Indian Journal of Chemistry
Vol. 61, July 2022, pp. 761-770

A review on triterpenoids from plant sources as potential antiviral agents

Narayana Rao Gundoju[a,*], Hemambika Sadasivuni[b], Boddu Rama Krishna[c], Tiruveedhula Somasekhar[d] & Ramarao Vangara[a]

[a]Department of Chemistry, M. R. Degree College, Fort, Vizianagaram-535 002, Andhra Pradesh, India

[b]Department of Science & Humanities, St. Martin's Engineering College, Kompalli, Secunderabad-500 100, Telangana, India

[c]Department of Energy Engineering and School of Energy and Chemical Engineering, Ulsan National Institute of Science and Technology, Ulsan 44919, Republic of Korea.

[d]Department of Chemistry, S.V.R.M College Nagaram, Guntur-522 268, Andhra Pradesh, India

*E-mail: gnarayanarao16@gmail.com

Received 13 December 2021; accepted (revised) 2 June 2022

Viral infections are considered as leading a health issue globally. Numerous numbers of biologically active anti-viral agents have been identified from plants and other organisms. Particularly, terpenoids are a major component of the plant secondary metabolites and a complexity of these structures is accompanied by the potency of their biological activities. It is believed that most of the terpenoids possess the bioactivity against viral infections and cancer diseases. Hence, affected by the pressing a need elevated by the spreading of seriously life-threaten viruses, this review highlights the importance of terpenoids and their activity as antiviral agents that can be employed to treat current lethal diseases such as HIV, H1N1, SARS-CoV and HSV.

Keywords: Triterpenoids, Natural sources, Antiviral bioactivity

Terpenes are largest and a family of structurally diverse natural products, which have been discovered in the metabolites of plants, animals, and microorganisms[1,2]. More than 55,000 triterpenes have been found to a date and most of them are found in higher plants. Isoprene unit is the basic building block of all terpenoids, which are classified by the quantity of isoprene units, for an example, hemiterpenes(C5), monoterpenes(C10), sesquiterpenes(C15)), diterpenes (C20), sesterpenes(C25), triterpenes(C30), and polyterpenes(>C30). A terpene has been exhibiting the variety of biological activities including anti-cancer, anti-bacterial, anti-fungal, anti-viral, anti-hyperglycaemic, anti-inflammatory, anti-oxidant, anti-parasitic and immunomodulatory[3,4]. As a raw material, terpenoids were also used various purposes, in particularly food additives, pharmaceuticals, cosmetics, traditional medicines, a natural flavour and fragrance agents[5,6]. The biosynthesis of terpenes involves mainly two pathways. The Mevalonic-acid pathway, which mostly produces sesquiterpenes, sterols and ubiquinones, and Methyl-erythritol phosphate pathway, which the majority of compounds is a hemiterpenes, monoterpenes and diterpenes[7]. The triterpenoids are rich and complex structures have prompted the drug discovery through inspiring chemical and biological research efforts. Total syntheses of these natural products have been a challenging goal for many chemists. It has been inspired by the invention of new chemical entities and advanced synthetic strategies. A literature survey reveals that triterpenoids have been found with significant anti-viral activities[8-10].

Current trends in clinical and medical sciences are continually looking highly interdisciplinary for new to disseminating in-depth information for all impressive specialists to prevent, treat or delay the viral contamination and fix the sicknesses they cause. Many viral infections are currently considered as the mortality causing diseases. Some viral infections, like hepatitis B, poliomyelitis are forestalled by conceivable through the immunization, which is sometimes not enough for treating some transporters and patients. No powerful vaccination is available for many viral infections such as a hepatitis C, human immunodeficiency virus (HIV), SARS-CoV-2. This review mainly focuses on systematically surveys various classes of terpenoids and its anti-viral activity, which could be useful for a further optimization and development in this field of the drug discovery.

Results and Discussion

Anti-viral Activities of Terpenoids

Oleanolic acid (1) is a pentacyclic triterpenoid broadly appropriated in different pieces of the plants including *Rosa woodsii*, *Prosopis glandulosa*, *Phoradendron juniperinum*, *Syzygium claviflorum*, *Hyptis capitata* and *Ternstromia gymnanthera*. Oleanolic acid has repressed HIV-1 replication in intensely tainted H9 cells with an EC_{50} estimation of 3.7 μM and restrained H9 cell development with an IC_{50} estimation of 47.8 μM[11]. The lupane-type triterpenoids 3α-hydroxylup-20(29)- ene-23,28-dioic and (2) corrosive 3-epi-betulinic corrosive 3-O-sulfate (3) were accounted for from leaf tail concentrate of *schefflera heptaphylla*. The antiviral examines exhibited that the two confined (Fig. 1) intensifies 2 had an extensive more extensive antiviral range against the respiratory syncytial infection (RSV), herpes simplex infection type 1 (HSV-1), Flu and Cox B3 infections, while the compound (3) didn't show any critical antiviral activity[12-14]. The two lupane-type triterpenoids were somewhat toxic to HEp-2 cell, Vero cell and MDCK cell, and accordingly had lower antiviral selectivity files triterpenoids, an antiviral test utilizing a cytopathic impact decrease technique showed these two triterpenoids that more extensive antiviral action against respiratory syncytial infection (IC_{50} 12.8 and 11.0 μM) and H1N1 infection (IC_{50} 51.4 and 55.3 μM), Coxsackie B3 (Cox B3) infection (IC_{50} 25.7 and 35.3 μM) and herpes simplex infection type 1 (IC_{50} 38.6 and 44.1 μM), respectively. Lupenone (4) from *Euphorbia segetalis* displayed solid viral plaque inhibitory impact against HIV-1 and HIV-2. A triterpene 1β-hydroxy-2-oxopomolic acid (5) (Fig. 1) detailed from the $CHCl_3$-dissolvable part of *R. woodsii*, didn't show any anti- HIV activity[15].

