

Review

The sausage plant (*Kigelia africana*): Have we finally discovered a male sperm booster?

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Our world harbors a rich source of medicinal plants which are used in the treatment of a wide range of diseases. *Kigelia africana* popularly known as the Sausage tree, cucumber plant, *Kigelia pinnata*, is a multipurpose medicinal plant with many attributes and considerable potentials. Some of these include its use for treatment of gynaecological disorders, renal ailments, skin complaint, tumors and reproductive disorders in developing countries where western orthodox medicine are expensive and or inaccessible, and there is high poverty rate. Anecdotal reports of its use in treatment of many ailments of reproductive background abound, and scientific validation of this in the last decades remains promising. Against the background of increasing male-factor related infertility and the continued search for phytomedical source for treatment, the present review highlights the reports of researchers on the potential fertility-enhancing properties of *K. africana* (Lam.) Benth with a view to its future development as a male sperm booster to alleviate the oligo/azoospermia associated with male infertility and also its diverse applications even in improving yield in aquaculture.

Key words: *Kigelia africana*, fertility-enhancing properties, reproduction.

INTRODUCTION

An impressive improvement has occurred in global health status in the past century which has become a cause for celebration. Therefore, public-health professionals can feel proud of their contribution to these achievements even as they appreciate the complexity of the underlying driving forces, many of which lie outside traditional public-health work. But this satisfaction must be tempered by emerging concerns (Sen and Bonita, 2000) against the recent evidence suggesting that based on current trends, many low-income countries are unlikely to achieve desired health targets by 2015, due to devastating disease and overwhelmingly failing health systems (Travis et al., 2004).

Infectious diseases are important in public health for communities in Africa and the developing world (Sparg et al., 2000), and these diseases and subsequent deaths have devastating consequences for developing economies. The meager health budgets and lack of adequate medical facilities hinder efforts by poor African countries to match the overwhelming treatment and prevention burden presented by these diseases (Louw et al., 2002). This has in one way advanced the interest in indigenous herbal medicines/remedies as a potential source of treatment repertoires by the natives in time past. Currently, many research efforts towards our indigenous African systems (knowledge) is receiving

strong support by the various higher education and research bodies across the countries, especially in South Africa.

Traditional knowledge to solve health problems of mankind and animals exists in all countries of the world (Rukangira, 2001), with history dating back to as long as 3000 BC years ago (Sofowora, 1982). In most of the traditional medicine, the medicinal plant include the fresh or dried part, whole, chopped, powdered or an advanced form of the herb usually made via extraction by a solvent such as water, ethanol or an organic solvent which play a major role and constitute the backbone of traditional medicine (Mukherjee, 2002). This system has undergone numerous transformations according to the prevailing cultural, traditional and social indices in the community but what has remained as a recurrent decimal across regions is the continuous interest by the scientific community into the proper identification of the relevant plant/herbs that are useful.

WHY PLANT-BASED THERAPY?

Knowledge has been built for decades on the use of herbal medicinal products and extracts in the treatment of human diseases (Iwalewa et al., 2007). In Nigeria (Kafaru, 1994), South Africa (Mander, 1998) and Bangladesh (Apu et al., 2012), traditional medicine has become well acknowledged and established as a viable profession that has helped in solving the numerous fertility related problems plaguing the society. Ethno-medicinal plant-use data in many forms has been heavily utilized in the development of formulas and pharmacopoeias, providing a major focus in global health care as well as contributing substantially to the drug development process (Graham et al., 2000). The medicinal values of these plants lie in some chemical substances that produce definite physiological actions on the human body. Some of these bioactive constituents of plants are classified as alkaloids, tannins, flavonoids, saponins, phenolic compounds; and other compounds reported to possess diverse range of bioactivity (Edeoga et al., 2005; Iwalewa et al., 2007).

