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Genus Terminalia: A phytochemical and Biological Review

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Abstract

Context: *Terminalia* is the second largest genus of family Combretaceae. The plants of this genus were used in traditional folk medicine worldwide.

Objectives: This review is a comprehensive literature survey of different *Terminalia* species regarding their biological activities and their isolated phytochemicals. The aim of this review is to attract the attention to unexplored potential of natural products obtained from *Terminalia* species, thereby contributing to the development of new therapeutic alternatives that may improve the health of people suffering from various health problems.

Materials and methods: All the available information on genus *Terminalia* was compiled from electronic databases such as Medline, Google Scholar, PubMed, ScienceDirect, SCOPUS, Chemical Abstract Search and Springer Link.

Results: Phytochemical research has led to the isolation of different classes of compounds including, tannins, flavonoids, phenolic acids, triterpenes, triterpenoidal glycosides, lignan and lignan derivatives. Crude extracts and isolated components of different *Terminalia* species showed a wide spectrum of biological activities.

Conclusion: phytochemical studies on genus *Terminalia* have revealed a variety of chemical constituents. Numerous biological activities have validated the use of this genus in treatment of various diseases in traditional medicine. Further studies are needed to explore the bioactive compounds responsible for the pharmacological effects and their mechanism of action.

Keywords: *Terminalia*; Tannins; Flavonoids; Terpenoids; Combretaceae; Traditional medicine

Abbreviations: A549: Human lung epithelial cancer; AChE: Acetylcholinesterase; ACP: Acid phosphatase; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Bw: Body weight ; COLO-205: Human colon cancer ; COX-2: Cyclooxygenase-2 enzyme; DPPH•: 2;2-diphenyl-1-picrylhydrazyl radical; DU-145: Human prostate cancer; FRAP: Ferric reducing ability of plasma; GSH: Glutathione; HbA1c: Glycated hemoglobin; HCT-15: Human colorectal cancer; HL-60: Human promyelocytic leukemia ; IMR: Ischemic mitral regurgitation; iNOS: inducible nitric oxide synthase ; K562: Human immortalised myelogenous leukemia; MBC: Minimum bactericidal concentration; MDA-MB-231:M.D.anderson-metastatic breast cancer; MIC: Minimum inhibitory concentration; ORAC: Oxygen radical absorbance capacity; PPARα / PPARγ: Peroxisome proliferator-activated receptor alpha/ gamma ; STZ: Streptozotocin; T: Terminalia

Introduction

The genus *Terminalia* is the second largest genus of the Combretaceae after *Combretum*, with about 200 species. These plants are distributed in tropical regions of the world with the greatest genetic diversity in Southeast Asia [1]. Genus *Terminalia* gets its name from Latin *terminus*, since the leaves appear at the tips of the shoots [2]. *Terminalia* species range from shrubs to large deciduous forest trees. Mostly they are very large trees reaching in height up to 75 m tall [3]. Members of the genus *Terminalia* are widely used in traditional medicine in several continents in the world for the treatment of numerous diseases including, abdominal disorders, bacterial infections, colds, sore throats, conjunctivitis, diarrhea, dysentery, fever, gastric ulcers, headaches, heart diseases, hookworm, hypertension, jaundice, leprosy, nosebleed, edema, pneumonia and skin diseases [4]. The fruits of both *T. bellerica* and *T. chebula* are important components of triphala, a popular Ayurvedic formulation that possess numerous activities in the Indian traditional medicine [5]. *T. chebula* fruit possess an extraordinary power of healing and is called the "King of Medicine" in Tibet as it's used for the treatment of various diseases [6,7]. The Bark of *T. arjuna* are used as cardioprotective and anti-hyperlipidemic in folklore medicine [8]. In Africa, *T. mollis* is used to treat diarrhea, gonorrhea, malaria, and in HIV treatment, while *T. brachystemma* is used for the treatment of shistosomiasis and gastrointestinal disorders [9]. The diverse phytochemical constituents and various biological activities attracted us to perform a comprehensive literature survey of different *Terminalia* species regarding their phytochemical constituents, their ability to exert biological activities and the evidence-based information regarding the phytochemistry and biological activities of this genus. The present review is divided into two main sections, the first include a phytochemical review of various chemical constituents and their occurrence within the *Terminalia* species, the second comprises the numerous biological studies conducted for different species of the genus *Terminalia*.

Phytochemical Studies

Phytochemical studies performed on different *Terminalia* species have demonstrated the occurrence of several classes of active constituents, such as tannins, pentacyclic triterpenes and their glycoside derivatives, flavonoids and other phenolic compounds [10].

Literature survey has revealed that genus *Terminalia* is a rich source of tannins and pseudotannins, including gallic acid and its simple gallate esters, chebulic and non-chebulic ellagitannins, ellagic acid derivatives and ellagic acid glycosides (Table 1 and Figure 1).

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No.	Compound	Species	Part used (Type of extract)	Reference (s)
A.	**Gallic acid and simple gallate esters**			
1	Gallic acid	*T. chebula* *T. bellerica* *T. horrida* *T. muelleri* *T. nigrovenulosa* *T. arjuna* *T. superba* *T. macroptera* *T. mollis* *T. catappa* *T. oblongata* *T. pallida* *T. stenostachya* *T. myriocarpa*	Leaves (H_2O), fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves, fruits, bark (MeOH) Bark (EtOAc) Leaves (EtOH), fruits, bark Stem bark (CH_2Cl_2: MeOH) Leaves Leaves (MeOH) Leaves (H_2O) Leaves Fruits (EtOH) Leaves Leaves	[27, 82] [27] [27] [28, 50] [52] [83, 84] [18] [54] [9] [85] [86] [87] [49] [88]
2	Methyl gallate	*T. chebula* *T. bellerica* *T. horrida* *T. superba* *T. myriocarpa*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Stem bark (CH_2Cl_2: MeOH) Leaves	[27] [27] [27] [18] [88]
3	Ethyl gallate	*T. arjuna* *T. chebula* *T. myriocarpa*	Arial parts (MeOH) Leaves Leaves	[64] [59] [88]
4	1,6-di-*O*-galloyl-β-D-Glc	*T. chebula* *T. bellerica* *T. horrida*	Leaves (H_2O), fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27, 82] [27] [27]
5	3,4,6-tri-*O*-galloyl-β-D-Glc	*T. chebula* *T. bellerica* *T. horrida*	Leaves (H_2O), fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27, 82] [27] [27]
6	1,3,4,6-tetra-*O*-galloyl-β-D-Glc	*T. chebula* *T. bellerica* *T. horrida*	Leaves (H_2O), fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27, 82] [5, 27] [27]
7	2,3,4,6-tetra-*O*-galloyl-β-D-Glc	*T. arjuna*	Leaves (EtOH)	[83]
8	1,2,3,4,6-penta-*O*-galloyl-β-D-Glc	*T. chebula* *T. bellerica* *T. horrida* *T. arjuna*	Leaves (H_2O), fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves (EtOH)	[27, 82] [27] [27] [83]
9	3,4,5-tri-*O*-galloyl-shikimic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
B.	**Chebulic acid and chebulic ellagitannins**			
10	Chebulic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH, EtOH) Fruits (MeOH) Fruits (MeOH)	[27, 33] [27] [27]
11	Neo-chebulic acid	*T. chebula*	Fruits (EtOH)	[33]
12	Chebulanin (1-*O*-galloyl-2,4-*O*-chebuloyl-β-D-Glc)	*T. chebula* *T. bellerica* *T. horrida* *T. brachystemma* *T. mollis*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves (MeOH) Leaves (MeOH)	[12, 27] [27] [27] [9] [9]
13	Chebulinic acid (1,3,6-tri-*O*-galloyl-2,4-*O*-chebuloyl-β-D-Glc)	*T. bellerica* *T. chebula* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [12, 27] [27]
14	Methyl neo-chebulanin	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27, 60] [27] [27]
15	Methyl neochebulinate	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
16	Chebulagic acid (1-*O*-galloyl-2,4-*O*-chebuloyl-3,6-*O*-HHDP-β-D-Glc)	*T. chebula* *T. bellerica* *T. horrida* *T. catappa*	Fruits (MeOH), seeds Fruits (MeOH) Fruits (MeOH) Leaves (H_2O)	[27, 89] [5, 27] [27] [34]
17	Methyl neochebulagate	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
18	1,6-di-*O*-galloyl-2,4-*O*-chebuloyl-β-D-Glc (or 1,3-)	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
C.	**Non-chebulic ellagitannins**			

