Anti-inflammatory and Anti-tumor Activities of Parthenolide: An Update

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Abstract
Parthenolide (PTL), the secondary metabolite of feverfew plant (Tanacetum parthenium), has been used in various medical purposes globally. Inflammation represents a physiological response to injury and helps to restore tissue homeostasis. Inflammation and cancer both are cellularularly associated with genotoxicity, invasion, metastasis, and abnormal tissue repair mechanisms. PTL inhibit major cellular inflammatory and proliferation pathways like NFκB, STAT3, and MAPK along with the activity and expression of several inflammatory mediators including COX. NFκB pathway plays a key role in controlling cell cycle progression and apoptosis together with metastasis and cancer of various types. Elevated NFκB, Wnt/β-catenin pathways are crucial factors of tumorogenesis. PTL inhibits NFκB and Wnt/β-catenin pathways, and thereby promotes apoptosis and suppresses cell proliferation. Experimental data showed that PTL protects normal cells from apoptosis; whereas in cancer cells it induces apoptotic cell death. Hence, parthenolide could be useful in controlling inflammatory diseases alone or together with tumorogenesis due to its evident anticancer potency and anti-inflammatory nature.

Keywords: Parthenolide; Feverfew; Inflammation; Cancer; Tumor; NFκB

Abbreviations: AML: Acute Myelogenous Leukemia; ARE: Antioxidant Response Element; COX: Cyclo-Oxygenase; FRA-1: Fos Related Antigen-1; HO-1: Heme Oxygenase-1; HDAC1: Histone Deacetylase-1; iNOS: Inducible Nitric Oxide Synthase; IL1: Interleukin-1; IKK: IκB kinase; IKCe: IkB Kinase Complex; iNKT: Innate Amino-Terminal Kinases; LT: Leukotrienes; LPS: Lipopolysaccharide; MAPK: Mitogen-Activated Protein Kinases; Nrf2: Nuclear Factor (Erythroid-derived 2)-like 2; NFκB: Nuclear Factor Kappa B; PTL: Parthenolide; PGE2: Prostaglandin E2; PKC-a: Protein Kinase C-α; ROS: Reactive Oxygen Species; GSH: Reduced Glutathione; SRF: Serum Response Factor; STAT: Signal Transducers and Activators of Transcription; TCR: T-cell Receptor; TRXR: Thioredoxin Reductase; TRAF: TNF Receptor Associated Factor; TNFa: Tumor Necrosis Factor Alpha; TYK: Tyrosine Kinases; VEGF: Vascular Endothelial Growth Factor; XBP1: X-box Binding Protein-1

