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SWEET WORMWOOD IN THE TREATMENT OF BREAST CANCER

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ABSTRACT

Cancer is an abnormal growth of cells which tends to proliferate in an uncontrolled way and in some cases to spread. Many anticancer drugs are available in market with a lot of side-effects. So our objective is to introduced a drug "sweet wormwood" (Artemisia annua) that is 1,000 times better than chemotherapy. In chemotherapy, for every 5 cancer cells 1 normal cell may be destroyed but a recent study found that wormwood can kill up to 12,000 cancer cells for every 1 healthy cell it may affect. The active ingredient that makes sweet wormwood such a cancer healer is artemisinin. The special super concentrated compound of wormwood and iron can target cancer cells while leaving healthy cells alone. The compound is specially effective in combating breast cancer. Wormwood and iron together is said to act as a "Trojan horse", creating a literal "time bomb" for cancer cells. Cancer cells are not as successful as healthy cell in disposing of free floating iron molecules. This weakness causes the presence of iron in general to create stressful environment for cancer cells. This compound works on a general property of cancer cells, their high iron content. Breast cancer cells in particular can sometimes contain up to 15 times more iron receptors than surrounding cells, which is why this iron-artemisinin duo may have an even more profound effect on breast cancer. "Artemisinin reacted with iron to form free radicals which cause cell death". The artemisinin and its derivatives are toxic to the malarial parasites at nanomolar concentrations, causing specific membrane structural changes in the erythrocyte stage that kills the parasites. The WHO recommends artemisinin- based combination therapies as first line treatment for *P. falciparum* malaria because it reacts with the high levels of iron in the parasites to produced the free radicals which then destroy the cell walls of malarial- parasite. Act as anti malarial, anti parasitic, anti fungal, anti microbial, anti-inflammatory.

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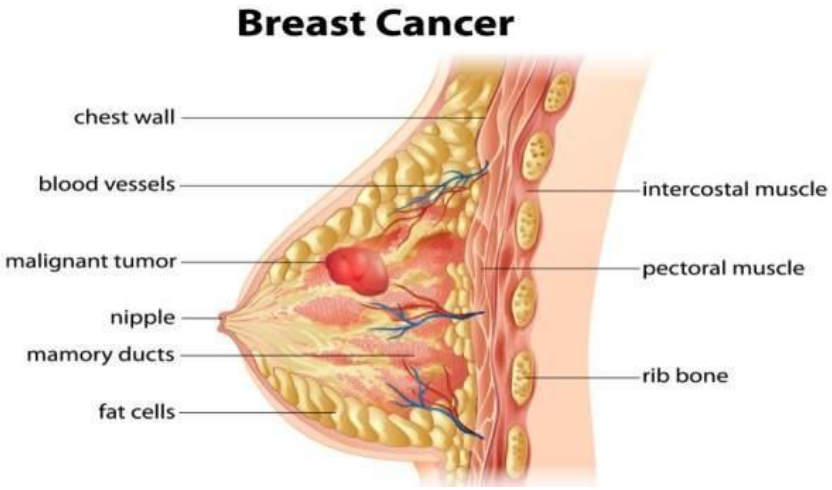
INTRODUCTION

Cancers begins in cells. Cells grow and divide to form new cells. When normal cells grow old or get damaged, they die and new cells take their place. When healthy cells in the breast show changes due to mutation in DNA and grow out of control, forming mass or sheet of cells called tumor. A tumor can be malignant- can grow and spread to other parts of the body (cancerous), benign – can grow but will not spread (non-cancerous). When breast cancer cells move to other parts of body through the blood vessels and/ or lymph vessels is called metastasis. Breast cancer can be invasive- that spread into surrounding tissues or non invasive- does not spread beyond the milk ducts or lobules in the breast



Types of breast cancer

Most breast cancer starts in the ducts or lobes and called ductal or lobular carcinoma.

Lobular carcinoma – starts in the lobules.

Lobular carcinoma in situ – Located only in the lobules.

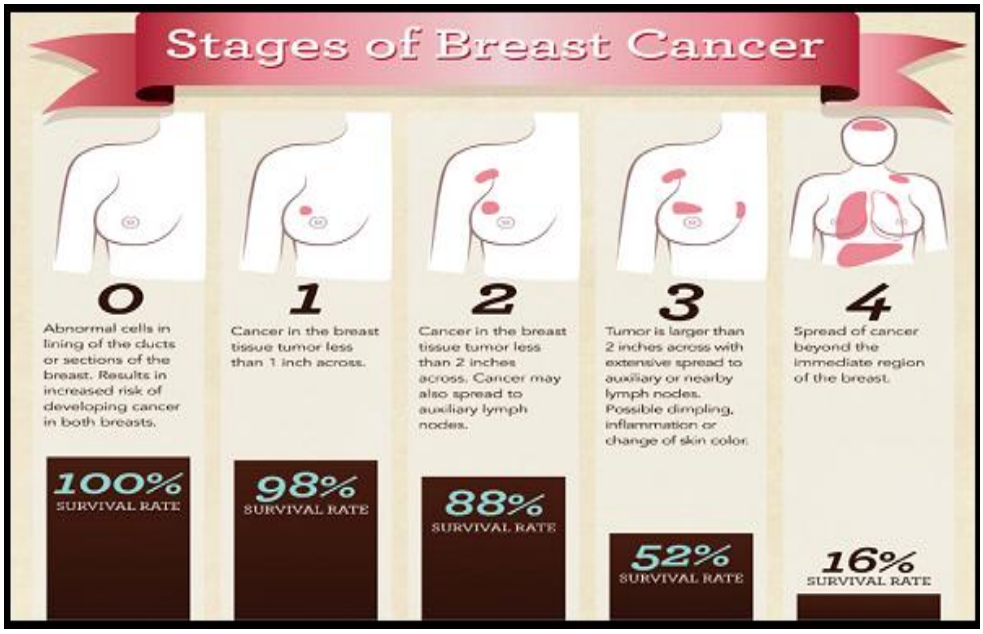
Ductal carcinoma- this cancer starts in the cells lining the milk ducts.

