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A review on the genus *Koelreuteria*: Traditional uses, Phytochemistry and Pharmacological activities

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Abstract

Koelreuteria plants have been used as a Chinese and Taiwanese folk medicine for the treatment of hepatitis, enteritis, cough, pharyngitis, allergy, hypertension, hyperlipidemia, diarrhea, malaria, urethritis and eye related diseases. The plants are distributed in Taiwan, Fiji, Northern China, Korea and Japan. The present study focused on the phytochemistry and pharmacological activities of the genus *Koelreuteria* to explore active constituents, therapeutic activities, and outlook for research. Extracts and essential oils of the genus *Koelreuteria* showed variety of bioactive metabolites including phenolic acids, flavonoids, lignans, steroids, terpenoids, etc. Scientific studies on extracts and essential oils demonstrated a range of pharmacological actions, as anticancer, antioxidant, antibacterial, antifungal, anti-hyperlipidemia, hepatoprotective and anti-Alzheimer's disease. Some indications have been verified through pharmacological activities, such as protein tyrosine kinase (PTK), topoisomerase 1, dihydrodiol dehydrogenase (DDH) protein expression, xanthine oxidase (XOD), tyrosinase, lipoxygenase and human low-density lipoprotein (LDL) inhibitory activities and induction of heme oxygenase-1 (HO-1) by this genus. The accessible literature revealed that, most of the genus activities could be attributed to the active flavonoids, lignans, terpenoids and essential oil. However, to confirm their pharmacological activities against human cancer cell lines and microbial diseases, more investigations are necessary to evaluate the molecular mechanisms of the identified active compounds. More evaluations and clinical trials should be carried out that might be incorporated into medicinal practices.

Key words: *Koelreuteria*, Ethnomedical use, Phytoconstituents, Pharmacological activity, Bioactive compounds.

1. Introduction

About 1900 species make up family Sapindaceae (Soapberry family) and are mainly found in the tropical regions; only few genera are found exclusively in temperate zones **[1]**. This family members are significant suppliers of medicines, oils, and nuts. Many species can be used as a soap alternative because they have saponins in their fruits, seeds, and other tissues. Many other members are cultivated for their edible fruits **[2]**. The genus *Koelreuteria* belongs to Sapindaceae or Soapberry family. The genus comprises three species of trees, including *K. elegans* (Seem.) A.C. Sm. (*K. formosana* Hayata or *K. henryi* Dumm.), *K. paniculata* Laxm. and *K. bipinnata* Franch. **[3]** (Fig. 1). For many years, the *Koelreuteria* genus members have been used as traditional medicines in various nations to cure a wide range of ailments and diseases **[4]**. They are regarded as well-known decorative tree species that are employed in landscape design **[5]**. Certain substances obtained from the genus *Koelreuteria* have been shown to have insecticidal **[6]** and anti-inflammatory effects for gout **[7]**. Moreover, leaves of some species are used as yellow and black hair dyes [8, 9]. Numerous researchers have investigated the chemical constituents and pharmacological characteristics of *K. elegans* and *K. paniculata*, while there are no available reports concerning the chemical or biological properties of the *bipinnata* species. Therefore, this review outlines traditional uses, phytochemical and pharmacological properties of these two species. Over 400 compounds have been found as a consequence of the phytochemical investigations, including, phenolic acids, flavonoids, lignans, terpenoids, fatty acids, sterols, vitamins, carotenoids, etc. **[5, 8-32]** and the most abundant active metabolites were kaempferol, quercetin (and their glycosides), galloyl derivatives, saponins (a, b and c), pyrogallol, paniculatonoid (a and b), austrobailignan-1, eicosenoic, oleic, linoleic and palmitic acids. Furthermore, a plenty of studies has been done on the pharmacological properties of the genus *Koelreuteria* such as anticancer, antioxidant, antibacterial, antifungal, anti-hyperlipidemia, hepatoprotective, anti-apoptotic and anti-Alzheimer's disease. Although many metabolites from the genus *Koelreuteria* have been discovered, a small number have undergone bioactivity assays. Those gaps present an excellent research opportunity to learn more about the pharmacology and

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phytochemistry of the genus *Koelreuteria*. This may open the possibility of discovering new medication sources for future uses. The goal of the current work was to assemble an up-to-date and comprehensive analysis of the genus *Koelreuteria* that covers traditional uses, phytochemistry, and pharmacology based on information obtained from previous related literature, that would offer the proof needed for future studies on the genus *Koelreuteria* or its active components in pharmacological and clinical applications.

2. Materials and methods

Data on studies of the genus *Koelreuteria* was collected via the Internet (using Google Scholar, Elsevier, PubMed, PubChem, LIPID MAPS, Web of Science, and others) and libraries. The presented data emphasizes bioactive compounds, and pharmacological activities of the genus *Koelreuteria*.

3. Traditional uses

Genus *Koelreuteria* has an extended record as traditional medicines for cure of several conditions (**Error! Reference source not found.**). Although the plants are distributed in many regions such as Taiwan, Fiji, Northern China, Korea and Japan, the available published articles showed that Chinese and Taiwanese people used different parts of the plant for treatment of various conditions. In traditional medicine, roots, bark, twigs, and leaves of *K. elegans* were used in the case of gastrointestinal disorders, such as diarrhea, enteritis, hepatitis, promotion of liver functions and malaria **[5, 29, 33, 34]**. *K. elegans* has been used to treat some cardiovascular diseases, like hypertension and hyperlipidemia **[29].** It was also useful for respiratory cases including pharyngitis and cough **[29]**. *K. elegans* roots and aerial parts were employed in the treatment of allergy and some urinary tract inflammations such as urethritis **[5, 29, 33, 34]**. They were also reported to have anti-cancer and anti-proliferation activity **[29, 35]**. *K. paniculata* was an important source for yellow and black dyes and was apparently used for eye ailments **[8]**. Taiwanese and Chinese people used the seeds of *K. elegans* and *K. paniculata* as insecticides and the leaves as anti-fungal and anti-bacterial **[21, 35]**. Additionally, the leaves of *K. elegans* were used as a black hair dye **[5, 9]**.

4. Phytoconstituents

The secondary metabolites produced by different species of the genus *Koelreuteria* were subjected to numerous studies that almost focused on the aerial parts of the genus. Phytochemical screening of the essential oils and extracts of the genus revealed the richness of those species in flavonoids, phenolic acids and terpenoids. All the resulting compounds are listed in Table 2. Chemical structures of main compounds that were isolated and identified from the genus are documented (Fig. 2-Fig. 5).

4.1. Flavonoids

Flavonoids, a vital group of natural products, possess notable biological activities; remarkably, that they are polyphenolic plant secondary metabolites **[36]**. Genus *Koelreuteria* is rich in flavonoids, which are mainly kaempferol and quercetin, beside their glycosides and derivatives. Flavonoids in the genus *Koelreuteria* are predominantly distributed in the leaves, flowers and seeds. About 32 flavonoids (**1**-**32**) have been isolated from the genus, and their chemical structures are displayed in Fig 2. Kaempferol aglycone (**1**) was isolated from the ethyl acetate (EtOAc) fraction of ethanol extract of *K. elegans* leaves and twigs **[10]**, as well as the leaves and flowers of *K. paniculata* **[8, 25]**. Kaempferol attached to rhamnose sugar was identified in the genus. Leaves of *K. elegans* afforded kaempferol-3-O-rhamnoside (afzelin, **2**) **[10]**, in addition the leaves and aerial parts of *K. paniculata* **[8, 21, 30]**. Both kaempferol-3-O-rhamnoside and kaempferol-7-O-rhamnoside (**7**) were separated by Mostafa *et al.* **[23, 24]** from the aerial parts of *K. paniculata*.

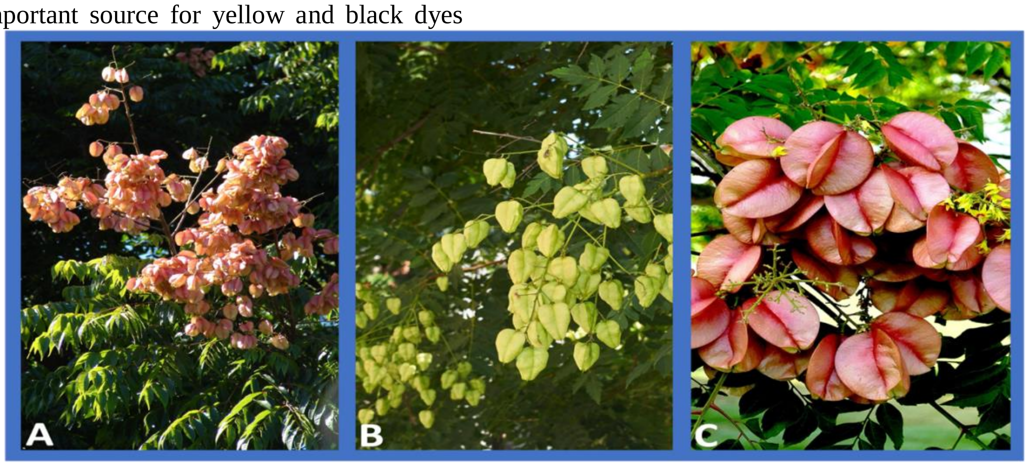

Fig. 1. Branches and fruits of: A, *Koelreuteria elegans* (reproduced from Sown); B, *Koelreuteria paniculata* (reproduced from Seedsandall); C, *Koelreuteria bipinnata* (reproduced from Wikipedia).

Table 1: Traditional uses of the genus *Koelreuteria*.

System/activity	Part used	Traditional use	Country	Reference
Koelreuteria elegans				
Gastrointestinal	Roots, bark, twigs, and leaves	Diarrhea and malaria	Taiwan	**[5, 33]**
	The plant	Enteritis and hepatitis	Taiwan	**[29]**
	Roots, bark, twigs, and leaves	Promotion of liver functions and malaria	Taiwan	**[34]**
Cardiovascular	The plant	Hypertension and hyperlipidemia	Taiwan	**[29]**
Respiratory	The plant	Pharyngitis and Cough	Taiwan	**[29]**
Urinary	Roots, bark, twigs, and leaves	Urethritis	Taiwan	**[5, 33, 34]**
Immunity	The plant	Allergy	Taiwan	**[29]**
Neoplasm	The plant	Cancer	Taiwan	**[29]**
	The plant	Anti-proliferation	Taiwan	**[35]**
Insecticidal	Seeds	Insecticides	Taiwan	**[35]**
Antimicrobial	Leaves	Anti-fungal and anti-bacterial	Taiwan	**[35]**
Hair dye	Leaves	Black hair dye	Taiwan	**[5, 9]**
Koelreuteria paniculata				
Insecticidal	Seeds	Insecticides	Northern China	**[21]**
Antimicrobial	Leaves	Anti-fungal and anti-bacterial	Northern China	**[21]**
Occular	The plant	Eye aliments	China	**[8]**
Hair dye	The plant	Yellow and black hair dye	China	**[8]**

Table 2: Chemical compounds isolated and identified from the genus *Koelreuteria*.

Part used	Extracts	Compound groups	Compounds	Ref.
			K. elegans	
Leaves, twigs	Ethanol extract	Flavonoids	Kaempferol, quercetin, kaempferol-3-O-*α*-rhamnoside, kaempferol-3-O-*α*-arabinoside	**[10]**
Leaves	Ethanol extract	Lignans	Austrobailignan-1, austrobailignan-2, furo[3’,4’:6,7]naphtha[2,3-d]-1,3-dioxol-6(8H)-one,5-(7-methoxy-1,3-bemodioxol-5-yl) named as koelreuterin-1	**[26]**
Leaves	Acetone extract	Flavonoids	Kaempferol-3-O-*β*-D-glucopyranoside, kaempferol-3-O-*α*-L-arabinopyranoside, quercetin-3-O-*α*-L-arabinopyranoside, quercetin-3-O-*β*-D-glucopyranoside, quercetin-3-O-*β*-D-galactopyranoside, apigenin-4’-O-*β*-D-glucopyranoside, kaempferol-3-O-(2’’,3’’-di-O-galloyl)-*α*-L-rhamnopyranoside	**[18]**
		Lignans	Austrobailignan-1, austrobailignan-2, (+)-sesamin, hinokinin 7-O-*β*-D-glucopyranoside	
		Chlorophyll derivatives	Pheophorbide a, pheophorbide b, methyl pheophorbide a, methyl pheophorbide b	
		Sterols	*β*-Sitosterol, *β*-stigmasterol	
		Tocopherols	*α*-tocopherol, *α*-tocopheryl quinone	
		Phenolic acids	Methyl gallate	
Leaves	Acetone extract	Phenolic acids	1,3,4,5-Tetra-O-galloylquinic acid	**[14]**
Leaves	Ethanol extract	Flavonoids	Kaempferol-3-O-*α*-arabinoside, astragalin, apigenin-4’-O-*β*-D-glucopyranoside	**[15]**
		Lignans	Austrobailignan-1	
Branches, leaves	Aqueous ethanol extract	Phenolic acids	Gallic acid, caffeic acid	**[20]**
Leaves	Ethanol extract	Lignans	Austrobailignan-1	**[29]**
Leaves, twigs	Aqueous methanol extract	Phenolic acids	1, 3, 4, 5-Tetra-O-galloylquinic acid butyl ester, methyl gallate, 6-O-[galloyl 4-methyl ether]-(*α*/*β*)-D-glucopyranose, 3, 5-di-O-galloylquinic acid butyl ester, 3,4,5-tri-O-galloylquinic acid butyl ester, 3-O-galloyl quinic acid butyl ester, 4-O-galloyl quinic acid butyl ester, gallic acid	**[9]**
		Lignans	Austrobailignan-1	
		Sterols	*β*-Sitosterol	
Leaves, twigs	Aqueous methanol extract	Flavonoids	3''-Galloyl quercetrin, quercetin, isorhamnetin-3-O-*β*-D-$^{4}C_{1}$-arabinopyranoside, isorhamnetin-3-O-*α*-L-$^{1}C_{4}$-rhamnopyranoside, quercetrin, guaijaverin, azaleatin	**[5]**
		Phenolic acids	Methyl gallate, 1, 3, 4, 5-tetra-O-galloylquinic acid butyl ester, 1,3,4,5-tetra-O-galloylquinic acid, gallic acid	
		Triterpenes	Oleanolic acid, oleanolic acid-3-O-*β*-D-$^{4}C_{1}$- glucopyranoside, 3-O-[O-*α*-L-rhamnopyranosyl-(1-2)-O-*β*-D-glucopyranosyl-(1-2)- *β*-D-$^{4}C_{1}$-glucopyranosyl] oleanolic acid	

Table 2 Continued.

