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REVIEW

Review on Phytochemistry and Pharmacology of the Genus *Licaria* (Lauraceae)

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ABSTRACT

The genus *Licaria* (Lauraceae) is a flowering plant genus, comprises 40 species and endemic to Central and South America. Most of the species have been used as traditional medicine. Phytochemicals isolated from *Licaria* species are lignans, neolignans, alkaloids, lactones, triterpenes, and arylpropanoids. The purpose of this review is to examine in detail from a phytochemical and pharmacological point of view what is reported in the past and current literature obtained from plants belonging to the *Licaria* genus.

Keywords: *Licaria*, Lauraceae, Phytochemistry, Pharmacology, Neolignans

INTRODUCTION

The genus *Licaria* (Lauraceae) is a Neotropical genus consisting of 40 species distributed from southern Florida, Mexico to the south of Brazil and Bolivia. In Brazil, the occurrence of 20 species and two subspecies, mostly in the Amazon region. These trees have a resilient wood, useful as timber for construction and as firewood (1). The genus evergreen monoecious, hermaphrodite, trees or rarely bushes. It is characterized by the combination of flowers with three 2-locellate stamens, a well-developed cupule, often with a double margin and alternate and opposite leaves. The fruit is a bay with tepals deciduous and an underlying dome double border (2). Most of *Licaria* species have ben used in the ethnomedical folk traditions of indigenous Central and South America for various ailments such as indigestion (3), diarrhea (4), stomachache (5), and as stimulant (3). To date, comparative phytochemical data are available for only eleven *Licaria* species. Several bioactive substances including lignans, neolignans, alkaloids, lactones, triterpenes, essential oils, arylpropanoids, and other components, have been isolated from different species of *Licaria*. Literature reviews show that several of them have been reported with

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interesting pharmacological activities such as cytotoxicity (6), antibacterial (7), antimalarial (8), anti-leishmanial (4), antioxidant, and antiplatelet inhibitory activities (9). The aim of this review is to examine from phytochemical and pharmacological perspectives the different *Licaria* species for which the extraction, isolation, structural characterization and description of the biological activity of individual compounds are reported in the literature. In addition, the chemical compositions of the essential oils of *Licaria* species are also reported. A substructure search performed using the SciFinder Scholar database and searches by keywords in PubMed, Medline, and Scopus, indicated that to date 14 species have been cited in this perspective. The discussion on phytochemistry, pharmacology and essential oils compositions of each plant is provided.

PHYTOCHEMISTRY AND PHARMACOLOGY

A review on the literatures revealed that few phytochemial studies have been carried out on *Licaria* species prior to the current study. Phytochemical investigations have been conducted on eleven species species of *Licaria* which are *L. aritu* Ducke, *L. armeniaca* (Nees) Kosterm., *L. aurea* (Huber) Kosterm. *L. brasiliensis* (Nees) Kosterm., *L. canella* (Meisn.) Kosterm., *L. chrysophylla* (Meisn.) Kosterm., *L. macrophylla* (A.C. Smith) Kosterm., *L. mahuba* (A. Samp.) Kosterm., *L. puchury-major* (Mart.) Kosterm., *L. rigida* Kosterm., and *L. triandra* (Sw.) Kosterm. The studies have reported the presence of several classes of natural products including lignans, neolignans, alkaloids, lactones, triterpenes, and arylpropanoids. The phytochemical studies of Licaria species are listed in Table 1 and the chemical structures are shown in Figure 1.

Table 1. Chemical constituents isolated from the genus *Licaria*

Compounds	Species	Part
Neolignans		
Licarin A **1**	*L. aritu*	Wood
	L. puchury-major	Seeds
Licarin B **2**	*L. aritu*	Wood
(2*S*,3*S*,3a*R*,5*R*)-3α-Allyl-5-methoxy-2-(3',4'-methylenedioxyphenyl)-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxo-benzofuran **3**	*L. armeniaca*	Trunk wood
(2*S*,3*S*,3a*R*,5*R*)-3α-Allyl-5,7-dimethoxy-2-(3',4'-methylenedioxy-phenyl)-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxo-benzofuran **4**	*L. armeniaca*	Trunk wood
Armenin A **7**	*L. armeniaca*	Trunk wood
Armenin B **8**	*L. armeniaca*	Trunk wood
	L. puchury-major	Seeds
(7*S*,8*R*, l'*S*,2'*S*, 3'*S*)-2'-Acetoxy-l'-allyl-3',5'-dimethoxy-8-methyl-7-piperonyl-bicyclo [3.2.1]-oct-5'- en-4'-one **9**	*L. armeniaca*	Trunk wood
3a-allyl-5-methoxy-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxobenzofuran **12**	*L. armeniaca*	Trunk wood
Dimethoxy-2-(3,4-methylenedioxyphenyl)-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxobenzofuran **13**	*L. armeniaca*	Trunk wood
(1*S*,5*R*,6*S*,7*R*,8*R*)-8-acetoxy-1-allyl-3,5-dimethoxy-7-methyl-6-(3'-methoxy-4',5'-methylenedioxyphenyl)-4-oxobicyclo[3.2.1]oct-2-ene **17**	*L. armeniaca*	Fruits
(1*S*,5*R*,6*S*,7*R*)-1-Allyl-3-methoxy-7-methyl-6-(3'-methoxy-4',5'-methylenedioxyphenyl)-4,8-dioxobicyclo[3.2.1]oct-2-ene **18**	*L. armeniaca*	Fruits
(1*S*,5*R*,6*S*,7*R*)-1-Allyl-3-methoxy-7-methyl-6-(3',4',5'-trimethoxyphenyl)-4,8-dioxobicyclo[3.2.1]oct-2-ene **19**	*L. armeniaca*	Fruits
Grandisin **20**	*L. aurea*	Fruits
de-O-Methylgrandisin **21**	*L. aurea*	Fruits
dide-O-Methylgrandisin **22**	*L. aurea*	Fruits
Virolongin A **23**	*L. aurea*	Fruits
Virolongin B **24**	*L. aurea*	Fruits
	L. chrysophylla	Bark/fruits calyx
Eusiderin A **27**	*L. chrysophylla*	Bark/fruits calyx

