

Minireview

The sausage tree (*Kigelia pinnata*): ethnobotany and recent scientific work

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Kigelia pinnata (Bignoniaceae), colloquially called the Sausage Tree, or Worsboom, on account of its large fruits, has a variety of medicinal uses throughout Africa where it grows as an endemic species in many areas. Chemical examination has resulted in the isolation of iridoids and naphthoquinoids as important secondary metabolites but flavonoids and lignans have also been isolated. Investigation into the biological activity of *K. pinnata* has focussed on its antibacterial activity and its cytotoxic effects against cancer cell lines. These are related to the traditional uses of bark and fruit extracts for treating diseases caused by micro-organisms and as a remedy for skin cancer. The iridoids and naphtho-

quinones have been shown to display antibacterial activity and also the ability to inhibit the growth of yeasts. Considerable *in vitro* cytotoxicity has been demonstrated by extracts of the fruits and barks and the iridoid-related compound norviburtinal and the naphthoquinone isopinnatal have been shown to be two of the compounds responsible. Although little ethnopharmacological evidence exists, the naphthoquinones are active against several protozoal species associated with disease. The compounds also show cytotoxicity against mammalian cell lines. More research is needed to investigate further the reputed effects on the skin of extracts of this plant.

Introduction

Kigelia pinnata (Jacq.) D.C. is also commonly referred to in the scientific literature as *K. africana* (Lam.) Benth. *Kigelia* is now generally considered to be a highly variable monospecific genus of the Bignoniaceae (Mabberley 1987), although several species have been reported in the past (Neuwinger 1996). It is a reasonably large tree, attaining 20m in height and grows in moist places, such as river banks, throughout the savannah areas of tropical Africa. It has a large range from Senegal across to Ethiopia and south to the northern parts of South Africa.

K. pinnata is often planted in botanical gardens in the tropics because of its spectacular fruits. These can weigh several kilograms and resemble large sausages, hence giving the tree its common English name of 'Sausage Tree'. In Afrikaans it is known as 'Worsboom', 'Kalabasboom' or 'Komkommerboom', in Zulu as 'Umfongothi', in Northern Sotho as 'Modukguhlu' and in Venda as 'Muvevha' (Hutchings *et al.* 1996, Van Wyk *et al.* 1997). Over one hundred other African local names are given by Neuwinger (1996), emphasising its widespread distribution within Africa and also its ethnobotanical importance.

Ethnobotanical uses of *K. pinnata* with particular reference to its medicinal uses

K. pinnata is mentioned in all the reference books dealing with economic plants of the parts of Africa where it grows. Details can be found in Irvine (1961), Watt and Breyer-Brandwijk (1962), Burkill (1985), Hutchings *et al.* (1996) and Neuwinger (1996). The account of uses which is given below is not exhaustive but is a summary of those most relevant to the laboratory studies which have been carried out. A comprehensive account of the ethnobotany of *K. pinnata* can be located on the SEPASAL database of the Royal Botanic Gardens Kew at: <http://www.rbgekew.org.uk/ceb/sepasal>.

There are some uses which are widespread but some are more localised. If a particular medicinal use is well-referenced but is confined to a particular geographical area, it may indicate that chemical varieties may exist, and this may support those who contend that several species should be recognised. However, no systematic study of the chemistry of the species from different areas has yet been carried out so that, at present, this hypothesis is confined to the realms of speculation.

The leaves are not one of the parts of the plant which feature prominently in its traditional use. In West Africa they are

used to make a drink to treat gastrointestinal ailments (Burkill 1985, Irvine 1961).

The use of a macerate in water of the stem bark as a treatment for dysentery and for sexually-transmitted diseases (STDs) such as syphilis is reported from many different areas. Another common use of the bark is as a powder or a water macerate to treat sores or fungal infections on the skin. In West Africa alone the bark extract is used to treat snakebite, mainly it appears to soften the skin before the administration of other plant-based remedies (Burkill 1985). In the same geographical area the bark has some reputation as a treatment for convulsions and this relates to similar uses in east Africa (Neuwinger 1996). In southern Africa the bark is used for ulcers, pneumonia and toothache (Hutchings *et al.* 1996).

The root bark is used in much the same way as the stem bark. In west Africa there are additional applications in getting rid of tapeworms and for gynaecological complaints (Burkill 1985).

