

REVIEW

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# Biological activities of limonoids in the Genus *Khaya* (Meliaceae): a review

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## Abstract

**Background:** Limonoids are a class of highly oxygenated modified triterpenoids with a diverse range of biological activities. Although with restricted occurrence in the plant kingdom, these compounds are found extensively in the Meliaceae and Rutaceae families. Limonoids are of great interest in science given that the small number of plant families where they occur exhibit a broad range of medicinal properties that promote health and prevent disease.

**Main text:** The Meliaceae family includes the genus *Khaya* and comprises tree species that have been used in traditional medicine to treat several ailments. In recent years, the genus *Khaya* has attracted much research interest owing to the presence of limonoids in different plant parts of a few species that can serve as therapeutic molecules in the pharmaceutical industry. In this study, a literature search over the past two decades (2000–2020) was conducted on the biological activities of limonoids in the genus *Khaya* using different databases such as Google Scholar, PubMed, Scopus and ISI Web of Science. The taxonomy, geographical distribution and the various traditional uses of the genus are presented in detail. This study reveals that the currently documented biological activities of limonoids both in vivo and in vitro are limited to four species (*K. anthotheca*, *K. grandifoliola*, *K. ivorensis* and *K. senegalensis*) in the genus *Khaya*, and include anticancer, antimalarial, hepatoprotection, anti-inflammatory, neuroprotection, antimicrobial, antifungal and antifeedant. The most well-researched species, *K. senegalensis*, has the most notable biological activities and traditional uses in the genus *Khaya*.

**Conclusion:** The present detailed and up-to-date review of recent literature on the biological activities in the genus *Khaya* reveals the potentials of limonoids for drug development in managing several ailments.

**Keywords:** Biological activities, Diseases, Drug development, *Khaya*, Limonoids, Meliaceae

## Background

Natural compounds from plants are continually investigated to discover new therapeutics in treating and preventing several human ailments [1]. Historically, medicinal plants have been efficient as a remedy for several ailments [2] and thus form an integral aspect of traditional medicines and various science fields [3]. As listed by the World Health Organization (WHO), there are up to 20,000 medicinal plants in 91 different countries worldwide [4]. Many of these plants have been evaluated and documented for potency and remedial capabilities

[5–7]. Research intensification in natural products derived from medicinal plants as a source of new drugs is mainly due to the plants abundant biologically active compounds (secondary metabolites) which have become central components in modern therapy [8]. These broad-range bioactive secondary metabolites are present in different plant organs such as fruits, stem, bark, leaves, seeds and roots [7], and are structurally and functionally diverse, thereby providing various prospects for developing novel drug leads in the pharmaceutical industry [4].

Among the plant secondary metabolites of significant importance are the limonoids, which are primarily found in the Meliaceae and Rutaceae (citrus) families and occur less frequently in Simaroubaceae and Cneoraceae

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families [9, 10]. In addition to their abundance, limonoids present in the family Meliaceae often referred to as meliacins, are of unique interest due to their structurally diverse and highly potent activity with relevant biological properties than those found in other families [2, 11, 12]. Interestingly, the genus *Khaya* (commonly known as African Mahogany) belonging to the family Meliaceae, is highly reputed for several biological activities that are attributed to limonoids present in different plant parts of different species [13]. On account of their extensive range of biological activities, including anticancer [14–16], antimalarial [17, 18], anti-inflammatory [16, 19], antifeedant [20, 21] among others, limonoids are increasingly gaining research interest.

There have been recent individual studies in *Khaya* species, mostly focusing on the plant extracts bioactivities and the composition of the constituents in various plant parts. However, to our knowledge, no study which presents all reported bioactivities with a focus on limonoids has been documented in the genus *Khaya* despite the significance of limonoids within the genus. Hence, the present review of recent literature aimed to present in-depth and current reports on the biological activities of limonoids in the different *Khaya* species and their significance in developing new therapeutics for different human ailments.

A literature search on the biological activities of limonoids in the genus *Khaya* was performed using different databases such as Google Scholar, PubMed, Scopus and ISI Web of Science. The literature search was limited to articles and other relevant materials over the past two decades (from 2000 to 2020) to present current studies in this review. Free, full-text articles available in English were used for the review, focusing mainly on the four species (*K. anthotheca*, *K. grandifoliola*, *K. ivorensis* and *K. senegalensis*) in the genus *Khaya* where limonoids have been reported. All chemical structures were drawn with ChemDraw Ver. 19.1 (PerkinElmer® Inc., Waltham, USA).

## Main text

### The genus *Khaya* at a glance

The genus *Khaya* belongs to the mahogany family Meliaceae comprising several economically important tree species, including *Toonia ciliata*, *Azadirachta indica*, *Swietenia macrophylla*, *Cedrella odorata* [22] and all *Khaya* species [23]. The genus *Khaya* consists of six recognized species: *K. anthotheca* (Welw.) C.DC., *K. grandifoliola* C.DC., *K. ivorensis* A. Chev., *K. senegalensis* (Desr.) A. Juss, *K. madagascariensis* Jum. & H.Perrier and *K. nyasica* Staph ex Baker f. [24], that are of high commercial and economic importance. The species of *Khaya* are native to Madagascar and tropical Africa and have been

introduced to Southern Asia and Australia from central Africa [25]. In their natural distributions, *Khaya* species are esteemed for timber, therapeutic products and attractiveness [22]. *Khaya* species have similar fruits and flowers, and the most apparent differences are seen in their leaflets. The scientific classification of *Khaya* species is presented in Fig. 1.

