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A Review on Natural Compounds for Lung Cancer

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Abstract
Lung cancer is the leading cause of cancer-related deaths throughout the globe for both man and women. Most of the patients are diagnosed with untreatable metastatic stage and their survival period is only 5 years. 80% of lung cancer patients suffer from non-small cell lung cancer (NSCLC) and the remaining 15% -20% suffer from small cell lung cancer (SCLC. The cancer of lung disease has a high death rate throughout the world. Natural compounds known as phytochemicals have been obtained from herbal medicines were used traditionally in the therapy of the cancer of the lung. Because they have less adverse effects and also most of the medicinal compounds are obtained from them. Most of the available drugs for the therapy of lung cancer are obtained from herbs. This review aims to find out some lead compounds from natural origin and also highlight their activity against lung cancer. Also checking their physical properties and determining their ADMET properties. It is a valuable attribute to use plants as an alternative for the treatment of lung cancer than commercial drugs because the patients also suffered to some extent and quality of the life of the patient reduced. These natural compound could be safe and effective for the treatment of lung cancer, helpful in prolonging the survival period, improve the life quality and also could bring a bright future for the patients of lung cancer. Therefore the data presented in this review will help come researchers to develop new and more effective compounds for lung cancer treatment.

Keywords: Lung cancer; Herbal medicines; Phytochemicals; Treatment.

Introduction

Lung cancer is the most common type of cancer disease and the major cause of cancer-related deaths throughout the world for both men and women. Most of the lung cancer patients are diagnosed with untreatable metastatic disease with a survival period of only 3 months to 1 year or 5 years. Among them, more than 80 % patients of lung cancers suffer from non-small cell lung cancer (NSCLC) and it has three subtypes namely, adenocarcinoma, squamous cell carcinoma and large cell carcinoma, among them adenocarcinoma is the most frequent subtype (Siegel et al.,2015). Compounds of natural origin, known as phytochemicals, these natural compounds are acquired from traditional medicinal herbs, which are used to treat different human diseases including cancers (Wu et al.,2015). Solamargine (SM), is a medicinal plant, glycoalkaloid is a general substance that is extracted from a medicinal plant solanum lycocarpum fruit, it has not just the ability to prevent inflammation but also it can prevent the uncontrolled cell division, this compound is used to treat several kinds of human illnesses including lung cancer (Martins et al., 2015). Studies have been shown that the chemical compounds from SM are active in inducing apoptosis and also prevent the growth of hepatoma SMMC-7721 cells by the activation and induction expression of caspase-3 (Ding et al.,2012). According to (Liang et al.,2007). Previous research work has been proved that SM is a very important medicinal herb, in A549 and H441 lung cancer cells, the abnormal action of human epidermal growth factor receptor 2(HER2) and topoisomerase II alpha (TOP2A) is regulated by the extract from SM and low toxic topoisomerase II inhibitor epirubicin. This mixture works together to simulate the apoptotic process in lung cancer cells.

Cancer of the lung is a lung disorder with high death rates around the globe. Due to which, patients of lung cancer are suffered to some extent and their life quality also decreases. The natural compounds from traditional herbal medicines are considered as the most effective ingredients for the treatment of cancer of the lung have less or no adverse reactions, also many other lead compounds obtained from them. Cancer is a group of different genetic disorders which are unified by some familiar alterations in different types of cells that produce signals for the cell growth (Luo et al., 2009). Several features pointed out for the cells that change and becomes cancerous. The process of apoptosis or programmed cell death is considered as the basic change that can point out the tumour formation (Hanahan et al., 2011). In lung cancer, a malignant tumour is formed that metastasize to other organs very early due to which the patients are diagnosed with an incurable metastatic stage with a survival period of only 5 years, also the patient is suffered to some extent and his life quality also decreases (D.W.Ford et al., 2013). Several factors may increase the risk of lung cancer such as excessive tobacco smoking, previous radiation therapy, exposure to radon gas, air pollution, and chemical elements like asbestos and another carcinogen like nickel, chromium, and arsenic (A.J.Alberg et al., 2013). Smoking is the major cause of lung cancer development because smokers are at more risk to be suffering from lung cancer as compared to non-smokers (W.N.Rom et al., 2000) and also lung cancer cases are higher in a man then women (Duarte et al., 2005).

