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Lignans in *Patrinia* with various biological activities and extensive application value: A review

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Abstract

Lignans in *Patrinia* have attracted the attention of researchers due to their diverse structure and remarkable activity. We searched the PubMed database for articles published from 2003 to 2023 using appropriate search terms: Patrinia, Lignans, Biological activity, and Chemical structures. In this paper, the active lignans and their action mechanisms were summarized over the past 20 years. The results showed that 56 lignans have been isolated and identified from *Patrinia*, including furofurans, dibenzyltyrolactones, tetrahydrofurans, arylnaphthalenes, benzofurans and biphenyl derivatives. 45 lignans had anti-oxidant, anti-inflammatory, anti-tumor, cytotoxicity, enzyme inhibitor, anti-Alzheimer's disease, neuroprotection, anti-bacterial, hepatoprotection and anti-diabetic activities. The anti-inflammatory mechanism involves AMPK, MAPK, NF-κB and JAK-STAT signaling pathways, and the antitumor mechanism involves Raf/MEK/ERK, Akt/JNK and AKT signaling pathways. Lignans in *Patrinia* are promising to be utilized in food and medicine.

Keywords: Lignans; *Patrinia*; Anti-inflammatory mechanism; Anti-tumor mechanism.

1. Introduction

There are about 20 species of *Patrinia* genus, mainly found in eastern to central Asia and northwestern North America. There are 10 species, 3 subspecies and 2 varieties in China, which are widely distributed throughout the country (The Editorial Committee of Chinese Flora, 1986).

Humans have been dependent on nature since ancient times for the fulfillment of their basic requirements such as shelters, foodstuffs and especially medicines (Adnan et al., 2020). It has a long history for the plant of *Patrinia* genus used as herb medicine in China, *P. scabiosaefolia* and *P. villosa* were first recorded in Shennong Materia Medica that have a pungent, bitter and slightly cold taste, and have the effects of clearing heat and detoxifying, eliminating carbuncle and discharging pus, removing blood stasis and relieving pain (Wang and Li, 2004).

In addition to its medicinal value, the young leaves of *Patrinia* can be eaten as wild vegetables, or picked and dried before flowering, such as *P. scabiosaefolia*, *P. villosa*, *P. punctiflora* and *P. heterophylla*, which have high nutritional value and are rich in a variety of vitamins, amino acids and minerals necessary for human body (Xiao et al., 2007).

In recent years, a series of lignans in *Patrinia* with diverse structures and significant activities have been found (Bai et al., 2018; Bai et al., 2017; Di et al., 2013; Gu et al., 2002; Huang et al., 2021; Jiang et al., 2017; Lee et al., 2018; Lee et al., 2020; Lee et al., 2016; Li et al., 2005; Li et al., 2003; Liu et al., 2015; Xiang et al., 2017; Yan et al.,

2016; Zhang et al., 2020). Active lignans discovered in *Patrinia* genus could be used as dietary supplements or functional food ingredients for health promotion and disease risk reduction (Gülsüm and Zeliha, 2019; Zeliha, 2018). In order to better expand that application value of lignans in *Patrinia*, it is necessary to summarize their structures, activities and mechanisms of active lignans discovered in *Patrinia* genus in the past 30 years. It is hoped that more and more attention to focus on the application value of lignans in *Patrinia*, promoting the utilization of lignans in food, medicine and other industries.

2. Phytochemistry

Lignins are natural compounds derived from the polymerization of two phenylpropyl derivatives (C6-C3) (Zalesak et al., 2019). According to different polymerization methods, lignans can be divided into ordinary lignans involving dibenzylbutanes, dibenzyltyrolactones, arylnaphthalenes, tetrahydrofurans, furofurans and dibenzocyclooctenes, neolignans involving benzofuran, bicyclooctane, futoenone, biphenyl and norlignans (Zalesak et al., 2019). 56 lignans were isolated and identified (Figure 1), including furofurans (1–10), dibenzyltyrolactones (11–20), tetrahydrofurans (21–28), arylnaphthalenes (29–34), benzofurans (35–42), biphenyl derivatives (43,44), and others (45–56). In addition, most of the substituents of lignans isolated from *Patrinia* were hydroxyl and methoxyl, and most of the linked glycosides were *β*-D-glucose.

Lignans reviewed in this paper have various biological activity (Table 1) including 18 kinds of activities such as antioxidant (32), anti-inflammatory (10), cancer cell toxicity (7), anti-tumor (4), enzyme inhibitor (7), anti-Alzheimer's disease (6), neuroprotection (5), antibacterial (4), hepatoprotection (3) and hypoglycemic (3) *etc*. The antioxidant activity is the main biological activity, followed by anti-inflammatory activity (Figure 2a). In addition, the relationship network between lignans and biological activities is established, which reflects the number of activities for each compound. Compound 1 showed eight biological activities, including cytotoxicity, anti-oxidation, hepatoprotection, enzyme inhibitor, anti-osteoporosis, anti-malaria, anti-inflammation, anti-Alzheimer's disease, anti-tumor and anti-diabetes. Compound 11 also showed eight biological activities, including cytotoxicity, anti-inflammatory, anti-diabetes, hepatoprotection, anti-tumor, anti-inflammatory, antioxidant and neuroprotection. Compound 3 showed six kinds of activities, including cytotoxicity, lipid-lowering, anti-tumor, anti-bacterial, anti-inflammatory and enzyme inhibition (Figure 2b).

3. Active lignans

3.1. Antioxidant activity

Antioxidants have been shown to reduce the risk of chronic diseases including cancer, liver injury (Selamoglu et al., 2015) and cardiovascular system by some scientific studies (Selamoglu et al., 2017). 32 lignans in *Patrinia* showed antioxidant activity with IC_{50} values ranging from 0.3 to 61.9 μM (Table 2). DPPH radical scavenging assay, ABTS cationic radical scavenging assay, metal ion reducing antioxidant capacity assay (CUPRAC, FRAP), thiobarbiturate reactive substance (TBARS) assay and modified irradiated riboflavin/ethylenediaminetetraacetic acid (EDTA)/Nitroblue tetrazolium (NBT) system were used to evaluate their antioxidant activities in vitro.

By comparing the structure and activity of lignans, it was found that active lignans contain a large number of phenolic hydroxyl groups, which may be related to its antioxidant capacity (Youssef et al., 2020). In general, the presence of phenolic hydroxyl groups increases the antioxidant capacity of a molecule, especially when they are located in positions where they can form intramolecular or intermolecular hydrogen bonds. Compound 7 had no hydroxyl group in its structure, and its IC_{50} was 61.9 μM, showing the weakest antioxidant activity. With the increase of hydroxyl group, the antioxidant activity increased, and compound 29 had four hydroxyl groups at the 4, 4′, 9 and 9′ positions. The IC_{50} value of compound 29 was 0.3 μM, indicating the strongest antioxidant activity. In addition, the action mechanism Showed that compound 11 played an antioxidant role by inhibiting the expression of antioxidant proteins Nrf2 and HO-1 (Wu et al., 2021), and compound 21 played an antioxidant role by activating p38 to up-regulate the NRF2-mediated HO-1 expression (Bajpai, Alam, et al., 2017).

