



COMPARATIVE STUDY AND REMIDIAL ASPECT ON LUNG CANCER OF THE ACTIVE COMPONENT(S) OF MEDICINAL PLANTS IN SPECIFIC TERRITORIES OF INDIA

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ABSTRACT

Cancer is a major health problem in both developed and developing countries, second only to cardiovascular disease. Lung cancer, in particular, is a disease with high morbidity and mortality, and is a major cause of death among all types of cancers the world over (- 18.2%), causing about 1.38 million deaths per year. The cause of such high mortality rate of lung cancer may be both internal (genetic, mutative, hormonal, poor immune conditions, etc) and external (such as food habits, heavy industrialization, population explosion, life- style, smoking, etc.). Due to high death rate and ill effects of chemotherapy and radiation therapy, many cancer patients seek alternative / complementary medical treatment with milder side effects. Some natural therapies such as direct use of certain medicinal plants or the use of active ingredients extracted from these plants are reported found beneficial in combating cancer. As such there exists a wide scope of deriving potential anticancer agents from these medicinal plants, which need extensive exploration in this area. Till date only a few medicinal plants have attracted the interest of concern therapist. In view of these facts, the objective of present article is to review the medicinal plants with antitumor potential against lung cancer, the status of lung cancer in specific territories of India and with comparison at Global level, and causes of lung cancer along with their remedial aspects, and mechanism of action.

KEY WORDS: Cancer, Medicinal Plants, Diet, Smoke, Population explosion



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INTRODUCTION

Cancer is a group of diseases caused by loss of cell cycle control and associated with abnormal uncontrolled cell growth¹, which may occur at any time, at any age, and in any part of the body. Cancer is the leading and sub leading cause of death in economically developed and developing countries, and is second most common disease after heart disease², and would overtake 70% of cancer deaths, in the developing world. Literature revealed that 14.1 million cancer patients were diagnosed in 2012, and this number is expected to be 15 million by 2020, about 8 million people died of cancer in 2012³, and this number would reach 13.1 million in 2030. In India, cancer has become one of the ten leading causes of death and their number is rising alarmingly and from the Year 2020 onwards more than 2 million new cancer patients will add every year. The most frequently observed cancer in Indian population are of lungs, breast, colon, rectum, stomach and liver⁴, and approximately 50-60% cancer patients die each year. According to Indian council of medical research (December 2011), 5,14,470 cancer deaths were noted in 2009, 5,24,911 in 2010 and 5,35,767 were reported in 2011 this number is expected to rise to 7,00,000 by 2015 and fivefold by 2025. A majority of cancer patients in India are between 30 to 70 years of age, such a high incidence of cancer may be both internal like genetic, hormonal and poor immune condition as well as external environmental factors such as food habits, heavy industrialization, population explosion, smoking, ultraviolet rays and life-style, smoking, etc. Lung cancer is the second most common cancer in world over which causes 19.4% (1.38 million) of the total deaths annually⁵. The incidence rates of lung cancer are generally higher among men than women, and 80% of all cancer cases are non-small cell lung carcinoma, while remaining cases are small cell lung carcinoma. Recently surgery, radiation, chemotherapy, hormones, immunotherapy including STAT3 pathway inhibition, cell cycle arrest, Htert silencing, chitin inhibition and ALK (anaplastic lymphoma kinase) gene inhibitor technique are used to cure different type of cancers. Although chemotherapy is most frequently used, but