rel-(7*S*,8*R*,1'*S*,4'*S*,5'*R*)-4'-Hydroxy-3,4,5,3',5'-pentamethoxy-6'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **29**	*L. brasiliensis*	Trunk wood
rel-(7*S*,8*R*,1'*S*,4'*R*,5'*R*)-4'-Hydroxy-3,4,5,3',5'-pentamethoxy-6'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **30**	*L. brasiliensis*	Trunk wood
rel-(7*S*,8*R*,1'*S*,5'*S*,6'*S*)-6-Acetoxy-3'-hydroxy-3,5'-dimethoxy-4,5-methylenedioxy-4'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **31**	*L. brasiliensis*	Trunk wood
rel-(7*R*,8*S*,1'*S*,5'*S*,6'*S*)-6-Acetoxy-3,4,5,3',5'-pentamethoxy-4'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **32**	*L. brasiliensis*	Trunk wood
rel-(7*R*,8*S*,1'*S*,5'*S*,6'*S*)-6'-Hydroxy-3,4,5,3',5'-pentamethoxy-4'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **33**	*L. brasiliensis*	Trunk wood
rel-(7*S*,8*R*,1'*S*,4'*R*,5'*S*,6'*S*)-6'-Acetoxy-4'-hydroxy-3,3',5'-trimethoxy-4,5-methylenedioxy-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **34**	*L. brasiliensis*	Trunk wood
Canellin A **35**	*L. canella*	Trunk wood
	L. rigida	Trunk wood
Canellin B **36**	*L. canella*	Trunk wood
Canellin C **37**	*L. canella*	Trunk wood
	L. rigida	Trunk wood
Chrysophyllin A **40**	*L. chrysophylla*	Trunk wood
Chrysophyllin B **41**	*L. chrysophylla*	Trunk wood
Chrysophyllon I-A **42**	*L. chrysophylla*	Trunk wood
Chrysophyllon I-B **43**	*L. chrysophylla*	Trunk wood
	L. chrysophylla	Bark
Chrysophyllon II-A **44**	*L. chrysophylla*	Trunk wood
	L. chrysophylla	Bark
Chrysophyllon II-B **45**	*L. chrysophylla*	Trunk wood
	L. chrysophylla	Bark
Chrysophyllon III-A **46**	*L. chrysophylla*	Trunk wood
Chrysophyllon III-B **47**	*L. chrysophylla*	Trunk wood
	L. chrysophylla	Bark
Eusiderin I **51**	*L. chrysophylla*	Bark/fruits calyx
Eusiderin J **52**	*L. chrysophylla*	Bark/fruits calyx
Eusiderin K **53**	*L. chrysophylla*	Bark/fruits calyx
Eusiderin L **54**	*L. chrysophylla*	Bark/fruits calyx
Eusiderin M **55**	*L. chrysophylla*	Bark/fruits calyx
Virolongin E **56**	*L. chrysophylla*	Bark/fruits calyx
Virolongin F **57**	*L. chrysophylla*	Bark/fruits calyx
Virolongin G **58**	*L. chrysophylla*	Bark/fruits calyx
Chrysophyllon IV-B **59**	*L. chrysophylla*	Bark
Chrysophyllon V1-B **60**	*L. chrysophylla*	Bark
Macrophyllin **61**	*L. macrophylla*	Trunk wood
Aurein **67**	*Licaria sp.*	Wood
Eusiderin **68**	*Licaria sp.*	Wood
	L. rigida	Trunk wood

