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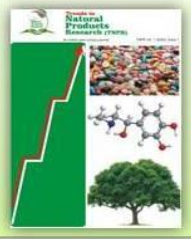

Towards harnessing the Therapeutic Potential of Kolaviron, a Biflavonoid Complex from *Garcinia kola Heckl*: A Review of its Bioactivity and Mechanisms of Action

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Abstract: Kolaviron, a bioactive biflavonoid complex found in the seeds of *Garcinia kola*, exhibits numerous therapeutic potentials. This paper provides an extensive review of the medicinal properties of kolaviron, and its significance in alternative medicine and drug development. The literatures on electronic databases, such as PubMed, Scopus, Web of Science, and Google Scholar, were thoroughly searched and analysed. The search keywords included "Kolaviron," "*Garcinia kola*," "bioactivity," and "therapeutic uses". The inclusion criteria for studies were those that investigated the bioactivity, safety, pharmacokinetics, and therapeutic potentials of kolaviron in preclinical (*in vitro and in vivo)* or clinical trials. The action mechanisms underlying the bioactivity of kolaviron have been partly elucidated. It modulates various signaling pathways involved in oxidative stress, inflammation, and cancer progression. Kolaviron was found to target multiple molecular targets and key transcription factors that regulate antioxidant defense systems or play crucial roles in immunoinflammatory pathways. In conclusion, this review highlights the therapeutic potential of kolaviron, emphasizing its diverse bioactivities such as antioxidant, anti-inflammatory, antimicrobial, antidiabetic and anticancer properties. These properties make it a promising candidate for the development of new therapeutic agents. However, further translational research is warranted to fully understand and harness its possible wide-ranging clinical applications.

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INTRODUCTION

Kolaviron is a bioactive flavonoid complex obtained from the seeds of *Garcinia kola* Heckel (Clusiaceae), a tropical plant native to West Africa. It has been used in traditional medicine for centuries to treat a variety of ailments, like respiratory infections, fever and liver disease. Recently, many scientific studies have investigated the bioactivity and therapeutic potential of kolaviron, revealing its wide-ranging beneficial effects on human health (Erukainure *et al*., 2021; Emmanuel *et al*., 2022; Tauchen *et al*., 2023). Kolaviron, which has a unique chemical composition of biflavonoids and polyphenolic compounds, has many pharmacological effects, such as antioxidant, anti-inflammatory, antimicrobial, antidiabetic, immunomodulatory and anticancer effects (Erukainure *et al*., 2021, Farombi *et al*., 2022). In addition, it shows cardioprotective effects (Oyagbemi *et al*., 2017, 2018) and potential for the treatment of infectious diseases (Dozie-Nwakile *et al*., 2021; Timothy *et al*., 2021)

Historically, *Garcinia kola*, the plant from which kolaviron is derived, has been significant in traditional African medicine. Commonly known as "bitter kola" due to its taste, it has been used for centuries in Nigeria and other West African countries as a remedy for various ailments including coughs, colds, fever, and liver diseases. It is considered an essential component of traditional medicine in West and Central Africa. Its anti-inflammatory, antioxidant, antibacterial, antifungal, and antimalarial properties make it a versatile treatment option for numerous conditions.

The discovery of Kolaviron, a bioactive complex in *Garcinia kola* seeds, is historically attributed to the research of Professor Maurice Iwu and his team at the University of Nigeria, Nsukka in the early 1990s. The team conducted comprehensive studies on the chemical composition, biological activities, and therapeutic potentials (Iwu, 1985; Iwu *et al*., 1987, 1990, 1994) Their pioneering research laid the foundation for further exploration into its potential health benefits for treating various diseases such as inflammatory disorders, diabetes, cancer, and cardiovascular diseases. The significant contributions of Professor E. O. Farombi and his team at the University of Ibadan, Nigeria is noteworthy. Farombi and his colleagues have carried out extensive research on kolaviron, focusing mainly on its protective properties against damage caused by chemical toxicants, oxidants and free radicals in the liver, kidney, cardiovascular, and other bodily systems (Farombi *et al*., 2000, 2002, 2004, 2005, 2009, 2023). They have also examined its effects on cancer cells, oxidative stress, and dyslipidemia. Recently, there has been a significant increase in kolaviron research as scientists investigate its chemical composition, action mechanisms, and potential therapeutic uses.

Due to promising findings in kolaviron research, there is growing interest in harnessing kolaviron bioactivity and therapeutic potential for developing new drugs and health products. This review article aims to provide a comprehensive overview of the current state of knowledge on kolaviron, covering its chemical composition, bioactivity, mechanisms of action, therapeutic potentials, safety, and toxicity. The article will also identify the gaps in knowledge and future research directions needed to fully harness the potential of kolaviron for human health.

Review and Search Methodology

The information in this review was obtained through an extensive literature review and search of relevant books and articles using the Web of Knowledge, SciVerse Scopus, and PubMed databases. The search was conducted from February to June 2023 (search period: 1960-2023), using specific keywords such as "*Garcinia kola*," "kolaviron," "Garcinia biflavonoids," "GB1," "GB2," "kolaflavanone," and "Bitter kola." Due to the lack of human clinical trials, both *in vitro* and *in vivo* studies were included in the review. This review aims to provide a comprehensive overview of scientifically available information on kolaviron, including studies using isolated substances and solvent extracts, as well as its reported biological activities and potential health benefits.

