Natural Products (Apigenin, Curcumin and Emodin) Cure Lung Cancer

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**To Cite This Article:** Bashir Ahmad. Natural Products (Apigenin, Curcumin and Emodin) Cure Lung Cancer. 2020 - 9(2). AJBSR.MS.ID.001375. DOI: 10.34297/AJBSR.2020.09.001375.

Received: April 28, 2020; Published: June 18, 2020

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**Abstract**

Lung cancer is the most common malignancy worldwide with over 1.8 million new cases diagnosed each year. As overall survival is only 15% for five years, therefore the appropriate therapy is compulsory for its treatment. A number of therapies are in practice for its treatment, but natural products (NPs) are considered safe and effective. Among these NPs, Apigenin, Curcumin and Emodin are reported for the treatment of lung cancer; therefore we summarized the studies of these NPs against lung cancer. This review will provide an outline for further research on these compounds against lung cancer.

**Keywords:** Lung cancer, Natural product, Apigenin, Curcumin, Emodin

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**Introduction**

Lung cancer is the most common malignancy worldwide with over 1.8 million new cases diagnosed each year [1]. Lung cancer incidence is the second highest while the leading cause of mortality in the United States. Approximately 85% lung cancers are NSCLC. Lung cancers. Nearly 80% of patients have regional or distal spread of disease at the time of diagnosis, accounting for poor overall survival [2]. Lung cancer screening is important and can shift the diagnosis to earlier and surgically resectable stage with significantly improved outcomes and cure but patients diagnosed with NSCLC are usually older and often have multiple age-smoking related comorbidities, poor functional status, borderline function, all factors that affect prognosis and health management [3]. Overall survival is poor and only around 15% of patients are alive 5 years after their initial diagnosis [1]. Lung cancer is among the malignancies with poor prognosis. In 2015, lung cancer was the fifth leading cause of mortality in United States, with the World Health Organization (WHO) reporting 1.7 million deaths worldwide [4].

A number of therapies are in practice for the treatment of cancer, natural products (plants derived compounds) are considered less toxic and more effective. [5] Medicinal plants are the vital sources for NPs [6,7] and it cure cancer through modulation of multiple pathways, including oxidative stress, intrinsic, extrinsic apoptosis pathway, cell cycle, inflammation, NF-kB, MEK-ERK etc. Among these NPs, Apigenin, Curcumin and Emodin are reported for the treatment of lung cancer; therefore we summarized the studies of these NPs against lung cancer.
Apigenin

Apigenin (AP) inhibits the proliferation and induced apoptosis in NCI-H460 cells time and dose dependently through inhibition of BCL-2 and upregulation of BAX and Caspase-3 [8]. In sphere forming NCI-H446 cells AP inhibit the self-renewal capacity which may have link with the down-regulation of uPAR expression [9]. AP inhibit the A549 cells proliferation and inhibit tumour growth through down-regulation of HIF-1 and VEGF [10]. AP alone or in combination with leptin inhibit the A549 cells proliferation and induces apoptosis through increase in ROS generation [11]. AP induces apoptosis in A549 cell though reactive oxygen species (ROS) generation, Mitochondrial membrane depolarization, Bcl2 down-regulation and Bax up-regulation, Cytochrome c (cyt c) decrease in mitochondrial fraction due to release to cytosol as result up-regulate the caspase 3,9 and PARP which lead to DNA fragmentation [12]. AP inhibit the proliferation of A549 and H460 NSCLC cells through downregulation of Akt and Xiap and upregulation of p21 and cyclin-dependent kinase inhibitor [13]. Another study reveal that the AP decrease the A549 cells viability and induces morphological changes time and dose-dependently through release of cyt-c, AIF and Endo G lead to activation of caspase-3,9 [14]. In H460 cells, AP induces apoptosis through ROS generation and Ca2+, MMP dissipation, down regulation of Bid, Bcl-2, procaspase-8, upregulation of Bax, AIF, cyt-c, caspase-3, GRP78 and GADD153 [15]. AP sensitize H1299 and A549 cells to TRIAL-induced apoptosis through upregulation of death receptor 5 (DR5) and death receptor 5 (DR5) in p53 dependent manner which lead to the upregulation of Bax and Bad, downregulate the Bclb and Bcl-2.