(7*S*,8*S*)-$\Delta^{8'}$-2',6'-Dimethoxy-3,4,-methylenedioxy-7.O.3',8.4',1'.O.7'-neolignan **75**	*L. puchury-major*	Seeds
Ferrearin B **76**	*L. puchury-major*	Seeds
Ferrearin C **77**	*L. puchury-major*	Seeds
rel-(7*S*,8*S*,1'*R*,2'*S*)-2'-Hydroxy-3,4-dimethoxy-3'-oxo-Δ4',8'-8.1',7.O.2'-neolignan **78**	*L. puchury-major*	Seeds
Ferrearin G **79**	*L. puchury-major*	Seeds
Oxaguianin **80**	*L. puchury-major*	Seeds
rel-(7*S*,8*S*,1'*R*,5'*R*)-5'-Methoxy-3,4-methylenedioxy-4'-oxo-Δ2',8'-8.1',7.O.2'-neolignan **81**	*L. puchury-major*	Seeds
3'-Methoxyburchellin **82**	*L. puchury-major*	Seeds
Eusiderin B **93**	*L. rigida*	Trunk wood
Triandrin A **94**	*L. triandra*	Seeds
Triandrin B **95**	*L. triandra*	Seeds
Burchellin **96**	*L. triandra*	Seeds
Lignans		
Magnolin **11**	*L. armeniaca*	Trunk wood
Alkaloids		
tri-O-Methylmoschatoline **10**	*L. armeniaca*	Trunk wood
Bracteoline **14**	*L. armeniaca*	Trunk wood
O-Methylbracteoline **15**	*L. armeniaca*	Trunk wood
α-Dehydroreticuline **16**	*L. armeniaca*	Trunk wood
Reticuline **83**	*L. puchury-major*	Seeds
Orientaline **84**	*L. puchury-major*	Seeds
Coclaurine **85**	*L. puchury-major*	Seeds
N-methylcoclaurine **86**	*L. puchury-major*	Seeds
Norjuziphine **87**	*L. puchury-major*	Seeds
Norisoboldine **88**	*L. puchury-major*	Seeds
Isoboldine **89**	*L. puchury-major*	Seeds
Glaziovine **90**	*L. puchury-major*	Seeds
Reticuline *N*-oxide [**91** *N*-Me (*S*)]	*L. puchury-major*	Seeds
Reticuline *N*-oxide [**92** *N*-Me (*R*)]	*L. puchury-major*	Seeds
Lactones		
(-)-Dihydromahubanolide B **65**	*L. mahuba*	Trunk wood
(-)-*iso*-Dihydromahubanolide B **66**	*L. mahuba*	Trunk wood
Miscellaneous compounds		
Sitosterol **5**	*L. armeniaca*	Trunk wood
	L. armeniaca	Trunk wood
	L. canella	Trunk wood
	L. macrophylla	Trunk wood
	L. puchury-major	Trunk wood
6,7-Dimethoxycoumarin **6**	*L. armeniaca*	Trunk wood
	L. armeniaca	Trunk wood
Dillapiole **38**	*L. canella*	Trunk wood
Elemicin **39**	*L. canella*	Trunk wood
2,3,4,5-Tetramethoxyallylbenzene **48**	*L. chrysophylla*	Trunk wood
2,3,4,5-Tetramethoxycinnamyl alcohol **49**	*L. chrysophylla*	Trunk wood
2,3,4,5-Tetramethoxycinnamaldehyde **50**	*L. chrysophylla*	Trunk wood
Borneol **62**	*L. macrophylla*	Trunk wood
Elemol **63**	*L. macrophylla*	Trunk wood
Nerolidol **64**	*L. macrophylla*	Trunk wood
Eugenol **69**	*L. puchury-major*	Trunk wood
Safrole **70**	*L. puchury-major*	Trunk wood
Syringic aldehyde **71**	*L. puchury-major*	Trunk wood
3,4-Methylenedioxycinnamaldehyde **72**	*L. puchury-major*	Trunk wood
3,4-Methylenedioxycinnamyl alcohol **73**	*L. puchury-major*	Trunk wood

***L. aritu* Ducke**

L. aritu is an arboreous Lauraceae species which occurs along the Manaus-Itacoatiara road, Amazonas State. The only literature report refers to the isolation from the benzene extract of the wood have characterize licarin A **1** and B **2** (10).

***L. armeniaca* (Nees) Kosterm.**

L. armeniaca is a tree up to 7 m, widely distributed in the Amazonian rainforest, Brazil. Four studies have been reported from this species. The first report was published in 1978 by Aiba and co-workers (11). These authors isolated two novel benzofuranoid neolignans, namely (2*S*,3*S*,3a*R*,5*R*)-3α-allyl-5-methoxy-2-(3',4'-methylenedioxyphenyl)-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxo-benzofuran **3** and (2*S*,3*S*,3a*R*,5*R*)-3α-allyl-5,7-dimethoxy-2-(3',4'-methylenedioxy-phenyl)-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxo-benzofuran **4**, together with sitosterol 5,6,7-dimethoxycoumarin **6**, armenin A **7**, and armenin B **8** from the benzene extract of trunk wood. Purification of the benzene/ethanol extract of the trunk wood by Alegrio et al. (12) have reported to have a novel neolignan (7*S*,8*R*, l'*S*,2'*S*, 3'*S*)-2'-acetoxy-l'-allyl-3',5'-dimethoxy-8-methyl-7-piperonyl-bicyclo [3.2.1]-oct-5'-en-4'-one **9**, including sitosterol 5,6,7-dimethoxycoumarin **6**, tri-*O*-methylmoschatoline **10** and magnolin **11**. In addition, Abdel-Hafiz and co-workers (13) have successfully isolated two neolignans, 3a-allyl-5-methoxy-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxobenzofuran **12** and dimethoxy-2-(3,4-methylenedioxyphenyl)-3-methyl-2,3,3a,4,5,6-hexahydro-6-oxobenzofuran **13**, including three alkaloids, bracteoline **14**, *O*-methylbracteoline **15** and α-dehydroreticuline **16**. Barbosa-Filho and co-workers (14) have studied on the fruits part. The isolation on ethanol/water extract have found three novel neolignans (1*S*,5*R*,6*S*,7*R*,8*R*)-8-acetoxy-1-allyl-3,5-dimethoxy-7-methyl-6-(3'-methoxy-4',5'-methylenedioxyphenyl)-4-oxobicyclo[3.2.1]oct-2-ene **17**, (1*S*,5*R*,6*S*,7*R*)-1-allyl-3-methoxy-7-methyl-6-(3'-methoxy-4',5'-methylenedioxyphenyl)-4,8-dioxobicyclo[3.2.1]oct-2-ene **18**, and (1*S*,5*R*,6*S*,7*R*)-1-allyl-3-methoxy-7-methyl-6-(3',4',5'-trimethoxyphenyl)-4,8-dioxobicyclo[3.2.1]oct-2-ene **19**.

***L. aurea* (Huber) Kosterm.**

L. aurea is a tree widely distributed in the Amazonian rainforest, Brazil. The ethanolic fruit extract of *L. aurea* have found to contain the diaryltetrahydrofuran type neolignans, grandisin **20**, de-*O*-methylgrandisin **21** and dide-*O*-methylgrandisin **22**, as well as virolongin A **23** and virolongin B **24**, as reported by Barbosa-Filho and co-workers (15). Bezerra and co-workers (16) also successfully isolated grandisin **20** from this species. Three years later, Marques et al. (17) were studied on wood part and successfully identified as aurein A-B **25-26**, eusiderin A **27**, virolongin B **24** and virolongin C **28**.

