# *Garcinia kola* (Bitter kola): Is it truly the Wonder Seed?

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**Abstract**

In search for new therapeutic agents, against several diseases such as inflammation, diabetes, hypertension, cancer, etc, scientists have embraced the importance and great values of medicinal plants. *Garcinia kola* seed is eaten raw with the belief that it promotes longevity. In folkloric medicine, extracts of this seeds are used for the treatment of laryngitis, cough, and liver diseases (Iwu, 1990).

Kolaviron (KV) (a biflavonoid fraction) has been isolated as one of the active components of *Garcinia kola* (Iwu, 1986). Basic medical research has shown KV to act as anti-inflammatory agent by inhibiting the production of nitric oxide, prostaglandin E2 and tumor necrosis factor-alpha (Aggarwal, 2004). In several models of hepatotoxicity, KV has been shown to elicit anti-tumor property via elevation of phase-II drug metabolizing enzymes, prevention of DNA oxidation, inhibition of lipid peroxidation process and pro-apoptotic effect by increasing bax/bcl2 ratio. The anti-hypercholesterolmic effect of KV in animals fed on high cholesterol diets has been established.

In addition, the antidiabetic activity of KV in rats rendered type-II diabetic has been confirmed. KV is known to inhibit α-amylase and glucose-6-phosphatase activities, thereby reducing fasting plasma glucose levels in diabetic rats. KV is a known chemo preventive agent against testicular damage caused by several toxicants. Experiments on the longevity effect of KV and involvement of regulator genes

is on-going. This review summarises the diverse biological activities of *Garcinia kola* and possible role as an emerging therapeutic agent.

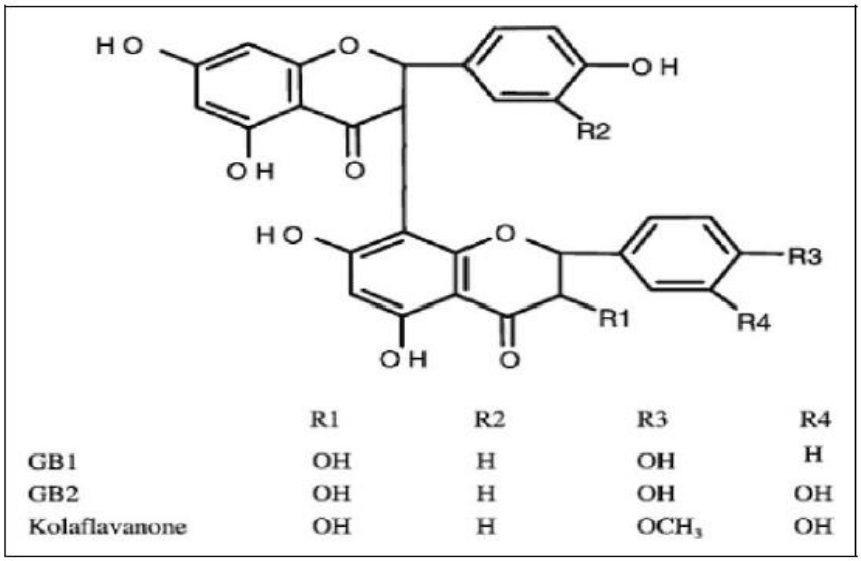
**Keywords**: Garcinia kola, Therapeutic agent, health, medicinal plant.

## Introduction

Bitter kola (*Garcinia kola)* is a medium sized tree that it is greatly treasured in West and Central Africa for its edible nuts (Hutchinson and Dalziel, 1956). The seed, universally known as 'bitter kola', is chewed by a lot of people and it is widely used at social and cultural ceremonies in many parts of Nigeria.

## Results and discussion

Extracts of the plant have been employed in a number of African herbal medicines. The chemical structure of Garcinia biflavonoid complex is also known as kolaviron (KV), is shown Figure 1.




| | R1 | R2 | R3 | R4 |
|---|---|---|---|---|
| GB1 | OH | H | OH | H |
| GB2 | OH | H | OH | OH |
| Kolaflavanone | OH | H | $OCH_3$ | OH |

**Figure 1: Chemical structure of kolaviron**
Source: Biflavanones of Garcinia: Pharmacological and biological activities (Iwu , 1986).

