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REVIEW

# Triterpenes in cancer: significance and their influence

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**Abstract** Natural products are enriched with numerous compounds with a broad spectrum of therapeutics indication suggesting the role of functional moieties as a core pharmacophore. This review highlights the role of triterpene in targeting signaling pathways in cancer. Advancement in cellular, biochemical, experimental, and computational approaches provides new insights into various pathways in cancer. In signaling network, triterpenes primarily target membrane receptors which control and modulates expression level of the biological responses. Triterpenes are immunomodulatory targeting nuclear factor kappa B, toll-like receptors, signal transducer and activator of transcription 3, and PI3K/Akt/mTOR. Triterpenes isolated from plants and fungus mainly focus on the process of apoptosis while other signaling areas in the cancer are still shrouded. Some of the triterpenes have already passed the clinical trial, whereas many more have been proven to yield effective results. This review would help the researchers to study the role of triterpenes in cancer, thus, helping them to discover and design efficacious therapeutics agents.

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**Keywords** Triterpenes · Receptor tyrosine kinase · PI3K/Akt/mTOR pathway · *Ganoderma lucidum* · Clinical trials

## Introduction

Alteration or the mutation in the critical genes controlling growth and differentiation result in uncontrolled cell proliferation causing cancer [1]. Cancer comprises of mutation in the DNA sequences, epigenetic silencing, and disorganization of the normal functioning of the cell [2]. Functioning of normal as well as cancer cells is regulated by switching on or off of membrane receptors which on receiving stimulus get phosphorylated and activate downstream signaling for cancer progression. The receptors in the cellular membranes are classified on the basis of ligands, how they recognize, their structure and biological response to stimulation. Important among the various receptors are receptor tyrosine kinases (RTK), which has high-affinity surface receptors regulating normal cellular processes as well in cancer pathways [3]. Structurally, RTKs have monomeric as well as multimeric subunit complexes in their receptors. Each monomeric unit has transmembrane spanning domain with N-terminal (extracellular) and C-terminal (intracellular) region. Both playing important roles in cancer signaling; with extracellular N-terminal act as ligand binding site and intracellular C-terminal region regulating the catalytic activity of kinase due to highly conserved nature that catalyzes receptor autophosphorylation [4]. As the external stimulus is received, the ligand binds and stabilize receptor dimerization that causes tyrosine to be trans-phosphorylated and produces a signal for the specific pathway [5]. Activation by phosphorylation of tyrosine residue forms binding site for phosphotyrosine-binding (PTB) domain and Src

homology 2 (SH2) domain, which results in initiation of the signals. Little irregularity in the process by mutation, genetic changes in the intracellular signaling in the RTKs may lead to cancer, diabetes, inflammation, arteriosclerosis, and angiogenesis [6, 7]. The conventional treatment of cancer includes various strategies as surgery, chemotherapy, and radiotherapy, but gene network involved in cancer limits their benefits [8]. All these strategies prove to be fruitful with some side effects [9]. Natural resources have potential to surmount the loopholes of earlier treatment. The prevention or the progression of cancer is controlled by targeting gene network, which creates havoc when uncontrolled during its functioning. Natural products drugs play a leading role in the pharmaceutical use and need isolation of more natural products to form drugs which target multiple sites [10]. Therefore to minimize the side effects, natural products are utilized to design the drugs, without detrimental effect. Nature is endowed with new therapeutic candidates found in plants, animals, and microorganism. Natural products the basis of various drugs [11], this increased the interest of researcher to explore more about natural products. In recent time, sequencing of genome and identification of molecular targets prepare the researcher to work for the discovery of new tools for the treatment of human anomalies. Thus, pharmaceutical companies emphasize for the discovery of such a drug which can target multiple genes. In this review among natural products, particularly, triterpenes were focused on their targets in cancer [12]. Some of the triterpene products were commercialized by various companies in the market while other products are still in various phases of clinical trials.

## Triterpenes

Terpenes are composed of the basic unit, known as isoprene. Terpenoids are categorized into various subclasses depending on the activities displayed by them such as anti-inflammatory, antitumorigenic, and hypolipidemic activity. Structurally, triterpenes are divided into their monoterpenes ($C_{10}$), sesquiterpenes ($C_{15}$), diterpenes ($C_{20}$), triterpenes ($C_{30}$), and tetraterpenes ($C_{40}$), where the carbon skeleton is cyclic, or contains mono, bi, tri, tetra, and pentacyclic structures, respectively. Triterpenes due to versatile medicinal value target anti-cancer, anti-inflammatory, antioxidative, antiviral, antibacterial and antifungal activities [13]. Triterpenes are a widespread group, produced as the arrangement of squalene epoxide in a chair–chair–chair–boat arrangement, lead by the process of condensation [14]. Triterpenes forms the vital composition in the formation of structures in plant membranes which stabilize the phospholipid bilayers in the cell membranes [14]. Pentacyclic triterpene represents the secondary metabolites present in the plant kingdom, found mainly in leaves, stem bark, fruits, and roots [15]. Different plants and fungus are the sources of triterpenes with myriads of medicinal values influencing numerous signaling pathways in cancer [13]. Triterpenoids from plants have been explored for their medicinal values up to some extent, but fungal triterpenes are still unexplored. Different plants and fungal triterpenes are *Ziziphus mauritiana* (betulinic acid), *Boswellia serrata* (boswellic acid), *Tripterygium wilfordii* (celastrol), *Glycyrrhiza glabra* (glycyrrhizin), *Mangifera indica* (lupeol), *Arctostaphylos uva-ursi* (oleanolic acid), *Ganoderma lucidum* (ganoderic acid) (Table 2). Terpenoids comprise of a unit, known as isoprene, which has isopentenyl pyrophosphate (IPP) and its isomer dimethylallyl pyrophosphate (DMAPP) as its activate form, important for the biosynthesis of various terpenoids. IPP formation takes place with acetyl-CoA via mevalonic acid as intermediate in the HMG-CoA reductase (HMGR) pathway. Furthermore, cyclizations of three prenyltransferases synthesize other products namely prenyl pyrophosphates, geranyl pyrophosphate (GPP), farnesyl pyrophosphate (FPP), and geranylgeranyl pyrophosphate (GGPP) [16]. Natural products are a reservoir of indispensable constituents with a broad range of activity. The different target of triterpenes includes nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$\kappa$B), tumor necrosis factor (TNF), Signal transducer and activator of transcription 3 (STAT3), Toll-like receptor (TLR), and PI3K/Akt/mTOR.

## Triterpenes and receptors

Through different means, RTKs get activated by dimerization using different strategies of a ligand for inducing active form. The receptor of epidermal growth factor (EGFR; ErbB) family encompass four members namely Her1, Her2, Her3, Her4. Irregularity in the ErbB signaling in humans lead to the development of anomalies like neurodegenerative diseases, multiple sclerosis, and tumor [17]. In cancer, mostly ErbB1 and ErbB2 are critically involved in cancer; some reports also highlight the involvement of ErbB2 in PI3K/AKT molecular signaling pathway. Insulin receptor (IR) gets activated by insulin and insulin-like growth factor (IGF-I, IGF-II) [18]. IR critically regulates glucose homeostasis and forms a vital link between cancer and diabetes [19]. Platelet-derived growth factor receptors (PDGF-R), act as key downstream mediators of Ras/mitogen-activated protein kinase (MAPK), PI3K, and phospholipase-$\gamma$ (PLC$\gamma$) pathways. Vascular endothelial growth factor receptor (VEGF), another receptor has a vital role in numerous signaling

pathways indispensable for the process of cell migration and angiogenesis. The fibroblast growth factor (FGF) are unable to activate FGF receptors (FGFR) without accessory molecule heparin sulfate proteoglycan (HSPG), and any perturbation leading to cancer [20]. RTK initiates myriads of downstream signaling leading to apoptosis, NF-κB, mTOR and cell cycle, and little aberration or deviation leads to a modulation in signaling leading to cancer [6]. To minimize the effects that lead to the abnormalities, natural products prove to have promising outcomes. Different studies exhibit the potential of numerous triterpenoids in cancers and inflammatory disease [14]. About one-fourth of total drugs synthesized belongs to natural sources and the United States alone synthesized more than 100 drugs. Triterpenoids target various factors responsible for progression and development of cancer.

