



The effects and mechanism of current chemotherapy drugs and natural agents in treating non-small cell lungs cancer.

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Abstract:

Non-small cell lung cancer (NSCLC) remains the most common cause of cancer-related mortality. Surgery, radiation, chemotherapy, treatments, and immunotherapy separate or in combination are commonly used to treat lung cancer. The heterogeneous nature of this disease hinders its diagnosis and treatment, requiring continuous advances in research aiming to understand its intricate nature. Furthermore, the development of novel immunotherapies based on the recently highlights the real possibility of definitively treating NSCLC different side effect, mechanism of drug and chemotherapy based regimens appear to have reached a therapeutic plateau. we review the research on using current chemotherapy drugs and natural compounds. we review the research on using current chemotherapy drugs and natural compounds (Wortmannin and Roscovitine, *Cordyceps militaris*, Resveratrol, OSU03013, Myricetin, Berberine, Antroquinonol) and the beneficial effects they have on various types of cancers including non-small cell lung cancer.

Keyword : NSCLC / Chemotherapy / Solid tumors / Natural compounds / Surgery / Radiation / cancer vaccine.

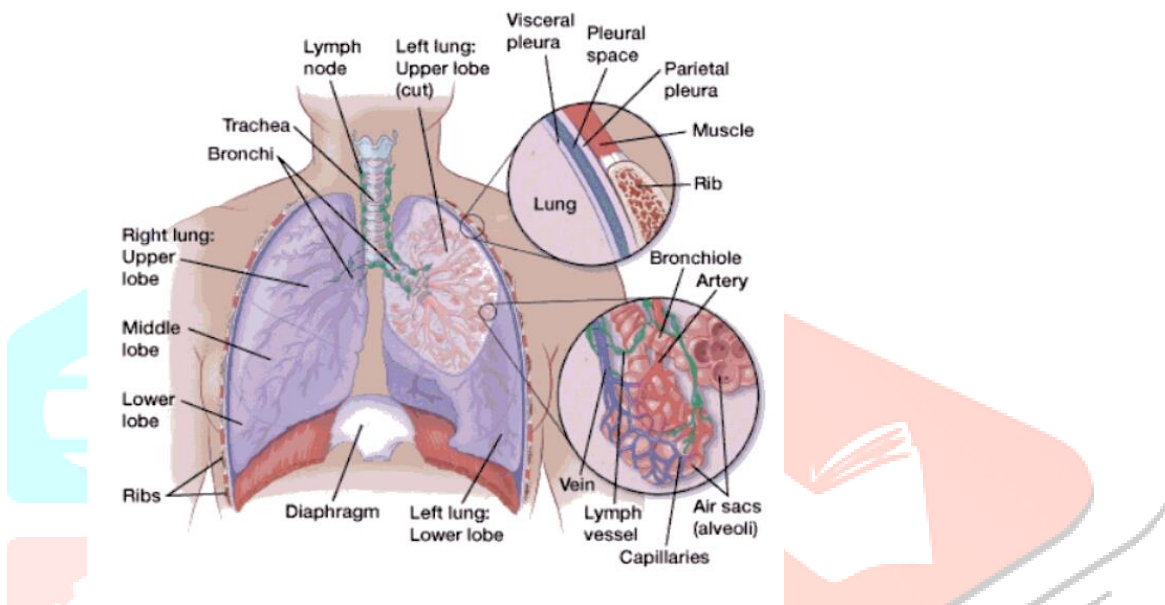
Introduction :

1) Lungs cancer :

Lung cancer is the major cause of cancer death and one of the leading causes of death worldwide. In 2018, accounted for more than 2 million deaths, according to the data reported by the World Health Organization (WHO) [1]. Lung cancer continues to be the leading cause of death in both men and women in the US, with over 158,900 deaths in 1999. Worldwide, lung cancer kills over 1 million people a year. It is estimated that about 90% of male lung cancer by smoking each year" (Hecht, 1999). The link between the smoking of cigarettes and lung cancer began to be suspected by clinicians in the 1930s when they noted the increase of this "unusual" disease. In the 1950s Doll and Hill in England and Cuyler Hammond and Ernest Wynder in the U.S provided further evidence for a causal association between smoking and lung cancer. Adenocarcinoma accounts for about 30 percent of primary lung tumours in male smokers and 40 percent in female smokers. Among non-smokers, these percentages approach 60 percent in males and 80 percent

in females. Early diagnosis is a must for providing appropriate prognosis and treatment options, thus explaining the importance of correct lung cancer evaluation.

A prospective evaluation of the incidence trend suggests that smoking habits are closely related to the appearance of lung cancer, although other environmental and genetic factors are also determinant. A remarkable increase of lung cancer cases in women has been noticed due to their rise in the number of smokers as a result of social changes, whereas the number of male smokers has traditionally been high. In Taiwan, liver, lung, stomach, colon, and oral cavity cancers are the five leading cancers responsible for cancer deaths among males; while lung, liver, cervix uteri, breast, and stomach are the five leading cancers responsible for cancer deaths among females. Major lifestyle variables associated with an increased cancer risk in Taiwan include habits like cigarette smoking, alcohol drinking, and betel nut chewing.



