Chapter

Introductory Chapter: Terpenes and Terpenoids

Shagufta Perveen

1. Terpenes and terpenoids

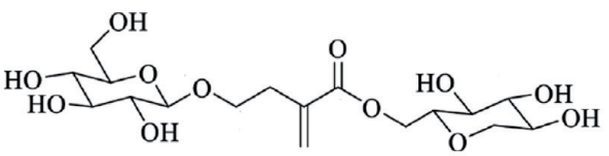
Terpenes are the largest class of secondary metabolites found in nature (plants, fungus, marine organisms, animals). Terpenes are mainly present as a main constituent of essential oils. It consists of isoprene units ($CH_2=C(CH_3)CH=CH_2$, C_5H_8) which are known as the building block of all types of terpenes, containing five carbon and eight hydrogen atoms. Monoterpenes have two isoprene units (C_{10}), sesquiterpenes have three (C_{15}), diterpenes have four (C_{20}), sesterpene have five (C_{25}), triterpenes have six (C_{30}) and tetraterpenes have eight isoprene units (C_{40}). Terpenes and terpenoids based chemical constituents are characterized by different chemical diversity with a wide range of therapeutic effects. This class of metabolites has been an enormous source of novel medicinal agents. Many terpenoids or terpenoid derivatives are used as traditional drugs with different medicinal values identified from different natural sources. *Artemisia annua* (sweet wormwood) a medicinal plant belongs to the family Asteraceae provided a drug artemisinin and its related derivatives which used as an antimalarial drug all over the world. Scientists Professor Tu Youyou was awarded Nobel Prize 2015 in Physiology or Medicine for her efforts toward the discovery of this important drug. Artemisinin and its derivatives are mainly sesquiterpenes (fifteen Carbons containing terpenes) which is known as a magical drug which served as the foundation for antimalarial treatment. Currently, many research groups have been reported the therapeutic potential of terpenes and its extract (terpene rich plant extracts) against anticancer, anti-inflammatory and SARS-CoV-2 and performed many tests and screenings. Many studies have been done for testing the efficacy of cannabis terpene for the treatment of this new viral infections [1, 2]. This chapter provides information about recently published terpenes which showed significant biological activities have unique skeletons.

2. Hemiterpene

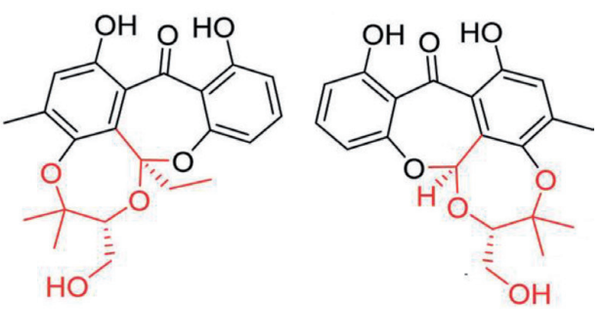
Hemiterpenes are the basic unit of terpenes and its consists of five carbon atoms ($CH_2=C(CH_3)CH=CH_2$) or one isoprene unit. It is usually found in different types of plants especially Coniferous, Willow and Oaks. Many types of hemiterpenes have isolated from different marine derived fungi (*Acremonium persicinum*, *Penicillium bialowiezense*) which are known as merohemiterpenoid]. Herein, we are discussing some of the recently published chemical diverse emiterpenes (**Table 1**, **Figure 1**).

Name	Source	Activity	Ref
Securiterpenoside G	*Securidaca inappendiculata* found in China	The potential anti-inflammatory activities of compounds were evaluated through inhibiting nitric oxide (NO) overproduction in LPS-stimulated mouse macrophage RAW264.7 model. Cell viability was measured by the MTT assay. None of them showed the obvious cytotoxicity at the dosage of 50 μM and significant anti-inflammatory activities (IC50 145.3, 57.5 μM, respectively). Dexamethasone was used as positive control (IC50 2.5 μM).	[3]
(±)-Cytorhizophin A, Cytorhizophin B	Endophytic fungus *Cytospora rhizophorae* from the plant *Morinda officinalis*	These compounds were evaluated for antimicrobial activities against the bacteria *Escherichia coli* and *Staphylococcus aureus*. However, all of them were found to be devoid of significant activity even at a concentration of 100 μg mL^{-1}.	[4]

Table 1.
Source and biological activities of some hemiterpenes.



Securiterpenoside G



Cytorhizophins A & B

Figure 1.
Structure of hemiterpene.

3. Monoterpenes

These types of terpenes consist on ten carbon atom or two isoprene units. Each type of monoterpenes has a particular aroma for the related plant such as: Citrus, grapes, rose etc. Many monoterpenes and their isomers have been isolated from different marine sources. Herein, we are discussing some of the recently published monoterpenes (**Table 2**, **Figure 2**).