Part used	Extracts	Compound groups	Compounds	Ref.
		K. paniculata		
Seeds	Glyceride oil	Fatty acids	Palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid, arachidic acid, eicosenoic acid	**[37]**
Fruits	Aqueous methanol extract	Triterpenes	O-α-arabopyranosyl-(1→3)hederagenin named as koelreuteria saponin A, O-α-rhamnopyranosyl-(1→3)-O-α-arabinopyranosyl-(1→4) and O-β-galactopyranosyl-(1→3)-β-glucuronopyranosyl(1→3)-gypsogenin named as koelreuteria saponin B	**[16]**
Leaves	Ethanol extract	Flavonoids	Kaempferol-3-O-α-rhamnoside, quercitrin-2"-gallate, quercitrin, hyperin, hyperin-2"-gallate	**[30]**
		Phenolic acids	p-Digalloyl acid, m-digalloyl acid, galloyl acid, ethyl galloyl acid, ellagic acid, Ethyl-p-digallate, ethyl-m-digallate	
		Sterols	β-Sitosterol, β-sitosterol-β-D-glucoside	
Seeds	Ethanol extract	Flavonoids	Paniculatonoid A, paniculatonoid B	**[31]**
Seeds	Aqueous ethanol extract	Triterpenes	O-α-rhamnopyranosyl-(1→3)-O-α-arabinopyranosyl-(1→4) and O-β-galactopyranosyl-(1→3)-β-glucuronopyranosyl(1→3)-gypsogenin named as koelreuteria saponin B	**[27]**
Leaves	Aqueous ethanol extract	Flavonoids	6,8-dihydroxy-afzelin, afzelin-3"-O-gallate, afzelin, quercetin, kaempferol	**[8]**
		Phenolic acids	Gallic acid, ferulic acid, ellagic acid, 3,5-di-O-galloyl-quinic acid, ,3,4,5-tri-O-galloyl-quinic acid, methyl gallate	
Leaves	Ethanol extract	Flavonoids	Kaempferol-3-O-α-L-rhamnoside, kaempferol-3-O-arabinopyranoside, quercetin-3'-O-β-D-arabinopyranoside, 3"-galloyl quercitrin, isorhamnetin, quercitrin, galloylepicatechin, catechin, hyperin	**[21]**
		Phenolic acids	p-digalloyl acid, m-digalloyl acid, 3"-O-galloyl-4'-O-galloyl-4-O-galloyl-gallic acid, Methyl p-digallate, methyl m-digallate, ethyl p-trigallate, ethyl p-heptagallate	
Seeds		Triterpenes	28-O-Isopentyryl-3β,16α,22β,28-tetrahydroxyl-oleanane-3-O-[α-L-rhamnopyranosyl-(1→3)-βD-galactopyranosyl-(1→4')]-3β-D-galacturonopyranoside, named paniculata saponin C	**[19]**
Seeds	Hexane extract	Fatty acids	Palmitic acid, stearic acid, oleic acid, linoleic acid, linolenic acid	**[38]**
Flowers		Flavonoids	Kaempferol, luteolin, kaempferol-3-O-D-glucopyranoside, kaempferol-3-O-(6"-acetyl)-β-D-glucopyranoside, hyperoside-2"-O-acetyl, hyperoside-2"-O-galloyl, hyperoside	**[25]**
		Phenolic acids	Gallic acid	
		Sterols	β-Sitosterol-β-D-glucoside	
Seeds	Aqueous ethanol extract	Flavonoids	Kaempferol-7-O-α-L-rhamnopyranosyl,3-O-α-L-[(2''→1''')-O-β-D-glucopyranosyl),(3''→1'''')-O-β-D-(6''''→9'''''')-p-coumaroylglucopyranosyl,(4''→1''''')-β-D-glucopyranosyl]rhamno-pyranoside	**[28]**
		Triterpenes	3-O-β-D-(2'-O-acetyl)-xylopyranosyl-20S,24R-epoxycycloartan-3β,6α,16β,25-tetraol(cyclogaleginoside A)	
Leaves	Methanol extract	Phenols	Catechol, 3-methoxycatechol, pyrogallol	**[17]**
		Phenolic acids	Gallic acid, isobutyl gallate	
		Terpenoids	Eugenol, phytol	
		Fatty acids	4-C-Methyl-myo-inositol, *n*-hexadecanoic acid, (Z,Z)-9,12-octadecadienoic acid, elaidic acid, oleic acid, octadecanoic acid, benzeneacetic acid, dibutyl itaconate, linoleic acid, di-*n*-octadecyl phosphite, dodecanoic acid, myristic acid, pentadecanoic acid, hexadecanoic acid-methyl ester, octadecanoic acid-methyl ester, cis-vaccenic acid, linolenic acid, bromoacetic acid-hexadecyl ester	
		Other volatiles	(S)-(2)-2-Methyl-1-butanol, meth allyl cyanide, phenol, 2-methoxy phenol, 2-methoxy-4-vinylphenol, 2,6-dimethoxyphenol, 6,8-dimethyl benzo cyclo octene, 2,4-di-tert-butylphenol, dibutyl phthalate, benzyl alcohol, 3-fluoro-2,5-dimethyl- 2,4-hexadiene, S-methyl methanethiosulphonate, methyl-benzene, benzoic acid, 3,5-dihydroxy-2-methyl- 4H-pyran-4-one, catechol, 2,3-dihydrobenzofuran, 3-ethyl-4-methyl-pyrrole-2,5-dione, 7,8-dimethyl-benzocyclooctene, 3,3,5,6-tetramethyl-1-indanone, 4-(2,6,6-trimethylcyclohexa-1,3-dienyl)but-3-en-2-one, 2,4-di-tert-butyl phenol, 1,6-anhydro-β-D-glucopyranose, D-allose, 1-(2,3,6-trimethylphenyl)but-3-en-2-one, 4,7,9-megastigmatrien-3-one, decahydro-1,1,4a,5,6-pentamethylnaphthalene, 1-ethoxy-butane, 1-methyl-2-cyclopenten-1-ol, 1-(3-methylphenyl)-ethenone, 3-ethyl-4-methyl-1H-pyrrole-2,5-dione, dodecamethyl-cyclohexasiloxane, 3-methyltridecane, (E)-2-tetradecene, tetradecane, cyclododecane, eicosane, tetradecamethylcyclo-heptasiloxane, pentadecane, 7-methylpentadecane, 5-methylpentadecane, 5,6,7,7a-tetrahydro-4,4,7a-trimethyl-2(4H)-benzofuranone, 3-methylpentadecane, hexadecene, cyclohexadecane, 1-nonadecene, 2-methylhexadecane, 3-methylheptadecane, octadecane, cyclopentadecane, octylcyclodecane,	

Table 2 Continued.

Part used	Extracts	Compound groups	Compounds	Ref.
			neophytadiene, 6,10,14-trimethyl-2-pentadecanone, 7,9-Di-tert-butyl-1-oxaspiro (4,5)deca-6,9-diene-2,8-dione, thiosulfuric acid (H_2S_2O3), S-(2-aminoethyl) ester, behenic alcohol, 7-pentadecyne, octadeca-methylcyclononasiloxane	
Aerial parts	Aqueous ethanol extract	Flavonoids	Kaempferol-3-O-*α*-rhamnoside, kaempferol-7-O-*α*-L-rhamnoside, 5-O-methyl-luteolin	**[23]**
		Phenolic acids	Gallic acid, methyl gallate, ethyl gallate	
		Sterols	*β*-Sitosterol, *β*-sitosterol-*β*-D-glucoside	
		Fatty acids	Methyl myo-inositol, palmitic acid monoglyceride	
		Other organic compounds	Loliolide	
Aerial parts	Aqueous ethanol extract	Flavonoids	Kaempferol-3-O-*α*-L-rhamnoside, kaempferol-7-O-*α*-L-rhamnoside, 5-O-methyl-luteolin	**[24]**
		Phenolic acids	Gallic acid, methyl gallate, ethyl gallate	
		Sterols	*β*-Sitosterol, *β*-sitosterol-*β*-D-glucoside	
		Triterpenes	3*β*-O-*β*-D-Xylopyranosyl-(1→3)-*α*-L-rhamnopyranosyl-(1→3)-*β*-D-xylopyranosyl-23-O-*β*-D-glucopyranosyl-hederagenin-28-O-*α*-L-rhamnopyranosyl-(1→6)-*β*-D-glucopyranosyl ester: paniculatosoid A, 3*β*-O-*β*-D-glucopyranosyl-(1→3)-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranosyl-22*α*-O-angeloyl-camelliagenin-A: paniculatosoid B, 3*β*-O-*α*-L-rhamnopyranosyl-(1→2)-*β*-D-glucopyranosyl-22*α*-O-angeloyl-camelliagenin-A: paniculatosoid C	
		Fatty acids	Methyl myo-inositol, palmitic acid monoglyceride	
		Other organic compounds	Loliolide	
Flowers	Ethanol extract	Carotenoids	Lutein, lycopene, *β*-carotene	**[32]**
Seeds	Aqueous ethanol extract	Triterpenes	16-O-2-Methylbutanoyl-A2-barrigenol, 3-O-[*α*-L-arabinofuranosyl(1→3)-*β*-D-galacto-pyranosyl(1→2)]-(6-O-methyl)-*β*-D-glucuronopyranosyl-28-O-2-methylbutanoyl-A2-barrigenol, 3-O-[*β*-D-galactopyranosyl (1→2)]-(6-O-methyl)-*β*-D-glucuronopyranosyl-28-O-2-methylbuta-noyl-A2-barrigenol, 3-O-[*α*-L-arabinofuranosyl (1→3)-*β*-D-galactopyranosyl (1→2)]-(6-O-methyl)-*β*-D-glucuronopyranosyl-22-O-2-methylbutanoyl-A2-barrigenol, 3-O-[*β*-D-galactopyranosyl (1→2)]-(6-O-methyl)-*β*-D-glucurono-pyranosyl-22-O-2-methyl-butanoyl-A2-barrigenol	**[22]**
Roots	Ethanolic, benzene/ethanol (1:1) and methanolic extracts	Triterpenes	Lupeol	**[39]**
		Terpenoids	Farnesol isomer a	
		Sterols	*γ*-Sitosterol-ribitol, Stigmast-4-en-3-one	
		Fatty acids	Linoleic acid, palmitic acid, methyl 9-cis,11-trans-octadecadienoate, oleic acid, acetic acid, dodecanoic acid, undec-10-ynoic acid-decyl ester, tiglic acid	
		Other volatiles	Ribitol, retinal aldehyde, lactose, 6-pentylpiperidin-2-one, 2-hydroxy-2-methylhept-6-en-3-one, phthalic acid-butyl undecyl ester, glycerol	
Leaves	Essential oil	Terpenoids	Linalool formate, *α*-cedrene, *β*-caryophyllene, aromadendrene, cedrane, (E)-*β*-farnesene, (E, E)-*α*-farnesene, caryophyllene oxide, phytol, isophytol, *α*-dehydro-ar-himachalene, (Z)-nerolidol, *α*-Copaen-11-ol, (E)-nerolidol, (2Z,6Z)-farnesal, (2E,6Z)-farnesal, (Z,Z)-farnesyl acetone, (5Z,9E)-farnesyl acetone, (5E,9E)-farnesyl acetone	**[11]**
		Fatty acids	(E)-Methyl 2-octenoate, (3E)-decen-2-one, *n*-decanoic acid, (3Z)-dexenyl-(3Z)-hexenoate, (2E,4E)-dodecadienal, *n*-dodecanoic acid, ethyl dodecanoate, methyl tetradecanoate, ethyl tetradecanoate, isopropyl tetradecanoate, methyl hexadecanoate, palmitic acid, ethyl hexadecanoate, hexadecyl acetate, methyl linolenate, methyl octadecenoate, (Z,Z)-linoleic acid, oleic acid	
		Other volatiles	(2E,4E)-Dodecadienol, trans-cadina-1,4-diene, n-hexadecanol, *n*-heneicosane, *n*-triacosane, *n*-tetracosane, *n*-untriacontane, *n*-pentacosane, *n*-hexacosane, *n*-heptacosane, *n*-octacosane, *n*-nonacosane	
Stem bark	Essential oil	Terpenoids	Linalool formate, *β*-caryophyllene, aromadendrene, cedrane, (E)-*β*-farnesene, (E, E)-*α*-farnesene, caryophyllene oxide, phytol, citronellyl anthranilate, (Z)-nerolidol, (E)-nerolidol, (2Z,6Z)-farnesal, drimenol, (Z,Z)-farnesyl acetone, (5E,9E)-farnesyl acetone, (5Z,9E)-farnesyl acetone	
		Fatty acids	*n*-Dodecanoic acid, ethyl dodecanoate, ethyl tetradecanoate, isopropyl tetradecanoate, methyl hexadecanoate, palmitic acid, ethyl hexadecanoate, hexadecyl acetate, methyl linolenate, methyl octadecenoate, (Z,Z)-linoleic acid, oleic acid	
		Other volatiles	*n*-Heneicosane, *n*-triacosane, *n*-tetracosane, *n*-pentacosane, *n*-hexacosane, *n*-heptacosane, *n*-octacosane, *n*-nonacosane	
Flower buds	Essential oil	Terpenoids	*α*-Cedrene, *β*-caryophyllene, aromadendrene, cedrane, (E)-*β*-farnesene, caryophyllene oxide, phytol, citronellyl anthranilate, (Z)-nerolidol, (E)-nerolidol, (2Z,6Z)-farnesal, (2E,6Z)-farnesal, (Z,Z)-farnesyl acetone, (5Z,9E)-	

Table 2 Continued.