The convergence point of these therapies with nanotechnology lays the foundation for achieving currently unmet needs. Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC) Cancer is a disease in which cells in the body grow out of control. When cancer starts in the lungs, it is called lung cancer. Lung cancers typically start in the cells lining the bronchi and parts of the lung such as the bronchioles or alveoli. A thin lining layer called the **pleura** surrounds the lungs. The pleura protects your lungs and helps them slide back and forth against the chest wall as they expand and contract during breathing.

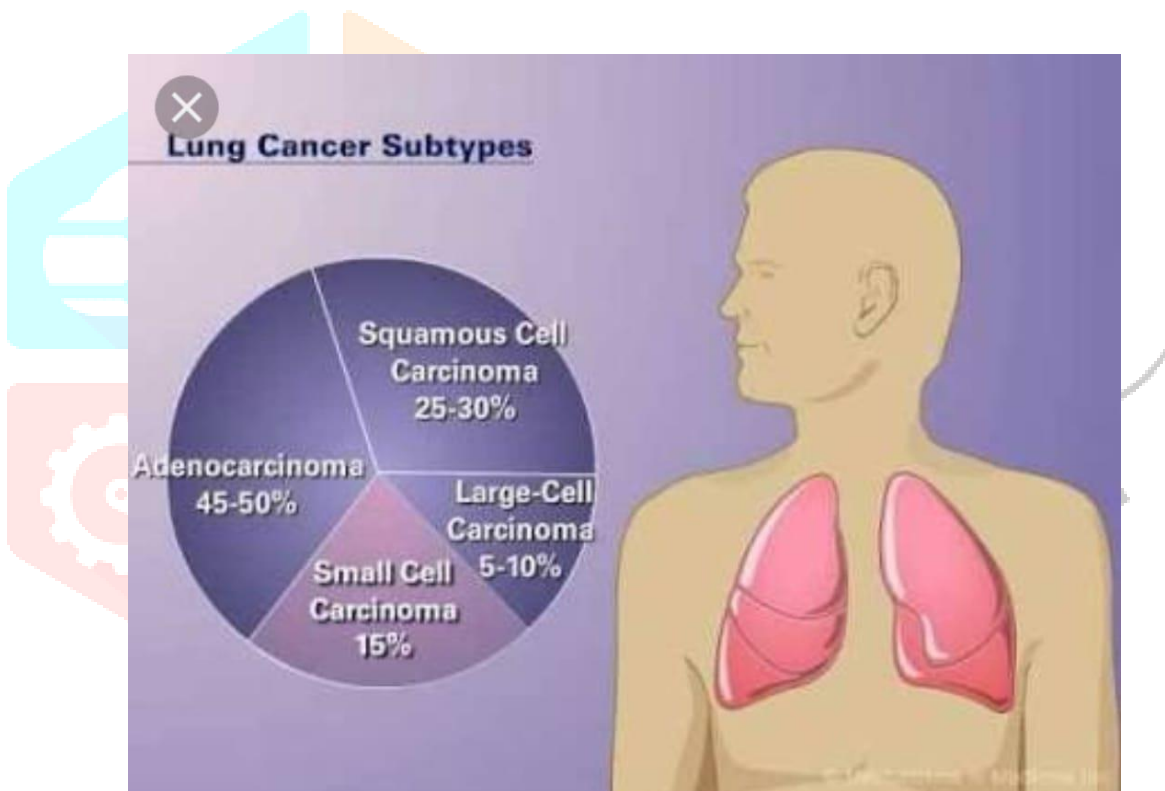
Lung cancer begins in the lungs and may spread to lymph nodes or other organs in the body, such as the brain. Lung cancer starts when abnormal cells grow out of control in the lung. They can invade nearby tissues and form tumours. Lung cancer can start anywhere in the lungs and affect any part of the respiratory system. The cancer cells can spread, or metastasize, to the lymph nodes and other parts of the body. Currently, the WHO differentiates several types of lung cancer which can be mainly classified into Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC). Currently, the WHO differentiates several types of lung cancer which can be mainly classified into Small Cell Lung Cancer (SCLC) and Non-Small Cell Lung Cancer (NSCLC).

There are two types of lung cancer Non-small cell lung cancer and small cell lung cancer.

a) Non-small cell lung cancer (NSCLC):

About 80% to 85% of lung cancers are NSCLC. The main subtypes of NSCLC are adenocarcinoma, squamous cell carcinoma, and large cell carcinoma.

- i. Adenocarcinoma : Adenocarcinomas start in the cells that would normally secrete substances such as mucus . This type of lung cancer occurs mainly in current or former smokers, but it is also the most common type of lung cancer seen in non-smokers .
- ii. Squamous cell carcinoma : Squamous cell carcinomas start in squamous cells, which are flat cells that line the inside of the airways in the lungs. They are often linked to a history of smoking and tend to be found in the central part of the lungs, near a main airway .
- iii. Large cell carcinoma : The Large cell carcinoma can appear in any part of the lung. It tends to grow and spread quickly, which can make it harder to treat. one type of lung cancer is known as Large cell carcinoma. The cells of this appear



large and abnormal under the microscope.