***L. brasiliensis* (Nees) Kosterm.**

L. brasiliensis is a tree popularly known as '*louro capitiu*', grows wild in the Forest Reserve of Jari, Municipality of Almerim, Brazil (18). Phytochemical studies on the hexane extract of the trunk wood of this species have led to the isolation of six new bicycle[3.2.1]octanoid neolignans, identified as *rel*-(7*S*,8*R*,1'*S*,4'*S*,5'*R*)-4'-Hydroxy-3,4,5,3',5'-pentamethoxy-6'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **29**, *rel*-(7*S*,8*R*,1'*S*,4'*R*,5'*R*)-4'-Hydroxy-3,4,5,3',5'-pentamethoxy-6'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **30**, *rel*-(7*S*,8*R*,1'*S*,5'*S*,6'*S*)-6-acetoxy-3'-hydroxy-3,5'-dimethoxy-4,5-methylenedioxy-4'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan**31**,*rel*-(7*R*,8*S*,1'*S*,5'*S*,6'*S*)-6-acetoxy-3,4,5,3',5'-pentamethoxy-4'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **32**, *rel*-(7*R*,8*S*,1'*S*,5'*S*,6'*S*)-6'-hydroxy-3,4,5,3',5'-pentamethoxy-4'-oxo-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **33**, and *rel*-(7*S*,8*R*,1'*S*,4'*R*,5'*S*,6'*S*)-6'-acetoxy-4'-hydroxy-3,3',5'-trimethoxy-4,5-methylenedioxy-Δ-1,3,5,2',8'-8.1',7.5'-neolignan **34** (18).

***L. canella* (Meisn.) Kosterm.**

L. canella is a botanical species popularly known as '*louro-pirarucu*'. Within the ethnic group Tacana of the Amazonian region, this species has the same name and use as *Aniba canelilla*, probably due to their aromatic barks. The barks of both species have ethnopharmacological uses to alleviate abdominal pain, intestinal cramps or discomfort, without diarrhea (8). The ethanol extract of the bark of this species showed activity *in vitro* against chloroquine sensitive *Plasmodium falciparum* (IC_{50} value of 3.8 μg/mL) and also resistant strains (IC_{50} value of 3.2 μg/mL). The extract of the stem demonstrated low activity against human myeloma cell line, RPMI 8226 cancer cells (8). Giesbrecht and co-workers (19) have reported the benzene/ethanol extract of the trunk wood to have three neolignans, canellin A **35**, B **36** and C **37**, as well as dillapiole **38**, elemicin **39** and sitosterol **5**.

***L. chrysophylla* (Meisn.) Kosterm.**

L. chrysophylla is a tree growing in Amazonian rainforest, Brazil. The first and up to now, four studies have been reported from this species. Ferreira and co-workers (20) have isolated chrysophyllin A **40** and B **41** from petroleum extract of the trunk wood. Both compounds were also found from the same species, reported by Lopes et al. (21). They also managed to obtain chrysophyllon I-A **42**, chrysophyllon I-B **43**, chrysophyllon II-A **44**, chrysophyllon II-B **45**, chrysophyllon III-A **46**, chrysophyllon III-B **47**, 2,3,4,5-tetramethoxyallylbenzene **48**, 2,3,4,5-tetramethoxycinnamyl alcohol **49** and 2,3,4,5-tetramethoxycinnamaldehyde **50** form the petroleum extract of trunk wood. Furthermore, Silva and co-workers (22) have reported on the other parts of this species which are from the bark and fruits calyx ethanolic extract. They found five new benzodioxane neolignans, eusiderin I-M **51-55**, three new β-aryloxy-arylpropane type neolignan, virolongin E-G **56-58**, together with known compounds, eusiderin A **27** and virolongin B **24**. In addition, Bezerra et al. (16) have studied on the bark extract of this species and successfully isolated chrysophyllon IV-B **59**, chrysophyllon V1-B **60**, chrysophyllon I-B **43**, chrysophyllon II-A **44**, chrysophyllon II-B **45**, chrysophyllon III-B **47**. They also found that the isolated compound have strong inhibition of supercoiled DNA relaxation induced by topo II-α at a concentration of 100 μM. These results indicate that no obvious correlation can be derived between the structure of these compounds and the inhibitory activity of DNA relaxation by DNA topoisomerase II.

L. macrophylla (A.C. Smith) Kosterm.

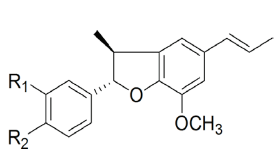
L. macrophylla is a tree which grows in the Amazon region, Brazil (23). Only one study has been reported in the literature about this plant in 1974, when Franca and coworkers (23) described the isolation and characterization of a novel neolignan, macrophyllin **61** from the trunk wood extracts. Besides, they also managed to get sitosterol **5**, borneol **62**, elemol **63**, and nerolidol **64**.

L. mahuba (A. Samp.) Kosterm.

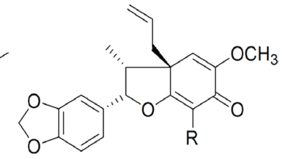
L. mahuba, an Amazonian Lauraceae has been reported to have (-)-dihydromahubanolide B **65** and (-)-*iso*-dihydromahubanolide B **66**. Synthesis of both compounds was achieved starting from (-)-methyl 5-hydroxymethyl-2,2-dimethyl-1,3-dioxolane-4-carboxylate which was readily available from L-(+)-tartaric acid, as published by Tanaka and Yamashita (24). Gottlieb and co-workers (25) also reported the phytochemical study from the wood of a *Licaria sp*. They were successfully identified two neolignans, namely aurein **67** and eusiderin **68**.