### *Khaya anthotheca*: description and distribution

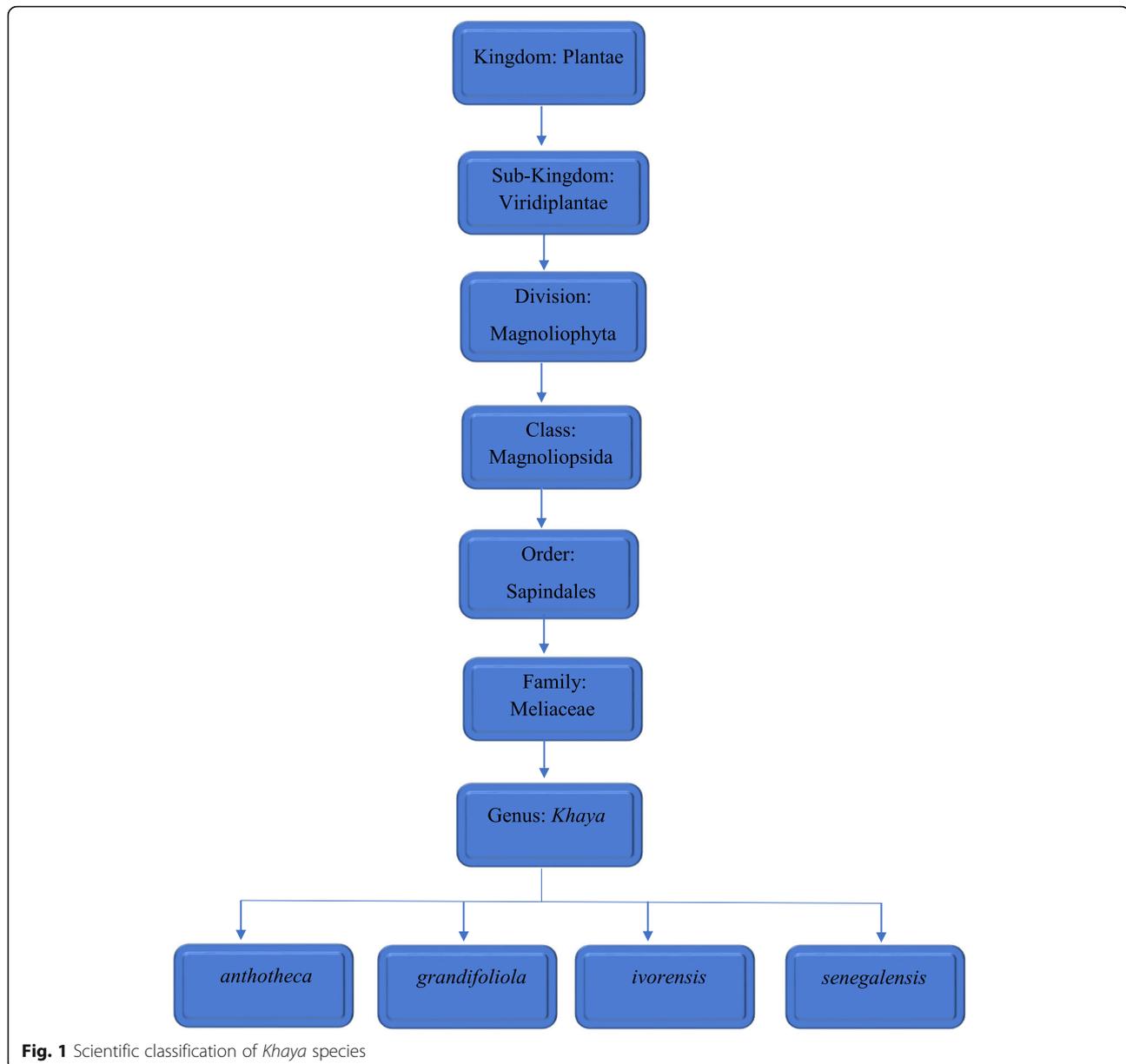
*Khaya anthotheca*, commonly known as East African Mahogany, is a large evergreen tree species native to tropical Africa [26]. The specific name *anthotheca* is derived from two Greek words, “*anthos*” and “*theca*” meaning flower and capsule, respectively. *Khaya anthotheca* is fast growing and grows up to 60 m in height (30 m in gardens) [23]. The leaves are spirally arranged, alternate, with 3–7 leaflets and dark-glossy green in colour. The bark of the tree is greyish brown. Stipules are absent, and the petiole is 3.5–7 cm long. The inflorescence is axillary with panicle that is 30–40 cm long and flowers are unisexual. The fruits are erect, nearly globose with woody capsules that are 4–10 cm in diameter, dehisce into 4–5 halves with many seeds [23]. Seeds are disk-shaped or quadrangular [23]. *Khaya anthotheca* is found at low to medium altitudes in riverine fringe and evergreen forests in Africa [27]. It occurs widely in Guinea Bissau east, Angola, Uganda, Zambia, Zimbabwe, Tanzania and Mozambique. It has been grown successfully in Cuba, the eastern part of South Africa, Puerto Rico, tropical America and tropical Asia [27].

### *Khaya grandifoliola*: description and distribution

*Khaya grandifoliola* commonly referred to as the large-leaf mahogany is a medium-large tree that grows up to 40 m in height and usually deciduous in dry seasons [28]. It is monoecious, and leaves are often arranged spirally with cluster ends, paripinnately compound with 3–5 leaflets in pairs. The flowers are unisexual, and the male and female flowers are much alike. The fruits are erect with woody capsules that are 6–9 cm in diameter, globose and dehisce by five halves with many seeds. Seeds are brown, flat and disk-shaped [28]. *Khaya grandifoliola* occurs naturally in the fringe between rain forest and the drier parts of savanna and occurs widely in western tropical Africa from Guinea-Bissau to Sudan and Uganda [29]. It is found in Nigeria, Benin, Congo, Sudan, Ghana, Togo, Ivory Coast and Uganda [28].

### *Khaya ivorensis*: description and distribution

*Khaya ivorensis*, commonly known as Lagos Mahogany or heavy African mahogany, is a tall evergreen forest tree (occasionally deciduous in drier climates) with a large buttressed trunk [30]. Like other species in its genus, *K.*



*ivorensis* grows up to 40–50 m in height. The leaves are compound, broad and are spirally arranged with 3–7 leaflets. The inflorescence is an axillary panicle which grows up to 20 cm long. The flowers are unisexual with a striking resemblance between the male and the female flowers. Fruits are greyish brown, erect with a woody capsule and are many-seeded [30]. The seeds are brown, disk-like shaped and flat. *Khaya ivorensis* occurs most abundantly in the evergreen forest. It is indigenous to Africa and naturally distributed from Sierra Leone and Liberia to Gabon [27]. It is found in Angola, Cameroon, Ghana, Ivory Coast and Nigeria and has been fairly grown in some plantations of tropical America and Asia.

#### ***Khaya senegalensis*: description and distribution**

*Khaya senegalensis* is commonly referred to as dry zone or Senegal mahogany [31]. It is an evergreen, medium-sized tree that grows up to 15–30 m in height and 1 m in diameter. In its natural distribution, *K. senegalensis* is usually grown as a roadside and ornamental shade tree [32]. The leaves are paripinnately compound, with leaflets in pairs of 2–6, spirally arranged but are clustered close to the end of branches. The flowers are regular, unisexual, sweet-scented and white. The fruits are pale-grey to greyish brown, erect, with a woody capsule of 4–6 cm in diameter and highly seeded. The fruit dehisces into four halves. The seeds are brown, quadrangular in

shape and are flat. *Khaya senegalensis* is naturally found in savanna woodland, usually in a wet area with an annual rainfall of 650–1800 mm [32]. The tree is native to Senegal, Nigeria, Ghana, Benin, Mali, Sudan, Togo, Gambia, Burkina Faso, Uganda, Ivory Coast, Cameroon, Niger and Guinea-Bissau. It has been successfully grown in South Africa, Malawi, India, Vietnam, Madagascar, Australia, Egypt, Indonesia and tropical America [22].

#### Uses of *Khaya* species in traditional medicine

*Khaya* species, which are timber trees in the family Meliaceae, have been used traditionally for treating several ailments (Table 1), including malaria, rheumatism, fever and back pain in Africa [19]. The crude extracts from different parts of these tree species have been reported to exhibit anti-inflammatory [19], antioxidative and anti-diabetic [13] and anti-hypertensive [44] activities among others, which justify their traditional use in the treatment of some ailments.

#### Limonoids in the genus *Khaya*

The word “limonoid” was derived from limonin more than a century ago when researchers isolated a primary bitter principle (limonin) in citrus seeds [9]. Limonoids are a class of highly oxygenated modified triterpenoids that exist extensively in the Meliaceae and Rutaceae plant families [45], and less frequently in Simaroubaceae and Cneoraceae families. Occasionally, limonoids have been reported in some species of the families Euphorbiaceae, Burseraceae, Boraginaceae and Flacourtiaceae, implying that these important secondary metabolites may be more varied and extensively spread than initially thought [11] (Figs. 2, 3, 4 and 5).