## Targets of triterpenoids

Terpenoids inhibit cell proliferation, induces the progression of tumor cell death by targeting multiple cancer-specific targets by the proteasome, B cell lymphoma 2 (Bcl-2), NF-κB, STAT3, TNF, angiogenesis, PI3K/Akt/mTOR, and (TLR) [12–21]. This review highlights the potential of triterpenes to modulate signaling in the cancer pathway. In addition to above, triterpenes target mTOR (mammalian target of rapamycin), ATM (ataxia telangiectasia mutated) which possesses PI3K-homologous kinase domain with conserved carboxyl-terminal tail [22]. Literature revealed that triterpenes in different plants and fungus mainly target the PI3K/Akt/mTOR and NF-κB signaling pathway in cancer.

## PI3K/Akt/mTOR pathway

Phosphatidylinositide 3-kinase is commonly known as PI3K or PtdIns3P. Membrane receptors such as receptor tyrosine kinases (RTK) is present on the cell surface, activates the PI3K signaling. Majorly, mutation and amplification of RTKs cause oncogenic activation of PI3K pathway. This includes EGFR (ERBB1) and HER2 (ERBB2), subunits of PI3K, Akt (Akt1) or activating isoforms of RAS. PI3K/Akt/mTOR pathway is crucial in promoting growth and differentiation specifically in adult stem cells and neural stem cells [23].

Loss-of-function or expressions of tumor suppressor gene phosphatase and tensin homolog (PTEN), resulted from phosphorylation by growth factors in phosphatidylinositol in the D-3 position of the inositol ring. Adapter signaling molecules maintains the structure of heterotrimeric guanosine triphosphate (GTP)-binding proteins which bind to D-3 phosphorylated phosphoinositides specifically. These signaling molecules when unphosphorylated remain in the cytoplasm but when phosphorylated gain the potential to combine to phosphoinositides which is newly formed, thus accumulating in the cell membrane. This activation leads to subsequent activation of numerous signaling cascades in the plasma membrane [25].

PI3K family is categorized by primary structure, regulation, lipid substrate specificity, and substrate preferences of Class I, II, III, and IV [26]. Different categories of PI3K are accountable for the production of D-3 phosphoinositides in response to growth factors. The PI3K and its downstream signaling proteins of class I produces phosphatidylinositol 3-phosphate (PI-3-P), phosphatidylinositol (3,4)-bisphosphate (PI-3,4-$P_2$) and phosphatidylinositol (3,4,5)-trisphosphate (PI(3,4,5)$P_3$. Class I are heterodimeric molecules comprising of the regulatory and catalytic subunit and further subdivided into IA and IB by the resemblance of the sequence. Class IA PI3K enzyme are a heterodimer of p110α, p110β, p110δ catalytic and p85 regulatory subunit [27] (Table 1). Regulatory subunit maintains the p110 low activity state in the quiescent cell and controls its activation by phosphotyrosine activation of the adapter proteins. There are eight isoforms of p85 containing two SH2 domain that show interaction with phosphotyrosines on activated RTKs. Platelet-Derived Growth factor receptor (PDGFR) and insulin receptor (IR) have binding sites for p85 and activate IA of PI3K [25].

p110γ is a Class Ib member, which gets activated by two subunits of the heterotrimeric G proteins, which get released into seven transmembrane receptors. Class II comprises mainly of three members (PI3KC2α, β, and g) characterized by a carboxyl-terminal phospholipids-binding domain and regulatory subunit has not been reported till now. The Class III kinases VPS34p is accountable for producing the majority of the cellular PI3P (Table 1). PI3P leads to the protein trafficking through the lysosome PI3K indulge in cell growth, proliferation, differentiation, motility, survival and other functioning of the body [25].

The pleckstrin homology domain of Akt interact and binds to PtdIns (3,4,5)P3 and PtdIns (3,4)P2, which are produced by activated PI3-kinase. PtdIns (3, 4, 5) P3 and PtdIns (3,4)P2 has been bound to plasma membrane leading to the Akt translocation in the plasma membrane. Association with PI(3,4,5)P3 at the membrane facilitates the phosphorylation by 3-phosphoinositide-dependent protein kinase 1 (PDK1) [28]. Thr308 and Ser473 residues are found to be active during interaction between pleckstrin homology (PH) domain and PtdIns (3,4,5)P3 recruitment in the plasma membrane [29]. Furthermore, it brings into light that full activation occurs upon phosphorylation of serine 473 by the TORC2 complex of the mTOR protein kinase. Phosphorylation of Thr308

**Table 1** PI3K and their subunits

| Class | Catalytic unit | Regulatory unit | Activation target | Products |
|---|---|---|---|---|
| Ia | p110α | P85 | RTK | PtdIns-3,4,5-P3 |
| | p110β | | RAS | PtdIns-3,4-P2 |
| | p110δ | | | PtdIns-3-P |
| Ib | p110γ | P101 | Heterotrimeric G proteins | PtdIns-3,4,5-P3 |
| | | – | – | PtdIns-3,4-P2 |
| | | – | – | PtdIns-3-P |
| II | PI3KC2a | – | RTK, integrins | PtdIns-3,4,-P2 |
| | | | | PtdIns-3-P |
| | PI3KC2b | | – | – |
| | PI3KC2g | – | – | – |
| III | VSP34p | – | – | PtdIns-3-P |

residue has been mediated by PDK1 with PH domain that binds to PtdIns (3,4,5)P3 [30]. PDK1 is the master kinase crucial for the activation of PKB belonging to AGC kinases including PKC, S6K, SGK (Fig. 1). It propagates and regulates the downstream signaling by the interaction of membrane phospholipids comprising of phosphatidylinositols, phosphatidylinositol (3,4)-bisphosphate (PtdIns(3,4)$P_2$) and phosphatidylinositol (3,4,5)-triphosphate. PI3K controls the downstream signaling of serine-threonine protein kinase, also known as protein kinase B, found to be important in apoptosis, cell proliferation, transcription and cell migration. Three isoforms including (PKBα), (PKBβ) and (PKBγ) are closely related to each other and have similar structure and size [31]. To date, no differences in the substrate selectivity have been clarified and believe to have similar substrate specificity. Structurally, it comprises of the N-terminal pleckstrin homology (PH) domain, a central catalytic domain and a C-terminal and in which PH domains can specifically bind to the D3-phosphorylated phosphoinositides regulatory region. PI3K Activation needs different adaptor molecules with the involvement in the process of phosphorylation. Upon PI3K activation and production of PI-P3, PI-P2 is recruited to the plasma membrane where it binds to the PH domain of the phosphoinositides. Phosphorylation of Thr 308 residue in the kinase domain is important for the activation event. On the other hand, phosphorylation of Ser 473 of C-terminus is required for maximum activity. In addition, PI3K pathway also activates and recruits other downstream signaling proteins, including mTOR, Glycogen synthase kinase 3 beta (GSK3β), and postsynaptic density protein 95 (PSD-95) [32]. Important downstream proteins which have an influence on PI3K encounter are GSK3, IRS-1 (insulin receptor substrate-1), PDE-3B (phosphodiesterase-3B), BAD, NF-kB transcription factors, mTOR, Raf-protein kinase, BRCA1, and p21 Cip1/WAF1 [33].

