

Bioactive constituents and medicinal importance of genus *Alnus*

Sushil Chandra Sati, Nitin Sati¹, O. P. Sati,

Department of Chemistry, ¹Pharmaceutical Sciences, H.N.B. Garhwal University, Srinagar Garhwal, Uttarakhand, India

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ABSTRACT

The genus *Alnus* has been reviewed for its chemical constituents and biological activities including traditional importance of some common species. The plants of this genus contain terpenoids, flavonoids, diarylheptanoids, phenols, steroids, and tannins. Diarylheptanoids are the dominant constituents within the genus *Alnus*, few of them exhibited antioxidant effects and inhibitory activity against nuclear factor kappaB activation, nitric oxide and tumor necrosis factor- α production, human umbilical vein endothelial cells, farnesyl protein transferase, cell-mediated low-density lipoprotein oxidation, HIF-1 in AGS cells, and the HIV-1-induced cytopathic effect in MT-4 cells. Some ellagitannins showed hepatoprotective activity even in a dose of 1 mg/kg which is ten-fold smaller compared with the dose of traditional flavonoid-based drugs. The members of genus *Alnus* are well known for their traditional uses in the treatment of various diseases like cancer, hepatitis, inflammation of uterus, uterine cancer, rheumatism, dysentery, stomachache, diarrhea, fever, etc. The aim of the present review is to summarize the various researches related to the chemistry and pharmacology of genus *Alnus*.

Key words: *Alnus*, antioxidant effects, diarylheptanoids, HIV-I, inhibitory activity

INTRODUCTION

Betulaceae or the Birch family includes six genera of deciduous nut-bearing trees and shrubs, including the birches, alders, hazels, hornbeams, and hop-hornbeams, numbering about 130 species. These are mostly natives of the temperate Northern Hemisphere, with a few species reaching the Southern Hemisphere in the Andes in South America. *Alnus* (alders) is an important genus belonging to Betulaceae which comprises 30 species worldwide. ^[1,2] Almost all plants of this genus have been traditionally used as folk medicine in Ayurveda, Unani, and Chinese medical systems.

OBJECTIVES OF THE REVIEW

Alnus is one of the genera having potential medicinal values.

Address for correspondence:

Dr. Sushil Chandra Sati,
Department of Chemistry, H.N.B. Garhwal University,
Srinagar Garhwal, Uttarakhand, India.
E-mail: sushilsati1983@gmail.com

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The plants of this genus have been found active against many live-threatening disorders like hepatitis, HIV-1 viral replication, and cancer. The aim of the present review is to delineate the various plants with their chemical constituents and biological activities. Various traditional uses of some common species have also been summarized. These informations can create a center of attention for scientists and herbologists for this genus, and consequently this database might play a major role in future research.

TRADITIONAL USES OF *ALNUS* SPECIES

The members of genus *Alnus* are well known for their traditional medicinal values. These have been used for the treatment of various diseases including cancer and as an alterative, astringent, cathartic, emetic, febrifuge, galactagogue, hemostatic, parasiticide, skin tonic, vermifuge, etc. *Alnus japonica* is a popular folk medicine in Korea for cancer and hepatitis.^[3] The bark of *Alnus glutinosa* is alterative, astringent, cathartic, febrifuge, tonic, and useful in mouth and throat inflammations, the vinegar extract of inner bark of plant produces a useful wash to treat lice and a range of skin problems such as scabies and scabs.^[4-6] The leaf, roots, and bark of *A. nepalensis* are used in dysentery, stomach ache, and diarrhea in Indian system of medicine (Ayurveda).^[7] A decoction of the root of *A. nepalensis* is prescribed to treat diarrhea and paste from the leaves is applied on cuts and wounds as a hemostatic.^[8] The mixture of leaves of *Alnus jorullensis* and branches of *Polylepis*

racemosa R. et P is used to treat inflammation of uterus, uterine cancer, and rheumatism.^[9] The bark of *Alnus hirsuta* is used in Korean and Chinese traditional medicine as remedies for fever, hemorrhage, alcoholism, and diarrhea.^[10,11] The decoction of *A. glutinosa* barks is used to treat swelling, inflammation, and rheumatism.^[12] It has also been used as an astringent, bitter, emetic, and hemostatic, and for the treatment of sore throat and pharyngitis.^[13,14] Contemporary indigenous healers used the bark of *Alnus rubra* for various medicinal teas.^[15,16]

CHEMICAL CONSTITUENTS OF GENUS *ALNUS*

The plants of the genus *Alnus* contain various types of plant secondary metabolites including terpenoids, flavonoids, diarylheptanoids, phenols, steroids, tannins, and many others. The plants and their chemical constituents have been summarized below, whereas the chemical structures of various compounds isolated from different parts of genus *Alnus* are drawn in Figures 1 to 8.

Chemical constituents of *Alnus japonica*

Luteolin 7,4'-dimethyl ether (pillion) (1); scutellarein-6,7,4'-trimethyl ether (salvigenin) (2); kaempferide (3); isohamnetin (4); rhamnazin (5); quercetin-7,3',4'-trimethyl ether (6); the 3,6,4'-trimethyl ether of 6-hydroxy-kaempferol (7); acacetin (8); apigenin-7,4'-dimethyl ether (9); scutellarein-6,4'-dimethyl ether (10); methyl (24E)-3,4-secodammara-4(28),20,24-trien-26-oic acid-3-oate (11); (24E)-3,4-secodammara-4(28),20,24-trien-3,26-dioic acid (12); (20S,24S)-20,24-dihydroxy-3,4-secodammara-4(28),23-dien-3-oic acid (13); (23E)-(20S)-20,25-dihydroxy-3,4-secodammara-4(28),23-