Uvaol (6), Ursolic acid (7) were isolated anther plant from the methanolic concentrate of leaves of *Crataegus pinatifida*, showed strong inhibitory action against HIV-1 protease at a concentration of 21.9 μM.19 HIV releases itself from an HIV-infected cell utilizing serine protease, trailed by the assault on different cells[16]. *Crataegus pinnatifida* was found to restrain the action of serine protease, trailed by diminishing diffusion rate of HIV in vivo. Maslinic acid (8) isolated from *C. pinnatifida* prominently affected restraining the movement of HIV-1 protease [16,17]. At the point when the fixation was 3.9 μM, the inhibitive rate is 100%. In this way, compound 8 is considered as a likely possibilitylike probability for the novel enemy of HIV therapeutics. Moronic acid (9) isolated from *Myrceugenia euosma* showed significant anti-HIV activity[18]. Pentacyclic triterpenes, 1β-hydroxymaprounic 3 p-hydroxy benzoate (10), and 2β-hydroxymaprounic 2,3-bis-p-hydroxybenzoate (11) revealed from the foundations of *Maprounea africana*[19], repressed HIV-1 RTase with an IC_{50} value of 3.7 μM. Celasdin B (12) isolated from (Fig. 2) ethanolic concentrate selection of *Celastrus hindsii* showed against HIV replication action in H9

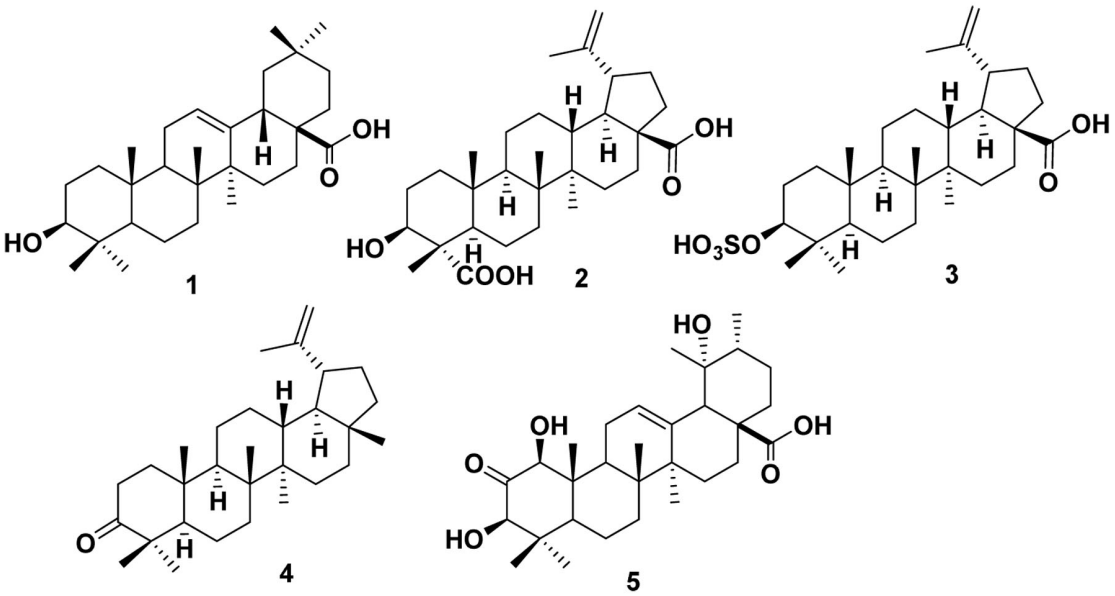

Fig. 1 — Terpenoids structures of 1-5

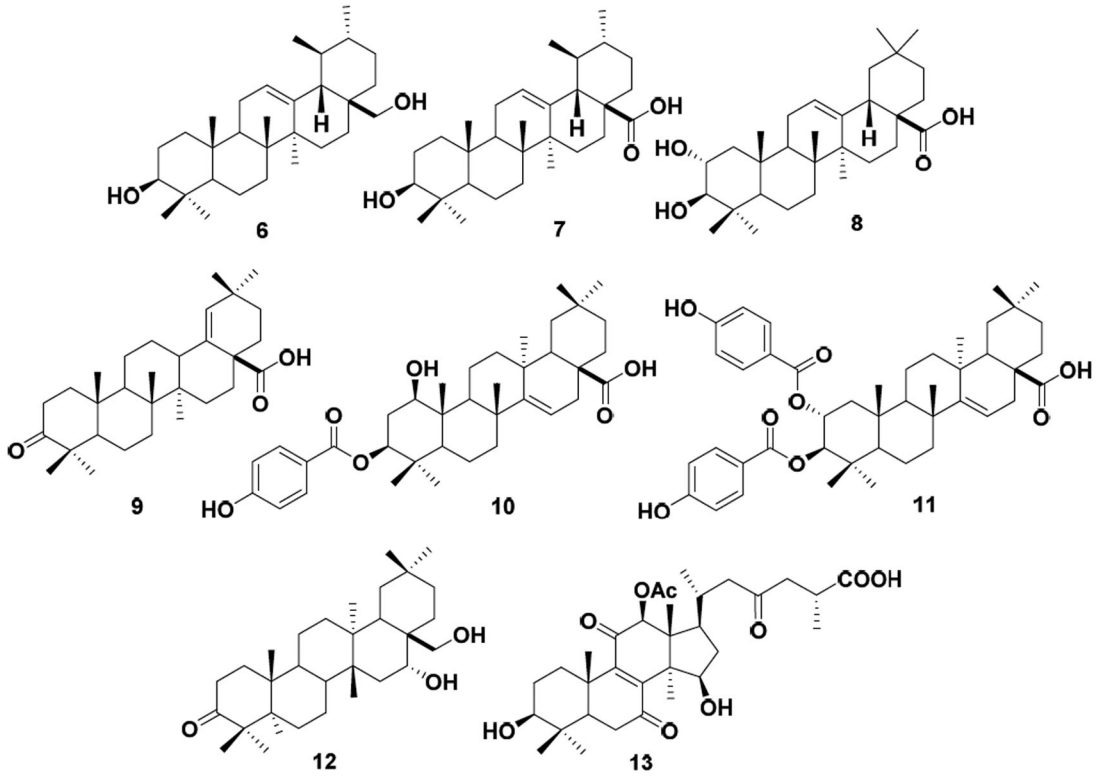

Fig. 2 — Terpenoids structures of 6-13

lymphocyte cells *in vitro*[20]. Oxygenated triterpenes, for example, α-ganoderic acid (13), separated from the methanolic concentrate of *Ganoderma lucidum*, were found to hinder HIV-1 instigated cytopathic impacts in MT-4 cells and furthermore had HIV-1 protease inhibitory activity[21].

