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Natural Triterpenes -Role in Cancer Treatment

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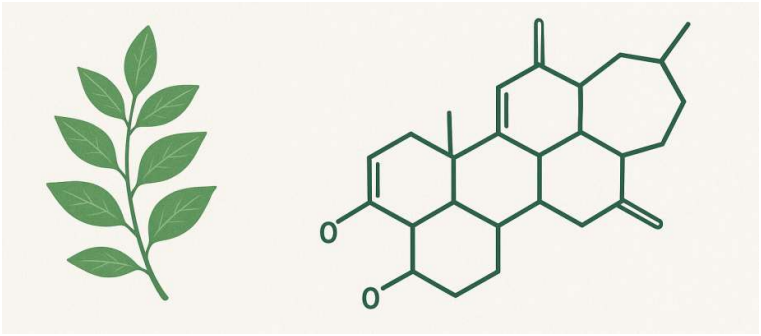

Abstract: The review highlights the biosynthesis and medicinal properties of several important triterpenes, which demonstrate their exceptional ability to modulate intracellular signaling pathways and control cancer. Terpenes are naturally synthesized bioactive molecules of herbal or marine origins. In nature, they are biosynthesized via the conjugation of isoprene units following head-to-tail arrangements, although exceptions are abundant. Substantial interest has been drawn recently due to their potent anticancer properties. Besides acting as anticancer agents, theycanalso control other diseases. About 20,000 triterpenes are hitherto known, which are built on ~ 100 scaffolds in nature. The majority undergo synthesis using the common intermediate, 3-oxidosqualene, by way of enzymatic catalysis. Within the plant kingdom, they are normally synthesized inside the higher plants, even of diverse families. In the marine world, they are primarily classified as sea cucumbers or similar species. As anticancer agents, triterpenes and their glycosides can inhibit tumor growth by exerting cytotoxicity, following apoptosis, or retarding cell division/mitosis. Uniquely, they wield anticancer actions without affecting normal cells. The major intracellular pathways frequently targeted are NF–κβ and STAT–3. It is further claimed that triterpenes can also prevent the intracellular switching mechanism during transformation from normal to tumor cells by deactivating proto-oncogenes or activating the tumor suppressor genes like p53 or others if administered previously. Numerous anticancer drugs have recently been synthesized by modifying different triterpene structures to enhance their medicinal efficacy.

Keywords: Triterpene, Marine triterpene, isoprene, Glycosides, Squalene, Cancers, Cytotoxicity, Intracellular signaling, NF–κβ, STAT-3, p53, Apoptosis, Anticancer effect, Bioavailability.

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Introduction:

Triterpenes are adverse group of organic compounds synthesized in plants, especially within the conifers. Itis also produced in a few insects and animals. The isolation of triterpenoids from marine sources has brought more recent attention owing to their prominent medicinal applicability. Among them, marine algae, marine fungi, sea cucumbers, and marine sponges rereported be rich sources exhibiting strong cytotoxicity toward many tumor or cancer cells [1,2]. A significant number of them are pentacyclic by nature, which are seen as more active in controlling or preventing malignancies. Factually, terpenes are the primary constituents of essential/fragrant oils of plants and flowers. About 30,000of them belong to different families, which play a significant role in plant metabolism by working as hormones, taking part in the growth, or helping synthesize important pigments like chlorophyll [3]. They provide defenses against predators and pathogens or act as allelopathic agents for survival[4].Recently, some of them have been seen as useful for medicinal needs to treat cancers, diabetes, inflammatory or cardiac diseases, or neurological disorders [5,6].Conceptually, an anti-cancer agent is supposed to inhibit or counter the progression or delay the advancement, imposing cytotoxicity/apoptosis to regulate the disease or exert retarding effect on the rapid growth/cell division/mitosis of the belligerent cancer cells. Reports show that triterpenoids, particularly the pentacyclic ones, exert extra cytotoxicity by interfering with specific signaling pathways deterring angiogenesis and associated undesired issues [7]. Controlling malignancies by using triterpenes and simultaneously keeping normal cells unharmed is the foremost approach to today's cancer research. Studies have shown that in that act, triterpenes Layan impressive role. Besides acting as anti-neoplastic agents, they also suppress inflammatory responses by down-regulating the cell cycle proteins like cyclin D1, CDK4, and cyclin B1, consequently arresting the cell cycle at G0/G1-2M phase. The action arises via the modulation of NF-κβ, AP-1, or STAT3 signaling pathways to control inflammation and associated metabolic problems, even cancers. The further benefits displayed are regulation of HIV infection, hepato-protection, antioxidant behavior, antibacterial, anxiolytic, analgesic, and anti-nociceptive activities [8 – 10].

Evidence points out that chronic inflammation is the prime source of cancer [9]. Inflammation is expressed in two stages, acute and chronic. The acute one starts at the initial stage, representing innate immunity mediated via the activation of the immune system that lasts for a short while. If it persists longer, in that situation, the chronic inflammatory condition builds up. It is this chronic status that becomes the underlying cause of too many persistent illnesses, cardiovascular, diabetes, pulmonary diseases, obesity, neurological problems, and cancers. The proponent of this inimitable idea was Prof. Rudolf Virchow, an eminent nineteenth-century Prussian scholar of medicine, often designated as the father of modern pathology [11]. He hypothesized Hata chronic inflammatory condition is the predisposing factor behind any cancers. This ingenious idea has been recognized afterwards, since one out of seven malignant cancers presumably originates from chronic inflammatory conditions. Based on this hypothesis, numerous molecular targets are aimed at tracing the crucial pathways of inflammation. Targeting intracellular pathways often bring succession keeping the cancer under control or preventing it. Besides inflammation, triterpenes have a significant role in cellular transformation, cell survival, proliferation, invasion, angiogenesis, as well as metastasis. A substantial number of them from the plant or marine sources can potently inhibit NF–κβ and STAT–3 activation pathways, signifying a great

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potential for cancer treatment [8-10]. It is noted that a substantial length of time (10 – 20 years) is required for a normal cello transform into a tumor/cancer. Initially, a normal one transforms the activation of proto-oncogenes along with the suppression of tumor suppressor genes like p53.In that course, the trans formed cell no longer behaves normally. On the contrary, it starts showing unusual behavior, different from the original. This undesired intracellular transformation makes the cell self-sufficient to grow, making it resistant to the anti-growth signals, leading to its uncontrolled proliferation. As a result, the transformed cells avoid apoptosis and undergo unres trained growth, becoming tumors [12 –13]. In that act, the event of angiogenesis further energizes the situation by supplying nutrition, enabling it to invade the surrounding tissues. The episode is labeled as metastasis, an invasion of distant tissues or organs, making the situation more lethal. Cancer is an overly complex disease involving multiple genes. It could be contained within one single cell or collaborate with the neighboring ones. Its inhibition or enhancement relies on the complex network of defense mechanisms, of which approximately 300 to 500 genes misbehave. In this undesired event, either the upregulation of wrongful products like anti-apoptotic proteins occurs, or the downregulation of tumor suppressor proteins arises [14]. In this situation, triterpenes used in many traditional Asian medicines are noticed to playa beneficial role in preventing or controlling lethality. They are biosynthesized inside the plants or marine life via the cyclization of Squalene [1,15]. Uniquely, a large section (~100) of prescription drugs is achieved from natural sources, which accounts for about ¼ of the total medications of the present-day. Often, they are structurally modified to enhance the anti-cancer performance [16,17].

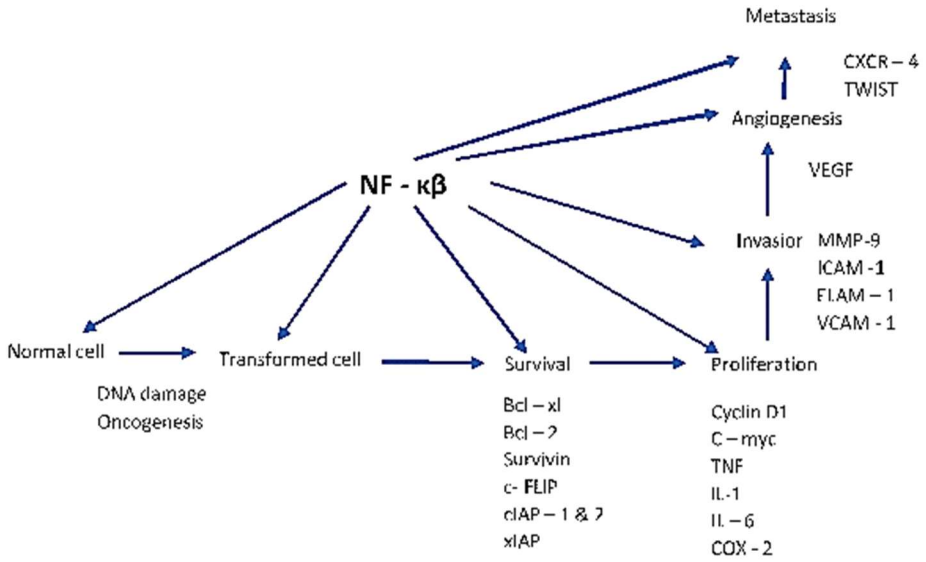

Fig 1.NF–κβ mediated inflammatory pathways imposing cell transformation and cancer cell survival, leading to metastasis.

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Terpenes:

Considering the molecular structure, if broken down thermally, each terpene molecule, irrespective of its nature, produces isoprene unit(s) since they are built through the conjugation of isoprene moiety ($CH_2 = C(CH_3) – CH = CH_2$).Around 1925, Ingold indicated that all naturally occurring terpenes are conjugated following the 'head to tail' arrangement where the head is the branched end of the isoprene unit[18].Even an important and useful guiding principle, the 'Isoprene rule', is not strictly followed in nature. The exceptions are plenty where the isoprene units are joined by tail-to-tail arrangement as seen in the case of Lavandula and Eremophila (Fig. 2a). Similarly, Carotenoids are seen to be joined via tail-to-tail at the mid part of the molecule (Fig.2 b). Although in the terpene family, unlike others, most of the Carotenoids do not follow the isoprene rule. Additionally, they have carbon atoms, which are also not multiples office. Generally, terpenoids bear the general formula of $(C_5H_8)_n$. The value of *n* decides the nature or category of the terpenoid molecule. For example, $n = 2 \rightarrow C_{10}H_{16}$ is Monoterpene; $n = 3 \rightarrow C_{15}H_{24}$ is Sesquiterpene; $n = 4 \rightarrow C_{20}H_{32}$ is Diterpene; $n = 5 \rightarrow C_{25}H_{40}$ – Sesterpene; $n = 6 \rightarrow C_{30}H_{48}$ is Triterpene; $n = 8 \rightarrow C_{40}H_{64}$ is Tetra terpenoids. Those having the number of carbon atoms more than 40 are considered Polycyclic terpenes [18].

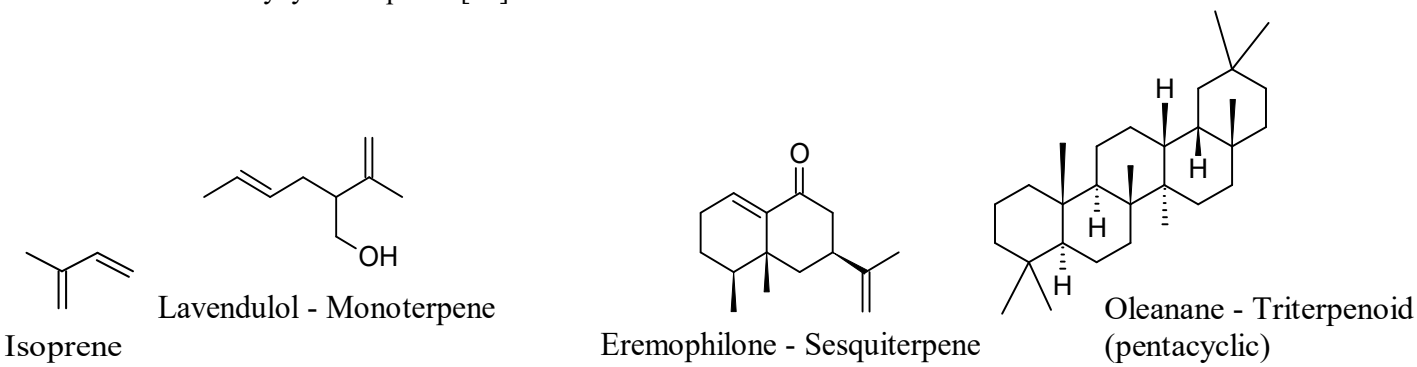

Fig 2 (a). The structural consideration of open-chain monoterpene is shown below.

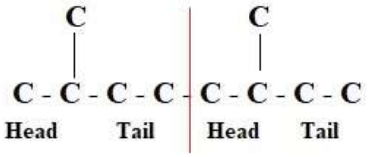

Fig. 2 (b)

Besides linear arrangements, isoprene units can also arrange themselves to make cyclic six-membered rings, as seen in Limonene, which exists in nature as two enantiomers having *(R) – and (S)* –configuration. *(R)* – form is in D (+) conformation, being the major naturally occurring component. The other monocyclic terpenoids are Menthol, Thymol, and Carvacrol (Fig. 3). In nature, bicyclic monoterpenes are synthesized by two sequential cyclization steps using Geranyl pyrophosphates, for example, Camphor, Borneol, Thujene, Pinene, Eucalyptol, Sabinene, Camphene, and many others. They can have ketone, alcohol, or other functional groups attached to them.

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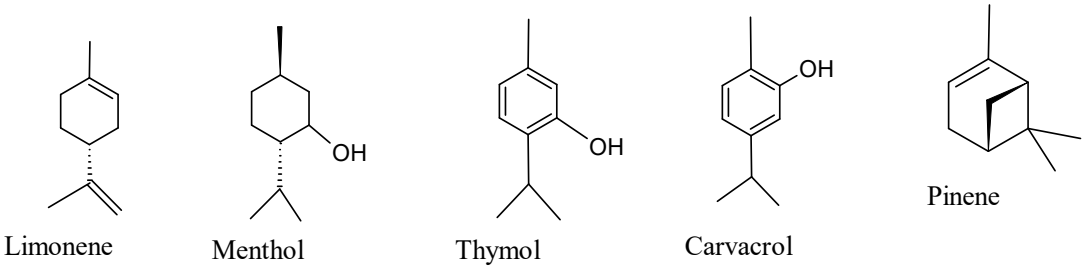

Fig - 3Triterpenes (C_{30}):

Among the affiliates of the Terpene family, triterpenes are the largest group available in nature, producing ~ 20,000 affiliates. Most of them occur in the vegetable kingdom [1]. Uniquely, some organisms can also synthesize a few. For example, Hopane has been synthesized by the bacteria [19]. About 100 different types of scaffolds of triterpenes are known in the plant world. The cyclization event leads to creating different configurations even if they are generated from the common intermediate, 2, 3-oxidosqualene (Fig. 4). The scaffolds undergo further modifications by enzymes like Cytochrome P450s, sugar transferases, acetyl-choline transferases, and others, creating more diversity, possibly due to natural needs. Most of the triterpenes are 6-6-6-5 tetracycles, 6-6-6-6-5 pentacycles, or 6-6-6-6-6 pentacycles, but acyclic, monocyclic, bicyclic, tricyclic, or hexacyclic components also originate from both plant and marine resources [20].

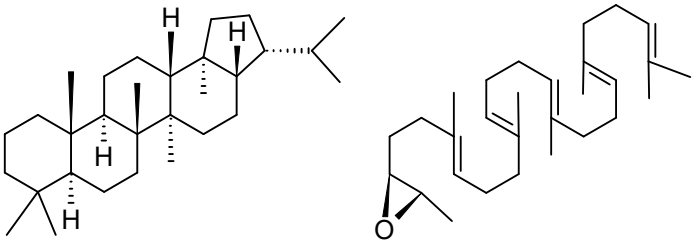

Fig 4.

