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Original Article

Triptolide Mediated Amelioration of Breast Cancer via Modulation of Molecular Pathways

Swadesh Sarkar[1,2], Santanu Paul[2]*

ABSTRACT

Triptolide is the main bioactive molecule isolated from a root extract of *Tripterigium wilfordii* Hook F. of Celastraceae family. Chemically, it is a diterpenoid triepoxide molecule and its chemical formula is $C_{20}H_{24}O_6$. Its five-membered unsaturated lactone ring (D-ring) is crucial for anti-tumor potential and carbonyl group at C-18 position is essential to exert important influence on the interaction between triptolide and the targeted protein(s). It is bio-synthesized from deoxy-D-xylullose-5-phosphate (DOXP) pathway in the cell. Triptolide can induce apoptosis in a number of breast cancer cells by up-regulating different pro-apoptotic and down-regulating different anti-apoptotic molecules. *In vitro* experiments indicate that it can down regulate several cell cycle related genes and induces S-phase cell cycle arrest. Triptolide treatment can also modulate the expression of different cell signaling molecules, e.g. ERK, NF-κB, FAK, VEGF, β-catenin, AKT etc. *In vivo* experiments indicate that triptolide can effectively reduce breast tumor growth in the mouse model. Apart from the single drug treatment, triptolide can effectively be applied in combination therapy. Application of Triptolide with other chemotherapeutic drugs, very efficiently check the proliferation of tumor cells which reduces the effective concentration of the commercially available drugs thus reducing their toxic side-effects. Although triptolide is very effective against a number of diseases, its higher degree of multi-organ toxicity limits its use of further clinical trial. Therefore, to reduce the toxic effects, a number of strategies have been developed which increase its water solubility and at the same time decrease the toxic effect. In this review article, we have addressed how triptolide participates in the antitumor processes in breast cancer cells.

Key words: Breast cancer, Cytotoxicity, *Tripterigium wilfordii*, Apoptosis, Triptolide, Molecular pathway.

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INTRODUCTION

Breast cancer is one of the main causes of death of women in the world. Its occurrence increases year by year. Steady increase of breast cancer incidence and mortality rate, eager researchers to search out novel anti-tumor chemotherapeutic drug. The application of chemotherapy in cancer treatment started in the 1940s by using nitrogen mustards and anti-folate drugs.[1] Thereafter, discovery of novel anti-cancer molecule has been major research endeavor to the researchers throughout the world. Compounds from natural origin have gained much attention in this regard as they possess no adverse side-effects. The finding of anti-cancer molecules from plant sources began in the 1950s with the discovery and development of the Vinca alkaloids, vinblastine (velban) and vincristine (oncovin); and the isolation of cytotoxic podophyllotoxins.[2] Traditional Chinese medicines comprising an extract of naturally occurring herbs promise an effective and useful alternative in cancer therapy. Extract of Chinese herb *Tripterygium wilfordii* Hook. F has been used for more than two centuries in traditional Chinese medicine for treating a variety of autoimmune and inflammatory diseases, including rheumatoid arthritis,[3] chronic hepatitis, chronic nephritis etc. Recent researches have revealed that this activity is attributed to the major diterpenoid presence in this extract–triptolide (PG490) Figure 1. This compound is responsible for the immunosuppressive and anti-inflammatory activities of this herb.[4-6] Mechanistic studies of triptolide has also revealed that this compound not only has an immunosuppressive and anti-inflammatory activities, but an anti-tumor efficacy as well. Anti-proliferative, cytotoxic and proapoptotic activities of this compound have been established in last two decades against a number of cancers.[7,8] In the present article we will explore the mechanism of the anti-breast cancer activities of this compound *in vitro* as well as *in vivo*.

Tripterygium wilfordii Hook F

Triptolide is derived from the root extract of Chinese herb *Tripterygeum wilfordii* Figure 2, belongs to the family Celastraceae. This plant is also known as 'lei gong teng' 'Thunder God vine' or 'Seven step vine'. It is a climbing vine; grow in China, Korea, Japan, and Taiwan. The entire plant is highly toxic

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and should not be used internally. This plant is used to kill maggots and larvae, etc. No edible uses of this plant are reported till date, although root pulp has shown some activity against a few diseases e.g. rheumatoid arthritis, and for dispelling wind and eliminating dampness etc. Seeds are sown in autumn and each individual seedling is transplanted on separate pot during the winter and finally to their permanent position in spring or early summer. It prefers a moist loamy soil with a range of pH from acidic to alkaline but tolerates chalky soils. This plant flowers in sunny condition. Flowers are small, white and develop in panicle with soft sweet fragrance.

