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A review on phenolic compounds in *Illicium* species and their pharmacological effects

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ABSTRACT

This review focuses mainly on findings of chemistry and pharmacological activities of phenolic compounds in Illicium plants. The continued chemical studies of Illicium species such as I.difengpi, I.verum, I.griffithii, I.henryi, and the related plants have resulted in isolation of phenylpropanoids, neolignans, phytoquinoids, flavonoids, neolignans and their glycosides which belong to the phenolic group of compounds. These compounds have been known to exhibit anti-inflammatory, antioxidant, anti-cancer, antimicrobial, antifungal and insecticidal activities.

Keywords: *Illicium* species; Neolignan; Phenolic; Phenylpropanoid; Phytoquinoid.

INTRODUCTION

Medicinal plants have been used to treat human diseases for centuries. Many plant-derived compounds have been used as drugs, either in their original or semi-synthetic form. Plant secondary metabolites can also serve as drug precursors, drug prototypes and pharmacological probes. More recently, the scientific community has shown an increasing interest in some medicinal plants due to their good therapeutic performance. In addition, the uses of plant-derived products as disease control agents have been studied, since they tend to have low mammalian toxicity, less environmental effects and have wide public acceptance[1]. Traditional Chinese medicine (TCM) has shown considerable scientific development which makes it a well known form of medication worldwide [2, 3].

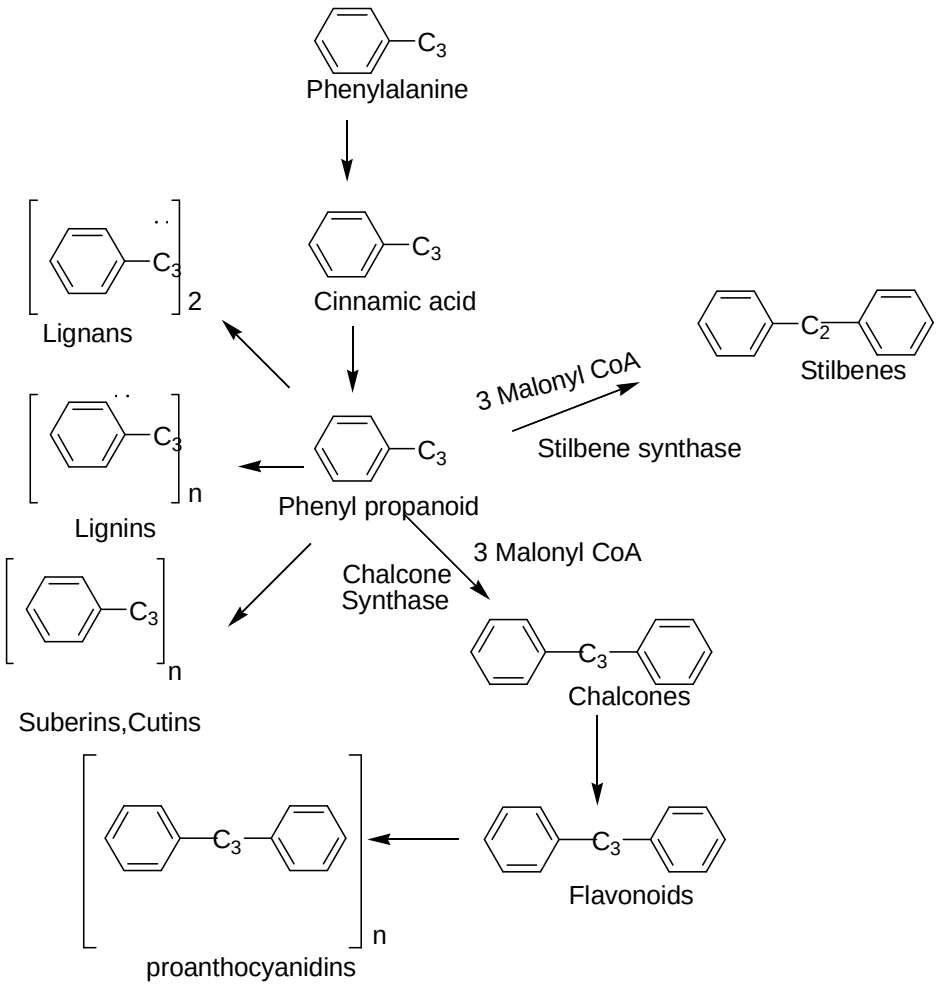
The genus *illicium* (Illiciaceae), contains about 40 species of evergreen trees and shrubs, mostly in eastern and southeastern Asia and a few in southeastern North America and tropical America. 27 of these species are found in China, about 14 of them endemic to various provinces: Guangdong, Guangxi, Hubei, Hunan, Jiangxi, Sichuan, Zhejiang, Fujian among other southern China areas [4]. The most frequently occurring species that are used medicinally are *I.difengpi, I.verum, I.griffithii* and *I.henryi.*

I. difengpi K. I. B et K. I. M., indigenous to China, is a shrub that grows in the mountainous areas of Guangxi Province. Its stem bark is listed in *Chinese Pharmacopeia* and has been applied as a traditional Chinese medicine to treat rheumatic arthritis by relieving lumbago and pain in the knees [5]. The drug is collected in spring and autum, and dried in the sun or at low temperature.