Suberosol (14) is a Lanostane-type triterpene, isolated from the ethanolic concentrate of the stems and leaves of *Polyalthia suberosa*, displayed anti-HIV replication activity in H9 lymphocyte cells[22]. The protostanes, garcisaterpenes A (15) and B (16) were confined from ethyl acetic acid derivation concentrate of bark and stems of *Garcinia speciosa,* showed critical inhibitory exercises against HIV-1 RTase and in the syncytium assay[23]. A ring-secocycloartene triterpenoid, nigranoic corrosive (17) secluded from the stems of *Schisandra sphaerandra*, repressed HIV-1 RTase and HIV-2 RTase [24]. Lancilactone C (18) separated from stems and roots of *Kadsura lancilimba*, additionally had inhibitory action against HIV replication in H9 lymphocytes [25]. The three new triterpenes, for example, lucialdehyde D (19), Ganoderone A (20), and Ganoderone C (21) were confined (Fig. 3) from the fruiting collections of *Ganoderma pfeifferi*, among these Ganoderone A (20) just showed solid inhibitory movement against. Vero cells (IC_{50} was 0.66 μM) against HSV with acyclovir as a standard[26].

Glycyrrhizin (22), from licorice root (*Glycyrrhiza radix*), has been known for some times an antiviral agent, its IC50 for HIV-1(IIIB) in MT-4 cells being 150 μM. Although the site of interaction of glycyrrhizin (at the envelope glycoprotein) has not been characterized[27], Twenty-seven triterpenoids (Fig. 4) saponins, uralsaponins (23-35), and 15 known analogues (36-49) were accounted from the foundations of *Glycyrrhiza uralensis* Fisch Uralsaponins Saponins containing a galacturonic acid (23-25) or xylose (26) build up detailed from *Glycyrrhiza* species interestingly. Mixtures 23, 29, 30, and 45 showed great inhibitory activity against the H1N1 infection A/WSN/33 (H1N1) in MDCK cells with IC_{50} values of 48.0, 42.7, 39.6, and 49.1 μM, respectively. Moreover, intensifies 45 and 49 showed hostility to HIV exercises with IC_{50} values of 29.5 and 41.7 μM, respectively. Mixtures (23-49) were additionally assessed against HIV activity. Mixtures 40, 42, 44, 45, 46, and 49 showed restraint paces of

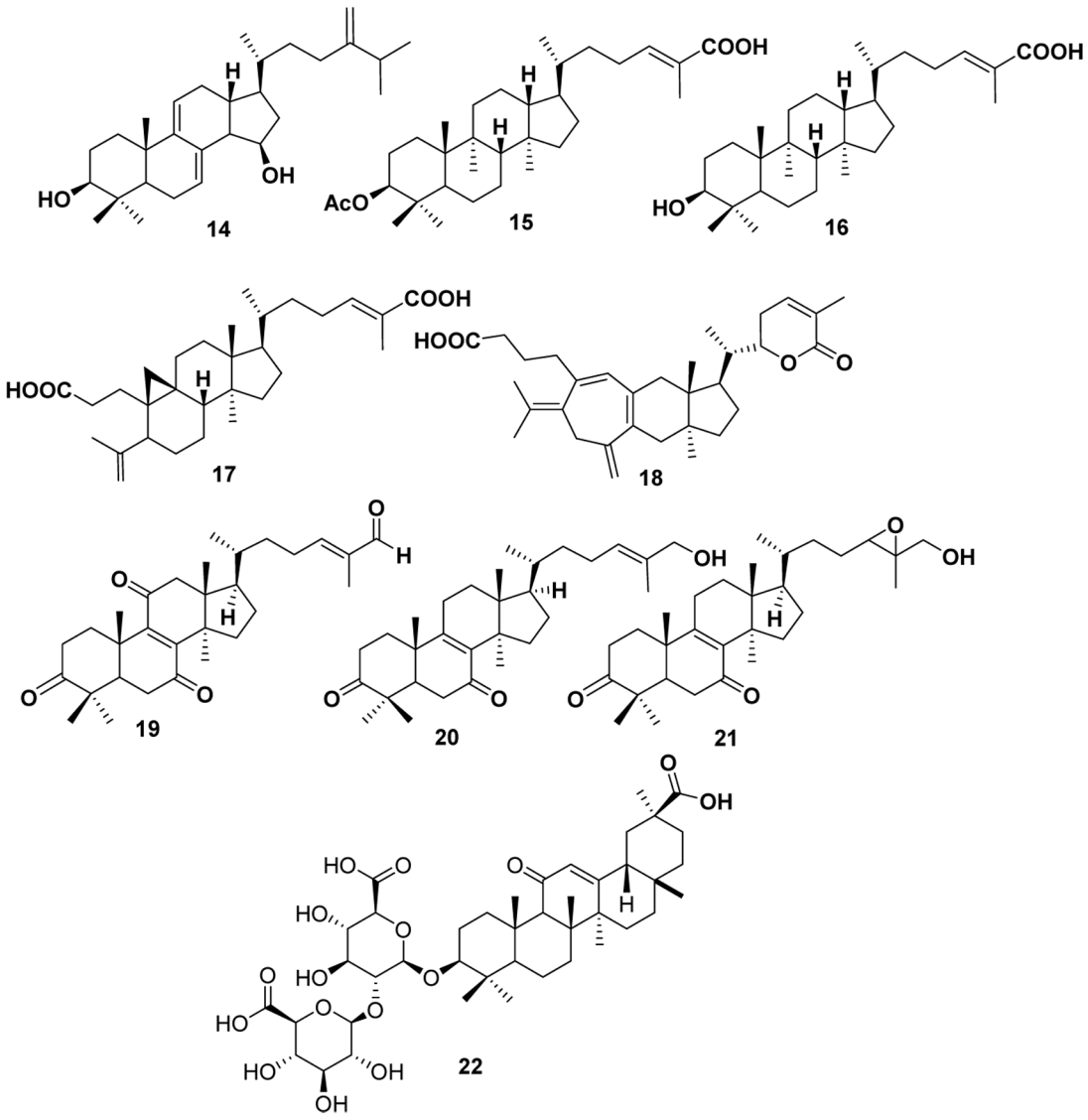

Fig. 3 — Terpenoids structures of 14-22

above half at 100 μM, and their IC_{50} esteems were accounted for. Glycyrrhetinic acid, the sapogenin of glycyrrhizic acid (48), hindered the HIV-1 infection with an IC_{50} estimation of 28.8 μM. By looking at the activity of glycyrrhetinic acid (no GluA), 52 (GluA), and 48 (GluA−GluA), it shows up as though GluA replacements decline the anti HIV activities of licorice saponins[28].