BIOSYNTHETIC PATHWAY OF TRIPTOLIDE

Triptolide is bio-synthesized from deoxy-D-xylullose-5-phosphate (DOXP) pathway.[9,10] This pathway is operating in plastids of higher plants, but absent in animal as well as fungi. In this pathway one molecule of glyceraldehyde-3-phosphate (GAP) (C_3) and one molecule of pyruvate (C_3) react to form one molecule of DOXP (C_5). DOXP is further converted to dimethylallyl pyrophosphate (DMAPP). DMAPP isomerizes to isopentanyl pyrophosphate (IPP) through isopentenyl-diphosphate-D-isomerase. One molecule each of DMAPP and IPP undergo head to tail condensation with the help of geranyl diphosphate (GPP) synthase to form GPP (C_{10}). GPP and one molecule of IPP react to form one molecule of the farnesyl diphosphate (FPP) (C_{15}) through condensation reaction by FPP synthase. Finally, FPP undergoes condensation reaction with another molecule of IPP to form C_{20} molecule geranylgeranyl diphosphate (GGPP) with the help of GGPP synthase. GGPP is the precursor molecule of triptolide as well as other diterpenoids.

TRIPTOLIDE CHEMISTRY

Triptolide is the major diterpenoid of *Tripterygeum wilfordii* responsible for its pharmaceutical properties. It was first isolated from the root extract and characterized in 1972 as a diterpenoid triepoxide lactone containing 18 (4→3) abeo-abietane backbones Figure 1. Just after its isolation, it was established as an anti-tumor,[11] anti-inflammatory,[12] immunosuppressive,[13,14] and anti-fertility drug.[15,16,17,18] As compared to other anti-tumor drug, triptolide has comparable or superior effects, especially against p53 mutated or multi-drug resistant cell lines.[19] Zhou and co-workers (2011) [20] recently demonstrated that the five-membered unsaturated lactone ring (D-ring) of triptolide is crucial for its anti-tumor potential and C18 carbonyl group may exert an important influence on the interaction between triptolide and the target molecule(s) responsible for initiating their cytotoxic effects. Its molecular formula is $C_{20}H_{24}O_6$ with a molecular mass 360.40 g·mol^{-1} and appears as white to off-white solid compound which is soluble in dimethylsulfoxide (DMSO) solvent system.

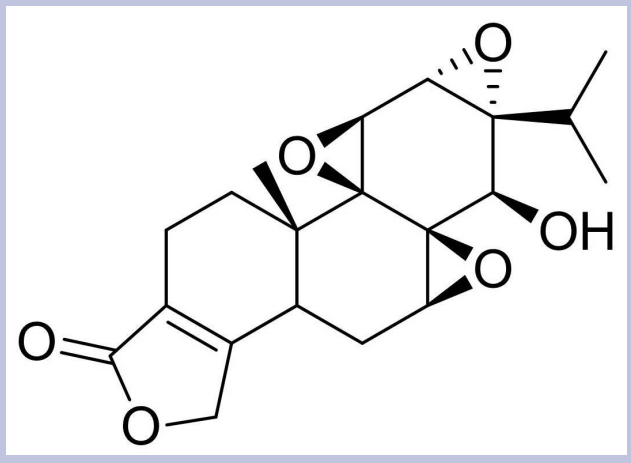

Figure 1: Chemical structure of Triptolide.

Figure 2: *Tripterigium wilfordii* Hook F. with mature inflorescence.

IN VITRO ANTI-BREAST CANCER EFFECTS OF TRIPTOLIDE

Several studies in the past revealed that triptolide is able to limit the proliferation of breast cancer cells *in vitro* as well as *in vivo*. A very preliminary study showed that triptolide inhibited the colony formation of two breast cancer cell lines MCF-7 and BT-20 in a dose dependent manner and IC_{50} values were 0.504μg/L and 0.774μg/L respectively.[21] Thereafter, a number of studies conducted by various scientific groups and indicated that it has prominent anti-breast cancer property by inducing apoptosis and modulating the expression of several cell signaling molecules *in vitro*.