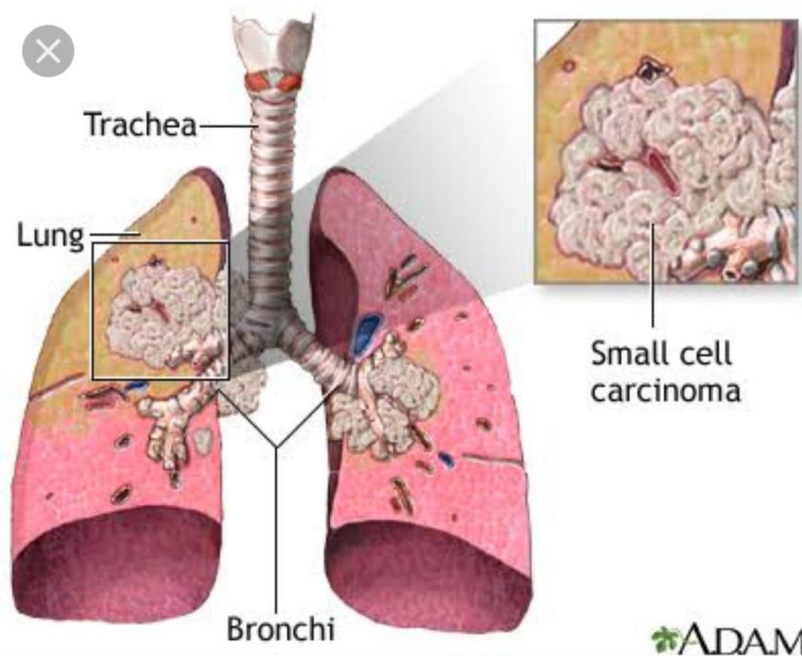
Table 1. Food and drug administration (FDA) approved chemotherapy drugs for the treatment of NSCLC sources, FDA and National Cancer Institute database .

Generic name (Brand Name)	Mechanism of action
Carboplatin (Paraplatin)	Alkylating agent
Docetaxel (Taxotere)	Mitotic inhibitor
Doxorubicin Hydrochloride (Adryamycin, Rubex)	Topoisomerase inhibitor
Gemcitabine Hydrochloride (Gemzar)	Antimetabolite
Lurtotecan (OSI-211)	Topoisomerase inhibitor
Mechlorethamine Hydrochloride (Mustargen)	Alkylating agent
Methotrexate (Trexal ITM, Rheumatrex)	Antimetabolite
Paclitaxel (Taxol)	Mitotic inhibitor
Paclitaxel -Albumin stabilized Nanoparticle Formulation (Abraxane)	Mitotic inhibitor
Pemetrexed Disodium (Alimta)	Antimetabolite
Vinorelbine Tartrate (Navelbine)	Tubuline-binding agent

Table 2. Active and completed nanomedicine -based chemotherapeutic drugs clinical trials.

Drug Name	Nano Delivery System	NSCLC stages	Phase	Clinical trial
Doxorubicin Hydrochloride Rubex	Pegylated Liposome	IIIB-IV	II	NCT01051362
	Serialized Liposome	IIIB	I	NCT00020124
Paclitaxel	Liposome	IIB-IV	IV	NCT02996214 NCT01023347
	Polymeric Michelle (Genexol-PM)			
Camptothecin	Aerosolized Liposome	IIB-IV	Pre-clinical	NCT00277082
Lurtotecan	Liposome	IIB	I	NCT00006036

b) Small cell lung cancer (SCLC) : About 10% to 15% of all lung cancers are SCLC and it is sometimes called **oat cell cancer**. This type of lung . cancer tends to grow and spread faster than NSCLC. About 70% of people with SCLC will have cancer that has already spread at the time they are diagnosed . Since this cancer grows quickly, it tends to respond well to chemotherapy and radiation therapy. Unfortunately, for most people, the cancer will return at some point



Symptoms :

Like other types of lungs cancer, symptoms can includes:

- Coughing that lasts or gets worse
- Chest pain that often hurts more when you cough, laugh, or take deep breaths
- Hoarseness or voice chages
- Horse, raspy sounds when you breathe
- Wheezing
- Weight loss, little appetite
- coughing up blood or mucus
- Shortness of breath
- Felling weaker or tired
- Lasting lung problems like bronchitis or pneumonia.
- Bone pain
- Headache
- Dizziness or balance problem
- Numbness or weakness in an arm or leg
- Yellow skin or eyes.

• Causes : Doctor aren't sure exactly what cause this disease. Many people who get it have smoked or been around smoke other things that make lungs cancer more likely are:

- Random a radioactive gas found naturally.
- Asbestos
- Mineral and metal dust
- Air pollution

- Radiators treatments to your chest or breast

- HIV / AID

• Diagnosis :

Imaging test help your doctor find tumour inside your lungs. They can also show whether the cancer has spread .

- X-rays use low doses of radiation to make image of structure inside your body.
- MRI, or magnetic resonance imaging, shows blood flow, organs, and structures .
- Ultrasound creates a picture by bouncing sounds waves off tissues inside you.
- PET scans use a radioactive compound or tracer that collects where your cells are very active .
- CT scans are powerfull X-rays that make detailed pictures of the tissue and blood vessels in the lung .

Sputum cytology is a lab test that checks the mucus you cough up for cancer cells .

2) Chemotherapy drug and treatment :

Chemotherapy is the application of chemicals or drugs to kill cancer cells, and its effects are systemic. So far, there are several different classes of anticancer drugs based on their mechanisms of action, and they include the following: a) alkylating agents which damage DNA; b) anti-metabolites that replace the normal building blocks of RNA and DNA; c) Mitotic inhibitors that inhibit mitosis and cell division; d) Topoisomerase inhibitors that inhibit either topoisomerase I or II which are the enzymes involved unwinding DNA during replication ; e) corticosteroid which are used for the treatment of cancer and to relieve mechanism and side effect from other drugs .