Chinese star anise (*Illicium verum* Hook) is widely used as culinary and medicinal fruit and is most popular in indigenous system of medicine. Its fruit is an important source of essential and volatile oil. Traditionally, the fruit has been used as carminative, digestive dyspepsia, antispasmodic, and stimulant, ant rheumatic and diuretic [6]. Studies done on this plant indicate its potential for medicinal uses[7]

I. griffithii is an important medicinal tree species of the temperate broad-leaved forests of Northeast India. Traditionally, dried seedless fruit is used as incense. It is used for sweet fragrance while preparing butter-salted tea or sugar tea. They are also used as medicine to cure cough, toothache and sinusitis (by inhaling the vapour or by boiling the fruits in water) and to improve the strength of local alcohol. The fruit is considered to be carminative, stomachic and glactagogic. It is also used in treating vomiting, dyspepsia, abdominal pain and food poisoning [8].

Figure 1: Biosynthesis of the main phenolic classes



I. henryi is a shrub distributed in the southwestern part of China, and its bark and roots have been used as a folk-medicinal herb for dispelling wind-evil and assuaging pain [9].

The pharmacological activities of these plants have been attributed to the presence of active compounds, predominantly phenolic compounds. This paper reviews the studies on *Illicium* species with respect to their isolated phenolic compounds and their pharmacological activities.

2. Phytochemistry

2.1 Biosynthesis and classification

Phenolic compounds represent a large group of molecules with a variety of functions in plant growth, development and defense. They include signaling molecules, pigments and flavors that can attract or repel, as well as compounds that protect against insects, fungi, bacteria viruses, ultra violet light and as structural materials of stability [10]. They are a very diversified group of phytochemicals derived from phenylalanine and tyrosine **(Fig .1)** [10, 11].

Phenolics are not uniformly distributed in plants at the tissue, cellular and subcellular levels. Insoluble phenolics are the components of cell walls, while soluble phenolics are compartmentalized within the cell vacuoles [12, 13]. At the tissue level, the outer layers of plants contain higher levels of phenolics than those located in their inner parts [14] .

Phenolic compounds can be classified into groups depending on the number of carbons in the molecule. They range from simple phenolics (C6), through betacyanins, to carbon polymers and oligomers like lignins and tannins(**Table.1**) [15].

Table 1: Some phenolic compounds and their major classification

Carbon	Class	Example
C6	Simple phenolics	Resorcinol (1,3-dihydroxybenzene)
C6-C1	Phenolic acids	Gallic acid, vanillic acid and salicylic acid.
C6-C3	Cinnamic acids, coumarins, isocoumarins	*p*-coumaric acid, ferulic acid, caffeic acid, berginin and umbelliferone.
C15 (Flavonoids) (C6-C3-C6)	Flavans, flavonones, anthocyanidin, anthocyanins, flavones.	Catechin, gallocatechin, kaemferol, quercitin, cyanidin, peonidin and petanin.
C6-C1-C6, C6-C2-C6	Xanthones, stilbenes	Xanthone, stilbene resveratol and pinosylvin.
C18	Betacyanins	Betanidin.
Oligomers	Lignans	(+)-pinoresinol and (+)-sesamin.
Polymers	Lignin	-
Oligomers and polymers (tannins)	Condensed, complex, and hydrolysable tannins.	Procyanidin B2, gallotannins,and acutissimin.

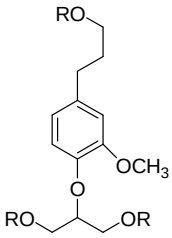
2.2. Phenolic constituents in *Illicium* species

Chemical investigations into the genus *Illicium* has yielded prenylated C_6-C_3 compounds [16-23], neolignans[24-26], flavonoids [27] and a large number of unique sesquiterpene lactones [28-30]. From a chemotaxonomic point of view, the illicium species are interesting sources, rich in biosynthetically unique sesquiterpenes which are considered as characteristic chemical markers [31]. In addition, the prenylated C_6-C_3 compounds, referred to as phytoquinoids, are considered to be characteristic constituents [32].

Phytochemical reports on *I. difengpi* published in 1992 revealed the isolation of Phenylpropanoids and their glycosides. 4-O-(2-Hydroxy-1-hydroxymethylethyl)-dihydroconiferyl alcohol (**1**) and its 6-p-coumaroyl-glucoside (**4**), 4-O-(1-carboxy-2-hydroxyethyl)dihydroconiferyl alcohol (**3**) and rhamnosyl glucoside of 2- hydroxyl safrole (**6**) were isolated from the stem barks of *I. difengpi*[33]. Compounds **2** and **5** were obtained as artifacts during acetylation of compounds **1** and **4** respectively. Six new constituents comprising three 2-phenyldihydrobenzofuranpropanol-type neolignans, two 1-phenyl-2-phenoxypropane-1,3-diols,and 4-O-(2-hydroxy-1-hydroxymethylethyl)dihydroconiferyl alcohol vanilloyl-glucoside were also isolated from the bark of *Illicium difengpi* together with three known neolignans[24]. Recently, several phenylpropanoids, neolignans and their glycosides classes of phenolic compounds (**7-19)**, have been reported from this plant [34-36].

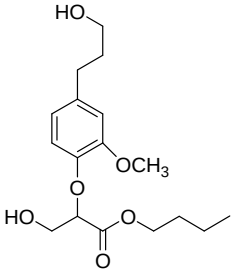
Similar classes of compounds, that is phenylpropanoids, neolignans and their glycosides (**20-43)**, have also been isolated from different species within *Illicium* genus; *I. arborescens*, *I. anisatum*, *I. henryi*, *I. tashiroi* and *I. verum(*[16, 37-40].

