EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 9
358-372
Year: 2022

EXTRACTION, ISOLATION AND CHARACTERIZATION OF ANTI-CANCER ALKALOID FROM *PAPAVER SOMNIFERUM* (MORPHINE)

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Article Received on 11/07/2022 **Article Revised on 01/08/2022** **Article Accepted on 23/08/2022**

ABSTRACT

Noscapine, a phthalideisoquinoline alkaloid derived from opium poppy, has been used in the treatment of various cancer types. Its low-toxicity profile has increased attention to this alkaloid. With regard to increasing demand for this compound, we developed a new method for isolation of noscapine from dried unripe seed capsules of *Papaver somniferum*. The poppy straw is an alternative source which is chemically used to extract the alkaloids. Noscapine was successfully isolated from unripe seed capsules for the first time and the purity of the isolated compound was determined to be over 98.99% by HPLC analysis. The proposed roles of alkaloids in plant metabolism, plant catabolism, or plant physiology are end products of metabolism or waste products, storage reservoirs of nitrogen, protective agents for the plant against attack by predators and growth regulators. Isolation of noscapine from opium was studied in literature. Sim showed the separation of alkaloids from opium in a step-wise process and produced noscapine as the last product.

KEYWORD: Alkaloid, Opium Poppy, Anti-Cancer, Bioactive Compounds, Chronic Cancer pain, Are-anesthetic Medication, Analgesic, Morphine, Nitrogenous Compounds.

INTRODUCTION

Important class of pharmaceutical compounds, they are alkaloids form, which can be found in natural products such as the opium poppy (unripe seed capsules), *Papaver somniferum.* Alkaloid, any of a class of naturally occurring organic nitrogen-containing bases. This group also includes some related compounds with neutral and even weakly acidic properties. Alkaloids have diverse and important physiological effects on humans and other animals. Well-known alkaloids include morphine, strychnine, quinine, ephedrine, and nicotine. Alkaloids are normally removed from natural products using solvent extraction. Alkaloids are small organic molecules, secondary metabolites of plants, containing nitrogen usually in a ring; about 20% of plant species consist of alkaloids.[1,2,9] They have diverse physiological effects: antibacterial, anti-mitotic, anti-inflammatory, analgesic, local anesthetic, hypnotic, psychotropic, and antitumor activity. The proposed roles of alkaloids in plant metabolism, plant catabolism, or plant physiology are end products of metabolism or waste products, storage reservoirs of nitrogen, protective agents for the plant against attack by predators and growth regulators. It is an odorless white solid of m.p. 234–236°C partially soluble in water (100 mM). As is known, caffeine has a stimulating effect and is found in plants such as coffee or tea. Caffeine is an alkaloid in the xanthine family. Alkaloid toxic effects are mainly due to their biotransformation into strong reactive structures by oxidases from the mammalian liver. The reactive pyrroles act by alkylating nucleic acids and proteins.[1]

AIM (OBJECTS)

1. A *Papaver somniferum* (Opium poppy) extraction and purification for Synthesis of the Anticancer Alkaloid Noscapine.
2. Anti-Cancer Drug Discovery and Development in Alkaloid Noscapine and Plant Collection *Papaver somniferum* in extraction and purification of Anti-Cancer Compounds.

Alkaloids are produced by a large variety of organisms including bacteria, fungi, plants, and animals. They can be purified from crude extracts of these organisms by acid-base extraction, or solvent extractions followed by silica-gel column chromatography.[4,5,8] Alkaloids" contain nitrogen in the heterocyclic and originate from amino acids. Compounds like proteins, nucleotides, nucleic acid, amines, and antibiotics are usually not called alkaloids. Natural compounds containing nitrogen in the exocyclic position (mescaline, serotonin, dopamine, etc.) are usually classified as amines rather than as alkaloids. Their characteristic examples are atropine, nicotine, and morphine.[1,2,3]

A simple process for isolating the alkaloids is highly desirable to evaluate product quality. This paper describes a method for the extraction and purification of noscapine that is present in the poppy straw. In this method, noscapine was obtained in purity suitable for use in pharmacopeia (98.99%). The chemical structure of this alkaloid is shown in Figure: - Alkaloids Compound.[4,6]

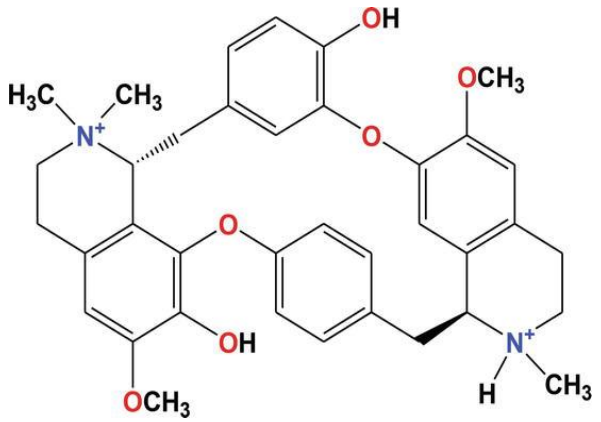


Fig. Alkaloid Compound.

OPIUM ALKALOIDS

Opium, narcotic drug that is obtained from the unripe seedpods of the opium poppy. The pharmacologically active principles of opium reside in its alkaloids, the most important of which, morphine, constitutes about 10 % by weight of raw opium. Other active alkaloids such as papaverine and codeine are present in smaller proportions. Opium alkaloids are of two types, depending on chemical structure and action. Morphine, codeine, and thebaine, which represent one type, act upon the central nervous system and are analgesic, narcotic, and potentially addicting compounds. Papaverine, noscapine (formerly called narcotine), and most of the other opium alkaloids act only to relax involuntary (smooth) muscles. This raw opium may be ground into a powder, sold as lumps, cakes, or bricks, or treated further to obtain derivatives such as morphine, codeine, and heroin. Opium and the drugs obtained from it are called opiates. The opium alkaloids (morphine, codeine, thebaine, noscapine, and papaverine) have been detected on poppy seeds; they are widely used by the food industry for decoration and flavor but can introduce opium alkaloids into the food chain.[5,8,11]

PAPAVER SOMNIFERUM

Papaver Somniferum is aayurvedic medicinal plant it can be use in narcotic drugs or moderate to severe visceral pain and also pre-anesthetic medication (analgesic and sedative). The opium poppy is an annual plant. Poppies have lobed or dissected leaves, milky sap, often nodding buds on solitary stalks, and four- to six-petaled flowers with numerous stamens surrounding the ovary. Which are kidney-shaped and grayish blue to dark blue; the seeds are used in bakery products and for seasoning, oil, and birdseed (*see* poppy seed). Native to turkey. Opium, morphine, codeine, and heroin are all derived from the milky latex found in its unripe seed capsule. It is also grown for its tiny nonnarcotic ripe seeds. Opium contains morphine, codeine, and thebaine, and also papaverine and noscapine (isoquinolines). *Papaver Somniferum* is a biosynthetic intermediate of the morphine pathway which is used by the pharmaceutical industry for synthesis of oxycodone, oxymorphone, buprenorphine, and naloxone, an opiate antagonist. *Papaver Somniferum* also known as codeine methyl enol ether is an opiate alkaloid, minor constituent of thebaine. *Papaver Somniferum* is chemically similar to both morphine and codeine, but has stimulatory rather than depressant effects.[12,15,18,19]

TAXONOMICAL CLASSIFICATION

- **Common Name: -** Opium poppy.
- **Family: -** Papaveraceae.
- **Subfamily: -** Fumarioideae
- **Species: -** genus *Papaver*
- **Colour: -** grayish blue to dark blue
- **Shaped: -** bisexual regular dish.
- **Part Used: -** Unripe Seed Capsules.
- **Active Principle: -** Morphine, Codeine, Thebaine, papaverine and noscapine.