Effects of Ttriptolide on Cell proliferation and apoptosis related proteins

Triptolide treatment altered the cellular morphology of MCF-7 cells as compared to the untreated cells. With increasing concentration, a significant reduction in the colony formation was associated with cell shrinkage and parts of the cell detachment were observed. MTT assay indicated that it efficiently decreased proliferation of MCF-7 cells in a time and dose dependent manner with LD_{50} 10ng/mL. It also induced chromatin condensation which was evidenced by nuclear fragmentation, PARP cleavage and Caspase-7 and -9 activations in a dose dependent manner. Triptolide treatment also modulated the membrane integrity of lysosomes, which was evidenced by leakage of lysosomal protein Cathepsin B in the cytosol Figure 4.[22] Lu *et al.* (2011) [23] experimentally proved that triptolide could induce apoptosis in MDA-MB-231 cells in a time and dose dependent manner by inducing Caspase-3 activity which was evidenced by increased levels of cleaved PARP. They showed that triptolide decreased the levels of cellular proteasomal activity in this cell line. In another study, triptolide treatment to MDA-435 cells effectively inhibited its proliferation in a dose dependent manner as indicated by [^{3}H] thymidine incorporation assay. The effect of triptolide (25ng/ml or 70nM) was much greater than conventional drug Taxol (100 ng/ml or 117 nM). Triptolide at 2ng/mL concentration was able to inhibit the proliferation of MDR-1 over-expressing MDA-435 cell line which was significantly resistant to Taxol. Apart from the anti-proliferative activity,

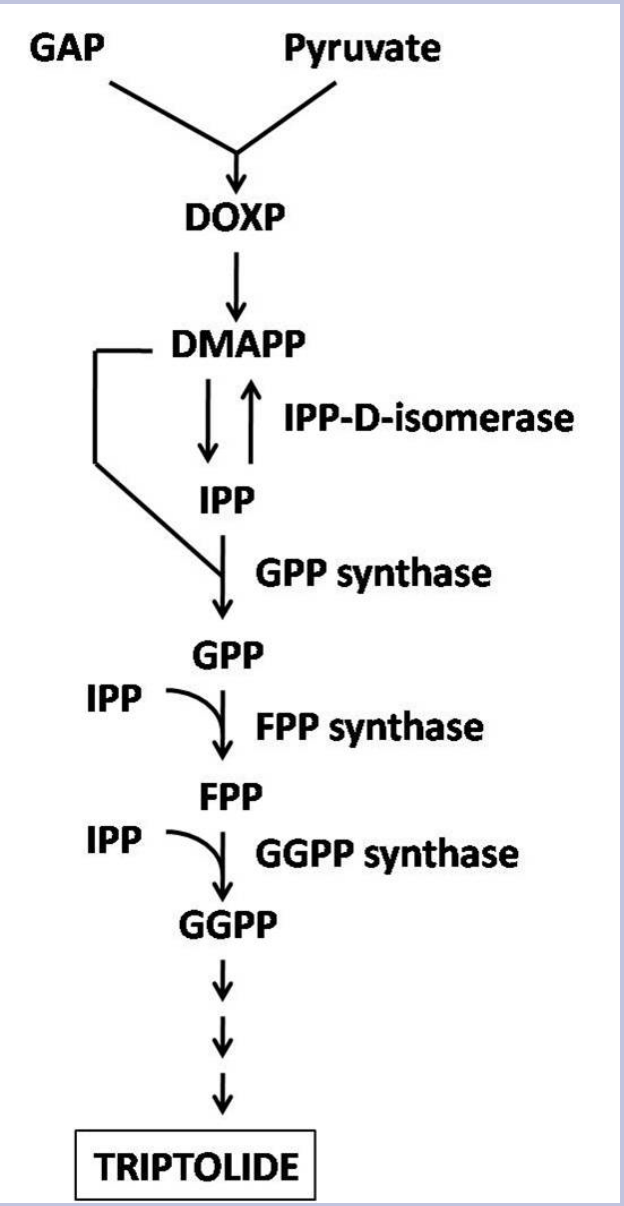

Figure 3: DOXP pathway- leading to Triptolide biosynthesis.