The most widely available triterpenes are synthesized inside fruits, vegetables, plants, animals, fungi, bacteria, and marine organisms. Generally, higher plants are the chief source. The majority of them belong to the Rhamnaceae, Cucurbitaceae, Gentianaceae, and Apocynaceae families, merged within the shrub categories, which can also synthesize tetracyclic components. Whereas those falling into the category of Ranunculaceae, Burseraceae, Capparidaceae, Celastraceae, and Lamiaceae family (herbs and flowering plants) produce significant levels of pentacyclic triterpenes [16,21]. They act as a part of a defense system protecting the plants from insects, microbes, or herbivores. Recently, triterpenes have drawn attention because of their performance as anticancer / anti-tumor agents, particularly those with pentacyclic structure [22,23]. A collection of reports regarding the chemo preventive/anticancer role of pentacyclic triterpenes is recorded including their molecular interactions to control or regulate the oncogenes, enzymes, cytokines, chemokines, reactive oxygen species (ROS), anti-apoptotic proteins, transcription factors, inflammatory enzymes which lead to the induction of apoptosis, suppression of angiogenesis, inhibition of signal transduction for controlling cellular proliferation and modulating the

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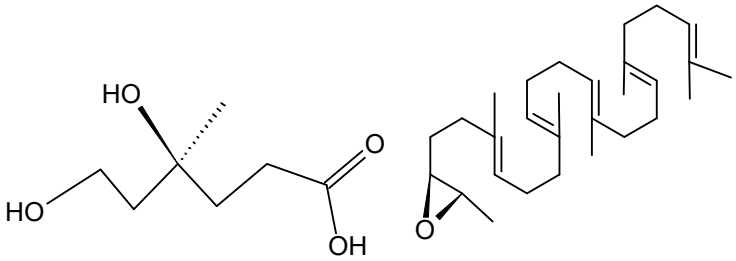
multidrug resistance (MDR) genes[16].Studies in vivo and in vitro indicate that pentacyclic ones are particularly effective against breast, prostate, colon, and several deadly cancers[16].Additional actions are also listed regarding other biological effects, bactericidal, anti-parasitic, fungicidal, anti-allergic, spermicidal, cardiovascular, anti-inflammatory, and numerous other agents. In a way, they offer substantial health benefits [16,23-25].

Sterols and triterpenes are naturally synthesized following the mevalonate pathway, producing long arrays of interactive compounds like geranyl pyrophosphate, farnesyl pyrophosphate, etc, which by enzymatic catalysis generate the most important viable intermediate, squalene, which is also a triterpene (Fig. 5). The compound undergoes catalytic cyclization by the enzymes generating 2, 3 oxidosqualene which is a common intermediate experiencing conversion to either sterols or triterpenes. The cyclization process of squalene or its 2,3-oxidized derivative, whether in plants, animals, or bacteria, follows a cascade of complex pathways leading to the ultimate generation of sterols or triterpenes [1,26].



Mevalonic acid 2,3-Oxidosqualene

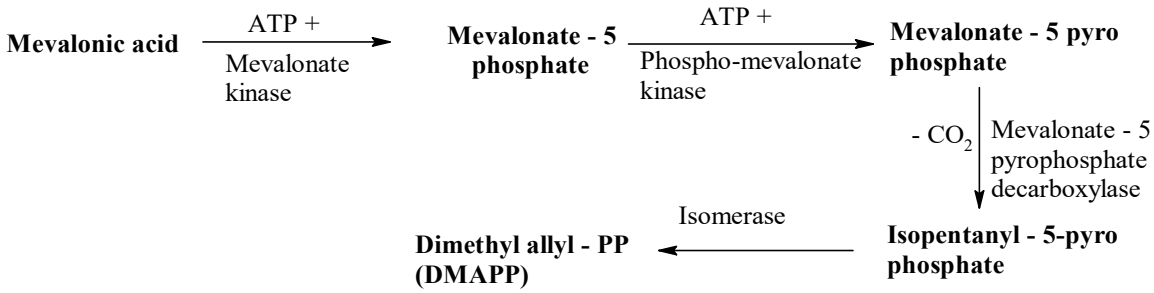


Fig 5. Mevalonate pathway

Biosynthesis:

The triterpenoids are biosynthesized from Squalene, which is itself a triterpene and acyclic by nature. Squalene was first isolated from shark liver oil. It exists in olive oil too and identified even in the plant leaves (Fig. 6). It is an important intermediate undergoing enzymatic reactions producing sterols or triterpenes [15,26,27]. Squalene has several benefits for health. It can act by itself as an anticancer agent. It is a good antioxidant that often synergizes with immune responses to vaccines [22]. In cosmetics, it provides protection to skin from UV damage also reduces wrinkles [28,29].

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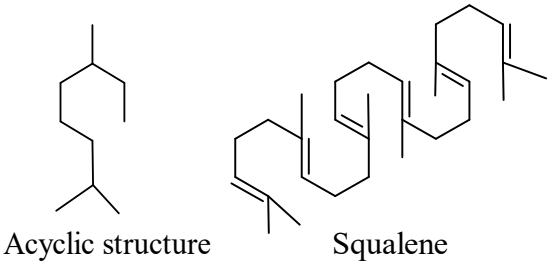

Fig 6.

The squalene, is biochemically synthesized by the condensation reaction of two molecules of Farnesyl pyrophosphate (FPP), following reduction by NADPH while eliminating the phosphate groups. Essentially, FPP acts as an active intermediate in the biosynthesis of squalene using the enzyme squalene synthase (Fig. 7).

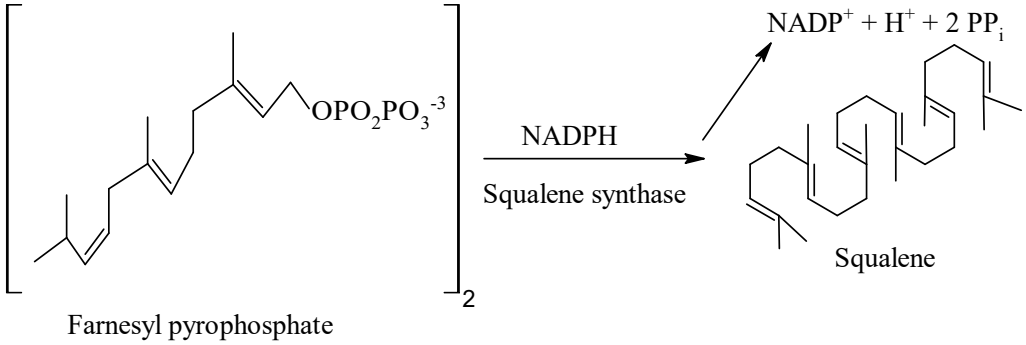

Fig 7.

FPP is initially synthesized by a similar way of condensation between Geranyl pyrophosphate (GPP) and 3-isopentenyl pyrophosphate, whereas GPP is produced via the condensation between dimethyl allyl pyrophosphate (DMPP) and 3-isopentenyl pyrophosphate as shown below. In all cases phosphate group has been eliminated. Farnesyl pyrophosphate synthase (FPS) sequentially catalyzes the reactions (Fig 8a).

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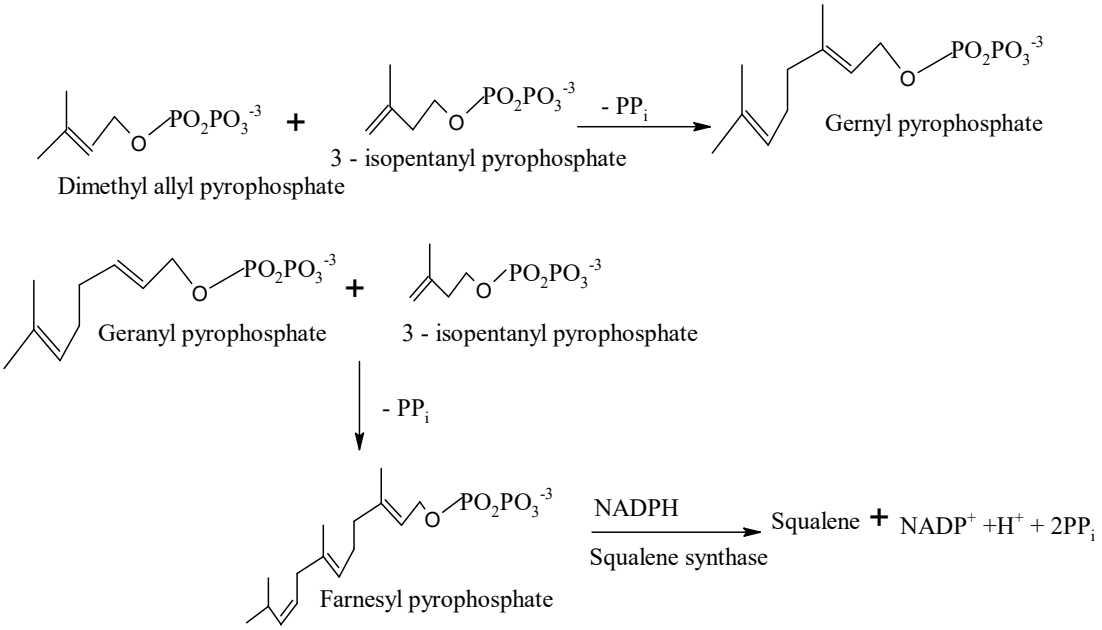

Fig 8a. Bio-synthetic pathways to produce Squalene

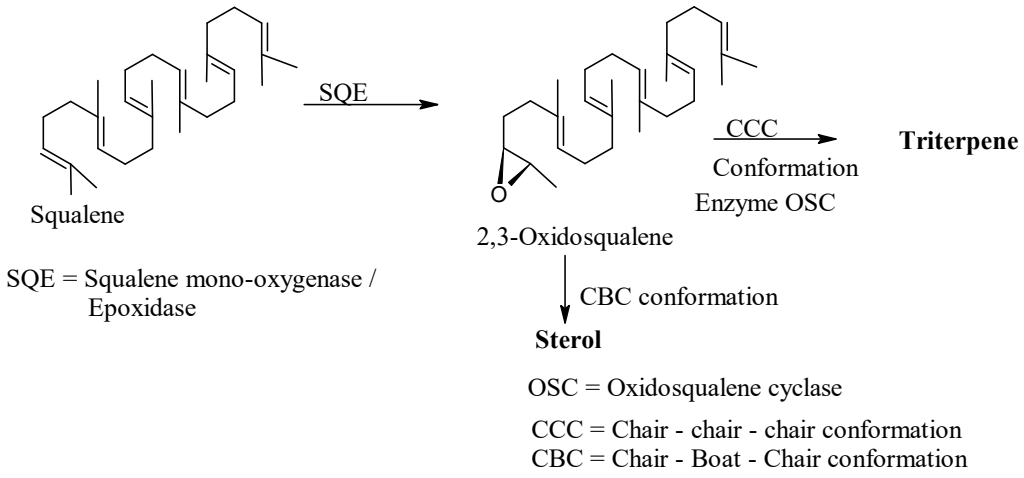

Fig 8.b. Squalene to Triterpene and Sterol Conversion

The cyclization of 2, 3 oxidosqualene is catalyzed by the enzymes Oxidosqualene cyclases that create sterol and triterpene scaffolds following chair – chair – chair (C – C – C) andchair – boat – chair (C-B-C) arrangements. The diversity of the triterpene scaffold arises via the cyclization of C–C–C conformational alteration, whereas the C-B-C conformational changes produce diversity within the sterol moiety. The cyclization following C–C–C conformational changes is initiated by the generation ofthe C–20 Dammarenyl cation (Fig. 9). Its further rearrangement creates a series of carbo-cationic intermediates (C-13 → C-14 → C-8 → C–9 → C–5 → C–4) producing various skeletal intermediates along the pathway [20].

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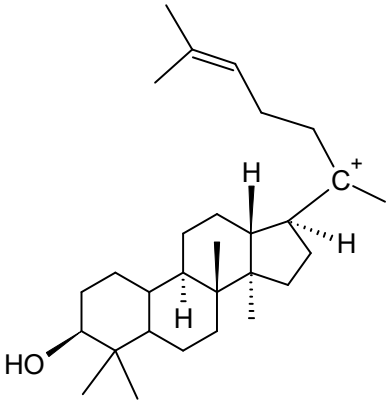

Dammerenyl cation

Fig 9.

The pentacyclic triterpenoids with Baccharane skeleton are also the result of the cyclization of 2, 3-epoxy squalene, forming six-membered rings. Further rearrangements produce numerous intermediate cations of tetracyclic triterpenes, which finally under goclosure, creating a fifth ring to form the 3β-hydroxylupanium ion. In that way, the Baccharane structure produces a group of pentacyclic triterpenes. The connection of C-18 and C–21of Baccharane creates five five-membered rings– E producing Lupane, a pentacyclic triterpene. Whereas a shift of C- 21 from C – 19 to C – 20 produces a six-membered ring making Oleanane, a pentacyclic triterpene that undergoes methyl shift making varieties of other pentacyclic triterpenes with the formation of six-membered cyclohexane ring, E as seen in 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), Pachysanane (C-28 from C-17 to C-16). Ursane and Taraxerane are formed from Oleanane when the Methyl group C-29 is shifted from C-20 to C-19. An equivalent Methyl shift rearranges Multiflorane to Bauerane [20] (Fig.10).

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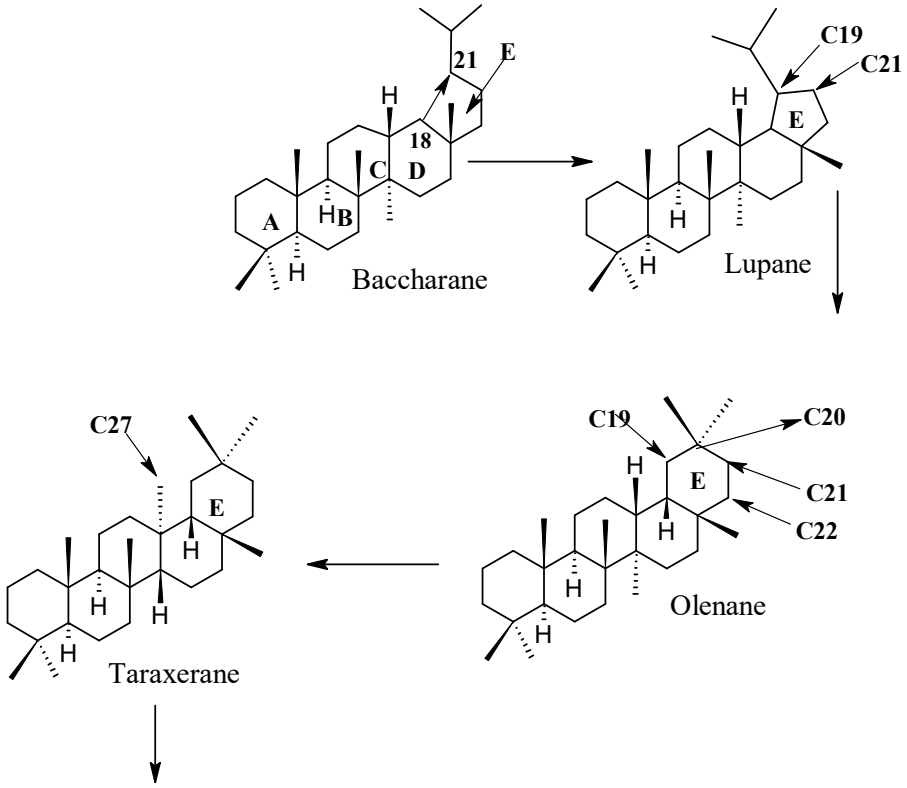

Fig 10. Arrow showing the cyclization process of Baccharane leading to variouspentacyclic triterpenes

The pentacyclic terpenes of Hopane moiety are also generated by the cyclization of 2,7-,6,11-, 10,15-, 14,19- and 18,22- carbon atoms of carbonium ion which are produced due to region selective protonation of 2,3- double bond of squalene creating various pentacyclic triterpene analogs like, Neohopane, Fernane, Gammacerane, Filicane and Adianane[2] (Fig – 11).

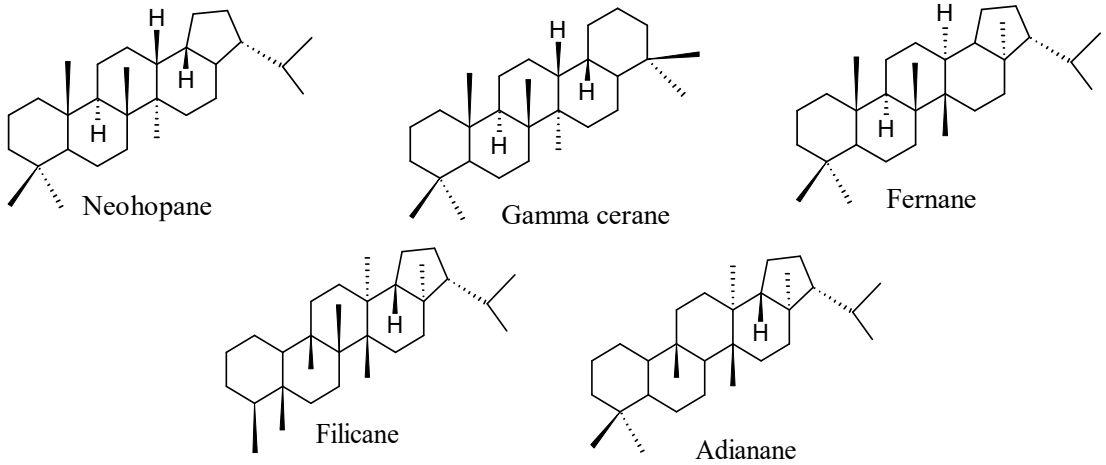

Fig 11.