Herbs have provided us some of the very important lifesaving drugs used in the armamentarium of modern medicine. Surprisingly, of the 400,000 plant species that Botanists have identified, only about 6% have been studied for biological activity, and about 15% have been investigated phytochemically (Cragg et al., 1997). This is against the backdrop of progress made in modern medicine, with more than 70% of the developing world's population still dependent on traditional medicine (Shaikh and Hatcher, 2005). This inadvertently shows a dire need for the in-depth review of the chemical constituents, pharmacological evaluation and biological activities and

probable mechanisms of action of herbal medicine.

Many western pharmaceutical agents are derived from tropical plant species, such as quinine from *Cinchona* spp., cancer-treating drugs from the rosy periwinkle (*Catharanthus roseus*), treatments for enlarged prostate gland from *Prunus africana*, forskolin which has a variety of medicinal uses, from the root of *Coleus forskohlii* and medicine for treating diabetes from *Dioscorea dumetorum* and *Harungana vismia* (Cunningham and Mbenkum, 1993; Colfer et al., 2006). The economic value therefore of traditional medicine is considerable, for example the bark of *P. africana* is exported from Cameroon, Equatorial Guinea, Madagascar, and Tanzania to the European Union (EU) under a systematic methodology that allows for sustainable management of the plant in the host countries while maintaining supply to the pharmaceutical industries in Europe (Clemente Muñoz et al., 2006). In 1999, the Forestry Department of Equatorial Guinea set an annual export quota for Prunus bark of 500 tonnes per year, upon consultation with the Convention on International Trade in Endangered Species (CITES) authorities in Malabo (Sunderland and Tako, 1999).

Herbs have been used since the beginning of time to aid in many different ailments. Of these ailments, fertility has been enhanced and even corrected by the use of certain herbs (Ramsey, 2000). The use of plant extracts as fertility enhancer in animals is now in the increase because of the shifting of attention from synthetic drugs to natural plant products (Dada and Ajilore, 2009). Hence, despite the increasing availability of conventional pharmacological therapies for management of fertility-related abnormalities in males, plant-derived herbal remedies have continued to increase the repertoire of available options for men seeking to improve their sexual life (Azu et al., 2009). This review is undertaken to highlight the significant milestone in the research on *Kigelia africana* geared towards improvement in male reproductive health. It is also intended to advance likely pathways for its proposed action.

K. AFRICANA PLANT

K. africana (Lam) Benth, herein after referred to as *K. africana*, belongs to the family Bignoniaceae, an exceptional indigenous medicinal plant, native to and widely distributed in Africa where it grows in open woodlands and wet areas including river banks/floodplains of Nigeria, Cameroon, Kenya, Guinea, and Senegal. It can also be found in open woodland from KwaZulu-Natal (South Africa) to Tanzania, Chad, and Namibia (Burkill, 1985). It represents an interesting example of a plant used in traditional medicine for many years, but which is now attracting interest and use far beyond its original geographical range (Kolodziej, 1997;

Owolabi and Omogbai, 2007). It is commonly called 'Sausage tree' or 'Cucumber tree' due to its long sausage-like fruit.

Description of *K. africana* tree, fruit, and seed

The tree is widely grown as an ornamental plant in the tropical regions for its decorative flowers and unusual fruit. It can grow to more than 20 m tall. The bark is grey and at first smooth but peels on older trees. The bark can be as thick as 5 mm. The wood is pale brown or yellowish in color, and not prone to cracking (Roodot, 1992). The leaves are opposite or in whorls of 30 to 50 cm in length, pinnate, with six to ten oval leaflets each up to 20 cm in length and 6 cm wide. Some birds/insects are attracted to the flowers where they use the strong stems as footholds. Their scent is most notable at night, indicating their reliance on pollination by bats which visit them for pollen and nectar. It flowers between the months of August and November (Joffe, 2003). Flowers are bisexual, very large; pedicel up to 11 cm long up curved at tip; calyx shortly tubular to campanulate, 2 to 4.5 cm long, suddenly widening and incurving upwards, limp 2-lipped, with the super or lip 2-lobed, the lower one 3-lobed and recurved (Grace et al., 2002).

