

MONOGRAPH FOR *Khaya senegalensis* (AUSTRALIAN MAHOGANY) BARK EXTRACT



BOTANICAL NAME

Khaya senegalensis is a species of tree that is native to Africa. The tree has also been introduced to Northern Australia

COMMON NAME(S)

African mahogany, dry zone mahogany, Gambia mahogany, khaya wood, Senegal mahogany, *cailcedrat*, *acajou*, *djalla* and *bois rouge*.

PART USED

Bark, leaves, seeds and gum.

TRADITIONAL USAGE

The bitter tasting bark is used for a variety of medical purposes. An extract of the bark of *Khaya senegalensis* is commonly used in African traditional medicine for pain and inflammation, against fever caused by malaria, stomach complaints and headaches. It is widely used in the treatment of fever, malaria, to cure skin rashes, wounds, mucous diarrhea, as an anti-microbial agent in venereal diseases or many other abnormalities. It is also used as an anti-helminthic and as a taeniocide (tapeworm remedy) in West Africa. In Senegal, this plant is used against fever, to treat fatigue, and to treat malaria. Decoctions or macerations of the bark is the most common preparations used in the treatment of

syphilis, vaginal discharge, leprosy and small pox, most likely because of its purgative properties. Syphilis and leprosy are also treated externally using leaf extracts. The gum from the plant has traditionally been used to treat dysentery, headache and menstrual pain (Sanogo, 1999).

DESCRIPTION OF THE PLANT & ACTIVE CONSTITUENTS

The main chemical groups in *K. Senegalensis* are fatty acids, carotenoids, coumarins, emodols, tannins, compounds reducers, anthracenosides, steroidal glycosides, flavonosides, carbohydrates, saponins, sterols and triterpenes, limonoids, anthocyanins, mono- and polysaccharides, mucilages and cardiac glycosides. Its bitter constituents, named "calicedrin" in West Africa, characterize the extract from the bark of *Khaya senegalensis*. It is used extensively as a bitter tonic for the treatment of a variety of pro-inflammatory disease. In this study, the effect of *Khaya senegalensis* bark extract (KSBE) was investigated on three human colorectal tumour cell lines with different COX profiles. This herbal medicine, popular in West Africa, was found to have great potential as a natural chemopreventive agent for colorectal cancer.

SCIENTIFIC STUDIES

The ethnopharmacological studies have been the basis of many investigations seeking to identify the natural chemopreventive agents in KSBE. Interestingly, studies

have shown that a total extract of *Khaya senegalensis* bark exerted as strong or even stronger anti-inflammatory effects than each of its fractions when applied as an anti-inflammatory ointment. *In vitro* data suggested that KSBE has potent anti-tumour effects and caused both cell cycle arrest and apoptosis, possibly via a COX-2-dependent pathway. Given the recent governmental removal and/or restriction from the market of selective COX-2 inhibitors of synthetic origin due to suspected cardiovascular toxicity, it is important to reassess natural products for a safer alternative. KSBE is one of the several anti-inflammatory plants used in West Africa that may have the potential to prevent colon cancer.

Studies on the bioactivity of *Khaya senegalensis* have reported effects on biochemical parameters; showing protective effects for vital organs, especially the liver and kidneys. Several authors have reported the effectiveness of different types of extract, aqueous or alcoholic, against some diseases (pest, infections, cancer, and diabetes). However, chronic administration poses tissue toxicity risks. *Khaya senegalensis* bark extract (KSBE) has been hypothesized to contain inhibitors of the cyclooxygenase-2 (COX-2) gene and to be useful in the prevention and treatment of colorectal cancer. KSBE displays anti-proliferative, anti-inflammatory and pro-apoptotic effects on colon cancer (HT-29, HCT-15 and HCA-7) cells. The diphenyl-2-picrylhydrazyl (DPPH) - free radical activity and the total phenolic content of KSBE were measured, followed by an investigation of cell growth inhibition, COX and prostaglandinE2 (PGE2) suppression. KSBE displays anti-proliferative, anti-inflammatory and pro-apoptotic effects on HT-29, HCT-15 and HCA-7 cells. It appears that both COX-dependent and COX-independent pathways of inflammation are activated by KSBE.

