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Pharmacological Property of Pentacyclic Triterpenoids

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PLANT terpenoids are utilized generally for their aromatic behaviour. They act as conventional herbal remedies and are under research for antineoplastic activity, antibacterial activity, anti-diabetic activity, anti-inflammatory activity, anti-platelet aggregate activity, antiviral activity, antioxidative activity, antiallergic, antihypertensive activity and additional pharmaceutical actions. Plants not only just deposit terpenes for herbariums defence yet in addition emanate essential mixtures in response to herbivory and numerous different abiotic and biotic stresses. Now a day, there is a phenomenal developing enthusiasm for natural triterpenes over the most recent couple of decades because of the revelation of their potential biological and pharmacological activities. Pentacyclic triterpenes are ancillary plant elements broadly spread in stem, leaves, bark and fruit peel. Specifically, the ursane, lupane and oleanane pentacyclic triterpenes show different pharmacological impact. Subsequently, these triterpenes are offering key components for the improvement of novel multi-targeted bioactive agents.

Keywords: Pentacyclic triterpenes, Antidiabetic activity, Antiviral activity, Antibacterial activity.

Introduction

There is an expansive scope of classes of normally happening compounds. Terpenoids likewise structure a gathering of normally happening compounds dominant part of which happen in plants, several of them have additionally been acquired from different sources (like marine animals). These are essential elements which give herbs and blooms their scent. They happen broadly in leaves and products of conifers, superior plants, eucalyptus and citrus. The word 'terpene' are the components separated from terpentine, was initially utilized to portray a blend of isomeric hydrocarbons of the atomic equation $C_{10}H_{16}$developed from the basic oils got from tissue and sap of trees and plants. However, there is a propensity to use progressively broad name 'terpenoids' which incorporate hydrocarbons and oxygenated derivatives of them. Anyway, the main use of the word terpene is nowadays by certain authors to speak to terpenoids.

Individual normal human utilization of triterpenes is evaluated to be roughly 250 mg for each dayin the Western world, and in the Mediterranean nations, the normal intake could achieve 400 mg for each day [1]. More than 30,000 triterpenes have been isolated thus far[2]. The free form of Triterpenes like sapogenins and bound to glycosides like saponins are generally foundin the nature. They can be categorized in assorted groups

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including ursanes, cucurbitanes, dammaranes, cycloartanes, friedelanes, euphanes, holostanes, isomalabaricanes, hopanes, lanostanes, lupanes, limonoids, oleananes, sqalenes, protostanes, tirucallanes and diverse compounds [3, 4, 5].In spite of the fact that triterpenoids were viewed as biologically inert for an extensive stretch of time, gathering evidence on their different types of pharmacological and biological properties combined with a low toxicity profile has started re-established enthusiasm concerning human wellbeing and ailment. Triterpenoids are utilized for therapeutic instances in numerous Asian nations for antipyretic, analgesic, hepatoprotective, anti-inflammatory, sedative, tonic and cardiotonic effects [6, 7, 8]. Current investigations have not just affirmed a portion of the previously mentioned pharmacological properties of a few triterpenoids, yet in addition recognized an assortment of extra biological actions including antiviral, antimicrobial, anti-oxidant, antipruritic, antiallergic, spasmolytic and antiangiogenic activity[9, 10]. Arising count of triterpenoids have been accounted for to display cytotoxicity against an assortment of malignant growth cells without demonstrating any lethality in common cells [3, 5, 11]. They likewise demonstrate antitumor viability in animal models of malignant growth preclinically [11]. Anenormous count of triterpenoids has been synthesized by structural change of natural components for the advancement of biological activity, and a portion of those semi-engineered analogs are viewed as the highest powerful anticarcinogenic and anti-inflammatory triterpenoids known to mankind [12]. The antitumor adequacy of a few triterpenoids is currently being assessed in phase I clinical trials [3]. Among the triterpenoids, tetracyclic and pentacyclic triterpenes are the most exorbitant. Pentacyclic triterpenes are separated into numeroussub-groups: gammaceranes, hopanes, lupanes, oleananes, ursanesand so on dependent on their carbon skeleton. From a natural perspective, pentacyclic triterpenes have earned much consideration, and a few of them, which include derivatives of pentacyclic triterpene, are being promoted as remedial specialists or nutritional supplementation all over the world [13]. Pentacyclic triterpenes have been found in devoured natural products, for example mango [14], apple peel [15, 16]strawberries [14], pearpeel[17], green pepper [18], guava [19], mulberry or olives [17, 20], yet in addition in aromatic herbs, e.g., basil [19, 21], oregano [17], lavender [17] and rosemary [22]. They have additionally been accounted for in trees, for example, eucalyptus leaves [21] and birch bark [16], just as in some oriental and conventional medication herbs broadly appropriated everywhere throughout the world [23, 24, 25]. Other than their less water dissolvability, these can be found as components of therapeutic herb decoctions where their bioavailability is viewed as adequate to advance natural movement [26]. To the extent wellbeing impacts, boswellic acids have picked up a specific intrigue. Mediterranean spices and their fruits further consist pentacyclic triterpenes which belong to theursane, oleanane and lupine groups [27], and for instance, maslinic acid obtained from the fruits and leaves of *Olea europaea*L., is the principle pentacyclic triterpene [28, 29, 30]. This compound is furthermore getting affirmation as a potential nutraceutical.

General Properties of Terpenoids

The greater sectionof the terpenoids are discoloured, odorous fluids and they are milder than aqua and volatile nature. A couple of them are solids for example camphor. Maximum are dissolvable in organic diluent and generally insoluble in aqua. The enormous majority of them are optically active. Generally, they are cyclic or open-chain unsaturated components having one or more double bonds and also having boiling point of 150^{o}-180^{o} C. Thus, they incur addition reaction with halogen, hydrogen, acids, and so forth. Various addition products have antiseptic characteristic. They in curde hydrogenation and polymerization. They are effectively oxidized about by all the oxidizing agents. In reaction of thermal decomposition, the vast majority of the terpenoids gives isoprene as one of the products.

Classification of Terpenoids

All the terpenoid hydrocarbons, which are natural, show their general equation $(C_5H_8)_n$. The classification of terpenoids can be done based on the value of n or numbers of carbon atoms present in the structure which are listed in Table 1.

Every class of terpenoid scan be additionally subdivided as indicated by the quantity of rings which are present inthe structure. Non-cyclic terpenoids generally contain open structure but one ring structure is observed in Monocyclic terpenoids and, two rings in Bicyclic terpenoids; similarly, three rings in the structure of Tricyclic terpenoids and four rings in Tetracyclic terpenoids.

Some examples of different classes of terpenoids are as follows:

Monoterpenoids

There are two kinds of monoterpenoids one is Acyclic monoterpenoids and another is Bicyclic monoterpenoids. Bicyclic monoterpenoids are additionallypartitioned into three classes: containing 6+3 membered rings, containing 6+4 membered rings and containing 6+5 membered rings, which is sub divided into two kinds, one is Bornane derivatives and other one is Non bornane derivatives. Instances of every class are:

Acyclic Monoterpenoids- Myrcene, Citral, Geraniol.