Name	Source	Activity	Ref
N-glucopyranosyl vincosamide, vincosamide	*Psychotria leiocarpa* Leaves found in Brazil	Vincosamide with a preliminary dose-dependent activity inhibiting at 50 μg mL^{-1} 99% of DENV infectious particles in the conditioned medium of infected HepG2 culture can be highlighted among the other isolated alkaloids as a potential anti-dengue agent.	[5]

Name	Source	Activity	Ref
Callistrilones H & I	*Callistemon rigidus* found in China	Compounds exhibited moderate inhibitory activities against HSV- 1 with IC_{50} values of 10.00 ± 2.50 and 12.50 ± 1.30 μM, respectively.	[6]
Plaxenones A & B	South African red seaweed *Plocamium maxillosum*	Plaxenones A and B were evaluated for activity against the metastatic breast carcinoma (MDA-MB-231) cell line and showed moderate antiproliferative effects with IC_{50} values of 10.78 ± 1.01 and 22.30 ± 1.13 μM, respectively.	[7]
Melodinines Y1		It showed cytotoxicity toward six cancer cell lines. The new modification of the isolated compounds expands the chemical diversity of this family. Cytotoxicity assays have demonstrated that compound significantly inhibited HL-60 cancer cell line, presenting with a great opportunity to discover promising natural agents for new antitumor leadings.	[8]

Table 2.
Source and biological activities of some monoterpenes.

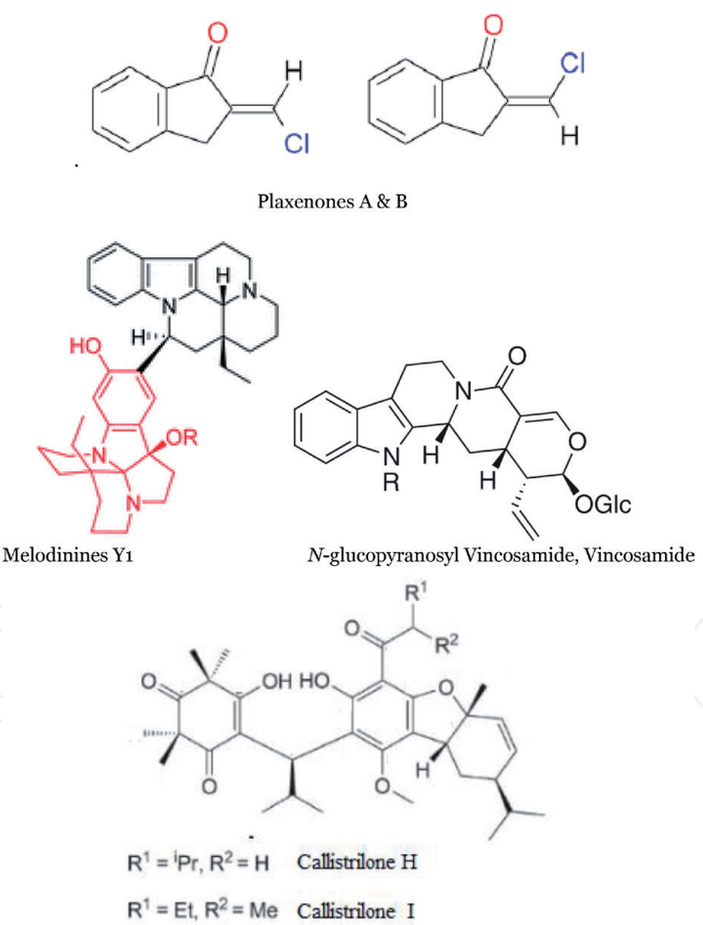


Figure 2.
Structure of monoterpene.

4. Sesquiterpenes

Sesquiterpenes are the class of terpenes with C15 carbon atoms having many uses like medicine, sanitary, agriculture, cosmetics and foods. These types of terpenes have many biological activities like, antibacterial, antifungal, antiviral and

ant insecticidal which provokes the researcher to work on the sesquiterpene rich natural sources. It is usually found in Asteraceae family plants. Herein we are tabulating few important sesquiterpene with their structure and biological information (**Table 3**, **Figure 3**).

Name	Source	Activity	Ref
Minusolide G	*Carpesium minus*	It exhibited cytotoxic activities against MDA-MB-231, A549, and HCT-116 cells with IC_{50} values of 6.1 ± 0.2, 8.4 ± 0.6, and 3.7 ± 0.6 μM, respectively. It induced the apoptosis of HCT-116 cells via suppression of PARP and promoting cleavage of PARP.	[9]
Penisarins A & B	Endophytic *Penicillium* sp. found in China	Penisarin B showed significant cytotoxicities against two human cancer cell lines, HL-60 and SMMC-7721, with IC_{50} values of 3.6 ± 0.2 and 3.7 ± 0.2 μM, respectively.	[10]
Cedrol	*Cedrus atlantica* Cedarwood oil	Cedrol-treated mice exhibited no significant differences in body weight and improved TMZ-induced liver damage. These results imply that cedrol may be a potential novel agent for combination treatment with TMZ for GBM therapy that deserves further investigation.	[11]

Table 3.
Source and biological activities of some sesquiterpenes.