19	Tellimagrandin(I) (2,3-di-*O*-galloyl-4,6-*O*-HHDP-α/β-D-Glc)	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
20	Corilagin (1-*O*-galloyl-3,6-*O*-HHDP-β-D-Glc)	*T. chebula* *T. bellerica* *T. horrida* *T. catappa*	Fruits (MeOH, EtOH) Fruits (MeOH) Fruits (MeOH) Leaves (H_2O)	[27, 90] [27] [27] [34]
21	Tercatain (1,4-di-*O*-galloyl-3,6-*O*-HHDP-β-D-Glc)	*T. catappa*	Leaves (Acetone)	[91]
22	Arjunin (3-*O*-galloyl-4,6-*O*-gallagyl-α/β-D-Glc)	*T. arjuna*	Leaves (EtOH)	[83]
23	Punicalin (4,6-*O*-gallagyl-α/β-D-Glc)	*T. bellerica* *T. chebula* *T. horrida* *T. arjuna* *T. catappa*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves (EtOH) Leaves (Acetone)	[27] [27] [27] [83] [91]
24	Punicalagin (2,3-*O*-HHDP-4,6-*O*-gallagyl-α/β-D-Glc)	*T. chebula* *T. bellerica* *T. horrida* *T. oblongata* *T. brachystemma* *T. macroptera* *T. catappa* *T. arjuna* *T. myriocarpa*	Leaves (H_2O), fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves (H_2O) Leaves (Acetone) Roots (EtOH) Leaves (Acetone, H_2O) Bark Leaves	[27, 90] [27] [27] [92] [9] [55] [61, 91] [93] [88]
25	2,3:4,6-bis-*O*-HHDP-1-*O*-galloyl-β-D-Glc	*T. arjuna*	Leaves (EtOH)	[83]
26	Tergallagin	*T. catappa*	Leaves (Acetone)	[91]
27	Terflavin (A) (4-*O*-flavogallonyl-6-*O*-galloyl-2,3-*O*-HHDP-α/β-D-Glc)	*T. chebula* *T. catappa* *T. macroptera*	Fruits (H_2O) Leaves (Acetone) Stem bark (EtOAc)	[90] [91] [94]
28	Terflavin (B) (4-*O*-flavogallonyl-6-*O*-galloyl-α/β-D-Glc)	*T. chebula* *T. bellerica* *T. horrida* *T. catappa* *T. macroptera*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves (Acetone) Stem Bark (EtOAc)	[27] [27] [27] [91] [94]
29	Terflavin (C) (4-*O*-flavogallonyl -2,3-*O*-HHDP-α/β-D-Glc)	*T. chebula* *T. catappa* *T. arjuna*	Fruits (H_2O) Leaves (Acetone) Bark	[90] [91] [93]
30	Calamansanin (4-*O*-flavogallonyl-6-*O*-galloyl-2,3-*O*-HHDP-α-D-Glc)	*T. calamansanai*	Leaves	[93]
31	Terchebulin	*T. chebula* *T. macroptera* *T. arjuna*	Fruits (H_2O) Roots (EtOH) Bark	[90, 95] [55] [93]
32	Isoterchebulin	*T. macroptera*	Stem bark (EtOAc)	[94]
33	4,6-*O*-isoterchebuloyl-α/β-D-Glc	*T. macroptera*	Stem bark (EtOAc)	[94]
34	Casurarinin	*T. chebula* *T. arjuna*	Fruits (H_2O) Bark (Acetone)	[90] [48]
35	Casuariin	*T. arjuna*	Bark	[96]
36	Castalagin	*T. arjuna*	Leaves	[93]
D.	**Ellagic acid and ellagic acid derivatives**			
37	Ellagic acid	*T. chebula* *T. bellerica* *T. horrida* *T. muelleri* *T. arjuna* *T. superba* *T. macroptera* *T. pallida* *T. paniculata*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Bark, fruits (MeOH) Leaves (EtOH), fruits Stem bark (CH_2Cl_2: MeOH) Leaves Fruits (EtOH) Heartwood (alc.)	[27] [27] [27] [28] [83, 84] [18] [54] [87] [97]
38	3-*O*-methyl ellagic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
39	3,3'-di-*O*-methyl ellagic acid	*T. chebula* *T. bellerica* *T. horrida* *T. superba* *T. paniculata*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Stem bark (CH_2Cl_2: MeOH) Heart wood (alc.)	[27] [27] [27] [18] [97]
40	3,4,4'-tri-*O*-methyl ellagic acid	*T. catappa*	Fruits, Leaves (EtOH)	[98]

41	3,4,8,9,10-Pentahydroxydibenzo[*b,d*] pyran-6-one	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
42	Flavogallonic acid	*T. chebula* *T. bellerica* *T. horrida* *T. myriocarpa*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves	[27] [27] [27] [88]
43	Methylflavogallonate	*T. chebula* *T. bellerica* *T. horrida* *T. myriocarpa*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Leaves	[27] [27] [27] [88]
44	3,4,3'-*O*-trimethyl flavellagic acid	*T. paniculata*	Heartwood (alc)	[97]
45	Gallagic acid.	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
E.	**Ellagic acid glycosides**			
46	3'-*O*-methyl-4-*O*-(β-D-xylopyranosyl) ellagic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
47	3,3'-di-*O*-methyl-4-*O*-(β-D-xylopyranosyl) ellagic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
48	3'-*O*-methyl-4-*O*-(n"-*O*-galloyl-β-D-xylopyranosyl) ellagic acid (n = 2, 3, or 4)	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
49	3,3'-di-*O*-methyl-4-*O*-(n"-*O*-galloyl-β-D-xylopyranosyl) ellagic acid. (n = 2, 3, or 4)	*T. chebula* *T. bellerica* *T. horrida* *T. superba*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH) Stem bark (CH_2Cl_2: MeOH)	[27] [27] [27] [18]
50	4'-*O*-galloyl-3,3'-di-*O*-methyl-4-*O*-(β-D-xylopyranosyl) ellagic acid	*T. superba*	Stem bark (MeOH)	[56]
51	3',4-di-*O*-methyl-3-*O*-(β-D-xylopyranosyl) ellagic acid	*T. superba*	Stem bark (MeOH)	[56]
52	3'-*O*-methyl-4-*O*-(α-L- rhamnopyranosyl) ellagic acid	*T. arjuna* *T. mollis*	Bark (MeOH) Stem bark (MeOH)	[99] [9]
53	4-*O*-(4"-*O*-galloyl-α-L-rhamnopyranosyl) ellagic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
54	4-*O*-(3",4"-di-*O*-galloyl-α-L-rhamnopyranosyl) ellagic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
55	3'-*O*-methyl-4-*O*-(3",4"-di-*O*-galloyl-α-L-rhamnopyranosyl) ellagic acid	*T. chebula* *T. bellerica* *T. horrida*	Fruits (MeOH) Fruits (MeOH) Fruits (MeOH)	[27] [27] [27]
56	3,3'-di-*O*-methyl-4-*O*-(β-D-glucopyranosyl-(1→4)-β-D-glucopyranosyl-(1→2)-α-L-arabinopyranosyl) ellagic acid	*T. alata*	Roots	[58]

Table 1: Tannins and pseudotannins and their occurrence within *Terminalia* species.

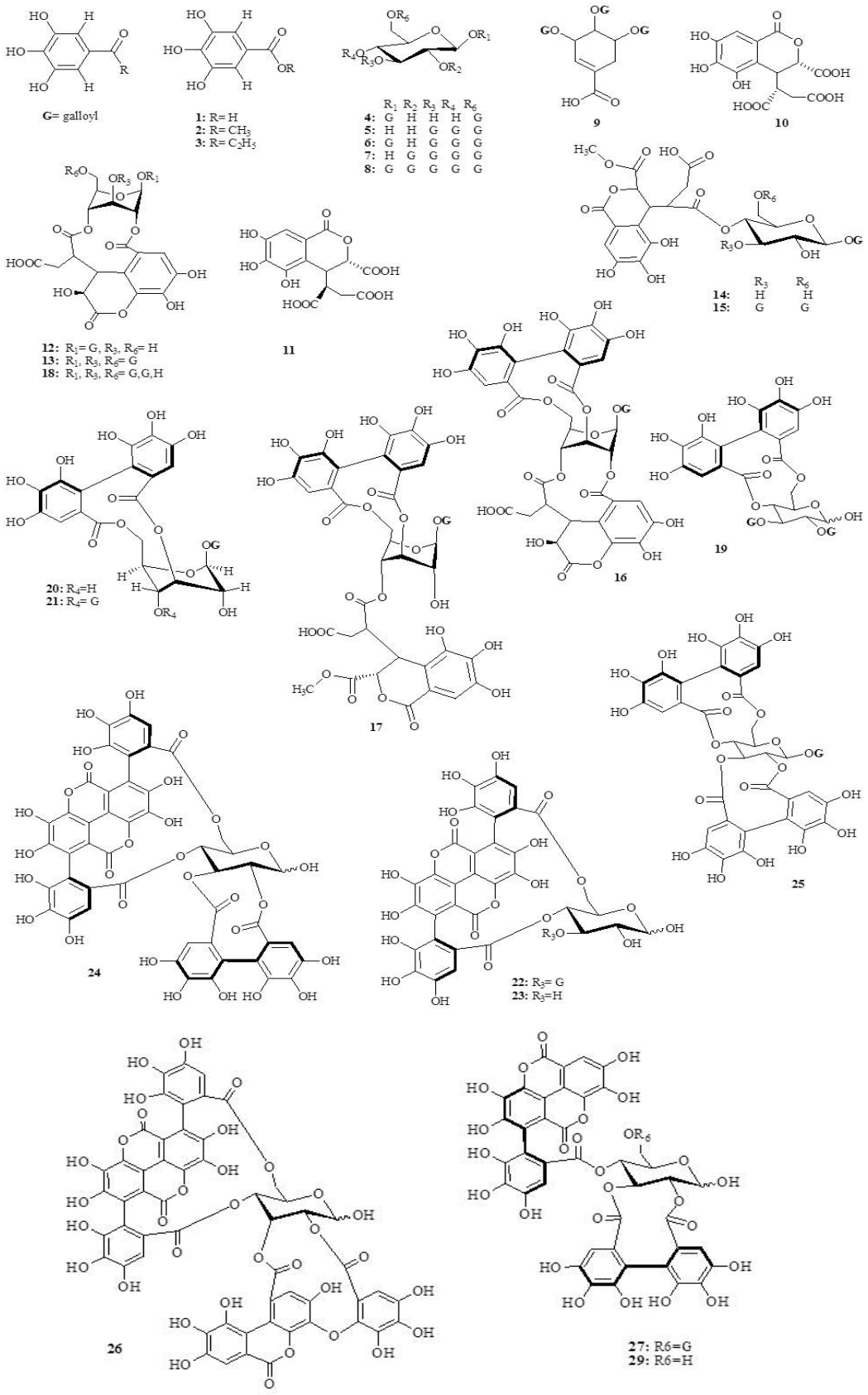
Phenolic acids (Table 2 and Figure 2), flavonoids (Table 3 and Figure 3), triterpenes and triterpenoidal glycosides (Table 4 and Figure 4) are also present in high amounts in various *Terminalia* species, few lignan and lignan derivatives have been isolated from genus *Terminalia* (Table 5 and Figure 5).

Biological Studies

Screening of available literature on genus *Terminalia* revealed numerous biological activities in various *in vivo* and *in vitro* models. Biological activities included anti-diabetic, anti-hyperlipidemic, antioxidant, anti-bacterial, anti-fungal, anti-viral, anti-inflammatory, anti-cancer, anti-ulcer, anti-parasitic, hepatoprotective and cardioprotective activities.