Colorectal cancer is the third most common cancer and the second leading cause of cancer deaths in the United States. An important strategy for combatting this deadly disease before tumours reach an invasive state is the use of a class of non-steroidal anti-inflammatory drugs (NSAIDs), which have shown great promise as chemopreventive agents. Epidemiological studies and clinical trials have demonstrated that NSAIDs reduce the incidence of colorectal cancer by 40%-50%. The mechanistic action of NSAIDs includes abating the prostaglandin synthesis pathway and cyclooxygenase (COX)-independent pathways. COX-2, one of the COX isoforms, has been suggested as a promising chemopreventive target for colorectal cancer. Recently, The US Food

and Drug Administration has placed severe limitations on the use of COX-2-specific inhibitors (e.g. celecoxib, rofecoxib and valdecoxib) due to cardiovascular toxicity. This emphasizes the importance of identifying safer COX inhibitors from natural sources (e.g. those which may be found in traditional medicinal plants).

COXs are the rate-limiting enzymes that catalyze arachidonic acid to form a variety of eicosanoids (e.g. prostaglandins, thromboxanes and leukotrienes). COX-1 is expressed constitutively in most tissues and plays a role in maintaining normal cellular physiological states. COX-2 is inducible by various inflammatory stimuli. COX-2 levels are elevated in both human colorectal adenomatous polyps and colon cancers. In addition, knocking out COX-2 reduces the incidence of intestinal tumours in the ApcMin mouse model. Treatment of colon cancer cell lines with COX-2-specific inhibitors and COX-2-null fibroblasts with different NSAIDs inhibits tumour cell proliferation. Interestingly, sulindacsulfone, a NSAID metabolite that does not inhibit either COX isoform, exerts anti-proliferative activity *in vitro* via apoptosis and inhibits azoxymethane-induced colonic carcinogenesis in the rat. Our data obtained on COX expression levels and PGE2 production suggest that one of the pathways by which KSBE inhibits tumour cell growth is through the disruption of PGE2 synthesis. PGE2 production was lowered even when the COX-2 protein expression levels remained the same, indicating that KSBE may also inhibit the enzymatic activities of COX.

Since 20-50% of human sporadic colorectal adenomas do not express COX-2, an investigation of KSBE in COX-null cell lines (e.g. HCT-15) was warranted. It was observed that KSBE suppressed the growth of HCT-15 cells, suggesting that KSBE may exert some of its effects through COX-independent mechanisms. The growth inhibition effect of KSBE was associated with an up-regulation of peroxisome proliferator-activated receptor (PPARs) and decreased expression of Cyclin D1. PPARs are important factors in controlling gene expression, critical to cell cycle regulation and cellular differentiation. PPAR ligand activation has been reported to have anti-tumour effects in several models of cancer. PPARs could be one of the downstream targets of KSBE in COX-null cell lines.

Dysregulation or inhibition of apoptosis has been reported to play an important role in a variety of cancers, including colorectal cancer. Previous studies have suggested that apoptosis induction is essential to the action of many chemotherapeutic agents in tumour cells. There are two

main apoptotic death pathways: the mitochondrial and the death receptor pathways. Both converge at the activation of caspase-3 via Bcl-2 mediation. Bcl-2 encodes an inner mitochondrial protein that antagonizes apoptosis. The results clearly demonstrated that KSBE strongly inhibited anti-apoptotic Bcl-2 protein expression in all three cell lines evaluated. This effect was more significant in the HCT-15 cells, most probably due to the high basal levels of Bcl-2 in this COX-null cell line. Furthermore, the increase in caspase-3 protein expression and activity level suggests that caspase-dependent apoptosis is involved in the inhibition of tumour cell growth by the constituents of KSBE.

MECHANISM OF ACTION

Bioactive applications (e.g. anti-inflammatory, anti-carcinogenic, anti-proliferative, anti-tumour and apoptotic activity).

TOXICITY

Decoctions of *Khaya senegalensis* prepared from the leaves and tree bark have been used in West African traditional medicine against several human and animal diseases for centuries without overt toxicity.

TOXICOLOGY

According to Nwosuet al. (2012), the aqueous extract of leaves of *Khaya senegalensis* is not toxic. At the end of a study conducted on rats in Nigeria, the authors reported that the LD50 of the extract is greater than 3000mg/kg body weight. Although other studies revealed that chronic treatment rather induces an increase of these parameters signing some hepatotoxicity. Long treatments also cause elevation of serum creatinine and blood urea, which reflects renal dysfunction.