they have side effects which prevent their extensive usage. Now-a-day approximately 70% of the world population is depending on medicinal herbs or traditional medicine. The use of traditional medicine has again increased dramatically, in the last two decades⁶. More than 50% of all modern drugs in clinical are use of natural products⁷. Cancer can be controlled by the intake of active ingredients of medicinal plants. There are at least 2,50,000 species of plants, out of which more than one thousand plants have been found to possess significant anticancer properties, while a large number of plants products are still remains to studies in details. In India the medicinal plants have been used to treat different type of cancer and some plant products are marketed as anticancer drugs based on the traditional uses and scientific reports, which may promote host resistance against infection by re-stabilizing body equilibrium and conditioning the body tissues. These plants may contribute novel compounds for preventive and curative medicine to modern science. The secondary metabolites are of specific interest to scientist because of their unique pharma-cophores and medicinal properties. secondary metabolites specially poly phenols are commonly used in treating or preventing specific ailments, such as atherosclerosis, diabetes mellitus, cancer and various type of communicable disease caused by different microbes. One of the reasons for these diseases could be the imbalance between reactive oxygen species and antioxidant defense systems, which may increase the oxidative burden over the body and lead to alter the metabolic activities of the cell and such processes are thought to play an important role in pathological processes of various diseases. Antioxidants neutralize the effect of free radicals through different ways and may provide defense towards various diseases. Plant and herb which exhibit antioxidant properties are therefore has widely been used for the treatment of various diseases. This paper high-lights the lung cancer context in specific territories of India, causes and their remedial aspects by specific medicinal plants and their active ingredients with a recent advances in understanding mechanism of action and structure function

relationship of nature derived anticancer agents.

2. Lung Cancer Global Status

The lung cancer is most commonly diagnosed cancer world over, accounting for 12.7% or 1.61 million of the total cancer cases in 2008 and this number rose to 13% or 1.8 million in 2012, which causes 1.6 million or 19.4% casualties in 2012, while this number was 1.38 million and 18.2 % of the total in 2008. In

contrast to the 5 year survival of 52 % in all cancers, the lung cancer survival rates continue to be poor ^{8,9}. The decline trend of age-adjusted lung cancer death rate in USA over a period of six decades has been noted in males whereas the same trend in female rising mainly because of the declining smoking habits in males & increasing smoking habits in females .The regional burden of lung cancer (cases and deaths) in the world is shown in Table-1 and figure 1and 2.

Table 1
The worldwide distribution 2008 of the incidence oo lung cancer

Region	Male		Female		Both Sexes	
	Cases	Deaths	Cases	Deaths	Cases	Deaths
World	1095	951	513	427	1608	1378
More developed region	482	411	241	188	723	599
Less developed regions	612	539	271	239	883	778
WHO Africa region (AFRS)	12	11	4	4	16	15
WHO Americas region (PAHO)	172	144	134	101	306	245
WHO East Mediterronean region (EURO)	21	19	5	4	26	23
WHO South-East Asia region (SEARD)	108	97	42	37	150	134
IARC Membership (21 countries)	456	386	233	180	689	566
United States of America	114	90	100	71	214	161
China	351	304	170	148	521	452
India	47	41	11	10	58	51
European Union (Eu-27)	207	182	80	70	287	252

Estimated numbers in thousands- (GLOBACON)

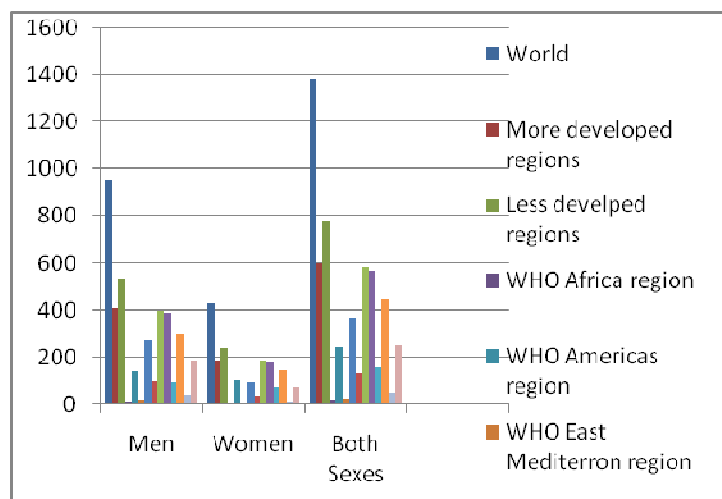


Figure 1
Graphical Representation of Data Shown in Table-1
(Total No of Cases)