Fig: - *Papaver Somniferum.*

METABOLISM

The alkaloids are organic nitrogenous compounds, derivatives of secondary metabolism, synthesized through the metabolic pathway of benzylisoquinoline. First, the amino acid phenylalanine, through the enzyme phenylalanine hydroxylase, is transformed into tyrosine. Tyrosine can follow two different routes: by tyrosine hydroxylase it can form L-dopamine (L-DOPA), or it can be reduced to form 4-phenylhydroxyacetaldehyde (4-HPAA). Subsequently, L-DOPA reacts with 4-HPAA and, through a series of reactions, forms - norcoclaurine, which carries the benzylisoquinoline skeleton that gives its name to this pathway. The conversion of - norcoclaurin to - reticulin is one of the key points, since from - reticulin morphine can be formed through the morphine route, noscapine through the path of the noscapina or berberina.[5,9,12,25]

PHYSIOLOGICAL ACTION OF OPIATES

Opiates (e.g., morphine and codeine) exert their main effects on the brain and spinal cord. Their principal action is to relieve or suppress pain. The drugs also alleviate anxiety; induce relaxation, drowsiness, and sedation; and may impart a state of euphoria or other enhanced mood. Opiates also have important physiological effects: they slow respiration and heartbeat, suppress the cough reflex, and relax the smooth muscles of the gastrointestinal tract.[22] Opiates are addictive drugs; they produce a physical dependence and withdrawal symptoms that can only be assuaged by continued use of the drug. With chronic use, the body develops a tolerance to opiates, so that progressively larger doses are needed to achieve the same effect. The higher opiates-heroin and morphine-are more addictive than opium or codeine. Opiates are classified as narcotics because they relieve pain, induce stupor and sleep, and produce addiction. The habitual use of opium produces physical and mental deterioration and shortens life. An acute overdose of opium causes respiratory depression which can be fatal.[25,28,31]

Opium was for many centuries the principal painkiller known to medicine and was used in various forms and under various names. Laudanum, for example, was an alcoholic tincture (dilute solution) of opium that was used in European medical practice as an analgesic and sedative. Physicians relied on paregoric, a camphorated solution of opium, to treat diarrhea by relaxing the gastrointestinal tract. The narcotic effects of opium are mainly attributable to morphine, which was first isolated about 1804. In 1898 it was discovered that treating morphine with acetic anhydride yields heroin, which is four to eight times as potent as morphine in both its pain-killing properties and its addictive potential. The other alkaloids naturally present in opium are much weaker; codeine, for example, is only one-sixth as potent as morphine and is used mainly for cough relief. Since the late 1930s, various synthetic drugs have been developed that possess the analgesic properties of morphine and heroin. These drugs, which include meperidine (Demerol), methadone, levorphonal, and many others, are known as synthetic opioids. They have largely replaced morphine and heroin in the treatment of severe pain.[22,25,29]

Opiates achieve their effect on the brain because their structure closely resembles that of certain molecules called endorphins, which are naturally produced in the body. Endorphins suppress pain and enhance mood by occupying certain receptor sites on specific neurons (nerve cells) that are involved in the transmission of nervous impulses. Opiate alkaloids are able to occupy the same receptor sites, thereby mimicking the effects of endorphins in suppressing the transmission of pain impulses within the nervous system.[23,24,26]

ANTI-CANCER PROPERTIES IN *PAPAVER SOMNIFERUM*

- Probably the most well-known plant-derived anti-cancer drug is Paclitaxel.
- The cytotoxic activity of this taxane dipertene found in extracts from the bark of Taxus brevifolia Nutt.
- Vina alkaloids include vincristine which was approved as chemotherapy treatment.
- *Papaver Somniferum* Plant alkaloids and natural products.
- *Papaver Somniferum* in present active compound of Anti-tumor antibiotics, Hormonal agents, Anti-metabolites and Biological response modifiers.
- Treatment of cancer in patients requires the use of different drugs like hormonal therapy, immunotherapy, targeted therapy, and others.[11,15,18]

CANCER

Cancer is a group of diseases associated with abnormal cell growth with the potential to plague or spread to other parts of the body. Major types of cancers include carcinomas, sarcomas, lymphomas, and leukemia. The risk of developing certain cancers can be reduced by not smoking, maintaining a healthy weight, limiting alcohol intake, eating plenty of vegetables, fruits, and whole grains, vaccination against certain infectious diseases, limiting consumption of processed meat and red meat, and limiting exposure to direct sunlight. These contrast with benign tumors, which do not spread and Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in bowel movements. Tobacco use is the cause of about 22% of cancer deaths. Another 10% are due to obesity, poor diet, lack of physical activity or excessive drinking of alcohol. Other factors include certain infections, exposure to ionizing radiation, and environmental pollutants. In the developing world, 15% of cancers are due to infections such as *Helicobacter pylori*, hepatitis B, hepatitis C, human papillomavirus infection, Epstein–Barr virus and human immunodeficiency virus (HIV).[23,25,28] Many genetic changes are required before cancer develops or approximately 5–10% of cancers are due to inherited genetic defects. Cancer is often treated with some combination of radiation therapy, surgery, chemotherapy and targeted therapy. Pain and symptom management are an important part of care. Palliative care is particularly important in people with advanced disease. The chance of survival depends on the type of cancer and extent of disease at the start of treatment. In children under 15 at diagnosis, the five-year survival rate in the developed world is on average 80%. The most common types of cancer in males are lung cancer, prostate cancer, colorectal cancer, and stomach cancer. In females, the most common types are breast cancer, colorectal cancer, lung cancer, and cervical cancer and If skin cancer other than melanoma were included in total new cancer cases each year, it would account for around 40% of cases or In children, acute lymphoblastic leukemia and brain tumors are most common. Cancer cell growth a subset of neoplasms. A

neoplasm or tumor is a group of cells that have undergone unregulated growth and will often form a mass or lump, but may be distributed diffusely. All tumor cells show the six hallmarks of cancer. These characteristics are required to produce a malignant tumor.[23,26,29]

They include

- Cell growth and division absent the proper signals.
- Continuous growth and division even given contrary signals.
- Avoidance of programmed cell death.
- Limitless number of cell divisions.
- Promoting blood vessel construction.
- Invasion of tissue and formation of metastases.

The progression from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression.