Ten triterpene saponins (50-59) (Fig. 5) have been isolated from a MeOH concentrate of the leaves of *Ilex oblonga*. In the three triterpenoid saponins, to be specific, siaresinolic acid 28-O-β-D-glucopyranosyl ester (56), oblonganoside K (57), and oblonganoside M (59), were principle dynamic segments against TMV (Tobacco Mosaic Virus) replication.

The inhibitory activity of mixtures 50-59 were considered in contrast to TMV at the concentration of ~0.25 μM, intensifies 56, 57, and 59 showed higher inhibitory movement against TMV replication than different mixtures with 84.5, 85.7, and 78.5% restraints individually. The EC_{50} estimations of mixtures 56, 57, and 59 were resolved to be 116, 96, and 107 μM individually. Considering the above outcomes, reasoned that the mixtures 56, 57, and 59 are principle dynamic parts against TMV[29].

Eight new cycloartane triterpenoids (60-67), (Fig. 6) named carinatins A−H, and the known mixtures secaubryolide (68) and dikamaliartane D (69) were reported from the leaves and twigs of *Gardenia carinata*. The anti HIV-1 exercises were

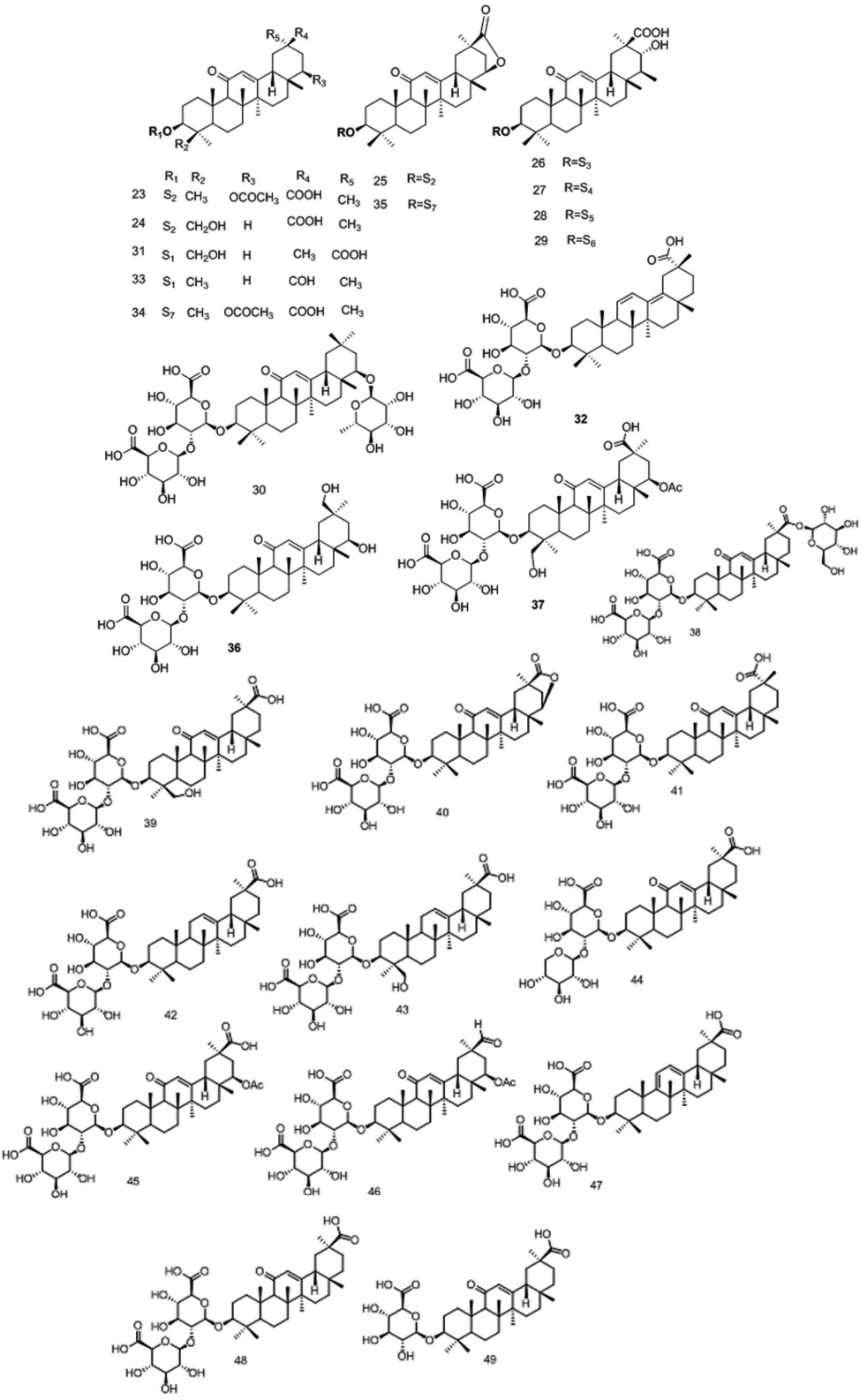

Fig. 4 — Terpenoids structures of 23-49

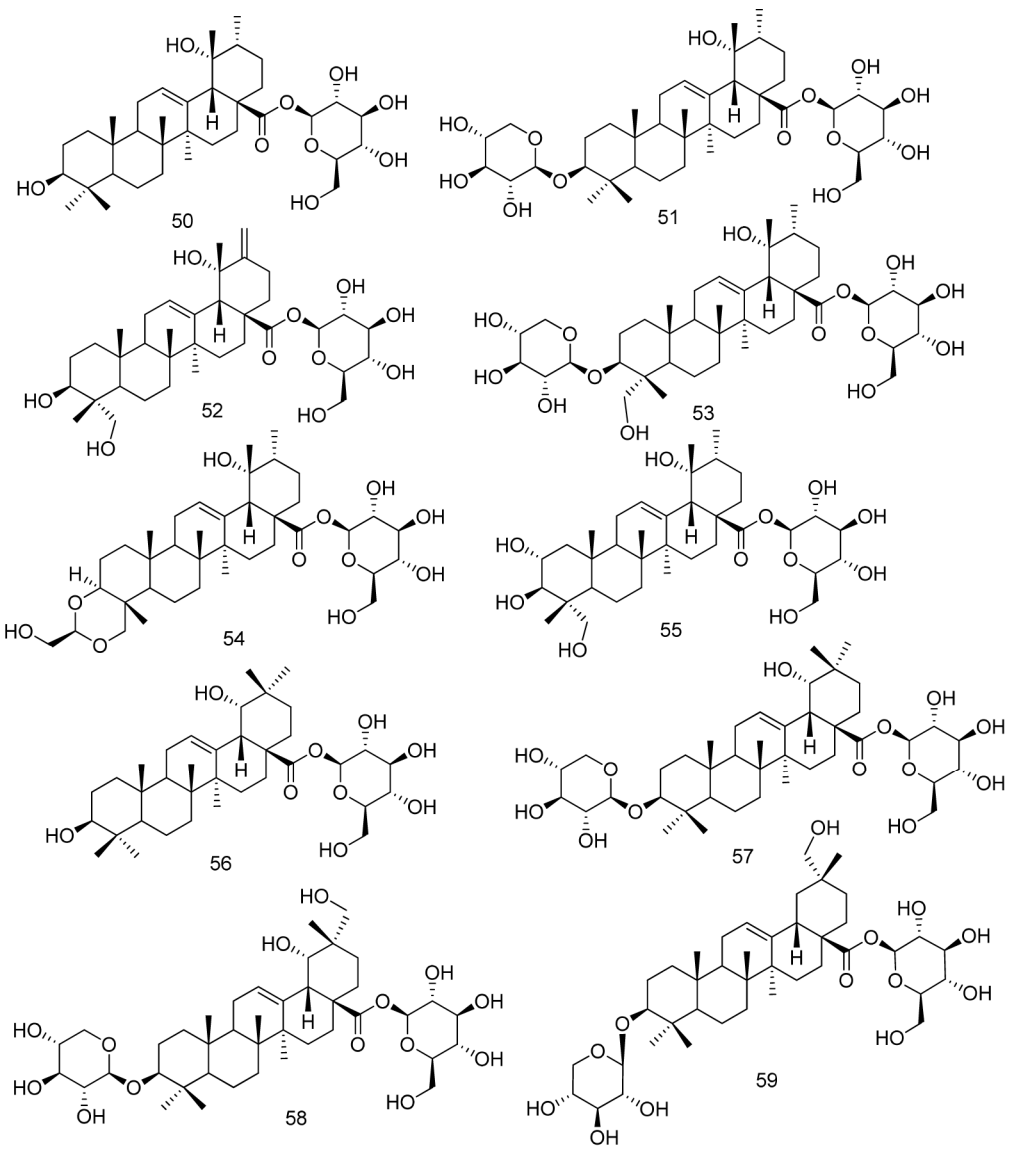

Fig. 5 — Terpenoids structures of 50-59