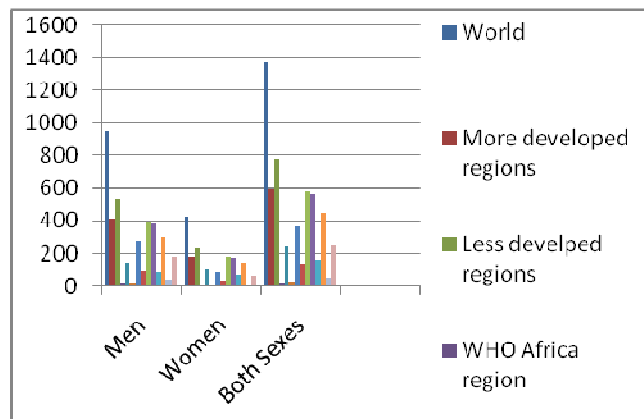


Figure 2
Graphical Representation of Data Shown in Table-1
(Total No. of Deaths)

3. Lung Cancer in India Scenario

Lung Cancer constituted 14.4% of all cancers in India[9]. On the basis of sporadic information collected from different hospitals of the country, incidence of lung cancer in hospital population was 27.4 per million in 1950 and in 1959 increased to 78.6 per million¹⁰. Lung cancer is frequently observed among all chest diseases¹¹. As per ICMR 2002, a total of 41000 lung cancer cases were diagnosed with a M:F ratio of 4.5:1 and varies with age and smoking status. The ratio increases progressively up to 51-60 years and then remains the same. In

India above 40% of patients with lung cancer are less than 50 years of age and 11% are less than 40 Years, while in younger age group lung cancer is commonly misdiagnosed as tuberculosis. Non-small cell lung cancer constitutes 75-80% of lung cancers and more than 70% of them are in stages III & IV while the small lung cancer constitutes 20% of all lung cancers and found in the extensive stage in 70% of patients at the time of diagnosis. The lung cancer in India as per Globacon report is shown in the Table-2

Table 2
Lung Cancer in India

Data Head	Male	Female	Both Sexes
Population (thousand)	610618	570793	1181412
Number of new cancer cases (thousands)	430.1	518.8	948.9
Age standardised rate (W)	92.9	105.5	98.5
Risk of getting cancer before age 75(%)	10.2	10.8	10.4
Number of cancer deaths (thousands)	321.4	312.1	633.5
Age-standardised rate (W)	71.2	65.5	68.0
Risk of dying from cancer before age (75%)	8.0	7.1	7.5

On the basis of data collected from different source, it has been noted that the total number of cancer patients in 2004 were 390809, in 2009 were 962832 , in 2010 were 979786 and 1193426 in 2011.Thus it is clear from the data that the cancer patients in both sexes increased gradually with time and their number would reached 1387069 in 2016, 1611625 in 2021 and 1869983 in 2026 as shown in table-3 figure-3. It has also been noted that female cancer patients dominant to male cancer patients

Table 3
Year- wise Total Cancer Ascendency in India.

	2004	2009	2010	2011	2016	2021	2026
Male	390809	454852	462408	589866	684918	799957	934268
Female	428545	507990	517378	603560	702151	811668	935715
Both Sexes	390809	962832	979786	1193426	1387069	1611625	1869983