- Ductal carcinoma in situ(DCIS) – Located only in the duct
- Invasive ductal carcinoma – spread outside the duct.

Less common types of breast cancer include:

- Medullary
- Metaplastic
- Papillary breast cancer
- Inflammatory breast cancer

Stages



Stage 0.

Stage 0 is used to describe non-invasive breast cancers, such as DCIS (ductal carcinoma in situ). In stage 0, there is no evidence of cancer cells or non-cancerous abnormal cells breaking out of the part of the breast in which they started, or getting through to or invading neighbouring normal tissue

Stage I

Stage I describes invasive breast cancer (cancer cells are breaking through to or invading normal surrounding breast tissue) Stage I is divided into subcategories known as IA and IB.

Stage IA describes invasive breast cancer in which:

- The tumor measures up to 2 centimeters AND
- The cancer has not spread outside the breast; no lymph nodes are involved Stage IB describes invasive breast cancer in which:
- There is no tumor in the breast; instead, small groups of cancer cells – larger than 0.2 millimeter but not larger than 2 millimeters – are found in the lymph nodes OR
- There is a tumor in the breast that is no larger than 2 centimeters, and there are small groups of cancer cells – larger than 0.2 millimeter but not larger than 2 millimeters – in the lymph nodes

Microscopic invasion is possible in stage I breast cancer. In microscopic invasion, the cancer cells have just started to invade the tissue outside the lining of the duct or lobule, but the invading cancer cells can't measure more than 1 mm.

Stage II

Stage II is divided into subcategories known as IIA and IIB.

Stage IIA describes invasive breast cancer in which:

- No tumor can be found in the breast, but cancer (larger than 2 millimeters) is found in 1 to 3 axillary lymph nodes (the lymph nodes under the arm) or in the lymph nodes near the breast bone (found during a sentinel node biopsy) OR
- The tumor measures 2 centimeters or smaller and has spread to the axillary lymph nodes OR
- The tumor is larger than 2 centimeters but not larger than 5 centimeters and has not spread to the axillary lymph nodes

Stage IIB describes invasive breast cancer in which:

- The tumor is larger than 2 centimeters but no larger than 5 centimeters; small groups of breast cancer cells -- larger than 0.2 millimeter but not larger than 2 millimeters -- are found in the lymph nodes OR
- The tumor is larger than 2 centimeters but no larger than 5 centimeters; cancer has spread to 1 to 3 axillary lymph nodes or to lymph nodes near the breastbone (found during a sentinel node biopsy) OR
- The tumor is larger than 5 centimeters but has not spread to the axillary lymph nodes.

Stage III

Stage III is divided into subcategories known as IIIA, IIIB, and IIIC.

Stage IIIA describes invasive breast cancer in which either:

- No tumor is found in the breast or the tumor may be any size; cancer is found in 4 to 9 axillary lymph nodes or in the lymph nodes near the breastbone (found during imaging tests or a physical exam) OR
- The tumor is larger than 5 centimeters; small groups of breast cancer cells (larger than 0.2 millimeter but not larger than 2 millimeters) are found in the lymph nodes OR
- The tumor is larger than 5 centimeters; cancer has spread to 1 to 3 axillary lymph nodes or to the lymph nodes near the breastbone (found during a sentinel lymph node biopsy)

Stage IIIB describes invasive breast cancer in which:

- The tumor may be any size and has spread to the chest wall and/or skin of the breast and caused swelling or an ulcer AND
- May have spread to up to 9 axillary lymph nodes OR
- May have spread to lymph nodes near the breastbone

Inflammatory breast cancer is considered at least stage IIIB. Typical features of inflammatory breast cancer include

- Reddening of a large portion of the breast skin
- The breast feels warm and may be swollen
- Cancer cells have spread to the lymph nodes and may be found in the skin

Stage IIIC describes invasive breast cancer in which:

- There may be no sign of cancer in the breast or, if there is a tumor, it may be any size and may have spread to the chest wall and/or the skin of the breast AND
- The cancer has spread to 10 or more axillary lymph nodes OR
- The cancer has spread to lymph nodes above or below the collarbone OR
- The cancer has spread to axillary lymph nodes or to lymph nodes near the breastbone.

Stage IV

Stage IV describes invasive breast cancer that has spread beyond the breast and nearby lymph nodes to other organs of the body, such as the lungs, distant lymph nodes, skin, bones, liver, or brain.

You may hear the words “advanced” and “metastatic” used to describe stage IV breast cancer. Cancer may be stage IV at first diagnosis or it can be a recurrence of a previous breast cancer that has spread to other parts of the body.

TNM staging system

TNM (Tumor, Node, Metastasis) is another staging system researchers use to provide more details about how the cancer looks and behaves. Your doctor might mention the TNM classification for your case, but he or she is much more likely to use the numerical staging system. Sometimes clinical trials require TNM information from participants, so talk to your doctor if you are considering participation in a clinical trial.

The TNM system is based on three characteristics:

- Size **(**T stands for tumor)
- lymph node involvement (**N** stands for node)
- Whether the cancer has metastasized **(**M stands for metastasis), or moved beyond the breast to other parts of the body.