3.2. Anti-inflammatory activity

Antibiotics are commonly used to treat inflammation, however, their clinical utility is limited by toxic side effects and drug resistance (Fan et al., 2023). The mechanism of natural products is complex, which can reduce drug resistance and side effects (Zou et al., 2023). 10 lignans in *Patrinia* showed anti-inflammatory activity (Table 3). Its anti-inflammatory activity was evaluated by measuring the release of NO and the production of pro-inflammatory factors (IL-6, IL-8, and NF-κB) in lipopolysaccharide (LPS)-induced mouse mononuclear macrophage leukemia cells (RAW264.7), the superoxide anion production of human neutrophils induced by N-formyl-methioyl-leucine-phenylalanine/cell relaxant B (fMLP/CB) and the release of NO from MH7A cells induced by (tumor necrosis factor-α) TNF-*α*.

Structure-activity relationship analysis showed that lignans containing furan rings had the best anti-inflammatory activity, and the anti-inflammatory activity of lignan aglycones was better than that of lignan glycosides (Wang et al., 2011). Among them, compounds 1, 2, 3, 8 and 10 contain two furan rings as furofurans, indicating that lignans containing furan ring structure have more prominent anti-inflammatory activity. Anti-inflammatory effects are mainly achieved by regulating AMPK, MAPK, NF-κB and JAK-STAT signaling pathways (Figure 3). Compound 1 significantly reduced the phosphorylated protein levels of protein kinase B (Akt) and c-Jun N-terminal kinase (JNK) (Yang et al., 2021). Compound 2 decreased the expression of iNOS and COX-2 in LPS-stimulated RAW 264.7 cells (Chang et al., 2019). Compound 11 attenuated the phosphorylation of MAPK, JNK and NF-κB in CLP rats and LPS-stimulated microglia in a concentration dependent manner, and upregulates Nrf2 and HO-1 (Al-Sayed et al., 2020). Compound 23 inhibitd the NF-κB pathway, thereby reducing the expression of influenza virus-induced pro-inflammatory cytokines IL-6, TNF-α, IL-8, MCP1, IP-10, and IFN-*α* (Li et al., 2015). The anti-inflammatory activity of compound 46 was regulated by the phosphorylation of the Janus kinase (JAK)/signal transductor and the transcription 1/3 activator (STAT1/3) signaling pathway (Gülsüm and Zeliha, 2019).

3.3. Anti-tumor and cytotoxic lignans

3.3.1. Anti-tumor activity

Cancer is a disease seriously endangering people's life and health worldwide, whose mortality rate is the second in all diseases (Zeng et al., 2022). There are four lignans in *Patrinia* showed antitumor activity. compound 1 had anti-ovarian (Ning et al., 2019) and cer-

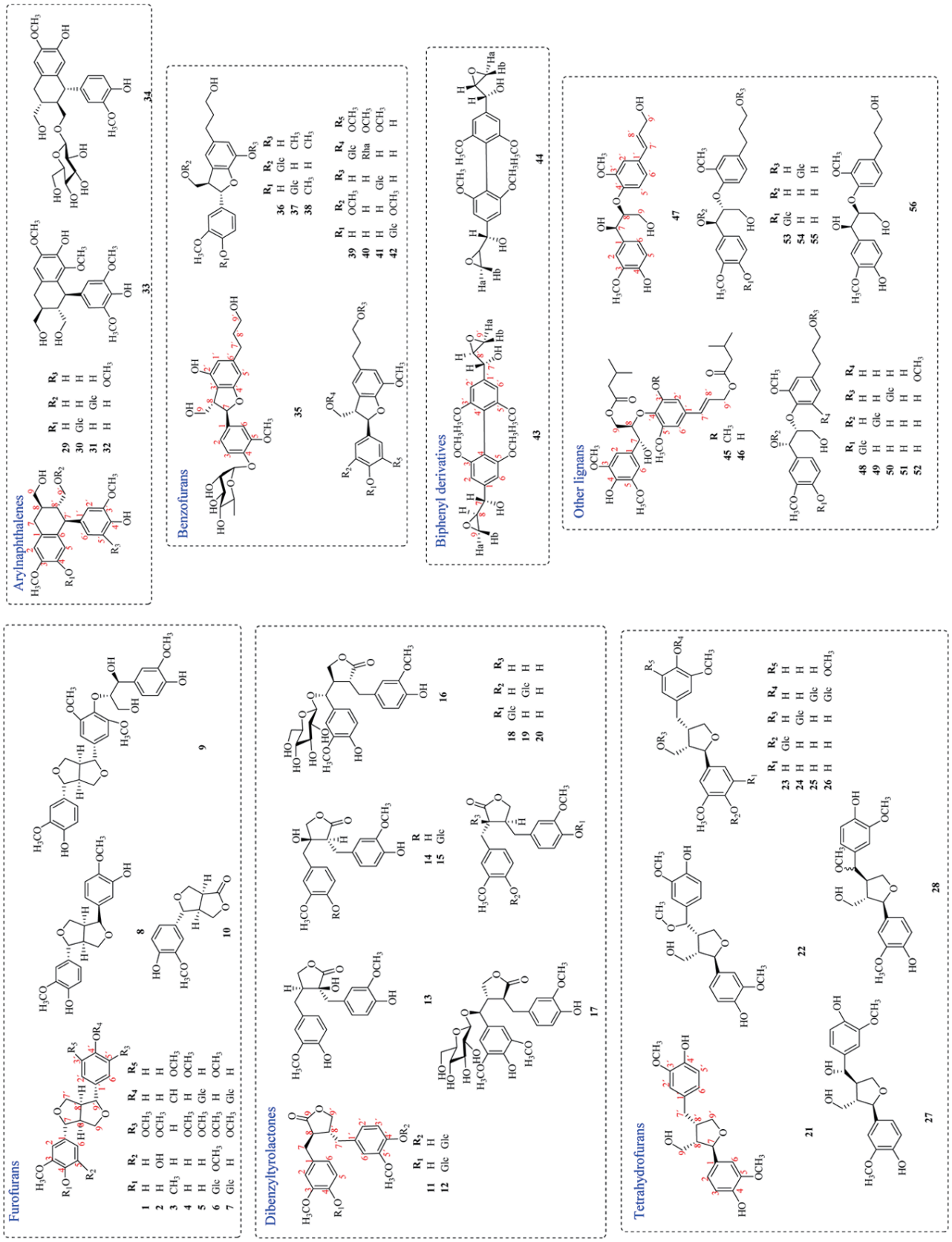

Figure 1. Structure of lignans in *Patrinia*.