L. puchury-major (Mart.) Kosterm.

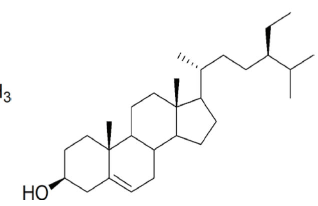
L. puchury-major is popular known in Brazil as '*puchuri*' or '*pixuri*'. Their seeds are used in folk medicine for stomach and intestinal ailments and also as a calmative in adults and children to treat insomnia, nervousness and irritability (26). The first phytochemical study of this species appeared in the literature in 1973 when Leao da Silva and co-workers (27) isolated and structurally characterized sitosterol **5**, eugenol **69**, safrole **70**, syringic aldehyde **71**, 3,4-methylenedioxycinnamaldehyde **72** and 3,4-methylenedioxycinnamyl alcohol **73** from trunk wood extract. In addition, Uchiyama and co-workers (28) have reported that the EtOH extract of the seeds of *L. puchury-major* showed the growth inhibitory activity against human leukemia Jurkat cells (53.3% inhibition at 30 μg/mL). Besides, acetone fraction was found to be the most active (82.7% inhibition at 30 μg/mL) and induced early apoptosis at 30 μg/mL within 24 h against Jurkat cells. Bioassay-guided fractionation of the ethanol extracts led to the isolation of one phenylpropanoid and ten neolignans. They were identified as apiole **74**, (7*S*,8*S*)-$\Delta^{8'}$-2',6'-dimethoxy-3,4,-methylenedioxy-7.O.3',8.4',1'.O.7'-neolignan **75**, ferrearin B **76**, ferrearin C **77**, licarin A **1**, *rel*-(7*S*,8*S*,1'*R*,2'*S*)-2'-hydroxy-3,4-dimethoxy-3'-oxo-Δ4',8'-8.1',7.O.2'-neolignan **78**, ferrearin G **79**, oxaguianin **80**, *rel*-(7*S*,8*S*,1'*R*,5'*R*)-5'-methoxy-3,4-methylenedioxy-4'-oxo-Δ2',8'-8.1',7.O.2'-neolignan **81**, armenin B **8**, and 3'-methoxyburchellin **82**. The cytotoxic activity of isolated compounds against Jurkat was tested by MTT assay and found that compounds **76**, **77**, **78** and **79** having furanocyclohexenone structure with hemiacetal in the molecule showed cytotoxic activity at 10 μM. These four neolignans induced early apoptosis at 10 μM within 24 h, while compound **75** also induced apoptosis at 100 μM within 48 h. Studies on this species was continued by Ohsaki and co-workers (6) and successfully isolated ten alkaloids from the seeds extract. They were identified as reticuline **83**, orientaline **84**, coclaurine **85**, *N*-methylcoclaurine **86**, norjuziphine **87**, norisoboldine **88**, isoboldine **89**, glaziovine **90** and reticuline *N*-oxide [**91** *N*-Me (*S*); **92** *N*-Me (*R*)]. The cytotoxicity of the obtained compounds was evaluated against vincristine-sensitive and -resistant P388 cells in the presence of P388/VCR(+) or the absence of P388/VCR(-) of low levels of vincristine. Norjuziphine **87**, norisoboldine **88**, and isoboldine **89** exhibited potent cytotoxic activity in the presence of vincristine P388/VCR(+).



1 $R_1 = R_2 = OCH_2O$
2 $R_1 = OCH_3$; $R_2 = OH$



3 R = H
4 $R = OCH_3$



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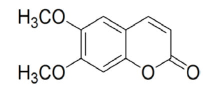

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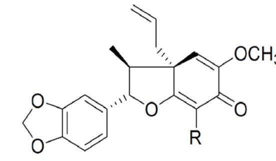
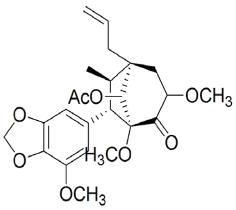


7 R = H
8 $R = OCH_3$



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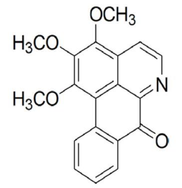

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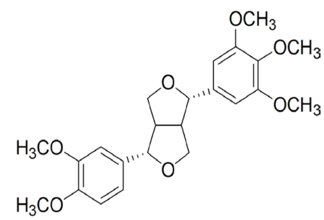

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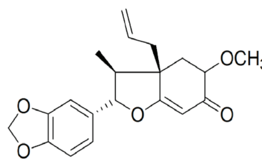

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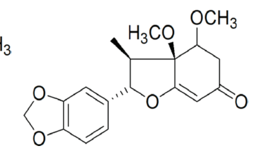

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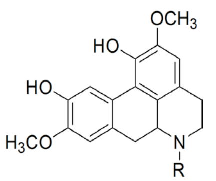
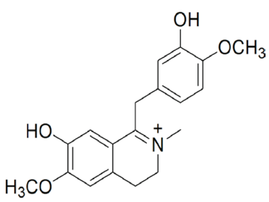


14 R = H
15 $R = OCH_3$



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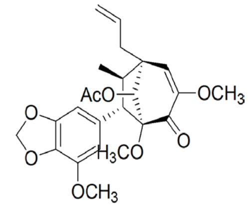

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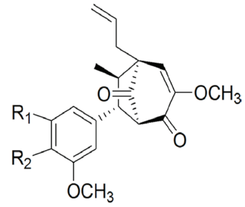
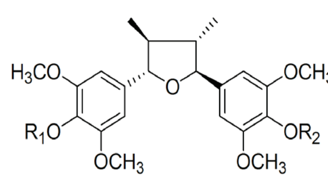
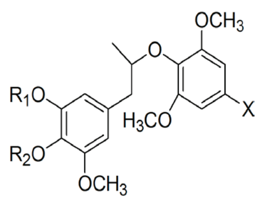
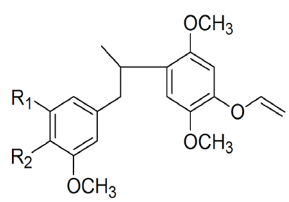


