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Review Article

Tetracarpidium Conophorum (African Walnut): A Review of Pharmaceutical Evidence on Cardiac Toxicity

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ABSTRACT

Objectives: *Tetracarpidium conophorum*, also known as African walnut, is a versatile climbing shrub with medicinal properties. In recent times, it has gained attention for its potential health benefits. This fruit not only promotes overall well-being but also aligns with certain lifestyle factors supported by scientific research. Its positive effects on heart health have been well-documented.

Study Approach: A comprehensive review of relevant literature was conducted, encompassing studies published from 2017 to 2023. The review specifically investigated the influence of *Tetracarpidium conophorum* on the cardiovascular system, with a particular emphasis on its potential implications for cardiac toxicity.

Findings: Four reports were identified as the most pertinent sources regarding the pharmaceutical evidence of *Tetracarpidium conophorum* on the cardiovascular system. These reports suggest that *Tetracarpidium conophorum* has a significant therapeutic effect on cardiac toxicity.

Conclusion: Based on the four identified reports, it can be inferred that *Tetracarpidium conophorum* has the potential to be a valuable ingredient in pharmaceuticals aimed at mitigating cardiac toxicity.

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Introduction

With the increasing global reliance on natural remedies, one of the current goals of researchers is to discover new products for the development of new drugs with high therapeutic efficacy and low toxicity profiles. In recent years, there has been a growing focus on medicinal plants to achieve this goal (Akomolafe *et al*., 2017). According to Hasler (1998), there has been a surge in consumer interest in physiologically active food components known as "functional foods". Gupta *et al*. (2004) reported the utilization of medicinal plants for addressing various health conditions such as diabetes, and erectile dysfunction, as well as cardiovascular, neurodegenerative, and inflammatory diseases.

Cardiovascular diseases are a leading global cause of death, highlighting the importance of researching cardiotoxicity and cardioprotective agents for better

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healthcare services. Cardiac toxicity refers to dysfunction of the heart as electric or muscle damage caused by toxins, potentially leading to arrhythmias or heart failure over time. Improving our understanding of cardiac toxicity and identifying protective agents can lead to better healthcare outcomes and quality of life.

Drug-related cardiotoxicity has been linked to synthetic antioxidants found in certain medications. These substances have been associated with various health risks, including cancer. To mitigate the risk of cardiovascular diseases, lifestyle changes such as exercise, low salt intake, and a healthy diet are often recommended. However, medication becomes necessary in critical stages (Balogun *et al*., 2019). As a result, there is a growing interest in exploring plant-based alternatives for treatment (Zhang *et al*., 2010).

Plants contain a wide variety of bioactive phytochemicals and secondary metabolites, making them a promising source for the development of modern synthetic drugs to treat various diseases. Balogun *et al*. (2016) stated that medicinal plants have demonstrated therapeutic potential due to the presence of diverse bioactive compounds. It is understood that all the constituents within a whole plant extract work together to achieve therapeutic efficacy, as emphasized by the World Health Organization (WHO, 1996). Considering the high costs and potential side effects associated with conventional drugs, there has been a growing interest in assessing the essential oils, nutritional value, and chemical composition of tropical plants, many of which possess medicinal properties (Repetto and Llesuy, 2002).

The tropical African walnut, known as *Tetracarpidium conophorum* (Mull. Arg.) Hutch. and Dalziel or *Plukenetia conophora* (Oyekale *et al*., 2015), belongs to the family Euphorbiaceae (Edem *et al.,* 2009). It is also sometimes found in the family *Olacaceae* (Adebona *et al.*, 1988). The walnut is generally referred to as the conophor tree or conophor nut (Janick and Paul, 2008). The plant is known by other names such as conophor tree, conophor nut, black walnut, and Nigerian walnut (Ekwe and Ihemeje, 2013; Nwaichi *et al.,* 2017). Scientific research (Nwaichi *et al*., 2017) and clinical trials (Edem *et al*., 2009) have shown that African walnut has properties that can help lower the risk of heart disease (Ayodeji and Aliyu,2018). However, there is still a lack of modern crop management techniques, production technologies, and value chains in Africa for the cultivation and marketability of African walnuts, which hinders their full economic potential (Nnodim *et al*., 2020). Current and future African walnut research and development programs should prioritize improved crop management and post-handling technologies, the cultivation of modern varieties with high yield and nutritional quality, value addition, and market access.

