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A REVIEW ON ANTICARCINOGENIC ACTIVITY OF "*CENTELLA ASIATICA*"

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ABSTRACT

In recent times, focus on plant research has increased all over the world. *Centella asiatica* is an important medicinal herb that is widely used in the orient and is becoming popular in the West. Triterpenoid, saponins, the primary constituents of *Centella asiatica* are manly believed to be responsible for its wide therapeutic actions. Apart from wound healing, the herb is recommended for the treatment of various skin conditions such as leprosy, lupus, varicose ulcers, eczema, psoriasis, diarrhoea, fever, amenorrhea, diseases of the female genitourinary tract and also for relieving anxiety and improving cognition. The present review attempts to provide comprehensive information on pharmacology and its anticarcinogenic activirty of the plant. As the plant shows the anticarcinogenic effect where the crude extract was found to be curing the ehrlich ascites tumor in mice and Asiatic acid helps in the treatment of skin cancer.

KEYWORD: Centella asiatica, Asiatic acid, cancer, asiaticoside, Bacopa monneri, Cytotoxic, Antitumour, breast cancer, ehrlich ascites tumor in mice.

INTRODUCTION

Centella asiatica

Kingdom : plantae

Order : Apiales

Family : Apiaceae

Genus : Centella

Species : C. asiatica

Centella asiatica, commonly known as centella, asiatica pennywort or Gotukola is a herbaceous, frost-tenderplant in the flowering plant familyApiacea.[1] It is native to the wetlands in Asia.[2][3] It is used as culinary vegetable and as a medicinal herb.

Centella asiatica has been used as a medicinal herb for thousands of years in India, China, Sri Lank, Nepal and Madagascar. Centella asiatica is one of the chief herb for treating skin problem, to heal wounds for revitalising the nerves and brain cells as primary known as a "brain food" in India.

Centella asiatica(Linn.) Urban system synonym hydrocotyle asiatica linn. Commonly known as Indian pennywort, belongs to the family Apiaceae(previously known as unbelliferae). in India the plant was earlier confused with *Bacopa monnieri* as both plants have been sold in the market by the same name "brahmi". However, the controversy has been resolved and it is concluded that brahmi is *B.monnieri* and mandookaparni is *C. Asiatica.*[4]

According to the report of export and import Bank of India *Centella asiatica* is one of the important medicinal plants in the international market of medicinal plant. However, the wild stock of this plant species has been markedly depleted, because of it large scale and unrestricted exportation coupled with limited cultivation and insufficient attempts for its replacement has been made moreover, it has been listed at 3:10 plant species by the international Union for conservation of nature and natural resources (IUCN)[5], and also as an endangered species.[6][7]

Morphological features

Centella asiatica (L.) Is a prostrate, faintly aromatic stoloniferous, perennial, creepersi herb, curtain height up to 15cm (6inches).

Stem is to glamorous stated routing at the notes *centella asiatica* processes extensively in shady, marshy, dam and wet places such as paddy field, rice banks forming a dense green carpet.[8]

The leaves, 1-3 from each node of stem long petioles, 2-6cm long and 1.5 - 5 cm wide, orbicular renniform, sheathing leaf base, crenate margin, glabrous on both sides.

Flower iron fascicled umbels, each umbel consisting of 3-4 white to purple and pink flowers, flowering occurs in the month of April- June.

Fruits are born throughout the growing season in approx 2 inch long, oblong, globular in shape and strongly thickned pericarp. Seeds have pedulous embryo which are laterally compressed.

Centella asiatica found throughout tropical and subtropical regions of India up to an altitude of 600m.

Chemical constituents

The scientific studies has to the claim of Indian system of medicine and a variety of biochemical components i.e., secondary metabolites has been found in *centella asiatica* and so far it is vividly medicinally important in modern medicine system also, *Centella asiatica* is reported to have following types of chemical compounds:-

Triterpenoids: Include asiatcoside, centelloside, Madecossoside, thankuniside, isothankunic acid, Centellose, asiatic, centellic and madecassic acids and Brahmoside, brahminoside, brahmicacid, the structure of their genin, brahmic acid (m.p. 293°) has been established as 2,6-hydroxy, 23-hydroxy-methyl ursolic acid. Asiaticoside and madecossoside predominated in the leaves with less in roots.[9]

Volatile and Fatty acids: The fatty oil consists of glycerides of palmitic, stearic, lignoceric, oleic, linoleic and linolenic acids.[10]

Alkaloids: An alkaloid, hydrocotylin (C_{22} H_{33} NO_8) has been isolated from the dried plants.[10]

Glycosides: Asiaticoside, madecossoside and centelloside have been isolated from the plant parts. On hydrolysis, these glycosides yield the triterpene acids, asiatic acid, madegascaric acid[11-13] and centellic acid, except this Centella acid, all the above are present in free form in the plant.