The huge, grey-brown fruit is a woody berry 30 to 100 cm long and up to 18 cm wide. It weighs between 4 to 10 kg and hangs from a long and fibrous stalk (Azu, 2010). The fruit is fibrous and pulpy, containing numerous hard seeds which are inedible to humans. However, several species of mammals eat the fruits/seeds, for example baboons, bush pigs, monkeys, porcupines, savannah elephants, giraffes and hippopotami. The seeds are dispersed via their dung. In Malawi, during famine the seeds are roasted and eaten by humans. Brown parrots and brown-headed parrots also eat the seeds (del Hoyo et al., 1997; Mukherjee, 2002; Owolabi and Omogbai, 2007).

Constituents of *K. africana*

The understanding of the phytochemical constituents of medicinal plants like *K. africana* is imperative not only because of the understanding of the scientific rationale for its usage but also for the discovery of novel compounds of pharmaceutical value (Fennell et al., 2004). Several phytochemical studies revealed that the extracts from many species of Bignoniaceae contained secondary metabolites such as saponins, tannins, flavonoids, quinones, alkaloids, anthralene derivatives, reducing sugars, glycosides, carbohydrates, querletin, kaempferol, α -sitosterol, terpenes, steroids, coumarins secondary metabolites and their derivatives (Gouda et

al., 2006; Choudhury et al., 2011). These bioactive constituents are reported present in the fruits of *K. africana* as an iridoid, verminoside and polyphenols like verbascoside (Picerno et al., 2005; Gouda et al., 2006), stem bark (Sofowara, 1984; Binutu et al., 1997), root bark (Binutu et al., 1997; Weiss et al., 2000) and the leaves (Gouda et al., 2006).

A notable number of bioactive compounds have been recorded from the Bignoniaceae family of plants that reportedly demonstrates a number of important activities which are beneficial to human beings. The various activities included mosquito larvicidal (Taura et al., 2004), anti-oxidant (Oltof et al., 2001; Jung et al., 2006; Olaleye and Rocha, 2007, 2008), anti-plasmodial (Zofou et al., 2011), antiprotozoal (Moideen et al., 1999; Weiss et al., 2000), anti-amoebic (Bharti et al., 2006), antidiarrheal (Galvez et al., 1993; Akah, 1998; Owolabi and Omogbai, 2009), anti-inflammatory (Picerno et al., 2005; Hussain et al., 2007; Owolabi and Omogbai, 2007), anti-microbial (Akunyili et al., 1991), antibacterial (Binutu et al., 1996; Grace et al., 2002; Ogbeche et al., 2002; Hussain et al., 2007; Owolabi et al., 2007), anti-depressant/central nervous system (CNS) stimulant effects (Owolabi et al., 2008), anti-cancer (Houghton et al., 1994; Jackson et al., 2000; Picerno et al., 2005; Bharti et al., 2006; Hussain et al., 2007), anti-diabetic, anti-nociceptive, anti-snake venom and neurotrophic (Rahmatullah et al., 2010) activities. However, efforts at the further elucidation of how these activities are executed *in vivo* or *in vitro* remains to be established by researchers.

***K. africana* and male fertility parameters**

Sexual difficulties are extremely prevalent among both men and women and are an important component of quality of life and subjective well-being of humans. They are associated with a number of biological, medical, and psychological risk factors and increase markedly with aging (Laumann et al., 1999; Leiblum, 1999). The main sexual problems are related to sexual desire and male erectile dysfunction. As a result, the use of herbs for treatment of diseases has become very common in developing countries, particularly in rural settings. However, during the last decade an increase in the use of plants has been observed in metropolitan areas of developed countries (Harnack et al., 2001).