Part used	Extracts	Compound groups	Compounds	Ref.
			farnesyl acetone, (5E,9E)-farnesyl acetone	
		Fatty acids	*n*-Decanoic acid, (3Z)-hexenyl-(3Z)- hexenoate, n-dodecanoic acid, ethyl dodecanoate, methyl tetradecanoate, ethyl tetradecanoate, isopropyl tetradecanoate, methyl hexadecanoate, palmitic acid, ethyl hexadecanoate, hexadecyl acetate, methyl linolenate, methyl octadecanoate, (Z,Z)-linoleic acid, linolenic acid, oleic acid, ethyl octadecenoate	
		Other volatiles	(2E,4E)-Dodecadienol, *n*-hexadecanol, *n*-heneicosane, *n*-triacosane, *n*-tetracosane, *n*-triacontane, *n*-untriacontane, *n*-pentacosane, *n*-hexacosane, *n*-heptacosane, *n*-octacosane, *n*-nonacosane	
Flowers	Essential oil	Terpenoids	*β*-Caryophyllene, aromadendrene, cedrane, (E)-*β*-farnesene, caryophyllene oxide, phytol, citronellyl anthranilate, (Z)-nerolidol, (E)-nerolidol, (2Z,6Z)-farnesal, (2E,6Z)-farnesal, (Z,Z)-farnesyl acetone, (5Z,9E)-farnesyl acetone, (5E,9E)-farnesyl acetone	
		Fatty acids	*n*-Dodecanoic acid, ethyl dodecanoate, methyl tetradecanoate, ethyl tetradecanoate, isopropyl tetra-decanoate, methyl hexadecanoate, palmitic acid, ethyl hexadecanoate, hexadecyl acetate, methyl linolenate, methyl octadecenoate, (Z,Z)-linoleic acid, oleic acid, ethyl octadecenoate	
		Other volatiles	(2E,4E)-Dodecadienol, *n*-hexadecanol, *n*-heneicosane, *n*-triacosane, *n*-tetracosane, *n*-pentacosane, *n*-hexacosane, *n*-heptacosane, *n*-octacosane, *n*-nonacosane	
Flowers	Ethanol extract	Terpenoids	γ-Terpineol, lavandulol acetate, δ-terpinyl acetate, *α*-terpinyl acetate, neryl acetate, *β*-caryophyllene, *α*-terpinyl isobutanoate, *β*-selinene, *α*-selinene, geranyl butanoate, *β*-eudesmol, *α*-eudesmol, dihydro-eudesmol, Epi-*β*-bisabolol, *β*-bisabolol, *α*-trans-bergamotene, (Z)-*α*-trans-bergamotol, (2Z,6Z)-farnesol	**[12]**
		Phenols	Pyrogallol	
		Fatty acids	(3Z)-Hexenyl butanoate, (2E,4E)-hexadienol isobutanoate, methyl nonanoate, (3Z)-hexenyl 2-methyl butanoate, ethyl decanoate, phenyl ethyl butanoate, phenyl ethyl 2-methylbutanoate, lauric acid, octyl hexanoate, decyl butyrate, phenyl ethyl hexanoate, δ-dodecalactone, palmitic acid, linoleic acid, ethyl palmitate, oleic acid.	
		Other volatiles	(2E,4E)-Nonadienol, *n*-tetradecane, *n*-dodecanol, tetradecanal, tetracosane	
Leaves	Ethanol extract	Terpenoids	γ-Terpineol, nerol, lavandulol acetate, δ-terpinyl acetate, *α*-terpinyl acetate, neryl acetate, *β*-caryophyllene, *α*-terpinyl isobutanoate, *β*-selinene, *α*-selinene, geranyl butanoate, *β*-eudesmol, *α*-eudesmol, dihydro-eudesmol, epi-*β*-bisabolol, *β*-bisabolol, *α*-trans-bergamotene, (Z)-*α*-trans-bergamotol, (2Z,6Z)-farnesol, geranyl acetone, linalool isovalerate, *α*-curcumene, γ-curcumene, *β*-curcumene, methyl eudesmate, (E)-nerolidyl isobutyrate	
		Phenols	Pyrogallol	
		Phenolic acids	Isobutyl cinnamate	
		Fatty acids	(3Z)-Hexenyl butanoate, (2E,4E)-hexadienol isobutanoate, methyl nonanoate, (3Z)-hexenyl 2-methyl butanoate, ethyl decanoate, phenyl ethyl butanoate, phenyl ethyl 2-methylbutanoate, lauric acid, octyl hexanoate, decyl butyrate, phenyl ethyl hexanoate, δ-dodecalactone, palmitic acid, linoleic acid, *α*-methyl benzyl butyrate, (3Z)-hexenyl hexanoate, isopropyl hexadecanoate	
		Other volatiles	(2E,4E)-Nonadienol, *n*-tetradecane, *n*-dodecanol, tetradecanal, isobutyl phenylacetate	
Stem bark	Ethanol extract	Terpenoids	γ-Terpineol, nerol, lavandulol acetate, δ-terpinyl acetate, *α*-terpinyl acetate, neryl acetate, *β*-caryophyllene, *α*-terpinyl isobutanoate, *β*-selinene, *α*-selinene, geranyl butanoate, *β*-eudesmol, *α*-eudesmol, dihydro-eudesmol, epi-*β*-bisabolol, *β*-bisabolol, *α*-trans-bergamotene, (Z)-*α*-trans-bergamotol, (2Z,6Z)-farnesol, geranyl acetone, linalool isovalerate, *β*-curcumene, methyl eudesmate, phytol, (6E,10Z)-pseudo phytol, (6E,10E)-pseudo phytol	
		Phenols	Pyrogallol	
		Phenolic acids	Isobutyl cinnamate	
		Fatty acids	(3Z)-Hexenyl butanoate, (2E,4E)-hexadienol isobutanoate, methyl nonanoate, (3Z)-hexenyl 2-methyl butanoate, ethyl decanoate, (3Z)-hexenyl butanoate, (2E,4E)-hexadienol isobutanoate, phenyl ethyl butanoate, phenyl ethyl 2-methylbutanoate, lauric acid, octyl hexanoate, decyl butyrate, phenyl ethyl hexanoate, δ-dodecalactone, palmitic acid, linoleic acid, *α*-methyl benzyl butyrate, (3Z)-hexenyl hexanoate, isopropyl hexadecanoate	
		Other organic compounds	(2E,4E)-Nonadienol, *n*-tetradecane, *n*-dodecanol, tetradecanal, isobutyl phenylacetate	
Leaves	Aqueous ethanol extract	Flavonoids	Quercetin, rutin, hesperidin, (−)-epicatechin	**[13]**
		Phenolic acids	Gallic acid, protocatehuic acid, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, salicylic acid, rosmarinic acid, ferulic acid	
Flowers	Aqueous ethanolic extract	Flavonoids	Quercetin, rutin, hesperidin, (−)-epicatechin	
		Phenolic acids	Protocatehuic acid, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, salicylic acid, rosmarinic acid, ferulic acid	

Table 2 Continued.

Part used	Extracts	Compound groups	Compounds	Ref.
Flower Buds	Aqueous ethanolic extract	Flavonoids	Quercetin, rutin, hesperidin, (−)-epicatechin	
		Phenolic acids	Protocatehuic acid, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, salicylic acid, rosmarinic acid, ferulic acid	
Stem Bark	Aqueous ethanolic extract	Flavonoids	Quercetin, rutin, (+)-catechin, (−)-epicatechin	
		Phenolic acids	Protocatehuic acid, vanillic acid, caffeic acid, syringic acid, p-coumaric acid, salicylic acid, rosmarinic acid	
Seeds	Glyceride oil	Fatty acids	Myristic acid, myristoleic acid, palmitic acid, palmitoleic acid, heptadecenoic acid, stearic acid, oleic acid, linoleic acid, eicosenoic acid, eicosapentaenoic acid, tricosanoic acid	**[40]**
		Sterols	Brassicasterol, campesterol, stigmasterol, Δ^7-campesterol, β-sitosterol, Δ^7-stigmasterol	
		Tocopherols	α-Tocopherol, β-tocopherol, γ-tocopherol	
		Phospholipids	Phosphatidic acids, phosphatidylserine, phosphatidylinositol, phosphatidylcholine, phosphatidylethanolamine, diphosphatidylglycerol	

Two new afzelin derivatives were separated from aqueous ethanol extract of *K. paniculata* leaves **[8]**. They were elucidated on the basis of chemical degradation, negative MS, UV, 1D and 2D NMR analyses as afzelin 3''-O-gallate (**8**) and 6,8-dihydroxy afzelin (**9**). Kaempferol-3-O-arabinoside (**3**) was isolated from the leaves of *K. elegans* by Abou-Shoer *et al.* **[10]**, Lee TH *et al.* **[18]** and Chiang *et al.* **[15]**, while it was detected in *n*-butanol fraction of *K. paniculata* leaves by Lin *et al.* **[21]**. The EtOAc fraction of the acetone extract of the leaves of *K. elegans* was subjected to a combination of silica gel and HPLC with various solvent systems to afford a new kaempferol galloyl glycoside namely kaempferol 3-O-(2'',3''-di-O-galloyl)-rhamnopyranoside (**5**) The identity of its structure was confirmed by MS^+, IR, UV, ^{1}H- and ^{13}C-NMR analysis **[18]**. Kaempferol-3-O-glucopyranoside (**4**) was separated by Lee *et al.* **[18]** and Chiang *et al.* **[15]** from the leaves of *K. elegans*. It was also separated from the flowers of *K. paniculata* beside its acetyl derivative kaempferol-3-O-(6''-acetyl)-glucopyranoside (**6**) **[25]**. Furthermore, Sutiashvili *et al.* **[28]** isolated a new kaempferol glycoside from the seeds of *K. paniculata*, kaempferol-7-O-rhamnopyranosyl,3-O-[(2''→1''')-O-glucopyranosyl),(3''→1'''')-O-(6''''→9'''''')-*p*-coumaroyl-glucopyranosyl,(4''→1''''')-glucopyranosyl]rhamnopyranoside (**10**), based on IR, UV, ^{1}HNMR, ^{13}CNMR, HSQC, HMBC and MS methods. Quercetin and its different glycosides were characterized in several studies of genus *Koelreuteria*. Quercetin aglycone (**11**) was isolated from the ethanol **[10]** and aqueous methanol **[5]** extracts of *K. elegans*, and the aqueous ethanol extract of *K. paniculata* **[22]** leaves, while its concentration in different parts of *K. paniculata* was compared and the leaves scored the highest concentration of quercetin followed by flowers, flower buds and stem bark **[13]**. Quercetin linked to arabinose (**12**) was detected in the leaves and twigs of *K. elegans* **[5, 18]** and *K. paniculata* **[21]**. In addition, quercetin-3-O-glucopyranoside (**13**) was isolated from *K. elegans* leaves **[18]**. The leaves of *K. paniculata* and *K. elegans* afforded Quercetin-3-O-galactopyranoside (hyperin\hyperoside, **14**) **[18, 21]**. Hyperin beside its galloyl derivative (**15**) were isolated from *K. paniculata* flowers **[25]**, and leaves **[30]**. Acetyl ester of hyperin (**16**) was also demonstrated **[25]**. Chemical investigation of the leaves of both species of *Koelreuteria* furnished quercetrin (**17**) and its galloyl derivatives (**18**, **19**) **[5, 8, 21, 30]**. Methyl ether of quercetin (azaleatin, **21**) was separated from *K. elegans* leaves and twigs **[5]**. Apigenin-4'-O-glucopyranoside (**26**) was isolated from *K. elegans* leaves **[15, 18]**. Isorhamnetin (**29**) was obtained from EtOAc fraction of *K. paniculata* leaves **[21]**. Additionally, two Isorhamnetin glycosides (**30**, **31**) were isolated from the leaves and twigs of *K. elegans* **[5]**. Luteolin (**22**) beside its methyl ether (**23**) were isolated from *K. paniculata*. The aglycone was afforded from the flowers **[25]**, while 5-O-methyl luteolin (**23**) was isolated from the arial parts **[23, 24]**. *K. paniculata* revealed the presence of flavan-3-ols and their galloyl esters in its different parts. Catechin (**27**) and galloylepicatechin (**28**) were detected in the leaves **[21]**. The report of Andonova and co-workers **[13]** depended on the study of flavonoids and phenolic acids in the leaves, flowers, flower buds and stem bark of *K. paniculata*. Epicatechin (**27**) was detected in all parts but was major in the flower buds, while catechin was identified only in the stem bark. Furthermore, Andonova's report focused on two additional flavonoids: rutin (**20**) and hesperidin (**32**). The leaves had the highest content of rutin, followed by hesperidin, while they were much less (11–14 times) in concentration in flower buds. Hesperidin was missing in stem bark **[12]**. Two new flavonoids were first isolated from the seeds of *K. paniculata*, paniculatonoid A and B (**24**, **25**) and their structures were confirmed by IR, UV, MS, ^{1}H- and ^{13}C-NMR methods **[31]**.

4.2. Phenolic acids

Phenolic acids in the genus *Koelreuteria* comprise derivatives of hydroxybenzoic and hydroxycinnamic acids, present as esters, glycosides, or glycoside-esters mainly distributed in the aerial parts of the plants. They occupy compounds **33-67** documented (

). Gallic acid besides its various derivatives were isolated or detected in genus *Koelreuteria.* Through chromatographic patterns from the HPLC and GC analysis, gallic acid (**33**) peak was detected from the leaves of both species of *Koelreuteria* **[13, 17, 20]**. It was isolated from the leaves of *K. elegans* **[5, 9]** and from the aerial parts of *K. paniculata* **[8, 23-25, 30]**. Methyl, ethyl and isobutyl esters of gallic acid (**34**, **35**, **36**) were detected in both plants. Compound **34** was isolated from the leaves of *K. elegans* **[5, 9, 18]** and *K. paniculata* **[8]**. Compound **35** was detected by Yang *et al.* **[30]** in the leaves of *K. paniculata*. Both **34** and **35** were identified in the aerial parts of *K. paniculata* **[23, 24]**. Isobutyl gallate peak was detected by GC-MS analysis in the leaves of *K. paniculata* **[17]**. Yang *et al.* **[30]** and Lin *et al.* **[21]** isolated two di-galloyl acids (**37**, **38**) from the aqueous ethanol extracts of *K. paniculata* leaves. Moreover, they isolated and elucidated several compounds of galloyl acid ester derivatives. Yang *et al.* **[30]** isolated ethyl-*p*-digallate (**41**) and ethyl-*m*-digallate (**42**), while Lin *et al.* **[21]** isolated methyl *p*-digallate (**39**), methyl *m*-digallate (**40**), ethyl *p*-trigallate (**43**), ethyl *p*-heptgallate (**44**) and 3''-O-galloyl-4'-O-galloyl-4-O-galloyl-gallic acid (**46**). Similarly, ellagic acid (**67**) was identified in the leaves of *K. paniculata* **[21, 30]**. 6-O-[galloyl 4-methyl ether]-glucopyranose (**45**) was isolated from the leaves of *K. elegans* **[9]**. Galloyl quinic acid derivatives were identified in genus *Koelreuteria.* Those compounds are composed of quinic acid as the central unit, attached with gallate ion multiples. 3,5-di-O-galloyl-quinic acid (**49**) and 3,4,5-tri-O-galloyl-quinic acid (**51**) were isolated from *K. paniculata* leaves **[8]**, while leaves of *K. elegans* afforded 1,3,4,5-tetra-O-galloylquinic acid (**53**) **[5, 14]**. Butyl esters of galloyl quinic acid compounds were also explored in aqueous methanol extract of *K. elegans* leaves **[5, 9]**. 3-O- galloyl quinic acid butyl ester (**47**), 4-O-galloyl quinic acid butyl ester (**48**), 3, 5-di-O-galloylquinic acid butyl ester (**50**) and 3,4,5-tri-O-galloylquinic acid butyl ester (**52**) **[9]**, as well as 1, 3, 4, 5-tetra-O-galloylquinic acid butyl ester (**54**) were detected **[5, 9]**.

By the aid of GC-MS analytical method of the aerial parts of *K. paniculata*, some phenolic metabolites were detected. Catechol (**64**), 3-methoxycatechol (**65**) and pyrogallol (**66**) peaks were determined in the leaves **[17]**. Similarly, Pyrogallol and isobutyl cinnamate (**59**) were elucidated in flowers, leaves and stem bark **[12]**. Pyrogallol peak scored higher quantity in the flowers than the other parts, while isobutyl cinnamate peak was missing in the flowers. By the same approach which depended on studying of metabolite peaks in different plant parts, Andonova and co-workers **[13]** used HPLC method for screening ten phenolic acids in different plant parts of *K. paniculata*. In the leaf extract, rosmarinic acid (**63**) appeared as the highest content, followed by vanillic acid (**57**). In the flower and flower bud extracts, p-coumaric (**60**) and rosmarinic acids were predominant, followed by salicylic (**55**) and protocatechuic (**56**) acids. Other phenolic acids (vanillic, caffeic (**61**), syringic (**58**), and ferulic (**62**) acids), were less represented in both generative parts. In the bark extract, ferulic acid was missing and the other seven phenolic acids were found in significantly lower amounts. Chlorogenic acid was not found in any of the tested samples. HPLC analysis of *K. elegans* branches and leaves showed a peak corresponding to caffeic acid **[20]**, while ferulic acid was isolated from the leaves of *K. paniculata* **[8].**

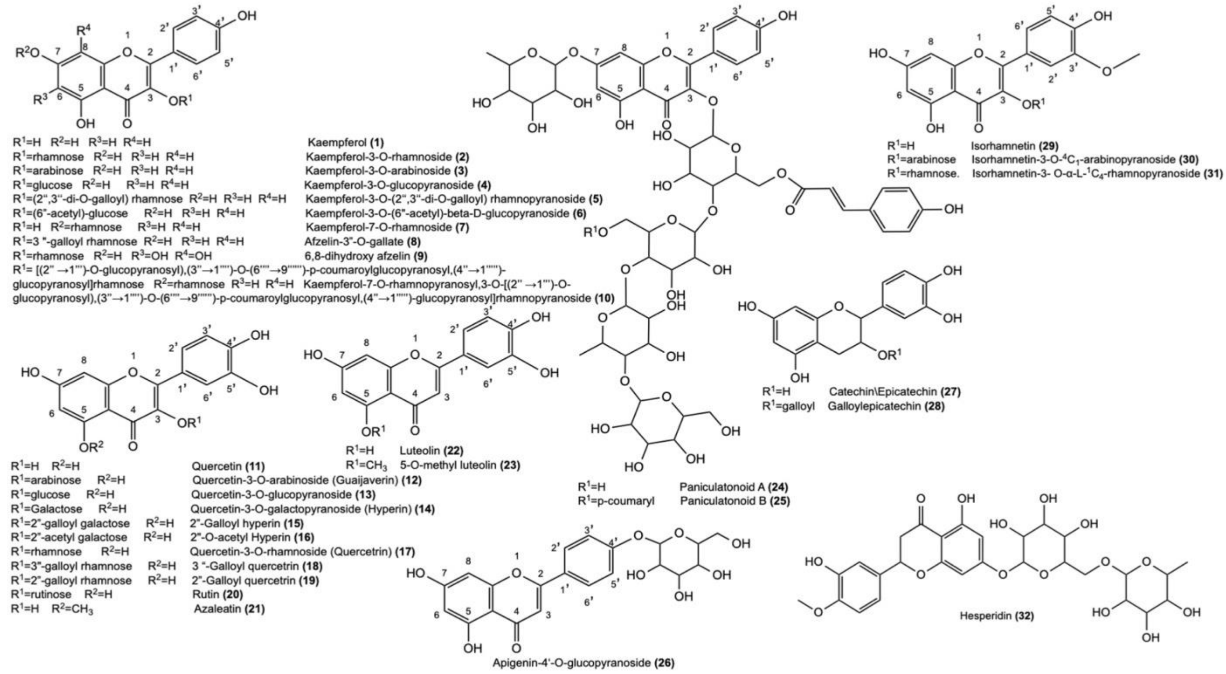

Fig. 2. Chemical structures of flavonoids (1-32) isolated from genus *Koelreuteria*.