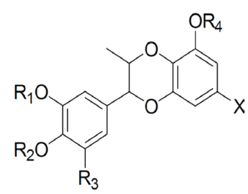
18 $R_1 = R_2 = OCH_2O$
19 $R_1 = R_2 = OCH_3$



20 $R_1 = R_2 = CH_3$
21 $R_1 = H$; $R_2 = CH_3$
22 $R_1 = R_2 = H$



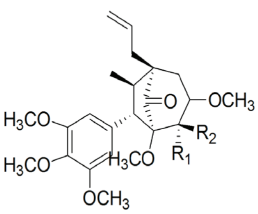




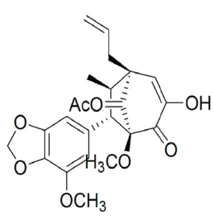
23 $R_1 = R_2 = CH_3$; $X = CH{=}CHCH_3$
24 $R_1 = R_2 = CH_3$; $X = CH_2CH{=}CH_2$
28 $R_1 - R_2 = CH_3$; $X = CH_2CH{=}CH_2$
56 $R_1 = R_2 = CH_3$; $X = CH{=}CHCH_2OH$
57 $R_1 = R_2 = CH_3$; $X = CH{=}CHCHO$
58 $R_1 = R_2 = CH_3$; $X = CHO$

25 $R_1 = OCH_3$; $R_2 = OCH_3$
26 $R_1 = R_2 = OCH_2O$

27 *trans*, $R_1 = R_2 = R_4 = CH_3$; $R_3 = OCH_3$; $X = CH_2CH{=}CH_2$
51 *trans*, $R_1 = R_2 = CH_2$; $R_3 = OCH_3$; $R_4 = CH_3$; $X = CH_2CH{=}CH_2$
52 *cis*, $R_1 = H$; $R_2 = H$; $R_3 = H$; $R_4 = H$; $X = CH_2CH{=}CH_2$
53 *trans*, $R_1 = R_4 = CH_3$; $R_2 = H$; $R_3 = OCH_3$; $X = CH_2CH{=}CH_2$
54 *trans*, $R_1 = R_2 = R_4 = CH_3$; $R_3 = OCH_3$; $X = CHO$
55 *trans*, $R_1 = R_2 = R_4 = CH_3$; $R_3 = OCH_3$; $X = CH{=}CHCH_2OH$
93 *trans*, $R_1 = R_2 = CH_2$; $R_3 = H$; $R_4 = CH_3$; $X = CH_2CH{=}CH_2$



29 $R_1 = OH$; $R_2 = H$
30 $R_1 = H$; $R_2 = OH$



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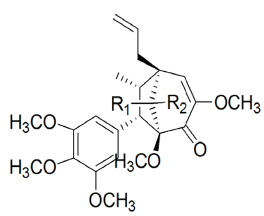
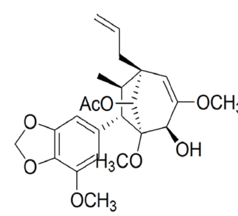


32 $R_1 = OAc$; $R_2 = H$
33 $R_1 = OH$; $R_2 = H$



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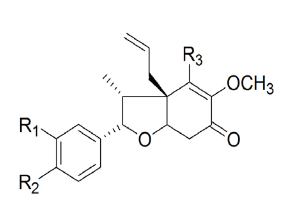
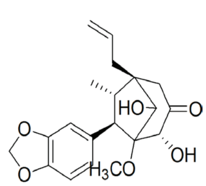


35 $R_1 = OCH_3$; $R_2 = OCH_3$; $R_3 = H$
36 $R_1 = R_2 = OCH_2O$; $R_3 = OCH_3$



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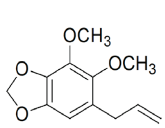

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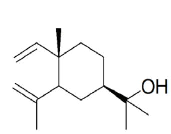

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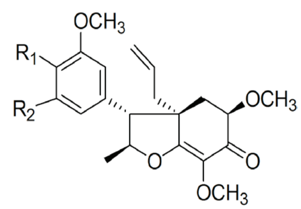
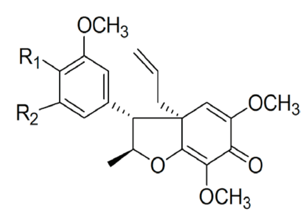