The T (size) category describes the original (primary) tumor:

- TX means the tumor can't be measured or found.
- T0 means there isn't any evidence of the primary tumor.
- Tis means the cancer is "in situ" (the tumor has not started growing into healthy breast tissue).
- T1, T2, T3, T4: These numbers are based on the size of the tumor and the extent to which it has grown into neighboring breast tissue. The higher the T number, the larger the tumor and/or the more it may have grown into the breast tissue.

The N (lymph node involvement) category describes whether or not the cancer has reached nearby lymph nodes:

- NX means the nearby lymph nodes can't be measured or found.
- N0 means nearby lymph nodes do not contain cancer.
- N1, N2, N3: These numbers are based on the number of lymph nodes involved and how much cancer is found in them. The higher the N number, the greater the extent of the lymph node involvement.

The M (metastasis) category tells whether or not there is evidence that the cancer has traveled to other parts of the body:

- MX means metastasis can't be measured or found.
- M0 means there is no distant metastasis.
- M1 means that distant metastasis is present.

Once the pathologist knows your T, N, and M characteristics, he or she can use them to assign a stage to the cancer. For example, a T1 N0 M0 breast cancer would mean that the primary breast tumor is less than 2 centimeters across (T1), has not involved the lymph nodes (N0), and has not spread to distant parts of the body (M0). This cancer would be grouped as stage I.

Tumours	**T0/Tis**	**T1**	**T2**	**T3**	**T4**
Tumour Size	**T0**: No primary tumour. **Tis**: Tumour only in breast ducts or lobules.	0-2 cm	2-5 cm	>5 cm	Tumor of any size with extension to chest wall/skin or ulceration ****inflammatory breast cancer** is staged as T4.
Nodes	**N0**	**N1**	**N1mi**	**N2**	**N3**
	No lymph node metastases.	Cancer cells present in 1-3 axillary lymph nodes.	Lymph node tumor > 2 mm.	Cancer cells present in 4-9 axillary lymph nodes.	Cancer cells in infra or supraclavicular lymph nodes, or in >10 axillary lymph nodes.
Metastasis	**M0**	**M1**			
	No evidence of cancer metastasis.	Cancer found in other areas of body.			

History

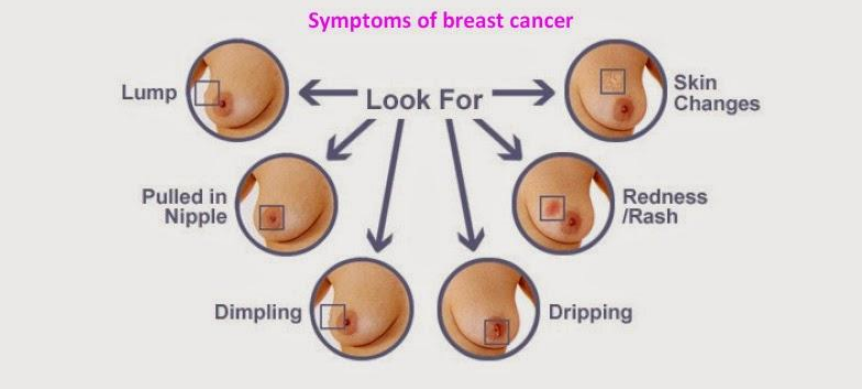
Breast cancer can be traced right back to ancient Egypt, with the earliest recorded case described on the 1600 BC Edwin Smith Papyrus. It has been mentioned in almost every period of recorded history. Because of the visible symptoms, unlike other internal cancers, breast lumps tends to manifest themselves as visible tumors. Earlier, it was a matter of taboo and embarrassment that meant detection and diagnosis was rare. Involvement of more women and actively bringing out the disease into the open is a recent phenomenon that is around three or four decades old. In the 1990's the symbol of breast cancer – the pink ribbon – brought out a revolution against this cancer. In 460 B.C., Hippocrates, described breast cancer as a humoral diseases. Thereafter in A.D. 200, Galen described the cancer as well. It was in 1757 that surgical removal of tumor could help treat breast cancer, as long as infected lymph nodes of armpits were removed. By mid 19th century, surgery was the available option for breast cancer. With advent of modern medicine, by 1995, less than 10% of breast cancer inflicted women had a mastectomy. This time also saw the development of novel therapies for breast cancer including hormone treatments, surgeries and biological therapies. Mammography was also developed for early detection. Scientist then isolated the gene that causes breast cancer: BRCA 1, BRCA 2 and ATM.

Epidemiology

Breast cancer has ranked number one among Indian females with age adjusted rate as high as 25.8% per 100,000 women and mortality 12.7% per 100,000 women. The age adjusted incidence rate of carcinoma of the breast was found as high as 41% per 100,000 women for Delhi, followed by Chennai (37.9), Bangalore (34.4) and Thiruvananthapuram (33.7). Breast cancer projection for India during time periods 2020 suggests the number to go as high as 1797900. Women from less developed regions (883,000 cases) have slightly more number of cases compared to more developed (794,000) regions. Earlier cervical cancer was most common cancer in Indian women but now the incidence of breast cancer has surpassed cervical cancer and is leading cause of cancer death. According to Globocan 2012, India along with U.S and China collectively accounts for almost one third of the global breast cancer burden. India is facing challenging situation due to 11.54% increases in incidence and 13.82% increase in mortality due to breast cancer during 2008-2012.