4.3. Lignans

Up to now, only five lignans (**68**-**71**) have been discovered in this genus. All the available literature revealed their presence exclusively in the *K. elegans*. An Early study exposed a new cyclolignan, named koelreuterin-1 (**68**), isolated from the leaves of *K. elegans*, its structure elucidation was based on extensive ^{1}H- and ^{13}C-NMR spectral analyses **[26]**. Lee *et al.* **[18]** succeeded to separate a new lignan glycoside, hinokinin 7-O-glucopyranoside **(71)**. The MS^{+}, IR, ^{1}H- and ^{13}C-NMR analyses were utilized to elucidate its structure. Austrobailignan-1 (**69**), the most common lignan detected in *K. elegans*, was isolated from the leaves of the plant **[9, 15, 18, 26, 29]**. Similarly, its stereoisomer: austrobailignan-2 (**69**) was highlighted in *K. elegans* studies **[18, 26]**. Moreover, the cyclolignan sesamin (**70**) was also separated **[18]**.

4.4. Triterpenoids

Sixteen triterpenoids were isolated and elucidated from the genus *Koelreuteria*. Their chemical structures were illustrated in Fig. 4 (**72**-**86**). The authors mainly focused their efforts on studying triterpenoids in the different parts of *K. paniculata.* The study of El Naggar *et al.* **[5]** represented the only available source of data related to triterpenoids in *K. elegans*. It encompassed the isolation of oleanolic acid (**72**), as well as two triterpenoid glycosides: oleanolic acid-3-O-$^{4}C_{1}$-glucopyranoside (**73**) and 3-O-[O-rhamnopyranosyl-(1-2)-O-glucopyranosyl-(1-2)-$^{4}C_{1}$-glucopyranosyl] oleanolic acid (**74**), from the leaves and twigs of the plant.

Early studies on *K. paniculata* showed two triterpenoid saponins, koelreuteria saponin A and B **(75, 76)**, isolated from aqueous methanolic extract of the fruits **[16]**. The compound **76** was purified from aqueous ethanolic extract of the seeds **[27]**. A new cycloartane glycoside, was isolated and identified as cyclogaleginoside A (**85**) **[28]**. Lei *et al.* **[19]** isolated a new saponin; paniculata saponin C from the seeds of *K. paniculata*. With the continued investigation of the chemical constituents of the seeds of *K. paniculata*, Lu *et al.* **[22]** succeeded to isolate five new barrigenol-type triterpenoids, 16-O-2-methylbutanoyl-A2-barrigenol, 3-O-[arabinofuranosyl-(1→3)-galactopyranosyl-(1→2)]-(6-O-methyl)-glucuronopyranosyl-28-O-2-methylbutan-oyl-A2-barrigenol, 3-O-[galactopyranosy(1→2)] -(6-O-methyl)-glucuronopyranosyl-28-O-2-methylbutanoyl-A2-barrigenol, 3-O-[arabinofuranosyl (1→3)-galactopyranosyl (1→2)]-(6-O-methyl)-glucuronopyranosyl-22-O-2-methylbutanoyl-A2-barrigenol and 3-O-[galactopyranosyl (1→2)]-(6-O-methyl)-glucuronopyranosyl-22-O-2-methylbutanoyl-A2-barrigenol (**80-84**). They were identified by using high-resolution electrospray ionization mass spectroscopy (HR-ESIMS), 1D and 2D NMR spectroscopic methods. Chemical investigation of the ethanolic extract of the aerial parts of *K. paniculata* revealed the isolation and identification of three new triterpenoid saponins; paniculatosoid A-C (**77-79**) **[24]**. The structures of the new triterpenoids were determined by HR-ESIMS, 1D and 2D NMR spectroscopic methods. Roots of *K. paniculata* were extracted using benzene/ethanol (volume ratio 1:1) solvents and applied to GC column **[39]**; a peak corresponding to lupeol (**86**) was afforded.

4.5. Sterols and carotenoids

Phytosterols are a common type of bioorganic molecules found in plants and previously recognized in food and pharmaceutical products **[41]**. About nine sterols were detected in genus *Koelreuteria*. They are listed in Table 2 and the chemical structures of the major compounds are displayed in Fig. 4 (**87-91**). *β*-sitosterol (**87**) is one of the most abundant, naturally occurring phytosterols in plants. Relatively, it represented the major isolated or detected sterol in this genus. It was isolated from the leaves of *K. elegans* **[9, 18]**, as well as, the aerial parts of *K. paniculata*, which afforded the compound besides its glycosidic form (**88**) **[23-25, 30]**. *β*-Sitosterol was the most abundant phytosterol in *K. paniculata* seed oil, followed by *β*-stigmasterol (**90**) **[40]**. *β*-Stigmasterol was also isolated from the leaves of *K. elegans* **[18]**. Wang *et al.* **[39]** investigated the active constituents of the roots of *K. paniculata* using GC. Peaks corresponding to *γ*-sitosterol-ribitol (**89**) and stigmast-4-en-3-one (**91**) were detected.

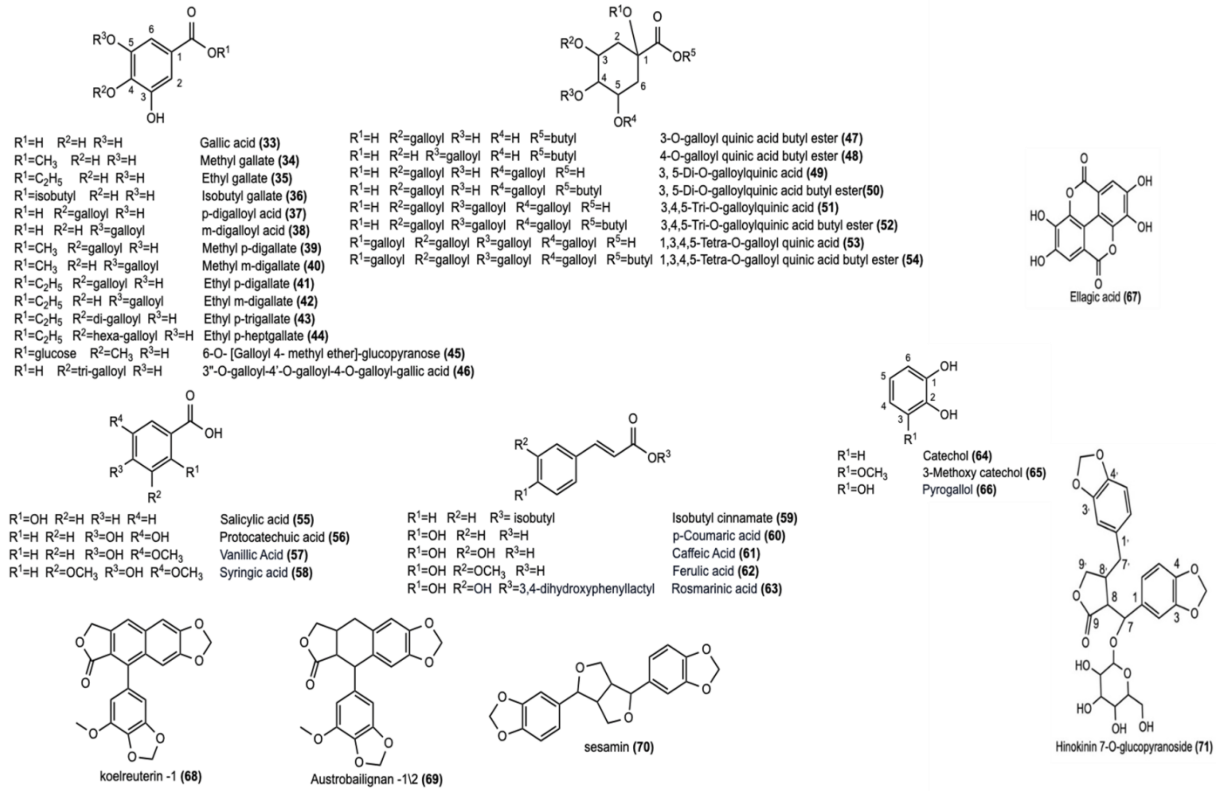

Fig. 3. Chemical structures of phenolic acids (33-67) and lignans (68-71) isolated from genus *Koelreuteria*.

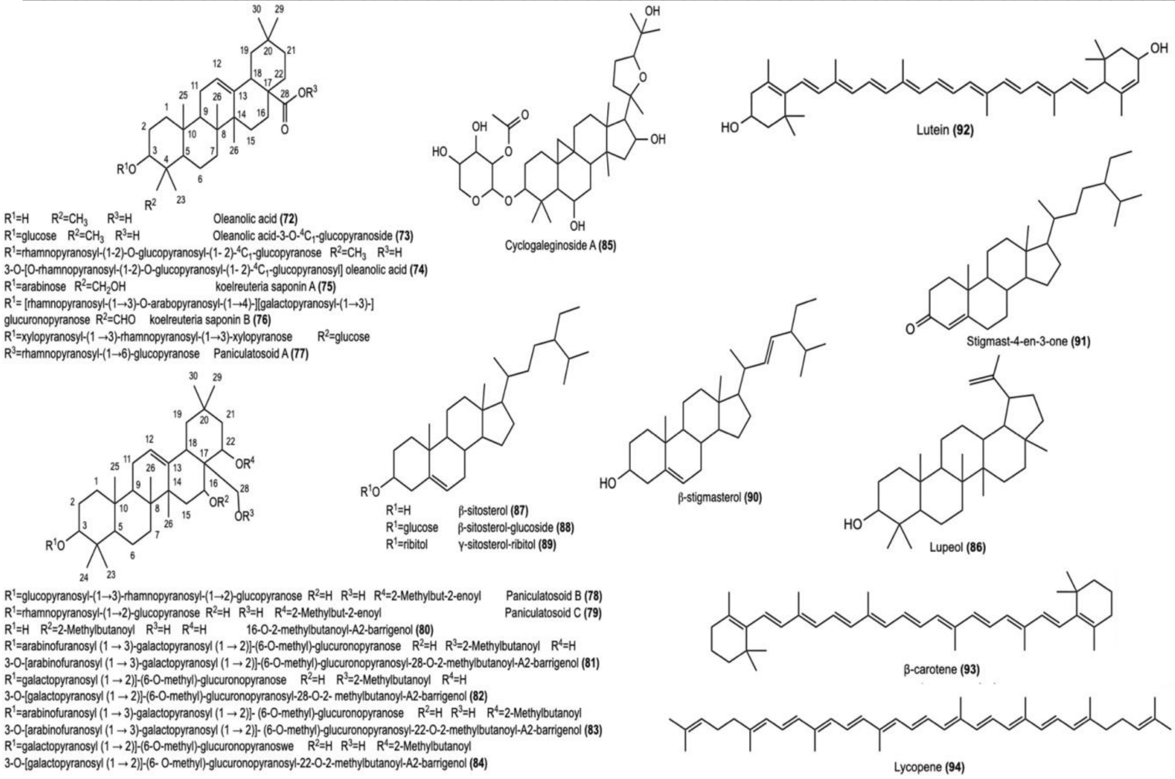

Fig. 4. Chemical structures of triterpenes (72-86), sterols (87-91) and carotenoids (92-94) isolated from genus *Koelreuteria*.

Limited studies have been carried out to investigate the carotenoids in genus *Koelreuteria*. Only three carotenoids lutein, *β*-carotene and lycopene (**92-94**, Fig. 4) have been isolated and quantified by HPLC analysis from the flowers of *K. paniculata* **[32]**. *β*-carotene was the compound with the highest concentration, followed by lycopene.

4.6. Fatty acids and volatiles

Fatty acids and volatiles are other characteristic components of the genus *Koelreuteria.* The studies depended mainly on analyzing the fatty acids and volatiles on various parts of *paniculata* species using GC-MS analysis. The chemical composition of the volatiles was dominated by aliphatics, sesquiterpenes, diterpenes, triterpenes, phenolic acids, and other aromatics. The chemical structures of the major fatty acids and volatiles are presented in

Fig. **5**. (**95-135**). Early studies showed the efforts of the authors for discovering the fatty acid constituents of *K. paniculata*. Hopkins *et al.* **[37]** analyzed the fatty acid content of of *K. paniculta* seed oil by the aid of GC, UV and IR analytical methods. Seven Fatty acids were discovered; palmitic (**95**), stearic (**97**), oleic (**98**), linoleic (**99**), linolenic (**100**), arachidic (**101**), and eicosenoic (**102**) acids; the latter was the most abundant (46%). Similar results were recorded except that arachidic and eicosenoic acids were absent and oleic acid was predominant (80.1%) **[38]**. The oil content of *K. paniculata* seeds in a recent study **[40]** was very close to the previous findings regarding fatty acid composition **[37]**. Eleven fatty acids were identified in *K. paniculata* seeds with the unsaturated fatty acids predominating in the oil (92.2%), and monounsaturated fatty acids being better represented than polyunsaturated fatty acids due to greater amount of omega-9 oleic and eicosenoic acids (41.8% and 46.5%, respectively).

The individual phospholipid composition of *K. paniculata* seeds was determined for the first time **[40]**. The highest amount was phosphatidylcholine (29.1%), followed by phosphatidylinositol (17.5%). Ghahari *et al.* **[17]** used GC-MS analysis to identify different phytochemicals in the fractions of methanol extract from the dry leaves of *K. paniculata*. They found a smaller number of the major components (over 3%), palmitic, linoleic, stearic acids, 1-ethoxy-butane (**103**), neophytadiene (**104**) and 4-C-methyl-myo-Inositol (**105**). Compound **105** and monoglyceride ester of palmitic acid (**96**) were isolated from the aerial parts of *K. paniculata* **[23, 24]**.

