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REVIEW ARTICLE ON ANTICANCER PROPERTIES OF MEDICINAL PLANTS: LAKSHMI TARU, VINCA ROSEA AND LAKSHMANPHAL

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ABSTRACT

Cancer is a disease in which some of the body's cells grow uncontrollably and spread other parts of the body. It can start anywhere in human body which is made up to trillions of cells. Even though various chemotherapeutic agents and other treatment options are available for treating cancer still it is emerging as one of the major cause of mortality either because of decreased effectiveness or increased side effects of the treatment and it is estimated that in India there will be increase in the incidence cancer cases by 12.8 per cent in 2025 as compared to 2020. It is important to change this situation. It is important to bring awareness about the medicinal plants with anticancer properties that has increased effectiveness and decreased side effects. In this article we discuss about cancer and its statistics, anticancer properties of three medicinal plants like Lakshmi taru, Vinca rosea and Lakshmanphal with their botanical description, mechanism of action, how to consume them and what are the side effects.

KEYWORDS: Cancer, Chemotherapy, Medicinal plants, Lakshmi taru, Vinca rosea, Lakshmanphal, mechanism of action.

INTRODUCTION

Cancer: Cancer is a disease in which some of the body's cells grow uncontrollably and spread to other parts of the body. It can start anywhere in human body, which is made up of trillions of cells. Conversation tumors spread into, or invade, nearby tissues and can travel to distant places in the body to form new tumors (metastasis).[1]

Statistics of Cancer 2023

According to the American Cancer Society statistics 2023 1,958,310 new cancer cases and 609,820 cancer deaths occurred in the United States. From 2014 through 2019 the incidence of prostate cancer increased annually by 3 per cent.[2]

In India: According to the National Cancer Registry Program, India the estimated number of cancer cases incidence in India 2022 was found to be 14,61,427. In India one in nine people are likely to develop cancer in their lifetime.[3]

Adults

Gender	Type of Cancer
Male	Lung Cancer
Female	Breast Cancer

Children between the age of 0 – 14 years lymphoid leukemia are likely to develop.

Gender	Percentage of lymphoid leukemia
Boys	29.2 %
Girls	24.2%

Medicinal plants with Anticancer Properties

Lakshmi Taru

Botanical Name : Simarouba glauca
Family : Simaroubaceae[4]

Fig: Lakshmi Taru[5]

Habit : Evergreen tree
Leaves : Unequally pinnate with broadly winged rachis.
Leaflets : Obovate – oblong having prominent nerves
Drupes 1-5, purple black, 12-13 mm long and seeds globular. Lakshmi taru is tropical tree grows up to 1000 Meters above sea level in all types of well drained soils, with an average annual rainfall of 1,769 millimeter in central region and 1,833 millimeter in eastern region.[6]

The tree grows well in sunny regions and need no special care. Simarouba leaves and leaf extracts are used traditionally by native populations in treating various ailments like fever, dysentery, cold etc. The decoction of the leaves is said to raise the natural immunity of the body so well that the patients could fend themselves off from common ailments. Simarouba glauca has very good anti bacterial, anti tumor properties. Hence Simarouba is very effective in reducing tumor size and secondary infection in cancer patients. In first / second stages of cancer it is effective in curing the cancer whereas in later stages it can increase the quality of life.[7]

Chemical Constituents: The combinations of secondary metabolites (therapeutic agents) are found in Lakshmi taru plant including alkaloids (quassinoids, quassin), glycosides, flavonoids, phenolic compounds, tannins, cardenolides and saponins. More specifically triolen (triglyceride), scopoletin, fraxidin (hydroxyl – coumarin), canthin -6-one (alkaloid), glaucarubinone (quassinoids), and free fatty acids (FFA) have also been evaluated from it.[6]

Pharmacological Action

The Glaucarubinone (GLU) activates pro apoptotic proteins including caspase – 9, Bax and p-53 which triggers apoptosis in multidrug resistant cell line KB cells and suppresses the ROS dependent ABC transporters. The polyphenolic constituents of Lakshmi taru may checks the over expression of a protein kinase called mammalian target of rapamycin (mTOR) which regulates several cellular activities like cell growth, development, differentiation cellular biosynthesis, maturity and cell death.[6]