Table 1. Lignans and lignans with bioactivity in *Patrinia*

Compound numbers	Name	Acitivity	Source	Ref.
1	Pinoresinol	Cytotoxicity	*P. scabiosaefolia*	(Deveci et al., 2019; Zhang et al., 2020)
		Anti-oxidant		(Deveci et al., 2019)
		Hepatoprotection		(Kim et al., 2019)
		Enzyme inhibitor		(Deveci et al., 2019; Salleh et al., 2019)
		Anti-osteoporosis		(Jiang et al., 2019)
		Anti-malarial		(Hashim et al., 2021)
		Anti-inflammatory		(Yang et al., 2021)
		Anti-AD		(Yu et al., 2019)
		Anti-tumor		(Ning et al., 2019; Zhou et al., 2022)
		Anti-diabetic		(Wikul et al., 2012)
2	Syringaresinol	Cytotoxicity	*P. scabiosaefolia*	(Lee et al., 2016; Ma et al., 2020; Zhang et al., 2020)
		Enzyme inhibitor		(Salleh et al., 2019)
		Anti-Inflammatory		(Chang et al., 2019; Kim et al., 2020)
		Anti-oxidant		(Liu et al., 2021; Ma et al., 2020; Tran Thu et al., 2022)
3	Eudesmin	Cytotoxicity	*P. scabiosaefolia*	(Zhang et al., 2020)
		Lipid-lowering		(Nam et al., 2018)
		Anti-tumor		(Jiang et al., 2017; Yu et al., 2019)
		Anti-biosis		(Yang et al., 2018)
		Anti-inflammatory		(Li et al., 2020)
		Enzyme inhibitor		(Park et al., 2021)
4	Medioresinol	Enzyme inhibitor	*P.scabiosaefolia*	(Salleh et al., 2019; Timalsina et al., 2021; Zhang et al., 2020)
		Anti-complementary		(Hou et al., 2017)
5	(+)-Pinoresinol-4-*O*-*β*-*D*-glucopuranoside	Anti-oxidant Anti-diabetic Hepatoprotection	*P.scabra*	(Di et al., 2013; Youssef et al., 2020)
6	Syringaresinol mono-*β*-D-glucoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
7	Pinoresinol-4,4′-di-*O*-*β*-*D*-glucopyranoside	Anti-oxidant	*P. scabra*	(Dinh Thi Huyen et al., 2022; Li et al., 2005)
		Estrogenic properties		(Wang et al., 2011)

(continued)

Table 1. *(continued)*

Compound numbers	Name	Acitivity	Source	Ref.
8	epipinoresinol	Anti-oxidant	*P. scabiosaefolia*	(Wang et al., 2019; Zhang et al., 2020)
		Anti-inflammatory		(Yu et al., 2019)
9	(7*R*,7′*R*,7″*S*,8*S*,8′*S*,8″*S*)-4,4″-dihydroxy-3′,3,3″,5′-tetramethoxy-7,9′:7′,9-diepoxy-4′,8″-oxy-8,8′-sesquineolignan-7″,9″diol	Anti-oxidant	*P. scabiosaefolia*	(Song et al., 2011; Zhang et al., 2020)
10	Salicifoliol	Anti-inflammatory	*P. scabiosaefolia*	(Yang et al., 2013; Zhang et al., 2020)
11	Matairesinol	Cytotoxicity Anti-inflammatory	*P. villosa*	(Al-Sayed et al., 2020; Huang et al., 2021; Wu et al., 2021)
		Anti-diabetic Hepatoprotection		(Yang and Wang, 2022)
		Anti-tumor		(Lee et al., 2022; Mahajan et al., 2021)
		Anti-oxidant		(Wu et al., 2021)
		Neuroprotection		(Yi et al., 2019)
12	Matairesinol-4,4′-di-*O*-*β*-*D*-glucopyranoside	–	*P. scabra*	(Li et al., 2005)
13	(+)-Nortrachelogenin	Anti-fibrosis	*P. scabiosaefolia*	(Pemmari et al., 2018; Zhang et al., 2020)
		Anti-oxidant		(Tebboub et al., 2018)
14	(−)-Nortrachelogenin	Anti-fungal	*P. scabiosaefolia*	(Lee et al., 2016; Li et al., 2003)
15	Nortracheloside	–	*P. scabra*	(Bai et al., 2017)
16	Patrinian A	Anti-AD Neuroprotection	*P. villosa*	(Liu et al., 2015)
17	Patrinian B	Anti-oxidant Anti-AD Neuroprotection	*P. villosa*	(Liu et al., 2015)
18	Styraxlignolide D	Anti-oxidant	*P. scabra*	(Di et al., 2013; Min et al., 2004)
19	Styraxlignolide E	Anti-oxidant	*P. scabra*	(Di et al., 2013; Min et al., 2004)
20	(2*S*,3*S*)-2*α*-(4″-hydroxy-3″-methoxybenzyl)-3*β*-(4′-hydroxy-3′-methoxybenzyl)-*γ*-butyrolactone	–	*P. scabra*	(Di et al., 2013)
21	Lariciresinol	Anti-tumor	*P. scabra*	(Gu et al., 2002; Ma et al., 2018)
		Plant growth inhibitor		(Nakano et al., 2002)
		Anti-fungal		(Bajpai, Shukla, et al., 2017; Hwang et al., 2011)
		Anti-oxidant		(Bajpai, Alam, et al., 2017)
22	4-[1-Ethoxyl-1-(4-hydroxy-3-methoxy)benzyl]methyl-2-(4-hydroxy-3-methoxy) benzyl-3-hydroxymethyl-tetrahydro-furan	–	*P. scabra*	(Bai et al., 2017)

(continued)

Table 1. *(continued)*

Compound numbers	Name	Acitivity	Source	Ref.
23	Lariciresinol 4-*O*-*β*-*D*-glucopyranoside	Anti-AD Neuroprotection	*P. villosa*	(Liu et al., 2015)
		Anti-inflammatory		(Li et al., 2015; Zou et al., 2021)
24	Lariciresinol 9-*O*-*β*-*D*-glucopyranoside	Anti-AD	*P. villosa*	(Liu et al., 2015)
25	Lariciresinol 4′-*O*-*β*-*D*-glucopyranoside	Anti-AD	*P. villosa*	(Liu et al., 2015)
		Cytotoxicity		(Lee et al., 2016)
26	Tortoside B	Anti-AD	*P. villosa*	(Liu et al., 2015)
27	Tanegool	Neuroprotection	*P. villosa*	(Liu et al., 2015)
		Anti-oxidant		(Lee et al., 2009)
		Enzyme inhibitor		(Ohtsuki et al., 2012)
28	Tanegool-7′-methyl ether	Neuroprotection	*P. villosa*	(Liu et al., 2015)
29	Isolariciresinol	Anti-oxidant	*P. villosa*	(Liu et al., 2015)
		Neuroprotection		(Cheng et al., 2020)
		Anti-inflammatory		(Cho et al., 2001)
		Enzyme inhibitor		(Lunder et al., 2019)
30	(−)-Isolariciresinol 4-*β*-*D*-glucopyranoside	–	*P. scabiosaefolia*	(Zhang et al., 2020)
31	(8*S*,7′*R*,8′*S*)-Isolarisiresinol 9′-*O*-*β*-*D*-glucopyranoside	–	*P. scabiosaefolia*	(Zhang et al., 2020)
32	5-Methoxy isolariciresinol	Anti-oxidants	*P. villosa*	(Bai et al., 2018)
33	lyoniresinol	Anti-oxidant	*P. villosa*	(Bai et al., 2018; Koga et al., 2007)
		Anti-fungal		(Moo-Puc et al., 2014)
34	(8*R*,7′*S*,8′*R*)-Isolarisiresinol 9′-*O*-*β*-*D*-glucopyranoside	Neuroprotection	*P. scabiosaefolia*	(Cheng et al., 2020; Zhang et al., 2020)
35	Patrinianeolignan I	–	*P. scabiosaefolia*	(Zhang et al., 2020)
36	Isodonoside VI	–	*P. scabiosaefolia*	(Zhang et al., 2020)
37	(7*S*,8*R*) Dihydrodehydrodiconiferyl alcohol 4-O-β-D-glucopyranoside	Antio-xidant	*P. villosa*	(He et al., 2014; Zhang et al., 2020)
		Cytoprotection		(Wang et al., 2017)
		Enzyme inhibitor		(Hong et al., 2014; Wu et al., 2012)
38	(7*S*,8*R*)-3′4,9′-Trihydroxy-4-methoxy-9-*O*-shikkyl-acyl-7,8-dihydrobenzofuran-1′-propyl lignan	–	*P. scabiosaefolia*	(Jiang et al., 2017)
39	(7*R*,8*S*)-3,3′,5-Trimethoxy-40,7-epoxy-8,5′-neolignan-4,9,9′-triol-9-*β*-*D*-glucopyranoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)