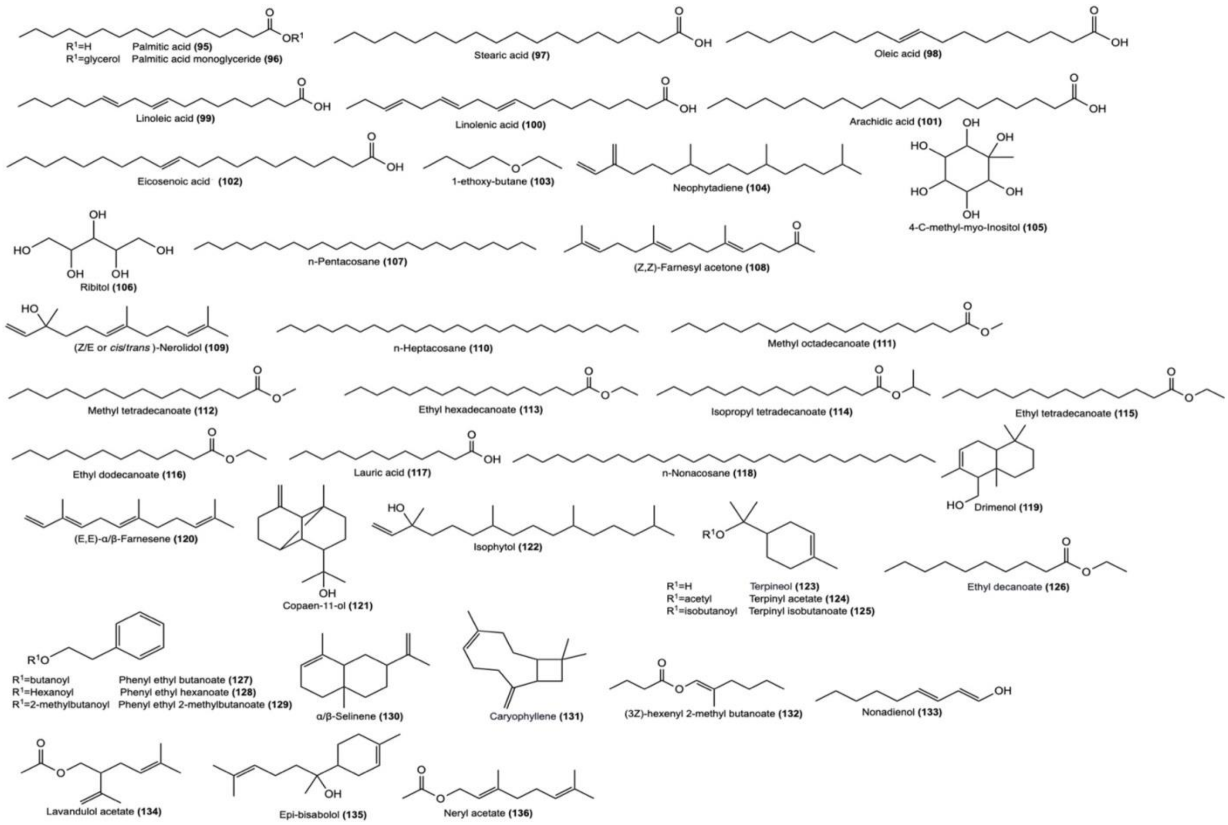

Fig. 5. Chemical structures of major fatty acids and volatiles (95-136) isolated from genus *Koelreuteria*.

K. paniculata roots were extracted using three different solvents and subjected to different spectroscopic analyses. GC-MS analysis revealed thirty-three, twenty-nine and twenty-three active substances from the ethanolic, benzene/ethanol (1:1) and methanolic extracts, respectively. The major constituents were listed in Table 2. Ribitol (**106**) was the major substance in the first and third solvents, while linoleic and palmitic acids represented the chief substances of the second solvent. TD-GC/MS results showed 81 active substances. Oleic acid was considered the main component **[39]**.

The metabolites prepared by hydrodistillation from four different aerial parts of *K. paniculata* were investigated and identified by GC-MS analysis **[11]**. Forty-four compounds were detected in the flower buds; eleven of them were considered the main constituents (**95**, **97**, **99**, **100**, **107**-**113**); linoleic (14.98 %) and palmitic acids (12.72 %) were the highest. Thirty-eight metabolites were detected in the flowers; twelve of them were major (**95**, **99**, **107**-**110**, **113**-**118**); (Z,Z)-farnesyl acetone (**108**) was the major compound (17.3 %). In the bark essential oil, thirty-six volatiles were identified; nine compounds were major (**95**, **107**, **108**, **110**, **113**, **116**, **118**-**120**) with drimenol (**119**, 16.19 %) and *n*-pentacosane (**110**, 10.54 %) being the highest. Finally, the constituents of the leaves were forty-nine compounds; comprising six main components (**109**, **120**-**122**); (E,E)-*α*-farnesene (**120**) scored 37.90%. It was stated that, thirty-two common components were identified for the four essential oils. Similarly, another study aimed to achieve the same goal but from the ethanol extracts of three aerial plant parts **[12]**. Forty components were identified in the flower extract; seven of them were in a concentration above 3% (**123**-**127**, **130**); *α*-terpinyl acetate (**124**, 16.42%) and *α*-terpinyl isobutanoate (**125**, 10.32%) were highlighted. Fifty components were identified in each of the leaf and bark extracts. Ten volatiles were major in leaves (**99**, **124**, **125**, **128**, **129**, **131**-**135**), while only five were above 3% in the bark (**124**, **129**, **132**, **133**, **136)**; *α*-terpinyl acetate (20.24%) and neryl acetate (**136**, 12.37%) scored the highest concertation in both extracts, respectively. By comparing the constituents of the two types of extracts **[11, 12]**, *β*-caryophyllene, lauric acid, palmitic acid, oleic acid, and tetracosane were common in the flowers; palmitic acid, lauric acid, and *β*-caryophyllene were common in the leaves; palmitic acid, *β*-caryophyllene, phytol, oleic acid, lauric acid, and tetracosane were common in the bark.

4.7. Tocopherols

Four tocopherols were identified in the genus *Koelreuteria*. The study of Lee TH *et al.* **[18]** involved the isolation of two tocopherols from the leaves of *K. elegans*, *α*-tocopherol and *α*-tocopheryl quinone. Three peaks were detected in the individual tocopherol composition of the studied glyceride oil of *K. paniculata* seeds **[40]**. The main representative of which was *β*-tocopherol (56.6% of the total tocopherol content), followed by γ-tocopherol (33.4%) and *α*-tocopherol (10.0%).

5. Pharmacology

The traditional medicinal applications from the genus *Koelreuteria* have inspired scientists to study many biological activities and validate the potential uses of the plant as therapeutic remedies. For a long time, several extracts from the genus *koelreuteria* and the isolated compounds have been investigated for their physiological and pharmacological properties, namely anticancer, antioxidant, anti-hyperlipidemic, anti-Alzheimer, anti-inflammatory, and antimicrobial and hepatoprotective activities among others (Tables 3-6)

Several works showed the anticancer properties. Indeed, several *in-vitro* investigations based on cell culture tests showed that both *K. elegans* and *k. paniculata* extracts and some of their active compounds exhibited antiproliferative effects against different cancer cell lines **[9, 10, 12, 15, 21, 26, 29, 42]**. Abou-Shoer *et al.* **[10]** was interested in determination of the anticancer activity of some *K. henryi* isolated compounds from its leaves and twigs using PTK inhibition assay and determination of structure activity relationship of those compounds. A bioassay-directed fractionation of the crude extract of *K. henryi* led to the discovery of kaempferol and quercetin as potent inhibitors of the PTK p56^{lck}. Two additional less potent inhibitors, kaempferol-3-O-*α*-rhamnoside and kaempferol-3-O-*α*-arabinoside, were also isolated for structure-activity studies. Comparison of their inhibitory activities showed that glycosylation of the 3-hydroxyl group of a flavonol markedly decreased the activity Likewise, PTK inhibitory activity was tested on *paniculata* species **[21]**. The study involved fractionation of the ethanol extract of the leaves and studying PTK inhibitory activity, the EtOAc and the *n*-butanol fractions showed half maximal inhibitory concentration (IC_{50}) 540 and 650 mg/mL, respectively. Further fractionation of EtOAc portion led to the isolation of two compounds, 3''-galloylquercitrin and quercetin-3'-O-*β*-arabinopyranoside. Both possessed the activity for PTK inhibition with IC_{50} 24 and 40 μg/mL, respectively.

The cytotoxicity of three cyclolignans isolated from *K. elegans* leaves and twigs **[26]**; koelreuterin-1, austrobailignan-1 and -2 on various human carcinoma cell lines was assessed using 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay. These compounds exhibited significant cytotoxicity against all tested cell lines, compared to two cytotoxic standard compounds; podophyllotoxin and doxorubicin. Austrobailignan-1 was the most cytotoxic compound which might be due to its structural similarity to podophyllotoxin. The new isolated molecule; koelreuterin-1 proved slight selective cytotoxicity against melanoma and ovarian carcinoma **[26]**. Podophyllotoxin is known for its cytotoxicity due to inhibition of tubulin polymerization and the disruption of microtubules **[43]**. Accordingly, the isolated cyclolignans were examined for their capability to prevent tubulin polymerization using turbidity and sedimentation assays **[26]**. Austrobailignan-1 scored the highest activity, followed by koelreuterin-1, concluding that the prevention of tubulin polymerization by the three compounds correlated quite well with their cytotoxicity.

Table 3: Anticancer activity of the genus *Koelreuteria*.

Part use	Extract/compound	Cell line	Method	Result	Ref.
		Koelreuteria elegans			
The plant	Ethanol extract Apigenin-4'-O-*β*-D-glucopyranoside Kaempferol-3-O-glucoside	Lung cancer cells (H838) Breast cancer cells (BT-20) Gastric cancer cells (KOTA-III)	Suppression of DDH protein expression determined by LCELISA and immunoblot analysis	Great suppressive effect on DDH expression. No marked inhibition of DDH expression. Intermediately suppressed DDH expression.	**[15]**
Leaves, twigs	Kaempferol, quercetin Kaempferol-3-O-*α*-rhamnoside Kaempferol-3-O-*α*-arabinoside		PTK inhibition	IC_{50} = 8 X 10^0 μg/mL IC_{50} = 4 X 10^2 μg/mL IC_{50} = 2 X 10^2 μg/mL	**[10]**

Table 3 Continued.

Part use	Extract/compound	Cell line	Method	Result	Ref.
Leaves, twigs	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Human lung carcinoma cells (A549)	MTT assay	ED_{50} = 4.9X10^{-1} μg/mL ED_{50} = 3.9X10^{-6} μg/mL ED_{50} = 4.6X10^{-1} μg/mL ED_{50} = 7.7x10^{-8} μg/mL ED_{50} = 3.1x10^{-4} μg/mL	**[26]**
	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Breast adenocarcinoma cells (MCF-7)		ED_{50} = 9.7 μg/mL ED_{50} = 5.2X10^{-5} μg/mL ED_{50} = 4.1 μg/mL ED_{50} = 1.1x10^{-6} μg/mL ED_{50} = 2.0x10^{-2} μg/mL	
	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Colon adenocarcinoma cells (HT-29)		ED_{50} = 2.9X10^{-1} μg/mL ED_{50} = 3.7X10^{-6} μg/mL ED_{50} = 1.0X10^{-1} μg/mL ED_{50} = 4.7x10^{-8} μg/mL ED_{50} = 5.6x10^{-4} μg/mL	
	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Human ovarian carcinoma cells (SK-OV-3)		ED_{50} = 6.7X10^{-3} μg/mL ED_{50} = 2.7X10^{-6} μg/mL ED_{50} = 8.32X10^{-1} μg/mL ED_{50} = 4.2x10^{-5} μg/mL ED_{50} = 2.5x10^{-3} μg/mL	
	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Human melanoma cells (SK-MEL-5)		ED_{50} = 3.5X10^{-3} μg/mL ED_{50} = 3.0X10^{-7} μg/mL ED_{50} = 7.7X10^{-1} μg/mL ED_{50} = 4.1x10^{-8} μg/mL ED_{50} = 2.8x10^{-4} μg/mL	
	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Epidermoid carcinoma cells (A431)		ED_{50} = 1.8X10^{-1} μg/mL ED_{50} = 3.6X10^{-6} μg/mL ED_{50} = 9.6X10^{-1} μg/mL ED_{50} = 1.1x10^{-6} μg/mL ED_{50} = 1.2x10^{-2} μg/mL	
	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Renal carcinoma cells (A498)		ED_{50} = 7.8X10^{-2} μg/mL ED_{50} = 3.2X10^{-6} μg/mL ED_{50} = 7.6X10^{-1} μg/mL ED_{50} = 3.4x10^{-7} μg/mL ED_{50} = 3.2x10^{-3} μg/mL	
	koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin Adriamycin	Prostate adenocarcinoma cells (PC-3)		ED_{50} = 1.5X10^{-1} μg/mL ED_{50} = 3.3X10^{-6} μg/mL ED_{50} = 3.1 μg/ml ED_{50} = 1.2x10^{-7} μg/mL ED_{50} = 1.0x10^{-2} μg/mL	
	Koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin		Turbidity assay	IC_{50} = 5.0 μM IC_{50} = 0.8 μM IC_{50} = 40.0 μM IC_{50} = 0.6 μM	
	Koelreuterin -1 Austrobailignan -1 Austrobailignan -2 Podophyllotoxin		Sedimentation assay	IC_{50} = 20.0 μM IC_{50} = 1 μM IC_{50} = 45 μM IC_{50} = 1 μM	
Leaves	Ethanol extract	Renal cell carcinoma (786-O-SI3)	MTT assay. Wound healing migration assay. Cell invasion and migration assays. Determination of MMP-2 and u-PA by zymography.	Delaying wound healing. Reducing invasion and migration. Suppressing the expression and activity of MMP-2 and u-PA.	**[42]**
Twigs	EtOAc fraction *n*-BuOH fraction Methanol fraction	Brine shrimp eggs	Brine shrimp lethality assay	LC_{50} = 75 μg/mL LC_{50} = 83 μg/mL LC_{50} = 132 μg/mL	**[9]**

Table 3 Continued.

