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Review Article

Phytochemistry and Biological Activities of the Genus *Knema* (Myristicaceae)

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ABSTRACT

Knema, a genus of the family Myristicaceae, usually found in Southeast Asia, has been used to treat sores, pimples, rheumatism, and cancer. A compilation of the research on isolation, structure elucidation, structural diversity, and bioactivities of *Knema* secondary metabolites reported between 1978 and 2016 are included in this review. Up to now, the reported constituents from the genus *Knema* included acetophenone, substituted stilbene, lignan, flavonoid, alkyl/acyl resorcinol, and phenylalkylphenol derivatives. Studies showed that *Knema* and its active principles possessed a wide range of biological activities such as antibacterial, antinematodal, anti-inflammatory, cytotoxicity, and acetylcholinesterase inhibitory activities. The increasing amounts of data support the application and exploitation for new drug development.

Introduction

The genus *Knema* (Myristicaceae) is commonly found in tropical countries like Asia, Africa, and Australia. It comprises approximately 60 species in Southeast Asia but the evergreen forests in Thailand carries at least 12 species of this genus.[1] They are tropical trees with characteristic red resin in their bark, usually referred to by a word meaning 'blood' in their local names. Some *Knema* species are used for medical purposes where the barks and seeds are used in traditional medicine for treatment of diseases pertaining to skin or mouth and throat sores. The seeds of *K. corlicosa* are employed to prepare medicinal salves.[2-3] Previously, the genus *Knema* also contains a variety of natural compounds including acetophenone, substituted stilbene, lignan, flavonoid, alkyl/acyl resorcinol, and phenylalkylphenol derivatives.[4-8] Plants in this genus exhibited antibacterial, antinematodal, cytotoxicity, and acetylcholinesterase inhibitory activities.[9-12] Given that the genus is reported to be rich in health benefits, this review paper aims to phytochemically and pharmacologically investigate the different *Knema* species through previous literature that had reported its extraction, isolation, structural characterization, and description of biological activity of individual compounds. The SciFinder Scholar database was used to search for a substructure and was done via keyword searches in PubMed, Medline, and Scopus. The results indicated that to date, there have been citations of 12 species in this perspective. Each plant would get a discussion on its phytochemistry and pharmacognosy and listed in alphabetical order.

Phytochemical Studies

Since 1978, compounds **1**–**97** (Figure 1) have been isolated from the plants of the genus *Knema*. Their structures were shown below, and their names and corresponding plant sources were discussed below. A literature survey revealed that only twelve species of *Knema* genus have been investigated worldwide which are *K. attenuata*,[14-16] *K. austrosiamensis*,[5,17] *K. elegans*,[3,4,18] *K. furfuraceae*,[4,7,9,11] *K. glauca*,[9-13] *K. globularia*,[8,19-20] *K. glomerata*,[21] *K. hookeriana*,[10,22-23] *K. laurina*,[5,12,24-27] *K. patentinervia*,[28] *K. stellata* subsp. *cryptocaryoides*,[29] and *K. tenuinervia*.[4,6] Most of the species produced anacardic acids and alkyl/acyl resorcinols.

K. attenuata Warb.

K. attenuata is a medium-sized tree species native to Western Ghats (India). Its medicinal importance is what this plant is known for. It is used as one of the ingredients of '*ashwagandadhi nei*' (medicated ghee) that is used to treat spleen disorders, breathing disorders, and tastelessness.[30] However, to the best of the authors' knowledge, only Joshi and coworkers reported on the phytochemical properties of this plant and described the isolation and characterization of a new lignin, attenuol (**1**) from the bark extract.[16]