(continued)

Table 1. *(continued)*

Compound numbers	Name	Acitivity	Source	Ref.
40	Massonianoside D	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
41	(7*R*,8*S*)-Dihydrodehydrodiconiferyl alcohol 4-*O*-*β*-*D*-glucopyranoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
42	(7*R*,8*S*)-glochidioboside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
43	2,6,2′,6′-tetramethoxy-4,4′-bis (1,2-trans-2,3-epoxy-1-hydroxypropyl) biphenyl	–	*P. villosa*	(Xiang et al., 2017)
44	2,6,2′,6′-tetramethoxy-4,4′-bis (2,3-epoxy-1-hydroxypropyl) biphenyl	Anti-inflammatory	*P. villosa*	(Liu et al., 2022; Xiang et al., 2017)
45	Patrineolignan A	Cytotoxic activity	*P. scabra*	(Di et al., 2013; Lee et al., 2020)
46	Patrineolignan B	Cytotoxic activity	*P. scabra*	(Di et al., 2013; Lee et al., 2020)
		Anti-inflammatory	*P. scabiosaefolia*	(Lee et al., 2018; Yan et al., 2016)
47	(7*R*,8*R*)-threo-1-(4-hydroxy-3-methoxyphenyl)-2-{4-[(*E*)-3-hydroxy-1-propenyl]-2-methoxyphenoxy}-1,3-propanediol	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
48	(7*S*,8*R*)-erythro-7,9,9′-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan-4-*O*-*β*-*D*-glucopyranoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
49	(7*S*,8*R*)-erythro-guaiacyl-glycerol-*β*-*O*-4′-dihydroconiferyl ether-7-*O*-*β*-*D*-glucopyranoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
50	(7*S*,8*R*)-erythro-guaiacyl-glycerol-*β*-*O*-4′-dihydroconiferyl ether-9′-*O*-*β*-*D*-glucopyranoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
51	Erythro-(7*S*,8*R*)-Guaiacyl-glycerol-*β*-*O*-4′-dihydroconiferyl ether	–	*P. villosa*	(Xiang et al., 2017)
52	(1*R*,2*S*)-rel-1-(4′-hydroxy-3′-methoxyphenyl)-2-[400-(3-hydroxypropyl)-2″, 6″-dimethoxyphenoxy]-1,3-propanediol	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
53	(7*R*,8*R*)-threo-7,9,9′-trihydroxy-3,3′-dimethoxy-8-*O*-4′-neolignan4-*O*-*β*-*D*-glucopyranoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
54	(7*R*,8*R*)-threo-guaiacyl-glycerol-*β*-O-4′-dihydroconiferyl ether-9′-O-*β*-D-glucopyranoside	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
55	(7*R*,8*R*)-threo-guaiacyl-glycerol-*β*-*O*-4′-dihydroconiferylether	Anti-oxidant	*P. villosa*	(Bai et al., 2018)
56	(7*R*,8*S*)-erythro-guaiacyl-glycerol-*β*-*O*-4′-dihydroconiferyl ether	Anti-oxidant	*P. villosa*	(Bai et al., 2018)

. "AD" stands for Alzheimer's disease; "–" indicates that the activity of the compound is not reported in the reference.

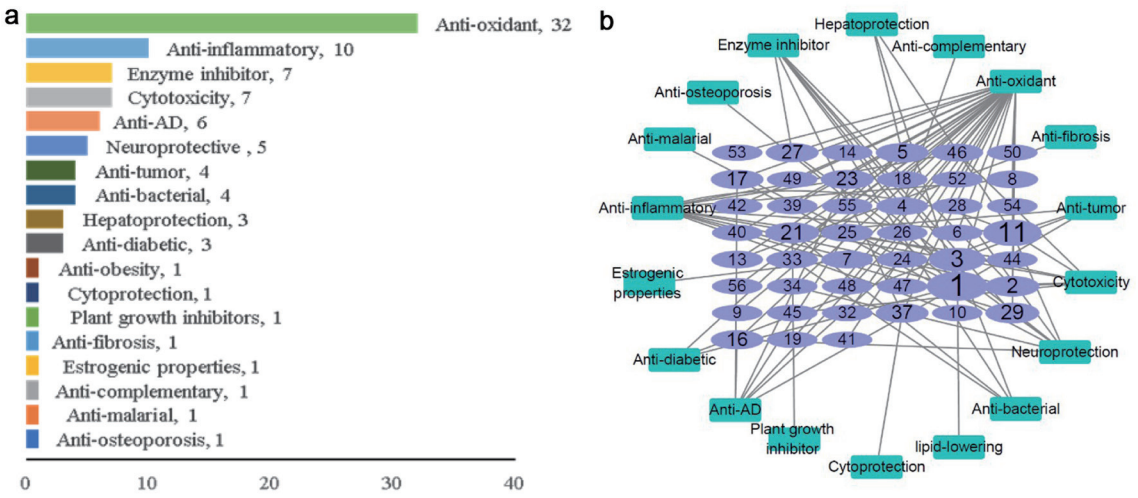

Figure 2. (a) The bioactivity of lignins. (b) The relationship network between lignins and biological activity. (The size of the ellipse represents the amount of biological activity of the compound, the green square box represents the biological activity, and each side line represents the biological activity of the compound).