Part use	Extract/compound	Cell line	Method	Result	Ref.
	n-BuOH fraction Austrobailignan -1 Methyl gallate	Breast carcinoma cells (MCF-7)	*In vitro* cell viability assay using crystal violet staining viability assay	IC_{50} = >100 μg IC_{50} = 40.4 μg IC_{50} = 48.6 μg	
		Colon carcinoma cells (HCT-116)		IC_{50} = >100 μg IC_{50} = 77.4 μg IC_{50} = 95.5 μg	
		Lung carcinoma cells (A-549)		IC_{50} = >100 μg IC_{50} = >100 μg IC_{50} = > 100 μg	
Leaves	Austrobailignan-1	Human non-small cell lung cancer (A549) Human non-small cell lung cancer (H1299)	Terminal deoxynucleotide transferase dUTP nicked-end labeling assay. Caspase activity assay. Immunoblot analysis. DNA relaxation assay. Comet assay. ATM and γH2AX western blot analysis.	IC_{50} = 41 and 22 nM on A549 and H1299, respectively Austrobailignan-1 caused cell cycle G2/M phase arrest and cell death in both cells. Austrobailignan-1 blocked topoisomerase 1 activity, initiated the DNA damage signaling pathway, regulated cell cycle related proteins and induced intrinsic mitochondria-mediated apoptosis	**[29]**
		Koelreuteria paniculata			
Leaves	EtOAc fraction *n*-BuOH fraction 3”-Galloylquercitrin Quercetin-3’-O-*β*-arabinopyranoside		PTK inhibition	IC_{50} = 540 μg/mL IC_{50} = 650 μg/mL IC_{50} = 24 μg/mL IC_{50} = 40 μg/ml	**[21]**
Flowers	Carotenoid fraction	Human skin fibroblast (BJ)	MTT assay after 24 and 72 hr.	IC_{50} = >1000 μg/mL (both)	**[32]**
		Breast cancer cell (MDA-MB-231)		IC_{50} = >1000 / 522.2 μg/mL	
		Human hepatocyte carcinoma (HepG2)		IC_{50} = >1000 / 459.9 μg/mL	
Leaves	Ethanol extract	Human colon adenocarcinoma (HT-29) Prostate adenocarcinoma cells (PC-3)	MTT assay	IC_{50} = 23.63 μg/mL IC_{50} = 80.56 μg/mL	**[12]**
Flowers				IC_{50} = 21.44 μg/mL IC_{50} = 58.76 μg/mL	
Bark				IC_{50} = 339.4 μg/mL IC_{50} = 182.8 μg/mL	
Seeds	Glyceride oil	Mouse embryonic fibroblast (BALB/3T3 clone A31)	MTT assay	CC_{50} = 5402 μg/mL	**[40]**
		Normal human epithelial (MCF-A10)		IC_{50} = 2284 μg/mL	
		Prostate adenocarcinoma cells (PC-3)		IC_{50} = 2221 μg/mL	
		Human colon adenocarcinoma (HT-29)		IC_{50} = 2274 μg/mL	
		PC-3 selectivity		1.03	
		HT-29 selectivity		1	

Note. DDH, dihydrodiol dehydrogenase; LCELISA, Live-cell enzyme-linked immunosorbent assay; PTK, Protein tyrosine kinase; MTT, 3-(4,5-dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide; MMP-2, Matrix metalloproteinase-2, u-PA, *urokinase*-type plasminogen activator and ATM, Ataxia telangiectasia mutated protein kinase.

With the continued attempts on studying the cytotoxic effect of cyclolignans **[29]**, the isolated austrobailignan-1 from the leaves of *K. elegans* was investigated for its antiproliferative effects on human non-small cell lung cancer A549 and H1299 and another possible cytotoxic mechanism. At lower concentrations (lower than 10 nM), austrobailignan-1 inhibited cell proliferation, while treatment with high concentrations (over 30 nM) exhibited apoptotic cell death, compared to camptothecin (a topoisomerase-1 inhibitor), with equipotent inhibitory activity. Accordingly, it was intended to evaluate topoisomerase-1 inhibitory activity of austrobailignan-1 and determine the cell death pathway **[29]**. It inhibited topoisomerase-1 activity, and then caused a DNA damage signaling pathway causing cell death (Fig. 6). The ethanol extract of *K. henryi* leaves together with four pure isolated compounds from the extract were tested on various human tumor cells **[15]**. The effect of the extract showed a great suppressive DDH expression leading to induction of apoptosis. Whereas only two compounds kaempferol-3-O-glucoside (astragalin) and apigenin-4'-O-β-glucopyranoside were effective. Astragalin inhibited intermediately DDH protein expression, while apigenin-4'-O-β-glucopyranoside caused cancer cell apoptosis through induction of poly (ADP-ribose) polymerase (PARP) cleavage. The ethanol extract of *K. formosana* leaves was tested on human renal cell carcinoma 786-O-SI3 **[42]**. It inhibited the invasion, motility, and migration of the cancer cells which was assured by delayed wound healing of the cells and reduction of *urokinase*-type plasminogen activator (u-PA) and Matrix metalloproteinase-2 (MMP-2) expression.

The carotenoid fraction obtained from the flowers of *K. paniculata* was examined for its antineoplastic potential on three different tumor cell lines **[32]**. MTT assay was performed for 24 and 72 hr. after treatment. The initial effect of the carotenoid fraction was established at IC_{50} over 1000 µg/mL towards all tested cell lines, which indicated a lack of antineoplastic activity. The most sensitive cell line was human hepatocyte carcinoma HepG2 with IC_{50} = 459.9 µg/ml, followed by breast cancer cell MDA-MB-231 with IC_{50} = 522.2 µg/ml after 72 hr. of treatment. The antiproliferative activities of the ethanol extracts of different parts of *K. paniculata* on two tumor cell lines were examined using cisplatin as anti-tumor standard by using of MTT assay **[12]**. The results showed enhanced antiproliferative effect of the flowers extract followed by the leaves extract on human colon adenocarcinoma HT-29, compared to cisplatin (2.5 µg/mL), while the bark extract exhibited weak inhibition effect on this cell line. Prostate cancer cells were less sensitive to all the extracts, compared to the standard (1.01 µg/mL). Similarly, Andonova *et al.* **[40]** continued the work on the anti-tumor activity of *K. paniculata*, the previous two cell lines, in addition to mouse embryonic fibroblast BALB/3T3 clone A31 and normal human epithelial MCF-A10 cell lines were used to evaluate the glyceride oil of the seeds. As the initial cytotoxicity of the cisplatin was detected at a concentration around 7.5 µg/mL, the first effect of the glyceride oil was recognized at a high concentration (over 1000 µg/mL) toward all tested cell lines indicating absence of cytotoxicity. The anti-proliferative selectivity (the ratio of the oil susceptibility to tumor and normal cell line) of the seed oil towards prostate adenocarcinoma cells PC-3 and human colon adenocarcinoma HT-29 cell lines was evaluated and no selectivity was found (1 and 1.03, respectively), compared to the higher ratio of cisplatin (1.68 on both cell lines). The aqueous methanol extract of *K. elegans* twigs was fractionated and the preliminary cytotoxic effect of the fractions was evaluated using brine shrimp lethality assay **[9]**. EtOAc, butanol, and methanol fractions showed good effect. The butanol fraction and its isolated compounds; methyl gallate and austrobailignan-1 were selected to evaluate their anticancer activity against several human tumor cells using *in vitro* cell viability assay. The results revealed that the butanol fraction didn't show cytotoxicity against both lung A-549 and colon HCT-116 carcinoma cells while it had weak cytotoxicity against breast adenocarcinoma cells MCF-7. Methyl gallate displayed weak cytotoxic effect against A-549 and good cytotoxicity against both HCT-116 and MCF-7. Austrobailignan-1 showed significant cytotoxic effect against HCT-116 and MCF-7, while it didn't show cytotoxic activity against A-549. The last result disagreed with the previous finding **[26]**.

5.2. Antioxidant activity

Numerous reports have assessed the antioxidative capacity of extracts and some of active compounds obtained from different parts of *K. elegans* and *K. paniculata* **[13, 14, 20, 32, 34, 44-48]**. The leaves ethanol extract of *K. elegans* was inspected for its anti-radical activites using 2,2-Diphenyl-1-picrylhydrazyl radical (DPPH), hydroxyl and superoxide radicals, in addition to ferric reducing antioxidant power (FRAP) assays **[44]**. *K. elegans* revealed a good radical scavenging activities, beside a potent reducing power effect at different concentrations. Moreover, HO-1 induction activity using luciferase reporter assay was tested **[44]**.

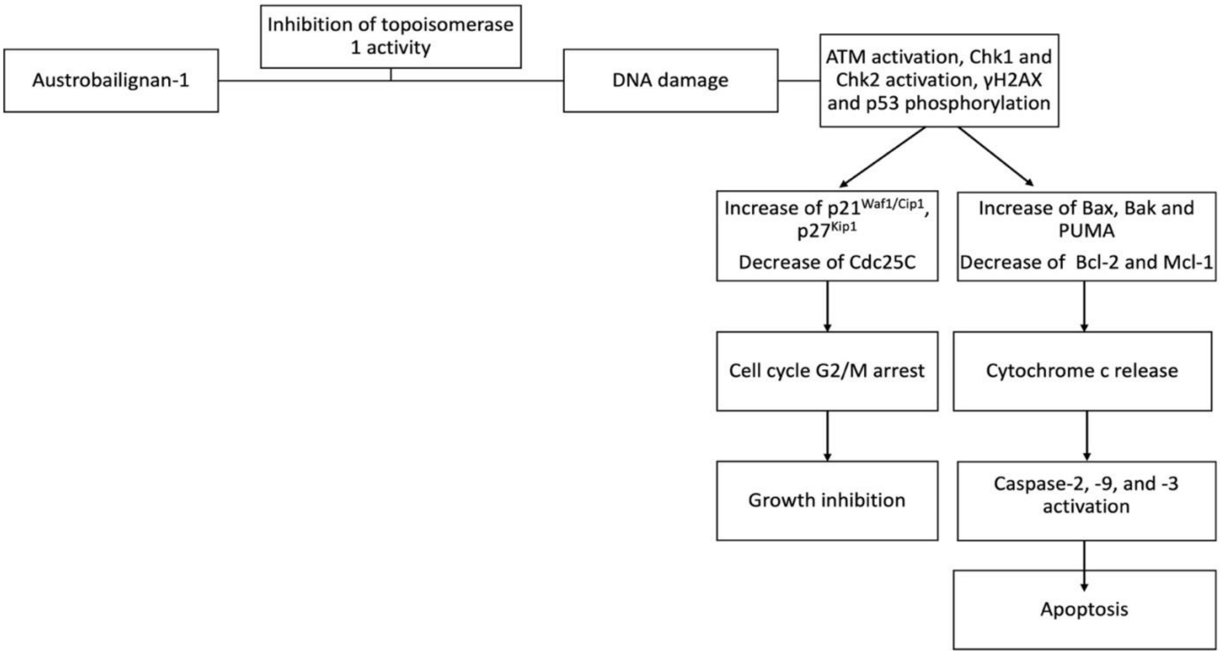

Fig. 6. Schematic representation of the anti-cancer mechanisms of austrobailignan-1 in human non- small cell lung cancer A549 and H1299 cell lines. ATM, Ataxia telangiectasia mutated; Chk1, Checkpoint kinase 1; Chk2, Checkpoint kinase 2; Cdc25c, Cell division cycle 25C; Bax, Bcl-2-associated X protein; Bak, Bcl-2 homologous antagonist/killer; PUMA, p53 upregulated modulator of apoptosis; Bcl-2, B-cell lymphoma 2 and Mcl-1, Myeloid cell leukemia-1.

The extracts from *K. elegans* at 1 mg/mL resulted in about 2-fold raise in the promoter activity of HO-1 using quercetin as the positive control. Lin *et al.* **[20]** agreed with the previous findings **[44]** regarding the ability of *K. formosana* to inhibit DPPH radical. They investigated how the plant ethanol extract protected human umbilical vein endothelial cells (HUVECs) from oxidized LDL-mediated dysfunction *in-vitro*. The study showed that, pretreatment with the extract hindered copper-induced oxidation of LDL and ApoB fragmentation in a dose dependent manner compared to trolox as a positive control. The extract reduced copper-induced lipid peroxidation indicated by reduction of malondialdehyde formation. Pretreatment with 100 µg/mL of *K. formosana* ethanolic extract almost completely inhibited oxidized LDL-induced reactive oxygen species formation. The extract restored the alternation of mitochondrial transmembrane permeability after treatment with oxidized LDL, however it didn’t show cytotoxicity to HUVECs **[20]**. DPPH assay was also made on the plant different aerial parts methanol extracts of *K. elegans* **[35]**. The bark extract was found to exceed the leaves in the scavenging activity followed by defatted seed cake extract. **Chen *et al.* [45]** extracted the leaves of *K. elegans* using acetone solvent, and evaluated its antioxidant effect using enzyme inhibitory assays. The extract exhibited good XOD and tyrosinase inhibitory activities, with a potent anti-lipoxygenase activity. Further tests were done with tyrosinase using high-performance liquid chromatography with diode-array detection (HPLC-DAD) method. After comparing the HPLC chromatograms of the extract before and after adding tyrosinase enzyme, it was observed that the heights of the peaks at 13.49 and 35.28 minutes were noticeably reduced by adding of tyrosinase as compared with the absence of tyrosinase, making evidence that there were compounds that interacted with tyrosinase enzyme causing its inhibition and antioxidant activity **[45]**. Accordingly, it was intended to determine the compounds that caused the antioxidant activity by the help of HPLC-DAD method which allowed them to detect and isolate the compounds simultaneously **[14]**. They applied HPLC-DAD method on DPPH radical and XOD enzyme. The results showed that, there was an obvious decrease in the intensities of the peaks after 10.1 and 12.9 minutes on adding DPPH and XOD, respectively. Using LC-MS and NMR, the decreasing peaks were identified as 1,3,4,5-tetra-O-galloylquinic acid. After the isolation of this compound, DPPH and XOD assays were done using quercetin as positive control. This compound was a very efficient scavenger against DPPH and XOD.

In the investigated fractions of the leaves methanol extract of *K. paniculata*, four studies of Kumar *et al.* **[46-49]** were involved in examining DNA protective and antioxidant potential of methanol mother extract in addition to five fractions; hexane, chloroform, EtOAc, *n*-butanol and aqueous fractions. First, those fractions were examined for their genoprotective ability against DNA damage produced by Fenton's reagent in pUC18 plasmid DNA and 4-nitroquinoline-1-oxide (4-NQO) in calf thymus DNA protection assays, in addition to DNA protective effect in lipid peroxidation assay using modified thiobarbituric acid reactive species assay.

Table 4: Antioxidant activity of the genus *Koelreuteria*.

Part use	Extract/compound	Method	Results	Ref.
		Koelreuteria elegans		
Branches, Leaves	50% Ethanol extract	DPPH assay	20 μg/mL displayed the strongest free radical scavenging activity	**[20]**
		Copper-induced oxidation and peroxidation	Inhibition	
Leaves	1,3,4,5-tetra-O-galloylquinic acid	DPPH assay XOD assays	IC_{50} = 7.1 μM IC_{50} = 6.7 μM	**[14]**
Flowers	Aqueous extract	DPPH assay Reducing power assay ORAC assay TEAC assay	EC_{50} = 0.04 mg/mL EC_{50} = 0.131 mg/mL 2.53 mmol Trolox/g 10.57 mmol Trolox/g	**[34]**
Leaves	Acetone extract	XOD assay Tyrosinase assay LOX assay	IC_{50} = 91.8 μg/mL IC_{50} = 289 μg/mL IC_{50} = 17.5 μg/mL	**[45]**
Leaves	Ethanol extract	DPPH assay Hydroxyl radical activity Superoxide radical activity	IC_{50} = 3.6 μg/mL IC_{50} = 0.36 μg/mL IC_{50} = 19.8 μg/mL	**[44]**
		Reducing power activity at: 25 μg of extract 50 μg of extract 75 μg of extract	 A= 0.827 A= 1.590 A= 1.952	
		Luciferase reporter assay at: 1 mg/ml of extract	Increased 2-fold	
Leaves Bark Defatted seed cake	Methanol extracts	DPPH assay	EC_{50} =0.022 mg/mL EC_{50} =0.023 mg/mL EC_{50} =0.025 mg/mL	**[35]**
		Koelreuteria paniculata		
Leaves	Chloroform extract Ethyl acetate extract	DPPH assay	IC_{50} = 121.98 μg/mL IC_{50} = 105 μg/mL	**[48]**
		ABTS assay	IC_{50} = 75.48 μg/mL IC_{50} = 62.12 μg/mL	
		Reducing power activity	IC_{50} = 60.94 μg/mL IC_{50} = 72.70 μg/mL	
		Superoxide radical activity	IC_{50} = N.D μg/mL IC_{50} = 167.59 μg/mL	
Leaves	*n*-Butanol extract Aqueous extract	DPPH assay	IC_{50} = 135.07 μg/mL IC_{50} = 111.04 μg/mL	**[47]**
		ABTS assay	IC_{50} = 72.65 μg/mL IC_{50} = 152.18 μg/mL	
		Reducing power activity	IC_{50} = N.D μg/mL IC_{50} = 132.79 μg/mL	
		Superoxide radical activity	IC_{50} = 145.56 μg/mL IC_{50} = 332.60 μg/mL	
Leaves	Methanol extract	DPPH assay ABTS assay Reducing power activity Superoxide radical activity	IC_{50} = 115 μg/mL IC_{50} = 54.54 μg/mL IC_{50} = 110 μg/mL IC_{50} = 135 μg/mL	**[49]**
	Hexane fraction at concentration of 200 μg/ml		Low inhibition percentage	
Leaves	Methanol extract Chloroform extract Ethyl acetate extract *n*-Butanol extract Aqueous extract	Peroxyl radical scavenging activity	IC_{50} = 36.44 μg/mL IC_{50} = 625.38 μg/mL IC_{50} = 36.44 μg/mL IC_{50} = 505.24 μg/mL IC_{50} = ND μg/mL	**[46]**

Table 4 Continued.