Chemical composition of kolaviron

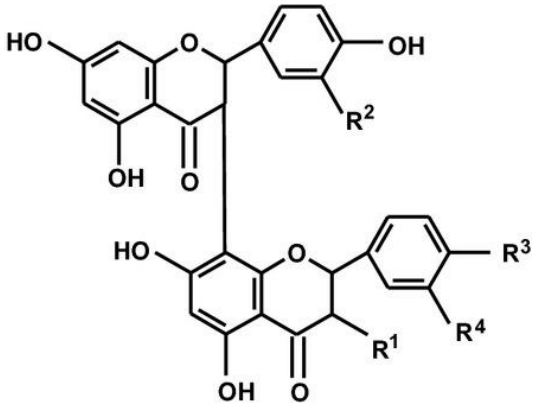
Kolaviron is a complex blend of bioflavonoids and other polyphenolic compounds found in *Garcinia kola* seeds. The most important constituents of kolaviron are biflavonoids, flavanone glycosides, and kolaflavanones (Iwu, 1985; Iwu *et al*. 1987, 1990). Biflavonoids, unique to the Garcinia genus, are the main bioactive components of kolaviron. They consist of two flavonoid molecules linked by a single bond, resulting in a characteristic dimeric structure (Iwu *et al*., 1990; Nworu *et al*., 2008; Emmanuel *et al*., 2022),

The most common biflavonoids found in kolaviron are GB1 and GB2, which consist of the flavonoids kaempferol and quercetin linked together by a single bond (Iwu *et al*., 1990; Nworu *et al*., 2008; Emmanuel *et al*., 2022). Kolaflavanones are another class of polyphenolic compounds present in kolavirone that are structurally similar to flavanones but have different chemical structures and carbon atom arrangements (Kumar and Pandey, 2013; Kolawole *et al*., 2018). The chemical structures of these kolaviron components are complex and contain multiple rings and functional groups. The unique structures of these

compounds are thought to contribute to the diverse bioactivity and therapeutic potential of kolaviron.
The chemical structure of kolaviron consists of two flavanone units linked together by a C-C bond between positions 4' of one flavanone and 8" of the other flavanone (Iwu *et al*., 1990; Nworu *et al*., 2008; Emmanuel *et al*., 2022). The two flavanone units are known as GB1 and GB2, which are connected by a butane-1,4-diol linker. The molecular formula of GB1 is $C_{30}H_{22}O_{11}$ (MW: 558.5g/mol), and its IUPAC name is (2R,3R)-8-[(2S,3R)-5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-2,3-dihydrochromen-3-yl]-3,5,7-trihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one (https://pubchem.ncbi.nlm.nih.gov/#query=GB1)

Extraction and purification methods of kolaviron

To obtain high yields and purity of kolaviron from *Garcinia kola* seeds, specific extraction and purification methods are necessary. The process involves several steps, including a crucial defatting stage. This step eliminates unwanted fats and oils from the seeds, thereby facilitating the extraction of kolaviron (Iwu, 1985; Iwu *et al*. 1990).
Many reported methods for extracting kolaviron involve grinding *Garcinia kola* seeds into a fine powder and then extracting with a suitable solvent such as acetone, ethyl acetate, ethanol or methanol. The most popular and initially discovered method is that of Iwu *et al*. (1990). *Garcinia kola* seeds are first peeled, cut and air-dried at 25-28°C before being grounded. The grounded seeds are defatted with petroleum ether (boiling point 40-60 °C) or n-hexane in a Soxhlet extractor for at least 24 h. Next, the dried press residue, now devoid of fat, is repacked into a soxhlet extractor and subjected to extraction with acetone. The concentrated extract is mixed with a double amount of water and the kolaviron is extracted with ethyl acetate (6 x 300 mL). This process results in a concentrated fraction which is partitioned with ethyl acetate to give kolavirone, a golden yellow solid (Iwu, 1985).
Crude kolaviron can also be subjected to column chromatography using silica gel as the stationary phase and a mixture of solvents such as ethyl acetate and methanol as the mobile phase. The purification of kolaviron can be achieved using various methods such as preparative thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC), and preparative HPLC. This method yields high amounts of kolaviron with purity up to 90%. Organoleptically, kolaviron has a bitter taste and a characteristic odour. It is soluble in organic solvents such as methanol, ethanol, and dimethyl sulfoxide (DMSO), but insoluble in water. Its appearance varies depending on the purity and concentration of the extract. Generally, kolaviron is a brownish-yellow powder or solid with crystalline structure.



	R1	R2	R3	R4
GB1	OH	H	OH	H
GB2	OH	H	OH	OH
Kolaflavanone	OH	H	OCH_3	OH

Figure 1: Structure of bioflavonoids of kolaviron

Structural features and Structural activity relationship of kolaviron

The structure-activity relationship (SAR) of kolaviron has been extensively studied to understand the key structural features responsible for its bioactivity (Iwu, 1985; 1986; Adaramonye *et al.,* 2005; Iwu *et al*., 1990). Kolaviron is composed of two major flavonoids, namely Garcinone C and Biflavonoid A. Garcinone C is a benzophenone derivative while Biflavonoid A is a flavonoid dimer consisting of two flavanone units linked by a C-C bond (Iwu, 1985; 1986; Adaramonye *et al.,* 2005; Iwu *et al*., 1990). These two compounds are responsible for the biological activities of kolaviron. The structural features of kolaviron play a crucial role in its bioactivity and therapeutic potentials. The biological activities of kolaviron such as antioxidant, anti-inflammatory, anti-cancer, anti-diabetic, anti-microbial and hepatoprotective properties are related to the unique structure of the biflavonoid complex (Chagas*et al*., 2022). The unique structural features of kolaviron include the presence of two flavonoid molecules linked together by a C-C bond and the presence of hydroxyl groups in both flavonoid molecules (Nijveldt *et al*., 2001; Shamsudin *et al*., 2022). The C-C bond is between the 3-position of one flavonoid and the 8-position of the other. The two flavonoids are composed of catechol and pyrogallol