USE IN PREGNANCY & LACTATION

In Senegal, this plant is used as an abortive remedy.

HERB/DRUG INTERACTIONS

There is a lack of studies on concurrent use of *Khaya senegalensis* and NSAIDs.

SUMMARY OF INDICATIONS & SUPPORTING STUDIES

Indication	Intervention	Outcome	Reference
Cancer	Bark or bark methanolic extract	Anti-proliferative and anti-inflammatory effect. Pro-apoptotic effect on HT-29, HCT-15, HCA-7 cells.	Androulakis et al. 2006, Zhang et al. 2007
Diarrhoea	Aqueous and methanolic extract of leaves	Anti-diarrhoeal effect. Decrease in bowel activity.	Nwosu et al. 2012
Bacterial infections	Aqueous extracts of leaves	Antioxidant and antibacterial potency against <i>Staphylococcus aureus</i> and <i>Bacillus cereus</i> .	Konate et al. 2011
Helminth infections	Bark Extract	Effective against some parasites: <i>Haemonchua</i> , <i>Cooperia</i> , <i>Oesophagostomum</i> and <i>Trichostrongylus</i> .	Chiezey et al. 2000, Okpara et al. 2004
Trypanosomiasis	Bark aqueous extract and methanolic stem bark extract	Decrease in parasitic burden (<i>Trypanosoma brucei</i>) within 6 days at 60-100mg per kg of bodyweight. Anti- <i>Trypanosoma evansi</i> activity.	Ibrahim et al. 2008 Umar et al. 2010 Shaba et al. 2011
Diabetes	Stem bark aqueous extract Leaves aqueous extract	Anti hyperglycaemic effect in rats. Inhibition of α -amylase activity at 45-75%.	Kolawole et al. 2012 Funke and melzig 2006

Table adapted from Takin et al. 2013, p.125.