Monocyclic monoterpenoids- Limonene, α-Terpineol, Menthol

Bicyclic monoterpenoids- The subdivisions of these class are:

- Containing 6+3 membered rings-Thujane, Carane
- Containing 6+4 membered rings-Pinane
- Containing 6+5 membered rings-Two types are there,
  - Bornanederivatives- Camphane
  - Non bornanederivatives- Isocamphane, Fenchane, Isobornylane

Sesquiterpenoids

Three types of sesquiterpenoids are there named Acyclic sesquiterpenoids, Monocyclic sesquiterpenoids and Bicyclic sesquiterpenoids. Instances of every class are:

Acyclic sesquiterpenoids- Farnesol

Monocyclic sesquiterpenoids- Zinziberene

Bicyclic sesquiterpenoids- Cadinene

Diterpenoids

Two types of diterpenoids are available, Acyclic diterpenoids and Mono cyclic diterpenoid. Examples of every class are:

Acyclic diterpenoids- Phytol

Mono cyclic diterpenoid- Vitamin A

Triterpenoids

Four types of triterpenoid are available Acyclic triterpenoid, Tricyclic triterpenoid, Tetracyclic triterpenoid and Pentacyclic triterpenoid. Examples of every class are:

Acyclic triterpenoid- Squalene

Tricyclic triterpenoid- Ambrein

Tetracyclic triterpenoid- Lanosterol

Pentacyclic triterpenoid- Amyrin

General Methods of Isolation

Isolation of Essential Oils from Plant Parts

a. Steam distillation method:

Dry steam is passed through the plant element, whereby the steam volatile compounds are volatilized, condensed and accumulate din collectors. It is used for essential oil extraction for a long period of time. Distillation is done with steam under low pressure which replaces the volatile components from the entire plant material.

b. Solvent extraction:

Solvents like hexane and ethanol is utilized to isolate essential oils. These are utilized for the plant parts having less amount of essential oil. Plant parts are treated with the solvent; it delivers a waxy aromatic component called a "concrete". At that point it is blended with alcohol, the oil particles are released. At that point it passes through a condenser then it is isolated out. This oil is utilized in scent industry or for aromatherapy purposes.

c. Maceration:

In this method the plant parts are changed over into moderately coarse powder and set in a closed vessel. To this, solvent is added and the mixture is permitted to stand for 1 week with vigorous shaking at definite time interval, then the liquid is strained. Solid residue is squeezed to recover any remaining liquid. Strained and expressed liquids are mixed. Advantage of this method is to capture more plant's essence.

d. Adsorption in purified fats/ enfleurage:

The fat is warmed to 500^{o} C on glass plates. By then the fat is covered with flower petals and it kept for a couple of days until it impregnated with essential oils. By then the old petals are supplanted by new petals, it repeated. Subsequent to expelling the petals, the fat is treated with ethanol when all the oils present in fat are dissolved in ethanol. The alcoholic distillate is then partially refined under reduced pressure to omit the solvent. Recently the fat is supplanted by coconut charcoal, because of more prominent stability and higher adsorptive capacity.

Separation of Terpenoid from Essential Oils

a. Chemical methods:

Essential oils containing terpenoid hydrocarbon + nitrosyl chloride in chloroform form crystalline adduct of hydrocarbons. Terpenoid containing aldehyde and ketone treated with $NaHSO_3$, phenyl

hydrazine or semicarbazone. After separation it is decomposed to get terpenoids. Likewise, essential oil containing alcohols with Phthalic anhydride, it results in diester then to terpenoids.

b. Physical methods:

With the help of Chromatography or Fractional distillation methods.

Bio Synthesis of Pentacyclic Triterpenoids:

The pentacyclic triterpenoids of baccharene type are the consequence of cyclization of the 2,3-epoxysqualene to frame a six-membered ring, subsequently, Wagner-Meerwein rearrangements produce the intermediate cation of tetracyclic triterpene 3β-hidroxybacchar-21-ene, and lastly closes the fifth ring to the pentacyclic 3β-hydroxylupanium ion. Thus, modifications in baccharane structure produce a group of pentacyclic triterpenes. The association of bond from C-18 to C-21 of baccharane closes the five membered ring E yielding the pentacyclic lupane. The shift of C-21 from C-19 to C-20 drives the formation of a six-membered ring E to produce oleanane. Oleanane may undergo methyl shifts to a variety of other pentacyclic triterpenes with cyclohexane ring E, for example, the development of taraxerane (C-27 from C-14 to C-13), multiflorane (C-26 from C-8 to C-14), glutinane (C-25 from C-10 to C-9), friedelane (C-24 from C-4 to C-5), and pachysanane (C-28 from C-17 to C-16). Ursane and taraxastane, including taraxastene, emerge from oleanane when methyl group C-29 migrates from C-20 to C-19; a corresponding methyl shift rearranges multiflorane to bauerane [31, 32].The chemical structures of baccharene type are appeared in Fig. 1.

The pentacyclic triterpenoids hopane type result of 2,7-, 6,11-, 10,15-, 14,19-, and 18,22-cyclization of the carbenium ion in a fivefold conformation, which is originated from regioselective protonation of the 2,3-double bond of squalene. This explains the fact that hopanes are usually not hydroxylated in the 3-position. Methyl changes in hopane structure lead to neohopane (C-28 methyl from C-18 to C-17), fernane (C-27 methyl from C-14 to C-13; C-26 ethyl from C-8 to C-14), adianane (C-25 methyl from C-10 to C-9) and filicane (C-24 methyl from C-4 to C-5). The production of a six-memberd ring due to shift of carbon atom C-17 from C-21 to C-22 produces gammacerane [31, 32]. Chemical structures of hopane type are provided in Fig. 2.

Pharmacological Activities Of Different Pentacyclic Triterpenoids

Anti-Cancer Activity

Betulinic acid (BA) is a pentacyclic triterpene of lupane group, low toxicity to normal cells and healthy tissues has shown Anti-proliferative activity in MGC-803, PC3, A549, MCF-7, NIH3T3, SGC-7901, HepG-2, LNCaP, DU-145, SK-MEL-2, SK-OV-3, HCT15, XF498 cell lines among others. BA and their analogues are able to induce apoptosis cell death through the intrinsic pathway affecting the mitochondrial membrane permeability and enhancing the release of cytochrome c. Moreover, cell death via ER pathway and ROS mediated mitochondrial pathway has been observed as other BA mechanism implicated in HeLa cells [33, 34, 35, 36]. In different investigations, it was seen that the treatment concurrent of 5-FU with BA or pursued by BA cause inhibitory impact on the development and apoptosis in ovarian-cancer cells OVACAR 432 by mitochondrial pathway[37].BA also responsible for arresting tumour growth, study claims that BA decreases the tumour size and reduced the expression of mRNA of Sp transcription factors, which regulated the expression of genes responsible for cancer growth (SP1, SP3 and SP4, VEGFR, survivin and microRNA-27) in nude mice xenografts bearing of estrogen receptor breast negative MDA-MB-231 cells [38]. Another study states that BA in combination with vincristine was able to suppress lung metastasis of murine melanoma B16F10 cells in C57BL/6 mice [39]. Another pentacyclic triterpenoid Oleanolenic acid (OA) inhibit the proliferation, induces apoptosis cell death and cell cycle arrested by inhibition of PI3K/AKT pathway in prostate cancer PC-3, DU145, and LNCaP, also OA was able to inhibit the tumour growth in nude mice bearing of PC3- cells through the inhibition of PI3K/AKT pathway [40]. In ovariectomized femaleC57BL/6 mice transplanted with MTTV- Wnt-1 mammary tumour cells Ursolic acid (UA)was able to inhibit the proliferation, reduce the tumour size, and induce apoptosis cell death through of modulation of Akt/mTOR and MAPKpathways[41]. UA also arrested breast cancer cell lines (MCF-7, MCF-7/ADR and MDA-MB-231) by inhibiting the growth [42]; also by suppressing the migration and metastasis by regulating mTOR,c-Jun N-terminal kinase (JNK) and Akt signalling [43]; also by consecration of apoptosis via mitochondrial death pathway and extrinsic death receptor pathway

TABLE 1. Classification based on the value of number of carbon atoms present in the structure.