dien-3-oic acid (14); (23E)-(20S)-20,25,26-trihydroxy-3,4-secodammara-4(28),23-dien-3-oic acid (15); (23E)-(12R,20S)-12,20,25-trihydroxy-3,4-secodammara-4(28),23-dien-3-oic acid (16); hirsutanonol 5-O-(6-O-galloyl)- β -D-glucopyranoside (17); 3-deoxy-hirsutanonol 5-O- β -D-gucopyranoside (18); hirsutanonol (19); hirsutanonol 5-O- β -D-glucopyranoside (20); 3-deoxy-hirsutanonol 5-O-(6-O- β -D-aposyl)- β -D-glucopyranoside (21); hirsutenone (22); 7-(3,4-dihydroxyphenyl)-5-hydroxy-1-(4-hydroxyphenyl)-3-heptanone-5-O- β -D-xylopyranoside (23); 1-(3,4-dihydroxyphenyl)-5-hydroxy-7-(4-hydroxyphenyl)-3-heptanone-5-O- β -D-xylopyranoside (24); 1,7-bis-(3,4-dihydroxyphenyl)-5-hydroxy-3-heptanone-5-O-[2-(2-methylbutenoyl)]- β -D-xylopyranoside (25); 1,7-bis-(3,4-dihydroxyphenyl)-5-methoxy-3-heptanone (26); oregonin (27); β -amyrin (28); 3-O-acetyl- β -amyrin (29); 3-O-acetyl taraxerol (30); glutinone (31); lupenone (32); quercitin (33); 5-O-methylhirsutanonol (34); glutinol (35); taraxerone (36); alnusjaponins A (37); alnusjaponins B (38); 5-O-galloyl(-)-shikimic acid (39); 2,3-(S)-hexahydroxydiphenyl-D-glucose (40); 4,6-di-O-galloyl-D-glucose (41); 1,4-di-O-galloyl- β -D-glucose (42); 4,6-(S)-valoneoyl-D-glucose (43); strictinin (44); gemin D (45); pedunculagin (46); praecoxin A (47); flosin A (48); stachyurin (49); casuarinin (50); 1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-O- β -D-glucopyranosyl(1 \rightarrow 3)- β -D-xylopyranoside (51); 1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-O- β -D-apiofuranosyl(1 \rightarrow 6)- β -D-glucopyranoside (52); 1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-O- β -D-glucopyranoside (53); 1,7-bis-(3,4-dihydroxyphenyl)-5-hydroxyheptane (54); 1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-O- β -D-glucopyranoside (55); platyphylloside (56);