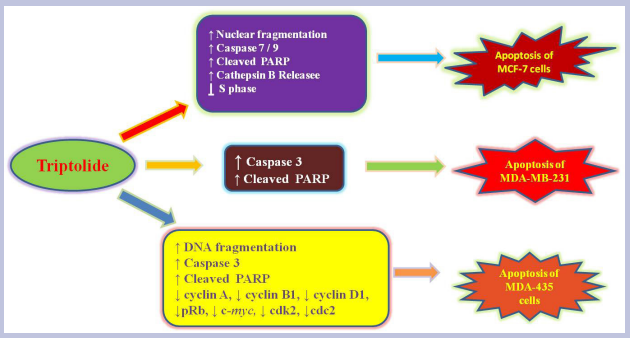

Figure 4: Apoptotic activities of Triptolide. Triptolide causes nuclear fragmentation, Caspase -7/9 activation, Cleavage of PARP, Release of Cathepsin B from lysozome, and cell cycle arrest at S phase to induce apoptosis of MCF-7 cells. It induces apoptosis of MDA-MB-231 cells by activating Caspase-3 and concomitant PARP cleavage. It also induces apoptosis by nuclear DNA fragmentation, Caspase-3 activation, PARP Cleavage and down regulation of several cell cycle related proteins e.g. Cyclin A, Cyclin B1, Cyclin D1, pRb, c-myc, cdk2, cdc2.

it caused DNA fragmentation which is a remarkable evidence of apoptosis. Western blot analysis indicated that triptolide treatment increased the level of cleaved Caspase-3 and cleaved PARP. Expression of some cell cycle related proteins were also down-regulated e.g. phosphorylated (nonfunctional) pRb, cyclin A, cyclin B1, cyclin D1, c-*myc*, cdk2, and cdc2 Figure 4.[24] In 2009, Liu and coworkers [25] indicated that the genetic backup of the cells also responsible for the triptolide sensitivity e.g. MCF-7 cells, carrying ERalpha-positive and wild-type p53 gene, was much sensitive to triptolide than that of MDA-MB-231 cells that carrying ERalpha-negative and mutant- p53 gene. The differential activity of triptolide on these two cell lines was evidenced by lower magnitude of IC_{50} values, more fragmented nuclei and only slightly S-phase arrest on cell cycle distribution in MCF-7 cells and no sub-G0/G1 peak Figure 4. All these data suggested that triptolide can effectively inhibit the proliferation and induce apoptosis in established breast cancer cell lines. Li and co-workers showed that not only in established cell line, triptolide was able to induce cytotoxicity in cultures of human primary breast cancer cells (BCCs) and breast cancer stem cells (BCSCs) *in vitro*. Human BCCs and BCSCs were treated with different concentration of triptolide for different time points. Results indicated that BCCs were more susceptible to triptolide than BCSCs as evidenced by the high degree of cytotoxicity and apoptosis.[26]

Effect of Triptolide on MAPK signaling pathway

MAPK pathway, particularly ERK pathway is involved in cellular growth and proliferation. Tan and co-workers (2013)[27] treated human breast cancer cell line MDA-MB-231 with triptolide and observed reduced cell viability in a concentration and time dependent manner. MAP Kinase pathway played a crucial role in this cell death phenomenon. They claimed that ERK was activated upon triptolide treatment which was correlated with the cell death. Phosphorylation of ERK depended on triptolide concentration and accompanied by Caspase 3/7 activation. Bcl_2 family member pro-apoptotic protein Bax was up-regulated and anti-apoptotic protein Bcl-xL was down regulated which were down-stream of ERK activation. Endoplasmic reticulum (ER) stress also played a vital role in this ERK activation. An expression of some common markers of ER stress, including PERK, eIF2α, Ire1α was modulated. p-PERK level was transiently up-regulated, which was followed by up-regulated expression of its target protein p-eIF2α, p-Ire1α Figure 5. Apart from the ER stress, ROS generation also took part in the ERK activation in this triptolide induced cell death. Recently, Li *et al.* (2015)[28] showed that triptolide dose dependently inhibited the proliferation of both MCF-7 and MDA-MB-231 cells. It down regulated the expression of estrogen receptor-α in MCF-7 cells and also down regulated the phosphorylation of ERK1/2 in a dose and time dependent manner. All these reports suggested that the ERK pathway plays a dual role in triptolide induced cell death.

Effect of Triptolide on NF-kB signaling pathway

NF-kB is a family of dimeric transcription factors. They possess RelA region that binds to the DNA. They interact with each other and bind the IkB inhibitor.[29] NF-kB plays significant role in cellular phenomenon, e.g. cell proliferation, inflammation, tumorigenesis etc.[30,31] Recent study indicated that it also takes part in modulating apoptosis e.g. mice lacking RelA region died during embryogenesis due to massive apoptosis in liver