Akt is a serine-threonine kinase regulating the cell proliferation, metabolism, migration, and survivability. Akt is considered as a central node connecting various upstream PI3K, PTEN, neurofibromin 1 (NF1), LKB1(human tumor suppressor), downstream tuberous sclerosis complex 2 (TSC2), Forkhead box O (FOXO) and eukaryotic translation initiation factor (eIF4E). Tumor suppressors such as PTEN, forkhead box protein (FOXO), LKB1, TSC2/TSC1, NF1, and Von Hippel–Lindau tumor suppressor (VHL) are the negative regulator of the Akt-mTOR pathway. Any perturbation upshot in a modification in the process of translation that regulate cellular processes of autocrine growth stimulation, communication with the extracellular environment and cell cycle progression [34]. The process of phosphorylation in Akt inactivates the BAD and procaspase-9 (proapoptotic factors), crucial in the process of apoptosis. Phosphorylation of the Akt inactivates FOXO, which has a key role in the regulation of gluconeogenesis and glycogenolysis by insulin signaling. Along with this, Akt activates IκB (IKK) in NF-κB signaling pathway [35]. In addition, Akt also activates and controls the downstream molecule interaction with mTOR kinase by inhibiting a complex formation by the tumor suppressor proteins (TSC1 and TSC2) [36]. mTOR phosphorylates p70 S6 kinase (p70 S6K) and eIF4E binding proteins and stimulates protein synthesis (Fig. 1). Subsequently, p70 S6K phosphorylates the ribosomal protein S6, which increases the process of translation of mRNAs with 5′-terminal oligopoly pyrimidine (5′TOP) tracts. This, in turn, phosphorylates the 4E-BPs and, releases the initiation factor eIF4E to promote cap-dependent translation which is encoded by cyclin D1, myc and VEGF [37]. Above all, mTOR also targets hypoxia-inducible transcription factor (HIF-1). Liu and his team reported Akt activity in the telomerase that stimulates telomerase activity and replication [38].

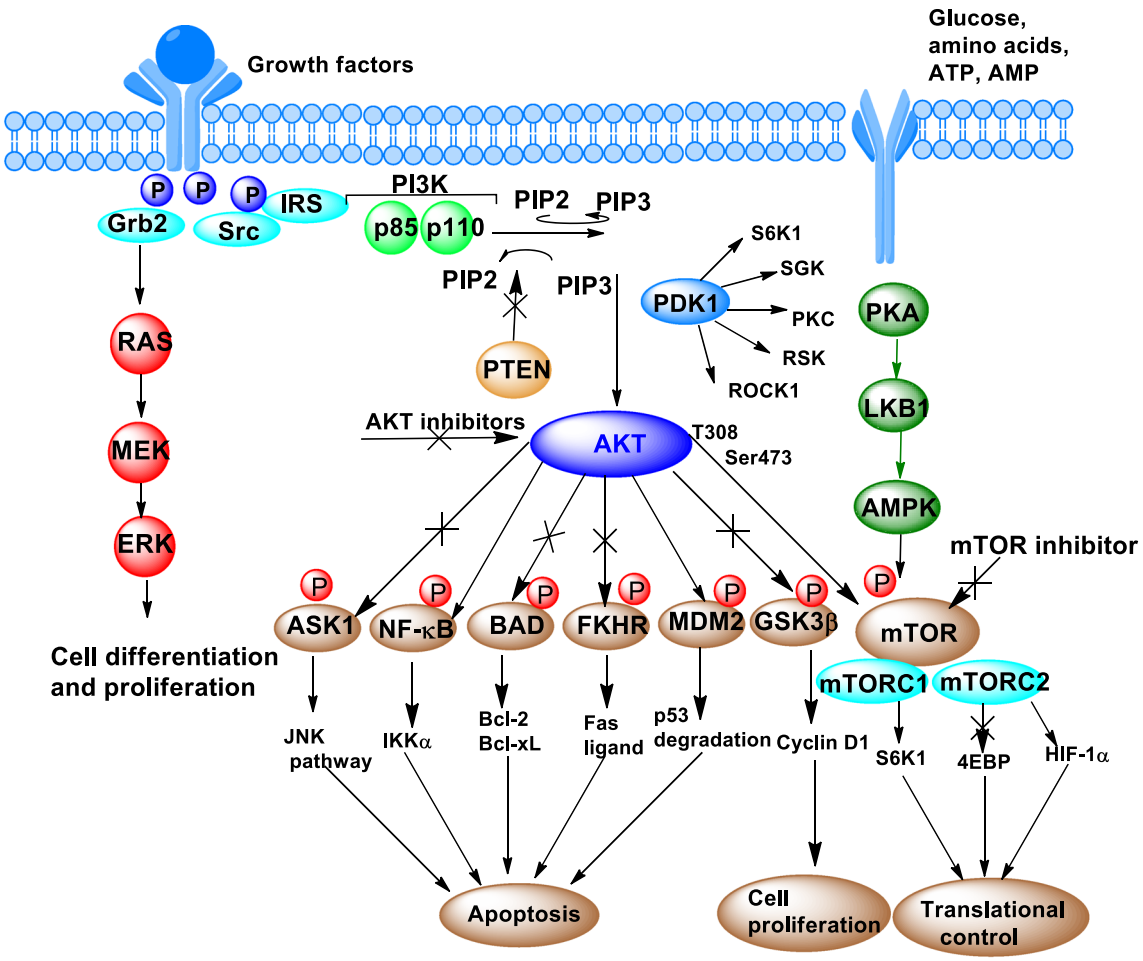


**Fig. 1** Mechanism of action of RTK and their downstream signaling in PI3K/Akt/mTOR pathway. Stimulus phosphorylates the RTKs which subsequently activate PI3K and its downstream proteins through binding of different adaptors, such as IRS1. PI3K phosphorylates PIP2. These events result in the formation of PIP3, which exhibits reversible characters by tumor suppressor gene, PIP3 phosphatase PTEN. Akt and PDK1 (3-phosphoinositide-dependent protein kinase 1) bind to PIP3 subsequently PDK1 phosphorylates the activation loop of AKT at T308. PDK1 is the master kinase crucial for the activation of /PKB belonging to AGC kinases including PKC, S6K, SGK and leads to activation of Akt. Akt furthermore enhances or repress different protein such as ASK1, NF-KB, BAD, FKHR, MDM2, GSK3β, which control the functioning of apoptosis and cell survivability. RTK signaling also activates mTORC1 and phosphorylates S6K1 and also inhibits 4EBP whereas mTORC2 phosphorylates HIF-1α and thus regulates the growth translation. This pathway highlighted the importance of mTOR pathway in cancer and diabetes 2 [24]