The fruits are the most commonly used parts of the plants. There are several reports of the poisonous nature of the unripe fruit but no scientific work has been carried out to determine the basis for this. Some uses are fairly prosaic such as the making of childrens' dolls in Tanzania or as support over a fire for cooking pots in Malawi (Burkill 1985). However, the fruits are extensively used, probably because of their shape and size, for a large number of reasons associated with indigenous religious and religio-medical practices. Thus the fruits are used as fetishes in many areas and rubbed to enlarge breasts or penises and in other rituals associated with increased fecundity, fertility and improved milk flow (Neuwinger 1996).

The ripe fruit is very fibrous and is not used to any extent by humans as a food, except in famine situations, although it is eaten by wild animals such as squirrels (Burkill 1985). In Tanzania, as in several other parts of Africa, an extract of the fruit is used to flavour beer and to increase its potency, thought to be due to the production of amyl alcohol (pentanol) during the fermentation (Watt and Breyer-Brandwijk 1962). The fruit also is reported quite widely to have effects which are more clearly medicinal rather than those associated with superstition or explainable by the Doctrine of Signatures (a theory originating from mediaeval Europe which proposed that the uses of a plant in disease were shown by its appearance e.g. the shape of the fruits of *K. pinnata* resemble an erectile penis and were therefore aphrodisiac). A decoction is used in many parts of Africa as a laxative and the powdered dried fruit is used extensively as a dressing for wounds, ulcers and sores. Commercial preparations for treating the skin are marketed in Zimbabwe and South Africa but no medical claims are made. However, it is widely believed that these creams reduce pigmentation in freckles and help sores to heal, the latter effect being possibly related to traditional wound-healing and antibacterial effects.

The fruit infusion is also taken as a remedy for rheumatism and back pains in Ivory Coast and some other countries (Burkill 1985). Of particular interest is the use of the fruit to treat cancer which is reported from Togo (Neuwinger 1996), and especially from southern Africa where it has a considerable reputation for being effective against solar keratoses,

which may develop into skin cancer, (Hutchings *et al.* 1996) and against less-defined cancer of the skin (Neuwinger 1996).

Chemical constituents of *Kigelia pinnata*

It is important to know which secondary metabolites are found in plants because these may provide a basis for its traditional uses, particularly if they are the same as, or similar in structure to, compounds from other species which display relevant activity. To some extent, the type of compounds likely to be present can be deduced from its taxonomic position and this can be seen to be the case with *K. pinnata*, which is a member of the Bignoniaceae, a family noted for the occurrence of iridoids and naphthoquinones in many constituent genera (Hegnauer 1964).

The iridoids (Figure 1) found in *Kigelia* correspond to the 9-carbon skeleton type, e.g. catalpol **1**, found in other members of the Bignoniaceae. The major iridoids found in the root bark and stem bark of *K. pinnata* are the catalpol derivatives esterified with phenylpropanoic acid derivatives at C-6 and these were identified as specioside **2**, verminoside **3** and minecoside **4** (Houghton and Akunyili 1993). Norviburtinal **5**, generally considered to be a breakdown product of the iridoids, has also been isolated from the roots,

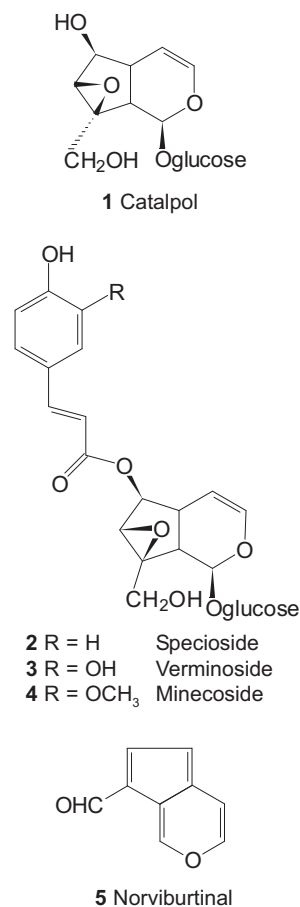


Figure 1: Iridoids from *Kigelia pinnata*

stembark and fruits (Joshi *et al.* 1982, Jackson *et al.* 2000).