According to the early cancer screening performed by the National Cancer Institute in 1976. Very low dosages (less than 20mcg/ml) of Sima rouba alcohol extract had toxic actions against cancer cells. Leaves and bark are used as a powerful digestive aid. Red and White are the two varieties of Simarouba both of which are equally good in treating cancer.[8] According to the research conducted by JSS College of Pharmacy they found that tricaproin (TCN) inhibited colorectal cancer cells growth in a time dose dependent manner. It reduced oncogenic Class – 1 histone deacetylases activity and there by inducing apoptosis in cells. Histone deacetylases (HDACs) are the key enzymes which are involved in chromatin remodeling and oncogenic behaviour of cells. It promote cancer cell proliferation, prevent apoptosis and increase cell migration through the modulation of histone acetylation. HDACs culminate in the down regulation of tumor suppressor gene such as p53, Bax, Bad, p21 etc by increasing chromatin tightening and it is caused due to removal of acetyl grows from the histone acetylation (which helps in packaging of DNA) by HDACs. They extracted SG leaves with hexane, chloroform, ethylacetate, 70% ethanol, water and anti cancer potential determined using sulforhodamine β assay.[8]

Preparation of Simarouba Decoction

Step 1: Take 3 Simarouba leaves per 10 kilogram body weight.
Step 2: Clean the Simarouba leaves with water to remove any impurities.
Step 3: Pour 250 ml of water into a Stainless Steel vessel and add leaves to it.
Step 4: Boil the mixture until it reaches the half the initial volume (i.e; 250 ml reaches to 125 ml).
Step 5: Cover the vessel using a Stainless Steel plate and leave it overnight.
Step 6: Next day morning, reheat the decoction and filter using a tea filter and consume it on empty stomach.
Step 7: To same leaf pieces add 250 ml of water and repeat step 4.
Step 8: Cover the vessel and leave it until evening.
Step 9: In the evening filter the decoction and consume it.
Step 10: Discard the leaves.
Step 11: Prepare the fresh decoction for next day starting from 1st step.
This decoction should be taken daily in morning and evening[7]

Other Medicinal uses of Simarouba

- Ulcers and bleeding in alimentary system.
- Gastritis caused by Helicobacter pylori.
- Hyperacidity, Dyspepsia.
- Amoebiasis, Diarrhea, Colitis.
- Chikungunya, H1N1, Herpes Colds, Hepatitis, Malaria, fever.
- Hemorrhage, Anemia, Rheumatoid arthritis[7]

Side Effects: High doses of Lakshmi taru leaves can cause vomiting and nausea. The person can also get high perspiration when the leaves or barks are consumed in higher doses. One can also experience an increased frequency in urination after consuming the extract of this plant in a large amount.[9]

Quantity to be Consumed: Take 3 leaves of Simarouba plant per 10 kilogram body weight. For example if the patient is of 60 kilograms then you need to take 18 leaves of Simarouba to prepare decoction.[7]

Vinca Rosea

Fig: Vinca Rosea[10]

Botanical name : Catharanthus roseus
Family : Apocynaceae
Synonyms : Ammocallis small, Lochnera Rchb.ex Endl.

Perennial herbs with oppositely or almost oppositely arranged leaves. Flowers are usually solitary in the leaf axils. Each has a calyx with five long, narrow lobes and a corolla with a tubular throat and five lobes.

Chemical Constituents: It is a main source of vinca alkaloids, now sometimes called catharanthus alkaloids. The plant produces about 130 of these compounds, including vinblastine and vincristine, two drugs used to treat cancer.