Part use	Extract/compound	Method	Results	Ref.
Flowers	Carotenoid fraction	DPPH assay	37.06 mMTE/g extract	**[32]**
		ABTS assay	368.86 mMTE/g extract	
Stem bark	Aqueous ethanol extract	DPPH assay	278.39 mmol TE/g DW	**[13]**
		ABTS assay	342.55 mmol TE/g DW	
		FRAP assay	637.62 mmol TE/g DW	
		CUPRAC assay	846.16 mmol TE/g DW	
		DNA nicking protection assay at 0.6, 1.25 and 2.5 µg/mL	61, 12 and 7 ng	
Leaves		DPPH assay	751.27 mmol TE/g DW	
		ABTS assay	645.88 mmol TE/g DW	
		FRAP assay	1838.92 mmol TE/g DW	
		CUPRAC assay	576.68 mmol TE/g DW	
		DNA nicking protection assay at 0.6, 1.25 and 2.5 µg/mL	41, 36 and 24 ng	
Flower		DPPH assay	1133.47 mmol TE/g DW	
		ABTS assay	1437.49 mmol TE/g DW	
		FRAP assay	4308.02 mmol TE/g DW	
		CUPRAC assay	1748.50 mmol TE/g DW	
		DNA nicking protection assay at 0.6, 1.25 and 2.5 µg/mL	35, 20 and 11 ng	
Flower buds		DPPH assay	904.12 mmol TE/g DW	
		ABTS assay	686.68 mmol TE/g DW	
		FRAP assay	2464.10 mmol TE/g DW	
		CUPRAC assay	731.81 mmol TE/g DW	
Seeds	Glyceride oil	DNA Nicking Protection Assay	The mount of nicked DNA was reduced	**[40]**

Note. DPPH, 2,2-Diphenyl-1-picrylhydrazyl radical; XOD, xanthine oxidase; ORAC, Oxygen radical absorbance capacity; TEAC, Trolox equivalent antioxidant capacity; LOX, Lipoxygenases, ABTS, 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid; FRAP, Ferric Reducing Antioxidant Power and CUPRAC, Cupric reducing antioxidant capacity.

Methanol, EtOAc and chloroform fractions protected DNA at 50 µg/mL against Fenton's reagent, while the other fractions protected DNA at 250 µg/mL. All the extract/fractions protected DNA at the highest examined concentration (250 µg/mL) against 4-NQO except the chloroform fraction, which showed very less protection at the highest concentration. EtOAc fraction displayed the highest capability to hinder peroxyl radicals and the lowest inhibition was exhibited by the aqueous fraction. Furthermore, the extract/fractions were examined for their superoxide anion, DPPH and 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid (ABTS) radical scavenging activity, beside FRAP effect. The mother methanol extract demonstrated the highest superoxide radical scavenging activity compared to the standard rutin while the hexane and chloroform portions were less represented. In DPPH assay, the results of the samples were compared to the standard ascorbic acid (IC_{50} = 55.88 µg/mL). The EtOAc fraction presented the highest DPPH inhibition effect, while the hexane fraction showed poor effect. *Butylated hydroxytoluene* (IC_{50} = 197.55 µg/mL) was used as standard compound in ABTS assay to compare the antioxidant activity of the different fractions. The methanol extract scored highest action and the hexane portion was less sensitive. Lastly, in FRAP study, the reductive potential of chloroform fraction (IC_{50} = 103.85 µg/mL) flourished the highest scavenging ability as compared to ascorbic acid, while hexane and *n*-butanol fractions were less potent. The HPLC analysis of the flowers of *paniculata* species was performed to isolate the carotenoid fraction and test the scavenging ability towards DPPH and ABTS radicals **[32]**. The tested fraction showed a good *in-vitro* antioxidant activity.

Tsai *et al.* **[34]** intended to optimize the aqueous extraction time of *K. henryi* flowers to achieve the maximum antioxidant potential using different evaluation methods; FRAP, DPPH, oxygen radical absorbance capacity (ORAC), and trolox equivalent antioxidant capacity (TEAC) assays. The results had better values in the 150 -min extract than the others. Accordingly, 150 -min extract was selected to evaluate the protective ability against hydrogen peroxide produced cellular oxidative injury. The pretreatment of mouse fibroblast L929 cells with the flower extract could repair the mitochondrial membrane capability as normal cells **[34]**. Based on Andonova *et al.* **[13]** studies which were concerned mainly with the comparison of different parts of *K. paniculata*, the *in-vitro* antioxidant potential of the ethanol aqueous extracts was estimated by the aid of DPPH, ABTS, cupric reducing antioxidant capacity (CUPRAC), and FRAP assays. It was revealed that the flower extract recorded the most pronounced antioxidant capacity in the four used methods, followed by the flower buds, leaves, and stem bark extracts. The arrangement was different in the CUPRAC assay, where the stem bark was second to the flower extract. In the same study, the DNA-protective capacity was tested on plant concentrations; 0.6, 1.25 and 2.5 µg/mL using *in vitro* DNA nicking protection assay and compared to trolox as a positive control. The bark extract showed the best protective effect with a nicked DNA band intensity; 7 ng at the highest tested concentration followed by flower and leaf extracts. The assay wasn't performed on the flower buds as they showed antioxidant activity similar to and lower than the flowers. Similarly, in a continuation of Andonova *et al.* **[40]** work on *K. paniculata*, the protective role against DNA nicking for the glyceride oil of the seeds was evaluated. The results showed that, 1 µL of the tested oil significantly reduced the amount of nicked DNA. Unlike the previous research of the authors, it was difficult to determine concentration-dependent DNA protection due to the limited solubility of the extract in aqueous solutions.

5.3. Antimicrobial activity

In the past decades, both species *K. elegans* and *K. paniculata* have been used traditionally as antibacterial and antifungal remedies. The effect was verified in various investigations showing the antimicrobial efficacy of the different extracts and separated compounds obtained from the genus plant parts **[5, 12, 17, 24, 50]**. The antimicrobial activity of each plant beside its extracts with their inhibition zones (IZ) and/or IC_{50} are summarized in table 5.

Eighteen fractions from the methanol extract of *K. paniculata* leaves were prepared by column chromatography and their antibacterial activity was evaluated against *Bacillus subtilis* and *Staphylococcus aureus* (Gram positive) and *Escherichia coli* and *Pseudomonas aeruginosa* (Gram negative) using standard antibiotics gentamicin (10 µg/disc) and chloramphenicol (30 µg/disc) as positive controls and dimethyl sulphoroxide (DMSO) (35 µL/disc) as negative control **[17]**. The antifungal activity was also assessed against *Pyricularia grisea* using Kirby–Bauer disc diffusion method. The fractions (35 µL) exhibited antibacterial activity only against gram positive organisms. Fraction 2 (from CH_2Cl_2) exposed the highest activity against *Bacillus subtilis* (20 mm), followed by fraction 12 (from *n*-BuOH, 16 mm). The latter exhibited the best activity against *Staphylococcus aureus* (18 mm) and *Pyricularia grisea* (36 mm). Fractions 4 and 5 (from EtOAc) revealed great results against *P. grisea* (32 mm and 33 mm, respectively). Remarkably, the total extract of the leaves of *K. paniculata* didn't show antimicrobial effect in the tested range against *P. grisea* **[17]**.

The antimicrobial effect of the pure phenolic compounds, ethyl gallate and methyl gallate isolated from the aerial parts of *K. paniculata* were evaluated **[23, 24]**. Both compounds demonstrated antimalarial efficiency against chloroquine-sensitive *Plasmodium falciparum* (IC_{50} 6.46 and 6.95 µM, respectively). and chloroquine-resistant *Plasmodium falciparum* (IC_{50} values of 9.34 and 4.18 µM, respectively).

Besides, ethyl gallate exhibited weak antibacterial effect against *Escherichia coli* (IC_{50} = 101 µM) using ciprofloxacin as positive control. Zazharskyi *et al.* **[50]** assessed the antibacterial efficiency of the leaves ethanol extract of *K. paniculata* (0.1 mL) against fifteen species of bacteria, *Enterococcus faecalis*, *Listeria ivanovii, Listeria innocua, Listeria monocytogenes, Rhodococcus equi* and *Corynebacterium xerosis* (Gram positive) and *Enterobacter aerogenes*, *Proteus mirabilis*, *Serratia marcescens*, *Salmonella typhimurium*, *Campylobacter jejuni, Yersinia enterocolitica, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Escherichia coli* (Gram negative), as well as, *Candida albicans* fungus using standard antibiotic azithromycin (15 µg) as positive control and 15.0 µg amphotericin as a control against the fungus.

It was reported that *Serratia marcescens*, *Campylobacter jejuni* and *Proteus mirabilis*, highly resistant to antibacterials, were susceptible to *K. paniculata* extract with inhibition zones 16.7, 13.3 and 8.9, mm, respectively, compared to *Enterobacter aerogenes*, *Klebsiella pneumoniae,* genus *Listeria*, *Pseudomonas aeruginosa* and *Candida albicans*, which were resistant to the extract. Moreover, *E. coli* was sensitive to the ethanol extract of the leaves (11.5 mm IZ) **[50]** which disagreed with the previous findings **[17]**.

Different parts of *K. paniculata* were compared to their antibacterial effect against nine pathogenic strains using 100 µL of chlorhexidine as a positive control and DMSO (5% (v/v) as a negative control **[12]**.

Table 5: Antimicrobial activity of the genus *Koelreuteria.*

Part use	Extract/compound	Activity	Tested strains	Results IZ (mm), IC_{50} (μM)	Ref.
			Koelreuteria elegans		
Leaves	Aqueous methanol extract	Antifungal activity	*Geotricum candidum*	IZ =14.1	**[5]**
			Candida albicans	NA	
		Antibacterial activity	*Staphylococcus aureus*	IZ =15.9	
			Bacillus subtilis	IZ =17.4	
			Enterococcus faecalis	IZ =16.3	
			Pseudomonas aeruginosa	NA	
			Salmonella typhimurium	IZ =10.1	
			Escherichia coli	IZ =9.3	
	1, 3, 4, 5-tetra-O-galloylquinic acid butyl ester	Antifungal activity	*Geotricum candidum*	IZ =25.1	
			Candida albicans	NA	
		Antibacterial activity	*Staphylococcus aureus*	IZ =21.7	
			Bacillus subtilis	IZ =27.2	
			Enterococcus faecalis	IZ =19.5	
			Pseudomonas aeruginosa	NA	
			Salmonella typhimurium	IZ =16.3	
			Escherichia coli	IZ =12.4	
	Methyl gallate	Antifungal activity	*Geotricum candidum*	IZ =17.8 mm	
			Candida albicans	NA	
		Antibacterial activity	*Staphylococcus aureus*	IZ =19.4 mm	
			Bacillus subtilis	IZ =21.3 mm	
			Enterococcus faecalis	IZ =18.9 mm	
			Pseudomonas aeruginosa	NA	
			Salmonella typhimurium	IZ =13.5	
			Escherichia coli	IZ =9.9	
	Guaijaverin	Antifungal activity	*Geotricum candidum*	NA	
			Candida albicans	NA	
		Antibacterial activity	*Staphylococcus aureus*	NA	
			Bacillus subtilis	NA	
			Enterococcus faecalis	NA	
			Pseudomonas aeruginosa	NA	
			Salmonella typhimurium	NA	
			Escherichia coli	NA	
			Koelreuteria paniculata		
Leaves	1 (Hexane fraction)	Antifungal activity	*Pyricularia grisea*	NA	**[17]**
		Antibacterial activity	*Bacillus subtilis*	IZ =15	
			Staphylococcus aureus	IZ =11	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	2 (CH_2Cl_2 fraction)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =20	
			Staphylococcus aureus	IZ =13	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	3 ($CHCl_3$ fraction)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	NA	
			Staphylococcus aureus	IZ =12	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	4 (EtOAc fraction 1)	Antifungal activity	*Pyricularia grisea*	IZ =32	
		Antibacterial activity	*Bacillus subtilis*	IZ =0.85	
			Staphylococcus aureus	NA	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	5 (EtOAc fraction 2)	Antifungal activity	*Pyricularia grisea*	IZ =33	
		Antibacterial activity	*Bacillus subtilis*	NA	
			Staphylococcus aureus	IZ =12	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	6 (EtOAc fraction 3)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =10	
			Staphylococcus aureus	IZ =10	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	

Table 5 Continued.

Part use	Extract/compound	Activity	Tested strains	Results IZ (mm), IC_{50} (μM)	Ref.
	7 (EtOAc fraction 4)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	NA	
			Staphylococcus aureus	NA	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	8 (Acetone fraction)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =0.95	
			Staphylococcus aureus	11	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	9 (BuOH fraction 1)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	NA	
			Staphylococcus aureus	NA	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	10 (BuOH fraction 2)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =0.90	
			Staphylococcus aureus	IZ =11	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	11 (BuOH fraction 3)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =10	
			Staphylococcus aureus	IZ =12	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	12 (BuOH fraction 4)	Antifungal activity	*Pyricularia grisea*	IZ =36	
		Antibacterial activity	*Bacillus subtilis*	IZ =16	
			Staphylococcus aureus	IZ =18	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	13 (MeOH fraction 1)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	NA	
			Staphylococcus aureus	NA	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	14 (MeOH fraction 2)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	NA	
			Staphylococcus aureus	IZ =13	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	15 (MeOH fraction 3)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	NA	
			Staphylococcus aureus	IZ =14	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	16 (MeOH fraction 4)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =0.8	
			Staphylococcus aureus	IZ =15	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	17 (MeOH fraction 5)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =10	
			Staphylococcus aureus	IZ =12	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
	18 (MeOH fraction 6)	Antifungal activity	*Pyricularia grisea*	NA	
		Antibacterial activity	*Bacillus subtilis*	IZ =0.9	
			Staphylococcus aureus	IZ =10	
			Escherichia coli	NA	
			Pseudomonas aeruginosa	NA	
Aerial parts	Ethyl gallate	Antimalarial activity	Chloroquine-sensitive *Plasmodium falciparum* protozoan	IC_{50}= 6.46	**[23, 24]**
			Chloroquine-resistant *Plasmodium falciparum* protozoan	IC_{50}= 9.34	
		Antibacterial activity	*Escherichia coli*	IC_{50}= 101	

Table 5 Continued.