The objective of this review is to analyze various studies and provide insights into the mechanisms of action and active compounds of African walnuts. Furthermore, it critically evaluates the pharmaceutical evidence regarding the effects of African walnuts on cardiac toxicity, underscoring the necessity for rigorous clinical trials to validate its therapeutic potential in mitigating cardiac toxicity. The findings in this review will add to the expanding knowledge of natural compounds that have the potential to revolutionize cardiovascular care, thus prompting further exploration of *Tetracarpidium conophorum'*s utilization as a complementary approach to promoting cardiac health.

Morphology

Tetracarpidium conophorum is a monoecious plant, typically ranging from 3-15 meters in length, although it can reach up to 30 meters. It exhibits separate male and female flowers on the same plant (Janick and Paul, 2008). The male flowers are located in a narrow raceme-like panicle that extends up to the length of the leaves. Near the base of this panicle, one or two female flowers can be found. The flowers are arranged alternately along the axis of the raceme inflorescence. The style of the female flowers is stout and quadrangular, and it bears four spreading stigmas (Ayodeji and Aliyu, 2018). The walnut tree typically has a large number of stamens, with approximately 40 in total (Janick and Paul, 2008). The plants are climbers that are typically found in the forest zones, both primary forests, which are the original and undisturbed forests, as well as secondary forests, which are forests that have regrown after previously being cleared or disturbed. The seeds of this plant are surrounded by a thick and hard testa, giving them extra protection. At maturity, the seeds are round in shape and have a dark brown colour (Okujagu *et al*., 2005). The seed has a diameter of about 2.5 cm, while the ripe fruit measures around 7 cm across and changes color from light green to brown (Janick and Paul, 2008). The walnut tree often grows wrapped around other trees for support, particularly cocoa and kola nut trees (Oyekale *et al*., 2015).

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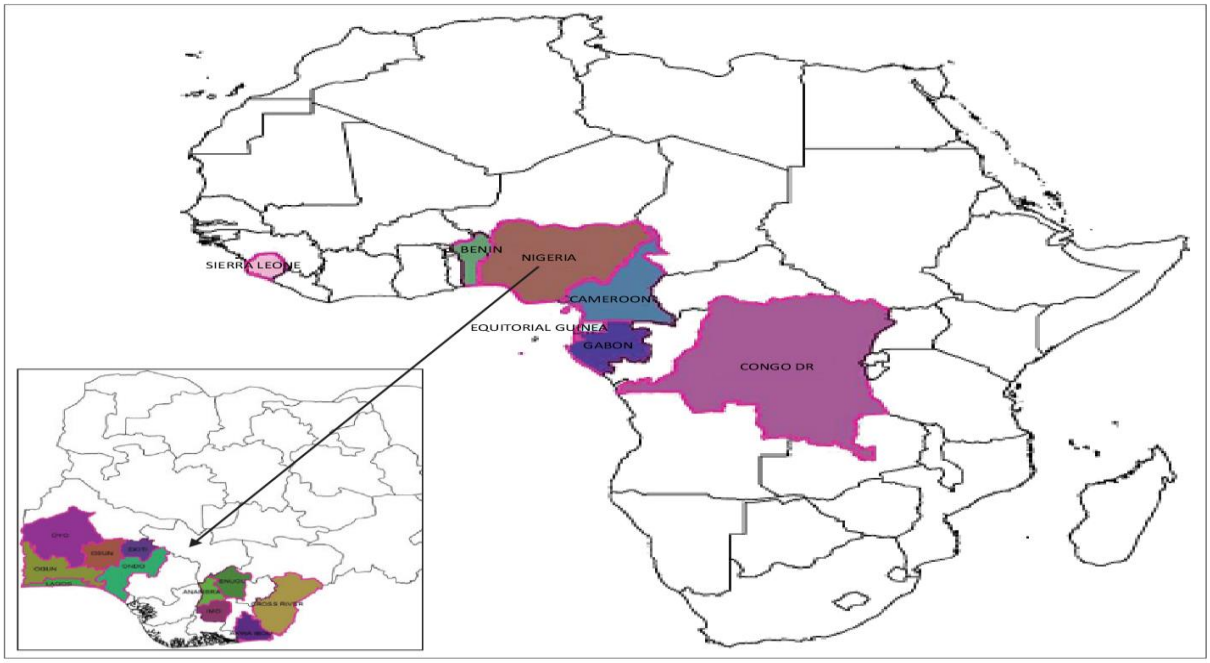
Figure 1: *Tetracarpidium conophorum* (African walnut) (Oke *et al*., 2020)