Chemotherapeutic drugs kill cancer cells but they also present offset cytotoxicity . However, the main drawback of chemotherapy is the development oresistance mechanisms. At this point, numerous studies have demonstrated the importance of autophagy andapoptosis, related to the very common p53 mutation in NSCLC . Autophagy, a “self-eating”process, has a dual role in the regulation of apoptosis in lung cancer .

a) alkylating agents which damage DNA :

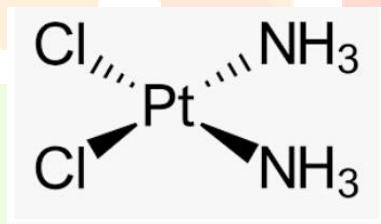
Alkylating agents performed a significant role in the development of chemotherapy. In the 1970s, several substances presenting this activity were identified and used as DNA cross-linkers, preventing the replication of tumorigenic cells. Examples of these drugs are Cisplatin, MitomycinC, Ifosfamide, Vindesine, Vinblastine, and Etoposide. Most studies combine cisplatin along with other alkylating or effective drugs against some characteristic patient mutations. Caution must be exercised regarding NSCLC, as it has shown 68% and 63% resistance against carboplatin and cisplatin and a similar percentage spectruagainst other alkaloids .

Table 1. Current regimen of treatment for lung cancer

Drug name	Generic name	Use
Xeloda	Capecitabine	anti-metabolite
Avastin	Bevacizumab	VEGF/VEGFR inhibits
Tarceva	Erlotinib	EGFR inhibitors
Taxol.	Paclitaxel	mitotic inhibitor
Taxotere	Docetaxel	mitotic inhibitor
Gemzar.	Gemcitabine	antimetabolite
Alimta	Pemetrexed	antimetabolite
Navelbine.	Vinorelbine	mitotic inhibitor
Platinol	Cisplatin	Alkylating agent
Neosar	Cyclophosphamide	Alkylating agent
Onxol	Paclitaxel	Mitotic inhibitors
Platinol -AQ	Cisplatin	Alkylating agents

i. Mechanism and effects of Cisplatin drug :

Name : Cisplatin

Molecular formula: $[\text{Pt}(\text{NH}_3)_2\text{Cl}_2]$ 

Structure formula :

Precautions:

- Before starting cisplatin treatment, make sure you tell your doctor about any other medications you are taking (including prescription, over-the-counter, vitamins, herbal remedies, etc.). Do not take aspirin, products containing aspirin unless your doctor specifically permits this.
- Cisplatin may be inadvisable if you have a history of severe allergic reaction to cisplatin, carboplatin, other platinum-containing formulations or mannitol.
- Do not receive any kind of immunization or vaccination without your doctor's approval while taking cisplatin.

Mechanism :

Most **chemotherapy drugs** kill **cancer** cells outright, or stop their reproduction and spread by inhibiting metabolic functions of the **cancer** cell. These **drugs** are called cytotoxic. They can also act on healthy cells (because they also divide) which is the basis for side **effects** and unwanted complications of therapy.

Side effects :

- **Most people do not experience all of the cisplatin side effects listed.**
- **Cisplatin** side effects are often predictable in terms of their onset, duration, and severity.
- Cisplatin side effects will improve after therapy is complete.
- Cisplatin side effects may be quite manageable. There are many options to help minimize or prevent the side effects of cisplatin.
- There is no relationship between the presence or severity of Cisplatin side effects and effectiveness of cisplatin.
- Nausea and vomiting. Nausea may last up to 1 week after therapy. Anti-nausea medication is given before the infusion, and a prescription is also given for use after.
- Low blood counts. Your white and red blood cells and platelets may temporarily decrease. This can put you at increased risk for infection, anemia, and/or bleeding. Nadir: Meaning low point, is the point in time between chemotherapy cycles in which you experience low blood counts.
 - Nadir: 18-23 days. Recovery: 39 days
- Kidney toxicity. Effects on kidney function are dose related, observed 10-20 days after therapy, and are generally reversible.
- Ototoxicity hearing loss, ringing in the ears.
- Blood test abnormalities (low magnesium, low calcium, low potassium)

Uses :

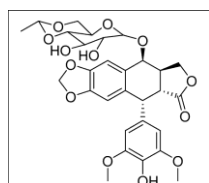
- Treatment of advanced bladder **cancer**, metastatic ovarian **cancer**, and metastatic testicular **cancer**.
- Testicular, ovarian, bladder, head and neck, esophageal, small and non-small cell lung, breast, cervical, stomach and prostate cancers.
- **Cisplatin** has been **used** as a treatment for cancer since its approval by the US Food .

ii) Mechanism and effects of Etoposide :

Name : Etoposide

Molecular formula : C₂₉H₃₂O₁₃

Structural formula :



Mechanism of action :

Etoposide inhibits DNA topoisomerase II, thereby inhibiting DNA re-ligation. This causes critical errors in DNA synthesis at the premitotic stage of cell division and can lead to apoptosis of the cancer cell. Etoposide is cell cycle dependent and phase specific, affecting mainly the S and G₂ phases of cell division. Inhibition of the topoisomerase II alpha isoform results in the anti-tumour activity of etoposide. The drug is also capable of inhibiting the beta isoform but inhibition of this target is not associated with the anti-tumour activity. It is instead associated with the carcinogenic effect.