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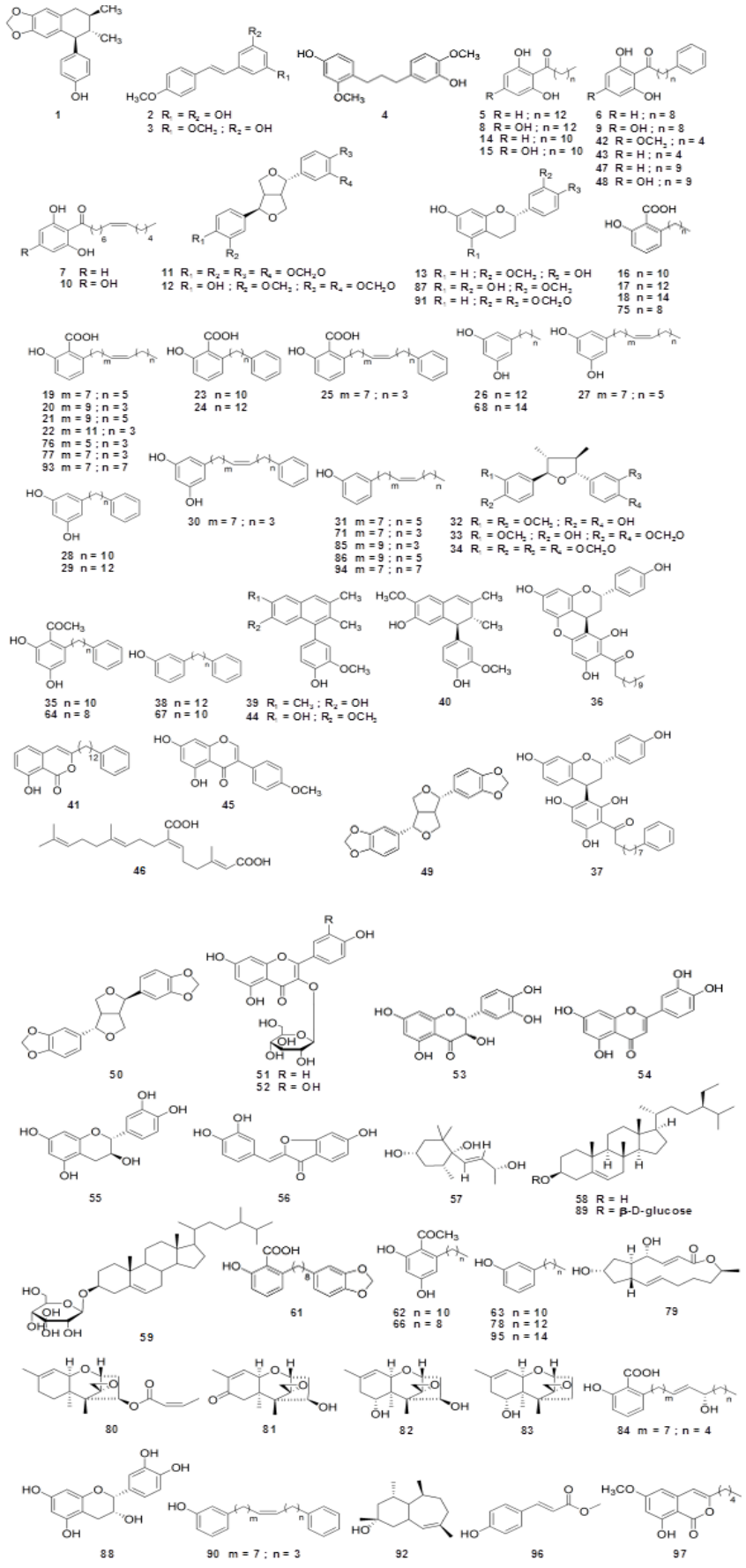