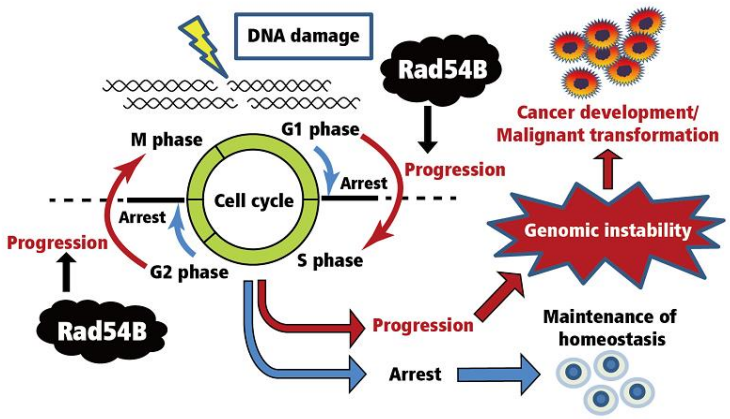


Fig: - Basic Mechanisms Of Cancer Cells.

CALCIFICATION OF CANCER: - The major types of cancer are **carcinoma, sarcoma, melanoma, lymphoma, and leukemia**. Carcinomas -- the most commonly diagnosed cancers originate in the skin, lungs, breasts, pancreas, and other organs and glands.[27,28,30]

- **CARCINOMA:-** Carcinoma is the most common type of cancer that starts in cells that make up the skin or the tissue lining organs, such as the liver or kidneys. Like other types of cancer, carcinomas are abnormal cells that divide without control. They are able to spread to other parts of the body, but don't always. It begins in the epithelial tissue of the skin, or in the tissue that lines internal organs, such as the liver or kidneys. Carcinoma arises from cells originating in the endodermal or ectodermal germ layer during embryogenesis. Specifically, carcinoma is tumor tissue derived from putative epithelial cells whose genome has become altered or damaged, causing the cells to transform and show abnormal malignant properties. Carcinomas may spread to other parts of the body, or be confined to the primary location. Survival rates can give you an idea of what percentage of people with the same type and stage of cancer are still alive a certain amount of time (usually 5 years) after they were diagnosed.[30,35,38]

Signs and Symptoms Carcinoma Cancer

- Scaly and dark skin patches.
- Open sores with raised borders.
- Firm growths.
- Spots that resemble age spots.
- Wart-like growths.
- Horn-like growths.
- Sores growing in scars.

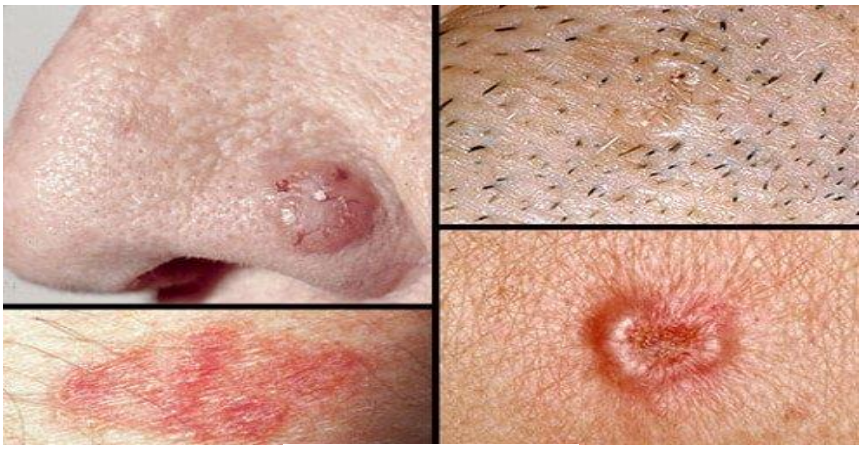


FIG:- Carcinoma Cancer.

❖ **SARCOMA: -** sarcoma is a type of cancer that starts in tissues like bone or muscle. Bone and soft tissue sarcomas are the main types of sarcoma. Soft tissue sarcomas can develop in soft tissues like fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues. Sarcoma is considered stage IV when it has spread to distant parts of the body. Stage IV sarcomas are rarely curable. But some patients may be cured if the main (primary) tumor and all of the areas of cancer spread (metastases) can be removed by surgery. The best success rate is when it has spread only to the lungs. 5-year relative survival rates for soft tissue sarcoma.[23,31,32]

Signs and Symptoms Of Sarcoma Cancer

- A lump that can be felt through the skin that may or may not be painful.
- Bone pain.
- A broken bone that happens unexpectedly, such as with a minor injury or no injury at all.
- Abdominal pain.
- Weight loss.

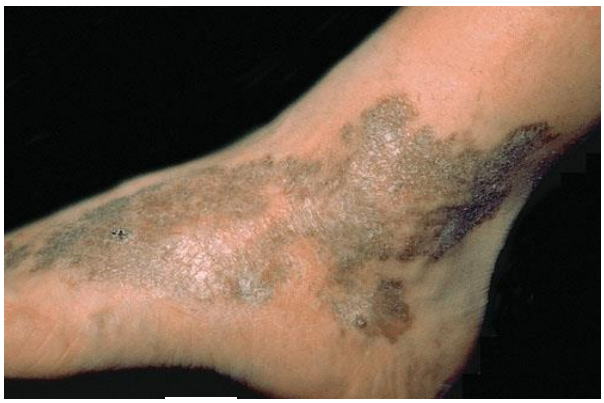


FIG: - Sarcoma Cancer.

❖ **MELANOMA: -** Melanoma, the most serious type of skin cancer, develops in the cells (melanocytes) that produce melanin-the pigment that gives your skin its color. Melanoma can also form in your eyes and, rarely, inside your body, such as in your nose or throat. Melanoma occurs when the pigment-producing cells that give colour to the skin become cancerous. Symptoms might include a new, unusual growth or a change in an existing mole. Melanomas can occur anywhere on the body. Treatment may involve surgery, radiation, medication or in some cases, chemotherapy.[23,35]

5-year relative survival rates for melanoma skin cancer. The overall average 5-year survival rate for all patients with melanoma is 92%. This means 92 of every 100 people diagnosed with melanoma will be alive in 5 years. In the very early stages the 5-year survival rate is 99%. Once melanoma has spread to the lymph nodes the 5-year survival rate is 63%.[35,38,41]

Signs and symptoms of melanoma Cancer: - Melanoma is a skin cancer that can show up on the skin in many ways. It can look like a-

- Changing mole.
- Spot that looks like a new mole, freckle, or age spot, but it looks different from the others on your skin.
- Excessive sweating, especially at night.
- Spot that has a jagged border, more than one color, and is growing.
- Border. The edges are ragged, notched, uneven, or blurred.
- Hair loss and skin problems.
- Dome-shaped growth that feels firm and may look like a sore, which may bleed.
- Dark-brown or black vertical line beneath a fingernail or toenail.
- Band of darker skin around a fingernail or toenail.
- Fever, Nausea, Vomiting and Bleeding.
- Slowly growing patch of thick skin that looks like a scar.

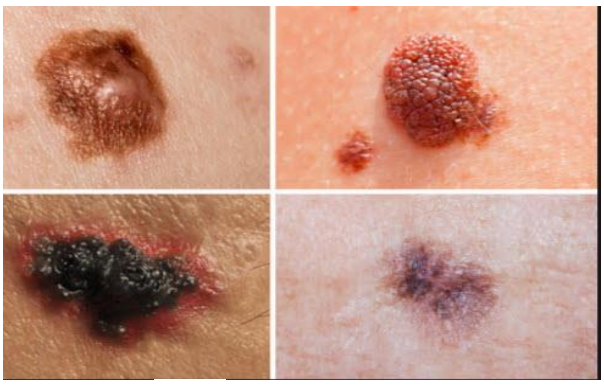


FIG: - Melanoma Cancer.