Anti-diabetic activity

T. chebula showed a strong anti-diabetic activity, compounds isolated from the fruits, such as corilagin and ellagic acid acted as α-glucosidase inhibitors [11]. Additionally, chebulanin, chebulagic acid and chebulinic acid possessed a potent intestinal maltase inhibitory activity, with IC_{50} values of 690 μM, 97 μM and 36 μM, respectively [12]. In another study, *T. chebula* fruits and seeds exhibited a dose-dependent reduction in blood glucose in STZ-induced diabetic rats [13]. Furthermore, ellagitannins and gallotannins isolated from *T. bellerica* and *T. chebula* fruit extracts enhanced the PPARα and/or PPARγ signaling [5]. The aqueous extract of *T. paniculata* bark reduced the elevated blood glucose, HbA1c, creatinine, urea, ALT, AST levels and reversed the abnormal status of endogenous antioxidants and the lipid profile levels towards their normal levels in STZ-induced diabetic rats in comparison with the untreated diabetic rats [14]. Nampoothiri [15] reported that the methanolic extract of *T. bellerica* fruits exhibited a potent α-amylase and α-glucosidase inhibitory activities. Moreover, the anti-diabetic activity of *T. bellerica* fruit extract is attributed to its gallic acid content, as it induced a dose-dependent reduction in blood glucose level with a simultaneous increase in plasma insulin (62.92%), C-peptide (79.74%), total protein (42.41%) and albumin (51.52%) in STZ-induced diabetic rats when compared to the untreated


G= galloyl
1: R= H
2: R= CH3
3: R= C2H5
4: G H H H G
5: H H G G G
6: G H G G G
7: H G G G G
8: G G G G G
9
10
12: R1= G, R3, R6= H
13: R1, R3, R6= G
18: R1, R3, R6= G,G,H
11
14:
15:
16
17
19
20: R4=H
21: R4= G
22: R3= G
23: R3=H
24
25
26
27: R6=G
29: R6=H

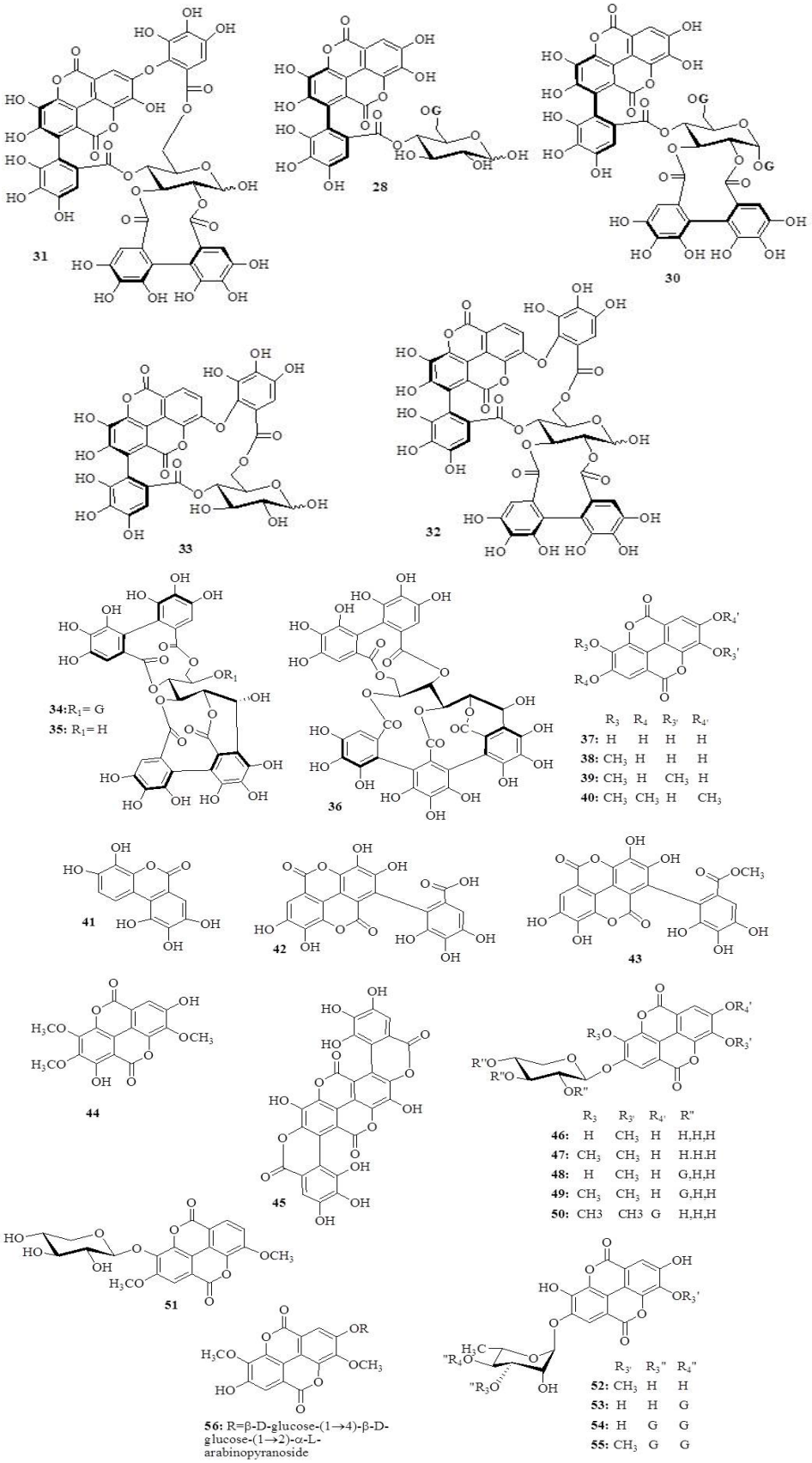


Figure 1: Chemical structures of tannins and pseudotannins isolated from different *Terminalia* species.

No.	Compound	Species	Part used (Type of extract)	Reference (s)
57	Caffeic acid	*T. chebula*	Leaves	[90]
58	Ferulic acid	*T. chebula* *T. catappa*	Leaves Fruits, leaves (EtOH)	[90] [98]
59	Vanillic acid	*T. chebula* *T. catappa*	Leaves Fruits, leaves (EtOH)	[90] [98]
60	Coumaric acid	*T. chebula* *T. catappa*	Leaves, fruits Leaves (H_2O)	[90] [85]
61	*p*-hydroxybenzoic acid	*T. catappa*	Leaves (H_2O)	[85]
62	3,4-dihydroxybenzoic acid	*T. nigrovenulosa* *T. catappa*	Bark Leaves (H_2O)	[75] [85]

Table 2: Phenolic acids and their occurrence within *Terminalia* species.

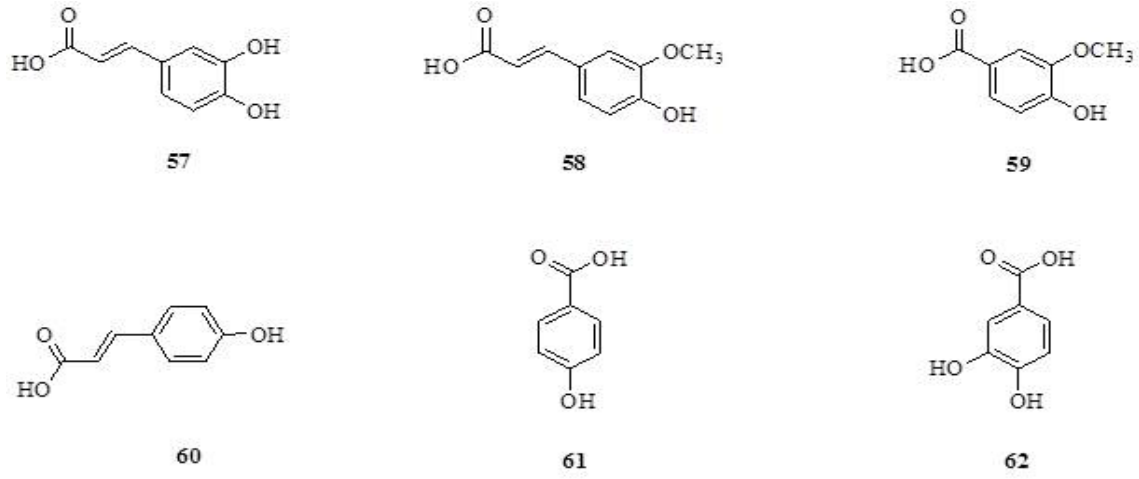


Figure 2: Chemical structures of phenolic acids isolated from different *Terminalia* species.

No.	Compound	Species	Part used (Type of extract)	Reference (s)
A.	**Flavonols**			
63	Quercetin	*T. arjuna* *T. muelleri* *T. macroptera* *T. bellerica* *T. chebula*	Fruits (MeOH) Bark, fruits, leaves (MeOH) Leaves Bark, fruits, leaves (MeOH) Leaves	[28] [28] [54] [28] [100]
64	Kaempferol	*T.arjuna*	Bark	[101]
65	Kaempferol 3-*O*-rutinoside	*T. myriocarpa*	Leaves	[88]
66	Rutin (Quercetin-3-*O*-rutinoside)	*T. chebula* *T. myriocarpa*	Leaves Leaves	[100] [88]
B.	**Flavones**			
67	Luteolin	*T. arjuna* *T. chebula*	Arial parts (MeOH) Fruits	[64] [59]
68	Apigenin	*T. arjuna*	Leaves (MeOH)	[102]
69	Arjunolone (6,4'-dihydroxy-7-*O*-methyl-flavones)	*T. arjuna*	Stem bark	[103, 104]
70	Baicalein (5,6,7-trihydroxy-flavones)	*T. arjuna*	Stem bark	[103, 104]
71	Orientin	*T. mollis* *T. catappa* *T. myriocarpa*	Leaves (Acetone) Leaves Leaves	[9] [105] [88]
72	Isoorientin	*T. brachystemma* *T. catappa* *T. macroptera.* *T. myriocarpa*	Leaves (Acetone) Leaves Leaves Leaves	[9] [105] [54] [88]
73	Vitexin	*T. arjuna* *T. catappa* *T. myriocarpa*	Leaves (MeOH) Leaves Leaves	[102] [105] [88]

74	Isovitexin	*T. arjuna* *T. brachystemma* *T. catappa* *T. myriocarpa*	Leaves (MeOH) Leaves (Acetone) Leaves Leaves	[102] [9] [105] [88]
75	2"-*O*-galloylvitexin	*T. mollis* *T. catappa*	Leaves (MeOH) Leaves	[9] [105]
76	2"-*O*-galloylisovitexin	*T. catappa*	Leaves	[105]
77	Arjunone (5,7,2',4'-tetra-*O*-mrthyl-flavones)	*T. arjuna*	Fruits (EtOH)	[106]
C.	**Flavans**			
78	7,3'-dihydroxy-4'-*O*-methyl-flavan	*T. argentea*	Bark (EtOH)	[107]
79	7,4'-dihydroxy-3'-*O*-methyl-flavan	*T. argentea*	Bark (EtOH)	[107]
80	7-hydroxy-3',4'-methylenedioxy-flavan	*T. bellerica*	Fruits	[108]
D.	**Flavanones**			
81	8-methyl-5,7,2',4'-tetra-*O*-methyl-flavanone	*T. alata*	Roots (EtOH)	[109]
82	5,7,2'-tri-*O*-methyl-flavanone 4'-*O*-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside	*T. alata*	Roots	[58]
E.	**Flavan-3-ol**			
83	Catachin	*T. arjuna* *T. mollis* *T. brachystemma*	Leaves, stem bark Stem bark (MeOH) Leaves (Acetone)	[84] [9] [9]
84	Gallocatechin	*T. arjuna* *T. catappa* *T. mollis*	Stem bark Bark Stem bark (MeOH)	[84] [93] [9]
85	Epicatechin	*T. arjuna* *T. catappa* *T. mollis*	Stem bark Bark Stem bark (MeOH)	[84] [93] [9]
86	3-*O*-galloyl-epicatechin	*T. catappa*	Bark	[93]
87	Epigallocatechin	*T. arjuna* *T. catappa* *T. mollis*	Stem bark Bark Stem bark (MeOH)	[84] [93] [9]
88	3-*O*-galloyl-epigallocatechin	*T. catappa*	Bark	[93]
F.	**Chalcones**			
89	2-*O*-β-D-glucosyloxy-4,6,2',4'-tetramethoxychalchone	*T. alata*	Roots (EtOH)	[109]
G.	**Anthocyanidins**			
90	Pelargonidin	*T. arjuna*	Bark	[101]
H.	**Leucoanthocyanidins**			
91	Leucocyanidin	*T. arjuna*	Bark (MeOH)	[110]