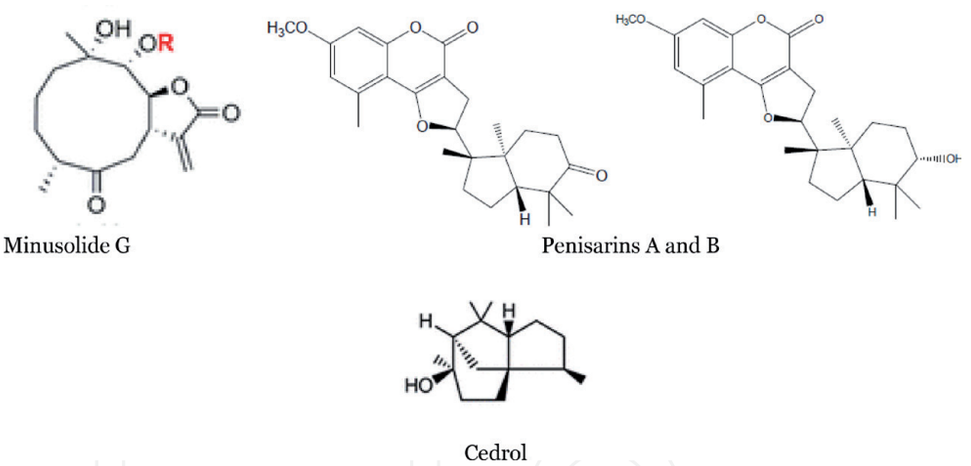


Figure 3.
Structure of sesquiterpene.

5. Diterpenes

It consists on C20 carbon atom having four isoprene units. These are very famous class of compounds as many are using in market for curing cancer

Name	Source	Activity	Ref
Kaemgalangols B-D	Edible rhizomes of *Kaempferia galanga* found in India	The antiproliferative activity of compounds was screened against CCRF-CEM leukemia cells using a fixed concentration of 30 μM. Dose response curve of (2*R*)-ent-2-hydroxyisopimara-8(14),15-dien showed IC_{50} values of ≤ 50 μM against CCRF-CEM, MDAMB-231-pcDNA and HCT116 (p53+/+).	[12]

Name	Source	Activity	Ref
Wickerols A & B	Fungus *Trichoderma atroviride* FKI-3849 from a soil sample	Wickerol A was highly active against two A/H1N1 viruses, but not active against two A/H_3N_2 viruses or a B-type virus.	[13, 14]
Nukiangendines A & B	*Abies Nukiangensis* found in China	Compounds were subjected to an in vitro bioassay for anti-hepatitis C virus (HCV) infection activity. Nukiangendine A exhibits a significant effect at 10 μM with an inhibition rate of 70.0%, compared to 99.0% for sofosbuvir (the positive control) at 0.01 μM.	[15]
Stachyonic acid A & B	*Basilicum polystachyon*	Stachyonic acids A & B was tested for cytotoxicity against human cells, breast and melanoma along with primary neonatal foreskin fibroblast cells. Mixture of both showed limited cytotoxicity toward all cell lines investigated. Stachyonic acid A, was found to display potent inhibitory activity against dengue virus.	[16, 17]
Andrographolide	*Andrographis paniculata* from Thailand	The study demonstrated anti-SARS-CoV-2 activity of *A. paniculata* and andrographolide using a Calu-3-based anti-SARS-CoV-2 assay. Potent anti-SAR-CoV-2 activities, together with the favorable cytotoxicity profiles, support further development of *A. paniculata* extract and especially andrographolide as a monotherapy or in combination with other effective drugs against SARS-CoV-2 infection.	[18]

Table 4.
Source and biological activities of some diterpenes.

disease such as; Taxol and etc. Herein, we are summarizing few recently published diterpenes structures, sources, origin and biological activities (**Table 4**, **Figure 4**).

6. Sesterpenes

Sesterpenes are the small class of terpenoids family which consists on twenty-five carbon atoms (tricyclic 5-8-5 carbotricyclic core, five isoprene units). These types of constituents usually found in plants, fungus culture, insects and marine organism. Sesterterpenes type compounds has complex structures due to the presence of many ring systems which makes its unique skeletons. These compounds have significant biological activities such as cytotoxic, nematocidal, anti-influenza, enzyme inhibition, anti-inflammatory and antimicrobial activities. In this chapter we are discussing, some recently published sesterterpene, including their structures, source, origin and pharmacology (**Table 5**, **Figure 5**).