In some South American species of the Bignoniaceae, naphthoquinones are present in quite large amounts and give a colour to the wood. The characteristic compound of several species of *Tabebuia*, a related genus of the Bignoniaceae, is lapachol **6** (Figure 2), which is known to be cytotoxic and at one time was considered as a treatment for cancer by the National Institute of Health in the USA. It has been reported present in small amounts in the wood, and roots of *K. pinnata* by several investigators (Binutu *et al.* 1996, Govindachari *et al.* 1971, Inoue *et al.* 1981, Joshi *et al.* 1982).

Three furanonaphthoquinones kigelinone **7**, 2-acetylnaphtho[2,3-b]furan-4,9-quinone **8** (Binutu *et al.* 1996) and 2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-quinone **9** (Moideen *et al.* 1999) have been isolated from *K. pinnata* stembark and rootbark (Figure 2).

Two pairs of monoterpenoid-naphthoquinone compounds (Figure 2) named pinnatal **10** and isopinnatal **11** and kigelinol **12** and isokigelinol **13**, unique to *K. pinnata*, have been isolated from the roots and fruit (Joshi *et al.* 1982, Akunyili and Houghton 1993).

The flavonol quercetin **14** and four flavonones luteolin **15**, its 6-OH analogue **16** and corresponding 7-O-glucosides **17**,

18 were isolated from the leaves and fruits of *K. pinnata* (El-Sayyad 1981). Three isocoumarins 6-methoxymellein **19**, kigelin **20** and 6-demethylkigelin **21** were isolated from the roots of the plant (Govindachari *et al.* 1971). The lignan kigeliol **22** was isolated from the wood (Inoue *et al.* 1981) and was the only lignan reported until 1999 when the neolignan balanophonin **23** was isolated from the stembark (Moideen *et al.* 1999) (Figure 3).

The common steroids β -sitosterol **24** and stigmasterol **25** have been isolated by various workers from the bark and root of *K. pinnata* (Govindachari *et al.* 1969, Inoue *et al.* 1981, El-Sayyad 1981, Joshi *et al.* 1982, Jackson *et al.* 2000). γ -sitosterol **26** was reported present in *K. pinnata* fruit by Khan (1998) (Figure 4).

Biological studies on *K. pinnata*

Most of the studies on the biological activity of *K. pinnata* extracts and constituents have been connected in some way to its traditional uses.

The use of extracts of *K. pinnata* bark in many parts of Africa as a treatment for STDs is mentioned above. An unpublished ethnobotanical survey amongst traditional healers amongst the Igbos in south eastern Nigeria conducted