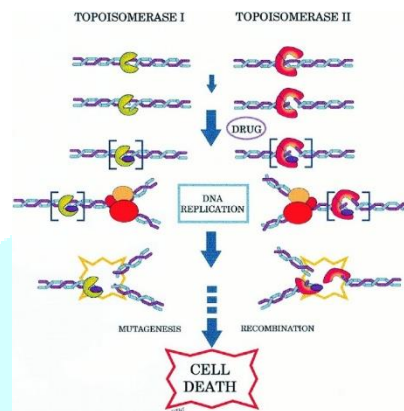
DNA topoisomerase 2-alpha

Inhibitor

Humans

DNA topoisomerase 2-beta

Inhibitor



Humans

Side effects :

- Nausea, vomiting, diarrhea, dizziness, tiredness, weakness, changes in taste, loss of appetite, and pain/redness at the injection site may occur. Nausea and vomiting can be severe.
- In some cases, your doctor may prescribe medication to prevent or relieve nausea and vomiting.
- Eating several small meals, not eating before treatment, or limiting activity may help lessen some of these effects.
- If any of these effects persist or worsen, tell your doctor or pharmacist promptly.
- Temporary hair loss

Tell your doctor right away if you have any serious side effects, including:

- numbness/tingling of arms/legs sudden vision changes, eye pain, stomach/abdominal pain, yellowing eyes/skin, dark urine, painful/difficult swallowing, redness/swelling of your veins.

Uses :

- Etoposide is used to treat testicular cancer and certain forms of lung cancer (such as small cell lung cancer).
- Etoposide works by slowing the growth of cancer cells.
- Etoposide works by slowing **cancer** cell growth. It is also commonly known as VP-16.
- OTHER This section contains uses of this drug that are not listed in the approved professional labeling for the drug but that may be prescribed by your health care professional.
- Use this drug for a condition that is listed in this section only if it has been so prescribed by your health care professional.
- This drug may also be used to treat certain types of leukemias, **lymphomas**, **ovarian cancer**, **testicular cancer**, and a certain type of **prostate cancer**.

B) anti-metabolites that replace the normal building blocks of RNA and DNA:

Antimetabolites are molecules preventing the synthesis of DNA and RNA by binding and stabilizing the enzymes involved in this process or replacing nucleotides in the nucleic acid growing chain. Regardless of the increase in drug doses, a plateau effect is early achieved at low concentrations. Several molecules with this activity are currently (antifolates, fluoropyrimidines, deoxynucleotide analogs, and thiopurines), available although a reduced number of them is used for treating NSCLC.

Effects and mechanism of fluoropyrimidine :

Name : Fluoropyrimidine

Molecular formula : $C_4H_3FN_2$

Mechanism :

The main mechanism of 5-FU activation is the conversion to fluorodeoxyuridine monophosphate (FdUMP), which inhibits the enzyme thymidylate synthase (TYMS), an important part of the folate–homocysteine cycle and purine and pyrimidine synthesis (see Pharmacodynamics) [2]. The conversion of 5-FU to FdUMP can occur via thymidylate phosphorylase (TYMP) to fluorodeoxyuridine and then by the action of thymidine kinase to FdUMP or indirectly by fluorouridine monophosphate (FUMP), or fluoridine (FUR) to fluorouridine diphosphate (FUDP) and then ribonucleotide reductase action to fluorodeoxyuridine diphosphate and FdUMP. An important consideration in the use of 5-FU and related drugs is the development of drug resistance by the tumor. Some resistance mechanisms involve expression changes in pharmacodynamic gene candidates [*TYMS* and tumor protein p53 (*TP53*)]. Drug resistance can also involve changes in drug transport.

Side effects :

- fatigue, nausea, diarrhea and lab.
 - abnormalities.
 - inflammation of the mouth, loss of appetite, low blood cell counts, hair loss, and inflammation of the skin.
- When used as a cream, irritation at the site of application usually occurs.

Uses : The **fluoropyrimidine** chemotherapeutics (5-fluorouracil (5-FU) and its prodrug, capecitabine) are commonly used for treatment of multiple malignancies including breast cancer and multiple gastrointestinal tumors.

C) Mitotic inhibitor :

Mitotic inhibitors are anti-cancer drugs preventing cell mitosis. Targeting mitosis is an approach based on the high proliferation rate of cancer cells compared to healthy cells, although off-site cytotoxicity is still considerable. These types of treatments aim to destabilize or stabilize the microtubules—protein polymers that play a fundamental role during the final phase of mitosis. The destabilizing and stabilizing mitotic inhibitors act in different phases of mitosis. Its nonspecific activity affects healthy dividing cells and other cells such as neurons, where intracellular transport processes are linked to the activity of microtubules. Its nonspecific activity affects healthy dividing cells and other cells such as neurons, where intracellular transport processes are linked to the activity of microtubules. In addition to this formulation, the use of extracellular vesicles (EVs) has recently shown promising results in the encapsulation of antitumor drugs. This type of vesicles, which includes exosomes, micro vesicles, and apoptotic bodies, has advantages in terms of biocompatibility, immunogenicity, and cytotoxicity. Mitotic inhibitors are derived from natural substances such as plant alkaloids, and prevent cells from undergoing mitosis by disrupting microtubule polymerization, thus preventing cancerous growth. The examples include paclitaxel, docetaxel, vinblastine, vincristine, and vinorelbine.