moieties, respectively. SAR studies have revealed that the presence of both catechol and pyrogallol moieties is essential for the antioxidant activity of kolaviron (Kelly *et al*., 2022). These features are responsible for its diverse biological activities and make kolaviron a potential therapeutic agent for the management of various diseases. For instance, the presence of hydroxyl (-OH) groups in the structure of any flavonoid makes it highly polar and water-soluble (Karak *et al*., 2019). This property allows kolaviron to easily interact with water molecules in biological systems, making it readily available for absorption and distribution in the body. The presence of the C-C bond in kolaviron makes it resistant to degradation by enzymes in the body, thereby increasing its bioavailability and half-life (Kumar and Pandey, 2013). Another important property of kolaviron is its antioxidant activity. This compound has been shown to scavenge free radicals and protect cells from oxidative damage (Erukainure *et al*., 2021). The antioxidant activity of kolaviron is attributed to the presence of phenolic groups in its structure, which can donate hydrogen atoms to neutralize free radicals (Erukainure *et al*., 2021). The hydroxyl groups present in both flavonoid molecules also contribute to the antioxidant activity of kolaviron by donating hydrogen atoms to scavenge free radicals and prevent oxidative damage to cells (Vo *et al*., 2019) Furthermore, the structural features of kolaviron also play a role in its anti-inflammatory activity. Kolaviron inhibits the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α) by blocking the nuclear factor-kappa B (NF-κB) pathway (Farombi *et al*., 2009). This mechanism is facilitated by the presence of hydroxyl groups in both flavonoid molecules that interact with NF-κB to inhibit its activation. Another important structural feature of kolaviron is the presence of a prenyl group on one of the flavonoids. SAR studies have shown that prenylation enhances the bioactivity of kolaviron by increasing its lipophilicity and cellular uptake (Sippl and Ntie-Kang, 2020). Prenylation also increases the stability of kolaviron by protecting it from degradation by enzymes. The addition of prenyl groups to kolaviron helps shield it from enzymatic degradation, thereby increasing its stability (Ogunwa *et al*., 2019)

Pharmacological properties of kolaviron

Kolaviron has been extensively studied for its pharmacological properties, such as antioxidant and free radical scavenging activities, anti-inflammatory and antimicrobial actions, anticancer and hepatoprotective effects, immunomodulatory and adjuvant functions, cardiovascular protection, antidiabetic benefits, and neuroprotective properties (Erukainure *et al*., 2022; Farombi *et al*., 2022). The pharmacological properties of kolaviron make it a promising therapeutic agent for various diseases.

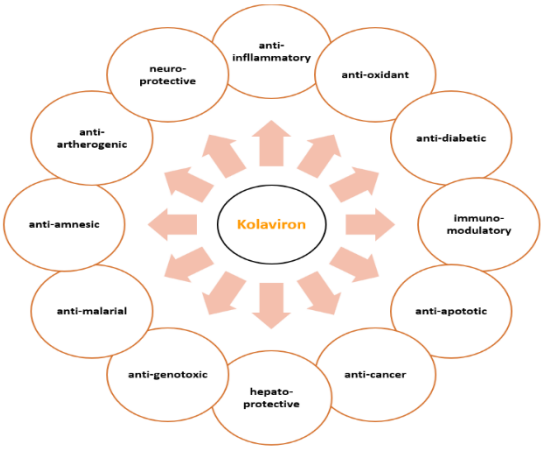


Figure 2: Pharmacological properties of kolaviron

Antioxidant and Free Radical Scavenging Activities

The recruitment of inflammatory cells at the infection site leads to excessive reactive oxygen species (ROS) production, which is important in the pathogenesis, development, and progression of inflammatory diseases (Griffith *et al*., 2009; Akki*et al*., 2020). Kolaviron has been reported to possess potent antioxidant and free radical scavenging activities both *in vitro* and *in vivo* (Ayepola *et al*., 2014). It effectively inhibited H_2O_2 and was shown to be better than butylated hydroxyanisole (BHA) and β-carotene (Farombi *et al*., 2002). Furthermore, kolaviron significantly scavenges superoxide generated by phenazine methosulfate NADH and hydroxyl radicals, as evidenced by the substantial inhibition of deoxyribose oxidation (Farombi, 2011). *In vivo*, kolaviron decreased background levels of protein oxidation marker (2-aminoadipic semialdehyde) in plasma and liver, as well as γ-glutamyl semialdehyde (GGS) and malondialdehyde in the liver (Farombi *et al*., 2004). Kolaviron showed ability to reduce the damage to proteins and lipids caused by Fe^{3+}/EDTA/ascorbate mixtures ex vivo (Farombi *et al*., 2004), and dose-dependent inhibition of intracellular ROS production induced by H_2O_2 (Nwankwo *et al*. 2000). Several other studies have demonstrated the antioxidant and free radical scavenging activities of kolaviron. In one study (Kehinde *et al*., 2016), kolaviron was found to scavenge free radicals such as DPPH (2,2-diphenyl-1-picrylhydrazyl) and ABTS (2,2'-azino-bis (3-ethylbenzothiazoline-6-sulphonic acid)) in a dose-dependent manner. The study also showed that kolaviron had a higher antioxidant activity than vitamin E and vitamin C. Another study investigated the effect of kolaviron on lipid peroxidation, a process that can lead to

oxidative damage of cell membranes (Farombi *et al*., 2000; Farombi *et al*., 2000). The study reported that kolaviron dose-dependently inhibited lipid peroxidation. The researchers suggested that kolaviron could be used as a natural antioxidant to prevent lipid peroxidation. Kolaviron has also been reported to increase the activities of endogenous antioxidants such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) (Abarikwu, 2014; Olatoye and Akindele, 2023). These enzymes play important roles in protecting cells against oxidative stress.