Catharanthus roseus is also cultivated as an ornamental plant in gardens. Several cultivators have been bred to produce flowers in many shades of pink, red, lilac and white or in light shades with dark throats.[11]

To fight against cancer vinca alkaloids also plays a major role. Four major vinca alkaloids are in clinical use: Vinblastine (VBL), vinorelbine (VRL), Vincristine and Vindesine (VDS). United States approved VCR, VBL and VRL for use. A new synthetic vinca alkaloid called Vinuflunine which has been approved for the treatment of second line transitional cell carcinoma of the urothelium in Europe.[12]

Pharmacological Action

Interactions with tubulin and disruption of microtubule function are the main mechanisms of vinca alkaloid to cause toxicity. It directly arrest metaphase by comprising the mitotic spindle apparatus. The vinca alkaloids connect to binding sites on tubulin which occurs rapidly and can be reversed, that they are separate from those of the taxanes, colchicine, podophyllotoxin and guanosine - 5'-tri-phosphate. For per mole of tubulin dimer there are two vinca alkaloid binding sites. In each microtubule there are nearly 16-17 high affinity binding sites and are located at the ends of microtubule congregation by binding to these sites. The decreases in rates of both growth and shorten at the assembly end of the microtubule is one of the most important effect of low drug concentration which produce "kinetic cap" which suppresses function.[12]

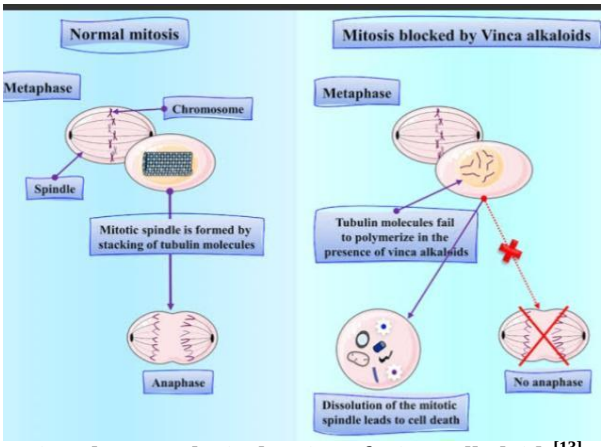

Fig: Pharmacological action of Vinca alkaloids[13]

Disturbance of microtubule dynamics (at the ends of mitotic spindle), causing metaphase arrest effects of vinca alkaloids occur at drug concentration below than the concentration that decrease mass of the microtubule. They can also invitro malignant angiogenesis Eg: 0.1 to 1.0 pmol/L of VBL blocked all essential steps in angiogenesis like endothelial proliferation, chemotaxis and spreading on fibronectin. But these concentrations are not effective on normal fibroblasts and lymphoid tumors. Low doses of VBL has increased antitumor response when it is combined with antibodies. This combinations is also effective against vascular endothelial growth factor. Mitotic block and apoptosis can be caused by vinca alkaloids by inhibiting cell proliferation by binding to microtubules. VCR and related compounds bind to tubulin and polymerization which causes destabilization of microtubules.[12]

VCR likely reflects a combination of higher level of sensitivity of pediatric malignancies to VCR and better tolerance to higher doses of VCR in children and VCR is commonly used for pediatric malignancies treatment. In both children and adults for the treatment of acute lymphocytic leukemia both Hodgkin's and non-Hodgkin lymphomas, lymphoid, lymphoid blast crisis of chronic myeloid leukemia VCR is an essential component of the chemotherapy regimen. In multimodality therapies of Wilms tumor, Ewing sarcoma, newblastoma and rhabdomyosarcoma and in adult for the treatment of small – cell lung cancer, multiple myeloma VCR plays a vital role. For some types of advanced lymphomas and germ cell malignancies chemotherapy regimens VBL has been a mainstay component. To treat Kaposi sarcoma breast, bladder and some brain malignancies it can be used alone or in combination with other agents.