Introduction
Parthenolide (PTL) is a multifunctional naturally occurring compound, isolated from Mexican Indian asteraceae family plants and has been widely used in native folk medical practices, including treatment of inflammation [1], stomach ache, tooth ache, menstrual irregularities, fever, rheumatoid arthritis [2] and migraines [3,4] due to its anti-inflammatory properties [5]. Sesquiterpene lactones are secondary metabolites found in asteraceae family plants. PTL is the principal component of sesquiterpene lactones present in medical plants such as feverfew (Tanacetum parthenium) [6]. PTL contains an α-methylene-γ-lactone ring and an epoxide, both of which are able to interact readily with nucleophilic sites of biological molecules [7]. These functional groups can react with nucleophiles, especially with cysteine thiol groups in a Michael addition reaction. Being the primary bioactive component of feverfew, PTL is used as prophylic treatment for migraine having positive therapeutic effects in clinical trials [8]. PTL has anti-leishmaniasis properties too [9]. Pareek et al. reported that feverfew has been used for psoriasis, allergies, asthma, tinnitus, dizziness and vomiting [10]. PTL has also been reported to improve endotoxic shock and prevent inflammation in immune glomerulonephritis [11,12]. In in vitro experiments scientists have shown the nuclear factor kapp B (NFκB) inhibiting abilities of PTL [13]. Zhang et al. showed that PTL inhibits the activation of NFκB and ERK signaling pathways, as well as the expression of inflammatory and osteo-clastogenic genes in lipo-polysaccharide (LPS)-stimulated hPDLcs in vitro [14]. It also inhibits proliferation and eliminates various cancer cells predominantly by inducing apoptosis [15]. It was recently reported that PTL inhibits the in vitro growth of tumor cells in a cytostatic manner [16]. In vitro, it preferentially inhibits mammosphere growth. The decrease of sphere growth was due to the inhibition of NFκB activity [17]. PTL and its derivatives may be effective anticancer agents against cholangiocarcinoma for the reason that they can effectively induce apoptosis in cholangiocarcinoma cells [18,19]. PTL-induced apoptosis was enhanced by the PKC-α inhibitor Ro317549 (Ro) through inhibition of Nrf2 expression and its nuclear translocation, resulting in suppression of HO-1 expression. Both in combination, PTL and Ro efficiently enhanced cancer cell growth inhibition compared to treatment with either agent alone in an in vivo tumor xenograft model [19]. Carlisi et al. established that both PTL and its soluble analog dimethylaminoparthenolide (DAMPT) arrested the cell growth of triple negative breast cancer stem cells by suppressing Nrf2, SOD and catalase, and inducing ROS generation and mitochondrial dysfunction, which ultimately leading to apoptotic and necrotic cell death [20]. It has also been observed that pre-incubated HCT116 cells with PTL resulted in the absence of activation of NFκB after TNFα treatment in both p53-proficient and p53-deficient cells [21]. Therefore, parthenolide might be represented a new class of cancer chemotherapeutic agent. This review aims to summarize the medicinal and clinical usages of PTL and its effects on relevant cellular signaling molecules to control inflammatory and tumorgenic pathophysiology.

Anti-inflammatory activity of parthenolide
The sesquiterpene lactone PTL from the anti-inflammatory medicinal herb Feverfew (Tanacetum parthenium) could be effective...
against variety of inflammatory responses. The anti-inflammatory properties of PTL, like platelet aggregation [22] and carrageenan-induced mouse and rat paw edema [23], have been summed up by investigations of various scientists. Feverfew appears to be an inhibitor of prostaglandin synthesis [24], leukotrienes (LT) and expression of pro-inflammatory cytokines [25]. PTL inhibited histamine release from rat peritoneal mast cells [26]. Further studies revealed that it inhibits inflammatory mediators including activity and expression of cyclo-oxygenase (COX) specifically COX-2, which also enhances cancer stem-like cells' characteristics such as higher colony formation efficiency and over expression of stemness-associated genes [27-29]. The compound was found to inhibit activation of transcription factor NFκB by both at the transcriptional level and by direct inhibition of associated kinases (IKK-β) [30,31]. NFκB transcription factors regulate several important physiological processes, like immune and inflammatory responses, cell growth and apoptosis. In normal unstimulated cell, NFκB dimers are located in the cytoplasm associated with IκB inhibitor proteins in inactive form. In response to pro-inflammatory molecules like TNF-α, cytotoxic drugs, ionizing radiations and oxidative stress, IκB gets phosphorylated rapidly and finally degraded through ubiquitination and proteasomal degradation [32-34]. The free NFκB dimer translocates to the nucleus and modulates expression of specific genes. Recent research showed that PTL could down regulate NFκB through one of the following ways either inhibiting IκB kinase complex (IKC) or binding with the catalytic subunit of IKK complex i.e., IκK-β subunit as a consequence of inactivation of NFκB signaling pathway [35]. Cellular inflammatory processes are associated with the release of cell-derived intermediaries, including cytokines of the IL-1 and IL-6 families, from the site of inflammation. Sobota et al. showed that parthenolide is also an effective inhibitor of these inflammatory cytokines IL-1 and IL-6. It hinders IL-6 induced gene expression by blocking STAT3 phosphorylation on Tyr705 [36]. PTL inhibits LPS-induced COX-2 protein, mRNA expressions in alveolar macrophage cells, production of IL-1β and prostaglandin E2 (PGE2) inhibits LPS-induced COX-2 protein, mRNA expressions in alveolar macrophage cells, production of IL-1β and prostaglandin E2 (PGE2) in human bronchial epithelial cells [27]. Studies showed that PTL inhibits production of IL-1α, IL-1β, TNFα, IL-6, and MCP-1 in human monocytes, keratinocytes, and vascular smooth muscle cells [28].

