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Review Article

BETULINIC ACID: A REVIEW ON POTENT ANTI-CANCER AGENT

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ABSTRACT

Betulinic acid is the pentacyclic triterpenoid, which occurred naturally and exhibit potent anticancer activity. It gets lot of attention due to its different biological and medicinal properties. It has capability to induce apoptotic cell expiry in malignant cells by activating mitochondrial track of apoptosis. Betulinic acid target towards mitochondria hence, hold the novel position in management of public malignancies.

Keywords: Apoptosis, Betulinic acid, Anticancer activity, Mitochondria.

INTRODUCTION

Organic molecules are comes from nature ,which remain explained through alive materials obtained since developed plants, toadstools, bacteria, aquatic creatures and animals as well as show a unusually varied series of chemical multiplicity or a variety of biological properties. Usual resources must remain in practice intended for combating human diseases from ancient time. Since previous 15 years attention in medicines of plant source has been bracing as well as rising progressively, and the drug investigators remain discovering the probable natural goods to treat life threating ailments like tumor.[1] Anticancer action of natural goods has remained related their aptitude to activate cell demise ways together with apoptosis in tumor cells. Apoptosis is nothing but, cell's inherent death program. It plays a dynamic character in maintaining flesh homeostasis as well as extremely preserved between dissimilar classes.[2] Apoptosis is phenomenon which takes a part in the guideline of numerous biological methods; faulty apoptosis signaling may lead toward many extreme conditions.[3] Betulinic acid is a naturally occurred product that shows potent anticancer actions through activating the mitochondrial route toward apoptosis. Mitochondria targeted mediators like betulinic acid might expose new opinions to overwhelm certain methods of drug resistance.[4] Betulinic acid is a 3b-hydroxy-lup-20(29)-en-28-oic acid and broadly dispersed pentacyclic lupane-type triterpene. Betulinic acid is existing in the external bark of a variety of tree species up to 2.5%. Those are appreciated intended for timber resolutions.[5] Betulin is a foremost component of white-barked birch trees having yields up to 22%.[6,7] Betulin can be simply rehabilitated into betulinic acid synthetically.[8] Researcher of University of Illinois reported that betulinic acid executed malignance cells in mice. Meanwhile formerly, several research laboratory tests conducted on betulinic acid to regulate antitumor possessions, particularly with melanoma cells. This review concentrates on the pharmacological assets of betulinic acid.[9]

Mechanism Action of Betulinic Acid

Number of studies completed from past years intended to explain mechanisms of betulinic acid-mediated anticancer movement. One distinguishing parameter about cytotoxicity is its aptitude to produce the mitochondrial passage of apoptosis in tumor cells. Apoptosis is an inherent database of cell death which existing in each cell as well as controlled by distinct motioning paths.

Apoptosis Pathways

Apoptosis way can be invented close to the mitochondria through discharge of apoptogenic factors like cytochrome c, Smac or AIF from the mitochondrial inter membrane space into the cytosol (intrinsic pathway).[10] They also stated that Smac encourages apoptosis by neutralizing "Inhibitor of Apoptosis Proteins" (IAP)-mediated inhibition of caspase-3 and -9.[10] Apoptosis can be activated through ligation of death receptors like CD95 or TRAIL receptors by their cognate ligands, i.e. CD95 ligand or TRAIL (extrinsic pathway).[11-12] The BH3 area individual protein Bid links the receptor to the mitochondrial pathway. Bid is a activated through caspase-8-mediated cleavage and translocate to mitochondria to endorse cytochrome c release.[113,14,15]