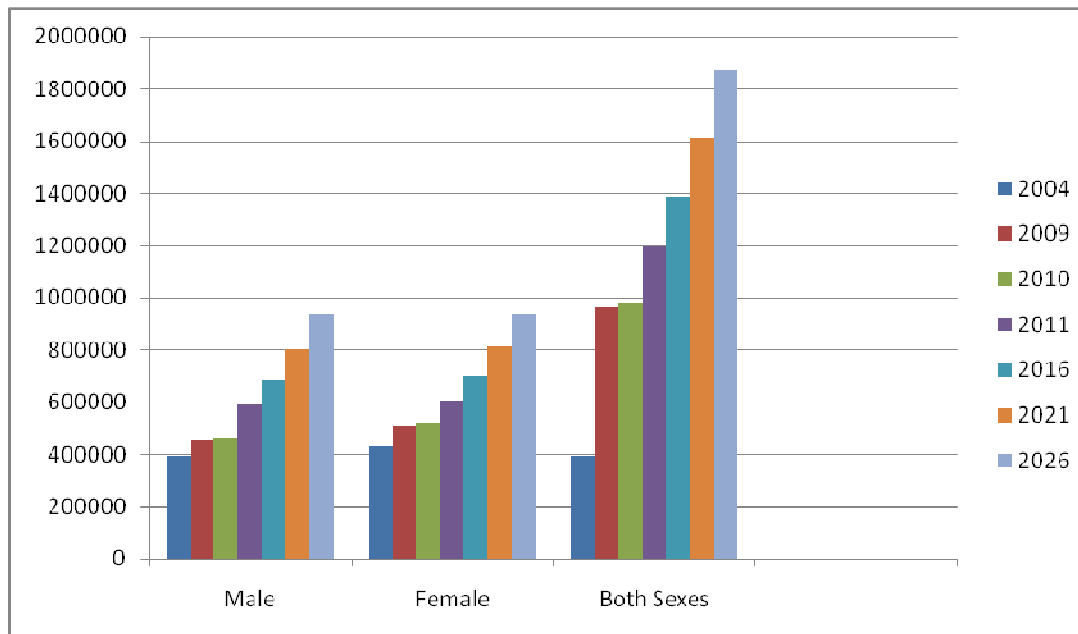


Figure 3
Year -wise Total Cancer Ascendency in India.

National Cancer Registry Program of the Indian Council of Medical Research (ICMR 1988-1989) showed varying degree of cancer incidences in specific territory of India and found that the most common form of malignancies in male during 1989 in Delhi, Bombay, Bhopal, Madras, Bangalore were trachea, bronchi and lungs. Now efforts have also been made to calculate the total number of cancer patients in a specific territories of India during 2016-2026. (Table -4, Figure-4) on the base- data for the year 2011

Table 4
Projected Annual Number of cancer cases in Males & Females in Specific Territories of India during THE years 2016-2026(Base 2011).

Territory	2011		2016		2021		2026	
	Male	Female	Male	Female	Male	Female	Male	Female
<i>UP</i>	89484	85032	102751	99830	118373	116264	136900	135436
<i>Bihar</i>	44146	42209	101357	49903	59537	58205	68690	67600
<i>Rajasthan</i>	29502	31161	34623	36640	40655	42709	47813	49751
<i>Haryana</i>	12474	11925	14445	13975	17076	16382	20441	19278
<i>Delhi</i>	8551	7658	10999	9598	14169	11931	18062	14730

