2).67-81.