Fig. 2: Some phenylpropanoids, neolignans and their glycosides isolated from *Illicium* plants

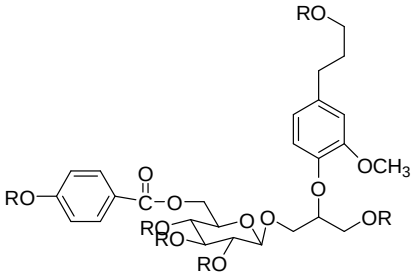


1 :R=H

2 :R=Ac

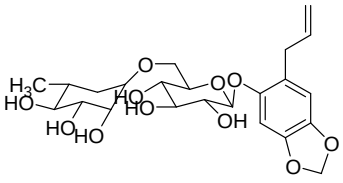


3



4 :R=H

5 :R=Ac



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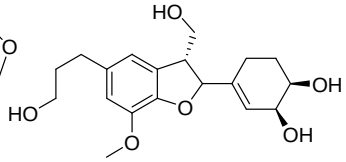
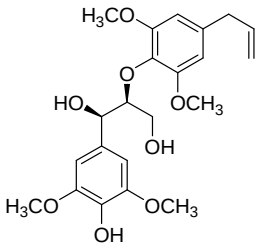
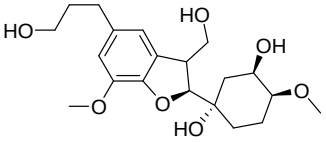


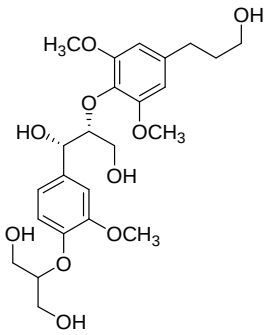
Difengpiol A (7)



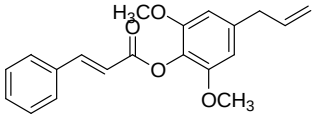
(7R,8S)-4,7,9-trihydroxy-3,5,3',5'-tetramethoxy-8-O-4'-neolignan-8'-ene (10)



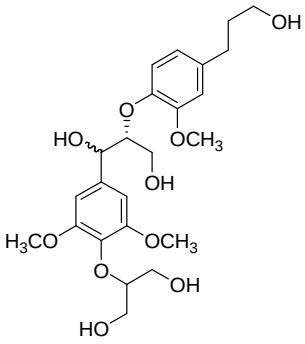
Difengpiol B(8)



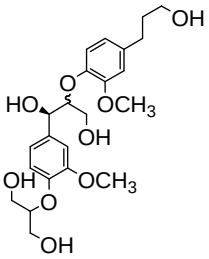
(7S,8R)-4-O-(glycer-2- yl)-7,9,9'-trihydroxy-3,3',5'-trimethoxy-8-O-4'-neolignan (11)

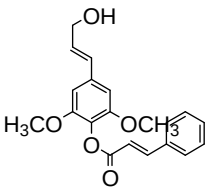


Difengpin (9)



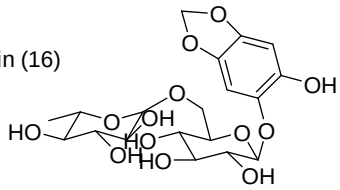
(12) 7R,8R
(13) 7S,8R
(7S,8R)-4-O-(glycer-2-yl)-7,9,9'-trihydroxy-3,5,3'-trimethoxy-8-O-4'-neolignan



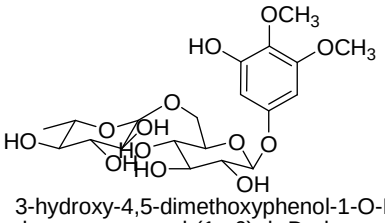


Neodifengpin (16)

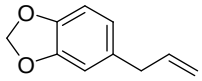
(14) 7R,8R
(15) 7R,8S
} -4-O-(glycer-2-yl)-7,9,9'-trihydroxy-3,3'-dimethoxy-8-O-4'-neolignan.



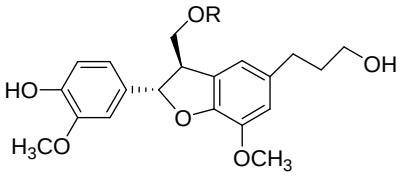
2-hydroxy-4,5-methylenedioxyphenol-1-O-R-L-rhamnopyranosyl-(1→6)-b-D-glucopyranoside (17)



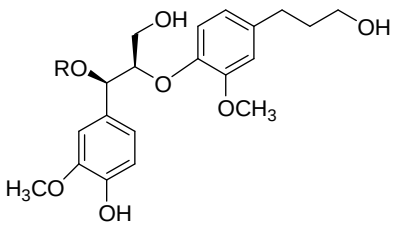
3-hydroxy-4,5-dimethoxyphenol-1-O-R-L-rhamnopyranosyl-(1→6)- b-D-glucopyranoside (18)



safrole (19)



20 :R=3-acetyl-Xyl { Dihydrodehydrodiconiferyl alcohol 9-O-b-D-(3''-O-acetyl)xylopyranoside }



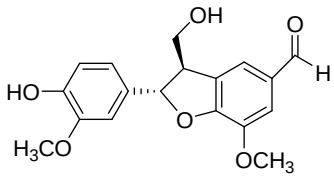
21 :R=Xyl { Dihydrodehydrodiconiferyl alcohol 9-O-b-D-xylopyranoside }