mTOR is a 289-kDa serine-threonine kinase regulating cell proliferation, cell survival, autophagy, transcription, and protein synthesis of PI3K related kinase family [39]. mTOR exists in two distinct complexes (mTORC1, mTORC2) which amalgamate both intracellular and extracellular signals and regulates downstream signaling. mTOR complex 1 (mTORC1), contains mTOR, Raptor, GβL, and DEPTOR and is inhibited by rapamycin. Rapamycin binds to FK506-binding protein which later on binds FKBP12-rapamycin binding domain (FRB) of mTOR and inhibits mTORC1 functions [40]. In contrast to mTORC1, FKBP12-rapamycin does not exhibit interaction and inhibits mTORC2, thus categorizes into rapamycin-sensitive and rapamycin-insensitive [41]. The role of mTOR highlighted in the process of protein synthesis by promoting phosphorylation eIF4E binding protein and S6K1. mTOR catalytically degrades the cells of unnecessary cellular components through the action of lysosomes called autophagy that is repressed by mTORC1 [42]. Blocking the Akt/mTOR pathway impedes the proliferation of tumor cells by modulating apoptosis in response to other cytotoxic agents. Chemoresistance remains a major problem in cancer therapy. Literature marks Akt an anti-apoptotic, which plays a significant role in cell survival. Page research group demonstrated the overexpression of ovarian cancer with Akt1 or Akt2 activity, which was highly resistant to paclitaxel [43]. Friedrichs research group demonstrated that hampering of Akt/mTOR pathway by

rapamycin reinstate the susceptibility to tamoxifen in breast cancer cells [44]. Currently, available mTOR inhibitors by Novartis, Wyeth Research, RAD001, and CCI-779 respectively, are being assessed in cancer patients. Mechanistically, these products target the immunophilin FK506 binding protein, FKBP12, which interact and attach to the active site of mTOR, thus prevents the process of phosphorylation in S6K and 4EBP1 [45]. Reports also indicate minor toxic effects of rapamycin derivatives, but RAD001 proves to be effective in minimizing the impact of prior therapies such as heritable hamartoma syndrome featured by perturbation of the Akt/mTOR pathway. RAD001 enhances the cisplatin-induced apoptosis process by inhibiting p53-induced p21 expression. Furthermore, doses with less content of DNA-damaging agents exhibits to synergize with RAD001 and plausible agent to minimize the side effects of conventional therapies [46].

## NF-κB pathway

Nuclear factor kappa B (NF-$\kappa$B) is a transcription factor regulating expression of genes caught in various physiological processes [47]. During inactivated phase, NF-$\kappa$B complex is formed with inhibitor protein of κB (IBs), which is present in the cytoplasm, and any external stimuli cause activation of the complex. Furthermore, ubiquitination and degradation of IBs causes translocation of NF-$\kappa$B complex from cytoplasm to the nucleus. Minute aberration in the NF-$\kappa$B signaling pathway results in several anomalies leading to the death. Constitutive activation of NF-κB is usually observed in several types of cancer [48]. IKK complex comprise of three subunits namely key regulatory element possessing two kinase subunits, IKK-α (IKK1) and IKK-$\beta$ (IKK2), and third regulatory subunit NF-$\kappa$B Essential Modulator or IKKc [47]. Different plant based triterpenes were involved in the NF-$\kappa$B pathway, but few of fungal triterpenes were reported to target this way (Table 3). Ganoderic acid, triterpene of *G. lucidum* revealed that isoform GA-A, GA-H hampers NF-κB signaling and inhibits the progression of breast cancer [47].

*Nuclear factor of activated T-cells (NF-AT)* is $Ca^{2+}$ dependent transcription factors, controlling lymphokine gene expression in T cells. Stimulation of the T cell receptor translocates NF-AT from the cytoplasm to the nucleus. Impressic acid from *Acanthopanax koreanum*, and 3 α-acetoxy-25-hydroxy-olean-12-en-28-oic acid, and lantanolic acid from *Liquidambar formosana* causes inhibition of NF-AT. Rios research group mechanistically showed that inhibitory action is due to oxy methylene group at C25 along with an acetoxyl group at C3 in NF-AT [49].

## Signal transducer and activator of transcription 3

Signal transducer and activator of transcription (STAT) proteins regulates the functioning of differentiation, development, immune response, proliferation, and apoptosis [50]. STAT3 are DNA-binding factors that bind selectively to the promoter region of the IL-6-responsive element, one of the major targets of triterpenoids. STAT3 proteins behave in a unique fashion and transduce the extracellular signals and modulate the transcription process. STAT gets phosphorylated on tyrosine 705 by receptor-associated kinases in response to various growth factors and cytokines. Constitutive STAT3 activation results in various human cancers and demonstrates its anti-apoptotic as well as proliferative activity [51]. STAT3 regulates the expression of c-myc and cyclin D1, Bcl-xL, Bcl -2 and surviving and promote angiogenesis [52]. Irregularity in STAT3 signaling due to genetic mutation results in different kinds of cancer [53]. Cucurbitacins inhibit activation of STAT3, particularly cucurbitacin E break the symmetry of structure of actin and vimentin in cytoskeleton and inhibits the proliferation of prostate cancer cells and recognized as anti-tumor agent [54]. Cucurbitacin R target and inhibits the activation of STAT3 in peripheral human blood lymphocytes stimulated with IL-6 [55]. Ursolic acid inhibits the activation of IL-6 inducible STAT3 in dose and time-dependent manner in multiple myeloma cells. Ursolic acid inactivates the myeloma cell, which results in suppression of kinases c-Src, Janus-activated kinase 1, Janus-activated kinase 2, and extracellular signal–regulated kinase ½ [56].

## Tumor necrosis factor (TNF)

Numerous factors instigate the process of apoptosis and foremost among them is tumor necrosis factor (TNF) acting on the receptors. The tumor necrosis factor (TNF) family includes TNF-alpha (TNFα), TNF-related apoptosis-inducing ligand (TRAIL), Fas ligand (FasL) cytokines indulged in numerous cellular processes [57]. Upon stimulation by the ligand, TNF receptors form trimers by proper orientation of the monomers into the groove of monomers. Ligand-mediated trimerization by the TNF family ligands causes recruitment of several intracellular adaptors. This process leads to a structural change in the receptor, intricating in the dissociation of inhibitory protein silencer of death domain (SODD) from the intracellular death domain. As a result, dissociation causes the adaptor protein TRADD to tie up with death domain that activates multiple signal transduction pathways. TRADD activates

and initiates kappa B (NF-κB), MAPK, JNK, and caspases transcription factor.

The exact mechanism behind the activation of NF-κB is not yet clear, but some studies demonstrated that death receptors (DR4, DR5, FADD, TRADD) trigger their activation [58]. TNF triggers the activation of Ikappa B (IκB) kinase (IKK)/NF-κB and mitogen-activated protein kinase (MAPK)/AP-1 pathways, essential for the expression of pro-inflammatory cytokines. TNF induces the activation of JNK, which evokes the moderate response of the p38-MAPK and accountable for minimal activation of AP-1. TNF has emerged as a hot spot for tumor progression, invasion, and metastasis [59]. Agents are targeting TRAIL receptors DR5 undergone both preclinical models and phase I clinical trials and considered possible targets for the development of antitumor agents [60]. Many trials verified their safety, tolerability and therapeutic efficacy of TRAIL in patients. Several studies have demonstrated that DR5 expressed in the primary tumor and cancer cell lines [61].