Structurally, limonoids are derived from triterpene by the loss of four carbon atoms from a side chain of apoeuphane or apotirucallane skeleton, forming 17 $\beta$ -furan ring after cyclization [2, 10]. Hence, they are alternatively regarded as tetranortriterpenoids [45] and are classified by an intact ring system and those in which one of the four rings (A, B, C, or D) has been oxidized [46]. Limonoids are of great interest in science given that

**Table 1** Uses of *Khaya* species in traditional medicine

Ailment	<i>Khaya</i> species	Part used	Country	References	
Rheumatism	<i>K. ivorensis</i>	Bark	Nigeria	[33]	
Fever	<i>K. grandifolia</i>	Stem bark	Nigeria	[33]	
Pile	<i>K. senegalensis</i>	Bark	Nigeria	[33]	
Malaria	<i>K. grandifolia</i>	Leaves	Cameroon,	[34]	
		Seeds	Cameroon	[34]	
		Leaves	Togo	[35]	
Anaemia	<i>K. senegalensis</i>	Bark	Burkina-Faso	[31]	
		<i>K. ivorensis</i>	Bark	Nigeria	[36]
			Bark	Burkina-Faso	[31]
Nervous system and mental disorder	<i>K. senegalensis</i>	Bark	Ghana	[37]	
Liver problem	<i>K. grandifolia</i>	Stem bark	Cameroon	[38]	
Worm infestations	<i>K. anthotheca</i>	Bark	Madagascar	[39]	
Microbial infections	<i>K. anthotheca</i>	Bark	Madagascar	[39]	
		Leaves	Madagascar	[40]	
Diarrhoea	<i>K. senegalensis</i>	Bark	Burkina-Faso	[31]	
		Stem bark	Cote-d'Ivoire	[41]	
Haemorrhoids	<i>K. senegalensis</i>	Root	Togo	[35]	
Epilepsy	<i>K. senegalensis</i>	Stem bark	Togo	[35]	
Boil	<i>K. senegalensis</i>	Bark	Mali	[42]	
Hypertension	<i>K. senegalensis</i>	Stem bark	Togo	[35]	
Diabetes	<i>K. senegalensis</i>	Stem bark	Togo	[35]	
Wounds	<i>K. senegalensis</i>	Stem bark	Cote-d'Ivoire	[41]	
		Bark	Mali	[42]	
Snake/insect bite	<i>K. senegalensis</i>	Bark	Mali	[42]	
Sexually transmitted infections	<i>K. senegalensis</i>	Stem bark	Guinea	[43]	



**Fig. 2** *K. anthothecca*. **a** Tree. **b** Leaves. Source: Google images

the small number of plant families where they occur exhibit a broad range of biological activities that promote health and prevent disease.

Several chemical investigations have revealed that the genus *Khaya* is highly characterized by abundant, structurally diverse and biologically active rings D, B, D-Seco limonoids like gedunins, mexicanolide, phragmalin and andirobins in various parts of the tree, mainly the stem bark (Figs. 6, 7, 8 and 9). For instance, [50] isolated six new limonoids (khayasenelide A-F) in addition to six known limonoids (1-O-deacetyl-2 $\alpha$ -hydroxykhayanolide E, 1-O-deacetylkhayanolide E, senegalensins A, khayanolide B, khaysenegain E and khaysenegain I) from the stem bark of *K. senegalensis* [47] isolated two new limonoids (14,15-didehydroruageanin A and 3-O-methylbutyrylseneganolide A) from the fruits of *K. ivorensis*. From the stem bark of *K. anthothecca*, [48] isolated

four new limonoids namely anthothecanolide, 3-O-acetylanthothecanolide, 2,3-di-O-acetylanthothecanolide and 6R,8 $\alpha$ -dihydroxycarapin. In another study, three limonoids (17-epi-methyl-6-hydroxyangolensate, 7-deacetoxy-7-oxogedunin and 7-deacetoxy-7R-hydroxygedunin), with hepatoprotective activity, were isolated from the stem bark of *K. grandifoliola* [49].

#### Biological activities of limonoids in the genus *Khaya*

##### Anticancer activity

Globally, cancer in whichever form is one of the leading causes of mortality. In the next two decades, it is estimated to increase by about 70% worldwide with the most significant impact on low income and developing countries [51]. Several efforts such as surgery, chemotherapy and radiotherapy have been used in the fight against cancer in the past few decades. However, cancer



**Fig. 3** *K. grandifoliola*. **a** Tree. **b** Leaves. Source: Google images



**Fig. 4** *K. ivorensis*. **a** Tree. **b** Leaves. Source: Google images

treatment remains a significant challenge owing to tumour diversity, damage to normal cells, resistance and recurrence of tumours even after years of remission [52].

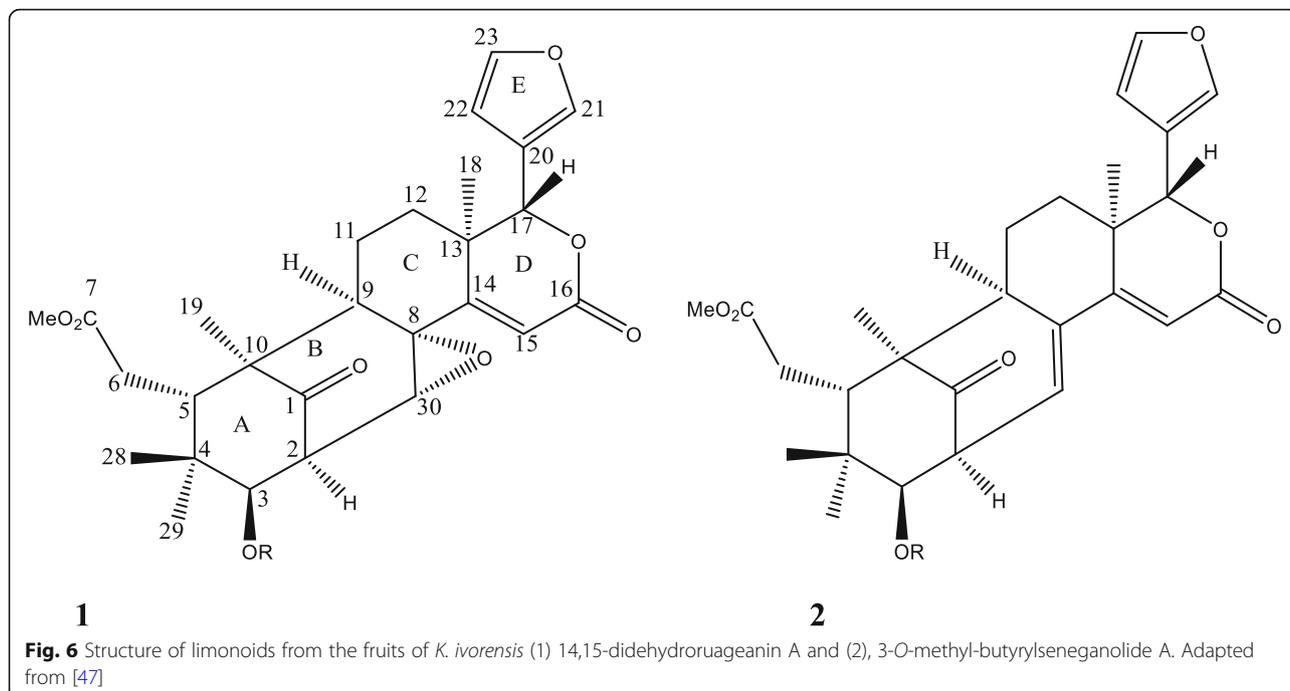
Studies have indicated that bioactive compounds in medicinal plant extracts with anticancer potentials are currently attracting researchers' attention in the fight against cancer. Verma et al. [15] examined the inhibitory capability and mechanism of action of anthothocol, a limonoid from *K. anthotheca* and anthothocol encased poly (D,L-lactic-co-glycolic acid) nanoparticles (Antho-NPs) on pancreatic cancer stem cells and cell lines obtained from human and *Kras*<sup>G12D</sup> mice.