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Triterpenes from marine sources: The other major sources of triterpenes are from marine resources like marine sponges, sea cucumbers, marine algae, and marine fungi, which are now considered to be a goldmine of cancer research and treatment. Malabaricol is the triterpene component of yellow pigment in the plant *Ailanthus malabarica* (Simaroubaceae family) from which the entire group of compounds is named. Malabaricane is the name given to the hydrocarbon system (*3S*, 3aR*, 5aS*, 9aS*, 9bS**)-3a, 6, 6, 6, 9a-tetramethyl-decyl) perhydro-obenzyl[e]indene having the tricyclic ring*trans-ant-trans* ring junction. In that way, Malabaricanes are characterized as tricyclic triterpenoid cores with conjugated polyene side chains. On the other hand,the Isomalabaricane skeleton is embedded in 4, 4, 8, 10-tetramethyl-perhydrobenz[e]indene, having *trans-syn-trans* ring junction,which leads to offering a twist to form an unfavorable twist-boat conformation of the central ring. Isomalabaricane triterpenes are first isolated from the Fijian sponge *Jaspersstellifera* and the Somalian marine sponge *Stellata* sp. Since then, many of them are isolated and identified from several genera of marine sponges. Isomalabaricane triterpenoids have polyene-conjugated functionality [2,26,29].

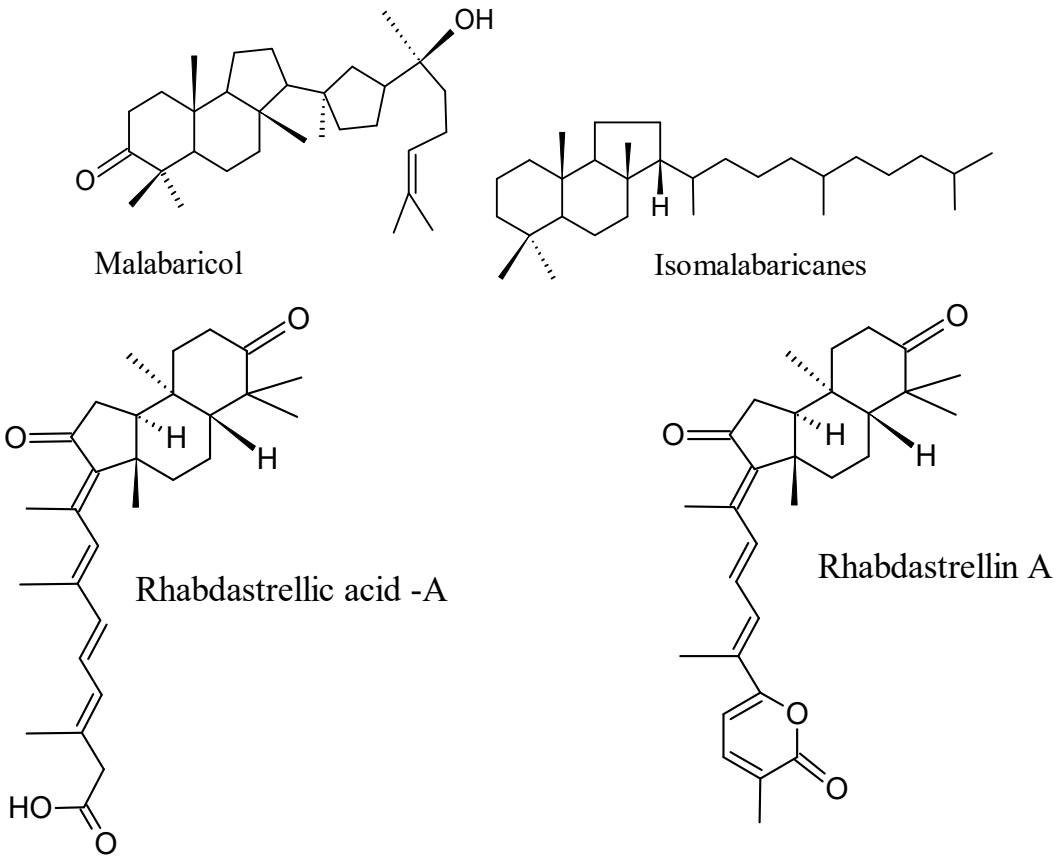

Fig 12.

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Table 1. Effect of Stelletins on cancer cell lines

Compounds	Cancer cell lines	IC_{50}
Stelletin A	Murine leukemia cell (P388)	2.1 nM
Stelletin A	Human leukemia cell (HL-60)	0.9 µM
Stelletin A	Human prostate cancer cell(LNCaP)	260 µM
Stelletin B	Human colon tumor (HCT-116)	0.043 µM
Stelletin E	Human colon tumor (HCT-116)	0.039 µM
Stelletin L	Human stomach cancer (AGS)	3.9 µM
Stelletin M	Human stomach cancer (AGS)	2.1 µM
Rhabdastrellic Acid – A	Human leukemia cell (HL-60)	1.5 µM
Rhabdastrellin A	Human leukemia cell (HL-60)	8.7 µM

Those belong to Iso malabaricane type triterpenoids (Stellittins, Stelliferins, and Geoditins) or polyether triterpenes (Sodwanones, Raspacionins, Sipholenols, Sipholenonoes, and Siphonellinols), triterpenes glycosides (Saponins), and tetracyclic triterpenes, all of them have shown potent anticancer potential [2,16] (Fig. 13). Interestingly, each one has a large potency on some specific cells. For example, Stelletin-A shows a strong cytotoxic effect on the murine leukemic cell line, P388 (IC_{50} ~2.1 nM). Reports indicate that Stellet in A and B both have cytotoxicity on various human cell lines, including HL-60 (Table 1), but less potent on androgen-dependent human prostate cancer cell line, LNCaP (IC_{50} ~ 260 µM). Comprehensive studies involving 60 distinct types of cancer cell lines have demonstrated that, in addition to Stelle tin A and B, other derivatives such as Stelle tin C, D, E, and F exhibit nearly identical potency, with a mean IC50 of approximately 0.98 µM [29,30]. In the case of human colon tumor HCT-116, the IC_{50} lies within 0.09 – 0.98 µM for Stelletin C, D, E, and F. When tested using polyether triterpenes on breast cancer cell lines, the potency (IC_{50}) lies within ~ 4 - 22µM. A large group of marine-derived triterpene glucosides shows enormous therapeutic potential against versatile cancer cells (IC_{50} ~ 0.2 – 2.2 µM), imposing cell death even with one hour exposure [31,32]. Apoptotic cell death is a normal stress-related response for cells facing cytotoxic agents. The effect is mediated either by the specific receptor-mediated pathway activating Caspase-8 or via a receptor-independent way involving cyclin-kinase inhibitors p53/p21. Eventually, both cause the translocation of pro-apoptotic Bax protein to mitochondria, dissipating mitochondrial membrane potential and simultaneously activating Caspase-3, thereby turning the apoptotic machinery on, leading to cell death [32].

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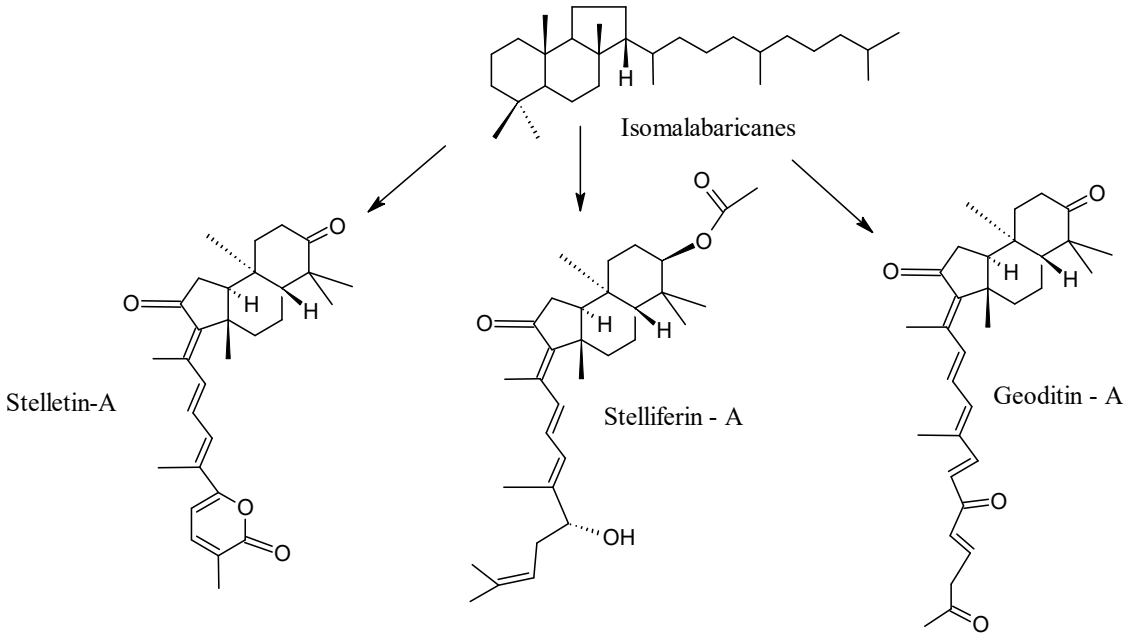

Fig 13. Isomalabaricanes-derived triterpene

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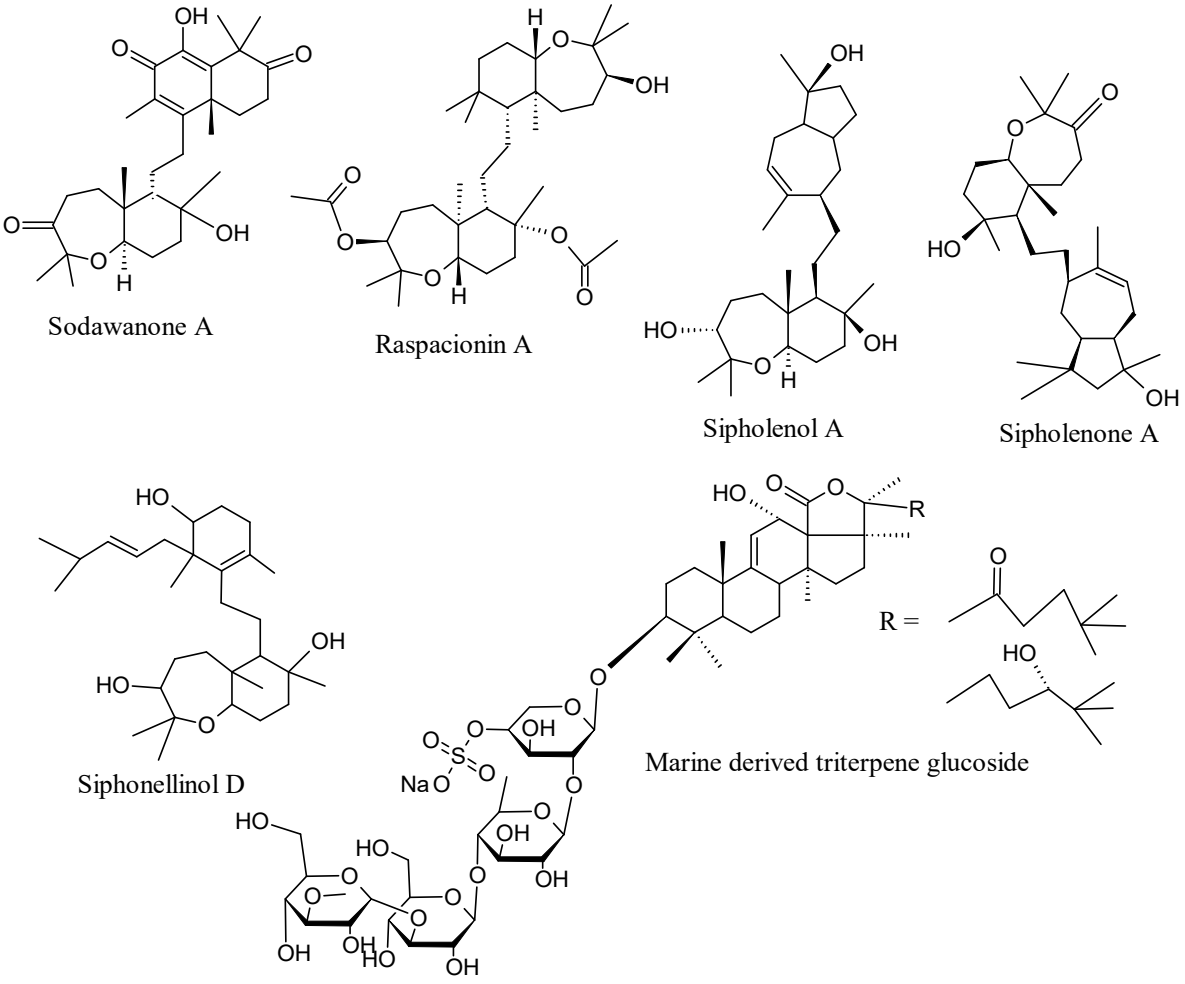

Fig 14. Polyether triterpenes and triterpene glucosides

Triterpenes on cancer: Load so fevidence validates the use of triterpenes of herbal origin to control cancer. In the majority of cases, they exhibit cytotoxicity toward the cancer/tumor cells without imposing much adverse effects on normal tissues or organs. However, few marine-derived components are seen to be toxic to both cancerous and normal cells. But the triterpenes from plants or their synthetic mimetics, particularly with pentacyclic structures exhibit broad pharmacological activities, includingthe anticancer effect. The most widely studied compounds are Ursolic acid (UA), Betulinic acid (BA), Oleanolic acid (OA), Cucurbitacin B (CuB), Masolinic acid (MA), and Asiatic acid (AA), which show potent anti neoplastic behavior (Fig. 15). They regulate cancer cell growth, angiogenesis, transformation, invasion, survival, and metastasis by modulating cytokine generation, oncogene expression, anti-apoptotic proteins, and ROS intermediates while controlling signaling pathways [16].