Class	Molecular formulae	Value of n	No. of carbon atoms
Isoprene or Hemiterpene		1	5
Monoterpenoids	$C_{10}H_{16}$	2	10
Sesquiterpenoinds	$C_{15}H_{24}$	3	15
Diterpenoids	$C_{20}H_{32}$	4	20
Sesterpenoids	$C_{25}H_{40}$	5	25
Triterpenoids	$C_{30}H_{48}$	6	30
Tetraterpenoids	$C_{40}H_{64}$	8	40
Polyterpenoids	$(C_5H_8)n$	>8	>40

[44] and also by suppressing expression of FoxM1 protein [45].It can also arrest cervical cancer in cell lines study (HeLa and SiHa) through mitochondrial intrinsic pathway along with suppression of ERK1/2 MAPK pathway [46] and also by enhancing of chemotherapeutic efficiency [47].Another study stated that UA is effective against colorectal cancer in cell lines (CO115, Caco-2, CT26, DLD1,SW620, HCT116, SW480,HT29andHCT15) by downregulation of Bcl-2, surviving and Bcl-xL activity [42]; also by influencing PI3K signalling pathway [48] and via p53-independent upregulation of death receptors [49, 50] as well as autophagy through JNK pathway [51] and cyclooxygenase 2 (COX-2) pathway [52].Gastric cancer in cell lines (SNU-484, AGS, SGC7901 andBGC823) and Hepatic cancer in cell lines (Huh7, HepG2, Hep3B andH22)both are evidenced to cured by UA via downregulation of Bcl-2 [43, 53]by activation of caspase-3,-8, and -9 and through inhibition of cyclooxygenase-2 [54].Glioma has been cured by UA in cell lines (U251, 1321N1 andU87) by suppressing TGF-1/miR-21/PDCD4 pathway [55], also by inhibiting of the endogenous reverse transcriptase (RT) [56]. Lung cancer was also cured by UA in cell lines (H3255, A549, H640, Calu-6 andASTC-a-1) by suppressing the expression of AEG-1 and inhibition of NF-kB [57].Multiple myeloma in cell lines (MM1.S, RPMI8226 and U266) has been cured by UA through inhibiting STAT3 activation pathway by expressingSHP-1(Src homology phosphatase-1), an SH2 domain-containing protein tyrosine phosphatase [58]. Ovarian cancer was cured by UA in cell lines (SK-OV-3and CAOV) after suppression ERK activity and ERK 1/2expression, also by upregulating BAX (Bcl-2-like protein 4) expression and down-regulating of Bcl-2 expression [59] and by activation of caspases and phosphorylation of GSK3 beta [60]. UA also showed activity in Raji cell line and mice on viral-induced cancer by inhibiting activation of TPA (12-O-tetradecanoylphorbol-13-acetate) induced Epstein-Barr virus [61, 62, 63].

Anti-Inflammatory Activity

Ursane-type triterpenoids as such β-Boswellic acid and Aβ-Boswellic acid inhibit 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced inflammation in mice [64]. Besides β-Boswellic acid can likewise inhibit impacts of LPS and it is a selective inhibitor of COX-1 with IC_{50} values of 15 μmol/lit[65]. Moreover, this triterpenoid decreases 2-fold the platelet-type 12-LOX catalysis. 12-ursene 2-diketone isolated of *Boswellia serrata*. Triana and Planch (Burseraceae) is able to inhibit key inflammatory mediators, such as TNF-α, IL-6 and IL-1β,

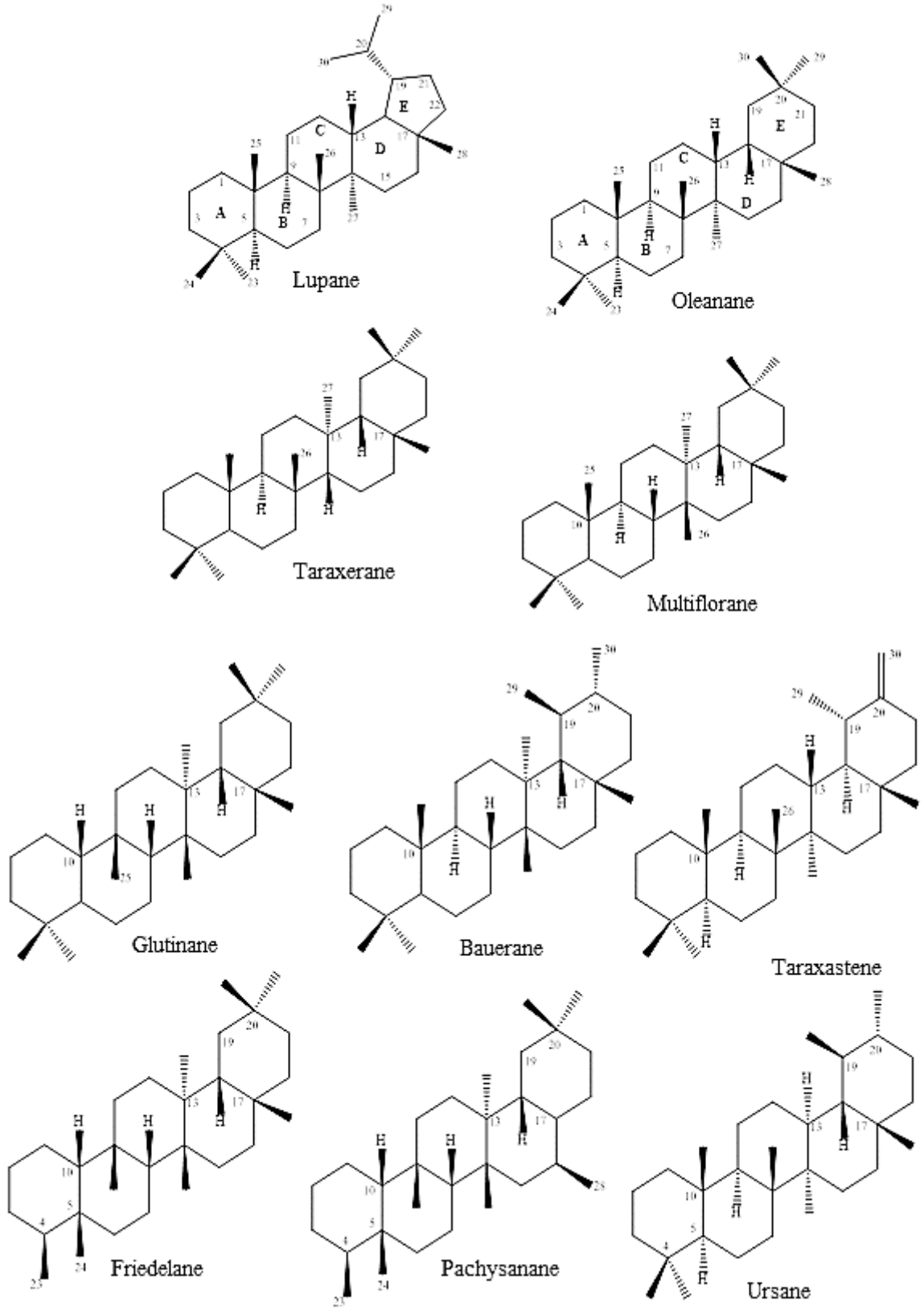


Fig. 1. Pentacyclic Triterpenoids of Baccharene Type.