performed by utilizing the HIV-1 converse transcriptase (RT) test and the syncytium inhibition assay utilizing the MC99 virus and 1A2 cell line framework. Compounds 60, 61, 64, 65, 66, and 69 displayed significant inhibitory activities by essentially decreasing the quantity of syncytium developments in the syncytium restraint measure. Compound 69 showed the most intense enemy of HIV-1 movement with a successful fixation at half (EC_{50}) estimation of <8.3 μM. The inhibitory movement noticed was not influenced by the cytotoxicity of the compound (> 7). In the opposite transcriptase test, just mixtures 62 and 69 were fairly dynamic against HIV-1 converse transcriptase, with IC_{50} values of 85.7 and 68.7 μM, respectively. These outcomes showed that the mixtures 60, 61, 64, 65, 66, and 69 perhaps hindered syncytium arrangements by meddling with HIV-RT as well as by different implies that need further investigations[29].

A ring-secocycloartene triterpenoid, nigranoic acid (3,4-secocycloarta-4(28),24-(Z)- diene-3, -26-dioic acid) (70) (Fig. 6) was isolated from the stems of Chinese conventional restorative plant *Schisandra sphaerandra*[30]. Nigranoic acid was discovered to be dynamic in a few opposite transcriptase and polymerase examines, in which fagaronine chloride was received as a positive-control substance.

