Role of Natural Compounds in Treating Lung Cancer through Apoptotic Pathway

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***Abstract*: Lung cancer is a type of death- causing disease which has high mortality rates across the world. Small-cell lung cancers and non-small-cell lung cancers are the types of lung cancer. The most common methodology for treating lung cancer are chemotherapy, radiotherapy and surgery but they have certain side effects. Treatment of lung cancer remains challenging as a result of drug resistance and multiple side effects. Naturally occurring compounds which are mainly found in vegetables, fruits and dietary supplements are used in treatment of lung cancer. Natural compounds are found to be better and more potent activity in lung cancer, as well as natural compounds have certain side effects. Discuss some important terms of natural products that are molecular targets of natural products with their anti - lung-cancer activities, anti-tumor activities and as well as discuss clinical trials for treating lung cancer using the natural product. Discussion about ethno pharmacological effects of natural compounds specialized in apoptosis, metastasis, angiogenesis as well as their efficacy in medical testing. Apoptosis is the process that is used in treatment of lung cancer for control the upregulating growth of cancerous cells. This review provides general and effective information on the use of natural compounds such as green tea, flavonoids, genistein, etc. to prevent lung cancer progression and their role in the treatment of lung cancer**.

***Keywords*: natural products and their constituents, apoptosis, lung cancer, antitumor, etc.**

Introduction

Lung cancer is categorized as metastatic in which uncontrolled growth can multiply beyond the lung into nearby tissue or other parts of the body [1]. On the basis of histological observation, the two main categories of lung cancer are non-small cell lung cancer and small cell lung cancer and the non-small cell lung cancer are also divided main 3 types such as adenocarcinoma, large cell carcinoma, squamous cell carcinoma and other [2, 3]. The most common signs and symptoms of lung cancer are coughing, shortness of breath, pain in chest, and losing weight [4]. Natural products and their bioactive components play an essential role in the treatment of lung cancer, but they also have side effects. Various molecules of natural products have shown themselves useful and effective in chemotherapy. Using this natural product may increase the duration of survival and also improve the quality of life (QoL) of patients. In this review, the effect of natural compounds and the molecular regulation mechanisms, their antitumor effects, and anti-lung activities on lung cancer has been discussed. In the treatment of lung cancer, early diagnosis very efficiently increases the survival times of patients. The causes of lung cancer were not explained earlier until the process of metastasis was introduced. The main strategies are used in the treatment of lung cancer are Chemotherapy, radiotherapy, and surgery. Although, standard chemotherapies have a toxic effect on lung cancer patients and may result in limited survival benefits. Anti-tumor and herb Phyto-chemicals, these plant-based agents are used for treatment because these agents are less toxic, and the high result has attractive ongoing reports and investigations [5].

2. Apoptosis

The word "apoptosis" comes from the Greek word "απο" and "*πτωσιζ* " that means "dropping off" and it refers to the falling of leaves from trees in autumn. In necrosis, it is used to explain the situation where a cell actively pursues a pathway to death after receiving some stimuli [6]. In the 1970s, Kerr et al described Apoptosis. It remains one of the most investigated processes in biological research [7]. Human beings are selective processes, apoptosis essential in both physiological and pathological conditions [8, 9]. Morphological alterations of apoptotic cell death that concern both the nucleus and the cytoplasm are remarkably similar across cell types and species [10, 11]. Typically, several hours are required from the initiation of cell death to the final cellular fragmentation. However, the time taken depends on the type of cell, the stimulus, and the apoptotic pathway [12].

2.1. Apoptosis and natural product molecules

Apoptosis is a form of programmed cell death that participates in many morphological expressions, like, cell shrinkage, plasma and nuclear membrane blebbing dissolution of the nuclear lamina, and biochemical processes, responsible for the apoptosis activation [13]. The roots and fruit of ***Toona sinensis*** (*Meliaceae*) in Chinese medicines have been used in cancer therapy. Toona showed that glucose takes in adipocytic isolation 3T3-L1 fats and improves anti-diabetic activity [14]. Medicinal plants and their bioactive compounds are also referred to as powerful inducers in cell apoptosis of lung cancer. Acacetin (5,7-dihydroxy-4′-methoxy-flavonoids.) A flavonoid compound is the natural compound derived from *Robinia pseudoacacia* (black locust) that can inhibit the cell proliferation of A549 cell line (IC50 = 9.46 micront). Through the regulation of p53 and p21/ WAF1 proteins, acacia-induced apoptosis and cell cycle at the concentrations of 5 / 10 μM in A549 cells [15]. Widely used Chinese herbal medicine has considerably

suppressed the proliferation and growth of A549 cells, partially due to the cytokine-induced NFκB activation inhibition i.e, tumor necrosis factor-alpha (TNF-α, cachexin) [16].