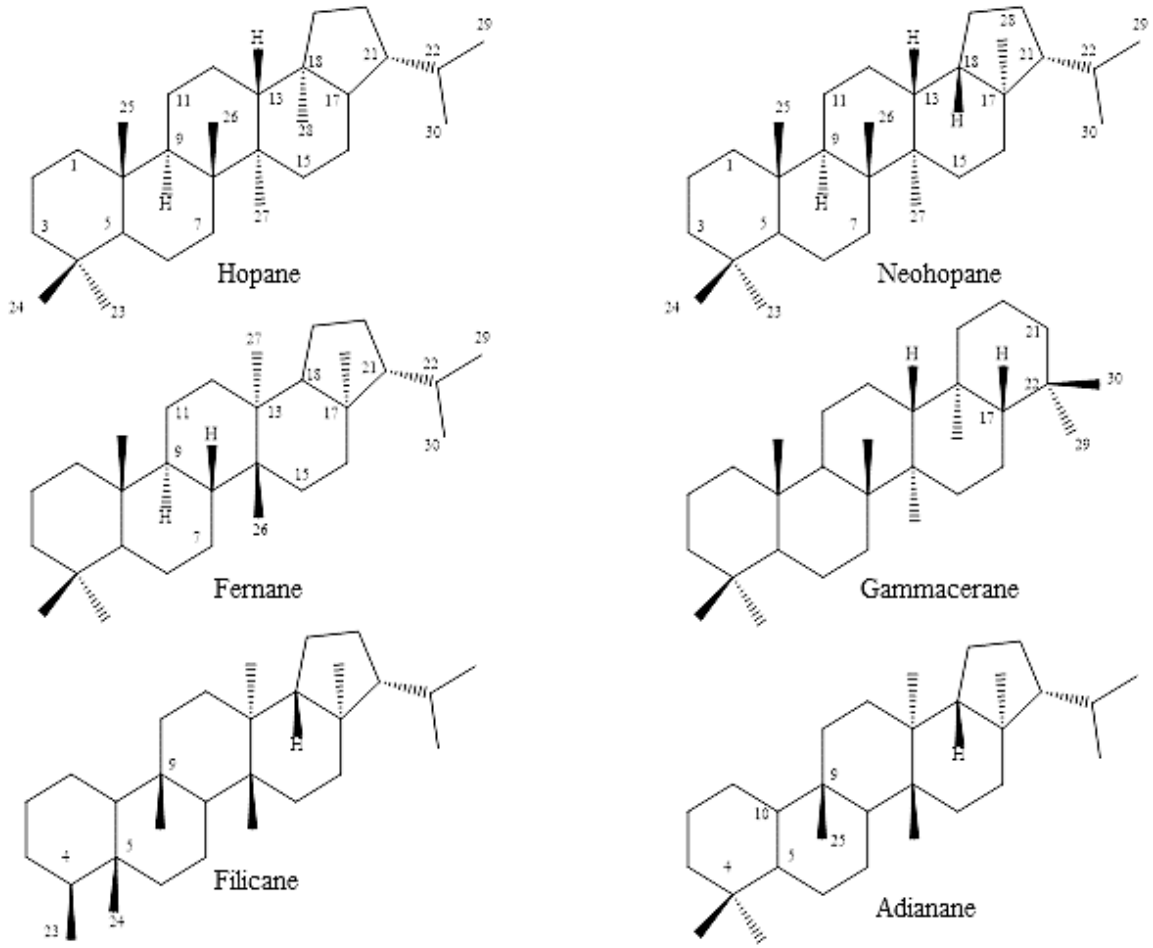


Fig. 2. Pentacyclic Triterpenoids of Hopane Type

avoiding phosphorylation of mitogen activated protein kinases, c-jun N-terminal kinase and p38 [66]. Betulinic acid from the herb *Bacopa monnieri* exhibit anti-inflammatory effect[67]. Another study found the percentage inhibitory activity of UA 86.8±1.23, 53.0±0.43, 46.2±0.23 having IC_{50} of 2.82µmol/lit; OA 60.2±0.42, 60.2±0.42, 88.8±0.42 with IC_{50} of 0.84µmol/lit; MA (maslinic acid) 37.2 ± 0.90, 53.0 ± 1.23, 69.9 ± 0.35 with IC_{50} of 2.81µmol/lit, by using concentrations 1, 3 and 10 mg/ml respectively on throbine-induced platelet aggregation. On ADP-induced platelet aggregation, percentage inhibitory activity found for OA 21.1±0.26, 27.5±0.31, 80.8±0.79 with IC_{50} of 5.98µmol/lit; for UA 0.00±0.61, 60.1±4.38, 76.7±0.76 with IC_{50} of 3.00µmol/lit, using concentrations 1, 3 and 10 mg/ml. On epinephrine-induced platelet aggregation, percentage inhibitory activity found for MA 0.00± 0.90, 35.9±1.32, 87.0±1.53 with IC_{50} of 4.99µmol/lit, using concentrations 1, 3 and 10 mg/ml [68].

Antidiabetic Activity:

Ramírez-Espinosa et al. reported that 50 mg/kg doses of ursolic, oleanolic, moronic and morolic acids demonstrated a noteworthy antidiabetic activity in streptozotocin-nicotinamide diabetic rats in comparison with control group[14, 69].Apart from that some Oleanane Compounds of pentacyclic triterpenoids from natural sources are there which possess potent antidiabetic activity viz. Gymnemic acid IV and Dihydroxy gymnemic triacetate obtained from *Gymnema sylvestre* respectively reduces blood glucose levels by 13.5 -60.0%, 6 h after administration at doses of 3.4- 13.4 mg/kg, where

13.4 mg/kg increased plasma insulin levels in streptozocin induced (STZ)-diabetic mice; and at 20 mg/kg dose plasma glucose (> 50%), HbA1c (39.56%) decreases in diabetic rats. Increases plasma insulin (50%), muscle glycogen (77.1%) and liver glycogen (59.09%) in diabetic rats[70, 71]; Maslinic acid present in *Olea europaea* exhibits antidiabetic effect by inhibiting glycogen phosphorylase there by reduces blood glucose levels in KK-Ay mice at 4 h and 7 h compared to control and intragastric administration of the same (5 or 50 mg/kg) for 14 consecutive days in STZ-diabetic rats lowers blood glucose levels, reduces infarct volumes and improves neurological scores for both doses[72, 73]; Arjunolic acid from *Terminalia arjuna*, reduces hyperglycaemia, membrane disintegration, oxidative stress, vascular inflammation and prevents oxidative stress-induced signalling cascades, leading to cell death in STZ-induced diabetic rats at a dose 20 mg/kg and at the same dose for 14 days, has a beneficial role against diabetic nephropathy [74, 75, 76];3β-Taraxerol from *Mangifera indica* produces a time-dependent increase in glucose transporter type 4 (GLUT4) with a maximum increase observed at 18 h, which was sustained until 24 h, maximum translocation of GLUT4 from cytosolic fraction to the plasma membrane fraction, increases glycogen synthesis involving the activation of PKB and suppression of GSK3β in 3T3-L1 adipocytes[77]; Elatoside E, elatoside A, tarasaponin VI, stipuleanoside R1, chikusetsusaponin IV, stipuleanoside R2, Elatosides G, H and I from *Aralia elata* shows hypoglycaemic activity at a dose100 mg/kg of each compound in oral glucose/sucrose tolerance test in rats[78, 79]; Sengins II and III from *Polygala senega* alleviates blood glucose level in normal mice 4 h after intraperitoneal administration and significantly lowers the glucose level of KK-Ay mice [80]; Kaika saponin III from *Pueraria thunbergiana* at 5 and 10 mg/kg, exhibits significant hypoglycaemic activity in STZ-induced diabetic rats[81]; 3-O-[(α-L-Rhamnopyranosyl) (1→2)]-[β-D-glucuronopyranosyl-6-O-methyl ester]-olean-12-ene-28-olic acid from *Acanthopanax senticosus* inhibits α-glucosidase (EC.3.2.1.20) (from Saccharomyces sp.) with IC_{50} value of 908.5 µmol/lit[82];Beta-vulgarosides II, III and IV obtained from the plant *Beta vulgaris* at 100 mg/kg, produces hypoglycaemic activity at a single oral administration in oral glucose tolerance tests in rats [83]; Kalopanax saponin A from *Kalopanax pictus* at decreases serum glucose by 93% at 25 mg/kg, in STZ-induced diabetic rats[84]; 3-O-Acetyloleanolic acid from *Eysenhardtia platycarpa* at a dose 31 mg/kg, decreases (26.3 ± 3.7%) glucose level of STZ-induced diabetic rats after 7 h of treatment[85].Some active Ursane compounds from *Eriobotrta japonica* herb are 2α-Hydroxy-3-oxours-12-en-28-oic acid and 3-Epicorosolic acid methyl ester both inhibits 11β-Hydroxysteroid dehydrogenase 1 activity, which displays hypoglycaemic activity and stimulates insulin release, where Tormentic acid inhibits glycosuria [86, 87]; 2α-Hydroxyursolic acid and Pomolic acid both exhibits hypoglycaemic activity[88]; Euscaphic acid and the total triterpene acid fraction of the herb *Eriobotrtaja ponica* exhibits hypoglycaemic effect in alloxan-diabetic mice [89, 90];Asiatic acid from *Centella asiatica* herb mitigates hyperglycaemia in STZ-induced diabetic rats at dose of 25 mg/kg for two weeks[91]; Corosolic acid from *Lagerstroemia speciosa* and Euscaphic acid, 2α,19α-Dihydroxy-3-oxo-12-ursen-28-oic acid, Ursolic acid, p-Coumaroylursolic acid obtained from *Sanguisor batenuifolia* all exhibits α-glucosidase inhibiting activity[92, 93]. 23-Hydroxyursolic acid from *Lagerstroemia speciose* exhibits hypoglycaemic activity [94]. Some Lupane Compounds belong to pentacyclic triterpenoids group, viz. Bacosine from *Bacopa monnieri* and ethanolic extract of *Aegle marmelo s*herb both exhibited hypoglycaemic effect [85, 95]. Glycyrrhizic acid decreases blood glucose level and increased serum insulin level at 100 mg/kg for 2 weeks in STZ-induced diabetic rats [96] and at 4.1g/kg for 7 weeks in genetic diabetic KK-Ay mice [97]; also it restores postprandial glucose level when 30 mM was given 30 mins before the administration of glucose solution in Wild type ddY mice [97]. Apart from that Glycyrrhizic acid also minimizes plasma total cholesterol and TG (Triglycerides) levels; reduces Apo B and cholesterol-ester-transport protein and enhances Apo A-1 level Decreases hepatic HMG-CoA reductase expression at doses 100 mg/kg for 4 weeks[98] and at doses 100 mg/kg for 28 days it leads to the up-regulation of LDL expression in the heart, kidney, abdominal muscle, quadriceps femor is and subcutaneous and visceral adipose tissues in high-fat-diet-induced dyslipidaemia; improves serum lipid parameters, inclusive diminishing in serum free fatty acid, total cholesterol, TG and LDL levels, whereas HDL levels were exalted and suppress lipid deposit in both abdominal muscle