7. Meroterpenes

Meroterpenes are mainly found in marine organisms and abundant in brown algae and other natural sources like microorganisms and invertebrates (sponges and

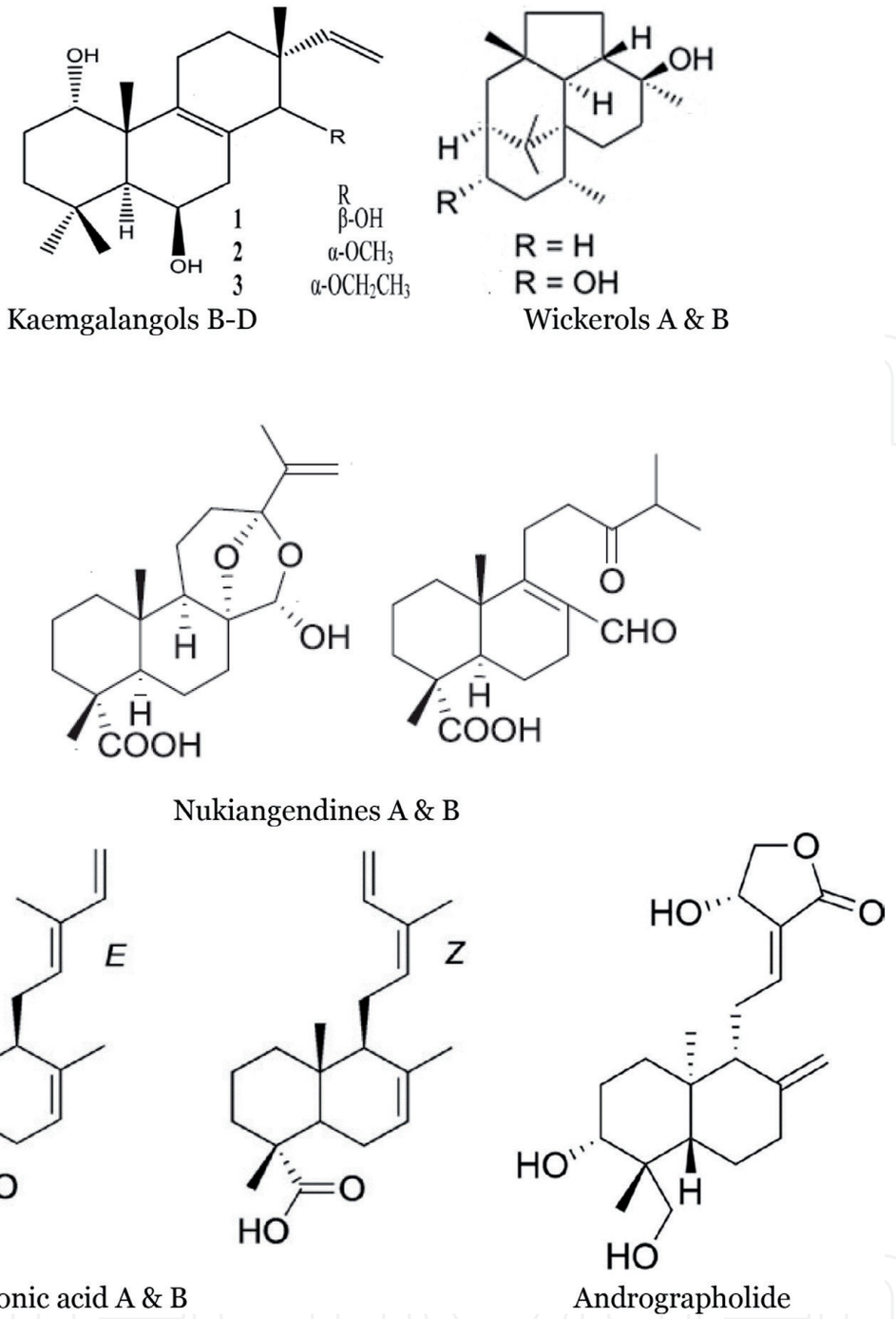
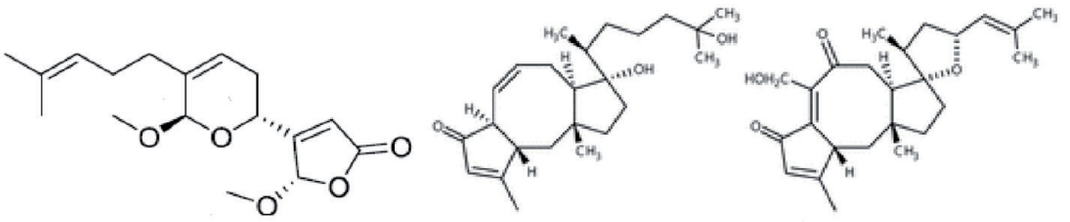


Figure 4.
Structure of diterpene.