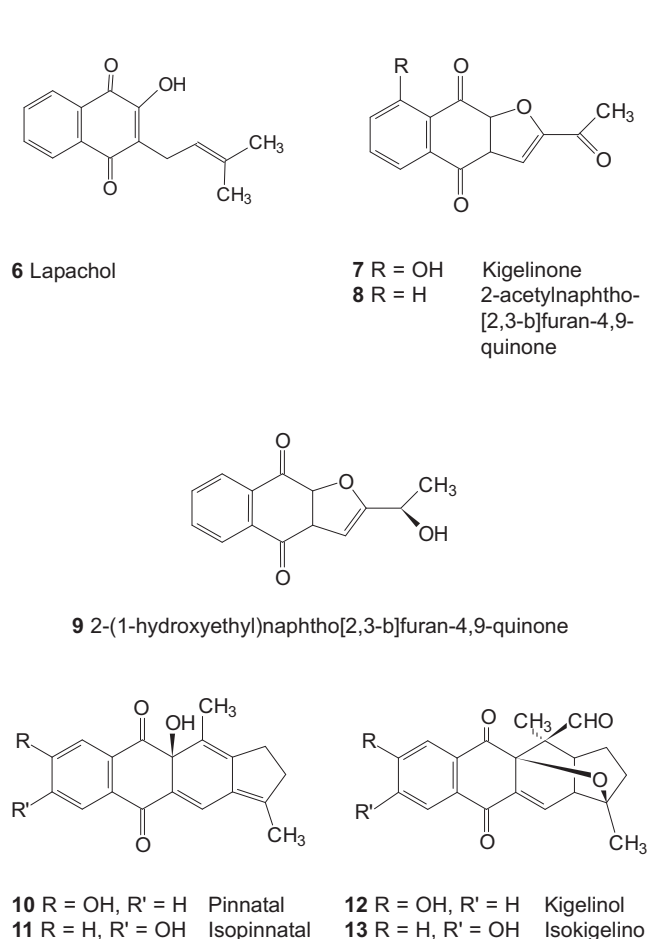


Figure 2: Naphthaquinoids from *Kigelia pinnata*

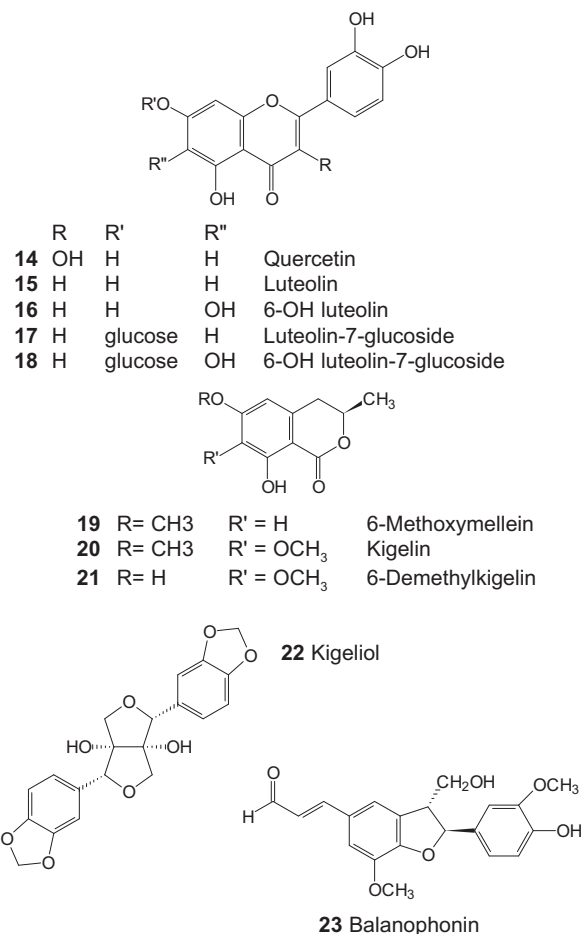


Figure 3: Flavonoids and other shikimate-derived compounds from *Kigelia pinnata*

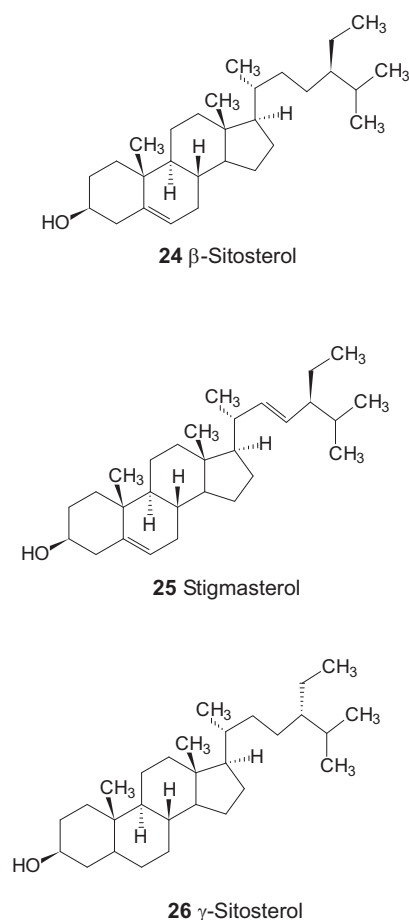


Figure 4: Flavonoids and other shikimate-derived compounds from *Kigelia pinnata*

by Dr Akunyili from University of Nigeria, Nsukka, revealed that they use an aqueous or dilute alcohol extract of *K. pinnata* rootbark as a treatment for STDs. Extracts of the roots equivalent to those obtained using the traditional methods were found to contain the iridoids specioside **2** and minecoside **4** as major constituents. The extracts, as well as two of the isolated iridoids, were tested and also their 1/10 and 1/100 dilutions, against four representative species of bacteria viz. *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli* and *Pseudomonas aeruginosa*, and the yeast *Candida albicans* in the absence and presence of the enzyme emulsin. This enzyme converts catalpol-type iridoids to their more antimicrobially active non-sugar containing aglycones. The growth of the organisms in culture broth was assessed by measuring the turbidity of the solution (Akunyili *et al.* 1991). The results showed that the aqueous extract had strong activity, even in the absence of emulsin, against all the bacteria tested but especially against the yeast *C. albicans*. This is of interest since *Candida* infections are common opportunistic infections of the genito-urinary tract and the traditional use of this plant extract might alleviate this in sexually-transmitted diseases. Both isolated iridoids also showed activity in the same way but did not seem

to account for all the activity shown by the extracts.