Flavanoids: Flavanoids, 3-glucosylquercetin, 3-glucosylkaemferol and 7-glucosylkaemferol have been isolated from the leaves.[12] The plant is reported to contain tannins, sugars, inorganic Acids[14] and resin[10], amino-acids, viz. aspartic acid, glycine, glutamic acid, α-alanine and phenylalanine[15] The total ash contains chloride, sulphate, phosphate, iron, calcium, magnesium, sodium and potassium. The leaves are rich in vitamins such as vit.B, vit.C[16] and vit.G.

PHARMACOLOGICAL USES

Several research workers have reported different biological activities of C. asiatica. These have been given under following headings;

- Wound Healing
- Cytotoxic and Antitumour
- Memory Enhancing
- Cardioprotective
- Radioprotective
- Antidepressant
- Sliming
- Striaegravidarum
- Immunomodulating
- Antiprotozoal
- Mental-retardation
- Antitubercular and Antileprotic

CANCER

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body.[17][18] These contrast with benign tumors, which do not spread to other parts of the body.[18]

Cancers are a large family of diseases that involve abnormal cell growth with the potential to invade or spread to other parts of the body.[17][18] They form 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.[19] [20]

All tumor cells show the six hallmarks of cancer. These characteristics are required to produce a malignant tumor. They include:[21]

- 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[21]

The progression from normal cells to cells that can form a detectable mass to outright cancer involves multiple steps known as malignant progression.[21] [22]

Signs and symptoms

When cancer begins, it produces no symptoms. Signs and symptoms appear as the mass grows or ulcerates. The findings that result depend on the cancer's type and location. Few symptoms are specific. Many frequently occur in individuals who have other conditions. Cancer is a "great imitator". Thus, it is common for people diagnosed with cancer to have been treated for other diseases, which were hypothesized to be causing their symptoms.[23]

People may become anxious or depressed post-diagnosis. The risk of suicide in people with cancer is approximately double.[24]

Causes

The majority of cancers, some 90-95% of cases, are due to genetic mutations from environment and lifestyle factor.[2] The remaining 5–10% are due to inherited genetics. [2]Environmental, as used by cancer researchers, means any cause that is not inherited genetically, such as lifestyle, economic and behavioral factors and not merely pollution.[25] Common environmental factors that contribute to cancer death include tobacco (25–30%), diet and obesity (30–35%), infections (15–20%), radiation (both ionizing and non-ionizing, up to 10%), stress, lack of physical activity and pollution.[2][26] Excepting the rare transmissions that occur with pregnancies and occasional organ donors, cancer is generally not a transmissible disease.[27]

Heredity

The vast majority of cancers are non-hereditary (sporadic). Hereditary cancers are primarily caused by an inherited genetic defect. Less than 0.3% of the population are carriers of a genetic mutation that has a large effect on cancer risk and these cause less than 3–10% of cancer.[28] Some of these syndromes include: certain inherited mutations in the genes *BRCA1* and *BRCA2* with a more than 75% risk of breast cancer and ovarian cancer,[28] and hereditary nonpolyposis colorectal cancer (HNPCC or Lynch syndrome), which is present in about 3% of people with colorectal cancer,[29] among others.

Hormones

Some hormones play a role in the development of cancer by promoting cell proliferation.[30] Insulin-rlike growth factors and their binding proteins play a key role in cancer cell proliferation, differentiation and apoptosis, suggesting possible involvement in carcinogenesis.[30]

Hormones are important agents in sex-related cancers, such as cancer of the breast, endometrium, prostate, ovary and testis and also of thyroid cancer and bone cancer.[30] For example, the daughters of women who have breast cancer have significantly higher levels of estrogen and progesterone than the daughters of women without breast cancer. These higher hormone levels may explain their higher risk of breast cancer, even in the absence of a breast-cancer gene.[30] Women who take hormone replacement therapy have a higher risk of developing cancers associated with those hormones.[30] On the other hand, people who exercise far more than average have lower levels of these hormones and lower risk of cancer.[30] Osteosarcoma may be promoted by growth hormones.[30] Some treatments and prevention approaches leverage this cause by artificially reducing hormone levels and thus discouraging hormone-sensitive cancers.[30]