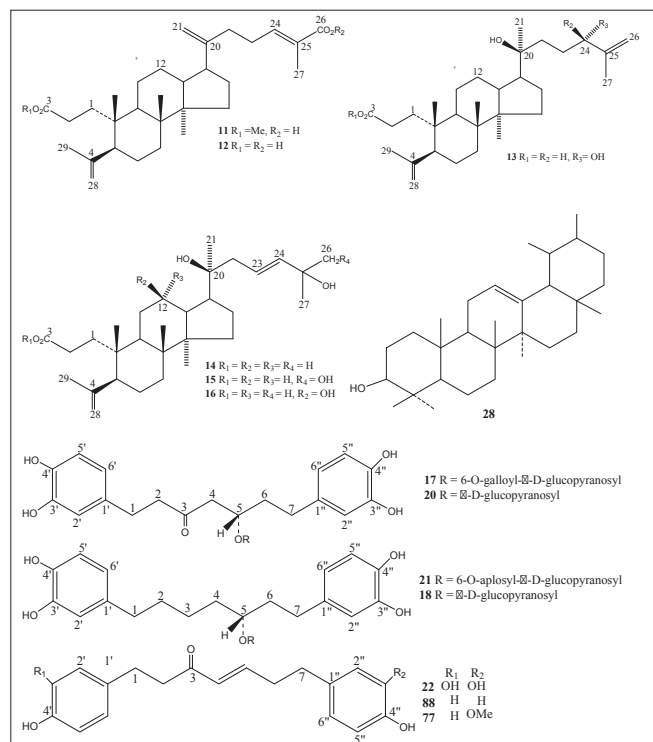


Figure 1: Chemical structures of compounds isolated from genus *Alnus*

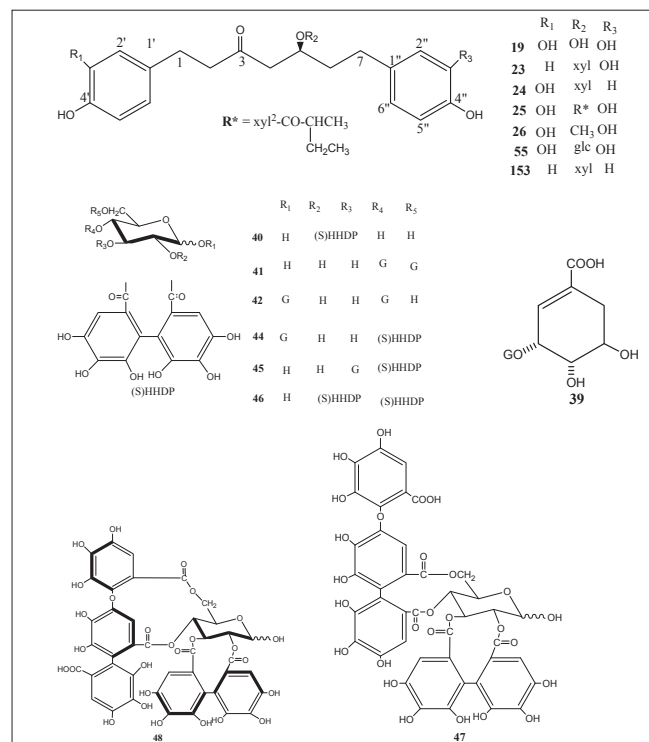


Figure 2: Chemical structures of compounds isolated from genus *Alnus*

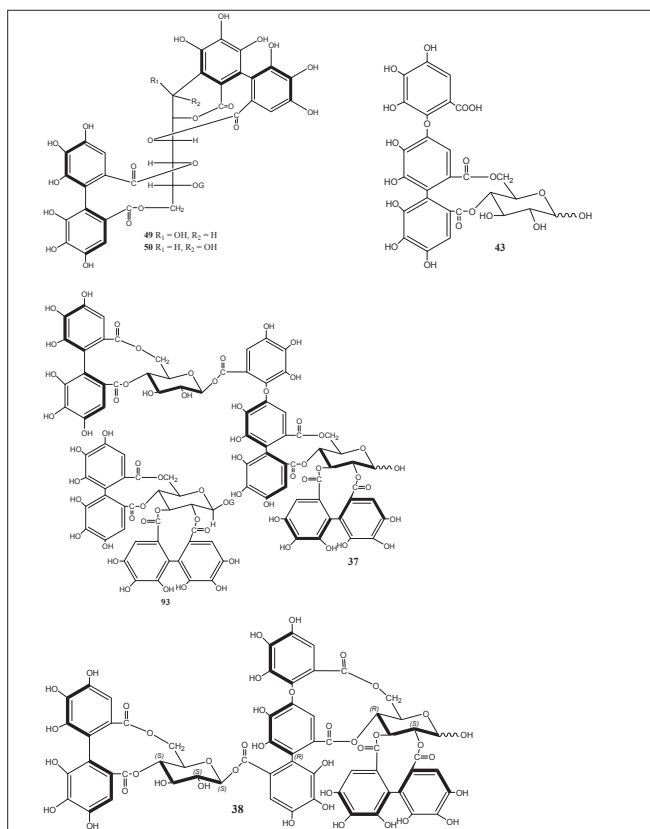


Figure 3: Chemical structures of compounds isolated from genus *Alnus*

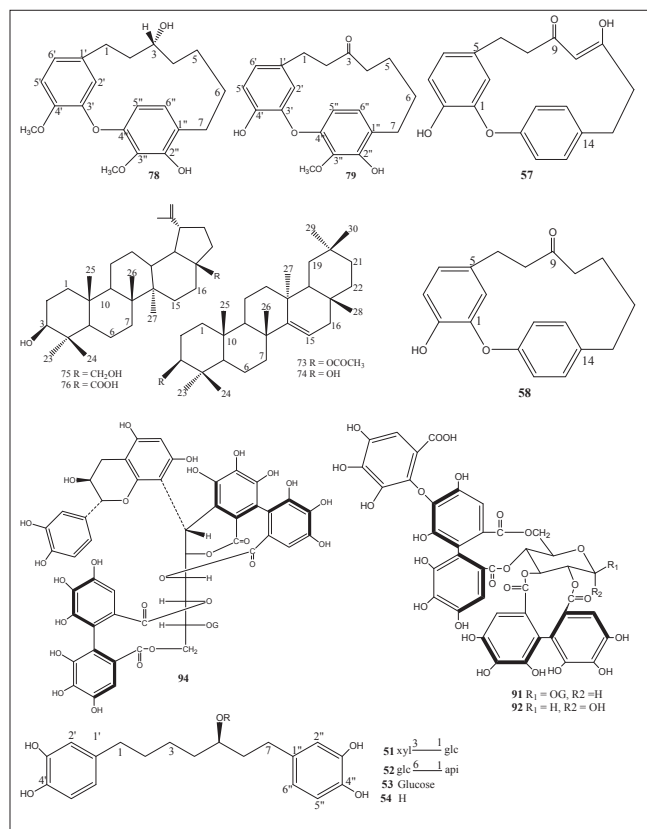


Figure 4: Chemical structures of compounds isolated from genus *Alnus*

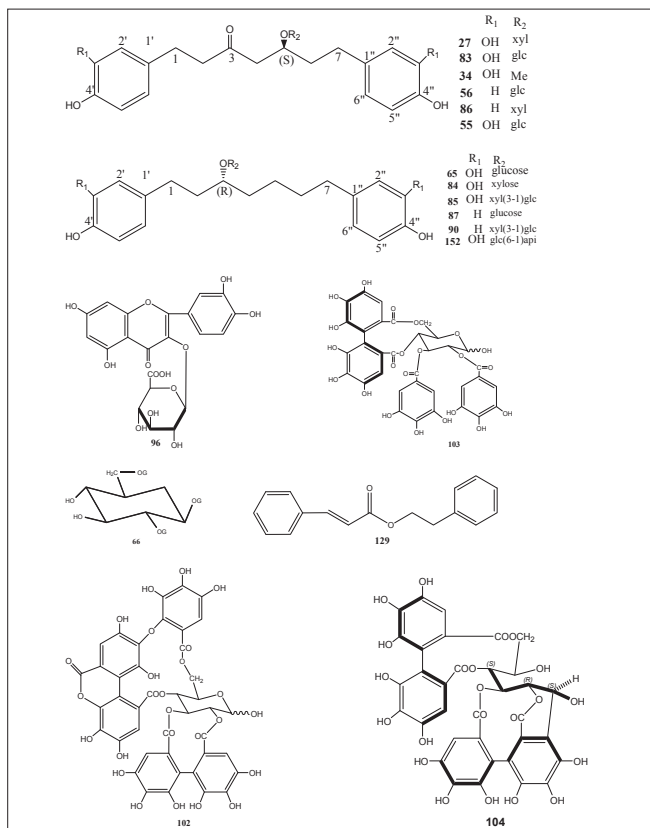


Figure 5: Chemical structures of compounds isolated from genus *Alnus*

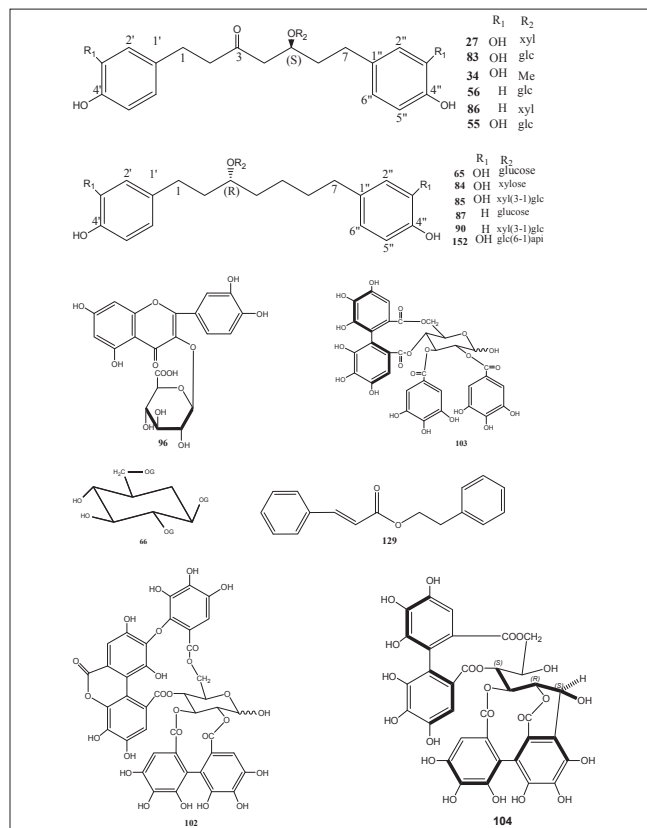


Figure 6: Chemical structures of compounds isolated from genus *Alnus*

garugamblin-3 (57); acerogenin L (58); oregonoyl A (59); oregonoyl B (60); platyphyllone (61) and platyphyllonol-5-xylopyranoside (62).^[17-30]

Chemical constituents of *Alnus hirsuta*

(5S)1,7-Bis-(3,4-dihydroxyphenyl)-heptane-5-hydroxy-3-one {hirsutanonol} (19); hirsutanone (22); (5S)1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-O- β -D-xylopyranoside {oregonin} (27); (5S)-O-methylhirsutanonol (34); pedunculagin (46); praecoxin A (47); (5R)1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-O- β -D-glucopyranoside (53); (5S)1,7-bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-O- β -D-glucopyranoside (55); platyphylloside (56); gentisic acid 5-O- β -D-(6'-O-galloyl)glucopyranoside (63); tellimagrandin I (64); rubranoside A (65); 1,2,6-tri-O-galloyl- β -D-glucose (66); 1,4,6-tri-O-galloyl- β -D-glucose (67); 1-desgalloyleugeniin (68); 1-desgalloylrugosin F (69); rugosin F (70); hirsunin (71); (5R)-1,7-bis(3,4-dihydroxyphenyl)-heptane-5-ol (72); taraxeryl acetate (73); taraxerol (74); betulin (75); betulinic acid (76); 1-(4-hydroxyphenyl)-7-(4-hydroxy-3-methoxyphenyl)-4-hept-3-one (77); 2-oxytrycyclo[13.2.2.13,7]eicosa-3,5,7(20),15,17,18-hexaen-10-16-diol (78); 