There are two major categories of Lung cancer namely, non-small cell lung carcinoma (NSCLC), more than 80% lung cancer incidences occurred, and 15 -20% small cell lung cancer (SCLC) incidences occur throughout the globe. Several chemotherapeutic agents have been identified for remediation of the cancer of lung which has been proven effective in lung cancer treatment (Greenberg et al., 2013). This strategy has been proven effective in those patients who have a highly metastatic stage in which the aberrant expression of the ALK gene has occurred (Shaw et al., 2014). Also, tumour-associated biomarkers have grown through studies which have

the main focus to decrease the rate of mortality of the patients of lung cancer, through the disease diagnosis at initial stages (Zhang et al., 2013). A traditional Chinese medicinal plant Selaginella tamariscina that can prevent the proliferation of cancerous cells in lung tissues (Yang et al., 2007). Sesbania grandiflora is another traditional medicinal herb and the methanolic fraction of this medicinal plant can induce anti-metastatic effects on the cancerous cells of lungs. These natural compounds can induce the process of programmed cell death along with the production of a large number of reactive oxygen species (ROS) (Pajaniradje et al.,2014).

Cancer is a disease in which the cell growth becomes abnormal, these cells are highly capable of invasion and proliferation to other organs. Ones the cancerous cells formed they spread to other parts of the body with the help of blood vessels and lymphatic ducts. Globally, lung cancer is considered the most common cause of cancer-related deaths (Jemal et al.,2007). Lung cancer has a very high mortality rate because the disease cannot be diagnosed in early stages and the cancerous cells have a great ability to invade locally and also these cells spread to other distant organs particularly the adrenal glands, liver and bones very early (Lee et al .,2007). Different therapies are available to prolong patient life and also used to eliminate the cancer cells, including surgery, radiation, and drugs (Smith et al.,2000). However, these treatments decrease the quality of the life of patients and also these therapies has other side effects. Medicinal plant extracts have been used for the treatment of several types of human illnesses due to their less adverse effects as compared to other available drugs (Newman et al.,2000). The apoptotic process of cell death is considered as an important mechanism to eliminate the cancerous cells. Some recognizable changes occur in apoptotic cells, such as chromatin condensation, nuclear fragmentation, and blebbing (Nagata S. 2000). Both extrinsic and intrinsic pathways are involved in programmed cell death that is used to remove the most damaged cells. From many years apoptosis has been an effective approach to remove cancer cells (Fesik SW. 2005).

Lung cancer is a very frequent type of cancer disease, both males and females can suffer from it. In China, approximately 520,000 cancer incidences, and 450 000 mortalities have occurred per year. (Tan X, Qin W, Zhang L et al.,2011). Thus, a new, effective and longer-lasting, treatment is required for lung cancer that could help prolong the patient's survival period and improving their life quality and also could bring a bright future for lung cancer patients. Products of natural origin have been used for cancer chemotherapy for many years, and an in-depth analysis is needed for their mechanism of action on lung cancer cells. (Qiu JX, He YQ, Wang Y et al.,2013). Chonglou (Paris polyphylla var. chinensis), a traditional Chinese medicine herb, that has been used for the removal of several types of cancer diseases including lung cancer for many years (Sun et al.,2007). The main constituents of the saponins extract from the rhizoma of Chonglou, known as Rhizoma Paridis saponins (RPS), were identified as polyphyllin D, formosanin C, dioscin, Paris H, and Paris VII. RPS has been proved as an effective constituent against cancer through various studies. (The Zhang W, Zhang D, Ma X et al.,2014) .The extracts of this medicinal plant can induce apoptosis, effective in cell cycle distribution, prevents the mechanism of angiogenesis, and also brings an improvement in immune function in cancer cells (Shuli M, Wenyuan G, Yanjun Z et al.,2011). RPS could also able to inhibit the process of metastasis through the induction of cell cycle arrest and programmed cell death of the NSCLC cells.