Causes

- Drinking of excessive alcohol – more than one drink a day
- Use of oral contraceptives – excessive consumption of birth control pills for more than 10 yrs e.g. saheli, mala D
- Exposure to carcinogens - smoking
- Gender – being female
- Heredity – family history of cancer can increased the risk of it. A women who has a first degree female relative (mother, sister or daughter) with breast cancer has almost twice the risk of getting breast cancer. If someone has more than one first degree female relative with a history of breast cancer, her risk is about 3-4 times higher.
- Inherited genes – like BRCA1 and BRCA2. Everyone has BRCA1 and BRCA2 genes. The function of these genes is to repair cell damage and keep breast, ovarian and other cells growing normally. But when these genes contain mutations that are passed from generation to generation, the genes then don't function normally and breast, ovarian and other cancer risk increases.
- Late menopause – after 40 yrs
- Early onset of menstruation – before 12 yrs
- Dense breast tissue – dense tissue make it harder to evaluate the results of mammogram and also associated with increase the risk of breast cancer.
- Greater Exposure to estrogen – women more susceptible to it. Estrogen tells cells to divide; the more the cells divide, the more likely they are to be abnormal in some way, possibly becoming cancerous.
- Obesity – before menopause, being overweight or obese modestly decreases the risk. After menopause, being overweight increases the risk.
- High fat diet – saturated fat is linked to a greater risk of hormone-receptor-positive breast cancer as well as HER2- negative
- Physical inactivity – physically active women have a low risk of breast cancer than inactive women.
- Having never been pregnant -
- Post menopausal hormone therapy – women taking medication that combine estrogen and progesterone in order to treat the sign and symptoms of menopause have an increased risk of breast cancer.
- Having children after 30 yrs of age
- DNA mutation – mistake in the DNA, may provide the wrong set of instructions, leading to faulty cell growth or function. It happens over the course of a lifetime called somatic alterations.
- No breast feeding – as breast feeding makes breast cells more resistant to mutation that can cause cancer. Hence no breast feeding cannot develop resistance.
- Age – women over age 40 are more likely to get it than younger women.



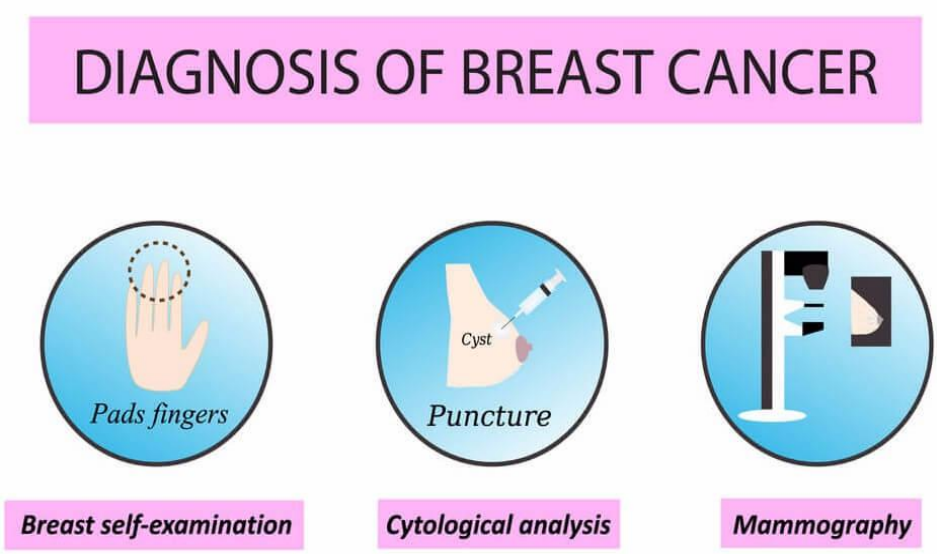
Symptoms

change how the breast looks or feels including -

- A lump in or Early breast cancer usually does not cause symptoms but as tumor grows, it can near the breast or underarm area
- A change in the size or shape of the breast
- A nipple turned inward into the breast
- Fluid discharge from the nipple (bloody)
- Scaly, red or swollen skin on the breast, nipples or areola.
- Skin irritation
- Unintentional weight loss
- Vaginal pain
- Enlarged lymph nodes in the armpits
- Breast pain
- Rashes on breast, itchiness

Diagnosis

❖Self examination – examined by touching the breast with hand.
❖Clinical examination – physical examination of both the breast and lymph nodes in the armpit is done by a doctor, he checks for all the abnormalities. It should be done every 6-12 months
❖Biopsy – removing a sample of breast cells for testing
❖Ultrasound – it is done to detect the formation of any new lumps or cyst or any solid mass
❖Mammography – it uses special X-rays images to detect abnormal growth or changes in the breast tissue.
❖MRI for breast – it is used for detection, assessment, staging and management in selected patients. MRI is more sensitive as compared to mammography.



Treatment

Treatment depends on the stages of cancer. It may consist of chemotherapy, radiation, hormone therapy and surgery.

Surgery

- Mammaplasty – plastic surgery to increase or reduce the size of the breast or to reconstruct a breast.
- Tissue expansion – inserting a balloon under the skin and then gradually expanding it to stretch and grow the skin and surrounding tissue.
- Lymph node dissection – surgical removal of lymph node.
- Lumpectomy – surgical removal of a lump (tumor) in the breast
- Mastectomy – surgical removal of some or all the breast.

Side effects

✓Pain and discomfort
✓Infection
✓Seroma – fluid collection in breast or armpit and cause swelling
✓Lymphoedema.

Medical procedure

Radiation therapy – treatment that uses X-rays and other high energy rays to kill abnormal cells.