REFERENCES

- Abubakar, M.G., Lawal, A. and Usman, M.R. Hepatotoxicity studies of sub-chronic administration of aqueous stem bark of *Khaya senegalensis* in Albino rats. *Bajopas*, 2009; 3(1): 26-28.
- Adakole, J.A. and Balogun, J.B. Acute ecotoxicity of aqueous and ethanolic extract of leaves of *Khaya senegalensis* on chironomid larvae. *Braz. J. Aquat. Sci. Technol.*, 2011; 15(2): 41-45.
- Adebayo, J.O., Yakubu, M.T., Egwim, E.C., Owoyele, V.B. and Enaibe, B.U. Effect of ethanolic extract of *Khaya senegalensis* on some biochemical parameters of rat kidney. *J. Ethnopharmacol.*, 2003; 88: 69-72.
- Adesogan, E.K. The chemical constituents of *Khaya senegalensis*. Symposium: Traditional pharmacopoeia and African Medicinal Plants, Dakar, Senegal, March 1968.
- Adjanohoun, E.J., Ahyi, M.R.A. and Ake Assi, L. Contribution aux études ethnobotaniques floristiques au Togo. *ACCT*, 1996; 389-392.
- Ali, S.A.M., Elbadwi, S.M.A., Idris, T.M. and Osman, K.M. Hepatoprotective activity of aqueous extract of *Khaya senegalensis* bark in rats. *J. Med. Plants Res.*, 2011; 5(24): 5863-5866.
- Androulakis, X.M., Muga, S.J., Chen, F., Koïta, Y., Touré, B. and Wargovich, M.J. Chemopreventive Effects of *Khaya senegalensis* Bark Extract on Human Colorectal Cancer. *Anticancer Res.*, 2006; 26: 2397-2406.
- Arbonnier, M. 2002. Trees, shrubs and lianas of West African dry zones. The Netherlands: Cirad/Margraf Publishers, pp. 189- 426.
- Athanasiadou, S., Githiori, J. and Kyriazakis, I. Medicinal plants for helminth parasite control: facts and fiction. *Animal*, 2007; 1(9): 1392-1400.
- Ayo, R.G., Audu, O.T. and Amupitan, J.O. Physicochemical characterization and cytotoxicity studies of seed extracts of *Khaya senegalensis* (Desr.). *Afri. J. Biotechnol.*, 2007; 6(7): 894-896.
- Azaizeh, H., Fulder, S., Khalil, K. and Said, O. Ethnomedicinal knowledge of local Arab practitioners in the Middle East region. *Fitoterapia*, 2003; 74: 98-108.
- Bickii, J., Njifutie, N., Foyere, J.A., Basco, L.K. and Ringwald, P. In vitro antimalarial activity of limonoids from *Khaya grandifoliola* C.D.C. (Meliaceae). *J. Ethnopharmacol.*, 2000; 69: 27-33.
- Chiezey, N.P., Gefu, J.O., Jagun, A.G., Abdu, P.A., Alawa, C.B.I., Magaji, S.O., Adeyinka, I.A., Edivie, L.O. 2000. Evaluation of some Nigerian plants for anthelmintic activity in young cattle. Proceedings of the International Workshop on Ethnoveterinary Practices, 14-18 August, Kaduna, Nigeria.
- Daniel-Yves, A. 2002. Initiation à l'agroforesterie en zone sahélienne: les arbres des champs du Plateau Central au Burkina Faso. KARTHALA Editions. Paris France. 220 p.
- Djoueche, C.M., Azebaze, A.B. and Dongmo, A.B. Investigation of plants used for control of gastrointestinal parasites in Cameroon. *Tropicicultura*, 2011; 29(4): 205-211.
- El Badwi, S.M.A., Bakhiet, A.O. and Abdel Gadir, E.H. Haemato-biochemical Effects of aqueous extract of *Khaya senegalensis* stem bark on Gentamicin-Induced Nephrotoxicity in Wistar Rats. *J. Biol. Sci*, 2012; 12:361-366.
- Elisha, I.L., Makoshi, M.S., Makama, S., Dawurung, C.J., Offiah, N.V., Gotep, J.G., Oladipo, O.O. and Shamaki, D. Antidiarrheal evaluation of aqueous and ethanolic stem bark extracts of *Khaya senegalensis* A. Juss (Meliaceae) in albino rats. *Pak. Vet. J.*, 2013; 33(1): 32-36.
- Full, A.B., Vanhaelen-Faster, R., Vanhaelen, M., Lo, L., Toppet, M., Ferter, A. and Fondou, P. In vitro antisickling activity of a rearranged limonoid isolated from *Khaya senegalensis*. *Plant Med.*, 1999; 63(3): 209-212.
- Funke, I. and Melzig, M.F. Traditionally used plants in diabetes therapy - phytotherapeutics as inhibitors of a-amylase activity. *Braz. J. Pharmacogn.*, 2006; 16(1): 1-5.
- Ibrahim, M.A., Njoku, G.C. and Sallau, A.B. In vivo activity of stem barks aqueous extract of *Khaya senegalensis* against *Trypanosoma brucei*. *Afr. J. Biotechnol.*, 2008; 7: 661- 663.
- Karou, D., Dicko, M.H., Simpore, J. and Traore, A.S. Antioxidant and antibacterial activities of polyphenols from ethnomedicinal plants of Burkina Faso. *Afr. J. Biotechnol.*, 2005; 4: 823-828.