The study established that anthothocol and antho-NPs repressed the spread of cancer stem cells and cell lines in a dose-dependent form without affecting the normal

human pancreatic ductal epithelial cells. Additionally, anthothocol alone and antho-NPs were reported to cause apoptosis on pancreatic stem cells and cell lines and prevented colonies formed by cancer cells in a dose-dependent manner. The study reported that antho-NPs prevented the expression of pluripotency maintaining factors (cMyc and Nanog) and hindered self-renewing ability of stem cell markers (CD44 and CD24) in pancreatic cancer stem cells. Similarly, in pancreatic cancer stem lines isolated from human and *Kras*<sup>G12D</sup> mice, antho-NPs inhibited pancreatic cancer stem cells' growth by hindering spheroids' cell viability. Also, in a dose-dependent manner in the pancreatic cancer stem cells and cell lines, antho-NPs inhibited epithelial-mesenchymal transition (a key driver of metastasis) and



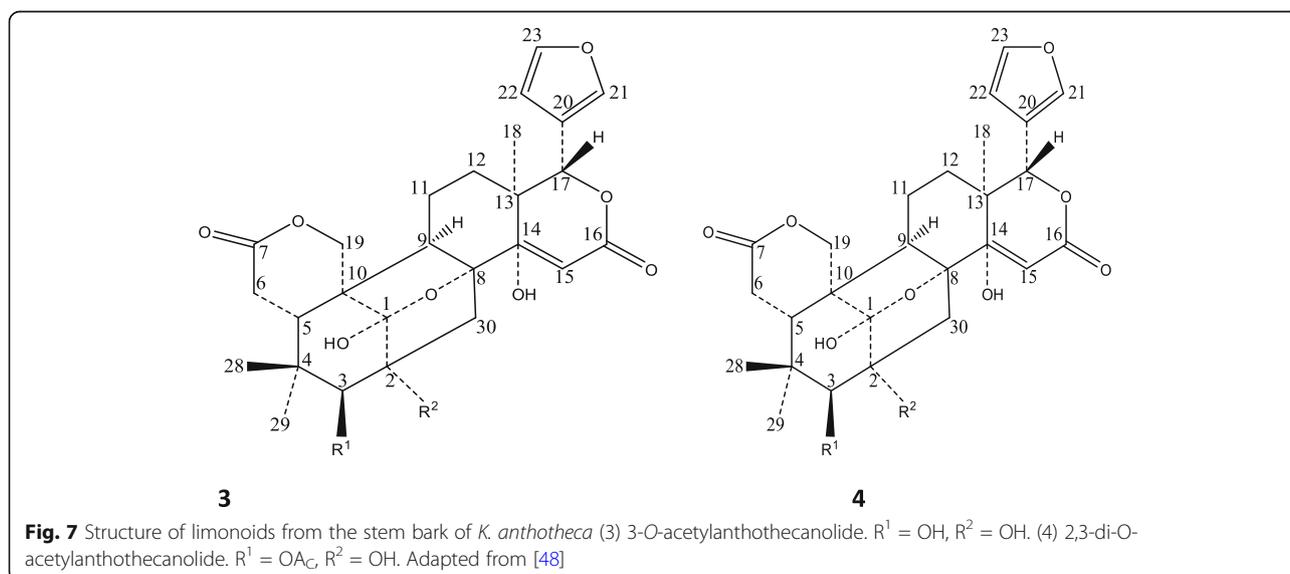
**Fig. 5** *K. senegalensis*. **a** Tree. **b** Leaves. Source: Google images

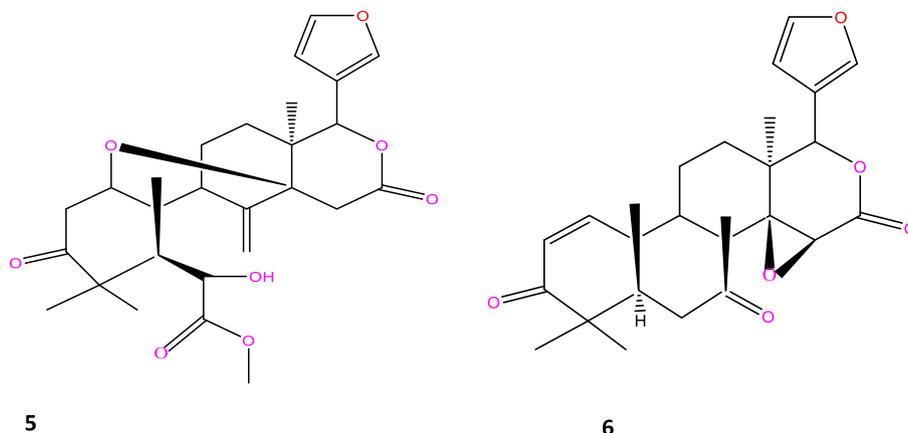


hindered the expression of sonic hedgehog signaling pathway that leads to the production of tumours. The results suggest that anthothecol and antho-NPs are potent in preventing and treating human pancreatic cancer. The mechanism via which antho-NPs caused inhibition of cell proliferation of pancreatic cancer stem cells and cell lines was attributed to the disruption of Gli-DNA binding activity.

In another study by [14], the antitumor activity of a limonoid (3 $\alpha$ ,7 $\alpha$ -dideacetylkhivorin) obtained from the methanol extract of the stem bark of *K. senegalensis* was examined on human breast (MCF-7), colon

(Caco-2) and cervical (SiHa) cancer cell lines. They reported that 3 $\alpha$ ,7 $\alpha$ -dideacetylkhivorin, in a dose-dependent manner, prevented the proliferation of MCF-7, Caco-2 and SiHa cell lines. The highest concentration examined (200 ppm) prevented 66%, 70% and 61% cell growth for MCF-7, Caco-2 and SiHa, respectively. Further, the IC<sub>50</sub> values leading to inhibition of cell proliferation were reported as 0.14  $\mu$ M, 0.07  $\mu$ M and 0.11  $\mu$ M, for MCF-7, Caco-2 and SiHa, respectively. The results suggest that 3 $\alpha$ ,7 $\alpha$ -dideacetylkhivorin is a potent anticancer agent against several human cancers.