22 :R=H { (-)-dihydrodehydrodiconiferyl alcohol }

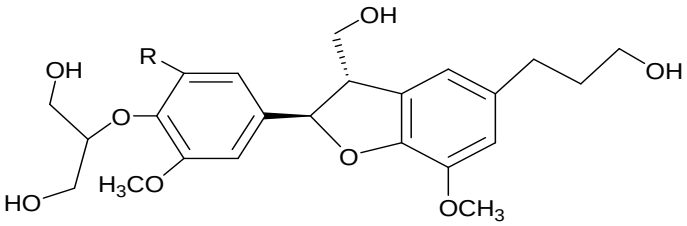
23 :R=Rha { dihydrodehydrodiconiferyl alcohol 9-O-a-L-rhamnopyranoside }

24 :R=Rha { threo-4,9,9'-trihydroxy-3,3'-dimethoxy-8-O-4'-neolignan 7-O-a-rhamnopyranoside }

25 :R=Glu { threo-4,9,9'-trihydroxy-3,3'-dimethoxy-8-O-4'-neolignan 7-O-b-D-glucopyranoside }

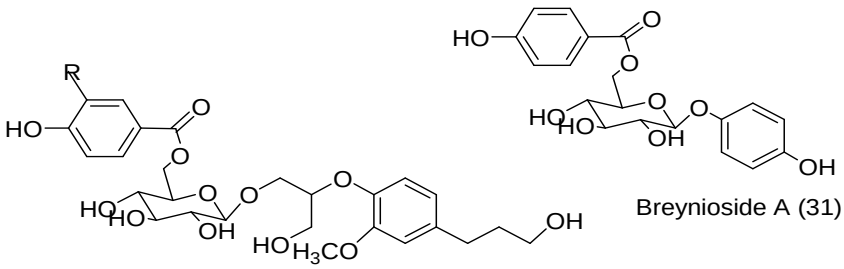


Ficusal (26)



27 :R=MeO {Sakuraresinol}

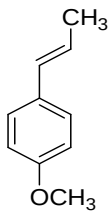
28 :R=H { 2,3-dihydro-2-[3'-methoxy-4'-(1'',3''-dihydroxy-2''-propyloxy) phenyl]-3-(hydroxymethyl)-7-methoxybenzofuran-5-propanol }



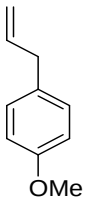
Breynioside A (31)

29 :R=H {4-O-[2'-hydroxy-1'-(hydroxymethyl) ethyl]dihydroconiferyl alcohol 6''-(p-hydroxybenzoyl)-b-d-glucopyranoside}

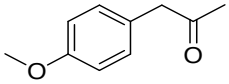
30 :R=MeO { 4-O-[2'-hydroxy-1'-(hydroxymethyl)ethyl] dihydroconiferyl alcohol vanilloyl-Glucoside }



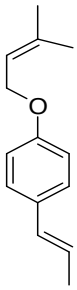
trans-Anethol(32)



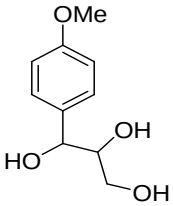
Estragole (33)



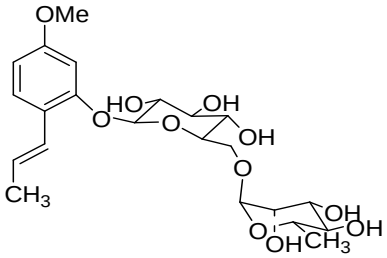
p-anisylacetone(34)



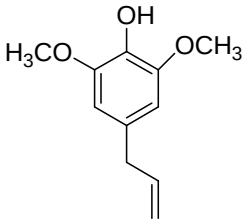
Foeniculin(35)



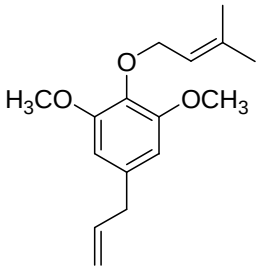
Phenylpropanoid (36)



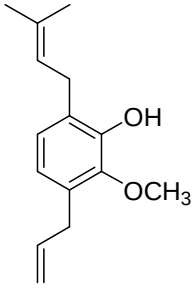
Phenylpropanoid glycoside (37)



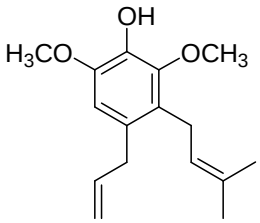
4-Allyl-2,6-dimethoxyphenol (38)



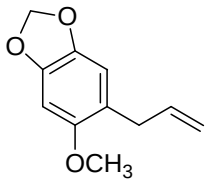
1-Allyl-3,5-dimethoxy-4-(3-methylbut-2-enyloxy)benzene (39)



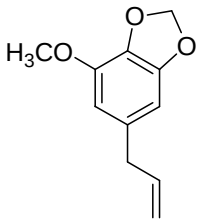
4-Allyl-2-methoxy-6-(3-methyl-2-butenyl)phenol (40)



4-Allyl-2,6-dimethoxy-3-(3-methyl-2-butenyl)phenol (41)



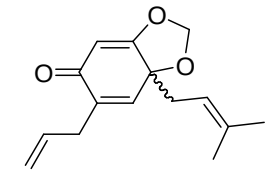
1-Allyl-2-methoxy-4,5-methylenedioxybenzene(42)



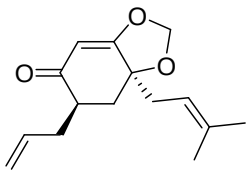
5-Allyl-1-methoxy-2,3-methylenedioxybenzene (43)

Phytoquinoids, being characteristic constituents of this genus, have also been extensively investigated among different Illicium species. A number of these compounds (**44-64**) have been isolated from illicium plants such as *I.tashiroi* [16-21], *I.anisatum* [22], *I.arborescens* [16], *I.simonsii* [23] and *I.oligandrum* [41, 42]. From the chemical viewpoint, phytoquinoids belong to cyclic prenylated tetrahydrofurano-type and non-cyclic prenylated C6-C3 compounds as reported [18].