and quadriceps femor is [99, 100, 101]. Glycyrrhetinic acid at doses 100 mg/kg for 45 days diminishes the elevated plasma glucose and glycosylated haemoglobin (HbA1c) and decreases plasma insulin and haemoglobin. Improves the action of hepatic gluconeogenic enzymes such as glucose 6-phosphatase, fructose 1,6-biphosphatase, and abates the action of glucokinase and glucose 6-phosphatase dehydrogenase and at doses 100 mg/kg for one week decreases the postprandial plasma glucose levelin STZ-induced diabetic rats [102, 103] but at doses 5 µg for 30 mins prolongs insulin secretion and cell viability in high glucose (20 mm) stimulated cells. Raises mRNA level of insulin receptor substrate-2, pancreas duodenum homeobox-1 and glucokinase in islet cells isolated from male C57BL6J mice [104]. Betulinic acid at 50 mg/kg for 15 weeks decreases body weight, blood glucose, abdominal fat procurement, plasma TG and total cholesterol level as compared with non-treatment group, it also increases the plasma insulin and leptin levels, and decreases the ghrelin level in high-fat-diet-induced dyslipidaemia [105]; at 20 mg/kg for 2 weeks it rises the ROS (Reactive oxygen species) level and decreases the SOD (Superoxide dismutases), NO (Nitric oxide) level, and eNOS (Endothelial nitric oxide synthase) activities in rat aortic rings in L-NAME-induced hypertensive rats [106]; and at 1 µg for 24 hrs it suppress the proliferation of human aortic smooth muscle cell induced by high glucose, diminishes the protein and mRNA expression of MMP-2 (Matrix metalloproteinase-2) and MMP-9 levels in a dose-dependent manner, decreases the intracellular ROS levels; inhibits the nuclear translocation and phosphylation of IκB-α of NF-κB(Nuclear factor kappa B) induced by high glucose condition in Human aortic smooth muscle cell[107]. Oleanolic acid (OA) at 100 and 200 mg/kg for 40 days diminishes blood glucose levels, enhances oral glucose tolerance tests, diminishes total cholesterol, TG, LDL (Low density lipoprotein) levels, enhances HDL and improves serum insulin levels; at 80 mg/kg for 5 weeks it restores glycogen level to near normal by prolonging the action of glucokinase and hexokinase in hepatic tissues and muscle; at 100 mg/kg for 1 week it protects hepatic cell death by maintaining the mitochondrial membrane potential and the phosphylation of ERK (Extracellular-signal-regulated kinases) pathway; andat 60 mg/kg for 5 weeks it enhances the creatinine clearance with concomitant reduction of plasma creatinine concentration, renal mean arterial blood pressure in STZ-induced diabetic rats [108, 109, 110, 111, 112]. OA at 10 mg/kg daily for 15 weeks elevates the glucose tolerance and decreases visceral adiposity, body weights, plasma level, increases plasma leptin levels, and decreases the plasma ghrelin level, which modulates carbohydrate and fat metabolism in high-fat-diet-induced dyslipidaemia [113]; at 20 mg/kg for 90 mins it enhances insulin levels in Wistar rats [114]; at 100 mg/kg for 40 days it retrieves the ALT (Alanine amino transferase),serum levels of AST (Aspartate amino transferase), and alkaline phosphatase in alloxan-induced diabetic rats [115]; at 60mg/kg for 5days it attenuates the raised systolic blood pressure, cardiac lipid peroxidation induced by dexamethasone, decreases the nitrite level in plasma compared to the non-treatment group [116]; at 50 µg for 1 hour it enhances insulin secretion in both beta and islet cells in INS-1 832/13 and islets cells isolated from Wistar rats [117]. Ursolic acid (UA) at 500 mg/kg for 8 weeks attenuates high fat-diet induced glucose intolerance and lipid accumulation in the liver, preserves the islet structure and insulin content in the pancreatic section in high-fat-diet-fed mice [118].UA at 0.01% and 0.05% w/w for 4 weeks; and 0.2% w/w for 11 weeks exhibits improvement in blood glucose, glycosylated haemoglobin, glucose and insulin tolerance, plasma leptin and aminotransferase activity, also increases plasma and pancreatic insulin concentration; and results in a 53% reduction in atherosclerotic lesion formation, reduces monocyte recruitment into MCP-1 (Monocyte chemotactic protein-1) loaded Matrigel plugs respectively in STZ-nicotinamide induced diabetic mice [119, 120]. Apart from that UA at 0.05% w/w for 4 weeks; 50 mg/kg for 8 weeks; and 0.1% w/w for 12 weeks exhibited improved blood glucose levels, glucose intolerance and insulin sensitivity which results in significant elevation in insulin levels and preserving pancreatic ß-cell function, it also reduces the plasma total cholesterol, free fatty acid, and TG concentration, and normalises hepatic TG concentrations; Reduces blood glucose and glycated haemoglobin levels. Significantly reduces aortic arch injury and the accumulation of advanced glycated end products in the aorta; and ameliorates the accumulation of type IV collagen in the kidneys and glomerular hypertrophy respectively in STZ-induced diabetic rats [121, 122, 123, 124]. UA also acts as insulin-

mimetic agent at 50 µg/ml and insulin-sensitizer at 1 µg/ml which increases the activity of insulin on tyrosine phosphorylation of insulin receptor B-sub unit in Chinese-hamster ovary cells expressing human insulin receptor; and at 1 µg/ml for 20 min it results in an increase in the number of insulin receptors activated by insulin, and enhanced the effect of insulin on the translocation of GLUT 4 in 3T3-L1 adipocyte [125]. Betulin at 3 µg/ml for 6 hr inhibits the maturation of sterol regulatory element-binding proteins (SREBP) and decreases the biosynthesis of cholesterol and fatty acid in rat hepatocytes CRL-1601; at 30 mg/kg/day for 6 weeks, decreases serum and tissue lipid contents in ameliorates diet-induced obesity, improves glucose tolerance and increases insulin sensitivity, minimises the size and improves the stability of atherosclerotic plaques in western-type diet-fed mice with LDL receptor knockout, high-fat diet-fed mice [126]. Lupeol at doses 20, 30 and 40 mg/kg/day reduces serum glucose, nitric oxide and glycated haemoglobin levels [127].