Table 2. Lignans with antioxidant activity

Compound numbers	Methods	IC_{50}/EC_{50} (μM)	Source	Ref.
1	DPPH, ABTS and CUPRAC assays	9.72 ± 0.14 18.45 ± 0.2 11.15 ± 0.08	*Porodaedalea pini*	(Deveci et al., 2019)
2	DPPH assay DPPH and ABTS assays	17.34 ± 0.44 25.30 ± 2.05, 40.13 ± 2.27	*Portulaca oleracea* L. *Liparis nervosa*	(Ma et al., 2020) (Liu et al., 2021)
5	FRAP and ABTS assays	418.47μmol/g 1091.3μmol/g	*Prunus domestica*	(Youssef et al., 2020)
6	DPPH, ABTS and FRAP assays	9.9 ± 1.02 12.7 ± 1.40 19.94 ± 4.0	*Patrinia villosa* Juss.	(Bai et al., 2018)
7	TBARS assay	61.9 ± 3.9	*Pandanus tonkinensis*	(Dinh Thi Huyen et al., 2022)
8	DPPH assay	18.92 ± 0.06	*Lancea tibetica*	(Wang et al., 2019)
9	ROS in (HBZY-1) cells	–	*Euryale ferox* Seeds	(Song et al., 2011)
11	A model of sepsis *in vitro*	The expression of antioxidant proteins Nrf2 and HO-1 was inhibited	–	(Wu et al., 2021)
13	DPPH assay	38.6 ± 2.7	*Galactites elegans*	(Lee et al., 2016)
16	DPPH, ABTS and FRAP assays	27.5 ± 3.72 0.3 ± 0.04 27.53 ± 8.4	*Patrinia villosa* Juss.	(Liu et al., 2015)
17	DPPH, ABTS and FRAP assays	9.0 ± 1.91 0.6 ± 0.08 34.15 ± 8.8	*Patrinia villosa* Juss.	(Liu et al., 2015)
18	DPPH assay	278	*Styrax japonica*	(Min et al., 2004)

(continued)

Table 2. *(continued)*

Compound numbers	Methods	IC_{50}/EC_{50} (μM)	Source	Ref.
19	DPPH assay	194	*Styrax japonica*	(Min et al., 2004)
21	DPPH assay	–	*Rubia philippinensis*	(Bajpai, Alam, et al., 2017)
27	Irradiated riboflavin/ (EDTA)/(NBT) assay system	13.4 (EC_{50})	*Magnolia fargesii*	(Lee et al., 2009)
29	DPPH, ABTS and FRAP assays	5.6 ± 0.16 0.3 ± 0.06 < 5	*Patrinia villosa* Juss.	(Liu et al., 2015)
32	DPPH, ABTS and FRAP assays	46.1 ± 1.93 5.1 ± 0.30 143.34 ± 2.7	*Patrinia villosa* Juss.	(Bai et al., 2018)
33	DPPH, ABTS and FRAP assays	8.0 ± 0.81 5.5 ± 0.04 57.43 ± 7.1	*Patrinia villosa* Juss.	(Bai et al., 2018)
37	ABTS assay	193.85 mmol/l	*Rosa soulieana*	(Lunder et al., 2019)
39	DPPH, ABTS and FRAP assays	5.3 ± 1.35 0.2 ± 0.03 < 5	*Patrinia villosa* Juss.	(Bai et al., 2018)
40	DPPH, ABTS and FRAP assays	>100 15.1 ± 1.56 18.36 ± 2.6	*Patrinia villosa* Juss.	(Bai et al., 2018)
41	DPPH, ABTS and FRAP assays	>100 9.9 ± 1.02 42.77 ± 2.8	*Patrinia villosa* Juss.	(Bai et al., 2018)
42	DPPH, ABTS and FRAP assays	90.9 ± 2.41 6.3 ± 0.53 78.42 ± 4.5	*Patrinia villosa* Juss.	(Bai et al., 2018)
47	DPPH, ABTS and FRAP assays	15.4 ± 0.77 0.5 ± 0.08 20.95 ± 9.2	*Patrinia villosa* Juss.	(Bai et al., 2018)
48	DPPH, ABTS and FRAP assays	>100 25.1 ± 0.78 16.49 ± 4.2	*Patrinia villosa* Juss.	(Bai et al., 2018)
49	DPPH, ABTS and FRAP assays	>100 23.2 ± 1.42 8.26 ± 3.4	*Patrinia villosa* Juss.	(Bai et al., 2018)
50	DPPH, ABTS and FRAP assays	>100 35.8 ± 0.94 12.86 ± 4.8	*P. villosa*	(Bai et al., 2018)
52	DPPH, ABTS and FRAP assays	70.1 ± 2.45	*Patrinia villosa* Juss.	(Bai et al., 2018)

(continued)

Table 2. *(continued)*

Compound numbers	Methods	IC_{50}/EC_{50} (μM)	Source	Ref.
		26.2 ± 1.48		
		12.86 ± 4.8		
53	DPPH, ABTS and FRAP assays	>100	*Patrinia villosa* Juss.	(Bai et al., 2018)
		15.5 ± 0.08		
		15.28 ± 3.7		
54	DPPH, ABTS and FRAP assays	94.4 ± 2.38	*Patrinia villosa* Juss.	(Bai et al., 2018)
		12.5 ± 0.83		
		42.58 ± 4.9		
55	DPPH, ABTS and FRAP assays	58.3 ± 3.20	*Patrinia villosa* Juss.	(Bai et al., 2018)
		27.4 ± 1.71		
		<5		
56	DPPH, ABTS and FRAP assays	33.7 ± 2.8	*Patrinia villosa* Juss.	(Bai et al., 2018)
		12.7 ± 1.40		
		206.88 ± 6.8		

DPPH (1,1-diphenyl-2-picryl-hydrazyl radical); ABTS (2,2′-Azinobis-(3-ethylbenzthiazoline-6-sulphonate)); FRAP (ferric reducing antioxidant power); EDTA (Ethylenediaminetetraacetic acid); NBT (Nitro blue tetrazolium chloride); ROS (Reactive oxygen species); IC_{50} (Half maximal inhibitory concentration); EC_{50} (Concentration for 50% of maximal effect).

Table 3. Lignans with anti-inflammatory activity

Compound numbers	Methods	IC_{50} (μM)	Source	Ref.
1	TNF-α-induced MH7Acells	6.25 ± 0.42	*Dendropanax dentiger*	(Yang et al., 2021)
	(fMLP/CB)-induced neutrophils	6.81 ± 1.07	*Machilus japonica*	(Li et al., 2020)
	LPS-stimulated production of TNF-α both in neutrophils and monocytes/macrophages	–	*Forsythia*	(Michalak et al., 2018)
2	LPS-induced RAW264.7 cells	26.56 ± 1.28	*Acanthopana sessiliflorus*	(Kim et al., 2020)
	LPS-induced RAW264.7 cells	9.18 ± 1.90	*Neonauclea reticulata*	(Chang et al., 2019)
3	fMLF/CB-induced human neutrophils	8.71 ± 0.74	*Machilus japonica*	(Li et al., 2020)
8	LPS-stimulated production of TNF-α both in neutrophils and monocytes/macrophages	–	*Forsythia*	(Michalak et al., 2018)
10	LPS-induced RAW264.7 cells	311.6 ± 14.1	*Lindera akoensis*	(Yang and Wang, 2022)
11	LPS-stimulated production of TNF-α both in neutrophils and monocytes/macrophages	–	*Forsythia*	(Michalak et al., 2018)
	fMLF/CB-induced human neutrophils	2.7 ± 0.3	*Cupressus macrocarpa*	(Al-Sayed et al., 2020)
23	influenza A virus-induced pro-inflammatory	–	*Isatis indigotica*	(Li et al., 2015)
29	LPS-induced RAW264.7 cells	123.8	*Coptis japonica*	(Cho et al., 2001)
44	LPS-induced RAW264.7 cells	10.62 ± 1.25	*Tripterygium regelii*	(Liu et al., 2022)
46	LPS-induced RAW264.7 cells	22.14	*Patrinia scabra*	(Lee et al., 2018)
	LPS-induced RAW264.7 cells	17.8	*Patrinia scabra*	(Yan et al., 2016)

TNF (Tumor Necrosis Factor); LPS (Lipopolysaccharides); RAW264.7 (Mouse Mononuclear Macrophages Cells).