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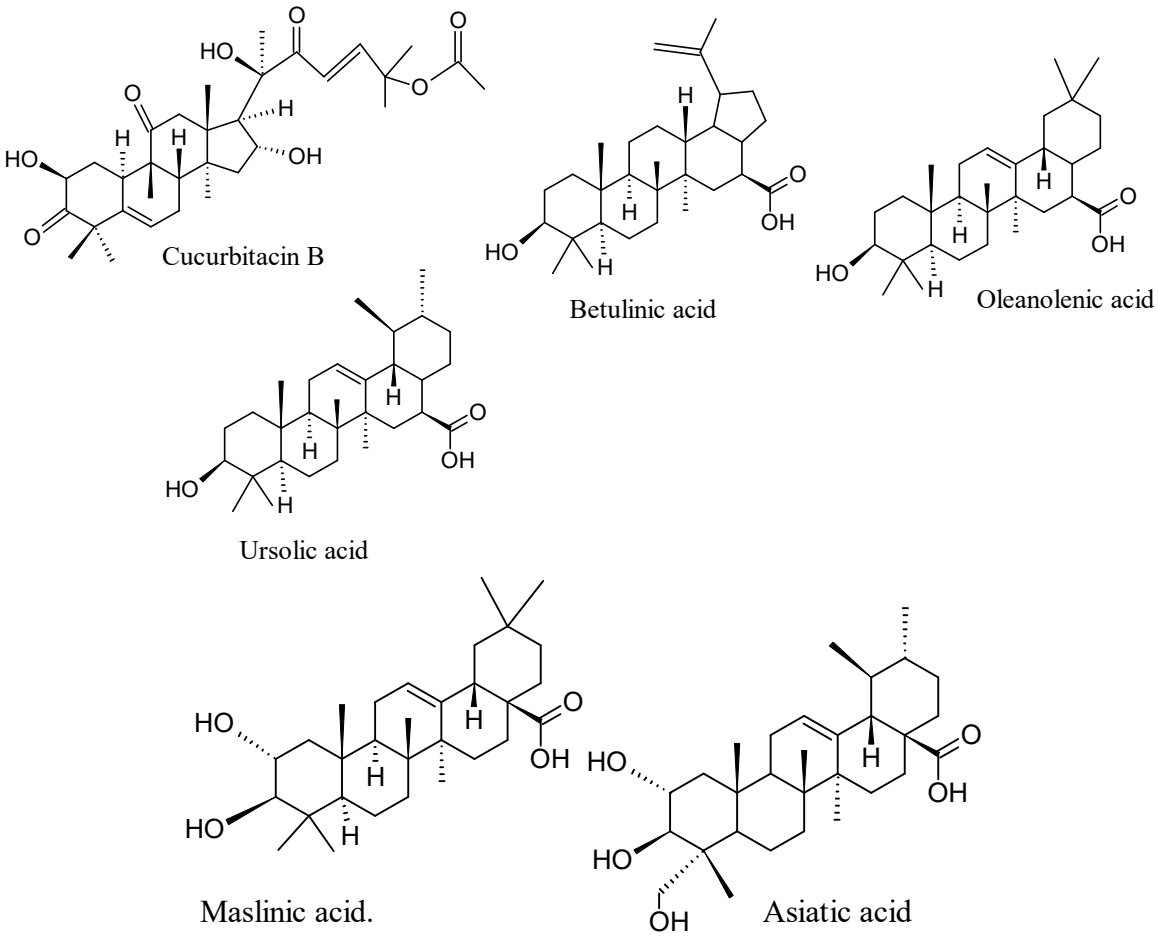
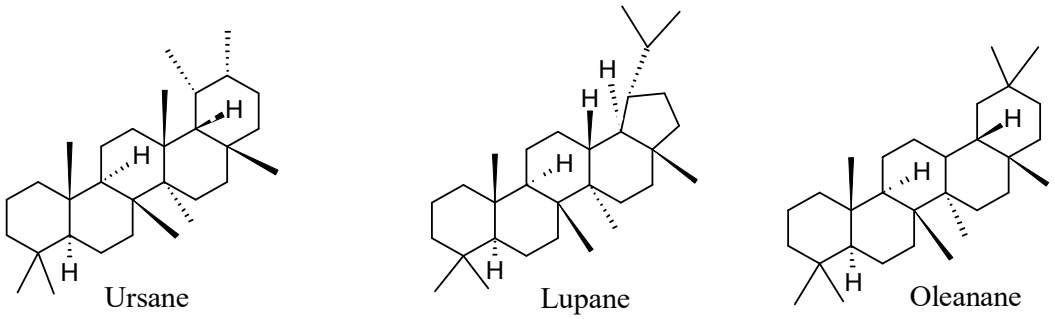


Fig 15. Notable plant triterpenes

Ursolic acid (UA)–Studies haveshown that naturally occurring pentacyclic triterpenes having Oleanane / Ursane scaffold can efficiently inhibit tumor progression compared to those with Lupane moiety (Fig. 16). In that order, A is seen as a very potent one.



Structural scaffold

Fig 16.

UA is a ubiquitous pentacyclic triterpene naturally synthesized in many herbal plants, leaves, and edible berries. It has a prominent medicinal role beneficial to health. Studies have confirmedits anti-

inflammatory, anti-proliferative, pro-apoptotic, antioxidant, anti-metastatic, and anti-angiogenic effects when tested in vitroorin vivo experiments. Researchhas identifiedvarious signaling pathways (NF–κβ, STAT3, AKT, and COX–2) interlinkingwith the progression of disease. For example,NF–κβacts as a potent regulator. Its activation and upregulation are linked to inflammatory diseases,even cancers. In addition, toworking against cancerswhilefollowing various intracellular pathways, UA and others of that category tend to work by inhibiting ubiquitin-specific enzymes (USP), particularly USP7[33]. Regardingthe inhibiting capacity toward USP7, Ursolic acid (UA) is seenverypotent(UA →IC_{50} ~ 7.0 ± 1.5 µmol / L, OA → 12.5 ± 1.0 µmol / L, BA → 33.3 ± 2.6 µmol / L) when tested against the proliferation of human myeloma cell lines (RPMI8226). The mechanism reveals that the UA molecule, after binding with USP7, inhibits the deubiquinating proteases (DUBs). USPs belong to the family of DUB,of sixty members. It has been identified that the majority of the USPs are related to the developmentof various cancers, in which they are often overexpressed, and USP7 is predominant among them. The inhibition of USP7 helps stabilize p53, a tumor suppressor protein, enabling the arrest of the cell cycle byinducingapoptosis in cancer cells.Computational molecular docking analysis points out that UA interacts with Met328, Tyr367, Ala369, and Val393 within the binding pocket of USP7[34]. As perthe binding nature,the crucial factors are H-bonding between - CO_2H at the 17th position of UA also Glu371, and - OHat the 3 positions of UA,including the Gln351 of USP7. Computational analysisconfirms that the – CO_2H at 17 and – OH at 3 positions of UAare extremely essential for the proper interaction withUSP7.The absence of them within the Ursane moiety makes UA fully inert. The action of UA isversatile.Since it also modulates the signaling events of Nrf2, NF-κβ, STAT3, and AKT. The identification of USP7 as a target of UA for cancer therapy is new. Evidencesuggests that the upregulation of p53 expression by UA brings degradation of MDM2 (Mouse double minute 2 homolog, which human also has) and the reduction of DNA methyl transferase (DNMT1), which is suspected to occur due to the inhibition of USP7. The other substrates of USP7 are Phosphatase and Tension Homolog (PTEN),Forkhead box protein – O4(FOXO4), andUbiquitin-like containing PHD and ring finger domain 1(UHRF1) proteins. So, there lies a large possibility of UA modulation of versatile signaling pathways to control the progression of cancers [35].

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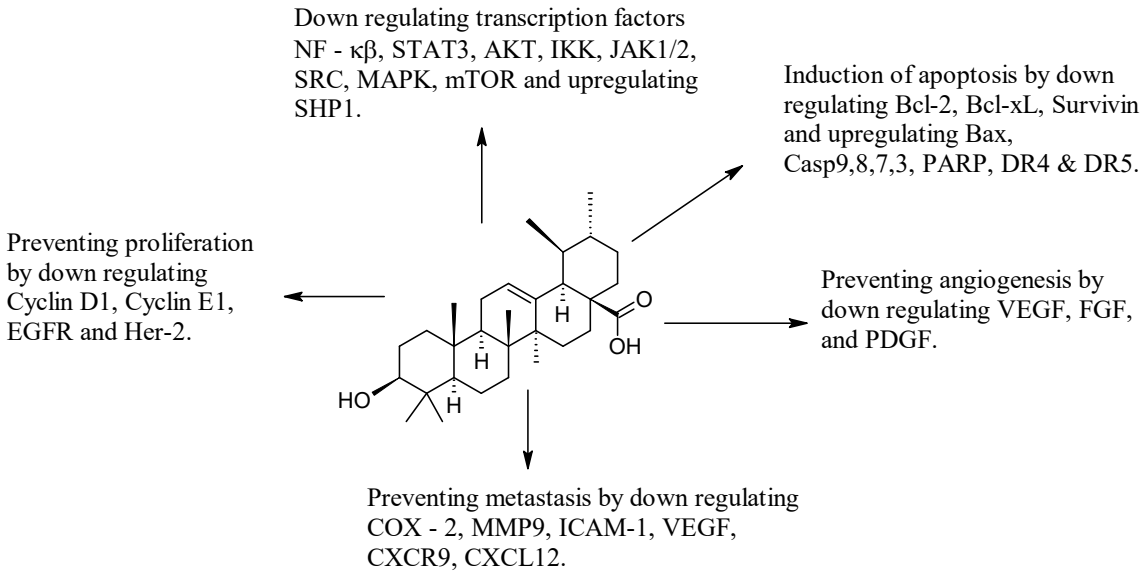

Fig 17.Signaling cascade modulated by UA in cancer cells

Table 2.Anti-tumor effects of UA on several cell lines

Cell lines	**Intra-cellular effects**
Multiple myeloma	Activation of STAT3 and upstream activation of JAK1/2 kinases & cSRC
Prostate carcinoma	Suppression of TNF induced activation of NF-κβ and IL-6 induced STAT3 activation in LnCaP cells. Downregulation of CXCR4 irrespective of HER2 Status. Induced apoptosis via Beclin-1 and Akt/mTOR pathway.
Breast carcinoma	Inhibiting proliferation by inducing apoptosis. Induces apoptosis within MDM-MB-231 Cells via Fas receptor, Casp3, PARP, and mitochondrial pathway. Suppressing Migration and invasion by modulating C-jun N-terminal kinase, Akt, and mammalian target of rapamycin signaling. Inhibiting the expression of FoxM1 in MCF-7 cells.
Hepatocellular carcinoma	Suppressing angiogenesis by inhibiting HIF-1α, βFGF, VEGF, IL-8, ROS and NO. Preventing hepatoma growth, cell cycle arrest at S phase and inducing apoptosis by activating Casp-3.
Ovarian carcinoma	Suppressing cell proliferation, upregulating phosphorylation of ERK, inducing Casp – 9 & 3, cleaving PARP, downregulating Survivin and c-Myc.

Colorectal carcinoma	Causing TRAIL-induced apoptosis, modulating autophagy by the JNK pathway, Downregulating NF-κβ and others like Cyclin D1, MMP-9, ICAM-1, VEGF, c-FLP, Survivin, Bcl-2, Bcl-xL, inducing apoptosis by modulating purinergic receptor P2Y (2) / Src / p38 / COX-2 pathways, reversing multidrug resistance.
Lung carcinoma	Inducing apoptosis in cell lines A549, H3255, and Calu-6.
Pancreatic carcinoma	Inhibiting the cell proliferation of MIA-PACA-2, PANC – 1 and Capan – 1 following P13K/AKT/NF-κβ and JNK pathways, inducing cytotoxicity and p53, p21waf1 and NOXA in AsPC cells.
Bladder carcinoma	Inhibiting cell proliferation at the G1 phase and inducing apoptosis with increasing Production of ROS. Apoptosis is caused by the activation of ASK1 – JNK Signaling. Proliferation is inhibited by inducing AMPK kinase.
Neuronal glioblastoma	Inhibiting proliferation and inducing apoptosis in glioblastoma cells (U251) by Suppressing TGF – β1, miR-21 and PDCD4 pathway.
Chronic Myelogenous Leukemia cells (HL-60)	Inducing apoptosis by downregulating Akt, upregulating PTEN, and activating Mitochondrial pathway, inducing differentiation in HL60 monocytes, upregulating C/EBPβ via ERK activation, reversing multidrug resistance.

Maslinic acid (MA) (Fig 15) –The compound is also called Crategolic acid ([2α, 3β] -2, 3-dihydroxyolean-12-en-28oic acid) (Fig. 15). It is naturally synthesized within several berries but is particularly seen at high levels in the olives (MA ~ 73.25 % and OA is ~ 25.75 %) [36,37]. It is a pentacyclic triterpene with a similar scaffold to UA.It is categorized as a phytoalexin due to its antioxidative and antimicrobial behavior, tending to accumulate at the site of pathogenic infection. Further, the compound exhibits strong anti-neoplastic properties. It potently inhibits cell proliferation, inducing apoptosis in cancer cell lines (Table 3). It might be a reason behind the traditional anticancer role of olive. Table -3shows that MA can inhibit the proliferation of several cancer cells in vitro.

Table 3. In vitro antiproliferative effect of Maslinic acid (MA)

Cellular origin	**Cell line**	**IC_{50} (μM)**
Human colorectal adenocarcinoma	HT-29	101
	Caco -2	15.4
Human hepatocellular carcinoma	HepG2	69.1

Human breast adenocarcinoma	MCF - 7	136.0
Human salivary gland Adenoid cystic carcinoma	ACC-2 (low Metastasis) and ACC- M (high metastasis)	43.7 45.8
Human uterus leiomyo-Sarcoma.	SK-UT-1	59.1
Human synovial sarcoma	SW982	45.3
Human transitional Urinary bladder papilloma	RT4	42.7
Human transitional Urinary bladder carcinoma	T24 253J	33.0 71.8
Prostate cancer	DU-145	25.0

Studies have further shown that MA can exert a wide range of biological effects besides being an anticancer compound. It also acts as an antidiabetic, antioxidant, cardio-protective, neuroprotective, anti-inflammatory, and antiparasitic agent. In addition, it is seen to be effective against bronchitis and also behaves as a diuretic, digestive, as well as antipyretic substance [38,39].MA exists ata high level in mustard leaves (1740 mg / Kg), spinach (1260 mg / Kg), and eggplant (900 mg / Kg) in terms of dry weight [36]. The antitumor effect of MA proceeds by cell cycle arrest, activating both intrinsic as well as extrinsic apoptotic pathways. During cell cycle arrest, the population is enhanced at the G0/G1 phase but considerably reduced at the S phase [40]. Further, apoptosis possibly occurs via the participation of death receptors following an extrinsic pathway. It also occurs due to the disruption of the mitochondrial membrane, which is categorized as an intrinsic pathway. Both pathways converge and activatecaspase-3, a potent effector. It has been identified that both pathways are affected by MA. Essentially, the apoptosis takes place by the activation of caspase-3, which is visualized by the changes in cellular morphology, shrinking of cells, and chromatin condensation. However, the major attention is drawn to the disruptive mitochondrial apoptotic pathway since it is a reservoir of pro-apoptotic proteins which, after release in the cytosol, triggercaspase-3 activation leading to the regulation of the Bcl-2 family [9]. Experiments in HT – 29 show that MA activated Bax (pro-apoptotic protein) but simultaneously inhibited the action of Bcl-2 (anti-apoptotic protein). Additionally, the disruption of mitochondria releases cytochrome C that binds to Apaf-1, causing sequential activation of caspase-9 and 3. Moreover, MA can act by following the death receptor, which is proven experimentally using the pancreatic cell line Panc-28[37,41]. It also synergizes the action of TNF–α regarding the inhibitory effect on cell proliferation as well as the induction of cell death [42]. The compound, in addition, affects NF–κβ by inhibiting IKBα phosphorylation, leading to the inhibition of NF-κβ translocation and DNA binding to the nucleus. This explains the dose-dependent lowering of COX-2 expression, which is the underlying reason behind its anti-inflammatory action. COX–2 is often overexpressed in premalignant or malignant tissues [42]. The unique behavior of MA is also noticed while working as an adjuvant of the anticancer drug doxorubicin, enhancing the drug sensitivity, helping accumulate intracellularly [43]. MA reduces the metastatic potential of both basal and

EGF-imposed migration of human prostate cancer cell line DU-145 in a dose-dependent manner. The compound reduces the secretion of pro-MMP-2 and pro-MMP-9, including their mRNA expression level. Detailed experiments further indicate that the anticancer effect of MA follows multiple different pathways, which depend on the nature of the tumors [44].