## Toll-like receptor (TLR)

TLRs are members of interleukin-1 receptors (IL-1Rs) superfamily proteins, membrane-spanning, single receptor usually expressed in sentinel cells having a role in defense mechanism. The amino acids present in three conserved boxes of Toll/IL-1R (TIR) domain (TIR) motif are crucial for signaling. TLR triggers signals important in NF-κB, MAP kinases, and others genes playing vital role eliminating Gram-negative bacterial infection which provides an edge to study immune system [62]. TLR are the non-catalytic receptors, recognize structurally conserved molecules derived from microbes in the innate immune system. They recognized specific molecular pattern present in the microbial pattern and induced an antimicrobial immune response [63].

## Terpenoids influencing different pathways

### Apoptosis

Apoptosis is highly regulated and controlled process, depicted by distinct morphological and energy-dependent biochemical mechanism [24]. Events include blebbing, DNA fragmentation, cell shrinkage, the nuclear fragmentation which result in cell death [64]. Triterpenes target the process of apoptosis, either through the intrinsic or extrinsic mitochondrial-dependent manner. Intrinsic pathways mainly target and hamper the anti-apoptotic and pro-apoptotic factor of bcl-2, marked by chromosomal translocation in Bcl-2. During abnormal conditions, mechanism gets hampered, Bax migrates to the mitochondria inhibiting Bcl-2 which consequence in the release of cytochrome c by forming a channel. Furthermore, cytochrome c binds to protein Apaf-1 (apoptotic protease activating factor-1) and ATP, which forms a complex known as apoptosomes which, in turn, binds and activates caspase-9 [65]. This activation of caspases, in turn, initiate a signaling cascade of events which cleaves and activates other caspases engrossed with proteolytic activity. This activity does result in cell death or cell differentiation [66]. Numerous factors also initiate signaling cascade directly by stimulating apoptosis, importantly tumor necrosis factor and its receptors [67].

### Angiogenesis

The Vascular system supplies nutrients to tissues and removes the waste product and plays a key role in metabolism in the body. Angiogenesis is the fundamental step in tumor formation, characterized by poor vascularisation network in term of blood or lymphatic vessels [68]. As the tumor cells lost the ability of controlled division, it needs to supply blood and remove waste materials by growing vascular network. Tumor angiogenesis is regulated and controlled by growth factors to support neovascularization, such as VEGF, basic Fibroblast Growth Factor (bFGF) and factor regulating is HIF-1. The HIF-1 comprises of HIF-1α and β subunits. The HIF-1α expression can be stimulated by the loss of function of VHL and PTEN and low concentration of oxygen. The growth factors can induce the HIF-1α expression through activation of PI3K signaling [69].

### Anti-inflammatory

Inflammation is an indicative process which causes increased blood flow and vascular permeability, activation of defense mechanisms, sensibilization, and activation of receptors. The mediators initiate and modulate the signaling network leading to obesity, cardiovascular disease, and cancer. Anti-inflammatory compounds may block the biosynthesis of proinflammatory action mediated by enzyme action or blocking receptor interaction [70]. Triterpenes isolated from virgin olive oil exhibits antitumoral and anti-inflammatory activity. Triterpenes (maslinic acid) enhances the production of IL-8, IL-1α, and IL-1β and exhibits inflammatory action. It promoted IFN-γ response, without altering expression level of NF-κβ or NO [71].

### Triterpenoids from plants

Terpenoids are the diverse class of chemicals produce by the plant with numerous therapeutic effects. Secondary

metabolite majorly, terpenoids protects the organism from the abiotic and biotic environment. Saikosaponin C is isolated from *Radix bupleuri* having the potential of inducing an effect on viability and growth on human umbilical vein endothelial cells. Saikosaponin C enhances the gene expression responsible for cell migration and capillary tube formation in the endothelial cell (MMP2, VEGF, and the p42/p44 MAPK) [72]. Immunohistochemistry studies of celastrol demonstrate the decrease in the level of VEGFR1 and VEGFR2 expression, but no change in VEGF expression [73]. In vivo study conducted by Kimura and his research group demonstrated that *G. lucidum,* when administered, inhibit primary solid tumor in liver and spleen, whereas secondary tumor in lung cancer in mice [74].

Programmed cell death is a regulated intracellular event crucial for plant and animal tissue development. Natural sources and their products with scaffold and group modification form the basis to design and synthesize effective drugs (Fig. 2). Among the numerous natural products, terpenes are the most highly valued compounds. The terpenes present in β-eudesmol (sesquiterpenes) results in inhibition of different pro-apoptotic events JNK, MAPK, and downregulation of Bcl-2, cytochrome *c* and a decrease in matrix metalloproteinases (MMP) [102]. Oridonin (diterpenoid isolated from *Rabdosia rubescens*) inhibits mTORC1 by reducing p-mTOR and p-p70s6k levels in A549 and NCI-H292 non-small cell lung cancer cell lines [103]. Myriad of evidence indicates the role of terpenes in inhibiting the process of apoptosis by inhibiting JAK2, STAT3 inhibition by acetyl 11-keto-β-boswellic acid from *Boswellia serrata* [80, 81]. Inspite of above, terpenes also induces apoptosis by blocking the NF-κB and involve different factors bcl2, BCL-xl, c-myc, cyclin D1 from nimobolide from *Azadirachta indica,* betulinic acid from *Pusatilla chinesis* (Table 2).

*Alisol B* is a triterpene derived from *Alisma Plantago-aquatica* with glucocorticoid-like structure, inhibiting prostate cancer by mitochondrial dysfunction. It destroys human gastric cancer by inhibiting phosphorylation with an increased Bax expression and reducing mitochondrial membrane potential accompanying activation of caspases. Alisol B also boosts $Ca^{2+}$ concentrations by blocking sarco/endoplasmic reticulum $Ca^{2+}$ inhibitor pumps which cause autophagy resulting in phosphorylation of AMPK and mTOR [96]. Alisol B acetate inhibits SGC7901 cell line (gastric) proliferation in dose and time dependent manner. The process of apoptosis in the SGC7901 cells was analyzed resulting in modulation of biochemical events such as loss of mitochondrial membrane potential, and disturbances in the behavior of cell cycle [95].

*Betulinic acid (BA),* a pentacyclic lupane-type triterpene present in the outer bark of a variety of tree species [104] inhibits the activation of NF-κB, cyclooxygenase-2, and MMP-9 induced by TNFR 1, TNFR-associated factor 2, NF-κB-inducing kinase, TNFR-associated death domain, and IκBα kinase [75]. Betulinic acid modulates the functioning of mitochondria, exhibiting antiangiogenic property by inhibiting growth factor in endothelial cells. Betulinic acid activates proteasome-dependent degradation of Sp1, Sp3, Sp4 protein that regulates the vascular endothelial growth factor (VEGF) expression [76].

*Cucurbita pepo (Pumpkin)* is used as a remedy to treat gastritis, constipation and expel worm from the intestine. Cucurbitacins is a tetracyclic triterpenoid obtained from *Cucurbitaceae* family. Cucurbitacin B is known to inhibit the STAT3, STAT5 and JAK2 phosphorylation in the pancreatic cancer cell lines (Panc-1 and MiaPaCa-2). Cucurbitacin B inhibits JAK-STAT pathway by modulating the downstream proteins such as c-myc, cyclins, survivin and p53, Bcl-xL and Bcl-2 [85]. Cucurbitacin E (CuE) activated 5′ adenosine monophosphate-activated protein kinase (AMPK), which induces suppression of mTORC1/p70S6K signaling and autophagy induction [86].