They can also perform many other biochemical activities which may or may not be related to microtubule effects

like proteins and nucleic acids synthesis inhibition, oxidized glutathione elevation, alteration of membrane lipids and lipid metabolism elevation of cyclic adenosine monophosphate (CAMP), inhibitors of calcium – calmodulin – regulated CAMP phosphodiesterase. Vinca alkaloids depolymerize and destabilize the microtubules and mitotic spindles respectively which causes cell death. Antimitiotic drugs which target microtubules are classified into two main groups: Microtubule – destabilizing agents and Microtubule – stabilizing agents. Vinca alkaloids like vinblastine, vincristine and vinorelbine are the examples of microtubule destabilizing agents.[14]

Medicinal Uses

The vinca alkaloids have been generally included in combinations chemotherapy regimens for medicinal therapies.

VBL : Integral part of medicinal treatment regimens for testicular carcinoma and both Hodgkin and non-Hodgkin lymphomas, breast cancer and germ cell tumors.

Side effects : Toxicity to white blood cells, nausea, vomiting, constipation, fever, wheezing, dyspnea, chest or tumor pain and also rarely associated with ADH secretion.

VRL : Same as VBL. It has antitumor activity in patients with breast cancer and can be affected on bone tumor cells, osteosarcoma. It decreases the stability of lipid bilayer membranes. In US it has been approved for the initial treatment of patients with advanced lung cancer.

Side effects : Decreasing resistance to infection, bruising or bleeding, anemia, constipation, diarrhea, nausea, numbness in hands and feet (also called peripheral neuropathy) and inflammation at the site of injection.

VCR : has been approved to treat acute leukemia, rhabdomyosarcoma, neuroblastoma, Wilm's tumor, Hodgkin's disease and other lymphomas.

Side effects : Peripheral neuropathy, suppression of bone marrow activity, constipation, nervous system toxicity, nausea and vomiting.

VDS : Has similar effects to VBL. In acute lymphocytic leukemia, blastcrisis of chronic myeloid leukemia, malignant melanoma, pediatric solid tumors and metastatic renal, breast, esophageal and Colorectal carcinomas.

Vinuflunine : Recently a new synthetic vinca alkaloid, vinuflunine was developed through the addition of two fluor molecules by superacidic chemistry. Vinuflunine is the first fluorinated microtubule inhibitor that belongs to vinca alkaloids. This compound has been used in Europe for the treatment of second – line transitional cell carcinoma of the urothelium (TCCU), is being developed for other malignancies.[12]

Dosing : Currently, there is no clinical data supporting specific dose of vinca. Traditional recommendations are: Boil 10 leaves and 10 flowers of vinca rosea and consumers it as tea. 9 pink coloured flowers in 0.5 litres of water for 3 hours as a solar tea and it has to be consumed or sipped throughout the day. Vincristine and vinblastine (pure alkaloids) preparations are available along with therapeutic dose recommendations.[15]

Pregnancy/Lactation*:* Avoid use. Abortifacient effects have been documented.[15]

Side Effects: Nausea, vomiting and other stomach and intestinal symptoms. It can also cause nerve, kidney and liver damage. Large amounts can cause very low blood pressure.[16]

Lakshmanphal

Description

Scientific name : Annona muricata

Family : Annonaceae

Location : Africa, South America and Southeast Asia.

Common names : Soursop, graviola, guanabana or Brazilian paw[17]

Chemical constituents[18]

Compound	Plant Part
Acetogenins	Leaf, pericarp, pulp, root stem
Alkaloids	Leaf, pericarp, pulp, root, stem
Arginine	Leaf, pulp, root, stem
Aromatic amino acids	Leaf, pulp, root, stem
Flavonoids	Leaf, pericarp, pulp, root

Fig: Lakshmanphal[19][20]

Leaves: Large, glossy, dark green leaves.

Fruits: edible, green heart – shaped fruits. Soft, curved spines cover the leathery skin of fruits each of which

may contain 55-170 black seeds distributed in creamy white flesh with a characteristic aroma and flavor.
Coria – Tellez et al. have reported 212 bioactive compounds in A. muricata extracts. Reports in the literature indicate that seventy four of these bioactive compounds exhibits a variety of anti cancer effects in preclinical cell culture and animal model systems.