Asiatic acid (AA) (Fig. 15)–It is a natural aglycone of urace-type pentacyclic triterpene. AA is synthesized innumerous edible medicinal herbs. One of them is *Centella asiatica* (Indian pennywort / *Thankuni)* of the Apiaceae family, synthesizing abundant levels of AA. This triterpene possesses a vast number of pharmacological properties, enabling it to regulate anti-inflammatory, antioxidant, as well as induction of apoptosis in several cancer cells [24,45]. In addition to its anticancer role, AA shows nootropic (enhancement of cognitive function), antihypertensive, neuroprotective, cardioprotective, and antimicrobial effects [46,47]. The compound works by modulating enzymes, receptors, growth factors, transcription factors, apoptotic components, and cell signaling pathways to exert its pharmacological role. It even helps heal wounds and protects from liver fibrosis, cerebral ischemia, dementia, hyperglycemia, Alzheimer's, and Parkinson's disorders [46,48]. Structurally, the compound possesses three – OH groups at C–2, C–3, and C–23, an olefinic bond at C-12, and – CO_2H at C-28 positions. Few AA derivatives are synthesized by modifying at C–11 and C–28 positions. Some exhibit more potent bioactivities along with higher bioavailability [47]. Studies in vitro show that AA is effective in exerting apoptosis /inhibiting cell growth in the case of liver, breast, skin, brain, and gastrointestinal tumor cells [49-52]. The anticancer effect is supported by its ability to inhibit NF–κβ, p38-MAPK, and ERK kinase in many cancer cell lines in vitro. Experiments further indicate that it enables modulating intracellular signaling pathways, including CDKs or cyclins that regulate EGFR, c–myc, cell proliferation, VEGF, and p53 and p21 proteins involved in the suppression of tumors. Additionally, AA influences apoptotic mediators like Bcl-2, Bcl-X, caspases, and death receptors, inflammatory mediators (NF-κβ and COX–2), protein kinases (JNK, Akt, and AMPK), and oncogenes (MDM2) [49]. Following the in vitro studies regarding capabilities, AA can be compared to the widely known, clinically used synthetic drug,5-fluorouracil (5–FU). However, a few modified AA derivatives show strong antiproliferative effects in several cancer cell lines. Those compounds induce ROS generation, activate caspase-3 and –9 to exert apoptosis, and regulate mitochondrial pro-apoptotic proteins, also arrest the cell cycle at the G1 phase in the case of HepG2 cells. It has been noticed that linking - $CONH_2$ at C–28 and > C = O group at C–11 potentiates the overall anticancer effects [48-52]. Studies further demonstrate that substituting – $CONH_2$ and – $COCH_3$ on – OH groups of C- 2, C – 3, and C – 23 in AA molecule provides a strong inhibitory effect regarding the cell growth of cancer cells (HeLa, HepG2, B16F10, SGC7901, A549, MCF7, and PC3) [47]. In that regard, several derivatives (A_1, A_2, A_3, and A_4) are prepared by modifying AA in several ways to find their efficacy for preventing the growth of non-small cell lung cancer cell lines (A549 and PC9/G). All of them strongly inhibit cell growth in a dose-dependent manner. AA also has a similar function by downregulating the Ras / Raf / MEK / ERK pathway, including cell cycle arrest at the G1/ S and G2 / M phases [49]. It exerts apoptosis, loss of mitochondrial membrane potential generates free radicals along with improved microtubule-associated protein and reduces p62 expression. When administered orally, AAor its derivatives reduce tumor volume and expression of proliferating cell nuclear antigen by promoting apoptosis in mouse lung cancer xenografted models.

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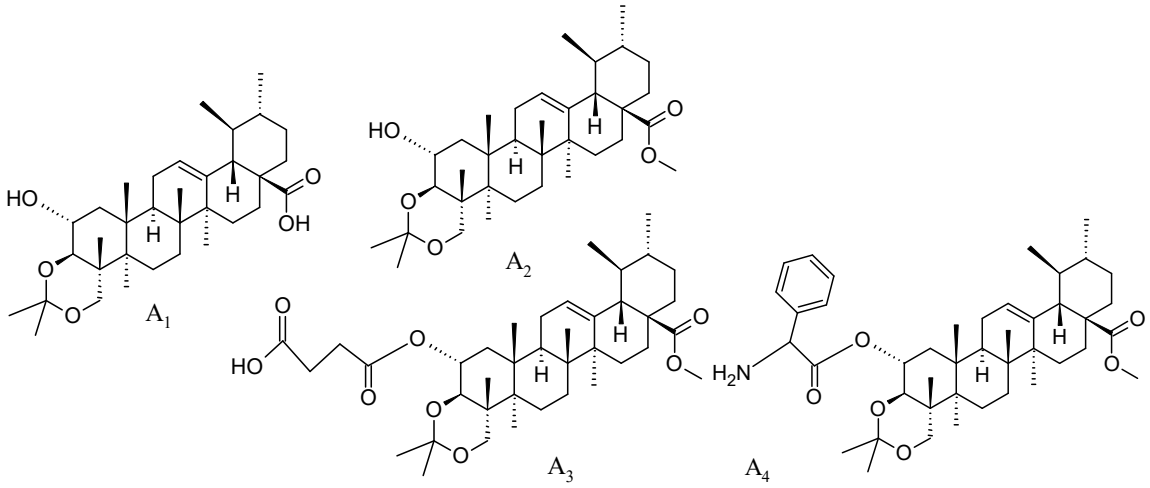

Fig. 18. Anticancer derivatives of AA

Betulinic Acid (BA) (Fig.15)– BA is also a pentacyclic triterpene belonging to the Lupane group. It plays alarge pharmacological role in cancer biology. Records indicate that the compound imposes anti-proliferative, anti-angiogenic, anti-metastatic, and apoptotic effects that help control several types of cancers. In addition to its beneficial effects, A is less toxic to normal cells or tissues. The chief sources of BAare found within the herbal kingdom [16,53]. They are largely available in the families of Rhamnaceae (Ziziphus / Jujube), Myrtaceae (Syzium / Clove), Betulaceae (Betula / Birch tree), Ebenaceae (Diospyros / Persimmon), Lamiaceae (Rosemary), and Paeoniaceae (Peony). Besides the original BA molecule, numerous semisynthetic analogs have been constructed to gain better anti-neoplastic effects. Experiments indicate that one of the cytotoxic abilities exerted by BA is the induction of apoptosis by directly perturbing the mitochondrial membrane. Perturbation of mitochondrial function is by far the most crucial event imposed by BA that in turn induces apoptosis, subsequently enabling to activation of the caspases, leading to DNA fragmentation. Isolated mitochondria from the cells, when treated with BA, cleave caspase-3 and caspase-8in the cytosol extract. This cleaving event possibly helps generate reactive oxygen species (ROS). The generation of ROS is noticed to be linked with cell death, which can be prevented by the prior treatment with antioxidants before administering BA. ROS activates the pro-apoptotic p38 and SAP/JNK kinases without the change of phosphorylation of ERK, indicating its action is upstream of MAPKs during the signaling event of BA. Further, BA can modulate the expression of pro-apoptotic protein Bax within several tumor cells by upregulating it. Additionally, it also modulates the action of NF-κβ, which is the major factor for stress-induced transcriptional events. But certainly, by activating NF–κβ, the molecule affects the overall immune system. As per its further activities, it also inhibits the enzyme Aminopeptidase N, involved in regulating angiogenesis. The enzyme is overexpressed in various cancers. It is claimed that the anti-angiogenic effect of BA occurs by blocking the growth factor-induced angiogenesis of endothelial cells, probably by affecting the mitochondrial functions [54-56].

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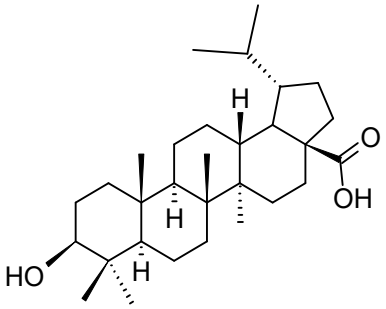

20,29-dihydro - betulinic acid

Fig 19.

The anti-angiogenic property could be due to the activation of selective proteasome-dependent degradation of transcription factors specific protein 1 (Sp1), Sp3, and Sp4 that regulate the expression of VEGF. The anti-angiogenic effect is seen more potent in favor of 20, 29-dihydro-betulinic acid rather than BA itself. Regarding further action, BA inhibits Topoisomerase-I,thus helping with apoptosis in neoplastic cells. The anti-tumor action is also observed to be mediated by controlling the cell cycleon many occasions. The anticancer activity of BA or its analogs is witnessed in several human cancers like neuroblastoma, glioblastoma, medulloblastoma, Ewing tumor (bone), leukemia, and several carcinomas, for example, colon, breast, hepatocellular, head and neck, prostate, renal, ovarian, and cervix carcinoma [53]. Interestingly, BA is also seen to be effective against several drug-resistant cancers. It synergizes the effect of different cytotoxic agents, suppressing the tumor growth, including ionizing radiation, chemotherapeutic drugs, and death receptor ligand TRAIL. BA strongly cooperates with vincristine (Vinka alkaloid), reducing the lung metastasis in the metastatic melanoma model, acting as an enhancer. The compound is even claimed to have a preventive role against cancers [57]. Alarge variety of BA derivatives are synthesized in recent days, which exhibit high retention concentrations within tissues and plasma compared to the natural analog, which seems more effective in curing or controlling any neoplasia.

Table 4. In vitro cytotoxic effect of BA on human cancer cells

Type of Cancers	**ED_{50} (µg / ml)**
Melanoma	1.1 – 4.8
Neuroblastoma	2 – 10
Medulloblastoma	3 – 15
Glioblastoma	5 – 16
Head & Neck cancer	8.0
Ovarian carcinoma	1.8 – 4.5
Cervix carcinoma	1.8
Lung carcinoma	1.5 – 4.2
Leukemia	2 – 15

Oleanolic acid (OA) (Fig. 15)–OA is also a pentacyclic triterpene and a close analog of UA. In nature, the compound exists either as saponin, aglycone, or in free acid form. In case of food, the major source of OA is olive oil, garlic, various fruits, vegetables, greens, and plants [58]. It is completely nontoxic and has scores of pharmacological functions displaying hepatoprotective, antiviral (including HIV and HCV), and antitumor activities. Additionally, it has potent anti-inflammatory effects. Numerous works have reported that OA exerts antiproliferative and apoptosis effects on a number of cancer cells of prostate, bladder, pancreatic, gastric, colorectal etc, by interfering with different intracellular signaling pathways. Experiments indicate that OA induces apoptosis/cell death by affecting the mitochondrial membrane potential (MMP). Generally, in normal cells MMP is stabilized by the Bcl-2 family of proteins, which are Bax (pro-apoptotic) and Bcl-2 (anti-apoptotic).In the event of cellular stress, Bax undergoes activation that encourages in making of pores on the outer surface of the mitochondrial membrane, thereby releasing Cytochrome Calong with several other parameters like anti-proliferative factor – 1 (Apaf-1), Caspase-9, and ATP while further activating Caspase-3, essentially bringing morphological changes of the apoptotic cells. Simultaneously, JNK undergoes activation in the MAPK pathway, causing further release of Bax from mitochondria, which also helps exert apoptosis. It is known that AKT has an important role in preventing apoptosis by regulating the expression of Bcl-2. In this complex signaling event, OA induces apoptosis via mitochondria-dependent regulation of AKT (protein kinase B) and JNK (c–Jun N-terminal kinase). In that event, OA increases JNK phosphorylation in gastric cancer cells (MKN-28), increasing mRNA expression of Caspase-3 and 9 andApaf-1, preventing cellular proliferation [58,59].

In the case of prostate cancer cells (PC3, DU145, LNCaP), OA prevents cell proliferation, induces apoptosis, and cell cycle arrest by inhibiting the PI3K/AKT pathway [60]. The administration of OA arrests PC3 tumor growth in nude mice, which proceeds via the inhibition of the PI3K/AKT pathway. Similar antiproliferative, cell cycle arrest, and apoptosis events are also noticed during the experiments using human osteosarcoma cell lines (MG63 and Saos-2)[60]. This inhibition follows the mTOR pathway. OA causes cell cycle arrest at the G1 to S phase transition through the inhibition of Cyclin D1. The downstream target of mTOR complex 1 (mTORC1) is also downregulated. The phosphorylation of p70 ribosomal S6 kinase1(p70S6K1) (T389) and S6 (S235/236), mediators of mTORC1 signaling to control protein translation events as well as cell growth, is inhibited by OA. OA prevents phosphorylation of AKT, which is a survival factor and a substrate for mTORC2. The inactivation of AKT leads to apoptosis by OAin sarcoma cells, which is demonstrated by the increase of V-FITC binding, cleavage of poly ADP ribose polymerase also along with the activation of Caspase-3 [59,61–63]. The events indicate that OA is a promising molecule that acts by following the mTOR signaling pathway while displaying its antitumor role in osteosarcoma cells.

OA is also seen as effective in inducing apoptosis and enabling it to prevent the proliferation of non-small lung cancer cell lines, particularly those that are multidrug resistant (A459 and H460). Treatment with OA increases the expression level of Bax while keeping Bcl-2 unaltered. It decreases the expression level of anti-apoptotic protein, Surviv in. The event thus changes the ratio of Bcl-2 / Bax, imbalancing the situation, thereby exerting apoptosis and subsequent death of cancer cells [64].
It is also identified that OA can prevent or lessen the incidence of metastasis in the case of several cancers when tested both in vitro and in vivo. In mice model, it reduces of the lung metastasis of melanoma

(B16F10) and osteosarcoma (MG63 and Saos-2) cell lines [64,65]. It also shows ability to inhibit the migration and invasion of glioma (U-87 MG) cell lines and even primary cell lines from the patients following the mitogen-activated protein kinase / extracellular signal-regulated kinase (MAPK/ERK) signaling pathway. It is known that MAPK/ERK is involved in the regulation of vascular endothelial growth factor (VEGF), which is important for angiogenic action, particularly for glioma cells. MAPK/ERK activation boosts proliferation via protein kinase C (PKC) that regulates the initiation as well as progression, while disrupting epithelial-mesenchymal transition (EMT). Treating with OA blocks that episode. This event is associated with the expression level of Vimentin, N – N-Cadherin, and Twist 1. These proteins are involved in the case of cell adhesion and matrix interaction. OA also deters the MAPK/ERK pathway within the glioma cells by inactivating it. The reactivation by the lentiviral vector (Lv-MEK) rescues the inhibitory effect of OA, bringing back the migration and invasion activity of U-87 cells [60]. The phenomena surely confirm that OA can be used as an anti-cancer agent, particularly for metastatic ones, like in the case of glioma.

Cucurbitacins: It isa tetracyclic triterpene with cucurbitane nucleus having the skeleton of 19-(10→9β)-abeo-5α-lanstone base with varying substitutional position of the oxygen, resulting in creatinga mild to extremely bitter taste having physiologically active components. Approximately forty variants of the molecule have been identified. The variants are widely distributed in various plants, fruits, and vegetables. They are synthesized inside those belonging to the Cucurbitaceae or Brassicaceae family, like pumpkins or gourds. Besides those, some derivatives are synthesized in the families of Begoniaceae, Rosaceae, Datiscaceae, Primulaceae, Rubiaceae, etc [16,66].Few marine mollusks also produce Cucurbitacin derivatives. Significant number of them express potentanti-neoplastic behavior and other pharmacological properties like anti-inflammatory, antifungal, hepatoprotective, and laxative activities [67]. Its potential effect also includes to bean eco-friendly pesticides with less toxicity to animals or humans. Uniquely even acting as potent anti-neoplastic agents, most of the derivatives have less toxicity toward normal cells. Physiochemically, the molecules are hydrophobic, thus can readily solubilize in most of the organic solvents, showing λ_{max} at 228 – 234 nm of the far UV range. Studies on cancer cells indicate that Cucurbitacin B (CU-B) and Cucurbitacin E (CU-E) are the most effective components regarding the anti-cancer effect.