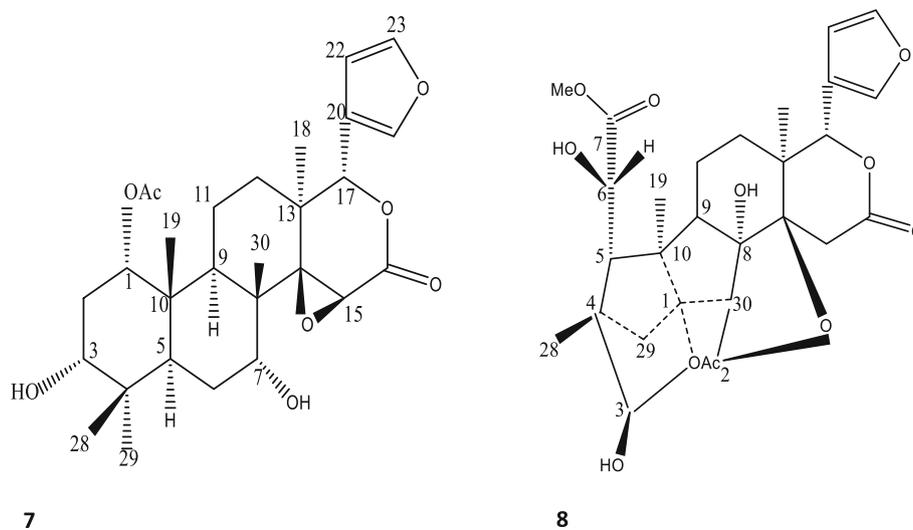
**Fig. 8** Structure of limonoids from the stem bark of *K. grandifoliola* (5) 17-epi-methyl-6-hydroxyangolensate. (6) 7-deacetoxy-7-oxygedunin. Adapted from [49]

As reported by [16], in vitro cytotoxicity screening of khayasenelide G, a limonoid isolated from the stem bark of *K. senegalensis* evaluated against human cancer cell lines (MDA-MB-231 and HepG2), showed effective cytotoxicities against the tumour cell lines with  $IC_{50}$  values of 6.02 and 8.98  $\mu$ M, respectively.

In vitro cytotoxic activity of different extracts of *K. grandifoliola* leaves was evaluated on liver carcinoma (HEPG2), breast carcinoma (MCF7), cervix carcinoma (HELA), larynx carcinoma (HEP2) and colon carcinoma (HCT116) cell lines by [25]. The authors revealed that the ethanolic leaf extract of *K. grandifoliola* exhibited cytotoxic effects against HEPG2, MCF7 HEP2 and HCT116 carcinoma cell lines and the results were comparable to the effects exhibited by the standard

(doxorubicin) while the chloroform extract showed high toxicity effects against HCT116 only. These cytotoxic effects of *K. grandifoliola* leaf extracts were attributed to two isolated limonoids  $\beta$ -sitosterol-3-*O*- $\beta$ -D-glucopyranoside and  $\beta$ -stigmasterol-3-*O*- $\beta$ -D-glucopyranoside in the chloroform extract.

Additionally, a study conducted by [47] on the cytotoxic activity of limonoids from the fruit of *K. ivorensis* against five cancer cell lines, revealed that some limonoids showed cytotoxicity against the cancer cell lines. Three limonoids (3-*O*-methyl-butyrlyseneganolide A, seneganolide A and 1,3-dideacetylkhivorin) demonstrated cytotoxicity against lung cancer (A-549), myeloid leukaemia (HL-60), hepatocellular carcinoma (SMMC-7721), colon cancer (SW480) and breast cancer (MCF-



**Fig. 9** Structure of limonoids from the stem bark of *K. senegalensis*. (7) 3a, 7a-dideacetylkhivorin. (8) 1-*O*-acetylkhayanolide. Adapted from [14]. All structures were drawn with ChemDraw

7), with  $IC_{50}$  values range of 21.1  $\mu\text{M}$  and 39.5  $\mu\text{M}$ . In another similar study by [53], the cytotoxic activity of two limonoids (ivorenoids C and F) isolated from the ethanolic extract of the stem of *K. ivorensis* against human leukaemia (HL-60) and murine leukaemia (P388) was reported to have shown moderate cytotoxicity against the cancer cells with  $IC_{50}$  values of 0.19  $\mu\text{M}$  for HL-60 and 0.63  $\mu\text{M}$  for P388.

#### **Antimalarial activity**

Malaria, caused by a protozoan parasite of the genus *Plasmodium*, is a major public health problem globally, especially in tropical and sub-tropical countries where high morbidity and mortality are recorded [54]. According to the WHO report in 2016, over 216 million malaria cases were reported across 91 countries globally, and over 445,000 deaths resulting from malaria infection were recorded yearly [55]. It is estimated that 90% of the malaria cases and mortalities occur in sub-Saharan Africa [54]. Children below the age of five are highly susceptible to malaria as death resulting from malaria occurs every 2 min in children [55]. The global burden of malaria has lingered owing to increased drug-resistant parasite strains in several parts of the world where the *Plasmodium* is prevalent. Malaria cases keep rising in the remote and rural areas of sub-Saharan Africa, where cheap drugs and medical centres are not available. As a result, most people rely on herbal medicine for the treatment of malaria [56]. In that regard, several limonoids in different parts of *Khaya* species have been effective against different *Plasmodium* strains.

Bickii et al. [17] evaluated the in vitro antimalarial activity of limonoids purified from the crude extracts of seeds and bark of *K. grandifoliola* against a chloroquine-resistant strain (W2/Indochina) of *Plasmodium falciparum*. The results showed that five limonoids (methylangolensate, gedunin, 1-deacetylkhivorin, 7-deacetylkhivorin and 6-acetyl-swietenolide) were active against the chloroquine-resistant strain of *P. falciparum* with  $IC_{50}$  values range of 1  $\mu\text{g/ml}$  and 10  $\mu\text{g/ml}$ . The authors further reported that the antimalarial activities of the purified limonoids were comparable to the results of other limonoids obtained from other plants such as *Azadirachta indica*, *Cedrela odorata* and *Guarea multiflora* in the Meliaceae family used in treating malaria.

In another study by [18], the antimalarial efficacy of two limonoids (anthothochol and gedunin) from “whole plant” of *K. anthotheca* was assessed against the W2-strain of *P. falciparum* using [ $^3\text{H}$ ]-hypoxanthine and 48-h culture assay in vitro. The results revealed that anthothochol demonstrated potent antimalarial activity in the two assays with  $IC_{50}$  values of 1.4  $\mu\text{M}$  and 0.17  $\mu\text{M}$ . Similarly, gedunin was also reported to be effective

against the *Plasmodium* strain in the two assays with  $IC_{50}$  values of 3.1 and 0.14  $\mu\text{M}$ .

#### **Hepatoprotective activity**

In humans, the liver is considered a major detoxification site and therefore, it is a principal drug exposure target in the body [57]. Liver injuries induced by drugs and liver cirrhosis have been reported to be the ninth main cause of mortality in western and developing countries [38]. Efficient and less-harmful treatments of liver injury, especially with the use of natural compounds, are of interest in the pharmaceuticals [49].