Figure 2: *Tetracarpidium conophorum* in its natural habitat (Ayoola *et al*., 2011)

Origin and Distribution

The African Walnut, scientifically named *Plukenetia conophora or Tetracarpidium conophorum* belongs to the Euphorbiaceae family and has a lengthy history as a sporadic natural fruit (Oke *et al*., 2020). *Tetracarpidium conophorum* is a notable indigenous plant that thrives in the tropical regions of western and central Africa. It is commonly found in a variety of countries, including Togo, Sierra Leone, Nigeria, Cameroon, the Republic of the Congo, and the Democratic Republic of Congo. In Nigeria, it can be found specifically in Akwa Ibom, Cross River, Lagos, Kogi, Osun, and Oyo states. However, one major challenge that hinders its market value is the lack of suitable storage facilities. This limitation necessitates the consumption of the nuts within 1-2 days after cooking, otherwise, they develop an unpleasant odor that renders them unsuitable for sale and consumption (Edem *et al*., 2009). It typically blossoms around November and early January and fruits are produced between February and September. The peak production of African walnuts occurs in July (Oyekale *et al*., 2015). The development of the seed takes approximately 4–6 months (Akpuaka and Nwankwor, 2000).



Source: Nkwonta 2015

Figure 3: Geographical distribution of *Tetracarpidium conophorum* Countries in Africa and states in Nigeria (Nkwonta, 2015).

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Table 1: Scientific Classification of *Tetracarpidium conophorum*

Scientific Classification

Rank	Name	Author
Kingdom	Plantae	Haeckel, 1866
Phylum	Spermatophyta	
Class	Magnoliopsida	Cronquist *et al*., 1996
Subclass	Dilleniidae	
Order	Euphorbiales	
Family	Euphorbiaceae	de Jussieu, 1789
Genus	Plukenetia	
Species	Conophora	Mull.Arg.

SYNONYM: *Tetracarpidium conophorum* (Mull.Arg.) Hutch. and Dalziel

Scientific classification of *Tetracarpidium conophorum* (Govaerts, 2023)

Methodology

A literature survey was conducted on various research databases to investigate the effects of the plant on the cardiovascular system and its toxicity. The search utilized specific keywords to explore this topic which includes; "*Tetracarpidium conophorum* and cardiac toxicity" "*Tetracarpidium conophorum* and cardiac health" "*Tetracarpidium conophorum* on heavy metals induced cardiac toxicity", "*Tetracarpidium conophorum* on iron, salt and cadmium induced cardiac toxicity", "*Tetracarpidium conophorum* on doxorubicin-induced cardiac toxicity". A summary of the findings is provided (Table 2).

Findings

Four (4) reports have been identified as the most suitable research studies that support the pharmaceutical evidence of *Tetracarpidium conophorum* on the cardiovascular system, indicating its essential therapeutic role in mitigating cardiac toxicity.