2-oxytrycyclo[13.2.2.13,7]eicosa-3,5,7(20),15,17,18-hexaen-10-one (79); rhoiptelol B (80); (5R)1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-O- β -D-xylopyranoside (81); hirsutoside (82); hirsutanonol 5-O-beta-D-glucopyranoside (83); rubranoside B (84); rubranoside C (85); platyphyllonol 5-O-beta-D-xylopyranoside (86); aceroside VII (87); platyphyllone (88); (5R)-1,7-bis(3,4-dihydroxyphenyl)-heptane-5-O- β -D-glucoside (89) and (3R)-1,7-bis-(4-dihydroxyphenyl)-3-heptanol-3-O- β -D-glucopyranosyl(1 \rightarrow 3)- β -D xylopyranoside (90).^[11,30-44]

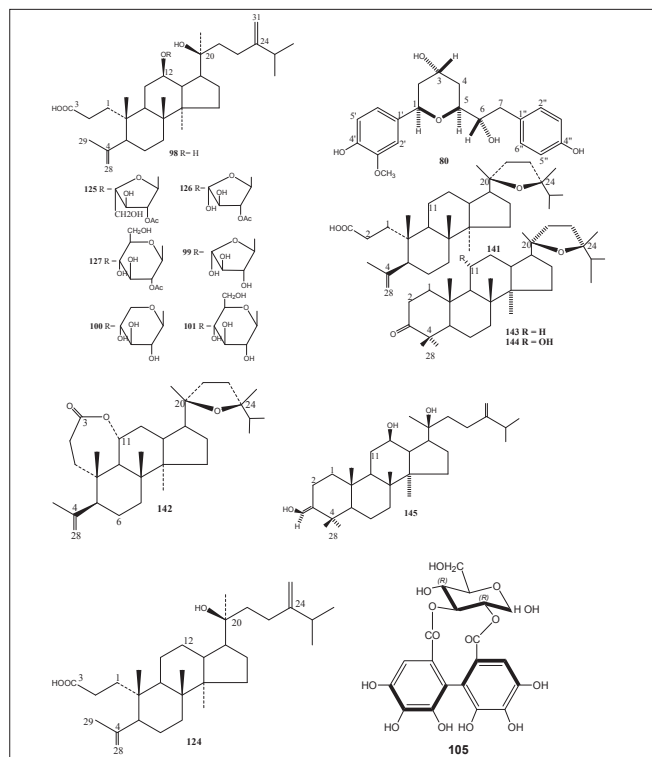


Figure 7: Chemical structures of compounds isolated from genus *Alnus*

Chemical constituents of *Alnus sieboldiana*

Strictinin (44); pedunculagin (46); stachyurin (49); casuarinin (50); 1,2,6-tri-O-galloyl- β -D-glucose (66); 1-O-galloyl-2,3-(S) hexahydroxydiphenoyl-4,6-(s)tergalloyl- β -D-glucose (91); 2,3-(s) hexahydroxydiphenoyl-4,6-(s)tergalloyl- β -D-glucose (92); 1(β)-O-galloylpedunculagin (93); stenophyllanin A (94); pinocembrin (95); quercetin-3-O- β -D-glucuronide (96); alnuserrudiolone (97); alnustic acid (98); alnustic acid 12-O- α -L-arabinofuranoside (99); alnustic acid 12-O- β -D-xylopyranoside (100); alnustic acid 12-O- β -D-glucopyranoside (101); alnusiin (102); tellimagrandin I (103); casuarinin (104); 2,3-O-(S)-hexahydroxydiphenoyl-D-glucose (105); 3,5,7-trihydroxy-6-methoxyflavone (106); 5-hydroxy-6,7,8-trimethoxyflavone (107); 5-hydroxy-3,6,7-trimethoxyflavone (108); 3,5,7-trihydroxy-6-methoxyflavanone (109); chrysin (110); izalpinin (111); tectochrysin (112); pinobanksin (113); strobopin (114); naringenin (115); pinosylvin (116); pinosylvin monomethyl ether (117); pinosylvin dimethyl ether (118); yashabushidiol A (119); yashabushidiol B (120); yashabushiketodiol A (121); yashabushiketodiol B (122); yashabushitriol (123).^[29,45-54]