Part use	Extract/compound	Activity	Tested strains	Results IZ (mm), IC_{50} (µM)	Ref.
	Methyl gallate	Antimalarial activity	Chloroquine-sensitive *Plasmodium falciparum* protozoan Chloroquine-resistant *Plasmodium falciparum* protozoan	IC_{50}= 6.95 IC_{50}= 4.18	
Flower	Ethanol extract	Antibacterial activity	*Escherichia coli at 150, 100* µL *Salmonella enterica at 150, 100* µL *Klebsiella at 150, 100* µL *Pseudomonas aeruginosa at 150, 100* µL *Proteus vulgaris at 150, 100* µL *Staphylococcus aureus at 150, 100* µL *Bacillus subtilis at 150, 100* µL *Bacillus cereus at 150, 100* µL *Listeria monocytogenes at 150, 100* µL	NA NA NA NA IZ =10.04, 6.05 NA IZ =14.03, 11.03 IZ =14.06 mm, NA NA	**[12]**
Leaves		Antibacterial activity	*Escherichia coli at 150, 100* µL *Salmonella enterica at 150, 100* µL *Klebsiella at 150, 100* µL *Pseudomonas aeruginosa at 150, 100* µL *Proteus vulgaris at 150, 100* µL *Staphylococcus aureus at 150, 100* µL *Bacillus subtilis at 150, 100* µL *Bacillus cereus at 150, 100* µL *Listeria monocytogenes at 150, 100* µL	IZ =9.02, 6.02 NA NA NA NA NA NA NA NA	
Bark		Antibacterial activity	*Escherichia coli at 150, 100* µL *Salmonella enterica at 150, 100* µL *Klebsiella at 150, 100* µL *Pseudomonas aeruginosa at 150, 100* µL *Proteus vulgaris at 150, 100* µL *Staphylococcus aureus at 150, 100* µL *Bacillus subtilis at 150, 100* µL *Bacillus cereus at 150, 100* µL *Listeria monocytogenes at 150, 100* µL	NA NA NA IZ =14.02, 5.03 IZ =8.04, 6.02 mm NA IZ =18.04, 11.03 IZ =14.03, 6,02 NA	
Leaves	Ethanol extract	Antibacterial activity	*Enterococcus faecalis* *Proteus mirabilis* *Seracia marcescens* *Salmonella typhimurium* *Campylobacter jejuni* *Escherichia coli* *Listeria ivanovii* *Listeria innocua* *Listeria monocytogenes* *Rhodococcus equi* *Corynebacterium xerosis* *Enterobacter aerogenes* *Yersinia enterocolitica* *Klebsiella pneumoniae* *Pseudomonas aeruginosa*	IZ =8.4 mm IZ =8.9 mm IZ =16.7 mm IZ =10.7 mm IZ =13.3 mm IZ =11.5 mm IZ = NA IZ = NA IZ = NA IZ = NA IZ = NA IZ = NA IZ = NA IZ = NA IZ = NA	**[50]**
		Antifungal activity	*Candida albicans*	IZ = NA	

Note. IZ, Inhibition zone; IC_{50}, Half maximal inhibitory concentration; EtOAc, Ethyl acetate and NA, No activity

A dose of 100 and 150 µL of ethanol extracts were applied using agar diffusion method. The stem bark extract revealed the highest activity against *Bacillus subtilis* (18 mm IZ) and *Bacillus cereus* (14 mm IZ) at the high tested concentration, which is quite similar to the flower extract (14 mm IZ for both). The gram-negative *Proteus vulgaris* was more sensitive to the flower extract (10 mm IZ) followed by the bark extract (8 mm IZ). Interestingly, *B. cereus* and *P. vulgaris* were resistant to the standard chlorhexidine. Conversely, *K. paniculata* leaves extract didn't inhibit the tested cultures except for *Escherichia coli* (9 mm IZ). There was an agreement **[12]** with the previous findings **[17, 50]** that, *Pseudomonas aeruginosa* was resistant to *K. paniculata* leaves extract. Attractively, *K. paniculata* stem bark extract showed an inhibitory zone against *Pseudomonas aeruginosa* (14 mm IZ) **[12]**.

The only available literature related to the antimicrobial effect of *K. elegans* was conceived by El Naggar *et al.* **[5]**. The study investigated the antimicrobial effect of the leaves' aqueous methanol extract, beside three isolated pure compounds; 1, 3, 4, 5-tetra-O-galloylquinic acid butyl ester, methyl gallate and guaijaverin. This effect was assessed against six bacterial strains; *Staphylococcus aureus*, *Bacillus subtilis*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Salmonella typhimurium* and *Escherichia coli*, and two fungal strains; *Candida albicans* and *Geotricum candidum* using standard antibiotics; ampicillin (gram positive bacteria) and gentamicin (gram negative bacteria) with amphotericin B (antifungal). The results showed that, 1, 3, 4, 5-tetra-O-galloylquinic acid butyl ester scored the highest inhibitory zones against most of the examined microorganisms, followed by methyl gallate. Guaijaverin exhibited no inhibitory zones against all the examined microorganisms. Gram positive *B. subtilis* was the most sensitive microorganism to all the tested samples, while *C. albicans* and the gram-negative *P. aeruginosa* were resistant **[5]**.

5.4. Other pharmacological activities

5.4.1. Hepatoprotective activity

Table 6: Other pharmacological activities of the genus *Koelreuteria*.

Part use	Extract/compound	Activity	Experimental approach	Results	Ref.
			Koelreuteria elegans		
Leaves	Aqueous methanolic extract	Hepatoprotective activity	Determination of hepatic function after treatment with the plant extract + CCl_4	ALT= 76.4 U/m AST= 188.2 U/m GGT= 13.5 U/L ALP= 46.1 IU/L TB= 0.58 mg/dl Vitamin C= 2.45 µg/ml SOD= 299.5 U/ml CAT= 16929 U/ml GSH= 41.24 mg/dl	**[5]**
Leaves and fruits	Methanolic extract	Anti-Alzheimer's activity	Rats were injured using intracerebroventricular (ICV) injection of streptozotocin (STZ) Morris water maze test Histopathological examination Measuring neuroinflammatory mediators TNF-α, NF-κB and IL-1β	Leaves and fruits extracts revealed great effect on memory function and spatial learning in behavioral experiments of the injured STZ tested mice. The extracts revealed pronounced improvement in hisopathological profile of the cerebral cortex of the injured tested mice. Both extracts reduced all the assessed inflammatory markers and neurodegeneration in AD. The fruit extract was more potent in ameliorating the damaging effect of STZ in a mice model of AD	**[51]**
			Koelreuteria paniculata		
Seeds	3-O-[*α*-L-arabinofuranosyl (1→3)-*β*-D-galactopyranosyl (1→2)]-(6-O-methyl)- *β*-D-glucuronopy- ranosyl-28-O-2-methylbutanoyl-A2-barrigenol 3-O-[*β*-D-galactopyranosyl (1→2)]-(6-O-methyl)-*β*-D-glucuronopyranosyl-22-O-2-methylbutanoyl-A2-barrigenol	Anti-Alzheimer's activity	Y maze test Novel object recognition test Morris water maze test Passive avoidance test Western blot method	Inhibit the damage of working memory, spatial memory, long-term memory and learning ability, but not recall memory and visual recognition. Enhance the expression of PP2A Inhibit the damage of working memory, spatial memory, long-term memory and learning ability, but not recall memory and visual recognition. Enhance the expression of PP2A. Enhance the expression of p-GSK-3*β*.	**[22]**

Note. AST, Aspartate transaminase; ALT, Alanine transaminase; ALP, Alkaline phosphatase; GGT, Gamma glutamyl transferase; TB, Total bilirubin; SOD, Superoxide dismutase; GSH, Glutathione; CAT, Catalase; PP2A, *Protein phosphatase 2A* and p-GSK-3*β*, phospho-Glycogen synthase kinase 3 beta.

Many studies were concerned in natural products as food supplements or therapeutic remedies for protecting and enhancing liver functions. *K. elegans* was considered as an example of those natural products due to its nourishment of phenolic acids and flavonoids and consequently, its antioxidant characteristics. The hepatoprotective effect of the leaves aqueous methanol extract was explored in CCl_4 induced liver toxicity in male Albino mice model and monitoring serum hepatic health indicating parameters after fourteen days of administration **[5]**. A dose of 200 µL/Kg b.wt of CCl_4 injected in the control group of mice caused disturbance of liver function; aspartate transaminase = 274 U/mL, alanine transaminase = 113.3 U/mL, alkaline phosphatase = 47.7 IU/L, gamma glutamyl transferase = 14.2 U/L, total bilirubin = 0.88 mg/dL, vitamin C=1.79 µg/mL, superoxide dismutase = 163.5 U/mL, Catalase = 13535 U/mL and glutathione = 26.8 mg/dL. Administration of 300 mg/Kg b.wt of the *K. elegans* extract with 200 µL/Kg b.wt of CCl_4, enhanced the liver functions and made the range of the parameters close to the normal values compared to the liver injury and the normal control groups.

5.4.2. Anti-Alzheimer's disease activity

Alzheimer's disease (AD) is a chronic neurodegenerative condition recognized by cognitive dysfunctions, impairment of learning and memory, and personality changes **[52, 53]**. Leaves and fruits methanol extracts of *K. elegans* revealed great effect in ameliorating the damaging effect of STZ in a mice model of AD. This great improvement was observed on memory function and spatial learning in behavioral experiments of the injured STZ tested mice, in addition to the noticeable enhancement in hisopathological profile of the cerebral cortex of the injured tested mice. Both samples lowered all the examined inflammatory markers and neurodegeneration in AD, whereas, the fruit extract was more potent **[51]**.

The isolated five barrigenol-type triterpenoid compounds from the seeds of *K. paniculata* (**80-84**, Fig. 4) were evaluated for their anti-AD activity using okadaic acid (OA) induced learning and memory impairment in mice **[22]**. Y maze test was used to evaluate the impairment of working memory, novel object recognition test and Morris water maze test were performed to evaluate spatial memory deficits, and passive avoidance test to evaluate long-term memory and learning ability. Injecting a dose of 100 ng/mouse of OA to the model group and the drug administered groups caused *protein phosphatase 2A* (PP2A) inhibition and glycogen synthase kinase 3 beta (GSK-3*β*) overactivation, producing hyper-phosphorylation of tau protein, then learning and memory impairment which caused failing in the mice behaviors towards the used models compared with the normal control group. Compounds 80-84 were injected in a dose of 0.5 mg/kg. The results showed that compounds 81 and 84 increased the expression of PP2A besides, compound 84 enhanced hippocampus phospho-glycogen synthase kinase 3 beta (p-GSK-3*β*) expression leading to renormalization of GSK-3*β* and PP2A levels, causing more reduction in hyperphosphorylation of tau. Furthermore, compounds 81 and 84 prevented the defect of working memory, long-term memory, spatial memory and learning ability, but had no effect on recall memory and visual recognition, in AD mice model **[22]**.

6. Conclusion

This scientific review focused on the phytochemistry and pharmacological activities of the genus *Koelreuteria*. Recent years have spotted a rise in the popularity of *Koelreuteria*, which has led to several scientific studies to give rigorous and experimental support for many of its traditional medicinal uses in the treatment of diseases. Even yet, there are just three species in the genus *Koelreuteria* which are distributed in Taiwan, Fiji, Northern China, Korea, and Japan, only *K. elegans* and *K. paniculata* are broadly studied but no phytochemical or pharmacological studies are available related to the *bipinnata* species. According to the literature, *Koelreuteria* plants have long been used in traditional medicine for a variety of conditions including enteritis, hepatitis, diarrhea, pharyngitis, cough, allergy, hyperlipidemia, hypertension, urethritis, malaria, eye related diseases. In recent decades, there has been an abundance of research conducted on the genus *Koelreuteria*, leading to important discoveries on the phytochemistry and pharmacology of the plant. Based on the information that is currently accessible, over 400 compounds have been found comprising phenolic acids, flavonoids, lignans, terpenoids, fatty acids, steroids, vitamins, carotenoids, etc. It is believed that the most abundant active compounds of the genus *Koelreuteria* are kaempferol, quercetin (and their glycosides), methyl gallate, gallic acid, saponins (a, b and c), pyrogallol, paniculatonoid (a and b), austrobailignan-1, and eicosenoic, oleic, linoleic and palmitic acids. Besides, it has been established that flavonoids and phenolic acids exhibit notable antioxidant, hepatoprotective, antitumor, hyperlipidemic and antimicrobial activities, lignans show antitumor and antioxidant activity and terpenoids display anti-Alzheimer and antitumor activities. It is nevertheless notable, that a number of gaps need to be filled in order to properly apply the genus *Koelreuteria*. The first gap is that more studies on the phytochemistry and analytical techniques of the compounds and crude extracts from the genus *Koelreuteria* is required. The pertinent research on the genus extracts or compounds will offer a strong scientific base as well as fresh perspectives on the clinical applicability, drug discovery, and quality assessment of upcoming pharmaceuticals. The second gap would be supplied by further pharmacological investigations of various chemical components from the different parts of the genus *Koelreuteria*. For these reasons, pharmacological mechanisms should be the primary area of study for researchers with an emphasis on the phytochemistry of the genus *Koelreuteria* in subsequent investigations. Finally, this review has highlighted the genus *Koelreuteria* potential for use in novel therapeutics and served as a foundation for further study into the use of medicinal plants.

Abbreviations

4-NQO	4-nitroquinoline-1-oxide	IL-1β	Interleukin-1 beta
ABTS	2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid	IZ	Inhibition zone
AD	Alzheimer's disease	LDL	Low-density lipoprotein
ATM	Ataxia telangiectasia mutated	Mcl-1	Myeloid cell leukemia-1
Bak	Bcl-2 homologous antagonist/killer	MMP	Matrix metalloproteinase
Bax	Bcl-2-associated X protein	MS	Mass spectroscopy
Bcl-2	B-cell lymphoma 2	MTT	3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide
Cdc25c	Cell division cycle 25C	NA	No activity
Chk1	Checkpoint kinase 1	NF-κB	Nuclear factor kappa B
Chk2	Checkpoint kinase 2	OA	Okadaic acid
CUPRAC	Cupric reducing antioxidant capacity	ORAC	Oxygen radical absorbance capacity
DDH	Dihydrodiol dehydrogenase	p-GSK-3*β*	Phospho-glycogen synthase kinase 3 beta
DMSO	Dimethyl sulphoroxide	PARP	Poly (ADP-ribose) polymerase
DPPH	2,2-Diphenyl-1-picrylhydrazyl radical	PP2A	Protein phosphatase 2A
EtOAc	Ethyl acetate	PTK	Protein tyrosine kinase
FRAP	Ferric Reducing Antioxidant Power	PUMA	p53 upregulated modulator of apoptosis
GSK-3*β*	Glycogen Synthase Kinase 3 beta	STZ	Streptozotocin
HPLC-DAD	High-performance liquid chromatography with diode-array detection	TEAC	Trolox equivalent antioxidant capacity
HO-1	Heme oxygenase-1	TNF-α	Tumor necrosis factor alpha
HR-ESIMS	High-resolution electrospray ionization mass spectroscopy	u-PA	Urokinase-type plasminogen activator
HUVECs	Human umbilical vein endothelial cells	XOD	Xanthine oxidase
IC50	Half maximal inhibitory concentration		

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