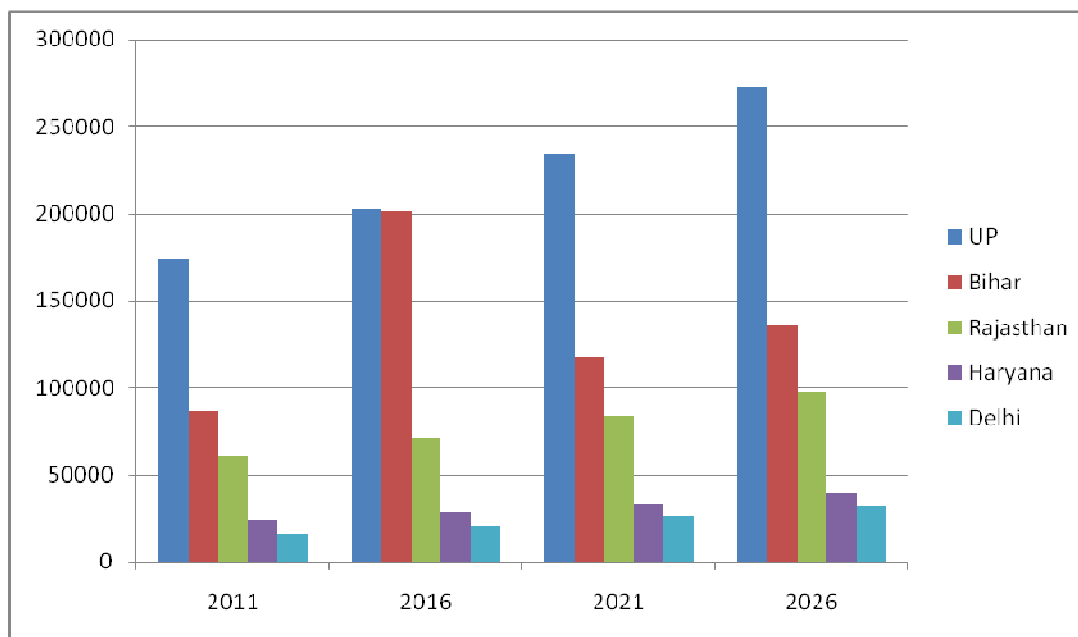


Figure 4
Graphical Representation of Data shown in Table -4

Data obtained from figure clearly indicate that UP has highest cancer patients and lowest in Delhi. In U.P, total number of cancer patients were 174516 in 2011, and would be approximately 202581 in 2016, 234637 in 2021 and 272336 in 2026. Bihar had the second highest number of cancer patients with 86355 in 2011 and would be approximately 101357 in 2016, 117742 in 2021 and 136290 in 2026. Third highest cancer patients were noted in Rajasthan with the number 60663 in 2011 and this number approximately would become 71263 in 2016, 83364 in 2021 and 97564 in 2026. Haryana occupied the fourth position with a total number of 24399 in 2011 and their number would be 28420 in 2016, 33458 in 2021 and 39619 in 2026. While Delhi had the least no. of cancer patients among experimental territories with 16209 in 2011 and their number approximately would be 20597 in 2016, 26100 in 2021 & 32792 in 2026. These differences may be due to environmental effect, nature of food & life style etc.

4. Causes of Cancer

The cancer causes are diverse, complicated and only partially understood. The cancer casualties that are directly or indirectly affected by tobacco use (25-30%), dietary and obesity (30-35%), exposure of radiation 10%, infection (15-20%). Lack of physical activity, obesity

and environmental pollutants¹². These factors may directly damage the genes or combine with existing genetic faults within the cell to cause cancerous mutations¹³. Approximately 5-10% of cancers can be traced directly to inherited genetic defects [Retrieved 2013]

5. Main Causes of Lung cancer in India

5.1 Smoking and lung cancer

In India, tobacco caused 100 million deaths in 20th century if current trends continue, it may cause one billion death in 21st century. In India Tobacco smoking (mainly in the form of beedi, cigarettes & hukka) is the major cause of lung cancer and 90% cases result from tobacco exposure, which include 87% active exposure and 3% passive exposure. The percentage of tobacco-related products smoked in India are beedi [28.4- 79%], cigarettes [9 - 53.7%], hukka [3.4 - 77.3%] and mixed [7.5 - 13.6%]¹⁴⁻¹⁶. According to National Family Health Survey¹⁷, the ascendancy of tobacco use (all forms) was 57% in men & 10.8% in women. In India, one third of men (33.4%) and 1.4% of women were beedi / cigarette smokers. The number of active adult smokers are higher in the rural areas (31.3%) as compared to urban area (21.5%)¹⁸. Tobacco is the most important identified cause of cancer and is responsible to 30 to 50% cancer in men and about 10-15% of cancer in women, in different registry area