Side effects –

Because it affects healthy cells along with cancer cells.
✓skin may become red, pinker or darker over time
✓skin may feel tender, dry, itchy and sore, peel.
✓Swelling of breast
✓Pain in the breast or chest area.
✓Sore throat
✓Tiredness and fatigue
✓Lymphoedema – swelling of arm, hand.
✓Weakening of the bone.

Medications

Estrogen modulator – mimics the effect of oestrogen on various tissues, including the breast, bones and reproductive organs.

Side effects –

- Abnormal vaginal bleeding or discharge
- Pain or pressure in the pelvis
- Leg swelling or tenderness
- Chest pain
- Shortness of breath
- Weakness, tingling in face, arm, leg
- Dizziness
- Headache
- Mood swings

Chemotherapy – kill cell that are growing or multiplying too quickly.

Side effects

- ✓ Effect on blood – Chemotherapy drugs affect the number of healthy blood cells in the body by reducing the ability of bone marrow to make them.
  - Risk of infection – (neutropenia) not having enough WBC's can increase the risk of getting an infection.
  - Anaemia – having too few red blood cells is called anaemia. A blood transfusion may be necessary during the treatment.
  - Bruising and bleeding – drugs can reduce the number of platelets, which help the blood to clot. Patient may bruise more easily, have nosebleeds or gums may bleed when brushed teeth.
- ✓ Hair loss – it is one of the most distressing side effect of chemotherapy
- ✓ Hand-foot syndrome (Palmar-plantar) – usually affects the palms of the hands and soles of the feet, but may have symptoms in other areas such as the skin on the knees or elbows.

common symptoms are –

- burning sensation
- tightness
- redness
- swelling
- numbness
- thick calluses and blisters on palms and soles
- discomfort
- itching
- rash
- difficulty walking or using the hands
- nails lifting from the nails bed
- slow-healing wounds

- ✓ **peripheral neuropathy –** nerves of fingers and toes are damaged
- ✓ **sickness, nausea and vomiting**
- ✓ **mouth and dental problems – causing** :
  - mouth ulcer
  - dry mouth
  - infections
- ✓ **Digestive system –** some people get constipated while others have diarrhea, heartburn, indigestion.
- ✓ **Effect on fertility –** chemotherapy causes changes in the ovaries, which can affect the ability to become pregnant

Hormone based chemotherapy – treats hormone sensitive cancers. It is a treatment that blocks the effect of estrogen on breast cancer cells of ER+ type.

Drugs commonly use for hormone therapy include –

- ✓ Tamoxifen
- ✓ Aromatase inhibitors
- ✓ Goserelin
- ✓ Fulvestrant

Common side effects

✓Hot flushes
✓Night sweats
✓Vaginal dryness
✓Reduced libido (sex drive)
✓Mood changes
✓Joint/muscle pain and stiffness
✓Headaches
✓Tiredness or fatigue
✓Effects on the bones

Specialists

- Oncologist – specializes in cancer
- Radiation oncologist – treats and manages cancer by prescribing radiation therapy.
- Palliative medicine – focuses on improving quality of life for those with severe illnesses.
- Primary care provider (PCP) – Prevents, diagnoses and treats diseases.
- Plastic surgeon – reconstructs defective, damaged or missing body parts.
- Surgeon – performs operations to treat disease.

Sweet wormwood

Scientific name – *Artemisia annua*
Family – Asteraceae
Common name – Artemether, Artemisinin, sweet annie.

Botany –

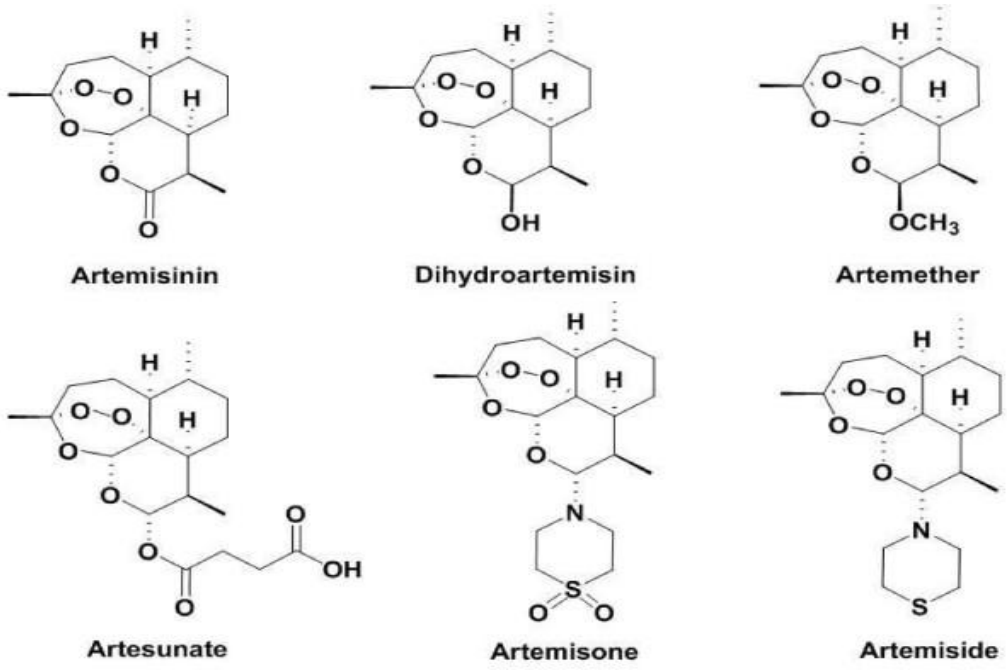
A. annua belongs to the Asteraceae family and is an annual herb native to china, commonly found in the northern parts of the Chahar as part of the natural vegetation. it also grows in several countries including Argentina, Australia, France, Italy, Spain, U.S.