Antioxidant Activity

A bioassay-guided fractionation of the bark of *Betula platyphylla* var. japonica (Betulaceae) resulted in the isolation of a new lupine type triterpene, 27-hydroxybetunolic acid and 18 know triterpenoids, which showed significant antioxidant activities with IC_{50} values in the range 4.48-43.02 µmol/lit in a DPPH radical-scavenging assay [128]. 2-Oxopomolic acid from *Sanguisor batenuifolia* exhibits antioxidant activity [129]. Betulin at 35 mg/kg/day for 21 days reveals an antiperoxidative effect, resulting in the protection against peroxidative damage to the red-cell membrane through antioxidant activity in male albino rats of wistar strain [130].

Antiviral Activity

Ursolic acid can perform as an inhibitor of HIV-1 protease, with IC_{50} near 1 µmol/lit to inhibit HIV [131]. OA along with its derivatives were likewise fit to inhibit HIV-1 protease, with an IC_{50}value of 4-20 µg/ml [132]. Likewise, ex-vivo investigations demonstrated that PBMC (peripheral blood mononuclear cells) of HIV-contaminated patients incubated with various doses of OA, displayed noteworthy decrease of viral replication, which was similar to the drug, azidothymidine (AZT) with EC_{50} of 22.7 µmol/lit and 24.6 µmol/lit, respectively [133]. Another investigation express that OA obtained from *Ligustri lucidi*is by all accounts powerful at extruding intracellular HCV (Hepatitis C virus) with an IC_{50}value 5.5 µg/ml and a high selectivity index (SI) 30.8 and the UA having similar impact on HCV withIC_{50} of 33.8 µg/ml and SI of 6.7[134].

Antiprotozoal Activity

A study demonstrates that a pentacyclic triterpenoid UA, revealed antimalarial activity with IC_{50}value 28 µg/ml and 36.5 µg/ml against *Plasmodium falciparum* chloroquine-sensitive and chloroquine-resistant strains, respectively; whereas, in OA IC_{50}value for chloroquine-resistant and chloroquine-sensitive strains were noted88.8 µg/ml and 70.6 µg/ml, respectively. In another study the potency of UA, obtained from *Mitragyna inermis*, against *Plasmodium falciparum* chloroquine-sensitive and chloroquine-resistant strains, found to be IC_{50} 15 µg/ml and 18 µg/ml[135].One study suggests that UA obtained from roots of *Salvia cilicica* was essentially dynamic against intracellular amastigote forms of *L. major* and *L. donovani*, with IC_{50}7.0nmol/lit and 12.7 nmol/lit, respectively in comparison to the standard drug Pentostam, whose IC_{50} was found to be 10.6 nmol/lit and 9.8 nmol/lit, respectively. *L. (L.) amazonensis* promastigotes were found to be highly sensorial to UA and OA, projecting an IC_{50}value5 µg/ml and 10 µg/ml, respectively [136]. Moreover, both UA and OA were dynamic against the intracellular form of *L. (L.) amazonensis*, exhibiting an IC_{50}value11 µg/ml and 27 µg/ml, respectively [137].

Cardioprotective Activity

Madecassoside present in *Centella asiatica* herb exhibits cardioprotective effect through suppression of inflammatory mediators in cardiomyocytes and protection against myocardial ischemia-reperfusion injury in vivo [138, 139]. The impact of UA has been reported that it is capable of lowering the heart rate by 32% in genetically hypertensive rats after administration [140].

Hepatoprotective Activity

Betulin at 1 µm for 24 h exhibits hepatoprotective activity through decreasing the production of superoxide anion against ethanol-induced cytotoxicity in human hepatoma cell line HepG2 [141]; and at same dose it also performing the same activity against ethanol toxicity in Rat liver stellate cell line CFSC-2G [142]. The protective effect of ursolic acid was found to be concentration dependent, almost 71%–74% protection was reported at a concentration of 100 mg/ml [143].

Anti-Bacterial Activity

The capability of UA against *S. sobrinus* and *S. mutans* was strengthened with a MIC (minimum inhibitory concentration) of 2.0 µg/ml, showing that these components can restrict caries in teeth [144]. OA isolated from *Lantana hispida* was observed to be viable at showing a MIC value of 25 µg/ml against *Mycobacterium tuberculosis*[145]; moreover, a MIC of 50 µg/ml was accounted for when OA was utilized against *M. tuberculosis* isoniazid, streptomycin, ethambutol and rifampin resistant strains and similarly as OA, UA isolated from leaves of *Chamaedorea tepejilote* was found to be effective to inhibit *M. tuberculosis* at 100 µg/ml [146]. The decent variety of the antibacterial characteristics of UA and OA has additionally been outlined contrary to other human bacterial pathogens, for example, *Staphylococcus aureus* methicillin-resistant and methicillin-sensitive (MIC of 64 µg/ml and 8 µg/ml, respectively), *Bacillus subtilis* (MIC of 8 µg/ml), *B. cereus* and *Enterococcus faecalis* (MIC of 6.25–8.00 µg/ml), *S. pneumonia* (MIC of 16 µg/ml) [147], *E. faecium* (MIC of 8 µg/ml), and *Pseudomonas aeruginosa* (MIC of 256 µg/ml)[148, 149, 150].

Analgesic Activity

A pentacyclic triterpene compound identified as taraxerol obtained from the petroleum ether (40°-60°C) extract of the fruits of *Dregea volubilis* has shown analgesic activity at 5 mg/kg body weight with inhibition 45.42%, taking aspirin (inhibition 66.57%) as standard in Swiss albino mice[151].

Other Pharmacological Activities

Lupeol and lupenone from *Pueraria lobate* reduces inducible nitric oxide synthase (iNOS), nitric oxide (NO) production and COX-2 protein levels in lipopolysaccharide(LPS)stimulated RAW 264.7 cells, and inhibits intracellular reactive oxygen species (ROS) generation by tert-butylhydroperoxide [152]. Lupeol from *Aegle marmelos* plant exhibits anti-dyslipidaemic activity [153]. Betulin at doses 1 and 10 µg for 24 h inhibits the production of TNF-α, and TGF-β1 and ROS, which results in the downregulation of the production of TIMP-TIMP-2 and MMP-2; it also inhibits the activation of the p38 MAPK and the JNK transduction pathways; and the phosphorylation of IκB and Smad 3 and attenuates the activation of TGF-β1 and NFκB/IκB transduction signalling as well in rat liver stellate cell line CFSC-2G [142].

Some Semisynthetic Pentacyclic Triterpenoids

Semisynthetic lupane triterpenoids, betulinin and betulinic acid derivatives, as well as pentacyclic terpenoids isolated from *Momordica balsamica* and *Diospyros rubra* Lec. (Ebenaceae), and tirucallane triterpenoids of *Schinus terebinthifolius* Raddi. (Anacardiaceae) have shown potent activity against Leishmania [154, 155, 156]. 2-cyano-3,12-dioxoolean-1,9-dien-28-oic acid, semisynthetic derivative of OA; CBA-Me, and five new synthetic derivatives of BA were synthesized (structures are replicated in Fig. 3), where they exhibit pharmacological activities like the new analogues of BA and OA suppress the manufacturing of nitric oxide and conduce the phase 2 cytoprotective enzyme NQO1. The chemical names of the above said new analogues are BA (3-Hydroxylupa-1,20(29)-dien-28-oic acid), TP-290 (CBA-Me) (Methyl 2-cyano-3-oxolupa-1,20(29)-dien-28-oate), TP-291 (CBA) (2-Cyano-3-oxolupa-1,20(29)-dien-28-oic acid), TP-292 (CBA-Im) (1-(2-Cyano-3-oxolupa-1,20(29)-dien-28-oyl)imidazole), TP-295 (Methyl 2-methoxycarbonyl-3-oxolupa-1,20(29)-dien-28-oate), TP-296 (Methyl 30-hydroxy-2-methoxycarbonyl-3-oxolupa-1,20(29)-dien-28-oate), TP-297 (Methyl 2-carboxy-3-oxolupa-1,20(29)-dien-28-oate), CDDO (2-Cyano-3,12-dioxoolean-1,9-dien-28-oic acid), whose IC_{50} for Nitric oxide inhibition were found to be >10.0, 0.0014, 0.0006, 0.001, >10.0, >10.0, 10, 0.0014 µmol/lit, respectively. Newly synthesized derivatives of BA containing an additional cyano-enonepharmacore (CBA-Im,CBA and CBA-Me) are potential inhibitors of nitric oxide production in primary mouse macrophages reinforced with IFN-g (with IC_{50} 1 nmol/lit).CBA-Im,CBA, and CBA-Me additionally suppress the induction of iNOS protein in a dose-dependent manner in RAW264.7 cells invigorated with IFN-g, invigorated TP- 295-297 are just dynamic at higher concentrations [157].