❖ **LYMPHOMA:-** Lymphoma cancer is very treatable, and the outlook can vary depending on the type of lymphoma and its stage. Lymphoma cancer a disease-fighting white blood cell called a lymphocyte develops a genetic mutation. Lymphoma is different from leukemia. Each of these cancers starts in a different type of cell. Most commonly, non-Hodgkin lymphoma starts in a lymph node at one or more places in the body. It can spread through the lymphatic system from one group of lymph nodes to another. Anxiety and depression occur at a higher rate among people with blood cancers like lymphoma than in the general population. Approximately 25 percent of people with lymphoma may experience persistent mental health symptoms, even after diagnosis and treatment. It can also spread to other lymph tissue, particularly in the bone marrow and spleen, or to lymph nodes in the liver. The overall 5-year relative survival rate for people with NHL is 72%. But it's important to keep in mind that survival rates can vary widely for different types and stages of lymphoma.[30,31,35]

Signs and symptoms of Lymphoma Cancer

- Painless swelling of lymph nodes in your neck, armpits or groin.
- Persistent fatigue.
- Fever.
- Night sweats.
- Nausea or Vomiting.
- Losing weight without trying.
- Hair loss and skin problems.
- Shortness of breath.
- Unexplained weight loss.
- Itchy skin.

Fig:- Lymphoma Cancer.

❖ **LEUKEMIA:-** Leukemia is a cancer of the blood and bone marrow, cancer of the body's blood-forming tissues, including the lymphatic system.. In simple terms, cancer is defined as the normally grow and divide in an orderly way, as your body needs them. But in people with leukemia, the bone marrow produces an excessive amount of abnormal white blood cells, Cancer can develop anywhere in the body. In leukemia, this rapid, out-of-control growth of abnormal cells takes place in the bone marrow of bones. Leukemia or myelodysplastic syndromes (MDS) can cause bone or joint pain, usually because your bone marrow has become overcrowded with cancer cells. At times, these cells may form a mass near the spinal cords nerves or in the joints. Treatment is highly variable. For slow-growing leukaemias, treatment may include monitoring. For aggressive leukaemias, treatment includes chemotherapy that's sometimes followed by radiation and stem-cell transplant.[31,35,36,38]

Signs and Symptoms of Leukemia cancer

- Fever or chills.
- Nausea or Vomiting.
- Bleeding; Bruise; Infection
- Hair loss and skin problems.
- Persistent fatigue, weakness.
- Frequent or severe infections.
- Losing weight without trying.
- Swollen lymph nodes, enlarged liver or spleen.
- Easy bleeding or bruising.
- Recurrent nosebleeds.
- Tiny red spots in your skin (petechiae).
- Excessive sweating, especially at night.
- Bone pain or tenderness.

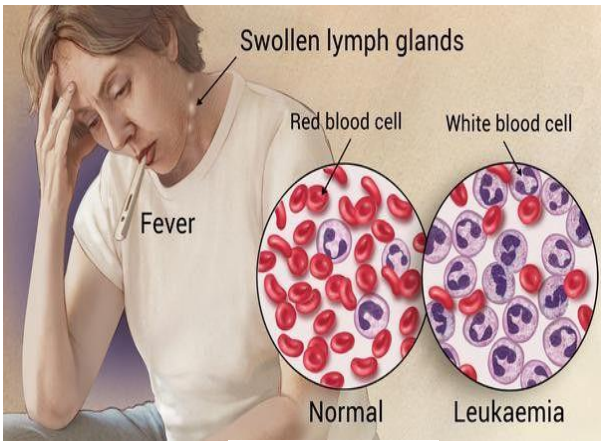


Fig:- Leukemia Cancer.

Cause bone or joint pain because bone marrow has overcrowded with cancer cells.

CAUSES OF CANCER:- Annually, it caused about 8.8 million deaths (15.7% of deaths). The majority of cancers, some 90–95% of cases, are due to genetic mutations from environmental and lifestyle factors. Cancer death include tobacco use (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), lack of physical activity, and pollution. The remaining 5–10% is due to inherited genetics. Environmental refers to any cause that is not inherited, such as lifestyle, economic, and behavioral factors and not merely pollution.[25,31,35]

It is not generally possible to prove what caused a particular cancer because the various causes do not have specific fingerprints and most cancers are related to environmental, lifestyle, or behavioral exposures.[For example, if a person who uses tobacco heavily develops lung cancer, then it was probably caused by the tobacco use, but since everyone has a small chance of developing lung cancer as a result of air pollution or radiation, the cancer may have developed for one of those reasons. Excepting the rare transmissions that occur with pregnancies and occasional organ donors, cancer is generally not a transmissible disease.[32,33,36,37]

- ❖ Genetics-Cancer syndromes.
- ❖ Physical and chemical agents-Smoking, Drinking and Materials.
- ❖ Lifestyle-Alcohol, Diet, fast food, and Obesity.
- ❖ Hormones changes.
- ❖ Infection and inflammation-Viruses, Bacteria and Inflammation.
- ❖ Radiation- Non-ionizing radiation, Ionizing radiation.
- ❖ Rare causes- transplantation, Trauma and Maternal-fetal transmission.

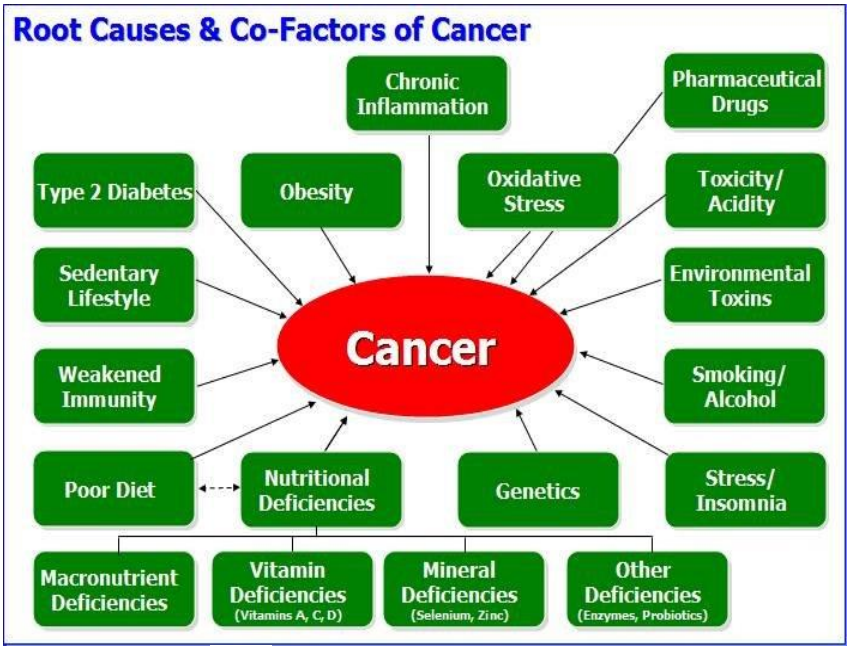


Fig:- Causes & Co-Factors of Cancer.