History

The herb A. annua has been used medicinally to treat fevers for more than 2,000 yrs and to treat malaria for more than 1,000 yrs in china. Artemisinin, the most studied derivative, and its semisynthetic derivatives, arteether, artemether, and artesunate, have been clinically evaluated and are the only antimalarial drugs to which clinical resistance has never been documented. Artemisinin was isolated from A. annua in 1972, and its structure was elucidated in 1979.

Chemistry

Numerous and extensive phytochemical investigations have been conducted on the herb. In general, most studies examine the sesquiterpine artemisinin and its derivatives, arteether (lipid soluble ethyl ether derivatives of DA), artemether (lipid soluble methyl ether derivative of artemisinin and is more active than artemisinin), artesunate (water soluble hemisuccinate derivatives of artemisinin), and dihydroartemisinin. Some 38 amorphane and cadinane sesquiterpenes have been isolated from A. annua. Most of the medicinal components of the plants are found in the leaves, stems, flowers, and seeds. The sesquiterpene trioxane lactone, artemisinin which contain a peroxide bridge essential for its medicinal activity, is the main active compound in A. annua. Dihydroartemisinin is the reduced form and the active metabolite of artemisinin. The highest concentration of artemisinin is found in its leaves prior to flowering. Study showed that 40% of artemisinin may be extracted from the aerial parts of the plant by simple tea preparation method. Antiviral activity is associated with sterols sitosterols and stigmasterols of A. annua. The plant's essential oil is composed of linalool, 1,8-cineol, p-cymene, thujone, and camphor. In addition, 17 methoxylated flavones and 4 coumarins have been found in the plant. Flavones such as casticin, chrysoplenetin, chrysophenol-D, and cirsilineol in A. annua are thought to enhance the antimalarial activity of artemisinin.



Pharmacology

Malaria –

Artemisinin and its derivatives are toxic to the malarial parasites at nanomolar concentrations, causing specific membrane structural changes in the erythrocyte stage that kill the parasite. In general, the mechanism of action involves 2 steps:

Activation followed by alkylation. Iron activates artemisinin in to a free radical through an iron-mediated cleavage. The second step, alkylation, involves the formation of covalent bonds between the artemisinin- derived free radicals and the malarial proteins.

Anti-parasitic –

Wormwood is used to eliminate intestinal worms, especially pinworm and roundworms. Pinworms are the most common worm infection with pinworm eggs spread directly from person to person. Roundworms, or nematodes, are parasites that also infect human intestines. Pinworms can cause extreme itching in the anal region while roundworms can cause cough, shortness of breath, abdominal pain, nausea and diarrhea, blood in the stool, weight loss.

Cancer –

The endoperoxide bridge is required for the anticancer activity of artemisinin and its derivatives through the formation of a free radical, which causes molecular damage and cell death.

In vitro data –

Of 9 terpenoids and flavonoids from wormwood, only artemisinin exhibited cytotoxicity toward the human tumor cell lines P-388, A-549, HT-29, MCF-7 and KB.

Artemisinin inhibited the growth of Ehrlich ascites and HeLa tumor cells with an IC_{50} of 0.98 mcmol/L, unlike deoxyartemisinin which lacks the endoperoxide bridge.

Dimmers of dihydroartemisinin were cytotoxic to Ehrlich ascites and HeLa tumor cells. The endoperoxide bridge and an ether linkage played a role in cytotoxicity. Artemisinin derivatives were subjected to the National Cancer Institute 60-cell screening program.

Artemisinin derivatives may be effective in treating cancers that overexpress the transferrin receptors. This mechanism of action involves the influx of iron in tumor cells, which then causes the formation of free radicals from artemisinin that causes molecular damage leading to cell death. A combination of dihydroartemisinin and halotransferrin resulted in rapid cell death in human leukemia cell line with little effect on normal cells. When compared with controls, dihydroartemisinin 200 mcmol decreased MOLT-4 lymphocyte growth 50% in 8 hrs. Cell death reached 100% in 8hrs when cells were exposed to the combination of dihydroartemisinin 200 mcmol and halotransferrin 12 mcmol. Dihydroartemisinin alone and in combination with halotransferrin had a similar effect on lymphocytes or normal cells, but the addition of halotransferrin did not enhance cell death in normal cells.

Artesunate, the semisynthetic derivative of artemisinin, induced apoptosis in human umbilical vein endothelial cells. Overexpression of the bcl-2 protein protects cells from apoptosis, where as activation of Bax drives apoptosis. Artesunate activated Bax, causing cell apoptosis and inhibiting the expression of the bcl-2 protein in a concentration and dose –dependent manner.