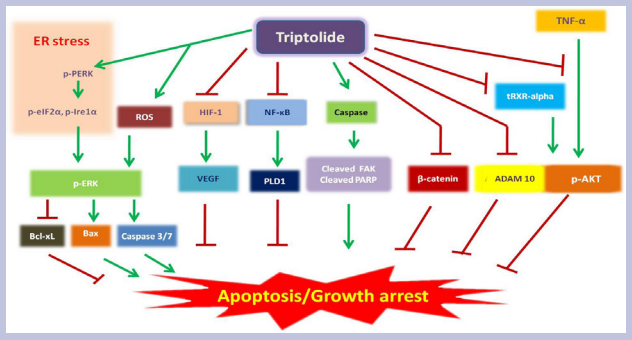

Figure 5: Mechanism of Triptolide induced cell death. Triptolide is able to induce cell growth arrest/apoptosis by modulating ERK signaling pathway, cleavage of FAK and PARP. Triptolide inhibits/blocks several cellular signaling pathways e.g. HIF-1 induced VEGF activation, NF-κB signaling pathway, Wnt/β catenin pathway, cleavage of ADAM 10. Triptolide also inhibits TNF-α induced and tRXR-alpha induced p-AKT activation.

cells.[32] Several studies showed that NF-kB significantly inhibit apoptosis induced by TNFα and chemotherapy.[33,34,35] Recently, Wang and coworkers[36] showed that NF-kB effectors e.g. TRAF-1 (TNFR-associated factor 1), TRAF2, c-IAP1 and c-IAP2 are required to suppress TNF-α -induced apoptosis. Triptolide sensitized a number of tumor cells, including MCF-7 to TNF-α induced apoptosis through the inhibition of NF-kB. It inhibited transactivation of NF-kB, but do not interfere with its DNA binding property. Triptolide blocked the induction of c-IAP2 and c-IAP1 by TNF-α and thus enhanced TNF-α induced apoptosis. [37] Another study indicated that triptolide induced apoptosis and NF-kB down regulation requires wild type p53 gene.[38] Phospholipase D (PLD1) is an important molecule in cell proliferation and tumorigenesis. Triptolide effectively inhibited PLD1 and PLD2 in a dose dependent manner at nano-molar concentrations as evidenced by promoter activity and RT-PCR assay. Triptolide abolished the protein level of PLD in dose and time dependent manner and inhibited both basal level and PMA induced PLD activation in MDA-MB-231 cells. The mechanistic study indicated that triptolide actually inhibited the transactivation of upstream gene NF-kB in a dose dependent manner which ultimately blocked the activation of its target gene PLD1 but an expression of PLD2 remained unaltered Figure 5.[39]

Effect of Triptolide on cell adhesion molecules

Focal adhesion kinase (FAK) is a non-receptor tyrosine kinase that regulates the adhesion and survival of breast cancer cells. FAK is over expressed in MCF7 cell line. Treatment of triptolide to MCF-7 effectively reduced the anchorage dependent growth in a concentration as well as time dependent manner. The mechanistic study indicated that triptolide was able to cleave the FAK and PARP in a concentration and time dependent manner which was not inhibited even in the presence of pan-caspase inhibitor, zVAD-fmk.[40] Vascular Endothelial Growth Factor (VEGF) is also responsible for the adhesion and survival of breast carcinoma cells. A two cell-based model with luciferase reporter gene assay were established to evaluate the HIF-1 inhibition activity of triptolide which indicated that triptolide can effectively inhibit the HIF-1 gene as well as its target gene VEGF in breast cancer cell model Figure 5.[41]

The effect of Triptolide on others cell signaling molecules

GD3 takes part in metastasis in multiple ways and is also responsible for the biosynthesis of ganglioside GD2, a novel breast cancer stem cell marker. Sarkar *et al.*[42] exhibited that GD3 synthase (GD3S) could serve as a potential druggable target in metastatic breast cancer. They observed that triptolide could efficiently inhibit the GD3S function. Thus, triptolide effectively blocked the initiation and maintenance epithelial-mesenchymal transition (EMT) and check the metastasis.

MDA-MB-231, BT-474 and MCF7 cells, treated with triptolide, showed significantly reduced cell viability. At 50nM concentration triptolide effectively induced apoptosis in all these cell lines. Western blot analysis indicated that triptolide was able to down-regulate the expression of β-catenin protein in a concentration dependent manner, thus blocking the Wnt- β-catenin pathway. [43]