Table 3. Flavonoids and their occurrence within *Terminalia* species.

diabetic rats [16]. The ethanolic leaf extracts of *T. arjuna, T. catappa, T. bellerica* and *T. chebula* had a potent α-glucosidase inhibition activity [17]. Gallic acid and methyl gallate isolated from *T. superba* stem bark showed a significant α-glucosidase inhibitory activity [18]. Additionally, the methanolic and the aqueous extracts of *T. catappa* fruits exhibited significant anti-hyperglycemic activities and showed an improvement in body weight and lipid profile as well as regeneration of β-cells of the pancreas [19]. Also, *T. pallida* fruit extract showed a significant anti-diabetic activity in alloxan-induced diabetic rats at a dose of 0.50 g/kg bw [20].

Anti-hyperlipidemic activity

The oral administration of gallic acid isolated from *T. bellerica* fruit at a dose of 20 mg/kg bw significantly reduced the serum total cholesterol, triglyceride and LDL-cholesterol levels [21]. Moreover, *T. chebula* fruits possessed anti-hyperlipidemic activity against cholesterol-induced hypercholesterolemia and atherosclerosis in rabbits [22]. In addition, the ethanolic extract of *T. arjuna* tree bark reduced the serum total cholesterol, LDL, VLDL, triglycerides and raised HDL levels in diet-induced hyperlipidemic rabbits [23]. Also, it was shown that *T. bellerica, T. chebula* and *T.arjuna* had anti-hyperlipidemic activities *T. arjuna* the most potent one caused an inhibition of rabbit atheroma after oral administration in hyperlipidemic rabbits [24].

Antioxidant activity

Most *Terminalia* species were reported to possess an antioxidant activity. The antioxidant activity of the *T. arjuna* bark was studied and the results of DPPH• assay, superoxide radical scavenging activity and lipid peroxidation assay were comparable with the standard antioxidant ascorbic acid [25]. *T. chebula* fruit extract possessed a potent antioxidant activity and can be used as a radio-protector as it protected from γ-irradiation-induced oxidative stress in rats by the reduction of radiation-induced cellular DNA damage [26].

The antioxidant activities of the methanolic fruit extract of *T. bellerica* and its isolated compounds was examined using DPPH•, oxygen radical absorbance capacity (ORAC) and ferric reducing ability of plasma (FRAP) *in vitro* assays. Chebulic ellagitannins showed the highest antioxidant activity [27]. Moreover, the high antioxidant activity of the aqueous methanolic extracts of the leaves, bark and fruits of *T. arjuna*, *T. bellerica, T. chebula and T. muelleri* were attributed to their high phenolic contents (72.00-167.20 mg/g) [28].

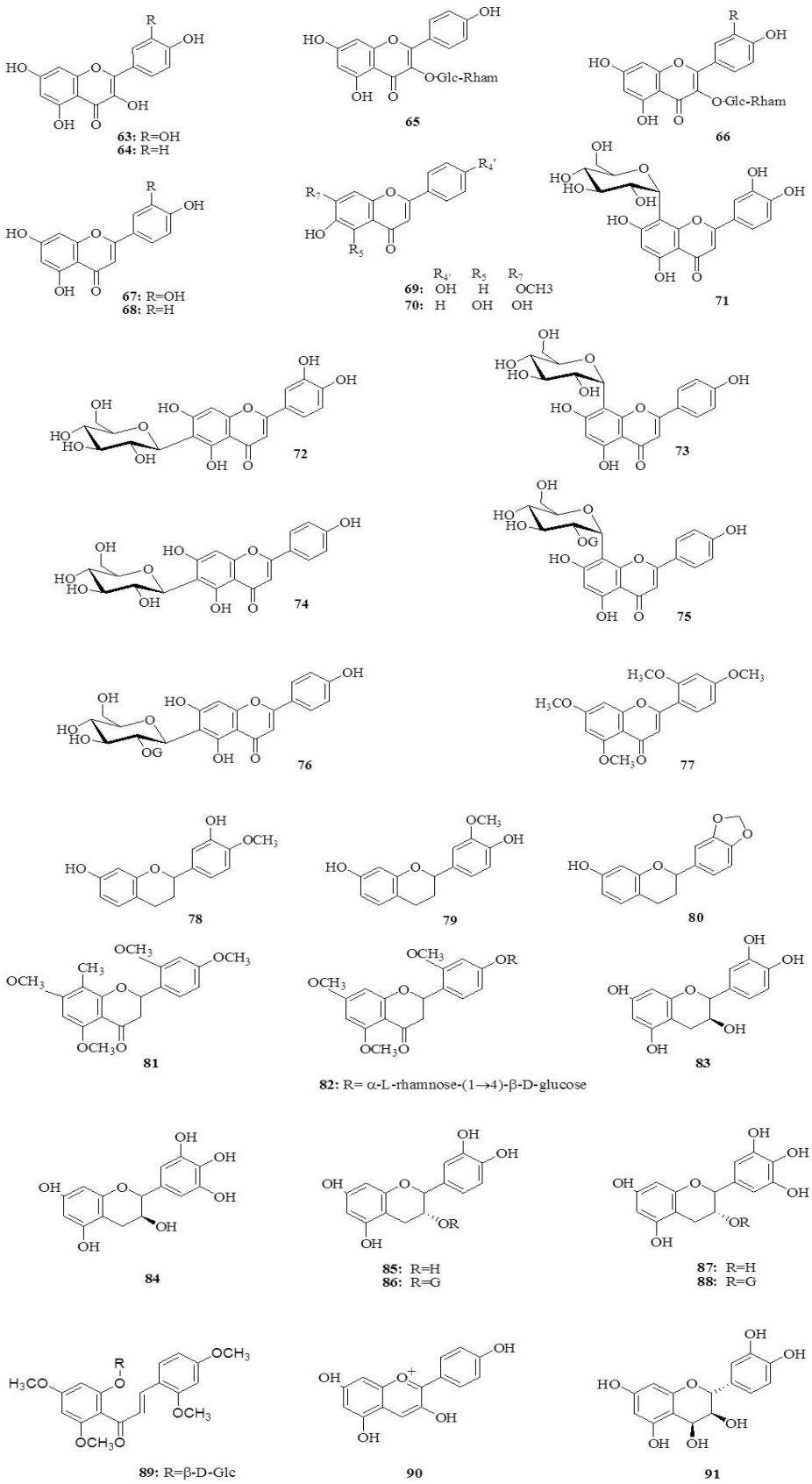
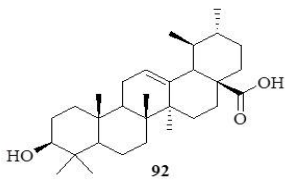


Figure 3: Chemical structures of flavonoids isolated from different *Terminalia* species.

No.	Compound	Species	Part used (Type of extract)	Reference (s)
A.	**Triterpenes**			
92	Ursolic acid	*T. brachystemma* *T. catappa*	Leaves (*n*-hexane) Leaves (EtOH)	[9] [42]
93	2α-hydroxyursolic acid	*T. chebula* *T. mollis*	Leaves (Acetone) Stem bark (*n*-hexane)	[111] [9]
94	2α,3β,23-trihydroxyurs-12-en-28-oic acid	*T. catappa*	Leaves (EtOH)	[42]
95	Asiatic acid	*T. brassii* *T. complanata*	Wood (Et_2O) Wood (Et_2O)	[112] [112]
96	Oleanolic acid	*T. arjuna* *T. superba*	Root bark Stem bark (CH_2Cl_2: MeOH)	[84] [18]
97	Methyl oleonate	*T.arjuna*	Fruits	[106]
98	Arjunic acid	*T. arjuna* *T. macroptera*	Fruits, roots, stem bark Bark	[84, 113], [114]
99	Arjunolic acid (2α,3β,23-trihydroxyolean-12-en-28-oic aid)	*T. arjuna* *T. brassii* *T. complanata*	Bark (pet. ether) Wood (Et_2O) Wood (Et_2O)	[32] [112] [112]
100	23-*O*-galloyl-arjunolic acid	*T. macroptera*	Stem bark (EtOAc)	[114]
101	Arjungenin (2α,3β,19α,23-tetrahydroxyolean-12-ene-28-oic acid)	*T. arjuna* *T. bellerica* *T. macroptera*	Bark (EtOH) Stem bark (MeOH) Bark	[113] [115] [114]
102	Tomentosic acid (2α,3β,19β,23-tetrahydroxyolean-12-ene-28-oic acid)	*T. arjuna* *T. tomentosa (T. alata)*	Stem bark Heart wood	[84] [116]
103	Sericic acid (2α,3β,19α,24-tetrahydroxy-olean-12-en-28-oic acid)	*T. sericea* *T. macroptera*	Roots Stem bark	[117] [114]
104	Belleric acid (2α,3β,23,24-tetrahydroxy-olean-12-en-28-oic acid)	*T. bellerica*	Stem bark (MeOH)	[115]
105	Bellericagenin A (2α,3β,7α,23-tetrahydroxyolean-12-en-28-oic acid)	*T. bellerica*	Stem bark	[118]
106	Bellericagenin B (2α,3β,19α,23,24-pentahydroxyolean-12-en-28-oic acid)	*T. bellerica*	Stem bark	[118]
107	Terminolic acid (2α,3β,6β,23-tetrahydroxyolean-12-en-28-oic acid)	*T. macroptera* *T. glaucesence* *T. catappa* *T. laxiflora* *T. avicennioides*	Stem bark Heartwood (Et_2O) Heartwood (Et_2O) Heartwood (Et_2O) Heartwood (Et_2O)	[114] [119] [119] [119] [119]
108	Maslinic acid (2α,3β-dihydroxyolean-12-en-28-oic acid)	*T. chebula*	Leaves (Acetone)	[111]
109	3-acetylmaslinic acid	*T. alata*	Root bark	[120]
110	2α-hydroxymicromeric acid	*T, chebula*	Leaves (Acetone)	[111]
111	Terminic acid (3β,13β-dihydroxylup-20-en-28-oic acid)	*T. arjuna*	Root bark (*n*-hexane)	[121]
112	Friedelin	*T. arjuna* *T. glaucescens* *T. mollis* *T. alata*	Fruits Stem bark Stem bark (*n*-hexane) Roots	[106] [122] [9] [58]
113	β-sitosterol	*T. chebula* *T. superba* *T. bellerica* *T. glaucescens* *T. phanerophlebia T. sambesiaca* *T. arjuna*	Stem bark Stem bark (CH_2Cl_2: MeOH) Fruits Stem bark Leaves (EtOH) Leaves Stem bark, fruits	[123] [18] [124] [122] [36]. [125] [84]
114	β-sitosterone	*T. phanerophlebia*	Leaves (EtOH)	[36]
115	Stigmasterol	*T. superba* *T. glaucescens* *T. arjuna*	Stem bark (CH_2Cl_2: MeOH) Stem bark Leaves (MeOH)	[18] [122] [102]
116	Stigma-4-ene-3,6-dione	*T. phanerophlebia*	Leaves (EtOH)	[36]
117	Terminalin A	*T. glaucescens*	Stem bark	[122]
B.	**Triterpenoidal glycosides**			
118	2α,3β-dihydroxyurs-12,18-dien-28-oic acid-28-*O*-β-D-glucopyranoside	*T. arjuna*	Bark (MeOH)	[99]
119	2α,3β,23 trihydroxyurs-12,18-dien-28-oic acid-28-*O*-β-D-glucopyranoside	*T. arjuna*	Bark (MeOH)	[99]
120	2α,3β,23 trihydroxyurs-12,19-dien-28-oic acid-28-*O*-β-D-glucopyranoside	*T. arjuna*	Bark (MeOH)	[99]
121	Quadranoside VIII (2α,3β,23-trihydroxyurs-12,19-dien-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. arjuna*	Bark (MeOH)	[99]
122	Kajiichigoside F1 (2α,3β,19α-trihydroxyurs-12-en-28-oic acid-28-β-D-glucopyranoside)	*T. arjuna*	Bark (MeOH)	[99]