Figure 1. Chemical structures of the compounds isolated from the genus *Knema.*

K. austrosiamensis de Wilde

K. austrosiamensis is endemic to Thailand. Gonzalez and coworkers reported phytochemical characteristics from its wood extracts and provided the derivatives of resveratrol: 3,4′-dimethoxy-5-hydroxystilbene (**2**), 3,5-dihydroxy-4′-methoxystilbene (**3**), 1-(2-methoxy-4-hydroxyphenyl)-3-(3-hydroxy-4-methoxyphenyl)-propane (**4**); three acylresorcinols: l-(2,6-dihydroxyphenyl)-tetradecan-l-one (**5**), 1-(2,6-dihydroxyphenyl)-9-phenylnonan-l-one (**6**), (*Z*)-1-(2,6-dihydroxyphenyI)-tetradecan-l-one (**7**); three acylphloroglucinols: 1-(2,4,6-trihydroxyphenyl)-tetradecan-1-one (**8**), l-(2,3,6-trihydroxyphenyl)-9-phenylnonan-l-one (**9**), (2)-1-(2,4,6-trihydroxyphenyl)tetradecen-l-one (**10**); (+)-episesamin (**11**); (+)-xanthoxylol (**12**) and (±)-7,4′-dihydroxy-3′-methoxyflavan (**13**).[17] Three years later, they managed to get 1-(2,6-dihydroxyphenyl)dodecan-l-one (**14**), and 1-(2,4,6-trihydroxyphenyl)dodecan-1-one (**15**).[5]

K. elegans Warb.

K. elegans is a tree with a spreading crown that can grow up to 20 metres tall and harvested from the wild as a source of its oil. It is widely distributed in Myanmar, Thailand, Cambodia, and Vietnam. Spencer and colleagues had conducted the first phytochemical study of this plant.[3] They isolated ten anacardic acids (**16-25**), five resorcinols (**26-30**), one cardanol (**31**), and three lignans (**32-34**) from the seed oil. Ten years later, Pinto and coworkers obtained 2-hydroxy-6-(12-phenyldodecyl)benzoic acid (**24**), 3-(8-pentadecenyl)phenol (**31**), and 2,4-dihydroxy-6-(10-phenyldeceyl)acetophenone (**35**) from the stem bark extract of *K. elegans*.[4] Studies on the β-inhibitors of DNA polymerase from plant extracts for DNA polymerase brought on the discovery of a methyl ethyl ketone extract that was made from the trunk wood of *K. elegans*, which had shown strong inhibition of DNA polymerase β. The extract then underwent bioassay-guided fractionation that had produced two potent polymerase β-inhibitors, (+)-myristinins A (**36**) and D (**37**), which is identified as flavans with unusual structures.[18]

K. furfuraceae Warb.

K. furfuraceae is a tree found in Peninsular Malaysia, Singapore, and Thailand. Especially in Thailand, the stem bark extract is employed as a popular natural remedy for sores, pimples, and cancers.[4] Pinto and coworkers isolated 2-hydroxy-6-(12-phenyldodecyl)benzoic acid (**24**), 3-(12-phenyldodecyl)phenol (**38**), dehydroguaiaretic (**39**), (+)-*trans*-1,2-dihydrodehydroguaiaretic acid(**40**), and 8-hydroxy-(12-phenyldodecyl)isocoumarin (**41**) from the stem bark extract.[4] In the same year, they also reinvestigated the stem bark extract and isolated compounds **24**, **38**, **39**, **40**, and **41**. Zahir and coworkers have reported two new phenylacylphenols; knerachelins A (**42**) and B (**43**) from the leaves extract of *K. furfuraceae*.[9] Rangkaew and coworkers reported of furfuracin, which is a new arylnaphthalene lignan (**44**) obtained from the leaves extract whereas the stem extract produced (+)-*trans*-1,2-dihydrodehydroguaiaretic acid (**40**), fragransin A_2 (**34**), biochanin A (**45**), gingkolic acid (**19**), anarcardic acid (**18**), 2-hydroxy-6-(12-phenyldodecyl)benzoic acid (**24**), and 2-hydroxy-6-(12-phenyldodecen-8′Z-yl)benzoic acid (**25**).[11]