3. Reversion of Multidrug Resistance

MDR, Multidrug resistance (medicates through altered expression of topo-isomerase 2) is one of the major complexities of chemotherapy against cancers [17]. The cellular overproduction (ABCB1) of p-glycoprotein (p-gp) is one important factor that participated in MDR, the transporter for various anticancer drugs outward the cell. Up to now, several reverse agents are determined to reverse MDR by intermeddling with the p-gp function [18, 19, 20]. On the other hand, some reversal agents of MULTIDRUG RESISTANCE may bring pharmacokinetics change and lead to some adverse effects. Gemcitabine (Gemzar), docetaxel is some anticancer or chemotherapy drugs that prevent and use for lung cancer treatment and (navelbine) vinorelbine (NVB) can over express MDR (multidrug resistance-associated proteins), including p-gp. While this outcome helps cause MDR in lung cancer treatment (NSCLC), new reversal agents of MDR should be used in medication to avoid MDR and also improve the effects of lung cancer therapy.

NATURAL COMPOUNDS-

Green tea polyphenol (Epigallocatechin-3- gallate)

Tea is the most regular beverage which is extracted from the plant C. Sinensis that is consumed worldwide for the treatment of lung cancer. Essential data comes from experimental studies that suggest that green tea can prevent cancer-causing effects [21, 22]. All activities involved a major component of EGCG (Epigallocatechin-3-gallate) an active compound of green tea. EGCG involved some mechanisms which showed that EGCG-inducing the apoptosis and modulating the cell cycle arrest in carcinogenic -metabolizing enzymes and regulate signaling pathways of cell and inhibited the transcription factors in cancer cells, which gives the result in the interdict development of cancer, which improve the prevention and treatment of cancer by green tea (EGCG).EGCG (Epigallocatechin-3-gallate)and Guanosine triphosphate (GTP), is a bioactive compound of Green tea can help the prevention and treatment of lung cancer. Dietary supplementation of EGCG (0.1, 0.3, and 0.5%) inhibited the growth of tumors in nude mice implanted with thymus H1299 cells. Increase phosphorylated H2AX variants, tumor cell apoptosis, and also increased 8-hydroxy-2′-deoxyguanosine (8-OHdG) biomarker for oxidative stress through ECGC treatment. This experimental report presents the first evidence that epigallocatechin-3-gallate introduces the generation of ROS (reactive oxygen species), leading to DNA oxidative damage of tumor cells. EGCG (Epigallocatechin-3-gallate) compound of green tea is referred to as a powerful antioxidant compound [23]. DFMO (alpha difluoromethyl ornithine) and Polyphenon E(green tea extract) showed inhibition activity analyzed in A/J mice when injected with B(a)P. Polyphenon E reduced the tumor load in animal and also reduced the largest tumor.[24].

Isothiocyanates

Isothiocyanates (ITCs), the natural compound found in cruciferous vegetables. Some cruciferous vegetables are broccoli, Japanese radish, and cauliflower, etc. It is converted into glucose and ITC by the action of enzyme myrosinase .Different studies focused on some biological isothiocyanates such as phenethyl isothiocyanate (PEITC), Benzyl isothiocyanate (BITC), and sulforaphane (SFN) for their chemopreventive and anti-tumor effects [25] In recent time, BITC(Benzyl isothiocyanate)is a form isothiocyanates can inhibit gefitinib-resistant human cancer growth (NSCLC), activation of CASP(caspase-3), introduce the apoptosis, arrest the cell-cycle in M phase,(reactive oxygen species) ROS generation, depletion of glutathione(GSH)depletion, inhibition the activity of protein kinase, activation of NF-κB transcription, and mitogen-activated protein kinase activation (MAPK) and activation of protein (AP)-1. Phenethyl isothiocyanate reduces the first phase of enzymes which is involved in the activation of various cancer-causing substances, and it is also involved in the activation of the second phase of enzyme activity, which is responsible for oxidative stress and various carcinogenic metabolize activity and also inhibited human leukemia cells growth by inducing apoptosis. Isothiocyanates (ITCs) are naturally occurring compounds which show anticancer properties by inducing apoptosis and inhibiting the cell-cycle stage. Numerous studies showed that various mechanisms have been used to determine the ITC against the mechanism of lung cancer. Significantly, researchers think that tubulin is the protein in the body that is one of the targets for ITC (isothiocyanates) binding. And also have a covalent binding of phenethyl isothiocyanates, Benzyl isothiocyanate, sulforaphane tubulin. Binding with cell apoptosis reduces the cell ability and cell cycle arrest in the m phase [26]