Table 2: **Pharmaceutical evidence of *Tetracarpidium conophorum* on cardiac toxicity**

Serial Number	Pharmaceutical evidence of *Tetracarpidium conophorum*	Research evidence
1.	*Tetracarpidium conophorum* extract has an ameliorating effect on iron (II) chloride-induced heart damage because it contains some phytochemicals such as tannins, terpenoids, and flavonoids.	(Innih *et al*., 2021)
2.	*Tetracarpidium conophorum* (Walnut) is responsible for the maintenance of normal structural and/or architectural integrity of cardiac tissue / myocytes through protecting the heart from the doxorubicin-induced myocardial infarction.	(Ezugwu *et al*., 2021)
3.	Aqueous extracts of *Tetracarpidium conophorum* have the potential to ameliorate salt-induced hypertension and reduce lipid peroxidation in Wistar rats.	(Bassey *et al*., 2018)
4.	*Tetracarpidium conophorum* (Walnut) was reported to have hepatoprotective and cardioprotective properties in the management of cadmium chloride-induced hypertension in albino rats and has some biological activities comparable to Nifedepem which served as the standard drug as was used in the study for the treatment of hypertension.	(Nnadi and Igbokwe, 2022)

Therapeutic Effects

Studies have increasingly focused on the therapeutic effects of *Tetracarpidium conophorum* on various body systems due to its wide range of medicinal properties. According to Akomolafe *et al*. (2017), aqueous extract from *Tetracarpidium conophorum* inhibited and reduced the activities of the key enzymes linked to erectile dysfunction and oxidative stress-induced lipid peroxidation in penile and testicular tissues of rats. The *Tetracarpidium conophorum* seed extracts administered orally to alloxan-induced diabetic Wistar rats had positive effects on the hypoglycemia of the rats. Further evidence for its potential use in the treatment and prevention of diabetes was found through its impact on blood lipid and glucose levels in rats with diabetes (Airaodion *et al*., 2022).

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Tetracarpidium conophorum seeds possess good glycemic control of diabetes mellitus and protect the liver against oxidative damage in diabetes-induced liver damage in rats treated with streptozotocin research carried out by Ajilore *et al.* (2020). Suara *et al*. (2016) further established an antibacterial property in *Tetracarpidium conophorum* methanol leaf extract which was active against *Bacillus subtilis* and Proteus mirabilis which is a causative agent of skin diseases. Kanu *et al*. (2015) reported that extract from *Tetracarpidium conophorum* leaves had more capacity to diminish lipid peroxidation in conceptive organs and frill organs. In this way, the plant might be valuable in the treatment of reproductive cellular damage (Oke *et al*., 2020). Omega 3 and Omega 6 are two fundamental fatty acids required by the body for cell development, immune function, blood clotting, and disease prevention which the body cannot make alone (Gourmetguide, 2014). These fatty acids are present in African walnuts.

Studies have also shown *Tetracarpidium conophorum* has anti-malarial properties (Dada and Ogundolie, 2016), anti-cancer properties (Nwaoguikpe and Ujowundu, 2016), energizing properties (Aladeokin and Umukoro, 2011) and anti-lipidemic properties (Ezealisiji *et al*., 2016) which make up its medicinal impacts.

Discussion

Tetracarpidium conophorum (African walnut) a native to the tropics of Western and Central Africa and commonly cultivated in Western Nigeria is a walnut plant that comes from the Euphorbiaceae family and the Plukenetia genus. It is known as Ekporo by Efik and Ibibios of Cross River and Akwa-Ibom states (Ojobor *et al*., 2015), Ukpa by Igbos, Awusa by Yoruba, Okhwe or Okwe by Edo, Gawudi bairi by Hausas (Akpuaka and Nwankwo, 2000). In Sierra Leone, it is called musyabassa and in western Cameroon, it is known as kaso or ngak, among other local names. The plants are cultivated principally for the nuts which are cooked and consumed as snacks (Oke, 1995).