K. glauca Warb.

K. glauca is a tree commonly found in Thailand. Only one study has been reported in literature on this plant in 2009. Rangkaew and coworkers discovered a new acyclic diterpene acid, known as glaucaic acid (**46**) which was isolated and characterized from fruit extract along with four acylphenols, including 1-(2,6-dihydroxyphenyl)tetradecan-1-one (**5**), malabaricone A (**47**), dodecanoylphloroglucinol (**15**), and 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one (**48**); two lignans: sesamin (**49**) and asarinin (**50**), as well as a flavan, myristinin D (**37**). Besides that, myristinin A (**36**) and (±)-7,4'-dihydroxy-3'-methoxyflavan (**13**) were obtained from the leaves and stem, respectively.[12]

K. globularia Warb.

K. globularia is locally known as '*lueat raet*' in Thailand. The bark was used as a blood tonic whereas the oil seeds were used for the treatment of skin diseases. Besides that, it is also an essential ingredient for an external preparation that is used for curing scabies.[31] Three brief reports on this plant appeared in literature in the early 2000s. Wenli and coworkers described the isolation of kaempferol-3-*O*-β-D-glucopyranoside (**51**) and quercetin-3-*O*-β-D-glucopyranoside (**52**).[8] Two years later, they isolated eight compounds, namely taxifolin (**53**), luteolin (**54**), catechin (**55**), 3′,4′,6′ trihydroxyaurone (**56**), 7-megastigmene-3,6,9 triol (**57**), proanthocyanidin (**NMS**), β sitosterol (**58**), and daucosterol (**59**).[19] Recently, Sriphana and coworkers isolated two new diaryloctanes, which is known as kneglobularic acid A (**60**) and B (**61**). In addition to that, they also discovered a new acetophenone derivative from the hexane extract of the roots, known as kneglobularone A (**62**), along with 3-(12-phenyldodecyl)phenol (**38**), 3-undecylphenol (**63**), 6-tridecylsalicylic acid (**12**), and kneglomeratanone A (**64**).[20]

K. glomerata Merr.

K. glomerata is a tree widely distributed in Borneo, the Moluccas and the Philippines. Only one study has been reported in the literature about this plant in

1994. Zeng and coworkers described the isolation and characterization of one new phenylalkyl phenol; kneglomeratanol (**65**), and two new acetophenones; kneglomeratanones A (**64**) and B (**66**), together with 3-(12'-phenyldodecyl)phenol (**38**), 3-(10'-phenyldecyl)phenol (**67**), 5-pentadecylresorcinol (**68**), 5-(10'-phenyldecyl)resorcinol (**28**), 5-(12'-phenyldodecyl)resorcinol (**29**), 2,4-dihydroxy-6-(10'-phenyldecyl)acetophenone (**35**), 2-hydroxy-6-(12'-phenyldodecyl)benzoic acid (**24**), formononetin (**69**), biochanin A (**45**), and 8-*O*-methylretusin (**70**), which were isolated from the stem bark extract.[21]

K. hookeriana Warb.

K. hookeriana is a tree commonly found in countries like Indonesia, Malaysia, Singapore, and Thailand. The leaves of this plant are traditionally employed as a remedy for stomach problems whereas the sap is useful when casting nets and cloths are dyed. In addition to that, this plant also acts as a preservative for surface coating materials of valuable wooden, porcelain, and metallic wares.[22] The methanol extract of this species was purified via activity-guided chromatography using pine wood nematode *Bursaphelenchus xylophilus,* which had successfully brought on the discovery and characterization of two phenolic antinematodal compounds: 3-undecylphenol (**66**) and 3-(8*Z*-tridecenyl)phenol (**71**). Some years later, Geny and coworkers successfully isolated and characterized six new compounds: three acetophenone derivatives: khookerianone A-C (**72-74**); three anacardic acid derivatives: khookerianic acid A (**75**), B (**76**), C (**60**); four known anacardic acids: anagigantic acid (**16**), (*Z*)-2-hydroxy-6-(tridec-8-en-1-yl)benzoic acid (**77**), 2-hydroxy-6-tridecylbenzoic acid (**17**), (*Z*)-2-hydroxy-6-(pentadec-10-en-1-yl)benzoic acid (**20**); two cardanols; 3-tridecylphenol (**78**), and (*Z*)-3-(tridec-8-en-1-yl)phenol (**71**) from this species.[23]