It caused about 8.8 million deaths (15.7% of deaths), the majority of cancers, some 90–95% of cases, Cancer death include tobacco use (25–30%), diet and obesity (30–35%), infections (15–20%), radiation up to 10%, The remaining 5–10% is due to inherited genetics. Cancer patient's 5-year survival rate is 99%.[41,42,45]

CANCER SYNDROMES

- Ataxia telangiectasia.
- Bloom syndrome.
- BRCA1 & BRCA2.
- Fanconi anemia.
- Familial adenomatous polyposis.
- Hereditary breast and ovarian cancer.
- Hereditary non-polyposis colon cancer.
- Li-Fraumeni syndrome.
- Nevoid basal cell carcinoma syndrome.
- Von Hippel-Lindau disease.
- Werner syndrome.
- Xeroderma pigmentosum.

TREATMENT OF CANCER

- Surgery
- Radiation therapy
- Chemotherapy is the treatment of cancer with" anticancer drugs".
- Targeted therapy,
- Cancer immunotherapy
- Hormonal therapy (oncology)- Blocking estrogen or testosterone.
- Angiogenesis inhibitors.
- Synthetic lethality.
- Change life style- regularly Exercises, Maintain diet. Du doesn't take fast food, drinking alcohol, and smoking etc.

ANTI-CANCER DRUG: - Anticancer drug are available in market on hearable drug or allopathic drug (Marketed drug).

- **HERBAL DRUG:-** Apigenin from parsley, Vinca alkaloids, Curcumin from turmeric, Crocetin from saffron, Cyanidins from grapes, Gingerol from gingers, Diindolylmethane (DIM) /Indole-3-carbinol (I3C) from Brassica vegetables, Vitamin D from mushroom, Sulforaphane from cruciferous vegetables, Lycopene from tomato, Epigallocatechin gallate from green tea, Fisetin from strawberries, apples, Genistein from soybean, Kaempferol from tea, broccoli, grapefruit, Rosmarinic acid from rosemary, Triterpenoids from wax-like coatings of fruits and medicinal herbs, Vitamin E from plant oil.[12,25,26]

- **MARKETED DRUG: -** Medicines that are used as anticancer drugs are: Platinum-based drugs (cisplatin, carboplatin), L-Asparaginase (Crasnit's), Hydroxyurea (Hydrea).[39]

By Drug Class Type

- Chemotherapy.
- Targeted Therapy.
- Immunotherapy (Biologic Therapy).
- Hormonal Therapy.

By Indication: - The market value of Oncology Cancer Drugs Market in 2020 is $1, 34,884.8 million and The total market value of Oncology Cancer Drugs Market is $2,22,380.0 million in 2019-20.

- Bone Cancer - Denosumab, Dactinomycin.
- Brain Cancer- Bevacizumab, Temozolomide.

- Lung Cancer- Erlotinib Hydrochloride, Mobocertinib Succinate, Bevacizumab.
- Stomach Cancer- Doxorubicin Hydrochloride, Bleomycin.
- Colorectal Cancer- Eloxatin (Oxaliplatin), Cetuximab, Panitumumab.
- Breast Cancer- Raloxifene Hydrochloride, Tamoxifen Citrate, Soltamox.
- Prostate Cancer- Oxaliplatin, Bleomycin, Mitomycin.
- Rectal Cancer- Cetuximab, Eloxatin, Oxaliplatin, Stivarga.
- Liver Cancer- Atezolizumab, Ramucirumab, Stivarga.
- Esophagus Cancer- Leucovorin Calcium, Ramucirumab, Regorafenib
- Cervical Cancer- Bevacizumab, Bleomycin Sulfate, Zirabev.
- Kidney Cancer- Aldesleukin, Ipilimumab, Temsirolimus.
- Bladder Cancer- Atezolizumab, Doxorubicin Hydrochloride.
- Pancreatic Cancer- Sunitinib Malate, Mitomycin, Gemcitabine Hydrochloride.
- Other Cancers.

MATERIAL AND METHOD

Melting point was determined in open glass capillary tube by means of a BUCHI Melting Point B-540 apparatus. Infrared (FT-IR) spectra were taken using a PerkinElmer Spectrum One FT-IR spectrometer, Vmax in cm^{-1}. The ^{1}H and ^{13}C nuclear magnetic resonance were taken with a Bruker 500 NMR spectrometer. Chemical shifts are reported in ppm (δ). High resolution electro spray ionization mass spectra (HR-ESI-MS) were obtained with MeOH on a Bruker micrOTOF-Q. Elemental analyses were performed using a Thermo Finnigan FLASH 1112 SERIES EA instrument. The specific rotation was measured on an Optical Activity Ltd. A55 polarimeter instrument using 2 cm^3 cells with a 0.5 dm path length and the sample concentration is given in g/100 cm^3 unit. Chemical reagents for isolation were of analytical grade and purchased from Merck (Darmstadt, 90 Germany). All solvents were filtered through 0.45 μm membrane filters before being injected into the HPLC.[22,28,30,34]

- **Plant Samples: -** Different parts of *Papaver Somniferum* were collected from herbal medicinal garden, Raipur, in august 2019. The identity of plant was confirmed by Dr. Ram Sahu, associate professor in faculty of Pharmacognocy, Columbia Institute of Pharmacy Near vidhansabha, Village tekari Raipur, (C.G.) India-493111.
- **Plant Material: -** Poppy capsules were procured from herbal medicinal garden, Raipur, in august 2019. For this method, the capsules of *Papaver somniferum* are cut and dried in air in the field then harvested and crushed to straw. These capsules are grown from genetically engineered seeds and contain 1.5% (w/w) noscapine.

FIG:- PLANT MATERIAL OF POPPY CAPSULES (*Papaver somniferum*)

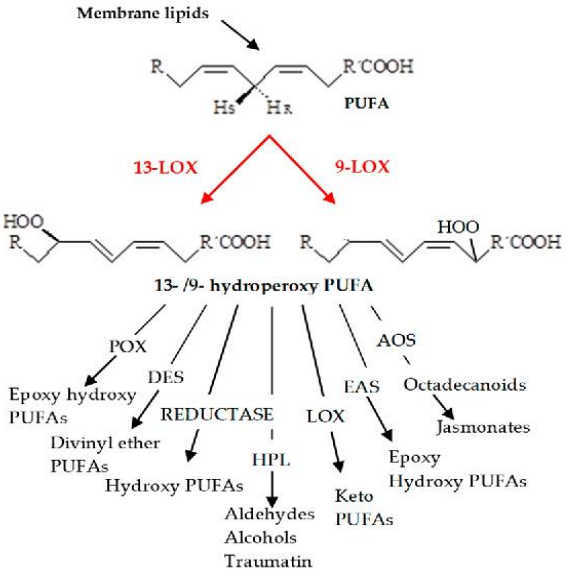
- **Sample Preparation:-** 200 mg of homogenized, powdered, dried poppy capsule was shaken with 50.0 cm^3 0.1 M hydrochloric acid for 2 hours. An aliquot of the extract was filtrated and the filtrate was filled to a vial. 50 mg of crude noscapine or pure noscapine was dissolved in 5 cm^3 of 10% acetic acid solution is added approximately and 100 cm^3 of demineralised water, sonicated to dissolve, then diluted to 250 cm^3 with demineralised water. It was mixed well and filled to a vial.[38,40]
- **Extraction:-** A three-neck round bottom flask was charged with 500 g of air-dried and ground poppy straw, 2000 cm^3 of ethanol, and 250 cm^3 of Purified/distilled water. The contents of the flask were stirred mechanically. The suspension was heated and refluxed for two hours at 80–85°C. The suspension was filtered. The alcohol extract was concentrated under reduced pressure to give 200 cm^3 of brown aqua phase. The pH of the solution was set 3.5 by adding acetic acid. 5.0 g of activated charcoal were added into this solution and contents was heated to 60°C and stirred

mechanically for fifteen minutes. This solution was filtered. The filtrate was extracted with chloroform (4 times 250 cm^3) and the extracts are combined. The chloroform extract was concentrated to give 15 g of dark brown residue. This residue was dissolved in 400 mL of 10% acetic acid solution and heated to 50°C. The pH of this solution was made 9.3 by adding 25% ammonia slowly. Crude noscapine was precipitated. The precipitate was filtered and dried in an oven at 105°C.[26,27,30,32]

FIG:- EXTRACT CRUDE OPIUM POPPY (*Papaver somniferum*).