*Saikosaponins a* (*SSa*), derived from the root of *Bupleurum falcatum* L. inhibits the receptor activation in the nuclear factor-κB ligand (RANKL) and induces osteoclastogenesis by suppressing MAPK and NF-κB pathways. It was observed to decrease NFATc1, c-fos and cathepsin marker protein in osteoclastogenesis. SSa inhibits IκBα and p65 phosphorylation in the NF-κB signaling pathway in RAW264.7 cells. In addition, SSa also suppressed RANKL induced phosphorylation in p-38, ERK, and JNK, which as a consequence hampers osteoclastogenesis [79].

*Azadirachta indica* is a plant of ethnobotanical importance used in various human diseases. The active compound nimbolide, the main constituent isolated from *Azadirachta,* has a basic limonoid skeleton with α, β-unsaturated ketone system, and a δ-lactone ring. Elumalai research group explicit the potential of nimbolide to reduce the IGF-I-mediated PI3K and MAPK signaling in MCF-7 and MDA-MB-231 cells (breast cancer cell lines). Mechanistically, it down-regulates the signaling of IGF-IRβ, insulin receptor substrate 2 (IRS-2), and PI3K, but on the other hand, it up-regulates the expression of insulin-like growth factor binding protein 3 (IGFBP-3) and PTEN. Nimbolide inhibits the protein expression of N-Ras, MEK, and pERK1/2 and p38 when treated in MCF-7 and MDA-MB-231 cells. Furthermore, in breast cancer, it decreases the β-catenin and c-Myc expression and repress cyclin in at G0/G1 in the cell cycle [97].

*Withanolide* is obtained from *Withania somnifera Dunal*, suppress the activation of NF-κB in the cancer signaling. As a consequence, it inhibited the kinase activation, phosphorylation, degradation of the IκBα subunit, as well as phosphorylation and nuclear translocation of

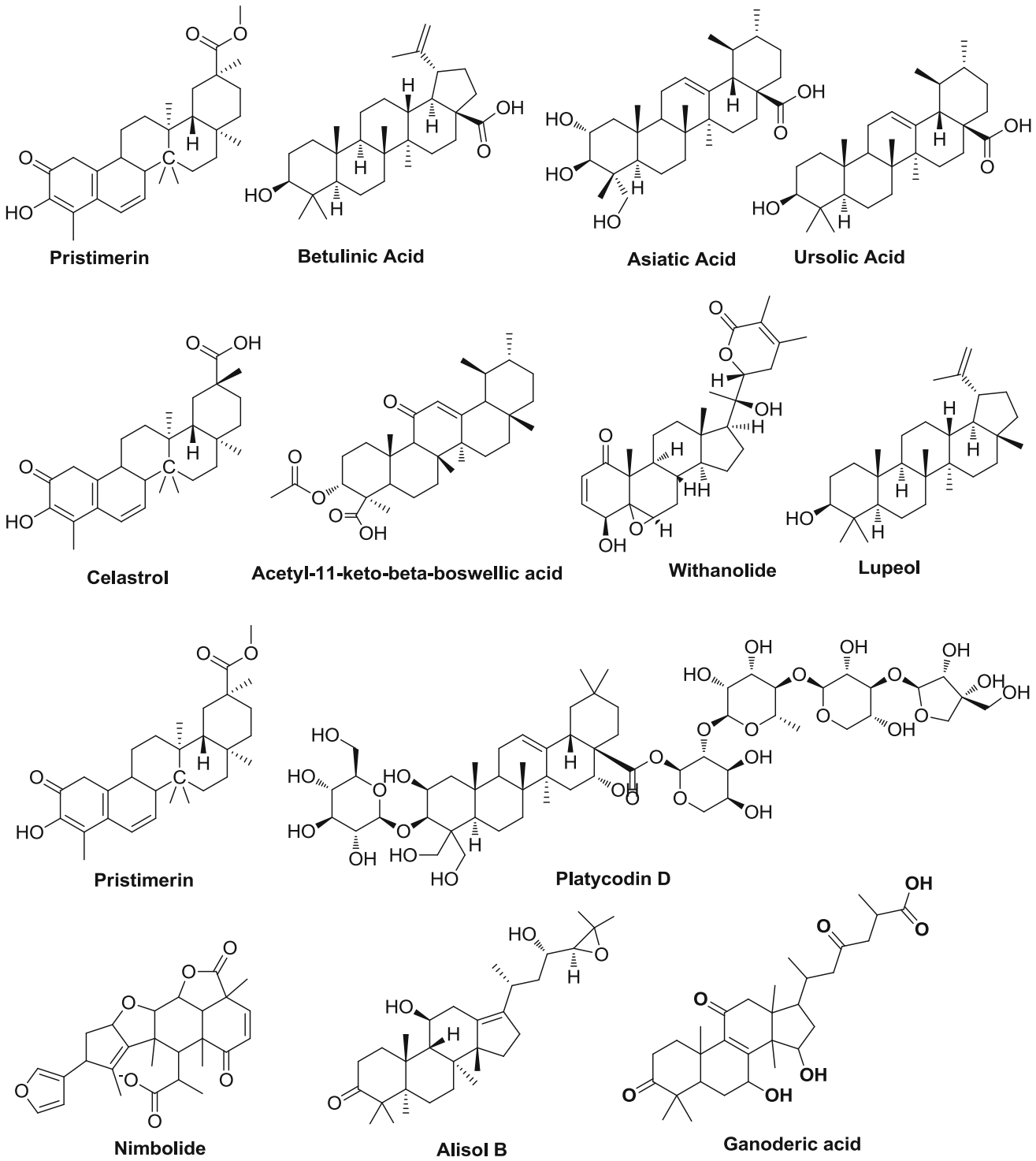


**Fig. 2** Chemical structure of triterpenoids

p65. Along with this, withanolide also inhibited the suppression of TNF, TNF receptor (TNFR) 1, TNFR-associated death domain and TNFR-associated factor 2 which activates the NF-κB [87]. A study conducted by Chitra research group concluded its potential to inhibit a number of receptors when administered in colon cancer, including mTOR, Akt, 4EBP1, p70-S6K, SK3β, β-catenin, Notch1 cleavage, and cyclin D1 [88].