Indole-3-carbinol

An autolysis product of glucosinolate (indole-3-carbinol) is a biologically active compound that has been reported to exert anticancer effects, which is present in vegetables like broccoli, cauliflower, rutabagas, etc. [27] .It is widely used for preventing and treatment of various types of cancers. After the procession protocol in A/J inbred mice, we determine how indole-3-carbinol inhibits tobacco carcinogen and prevents lung cancer. The reduction was observed at some stage in going on after initiation in tumor multiplicity, adenoma, adenocarcinoma, and hyperplastic foci after treatmen with bioactive compound indole-3-carbinol. This biological active compound (I3C) easily suppressed the growth of pulmonary adenocarcinoma. Also, the anticancer effects of indole- 3- carbinol were mediated through modulating the phosphatidylinositol-3-kinase signaling pathway [28]. Myo-inositol (MI; 56 μ mol/g/diet) and I3C (30 or 70 μ mol/g/diet) against VC that induced lung cancer were applied. With a higher dose at the lung surface, cancer prevalence, multiplicity, size, and adenoma with cellular pleomorphism, the lower dosage of indole-3-carbinol showed some effects, whereas the higher dose of indole-3-carbinol reduced the tumor multiplicity on the treatment of mice. Treatment with the higher dose of i3c inhibits many mechanisms such as IkB-alpha degradation, activation of NF-κB, COX-2, and caspase-3 activation [29]

Genistein

Genistein (4, 5, 7-trihydroxyisoflavone) is a major isoflavone found in soybean, and has been widely studied for its chemotherapeutic and chemopreventive effects. In recent times, experiments show that the derivatives of genistein, [7-difluoro methyl dimethoxy genistein], has suppressed the growth of lung cancer in a dose-dependent manner and no toxic effect [30]. When treatment of mice with a combination of gefitinib and genistein, the tumor growth was decreased in the xenograft model [31].For lung metastasis induced through B16F-10 melanoma cells in C57BL/6 mice, the inhibitory effects of dietary soybean such as isoflavones, and daidzein were studied. Comparison with untreated tumor-bearing animals, treatment with genistein (200 μmol/kg body weight) caused inhibition in lung tumor nodule formation and also inhibited the lung collagen hydroxyproline content and serum salicylic acid level. When tumor-bearing animals were treated with genistein the duration of tumor-bearing animals was increased [32].

Curcumin

Curcumin (diferuloylmethane) is found in the plant C. longa. Curcumin has various therapeutic properties such as antioxidant, anti-inflammatory, analgesic, antiangiogenic, and antiseptic have been generally studied [33].Being observed as a curcumin (0.6%) bioactive compound can reduce the expression of COX2 in subcutaneous tumors and also reduce the weight of intra lung tumors but can enhance the survival time . Curcumin may enhance the survival of Athymic nude mice (immunocompromised mice) and inhibit the tumor growth of orthotopic lung tumor model xenografts [34]. When oral intake of curcumin and phospho sulindac then inhibit lung cancer growth in human xenografts in nude mice; curcumin may also enhance the phosphor sulindac bioavailability and efflux transporters were inhibit [35]. Curcumin also improves cell survival rate, which participates in T-cell–mediated adaptive immune response and reduction in the growth of cancer cells. Low-dose of curcumin increased T cells (lymphocyte) derived from 3LL-tumor-bearing mice, especially, CD8+ T cells, but high-dose of curcumin (100-mg/kg body weight) reduced T cells (lymphocytes) which show the improvement of cytotoxicity and secretion of interferon-γ (IFN-γ) and proliferation against 3LL tumor cells. The results of the lung tumor-bearing model are cleared that curcumin may support the immune system by inducing an antitumor immune response. Curcumin can verify that it is an immunologically safe drug for cancer treatment. Some experimental evidence suggested that Curcumin can play a vital role in lung cancer therapy [36].