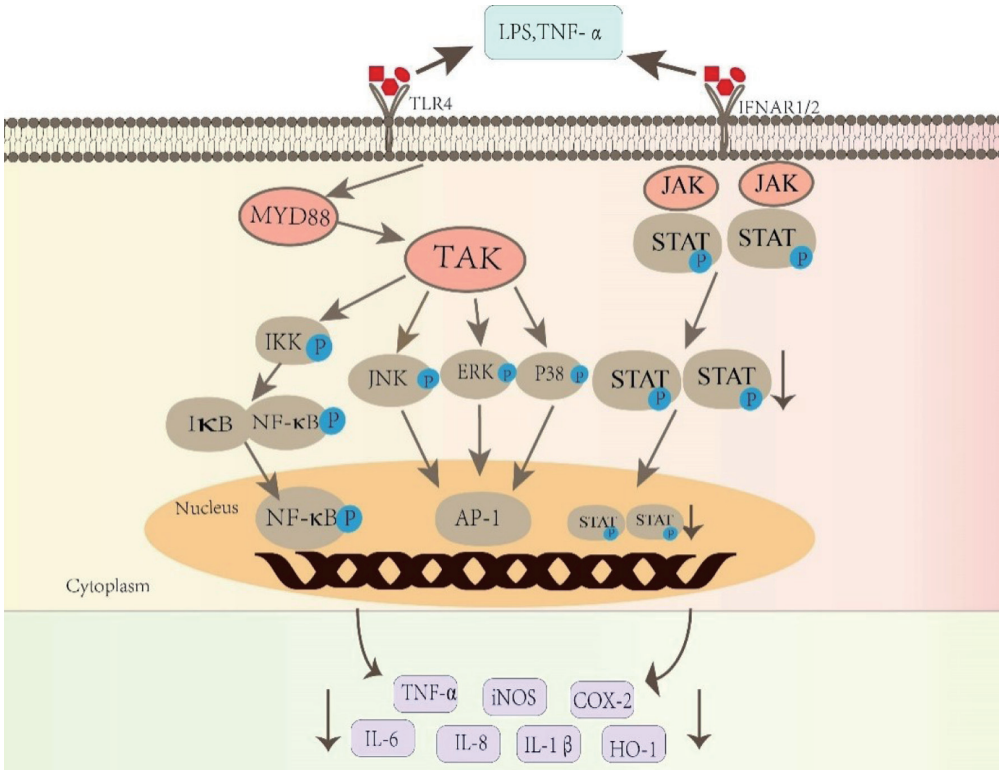

Figure 3. Anti-inflammatory pathways of active ingredients in *Patrinia*. IL-6 (Interleukin-6); IL-8 (Interleukin-8); TNF-α (Tumor Necrosis Factor-α); IL-1β (Interleukin-1beta); NF-κB (nuclear factor kappa-B); COX-2 (Cyclooxygenase-2); iNOS (Inducible nitric oxide sythase); HO-1 (Heme oxygenase 1); ERK (Extracellular regulated protein kinases); JNK (c-Jun N-terminal kinase); STAT Signal transducer and activator of transcription);MyD88 (Myeloid differentiation primary response protein 88); TAK (Transforming growth factor β-activated kinase); IκB (Inhibitor of NF-κB); IKK (Inhibitor of kappa B kinase); JAK (Janus kinase).

vical tumor (Zhou et al., 2022), Compound 3 had anti-nasopharyngeal (Yu et al., 2019) and lung tumor (Jiang et al., 2017), compound 11 inhibited the proliferation of pancreatic tumor cell lines (Lee et al., 2022), significantly reduced the activity of breast tumor and prostate tumor cell lines (Mahajan et al., 2021), and compound 21 had anti-human liver tumor activity (Lee et al., 2016).

Anticancer activity is mainly mediated by the regulation of Raf/MEK/ERK, Akt/JNK and AKT signaling pathways (Figure 4). Compound 1 inhibited phosphoric acid (p)-MEK and (p)-ERK expression in a concentration-dependent manner (Ning et al., 2019). Compound 3 significantly reduced EZH2 expression by inhibiting Akt signaling (Yu et al., 2019). Compound 3 induces apoptosis through the Akt/ JNK signaling pathway (Jiang et al., 2017). Compound 11 inhibited the expression of invasion genes through the MAPK and AKT signaling pathways and weakens the migration ability of cancer cells (Yang and Wang, 2022). Compound 21 induced apoptosis by inhibiting cell proliferation, possibly by activating the mitochondria-mediated apoptosis pathway (Ma et al., 2018).

3.3.2. Cytotoxic lignans

Seven lignans isolated and identified from *Patrinia* were cytotoxic to 28 different cancer cell lines, with IC_{50} values ranging from 1.8 to greater than 100 μM (Table 4). Compound 1 showed cytotoxicity against human breast cancer cell line (MCF-7) (Deveci et al., 2019), compound 2 showed cytotoxicity against human non-small cell lung cancer cell lines (A549) (Ma et al., 2020), compound 3 showed cytotoxicity against human colon cancer cell line (HCT-116) (Zhang et al., 2020). Compound 11 showed cytotoxicity against human hepatocellular carcinoma cell line (HepG2) (Al-Sayed et al., 2020), and compounds 1, 2, 11, 25 showed cytotoxicity against human skin melanoma cells (SK-MEL-2) (Lee et al., 2016). Compound 45, 46 showed cytotoxicity against human cervical cancer cells (HeLa) and human gastric cancer cells (MNK-45) (Di et al., 2013) (Table 4).

3.4. Other active lignans

In addition to the above activities, the lignans in *Patrinia* have enzyme inhibition, anti-AD, neuroprotection, antibacterial, Hepatoprotection, hypoglycemic, anti-osteoporosis, anti-malaria, lipid-lowering, anti-complementary, estrogen, anti-fibrosis, plant growth inhibition, and cytoprotection.

3.4.1. Lignans of enzyme inhibition

Seven lignans from *Patrinia* show enzyme inhibitory activity. Compound 1 has anticholinesterase activity (Deveci et al., 2019), compound 1, 2, 4 has the inhibitory activity of lipoxygenase (LOX) (Salleh et al., 2019), compound 3 inhibits the activities of glucuronic transferase 1A1 and 1A3 in human liver microsomes (Park et al., 2021), compound 4 has the inhibitory activity of α-amylase (Timalsina et al., 2021). Compound 27 inhibits glycogen synthase kinase-3β (Ohtsuki et al., 2012), compound 29 inhibits dipeptide peptidase 4 (Lunder et al., 2019), and compound 37 inhibits tyrosinase (Hong et al., 2014). (Table 5)