Further studies using a wider range of micro-organisms and compounds showed that the naphthoquinoids from the stembark also had a moderate antimicrobial effect. Kigelinone **7** and isopinnatal **11** were the most active compounds with minimum inhibitory concentrations (MIC) not less than $50\mu\text{g mL}^{-1}$ against any other the bacteria or yeasts tested (Binutu *et al.* 1996). However, it should be pointed out that the naphthoquinoids are unlikely to exist in sufficiently high concentrations in aqueous or dilute alcohol extracts such as those used in traditional medicine.

There thus seems some evidence that extracts of the roots and stembark of *K. pinnata* possess antimicrobial activity. As well as some justification for their traditional uses against genito-urinary infections, this observed effect may also be relevant to the use of such preparations in skin conditions which might be caused by micro-organisms such as dermatophytes (ringworm and associated conditions) or bacteria (complications of acne, boils and similar diseases).

As well as reports in the literature which are mentioned above, several independent anecdotal reports were received by our group of the usefulness of *Kigelia* extract in treating 'skin cancer', particularly amongst the white population in southern Africa. Although the nature of the extract and the part of the plant from which it was derived were at first unclear, further investigations revealed that a 50% ethanolic extract of the fresh fruits was most commonly used. Other findings included the information that the white population had learnt of this use of the plant from the indigenous ethnic groups in Zimbabwe and surrounding countries, a fact supported by literature reports (Neuwinger 1996, Hutchings *et al.* 1996). The precise definition of 'skin cancer' was unclear and there is a range of diseases with different severity which could be classified as such. These range from erodent ulcers, which are common in fair-skinned persons exposed to bright sunlight, and are not malignant *per se* but often develop into malignant growth, to melanoma which is often refractory to treatment, particularly once it has metastasised. As well as the ethnobotanical evidence, there were other indicators that *Kigelia* extracts might possess anticancer activity. A large number of related species of the Bignoniaceae are used for this purpose in traditional medicine (Hartwell 1968) and also some naphthaquinones from this family, e.g. lapachol **6**, have attracted interest as potential anticancer drugs. Studies were consequently initiated testing *K. pinnata* extracts *in vitro* for cytotoxicity against cultured melanoma cells using the SRB assay for cell viability. Initial studies showed that only the less polar dichloromethane extracts of the stembark showed significant effects but not extracts of the dried fruits (Houghton *et al.* 1994). Later studies, however, showed that the dichloromethane extract of the fresh fruits, and also the alcoholic extract of the fruit used in making commercial creams, also showed activity (Jackson *et al.* 1995).

Bioassay-guided fractionation, using the same cytotoxicity bioassay system, of the dichloromethane stembark extract, and also the fruit extract, showed that several compounds contribute to the effect (Jackson *et al.* 2000). The compound with the greatest activity, isolated from the most active fraction after separation on a silica gel column, was not a naph-

thoquinone but the iridoid-like compound norviburtinal **5**. The steroid β -sitosterol **24** was also found in the most active fraction but had negligible activity. Comparison of the activity of norviburtinal **5** with the amount present in the dose of extract having the same activity showed that it did not contribute to a large part of the effect e.g. norviburtinal **5** had an IC_{50} of $3.25\mu\text{g mL}^{-1}$ against G361 cells (144 hour exposure) but it was calculated that its concentration in the total dichloromethane extract (IC_{50} $2.1\mu\text{g mL}^{-1}$) was only $0.154\mu\text{g mL}^{-1}$, thus indicating that other cytotoxic compounds are present which await discovery. This was also shown by the fact that other fractions which did not contain norviburtinal **5**, which were not investigated further, also displayed appreciable activity.

Although norviburtinal **5** had a reasonably good level of activity against the melanoma cell lines tested, it was also cytotoxic against other cancer cell lines (Table 1), thus reducing its suitability as a lead compound for cancer chemotherapy. Although it does not appear to be used in traditional medicine for treating cancer, the rootbark dichloromethane extract also showed some activity and the naphthoquinone isopinnatal **11** was shown to play a major contribution to this (Jackson *et al.* 2000).