The decoctions of the bark, leaves, fruits, pericarp, seeds and roots have been extensively used in traditional medicine to treat multiple ailments including cancers by local communities in tropical Africa and South America. Due to aging and growing population majorly and also with carcinogens, infections, genetic mutations, hormones, immune conditions and adoption of behavioral and dietary risk factors such as smoking, unhealthy diet, physical inactivity and environmental pollutants. Extracts from Annona muricata are among a myriad of botanical products which have been shown promising medicinal values. Studies have linked the compounds derived from A. muricata to a variety of anti cancer effects including cytotoxicity.

Pharmacological Action

Graviola components modulate several cellular processes including inhibition of signaling pathways downstream of the epidermal growth factor receptor (EGFR), with others causing down regulation of phosphatidylinositol – 4,5-bisphosphate 3-kinase (PI3K / AKT), RAS, NF-KB and JAK/STAT. Further actions include inhibition of HIF-1α, GLUTI and GLUT4; proinflammatory cytokine expression (inflammation); and generation of reactive oxygen species (ROS) via upregulation of enzyme systems like catalase (CAT), superoxide dismutase (SOD) and heme – oxygenase (HO-1) expression.[17]

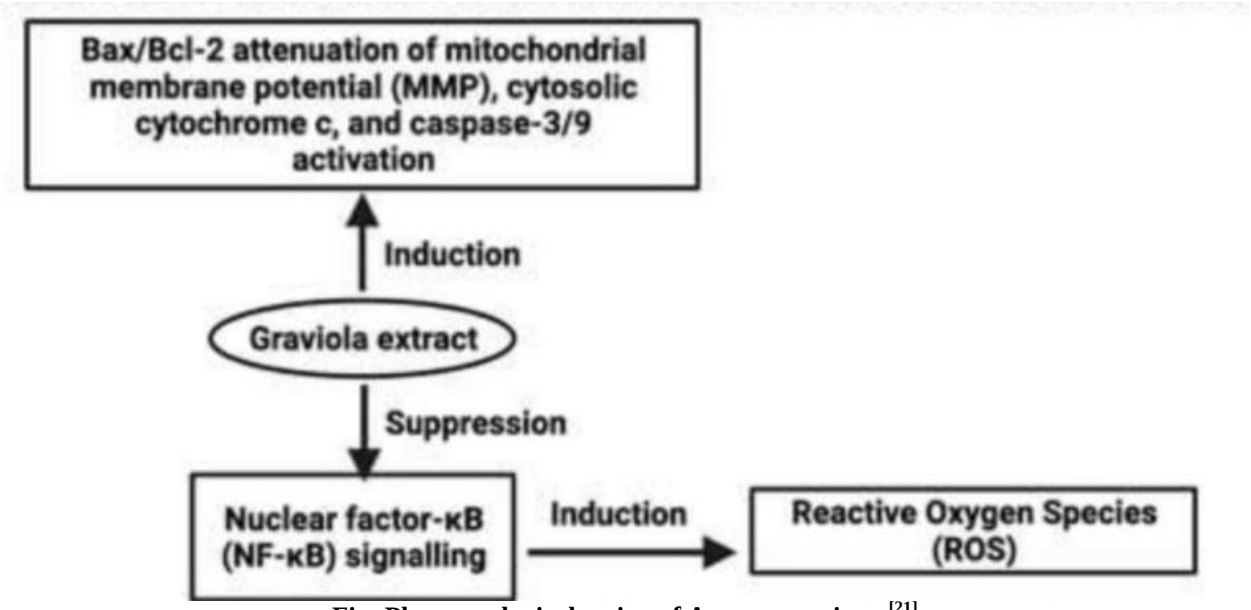

Fig: Pharmacological action of Annona muricata[21]

Cytotoxicity

Annonaceous actenogenins (AEGs) are extracted from various parts of A.muricata which are bioactive components. AEGs inhibit mitochondrial complex I which is involved in oxidative phosphorylation and ATP synthesis which results in cytotoxicity.[17] Actenogenins are potent anticancerous agents which play important role in lung, prostate, breast, colon and pancreatic cancers.[22]