Pentacyclic Triterpenoids As A Drug – Clinical Trials

Ursolic acid in the preliminary stage (phase I) is to assess its safety and adverse effects in cancer patients. As the water solubility are poor and bioavailability of ursolic acid is also low, it administered as a liposome. So, there is no published report of the results of these studies [158, 159, 160]—they all were held in The People's Republic of China. Ursolic acid liposomes showed acceptable toxicity and adverse effects—only one in 108 patients reported adverse

third stage activity. Skin problems, diarrhea and Nausea were the most common complaints. The common discussion on the result of all the studies was the major partto continue research during phase II trials.

Structure-Activity Relationships (Sar) Of Different Type Pentacyclic Triterpenoids

Oleanolic acid and its glucoronides from *Aralia elata*, was advised that the 3-O-glycoside moiety is crucial for the pharmacological activity; the 28-ester glucoside moiety significantly reduces the activity, and in the 3-O-oligoglycoside structure, the 3'-O- glucopyranosyl moiety recuces the activity, while the 4'-O-arabinofuranosyl moiety increases activity [78]. In case of the three groups, oleanane, ursane and lupane, it was again advised that the diversity of the structure skeleton among the three groups did not interfere with their inhibitory activities on glycogen phosphorylase, but the number of hydroxyl groups and their positioning do. It was found that introducing a hydroxyl groupat C-2 resulted in a loss of potency; both 2α-hydroxyoleanolic acid (IC_{50} = 28 μmol/lit) and 2β-hydroxyoleanolic acid (IC_{50} = 34 μmol/lit) were less potent than oleanolic acid (IC_{50} = 14 μmol/lit). The same trend was observed in both 2α-hydroxyursolic acid (IC_{50} = 20 μmol/lit) and 2β-hydroxyursolic acid (IC_{50} = 116 μmol/lit) compared to the parent compound, ursolic acid (IC_{50} = 9 μmol/lit). Also, in madecassic acid, it was observed that a hydroxyl group at C-6 was related to complete loss of activity. This study also suggested that the presence of a sugar moiety in the triterpene compounds resulted in a markedly decreased orloss in the activity comparing to their aglycones. Glycyrrhizic acid(IC_{50} = 822 μmol/lit) was 12-fold less potent than glycyrrhetinic acid(IC_{50} = 66 μmol/lit). Also, β-D-pyranoglucosyl 3β-hydroxyolean-12-en-28-oic acid (IC_{50} = 293 μmol/lit) was 20-fold less potent than its aglycone; oleanolic acid. The decrease in the activity was also observed in β-D-pyranoglucosyl3β-hydroxyurs-12-en-28-oic acid and β-Dpyranoglucosyl2α,3β-dihydroxyurs-12-en-28-oic acid. Structures are shown in Fig. 4 [161].

The structures of oleanane pentacyclic triterpenes (GiA-1, GiA-2, GiA-5 and GiA-7) from *G. inodorum* leaves (Fig. 5) are derivatives of (3β, 4α, 16β)-16, 23, 28-dihydroxyolean-12-en-3-yl-β-D-glucopyranosiduroic acid. GiA-1 has a -H at the C-21 position and -CH_3 at 4β position of the aglycone. GiA-2, GiA-5 and GiA-7 commonly have a -H at the C-21 position and -CH_2OH at 4β position of the aglycone. It was shown that -CH2OH at the 4β position of the aglycone is necessary for the inhibition of glucose absorption from the intestinal tract [162]. Oleanolic acid derivatives were synthesised and evaluated asPTP1B inhibitors (which is a negative regulator in the process of insulin signalling and a promising drug target for the treatment of diabetes and obesity) and several exhibited moderate to good activity against PTP1B, with compound 3-oxo-28-(phthaloyl-4′)-erythrane displaying the most promising inhibition (IC_{50} = 3.12 μmol/lit). A SAR analysis of these derivatives explained that the integrity of the Aring and 12-ene moieties was important in the retention of PTP1Benzyme inhibitory activity [163]. Ursane-type triterpenoids from Diospyros kaki with a 3α-hydroxy group were found to inhibitPTP1B activity, with IC_{50} values ranging from 3.1 ± 0.2 to 18.8 ±1.3 μmol/lit, whereas those with a 3α-hydroxy moiety were inactive [164].

The 3-O-glucuronidemoiety and the 28-carboxyl group in oleanolic acid glycosides are essential for hypoglycaemic activity; 3β-hydroxy group on theoleanolic acid and ursane structure inhibits PTP1B activity; CH_2OH at the 4β position of the oleanane aglycone decrease the absorption of glucose from GIT; C-3 position of betulinic acid enhances in TGR5 agonist activity; therefore C-3 substitution on pentacyclic triterpenoids increase their antidiabetic bioactivity.

Guideline For Research In Future:

Reflecting on the anti-proliferative impacts of pentacyclic triterpenoids for instance, ursolic acid inmalignant cells, the different molecular pathways influenced, and the production of those constituents in cranberries and many different fruits, there is a distinct requirement for future investigations onthose constituents as potent foods and drugs. Culturing on their bioavailability and the character of elements worked *in-vivo may* be very much required in evaluating the function of triterpenoids which may play in curing inflammatory diseases and cancers. The oral bioavailability of those components may not be familiar and need to be evaluated. Synergistic effects with constituents of many berries such as carotenoids and flavonoids must be noted, simultaneously with the result of progress of isolation of triterpenoids from many other fruits.

Conclusions

The constituents named, Pentacyclic triterpenes, with exceptional properties, which constitute under the most important groups of secondary metabolites due to their multiple