❖ **Purification:** - A Crude Poppy capsule was suspended in 50 cm^3 of toluene. The suspension was heated to 70–80°C. 5.0 g of activated charcoal was added and stirred mechanically for fifteen minutes at room temperature. The solution was filtered. The filtrate was concentrated under reduced pressure to give white precipitate and stirred mechanically for thirty minutes in an ice bath. The white precipitate was filtered and dried in an oven at 105°C. The resulting white solid corresponded to a yield of 90% and purity (by HPLC) of 98.99%.[35,38,41]

(a)



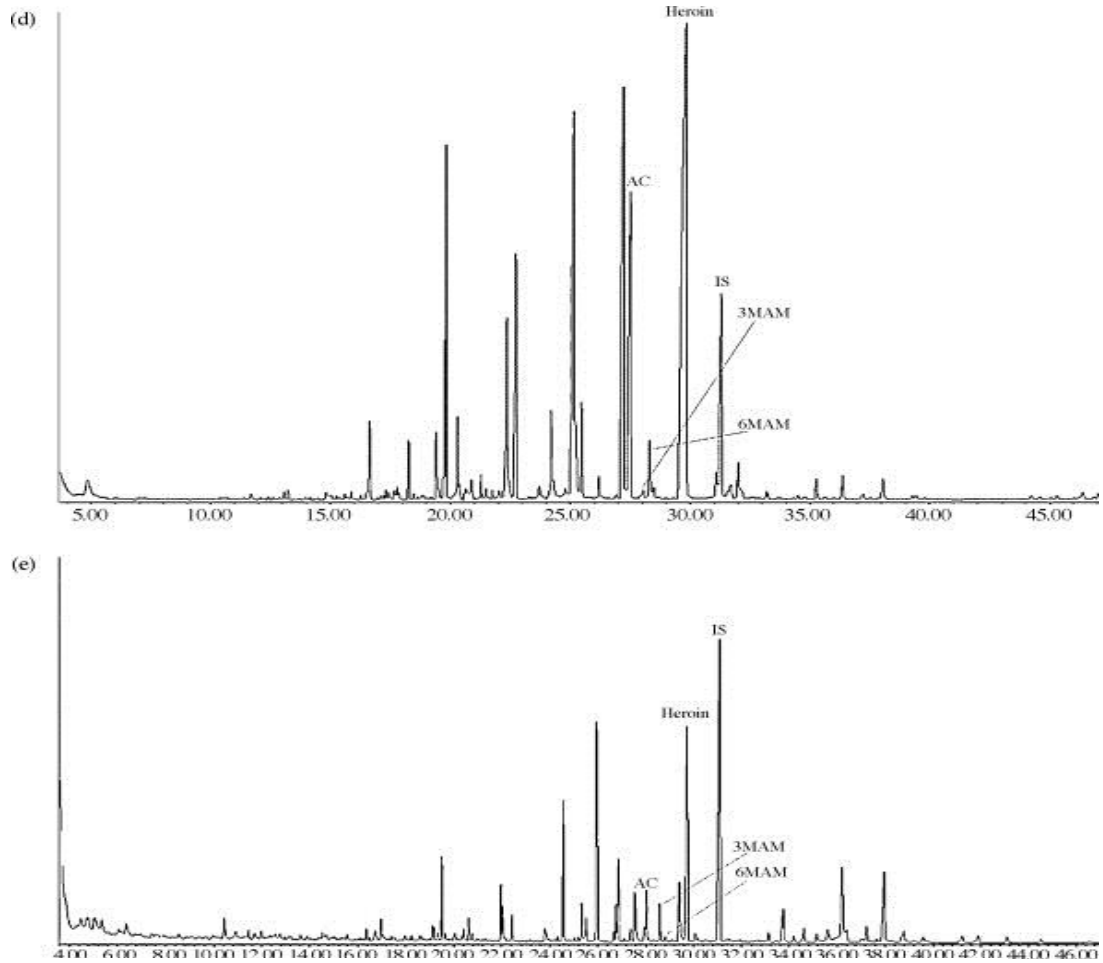
(b)

FIG:- PURIFICATION & PRODUCT CHARACTERIZATION OF OPIUM POPPY (*Papaver somniferum*).

❖ **Isolation:** - The Isolation procedure involves soaking the crude drug, in the form of either a powder or a decoction, Percolation, Reflux extraction, Soxhlet extraction, Supercritical fluid extraction, Ultrasound assisted extraction, and Microwave assisted extraction for a specified period of time, during which it undergoes fermentation and generates alcohol in situ; this facilitates the extraction of the active constituents contained in the plant material.[44,45]

That procedure is a set of predetermined steps that should be followed when workers are required to perform tasks such as inspection, maintenance, cleaning,

repair and construction and isolate all forms of potentially hazardous energy to ensure that an accidental release of hazardous energy does not occur. Control all other hazards to those doing the work. Ensure that entry to a restricted area is tightly controlled. The three most common types of Isolation procedure involves are: liquid/liquid, liquid/solid, and acid/base (also known as a chemically active extraction). The coffee and tea examples are both of the liquid/solid type in which a compound (caffeine) is isolated from a solid mixture by using a liquid extraction solvent (water).[23,25,29]



GRAPH: - ISOLATION & IDENTIFICATION OF UNIQUE MARKER COMPOUND FROM OPIUM POPPY (*Papaver somniferum*).