**Anticancer/anti-tumorogenic activity of parthenolide**

Drug discovery against cancer is ventured throughout the world, especially from the natural harvests. Recently, the anti-tumor property of parthenolide has attracted great interest among researchers. Parthenolide has been shown to inhibit growth or induce apoptosis in a number of tumor cell lines [16-18,40,41]. Many mechanisms have been proposed as being involved in the anti-tumorogenic effect of parthenolide, including inhibition of NFκB activation [17,41], suppression of STAT3 [36], inhibition of MAPK activity [37], sustained activation of JNK [42,43], activation of p35 [15,17], inhibition of nucleic acid synthesis [44,45], depletion of thiol, induction of oxidative stress [16,17], induction of mitochondrial dysfunction [16], disruption of intracellular calcium equilibrium, induction of cell cycle G2/M phase arrest [16,40], depletion of HDAC1 [43], and inhibition of tubulin carboxypeptidase activity [46,47]. Parthenolide also inhibits IL1 and TNFα-mediated NFκB activation [7] resulting in inhibition of IκB kinase mediated NFκB translocation [48]. PTL also induces apoptosis and autophagy-mediated growth inhibition in HeLa cells by repressing the PI3K/Akt signaling pathway and mitochondrial membrane depolarization, bringing on mitochondria-mediated apoptosis, ROS generation and autophagy by activation of caspase-3, up regulation of Bax, Beclin-1, ATG5, ATG3 and down-regulation of Bcl-2 and mTOR [49].

**Parthenolide and NFκB**

The molecular mechanism of PTL action has been showed associated with inhibiting NFκB mediated apoptosis that enables disruption in recruitment of IKK to the TNF receptor, resulting in blockade of IKK-dependent activation of NFκB, along with activation of the p53 pro-apoptotic pathway, and augmentation of reactive oxygen species (ROS) in cancer cells [43]. In addition to acute myeloid leukemia, PTL targets mammary breast cancer stem cells and could inhibit mammosphere growth for more than seventy two hours. The shrinkage in sphere growth is due to the inhibition of NFκB activity [17]. PTL and its derivatives may be effective anticancer agents against cholangiocarcinoma as it effectively induces apoptosis in these cells [18]. It has also been observed that pre-incubated HCT116 cells with parthenolide resulted in the absence of activation of NFκB after TNFα-treatment in both p53-proficient and p53-deficient cells [21]. PTL could antagonize Taxol-mediated NFκB nuclear translocation as well as activation and Bcl-xl up-regulation by selectively targeting IκB kinase activity. In A549 lung carcinoma cells, inhibition of NFκB by PTL resulted in activation of caspase 9 and 3 by the mitochondrial death pathway involving cytochrome-c release. Moreover, taxol-induced inhibition of A549 cell growth in mouse xenograft was potentiated with the treatment of PTL [50]. Another study in mouse xenograft model also showed PTL inhibiting tumor initiation and progression by CD44+ tumor initiating cells. It was found in one of the early events of PTL cytotoxicity that it is associated with attenuation of activity of the non-receptor tyrosine kinase, src and many src-associated signaling components that include: Csk, FAK, B1-arrestin, FGER2, PI3K, PKC, MEK/MAPK, CaMK, the transcription factor ELK-1 and Elk-1 dependent genes. Additionally, it was observed that PTL altered binding of a number of transcription factors involved in prostate cancer including: C/EBP-α, FRA-1, HOXA-4, c-MYB, SNAIL, SP1, SRF, STAT1/3, XBP1 and p53 [51]. Kim et al. showed that PTL inhibits IκBα phosphorylation and NFκB activation, resulting in the initiation of apoptosis and the ultimate repression of colitis-associated colon cancer development in vivo [52]. And, in *in vitro* experiments, using human multiple myeloma cells, Kong et al. (2015) showed that PTL treatment resulted in reduced level of p65 and ubiquitination of TNF receptor-associated factor 6 (TRAF6) [53]. It was also observed that PTL suppresses proliferation, invasion and tumor induced angiogenesis of glioblastoma cells. It reduces Akt phosphorylation and mitochondrial apoptotic signaling in addition to its inhibitory action on NFκB (Table 1) [54].