Name	Source	Activity	Ref
Manoalide derivatives	Sponge *Luffariella variabilis* from the South China Sea	manoalide derivatives demonstrated cytotoxic activities against several human cancer cell lines with IC_{50} values ranging from 2 to 10 μM.	[19]
Drophiobiolins A & B	*Dreschslera gigantea s* found in China	Both of the newly identified ophiobolins showed significant phytotoxicity. Drophiobolins A & B exhibited cytotoxicity against Hela B cells with an IC_{50} value of 10 μM.	[20]

Table 5.
Source and biological activities of some sesterpenes.



Manoalide sesterpene

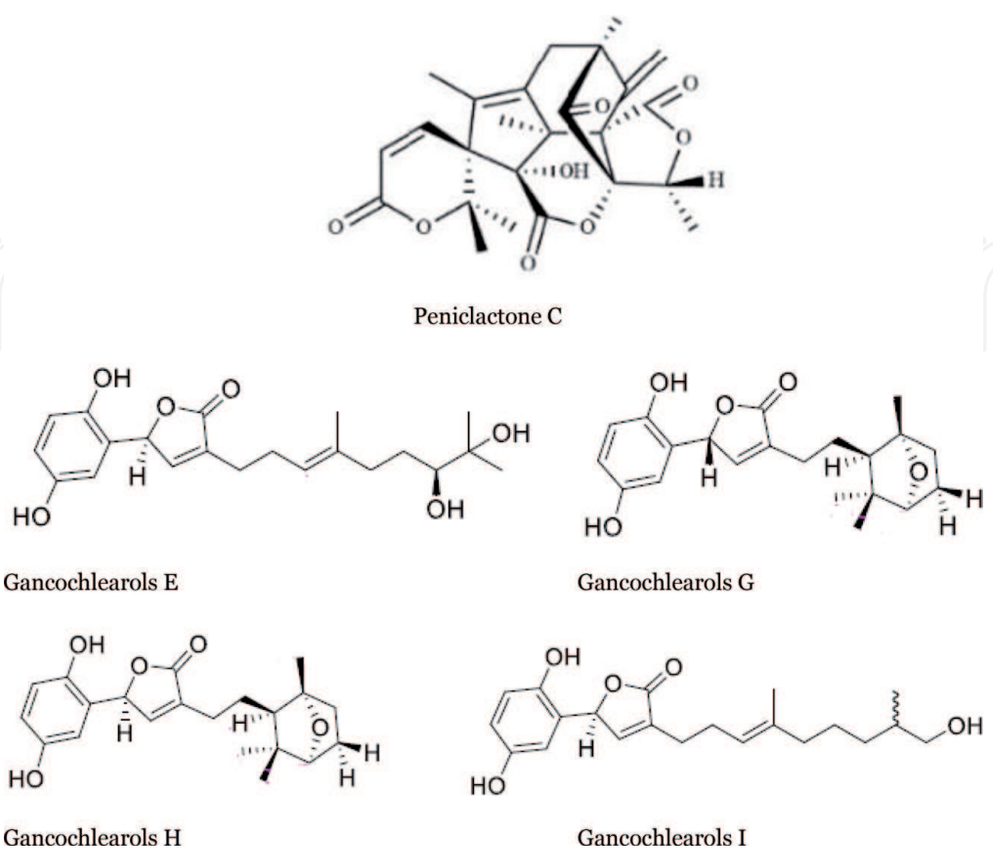
Drophiobiolins A & B

Figure 5.
Structure of sesterterpene.

tunicates). These types of compounds have many chemical diversities. Herein, we are discussing some recently published biological active meroterpenes (**Table 6**, **Figure 6**).

Name	Source	Activity	Ref
Peniclactone C	Endophytic fungus *Penicillium* sp. GDGJ-285	Bioassays showed that peniclactone C inhibited nitric oxide production in lipopolysaccharide-induced RAW 264.7 macrophage cells with an IC_{50} value of 39.03 μM.	[21]
Gancochlearols E – I	Ganoderma cochlear	Biological results revealed the significantly inhibitory effects of the Gancochlearols E – I on COX-2 activity and the migration of TNBC cells. In results not only enrich the structure type of meroterpenoids in Ganoderma, but also present novel structural template for developing nonsteroidal anti-inflammatory drug (NSAID) and anti-cancer drug against metastatic TNBC.	[22]

Table 6.
Source and biological activities of some meroterpenes.