Furthermore AP inhibit NF-kB, AKT and ERK activation. In xenograft model, AP and TRIAL in combination completely suppress the tumour growth compared to its alone treatment [16]. We show that AP significantly decreases GLUT1 expression in mice. Furthermore, AP induces growth retardation and apoptosis through metabolic and oxidative stress caused by suppression of glucose utilization in lung cancer cells. The underlying mechanisms were defined that the anticancer effects of AP were reversed by ectopic GLUT1 overexpression and galactose supplementation, through activation of pentose phosphate pathway-mediated NADPH generation. Importantly, we showed that severe metabolic stress using a glutaminase inhibitor, compound 968, was involved in the mechanism of sensitization by AP. Taken together, the combination of AP with inhibitors of glutamine metabolism may provide a promising therapeutic strategy for cancer treatment [17]. AP tocopherol derivative-containing D-alpha-tocopheryl polyethylene glycol 1000 succinate (TPGS) liposomes and tyroservicate in combination exhibit superior cyto-toxicity, suppress invasion of A549 cells, induced G2 arrest. Furthermore, the combinatory effect inhibits the tumour growth in A549 cells bearing mice [18]. In A549 cells, AP exert anti-proliferative, anti-migration and anti-vision trough PI3K/Akt signaling pathway and inhibition of its down-stream signaling genes expression of matrix metalloproteinases-9, glycogen synthase kinase-3β, and HEF1 [19]. Taken together the AP is a potential natural compound for the lung cancer chemoprevention.

Curcumin

Curcumin (Cum) induces apoptosis in human lung cancer cells through various mechanisms including synergistic induction of cell death and apoptosis with AP and also by blocking cell cycle progression at growth/mitotic (G2/M) phase of A549 cells [20], showed that by binding to purified microtubules Cum can depolymerize interphase microtubules and inhibit reassembly of cold depolymerized microtubules [20]. Another study demonstrated that the Cum induces apoptosis in A549 cells through downregulation of Microribonucleic acid (miRNA) and caspase-10 which is identified as a target of miRNA-186-5p and caspase-10 which is identified as a target of hsa-miR-186 and led the cells to apoptosis [23,24]. Examined the in vitro effects of Cum on human lung cancer cell line apoptosis. They showed that Cum increases the growth arrest and DNA damage (GADD) 45 and 153 in a p53-independent manner and also inhibits the growth of PC-9 cells and induces G1/S arrest of the cell cycle followed by strong induction of apoptosis. They further showed that expression of cydin dependent kinase inhibitor genes p21 and p27 is induced by Cum, while the expression of numerous other genes, including Bcl-2, cyclin D1, CDK2, CDK4, and CDK6, is inhibited by Cum. Upregulation of GADD45 and 153by Cum is one of the prime mechanisms of its anticancer activity [24]. Taken together all this information, Cum is potential therapeutic NP for the treatment of lung cancer.

Emodin

In TCM, constituents of rhubarb (Rheum palmatum) have found a wide range of therapeutic applications including antitumor [25]. Major compounds of therapeutic importance in rhubarb are derivatives of anthraquinone, including emodin [26]. Many reports suggest that emodin efficiently suppresses multiple cell signaling pathways and also inhibits cell proliferation, invasion, metastasis, and angiogenesis [27]. Emodin is the most important therapeutic agent for the treatment of NSCLC. In NSCLC, emodin increase the cisplatin induced toxicity through inhibition of induced ERK1/2 activation and ERCC1 protein induction via instability of ERCC1 protein [28]. In NCI-H446 small cell lung cancer cells, emodin suppressed the viability increased the apoptosis and induced changes in cell cycle through down-regulation of 8 genes and upregulation of 10 gene after 12 hours and 12 gene up-regulate and 24 were down regulated after 24 h. These genes were involved in signal transduction, metabolism, cytoskeleton organization, transport, cell adhesion, transcription regulation, immune response, cell
adhesion, RNA processing and cell cycle control [29]. Emodin exert a suppressive effect on NSCLC proliferation in concentration dependent manner through down regulation of Rad51 and ERCC1 [30]. Emodin induces growth inhibition and apoptosis in A549 cells through extrinsic pathway in which emodin upregulate the FASL while downregulate the C-myc and lead to DNA fragmentation [31]. In H1299 and A549 cells the emodin decrease cells viability and induces apoptosis through tribbles homolog 3 (TRIB3) induced ER stresses [32]. These studies show that the emodin has very potential therapeutic effect against lung cancer.

Conclusion
Lung cancer is the most common malignancy around the world. NPs cure the lung cancer through different mechanisms. Among these NPs, AP, Cum and Emodin has very potential effect for the treatment of lung cancer.

Conflict of Interest
The authors declare no conflict of interest.

Consent for publication
All authors agree to be published.

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