Cancer of the lung is the leading cause of cancer-related deaths throughout the globe non-small cell lung cancer incidences are more than 80% of all lung cancers. Non-small lung cancer is an umbrella term for several types of lung cancer which are adenocarcinomas, squamous cell

carcinomas and large cell carcinomas. (Jemal et al.,2008). Despite advances in the treatment strategy of lung cancer, that includes surgery, chemotherapeutic drugs, radiation therapy the lifetime of the patient is still poor and only 15% can survive (Erridge et al.,2007). Due to metastasis of cancerous cells to other organs, the survival period of lung cancer patients becomes lower and radical resection may be done for soft tissue sarcomas that remove the whole tumour and it is the only remedy needed which depends on the type of tumor (Wang et al.,2010). The metastasis process of cancerous cell to other organs consist of many steps in which adherence of cells occur, then invade locally, then migrate, proliferate and finally, vessel formation occurred (Yilmaz et al.,2007). Thus it is important to prohibit lung cancer proliferation to other organs which necessary for increasing the survival period of patients and also needed for the improvement of life quality. Cnidium monnieri is a medicinal plant from which a natural compound named Osthole can be obtained and many types of research proved that this natural compound is an active ingredient against many human cancer cell lines. Many studies have proved that osthole can prevent the relocation and proliferation of many cancer cells in lung tissues (e.g A549 cells of lungs).

Lung cancer is caused due to aberrant expression of some proteins that leads to activation of oncogenes and inactivation of tumour suppressor genes which results in uncontrolled cell division in lung tissues that finally forms a tumour which spread to other organs. [Ou et al.,2017] Due to which the signally pathways of the apoptotic process becomes irregular and the cells receive signals continuously. The apoptotic process is necessary for the elimination of damaged cells and also responsible for the normal process of cell growth. [Pucci et al.,2000]Due to disruption in the cell cycle the apoptotic processes becomes irregular in lung cancer cell lines (Meikvantz W, Schlegel R 1995), Several genetic factors are involved in the process of cell growth such as p53,p27,p16 these are some proteins which are responsible for the normal growth of cells. Along with other signally pathways are also involved in the process of apoptosis such as intrinsic and extrinsic apoptotic pathways. [Hassan et al., 2014]. A medicinal herb Calotropis gigantea (CG)is a type of flower which is mostly found in Asia and tropical Africa. The extract obtained from this plant is active in inducing the apoptotic process by the generation of reactive oxygen species in many cells of lungs (e.g A549 and NCI-H1299 cells). The extrinsic and intrinsic apoptotic signalling pathways are also activated by the action of CG extract. This extract is capable of preventing the abnormal cell growth in A549 and NCI-H1299 cells of lungs that inhibit uncontrolled cell division and causes program cell death.

Lung cancer-related deaths are quickly increasing throughout the world due to the long term history of smoking behaviour, laziness and western pattern diet or standard American diet (Jemal et al.,2011). Cancer is a fatal disorder many fatalities occurred because of cancer but the cancer of the lung is considered as the most common cause of deaths as compared to other types of cancers throughout the world (Khuri et al., 20010. Several strategies have been used for lung cancer therapy such as surgical procedures, radiotherapy, and chemotherapy. Although, these treatment strategies are not effective in the complete remission of cancer (Das et al., 2009) and cannot be effective to prolong the survival period of cancer patients. Therefore, a new, longer-lasting and effective treatment strategies are needed for early diagnosis and to target cancer, and also new improvements must be made to the available treatment procedures that can easily point out the responsible signalling pathways involved in the process of apoptosis and which should have less adverse reactions are immediately required to increase the treatment of cancer. In medical applications, nano-based particles are used to treat various human illnesses, which are known as nanomedicines. This nano-based material brings the innovation of several

nanoparticles which have some special properties and have several important functions like a diagnosis of disease and therapy (Rychahou et al.,2018). According to (Vivek et al.,2016) The nanotechnology for cancer disease consists of science and engineering having several medical applications like molecular imaging, disease diagnostics and treatment. Silver nanoparticles from the natural origin are one of the most favourable nanoproducts which have been used for nanomedicines in the past two decades because of their peculiar features. Extract from the leaves of Gossypium hirsutum is used for the synthesis of AgNPs. Silver nanoparticles which are synthesized biologically have proved that this nano-based material causes apoptotic cell death in human lung cancer cells.