Peniclactone C

Gancochlearols E

Gancochlearols G

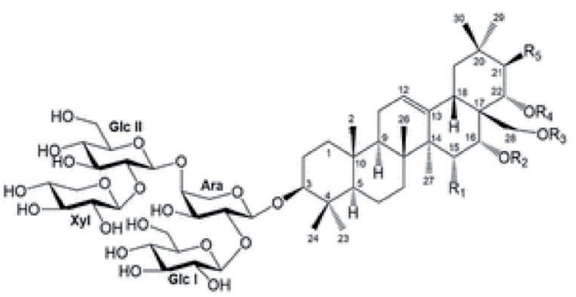
Gancochlearols H

Gancochlearols I

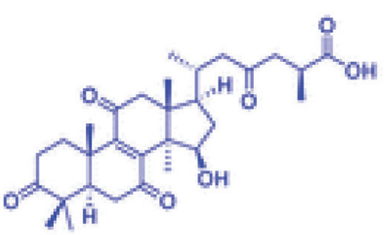
Figure 6.
Structure of meroterpene.

Name	Source	Activity	Ref
Arenarosides A	*Polycarpaea arenaria* found in Brazil	Compound displayed promising antiangiogenesis effects with IC_{50} values <5 μM in the test system used. It exhibited the most potent inhibitory effects, not only in cancer cell proliferation but also in angiogenic activities.	[23]
Ganoweberianones A & B	Fruiting bodies of Basidiomycete *Ganoderma weberianum*	These compounds were evaluated for Ganoweberianone A exhibited significant antimalarial activity against *Plasmodium falciparum* K1 (multidrug-resistant strain) with an IC_{50} value of 0.050 μM.	[24]
Longipetalol A	Dichapetalum longipetalum	Compound exhibited inhibitory effects on nitric oxide production in lipopolysaccharide-induced RAW264.7 macrophages.	[25]
Periploside A5	Root barks of *Periploca sepium*	Periploside showed significant suppressive effects on T lymphocyte proliferation with IC_{50} values ranging from 0.16 to 3.9 μM and displayed potent inhibitory activity on B lymphocyte proliferation with IC_{50} data at between 0.17 and 5.9 μM. IC_{50} data of Periploside A5 were 0.30 μM and 0.55 μM for T and B lymphocytes, and with the most favorite selective index values 176 and 96.9, respectively.	[26]

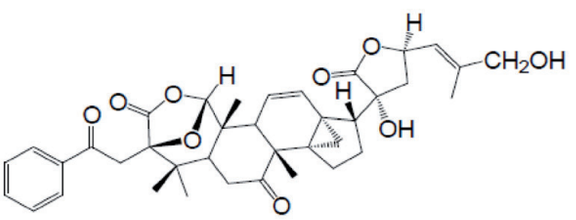
Table 7.
Source and biological activities of some triterpenes.



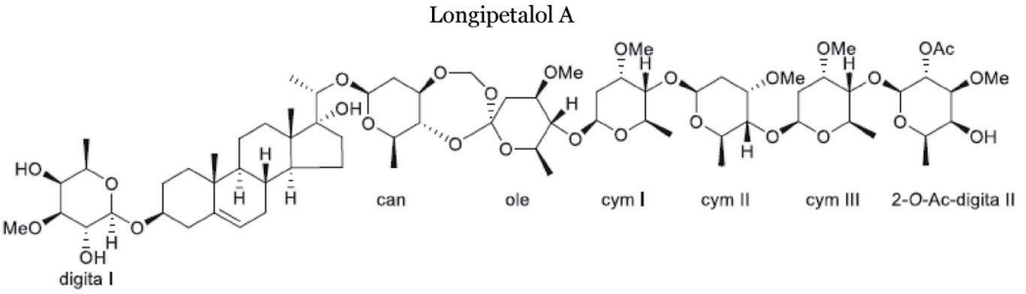
Arenarosides A



Ganoweberianones A



Longipetalol A



Periplosides A5

Figure 7.
Structure of triterpene.

8. Tripterpenes

A major class of secondary metabolites are known as triterpenes and it usually contains thirty carbons consisting of six isoprene units. Different class of triterpenes are known as lanostanes, euphanes,holostanes, tetranortriterpenoids, cycloartanes, cucurbitanes, dammaranes, tirucallanes, quassinoids, oleananes, lupanes, friedelanes, ursanes, hopanes, serratanes, isomalabaricanes which derived from the squalene biosynthesis (**Table 7**, **Figure 7**).

Author details

Shagufta Perveen
Department of Pharmacognosy, College of Pharmacy, King Saud University, Riyadh, Kingdom of Saudi Arabia

*Address all correspondence to: shagufta792000@yahoo.com; shakhan@ksu.edu.sa

References

[1] Diniz LRL, Castillo-P Y, Hatem A. Elshabrawy, Filho CSMV, de Sousa DP. Bioactive Terpenes and Their Derivatives as Potential SARS-CoV-2 Proteases Inhibitors from Molecular Modeling Studies. Biomolecules 2021;11(74). DOI: 10.3390/biom 11010074.