There have been a number of important approaches to restore sexual function which may improve not only sexual relationships but also the overall quality of life. In this regard, alternatives for the treatment of hypoactive sexual desire are scarce despite the intervention of testosterone (Seidman, 2000). But many people still prefer to use natural plants extensively to relieve sexual dysfunction. Ginseng, for example, is an essential

constituent in traditional Chinese medicine (Kim et al., 1976), and at least 6 million Americans use the root of this slow-growing perennial (Nocerino et al., 2000). Owolabi and Omogbai (2007) had previously reported that sexual complaints such as infertility, poor libido, sexual asthenia and impotence are treatable with preparations containing the fruits, roots or leaves of *K. africana*. This has further driven the quest for medicinal plants that were once considered of no value to be investigated, evaluated and developed into drugs with little or no side effects on the organisms (Adedeji et al., 2006b). The beneficial outcome of this is that even in the agricultural sector, specific plants can be used as fertility enhancer in aquaculture.

Dada and Ajilore (2009) used extract of *Garcinia kola* seed to enhance fertility in *Clarias gariepinus* while Adeparusi et al. (2010) used dried *K. africana* fruit meal to enhance fertility in male *C. gariepinus*. Dada et al. (2010) showed that dried *K. africana* fruit meal affects the fecundity, hatching rate and percentage survival of *C. gariepinus* and the authors ascribed this increase in fecundity observed in the study to the presence of biflavonoid and xanthone in the *K. africana*. These compounds are potent anti-oxidants which are capable of increasing the production of estrogen, the key hormone involved in the production and maturation of eggs in the ovary. Previous studies in male *C. gariepinus* have shown that dried *K. africana* fruit meal also improved fertility in male, by improving especially the sperm characteristics (Adeparusi et al., 2010). It further reported that the sperm count ($6.5 \pm 1.2 \times 10^9$ sperm/m) of male brood fish fed 100 g/kg powder of *K. africana*, percentage motility (92%) and fertilization ability (90.88 ± 1.03) were significantly ($p < 0.05$) higher than corresponding controls.

While there may be other co-founding factors necessary to determine reproductive competence, fertility-enhancing ability as such cannot only be assessed by sperm count and motility alone. However, the ability of spermatozoa to achieve maximum motility and morphological configurations are necessary prerequisites for eventual fertilization to take place. This promising pro-fertility effect of *K. africana* is expected to stimulate further studies on improving better outcomes as well as minimize the dependence on synthetic drugs as fertility enhancing agents in fishery/aquaculture.

Anecdotal reports on *K. africana* highlights its property of improving sexuality and fertility, and folkloric information in various tribes indicates that the fruits are hung on roofs of homes to represent a symbol of fertility (Owolabi and Omogbai, 2007; Owolabi et al., 2007). Oliver-Bever (1986) and Abioye et al. (2003) reported that the bark has strong aphrodisiac effect. To investigate this androgen-stimulating potential of *K. africana*, Azu et al. (2009) had carried out *in vitro* studies using extracts of

the fruits of *K. africana* in adult male Sprague-Dawley rats in the laboratory. *K. africana* fruit extract treatment to experimental animals after 28 days significantly increased ($p < 0.001$) the sperm count of rats and sperm motility was above 70%. This result is in tandem with the work of Abioye et al. (2003) as well as Ogbeche et al. (2002) where *K. africana* fruit extracts have been used to enhance fertility in rats as well as increase epididymal sperm motility/percentage pregnancy in male/female Sprague-Dawley rats, respectively. These data becomes pertinent, bearing in mind that viable sperm is an essential component of any successful animal production operation, and the success of reproduction is dependent on high quality gametes (Crus-Casallas et al., 2005) in men (Van der Steeg et al., 2007).

Previous studies in rats (Azu et al., 2010a, b) and *C. gariepinus* (Adeparusi et al., 2010) showed that treatment with *K. africana* fruit extracts resulted in significant increases in testicular and body weight compared with respective controls, suggestive of enhanced nutrient utilization. When this information is mirrored with hormonal changes following experimental intervention, newer insights can be gleaned to suggest that *K. africana* fruit extracts may become useful in stimulating spermatogenesis and androgen biosynthesis in experimental animals. Previous outcome following 28 and 56-day treatment with extracts of fruits of *K. africana* resulted in significant increase in serum testosterone levels ($p < 0.001$) which was more pronounced in the 8 weeks treatment compared to controls. Serum follicle stimulating hormone levels remained significantly high at the end of 4 and 8 weeks compared with the control, and this paralleled Luteinizing hormone (LH) readings (Azu et al., 2009).