- **Characterization: -** In general, color, odor, taste, size, shape, and special features, like touch, texture, fracture, presence of trichomes, and presence of ridges of crude drugs are studied under morphology. Aromatic odor of umbelliferous fruits and sweet taste of liquorice are the example of this type of evaluation. In this classification the crude drugs are classified according to kingdom, subkingdom, division, class, order, family, genus and species as follows. The opium poppy is an annual plant. Poppies have lobed or dissected leaves, milky sap, often nodding buds on solitary stalks, and four- to six-petaled flowers with numerous stamens surrounding the ovary.[22,26]

Papaver somniferum (opium poppy) and related species, (S)-reticuline serves as a branch-point intermediate in the biosynthesis of numerous isoquinoline alkaloids. Common Name – Opium poppy, Family - *Papaveraceae*, Subfamily – Fumarioideae, Species - genus *Papaver*, Colour - grayish blue to dark blue, Shaped- bisexual regular dish. Part Used- Unripe Seed Capsules, Active Principle: - Morphine, Codeine, Thebaine, papaverine and noscapine.[28,29,30]

- **HPLC Analysis: -** High-performance liquid chromatography (HPLC) is an important analytical method commonly used to separate and quantify components of liquid samples. In this technique, a

solution (first phase) is pumped through a column that contains a packing of small porous particles with a second phase bound to the surface. High-performance liquid chromatography is an analytical technique to separate, identify, and quantify components in a mixture. It is the single biggest chromatography technique essential to most laboratories worldwide.[12,22,23]

High-performance liquid chromatography work Sample carried by a moving gas stream of Helium or Nitrogen. High Performance Liquid Chromatography (HPLC) is a form of column chromatography that pumps a sample mixture or analytic in a solvent (known as the mobile phase) at high pressure through a column with chromatographic packing material (stationary phase). HPLC Calibration Know the procedure to calibrate the High Performance Liquid Chromatography (HPLC) including leakage test, flow rate, reproducibility and linearity, lamp energy and pump pressure drop in Pharmaceutical Quality Control.[24,26,28]

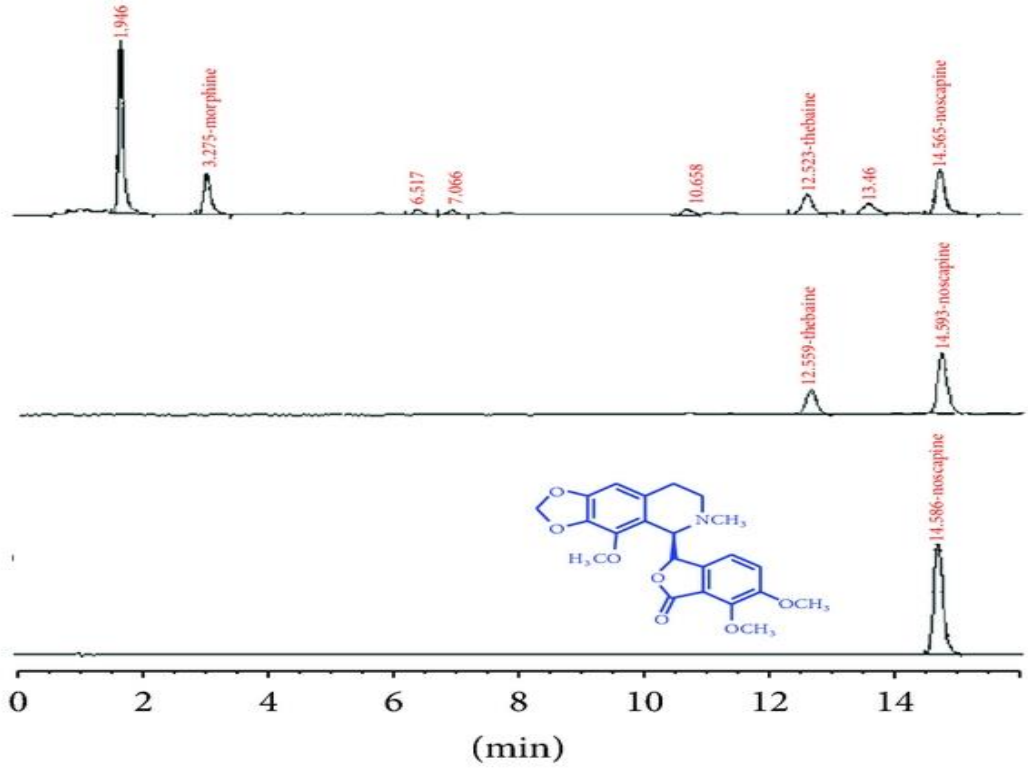
- **Chromatographic System: -** In chemical analysis, Chromatography is a laboratory technique for the separation of a mixture. The mixture is dissolved in a fluid (gas or solvent) called the *mobile phase*, which carries it through a system (a column, a capillary tube, a plate, or a sheet). Chromatography may be preparative or analytical. The purpose of preparative chromatography is to separate the components of a mixture for later use, and is thus a form of purification.[22,25,29]

An Agilent 1200 HPLC with UV-vis detection capabilities and a 0.01 cm^3 injection volume was used. The wavelength used during the analysis was 288 nm. A Eurospher-100 column measuring mm, 5 μm particle size and with C18 stationary phase was used. The column was heated and maintained at 40°C. The mobile phases consisted of water with 0.67% trifluoroacetic acid (TFA) and 0.67% TFA in a mixture of methanol, acetonitrile, and water (500/16/129 cm^3) using a gradient system. The flow rate was 1.0 mL/min and the applied elution program is described in Table: - Parameters of gradient elution program.[26,28,30]

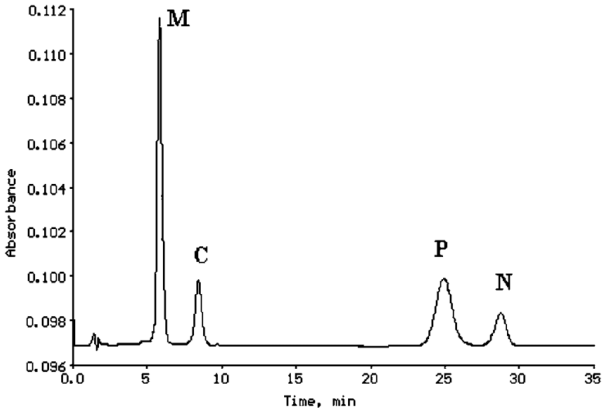
Table:- Chromatographic System on HPLC with UV-vis detection capabilities.

Time (min)	Flow rate (cm3/min)	Eluent A (v/v)	Eluent B (v/v)
0.0	1.0	89.5	17.5
14.4	1.0	55.20	58.9
14.5	1.0	1.5	85.8
16.4	1.0	00.0	15.5
16.5	1.0	84.0	16.0

Trifluoroacetic acid = (TFA) 0.67%, flow rate = 1.0 mL/min, methanol, acetonitrile and water using = (500/16/129 cm^3), injection volume =0.01 cm^3, particle size = 5 μm, stationary phase = C18, solid corresponded yield = 90%, purity (by HPLC) = 98.99%.



GRAPH:- CHROMATOGRAPH ON FLOW RATE (CM3/MIN), ELUENT A (V/V), ELUENT B (V/V) AND HPLC WITH UV-VIS DETECTION OF OPIUM POPPY (*Papaver somniferum*).



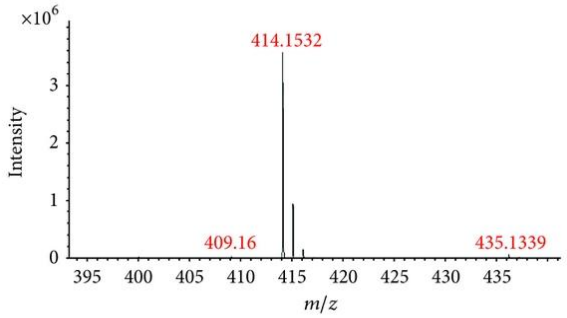
GRAPH:- CHROMATOGRAPHIC OBTAINED BY HPLC OF OPIUM POPPY (*Papaver somniferum*).