[2] Anil MS, Shalev N, Vinayaka AC, Nadarajan S, D Namdar, Belausov E, Shoval I, Mani KA, Mechrez G, Kolta H. Cannabis compounds exhibit anti-infammatory activity in vitro in COVID-19-related infammation in lung epithelial cells and pro-infammatory activity in macrophages. Scientifc Reports. 2021;11;1462. DOI: 10.1038/ s41598-021-81049-2

[3] Yang C, Wang Z, Qiu Y, Zha H,Yang X. New hemiterpene and furolactone-type lignan glycosides from *Securidaca inappendiculata* Hassk. Phytochemistry Letters. 2020; 37:42-46. DOI: 10.1016/j.phytol.2020.04.001

[4] Liu H, Tan H, Wang W, Zhang W, Chen Y, Li S, Liu Z, Lia H, Zhang W. Cytorhizophins A and B, benzophenonehemiterpene adducts from the endophytic fungus Cytospora rhizophorae. Organic Chemistry Frontries. 2019; 6:591-596. DOI: 10.1039/C8QO01306C

[5] Costa JO, Barboza RS, Valente LMM, Gomes TWM, Gallo B, Berrueta LA, Guimarães-Andrade IP, Gavino-Leopoldinod D, Assunção-Miranda I. One-Step Isolation of Monoterpene Indole Alkaloids from Psychotria leiocarpa. Leaves and Their Antiviral Activity on Dengue Virus Type-2. Brazilian Chemical Society. 2020:10(31): 2104-2113. DOI: 10.21577/0103-5053.20200111

[6] Cao J-Q, Wu Y, Zhong Y-L, Li N-P, Chen M, Li M-M, Ye W-C, Wang L. Antiviral Triketone-Phloroglucinol-Monoterpene Adducts from Callistemon rigidus. Chemistry & Biodiversity 2018;15: e1800172. DOI: 10.1002/ cbdv.201800172

[7] Knotta MG, de la Marec J.A, Edkinsc AL, Zhangd A, Stillmand MJ, Boltone JJ, Antunesf EM, Beukes DR. Plaxenone A and B: Cytotoxic halogenated monoterpenes from the South African red seaweed Plocamium maxillosum. Phytochemistry Letters. 2019;29:182-185. DOI: 10.1016/j. phytol.2018.12.009

[8] Fa-Lei Zhang, Juan He, Tao Feng, Ji-Kai Liu. Melodinines Y1–Y4, four monoterpene indole alkaloids from Melodinus henryi. RSC Advances. 2021, 11, 23-29. DOI:10.1039/D0RA09819A

[9] Zhu L, Liu X-Q, Lin Y-L, Wang W-L, Luo J-G, Kong L-Y. Cytotoxic Germacranolides from the Whole Plant of *Carpesium minus.* Journal of Natural Products. 2020 25;83(11):3230-3238. DOI: 10.1021/acs.jnatprod.0c00428

[10] Li W, Shao YT, Yin TP, Yan H, Shen BC, Li YY, Xie HD, Sun ZW, Ma YL. Penisarins A and B, Sesquiterpene Coumarins Isolated from an Endophytic *Penicillium* sp. Journal of Natural Products. 2020, 83(11):3471-3475. DOI: 10.1021/acs. jnatprod.0c00393

[11] Chang K-F, Huang X-F, Chang J-T, Huang Y-C, Lo W-S, Hsiao C-Y, Tsai N-M. Cedrol, a Sesquiterpene Alcohol, Enhances the Anticancer Efficacy of Temozolomide in Attenuating Drug Resistance via Regulation of the DNA Damage Response and MGMT Expression. Journal of Natural Products. 2020;23;83(10):3021-3029. DOI: 10.1021/acs.jnatprod.0c00580

[12] Elshamy AI, Mohamed TA, Swapana N, Yoneyama T, Noji M, Efferth T, Hegazy M-EF, Akemi

Umeyama. Cytotoxic polyoxygenated isopimarane diterpenoids from the edible rhizomes of *Kaempferia galanga* (kencur). Industrial Crops & Products 2020; 158:112965. DOI:10.1016/j.indcrop.2020.112965

[13] Yamamoto T, Izumi N, Ui H, Sueki A, Masuma R, Nonaka K, Hirose T, Sunazuka T, Nagai T, Yamada H, Ōmura S, Shiomi K. Wickerols A and B: novel anti-influenza virus diterpenes produced by *Trichoderma atroviride* FKI-3849. Tetrahedron. 2012;45(68):9267-9271. DOI:10.1016/j.tet.2012.08.066

[14] Deng J, Ning Y, Tian H, Gui J. Divergent Synthesis of Antiviral Diterpenes Wickerols A and B. Journal of American Chemical Society. 2020;142(10), 4690-4695. DOI: 10.1021/jacs.9b11838