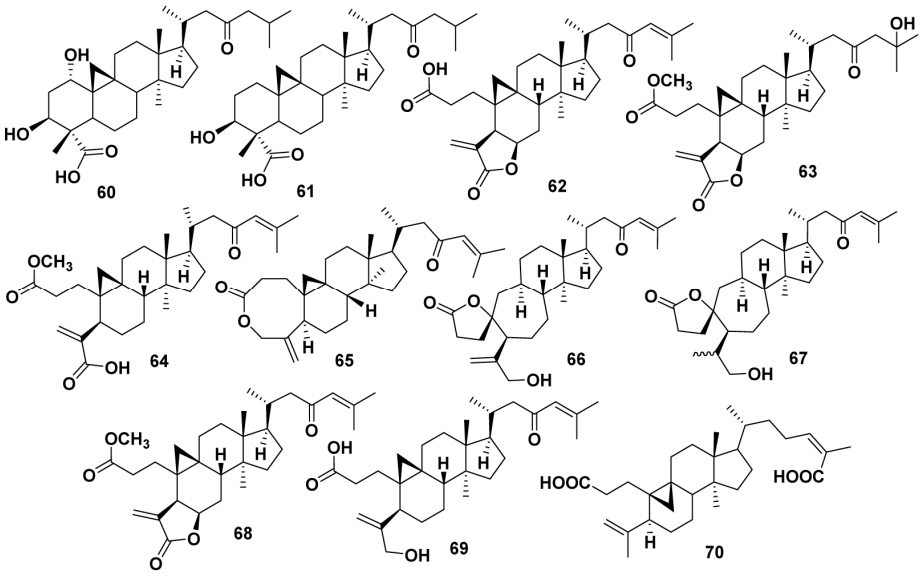

Fig. 6 — Terpenoids structures of 60-70

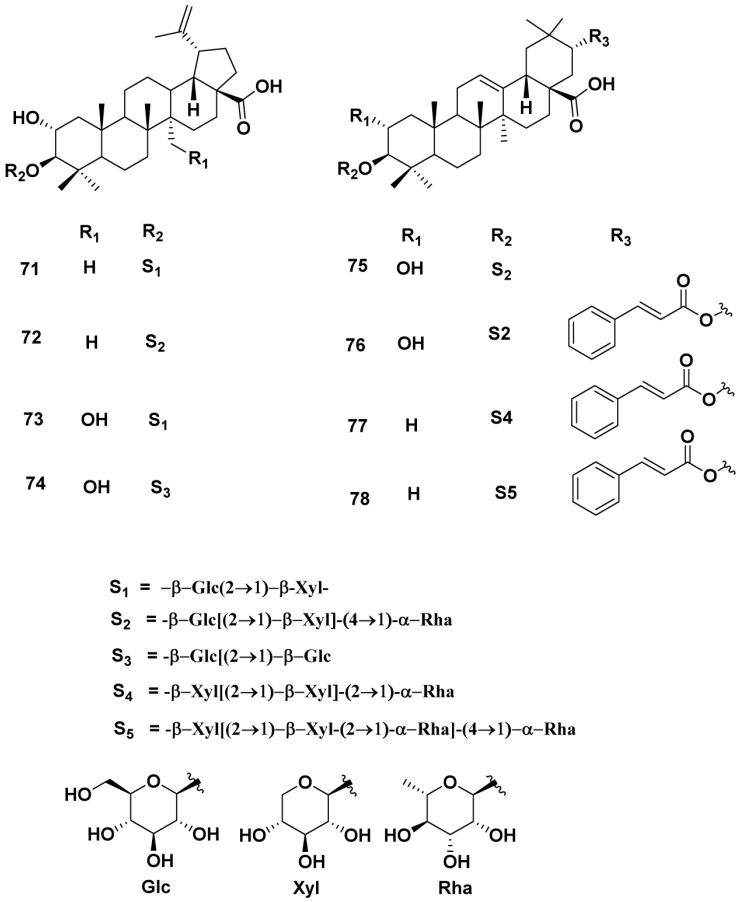

Fig. 7 — Terpenoids structures of 71-78

Christina *et al.*[31], first time detailed triterpene saponins (71-78) (Fig. 7) confined from the bark concentrate of Burkea Africana, discovered to be a promising antiviral lead with an IC_{50} values of 5.5 µg/mL without significant cytotoxicity in Madin Darby canine kidney cells. Their anti-H1N1 virus

activity on HK/68 and the 2009 pandemic H1N1 strain A/Jena/8178/09 uncovered the most powerful impacts by intensifies 77 and 78, with IC50 esteems somewhere in the range of 0.05 and 0.27 μM[30].

Five known triterpene acids, ursolic acid, epipomolic acid, maslinic acid, euscaphic acid, and tormentic acid (Fig. 8) were isolated from the Plant *Geum japonicum*. All the mixtures isolated from the EtOAc-dissolvable portion were tried for their anti HIV-1 protease action by HPLC measure. (2R, 19R)-Dihydroxy-3-oxo-12-ursen-28-oic acid (79), ursolic acid (7) and maslinic acid (8) showed more grounded movement than the others epipomolic acid (80) and tormentic acid (82), at the concentration of ~35 μM. aslinic acid (8) was the most dynamic, while eusaphic acid (81) didn't show any activity at this tried fixation.

Hong-Xi *et al*.[32], the primary report of hostile to HIV-1 action of this arrangement consequences of the examinations acquired in the investigation show that intensifies 79, 7, and 8 may contribute toward the anti HIV-1 protease action of the EtOAc-solvent part of *Geum japonicum*. Betulonic acid (83) (Fig. 9) was isolated from the ethyl acetate extracts of the heartwood of *Juniperus formosana*. Several biological properties have been observed from this compound, particularly exhibit activity against anti-severe acute respiratory syndrome-associated coronavirus (SARS-CoV) activities using a cell-based assay measuring. SARS-CoV-induced cytopathogenic impact on Vero E6 cells reference controls niclosamide and valinomycin were intense inhibitors at focuses somewhere in the range of 3.3 and 10 μM. The centralizations of the compound to hinder half of Vero E6 cell expansion (CC_{50}) and viral replication (EC_{50}) were measured[33]. The dynamic mixtures revealed from *Ganoderma pfeifferi*, lucialdehyde B (84), and ergosta-7,22-dien-3α-ol (85) were established to display strong inhibitory activity against herpes simplex virus. Callies *et al*.[34], first announced another enemy of HIV specialists, (86-91) and 3 known (92-94) (Fig. 9) pentacyclic lupane-type triterpenoids from the stem of *Cassine xylocarpa* and root bark of Maytenus cuzcoina. Among these showing comparable tritepenoids yet a portion of these showed inhibitory impacts of human immunodeficiency infection type 1 replication with IC_{50} values in the micromolar range, featuring compound 94 (IC_{50} 4.08 μM, individually) as the most encouraging anti HIV agents.

Cucurbitacin B (95) (Fig. 10) is a biologically dynamic constituent of *Ecballium elaterium*, is a trademark tetracyclic triterpene heighten that has a spot to Cucurbitacins (CUs) compounds, from the group of Cucurbitaceae. Hassan *et al*.[35], showed that Cucurbitacin B has powerful anti HSV-1 activity contrasted with that of acyclovir with IC_{50} values of 0.94 and 1.74 μM, respectively and selectivity lists (SI) is equivalent to 127.7 and more than 132.2, respectively. Besides, cytotoxicity contemplates uncovered that Cucurbitacin B could be utilized securely at a non-cytotoxic convergence of 120 μM. (S.T.S. Hassan). Tereticornate A (96) is an intense dynamic element of triterpene separated from the *Eucalyptus globules*. Brezáni et al.[36], considered antiviral properties of Tereticornate A compound (96, 102) (Fig. 10) displayed the strong activity against HSV-1 contrasted with the acyclovir with IC_{50} values