123	Arjunetin (2α,3β,19α-trihydroxyolean-12-en-28-oic acid-28-β-D-glucopyranoside)	*T. argentea* *T. arjuna*	Bark (EtOH) Stem, root bark (EtOH)	[107] [113, 126]
124	Arjunosides (I) (3-*O*-β-D-galactoside of arjunic acid) Arjunosides (II) (3-*O*-β-D-glucosyl-2-deoxy-α-L-rhamnoside of arjunic acid) Arjunosides (III) (28-β-D-glucuronopyranoside of arjunic acid) Arjunosides (IV) (3-*O*-α-L-rhamnoside of arjunic acid)	*T. arjuna*	Root bark (EtOAC, MeOH)	[84, 126]
125	2α,3β,19α-trihydroxyolean-12-en-28-oic acid-methylester-3-*O*-rutinoside	*T. alata*	Roots (EtOH)	[109]
126	2α,3β,19α-trihydroxyolean-12-en-28-oic acid-3-*O*-β-D-galactopyranosyl- (1→3)-β-D-glucopyranoside	*T. alata*	Roots	[127]
127	2α,3β,19β,23-tetrahydroxyolean-12-en-28-oic acid 3-*O*-β-D-galactopyranosyl-(1→3)-β-D-glucopyranoside-28-*O*-β-D-glucopyranoside	*T. alata*	Roots	[58]
128	Arjunolitin (2α,3β-23-trihydroxyolean-12-en-28-oic acid-3-*O*-β-D-glucopyranosyl-28-*O*-β-D-glucopyranoside)	*T. arjuna*	Stem bark	[110]
129	Tormentic acid-β-D-glucopyranoside	*T. argentea*	Bark (EtOH)	[107]
130	Chebuloside (I) (2α,3β,23-trihydroxyolean-12-en-28-oic acid-28-*O*-β-D-galactopyranoside)	*T. chebula*	Stem bark (MeOH)	[123]
131	Chebuloside (II) (2α,3β,6β,23-tetrahydroxyolean-12-en-28-oic acid-28-*O*-β- glucopyranoside)	*T. chebula*	Stem bark (MeOH)	[123]
132	23-galloylarjunolic acid-28-*O*-β-D-glucopyranoside	*T. macroptera*	Stem bark (MeOH)	[114]
133	Arjunglucoside (I) (2α,3β,19α,23-tetrahydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. bellerica* *T. chebula* *T. tropophylla* *T. macroptera* *T. arjuna*	Fruits, Stem bark Stem bark (MeOH) Roots (EtOH) Bark Stem bark	[115] [123] [128] [114] [126, 129]
134	Arjunglucoside (II) (2α,3β,23-trihydroxyolean- 12-en-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. arjuna*	Stem bark	[129]
135	Terminoside (A) (1α,3β,22β-trihydroxyolean-12-en-28-oic acid-3-*O*-β-D-glucopyranoside)	*T. arjuna*	Bark (EtOH)	[130]
136	Termiarjunoside (I) (1α,3β,9α,22α-tetrahydroxyolean-12-en-28-oic acid-3-*O*-β-D-glucopyranoside)	*T. arjuna*	Bark (EtOH)	[131]
137	Termiarjunoside (II) (3α,5α,25-trihydroxyolean-12-en-23,28-dioic acid-3-*O*-α -D-glucopyranoside)	*T. arjuna*	Bark (EtOH)	[131]
138	Sericoside (2α,3β,19α,24-tetrahydroxy-olean-12-en-28-oic acid -28-*O*-β- D-glucopyranoside)	*T. sericea* *T. tropophylla* *T. macroptera* *T. ivorensis*	Roots Roots (EtOH) Stem bark Bark	[117] [128] [114] [65]
139	Ivorenoside (A) (Dimer of 18,19-seco-2α,3β,19,19,24-pentahydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside and 2α,3β,19α,24-tetrahydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. ivorensis*	Bark	[65]
140	Ivorenoside (B) (Dimer of 18,19-seco-24-carboxyl-2α,3β,19,19-tetrahydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside and 2α,3β,19α,24-tetrahydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. ivorensis*	Bark	[65]
141	Ivorenoside (C) (2α,3β,19β,24-tetrahydroxyolean-11-oxo-olean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. ivorensis*	Bark	[65]
142	Bellericoside (2α,3β,23,24-tetrahydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. chebula* *T. bellerica*	Stem bark (MeOH) Stem bark (MeOH)	[123] [115]
143	Bellericaside (A) (2α,3β,7α,23-tetrahydroxyolean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside)	*T. bellerica*	Stem bark	[118]
144	Bellericaside (B) (2α,3β,19α,23,24-pentahydroxyolean-12-en-28-oic acid-28-*O*-β-D-galactopyranoside)	*T. bellerica*	Stem bark	[118]
145	2α,19α-dihydroxy-3-oxo-olean-12-en-28-oic acid-28-*O*-β-D-glucopyranoside	*T.arjuna*	Roots	[101]
146	1α,3β,23-trihydroxy-olean-12-en-29-oic acid-23-O-α-L-4-acetylrhamnopyranoside	*T. stulhamanii*	Stem bark (CH_2Cl_2)	[132]
147	1α,3β,23-trihydroxy-olean-12-en-29-oic acid-23-*O*-α-L-(4-acetylrhamnopyranosyl)-29-α-rhamnopyranoside	*T. stulhamanii*	Stem bark (CH_2Cl_2)	[132]
148	16,17-dihydroneridienone-3-*O*-β-D-glucopyranosyl-(1→6)-*O*-β-D-galactopyranoside	*T.arjuna*	Roots	[133]
149	Daucosterol (β-sitosterol-3-*O*-β-D-glucopyranoside)	*T. catappa* *T. arjuna* *T. bellerica*	Fruits, leaves (EtOH) Leaves (MeOH) Fruits (MeOH)	[98] [102] [5]

Table 4. Triterpenes and triterpenoidal glycosides and their occurrence within *Terminalia* species.



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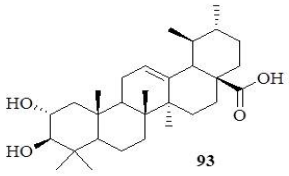

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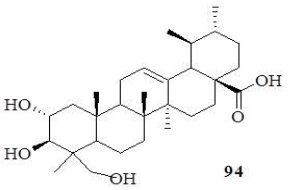

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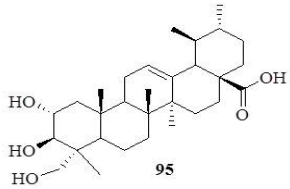

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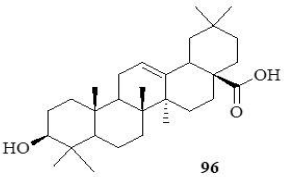

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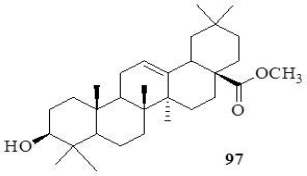

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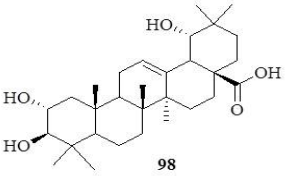

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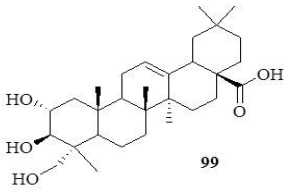

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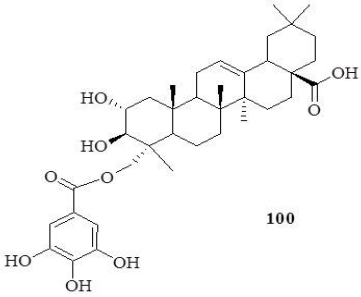

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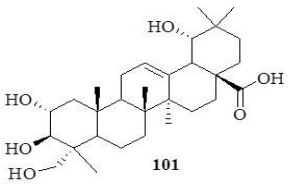

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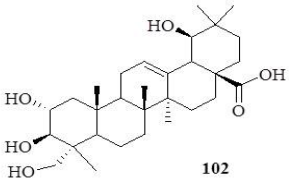