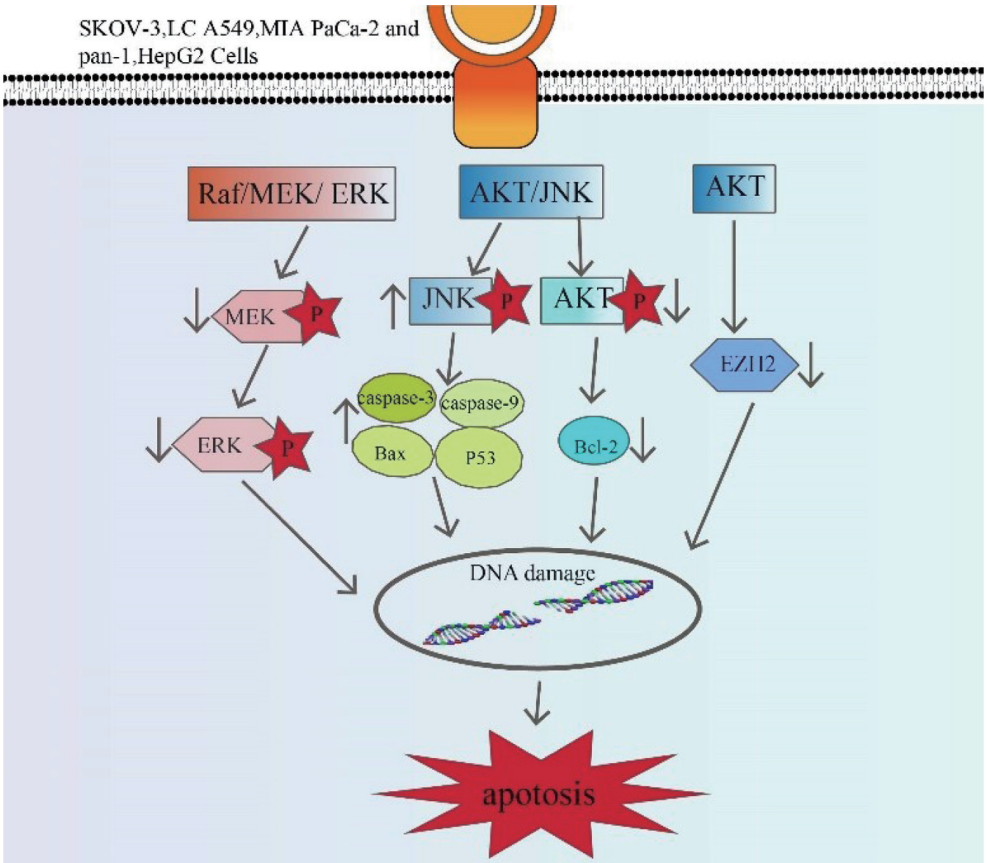

Figure 4. Anticancer pathways of active ingredients in *Patrinia*. MEK (Mitogen-activated extracellular signal-regulated kinase); BAX (BCL2-Associated X); BCL2 (B-cell lymphoma-2); EZH2 (Enhancer of zeste homolog).

Table 4. Lignans with cytotoxic activity

Compound numbers	Cancer cell line	IC_{50} (μM)	Source	Ref.
1	MCF-7	21.08 ± 1.01μg/ml	*Porodaedalea pini*	(Deveci et al., 2019)
	SK-MEL-2	37.96	*Euonymus alatus*	(Lee et al., 2016)
2	A549	>100	*Eleutherococcus sessiliflorus*	(Ma et al., 2020)
	SK-MEL-2	23.24	*Euonymus alatus*	(Lee et al., 2016)
3	HCT-116	41.92	*Patrinia scabiosaefolia*	(Zhang et al., 2020)
11	HepG2	15.1 μg/ ml	*Cupressus macrocarpa*	(Al-Sayed et al., 2020)
23	SK-MEL-2	42.86	*Euonymus alatus*	(Lee et al., 2016)
45	HeLa MNK-45	1.8, 2.3	*Patrinia scabra*	(Di et al., 2013)
	H460, Hela, SKM-1, NB4, Z-138, GIST-T1	–	*Patrinia scabiosaefolia*	(Jiang et al., 2017)
46	HeLa MNK-45	2.7, 3.1	*Patrinia scabra*	(Di et al., 2013)
	H460, H1975, H23, T24, Hela, A431, Du145, HCT116, SKM-1, MOLM-14, PF382, HEL, TMD8, JVM-2, Namalwa, Z-138, U-2 OS, GIST-T1	–	*Patrinia scabiosaefolia*	(Jiang et al., 2017)

MCF-7 (Michigan Cancer Foundation-7); SK-MEL-2 (Human skin melanoma cells); A549/ H1975 (Human lung cancer cells); HCT-116 (Human colorectal adenocarcinoma cells); HepG2 (Human hepatocellular carcinoma cells); HeLa (Human cervical carcinoma cell line); MNK-45 (Human gastric cancer cells); H460 (Human large-cell lung cancer cells); SKM-1 (Human acute myeloid leukemia cells); NB4 (Human acute promyelocytic leukemia cells); Z-138 (mature B-cell acute lymphoblastic leukemia cell line); GIST-T1 (Human gastrointestinal stromal tumor cell line); H23 (Human non-small-cell lung cancer (NSCLC) cell line); T24 (Human urinary bladder cancer cells); A431 (human epidermoid carcinoma cell line); Du145 (human prostate cancer cell); MOLM-14 (Myeloid leukemia cells); PF382 (human malignant T lymphoblast); HEL (Human Erythroleukemia Cell Line); TMD8/ JVM-2 (Diffuse large B-cell lymphoma cell line); Namalwa (Human Burkitt's lymphoma cells); U-2 OS (Human osteosarcoma cell line).

Table 5. Lignans with other activity

Activities	Compound numberss	Methods	IC_{50} (μM)	Source	Ref.
Enzyme inhibition	1	Anti-cholinesterase	AChE (13.73 ± 0.85%)	*Porodaedalea pini*	(Deveci et al., 2019)
			BChE (80.02 ± 0.73%)		
		lipoxygenase inhibitory	15.2,	*Piper stylosum*	(Salleh et al., 2019)
	2	lipoxygenase inhibitory	24.0	*Piper stylosum*	(Salleh et al., 2019)
	3	InhibitUDP-Glucuronosyltransferase 1A1 and 1A3	24.3, 26.6	*Magnoliae*	(Park et al., 2021)
	4	lipoxygenase inhibitory	18.5	*Piper stylosum*	(Salleh et al., 2019)
		α-Amylase Inhibitory	–	*Catunaregam spinosa*	(Timalsina et al., 2021)
	27	Glycogen Synthase Kinase-3β	1	*Taxus yunnanensis*	(Ohtsuki et al., 2012)
	29	Dipeptid peptidase 4	49.2 ± 7.0% (inhibition rate)	*Abies alba*	(Lunder et al., 2019)
	37	tyrosinase inhibitory	15.92 ± 0.70	*Castanea henryi*	(Wu et al., 2012)
		The inhibitory on the release of β-hexosaminidase from RBL-2H3 cells	52.3 ± 0.9	*Pinus thunbergii*	(Hong et al., 2014)
	1	ameliorated memory impairment in dementia model induced by cholinergic blockade	25 mg/kg	–	(Yu et al., 2019)
	16	Inhibition of self-induced Aβ aggregation	57.57–65.53% (inhibition range)	*Patrinina villosa*	(Liu et al., 2015)
	17				
	23				
	24				
	26				
Neuroprotective lignans	11	preventing LOHP-induced peripheral neuropathy	–	*Forsythia*	(Yi et al., 2019)
	16	Neuroprotection	50–100% (viability of cells)	*Patrinina villosa*	(Liu et al., 2015)
	23				
	27				
	28				
	29	the neuroprotective activity against the injury of HT-22 cells induced by L-Glutamate *in vitro*	–	*Selaginella picta*	(Cheng et al., 2020)