40 $R_1 = R_2 = OCH_2O$
41 $R_1 = R_2 = OCH_3$



42 $R_1 = R_2 = OCH_2O$
43 $R_1 = R_2 = OCH_3$

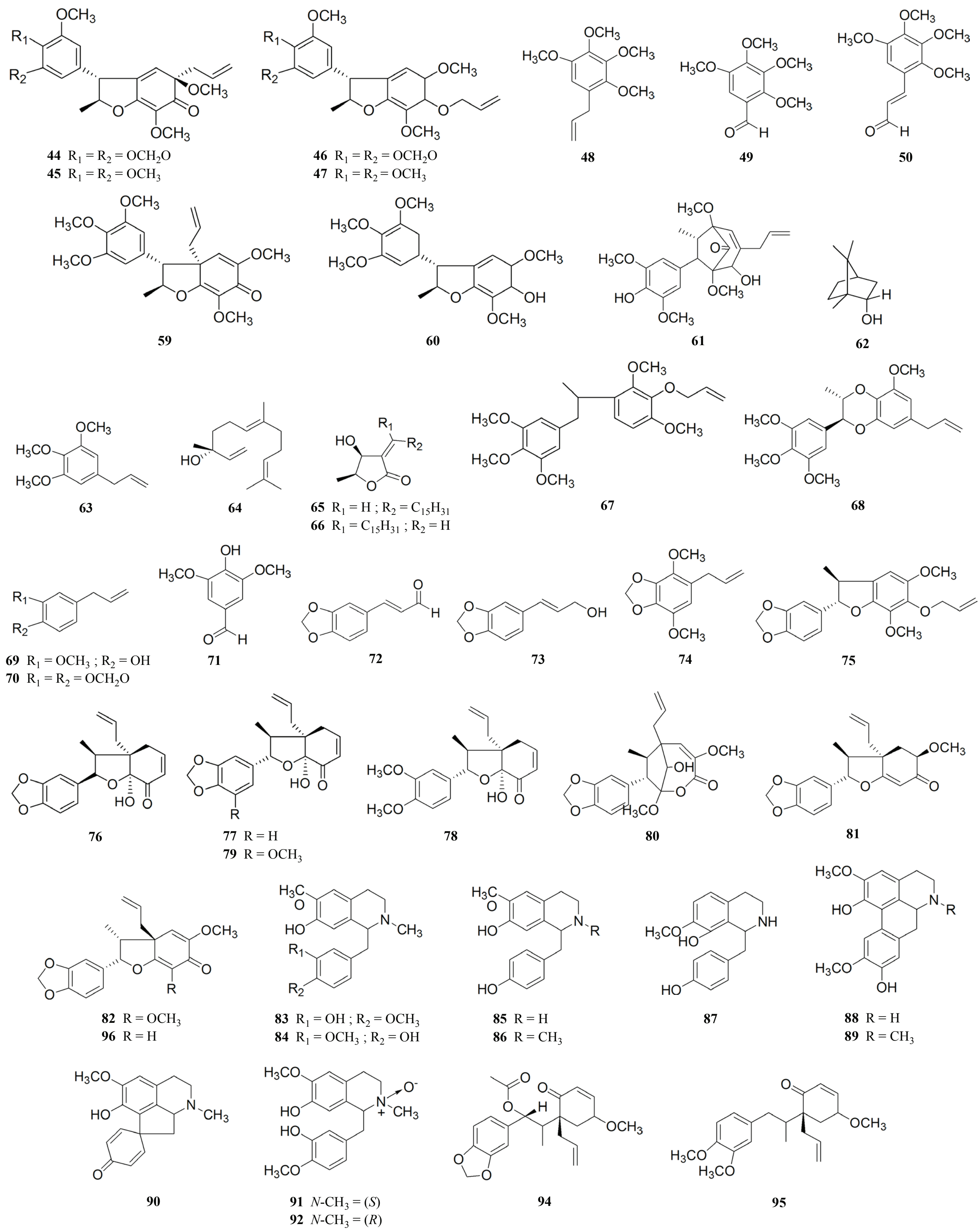


Figure 1. Chemical structures of the compounds isolated from the genus *Licaria*

Table 2. Essential oils compositions from the genus *Licaria*

Species	Locality	Parts/Major components
L. canella	Brazil	**Leaves:** Benzyl Benzoate (69.7-73.0%), α-copaene (4.5-4.9%), α-phellandrene (3.3-4.2%), α-pinene (3.0-3.5%) (4)
L. excelsa	Costa Rica	**Leaves:** α-Pinene (42.9%), β-pinene (22.0%) (31)
L. macrophylla	Brazil	**Wood:** Elemol (25.0%), nerolidol (5.0%), borneol (3.0%) (27)
L. martiniana	Brazil	**Leaves:** β-Caryophyllene (41.7%), β-selinene (7.9%), isovalerate linalool (5.9%), linalool (5.3%) (9)
	Brazil	**Stems:** β-Caryophyllene (21.4%), spathulenol (11.5%), linalool (6.5%), α-cadinol (5.9%), γ-cadinene (5.7%) (9)
L. puchury-major	Brazil	**Twigs:** Eugenol (61.0%), safrole (20.1%), eucalyptol (10.8%), α-terpineol (6.8%) (32)
	Brazil	**Leaves:** Eucalyptol (47.6%), safrole (21.7%), α-terpineol (11.7%) (32)
	Brazil	**Seeds:** Safrole (51.3%), eugenol (3.3%), methyl eugenol (2.9%) (33)
	Brazil	**Seeds:** Safrole (36.1%), 1,8-cineole (21.1%), limonene (12.2%), α-terpineol (10.7%) (34)
	Brazil	**Seeds:** Safrole (58.4%), dodecanoic acid (13.7%), α-terpineol (8.4%) (5)
L. salicifolia	France	**Leaves:** α-Phellandrene (17.2-22.0%), α-santalene (0.8-20.3%), *p*-cymene (1.5-17.4%), β-santalene (0.2-7.0%) (35)
	France	**Bark:** *p*-Cymene (10.1-13.0%), α-phellandrene (5.3-8.1%), 7-epi-α-santalene (7.3-7.6%), α-cadinol (4.5-6.5%), caryophyllene oxide (4.3-6.2%) (35)
	France	**Fruits:** α-Cantalene (2.0-19.0%), *p*-cymene (11.0-13.5%), α-phellandrene (5.8-13.0%), β-santalene (0.7-9.2%) (36)
L. triandra	Cuba	**Leaves:** Selin-11-en-4α-ol (15.1%), β-pinene (10.6%), β-caryophyllene (9.5%), spathulenol (5.6%) (29)
	Cuba	**Leaves:** β-Eudesmol (11.4%), caryophyllene oxide (3.0%) (29)
	Costa Rica	**Leaves:** α-Pinene (40.9%), β-pinene (28.5%) (*E*)-caryophyllene (6.5%) (30)

***L. rigida* Kosterm.**

L. rigida, collected at the Ducke Forest Reserve, near Manaus, Amzonas State, have been investigated by Fo et al. (7). They managed to isolate three neolignans from the trunk wood extract, namely eusiderin **68**, eusiderin B **93**, canellin A **35** and canellin C **37**.