**Biological activities of Kolaviron**

*Antioxidant activity*

Increased activities of free radicals which are generated in the body lead to various pathogenesis such as aging, inflammation, cancer and so on (Namiki, 1990). Several vascular diseases such as cardiovascular diseases, atherosclerosis are been caused by reactions of the free radicals to the different macromolecules such as DNA, protein, in the system through the process of oxidative modification (Bonanome, *et al*., 1992). Free radicals like $H_2O_2$, $O_2^{\cdot-}$ and $OH^{\cdot}$, which are generated in the body due to exposure of hazardous compounds such as xenobiotics or drugs are scavenged by antioxidants. These free radicals that are produced in the body are able to bind to biological macromolecules in the body such as DNA, protein and lipids. A product of lipid peroxidation of membrane, MDA also reacts with biomolecules such as nucleic acid thereby damaging the cells (Cuzzocrea *et al*., 2001). With the increased amount of free radicals, the system is compromised due to the overwhelming process of the antioxidant system. There is a need for the intake of antioxidant rich supplements to complement the endogenous antioxidant in the body of the individual. Natural products have been shown by several studies to contain a vast array of diverse classes of bioactive compounds which include tocopherols, polyphenols and flavonoids (Gordana *et al*., 2004). Flavonoids can serve as antioxidants which help to neutralize free radicals that damage body tissues and which can lead to heart disease, strokes and cancers (Li-chem *et al*., 2006). Flavonoid compounds which possess antioxidant and antiradical activities are capable of quenching free radicals, which may stimulate mutations and DNA damage. KV, a biflavonoid complex, can protect against these adverse effects because of its antioxidant activity.

Chemoprevention by natural products against oxidative damage and chemical carcinogens may be related to their intrinsic antioxidant properties. Most of these chemicals including hydrogen peroxide are known to cause DNA damage through an oxygen radical mechanism and can induce chromosomal aberrations, gene mutations and DNA strand breaks (McKelvey-Martin *et al*., 1993).

Natural antioxidants such as herbs, plants, and the different spices which are consumed everyday are being investigated for their pharmacological and biochemical properties (Jialal and Scaccini, 1992),

Gordana *et al*., 2004 which are shown to be more economical and accessible compared to the synthetic antioxidants which may even pose threat to the subject. Quite a number of these natural products have been tried and found to cause a great reduction in oxidative modification both *in vitro* and *in vivo* (Farombi and Owoeye, 2011).

Garcinia kola, which has been known for its antioxidant properties, was therefore tested to see its mechanism of action on reactive oxygen species and lipid peroxidation. Adaramoye *et al*. (2005) found out that different fractions of Garcinia kola extract, GB1, GB2, KV, KF had different scavenging power on hydrogen peroxide generated in the animal model. Hydrogen peroxide scavenging activity of KV in relation to Butylated Hydroxyl Toluene, BHT, a standard antioxidant was tested (Adaramoye, 2005) on human subjects to see the potency of KV. It was observed that the scavenging properties of KV was comparable with BHT but at a higher concentration of Garcinia kola also showed scavenging effects with KF being the least scavenger of $H_2O_2$ *in vitro (Figure 2)*.