Mechanism and effects of Vinblastine :

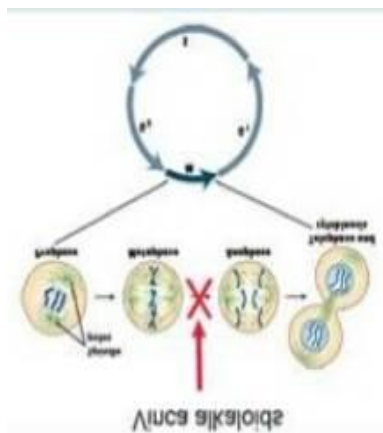
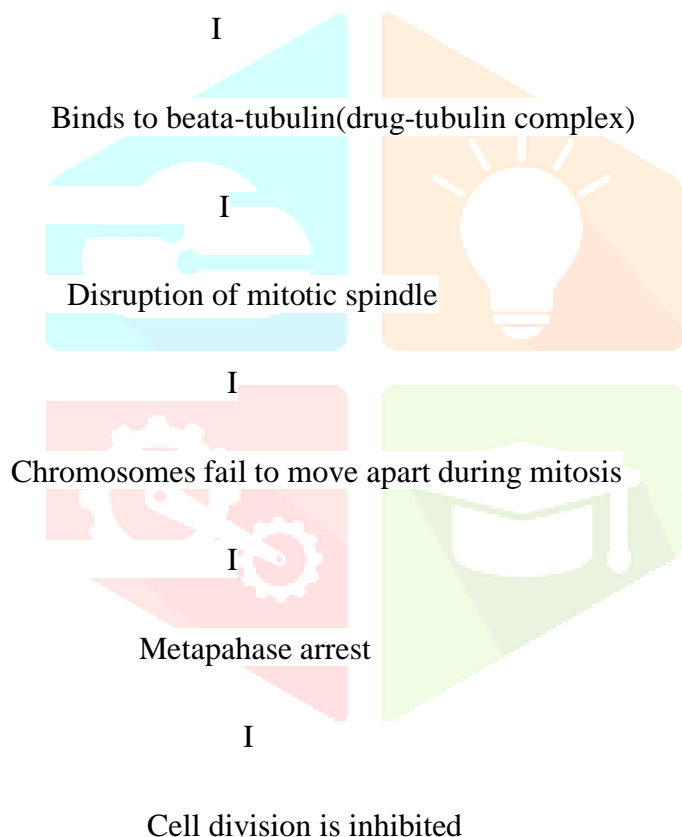
Name : vinblastine

Molecular formula : C₄₆H₅₈N₄O₉

Mechanism : The antitumor activity of vinblastine is thought to be due primarily to inhibition of mitosis at metaphase through its interaction with tubulin. Vinblastine binds to the microtubular proteins of the mitotic spindle, leading to crystallization of the microtubule and mitotic arrest or cell death.

Mechanism of action :

Vinblastine & vincristine



Effects :

- Most people do not experience all of the vinblastine side effects listed.
- Vinblastine's side effects are often predictable in terms of their onset and duration.
- Vinblastine's side effects should improve after treatment is complete.
- Vinblastine's side effects are usually quite manageable. There are many options to help minimize or prevent the side effects of vinblastine.
- Nausea and vomiting - usually moderate and occur within the first 24 hours of treatment
- Poor appetite
- Peripheral neuropathy (numbness in your fingers and toes) may occur with repeated doses. This should be reported to your healthcare provider.
- Diarrhea
- Fever
- Hair loss may occur, but your hair will most likely grow back when the treatments are completed. This usually begins 2-3 weeks after each treatment.
- Hearing loss
- Mouth sores
- Taste changes, metallic taste
- Headache
- Depression
- Jaw pain, bone pain, tumor pain
- High blood pressure (hypertension)
- Tiredness
- Shortness of breath, myalgias (muscle pain), and arthralgias (joint pain) may occur infrequently

Uses:

- This drug is given to treat Hodgkin lymphoma, non-Hodgkin's lymphoma, testicular, breast, lung (Non-small cell lung cancer), head and neck, and bladder cancers, melanoma, soft tissue sarcoma, Kaposi's sarcoma, mycosis fungoides (t-cell lymphoma), and choriocarcinoma. It can be used to treat fibromatosis and germ cell tumour.
- It is also used in the treatment of certain blood disorders such as histiocytosis

d) topoisomerase inhibitors that inhibit either topoisomerase I or II, which are the enzymes involved in unwinding DNA during replication and transcription :

Topoisomerases I and II relieve torsional strain incrementally within a domain by using controlled breakage of one or both strands, respectively; passage of DNA through the strand break; and reunion . Adjacent domains are not affected. The efficiency of topoisomerase is modified by domain size, binding site preference, and site accessibility. The intranuclear distribution of topoisomerase is not known. A large fraction of topoisomerase II is bound by the nuclear matrix and so is available only to local DNA sequences . The packaging of DNA into chromatin restrains approximately one negative-supercoil on the surface of each nucleosome .