[NCRP 2008]. Cigarette smoke has more than 60 carcinogenic molecules, out of these benzo- α -pyrene and N-Nitrosomine NNK are highly carcinogenic in nature and form adduct with DNA and protein which increase the chance of DNA mutation and interfere with proper function of protein¹⁹. The relative risk of developing lung cancer is 2.64 for beedi smokers, 2.23 for cigarette smokers and with 2.45 as the overall relative risk. Hooka smoking has also been associated with lung cancer with an odds ratio of 1.94²⁰. It has been noted that beedi is more carcinogenic²¹. Currently, it has been noted that 89 % of men & 33 % women ever smokers suffer lung cancer as compared to respectively 60% of men and 20% of women among control. The odds ratio (OR) for ever smoking was 5.0 (CI 3.11 – 8.04) among men and 2.47 (CI 0.79 – 7.75) among women. Smoking of beedi and hooka as well as cigarettes has similar ORs for cumulative consumption. The daily consumption of all forms of tobacco use was higher among the lower income quintile (41.8%) compared to higher income quintile (15.5%) and in the elderly population (43.9% among 65+ age group) compared to younger age group (14.7% among 18-24 age group). Environmental tobacco smoke carries a relative risk of developing lung cancer of 1.48 (1.13 – 1.92) in male and 1.2 in females (1.12 – 1.29), while the odds ratio of environmental tobacco smoke during childhood was found 3.9 (95% CI 1.9-8.2) and while OR in female is higher depend upon the number of smokers and duration of exposure is higher 5.1)^{22,23}.

5.2. Diet and Lung cancer

In India improper diet is one of the main reason of cancer causes. The role of dietary factor towards cancer varies greatly according to the type of cancer^{24,25}. It has been noted that some dietary factor with lowest intake of food rich in β -carotene, vitamin A and vitamin E have the highest risk of lung cancer²⁶⁻²⁹. The green vegetable and bananas have a protective effect on development of lung cancer³⁰, while pumpkins and onion have most invariable shielding effect on lung cancer and on the other hand dietary cholesterol and animal fat increases the risk of lung cancer³¹. Carrots and tomatoes decrease the risk of lung cancer about 20 - 25% which is due to α -carotene and lycopene³². It has been found that

flavonoids (found in apples) and iso thiocyanate (found in cruciferous vegetables) also reduce risk of lung cancer³³. Beans, chickpeas, lentils, and pulses have been significantly used to reduce cancer^{34,35}. The heavy consumption of red meat is the main cause of several types of cancer³⁶, which is due to the production of heterocyclamines at elevated temperature, and food stored in plastic container may also become carcinogenic due to the bis-phenol of plastic³⁷.