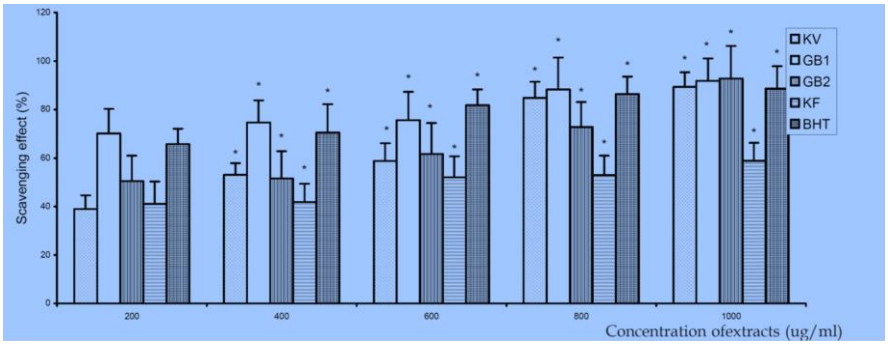



**Figure 2: The scavenging activity of flavonoids from Garcinia kola seeds on hydrogen peroxide radical in vitro**
Source: (Adaramoye *et al*., 2005)

Adaramoye *et al*., 2005, therefore suggests that KV, GB1, and GB2 were able to scavenge hydrogen peroxide radicals effectively. Kolaviron has been shown to scavenge $H_2O_2$ and was even more effective than compounds which were already known as standard antioxidants such as Butylated hydroxylanisole (BHA) and β-carotene which is found in tomatoes (Farombi *et al*., 2002). It has also been found to have the same effect as α-tocopherol. KV extract was also found to extensively scavenge superoxide radicals, which was generated by phenazine methosulfate

NADH (Hussain *et al*., 1982; Aruoma, 1999). In an experiment conducted by Farombi *et al*. (2002), it was discovered that kolaviron was able to mop up the hydroxyl radicals as shown by the significant inhibition of the deoxyribose oxidation.

Hydrogen peroxide is one of the highly reactive oxygen species which invades all protein, DNA, and poly unsaturated fatty acids in membrane and any other biological molecule it gets in contact with (Hussain *et al*., 1982; Aruoma, 1999). In the Hep G2 cells, reactive oxygen species production which was induced by $H_2O_2$ was independently inhibited by kolaviron dose when a fluorescence assay was carried out using 2, 7-dichlorofluorescein diacetate (Eddy *et al*., 1987; Nwankwo *et al*., 2000. This therefore showed that kolaviron and its components GB1 and GB2 act as effective and powerful antioxidants which in turn lead to scavenging of reactive oxygen species.

***Anti-diabetic activity***

Diabetes mellitus (DM) has been found to be one of the most degenerative diseases in the world (Ogbonnia *et al*., 2008). According to ADA (2011), it has been characterized by hyperglycemia, hypertriglyceridaemia and hypercholesterolaemia. DM is a complex disease which is exemplified by abnormal lipoproteins (Scoppola *et al*., 2001), decrease in activities of enzymes that scavenge reactive oxygen species (Kesavulu *et al*., 2000), and high oxidative stress which leads to damage of the β-cells of the pancreas (Nayeemunnisa, 2009). The management of diabetes has been of great interest in recent years (Erejuwa *et al*., 2012). Diabetic patients show several symptoms which include hyperglycemia, *polydipsia, polyuria* and *glucosuria*. When there is chronic hyperglycemia, it leads to several complications which include cardiovascular diseases, renal failure and retinopathy. Many drugs including the oral hypoglycaemic agents used to manage DM have been discovered to have adverse effects on different visceral organs in the body (Adaramoye *et al*., 2012). The unintended damage caused by these drugs has been shown to be due to the production of free radicals. Alloxan monohydrate and Streptozotocin-induced diabetic rats have been helpful as models in the diabetes research fields. Several studies have shown that there were significant increases in serum indices of renal, hepatic and cardiac toxicity in streptozotocin-induced diabetic rats (Adaramoye *et al*., 2012, Erejuwa *et al*., 2011; 2012).

These indices were further aggravated when these diabetic animals were treated with the antidiabetic drug, glibenclamide, GB although their serum glucose levels were significantly reduced. It was found out that the different fractions from Garcinia kola showed high significant hypoglycemic effect on the STZ-induced diabetic rats after 30 minutes of administration. The induction by STZ evoked a very high level of microsomal glucose-6-phosphatase which in turn caused an increase in hyperglycemia. Further research also conducted with kolaviron as a natural product in comparism with the standard antidiabetic drug, glibenclamide showed that there was significant decrease in the fasting blood glucose levels of STZ-diabetic animals as compared with the untreated diabetic group as shown in figure below (Adaramoye *et al*., 2012).