*Maslinic acid,* oleanolic acid, uvaol, and erythrodiol are the triterpenes isolated from *Olea europaea* L with

**Table 2** Different triterpenes with their targets

| Triterpenoids | Target | Reference |
|---|---|---|
| Betulinic acid | Cyclooxygenase-2, MMP-9, antiangiogenic, VEGF, NF-κB | [75, 76] |
| Asiatic acid | p21/WAF1, MAPKs, Bax/Bcl-2 ratios, caspase-9, ERK1/2, p38, cyclinB1, cyclinA, Cdc2, and Cdc25C NF-κB, IKK, p38, ERK1/2 | [77, 78] |
| Saikosaponins C | NF-κB, c-fos, cathepsin K, ERK, JNK, p-38 | [79] |
| Acetyl-11-keto-β-boswellic Acid | VEGF, focal adhesion kinase, extracellular signal-related kinase, Akt, mTOR, ribosomal protein S6 kinase, Src family kinase, NF-κB | [80, 81] |
| Celastrol | NF-κB, MMP9, VEGF, VEGFR, mTOR, S6K kinase | [82, 83] |
| Ganoderic acid | NF-κB, NFATc1, AP-1, ERK1/2, PI3K, Akt, uPAR, cdk4, uPA, MMP2, MMP-9, VEGF, TGF, IL-8. | [84] |
| Cucurbitacin | STAT3, STAT5, JAK2, JAK-STAT, c-myc, cyclins, survivin, p53, Bcl-xL, Bcl-2, AMPK, mTORC1/p70S6K | [85, 86] |
| Withanolide | TNF, TNFR 1, mTOR, Akt, 4EBP1, p70-S6K, SK3β, β-catenin, Notch1 cleavage, and cyclin D1, NF-κB | [87, 88] |
| Lupeol | NF-κB, PI3K, Akt, Ras protein, MAPK | [89, 90] |
| Pristimerin | NF-κB, Bax, Bcl-2, Bcl-xL, VEGFR2, ERK1/2, mTOR, ribosomal protein S6 kinase | [91, 92] |
| Platycodon D | MAPK, ERK, p38, JNK, NF-κB, PI3K, mTOR | [93] |
| Ursolic acid | STAT3, NF-κB, p53, mTORC1, PI3K, Bcl-2, Bax, PKC, | [94] |
| Alisol B | Bax, Bcl-2, cell cycle arrest, caspase-3, caspase-9, PI3K, CaMKK, AMPK, mTOR | [95, 96] |
| Nimbolide | IGF-IRβ, IGFBP-3, MEK, pERK1/2, p38, PTEN, Raf-1, PI3K, cell cycle | [97] |
| Glycyrrhizin | NF-κB, STAT3, TNF-α, interleukin-1β (IL-1β), ERK, JNK, and PI3K/AKT and Akt/mTOR/STAT3 | [98, 99] |
| *Ganoderma tsugae* | PI3K, Akt, MAPK, cyclins D1, p21, p27 | [100, 101] |

antitumor, cardioprotective, anti-inflammatory, and antioxidant activity [105]. Maslinic acid induces the process of apoptosis in HT29, colon cancer cells. Maslinic acid inhibits the process of cell proliferation significantly and leads to the apoptotic cell death by modulating the ratio of Bcl-2 and Bax. Apoptotic events consequence in the release of mitochondrial cytochrome-*c* with activation of caspases in the mitochondrial apoptotic pathway [106]. Maslinic acid acts as an antioxidant and prevents pro-inflammatory cytokine generation and oxidative stress. Maslinic acid inhibits the production of nitric oxide and (TNF-α) and demonstrates anti-inflammatory action. Furthermore, it suppresses the expression of (COX-2) and inducible nitric oxide synthase (iNOS),which potentially reduce neuroinflammation in rat astrocyte [107]. Erythrodiol and uvaol (intermediate of Oleanolic acid) actively modulate the apoptotic process by reducing mitochondrial potential and activation of JNK signaling in 1321N1 cells [108].

*Lupeol* is derived from vegetables such as cabbage, pepper and fruits like mango, and fig. Other medicinal plants enriched with lupeol include *Tamarindus indica, Celastrus paniculatus*, *Bombax ceiba.* This natural product has been seen to modulate NF-κB, PI3K and Akt signaling pathways, thus, portraying potent anti-tumor effect [90]. Saleem research group demonstrated the role of lupeol in inhibiting pancreatic cancer cells by modulating NF-κB/PI3K/Akt/MAPK. Lupeol treatment to pancreatic cells significantly reduce the Ras oncoprotein expression and modifies expression level of different signaling molecules concerned in PKCalpha/ODC, and PI3K/Akt pathways [89].

*Celastrol* is the active principle extracted from *Trypterygium wilfordii* Hook F. by Pang et al. [82]. They highlighted the potential of celastrol to repress angiogenesis-mediated tumor growth by inhibiting mTOR pathway. Pang research group observed that celastrol effectively suppressed mTOR and S6K kinase in human umbilical vascular endothelial cells (HUVECs) in a concentration-dependent manner in VEGF-triggered activation of the mTOR signaling cascade. Thus, inhibiting tumor angiogenesis by blocking the mTOR signaling pathway in endothelial cells [82]. Furthermore, it induced the process of invasion and migration by suppressing phorbol 12-myristate 13-acetate (PMA) in MCF-7 cells. Celastrol also inhibited the degradation of IκBα in NF-κB translocation by suppressing the expression of MMP-9 [83].

*Asiatic acid* triterpene derived from medicinal plant *Centella asiatica* which arrests S-G2/M phase in cell cycle, therefore, inhibiting cell growth. The cell growth arrest results in increased p21/WAF1 levels and reduction of cyclinB1, cyclin A, Cdc2, and Cdc25C in a p53-independent manner. In the process of apoptosis, it triggers the intrinsic mitochondrial-dependent apoptotic pathway by modulating the ratios of Bax/Bcl-2, cytochrome c release,

caspase-9 activation. Asiatic acid induces ERK1/2, p38, MAPKs, but not JNK [77]. Furthermore, asiatic acid inhibits the activation of NF-κB induced by lipopolysaccharide and decreased the nuclear p65 and p50 protein levels. Moreover, it also suppressed the expression of LPS-stimulated RAW 264.7 cells by phosphorylating the IKK, p38, ERK1/2 in a dose-dependent manner [78].

*Acetyl-11-keto-β-boswellic acid* (*AKBA*), pentacyclic triterpene isolated from a *Boswellia serrata* which suppresses VEGF and inhibits blood vessel formation. AKBA inhibits capillary-like structures in human umbilical vascular endothelial cells (HUVECs). Along with this, AKBA was also found to suppress Src family kinase, focal adhesion kinase, extracellular signal-related kinase, Akt, mTOR, and ribosomal protein S6 kinase [80]. On the contrary, AKBA enhanced the process of apoptosis by inducing cytokine expression which inhibited the process of invasion and suppressed osteoclastogenesis by inhibiting NF-κB pathway [81].

*Pristimerin* is a triterpenoid having the ability to inhibit tumor angiogenesis mainly by targeting the VEGFR2 expression, isolated from *Celastrus* and *Maytenus* species. Mu research group revealed the potential of pristimerin to suppress VEGF-induced phosphorylation of VEGF receptor 2 kinases via modulating the expression level of ERK1/2, mTOR and ribosomal protein S6 kinase in the cancer pathway. Moreover, pristimerin significantly inhibited the mTOR kinase activation in the mTOR pathway in endothelial cells leading to down streaming of ribosomal S6kinase in a dose-dependent manner. The inhibitory action resulted in the inhibition of progression of the process of cancer in terms of proliferation, capillary structure formation in the endothelial cells. Thus, pristimerin may be exerting its antiangiogenic properties via inhibition of the/mTOR/P70S6K signaling pathway [91]. A study conducted by Wang and his team highlighted the effect of pristimerin on pancreatic cancer cells both in monotherapy and in combination with gemcitabine. Pristimerin treatment arrested and modulates cell cycle at G1-phase with a decrease in cyclins D1, E, cdk2, cdk4 and cdk6 expression. In addition, pristimerin also controlled the process of apoptotic cell death by as cleaving caspase-3 which modulates the function of Bcl-2 family proteins and inhibiting the translocation NF-κB proteins [92].