In vivo studies have further confirmed the antioxidant activity of kolaviron (Farombi *et al*., 2013, Erukainure *et al*., 2021). For example, kolaviron was found to reduce lipid peroxidation and increase the levels of antioxidant enzymes in rats exposed to oxidative stress induced by carbon tetrachloride (CCl4) (Farombi, 2000; Farombi and Owoeye, 2011). In another study (Nkanu *et al*., 2019), kolaviron was shown to protect against oxidative damage in liver and

Anti-inflammatory Properties Kolaviron

Kolaviron's most notable pharmacological property is its anti-inflammatory activity, which has been extensively studied in various preclinical *in vitro* and *in vivo* studies (Farombi *et al*., 2009; Onasanwo and Rotu, 2016). Inflammation is a complex biological response that occurs in response to tissue damage or infection. While acute inflammation is a natural and necessary process for the body to heal itself, chronic inflammation can lead to a host of diseases such as cancer, diabetes, and cardiovascular disease. Therefore, the development of safe and effective anti-inflammatory agents is crucial for the prevention and treatment of these diseases. Kolaviron has been shown to possess potent anti-inflammatory properties through various mechanisms. One study (Abarikwu, 2014) demonstrated that kolaviron inhibited the production of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) in lipopolysaccharide (LPS)-stimulated macrophages. Another study found that kolaviron reduced the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS), the two enzymes involved in the inflammatory response (Abarikwu, 2014).

Furthermore, kolaviron has been shown to inhibit the activation of nuclear factor-kappa B (NF-κB), a transcription factor that regulates the expression of genes involved in inflammation. NF-κB activation is known to play a critical role in the pathogenesis of chronic inflammatory diseases, and therefore, inhibition of NF-κB activation by kolaviron represents a promising therapeutic strategy (Abarikwu, 2014).

In addition to its direct anti-inflammatory effects and as discussed in the preceding section, kolaviron has also been shown to possess antioxidant properties. Oxidative stress is known to contribute to the development of chronic inflammatory diseases, and therefore, the antioxidant activity of kolaviron may further contribute to its anti-inflammatory effects. Overall, the anti-inflammatory properties of kolaviron make it a promising candidate for the prevention and treatment of chronic inflammatory diseases. Further studies are needed to fully elucidate the mechanisms underlying its anti-anti-inflammatory activities.

Antimicrobial Activities of Kolaviron

The antimicrobial activity of kolaviron has been demonstrated against both Gram-positive and Gram-negative bacteria and fungi.

GB1, a biflavonoid component of kolaviron, has demonstrated antibacterial properties against methicillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci. The minimal inhibitory concentrations (MIC) were found to be 32 and 128 mg/ml respectively (Han *et al*., 2005). Further studies showed that the antibacterial activities of the methanol extracts, which contain kolaviron from *G. kola*, had an MIC range of 256 to 1024 µg/mL against multidrug resistant Gram-negative bacteria that overexpress active efflux pumps (Lacmata *et al*., 2012). Kolaviron demonstrated immunomodulatory and immunorestorative properties in both *in vitro* and *in vivo* studies involving immunocompetent and immunocompromised animal models (Nworu *et al*., 2008). These findings could potentially be use for clinical benefits in treating immunodeficient patients who may need antimicrobial agents.

Anticancer Properties

Kolaviron possesses anticancer properties, which can help to prevent or treat cancer. The anticancer properties of kolaviron have been attributed to its ability to induce apoptosis, inhibit angiogenesis, and modulate the immune system (Nworu *et al*., 2008; Erukainure *et al*., 2021). Apoptosis is a programmed cell death process that plays a critical role in the regulation of cell growth and differentiation. The dysregulation of apoptosis is a hallmark of cancer, and agents that can induce apoptosis in cancer cells have anticancer properties. Kolaviron has been reported to induce apoptosis in various cancer cell lines, including breast cancer, prostate cancer, and colon cancer cells (Farombi *et al*., 2023). The mechanism by which kolaviron induces apoptosis is believed to be through the activation of caspases, which are enzymes that play a central role in the execution of apoptosis.

Angiogenesis is the process by which new blood vessels are formed from pre-existing ones. Angiogenesis plays a critical role in tumour growth and metastasis, and agents that can inhibit angiogenesis have anticancer properties. Kolaviron inhibits angiogenesis *in vitro* and *in vivo* (Ogunwa *et al*., 2019). The mechanism by which kolaviron inhibits angiogenesis is believed to be through the suppression of vascular endothelial growth factor (VEGF), which is a key regulator of angiogenesis (Muhammad *et al*., 2017). The immune system plays a critical role in the recognition and elimination of cancer cells. Agents that can modulate the immune system have anticancer properties. Kolaviron has been reported to modulate the immune system by increasing the production of cytokines such as interleukin-2 (IL-2) and interferon-gamma (IFN-γ), which are involved in the activation of immune cells such as T cells and natural killer (NK) cells (Nworu *et al*., 2008).

Hepatoprotective properties of kolaviron

Kolaviron has demonstrated hepatoprotective properties, which aid in protecting the liver from damage caused by toxins or harmful substances. This property is attributed to the ability of kolaviron to enhance liver function and reduce oxidative stress (Oyenihi *et al*., 2015). The hepatoprotective effects of kolaviron have been shown against hepatotoxicity induced by various drugs and hepatotoxins, such as CCl4 (Farombi *et al*., 2000), diclofenac (Alabi *et al*., 2017), aflatoxin (Farombi *et al*., 2005), 2-acetyl aminofluorene (Adaramoye *et al*., 2009), and dimethylnitrosamine (Farombi *et al*., 2009).The hepatoprotective activities of kolaviron involve antioxidant and anti-inflammatory properties, as well as inhibition of lipid peroxidation (Farombi *et al*., 2000; 2005; 2009; Alabi *et al*., 2017). Kolaviron suppresses certain pro-inflammatory genes regulated by transcription factors, eliminating the expression of COX-2 and iNOS proteins in DMN-treated rat liver. It also prevents the DNA binding activity of NF-kB and AP-1 induced by dimethyl nitrosamine (Farombi *et al*., 2009). Additionally, kolaviron increases antioxidant levels, such as glutathione, regulates lipid profiles, and restores liver function biomarkers in drug-induced liver toxicity in rodents (Farombi *et al*., 2000; Adaramoye *et al*., 2009).