Kolaviron has also been shown to elicit a hypoglycemic effect in both fasted normoglycaemic and alloxan-induced diabetic rabbits (Iwu *et al*., 1990). HbA1c which expresses the percentage of hemoglobin which is bound to the glucose and also a measure for mean glucose concentration over a period of 6-8 weeks in the plasma of individuals who are known to be diabetic (Ghacha *et al*., 2001 ) was found to be reduced by KV even better than in GB-treated diabetic rats. Clinically, a higher amount of HBA1 in patients implies that the glucose level in the blood is poorly controlled which could be as a result of diabetes mellitus.

It was reported in the study below (Adaramoye, O.A, 2012), on the antidiabetic effects of KV that there was an increase in the HBA1c level after STZ administration. This increment was further significantly reduced by KV as shown in table 1.

**Table 1: Increase in the HBA1c level after STZ administration**

| Treatment | HBA1c |
|---|---|
| Normal | 4.2±0.3 |
| STZ only | 8.3±0.4* |
| STZ+KV | 5.0±0.4** |
| STZ+GB | 6.2±0.2** |

Values are means ± S.D. of 6 rats per group * significantly different from normal at $p< 0.05$ ** significantly different from STZ only at $p< 0.05$. STZ= Streptozotocin, KV= Kolaviron at 100 mg/kg, GB= Glibenclamide, HbA1c= Glycosylated hemoglobin

Source: Adaramoye, O.A. African health science 2012; (4): 498-506

**Hepatoprotective effects of Garcinia kola**

The liver and kidney are important organs which play an important role in the metabolism of xenobiotics in the body of an organism. The liver being the largest of the internal organs of the human body performs several functions, such as filtering poisons and waste from the blood, which are essential to life. One of the major functions of the liver is to store energy in the form of glycogen. When there is an infection in the liver, there are increased activities of enzymes such as Alanine Transaminase, Alkaline Phosphatase, Gamma Glutamyl Transaminase, and Aspartate Transferase which are predominantly found in the liver. As a result of toxicity of damage to this organ, the enzymes which are found therein may however leak out into the blood stream and thus cause elevation of the enzyme levels in the blood (Whitehead *et al*., 1999; Elizabeth and Harris, 2005).

Wojcicki *et al*., (1984) and Pickering *et al*. (1975) observed that GalNH2 induces liver damage and this causes inflammation of the liver which is similar to viral hepatitis and thus indicates its severity. The lesion that appears in the liver cells is being portrayed by inhibition of RNA and protein synthesis. Several natural products have served as sources of shelter and defense against xenobiotic toxicity and GalNH2 toxicity have also been researched into with positive results (Wojocicki *et al*., 1984 (Handa, 1990).

Study by Adaramoye and Adeyemi, 2006, showed the hepatoprotective effect of Garcinia kola on hepatocytes of mice. $GalNH_2$ – induced animals were pretreated with or without fractions of Garcinia kola. Results from the experiment showed significant elevation of serum indices alanine transaminase and aspartate transferase which is due to hepatotoxicity which was later reduced with the treatment with kolaviron. The activity of kolaviron was then compared with standard antioxidant Vitamin E which showed to have similar hepatoprotective effect with kolaviron. Results from the study are indicated in table 2.