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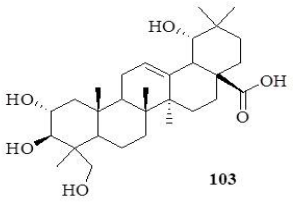

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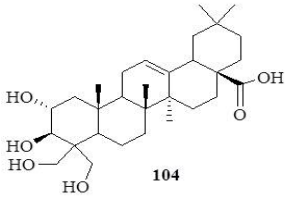

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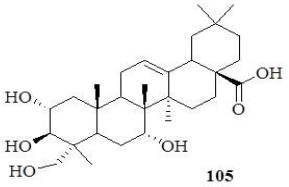

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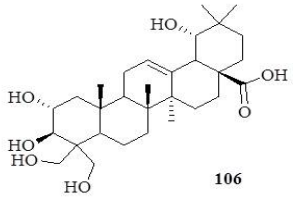

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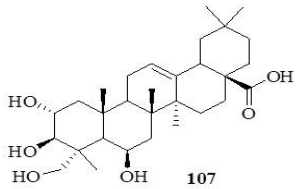

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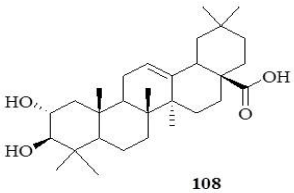

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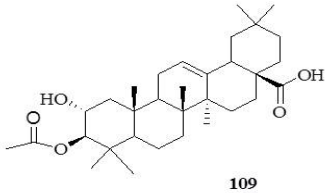

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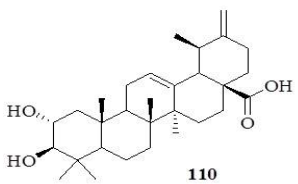

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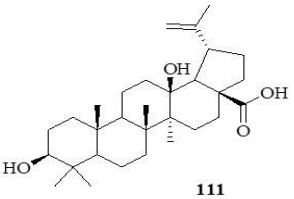

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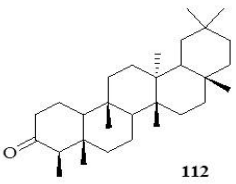

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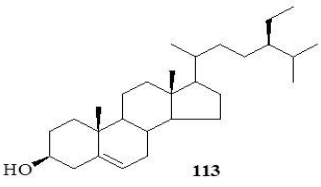

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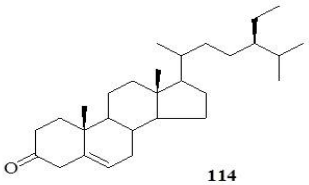

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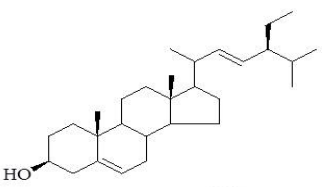

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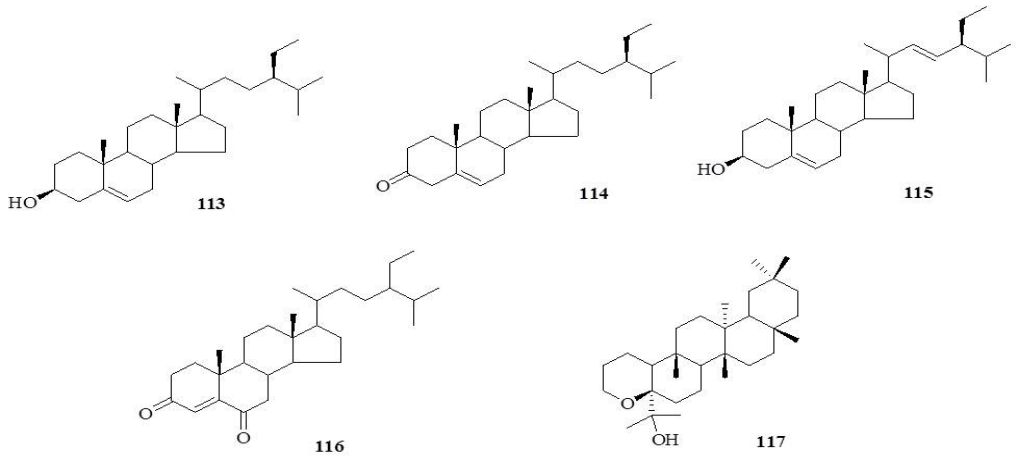
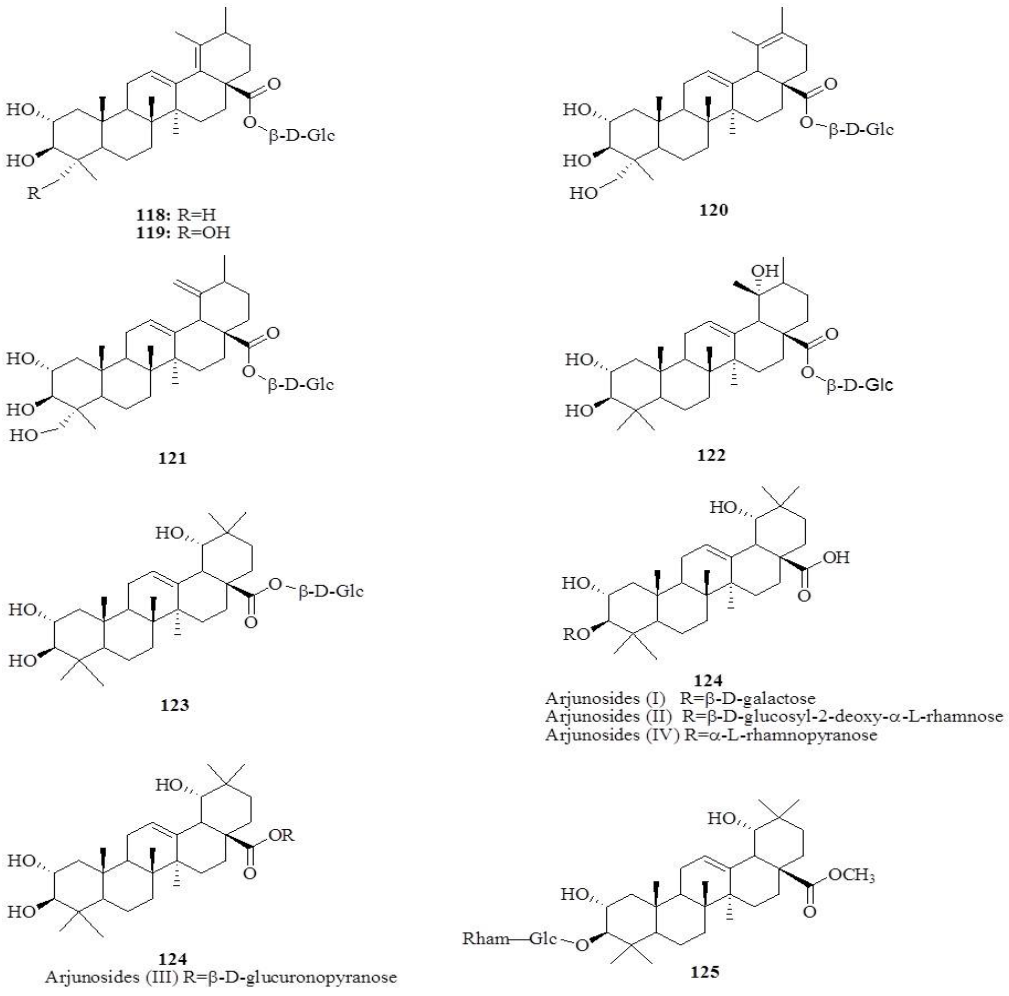
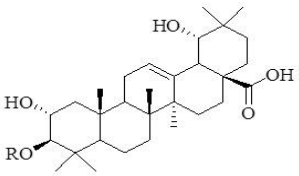
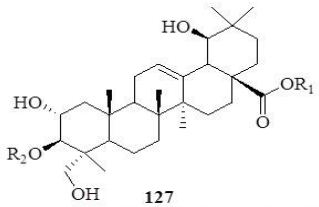


Figure 4A: Chemical structures of triterpenes isolated from different *Terminalia* species.

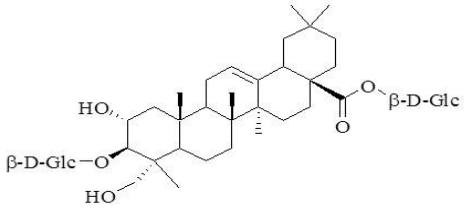




126
R= β-D-galactopyranosyl-(1→3)-β-D-glucopyranose



127
R_1=β-D-galactose(1→3)-β-D-glucose
R_2=β-D-glucose



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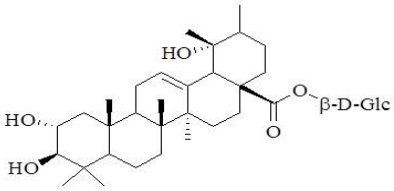

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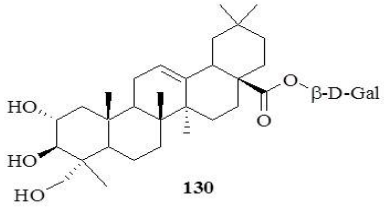

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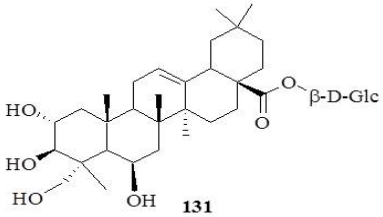

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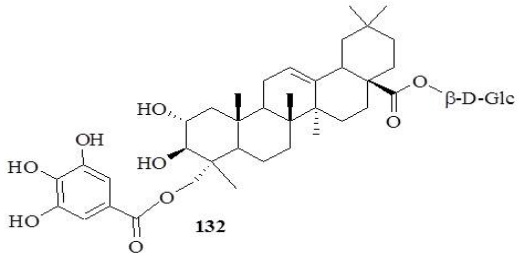

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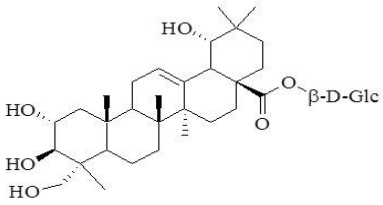

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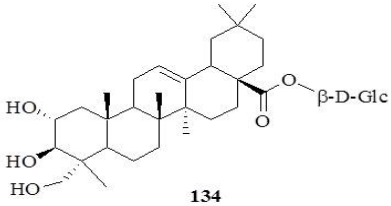