Chemical constituents of *Alnus pendula*

Pinocembrin (95); alnustic acid (98); 12-O- α -L-arabinofuranoside of alnustic acid (99); 12-O- β -D-xylopyranoside of alnustic acid (100); 12-O- β -D-glucopyranoside of alnustic acid (101); pinosylvin (116); monomethyl ether of pinosylvin (117); 12-deoxy alnustic acid {(20S)-20-hydroxy-24-methylene-3,4-secodammar-4-(28)-en-3-oic acid} (124); alnustic acid 12-O-(2'-O-acetyl)- α -L-arabinofuranoside (125); (12R, 20S)-12-O-(2'-O-acetyl- β -D-xylopyranosyl)-20-hydroxy-24-methylene-3,4-secodammae-4(28)-en-3-oic acid (126); (12R, 20S)-12-O-

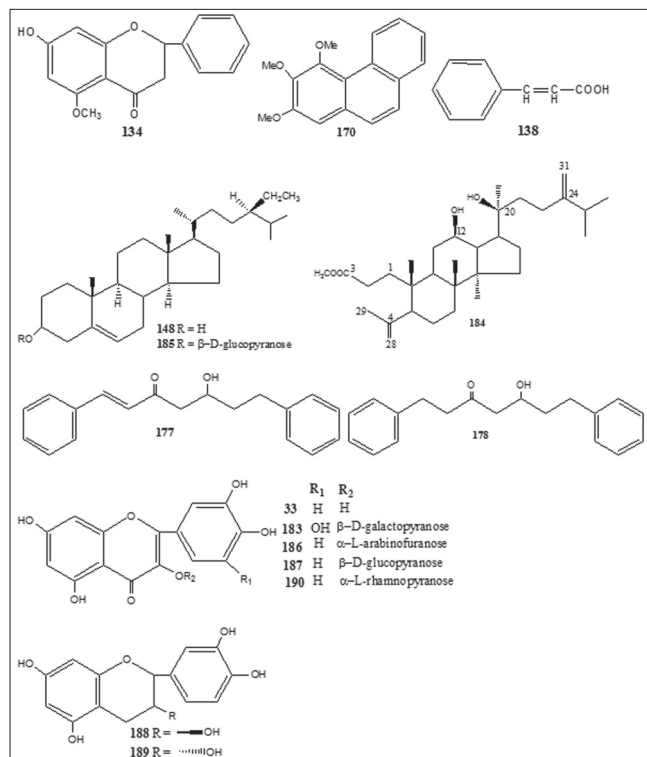


Figure 8: Chemical structures of compounds isolated from genus *Alnus*

(2'-O-acetyl- β -D-glucopyranosyl)-20-hydroxy-24-methylene-3,4-secodammae-4(28)-en-3-oic acid (127); alnustone (1,7-diphenyl-1,3-heptadien-5-one) (128); β -phenylethyl cinnamate (129); cinnamaldehyde (130); benzylacetone (131); β -phenylethyl alcohol (132); pinostrobin (133); alpinetin (134); galangin (135); eugenol (136); chavicol (137); cinnamic acid (138); β -phenylpropionic acid (139) and benzoic acid (140).^[55-58]

Chemical constituents of *Alnus serrulatoides* (Call.)

Alnuserrudiolone (97); alnustic acid (98); alnustic acid-12-O- α -L-arabinofuranoside (99); alnustic acid-12-O- β -D-xylopyranoside (100); alnustic acid-12-O- β -D-glucopyranoside (101); alnustic acid-12-O-(2'-O-acetyl)- α -L-arabinofuranoside (125); alnustic acid-12-O-(2'-O-acetyl)- β -D-xylopyranoside (126); alnustic acid-12-O-(2'-O-acetyl)- β -D-glucopyranoside (127); alnuseric acid {20S,24R}-20,24-epoxy-24-methyl-3,4-secodammar-4(28)-en-3-oic acid} (141); alnuselide {(11R,20S,24R)-20,24-epoxy-24-methyl-3,4-secodammar-4(28)-en-3-oic acid} (142); alnincanone (143); alnuserol (144) and alnuserrutriol (145).^[59-66]

Chemical constituents of *Alnus rubra*

Salvigenin (2); acacetin (8); hirsutanonol (19); oregonin (27); glutinone (31); lupenone (32); 7,4'-dimethoxy-5-hydroxyflavone (34); taraxerone (36); 1,7-bis-(3,4-dihydroxyphenyl)-heptan-3-one-5-O- β -D-glucopyranoside (55); platyphylloside (56); rubranoside A (65); (5R)-1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-ol (72); taraxeryl acetate (73); taraxerol (74); betulin (75); rubranoside B (84); rubranoside C (85); (5R)-1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-O- β -D-glucoside (89); pectolinaringenin (146); lupeol (147); β -sitosterol (148); diarylheptenone-1-(3',4'-dihydroxyphenyl)-7-(4"-hydroxyphenyl)-4-hepten-3-one (149); 1,7-bis(p-hydroxyphenyl)-4-hepten-3-one (150); apigenin (151); rubranoside D (152) and (s)-1,7-bis-(4-hydroxyphenyl)-heptane-3-on-5-O- β -D-xylopyranoside (153).^[67-70]