Immunomodulatory properties of kolaviron

Kolaviron has demonstrated a number of immunomodulatory effects in both *in vitro* and *in vivo* studies. For example, kolaviron can inhibit delayed-type hypersensitivity reactions, increase the antibody production, and modulate the complement system (Nworu *et al*., 2008). These effects suggest that kolaviron could have potential therapeutic applications for various immune-related conditions, such as allergies, autoimmune diseases, and cancer. Kolaviron possesses immunomodulatory properties, that can help regulate immune system function. This property is attributed to the ability of kolaviron to modulate the production of cytokines and other immune system cells and molecules (Nworu *et al*., 2008; Abarikwu *et. al*., 2014).

Cardiovascular protective properties of kolaviron

Kolaviron has been demonstrated to possess cardiovascular protective properties, which can help reduce the risk of cardiovascular disease (Adaramoye *et al*., 2005; Adoga *et al*., 2021). This property was attributed to kolaviron's ability to decrease oxidative stress and inflammation in cardiovascular system (Adoga *et al*., 2021) Oxidative stress and inflammation have been identified as significant factors in the pathways leading to the development of cardiovascular diseases (CVDs), in which endothelial and thromboembolic dysfunction are etiological factors (Stocker and Keaney Jr, 2005; Victor and Rocha, 2007; Victor *et al*., 2009; Kibel *et al*., 2020). Reactive oxygen species (ROS) are highly reactive chemical entities, regulated by enzymatic and non-enzymatic antioxidant defense mechanisms. ROS play a crucial role in heart cell homeostasis by controlling cell proliferation, differentiation, and excitation-contraction coupling (D'Oria *et al*., 2020). However, when ROS production exceeds the capacity of antioxidant defenses to neutralize them, oxidative stress occurs, leading to cellular and molecular dysfunctions and ultimately resulting in heart failure. Oxidative stress is a crucial factor in the development of hypoxia- and ischemia-reperfusion-related cardiovascular disorders (Farías *et al*., 2017; D'Oria *et al*., 2020; Valaei *et al*., 2021). Several pathways and enzyme systems, including xanthine oxidase (XO), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), uncoupled endothelial nitric oxide synthase, and the mitochondrial electron transport chain, have been associated with the generation of reactive oxygen species (ROS) in the cardiovascular system (Cammisotto *et al*., 2021; Knaus, 2021). Furthermore, inflammation occurs in the vascular tissue, involving inflammatory immune cells, cell surface interactions, and proinflammatory mediators (Moreira *et al*., 2015). As previously discussed, kolaviron has demonstrated anti-inflammatory, antioxidant, free-radical scavenging, and anti-lipid peroxidation properties, which are essential for protecting the cardiovascular system. Kolaviron activities strengthen the antioxidant enzyme systems that safeguard the vasculature and

cardiomyocytes against reactive oxygen species (ROS), such as superoxide dismutase (SOD), catalase, and glutathione peroxidases (Wang and Kang, 2020; Dubois-Deruy *et al*., 2020). In a study on rat models with reperfusion injury (Oyagbemi *et al*., 2016; Oyagbemi *et al*., 2018), kolaviron's cardioprotective effects were found to result from inhibiting the activation of p38 MAPK and enhancing the activation of Akt. This protected cardiomyocytes from apoptosis by decreasing the expression of Caspase 3, cleaved Caspase 3, and cleaved PARP (Oyagbemi *et al*., 2016; Oyagbemi *et al*., 2018).

Antidiabetic properties of kolaviron

Kolaviron possesses antidiabetic properties, which can help to regulate blood sugar levels. Iwu *et al*. (1990) reported that Kolaviron had significant hypoglycaemic effects in both normal and alloxan diabetic rabbits when administered intraperitoneally at a dose of 100 mg/kg, reducing fasting blood sugar levels in normoglycemic rabbits from 115 mg/100 mL to 65 mg/100 mL after 4 hours, and in alloxan diabetic rabbits from 506 mg/100 mL to 285 mg/100 mL at 12 hours. This property was attributed to the ability of kolaviron to enhance insulin sensitivity and reduce oxidative stress. Oyenihi *et al*. (2015) reported the protective effects of kolaviron on hepatic antioxidants, lipid peroxidation, and apoptosis in diabetic rats. Their results showed that kolaviron administration in diabetic rats increased the activity of catalase (CAT) (Oyenihi *et al*., 2015). In addition, kolaviron attenuated lipid peroxidation and apoptosis, and increased the levels of reduced glutathione (GSH) and the ratio of reduced to oxidized glutathione (GSH: GSSG) (Oyenihi *et al*., 2015; Olatoye and Akindele, 2023). The activities of glutathione peroxidase (GPX) and superoxide dismutase (SOD) were unaltered in diabetic rats (Oyenihi *et al*., 2015). Similar studies showed beneficial effects of kolaviron (Ayepola *et al*., 2014), and various solvent fractions of *Garcinia kola* on the metabolic, antioxidant, and anti-inflammatory parameters in streptozotocin (STZ)-induced rat models of type 1 diabetes mellitus (Idris *et al*., 2020).