Liang and Fu [44] showed that triptolide inhibited surface expression of IF-gamma induced programmed death-1-ligand 1 (PD-L1) in human breast cancer cells and thereby serving as a modulator to promote cancer cell-reactive immune responses. ADAM 10 is a type I transmembrane glycoprotein. It cleaves some plasma membrane proteins. It is highly expressed in several tumor cells. Triptolide treatment of MCF-7 cells expressing ectopic ADAM10 or dominant negative ADAM10 resulted in the reduced expression of ADAM10 and a concomitant increase in the cleaved ADAM10 product. SiRNA mediated knock down of ADAM10 and triptolide treatment reduced the growth of MCF-7 breast cancer cells. This result indicated that ADAM10 is a novel target of triptolide for breast cancer prevention. [45] 4T1 mouse breast cancer cell line was treated with triptolide to investigate its anti-neoplastic capacity. Triptolide was able to check the cellular proliferation of T41 cells and induced apoptosis at a significant level as evidenced by MTT assay and FITC-annexin V/PI staining respectively. The mechanistic study indicated that triptolide blocked the expression of ERalpha, p-ERalpha, ERbeta, and p-ERbeta, but MAPK signaling remained unaltered. [46]

Retinoid X receptor-alpha is a member of the nuclear receptor superfamily. Proteolytic cleavage of RXR-alpha resulted in the accumulation of truncated product tRXR-alpha, which promotes cancer cell survival by activating PI3K/Akt pathway. Triptolide treatment resulted in degradation of cellular tRXR-alpha, down regulation of p-Akt level and concomitant induction of cellular apoptosis in the cancer cells. Triptolide inhibited the TNFα induced Akt activation. These workers showed that triptolide significantly activated p38 which was involved in down-regulation of tRXR-alpha induced Akt activation Figure 5.[47]

IN VIVO ANTI-BREAST CANCER STUDY

Although a number of *in vitro* studies indicate that triptolide significantly inhibits proliferation, induces apoptosis in different breast cancer cell lines, its evidence of anti-cancer efficacy in animal models is significantly limited. A few *in vivo* studies show that triptolide efficiently inhibits/reduces tumor growth as it inhibits cellular proliferation *in vitro*. Yang and coworkers [24] used four types of cell lines (e.g. B16F10, TSU, MDA-435, or MGC80-3) to establish primary tumor in mice. MDA-435 human breast cancer cells ($5X10^6$ cells/site) were injected subcutaneously in the flank of BALB/c Nude/Nude mice (8 mice /group) of 5-6 weeks age-old. After 3 days of incubation, tumor xenografts reached a size of 100 mm. After that triptolide was injected intra-peritonially at a dose of 0.15mg/kg/day for 2-3 weeks. Results indicated that triptolide has an inhibitory effect on all the tumor lines tested, with an 80% inhibitory rate to MDA-435 tumor. This study also showed that triptolide effectively reduced the rate of metastasis *in vivo*. Recently [46] further proved the anti-tumor efficacy of triptolide in a mouse model. They developed tumor in a BALB/c mouse by injecting mouse tumor cells 4T1. They showed that triptolide at 200μg/kg dose effectively inhibited tumor growth in mice. In 2014, Li and colleagues [48] showed that triptolide could inhibit the breast cancer stem cells (BCSCs) implanted cancer. They implanted BCSCs subcutaneously in nude BALB/c mice and observed high rate of tumor formation. However, Triptolide treatment significantly inhibited tumor

growth compared to the mock treatment in these mouse models. All the above-mentioned experiments prove the anti-tumor effects of triptolide in xenograft models, but its mechanism of action in the animal model is still unclear.