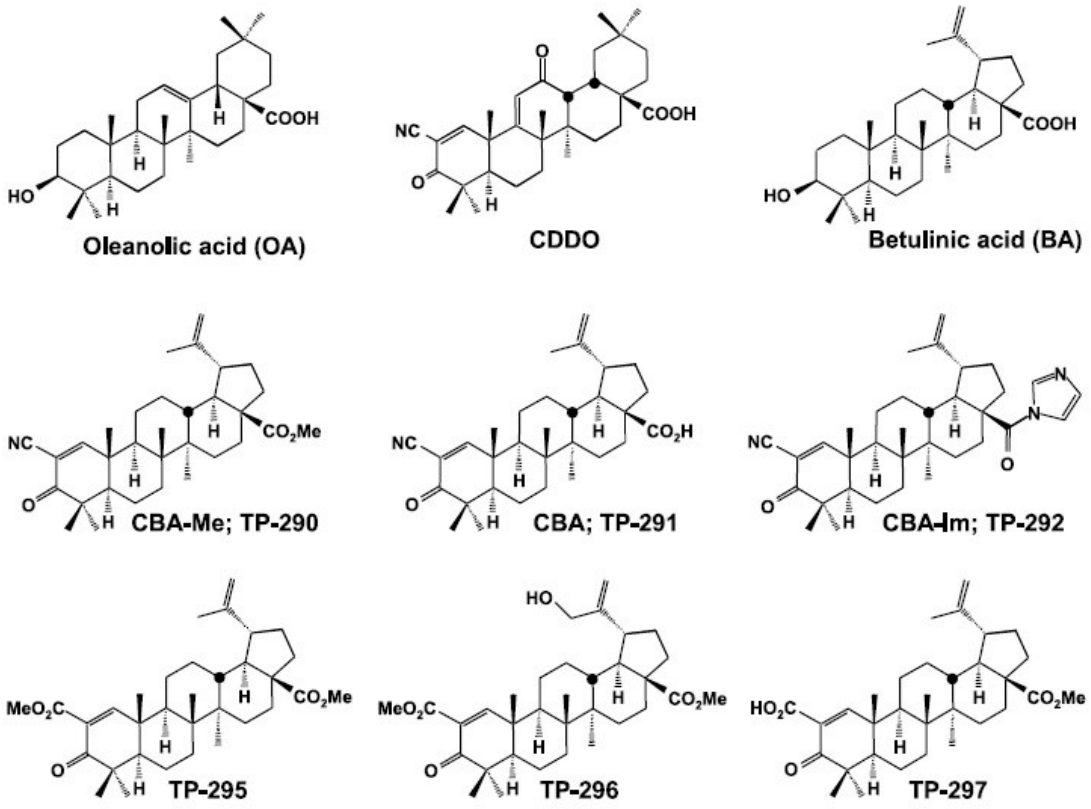


Fig. 3. Structures of OA, its synthetic derivative CDDO; BA, CBA-Me, and five new synthetic derivatives of BA.

biological activities and many established features. The common diets and foodstuffs contain many of them which can be used in the protocol of treatment of many deadly diseases. It is a generalized component of plant origin showing a wide range of pharmacological activities. From several *in vitro* and *in vivo* studies, it has been affirmed that many pentacyclic triterpenoids contain inedible and medicinal plants possesses biological activities such as antibacterial, antiviral, antioxidant, antidiabetic, anticancer, cardioprotective and neuroprotective properties which are result of the different signalling pathways interrupted by triterpenoids. Total syntheses of triterpenoids still represent a challenge due to complex structures, for this reason the semisynthetic chemistry is commonly used. In this way triterpenoids represent an interesting source of new compounds for the treatment of human diseases. The greatest attention amongst is engaged in its role in the treatment and prevention of diabetes, cancer, inflammation and so on. Except these, other interesting properties are anti-bacterial and protective impact over physiological conditions against chemical-damages have been reported.

This review introduces updated reports on the basis of literature of pentacyclic triterpenoids and a portion of its semi-synthetic analogs as potent natural products. Considering the immeasurable pharmacological actions explained of those compounds and its pervasive nature, there is cleaned for future investigation on the bioavailability of these components and appraise in diverse plant parts and fruits. Further research work is also essential on the improvement of many derivatives of synthetic products with less harmful effects and more pharmacological potential. Another fresh area is the mechanism of action of the therapeutic actions of these components; as well as its effectiveness as functional food factor.

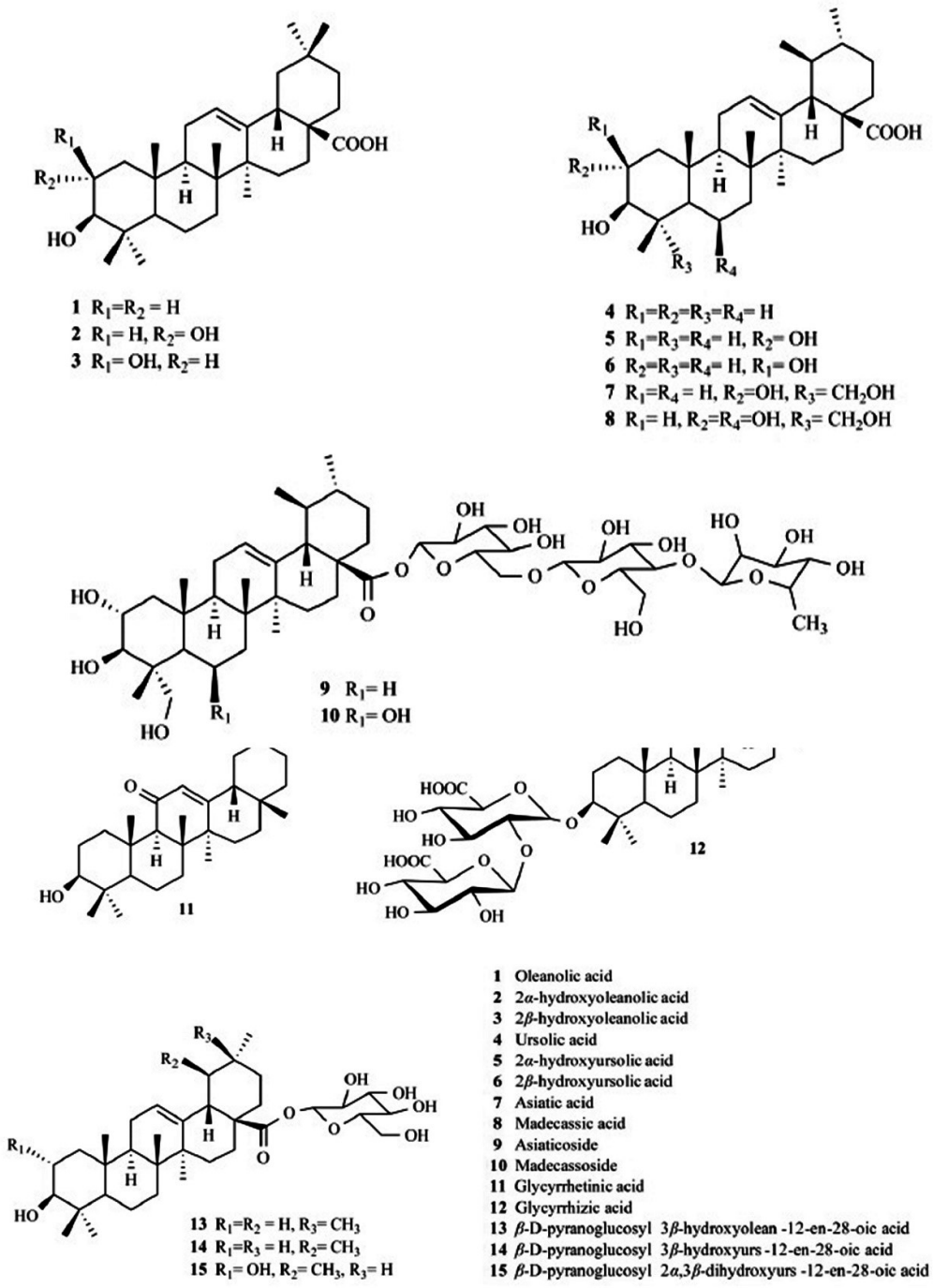
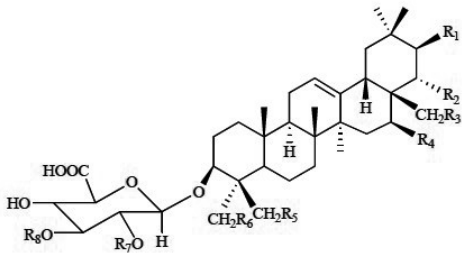


Fig. 4. Pentacyclic triterpenoids with variation on the inhibition of glycogen phosphorylase



Triterpene compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7	R_8
GiA-1	H	H	OH	OH	H	H	β-Glu	H
GiA-2	H	H	OH	OH	OH	H	H	H
GiA-5	H	O – NMAt	OH	OH	OH	H	H	β-Glu
GiA-7	H	O – NMAt	OH	OH	OH	H	H	H

β-Glu: β-glucopyranosyl; NMAt: *N*-methylanthraniloxy.

Fig. 5. Pentacyclic triterpenoids from Gymnema inodorum

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