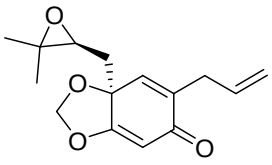
Fig. 3: Some phytoquinoids isolated from *Illium* plants



44. 4S-(+)
45.4R-(-) } illicinone-A



2S,4R-(-)-illicinone-B(46)



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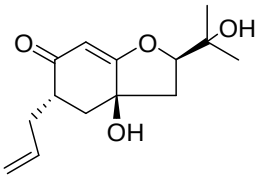
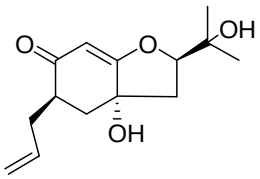


Illifunone-A (48)



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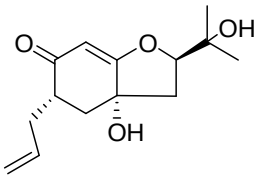
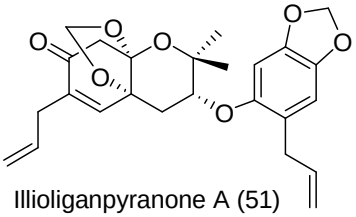
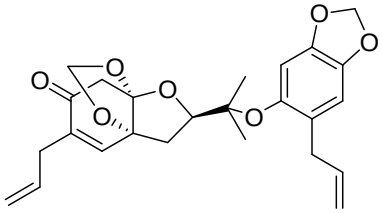


Illifunone-D (50)



Illioliganpyranone A (51)



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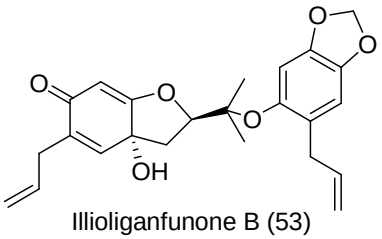
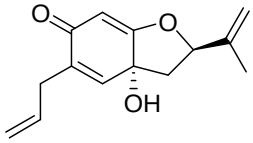


Illioliganfunone B (53)



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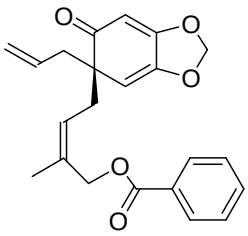

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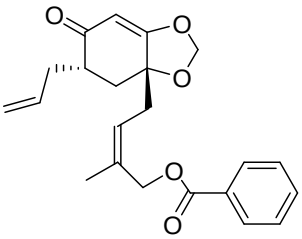
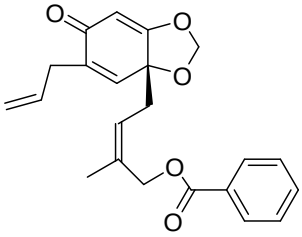
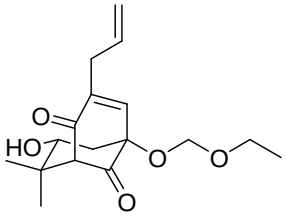


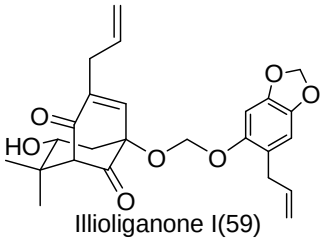
Illioliganone E (56)



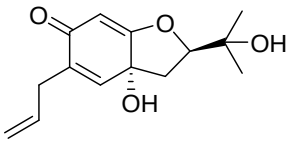
Illioliganone F (57)



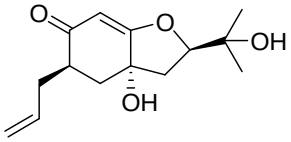
Illioliganone H (58)



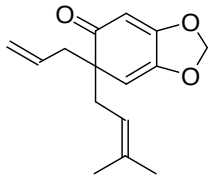
Illioliganone I(59)



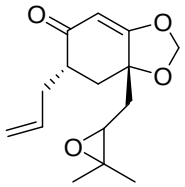
2,3-dehydroillifunone C (60)



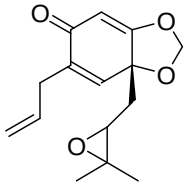
(2R, 4S, 11R)- illifunone C (61)



4-allyl-4-(3-methylbut-2-enyl)-1,2-methylenedioxycyclohexa-2,6-dien-5-one (62)



(2S, 4S)-illicinone D (63)



4R-illicinone C (64)