K. laurina Warb.

K. laurina is a tropical plant which is native to the Malaysian rain forest. The indigenous people of Malaysia has been traditionally using this plant for centuries to treat digestive and inflammatory diseases.[32] The leaves extract of this species was found by a recent pharmacological study to exert anti-inflammatory and neuroprotective effects in microglia cells and living brain tissue with H_2O_2 exposure.[25] Bioassay-guided fractionation of the extract successfully identified brefeldin A (**79**), 8-deoxytrichothecin (**80**), trichothecolone (**81**), 7α-hydroxytrichodermol (**82**), and 7α-hydroxyscirpene (**83**). Further investigation of the stem bark extract of this species by Akhtar and coworkers provided five derivatives of alkenyl phenol and salicylic acid.[13] They isolated two new compounds; (+)-2-hydroxy-6-(10′-hydroxypentadec-8′(*E*)-enyl)benzoic acid (**84**) and 3-pentadec-10′(*Z*)-enylphenol (**85**), along with known 3-heptadec-10′(*Z*)-enylphenol (**86**), 2-hydroxy-6-(pentadec-10′(*Z*)-enyl)benzoic acid (**20**), and 2-hydroxy-6-(10′(*Z*)-heptadecenyl)benzoic acid (**21**). Ismail and coworkers continued studying on this species and isolated five flavonoids (**13**, **54**, **55**, **87,** and **88**), one anacardic acid (**20**), together with β-sitosterol (**58**) and β-sitosterol glucoside (**89**).[27] Decades ago, Gonzalez and coworkers isolated anacardic acid derivatives: **19**, **23**, **30**, **90**, together with 7-hydroxy-3′,4′-methylenedioxyflavan (**91**).[5]

K. patentinervia de Wilde

K. patentinervia is locally called as '*penarahan*' in Malaysia, which produces a red exudate on the stems. Only one report has been cited in the literature about this plant in 2013. Taher and coworkers obtained a new widdrane sesquiterpene, 3β,6β,8α,10β-tetramethylwiddrane-2(3)-en-10α-ol (**92**) from the stem bark extract.[28]

K. stellata subsp. cryptocaryoides de Wilde

K. stellata is known to the locals as '*durogo*'. It is a dioeciously growing tree of medium-size commonly found in the lowland forests of Luzon, Sibuyan, and Mindanao in Philippines. The first and up to now, only phytochemical report about this plant was in 2015 as reported by Ragasa and coworkers.[29] They isolated mixtures of 2-[(*Z*)-heptadec-8-enyl]-6-hydroxybenzoic acid (**93**) and 2-[(*Z*)-pentadec-8-enyl]-6-hydroxybenzoic acid (**19**), 3-(heptadec-8-enyl)phenol (**94**), 3-(pentadec-8-enyl)phenol (**31**), 3-pentadecylphenol (**95**), saturated long-chain 4-hydroxycinnamate fatty acid esters (**96**), and β-sitosterol (**58**) from the dichloromethane leaves extract.

K. tenuinervia de Wilde

K. tenuinervia is an evergreen tree that can grow up to 25 metres tall, growing in China, India, Nepal, Thailand, and Laos. The tree was a source of oil and latex, while the stem bark was employed as a remedy for cancer in traditional Thai medicine.[6] Pinto and Kijjoa described the isolation and structural characterization of 2-hydroxy-6-(12-phenyldodecyl)benzoic acid (**24**), 3-(8*Z*-pentadecenyl)phenol (**31**), 2,4-dihydroxy-6-(10-phenyldecyl)acetophenone (**35**), and 8-hydroxy-6-methoxy-3-pentylisocoumarin (**97**) from the stem bark extract.[4]