6. Medicinal Plants for the Treatment of Lung Cancer

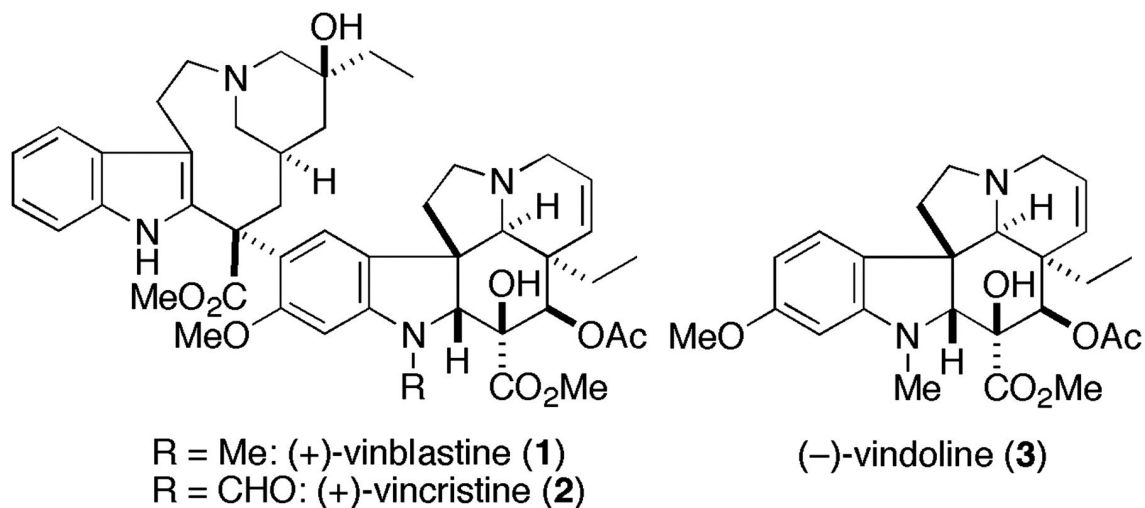
Herbal medicines are more frequently used against various types of tumor such as sarcoma, lymphoma, carcinoma, and leukemia because they have proven to be useful and effective in sensitizing conventional agents, prolong patient survival time, preventing side effects of chemotherapy and improving quality of life in lung cancer patients³⁸. The secondary metabolites of medicinal plants have also been extensively studied for their anti lung cancer activity⁴, for example vinblastine, vincristine, and vinca alkaloids extracted from *Catharanthus roseus*, paclitaxel from the leaves of various *Taxus species*, nimbolide from edible part of *Azadiracta Indica*, curcumin from *curcuma longa*, genistein, diadzein and anisitol from *Glycin max* seeds, kaempferol-3-galactoside, kaempferol-3-rhamnoglucoside, hentriocotane- β -sitosterol, lupal, flavanone glucosides, peonidine glucoside from *Bauhinia variegata*, gingerol from *Zingiber officinale*³⁹, embelin from *Embelia ribes*⁴⁰, carbazole alkaloid from *murraya koenigi*⁴¹, subamolide A from *Cinnamomum subavenium*⁴², davallic acid from *Davallia divuricata*⁴³, daphnodorin-B from *Daphne genkwa*⁴⁴, β -elemene extracted from *Curcuma wenyujin* (Zingiberaceae) rhizome, etc.

6.1 Catharanthus roseus

Catharanthus roseus, is a world over known medicinal plant used for the treatment of tumor, hypertensive, and arrhythmic disease⁴⁵. It comprises about 130 terpenoid indole alkaloids (Vinca alkaloids), in which Vincristine, Vindesine, Vinorelbine and Vinblastine are most notable for their medicinal benefits and used for the treatment of several kinds of cancer such as Hodgkin's disease, lymphosarcoma, choriocarcinoma,

neuroblastoma, carcinoma of breast and chronic leukemia⁴⁶. Vinblastine and vincristine exhibit significant cytotoxic activity and are used in the antitumor therapy as antineoplastic agents for the treatment of Hodgkin's disease, non-Hodgkin's lymphoma, lung cancer, breast cancer, acute leukemia, rhabdomyosarcoma, neuroblastoma, other lymphomas, also decrease the stability of lipid bilayer

membranes. These vinca alkaloids induce cell apoptosis, and inhibit the formation of tubulin (building block unit of protein) during cell division. These tubulin work to create spindle fibers (microtubules), which control the replication and division of the cell⁴⁷. Vinca alkaloids inhibit the growth of lung cancer by binding to tubulin in the mitotic spindle. It also induces apoptosis and inhibits angiogenesis.



CONCLUSION

Lung cancer, in particular, is a disease with high morbidity and mortality, which is increasing with alarming rate after heart disease. The cause of such high mortality rate of lung cancer may be both external (mainly tobacco) and internal factor. It is a second most common cause of death in world over among men, and most frequently treated by chemotherapy, but due to their severe side effects, which prevent their extensive usage. Now many cancer patients seek alternative medicinal herbs, which contribute novel secondary metabolites for preventive and curative medicine to modern science. Since the interaction of secondary metabolites has been tremendous increase in the treatment of lung cancer. Hence, search for new secondary metabolites from medicinal plants is very indispensable in recent time to develop noble drug or drug precursor.

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