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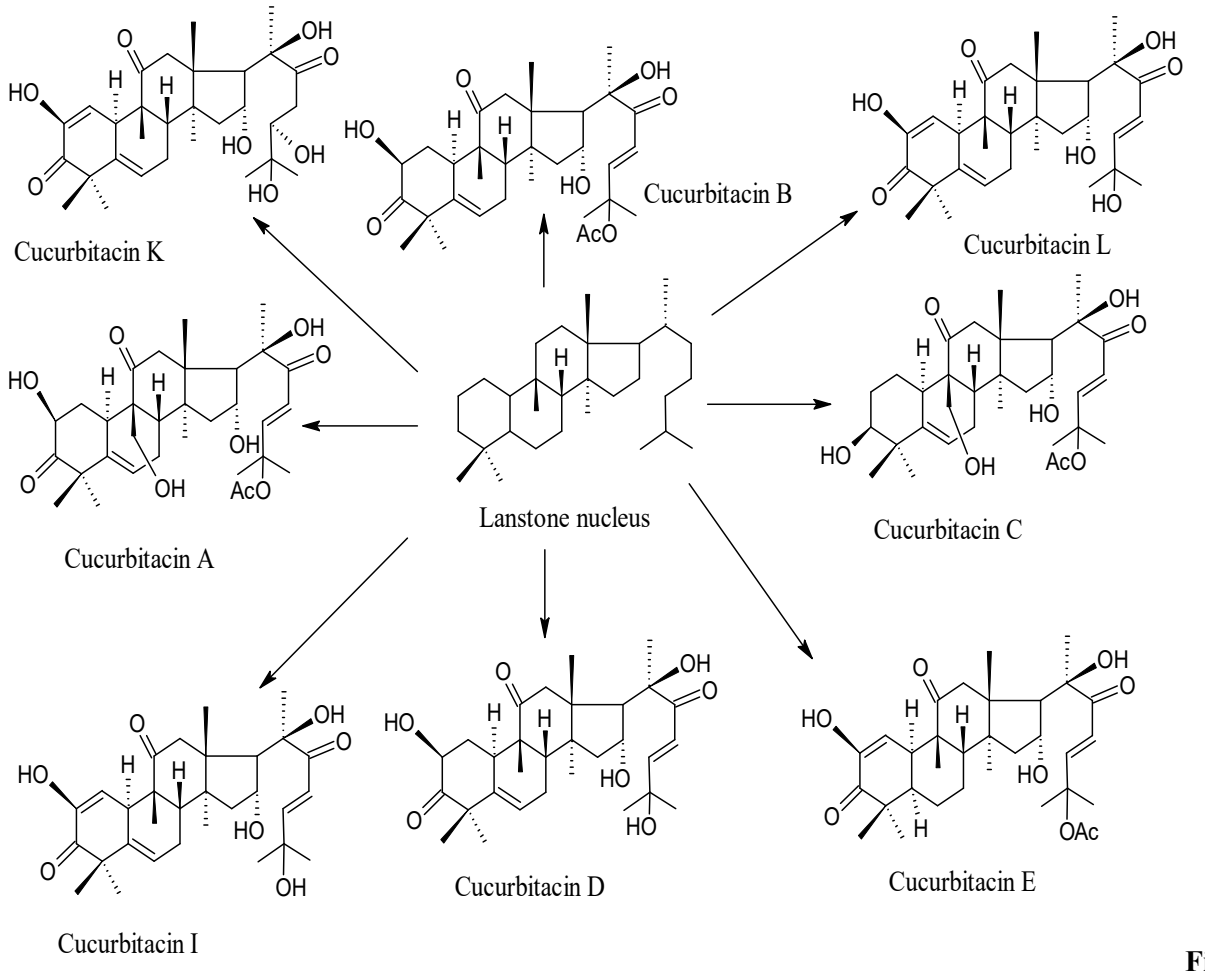

Fig 20.Chemical structure of Cucurbitacins – A, B, C, D, E, I, L & K

Binding to receptors and subsequent signaling event: Due to substantial hydrophobicity, the majority of the triterpenes bind tightly with plasma albumin, allowing their transport to the desired target organs [68,69]. The behavior is analogous to steroid binding and transport, and efficient drug distribution via circulation. Lakethe steroids, triterpenes bind to the cell surface receptors. Studies conducted while using either cell-free systems or intact cancer cells confirm the specificity of the binding. The binding to the cell surface receptor is seen as competitive. Inimitably, triterpenes interact with the same receptors used by steroids, like cortisol, estrogen, and others. The binding is associated with a positive entropy (ΔS+) change, confirming the involvement of hydrophobicity during interaction [68]. It is noticed that Cucurbitacin I binds efficiently with the Cortisol receptor in a competitive and dose dependent (IC_{50} ~ 120 nM) manner when conducted by using the radiolabeled, [H^3] cortisol to HeLa (cervical cancer) cells [68]. The cytotoxicity exhibited by Cucurbitacin I takes place via its binding with the glucocorticoid receptor and subsequent internalization of the ligand-receptor complex to exert intracellular effects. Using intact cells, it is proven that after the internalization of the ligand-receptor complex, Cucurbitacin I later forms cytoplasmic and nuclear complexes. The inhibitory effects on Bcl-2 and Bcl-XL and subsequent

apoptosis incurred in the tumor cells occur because of this event. Studies following various molecular models indicate that UA and OA perhaps exert the highest level of inhibition of Bcl-2 proteins. Studies also show that triterpenes isolated from the plant Morinda Lucida Benth (Mulberry) interact with the anti-apoptotic proteins overexpressed in cancer with high affinity, helping the apoptosis/cell death of malignant cells [69]. Experiments using several pentacyclic triterpenes and their glucosides from the *Ayurvedic* plant *Dendrophthoe falcata* (Indian mistletoe)indicate that the binding event is carried via the estrogen receptor to lead to the intracellular signaling actions [70].Normally, the extracellular binding of growth factors and other agonists activates the receptor-linked Janus kinases (JAK) that in turn phosphorylate specific tyrosine residues within the signal transducer and activator of transcription 3(STAT3) protein, boosting its dimerization through the SH2 domains. The phosphorylated dimerized proteins are transported by the Importin α/β complex to the nucleus for the sake of transcription. Evidence indicates that STAT proteins are necessary for tumor survival. It is known that STAT3 is constitutively phosphorylated and activated within human cancer cells. Thus, blocking STAT3 by triterpenes inhibits tumor growth and subsequent induction of apoptosis without affecting any normal cells. For this reason, in recent days, they are considered novel agents for cancer therapy, particularly when targeted to STAT3, even though they do not directly bind to that protein [71]. STAT3 has gained much attention since its constitutive activation leads to abnormal growth as well as the survival of tumors. It transduces intracellular signals after binding to the receptors of growth factors, steroids, cytokines, etc. Another important factor regarding cancer cell proliferation is the Bcl-2 family of anti-apoptotic proteins, cyclin-D1, c-myc, and others, necessary for survival and the cell cycling process. The agonist binding causes phosphorylation of the receptors on Tyr residues, and subsequently, STAT3 is recruited through its SH2 domains. In that course, Tyr705 in STAT3 undergoes phosphorylation by JAK kinases, src kinases, or even due to the kinase effect of phosphorylated receptors. Afterward, on dissociation from the receptor, two STAT3 molecules dimerize via reciprocal Tyr705-SH2 interactions. The dimer later trans locates to the nucleus for transcriptional reasons. The entire episode within the tumor could be blocked by the bioactive triterpenes, inducing apoptosis/cell death. But there exists a distinction between STAT3 inhibitor and the inhibitor of the STAT3 pathway. It is identified that Cucurbitacin I prevents phosphorylation of STAT3 without direct binding. A large number of triterpenes have been extracted from various resources, which shows a significant inhibitory role in the STAT3 pathway [71].

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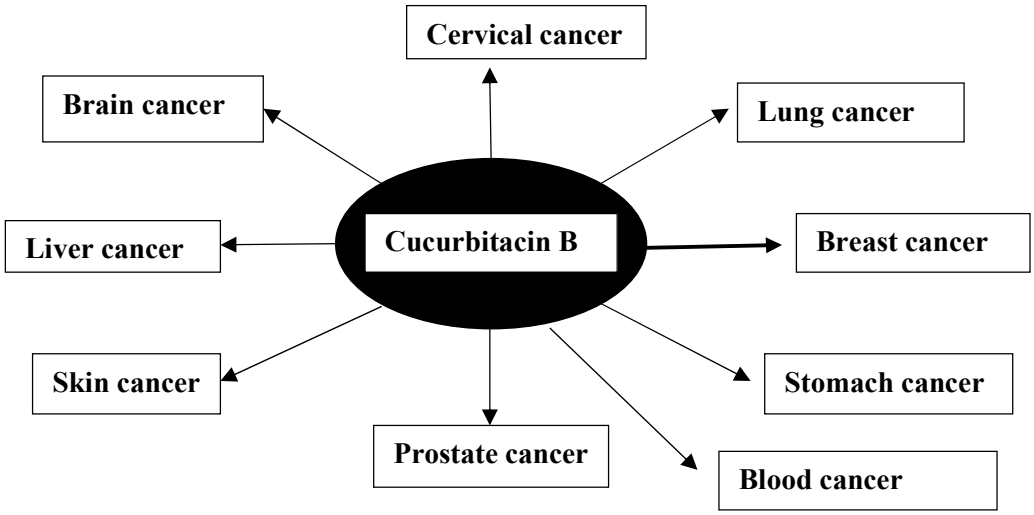

Fig 21. Effect of Cucurbitacin B on several types of cancers

Table 5. Sources of Cucurbitacins and effects on cancer cells.

Cucurbitacin	Plants	Effectiveness on cancer cell lines
Cucurbitacin A	Snake gourd	Lung cells (A549)
Cucurbitacin B	Snake gourd Buttercup squash Sponge cucumber	Leukemia & Lymphoma (HL60, U937, THP1, NB4, K562, BALL1, Reh, RCH, LY4, SP4, Jeko1, NCEB1, MD901 & Daudi). Hepatocellular (Hep-2). Breast (SKBR2, MCF-7, T47D and MDA-MB435). Lung (A549, SK LU1 & NCI-H460). Colon (COCA-2 & HCT-116). Brain (SF-268). Pancreatic cancer cell lines.
Cucurbitacin-glucosides	Bitter cucumber	Breast (ER^+MCF – 7 & ER^- MDA-MB231).
Cucurbitacin E & glucosides	Brahmi, Bitter cucumber, Pumpkin	Ovarian sarcoma (M5076) & Colon (HCT-116), Breast (MCF-7 & ZR-75-1). Lung (NCI-H460), Brain (SF-268), Prostate (PC-3). Hepatocellular (HepG2).
Cucurbitacin D	Chinese cucumber, Pumpkin.	Hepatocellular (HepG2), Leukemia & Lymphoma (HL60, U937, THP, BALL1, Reh, RCH, LY4, Daudi, MD901, SP49, Jeko1 & NCEB1). Breast (MCF-7), Colon (HCT-116), Lung (NCI-H460),

		Brain (SF-268).
Dihydro-Cucurbitacin B	Chinese cucumber, Tayuya.	Leukemia, Hepatocellular (HepG-2). Breast (Bcap37, Hela, SW620, SMMC-7721, K562 & MCF-7). Colon (HCT116 & Hk33).
Cucurbitacin I & glucosides	Balsam pear, Tayuya, Winter squash / Pumpkin & Bitter cucumber	Colon (HCT-116). Breast (MCF-7, MDA-MB-231, MDA-MB-468, Panc-1). Lung (NCI-H460). Brain (SF-268). Prostate (U251, A172). Hepatocellular (HepG2).
Cucurbitacin Q	Tayuya	Lung (A549). Breast human and murine (MDA-MB-435 & Src / NIH3T3).
Cucurbitacin R	Tayuya	Colon (HCT116 & Hke-3).

Effect on breast cancer: Reports show that CU-B or CU-E or any of its glycosides efficiently inhibit breast cancer cell proliferation in a dose dependent way by arresting them at G2/M cell cycle phase, enhancing the path of apoptosis [72,73]. When tested against six different cell lines (MDA-MB-231, ZR – 75-1, MCF – 7, T47D, BT474, MDA-MA-453) with varying expression of estrogen receptor (ER), Human epidermal growth factor receptor – 2 (Her2 / neu) and p53 mutation, the potency (IC_{50}) of CU-B lies within 3.03 x 10^{-8} - 41.8 x 10^{-8} M. The in vitro experiments are conducted after 15 – 20 minutes of exposure to CU-B (5 x 10^{-7} M), showing rapid and tremendous morphologic changes. The antitumor effect, indicating tumor volume contraction, is observed nan in vivo model using orthotopically implanted nude mice breast receiving CU-B intraperitoneally (1.0 mg / Kg) for six weeks. Interestingly, no damage or any adverse effects on any of the organs are noticed. However, as an additional effect, the compound shows a significant lowering of serum glucose level, authenticating the fact of its legendary antidiabetic role. The tumor growth arrest occurs by the downregulation of $p34^{cdc2}$/ Cyclin B1 complex with simultaneous upregulation of Phospho-STAT3 and p21 proteins. The compound, CU-B, also disrupts the actin filament, causing Estrogen receptor (ER) independent inhibition of phosphorylation of Protein kinase B (PKB) along with concomitant reduction of the expression of Surviv in, thus assisting the overall incidence of apoptosis. The report also confirms that CU-B inhibits Telomerase activity within several breast cancer cells [74]. The erosion of telomeres along with the inhibition of Telomerase is validated due to the simultaneous inhibition/reduction of human telomerase reverse transcriptase (hTERT) and cMYC proto-oncogene proteins, imposing cell cycle arrest at the G2/M phase [75]. The highest growth inhibition occurs for the cancer cells devoid of ER, like SKBR-3, rather than MCF-7 or T47D, which also undergo apoptosis during the event. The treatment with CU-B also induces autophagy and DNA breakdown in HER-2 breast carcinoma. Reports show that CU-B inhibits HER2 receptor and cell adhesion protein, Integrins, also initiates Integrin-mediated cell death by upregulating B1 and B2 through time-dependent Bax and Caspase-8 cleavage. It is also recorded that CU-B reduces the invasiveness of $HER2^{+}$ breast cancer cells through the reversal of EMT. CU-B inhibits the expression of TGFβ, SMAD, SNAIL, SLUG,

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ZEB1, and N-Cadherin and abolishes the expression of E-Cadherin. In that way, $HER2^+$ cells would not acquire any mesenchymal properties because of the lack of TGFβ. Further, CU-B induces autophagy in many breast cancer cells. It imposes DNA damage in HER2 breast cancer cells by ROS-mediated upregulation of γH_2AX and phosphorylation of ATM/ATR, causing p53-dependent apoptosis [76]

Effect on prostate cancer: Reports have confirmed the anti-cancer role of CU-B and CU-E derivatives on prostate cancer cells. The compound CU-B shows a significant inhibitory role (IC_{50} ~ 0.3 µM) on both PC-3 (hormone independent) and LNCaP (hormone dependent), human prostate cancer cell lines, exerting apoptosis via caspase 3 / 7 activation and PARP cleavage, with simultaneous arrest of the cells at Sub-G0/G1 phase. Interestingly, those compounds do not impose harmful effects on normal human prostate epithelial cells [77]. Prior treatment with CU-B for two weeks reduces ~ 79 % of the tumor volume in orthotopically implanted PC-3 tumors in nude mice. The underlying mechanism reveals that CU-B dose-dependently inhibits the phosphorylation of the enzyme, ATP citrate lyase (ACLY), both in vitro and in vivo nude mouse model. The overexpression of ACLY has been noticed in prostate cancer cells. Additionally, this enzyme is noticed to be the direct target of CU-B. Therefore, CU-B exerts the chemo preventive role by inhibiting the ACLY signaling event within these cancer cells. Other studies have demonstrated the inhibitory role of CU-E when tested on hormone-dependent human prostate cell lines LNCaP, indicating its potent cytotoxicity, inducing apoptosis. The compound exerts the effect through the induction of Cofilin-1, p-mTOR, p53, Caspase-9 expression, and AMP-activated protein kinase (AMPK) signaling while suppressing cell viability and provoking apoptosis [77,78].

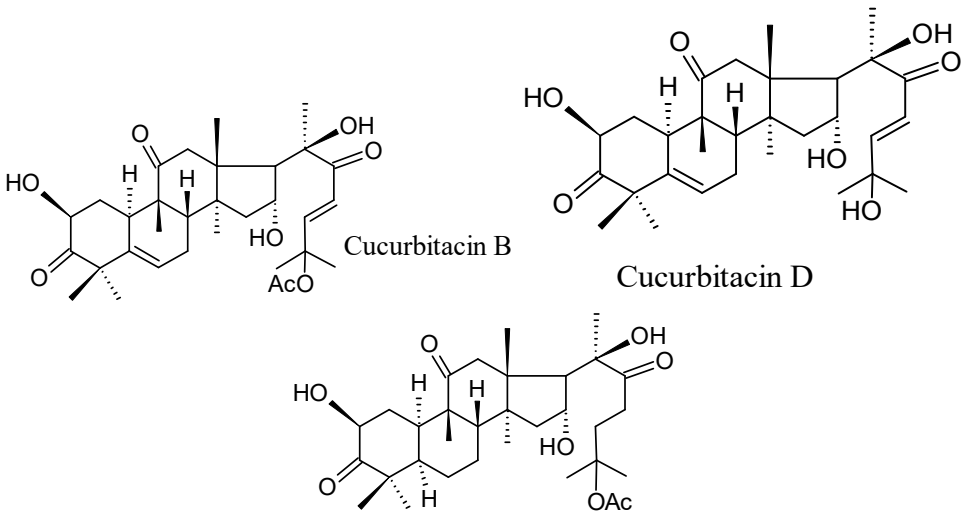

Fig 22.