COMBINATION THERAPY

In order to enhance anti-tumor efficiency and to reduce the adverse side-effects, combination therapy of two drugs is the alternative strategy.[48-53] Recent reports indicated that triptolide could effectively reduce the dose of many popular anti-cancer drugs. Lin and coworkers showed that triptolide and amino terminal fragment (ATF) of urokinase (uPA) synergistically reduced the growth of breast cancer cells MDA-MB-435. In general, amino terminal fragment (ATF) of urokinase (uPA) interferes with the interaction of uPA and its receptor uPAR and thereby inhibits the proliferation, migration and invasiveness of breast cancer cells. Triptolide (10ng/mL) treated with ATF of urokinase (10nM), significantly reduced the growth of human breast cancer cell line MDA-MB-231in comparison to any of the single drug.[54] Apart from the breast cancer, triptolide could enhance the efficacy of other anti-cancer drugs against other cancer models. Triptolide in combination with aspirin suppressed proliferation, induced apoptosis, effectively decreased mitochondrial membrane potential and colony formation of human cervical cancer cells. Co-treatment significantly decreased the expression of Bcl_2 and cyclin E gene and increased Bax and p21 gene expression at mRNA level.[55] Lin and co-workers [56] demonstrated that triptolide enhanced the anti-tumor potential of anti-angiogenic drug vasostatin120-180 (VAS). Combined therapy enhances the apoptosis efficacy of VAS by down regulating NF-kB and many anti-apoptotic genes (e.g. c-FLIP, cIAP, Bcl-2, Bcl-xl, and Mcl-1) as well as up-regulated Caspase-3, -8, -9 and many pro-apoptotic genes (e.g. Bax, Bak, and Bad). Cisplatin is a popular anti-cancer drug against an array of cancer types. Triptolide along with lower doses of cisplatin reduced viability and induced apoptosis in gastric cancer cells SC-M1 *in vitro* as well as *in vivo*. Apoptosis was accompanied by loss of mitochondrial membrane potential, cytochrome-C release and Caspase activation.[57] In another study, Cai and others showed that Triptolide in combination with curcumin synergistically inhibited the growth of ovarian cancer cells and apoptosis induced by loss of mitochondrial membrane potential, ROS generation and down regulation of Hsp27 and Hsp70 genes.[58] Not only chemotherapeutic drug, Triptolide could enhance the anti-tumor effect of ionizing radiation. Triptolide and ionizing radiation synergistically enhance the growth inhibition of pancreatic cancer cells AsPC-1, induced apoptosis via both mitochondrial and death receptor pathway and inhibited tumor progression *in vivo*.[59]

TRIPTOLIDE INDUCED TOXICITY

Triptolide possesses multiple pharmacological activities including anti-tumor, immunosuppressive, anti-fertility [60] etc. however, its side-effects, particularly toxicity greatly limits for further clinical use.[61] This triptolide induced toxicity is gender specific. Very recently, Liu and colleagues showed that triptolide causes greater toxicities in female rat as compared to male.[62] Toxicological study indicated that, triptolide possesses potential nephrotoxicity which is involved with oxidative stress.[63] NF-E2-related factor 2 (Nrf2), which is an antioxidant nuclear transcription factor, plays a protective role in defense against triptolide-induced toxicity.[64] Triptolide also possesses hepatotoxicity. Wang and coworkers [65] reported that hepatotoxic properties of triptolide associated with the insulin signaling pathway, glucose metabolism, cell cycle, oxidative stress and apoptosis. This hepatotoxic effect can be counteracted by the up-regulated expression of Nrf2 and its downstream target.[66] Cytochrome P450 reductase enzyme also plays a significant role to eradicate triptolide induced toxicity.[67] Mechanistic study by Qu and co-workers [68] indicates that spingolipid pathway plays a regulatory role in this triptolide induced nephro and hepatotoxicity. Sphingolipidomics study shows that the total levels of ceramides (Cers), sphingomyelins (SMs) and sphingosine (Sph) were all elevated, while dihydroceramides (dhCers) and hexosylceramides (HexCers) were all down-regulated after triptolide treatment. Trancriptomics study indicates that several enzymes, including kdsr, CerS2, CerS4, CerS5 and CerS6 in the liver and Cerk in the kidney are probably responsible for the TP-induced toxic effect, identifying them as possible novel therapeutic targets. However, this study also discovered several biomarkers for triptolide induced toxicity in the liver and kidney. Cardiotoxicity is another adverse side effect of triptolide treatment. *In vitro* and *in vivo* studies indicated that triptolide induced cardiac injury via oxidative stress by ROS production, Nrf2 activation and mitochondria mediated apoptotic signaling cascade which was evidenced by reduced ratio of Bax/Bcl-2, release of cytochrome c and, activation of caspase-3.[69] Apart from these, triptolide also causes reproductive toxicity.[70] All these results together indicate that triptolide causes multi-organ toxicity. In contrast to triptolide induced toxicity, cells possess any defense system against this cellular damage. *In vitro* and *in vivo* mechanistic study indicates that rapamycin induced autophagy greatly ameliorated the detrimental cardiac damage induced by triptolide.[71] Cytochrome P450 enzymes and GSH conjugation pathway also play significant roles in detoxification of triptolide.[72]