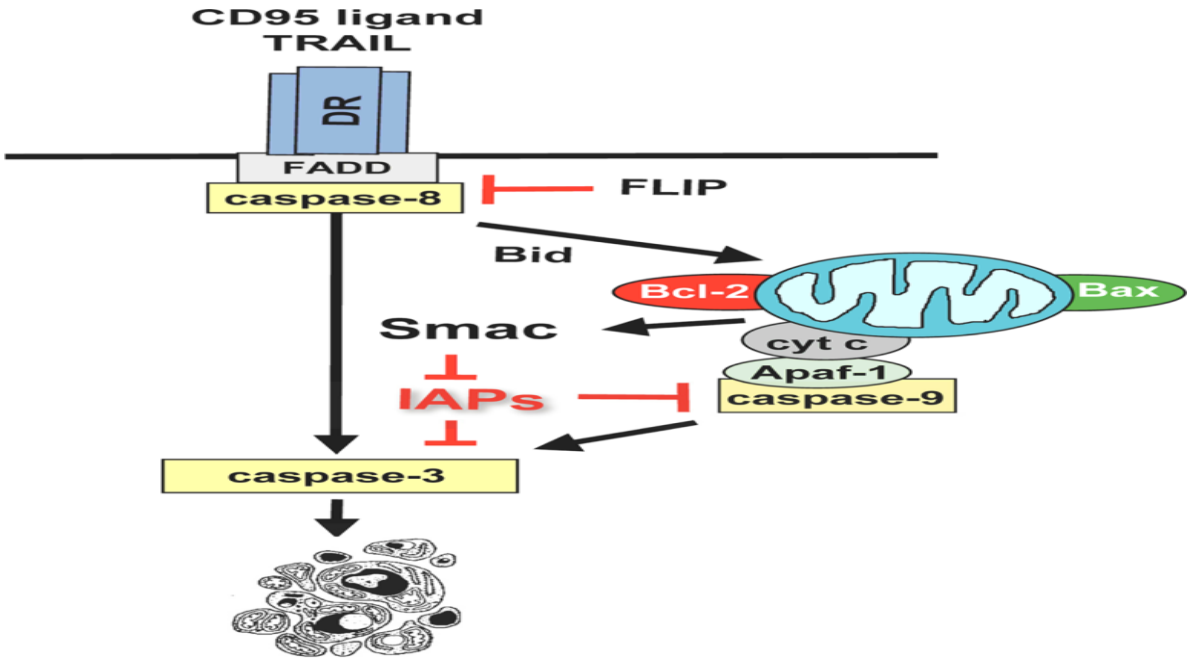

Figure1: Apoptosis Pathway

(Adopted From: Fulda S.2008. Betulinic Acid for Cancer Treatment and Prevention, *Int. J. Mol. Sci.9*, pp.1096-1107)

Stimulation of the Mitochondrial Lane through Anticancer Therapeutics

Intrinsic pathway of apoptosis is triggered upon management with chemotherapeutic mediators as the consequence of a DNA injury as well as cellular stress response. They studied about a key initial stage in the initiation of the mitochondrial corridor is the permeabilization of the outside mitochondrial membrane. Throughout progression, mitochondrial outer and inner membranes are permeabilized, which in turn effects towards discharge soluble protein from the mitochondrial interspace into the cytosol (cytochrome c, Smac or AIF).[16] Long lists of protein causes and additional heralds have been recognized that can positively or negatively adjust permeabilization of the external mitochondrial membrane. Therefore, factors openly encourage mitochondrial outside membrane permeabilization can performance as operative cytotoxic agents.[17]

Initiation of Mitochondrial Outer Membrane Permeabilization by Betulinic Acid

Betulinic acid used to bring apoptosis through direct mitochondrial agitations. When added to remote mitochondria in cell-free structures, betulinic acid encouraged forfeiture of mitochondrial membrane

potential in a way that was not pretentious by the caspase inhibitor zVAD.fmk as well as so far was kept via bongkrekic acid, an inhibitor of the permeability transition pore complex.[18] In intact cells, betulinic acid was accessible near trigger cytochrome c in a caspase-independent and permeability transition pore-dependent manner.[19]

They explained about antiapoptotic Bcl-2 family proteins like Bcl-2 and Bcl-XL repressed all mitochondrial as well as cellular entrances of apoptosis encouraged through betulinic acid, as did bongkrekic acid, representing that mitochondrial permeability transition is obligatory for these actions.[20] Perturbance of mitochondrial purpose establishes a dominant organizing occasion in betulinic acid persuaded apoptosis significant toward caspase beginning as well as apoptotic DNA fragmentation. Mitochondria from cells, which were treated with betulinic acid, heartened cleavage of together caspase-8 and caspase-3 in cytosolic extracts. Cytochrome c, allowed after mitochondria undertaking betulinic acid facilitated permeability transition, triggered caspase-3 but not caspase-8 in a cell-free system.[21] In count, initiation of caspases was controlled toward cells those previously had misplaced their mitochondrial membrane potential supplementary suggesting that mitochondrial adjustments were elaborate in betulinic acid encouraged twitch of caspases.[21] Overexpression of protein like Bcl-2 as well as Bcl- XL discussed confrontation towards betulinic acid close to mitochondrial dysfunction, protease activation, and nuclear fragmentation characterize these trials occurred downstream of protein like Bcl-2- or Bcl-XL measured barrier of apoptosis. Betulinic acid may overwhelm certain formulae of drug confrontation. Group of reactive oxygen species (ROS) upon action through betulinic acid has remained quantified to be complicated in introducing permeabilization. Near this end, species generation was noticed in malignance cell lines of dissimilar source that were preserved through betulinic acid.[22] They reported about development by antioxidants proceeding to administration of betulinic acid protected cells since undergoing apoptosis suggesting that ROS manufacture stood complicated in arbitrating cell death.[23] Betulinic acid has remained defined toward encourage apoptosis in a p53- and CD95-independent manner. Nearby, apoptosis upon exploit by betulinic acid was not allied with accretion of wild-type p53 protein besides, betulinic acid activated apoptosis independent of CD95-ligand/receptor interaction.[21-24]