Effect on lung cancer: When tested on non-small cell lung carcinoma cell line (NSCLC), CU-B showed moderate to potent cytotoxicity (IC_{50} ~ 0.13 µM) in 48 hrs and (IC_{50} ~ 0.04) for 72 hrs exposures to cells. It has been recorded that thiols (-SH groups) act as intermediates while imposing toxicity by the CU-B [79,80]. The workers also show that CU-B causes DNA damage and arrests the cell at G2/M phase. The

growth arrest is due to the inhibition of phosphorylation of STAT3, which imposes apoptosis. The inhibition of the STAT3 pathway results in the downregulation of Cyclin B1 and Bcl-2. Certainly, there are other factors relating to the growth and apoptosis involved due to the action of CU-B on NSCLC. Recent findings also show that its inhibition of PI3K and MAPK pathways is also noticed by the treatment with CU-B, which delays cell migration, alleviates invasion capacity, leading to dose dependent and time-dependent apoptosis. Studies also indicate that the compound prevents MMP release and FAK activation while activating/upregulating phosphor-AKT, - ERK, - JNK, and NF-κβ and p65 [81-87]. In that way, CU-B exerts strong anti-metastatic potential in those cells. Intraperitoneal administration of CU-B (0.1 mg / Kg body weight) three times per week significantly lowered the incidence, tumor volume, and frequency by almost 90 % in comparison to the vehicle control [81- 84].

Effect on liver cancer: Cu-B imposes anticancer activity on hepatocarcinoma cells. The anticancer action is mediated via the inhibition of HIF-1α and NF-κβ. Further studies also reveal that CU-B inhibits STAT3 dose and time-dependent manner, causing the cellular arrest at S-phase [76,83]. The event occurs through the activation of ERK1/2 and with simultaneous suppression of cyclin D1, CDC2, and c-RAF phosphorylation. It is also noted that CU-B causes DNA damage to induce apoptosis as well as autophagy in hepatocarcinoma cells. The underlying cause is increased upregulation of γH_2AX, phosphorylation of ATM/ATR and CHK1/CHK2, modulation of BCL2 family proteins, and cleavage of Caspase-7 and -9 [85].

Blood cancer: Experiments indicate that CU-B induces cell cycle arrest as well as differentiation in hematopoietic leukemia and lymphoma cell lines dose-dependently ($IC_{50} \sim 4 – 8 \times 10^{-8}$M). The identical effect is noticed for CU-D ($IC_{50} \sim 0.2 – 9.5 \times 10^{-8}$ M) [79]. Further studies involving CU-B show that in acute promyelocytic and myeloid leukemia, it arrests the growth at S phase, also alters the cytoskeleton, changing morphology and decreasing clonogenicity in immature blasts. The upregulation of CD11b signifies cell differentiation. The compound suppresses the activated MAPK/ERK pathway and also inhibits STAT3 activation in myeloid leukemia cell lines [86]. In an overall aspect, it imposes cell cycle arrest G2/M phase and subsequent apoptosis. The identical behavior is also noticed in the case of the human leukemic *Jurkat* cell line [87]. The compound and its analogs also induce autophagy.

Interaction with marine triterpene glycosides: Recent attention has also been drawn to marine triterpene glycosides due to their ability to prevent numerous diseases, particularly cancers. The structural role relating to their biological actions and mechanisms is not fully revealed. However, considering overall aspects, membranotropic and membranolytic activities could be liable for the cytotoxicity and apoptosis of tumor cells. The antitumor effects of stichoposide C (STC) and stichoposide D (STD) are often followed to identify the molecular mechanism involved during their interaction [88]

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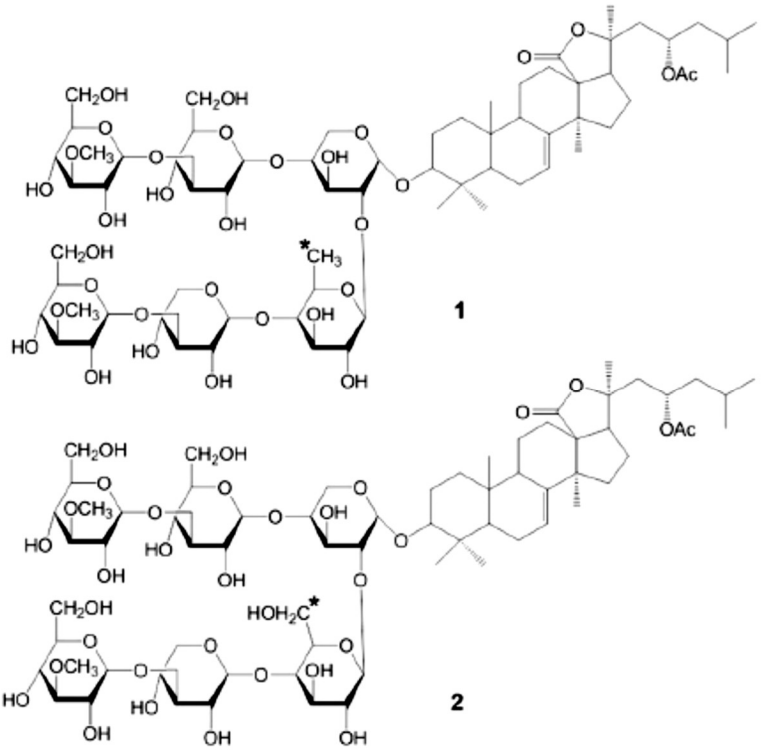
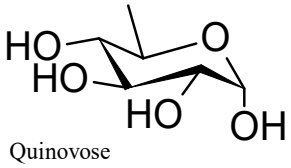


Fig 23. Structure of STC (compound-1) and STD (Compound-2)

The triterpene glycosides are widely available in marine invertebrates, particularly within echinoderms, octocorals, and sponges. STC (compound 1) and STD (compound 2) are hexaosides identified within the green fish sea cucumber. The compounds of those natures are also identified within the family of Stichopodidae (different family of sea cucumbers like Thelenota ananas). Structurally, STC and STD differ only in terms of sugar residue. STC is linked to quinovose (Fig.24), whereas STD has glucose as being second monosaccharide unit (shown with an asterisk in compounds – 1 and – 2). Frondoside A (Compound – 3) and cucumariosides are isolated from the edible variety of sea cucumbers (Cucumaria frondosa and C. Japonica).



Quinovose

Fig 24. Structure of quinovose

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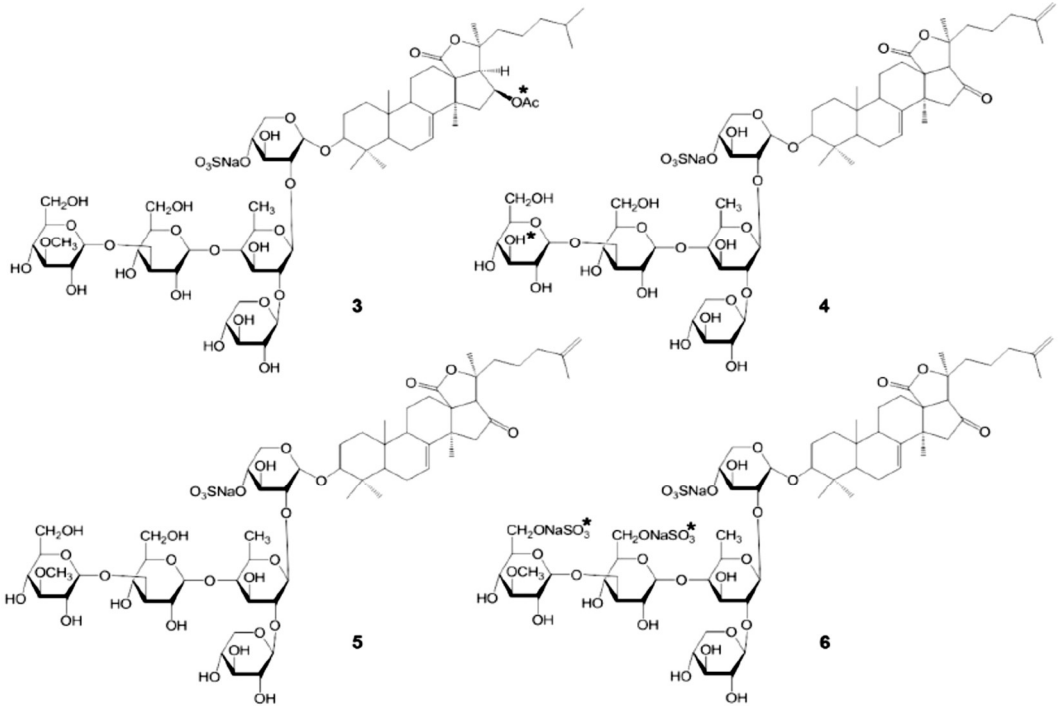

Fig 25. Structures of Frondoside-A (Compound-3 3) and Cucumariosides (Compounds 4 to 6)

Frondoside: A and Cucumariosides are pentosides having main structural differences being the functional group at C-16 of the aglycone (acetoxy or keto group) and the third carbohydrate unit within the carbohydrate chain (shown by an asterisk on compounds 3 and 4). Despite such structural similarity, the biological activity and mechanism of Frondoside and Cucumariosides are observed to be different. Within the last two decades, more than 100 triterpenes have been isolated from various marine sources [89]. They are grouped into four structural categories depending on their aglycone structure: 3 β – hydroxyholost-9(11)-ene aglycone skeleton (structure 7), 9βH–3β–hydroxyholost–7–ene skeleton (structure 8), holostone-type glycosides, and nonholostane glycosides (Fig. 26).

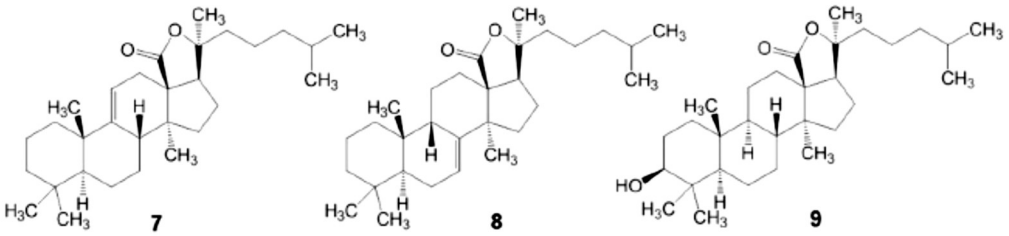

Fig 26. Structures of aglycone skeleton systems with 9(11) double bonds (compound – 7), 9β-H-7(8)-unsaturation (compound – 8)and 3β, 20S-dihydro-5α-lanstano-18(20)-lactone (compound – 9).

The holothurians (sea cucumbers) have carbohydrates and triterpenoids having lanostane derivatives, but the majority containholostane structures. Holostane type includes 3β, 20S-dihydroxy-5α-lanostano-

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18(20)-lactone (compound 9). The glycone containing natural ones from sea cucumbers has 2 to 6 sugar units linked to the C-3 of the aglycone unit. Quinovose, glucose, 3-O-methyl-glucose, xylose, and 3-O-methyl-xylose are the major sugars present in those glycosides. In oligosaccharide chains, the first one is xylose, and 3-O-methyl-xylose sits at the end. In some cases, sulfate groups are bonded to the oligosaccharide chain. Most of them are mono-sulfated, but some are di or tri-sulfated glycosides.

Interaction with cellular membranes: The triterpenes or their glycosides, whether originating from plants or marine sources, work by exerting membranolytic actions, rupturing the cell membranes, enhancing the cellular permeability to demonstrate any biological role. Even so, the exact mode of interaction is not yet fully understood. They interact with the cell membrane while attaching to the surface lipids, making a noncovalent sterol-lipid complex that, in turn, changes the micro-viscosity of the cell surface, including the bioactivity of the membrane proteins. It is, in fact, the basis of numerous ion or peptide channel formation by various sterols, triterpenes, and their glycosides. The stereo-structural positions of carbohydrates and subsequent linking with terpenoid conformation are identified to be the primary cause. Recent studies propose a possible three-step mechanism regarding the event of permeabilization effect exerted by the triterpenoids α – and δ – δ-hederin [88-91].

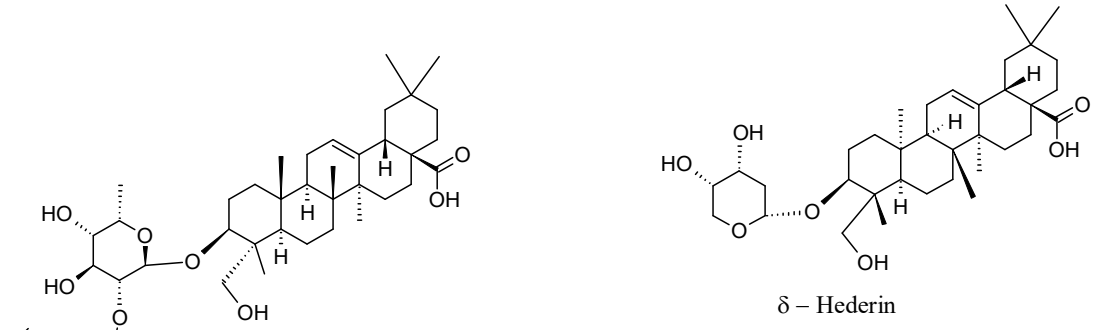

Fig 27.

The mechanism involves: 1) cholesterol-independent binding to the membrane, 2) interaction with cholesterol and asymmetric lateral distribution of saponin, and 3) pore formation as well as the budding of lipid bilayer owing to the enhancement of curvature stress [91].Further interest rests on the fact that at low concentrations (from 10^{-9} to 10^{-6} M) several marine triterpene glycosides from sea cucumbers or sponges are seen to act on specific membrane transport proteins and change their actions. For example, frondoside-A and cucumarioside-A2can inhibit ATP binding cassette (ABC) transporter, multidrug resistance protein-1 (MDR1) [92]. It is also noticed that membrane transporters can be modulated by the triterpene glycosides irrespective of their origins. This event is thus used as a therapeutic target. The transporter proteins could be the basis to explore any triggering molecules, which could be, by nature, a triterpene glycoside used specifically asprecise drugs.

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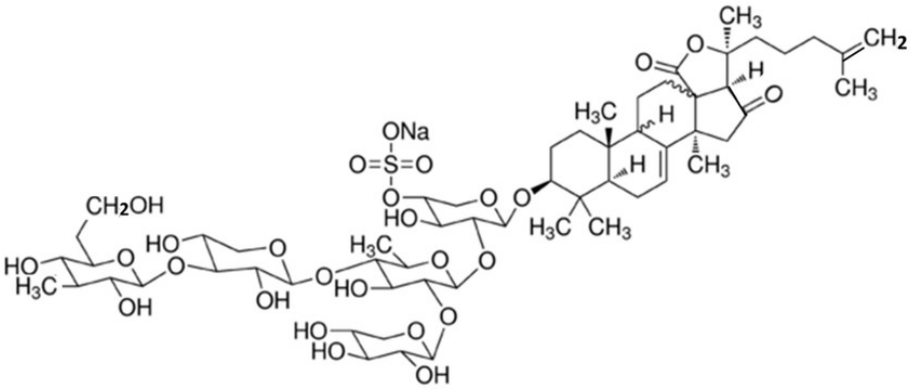

Cucumarioside A_2
Fig. 28.

As, selective inhibition of Na^+ - K^+ - ATPase and Ca^{+2} – ATPase within sarcoplasmic/endoplasmic reticulum along with increased Ca^{+2} influx via L- type voltage-gated calcium channels, transient receptor potential canonical (TRPC) channels and ryanodine receptor leads to the increase of cytosolic Ca^{+2} level which is the basis of positive inotropic effect often caused by several triterpene glycosides like Digoxin. It helps strengthen the contractions of the heart muscle, enabling it to pump more blood with lesser heartbeats, often used during congestive heart failure or when suffering from cardiomyopathy [93]. Additionally, other triterpene glycosides can inhibit voltage-gated Na^+ channels (Nav 1.2 and Nav 1.4). Further, they can induce K^+ currents through voltage-gated K^+ channels (Kv 1.4), calcium-activated K^+ channels (BK_{ca}), and human Ether-a`-go-go related gene (hERG) K^+ channels (Kv 11.1), which are responsible for the vasodilatory and antiarrhythmic actions [92,94]. The antiepileptic as well as neuroprotective effect of triterpene glycosides of plant origins (Ginsenoside Rh_2 and Rg_3, **Fig. 29**) from Panax ginseng is exerted by the inhibition of excitatory N-methyl-D-Aspartate (NMDA) receptors, nicotinic acetylcholine receptors (nAChR) along with the subsequent activation of inhibitory γ – amino butyric acid (GABA) receptors [95].