Chemical constituents of *Alnus crispa*

Kaempferol 3, 7-dimethyl ether (kumatakenin) (154); quercetin 3,7-dimethyl ether (155) and quercetin-3,7,4'-trimethyl ether (156).^[29]

Chemical constituents of *Alnus koehnei*

Salvigenin (2); kaempferide (3); quercetin-7,3',4'-trimethyl ether (6); 3,6,4'-trimethyl ether of 6-hydroxykaempferol (7); acacetin (8); quercetin-3,7-dimethyl ether (155); kaempferol (157); rhamnetin (158); isorhamnetin (159); quercetin-3,3'-dimethyl ether (160); the 3,6-dimethyl ether of 6-hydroxykaempferol (161), 6,4'-dimethyl ether of 6-hydroxykaempferol (162) and quercetagetin-3,6,4'-trimethyl ether (163).^[29]

Chemical constituents of *Alnus sinuate*

Kumatakenin (154); quercetin-3,7-dimethyl ether (155) and genkwanin (164).^[29]

Chemical constituents of *Alnus nepalensis*

(5S)1,7-Bis-(3,4-dihydroxyphenyl)-heptane-3-one-5-O- β -D-xylopyranoside {oregonin} (27); taraxerone (36); taraxerol (74); betulin (75); betulinic acid (76); lupeol (147) and β -sitosterol (148).^[71-72]

Chemical constituents of *Alnus fruticosa*

β -Amyrin (28); lupenone (32); β -sitosterol (148); glutin-5-en-3-ol (165) and α -amyrin (166).^[73]

Chemical constituents of *Alnus kamtschatica*

β -Amyrin (28); lupenone (32); β -sitosterol (148); glutin-5-en-3-ol (165) and α -amyrin (166).^[73]

Chemical constituents of *Alnus glutinosa*

Hirsutanonol (19); oregonin (27); genkwanin (164); rhododendrin {3-(4-hydroxyphenyl)-l-methylpropyl- β -D-glucopyranoside} (167) and glutinic acid (2,3-pentadienedioic acid) (168).^[74-77]

Chemical constituents of *Alnus maximowiczii*

Pinocembrin (95); pinosylvin monomethyl ether (117); pinosylvin dimethyl ether (118); 1,7-diphenylhept-3-en-5-one (169); 2,3,4-trimethoxyphenatheren (170); 1,7-diphenyl-hept-1-ene-3,5-dione (171); 1,7-diphenylheptane-3,5-dione (172); alnustinol (173); cryptomeridiol 11-o-monoacetate (174); β -eudesmol acetate (175) and elemol acetate (176).^[78]

Chemical constituents of *Alnus firma*

β -phenylethyl cinnamate (129); pinostrobin (133); alpinetin (134); cinnamic acid (138); yashabushiketol (177); dihydroyashabushiketol (178); trans-stilbene (179); triglycerides (180); 4-hydroxy-2,6-dimethoxyphenyl-6'-O-syringoyl- β -D-glucopyranoside (181); 4-hydroxy-2,6-dimethoxyphenyl-6'-O-vanilloyl- β -D-glucopyranoside (182); myricetin-3-O- β -D-galactopyranoside (183) alnustic acid methyl ester (184); β -amyrin acetate (29); β -amyrin (28); β -sitosterol (148); β -sitosterol 3-O- β -D-glucoside (185); pinocembrin (95); alnustinol (173); quercetin (33); quercetin-3-O- α -L-arabinofuranoside (186); isoquercitrin (187); (+)-catechin (188); (-)-epicatechin (189) and quercetrin (190).^[79-83]

Chemical constituents of *Alnus cordata* (Desf.)

Quercetol-3-sophoroside (191).^[84]

BIOLOGICAL ACTIVITIES OF GENUS *ALNUS*

Inhibitory activity against HIF-1 in AGS cells

Jin *et al.* (2007) investigated the triterpenoids and diarylheptanoids isolated from EtOAc-soluble fraction from the MeOH extract of the stem bark of *A. hirsuta* (Betulaceae), for their effects on the hypoxia-induced HIF-1 activation using an HIF-1 α -mediated reporter gene assay in AGS cells. Among the isolated compounds, two diarylheptanoids, 2-oxatrycyclo[13.2.2.13,7]eicosa-3,5,7(20),15,17,18-hexaen-10-16-diol (78) and 2-oxatrycyclo[13.2.2.13,7]eicosa-3,5,7-(20),15,17,18-hexaen-10-one (79), inhibited HIF-1 activation dose-dependently with 50% inhibitory concentrations (IC₅₀) values of 11.2 and 12.3 microM, respectively. These two compounds had no significant cytotoxicity to the AGS cells at the effective concentration for the inhibition of HIF-1 activation.^[10]

Antimicrobial activities

Middleton *et al.* (2005) tested antibacterial activity of *A. glutinosa*. The MeOH extract was found to be active against the following eight bacterial species: *Citrobacter freundii* NCTC 9750, *Escherichia coli* NCIMB 8110, *Escherichia coli* NCIMB 4174, *Klebsiella aerogenes* NCTC 9528, *Lactobacillus plantarum* NCIMB 6376, *Pseudomonas aeruginosa* NCTC 6750, *Staphylococcus aureus* NCTC 10788, and *Staphylococcus aureus* NCTC 11940 (MRSA), the most potent activity was against *E. coli* (NCIMB 8110) with an MIC value of 1.25×10^{-1} mg/ml. Despite the high MIC value against MRSA (1.00 mg/ml), this finding could be considered significant, at least qualitatively, because this activity was not due to a purified compound, but due to crude extract.^[14] In 1995, Saxena *et al.* tested the antimicrobial activity of methanol extract of the bark of *A. rubra* against Gram-positive and Gram-negative bacteria. Diarylheptanoid and its glycoside (oregonin) were identified as the two constituents responsible for this activity.^[69]