The microarchitecture of matrix attachments, protein-protein-mediated loops, the arrangement of promoter sites, and the disposition of topoisomerases and nucleosomes all mold the physiological or pathological response of a transcription unit. The expression of the *c-myc* gene is particularly sensitive to perturbations of its normal chromosomal milieu. Translocations, regional amplifications, and viral insertions and mutations, sometimes at vast distances either 5' or 3' from the *c-myc* promoters, all deregulate *c-my* transcription . Class I topoisomerases break only one strand of the DNA helix and are important in DNA synthesis. Class II topoisomerases cut both strands of DNA, using ATP (adenosine triphosphate) for fuel. The uncoiling process involves the relaxation of the coil of both DNA strands. After the cuts are made and replication or repair is complete, the strands are paired back together and the coil

reforms. Topoisomerase I inhibitors include camptothecin, topotecan, and irinotecan. Topoisomerase II inhibitors include doxorubicin, etoposide, and mitoxantrone.

Mechanism and effects of Etoposide

Name: Etoposide

Molecular Formula: $C_{29}H_{32}O_{13}$

Mechanism: topoisomerase II inhibitor

Topoisomerase inhibitors are chemical compounds that block the action of topoisomerase II, which are enzymes that control the changes in DNA structure by catalyzing the breaking and rejoining of the phosphodiester backbone of DNA strands during the normal cell cycle.

In recent years, topoisomerases have become popular targets for cancer chemotherapy treatments. It is thought that topoisomerase inhibitors block the ligation step of the cell cycle, generating single and double stranded breaks that harm the integrity of the genome. Introduction of these breaks subsequently leads to apoptosis and cell death.

Effects :

- pregnant should not handle this medication or breathe the dust from the capsules.

Notes: Approved by the FDA in 1983

Treatment :

- Several anticancer drugs applied to the treatment of lung cancer (bleomycin, doxorubicin, etoposide (VP-16), cisplatin, and methotrexate) have been reported to enhance Fas ligand (FasL) expression on the surface of Fas receptor-expressing cells, suggesting that apoptosis caused by these drugs may be mediated by means of Fas cross-linking .
- The 5-year survival rate for NSCLC is compared to 6% for small cell lung cancer.
- However, it is important to note that survival rates on several factors, including the subtype of lung cancer, and the stage of disease .
- Platinum drugs are effective for patients with a positive K-ras mutation, while a number of drugs are not useful for those with increased Her-2 expression .
- No Chemotherapy or radiation therapy is needed .if you are healthy enough for surgery, you can usually be treated by segmentectomy or wedge resection (removal of part of the line of the lungs)
- There is always a chance that lung cancer can recur even after it has been in remission for year or decades. Because of this ,many doctors will say that lung cancer is never truly, curlym.

3)Surgery and Radiotherapy:

Surgery is the main treatment option when NSCLC is diagnosed in the early stages I, II, and IIIA and the patient can tolerate it. However, only 15–20% of tumors can be radically resected, because the tumor is not always clearly identifiable. During surgery, the lobe or the section of the lung containing the tumor is removed, using imaging techniques such as video-assisted thoracoscopic surgery (VATS) and biopsies as support . Common treatments at these stages include chemotherapy and surgery-combined approaches, depending on the patient's conditions . Cisplatin-based chemotherapy is the preferred approach, although new drugs are being investigated. Surgery to remove the cancer might be an option for early-stage non-small cell lung cancer (NSCLC). It provides the best chance to cure the disease. But, lung cancer surgery is a complex operation that can have serious consequences, so it should be done by a surgeon who has a lot of experience operating on lung cancers.

Surgery to remove the cancer might be an option for early-stage non-small cell lung cancer (NSCLC). It provides the best chance to cure the disease. But, lung cancer surgery is a complex operation that can have serious consequences, so it should be done by a surgeon who has a lot of experience operating on lung cancers.

Types of lung surgery

Different operations can be used to treat (and possibly cure) NSCLC. With any of these operations, nearby lymph nodes are also removed to look for possible spread of the cancer. These operations require general anesthesia (where you are in a deep sleep) and are usually done through a large surgical incision between the ribs in the side of the chest or the back (called a **thoracotomy**).

- **Pneumonectomy:** This surgery removes an entire lung. This might be needed if the tumor is close to the center of the chest.
- **Lobectomy:** The lungs are made up of 5 lobes (3 on the right and 2 on the left). In this surgery, the entire lobe containing the tumor(s) is removed. If it can be done, this is often the preferred type of operation for NSCLC.
- **Segmentectomy or wedge resection:** In these surgeries, only part of a lobe is removed. This approach might be used if a person doesn't have enough normal lung function to withstand removing the whole lobe.
- **Sleeve resection:** This operation may be used to treat some cancers in large airways in the lungs. If you think of the large airway with a tumor as similar to the sleeve of a shirt with a stain a few inches above the wrist, the sleeve resection would be like cutting across the sleeve (airway) above and below the stain (tumor) and then sewing the cuff back onto the shortened sleeve.

However, we know that the median overall survival rate with radiotherapy alone is 9 to 11 months, and the 5-year survival rate is disappointingly low, at 3% to 10%. Approximately one out of every three patients with NSCLC has a locally advanced tumor that is surgically unresectable. Hence, radiotherapy remains a major therapeutic option for patients with such advanced lung cancer. Radiation therapy uses high-energy rays or particles to kill cancer cells.

Depending on the stage of the non-small cell lung cancer (NSCLC) and other factors, radiation therapy might be used.