With increasing male factor infertility in countries around the globe, coupled with declining semen quality, most potent herbal aphrodisiacs are available and have little or very little side effects (Indurwade et al., 2005). An aphrodisiac, defined as any food or drug that arouses the sexual instinct, induces veneral desire and increases pleasure and performance have been used by man since time immemorial (Yakubu et al., 2007) to solve the problem of erectile dysfunction (ED) or (male) impotence (Monga, 1999). Studies have implicated the saponin component of plants in enhancing aphrodisiac properties due to their stimulatory effect on androgen production (Gauthaman et al., 2002). In this case, the anabolic effect of *K. africana* fruit extracts earlier described is thought to be mediated via its increased androgen biosynthesis, as testosterone is known to be the hormone that induces masculinity in man. However, the precise mechanism for action of *K. africana* fruit extract on the testes still remains to be fully explained; whether it is via a local paracrine effect on the androgen receptors in the testes or mediated via the hypothalamic pathway are possibili-

ties (Azu et al., 2009). But we agree with the postulation that this could be linked to the abundance of flavonoids (which is an effective aromatase inhibitor) as reported by Jeong et al. (1999). *K. africana* is rich in bioflavonoids, saponins and tannins.

Phytochemical studies on *K. africana* fruit extract secondary metabolites revealed the presence of saponins which might be contributory to increasing the endogenous testosterone levels (Oyetayo et al., 2007) by raising the level of luteinising hormone.

In previous work by Azu et al. (2009), it was described that the lower dose of *K. africana* fruit extract (100 mg/kg) was more effective in enhancing the spermatogenic parameters than the 500 mg/kg dose. Similar observations albeit on toxicity were made by Hassan et al. (2011) where high dose of *K. africana* was observed to be toxic. The reason for this observation remains to be elucidated but may be due to a direct effect of some of the components in *K. africana* fruit extracts on the reproductive parameters. It may likely be that *K. africana* fruit extracts may have pro-oxidant and anti-oxidant effects which are mediated at dose-specific ranges and this might have been responsible for the higher doses not producing similar or better androgenic effects in the previous studies reported. It is also likely that the weight-lowering effects of high doses of *K. africana* fruit extract is possible due to presence of antinutrients that may cause poor feed utilization expressed as weight loss according to Muyibi et al. (2000).

Animal studies (in mice and rats) have proven *K. africana* ethanolic extract to be safe at certain doses not exceeding 4,000 mg/kg. Acute and sub-chronic toxicity studies revealed an lethal dosage (LD₅₀) of 3,981.07 mg/kg (fruits) (Azu et al., 2009); 4 g/kg (stem bark) (Owolabi et al., 2007) and 4,000 mg/kg (leaf extracts) (Hassan et al., 2011) in either sex. Therefore, it is reasonable to adduce that a study using the preparation can be carried out safely within these limits of established toxicity and treatment would be inexpensive. It should be mentioned however that different preparations of *K. africana* have been used by various authors in different experimental protocols. It is therefore possible that the difference in the test samples may have contributed to the differences in the results that have been obtained.