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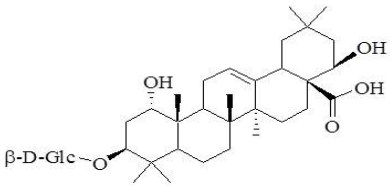

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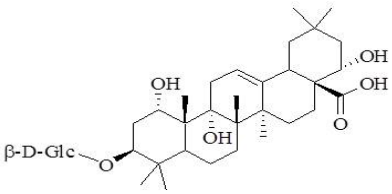

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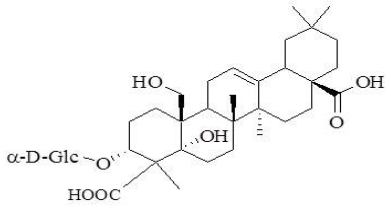

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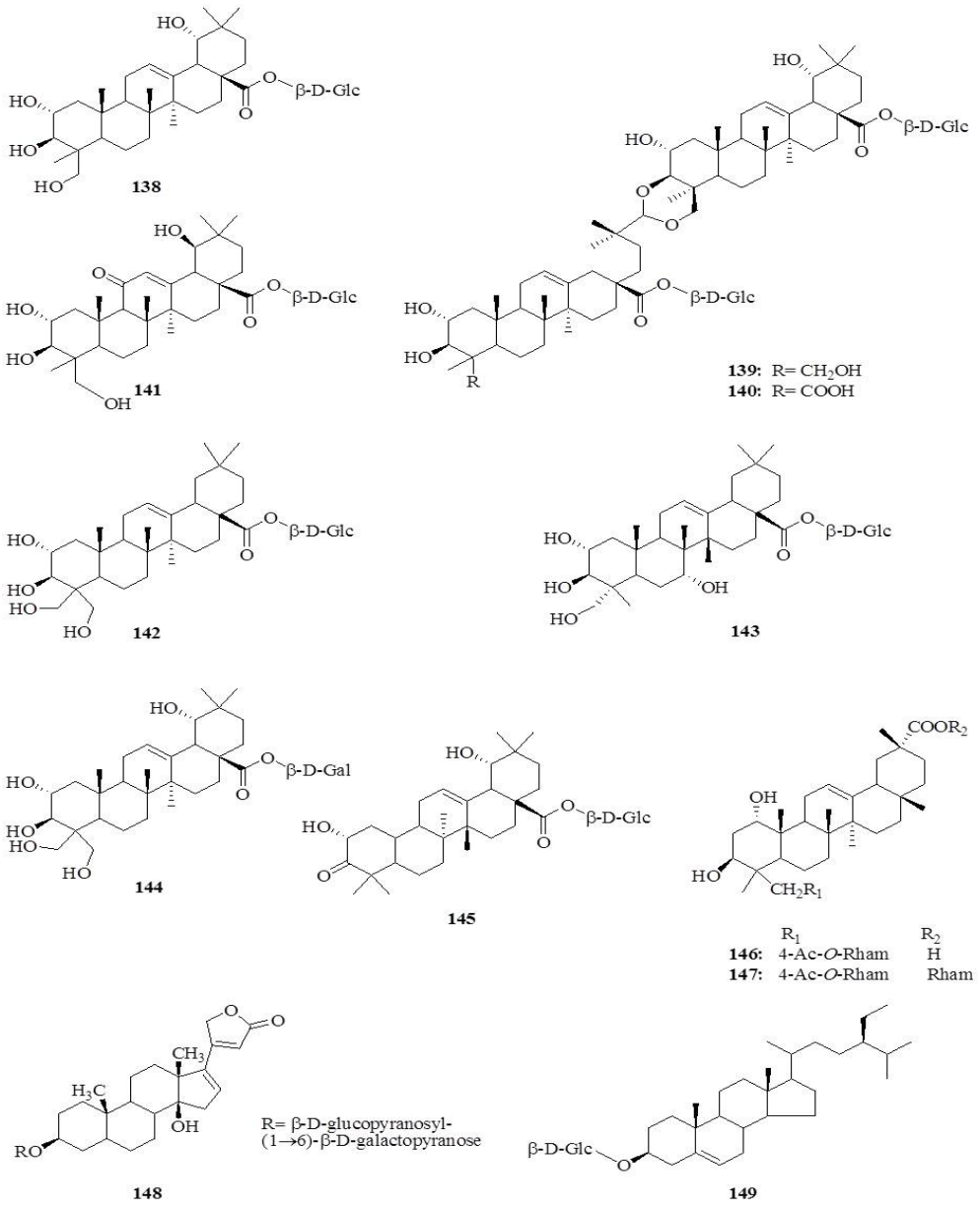

Figure 4B: Chemical structures of triterpenoidal glycosides isolated from different *Terminalia* species.

Hepato and nephro-protective activities

T. muelleri polyphenolic-rich fraction possessed hepato and nephro-protective activities in CCl_4-induced hepato- and nephrotoxicities in mice [29]. The ethanolic bark extract of *T. paniculata* possessed hepatoprotective activity and reduced the elevated serum biochemical parameters and lipid peroxides in paracetamol-induced liver damage in rats [30]. Also, oral administration of *T. arjuna* fruit extract inhibited the hepatic damage and oxidative stress in cadmium-induced hepatotoxicity in rats [31]. In addition, Manna demonstrated the protective role of arjunolic acid, isolated from the bark of *T. arjuna*, against sodium arsenite-induced oxidative stress in mouse hepatocytes [32]. *In vitro* treatment of hepatocytes with chebulic acid and neochebulic acid, isolated from *T. chebula* ethanolic fruit extract, significantly reduced the tert-butyl hydroperoxide-induced cell cytotoxicity, reactive oxygen species level, and increased the hepatic GSH [33]. Corilagin, isolated from *T. catappa* protected against galactosamine and lipopolysaccharide-induced hepatotoxicity in rats at a dose of 1 mg/kg by decreasing the oxidative stress and apoptosis [34]. Also, pre-treatment with *T. bellerica* leaf extract in CCl_4-induced hepato- and nephrotoxicities, exhibited a dose-dependent recovery in all the biochemical parameters, while gallic acid from its extract had a more pronounced effect at a dose of 200 mg/kg [35].

Anti-inflammatory activity

The ethanolic extract of *T. phanerophlebia* stem as well as its isolated compound β-sitosterol selectively inhibited cyclooxygenase enzyme

No.	Compound	Species	Part used (Type of extract)	Reference (s)
150	Isoguaiacin	*T. argentea*	Bark (EtOH)	[107]
151	Termilignan	*T. bellerica*	Fruits	[108]
152	Thannilignan	*T. bellerica*	Fruits	[108]
153	Anolignan (B)	*T. bellerica* *T. sericea*	Fruits Roots (EtOAc)	[108] [40]
154	4′-hydroxy-4-methoxy-7,7′-epoxylignan	*T. superba*	Stem bark (CH_2Cl_2: MeOH)	[18]
155	4,4′-dimethoxy-7,7′-epoxylignan	*T. superba*	Stem bark (CH_2Cl_3: MeOH)	[18]

Table 5. Lignan and lignan derivatives and their occurrence within *Terminalia* species.

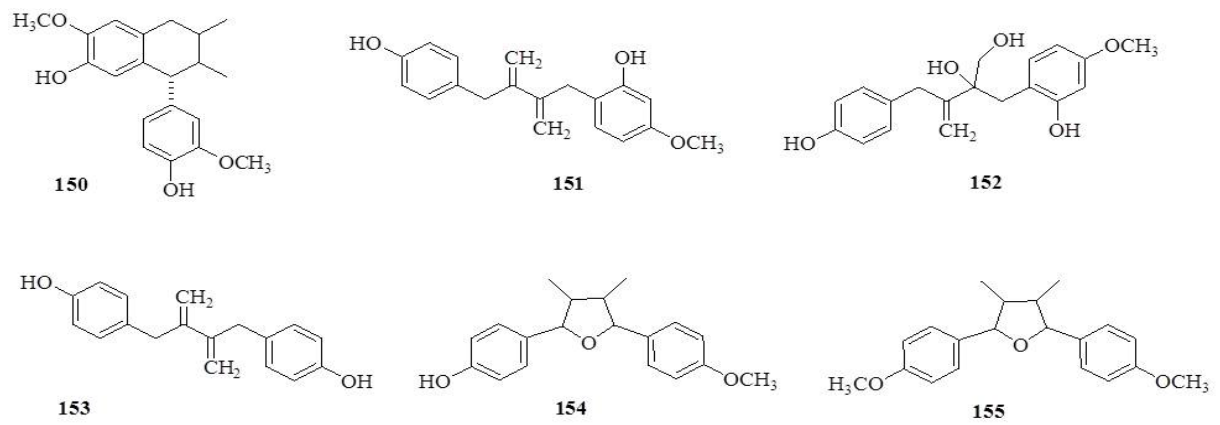

Figure 5: Chemical structures of lignans isolated from different *Terminalia* species.

(COX-2) [36]. The aqueous extract of *T. paniculata* bark significantly reduced the edema volume in carrageenan-induced rat paw edema [37]. Furthermore, the extract at a dose of 400 mg/kg also reduced the carrageenan-induced leukocyte migration and myeloperoxidase activity in air pouch exudates and exhibited anti-rheumatic and analgesic activities at a dose of 200 mg/kg. *T. ferdinandiana* fruit had a unique anti-inflammatory activities in lipopolysaccharide-activated murine macrophages, by inhibiting the expression of COX-2 and inducible nitric oxide synthase (iNOS), as well as by inhibiting the production of prostaglandin E_2 [38].

Chebulagic acid from *T. chebula* seeds, significantly suppressed the onset and progression of collagen-induced arthritis in mice [39]. Moreover, anolignan B isolated from the ethyl acetate root extract of *T. sericea* possessed an inhibitory activity against both COX-1 and COX-2 enzymes [40]. Punicalagin at a dose of 10 mg/kg and punicalin at a dose of 5 mg/kg isolated from the leaves of *T. catappa* possessed an anti-inflammatory activity against carrageenan-induced hind paw edema in rats [41]. Ursolic acid and 2α,3β,23-trihydroxyurs-12-en-28-oic acid isolated from *T. catappa* leaf ethanolic extract were responsible for its anti-inflammatory activity, as it caused a significant reduction (over 50%) of the edema induced in mice ear at 0.30 mg/ear dose [42].