Few examples of AGEs and against cancer cell lines[17]

AGEs	Cancer Cell Line
Annocatacin (A or B) or annocatalin	Hep G2 and Hep 2,2,15 hepatic cancer cell
Annomuricin A, B or E muricapentocin: annomutacin: annohexocin	Breast Cancer

Apoptosis: Leaf extracts of A.muricata activates caspase 3 which leads to apoptosis in breast MDA – MB – 468 cancer cells. Fruit extract of A.muricata induces apoptosis in breast T47D cancer cells.[17]

Component of A.muricata	Cancer cells	Mechanism of action
Annomuricin E (leaves)	Breast T47D cancer cells	Activation of caspases 3/7 and 9, upregulation and downregulation of BAX and BCL-2 at the mRNA and protein levels respectively.
Ethyl acetate extract of leaves	Colorectal HT-29 and HCT-116 cancer cells	Excessive accumulation of ROS followed by disruption of MMP, cytochrome C leakage, activation of the initiator and execution of caspases, upregulation of Bax and downregulation of Bcl2 protein.

Lakshmanphal selectively hunts down and kill 12 different types of cancer cells.[22] According to the researchers acetogenins are equipped with selective toxicity which means they can able to differentiate which cells are cancerous and which cells are resistant to drug (drug resistant).[23]

Restricts the production of ATP molecules in the cancer cells

In order to divide at extraordinary rate, the cancer cells require ATP in higher doses when compared to normal healthy cells. Annonaceous acetogenins are the bioactive compounds in Graviola can stop the production of ATP by the cancer cells that is required for the cancer cells growth and multiplication. Acetogenins interfere with the enzymatic reactions that are involved in ATP production by mitochondria of the cancerous cells. Acetogenins reduce angiogenesis which is the hallmark of cancer as a result it decreases the sprouting of blood vessels, causes the starvation of cancer cells by cutting off the flow of nutrients and oxygen. Low ATP production also impacts the blood vessels growth.[24]

Role of acetogenins in combating drug – resistant cancer cells

On long term chemotherapeutic treatment, the cancer cells develop immunity against the chemotherapy. They learn to recognize and resist the chemicals and develop multiple drug resistance (MDR). They develop pumping mechanism and pump out the toxic chemicals and as a result chemo drugs become ineffective and for this process the cancer cells require ATP for energy. As the acetogenins able to slow the production of ATP it can decreases the pumping mechanism and making the commercial cells sensitive to chemotherapy.[24]

Consumption of Lakshmanphal

It can be consumed rawly when it is ripen. Slight softness of the fruit when it is touched indicates that the fruit is ripen. It should be cutted into half and scoop the flesh the seeds should be discarded as these may be toxic. It can be stored in refrigerator and can also be used in smoothies. Lakshmanphal is commonly available in following forms.

- Fresh fruit
- Packaged fruit pulp
- Tincture extract from leaves and fruit
- Powdered leaf
- Bitters
- Capsules and tablets
- Dried whole leaves
- Tea bags[25]

Side Effects: On long term use of graviola may cause nerve damage and movement problems. It can also cause serious neuropathy that leads to Parkinson like symptoms like tremors or stiff muscles. It may be toxic to kidneys and liver. Those who consider taking graviola they need to first talk with doctor if they have hypertension or taking any anti hypertensive medications, diabetes and are pregnant and breast feeding.[26]

CONCLUSION

As the incidence of cancer is increasing day by day worldwide it is important to take preventive and curable measures in order to decrease the incidence of cancer occurrence. Even though various chemotherapeutic agents and treatment options are available still it is remaining as a major cause of mortality either because of decreased effectiveness or increased side effects. It is necessary to bring awareness about the herbal medicines like lakshmi taru, Vinca rosea and Lakshmanphal that play crucial role in treating and preventing cancer with increased effectiveness and decreased side effects. I hope that more research should be carried out about these herbal medicines, bring awareness and make it available for the cancer treatment. I hope that the world would become cancer free world.

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