Adverse cardiovascular effects caused by cardiac toxicity include arrhythmia, hypertension, myocardial ischemia, thromboembolism, heart failure, systolic dysfunction, and other related events (Truong *et al*., 2014). Chemotherapy treatment, specifically with the class of anthracyclines like doxorubicin, can cause cardiac toxicity (Huang *et al*., 2010; Volkova and Russel, 2011) and/or radiotherapy (Suchorska and Wiktoria, 2020); complications from anorexia nervosa; adverse effects of heavy metals (cadmium, iron) intake (Nigra *et al*., 2016); abusing or consuming high doses of powerful stimulants like cocaine over a prolonged period (Pergolizzi *et al*., 2021); or an incorrectly administered drug such as bupivacaine (de La Coussaye *et al*., 1993). The different types of cardiac toxicity include reversible, irreversible, acute, chronic, and late-onset. Irreversible damage is categorized as type 1 and reversible damage as type 2. Direct therapeutic evidence of *Tetracarpidium conophorum* on cardiac toxicity was demonstrated in cadmium, salt, iron-overload, and doxorubicin-induced cardiac toxicity (Table 2), where administration of *Tetracarpidium conophorum* ameliorated several effects such as tissue damage induced by the toxins. According to Innih *et al*., (2021), iron (II) chloride administered to the rats caused vascular ulceration, stenosis, and perivascular inflammatory infiltrates in the study which was carried out to investigate the effects of *Tetracarpidium conophorum* on iron overload-induced cardiac toxicity in Wistar rats. Post treatment with *Tetracarpidium conophorum* extract showed normal cardiomyocytes and vasculature which proves the healing effect of walnut on damaged cells. There was also dilation of blood vessels which is a mechanism to reduce blood pressure in the heart as it contains omega-3 called alpha-linolenic acid (ALA). It also proves the anti-inflammatory activity of walnuts.

The experimental studies of Ezegwu *et al*. (2021) revealed that the myocardium of Wistar rats experienced toxic damage from repeated doxorubicin administration. However, post-treatment with *Tetracarpidium conophorum* (African walnut) prevented the rise of serum marker enzymes induced by doxorubicin and restored the myocardial infarction caused by it. This finding supports the idea that *Tetracarpidium conophorum* plays a role in preserving the normal structure and integrity of cardiac tissue/myocytes, thereby protecting the heart from myocardial infarction.

Hypertension treatment primarily depends on synthetic medicines, but newer, more effective antihypertensive drugs have been introduced to the market with significant side effects (Balogun *et al*., 2016). Additionally, due to limited resources, the cost of synthetic drug treatment may not be affordable for many hypertensive patients in developing nations like Nigeria. Thus, it is crucial to explore natural remedies for preventing and managing hypertension (Arakawa *et al*., 2006; Tahraoui *et al*., 2007). The study of Bassey *et al*., (2018) was designed to investigate the antihypertensive effect of aqueous extract of *Tetracarpidium conophorum* in salt-induced hypertensive rats. The results of the study indicate that the anti-hypertensive effect observed in hypertensive rats is attributed to the presence of flavonoids,

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saponins, tannins, alkaloids, and phenols in the aqueous extract of *Tetracarpidium conophorum*.

Nnandi and Igbokwe (2022) carried out research on the protective effects of nutraceuticals from *Tetracarpidium conophorum* against cadmium-chloride-induced hypertension in albino rats. The results obtained showed that *Tetracarpidium conophorum* exhibits renoprotective, cardioprotective, and hepatoprotective effects in Wistar rats. This suggests that the nutraceutical properties of the walnut can protect against cadmium chloride-induced hypertension. This protective effect is evidenced by a significant reduction in total protein levels, conjugated bilirubin levels, and total bilirubin levels in the *Tetracarpidium conophorum* study group compared to the control, hypertensive, and standard groups.

Conclusion

Pharmaceutical evidence indicates that *Tetracarpidium conophorum* shows promising results in mitigating cardiac toxicity. Thus, prompting its consideration as a potential active ingredient in pharmaceuticals.

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