Neuroprotective properties of kolaviron

Kolaviron has been shown to possess neuroprotective properties, which can help to protect the brain from damage caused by oxidative stress or other harmful substances (Onasanwo *et al*., 2016; Adedara *et al*., 2020; Oyovwi *et al*., 2021). This property was attributed to the ability of kolaviron to enhance brain function and reduce inflammation. Many studies have demonstrated the ability of kolaviron to protect against oxidative stress and inflammation in the brain, which are key contributors to neurodegenerative diseases such as Alzheimer's and Parkinson's (Adewole *et al*., 2021). Kolaviron has also been shown to improve cognitive function and memory in animal models (Olajide *et al*., 2017). Kolaviron treatment was found to counteract cuprizone-induced behavioural deficits and improve cerebellar functions by reducing oxidative stress (Omotoso *et al*., 2020). Cuprizone (CPZ) significantly depressed locomotor and exploratory activities, causing increased oxidative stress (OS) and cerebellar toxicity. The study showed that KV intervention significantly enhanced behavioural functions and ameliorated CPZ-induced cerebellar degeneration. Moreover, it considerably regulated OS markers in the cerebellum of a rat model of demyelinating diseases (Omotoso *et al*., 2020). In a related study, KV effectively protected against CPZ-induced neurotoxicity and demyelination in the prefrontal cortex and hippocampus of Wistar rats by preventing ribosomal protein degradation (Omotoso *et al*., 2018). Exposure to multiwalled carbon nanotubes (MWCNTs) has been reported to cause neurotoxic effects. However, the co-administration of kolaviron and MWCNTs significantly improved locomotor, and exploratory activities in rats compared to those exposed to MWCNTs alone. This includes enhancements in the total distance travelled, maximum speed, total time mobile, mobile episodes, path efficiency, body rotation, absolute turn angle, and negative geotaxis. Furthermore, kolaviron significantly alleviated the reduction in acetylcholinesterase activity and antioxidant defense system, as well as the increase in oxidative stress and inflammatory biomarkers caused by MWCNT exposure in the cerebrum, cerebellum, and mid-brain of rats. The improvement of MWCNTs-induced neuronal degeneration in brain structures by kolaviron was confirmed through histological and morphometric analyses (Adedara *et al*., 2020; Adedara *et al*., 2021). It is thus suggested that kolaviron mitigated MWCNTs-induced neurotoxicity through anti-inflammatory and redox regulatory mechanisms.

Mechanisms of action of Kolaviron

The molecular mechanisms underlying the bioactivities of kolaviron have been investigated (Onasanwo and Rotu, 2016; Farombi, 2000; Nwankwo *et al*., 2000). Kolaviron exerts its pharmacological activities through several signalling pathways, including Nrf2, NF-κB, MAPK, PI3K/Akt, JAK/STAT, and Wnt/β-catenin (Abarikwu, 2014). Understanding these pathways is essential for developing kolaviron as a therapeutic agent for various diseases. Kolaviron scavenges free radicals and prevent oxidative stress-induced damage in cells.

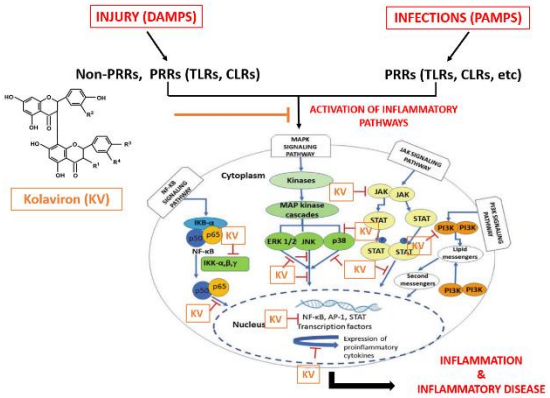


Figure 3: Some targets/mechanisms of action of kolaviron in the inflammatory signalling pathways.

Legend: KV = kolaviron; **DAMPs**= Damage-associated molecular patterns; **PAMPs**; Pathogen-associated molecular patterns; **PRRs** = pattern recognition receptors; **TLRs** = toll-like receptors; **CLRs** = C-type lectin receptors; **NF-κB** = nuclear factor-kappa B; **ERK1/2** = extracellular signal-regulated kinases, **IκBα** = inhibitor of kappa light polypeptide gene enhancer in B-cells, kinase beta.

This effect was attributed to its ability to upregulate antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx) and downregulate pro-oxidant enzymes such as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and xanthine oxidase (Teodoro *et al*., 2016). Kolaviron also inhibits lipid peroxidation and enhances the activity of endogenous antioxidants like glutathione (Farombi *et al*., 2009, 2018). These mechanisms are partly behind the reported antioxidant and anti-inflammatory properties, which are relevant in several disease models including reproductive toxicity, cardiotoxicity, diabetes mellitus, gastrotoxicity and hepatotoxicity. Kolaviron has also been shown to inhibit the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6) by suppressing the activation of nuclear factor-kappa B (NF-κB) (Olaleye *et al*., 2010). It was shown to reduce the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), the enzymes involve in producing nitric oxide and prostaglandins, respectively (Okoko, 2018). These mechanisms are involved in its anti-inflammatory, hepatoprotective, and neuroprotective effects.