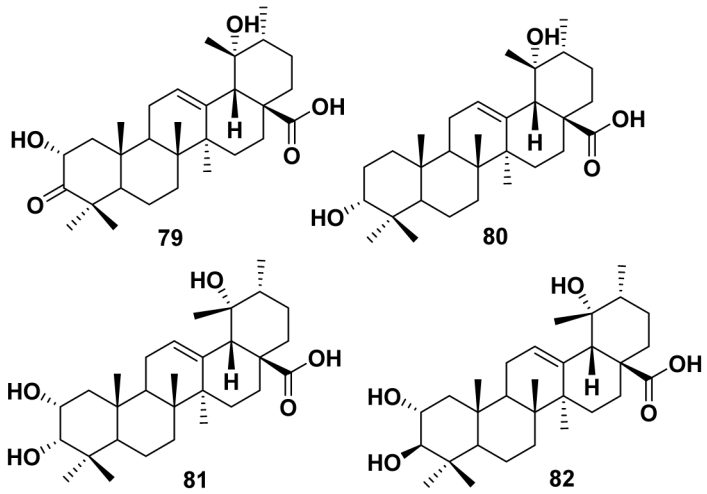

Fig. 8 — Terpenoids structures of 79-82

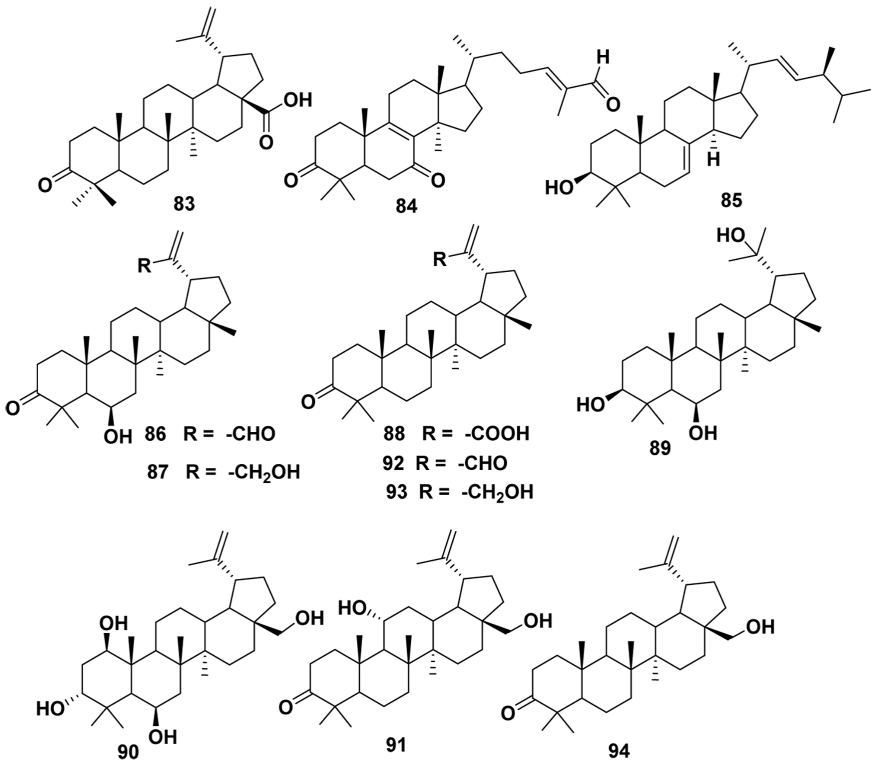

Fig. 9 — Terpenoids structures of 83-94

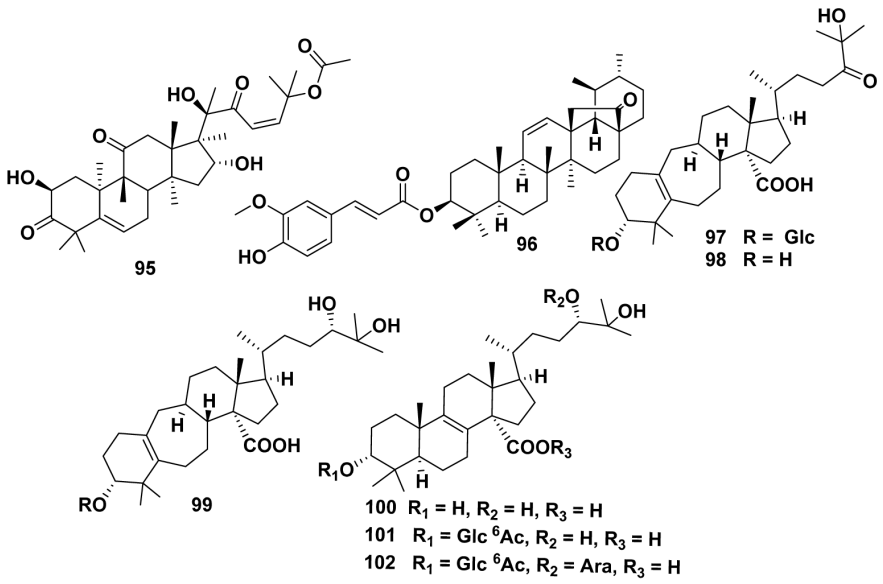

Fig. 10 — Terpenoids structures of 95-102

1.5 μM and 7.7 μM respectively and particular lists are 218.8 and 109.4, respectively. Xiao-Jing et al.[37], have separated and detailed twenty uncommon triterpenoids mixtures and tried for antiviral activity. Among every one of these mixtures, six mixtures displayed powerful activity against HSV-1 contrasted with the acyclovir as reference. The IC_{50} values confined of 97, 98, 99, 100, 101, 102 and acyclovir appeared as 11.1, 3.7, 11.1, 2.1, 6.4, 14.3 and 0.41 μM respectively[37].

Conclusion

To date, HIV, SARS, MERS, COVID-19 has become in demand diseases threatening human health. Improvement of significant expense productive and low toxicity, antiviral medications is perhaps the most pressing issues in the clinical field. Triterpene represents as a major and assorted gatherings of plant regular items, compound permits as promising antiviral medication because of their significant pharmaceutical values, broad spectrum of applications towards antiviral medication, high effectiveness, high cost-effective, high efficiency, low harmfulness. This review mainly focused on the current advantages and antiviral activity of 102 triterpenes, isolated from different plant sources and from macrofungi (*Ganoderma pfeifferi*). This provides new insight for further research and investigations on the antiviral drug development.