The hepatoprotective activity and molecular mechanisms of action of limonoids from the stem bark of *K. grandifoliola* were evaluated against acetaminophen (APAP)-induced hepatotoxicity in normal human liver L-02 cells line [49]. The results of the study showed that three isolated limonoids, namely 17-epi-methyl-6-hydroxylangolensate, deacetoxy-7R-hydroxygedunin and 7-deacetoxy-7-oxogedunin demonstrated protective activity against APAP-induced hepatotoxicity as the limonoids improved the cellular antioxidant defense system as well as modified the major processes involved in APAP cell-death mechanism. The increased expression of mitogen-activated protein kinase phosphatase (Mkp)-1 and the nuclear translocation of nuclear factor erythroid 2-related factor-2 (Nrf2) were identified as the molecular mechanism of action of protection of the isolated limonoids against APAP-induced hepatotoxicity.

#### **Anti-inflammatory activity**

Inflammation is an activated defense response in the body to living tissue injuries caused by a damaged immune system, microbial infections and other physical agents [58]. Although the basic purpose of inflammatory activation is to contain and get rid of the harmful agents, and eliminate defective tissue parts in order to heal the system, organ and tissue affected, the mediators responsible for these processes in the acute inflammation phase may not progress well, thereby resulting to chronic inflammation [5]. Chronic inflammation has been implicated in the development of several diseases such as arthritis, atherosclerosis and obesity-associated diabetes [19]. Several anti-inflammatory and non-steroidal drugs are available in treating inflammation and pain; however, there are several side effects reported with the use of non-steroidal anti-inflammatory medication. Medicinal plants having anti-inflammatory therapeutic activities with little or no side effects are recommended as a healthy alternative therapy to be exploited in the treatment of inflammation [5].

The anti-inflammatory activity of Khayandirobilde, a limonoid isolated from the stem bark of *K. senegalensis*,

was evaluated against lipopolysaccharide (LPS)-stimulated inflammation in mouse macrophages RAW 264.7 and BV-2 microglial cells [19]. Khayandirobilde suppressed several pro-inflammatory mediators in RAW 264.7 and BV-2 microglial cells. Khayandirobilde reduced the production of LPS-induced nitric oxide (NO) in RAW 264.7 and BV-2 with  $IC_{50}$  values of  $5.04 \pm 0.14 \mu\text{M}$  and  $4.97 \pm 0.5 \mu\text{M}$ , respectively. Additionally, at both protein and mRNA levels, Khayandirobilde decreased LPS-induced interleukin-6 (IL-6) and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), which are pro-inflammatory mediators [19]. These results suggest that this limonoid is capable of exerting anti-inflammatory activity by preventing inflammatory mediators' expression.

Khayasenelide G, another limonoid isolated from the stem bark of *K. senegalensis*, evaluated for its anti-inflammatory activity against LPS-induced inflammation in mouse macrophage cell line (RAW 264.7) showed significant anti-inflammatory activity by inhibiting NO activities in the cell line at an  $IC_{50}$  value of  $3.51 \mu\text{M}$  [16].

#### Neuroprotective activity

In the human brain, glutamate is involved in a number of physiological activities, including memory, learning, neuronal plasticity and central excitatory neurotransmission [59]. However, when glutamate is excessive, it can stimulate *N*-methyl-D-aspartate receptor resulting in a high inflow of  $Ca^{2+}$ , reactive oxygen species, impairment of mitochondrial activity, neurotoxicity and subsequent neuronal cell death [58, 59]. Moreover, damage to neuronal cells caused by excess glutamate has been implicated in neuropathological and neuropsychiatric maladies such as brain injury, stroke and several other neurodegenerative ailments, and neuroprotection against glutamate-induced neurotoxicity has been a healing approach in treating neurodegenerative disease [60].

In vitro neuroprotective activity of khasenegasin G and seneganolide A isolated from the seeds of *K. senegalensis* was evaluated against "glutamate-induced injury in primary rat cerebellar granule neuronal cells (CGCs)" using MTT assay [61]. The study reported that the two limonoids demonstrated significant neuroprotective activities at a concentration of  $10 \mu\text{M}$  ( $88.5 \pm 6.4\%$  and  $78.4 \pm 5.7\%$  cell viabilities, respectively) and  $1 \mu\text{M}$  ( $87.6 \pm 1.2\%$  and  $76.5 \pm 2.0\%$  cell viabilities, respectively). The neuroprotective activity demonstrated by the two limonoids was comparable to the positive control, edarovone, which showed a cell viability of  $86.7 \pm 5.6\%$  at  $50 \mu\text{M}$ .

Similarly, Khasenegasin Z, a new andirobin-type limonoid extracted from the seeds of *K. senegalensis*, showed neuroprotective activity when evaluated against glutamate stimulated damage in rat cerebellar granule neuronal cells with increased viability of  $83.3 \pm 6.0\%$  at  $10 \mu\text{M}$  and  $80.3 \pm 3.2\%$  at  $1 \mu\text{M}$  [62].

#### Antimicrobial activity

Globally, infectious diseases are among the leading cause of mortality and account for half of the deaths in tropical regions [63]. The increasing antibiotic resistance resulting from antibiotics' overuse is a common health challenge, particularly for human infectious diseases [64]. This has necessitated the search for healthier and efficient natural product alternatives in treating several microorganisms with little or no toxicity to humans [63]. Antimicrobials that are plant-based represent a wide range of underexploited alternatives that can be used to treat infectious diseases with no such side effects associated with synthetic antimicrobials [63].

Abdelgaleil et al. [65] investigated the in vitro antimicrobial efficiency of a limonoid (3-dideacetylkhivorin) isolated from the stem bark of *K. ivorensis* against three bacterial strains, viz. *Bacillus subtilis* (Ehrenberg) Cohn (IFO 3009), *Micrococcus luteus* (Schroeter) Cohn (IFO 12708) and *Salmonella enteritidis* (Gaertner) Castellani and Chalmers (IFO 3313). The result of the study revealed that 3-dideacetylkhivorin totally prevented the growth of *S. enteritidis* and *B. subtilis* at 1 and 2 mg/ml, and 2 mg/ml, respectively.

In another study by [66], four limonoids (3-deacetylkhivorin, 1-deacetylkhivorin, swietmanin B and 3 $\beta$ -acetoxy-1 oxo-methylmeliacate) isolated from the methanol extract of *K. senegalensis* were evaluated for their antimicrobial efficacy against *Staphylococcus aureus* (ATCC25923), *Pseudomonas aeruginosa* (ATCC27853) and two clinically isolated bacterial strains MRSA 92 and MRSA 98 using the 2-fold dilution method. The authors reported that the four limonoids (at a MIC value of  $12.5 \mu\text{g/ml}$ ) showed antimicrobial activities against MRSA 92, MRSA 98 and *P. aeruginosa*.

In the studies carried out by [39], in vitro antitrypanosomal and antileishmanial activities of two limonoids (Grandifolione and 7-deacetylkhivorin) isolated from the petroleum ether seed extract of *K. anthotheca* were evaluated against *Trypanosoma brucei brucei*, *Trypanosoma brucei rhodesiense*, *Trypanosoma cruzi* and *Leishmania donovani*. Both Grandifolione and 7-deacetylkhivorin showed activity against *Trypanosoma brucei rhodesiense* (with  $IC_{50}$  values of 10.66, 16.88  $\mu\text{g/ml}$ , respectively), *Trypanosoma cruzi* (with  $IC_{50}$  values of 20.97, 31.82  $\mu\text{g/ml}$ , respectively) and *Leishmania donovani* (with  $IC_{50}$  values of 13.31, 36.71  $\mu\text{g/ml}$ , respectively). The results justify the traditional use of *K. anthotheca* in treating microbial infections.