**Parthenolide and STAT**

It is previously discussed that the activation of STAT directs to cell proliferation, cell migration, transformation, apoptosis, cellular differentiation, adhesion, fetal development, inflammation, and immune response. In normal homeostasis, STAT tyrosine phosphorylation is short-term, lasting from 30 minutes to several hours, whereas in numerous cancer cell lines and primary tumors it is in NFκB contrary to that of normal homeostasis. It takes place due to the deregulation of positive effectors of STATs activation, such as upstream tyrosine kinases (JAK, TYK), or repression of negative regulators of STATs phosphorylation, e.g. phosphatases, suppressors of cytokine signaling or protein inhibitors of activated STATs [55,56]. The products of STATs-regulated gene transcription, including Bcl-xL and survivin permit cancer cells to proliferate and to inhibit cellular apoptosis episode [57]. In normal cells, survivin is expressed in low
levels whereas in cancer cells it is high and acts as an upstream signal on G2/M transition and cellular proliferation [58]. Survivin has been considered to be a key resistant factor in glioblastoma [59] and leukemia [59] because of its anti-apoptotic action, autophagy regulation, and G2/M cell cycle promoting effects. It was observed that, treatment with PTL led to substantial down regulation of survivin, G2/M cell cycle arrest and Chk2 upregulation in glioblastoma cells in vitro [61]. According to Sobota et al. PTL blocks STAT-3 and STAT-1 binding to the regulatory elements in DNA. Moreover PTL inhibits phosphorylation of tyrosine 705 residue which prevents translocation to the nucleus and subsequent gene activation by blocking STAT-3 dimerization (Table 1) [36].

Parthenolide and JNK/MAPK

JNK is one of the MAPK groups of protein which are responsive to stress stimuli such as cytokines, UV irradiation, heat shock etc., together with ERKs, p38 and ERK5. All MAPKs are activated by dual phosphorylation of threonine and tyrosine motifs within the sub-domain VIII of activation loop. Once activated, they translocate to the nucleus and phosphorylate target transcription factors, such as c-Jun. JNK involved in apoptosis, neurodegeneration, cell differentiation, proliferation and inflammatory conditions [61]. Won et al. showed that PTL inhibited JNK activation and led to UVB-induced apoptosis of JB6 murine epidermal cells [62]. But Zhang et al. demonstrated that inhibition of NF-κB activation and sustained JNK activation contribute to the sensitization of PTL effect on TNFα-induced apoptosis in human cancer cells [43]. The authors reported that PTL sensitizes human nasopharyngeal carcinoma (CNE1) cells to TNF-α induced apoptosis. Tang et al. and Varfolomeev et al. concluded that sustained JNK activation had resulted from NFkB inhibition [63,64]. Furthermore, it down-regulates the phosphorylated form of NF-kB, p38MAPK, and ERK1/2 protein levels [65]. Based on the literature data, it is evident that in normal cells, PTL protects cells from apoptosis whereas in cancer cells, it supports apoptotic cell death (Table 1).