Poppy straw sample Chromatogram:- Trifluoroacetic acid (TFA) 0.67%, Morphine 3.341, Codine 6.257, Thebaine 16.866, Papaverine 20.842, Noscapine 21.477, purity (by HPLC) 98.99%, particle size & C18 is 5 μm.

RESULT

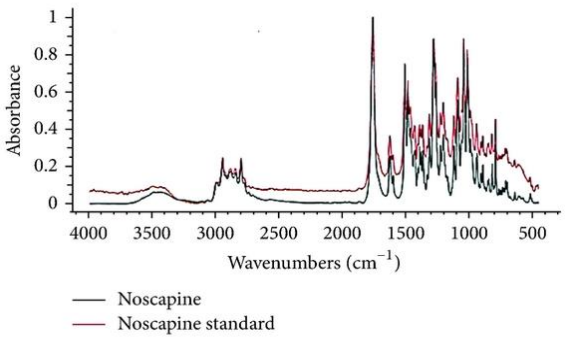
Noscapine was isolated as a white crystalline solid with negative rotation [α] ^{22D}= -176^{0c} (C=0.5 g/100 cm^3, $CHCl_3$). Several elution systems were tested in HPLC separation. The results indicated that when methanol-acetonitrile-water was used as mobile phase in gradient mode (Table), good separation results could be obtained. HPLC analysis of poppy straw, crude extract and pure noscapine show that noscapine was clearly separated and exhibited well-defined chromatogram with retention times of 13.596 min in the selected experimental conditions. The content of noscapine in the crude extracts was 50.8%. After purification treatment, the purity of the collected fraction peak 1 was found to be 98.99%.

Its molecular formula was determined as $C_{22}H_{23}NO_7$ on the basis of HR-ESI-MS (M/Z=414.1532 $[M^+H]^+$, calcd for $C_{22}H_{23}NO_7$ 414.1532). Figure shows the expected molecular ion peak at M/Z=414.1532, indicating formation of $[M^+H]^+$.



The chemical structure of peak fraction in Figure 2(c) was identified according to its FT-IR, ^{1}H NMR data ^{13}C NMR. These were well-matched with the literature. Figure shows infrared spectra of pure noscapine product and noscapine standard (purchased from Turkish Grain Board). IR spectra show numerous sharp bands between 700 and 1500 cm^{-1} which are assigned to deformation and stretching vibrations of the alkaloid ring system. Also, the strong band at 1755 cm^{-1} is the most characteristic for C=O stretching vibration.

The NMR spectrum of noscapine shows two one-proton doublets at 6.98 and 6.18 ppm assigned to the aromatic protons in the phthalidyl ring. The one-proton singlet signal at 6.32 ppm is attributed to aromatic proton in the isoquinoline ring. The three-proton singlets at 3.87 ppm, 4.15, and 4.19 ppm are ascribed to methoxy protons in isoquinoline and phthalidyl rings, respectively. The signal at 5.95 which is given as a two-proton singlet is accounted the methyl enedioxy protons. The singlet signal at 2.65 ppm is due to the -N-CH_3 protons. The -CH_2-CH_2- protons of isoquinoline ring are appeared as a multiplet at 2.34-2.39 ppm.



It caused about 8.8 million deaths (15.7% of deaths), the majority of cancers, some 90–95% of cases, Cancer death include tobacco use (25–30%), diet and obesity (30–35%), infections (15–20%), radiation up to 10%, The remaining 5–10% is due to inherited genetics. Cancer patient's 5-year survival rate is 99%.

The ^{13}C NMR spectrum of compound exhibited signals for aromatic carbons between 118.2-135.1 ppm, methylenedioxy carbon at 100.7 ppm, and carbonyl carbon at 168.0 ppm. The signals at 57.8, 58.44, and 63.21 ppm are ascribed to methoxy carbon atoms. The carbon atom which bonded nitrogen atom is observed at 47.20 ppm.

CONCLUSION

Since bioactive compounds occurring in plant material consist of multi-component mixtures, their separation and determination still creates problems. Practically most of them have to be purified by the combination of several chromatographic techniques and various other purification methods to isolate bioactive compound. Noscapine is isolated from opium. Recently, following seed development and gene studies, poppy seed including capsules that are rich in noscapine have been developed. To our knowledge, this is the first report on the isolation of noscapine from poppy capsules. The isolation method is very short compared with other

production methods from opium. Hence, poppy straw could be used as an accessible source of noscapine product with high yield. Its chemical structure was clearly confirmed by using various instrumental techniques. The obtained product has pharmacological purity and does not include impurities.

DISCUSSION

Cancer is a disease caused when cells divide uncontrollably and spread into surrounding tissues. Cancer is caused by changes to DNA. Most cancer-causing DNA changes occur in sections of DNA called genes. These changes are also called genetic changes. When Cancer is mad, you will know by the way that we act, and being hurt can make a Cancer feel frustrated about what's going on. We tend to ignore the ones who have hurt us and hide in our shell to feel upset and comprehend our feelings so we don't hurt anyone while being upset. Surgery. The goal of surgery is to remove the cancer or as much of the cancer as possible. Fears of cancer emanated from a core view of cancer as a vicious, unpredictable, and indestructible enemy, evoking fears about its proximity, the (lack of) strategies to keep it at bay, the personal and social implications of succumbing, and fear of dying from cancer.

The main reason cancer risk overall is rising is because of our increasing lifespan. And the researchers behind these new statistics reckon that about two-thirds of the increase is due to the fact we're living longer. The rest, they think, is caused by changes in cancer rates across different age groups. Cancers are actually one of the most emotionally intelligent signs, because they excel at recognizing and reasoning with their own and others' feelings. Cancer's use their emotional intelligence and intuition to assess other people and their emotions, and ultimately help them. Cancers are tough to get into arguments with because they are, after all, the emotional Crab. They will take whatever you say, exaggerate and inflate it, and then turn it around and use it against you, which make them one of the powerful zodiac signs that can fight. It caused about 8.8 million deaths (15.7% of deaths), the majority of cancers, some 90–95% of cases, Cancer death include tobacco use (25–30%), diet and obesity (30–35%), infections (15–20%), radiation up to 10%, The remaining 5–10% is due to inherited genetics. Cancer patient's 5-year survival rate is 99%.

Cancer is perhaps the most emotional, passionate, and moody of all of the star signs. Cancerians are badass, maybe even batshit. The water sign brigade is more into feelings than intellect or rationality. They thrive in intense and spiritual relationships, and they tend to forge few, but very deep, friendships. Cancers love people and love to entertain, but if they're feeling resentful and hurt by the negative treatment they've experienced at the hands of others, they'll retreat into their shell. Cancer individuals love being home, so being home alone isn't a burden but something they enjoy.

ACKNOWLEDGE

I am very thankful to Principal (Dr Amit Roy), & Columbia Institute of pharmacy tekari Raipur Chhattisgarh and my teachers for their valuable guidance. I would like to thank all monitors who participated in data collection for this study and structures involved into the project: Himanshu pandey, Saraswati Sahu, Dr.Trilochan Sathpathy (HOD–Pharmacology), Dr.Aashish Dewangan, Dr.Ram Sahu, Rajani Yadav, and Mogesh Dewangan. I am also thankful to my friends, school teacher and colleagues for their time to time support. Especially thanks to my family and also all India institutes of medical sciences, Raipur (C.G.) hospital staff for informatics support.

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