#### Antifungal activity

The major focus of integrated pest management is to effectively manage and control pests without causing harm to humans, animals and the environment. In recent

times, bioactive natural compounds, particularly secondary metabolites with antifungal activities that are nontoxic to humans, highly biodegradable and with very low persistence in the environment are considered alternatives to conventional pesticides in pest management and control [65].

Several plants with fungitoxic activities against pathogens have been reported in the literature. Using radial growth approach, [65] investigated in vitro antifungal activity of isolated limonoids from the diethyl ether of the stem bark of *K. ivorensis* against a plant pathogen fungus (*Botrytis cinerea* Pers.). The results revealed that the 10 limonoids (methyl angolensate, methyl 6-hydroxyangolensate, 3-deacetylkhivorin, 3,7-dideacetylkhivorin, 1,3,7-trideacetylkhivorin, 7-deacetylgedunin, 7-deacetoxy-7-oxogedunin, swietenine, 3-*O*-detigloyl 3-*O*-acetylswietenine and 3-*O*-acetylswietenolide) isolated from the stem bark of *K. ivorensis* exhibited antifungal activities at the test concentrations. It was reported that the highest fungal growth inhibition was demonstrated in methyl angolensate (62.8% at 1000 mg/L and 73.3% at 1500 mg/L) and 1,3,7-trideacetylkhivorin (64% at 1000 mg/L and 68.6% at 1500 mg/L).

#### **Antifeedant activity**

Some secondary metabolites found in plants have been reported to have vital adaptive implication in protection against herbivory, thus, serving as defense chemicals and protecting the plant against wounds caused by insect feeding [67]. These naturally occurring antifeedants in plants have been recognized as potential alternatives to traditional insecticides in pest management. Furthermore, the feeding inhibition conferred by these secondary metabolites in plants has been considered advantageous relative to conventional chemicals as they target the herbaceous host insect without damaging non-target insects or organisms and act with little or low environmental impact [68].

Limonoids in plant species including *K. senegalensis* [20, 68, 69] have been reported to show marked antifeedant activities against some insects. In the study of [21], the antifeedant effects of 15 limonoids (*Khayanone*, *Khayalactol*, *Seneganolide*, 2-hydroxyseneganolide, *Khayanolide A*, 1-*O*-acetyl*Khayanolide A*, *Khayanolide C*, *Khayanolide B*, 1-*O*-acetyl*Khayanolide B*, 6-dehydroxy*Khayanolide B*, *Khayanolide D*, *Khayanoside*, Methyl angolensate, Methyl 6-hydroxyangolensate and Methyl 6-acetoxyangolensate) isolated from ether and acetone extracts of the stem bark of *K. senegalensis* were evaluated against third-instar larvae of cotton leafworm *Spodoptera littoralis* (Boisd.) using the conventional choice leaf disc method. The isolated limonoids demonstrated antifeedant actions at concentrations ranging

between 100 and 1000 µg/ml. The highest antifeedant activity was demonstrated in *Khayalactol* with an anti-feeding percentage of 83.8% at 1000 µg/ml while at the same concentration, *Khayanoside* showed the least anti-feeding percentage of 15.1% (Table 2).

A great diversity of secondary metabolites like limonoids are produced in a narrowed taxonomic group in the kingdom Plantae, and many of them hold vital biological activities and pharmaceutical potentials [13]. Based on the available data published between 2000 and 2020, this review has summarized the several documented limonoids bioactivities, including anticancer, antimalarial, hepatoprotection, anti-inflammatory, neuroprotection, antimicrobial, antifungal and antifeedant in the genus *Khaya*. The study revealed *K. senegalensis* as the most well-researched species with the most prominent biological activities and traditional uses in the genus. Pharmacological investigations carried out on limonoids isolated from different plant part in the genus provided empirical support for some of its ethnomedicinal uses, mainly in treating malaria, fever, liver problem, microbial infections, and nervous disorder. Most of the investigated biological activities of limonoids in the genus are in vitro-based assays. However, only a few studies on anticancer, anti-inflammatory, hepatoprotective and neuroprotection activities have employed in vivo-based models.

The limonoids isolated from different parts in *Khaya* species showed potent cytotoxic effects in different cancer cell lines based on in vitro and in vivo studies and can be employed as a complementary agent in cancer treatment and management.

With the alarming spread of multi-drug and chloroquine-resistant strains of *Plasmodium*, the integration of limonoids from *Khaya* species as combination treatments in malaria control programmes could be exploited as they have demonstrated to be potent sources of cheap and effective antimalarial agents as revealed in this study.

Several phytochemicals in plants such as phyllanthin, silymarin, neoandrographolide, β-sitosterol and betalain, among others, have been reported to demonstrate potent hepatoprotective properties [88]. The pharmacological investigation of the hepatoprotective activity of limonoids provided empirical support for the ethnomedicinal use of *Khaya* in treating liver problems. In various central nervous system disorders such as epilepsy, Alzheimer's disease and ischemia, glutamate-induced oxidative damage is a key driver to neuronal degeneration and death [59]. In vitro studies on evaluation of neuroprotective activity revealed that limonoids in the genus *Khaya* showed potent neuroprotective effects in glutamate-induced injury in primary rat cerebellar granule neuronal cells. Further clinical studies need to be done to