***L. triandra* (Sw.) Kosterm.**

L. triandra is a tree 7-16 m high. It is frequent in woodlands on limestone or shale, 100-1000 m, flowering in September-November, fructifying in January-September. It grows wild in Florida and West Indies southward to Martinique (29). The leaves are used locally as folk medicine such as against indigestion, stomachache and as stimulant (3). Phytochemical investigation from the seeds of this species have afforded two new neolignans, identified as triandrin A-B **94-95** (18) as well as a known benzofuranoid neolignan, burchellin **96** as reported by Castro and Ulate (30).

Literatures revealed that few essential oils studies have been carried out on *Licaria* species. The chemical compositions of the essential oils of *Licaria* species have been conducted on seven species, which are *L. canella* (4), *L. excelsa* (31), *L. macrophylla* (27), *L. martiniana* (9), *L. puchury-major* (5,32,33,34), *L. salicifolia* (35), and *L. triandra* (29,31,36). The major components of the essential oil compositions from *Licaria* species are tabulated in **Table 2**. Monoterpenes hydrocarbon was found as the major group components, in the essential oil of *L. triandra* (Cuba: 42.9%; Costa Rica: 77.7%) (29,31) and *L. excelsa* (85.7%) (31). Meanwhile, oxygenated monoterpenes and benzenoids were found from the essential oil of *L. puchury-major* (seeds: 34.3%) (5) and *L. canella* (leaves: 71.3-74.9%) (4), respectively. In addition, sesquiterpene hydrocarbons were found from the essential oil of *L. martiniana* (47.0-65.8%) (9). Benzyl benzoate, eugenol, and safrole were the major components identified with more than 50% in the essential oils of *Licaria* species. Benzyl benzoate was found in 69.7-73.0% from the leaves oil of *L. canella* (4). Other studies have demonstrated that benzyl benzoate is effective at denaturing dust miteallergen (37) and can eradicates mites and reduce their populations (38). In addition, eugenol presented 61.0% from the twigs oil of *L.*

puchury-major (32). It has been shown in the pharmacological studies that eugenol demonstrated anesthetic, hypothermic, muscle-relaxant, antistress effect and anticonvulsant activities (39,40). Besides, the seeds oil from the same species has successfully found safrole in 51.3% (33) and 58.4% (5). Studies have revealed the genotoxic (41) and carcinogenic (42) potentials of safrole. The study of Taiwanese oral cancer patients suggests that safrole may form stable safrole-DNA adducts in human oral tissues following betel quid chewing, which may contribute to oral carcinogenesis (43).

The *in vitro* antibacterial activity of the essential oil of *L. triandra* was studied against five bacteria strains (*Bacillus cereus*, *Staphylococcus aureus*, *Listeria monocytogenes*, *Bacillus subtilis* and *Escherichia coli*) using the disc diffusion method. The essential oil showed weak activity against the bacteria tested (29). Palazzo and co-workers (31) have evaluated *in vitro* cytotoxicity activity of the essential oils of *L. excelsa* and *L. triandra* against human breast adenocarcinoma cells (MDA-MB-231/MDA-MB-231) and human breast ductal carcinoma cells (Hs 578T). The essential oil of *L. triandra* was found weak activity with 25% kill at 100 µg/mL, while *L. excelsa* oil found to be inactive. The evaluation of the anti-leishmanial activity of the essential oil of *L. canella* indicated moderate activity against *Leishmania amazonensis* with IC_{50} value of 19 µg/mL. Meanwhile, the essential oil displayed low cytotoxicity against *Artemia salina* with LC_{50} value of 5.25 µg/mL (4). Besides, the essential oils of *L. martiniana* showed weak antioxidant (DPPH >1000 µg/mL) and antiplatelet inhibitory activities (leaves 4.2%; stems 36.9%) at quantitative spectrometric assays (9).

CONCLUSION

In this review, we summarized the secondary metabolites isolated from the genus *Licaria* and their pharmacological properties. Most of the species produced lignans and neolignans. Apart from that, further phytochemical studies need to be carried out in the near future to provide a more detailed pattern of the natural constituents and of the biologically active principles in extracts. As a conclusion, it is evident that the genus *Licaria* comprises therapeutically promising and valuable plants, some of which are used in the traditional medicine of indigenous populations. Meanwhile, there are only few studies describing their pharmacological properties, this genus merits more attention in the on-going search for new bioactive compounds.

ACKNOWLEDGMENTS

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Licaria (Lauraceae) Türlerinin Fitokimyasal ve Farmakolojik Özellikleri Üzerine Bir Derleme

ÖZ

Licaria (Lauraceae) çiçekli bir bitki olup 40 cinsi vardır ve bu cinslerin bazıları Orta ve Güney Amerika'ya ait endemik bitkilerdir. *Licaria* (Lauraceae) türlerinin çoğu geleneksel halk ilacı olarak kullanılmaktadır. Licaria türlerinden izole edilen fitokimyasallar; lignanlar, neolignanlar, alkaloidler, laktonlar, triterpenler ve arilpropanoit'lerdir. Bu derlemenin amacı, *Licaria* türlerine ait bitkileri konu alan hem eski hem de güncel literatürün bitkilerin farmakolojik ve fitokimyasal özellikleri açısından ayrıntılı olarak incelenmesidir.

Anahtar kelimeler: *Licaria*, Lauraceace, Fitokimya, Farmakoloji, Neolignanlar

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