References

1 Jiang Z, Kempinski C & Chappell J, *Curr Protoc Plant Bio*, 1 (2016) 345.
2 Wang C, Liwei M, Park J-B, Jeong S-H, Wei G, Wan Y & Kim S-W, *Front Microbiol*, 9 (2018) 2460.
3 Gershenzon J & Dudareva N, *Nat Chem Biol*, 3 (2007) 408.
4 Paduch R, Trytek M, Król S K, Kud J, Frant M, Kandefer-Szerszeń M & Fiedurek J, *Pharm Biol* 54 (2016) 1096.
5 Caputi L & Aprea E, *Recent Pat Food Nutr Agric,* 3 (2011) 9.
6 Oldfield E & Lin F Y, *Angew Chem Int Ed Engl*, 51 (2012) 1124.
7 Astani A & Schnitzler P, *Iran J Microbiol*, 6 (2014) 149.
8 Chatow L, Nudel A, Nesher I, Hemo D H, Rozenberg P, Voropaev H, Winkler I, Levy R, Kerem Z, Yaniv Z & Nadav E, *Life*, 11 (2021) 290.
9 Perez R M, *Pharm Biol*, 2 (2003) 107.
10 Yamagishi T, Zhang D C, Chang J J, McPhail D R, McPhail A T & Lee K H, *Phytochemistry*, 27 (1998) 3213.
11 Lee K H, Lin Y M, Wu T S, Zhang D C, Yamagishi T, Hayashi T, Hall I H, Chang J J, Wu R Y & Yang T H, *Planta Med*, 53 (1988) 308.
12 Kashiwada Y, Zhang D C, Chen Y P, Cheng C M, Chen H T, Chang H C, Chang J J & Lee K H, *J Nat Prod*, 56 (1993) 2077.
13 Fujioka T, Kashiwada Y, Kilkuskie R E, Cosentino L M, Ballas L M, Jiang J B, Janzen W P Chen I S & Lee K H, *J Nat Prod*, 57 (1994) 243.
14 Tan G T, Pezzuto J M, Kinghorn A D & Hughes S H, *J Nat Prod*, 54 (1991) 143.
15 Min B S, Jung H J, Lee J S, Kim Y H, Bok S H, Ma C M, Nakamura N, Hattori M & Bae K, *Planta Med*, 65 (1999) 374.
16 Xu H-X, Zeng F-Q, Wan M & Sim K-Y, *J Nat Prod*, 59 (1996) 643.
17 Ito J, Chang F R, Wang H K, Park Y K, Ikegaki M, Kilgore N & Lee K H, *J Nat Prod*, 64 (2001) 1278.
18 Pengsuparp T, Cai L, Fong H H S, Kinghorn A D, Pezzuto J M, Wani M C & Wall M E, *J Nat Prod*, 57 (1994) 415.
19 Kurokawa M, Basnet P, Ohsugi M, Hozumi T, Kadota S, Namba T, Kawana T & Shiraki K, *J Pharmacol Exp Ther*, 289 (1999) 72.
20 Chaudhuri S K, Fullas F, Brown D M, Wani M C, Wall M E, Cai L, Mar W, Lee S K, Luo Y, Zaw K, Fong H H S, Pezzuto J M & Kinghorn A D, *J Nat Prod*, 58 (1995) 1.
21 Li H Y, Sun N J, Kashiwada Y, Sun L, Snider J V, Cosentino L M & Lee K H, *J Nat Prod*, 56 (1993) 1130.
22 Rukachaisirikul V, Pailee P, Hiranrat A, Tuchinda P, Yoosook C, Kasisit J, Taylor W C & Reutrakul V, *Planta Med*, 69 (2003) 1141.
23 Johnston M I & Hoth D F, *Science*, 260 (1993) 1286.
24 Taniguchi S, Imayoshi E, Kobayashi E, Takamatsu Y, Ito H, Hatano T, Sakagami H, Tokuda H, Nishino H, Sugita D, Shimura S & Yoshida T, *Phytochemistry*, 59 (2002) 315.
25 Niedermeyer T H J, Lindequist U, Mentel R, Gordes D, Schmidt E, Thurow K & Lalk M, *J Nat Prod*, 68 (2005) 1728.
26 Fiore C, Eisenhut M, Krausse R, Ragazzi F, Pellati D, Armanini D & Bielenberg J, *Phytother Res,* 22 (2008) 141.
27 Isao K, Kazuyuki H, Masahiro S, Jun-Liang Z & Masayuki Y, *Chem Pharm Bull*, 41 (1993) 1337.
28 Kongkum N, Tuchinda P, Pohmakotr M, Reutrakul V, Piyachaturawat P, Jariyawat S, Suksen K, Akkarawongsapat R, Kasisit J & Napaswad C*, J Nat Prod*, 76 (2013) 530.
29 Sun H D, Qiu S X, Lin L Z, Wang Z Y, Lin Z W, Pengsuparp T, Pezzuto J M, Fong H H S, Cordell G A & Farnsworth N R, *J Nat Prod*, 59 (1996) 525.
30 Mair C E, Grienke U, Wilhelm A, Urban E, Zehl M, Schmidtke M & Rollinger J M, *J Nat Prod*, 81 (2018) 515.
31 Xu H-X, Zeng F-Q, Wan M & Sim K-Y, *J Nat Prod*, 59 (1996) 643.
32 Wen C-C, Kuo Y-H, Jan J-T, Liang P-H, Wang S-Y, Liu H-G, Lee C-K, Chang S-T, Kuo C-J, Lee S-S, Hou C-C, Hsiao P-W, Chien S-C, Shyur L-F & Yang N-S, *J Med Chem*, 50 (2007) 4087.
33 Callies O, Bedoya L M, Beltrán M, Muñoz A, Calderón P O, Osorio A A, Jiménez I A, Alcamí J & Bazzocchi I L*, J Nat Prod*, 78, (2015) 1045.
34 Hassan S T S, Berchova-Bimova K, Petras J & Hassan K T S, *S Afr J Bot*, 108 (2017) 90.
35 Brezáni V, Lelakova V, Hassan S T S, Berchova-Bimova K, Novy P, Kloucek P, Marsik P, Dall'Acqua S, Hosek J & Smejkal K, *Viruses*, 10 (2018) 360.
36 Lv X-J, Li Y, Ma S-G, Qu J, Liu Y-B, Li Y-H, Zhang D, Li L & Yu S-S, *J Nat Prod*, 79 (2016) 2824.
37 Wu Z-J, Ouyang M-A, Wang C-Z, Zhang Z-K & Shen J-G*, J Agric Food Chem,* 55 (2007) 1712.