In lung cancer, a malignant tumour is formed which affects the lower respiratory tract and also metastasize to other distant organs very early after it forms due to which the lifetime of the patient is only 5% (R.L. Siegel, et al.,2018). Though active cigarette smoking is considered as the basic root for cancer of the lungs many other risk factors are also involved such as radon gas, air pollution, arsenic and other chemicals which are carcinogenic to humans (G. Fehringer, et al.,2017). Even though there are many FDA approved drugs for the treatment of lung malignancy available, but a new and safe natural compound with little side effects is needed in lung cancer therapy. Identification of some important compounds from natural origin having little adverse effects is needed for the treatment of lung cancer. Commercial products have several side effects which can decrease the quality of the life of the patient, now studies are concentrated towards natural products for cancer treatment. In recent years several types of research have been conducted to find out the toxic effect of several natural compounds has a history of traditional use in past years. A traditional medicinal herb Thuja orientalis L. can prevent inflammation of cancer cells by interrupting the NF-κB activation (P. Srivastava, et al.,2012, T.-H. Kim, et al., 2013). Due to inflammation the tumour progression occurs and as a result, phenotypical changes occur in cells and the tumour becomes more aggressive and acquires greater malignant potential. The leaf extract from Thuja orientalis L. plant has great anti-cancer ability against human lung cancer A549 cell line. Thuja orientalis L. extract is an effective ingredient that can prevent the uncontrolled growth of cancer cell and progression at different concentrations.

Cancer is a type of disease that produces no clinical symptoms or signs that is caused due to undesirable cell division. Due to disruption in the system of checks and balance on normal cell growth, the cells start to dividing uncontrollably and forms a mass of cells called a tumor (S. Demir, Y. Aliyazicioglu, I. Turan et al., 2016). In Malaysia cancer is considered as the most frequent disease and more cancer incidences occur than other human illnesses. In Malaysia, a research survey has been carried out by International Agency of Research for Cancer(IARC) in 2017 and reported that cancer is the most frequent disease and the fourth leading cause of cancer-related deaths in private hospitals. In 2017 the cancer incidences were 37,400 but in 2018 there were 43,837 cancer cases were reported, a very big change occurred in cancer incidences. Lung cancer is the leading cause of cancer-related deaths worldwide. According to (Goldatraw et al., 2016)Unfortunately, the currently available treatment strategies are not enough and the survival period of only 5 years is remains poor. Compounds from natural origin have been used traditionally as alternative medicines for many years. [J. K. Grover and S. P. Yadav,2004]. The common medicines are mostly used as holistic medicines. M. charantia is a natural herbal medicine which has some anti-cancer, anti-viral and anti-diabetic properties.[Manoharan et al.,2014]. Several types of research have been proved that a crude extract of M. charantia has anti-cancer properties (Li et al.,2012). Studies have also reported that the natural compound from

M.charantia can prevent cancer progression by interfering in the process of synthesis of proteins, synthesis of RNA and DNA configuration. There are two types of M.charantia found in China and India and were proved as an active product of antiproliferation in A549 lung cancer lines. Chinese hot aqueous extracts (CHA) has the capability of antiproliferation in A549 lung cancer cell line. Because of the rich bioactive chemical composition, CHA is considered as an apoptosis inducer in lung cancer cells. During the apoptotic process reactive oxygen species produced due to which CHA causes an active proliferative effect on the dividing cells.

According to (Globocan, 2012) Due to Lung cancer there are approximately 1.59 million deaths are reported in 2012 and it is the most common cause of cancer-related deaths. Cheng et al.,2005 said that, although the available treatment strategies have been improved it is still untreatable in the complete remission of cancer and quality of life of patient decreases after treatment. Bello et al. (2011) proposed that the people of South Africa have more risk to be suffered from the cancer of lungs because of their continuously changing living habits and bad conditions of communicable infections in that particular area. Because of genetic mutation in genes and proteins, cancer cells divide uncontrollably and forms a mass of cells called tumours that spread to other organs (Bonomi et al., 2013). Apoptosis is a natural mechanism to maintains a balance in cell growth and disruption to checks and balance on cell growth causes cancer. Another medicinal plant named Moringa oleifera (MO) endemic to India and South Africa, its common name is Drumstic plant from the family Moringaceae (Fahey, 2005; Goyal et al., 2007). Commonly the whole plant has medicinal importance's but its leaves have several important medicinal properties such as anticancer, antioxidant etc as compared to other parts of plant (Prasad and Elumalai, 2011; Sreelatha et al., 2011). The extract from leaves contains bioactive compounds which have anti-cancer properties. According to (Anand et al.,2014)Recently, the flower petals of this plant were used as a substrate for the synthesis of AuNP0 s and the nano-based material proved to be an active ingredient against the A549 cancer cells of lungs. MLAuNP has antiproliferative properties and is capable of inducing apoptosis in A549 cells. The nano-based material acts selectively and inhibits the action of mutated genes which are responsible for the progression of lung cancer.

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