Parthenolide and ROS

Cellular oxidative stress is defined as enhanced production of intracellular reactive oxygen species (ROS) and/or impaired function of the cellular anti-oxidant defense mechanisms [66]. The intracellular redox status plays an important role in survival and cell death [67]. Most of the cancer therapeutics is apoptosis inducers which disrupt the redox balance by depleting the intracellular thiol buffer system through the removal or redistribution of GSH [68]. The disturbed intracellular redox state elicits the downstream cellular apoptotic events, such as alternation of mitochondrial function and cell signaling pathways, which all lead to cellular death [69]. PTL has also been shown to play a dual role in regulating the intracellular redox state. In HeLa cells, PTL induced cellular apoptosis by enhancing ROS generation which is due to noticeable interactions of PTL with both cytosolic thioredoxin reductase (TrxR1) and mitochondrial thioredoxin reductase (TrxR2) [70]. However, some studies concluded that PTL reacts with the Cys thiols directly and may lead to depletion of intracellular GSH and protein thiols, and induction of ROS in some cancer cells [16,43], and some others suggest that PTL possibly increases GSH levels by activation of the Nrf2-ARE pathway in hippocampal HT22 cells [71]. Interestingly, studies of Li-Weber et al. demonstrated that PTL at low dose (up to 5 μM) neutralizes H2O2 generated by the T cell receptor signaling pathway in Jurkat T cells and protects cells from CD3-induced apoptosis, whereas, at high dose (10 μM), it induces O2·− and generates oxidative stress, leading to an increased number of cell death [72]. Zhang et al. (2004) examined the influence of PTL on mitochondrial function in colorectal cancer cells. PTL activates caspases, dissipates the mitochondrial membrane potential and releases the mitochondrial pro-apoptotic proteins [41]. Therefore, PTL may act as either a pro-oxidant or an antioxidant, under different conditions depending on its concentration and the cell type. It is clear that PTL affects several cellular pathways, modulates cellular redox state and appears to be an efficient drug for anti-cancer therapy (Table 1).

Crosstalk between inflammation and tumorigenesis

Earlier studies from our research group demonstrated that, Biochanin-A, an isoflavone, which is found in red clover, cabbage and alfalfa, is important for the prevention of phosphorylation and degradation of IκBα, thereby blocking NFkB activation and nuclear translocation. This in turn, leads to decreased transcription of the INOS and other pro-inflammatory genes, thus preventing inflammation. Moreover, Biochanin-A mediated inhibition of inflammatory cytokine production in RAW 264.7 cells [20,71].

Table 1: Effect of parthenolide on signaling molecules involving inflammatory, cellular proliferation and tumorigenic pathways.

<table>
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<th>Inflammatory Molecules</th>
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<th>Cell Proliferation/ Apoptosis associated Molecules</th>
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<td>C/EBPα, FRA-1, HOXA-4, c-MYB, SNAIL, SP1, SRF, STAT3, XBP1</td>
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<td>PKC-α, HO-1 [19]</td>
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release and inhibition of LPS mediated p38 MAPK phosphorylation with its specificity towards cancer cell growth inhibition, indicates the association between antiproliferative and anti-inflammatory actions of Biochanin-A [73]. Parthenolide is also working as an anti-inflammatory and anti-tumorogenic agent in similar manner to that of Biochanin-A. A sesquiterpene lactone 1-β,10-Epoxy-6-hydroxy-1,10H-inunolide (K100) was isolated from Cota palustina subsp. syriaca, an Eastern Mediterranean endemic plant. It was found to be analog of PTL, which inhibited endotoxin induced proinflammatory markers IL-6, MMP-9, and NO in normal mouse mammary SCP2 Cells and showed antiproliferative activity against breast adenocarcinoma MDA-MB-231 cells, indicating its anti-inflammatory and antitumor nature [74]. It indicates that, at least some biologically active components of plants including biochanin, PTL, or its analog may work by cross-talking between cellular inflammatory and proliferative pathways. Infection, leading to inflammation has been considered to be major conventional propulsive force of inflammation-induced tumorgenesis. Up to 20% of total cancer cases are allied with microbial infection worldwide [75]. Inflammation and cancer development are associated to each other in the course of processes involving genotoxicity, invasion, metastasis, abnormal tissue repair and also proliferative mechanisms [76]. Numerous experimental records signify that NFκB is involved in the development or progression of human cancers. Several members of NFκB and IkB families were derived from genes that are amplified or translocated in human cancers. The first member of the Rel/NFκB family was v-rel oncogene of the reticulo-endotheliosis virus T. In an in vivo experiment, REV-T virus was injected in mice in which results in aggressive lymphomas [77]. It was reported that NFκB may control apoptosis and cell cycle progression together with invasion and metastasis [78,79]. NFκB constitutively contribute in various tumors, such as breast cancer [80], pancreatic cancer [81], Hodgkin’s lymphoma [82] and other. Thus the inhibition of NFκB in cancer cells has become one of the major strategies in anticancer therapy in recent research. Receptor tyrosine kinases are one of most important cell surface growth factor play a crucial role in oncogenesis. Growth factor receptor tyrosine kinases along with ample range of input signals assemble on some major intracellular signaling surges [viz., the activation of STAT and this directs to cellular differentiation, adhesion, cell proliferation, transformation, fetal development, inflammation, immune response apoptosis and cell migration [55]. STAT signaling molecule more precisely STAT3, participates in tumorgenesis in multiple tissues, and is strongly linked to inflammatory processes in pancreatic, colon, gastric and lung cancers [83-88]. STAT3 promotes cell proliferation by up-regulating the expression of anti-apoptotic genes Bcl2 and Bcl2-like 1 (Bcl2L1) [84-85,88], and NFκB [90]. PTL markedly repressed vascular cell migration and capillary-like structure formation and suppressed the expression of angiogenic biomarker proteins VEGF, VEGF receptor 1 and VEGF receptor 2 in both the HUVECs and colorectal cancer cells. Additionally, PTL effectively inhibited tumor neovascularization in a HT-29 xenograft model [91]. In a model of constitutive Wnt activation, elevated NFκB signaling in epithelial cells enhanced Wnt/β-catenin activation and induced dedifferentiation, resulting in intestinal tumorgenesis [92]. Evidently it can be summarized that inflammatory mediators of cellular micro-environment (like cytokines) works individually or cumulatively to promote signals for tumorgenesis (Table 1).