Gastroprotective activity

Chebulinic acid isolated from *T. chebula* fruit showed a gastro protective effect against ulcers induced by cold restraint (62.90% gastro protection), aspirin (55.30%), alcohol (80.67%) and pyloric ligation (66.63%) induced ulcer models. Chebulinic acid significantly reduced free acidity (48.82%), total acidity (38.29%) and upregulated mucin secretion (by 59.75%). Additionally, chebulinic acid significantly inhibited H^+ K^+-ATPase activity *in vitro* with an IC_{50} value of 65.01 µg/ml compared to that of Omeprazole 30.24 µg/ml, proving its anti-secretory activity [43]. In addition, the methanolic extract of *T. arjuna* caused a significant reduction in the lesion index in diclofenac-induced ulcer, and a significant increase in pH, non-protein sulfhydryls, reduced glutathione, protein bound carbohydrate complexes, adherent mucus content with a significant decrease in the volume of gastric juice, free and total acidity, pepsin concentration, acid output, lipid peroxidase levels and myeloperoxidase activities [44]. The ethanolic extract of *T. pallida* exhibited a significant anti-ulcer activity against indomethacin, histamine and ethanol in Swiss albino rats by enhancing the antioxidant state of the gastric mucosa, thereby reducing mucosal damage [45].

Antimicrobial and Antiviral activity

Various *Terminalia* species were reported to exert a potent antimicrobial effect on different microorganism. *T. chebula* water extract had a significant antibacterial activity on *Helicobactor pylori* with MIC and MBC of 125 and 150 µg/ml respectively [46]. Additionally, the acetone extract of *T. chebula* exhibited a potent antibacterial activity on *Enterococcus faecalis, Bacillus sabtilis* and *Klebsiella pneumoniae* bacterias [47]. Casuarinin isolated from the bark of *T. arjuna*, showed a strong antiviral activity on *Herpes simplex* type 2 at a concentration of 25 µM and reduced the viral titers up to 100,000-fold by inhibiting the viral attachment and penetration [48]. Recently, Fyhrquist reported that the methanolic root and stem bark extracts of *T. sambesiaca* showed lower MIC values than its aqueous, butanol and chloroform fractions against mycobacterium [49]. The strong antibacterial activity of *T. muelleri* ethylacetate leaf extract was attributed to its gallic acid content [50].

The antifungal activity of different leaf extracts prepared from six *Terminalia* species (*T. prunioides*, *T. brachystemma*, *T. sericea*, *T. gazensis*, *T. mollis* and *T. sambesiaca)* were examined against numerous fungi. It was found that the acetone extracts possessed the highest antifungal activity. *T. sericea* extracts were the most active against nearly all tested microorganisms [51]. Another study revealed that anolignan B isolated

from the ethyl acetate root extract of *T. sericea* had a strong antimicrobial activity with MIC values ranging from 3.80 µg/ml against *Bacillus sabtilis* to 31 µg/ml against *Escherichia coli* [40]. Gallic acid isolated from the methanolic extract of *T. nigrovenulosa* bark showed a high antifungal activity against *Fusarium solani* [52]. Ethanolic root extract of *T. macroptera* had a significant antimicrobial activity, where the lowest MICs were obtained for *Shigella dysenteriae*, *Staphylococcus aureus* and *Vibrio cholera* with a significant activity against *Campylobacter* species [53]. Also, the leaf extract of *T. macroptera* showed an antimicrobial activity against *Neisseria gonorrhoeae* with an MIC value between 100 and 200 µg/ml, the diethyl ether fraction was the most active fraction with an MIC values between 25 and 50 µg/ml [54]. Moreover, it was assumed that punicalagin and terchebulin, the major compounds of the *T. macroptera* root extract were responsible for the *in vitro* activity of the extract against *Helicobacter pylori* [55]. The methanolic extract of *T. superba* stem bark, together with its major component 3',4-di-*O*-methyl-3-*O*-(β-D-xylopyranosyl) ellagic acid prevented the growth of various mycobacteria and fungal species [56]. Punicalagin, isolated from the acetone extract of *T. brachystemma* leaves, displayed a good antifungal activity against *Candida parapsilosis* (MIC=6.25 µg/ml), *Candida krusei* (MIC=6.25 µg/ml) and *Candida albicans* (MIC=12.50 µg/ml) [9]. *T. australis* methanol and aqueous extracts were effective against the several *Aspergillus* and *Candida* strains [57]. The compounds 5,7,2'-tri-*O*-methyl-flavanone-4'-*O*-α-L-rhamnopyranosyl-(1→4)-β-D-glucopyranoside and 2α,3β,19β,23-tetrahydroxyolean-12-en-28-oic-acid-3-*O*-β-D-galactopyranosyl-(1→3)-β-D-glucopyranoside-28-*O*-β-D-glucopyranoside isolated from the roots of *T. alata* were reported to have a strong antifungal activity [58].

Cytotoxic activity

T. chebula methanolic fruit extract showed a reduction in cell viability, inhibition of cell proliferation, and induction of cell death in a dose-dependent manner on many malignant cell lines. In addition, it induced apoptosis at lower concentrations, and necrosis at higher concentrations. Chebulinic acid, tannic acid and ellagic acid, with IC_{50} values of 53.20, 59.00 and 78.50 µg/ml respectively, were the most cytotoxic compounds of *T. chebula* fruit [59]. Furthermore, chebulagic acid isolated from the *T. chebula* fruit extract possessed an anti-proliferative activity against HCT-15, COLO-205, MDA-MB-231, DU-145 and K562 cell lines [60]. *T. catappa* leaf water extract, along with its isolated component punicalagin were effective against bleomycin-induced genotoxicity in Chinese hamster ovary cells [61]. Furthermore, *T. catappa* leaf extract exerted a dose-dependent inhibitory effect on the invasion and motility of highly metastatic A549 and Lewis lung carcinoma cells [62]. Moreover, the ethanol extract of *T. catappa* leaves significantly inhibited the cell migration capacity of oral squamous cell carcinoma cells [63]. Luteolin, gallic acid and gallic acid ethyl ester isolated from the bark, stem and leaves of *T. arjuna* methanolic extract possessed a strong antineoplastic activity [64]. Moreover, ivorenoside C isolated from the bark of *T. ivorensis* had an antiproliferative activity against MDA-MB-231 and HCT116 human cancer cell lines with IC_{50} values of 3.96 and 3.43 µM respectively [65]. Additionally, the acetone extract of *T. calamansanai* leaves inhibited the viability of HL-60 cells [66].

Cardioprotective activity

T. arjuna bark has been used widely in traditional medicine as a cardioprotective. The ethanolic extract of *T. arjuna* bark enhanced the cardiac intracellular antioxidant status in CCl_4-induced oxidative stress in rats [67]. The protective effect was comparable to that of vitamin C. In addition, The butanol fraction of *T. arjuna* bark extract exhibited a protective effect against doxorubicin-induced cardiotoxicity by increasing cardiac antioxidant enzymes, decreasing serum creatine kinase-MB levels and reducing lipid peroxidation [68]. Many clinical trials were also conducted to prove the beneficial effect of *T. arjuna* bark on the heart. A group of scientists showed that patients with refractory chronic congestive heart failure, when received *T. arjuna* bark extract as an adjuvant therapy, showed a long lasting improvement in the signs and symptoms of heart failure with an improvement in left ventricular ejection phase indices and quality of life [69]. Moreover, a clinical study was done to evaluate the role of *T. arjuna* in ischemic mitral regurgitation (IMR) following acute myocardial infarction. Patients receiving adjuvant *T. arjuna* showed significant decrease in IMR and reduction in anginal frequency [70]. In addition, pretreatment with *T. pallida* fruit extract ameliorated myocardial injury in isoproterenol-induced myocardial infarction in rats and exhibited cardioprotective activity [71]. Similarly, pretreatment with *T. chebula* extract ameliorated the effect of isoproterenol on lipid peroxide formation [72].

Anti-hypertensive activity

T. superba bark extract showed a potent antihypertensive activity in spontaneously hypertensive rats, as well as in glucose-induced hypertensive rats due to the withdrawal of sympathetic tone and the improvement of the antioxidant status [73,74].

Antiparasitic and molluscicidal activity

The *in vitro* nematicidal activity of *T. nigrovenulosa* bark against *Meloidogyne incognita* was attributed to 3,4-dihydroxybenzoic acid isolated from it. [75]. The ethyl acetate, acetone and methanol leaf and seed extracts of *T. chebula* showed *in vitro* ovicidal and larvicidal activities on *Haemonchus contortus* [76]. In addition, *T. chebula* fruit molluscicidal activity was due its tannic acid content that significantly inhibited the AChE, ACP and ALP activity in the nervous tissue of freshwater snail *Lymnaea acuminate* [77]. Additionally, ethanolic leaf extract of *T. catappa* possessed a molluscicidal activity against the snail intermediate hosts of schistosomiasis (*Biomphalaria pfeifferi* and *Bulinus globosus*) with *B. pfeifferi* being more susceptible [78].

Wound healing activity

Topical administration of *T. chebula* alcoholic leaf extract on the rat dermal wounds showed a beneficial effect in the acceleration of the healing process, by increasing the tensile strength of tissues by about 40% and decreasing the period of epithelialization [79]. Moreover, the tannin-rich fraction obtained from *T. chebula* fruits endorsed wound healing in rats due to the powerful antibacterial and angiogenic activity of the extract [80]. Topical application of *T. arjuna* hydro-alcholic extract resulted in a significant increase in the tensile strength of the incision wounds and epithelialization of excision wounds. This wound healing property was more pronounced in the tannin-rich fraction compared to the other fractions [81].

Conclusion

An extensive literature survey on genus *Terminalia* has revealed a variety of chemical constituents produced by this genus. Tannins, flavonoids, phenolic acids, triterpenes, triterpenoidal glycosides, lignan and lignan derivatives constitute the major classes of phytoconstituents of this genus [82-105]. In addition, the current review showed that most of the biological studies performed on different extracts and isolated compounds from different species of *Terminalia* were focused on the assessment of the antimicrobial, antioxidant, hepatoprotective, anti-

inflammatory, hypoglycemic, hypolipidimic, cytotoxic and wound healing activities of these species. The various pharmacological studies validated the folk medicinal uses of different *Terminalia* species. Although many phytochemical and biological investigations were reported from the genus *Terminalia,* the studies have focused mainly on certain species, with *chebula, bellerica, arjuna, catappa, horrida, superba, macroptera, pallida, ivorensis, sericea and alata* being the most phytochemically and biologically studied species, leaving a fertile area for further investigations on other species that have not been fully explored yet [106-133]. The present review provides a comprehensive understanding of the chemistry and biology of different *Terminalia* species, which may help in the discovery and development of new alternative medications for the treatment of various diseases and health problems.

Declaration of Interest

The authors have declared no conflicts of interest.

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