Biological Activities

Cytotoxicity activity

Furfuracin (**44**) tested against three types of human cancer cell lines: KB, MCF-7, and NCI-H187 showed that it was inactive. The (+)-*trans*-1,2-dihydrodehydroguaiaretic acid (**40**) (IC_{50} 17.7 μg/mL) and fragransinA_2 (**34**) (IC_{50} 16.2 μg/mL)

displayed weak cytotoxic activity against the KB cell line, while the isoflavone biochanin A (**45**) (IC_{50} 19.0 µg/mL) showed weak cytotoxic activity against the NCI-H187 cell line.[11] Sriphana and coworkers reported that the crude hexane and EtOAc extracts of the *K. globularia* roots exhibited cytotoxicity against the cells of NCI-H187 and Vero with IC_{50} ranging from 17-47 mg/mL.[20] Meanwhile, 3-Undecylphenol (**63**) revealed weak cytotoxicity against the cell lines of KB (oral human epidermal carcinoma), MCF-7 (breast cancer), and NCI- H187 (human lung cancer) with IC_{50} values between the range of 28 and 48 mg/mL, while 3-(12-phenyldodecyl)phenol (**38**) showed cytotoxic inactivity against the cell lines of KB and MCF-7 but weak cytotoxicity was shown against the NCI- H187 cell line (IC_{50} 25.6 mg/mL). However, compounds **63** and **38** showed cytotoxicity against Vero cells (African green monkey kidney) with IC_{50} values of 14.93 and 44.61 mg/mL, respectively. Kneglobularone A (**62**) and kneglomeratanone A (**64**) exhibited weak cytotoxicity against all cell lines with IC_{50} values between the range of 8 and 48 mg/mL. The 3-(12'-Phenyldodecyl)phenol (**38**) gave strong activity against A-549 (IC_{50} 1.85 µg/mL) and HT-29 (IC_{50} 2.62 µg/mL), while kneglomeratanone B (**66**) against MCF-7 (IC_{50} 1.12 µg/mL) cell lines.[21] Chinworrungsee and coworkers found that strong cytotoxic activity is displayed by the culture broth extract of the endophytic fungus (KLAR 5) obtained from a twig of *K. laurina* against cells of KB, BC-1, and NCI-H187 with IC_{50} values of 0.09, 0.03, and 0.31 µg/mL, respectively.[26] Cytotoxic activity against these cells were also shown by the mycelial extract of KLAR with IC_{50} values of 0.10, 0.02, and 0.29 µg/mL, respectively. Brefeldin A (**79**) showed high activity against the cells of the human epidermoid carcinoma of the mouth, human breast cancer (BC-1), and human small cell lung cancer (NCI-H187) with IC_{50} values of 0.18, 0.04, and 0.11 µM whereas 8-deoxytrichothecin (**80**) was selectively active against BC-1 (IC_{50} of 0.88 µM) and NCI-H187 cells (IC_{50} of 1.48 µM). Besides that, (+)-Myristinins A (**36**) and D (**37**) isolated from *K. elegans* had given IC_{50} values of 12 and 4.3 µM, respectively, in bovine serum albumin (BSA), which acts as inhibitors of DNA polymerase-β and IC_{50} values of 2.7 and 1.2 µM without BSA. In addition, compounds **36** and **37** applied at 9 µM concentration for 6 h, potentiated the cytotoxicity of bleomycin towards cultured $P388D_1$ cells, thus causing a reduction in the amount of viable cells by at least 30%. Strong Cu^{2+}-dependent DNA strand scission was induced by principles **36** and **37** in a DNA cleavage assay.[18]

Toxicity activity

The chloroform extract of aril and ethanol of the *K. attenuata* kernel showed toxicity against *Aedes albopictus* (LC_{50}, 141 ppm and 159 ppm; LC_{90}, 290 ppm and 342 ppm) and *Anopheles stephensi* (LC_{50}, 160 ppm and 162 ppm; LC_{90}, 445 ppm and 458 ppm). Meanwhile, the hexane extract of the kernel produced minimal toxicity against *Aedes albopictus* (LC_{50}, 239 ppm; LC_{90}, 484 ppm) whereas the ethanol extract of aril produced minimal toxicity against *Anopheles stephensi* (LC_{50}, 290; LC_{90}, 498).[15] Formononetin (**69**) isolated from *K. glomerata* showed strong activity in brine shrimp lethality test with an IC_{50} value of 0.18 µg/mL.[21]