Caspases play a crucial role in the apoptotic pathway. Kolaviron has been demonstrated to induce apoptosis (programmed cell death) in cancer cells by activating caspases (Adedara *et al*., 2013). Caspases are an evolutionarily conserved family of cysteine proteases, centrally involved in cell death and inflammatory responses. A deeper understanding of the mechanisms regulating caspase activation has facilitated initial attempts to modulate dysfunctional cell death and inflammation pathways in various communicable, inflammatory, malignant, metabolic, and neurodegenerative diseases (Van Opdenbosch *et al*., 2019). Kolaviron can also inhibit the proliferation of cancer cells by arresting the cell cycle at various stages, including G0/G1, S, and G2/M phases. Additionally, kolaviron can inhibit angiogenesis, which is the process of new blood vessel formation that is essential for tumour growth and metastasis (Farombi *et al*., 2023). One of the signalling pathways involved in the antioxidant activity of kolaviron is the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. Kolaviron activates Nrf2, which induces the expression of antioxidant enzymes such as heme oxygenase-1 (HO-1) and glutathione S-transferase (GST) (Onasanwo *et al*., 2016). These enzymes play a crucial role in protecting cells against oxidative stress. Another signalling pathway involved in the anti-inflammatory activity of kolaviron is the nuclear factor-kappa B (NF-κB) pathway. Kolaviron inhibits the activation of NF-κB, which is a transcription factor that regulates the expression of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (Abarikwu, 2014). By inhibiting NF-κB activation, kolaviron reduces inflammation. Kolaviron has also been reported to have anticancer activity through various signaling pathways. One of these pathways is the mitogen-activated protein kinase (MAPK) pathway (Abarikwu, 2014). Kolaviron activates MAPKs such as extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38, which regulate cell proliferation, differentiation, and apoptosis (Abarikwu, 2014). By activating these MAPKs, kolaviron induces apoptosis and inhibits cell proliferation in cancer cells (Farombi *et al*.,2023). In addition to these pathways, kolaviron has also been reported to modulate other signaling pathways such as the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway, the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, and the Wnt/β-catenin pathway (Akinmoladun *et al*., 2015).

From the above, it can be inferred that kolaviron exerts its bioactivities through various signaling pathways including Nrf2, NF-κB, MAPK, PI3K/Akt, JAK/STAT, and Wnt/β-catenin pathways. Understanding these pathways is crucial for developing kolaviron as a therapeutic agent for various diseases.

V. Therapeutic potentials of kolaviron

Kolaviron has been extensively studied for its bioactivity and potential therapeutic applications. Kolaviron holds considerable therapeutic potential in various diseases, particularly in disorders where inflammation is a significant causative factor. The multifaceted mechanisms of action, as discussed in the preceding sections, including antioxidant, anti-inflammatory, antimicrobial, and anticancer properties, make it a promising candidate for further exploration and development as a therapeutic agent. Recent studies have increasingly explored the potential effects of kolaviron on various diseases such as diabetes, cancer, cardiovascular and infectious diseases. This section offers a comprehensive overview of the potential therapeutic applications of kolaviron in treating these conditions.

1. **Cancer**: Kolaviron has demonstrated significant anticancer properties in various preclinical studies. It exhibits potent cytotoxic effects against a wide range of cancer through the induction of apoptosis (programmed cell death), inhibition of cell proliferation, and suppression of angiogenesis (the formation of new blood vessels that support tumour growth) (Ayepola *et al*., 2014; Suleiman *et al*., 2022). Additionally, kolaviron has been found to enhance the efficacy of conventional chemotherapeutic agents and reduce their associated side effects. These findings suggest that kolaviron holds great potential as an adjuvant therapy for cancer treatment.

2. **cardiovascular diseases**: Kolaviron possesses remarkable cardioprotective properties and has been investigated for its potential in managing various cardiovascular diseases (Akinmoladun *et al*., 2015; Adoga *et al*., 2021; Olatoye *et al*., 2021). Studies have shown that kolaviron can effectively reduce blood pressure by promoting vasodilation and inhibiting the production of vasoconstrictor substances (Uche and Osakpolor, 2018). Furthermore, it exhibits antioxidant and anti-inflammatory activities, which help protect against oxidative stress and inflammation-induced damage to the cardiovascular system (Oyagbemi *et al*., 2016). Kolaviron has also been reported to improve the lipid profile by reducing total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels while increasing high-density lipoprotein (HDL) cholesterol levels (Adaramoye *et al*., 2005). These multifaceted effects make kolaviron a promising candidate for the prevention and management of cardiovascular diseases such as hypertension, atherosclerosis, and myocardial infarction (Adoga *et al*., 2021; Olatoye *et al*., 2021).

3. **Diabetes**: Kolaviron has shown potential in the management of diabetes and its associated complications (Adaramoye. 2012; Salau *et al*., 2021; Oyenihi *et al*., 2022; Salau *et al*., 2023). It exerts antidiabetic effects by enhancing insulin secretion, improving glucose uptake, and protecting pancreatic beta cells from oxidative damage. Kolaviron also exhibits anti-inflammatory properties, which can help alleviate chronic low-grade inflammation commonly observed in individuals with diabetes. Moreover, kolaviron has been found to possess the hepatoprotective activity, protecting the liver from diabetes-induced damage. These findings suggest that kolaviron may have therapeutic implications in the prevention and treatment of diabetes and its complications (Adaramoye. 2012; Adoga *et al*., 2022).

4.**Infectious Diseases**: Kolaviron has demonstrated significant antimicrobial activity against a wide range of pathogens, including bacteria and viruses (Adaramoye *et al*., 2016; Erukainure *et al*., 2021; Dozie-Nwakile *et al.*, 2021; Oluyori *et al*., 2023). Kolaviron has also been reported to possess antiviral activity against several viruses, including human immunodeficiency virus (HIV), herpes simplex virus (HSV), hepatitis C virus (HCV), and SARS-CoV-2 (Awogbindin *et al*., 2015; Abodunrin *et al*., 2022); Oluyori *et al*., 2023. These antimicrobial properties make kolaviron a potential therapeutic agent for the treatment of infectious diseases.