Animal data –

Oral administration of ferrous sulphate enhanced dihydroartemisinin cytotoxicity in rats. Fibrosarcoma tissue was implanted in to the right flank of 50 female fisher rats. Eight days after implantation, rats were randomnized to receive 1 of 4 treatments: 1) ferrous sulphate 20 mg/kg in distilled water plus dihydroartemisinin 2mg/kg in peanut oil; 2) distilled water and dihydroartemisinin; 3) ferrous sulphate in distilled water and peanut oil; 4) distilled water and peanut oil. Body weight and tumor size were measured daily for 11 days. Ferrous sulphate was first administered, followed by dihydroartemisinin 6 hrs later. On day 4, treatment was increased to dihydroartemisinin 5 mg/kg until the treatment ended on day 10. The combination of dihydroartemisinin with ferrous sulphate decreased tumor size by 30%. The efficacy of artemisinin in preventing breast cancer development was examined for 40 weeks in rat treated with a single oral dose (50 mg/kg) of 7,12-dimethylbenz[a]anthracene (DMBA). The experimental group (n = 12) of rats fed a powdered rat chow containing 0.02% artemisinin and the control group (n = 22) received plain, powdered food. artemisinin delayed and in some rats prevented breast cancer development. In the artemisinin-fed rats that developed a tumor, tumor size was smaller, and there was a longer duration of time for tumor development when compared with controls. Research has shown artemisinin demonstrates anti-cancer potential even for cells lines that are drug and radiation resistant. Cancer cells typically uptake large amounts of iron than healthy cells in order to proliferate. Many cancer cells have a larger percentage of transferrin receptors on the cell surface. These receptors increase uptake of iron carrying protein transferrin via endocytosis. Once endocytosed, the artemisinin reacts with the iron, killing the cancer cells. Artemisinin and transferring bonded to artemisinin have been found to be extremely potent and selective in causing cancer cell death (Lai, 2005). It is hypothesized that artemisinin's anti-proliferative properties in cancer cell lines originates with artemisinin's interactions with iron and heme intermediaries (Zhang, 2009). Artemisinin has also been found to block estrogen receptors in breast cancer. Research has shown that artemisinin dimmers synthesized with liposomal nanoparticles demonstrate improved anti proliferative effects. The dimer has also been shown to decrease the growth factor receptor activity in triple negative breast cancer, a notoriously hard types to treat through hormone therapy (Zhang, 2013).

The study also showed that treating cells with artemisinin alters the expression of genes involved in development, proliferation and migration of breast cancer cells. In a healthy body, 'tumor suppressor genes' in our cells slow down the rate of spread of cells and protect us from cancer. Treating cells with artemisinin enhanced the expression of these genes. The researchers also observed increased expression of cancer-causing oncogenes after treating the cells with artemisinin.

The study revealed that small dosage of artemisinin was enough to inhibit breast cancer cells. Migration of cancer cells from its origin to other parts of the body causes cancer to spread rapidly, and it is a challenge to stop this. However, the study showed that cells treated with artemisinin had high quantities of E-cadherin, a protein that promotes cell-cell adhesions and thus prevents the migration of cells.

A similar 2015 comprehensive study on the cancer-healing effects of artemisinin conducted by Worcester Polytechnic Institute in the UK found that, "Artemisinin reacted with iron to form free radicals which cause cell death. The increased iron uptake of cancer cells leaves them susceptible to the free radicals artemisinin creates."

According to the Washington study report published in the journal *Cancer*, within 16 hours, all cancer cells exposed to doused holotransferrin perished with 16 hours.

"Most currently available drugs are targeted to specific cancers," Lai said. "This compound works on a general property of cancer cells, their high iron content."

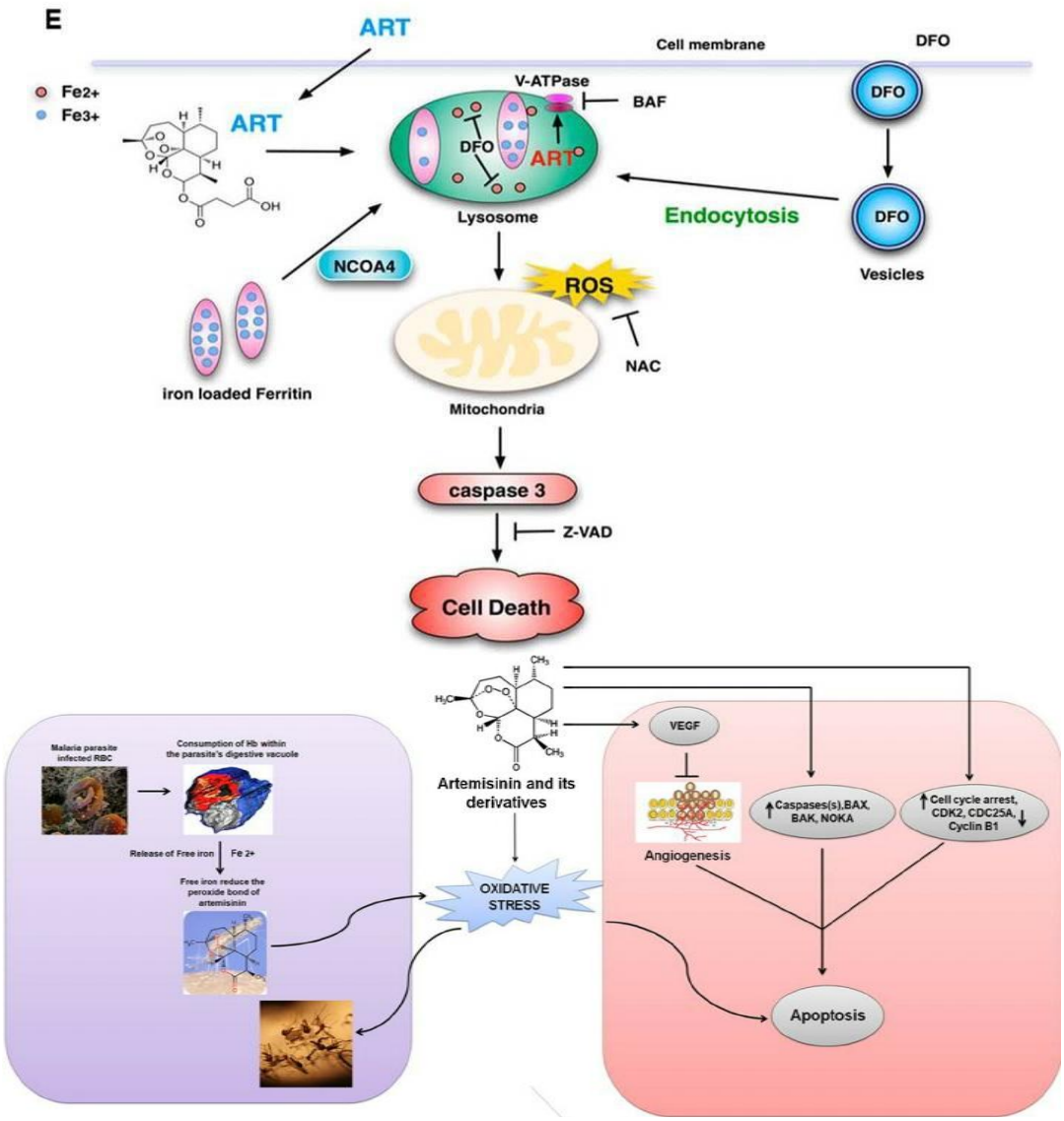
Breast cancer cells in particular can sometimes contain up to 15 times more iron receptors than surrounding cells, which is why this iron-artemisinin duo may have an even more profound effect on breast cancer.