General toxicity

n-Hexane, DCM, and MeOH extracts of *A. glutinosa* were tested for general toxicity using the brine shrimp lethality assay by Middleton *et al.* in 2005. All three extracts of *A. glutinosa* showed low levels of toxicity toward brine shrimps (LD₅₀ values were in the range of 1.29×10^{-1} to 8.30×10^{-1} mg/ml).^[14]

Inhibitory effects in human umbilical vein endothelial cells

Han *et al.* (2007) reported the inhibitory effects of two diarylheptanoids, 5-O-methylhirsutanonol (34) and oregonin (27), isolated from the methanolic extracts of *Alnus japonica* leaves, on the expression of adhesion molecules in human umbilical vein endothelial cells (HUVECs). 5-O-methylhirsutanonol and oregonin inhibited tumor necrosis factor (TNF)-alpha-induced upregulation of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1, which also prevented adhesion of monocytes to HUVECs, and slightly suppressed the mRNA expression of the inflammation-associated gene interleukin-1beta. A further study demonstrated the inhibitory effect of compound 5-O-methylhirsutanonol on DNA-binding of nuclear factor kappaB (NF- κ B) and on the phosphorylation and degradation of inhibitory factor κ B α in TNF-alpha-stimulated HUVECs. These results indicate that these two compounds may be useful in the prevention and treatment of atherosclerosis through attenuation of adhesion molecule expression by inhibition of NF- κ B activation.^[28]

Inhibition of cyclooxygenase-2 expression

Lee *et al.* (2000) examined the inhibitory effect of oregonin (27) and hirsutanonol (19) isolated from the bark of *A. hirsuta* on 12-O-tetradecanoylphorbol-13-acetate-induced cyclooxygenase-2 expression in immortalized human breast epithelial MCF10A cells.^[38]

Nitric oxide synthesis inhibitory activity

Lee *et al.* (2000) assessed the leaves extract of *A. hirsuta* for nitric oxide (NO) production inhibitory effects *in vitro*. Oregonin (27)

and hirsutanonol (19) were found to be potent inducible nitric oxide synthase (iNOS) inhibitors. These compounds showed inhibition of NO synthesis in dose-dependent manners by murine macrophage-like RAW 264.7 cells stimulated with interferon-gamma (IFN-gamma) plus lipopolysaccharide (LPS). Their IC₅₀ were 3.8 and 14.3 microM, respectively. The inhibitory effects of these compounds on NO synthesis were due to suppression of iNOS mRNA expression, as determined by Northern blotting.^[39]

Protective effects in human HepG2 cells

Park *et al.* (2010) assessed the diarylheptanoid derivatives isolated from the ethyl acetate-soluble fraction of the stem bark of *A. hirsuta* for their hepatoprotective effects against tert-butyl hydroperoxide (t-BHP)-induced toxicity in HepG2 cells. Of these isolates, compounds (27, 34, 57, and 79-84) significant hepatoprotective effects on t-BHP-induced damage to HepG2 cells, with (5S)-O-methylhirsutanonol (34) exhibiting the greatest protective effect (50.7+/-3.7% at a concentration of 10 μ M).^[43]

Inhibitory activity on lipopolysaccharide-induced nitric oxide production in BV2 microglia

Methanolic extract of *Alnus firma* barks significantly attenuated NO production in LPS-stimulated BV₂ microglia. Lee *et al.* (2010) found that 4-hydroxy-2,6-dimethoxyphenyl-6'-O-syringoyl- β -D-glucopyranoside, phenolic glycosides, and diarylheptanoids, isolated from the bark of *A. firma* showed significant inhibitory effect on LPS-induced NO production in BV₂ microglial cells at concentration ranging from 10 to 100 microM.^[80]

Inhibition against the HIV-1

Yu *et al.* (2007) observed that triterpenoids and flavonoids isolated from *Alnus firma* S. Z. inhibit HIV-1 virus replication and controlled its essential enzymes. In this study, the inhibition of HIV-1 viral replication and its essential enzymes, such as reverse transcriptase, protease, and alpha-glucosidase, were observed using 18 Korean plant extracts. Among the extracts, the methanol extract of *Alnus firma* leaves showed potent inhibition against the HIV-1-induced cytopathic effect (CPE) in MT-4 cells on microscopic observation (the minimum concentration for complete inhibition of HIV-1-induced CPE, IC = 50 μ g/ml). The alnustic acid methyl ester (183) exhibited inhibition against HIV-1 protease, with an IC₅₀ of 15.8 microM, quercetin (33) and myricetin 3-O-beta-D-galactopyranoside (182) displayed inhibition against HIV-1 reverse transcriptase, with IC₅₀ values of 60 microM. Based on these results, however, inhibition of viral replication by methanol extract of *Alnus firma* leaves was adjudged to be acutely related to the protease inhibition activation of the alnustic acid methyl ester as well as the reverse transcriptase inhibition activation of flavonoids.^[83]

Inhibitory activity against NF- κ B activation and NO and TNF- α production

Jin *et al.* (2007) investigated diarylheptanoids from the stem bark of *A. hirsuta* for their inhibitory activity against LPS-induced NF- κ B activation and NO and TNF-alpha production. Among them, compounds 2-oxytrycyclo[13.2.2.13,7]eicosa-3,5,7(20),15,17,18-

hexaen-10-16-diol (78), 2-oxytrycyclo[13.2.2.13,7]eicosa-3,5,7-(20),15,17,18-hexaen-10-one (79), and (5S)1,7-bis-(3,4-dihydroxyphenyl)-heptane-5-hydroxy-3-one {hirsutanonol} (19) displayed inhibitory activity against NF- κ B activation and NO and TNF- α production with IC₅₀ values of 9.2-9.9 μ M, 18.2-19.3 μ M, and 22.3-23.7 μ M, respectively, in RAW264.7 cells. These active compounds had no significant cytotoxicity in RAW264.7 cells at their effective concentrations. This supports the pharmacological use of *A. hirsuta*, which has been employed as a herbal medicine for the treatment of inflammatory diseases.^[85]