5. **Neurological Disorders**: Emerging evidence suggests that kolaviron may have neuroprotective effects and could be beneficial in the management of neurological disorders. Studies (Erukainure *et al*., 2021) have shown that kolaviron possesses antioxidant and anti-inflammatory properties, which can help protect neurons from oxidative stress and inflammation-induced damage. Kolaviron has been found to enhance memory and cognitive function in animal models of Alzheimer's disease (Ishola *et al*., 2017). These findings indicate that kolaviron holds promise as a potential therapeutic agent for neurodegenerative disorders.
The study of the neuroprotective effect of kolaviron on behavioural impairment, neurodegeneration, oxidative stress, and neuroinflammation in the acute 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTD)-induced PD model has been conducted (Farombi *et al*., 2020). Kolaviron was found to alleviate the frequently observed MPTP-associated hyperkinesia, inefficient gait, immobility, and inability to navigate sizable holes on the walking path. It also reduced habitual clockwise rotations with minimal diversion of movements and improved balance (Farombi *et al*., 2020). The study demonstrated that Kolaviron mitigated MPTP-induced striatal oxidative stress, depletion, and

degeneration of dopaminergic terminals. It also decreased DJ-1 secretion and increased the expression of caspase-3. Furthermore, Kolaviron was shown to promote a cytoprotective antioxidant response and prevent MPTP-induced neuroinflammation by blocking striatal infiltration of peripheral CD45R positive cells (Farombi *et al*., 2020).Evidences suggest that kolaviron displays a broad spectrum of bioactivities and holds potential as a therapeutic agent for various diseases. Numerous research findings support its therapeutic use in disorders such as hepatoprotection, chemoprotection, nephroprotection, immunomodulation, antioxidant and free-radical scavenging activities. Kolaviron has proven effective in protecting the liver from inflammatory damage induced by toxins or diseases like hepatitis. Additionally, it has demonstrated chemoprotective effects by inhibiting cancer cell growth and inducing apoptosis. The nephroprotective properties of kolaviron have been demonstrated by its ability to lessen oxidative stress and inflammation in the kidneys, potentially preventing kidney damage and enhancing renal function (Adedara *et al*., 2015; Alabi *et al*., 2018). Additionally, kolaviron displays immunomodulatory effects by adjusting immune responses and boosting the body's defense mechanisms against infections and autoimmune diseases. However, despite these potential therapeutic benefits, more preclinical and clinical studies are needed to fully understand its efficacy, safety profile, and optimal dosage regimens in various disease contexts.

VI. Safety and toxicity of kolaviron

To evaluate the feasibility of kolaviron as a therapeutic agent, it is crucial to thoroughly examine its safety and potential toxicity. This section will present a review of existing literature concerning the safety profile and toxicity of kolaviron. Understanding the potential adverse effects of kolaviron is essential for determining its suitability for further development. The existing preclinical data indicates that kolaviron has a promising acute safety profile, showing no noticeable genotoxic or mutagenic effects (Farombi *et a*l., 2004b; Kalu *et al*., 2016; Olatoye and Akindele, 2023). However, it is necessary to conduct thorough evaluations of sub-chronic and chronic toxicity, reproductive and developmental toxicity, and potential drug interactions. The data currently experience for human-safe use is anecdotal, originating from its routine use as a masticatory adaptogen (Nworu, 2007, 2008; Esimone *et al*., 2007) and its historical use in African traditional medicine. However, it's crucial to establish clinical evidence base to empirically confirm its safety and tolerability in humans. These efforts are vital steps towards utilizing the therapeutic potential of kolaviron while guaranteeing its safe use in healthcare. Based on the available evidence from empirical animal studies and human experience over the years, kolaviron appears to have a favourable safety profile with minimal toxicity (Nworu *et al*., 2008; Ishola *et al*., 2017). Acute and sub-chronic animal studies have consistently shown that kolaviron does not induce significant adverse effects even at high doses (Nworu *et al*., 2008). In a ninety-day oral toxicological profiling of Kolaviron, KV did not elicit any adverse effect on histopathological presentations of vital organs which were generally non-abnormal (Olatoye and Akindele, 2023).

VII Future Perspectives

Several future perspectives should be considered for exploring the therapeutic potentials of kolaviron. Firstly, comprehensive studies are needed to clarify the exact molecular targets and signalling pathways that kolaviron utilizes to exert its bioactivities. This can be achieved through advanced techniques such as proteomics, genomics, and metabolomics. Additionally, investigations into the pharmacokinetics of kolaviron are necessary to determine its optimal dosage and administration routes for different therapeutic purposes.

Furthermore, the potential synergistic effects of kolaviron with other natural compounds or conventional drugs should be explored. Combination therapies may enhance the efficacy of kolaviron and reduce potential side effects. Moreover, preclinical and clinical trials are essential to evaluate the safety and efficacy of kolaviron in humans. These studies will provide valuable insights into its therapeutic potential and pave the way for its development as novel drug or nutraceutical.

Finally, considering the increasing interest in natural products and their potential health benefits, it is crucial to promote sustainable sourcing and cultivation practices for *Garcinia kola*. Conservation efforts should be implemented to ensure the long-term availability of this valuable medicinal plant. Additionally, collaborations between researchers, pharmaceutical companies, and regulatory agencies are necessary to facilitate the translation of kolaviron's therapeutic potentials into practical applications for the benefit of human health.

VII. Conclusion

This review provides a comprehensive overview of Kolaviron's bioactivity and its mechanisms of action. The paper highlights the wide-ranging therapeutic potentials of kolaviron, including its antioxidant,anti-inflammatory, immunomodulatory,

anticancer and chemoprotective, antidiabetic, neuroprotective, nephroprotective, hepatoprotective properties among others. The underlying molecular mechanisms through which kolaviron exerts its effects, such as modulation of oxidative stress, inflammation pathways, cell cycle regulation, and apoptosis were explored. This review further highlights the significant therapeutic potential of kolaviron and stresses the necessity for additional research to fully exploit its benefits.

DECLARATION OF PATIENT CONSENT

Patient's consent was not required as there were no patients in this study.

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None to declare

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