3. Pharmacological effects

3.1 Anti-inflammatory activities

Neolignans and their glycosides isolated from the stem bark of *I. difengpi* exhibited moderate anti-inflammatory activities with IC_{50} values ranging from 1.62 to 24.4μm. The anti-inflammatory activities were evaluated by measuring the inhibitory ratios of β-glucuronidase release in rat polymorphonuclear leucocytes (PMNs) induced by platelet-activating factor (PAF) in vitro,Ginkgolide B being used as a positive control. (7R,8S)-4,7,9-trihydroxy-3,5,3'5'-tetramethoxy-8-O-4'neolignan-8'-ene (**10**),(7S,8R)-4-O-(glycer-2-yl)7,9,9'-trihydroxy-3,3',5'-trimethoxy-8-O-4'-neolignan (**11**) and 3-hydroxy-4,5-dimethoxyphenol-1-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (**18**) showed positive results [35]. It is important to note that only a few of the isolated compounds from *I. difengpi* have been assayed for anti-inflammatory activities. Similar classes of compounds from other plants within the genus are effective as anti-inflammatory agents. For example, phenylpropanoids and phytoquinoids from *Illicium* species were reported to potential anti-inflammatory agents against mast cell-mediated inflammatory diseases. Two phenylpropanoids,1-allyl-3,5-dimethoxy-4-(3-methyl-but-2-enyloxy)benzene (**39**) and 4-allyl-2,6-dimethoxy-3-(3-methyl-2-butenyl)phenol(**41**), and two phytoquinoids, 4 R-(-)-illicinone-A**(45**) and 2 S,4 R-(-)-illicinone-B(**46**) isolated from *Illicium* plants significantly inhibited histamine release from rat basophilic leukemia (RBL-2H3) cells stimulated with A23187. Furthermore, these compounds caused a decline in TNF-alpha levels in culture supernatants of RBL-2H3 cells following treatment with A23187. It was therefore suggested that these compounds might be useful as anti-inflammatory agents against cell mediated inflammatory diseases [43].

I. verum extracts (IVE) were investigated for the anti-inflammatory effects in the human keratinocyte HaCaT cell line. IVE successively exerted anti-inflammatory effects by suppressing the expression of TNF-α/IFN-γ-induced chemokines, pro-inflammatory cytokines, and adhesion molecules via blockade of NF-κB, STAT1, MAPK, and Akt

activation, suggesting that IVE may be a useful therapeutic candidate for inflammatory skin diseases, such as atopic dermatitis [44].

While comparing the anti-inflammatory and analgesic effects of two injections of extracts isolated from the root bark of *I. angustisepalum* A. C. Smith and *I. Jiadifengpi* B.N. Chang, both injections displayed marked anti-inflammatory and analgesic effects. The injection of extract isolated from the root bark of *I. Jiadifengpi* B.N. Chang, however, showed better anti-inflammatory and analgesic effects than that of *I. angustisepalum* A. C. Smith [45].

3.2 Antioxidant activities

It is well known that oxidation damages various biological substances and subsequently causes many diseases such as cancer, liver disease, Alzheimer's disease, premature ageing, arthritis, inflammation, diabetes, Parkison's disease and atherosclerosis [46]. Many *Illicium* plants have been evaluated and reported to posses antioxidant properties. Extracts of star anise *(I.verum*) have been evaluated and found to posses greater potential as a natural antioxidant. Kareti Srinivasa Rao et al., 2012 [47] reported excellent antioxidant activities of the total phenolic contents of both microwave assisted and conventional extract of star anise. A significant relationship between the antioxidant capacity and the total phenolic and flavonoid content was found [47]. Ethanol extracts, ethyl acetate fraction, volatile oil and water extracts of fruits of illicium verum have also been assessed for free radical scavenging activity against 1,1-diphenyl-2-picrylhydrazyl(DPPH) radical and found to be effective[48-50].

(7R,8S)-4, 7,9-trihydroxy-3,5,3'5'-tetramethoxy-8-O-4'neolignan-8'-ene(**10**), a neolignan, isolated from *I. difengpi* displayed antioxidant activity with an IC_{50} value of 42.3μM when assessed by measuring its inhibition activity on liver microsomal lipid peroxidation induced by Fe^{2+}-Cys system in vitro[35].

The antioxidant activity of hexane, ethyl acetate and methanol extracts of *I. griffithii* seeds were determined using 1,1-diphenyl-2- picrylhydrazyl (DPPH), phosphomolybdenum, cupric ions (Cu2+) reducing antioxidant capacity (CUPRAC), ferric reducing antioxidant power (FRAP), reducing power, lipid peroxidation, hydroxyl and N,N-Dimethyl-p-phenylenediamine (DMPD) methods. Extracts were analyzed for total phenolic content (TPC) and total flavonoids content (TFC) using a spectrophotometric analysis. Total phenolic content 164.91 ± 12.67 GAE mg/g (as gallic acid equivalents) and total flavonoids content 63.94 ± 0.16 CE mg/g (as catechin equivalents) were estimated in the methanol extract of seeds. Among the extracts tested for antioxidant activity, methanol extract showed maximum activity on DPPH (70.96 ± 1.88), CUPRAC (0.988 ± 0.07), reducing power (0.236 ± 0.02), lipid peroxidation (36.95 ± 2.36), hydroxyl (47.52 ± 1.94) and DMPD (64.30 ± 0.31). It also exhibited high activity at 300 μg/ml on total antioxidant activity (0.159 ± 0.04 GAE mg/g) and FRAP (0.297 ± 0.03 mM Fe2+/g). The results indicated that the methanol extract of *I. griffithii* seeds is having more of natural antioxidants and it can be considered for further clinical use[51].