- Kolawole, O.T., Kolawole, S.O., Ayankunle, A.A. and Olaniran, O.I. Anti-hyperglycemic Effect of *Khaya senegalensis* Stem Bark Aqueous Extract in Wistar Rats. *European J. of Medicinal Plants*, 2012; 2(1): 66-73.
- Konaté, K., Kiendrébéogo, M., Ouattara, M.B., Souza, A., Lamien-Meda, A., Nongasida, Y., Barro, N., Millogo-Rasolodimby, J. and Nacoulma, O.G. Antibacterial potential of aqueous acetone extracts from five medicinal plants used traditionally to treat Infectious Diseases in Burkina Faso. *Curr. Res. J.Biol. Sci.*, 2011;3(5): 435 - 442.
- Le Strange, J.N. 1977. The Useful Plants of West Tropical Africa. The Crown Agents, London, p. 325.
- Lompo, M. 1993. Etude pharmano-toxicologique chez la souris et le rat de *Khaya senegalensis* (Desr.) A. Juss (Meliaceae) utilisé en thérapeutique au Burkina Faso. Mémoire de D.E.A. *Physiol. Anim. Appl. Université de Ouagadougou*.
- Nacoulma, O.G. 1996. Medicinal plants and their traditional uses in Burkina Faso. Ph.D. Thesis, University of Ouagadougou, pp: 328.
- Ndiaye, S.S. 2013. *Khaya senegalensis* ou hay enwolof. Retrieval on 2013/04/28 at <http://sambamara.com/>
- Nwosu, C.U., Hassan, S.W., Abubakar, M.G. and Ebbo, A.A. Anti-diarrhoeal and toxicological studies of leaf extracts of *Khaya senegalensis*. *J. Pharm. Toxicol.*, 2012; 7(1): 1-10.
- Okpara, J.O., Anagor, P.O., Okpalia, E.J., Abdullahi, A. and Ahmed, M.S. 2004. The anthelmintic efficacy of medicinal herb extracts against gastrointestinal helminths of sheep. Rapport de la 9th Annual Conference of Animal Science Association of Nigeria (ASAN), 13- 16 Sept. 2004. Ebonyi State University, Nigeria.
- Sabllassou, K., Aklidikou, A.K. and Gbeassor, Von Maydell, H.J. 1983. Arbres et Arbustes du Sahel. Leurs caractéristiques et leurs utilisations. G.T.Z. ESCHBORN, 283-284.
- Sale, M., De, N., Doughari, J.H. and Pukuma, M.S. In vitro assessment of antibacterial activity of bark extracts of *Khaya senegalensis*. *Afr. J. Biotechnol.*, 2008; 7: 3443-3446.
- Shaba, P., Pandey, N.N., Sharma, O.P., Rao, J.R., Mishra, A.K. and Singh, R.K. Antitrypanosomal activity of methanolic extract of *Khaya Senegalensis* tree bark against *Trypanosoma evansi*. *Int. J. of Food, Agri. And Vet. Sc.*, 2011; 1(1): 21-26.
- Sokpon, N. and Ouinsavi, C. Utilisations du *Khaya senegalensis* en médecine traditionnelle au Bénin. *Rev. Med. Pharmaco. Afric.*, 2002; 16: 9-19.
- Sule, M.S., Abdulraheem, R.B. and Aminu, B.M. Potency of aqueous stem bark extract of *Khaya senegalensis* against liver diseases in rats. *Bajopas*, 2008; 1(1): 29-31.
- Takin, M.C., Attindehou, S., Sezan, A., Attakpa, S.E. and Baba-moussa, L. Bioactivity, therapeutic utility and toxicological risks of *Khaya Senegalensis*. *IJPBR*, 2013, 1 (4): 122-129.
- Tchacondo, T., Karau, S.D., Batawila, K., Agban, A., Ouro-Bang'na, K., Anani, K.T., Gbeassor, M. and de Souza, C. Herbal remedies and their adverse effects in tern tribe traditional medicine in Togo. *AJT CAM*, 2011; 8(1): 45-60.
- Umar, I.A., Ibrahim, M.A., Fari, N.A., Isah, S. and Balogun, D.A. In-vitro and -vivo anti *Trypanosoma evansi* activities of extracts from different parts of *Khaya senegalensis*. *J. Cell Ani. Bio.*, 2010; 4(6): 91-95.
- Von Maydell, H.J. 1983. Arbres et Arbustes du Sahel. Leurs caractéristiques et leurs utilisations. G.T.Z. ESCHBORN, 283-284.
- Yakubu, M.T., Adebayo, O.J., Egwim, E.C. and Owoyele, V.B. Increased liver alkaline phosphatase and aminotransferase activities following administration of ethanolic extract of *Khaya senegalensis* stem bark to rats. *Biokemistri*, 2005; 17(1): 27-32.
- Yuan, T., Zhang, C-R., Yang, S.P. and Yue, J-M. Limonoids and Triterpenoids from *Khaya senegalensis*. *J. Nat. Prod.*, 2010; 73: 669-674.
- Zhang, H., Wang, X., Chen, F., Androulakis, X.M. and Wargovich, M.J. Anticancer activity of Limonoids from *Khaya senegalensis*. *Phytoter. Res.*, 2007; 21: 731-734.