It is of interest to note that 2mg extracts of *K. pinnata* fruits from Nigeria have also shown antitumour effects when given intraperitoneally to mice with fore-stomach tumours induced by benzopyrene (Azouine *et al.* 1997). The extract alone showed little toxicity when it was given to the mice and so these studies give further evidence of the relative safety and efficacy against cancer of the ethanolic extract of the fruits, although individual compounds were not isolated.

A paper by Khan (1998) ascribed some *in vitro* cytotoxic activity found in an extract of the fruits to the steroid γ -sitosterol **26** but this has not been confirmed by other studies. It is interesting to note that the related β -sitosterol **24** was found in the active fraction of *K. pinnata* fruit and bark but showed no activity (Jackson *et al.* 2000).

There are no records of the traditional use of *Kigelia pinnata* against protozoal diseases such as malaria, leishmaniasis, sleeping sickness or Chaga's disease although the reports of the use of the bark in dysentery could suggest activity against *Entamoeba histolytica*, the cause of amoebic dysentery. However, the occurrence of novel naphthoquinones prompted the investigation of antiprotozoal activity of extracts and isolated naphthoquinoids since naphtho-

quinones exhibit antiprotozoal activity (Croft *et al.* 1985). This activity is due to the increase of oxygen consumption and stimulation of hydrogen peroxide production in the protozoal cell (Meshnick *et al.* 1987). Protozoa do not have the same biochemical mechanism as mammalian cells for dealing with excess peroxide and consequent oxygen free radicals and so this process is used as a target in the search for novel antiprotozoal compounds. Bioassay guided fractionation of extracts of *K. pinnata* rootbark and stembark was carried out using *in vitro* cultures of *Trypanosoma cruzi* (the organism associated with Chaga's disease) and *T. brucei rhodesiense* and *T. brucei brucei* (associated with sleeping sickness) (Moideen *et al.* 1999). Similar studies were carried out with *Leishmania major* (associated with leishmaniasis) (Moideen 1998) and *Plasmodium falciparum* (the causative agent of malaria) for which the chloroquine-resistant K1 strain was used (Weiss *et al.* 2000). No great dose-related activity for extracts of compounds could be found against *T. cruzi* or the amastigote forms of *Leishmania major* or *Trypanosoma* but some activity was observed against the other protozoa. In all cases the dichloromethane extract of the plant material proved to be the most active and the greatest activity was shown by 2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-quinone **9**, with isopinnatal **11** also showing some activity. The neolignan balanophonin **23**, which was also present in the bark extracts tested, showed no appreciable activity. In the case of activity against *Trypanosoma* the activity of the furanoquinone was of the same order of magnitude as the positive control, pentamidine, but the activity of the compounds against *Leishmania* and *Plasmodium* was considerably less than that displayed by the positive control substances (Table 2). The *in vitro* cytotoxicity of the compounds was also tested using cultured mammalian KB cells and the values obtained suggested that the compounds had a general cytotoxic effect which tended to preclude any clinical usefulness. It should be noted, however, that the selectivity against *Trypanosoma* was more promising (Table 3) and indicated that the active compounds might prove useful lead compounds for further studies against these organisms.

The traditional uses of *K. pinnata* bark and fruits as a treatment for oedema, ulcers and other sores might indicate antibacterial, wound-healing and anti-inflammatory effects. In addition to the antibacterial activity discussed above, there is a report on the anti-inflammatory effect on rats of the ethanolic extract of the *K. pinnata* fruits (Azouine *et al.* 1997). The test used was the size of oedema induced by injection of a standard dose of albumen into a rat paw. The extract at 100mg kg^{-1} gave a significant 54% reduction in the circumference of the paw compared with the albumin alone which was comparable with a dose of 10mg kg^{-1} of the positive control indomethacin. No work has been done to elucidate the compounds responsible.

Anecdotal reports from southern Africa also exist concerning the ability of *K. pinnata* fruit extract to reduce skin pigmentation, particularly where this takes the form of freckles. No tests have yet been carried out to investigate the validity of this claim but it is of interest to note that quinones are used for skin lightening in dark-skinned people and that quinone derivatives are present in *K. pinnata*.