[15] LiLi-Y, Zhang O, Wu J-J, Xue L-J, Chen L-M, Tian J-M, Xu Z-N, Chen Y, Yang X-W, Hao X-J, Li J. Nukiangendines A and B, two novel 13,14-*seco*-abietanes from *Abies nukiangensis.* Tetrahedron Letters. 2019;10(60):751-753. DOI: 10.1016/j.tetlet.2019.02.008

[16] Tan YP, Houston SD, Modhiran N, Savchenko AI, Boyle GM, Young PR, Watterson D, Williams C.M. Stachyonic Acid: A Dengue Virus Inhibitor from *Basilicum Polystachyon*. Chemistry A Eurpion Journal 2019; 25:5664-5667. DOI:10.1002/chem.201900591

[17] Yuen P. Tan, Sevan D. Houston, Naphak Modhiran, Andrei I. Savchenko, Glen M. Boyle, Paul R. Young, Daniel Watterson, Craig M. Williams. Stachyonic Acid: A Dengue Virus Inhibitor from *Basilicum Polystachyon*. Chemistry A Eurpion Journal 2019;25,5664-5667. DOI:10.1002/chem.201900591

[18] Sa-ngiamsuntorn K, Suksatu A, Pewkliang Y, Thongsri P, Kanjanasirirat P, Manopwisedjaroen S, Charoensutthivarakul S, Wongtra koongate P, Pitiporn S, Chaopreecha J, Kongsomros S, Jearawuttanakul K, Wannalo W, Phisit K, Chuti pongtanate S, Borwornpinyo S, Thitithanyanont A, Hongeng S. Anti-SARS-CoV-2 Activity of *Andrographis paniculata* Extract and Its Major Component Andrographolide in Human Lung Epithelial Cells and Cytotoxicity Evaluation in Major Organ Cell Representatives. Journal of Natural Products. 2021;84(4):1261-1270. DOI: 10.1021/acs.jnatprod.0c01324

[19] Luo X, Wang Q, Tang X, Xu J, Wang M, Li P, Li G. Cytotoxic Manoalide-Type Sesterterpenes from the Sponge *Luffariella variabilis* Collected in the South China Sea. Journal of Natural Products. 2021;84(1):61-70. DOI: 10.1021/acs.jnatprod.0c01026

[20] Zatout R, Masi M , Sangermano F, Vurro M, Zonno MC, Santoro E, Viola Calabrò V, Superchi S, Evidente A. Drophiobiolins A and B, Bioactive Ophiobolan Sestertepenoids Produced by *Dreschslera gigantea.* Journal of Natural Products. 2020;83(11):3387-3396. DOI: 10.1021/acs.jnatprod.0c00836

[21] Mo T-X, Huang X-S, Zhang W-X, Schäberle TF, Qin J-K, Zhou D-X, Qin X-Y, Xu Z-L, Li J, Yang R-Y. A series of meroterpenoids with rearranged skeletons from an endophytic fungus *Penicillium* sp. GDGJ-285. Organic Chemistry Frontiers. 2021. DOI: 10.1039/d1qo00173f

[22] Li Y-P, Jiang X-T, Qin F-Y, Zhang H-X, Cheng Y-X. Gancochlearols E-I, meroterpenoids from *Ganoderma cochlear* against COX-2 and triple negative breast cancer cells and the absolute configuration assignment of ganomycin K. Bioorganic Chemistry 2021;109: 104706. DOI: 10.1016/j.bioorg.2021.104706

[23] Nguyen N-L, Vo T-H, Lin Y-C, Liaw C-C , Lu M-K , Cheng J-J, Chen M-C, Kuo Y-H. Arenarosides A-G, Polyhydroxylated Oleanane-Type Saponins from *Polycarpaea arenaria* and their Cytotoxic and Antiangiogenic Activities. Journal of Natural Products. 2021;84(2):259-267. DOI: 10.1021/acs.jnatprod.0c00919

[24] Isaka M, Chinthanom P, Vichai V, Sommai S, Choeyklin R. Ganowe berianones A and B, Antimalarial Lanostane Dimers from Cultivated Fruiting Bodies of the Basidiomycete Ganoderma weberianum. *Journal of Natural Products* 2020;83(11):3404-3412. DOI: 10.1021/acs.jnatprod.0c00879

[25] Zhang D-L, Li M, Han G-F, Li S-Y, Jin D-J, Tang S-A. Longipetalol A: A Highly Modified Triterpenoid from *Dichapetalum longipetalum.* Journal of Natural Products. 2021. DOI: 10.1021/acs.jnatprod.1c00068.

[26] Shao X-C, Chen Z-H, Liu S-S, Wu F, Mu H-Y, Wei W-H, Feng Y, Zuo J-P, Zhang J-Q, He S-J, Zhao W-*M. minor* immunosuppressive spiroorthoester group-containing pregnane glycosides from the root barks of *Periploca sepium*. Bioorganic Chemistry 2021; 108:104641. DOI: 10.1016/j.bioorg.2021.104641