Plant extracts with proven antioxidant activity are usually composed of phenolic moiety. Organic acids, carotenoids and tannins can also be present and act as antioxidants or have a synergistic effect with phenolic compounds[52].The antioxidant activity of phenolic is mainly due to their redox property, which allows them to act as reducing agents, hydrogen donors and singlet oxygen quenchers [53, 54]. Natural polyphenols have chain-breaking antioxidant activities that are believed to prevent many degenerative diseases, including arthritis, atheroscelerosis, ischemia, cancer among others [55, 56]. The number of studies on the antioxidant activity of Chinese medicinal plants has especially increased remarkably due to the potential of the plants being used as a rich and natural source of antioxidant compounds[53].

3.3 Anti-cancer activities

Six phenylpropanoids (**38-43**) and seven phytoquinoids (**44-50**) isolated from three *Illicium* plants, *I.tashiroi*,*I.anisatum* and *I.arborescens*, showed inhibitory activity against the EBV-EA activation even at 1×10 mol ratio [57] . The inhibitory activity of their compounds was found to be more than that of β-carotene (IC_{50} 400), a vitamin A precursor commonly used in cancer prevention studies as a standard reference. Two phenylpropanoids having prenyl group,4-allyl-2-methoxy-6-(3-methyl-2-butenyl)phenol **(40**) and 4-allyl-2,6-dimethoxy-3-(3-methyl-2-butenyl)phenol (**41**) showed more potent activities as antitumor promoters(100% inhibition of activation at 1×10^3 mol ratio/TPA, and 76.8–77.8%, 37.1–38.9% and 19.0–20.3% inhibition of activation at 5×10^2, 1×10^2 and1×10 mol ratio/TPA, respectively) on EBV-EA activation (IC_{50} 224 and 217, respectively). Furthermore, the inhibitory activity of 1-allyl-3,5-dimethoxy-4-(3-methylbut-2-enyloxy)benzene **(39**) with *O*-prenyl side chain was slightly more (IC_{50}

263) than that of non-prenylated phenylpropanoids (**38**). Hence, the prenylated phenylpropanoids might be valuable as potential cancer chemopreventive agents.

3.4 Antimicrobial and antifungal activities

The antimicrobial activity of the organic extracts of *I. griffithii* were determined using disc diffusion assay against Gram-positive bacterial strains (three reference cultures and three clinical isolates), Gram-negative bacterial strains (nine reference cultures and six clinical isolates), and six fungi. Ethyl acetate extract of its fruits was effective against most of the tested reference cultures such as *Staphylococcus aureus*, *Yersinia enterocolitica*, *Vibrio parahaemolyticus*, *Bacillus subtilis*, *Salmonella paratyphi*, *Enterococcus feacalis*, *Xanthomonas oryzae* and *Pseudomonas aerugenosa*, whereas methanol extract showed activity only against *Staphylococcus aureus*, *Bacillus subtilis* and *Xanthomonas oryzae*. The hexane and ethyl acetate extracts of fruits were more effective against most of the clinical isolates, whereas methanol extract was effective only against *Klebsiella pneumoniae* ESBL. Gas chromatography-mass spectrometry studies on hexane and ethyl acetate extract of fruits resulted in the identification of 31 and 39 compounds respectively mainly Phenylpropenes and phenols. Other classes of compounds present included sesquiterpenes, monoterpene alcohols, esters,fatty acids and diterpene hydrocarbons. Thus, antimicrobial activity of seed and fruit extract might be related to their phenolic compounds[58].

Star anise (*Illicium verum* Hook f) has also been shown to possess potent antimicrobial properties. Chemical studies indicated that a major portion of this antimicrobial property was due to anethole (**32**) present in the dried fruit. Studies with isolated anethole (compared with standard anethole) indicated that it is effective against bacteria, yeast and fungal strains[59].

The diethyl ether (EE) fraction obtained from partition extraction and supercritical CO_2 extracts (SFE) of *I. verum* revealed an antibacterial activity with a minimum inhibitory concentration value of 0.15–0.70 mg/ml and 0.11 mg/ml, respectively. The EE fraction of *I. verum* showed synergetic effects with some commercial antibiotics. The antimicrobial mechanism was investigated with killing curves and scanning electron microscopy observation. The chemical components of the extracts analyzed by spectrophotometry showed that (*E*)-anethole (**32**) was the most abundant in the extracts and exhibited antibacterial activity against different clinical isolates. Other compounds present include anisyl acetone (**34**), anisyl alcohol, and anisyl aldehyde. Four standards—(*E*)-anethole, anisyl aldehyde, anisyl acetone, and anisyl alcohol—were also tested for their antimicrobial activities to determine the antibacterial composition. (*E*)-anethole had a higher antibacterial activity than the other standards against *A. baumannii*, with an MIC value of 0.11 mg/mL, which is same as in the SFE extracts. Anisyl aldehyde and anisyl alcohol possessed a broader antimicrobial activity against all of the test bacteria, with an MIC range of between 1 and 2 mg/mL and 3 and 6 mg/mL, respectively. Anisyl acetone showed antimicrobial activity against *A. baumannii* and *P. aeruginosa*, with MIC values of 2 and 4 mg/mL, respectively. The antimicrobial activity results obtained for the standards were consistent with the results obtained in the EE fraction [38].