CONCLUSION

Breast cancer is still a very common cancer type in women. Predominant anti- breast cancer drugs have prominent side effects and there is a chance of recurrence of resistance sub type due to long term use. Plant derived compounds have gained much attention in this regard as they have multiple cellular targets and lower cytotoxicity. Therefore, identification and use of active bio-molecules have emerged as potential therapeutic and preventive strategy which assures high selectivity to breast carcinoma cells, bestowing no side effects and thereby perceived to hold high disease free survival rates of treated patients. Triptolide, the active principle in the root extract of Chinese wonder plant *Tripterigium wilfordii* Hook. F has attracted much attention in this regard due to its multiple pharmacological activities including anti-tumor, immunosuppression, anti-inflammation, etc. Recent researches indicate that triptolide induces its anti-tumor effects through the induction of apoptosis,[73,74] perturbation of cell cycle progression [75,76] interference with multiple cellular signaling systems, e.g. MAPK,[77,78] PI3K/AKT,[79] NF-kB.[80,81] Not only breast cancer, triptolide significantly inhibits almost all cancer types, e.g. colon cancer,[82] pancreatic cancer,[83] ovarian cancer,[84,85] leukemia,[86] cervical cancer[87] etc. Apart from its own biological activities triptolide modulates the activity of different popular commercial anti-tumor drugs that indicates its chemo-sensitizing property.[54-59] A major problem associated with the anti-tumor activity of triptolide is its lower solubility in water and greater cytotoxicity that limits its use of clinical study. Therefore, to increase its bioavailability, Xu and colleagues [88] developed polymeric micelles that reduce the triptolide toxicity and increase Poly (D, L-lactic acid) nanoparticles are another very promising carripaire for triptolide that can reduce renal toxicity in rats.[89] Zhang and coworkers [90] developed triptolide-loaded solid lipid nanoparticles those are effective for accurate triptolide delivery and reduce toxicity in male rats. Although triptolide has been approved for phase I clinical trial in pancreatic cancer treatment, its anti-breast cancer activity and mode of action is still a major area of research. We hope triptolide could be used in the therapeutic intervention of breast cancer in the future.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ABBREVIATION USED

ADAM10: A disintegrin and metalloproteinase domain-containing protein 10; **ERK:** Extracellular signal regulated kinases; **NF-κB:** Nuclear factor-κB; **FAK:** *Focal adhesion kinase*; **VEGF:** Vascular endothelial growth factor; **AKT:** Protein kinase B; **LD50:** 50% Lethal dose; **PARP:** *Poly (ADP-ribose) polymerase*; **pRb:** Retinoblastoma *protein*; **c-myc:** Myelo cytomatosis gene; **cdk:** Cyclin dependent kinases; **cdc:** Cell division cycle; **DNA:** Deoxyribonucleic acid; **Bcl-xL:** B-cell lymphoma-extra large; **IAP:** Inhibitors of apoptosis proteins; **PLD1:** Phospholipase D1; **FITC:** Fluorescein isothiocyanate; **PI:** Propidium iodide; **SiRNA:** Small interfering RNA; **PERK:** *Protein* kinase R (PKR)-like endoplasmic reticulum kinase; **eIF2α:** Eukaryotic translation initiation factor 2 alpha; **Ire1α:** Inositol-requiring enzyme 1α; **HIF-1:** Hypoxia-inducible factor 1; **zVAD-fmk:** Carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]- fluoromethylketone; **ROS:** Reactive oxygen species; **GD3:** Disialoganglioside; **FLIP:** FLICE-inhibitory *protein*; **Bcl-2:** *B-cell lymphoma 2*; **Mcl-1:** Myeloid cell leukemia-1; **PI3K:** Phosphoinositide-3-kinase.

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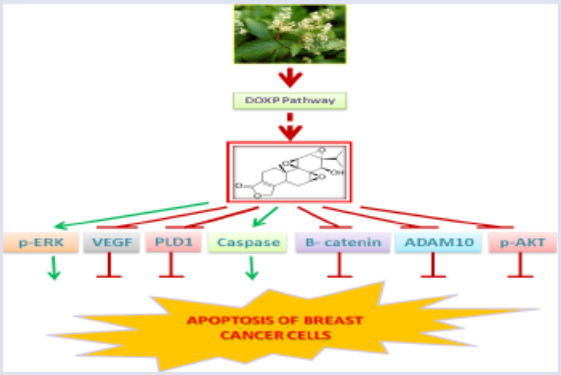
GRAPHICAL ABSTRACT



SUMMARY

- Triptolide, a diterpenoid triepoxide down regulates several cell cycle related genes and induces S-phase cell cycle arrest.
- It also modulates the expression of different cell signaling molecules, e.g.
- ERK, NF-Î°B, FAK, VEGF, Î²-catenin, AKT etc which ultimately cause death of the breast cancer cells
- Triptolide can effectively reduce breast tumor growth in the mouse model.

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