Antimicrobial activity

The chloroform extract of aril and hexane of *K. attenuata* seeds showed antimicrobial activity against *Staphylococus aureus* (MIC 12536 and 12541 µg/mL) and moderate antifungal activity against *Candida albicans*.[16] Knerachelins A (**42**) and B (**43**) were obtained from the leaves extract of *K. furfuraceae* showing antibacterial activity against *Staphylococcus aureus* and *Streptococcus pneumoniae* with MIC values of 8.0 and 4.0 µg/mL, respectively.[9]

Antioxidant activity

In addition, the *K. attenuata* chloroform extract of aril displayed DPPH and H_2O_2 scavenging activities of 15.0 µmoles/15 min/100 mg and 12.4 µmoles/10 min/100 mg extracts respectively as well as a reducing power of 94.6 A_{700}/20 min/100 mg. Besides that, the chloroform extract also displayed a maximum concentration of phenolics (96.1 mg/g) and flavonoids (64.2 mg/g).[14] The methanol extract of *K. laurina* also showed a peroxide value of 158.0 peroxide/1 kg sample, having potential DPPH free radicals with an IC_{50} value of 39.7 ppm.[24]

Anti-apoptotic proteins

Significant binding properties were shown by anacardic acid derivatives **16**, **17**, **20**, **60**, **75**, **76**, and **77** with K_i values between 0.2 and 18 µM. The results of the protein-ligand NMR experiments showed that anacardic acid **17** the most active compound did not have any interactions with Bcl-xL and Mcl-1, the anti-apoptotic proteins but had interacted with the pro-apoptotic protein, Bid.[23]

Antinematodal activity

Alen and coworkers studied *in vivo* antinematodal activity against *Bursaphelenchus xylophilus* and found that the extracts of this species exhibited very strong activity at minimum effective dose (0.7 mg/cotton ball).[10]

Antituberculosis activity

The acylphenols; malabaricone A (**47**), 1-(2,4,6-trihydroxyphenyl)dodecan-1-one (**15**), and 1-(2,4,6-trihydroxyphenyl)-9-phenylnonan-1-one (**48**) exhibited one common attribute, which is

antituberculosis activity against *Mycobacterium tuberculosis* with each having MIC values of 25, 50, and 100 µg/mL.[11]

Antiviral activity

The acylphenol, 1-(2,4,6-trihydroxy-phenyl)dodecan-1-one (**15**) had an IC_{50} value of 3.05 µg/mL for antiviral activity against herpes simplex virus type 1.[11]

Acetylcholinesterase inhibitory activity

Strong activity of acetylcholinesterase inhibition was displayed by 2-Hydroxy-6-(10′(*Z*)-heptadecenyl)benzoic acid (**21**) with an IC_{50} value of 0.57 µM.[13]

Antimalarial activity

An IC_{50} value of 2.78 µg/mL was obtained from the activity of Malabaricone A (**47**) against the malarial parasite, *Plasmodium falciparum* indicating that it is actively against the parasite.[11]

Conclusion

In this review, we summarized the secondary metabolites acquired from the genus *Knema* and their pharmacological properties. Most of the species produced anacardic acids and alkyl/acyl resorcinols exhibited cytotoxicity activity. Apart from that, further phytochemical studies are required in future studies in order to give a detailed idea of the natural constituents and the biologically active principles in the extracts. As a conclusion, it was evident that the genus *Knema* comprises plants that are therapeutically promising and valuable with some of them being used in the indigenous people's ethnomedical traditions. Meanwhile, only few studies were found to have described their pharmacological properties. This genus deserves to be given more attention in the on-going search for new bioactive compounds.

Conflict of interests

The authors claim that there is no conflict of interest.

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