Variation of NF-κB Action through Betulinic Acid

Betulinic acid controls movement about record factor nuclear factor- κB, a important controller of stress persuaded transcriptional beginning. Betulinic acid was acknowledged as a strong activator of NF-κB in a quantity of tumor cell lines.[26] BA encouraged NF-κB initiation intricate amplified IKK action, phosphorylation of IκBα at serine 32/36 pursued through squalor of IκBα and nuclear translocation of the NF-κB subunit p65.[27] Specific result of activation of NF-κB by betulinic acid encourages betulinic acid-induced apoptosis in a cell type-specific manner. By contrast, betulinic acid was exposed to interfere with NF-κB activation and NF-κB regulated gene expression activated by carcinogens and inflammatory stimuli.

These conclusions may deliver a molecular basis for the skill of betulinic acid to suppress inflammation and moderate the immune response. Collectively, these results point to a context-dependent function of NF-κB in the regulation of betulinic acid-mediated apoptosis.

Antitumor Activity

Betulinic acid remained an extremely discriminating growth inhibitor of human cancer, malignant tumor cells as well as neuroectodermal cell as well as carried to persuade apoptosis in these cells. Anticancer mediators through dissimilar manners of action require triggering apoptosis in chemo selective cells.[28] After alternating mitochondrial functionality like permeability transition (PT) require to play a main part in the apoptosis procedure counting cell death brought through antitumor agents.[29,30] It is a novel cytotoxic agent contrary to neuroectodermal tumor cells composed with neuroblastoma, medulloblastoma, glioblastoma and Ewing's sarcoma cells, which denote the most common solid tumors of childhood.[31]

Betulinic acid from the methanol extracts of *Dillenia indica* L. fruits. The extract represented important anti leukemic movement in human leukemic cell lines U937, HL60 and K562.[32-33] It was secluded from the methanolic extract of the midair portion of Vietnamese *Orthosiphon stamineus* as well as verified for its cytotoxicity near extremely liver metastatic murine colon 26-L5 cancerous cells. It was revealed that betulinic acid displays the cytotoxicity with an ED50 value of 75.4 μg/ml.[34] Betulinic acid was secluded from the methanol extract of the dried leaves of *Nerium oleanderand* as well as confirmed for its *in vitro* antitumor action on the basis of the cell growth inhibitory activities near three kinds of human cell line.[35]

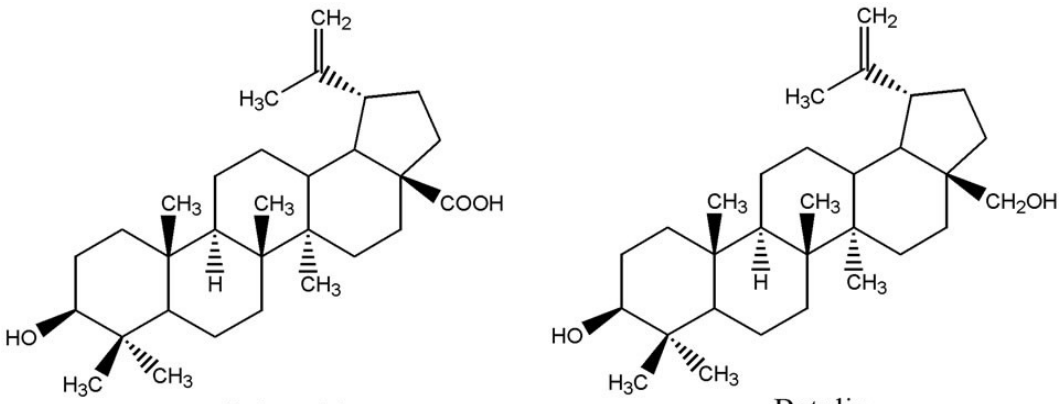

Figure2: Structure of Betulinic Acid and Betulin

Betulinic acid condensed nanoparticles for in vivo antitumor treatment, two possessions are predictable to increase the uptake of the betulinic acid loaded nanoparticles by tumor cells: (1) the appropriate size (120 nm) to reduce renal clearance of the drug (2) BSA has many rewards such as low toxicity, excellent biocompatibility and biodegradability.[36]

CONCLUSION

Betulinic acid is natural compound and shows the potent anticancer action. It shows antitumor activity through apoptosis pathway. Betulinic acid enhances its antitumor activity in combination with ligand like CD95&TRAIL. It show relative cytotoxicity in comparison of normal cells and hence betulinic acid is new promising potent anticancer agent to treat the cancer.

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