Inhibitory activity on farnesyl protein transferase

Kang *et al.* (2004) reported that diarylheptanoid isolated from the fruits of *Alnus japonica* very mildly inhibited FPTase and the inhibitory activity very much depends on the structure of diarylheptanoids.^[86]

Hepatoprotective activity

Buniatian *et al.* studied hepatoprotective properties of altan (obtained on the basis of ellagitannins from the cones of black alder *A. glutinosa*) on the model of acute liver damage induced with tetrachloromethane. It was found that altan exhibits the hepatoprotective activity even in a dose of 1 mg/kg which is ten-fold smaller than the dose of traditional flavonoid-based drugs. Altan limits cholepoiesis disorder, has an anti-inflammatory and membrane stabilizing effect, and recovers physiological antioxidant system.^[87]

Inhibitory activity against cell-mediated low-density lipoprotein oxidation

Kang *et al.* (2006) evaluated the inhibitory activity of two cyclic diarylheptanoids, garugambin-3 (57) and acerogenin L (58), isolated from the MeOH extract of the fruits of *Alnus japonica* Steud., against human low-density lipoprotein (LDL) oxidation in the thiobarbituric acid-reactive substance assay with IC₅₀ values of 2.9 and 1.7 μ M, respectively, and they also inhibited cell-mediated LDL oxidation more than five times more strongly than that of a well-known antioxidant, probucol, at a concentration of 10 μ M. Compound (57) had no effect on the anti-atherogenesis in LDL receptor-deficient mice.^[27] Lee *et al.* (2005) assessed the antioxidant effects of diarylheptanoid derivatives from *Alnus japonica* on human LDL oxidation.^[88]

Inhibition of diacylglycerol acyltransferase

During the screening for diacylglycerol acyltransferase (DGAT) inhibitors from natural products, Chung *et al.* found that the lupine-type triterpenoid betulinic acid (76) isolated from the methanol extract of *A. hirsuta* potently inhibited DGAT in the rat liver microsomes with an IC₅₀ value of 9.6 and 8.1 μ M using [(14)C]oleoyl-CoA as a substrate. A decrease in the apparent V_{max} was observed with betulinic acid (76), whereas the apparent K_m remained constant. Therefore, a Lineweaver-Burk plot of DGAT inhibition by betulinic acid (76) showed a noncompetitive type of inhibition. In the cell-based assay, betulinic acid (76) inhibited triglyceride (TG) formation by human HepG2 cells. These findings suggest that betulinic acid (76) may be a potential lead compound in the treatment of obesity.^[89]

Cytotoxic activities

Choi *et al.* (2008) analyzed the cytotoxic activities of compounds [(19), (22), (27), and (51) to (57)] isolated from the bark of *Alnus japonica* against murine B16 melanoma, human SNU-1 gastric cancer, human SNU-354 hepatoma cancer, and human SNU-C4 colorectal cell lines. The diarylheptanoids showed potent cytotoxic activities against murine B16 melanoma cells and human SNU-C1 gastric cancer cell when the cell viability was analyzed by MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide) assay.^[90]

Melanogenesis inhibitory activities

Cho *et al.* (2003) examined the inhibitory effect of diarylheptanoid isolated from the bark of *A. hirsuta* Turcz. on melanogenesis by measuring the melanin level and tyrosinase activity in B16 melanoma cell. Melanin level and tyrosinase activity were reduced by 75 to 85% on addition of diarylheptanoids to incubation medium of the melanoma cell. On the other hand, melanin level and tyrosinase activity were reduced by 13 to 43% on the addition of diarylheptanoids to incubation medium of the melanoma cell treated with melanogenesis stimulator, α -MSH and forskolin. These melanogenesis inhibitory effects were significantly different compared with control.^[91]

Antitumor activity

Sheth *et al.* (1973) reported that betulin (75) isolated from *Alnus oregona* showed antitumor activity for the Walker 256 (5WA16) tumor systems.^[92]

Immunological properties

Joo *et al.* (2009) demonstrated that hirsutenone (22) may have ideal properties as a new calcineurin inhibitor. It is small in molecular weight and possesses a potential comparable with that of cyclosporine A for the inhibition of allergen-induced T-cell and mast cell activation. Moreover, due to its lipophilic properties, hirsutenone (22) has a high affinity for the skin compartment and a low potential for absorption into the systemic circulation. Thus, hirsutenone (22) is an attractive source for developing a topical drug for T cell-based anti-atopic dermatitis by its actions as a calcineurin inhibitor.^[93-95]

Antiviral activity

Tung *et al.* investigated anti-influenza components from the bark of *Alnus japonica*. Antiviral testing of isolated compounds were performed against KBNP-0028 (H9N2) avian influenza virus. Result of study showed that platyphyllone (61) was strongly active (EC₅₀ = 29.9 μ M), and platyphyllonol-5-xylopyranoside (EC₅₀ = 105.0 μ M) (62) was moderately active against KBNP-0028 as compared with the positive control, zanamivir (EC₅₀ = 16.9 μ M), respectively.^[96]

CONCLUSION

The genus *Alnus* is widespread all over the world, and many species of this genus have been used as traditional herbal medicines.

The chemical investigation of *Alnus* species has revealed many components from this genus with significant bioactivities. On the basis of the above discussion, it may be concluded that all the members of genus *Alnus* have different biological activities. The genus is well known for its traditional medicinal uses including cancer, hepatitis, inflammation of uterus, uterine cancer, rheumatism, dysentery, stomachache, diarrhea, fever, etc. The plants contain variety of bioactive constituents, i.e., triterpenoids, flavonoids, tannins, phenols, steroids, diarylheptanoids, etc. Among them, diarylheptanoids (hirsutenone, oregonin, (5S)-O-methylhirsutanonol, 2-oxatrycyclo[13.2.2.13,7]eicosa-3,5,7(20),15,17,18-hexaen-10-16-diol, 2-oxatrycyclo [13.2.2.13,7] eicosa-3,5,7-(20),15,17,18-hexaen-10-one, garugamblin-3, acerogenin L, etc.) are highly potent bioactives.

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