- As the main treatment (sometimes along with chemotherapy), especially if the lung tumor can't be removed because of its size or location, if a person isn't healthy enough for surgery, or if a person doesn't want surgery.
- After surgery (alone or along with chemotherapy) to try to kill any small areas of cancer that surgery might have missed.
- Before surgery (usually along with chemotherapy) to try to shrink a lung tumor to make it easier to operate on.
- To treat cancer spread to other areas such as the brain or bone.

3) Natural compound :

Natural compounds have long been a source of anticancer compounds. Herbal medicines are generally low in cost, plentiful, and show very little toxicity or side effects in clinical practice. Several natural products, in particular, phytochemicals, have been identified as sources for the development of anticancer agents¹⁴. Their mechanisms of action vary greatly; however, many of them suppress cancer cell growth, and a few also modulate metabolism. To discover novel potential anticancer compounds targeting mitochondrial metabolism in cancer cells, we employed a large natural chemical library consisting of compounds from various chemical classes. Consistent with their *in vitro* inhibitory effects, gracillin displayed potent anti-tumor effects *in vivo* with a limited toxicity. These results suggest the potential of gracillin as an antitumor agent targeting mitochondrial respiration.

The natural product is a chemical compounds or substance produced by a living organisms that is, found in nature . In the broadest sense, natural products include any substance produced by life. In clinical treatment, most NSCLC patients respond poorly to conventional chemotherapy because of the emergence of resistance. Hence, there is an urgent need to develop novel treatment strategies to improve the sensitivity of cancer cells to chemotherapy-induced cell death. The natural compounds example of drug (Wortmannin and Roscovitine, *Cordyceps militaris*, Resveratrol, OSU03013, Myricetin, Berberine, Antroquinonol) and the beneficial effects they have on various types of cancers including non-small cell lung cancer.

4.i)Wortmannin and Roscovitine :

The purine analogues roscovitine is a small molecule that inhibits the activity of cyclin-dependent kinases (CDKs) *via* direct competition in the ATP-binding site. Similarly, roscovitine induces apoptosis in A549 cells in a dose-dependent manner. Meanwhile, wortmannin, a fungal metabolite, is a potent specific PI3K inhibitor, which binds to the p110 catalytic subunit of PI3K and irreversibly inhibits the enzyme , something which could chemosensitize three human tumour cell lines (A549, HCT116 and HeLa cells). Taken together, these results provide evidence for the potential application of a roscovitine and wormannin combination in clinical treatment for solid tumours .

Mechanism : Roscovitine [CY-202, (R)-**Roscovitine**, Seliciclib] is a small molecule that inhibits cyclin-dependent kinases (CDKs) through direct competition at the ATP-binding site. It is a broad-range purine inhibitor, which inhibits CDK1, CDK2, CDK5 and CDK7, but is a poor inhibitor for CDK4 and CDK6.

4.ii)Berberine

On the basic effects of the amount of berberine present in Amy compound, route of administration and type of organ LD50 value varies. Some data accumulated by Kulkarni et al (1972) ,which gives following information. The LD50 value of powdered root *Breweria vulgaris* which is known as barberry is 2,600 mg/kg in mice on oral . The berberine sulfate isolated from *Breweria aristata* on intraperitoneal administration in rats have, LD50 values equal to 305 mg/kg. Berberine appear to Activate AMP-activated protein kinase can help regulate how the body used, blood sugar, Research believe that this activation can help issues, such as obesity . The main **side effects** are related to digestion, and there are some reports cramping, **diarrhea**, flatulence, **constipation** and stomach pain .

Mechanism : Berberine is known as an AMP-activated protein kinase (AMPK) activator. Its insulin-independent hypoglycemic effect is related to inhibition of mitochondrial function, stimulation of glycolysis and activation of AMPK pathway. Additionally, **berberine** may also act as an α -glucosidase inhibitor.

4.iii)Myricetin :

The health benefit of myricetin exert a wide variety of biological effect, including antioxidants and free radical - scavenging activities. Report indicates that myricetin has anti-cancer and anti-inflammatory properties and may improve bone-health.

However, it can also act a pro-oxidant in the presence of certain ions such as copper. In this form (myricetin -copper complexes), myricetin is toxic to cancer cells causing cell . Copper myricetin complexes produce reactive oxygen species that break DNA cancer cell .

5) Cancer vaccines :

The cancer vaccine has been traditionally related to the treatment of infectious diseases, aiming at humoral immunity against pathogens. There are five main type of vaccines i. cellular vaccine, protein vaccine, mRNA vaccine, DNA vaccine and peptide vaccines.

Mechanism of Cima -vax EGF: Cima Vax is an active vaccine with which patients are immunized with epidermal growth factor, thus raising antibodies targeting EGF itself. The epidermal growth factor receptor (EGFR) is hijacked by many types of cancer, including cancers of the lung, colon, kidney, and head and neck. The concentration of EGF in the blood are reduced. Thus Cima-vax does not target directly, but is expected to work against these cancers by denying the cancer the growth stimulus they require.

6) Conclusion : Chemotherapy now actually accepted from of therapy for stage IIIB/IV NSCLC, and there is growing interest in its used in earlier stages of the disease when combine with other therapy .surgery or radiotherapy is the standard option for patients with early stages of NSCLC .in summary the number of available treatment for NSCLC continues to expand, drawn by the improvements introduce by nano technology .chemotherapy can treat cancer cells that are spread all over the body but they have extremely toxic side effect. Lungs cancer is leading to cause of death over the world and the only chance of pure for patients affected from this type of cancer is surgical resection.

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