Oxidative stress is known to play a role in a number of conditions detrimental to male fertility (Zalata et al., 1998). The pathologic phenomenon of oxidative stress results from an imbalance between the production of reactive oxygen species and the defense systems that function to scavenge or destroy them (Favier et al., 1994; Agarwal et al., 2007). It is proposed that *K. africana* fruit extract exhibits antioxidant activities by its ability to significantly reduce testicular malondialdehyde (MDA) levels as well as augment endogenous glutathione in an animal experimental model. Azu et al. (2010c) showed

that MDA levels were significantly reduced ($p < 0.001$) when compared with the controls in Sprague-Dawley rats treated for 8 weeks with *K. africana* fruit extract. Similarly, there was corresponding and significant ($p < 0.001$) increase in glutathione levels in the same experimental animals. It is known that the lipid composition of the sperm membrane exert a significant effect upon the functional quality of spermatozoa. Hence, while the sperm cell plasma membrane is high in polyunsaturated fatty acids, it makes it especially vulnerable to free radical attack (Zalata et al., 1998; Suzuki and Sofikitis, 1999).

K. africana fruit extract (KAFE) at doses of 100 and 500 mg/kg induced an up-regulation in glutathione (GSH) levels especially at long term duration, and this may be attributed to its inherent flavonoid content. There is supporting evidence that some flavonoids can also elevate intracellular basal level of GSH, thereby allowing better tolerance of free radicals (Durgo et al., 2007). Flavonoid activities depend heavily on their antioxidant and chelating properties. Bearing in mind that sperm morphology, count and motility are highly associated with the production and activity of free radicals and antioxidant enzymes (Krishnamoorthy et al., 2007), it becomes more plausible to agree that the ability of KAFE to up-regulate GSH, lower MDA levels and enhance testicular catalase activities does confer a strong antioxidative role to its components. However, the lower dose of 100 mg/kg was more effective than the higher dose of 500 mg/kg and the reason for this is not yet known. This may suggest that *K. africana* fruits extracts does not have a dose-dependent effect on the various parameters examined. The antioxidant pathway may provide a rationale for the use of this plant in folk medicine for treatment of inflammatory disorders and male infertility, since oxidative stress plays very crucial roles.

It is possible that the single compounds found in *K. africana* may be acting synergistically in the body and mediating greater benefit than has been observed. However, very few studies have yet to be conducted in this area especially in humans and using cell cultures. Given this scenario, it is not possible to draw a conclusion on how *K. africana* works to show whether it will be effective to treat hypo-spermatogenesis.

FUTURE PERSPECTIVES

At present, it is difficult to ascertain if the androgen-stimulating effect of *K. africana* fruit extract would ultimately influence sexual desires directly or indirectly as experimental data still requires additional and rigorous investigations. Certainly, sexual desire may be affected directly by increasing serum testosterone levels or by having a testosterone-like effect, or indirectly by affecting behavioral depression, and stress (Kumar et al., 2001). It

is well known that low serum testosterone levels are related to low sexual desire, and that an increase in serum testosterone levels results in resumption of sexual activity (Jannini et al., 1999). But again, an increase in testosterone levels over normal values may have undesirable effects such as the possibility that testosterone may be a promoter of prostate cancer (Nelson and White, 2002). Furthermore, because previous reports also support the positive effects of *K. africana* fruit extract on follicle stimulating hormone (FSH) and LH (Azu et al., 2009, 2010, 2010b), both hormones involved in the pituitary-hypothalamo-testicular regulation of spermatogenesis, which is in concordance with Morakinyo et al. (2008) that their derangements would result in testicular steroidogenic disorder. Put together, further work is expected to shed light on any demonstrated effects of *K. africana* fruit extracts on other associated male reproductive organs like the prostate gland and seminal vesicle, a target organ for androgens as this may assist in the elucidation of action. However, this plant has great potential to be developed as drug by pharmaceutical industries but before recommending its use in modern system of medicine, further research and clinical trials are to be done.

CONCLUSION

While the precise mechanism of anti-oxidant, anti-inflammatory phyto-medicine shares common molecular targets with steroidal drugs; as both non-steroidal anti-inflammatory drugs and phytomedicine constituents such as sterols, flavonoids are able to inhibit processes that lead to inflammation (such as production of free radicals), the implication for the future development of *K. africana* as a potent fertility-enhancing drug remains very bright. This is against the background of remarkable progress in our understanding of role of phytoestrogens, sex steroids and human physiology.

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