Table 1: *In vitro* cytotoxicity of norviburtinal **5** against cultured cell lines (Jackson *et al.* 2000)

Cell line	IC_{50} value $\mu\text{M}^*\dagger$
G361 melanoma	22
StML11a melanoma	50
C32 melanoma	50
ACHN renal cancer	48
Colo668 colon cancer	22

* measured using the SRB assay. Figure given is the mean of three separate determinations.

† IC_{50} value for vinblastine sulphate (positive control) against these cell lines is $0.95\text{--}1.65\mu\text{M}$

Table 2: *In vitro* antiprotozoal activity (IC₅₀ in μ M) of compounds isolated from *Kigelia pinnata* stem bark (Moideen 1998, Moideen *et al.* 1999, Weiss *et al.* 2000)

Compound	<i>Leishmania major</i> promastigotes	<i>Trypanosoma brucei</i> <i>brucei</i> trypomastigotes	<i>Trypanosoma brucei</i> <i>rhodesiense</i> trypomastigotes	<i>Plasmodium falciparum</i> K1 (chloroquine resistant)
2-(1-Hydroxyethyl)-naphtho [2,3-b]furan-4,9-quinone 9	1.77	0.12	0.045	5.23
Isopinnatal 11	1.74	0.37	0.73	25.1
Kigelinol 12	24.4	4.21	21.3	>100
Isokigelinol 13	12.46	1.36	11.1	>100
Balanophonin 23	2.76	ND	ND	>100
Positive control (Pentamidine)	0.578	0.007	0.016	0.228 (Chloroquine phosphate)

ND = not done

Table 3: Selectivity ratio of cytotoxicity of compounds isolated from *Kigelia pinnata* stem bark between protozoa and mammalian cell lines (Moideen 1998, Moideen *et al.* 1999, Weiss *et al.* 2000)

Compound	IC ₅₀ KB/ED ₅₀ <i>L. major</i> promastigotes	IC ₅₀ Vero/ED ₅₀ <i>L. major</i> promastigotes	IC ₅₀ KB/ED ₅₀ <i>Trypanosoma</i> <i>brucei brucei</i> trypomastigotes	IC ₅₀ Vero/ED ₅₀ <i>Trypanosoma</i> <i>brucei brucei</i> trypomastigotes	IC ₅₀ KB/ED ₅₀ <i>T. brucei</i> <i>rhodesiense</i> trypomastigotes	IC ₅₀ Vero/ED ₅₀ <i>T. brucei</i> <i>rhodesiense</i> trypomastigotes	IC ₅₀ KB/ED ₅₀ <i>Plasmodium</i> <i>falciparum</i> K1 (chloroquine resistant)
2-(1-Hydroxyethyl)- naphtho[2,3-b]furan -4,9-quinone 9	2.2	1.86	33.6	85.5	28.2	71.8	0.70
Isopinnatal 11	8.5	9.42	41.8	20.0	46.2	22.2	0.59
Kigelinol 12	6.1	5.0	35.1	7.0	28.9	5.7	ND
Isokigelinol 13	13.4	9.23	122.6	15.1	84.7	10.4	ND
Balanophonin 23	3.72	5.76	ND	ND	ND	ND	ND
Positive control (Pentamidine)	7.4	284	710	284	435	174	861 (Chloroquine diphosphate)

ND = not done

Conclusions

Kigelia pinnata is 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. Experiments into the effect of *Kigelia* extracts, and some of the pure compounds contained therein, on microorganisms and cancer cells have shown that the traditional use of this plant is given considerable justification. In addition, there exists some evidence for its anti-inflammatory reputation.

The chemical basis of these effects, particularly in the area of anticancer and anti-inflammatory activity, has not been elucidated to any great extent. As well as the possibility of the discovery of novel single chemical entity drugs, this exercise is necessary so that extracts can be standardised for minimum content of active constituents to assure the user of efficacy. In some cases, standardisation will also indicate safety, if the content of toxic compounds is specified to be non-detectable or to be kept below a specified level. It would not be surprising if deeper investigations revealed

that other compounds were present which had cytotoxic effects which might underlie its reputation as an anticancer drug. Similarly, work needs to be carried out to determine whether the use of extracts to remove pigmentation has any scientific basis and, if so, which compounds are responsible.

It would be useful to screen samples of *Kigelia* obtained from different locations for chemical content and biological activity to find out whether variation exists and, if it does, whether it is responsible for the different traditional uses reported from different areas.

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