*Ursolic acid (UA)* is a triterpene (pentacyclic acid) found in epicuticular waxes of apples. UA has been observed to activate the independent mTOR complex 1 (mTORC1) expressed by resistance exercise, thus behaving as an effective stimulator of muscle protein anabolism by PI3K/mTOR signaling [94]. Furthermore, ursolic acid was also found to improve cognitive impairments resulting due to high-fat diet by blocking endoplasmic reticulum stress as well as IK-B kinase b/nuclear factor-KB-mediated inflammatory pathways. Therefore, delving deeper into the mechanism of action of a ursolic acid in correcting cognitive functions can pave the path for prevention and management of cognitive deficits resulting as a complication of type 2 diabetes [109].

*Platycodin D (PD)* is an active triterpenoid saponin isolated from the roots of *Platycodon grandiflorus* which is a potent inhibitor of migration, invasion, and growth. This therapeutic activity can be attributed to its ability to suppress EGFR-mediated and MAPK pathways in human breast cancer cells (MDA-MB-231). PD strongly inhibited the phosphorylation process of ERK, p38, and JNK and blocked the PI3K/mTOR signaling. Along with this, PD is also known to inhibit the DNA binding activity of NF-kB [93].

*Glycyrrhizin (GA)* is the triterpene glycoside, important bio-constituent of licorice (*Glycyrrhiza glabra*) isolated from root. Glycyrrhizin exhibits anti-inflammatory effects in carrageenan-induced pleurisy by decreasing the production of TNF-α and interleukin-1β. Additionally, Glycyrrhizin activates and reduces the expression of NF-κB, STAT3 in the lungs [98]. A study conducted by Chaun research group demonstrated the alleviation in liver injury and fibrosis by treatment of Glycyrrhizin, which regulates the $CD4^{+}T$ cell response in ERK JNK, and PI3K/AKT pathways [110]. Furthermore, GA inhibits leukemia cell (TF-1) growth and migration via blocking signaling in the Akt/mTOR/STAT3 pathway [99].

*Esculentoside (EsA),* saponin triterpene isolated from roots of *Phytolacca esculenta.* EsA inhibits interleukins (IL-1β and IL-6), TNF, and prostaglandin $E_2$ in cancer cells [111].

## Fungal triterpenes

*Ganoderma lucidum* is a basidiomycetes fungus with numerous medicinal properties known from ancient time. Majorly, fungus comprises of terpenes, proteins, polysaccharides constituents which actively participates and modulates signaling in cancer [65]. *G. lucidum* inhibits the activation of NF-κB proteins in the reporter gene assay in MDA-MB-231 cells in a dose–response manner. The investigation carried by Jiang research group highlighted the inhibitory effect of *G. lucidum* on NF-κB mediated pathway in the suppression of breast cancer cells. *G. lucidum* potently inhibited the proliferation of breast cancer MDA-MB-231 cells by down-regulating NF-κB pathway signaling [112]. Along with this, *G. lucidum* suppressed the phosphorylation of some specific residues Ser473 which directly inhibits the NF-κB activity in MDA-MB-231 cells [112]. *G. lucidum* was also seen to modulate the phosphorylation of ERK1/2, PI3K or Akt subsequently

**Table 3** Triterpenoids under clinical trials

| Triterpenoids | Type of cancer | Phase | Status | Sponsors |
|---|---|---|---|---|
| CDDO-Me | Solid tumors | I | Terminated | MD Anderson Cancer Center, US |
| CDDO | Solid Tumors | I | Completed | National Cancer Institute, US |
| CDDO-Me | Liver disease | I/II | Terminated | Reata Pharmaceuticals, Inc. |
| Ginsenoside | Breast cancer | II | Ongoing | Southern Illinois University |
| Ginsenoside | Hypertension | II | Completed | St. Michael's Hospital, Toronto |
| Ginsenoside | Ischemic Stroke | II/III | Completed | Xijing Hospital, China |
| Betulinic acid | Dysplastic nevus syndrome | I/II | Ongoing | University of Illinois |
| Escin | Arm lymphedema | II | Completed | University of Wisconsin, US |
| Glycyrrhizin | Hepatitis C | III | Ongoing | Schering-Plough |
| Glycyrrhetinic acid | End stage renal disease | II | Ongoing | University Hospital Inselspital, Switzerland |
| Glycyrrhetinic acid | Apparent Mineralocorticoid Excess | II/III | Completed | Brigham and Women's Hospital, US |
| Ursolic acid | Metabolic Syndrome X | II | Ongoing | University of Guadalajara |
| Oleanolic acid | Gastrointestinal Satiation Peptides | I | Completed | University Hospital, Basel, Switzerland |

inhibiting the AP-1 and NF-κB, resulting in the down-regulation of expression level of uPA, uPAR, MMP-9, VEGF, IL-8, nitric oxide (NO) and integrin in different cancer cell lines [84]. Another study demonstrated that triterpenes of *G. lucidum*, ganoderic acid-T (GA-T) inhibited NF-κB signaling and reduced the expression of MMP-9, iNOS, and uPA, resulting in inhibition of invasion of HCT-116 cells [113]. Similarly, another triterpene of *G. lucidum,* lucidenic acid B demonstrated lucidenic acid B (active triterpene of *G. lucidum*) inhibit PMA-induced invasion to reduce AP-1 and NF-κB by down-regulating MMP-9 expression of hepatoma HepG2 cells [114].

### Ganoderma tsugae

*Ganoderma tsugae* is a flat polypore fungus of the genus *Ganoderma,* which phosphorylates the human epidermal growth factor receptor 2 (HER2) which activates the variety of proteins such as PI3K/Akt and Ras/mitogen-activated protein kinase (MAPK) proteins in downstream signaling in cancer [101]. *In vitro* studies of *G. tsugae* indicated that administration of *G. tsugae* extract (GTE) induced G1 phase arrest via modulating cyclins D1, E, p21, and p27 in the cell cycle in ovarian cancer and breast cancer cells. *G. tsugae* arrests cyclin and cdks in HER2/PI3K/Akt signaling which inhibit the growth of HER2 overexpressing cancer cells [100].

## Triterpenoids in clinical trails

Different triterpenoids such as ganoderic acid, nimbolide, betulinic acid, diosgenin, pristimerin, boswellic acids, celastrol, ursolic acid, platycodin D, saikosaponins, 2-cyano-3, withanolide, momordin, 12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO) and its methyl ester CDDO-Me possess anticancer and anti-inflammatory activities. Triterpenoids are multifunctional and target numerous signaling pathways and control the survivability of the cell. This makes triterpenes successful and undergone different clinical phases sponsored by various companies (Table 3).

## Conclusion

Natural products are accredited with a broad spectrum of medicinal properties from ancient time. The multitargeting role of triterpenes in cancer highlighted and enhances more opportunities for drug development. Triterpenes target and hamper various accessory proteins associated with the signaling pathways in numerous diseases. Successful clinical phase trials of different triterpenes highlighted them in the field of drug development. Fungal triterpenes need to explore more in cancer and may provide an opportunity for novel work in this area. This attempt of highlighting the role of terpenes in the cancer signaling makes them an alternative tool to design an effective drug. Presently the group is engaged in the quantification of the terpenes available in the areas of Punjab with extreme climatic conditions based on the premise that mycoconstituents of this region will be more in quantity and effective in analyzing its effect on different disorders.

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**Compliance with ethical standards**

**Conflict of interest** None.

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