Flavonoids

Flavonoids are polyphenolic compounds that have been used as nutraceuticals for many years for the various favorable properties on human health. Flavonoids are mainly found in vegetables, fruits, whole grains, and plant extracts. Flavonoids are the part of polyphenols that responsible for the plant pigmentation in plants ., apart from this, Flavonoids also have been proved to be responsible for several biochemical functions in seed maturation, protection from different biotic/abiotic stresses, and heat acclimation and freezing tolerance. Flavonoids were developed as a detoxifying and defensive system in plants [37]. Some important flavones are diosmetin apigenin and luteolin which showed potent inhibitory effects on the proliferation, activation of apoptosis, and cell cycle regulation, but also invasion and metastasis [38]. Dietary flavonoids may be used as preventive/therapeutic agents against different human cancers because of their interfering capacity with epigenetic pathways [39]. Flavonols were proved to have significant anti proliferative effects [40], apoptosis also affecting tight junction protein key elements of carcinogenesis [41], invasion and metastatic processes [42]. Flavanones, including hesperidin and naringin, are retrieved in high concentration in citrus, the main biological effects being related to the anti-inflammatory effects [43]. Furthermore, flavanone derivatives have been shown to play a critical role in the cell cycle regulatory proteins expression control [44].

Fisetin (3,3′,4′,7-tetrahydroxyflavone1)

Fisetin is a naturally occurring flavonoid found in fruits and vegetables like grapes, onion, apple, etc [45]. Fisetin (3,3′,4′,7-tetrahydroxyflavone) has been described as immunotherapy and chemopreventive in most cancers. Fisetin is the main flavonoid that has antioxidant, antitumor and anticancer activities. Numerous studies by different researchers have studied and explained the chemotherapeutic role of flavonoid groups against several types of human cancers [46]. Initial research examining the fisetin's effect in lung cancer has been shown to fisetin is an effective inhibitor of adhesion, migration, and invasion of human A549 cells of lung cancer[47].After the administration of fistein reported that Fisetin play a promise and important role in human lung cancer (NSCLC) cell (A549) , inhibited cell growth, reduced colony development, phosphorylation inhibition (p70S6K1,mTOR, protein kinase B), reduced PI3K protein expression as well as suppressed constituents of mTOR signaling complex. Fisetin- treated cell showed a significant decrease in TSC2 phosphorylation as well as increase AMPK- alpha phosphorylation [48].

4. Clinical trials of the natural compound for lung cancer treatment

Complementary and alternative medicine (CAM), involve natural product compounds, the improved survival rate in patients with cancers [49].In recent times, 453 patients of cancer in a longitudinal study give evidence that 77% of cancer patients use herbal medicines with conventional treatment to reduce the toxic effect of therapy and also reduce the symptoms of cancer, and also recover the immune system, and even eliminate cancer directly [50]. However, natural occurring herbal drugs have not affected bone marrow inhibition, one-year survival rate, median time to progression, and mean cycles of chemotherapy applied. Natural product molecules can improve the QoL (quality of life) of lung patients with cancer. 294 patients with lung cancer (NSCLC), treated with Shenfu injection of traditional Chinese medicine, based on the functional analysis of lung cancer therapy (FACT-L), health positively affected by Chinese medicine, when these medicinal drugs used in addition to with psychological, functional, and extra attention when performing traditional chemotherapy ($P < 0.05$) [51].

Conclusion

In this review, it has been discussed that a significant number of herbal compounds are potentially useful in the treatment of lung cancer. The use of natural products including (1) green tea, (2) cruciferous vegetables (isothiocyanates), (3) turmeric (curcumin), (4) Fisetin, (5) flavonoids appears to be promising. These dietary natural products and their active components could affect the growth and progression of lung cancer in various ways such as inhibiting tumor cell growth and metastasis, caring against lung cancer, immune-modulating and enhancing effects of chemotherapeutic drugs. In the future, attention ought to be paid to the isolation of active compounds, the illustration of deed mechanisms, bioavailability, potential toxicity, and unpleasant effects, and more studies are necessary about the clinical efficiency of dietary natural products and their bioactive compounds

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Conflict of Interest

The authors declare that there is no conflict of interest.

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