The preliminary studies of crude ethanolic extract from the fruit of *I. verum* Hook showed antimicrobial activity against *S. aureus* ATCC 25923, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *C. albicans*, *A. flavus* and *T. mentagrophytes*, which was determined by the agar diffusion method. Further extractions from the fruit consisted of three parts: hexane, dichloro-me-thane and methanolic extracts. Crude hexane and crude dichloromethane extracts showed antifungal activity against *T. mentagrophytes*. Crude dichloromethane and crude methanolic extracts showed antibacterial activity against *S.aureus* ATCC 25923. Isolation was possible only from hexane extract, which resulted in one active compound. From spectroscopic evidence, hexane extract appeared to be anethole and it antifungal activity was determined using the agar dilution method. The MIC against *C. albicans*, *A. flavus* and *T. mentagrophytes* was found to be 2,500, 2,500 and 625 mg/mL, respectively[60].

In order to identify natural products for plant disease control, the essential oil of star anise (*I. verum* Hook. f.) fruit was investigated for its antifungal activity on plant pathogenic fungi. The fruit essential oil obtained by hydro-distillation was analyzed for its chemical composition by gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS). *trans*-Anethole (89.5%), 2-(1-cyclopentenyl)-furan (0.9%) and cisanethole (0.7%) were found to be the main components among 22 identified compounds, which accounted for 94.6% of the total oil. The antifungal activity of the oil and its main component trans-anethole against plant pathogenic fungi were determined. Both the essential oil and trans-anethole exhibited strong inhibitory effect against all test fungi indicating that most of the observed antifungal properties was due to the presence of *trans*-anethole (**32**) in the oil, which could be developed as natural fungicides for plant disease control in fruit and vegetable preservation [61] .

The mechanism of action of (*E*)-anethole is not fully understood but is speculated to involve membrane disruptions by the lipophilic compound [62]. Chemical components exert their toxic effects against the test strains through disruption of the bacterial membrane integrity. The active components are able to destroy the cellular integrity and thereby inhibit respiration and iron transport processes. They might also increase membrane permeability in bacterial mitochondria [63].

Phenolic compounds are known to be synthesized by plants in response to microbial infection. It is therefore possible that they can act as effective antimicrobial substances against a wide array of microorganisms. However, the antimicrobial activity of plant extracts depend not only on phenolic compounds but also by the presence of different secondary metabolite especially those hydroxyl groups on the active constituents, because of the ability of these substances to bind to bacterial adhesions and disturb the availability of receptors on the surface [64]. Phytochemical studies have shown that plants with antimicrobial activity contain bioactive constituents such as tannins, flavonoids, alkaloids and saponins[65]

3.5 Insecticidal activities

The essential oil of *I. difengpi* stem bark was found to possess strong insecticidal activities against the maize weevil, *Sitophilus zeamais* (Motschulsky) (Coleoptera: Curculionidae) and red flour beetle, *Tribolium castaneum* Herbst (Coleoptera: Tenebrionidae). Bioactivities-directed chromatographic separation on repeated silica gel columns led to the isolation of two compounds: safrole (**19)** and linalool. Safrole showed pronounced contact toxicity against both insect species (LD50 = 8.54 for *S. zeamais*; 4.67 μg/adult for *T. castaneum*) and was more toxic than linalool (LD50 = 24.88 for *S. zeamais*; 8.12 μg/adult for *T. castaneum*) [36].

The insecticidal activities of materials derived from the fruit of star anise, *I. verum*, against adults of *Blattella germanica* were also examined by direct contact application and fumigation methods, and compared with those of DDVP, deltamethrin and hydramethylnon. The biologically active constituent of the *Illicium* fruit was characterized as the phenylpropene, (E)-anethole, by spectroscopic analysis. In a filter paper diffusion test with females, (E)-anethole (**32**) caused 80.3% mortality at 0.159 mg cm-2 at 1 and 3 days after treatment (DAT), whereas 16.7% mortality at 3 DAT was achieved at 0.079 mg $cm^{-2.}$ DDVP and deltamethrin gave > 90% mortality at 0.019 mg cm-2 at 1 DAT. At 0.009 mg cm-2, DDVP and deltamethrin showed 73.3 and 60% mortality at 1 DAT, respectively, but 93.3 and 76.7% mortality at 3 DAT. Hydramethylnon exhibited 0 and 93.3% mortality at 0.159 mg cm-2 at 1 and 3 DAT, respectively, whereas 6.7% mortality at 3 DAT was observed at 0.079 mg cm-2. In a fumigation test with females, (E)-anethole (**32**) was much more effective in closed cups than in open ones, indicating that the insecticidal activity of the compound was largely attributable to fumigant action. (E)-Anethole and DDVP caused 100% mortality at 0.398 and 0.051 mg cm-2 4 and 1 h after treatment, respectively. (E)-Anethole showed 46.7% mortality at 0.199 mg cm-2 at 3 DAT, whereas deltamethrin and hydramethylnon at 0.796 mg cm-2 was ineffective for 3-day period (Chang kS et al.2002). Further studies showed that *I.verum* extracts (anise oil and (*E*)-anethole) were highly toxic to both life stages (larvae and adults) of a museum insect pest *Demestes maculates* [62]

3.6. Other pharmacological activities

Other medicinal benefits of *Illicium* genus include anti-Hepatitis B virus activities [37]. In addition, some of the phytoquinoids isolated from this genus have choline acetyltransferase increasing and cytotoxic activities [19-21, 42].

CONCLUSION

Ilicium species are a rich source of phenolic compounds, mainly phenylpropanoids, neolignans and their glycosides, flavonoids and phytoquinoids. Besides, these compounds have been linked to most of the pharmacological activities associated with these plants. As a result, *Illicium* plants should be explored further as an alternative source of medicine.

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