The Worcester report states that "further research of the plant has found that the plant [itself as opposed to just artemisinin extract] may potentially kill cancer cells and behave as an antagonistic agent for estrogen-receptors in breast cancer."

The Worcester report also found that artemisinin delivered through liposomal nanoparticles, which become more water-soluble as pH decreases, can greatly improve the "anti-proliferative effects of the artemisinin on ER-positive breast cancers." Lower pH environments are the likeliest places for cancer tumors to grow.

The exciting finding by University of Washington researchers provides further proof of the powerful effect of artemisinin on cancer and the powerful effect of combining naturally-occurring herbals with other essentials, such as iron, to combat cancer cell growth.

Mechanism of action



Artemisinin, the natural endoperoxide of A. annua, and its semisynthetic derivatives are considered to be the primary active constituents for antimalarial and anticancer activity. Also the polymethoxyflavonoids are indicated as important compounds with potential anticancer activity. Different genes which influence the sensitivity or the resistance to treatment have been identified. these genes could potentially function as the markers indicating the expected efficacy of a clinical therapy. In contrast to popular belief that the cytotoxic activities would only be due to the nonspecific generation of reactive oxygen species, it has become clear that artemisinin- related endoperoxide additionally have various specific molecular targets and can significantly influence the expression of key regulatory proteins of cell cycle. Artemisinin- related endoperoxides were found to significantly inhibit angiogenesis and also to induced apoptosis. Iron plays a crucial role in the cytotoxic activities of the artemisinin- related endoperoxide through the generation of both ROS and carbon- centered radicals. In general the addition of the iron has been shown to enhance both the cytotoxicity and selectivity of treatment.

AMDT is a sesquiterpene found in the hairy roots of A. annua. It has been demonstrated that it induces apoptosis through the mitochondrial dependent pathway in human lung 95-D cells. Cytotoxicity of this compound also found in ovary, liver, and cervix cancer cells.

Dose

Clinical trial and WHO documentation include oral and intravenous dosage forms of artesunate. Parenteral preparations are available for oil-soluble artemether and the newly marketed artemotil. Treatment includes administering four tablets initially, repating dosage in 8hrs, and then taking twise daily for the next two days. The combination has proven to be effective, with reported cure rates upto 98%.

The therapeutic dose ranges from 200mg a day upto 1,000mg a day depending on cancer type and the source of herb. In laboratories studies, significant cell toxicity is shown to have been affected at dosage as little as 1-2 mg/kg body weight. The exect dosage is highly controversial. In addition to the lack of clinical trials and individual variations, the dosage is highly dependent on the purity and potency of the herb it self. The same 100 mg capsule from one manufacturer may have different and varied effects from other manufacturer.

Artemisinin should always be taken with food. Cod liver oil, cottage cheese , or fish oil may be administered at the same time to enhance absorption. Generally, 400-800mg/day can be used at least 6-12 months.

Contraindications

Avoid use in women during first trimester of pregnancy because of potential teratogenicity. Artemisinin derivatives, in particular artemether have a toxic effect on embryos.

Adverse reactions

Clinical trial data documents GI complaints such as abdominal pain, diarrhea, nausea, and vommeting. Rashes have been reported as well as pain and abscess development at the injection site. Metabolic changes include hypoglycemia. Cardiovascular changes include bradycardia and prolongation of the QT interval.

Conclusion

Sweet wormwood extract, Artemisinin, are largely non toxic, with related compounds having been administered to over 2 million patients; both children and adult, world-wide without reports of significant serious side effects, and artemisinins are very inexpensive when compared to conventional cancer drugs.

Studies into the effectiveness of Sweet Wormwood as a cancer treatment are ongoing, but the outlook is good. The research indicates that this treatment may be particularly effective for more aggressive forms of cancer, where cell division and replication is more rapid and the cancer cells will be more dependent on iron to survive and thrive.

While the current research is concentrating on breast cancer, all indications point to Sweet Wormwood therapy being effective against a wider range of cancers, including pancreatic cancer and leukemia, colonal.

Once again it seems that the natural world holds the answers to restoring, and maintaining, our total health. Sweet Wormwood is just the latest rediscovery that illustrates how much we have forgotten about the nature of natural healing.

The plants and herbs that form the garden of God's creation hold the secrets we need to remain healthy and cancer free.

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