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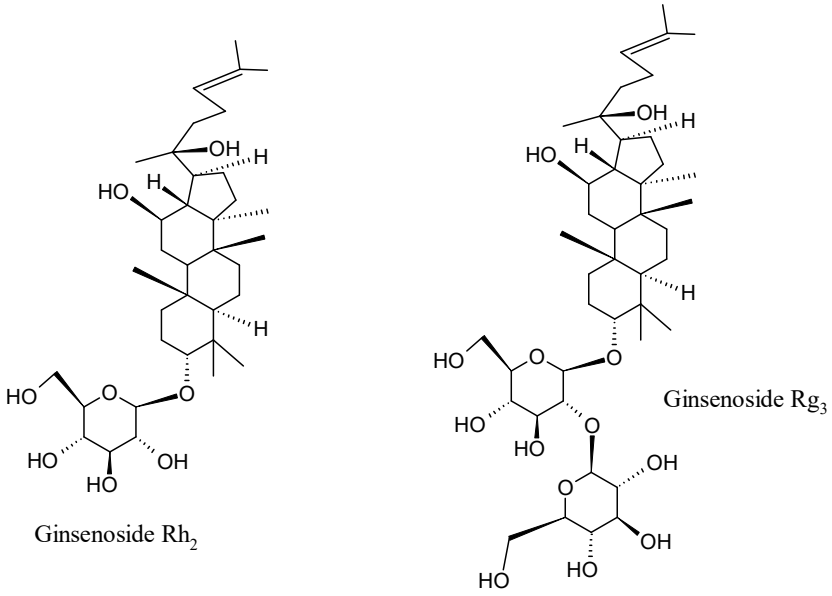
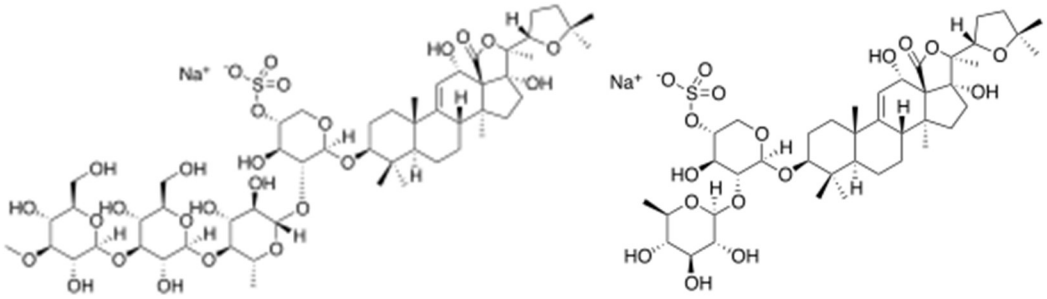


Fig. 29. Triterpene glycosides from Panax ginseng

Molecular structure and effect of marine triterpene glycosides on cancers –Many triterpene glycosides of marine sources, particularly from the sea cucumbers, have shown versatile pharmacological roles, which include anticancer. In laboratory experiments, it is noticed that Holothur in mixture (A and B) inhibits the growth of Sarcoma–180tumor cells in tumor-bearing mice [96]. Further, Krebs-2 Ascitic tumor cells, when previously treated with Holothurin, failed to produce any tumor in healthy mice [88]. Additionally, Holothurin A inhibits the growth of epidermal carcinoma, KB tumor cells in vitro [97].



Holothurin A **Holothurin B**

Fig 30.

A large majority of glycosides belonging to Holothurin A and B categories inhibit the growth of Sarcoma–37 cell lines [97]. Although ample instances areavailable, the exact mechanism behind the inhibitory role remains unestablished. Studies indicate that certain specific groups within the molecular structure are responsible for or necessary for the cell surface interaction. It is identified that presence of 18(20)-lactone in the aglycone with one neighboring oxygen atom (asterisk in below, Fig -30) could be significant for the bioactivity of the compound holding 9(11) – double bond [98] It is also noticed that glycosides having 7(8) double bonds within aglycone without 16- keto group are more active for

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hemolytic effect than those having it. So, the structural nature of aglycones dictates the bioactivity of marine triterpenes.

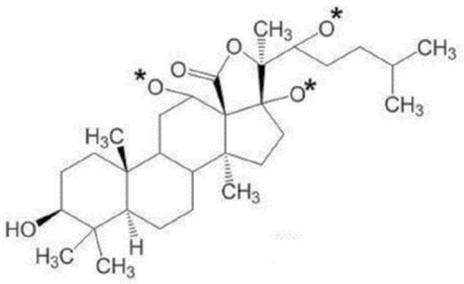
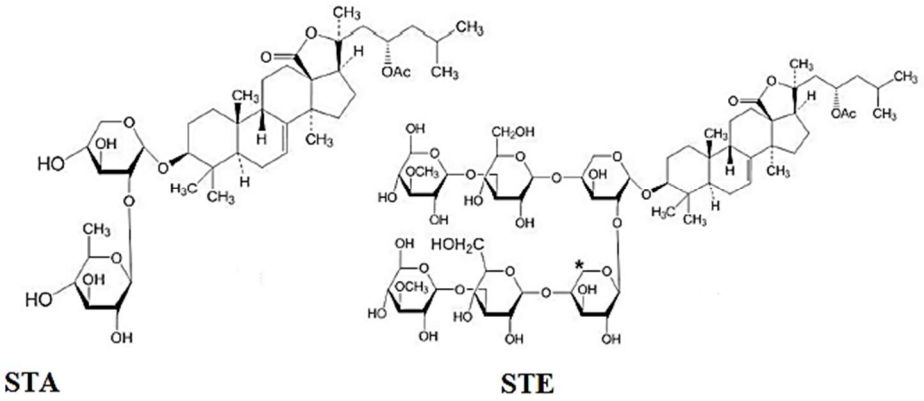


Fig 31. Structure containing 18(20)-lactone in aglycone showing oxygen

Some suggest that the bioactivity of marine triterpene glycosides relies mainly on membranolytic actions. Reports further indicate that the membranolytic effect occurs due to the formation of complexes between the glycosides and 5(6) unsaturated sterols within the target cellular membrane [98]. In that situation, a linear tetrasaccharide chain will be necessary to modify the cell membrane nature or structure [98]. STA, which has two monosaccharide units, and STE, having xylose residue as the second monosaccharide unit, is seen to possess more hemolytic effects. It is also reported that glycosides with quinovose moiety, being the second monosaccharide, have more hemolytic power than the others.



STA **STE**

Fig 32.

Uniquely, the sulfate group attached to the sugar chain within triterpene glycosides also influences the bioactivity [92,99,100]. Sulfate linked to the C-4 of the first xylose of unbranched glycosides with linear tetrasaccharide arrangement (compound A) does not alter much of the bioactivity, whereas its absence (compound B – asterisk position) significantly reduces the effect. On the other hand, the presence of sulfate at the C-4 position of the first xylose of branched chain pentosides having a 3-O-methyl group on the terminal monosaccharide chain would increase the activity, while the same sulfate group lowers the effect of branched chain pentosides that contain glucose at the terminal. Sulfate linked to the C-6 position

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of terminal glucose or 3–O–ethyl glucose residues in triterpene glycosides considerably reduces the biological effects [92,99].

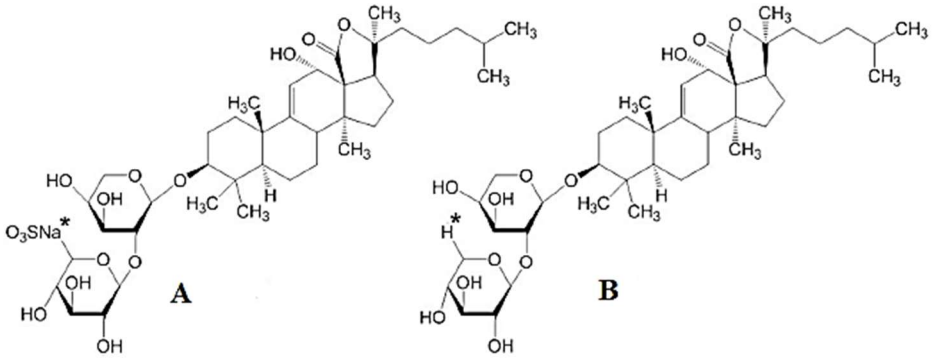

Fig 33.

There are a few more important marine-derived triterpenoid glycosides that could also be effective for anticancer drug therapy. For example, Echinoside A (EA) and DS-echinoside A (DSEA) or Phillinopside A (PA) and E (PE) (Fig.34).

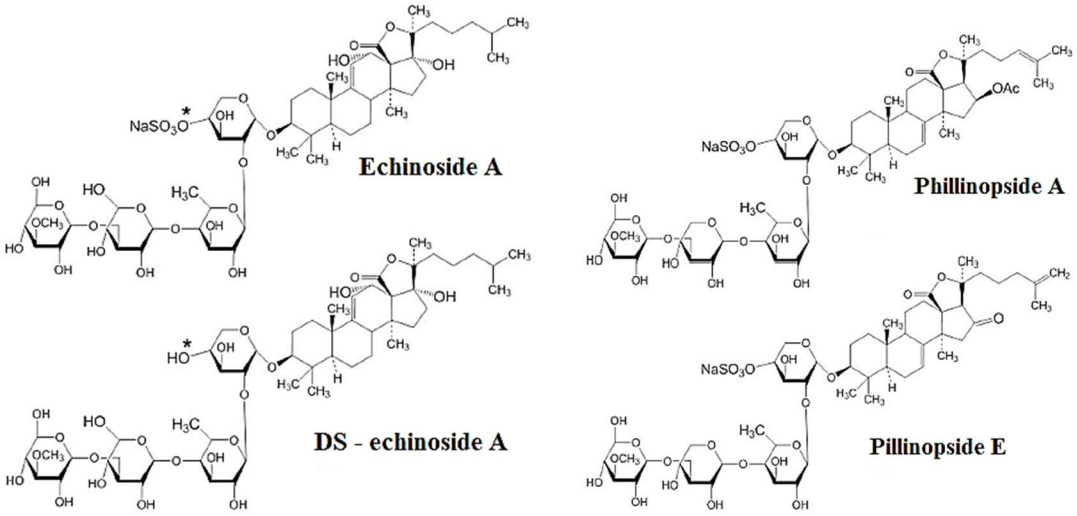

Fig 34.

EA and DSEA are derived from holostane glycoside type, holding 18(20) lactonemoieties. Both possess identical aglycone moieties except for the differences regarding carbohydrate chains. EA has sulfate at C–4 of the first xylose, whereas DSEA holds no sulfate. They are isolated from the sea cucumber (Holothuria nobilis) exhibit strong anticancer actions while noncovalently binding to topoisomerase 2α to DNA, exerting double-strand breaks and imposing subsequent apoptosis. This marine-originated topoisomerase inhibitor inhibits cell proliferation while arresting the cell cycle at G_0 / G_1 phase, subsequently inducing apoptosis. In that regard, DSEA exerts more potent anticancer action, signifying the fact that the sulfate group at C– 4 positions of the first xylose intends to reduce the potency. DSEA inhibits the metastasis of HepG2 cells, which includes cell migration, cell adhesion, and invasion as well.

It suppresses MMP-9 and VEGF expression while enhancing the expression of TIMP by blocking NF–κβ signaling. The event indicates that desulfation at xylose could be related to the targeting of NF–κβduring metastasis of tumors [92].

On the other hand, PA from sea cucumber (*Pentacta quadrangularis*) shows anticancer effect both in vivo and in vitro experiments by inhibiting autophosphorylation of receptor tyrosine kinases that include growth factor receptor, platelet-derived growth factor receptor β, and fibroblast receptor [92,101,102]. But PE, another sulfated saponin from the sea cucumbers, inhibits cell adhesion, migration, and invasion by inhibiting vascular endothelial growth factor receptor 2 signaling, causing suppression of Akt, ERK, focal adhesion kinase, and paxillin (Zinc finger protein helps adhere cells to the extracellular matrix) [101].It is further noted that PE specifically interacts with the extracellular domain of the kinase insert domain-containing receptor (KDR)to block the interaction with VEGF while inhibiting downstream signaling. Specifically, PE suppresses $\alpha_v\beta_3$ integrin-driven downstream signaling, thus disturbing the physical interaction between KDR and $\alpha_v\beta_3$ integrin in human microvascular endothelial cells, followed by the disruption of actin cytoskeleton organization, decreasing the cell adhesion to Vitronectin [92,103].

Table 6. Mechanism behind the anticancer effect of a few marine triterpene glycosides

TRITERPENE	Biological actions	Mechanism	Cell lines
Frondoside A	Inhibition of the cell Proliferation and Induction of apoptosis	Increased expression of p21 caspase Independent pathway, mitochondrial Pathway, increased expression of p53, Decreased expression of Bcl-1 and Mcl-1, increased expression of Bax.	As pC-1, HL-60, MDA-MB.
	Antimetastatic activity	Inhibition of MMP-9, inhibition of Prostaglandin receptor EP2 and EP4	MDA-MB-231, Line 66.1
Stichoposide C And D.	Induction of apoptosis	Extrinsic and intrinsic pathways, Activation of ceramide synthase 6, Ceramide generation.	HL-60, K562.
Cucumioside A2-2, A4-2	Induction of apoptosis	Caspase-dependent pathway	HL-60
Echinoside A	Induction of apoptosis Cell cycle arrest	Inhibition of the noncovalent binding of Topoisomerase 2α to DNA, increased expression ofp16, p21, and c-myc, Decreased expression of cyclin D1.	HepG2 and Human cancer Cells.
Ds-echinoside A	Antimetastatic actions	Inhibition of NF-κβ dependent MMP-9 And VEGF expression	HepG2
Phillinopside A	Induction of apoptosis	Inhibition of receptor tyrosine kinase autophosphorylation	Sarcoma – 180, BEL-7402, MCF-7.
Phillinopside E	Antimetastatic action	Inhibition of VEGFR-2 signaling, Inhibition of interaction between KDR And $\alpha_v\beta_3$ integrin.	

The difference in sugar moiety also shows dissimilar biological action, although the overall effect converges to the same anticancer role. For example, STC exhibits an anticancer effect due to the production of ceramide by a different mechanism than STD due to its difference in sugar moiety. The Structural differences of Frondoside, a Cucumarioside analog, also show different intracellular bioactivities, although both exert membranolytic, cytotoxic, and apoptotic effects [92].

Bioavailability of pentacyclic triterpenes: Bioavailability indicates a fraction of orally administered dose that would reach systemic circulation as an intact drug molecule after its absorption and site-specific metabolic degradation [7]. Foods including vegetables having plant matrices play a critical role in that regard because prior to reaching the intestine, they experience digestion via the mouth, stomach, and duodenum. In that course, interactions with proteins, carbohydrates, and fibers would reduce the absorption of triterpenes due to their lipophilic nature. But in that event, the presence of fat is an important matter since it helps solubilization and micellarization of lipophilic triterpenes, which is an important step for absorption. The bioavailability of triterpenes can be enhanced by lowering their solubility in gastrointestinal fluid and inhibiting their metabolism. Bioavailability differs whether those compounds are administered in pure form or along with the complex matrix, like foods. In case of pentacyclic triterpenes, the bioavailability could be increased with high-fat meals [7,104,105].

Abbreviation:

NF – κβ (Nuclear factor κβ), AP – 1 (Activator protein – 1), STAT - 3 (Signal transduction and activator of transcription factor 3), CDK – 4 (Cyclin dependent kinase 4), ATP (Adenosine triphosphate), NADPH (Nicotinamide adenine di-phosphate reduced form), ROS (reactive oxygen species), NRF2 (Nuclear factor erythroid 2-related factor 2), AKT (Protein kinase B, Threonine/ Serine – specific kinase), MMP (matrix metalloproteases), IKK (IkB kinase), JAK (Janus kinase), Src (Non receptor tyrosine kinase – proto-oncogene), MAPK (Mitogen activated protein kinase), mTOR (Mammalian target of Rapamycin), SHP-1 (Src homology region 2 domain-containing phosphatase-1), EGFR (Endothelial growth factor receptor), PDGF (Platelet derived growth factor), FGF (Fibroblast growth factor), VEGF (Vascular endothelial growth factor), ICAM (Intracellular adhesion molecule), CXCR (Chemokine receptor), CXCL (Chemokine ligand), COX (Cyclooxygenase), CASP (caspase enzyme), SHP (Src homology region 2 domain containing phosphatase), TNF (Tumor necrosis factor), VCAM (Vascular cell adhesion protein), IL (Interleukin), c-FLIP (FLICE like regulatory protein or CASP8), TWIST (Twist related protein / basic helix-loop-helix transcription factor), TRAIL (TNF – related apoptosis-inducing ligand), PARP (poly-[ADP-ribose] polymerase), USP (Ubiquitin specific enzymes), NO (Nitric oxide).

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