(continued)

Table 5. *(continued)*

Activities	Compound numberss	Methods	IC_{50} (μM)	Source	Ref.
Anti-bacterial	3	inhibited the growth of *H. pylori*	–	–	(Yang et al., 2018)
	14	Anti-*Candida albicans*	25 μg/ml (MIC)	*Partrinia scabiosaefolia*	(Li et al., 2003)
		Anti-*Escherichia coli* O157	–	–	(Lee et al., 2016)
	21	Anti-pathogens *Staphylococcus aureus* KCTC1621 and *Escherichia coli* O157:H7.	125~250 μg/ml (MIC)	*Rubia philippinensis*	(Hwang et al., 2011)
		Anti-*Candida albicans* Anti-*Trichosporon beigelii* Anti-*Malassezia furfur*	25, 12.5, 25 μg/ml (MIC)	*Sambucus williamsii*	(Bajpai, Shukla, et al., 2017)
	33	Anti-trichomoniasis vaginalis	17.57	*Maytenus phyllanthoides*	(Moo-Puc et al., 2014)
Hepatoprotection	1	Improve nonalcoholic fatty liver disease	–	*Lysimachia vulgaris*	(Kim et al., 2019)
	5	Improve the hepatotoxicity model induced by CCl_4	50 mg/kg	*Prunus domestica*	(Timalsina et al., 2021)
	11	Prevent hepatocyte apoptosis		–	(Yang and Wang, 2022)
Anti-diabetic	5	Inhibition of α-glucosidase	48.13 μg/ml	*Prunus domestica*	(Timalsina et al., 2021)
	11	Inhibition of DPPH-4	–	–	(Yang and Wang, 2022)
lipid-lowering	3	impairs adipogenic differentiation	–	–	(Nam et al., 2018)
Anti-osteoporosis	1	promotes MC3T3-E1 cell proliferation and differentiation	–	–	(Jiang et al., 2019)
Anti-malarial	1	Anti-malarial	24.2	*Morinda morindoides*	(Hashim et al., 2021)
Anti-complementary	4	complement inhibitors	0.07–0.82 mM	*Anchusa italica*	(Hou et al., 2017)
Estrogenic properties	7	Estrogenic properties	–	*Eucommia ulmoides*	(Wang et al., 2011)
Anti-fibrosis	13	Attenuating on Bleomycin-Induced Dermal Fibrosis	–	*Pinus sylvestris*	(Pemmari et al., 2018)
plant growth inhibitors	21	plant growth inhibitors	–	*Prosopis juliflora*	(Nakano et al., 2002)
Cytoprotection	37	reduce acetaminophen-induced HepG2 cell injury	30.5~46.0% (inhibition rate)	*Litsea cubeba*	(Wang et al., 2017)

AChE (Acetylcholinesterase); BChE (Butyrylcholinesterase); MIC (Minimum Inhibitory Concentration); RBL-2H3 (Rat basophil leukemia cell line); HT-22 (Mouse hippocampal neurons cell); CCL_4 (Carbon tetrachloride); MC3T3-E1 (Mouse embryonic osteoblast precursor cells).

3.4.2. Anti-AD lignans

The deposition of amyloid-beta (Ab) peptide in neuronal cells is a defining feature of the diagnosis of Alzheimer's disease (Lee et al., 2022). Compound 1 could improve memory impairment in cholinergic block-induced dementia models (Yu et al., 2019), and compounds 16, 17, 23, 24 and 26 could inhibit deposition of amyloid-beta (Ab) peptide in neuronal cells (Liu et al., 2015). (Table 5)

3.4.3. Neuroprotective lignans

Six lignans from *Patrinia* showed neuroprotective activity. Compound 11 had a protective effect against oxaliplatin (LOHP)-induced neurotoxicity (Yi et al., 2019), compound 16, 23, 27, 28 had neuroprotective activity (Lee et al., 2018), and compound 29 had neuroprotective activity against L-glutamate-induced HT22 cell damage (Cheng et al., 2020). (Table 5)

3.4.4. Anti-fungal lignans

Four lignans from *Patrinia* showed antibacterial activity. Compound 3 had an inhibitory effect on the growth of *Helicobacter pylori* (Yang et al., 2018). Compound 14 was resistant to *Candida albicans* (Li et al., 2003) and had antibacterial effects on *Escherichia coli* by destroying and disturbing the cytoplasmic membrane (Heejeong Lee et al., 2016). Compound 21 had antibacterial activity against *Staphylococcus aureus* and *E. coli* (Hwang et al., 2011) and could damage the fungal plasma membrane against *Candida albicans*, *Trichosporon beigelii* and *Malassezia furfu*r (Bajpai, Shukla, et al., 2017). Compound 33 had anti-trichomoniasis vaginalis activity (Moo-Puc et al., 2014).

In addition, Compounds 1 and 5 had liver protective activities (Kim et al., 2019; Youssef et al., 2020)to relieve liver fibrosis (Badr et al., 2019). Compounds 5 and 11 had hypoglycemic activities (Youssef et al., 2020; Yang and Wang, 2022), compound 1 also had anti-osteoporosis (Jiang et al., 2019) and antimalarial activities (Hashim et al., 2021). Compound 3 blocked adipogenesis by inhibiting S6K1 signaling pathway (Nam et al., 2018). Compound 4 had Anti-complementary activity (Hou et al., 2017), compound 7 could activate the transcription of estrogen response reporter gene and induce the expression of estrogen response gene (pS2) mRNA (Wang et al., 2011). Compound 13 could improve bleomycin-induced fibrosis (Pemmari et al., 2018). Compound 21 had the activity of inhibiting plant growth (Nakano et al., 2002), and compound 37 had a protective effect on HepG2 cell damage induced by acetaminophen (Wang et al., 2017) (Table 5).

4. Conclusion and prospects

Lignans are widely distributed in natural plants (flaxseed, sesame, *Schisandra chinensis*, *Magnolia officinalis* and *forsythias*), and their edible and medicinal values are also being continuously developed. Literature studies have shown that lignans play important roles in imparting the biological activities to plants of *Patrinia* (Bai et al., 2018; Liu et al., 2023a). It is evident from the discussed literature that lignans in *Patrinia* have abundant biological activities, mainly showing antioxidant, anti-inflammatory, anti-tumor, anti-Alzheimer's disease and neuroprotective activities, *etc.* The anti-inflammatory and anti-tumor mechanisms showed the characteristics of multi-pathway and multi-target. Among them, antioxidant is the main biological activity of the lignans. In addition, the research on the chemical constituents of the *Patrinia* was mainly focused on *P. s cabiosifolia*, *P. villosa*, and *P. scabra*. It is hoped that researchers should use new science and technology to quickly explore the active ingredients and action mechanism of *Patrinia* plants (Liu et al., 2023), which will be conducive to better exploitation and utilization of *Patrinia* resources.

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