**Table 2: The effect of kolaviron and its fractions on the level of malonaldehyde, ALT and AST generated in the serum**

| Treatment | LPO | ALT | AST |
|---|---|---|---|
| Control | 0.73±0.02* | 0.50±0.04* | 8.21±1.04* |
| KV+GalNH2 | 0.54±0.03* | 0.60±0.06* | 12.44±2.68* |
| FI+GalNH2 | 0.58±0.01* | 0.53±0.03* | 13.32±0.99* |
| FII+GalNH2 | 0.69±0.07* | 0.52±0.06* | 11.01±3.05* |
| FIII+GalNH2 | 0.98±0.01 | 1.44±0.05 | 18.95±2.09 |
| Vit. E+GalNH2 | 0.72±0.01* | 0.63±0.08* | 12.54±1.56* |
| GalNH2 | 1.07±0.01 | 1.79±0.05 | 20.41±3.35 |

Results are means ±S.D. of 5 animals.
Source: (Adaramoye & Adeyemi, 2006)

**Hypolipidemic and anti-hypertensive effects of *Garcinia kola***

Hypertension or high blood pressure is a medical condition in which the constricted arterial blood vessels increase resistance to blood flow, thereby causing an increase in blood pressure against the vessel wall. The systolic and diastolic blood pressures in normal blood pressure at rest is within the range of 100-140 mmHg and 60-90 mmHg, respectively whilst those in high blood pressure are >140-210 mmHg and >90-140 mmHg, respectively. Kolaviron has been found to help in vaso-relaxation of the blood vessels. Experiments carried out on the isolated rat mesenteric arteries showed that KV helps in the relaxation by blocking the calcium ion pump to avoid the entry of $Ca^{2+}$ from the intracellular milieu (Adaramoye and Medeiros, 2009). This dietary cholesterol which reduces fatty acid oxidation, leads to accumulation of the cholesterol in form of triglyceride in the blood and liver (Fungwe *et al*., 1993). Study conducted on rats fed with dietary cholesterol indicated that KV may help reduce the occurrence of coronary heart disease (Adaramoye *et al*., 2005).

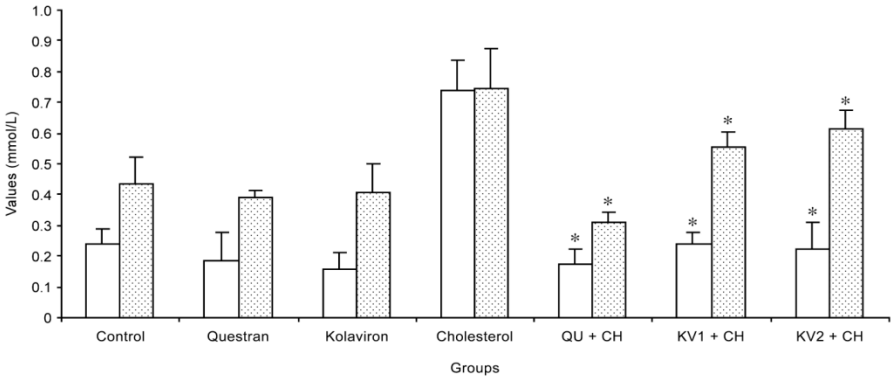



**Figure 3: Effect of kolaviron on post-mitochondrial fraction low-density lipoprotein–cholesterol and total cholesterol in cholesterol- fed rats. Data are the mean SD. ****P* **< 0.05 compared with the cholesterol-only fed group. KV1, KV2, 100 and 200 mg/kg kolaviron, respectively; QU, Questran; CH, cholesterol**

## Conclusion

A number of constituents have been extracted and characterized from Garcinia kola seed. Biological activities of these extracts have also been tested and observed to possess antidiabetic, anti-hypertensive, hepatoprotective, anti-scavenging properties. Kolaviron shows promise in the prevention of development of coronary heart diseases. This properties of kolaviron showed that this compounds might confirm protection of the visceral organs in the animals.

This review further shows an insight into the usage of naturally occurring plant materials as sources of antioxidants. Importantly is the bioavailability of the Garcinia Kola seed for human consumption. These natural plants are economical and easily accessible. The presence of the biflavonoid complex of *Garcinia kola* shows high potency for diseases which are caused by the generation of the oxyradical species in living organisms as compared to monoflavonoids. Intake of two to three seeds of bitter kola daily is advisable for normal consumption to give a recommended daily allowance.

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