**Table 2** Other (non-limonoid) reported bioactivities in the genus *Khaya* for the period 2000–2020

<i>Khaya</i> species	Activity	Part	Solvent	Phytochemicals detected	References
<i>K. senegalensis</i>	Anti-diabetic at 300 mg/kg BW on T2D induced male Sprague-Dawley rats	Root	Ethanol	N.r.	[69]
<i>K. senegalensis</i>	Immunostimulating activity against amastigotes (EC <sub>50</sub> = 3.85 and 3.98 mg/ml for catechin-(4a,6)-catechin and catechin-(4a,8)-catechin, respectively)	Bark	Methanol	Catechin-(4a,6)-catechin and catechin-(4a,8)-catechin	[70]
<i>K. senegalensis</i>	Anthelmintic against gastrointestinal nematodes of sheep. LC <sub>50</sub> 0.69 mg/ml (aqueous), LC <sub>50</sub> 0.51 mg/ml (ethanolic).	Bark	Ethanol, Aqueous	N.r.	[71]
<i>K. senegalensis</i>	Anticoccidial at 400 mg/kg and 800 mg/kg against experimentally induced coccidiosis in broiler chicken	Stem bark	Aqueous	Tannins, saponin, cardiac glycosides and steroids	[72]
<i>K. senegalensis</i>	Antidiarrheal in castor oil-induced diarrhoea in albino rats	Stem bark	Ethanol, Aqueous	Flavonoids, tannins and cardiac glycosides	[73]
<i>K. senegalensis</i>	Anti-ulcer at 200, 400, 800 mg/kg against ethanol-induced gastric ulceration in Wistar rats	Stem bark	Methanol	Alkaloids, carbohydrate, glycosides, flavonoids, steroids, tannins and triterpenes	[74]
<i>K. senegalensis</i>	Nematocidal at 60 mg on root-knot nematodes in cowpea	Bark	NA	N.r.	[75]
<i>K. senegalensis</i>	Anti-Trypanosoma against <i>T. brucei brucei</i> in infected Wistar rats	Stem bark	Methanol	N.r.	[76]
<i>K. senegalensis</i>	Antidermatophytic (MIC 1.2–2.4 µg/ml) against <i>Trichophyton mentagrophyte</i> , <i>Trichophyton verrucosum</i> , <i>Trichophyton terrestre</i> and <i>Microsporum canis</i>	Stem bark	Methanol, Aqueous, Chloroform	Alkaloids, glycosides, tannins, flavonoids, saponins, steroids and anthraquinone	[77]
<i>K. senegalensis</i>	Antioxidant with IC <sub>50</sub> 3.37 ± 0.61–9.900 ± 1.2 mg/ml for DPPH	Leaves	Aqueous, ethanol, methanol and Butanol	Flavonoids and phenols	[78]
<i>K. senegalensis</i>	Antioxidant with IC <sub>50</sub> 46, 37 and 64 µl for leaves, root and stem bark, respectively for xanthine assay; IC <sub>50</sub> 178, 91 and 122 µl for leaves, root and stem bark, respectively for 2-deoxyguanosine assay	Leaves, root, stem bark	Methanol	Catechin, rutin, quercetin rhamnoside, catechin and procyanidins	[79]
<i>K. grandifoliola</i>	Gastric antisecretory at 50–500 mg/kg in HCl/ethanol-induced gastric lesions in male Wistar rats	Stem bark	Aqueous	Tannins, alkaloids, saponins, flavonoids, anthocyanins, phenols, quinones, coumarins, sterols, triterpenoids, and glycosides	[80]
<i>K. grandifoliola</i>	Desmutagenic and antimutagenic activities in ethyl methanesulphonate and ribose lysine induced mutagen in <i>Salmonella typhimurium</i> TA100 (His).	Leaves, flower	Ethanol	Quercetin 3-O-rhamnoglucoside, quercetin 3-O-rhamnoside, quercetin 3-O-glucoside, quercetin and 6-methoxycoumarin-7-O arabinofuranoside	[81]
<i>K. grandifoliola</i>	<i>In vivo</i> antiviral activity at 100 µg/ml in hepatitis C virus	Bark	Methylene chloride/methanol (50:50 v/v)	Benzene, 1,1'-(oxydiethylidene) bis (1), carbamic acid, (4-methylphenyl)-, 1-phenyl (2) and 6-phenyl, 4-(1'-oxyethylphenyl)	[29]
<i>K. grandifoliola</i>	Insecticidal activity 85% against <i>Rhyzopertha dominica</i> and 80% against <i>Tribolium castaneum</i>	Essential oil from stem bark	<i>n</i> -hexane	α-pinene, limonene, β-carophyllene, β-pinene, α-phellandrene and citronellol	[82]
<i>K. grandifoliola</i>	Molluscicidal activity (100% at 1 g/L) against freshwater snails.	Bark	Ethanol	N.r.	[83]
<i>K. grandifoliola</i>	Immunomodulatory activity at 200 µg/ml on human peripheral blood mononuclear cells.	Polysaccharide fractions of stem bark	Ethanol	Glucose, galactose, arabinose and rhamnose	[84]
<i>K. anthotheca</i>	Antiplasmodial activity (IC <sub>50</sub> 0.955 µg/ml) against <i>Plasmodium falciparum</i> and antitrypanosomal activity (IC <sub>50</sub> 5.72 µg/ml) against <i>Trypanosoma brucei rhodesiense</i>	Seeds	Petroleum ether	N.r.	[39]

**Table 2** Other (non-limonoid) reported bioactivities in the genus *Khaya* for the period 2000–2020 (Continued)

Khaya species	Activity	Part	Solvent	Phytochemicals detected	References
<i>K. anthothecca</i>	Antiplatelet activity ( $EC_{50}$ $0.97 \pm 0.03$ $\mu\text{g/ml}$ ) in adrenaline (epinephrine) induced platelet aggregation in equine platelets.	Leaves	Acetone	N.r.	[85]
<i>K. anthothecca</i>	Antioxidant ( $EC_{50}$ 0.10) for TEAC assay and ( $EC_{50}$ $176.40 \pm 26.56$ $\mu\text{g/ml}$ ) for DPPH assay.	Leaves	Acetone	N.r.	[85]
<i>K. ivorensis</i>	Antioxidant ( $IC_{50}$ 2.08–4.48 $\mu\text{g/ml}$ ) for DPPH and ( $IC_{50}$ 2.78 $\mu\text{g/ml}$ ) for ABTS assay.	Stem bark, root	Ethanollic	Alkaloids, flavonoids, tannins, saponins, steroids and triterpenoids.	[86]
<i>K. ivorensis</i>	Terminical activity (100% mortality at 200 and 400 mg/ml) against subterranean termites.	Stem bark	Ethanollic, aqueous	N.r.	[87]

N.r. not reported

elucidate the mechanism via which the neuroprotective effect of limonoid is mediated, after which limonoids can then be explored as potential agents in the treatment of neurological disorders. The antimicrobial and antifungal activities of limonoids against several important pathogens support the traditional use of *Khaya* species in treating several microbial infections, including sexually transmitted infections and diarrhoea.

## Conclusion

Though limited in their occurrence in the plant kingdom, limonoids are abundant in the *Khaya* species. The study revealed *Khaya senegalensis* as the most well-researched species with the most documented biological activities and traditional uses in the genus. In addition to the several uses of *Khaya* species in traditional medicine, the biological activities of limonoids, as outlined in this study, display great potentials for drug discovery.

While investigations on the biological activities of limonoids in the genus *Khaya* have focused mostly on the stem bark of *K. senegalensis*, other tree parts and species in the genus may also contribute as alternative sources of bioactive compounds. Therefore, there is a need for more investigations on other tree parts and species to discover and develop more biologically active compounds that may be of significant pharmaceutical implications. Additionally, clinical investigations using in vivo approaches should be carried out on the reported bioactivities of limonoids in the genus *Khaya* to validate their use as potential treatments for different human ailments.

## Abbreviations

ABTS: 2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); Antho-NPs: Anthothecol encased poly ( $D,L$ -lactic-co-glycolic acid) nanoparticles; BW: Body weight; DNA: Deoxyribonucleic acid; DPPH: 2,2-Diphenyl-1-picrylhydrazyl;  $EC_{50}$ : Half maximal effective concentration;  $IC_{50}$ : The half maximal inhibitory concentration;  $LC_{50}$ : Lethal concentration required to kill 50% of the population; LPS: Lipopolysaccharide; MIC: Minimum inhibitory concentration; Mkp-1: Mitogen-activated protein kinase phosphatase; mRNA: Messenger ribonucleic acid; MTT: 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2-related factor-2; T2D: Type 2 diabetes; TEAC: Trolox equivalent antioxidant capacity; WHO: World Health Organization

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## Authors' contributions

TLO and CAO conceptualized, designed and wrote the manuscript. AEA has substantively revised the manuscript and was a major contributor in writing the manuscript. All authors have read and agreed to the published version of the manuscript.

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## Competing interests

The authors declare no competing interest.

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