### Summary and Conclusion

PTL is the secondary metaboflave of feverfew plant (Tanacetum parthenium) which has been used in various medical practices worldwide. It can inhibit major cellular inflammatory and proliferation pathways like NFκB, STAT3, MAPK, etc. via blocking them at the transcription level. PTL inhibits the activity and expression of several inflammatory mediators including cyclo-oxidase (COX). Inflammation represents a physiological response to injury and helps to restore tissue homeostasis. As a result of those cellular immune and inflammatory responses, cell growth, cellular apoptotic signal modulation starts. Acute or prolonged inflammatory processes may lead to increased tissue damage and uncontrolled amplification of inflammatory responses which further proceed towards cancer. Cancer is a multi-factorial class of diseases characterized by uncontrolled cell growth that constitutes the greatest cause of mortality and morbidity worldwide. Inflammation and cancer both are associated with genotoxicity, invasion, metastasis, and abnormal tissue repair mechanisms. In fact, NFκB pathway regulates pro inflammatory cytokine production, leukocyte recruitment and cell survival [93]. In addition, NFκB also controls cell cycle progression and apoptosis together with metastasis and cancer of various types. Elevated NFκB, Wnt/β-catenin pathways are crucial factors of tumorgenesis. PTL inhibits NFκB and Wnt/β-catenin pathways, which exert promising anticancer effects by promoting apoptosis and inhibiting cell proliferation. Furthermore parthenolide altered binding of a number of transcription factors including: C/EBP-α, FRA-1, HOXA-4, c-MYB, SNAIL, SP1, SRF, STAT1/3, XBPI and p53. It depletes GSH and increases cellular oxidative redox status also. The disturbed intracellular redox state elicits the downstream cellular apoptotic events, altered mitochondrial function and cell signaling pathways, which all lead to cellular death. Evidently, literature data showed that PTL protects normal cells from apoptosis; whereas it induces apoptosis in cancer cells. PTL has been shown to target acute myelogenous leukemia (AML) stem cells and their progenitors while sparing normal hematopoietic cells [94]. Therefore, parthenolide have become a strong candidate for future anti-cancer therapy in addition to its evident anti-inflammatory nature.

### References


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