Genetics

Cancer is fundamentally a disease of tissue growth regulation. In order for a normal cell to transform into a cancer cell, the genes that regulate cell growth and differentiation must be altered.[32]

The affected genes are divided into two broad categories. Oncogenes are genes that promote cell growth and reproduction. Tumor suppressor genes are genes that inhibit cell division and survival. Malignant transformation can occur through the formation of novel oncogenes, the inappropriate over-expression of normal oncogenes, or by the under-expression or disabling of tumor suppressor genes. Typically, changes in multiple genes are required to transform a normal cell into a cancer cell.[33]

Genetic changes can occur at different levels and by different mechanisms. The gain or loss of an entire chromosome can occur through errors inmitosis. More common are mutations, which are changes in the nucleotide sequence of genomic DNA.

Large-scale mutations involve the deletion or gain of a portion of a chromosome. Genomic amplification occurs when a cell gains copies (often 20 or more) of a small chromosomal locus, usually containing one or more oncogenes and adjacent genetic material. Translocation occurs when two separate chromosomal regions become abnormally fused, often at a characteristic location. A well-known example of this is the Philadelphia chromosome, or translocation of chromosomes 9 and 22, which occurs in chronic myelogenous leukemia and results in production of the BCR-ablfusion protein, an oncogenic tyrosine kinase.

Small-scale mutations include point mutations, deletions, and insertions, which may occur in the promoter region of a gene and affect its expression, or may occur in the gene's coding sequence and alter the function or stability of its protein product. Disruption of a single gene may also result fromintegration of genomic material from a DNA virus or retrovirus, leading to the expression of *viral* oncogenes in the affected cell and its descendants.

Replication of the data contained within the DNA of living cells will probabilistically result in some errors (mutations). Complex error correction and prevention is built into the process and safeguards the cell against cancer. If a significant error occurs, the damaged cell can self-destruct through programmed cell death, termed apoptosis. If the error control processes fail, then the mutations will survive and be passed along to daughter cells.

Some environments make errors more likely to arise and propagate. Such environments can include the presence of disruptive substances called carcinogens, repeated physical injury, heat, ionising radiation or hypoxia.[34]

Metastasis

Metastasis is the spread of cancer to other locations in the body. The dispersed tumors are called metastatic tumors, while the original is called the primary tumor. Almost all cancers can metastasize.[35] Most cancer deaths are due to cancer that has metastasized.[36]

Metastasis is common in the late stages of cancer and it can occur via the blood or the lymphatic system or both. The typical steps in metastasis are local invasion, intravasation into the blood or lymph, circulation through the body, extravasation into the new tissue, proliferation and angiogenesis. Different types of cancers tend to metastasize to particular

organs, but overall the most common places for metastases to roccur are the lungs, liver, brain and the bones.[35]

Diagnosis

Most cancers are initially recognized either because of the appearance of signs or symptoms or through screening. Neither of these leads to a definitive diagnosis, which requires the examination of a tissue sample by a pathologist. People with suspected cancer are investigated with medical tests. These commonly include blood tests, X-rays, (contrast) CT scarns and endoscopy.

The tissue diagnosis from the biopsy indicates the type of cell that is proliferating, its histological grade, genetic abnormalities and other features. Together, this information is useful to evaluate the prognosis and to choose the best treatment.

Cytogenetics and immunohistochemistry are other types of tissue tests. These tests provide information about molecular changes (such asmutations, fusion genes and numerical chromosome changes) and may thus also indicate the prognosis and best treatment.

Classification

Cancers are classified by the type of cell that the tumor cells resemble and is therefore presumed to be the origin of the tumor. These types include:

Carcinoma: Cancers derived from epithelial cells. This group includes many of the most common cancers and include nearly all those in the breast, prostate, lung, pancreas and colon.

Sarcoma: Cancers arising from connective tissue (i.e. bone, cartilage, fat, nerve), each of which develops from cells originating in mesenchymal cells outside the bone marrow.

Lymphoma and leukemia: These two classes arise from hematopoietic (blood-forming) cells that leave the marrow and tend to mature in the lymph nodes and blood, respectively.[37]

Germ cell tumor: Cancers derived from pluripotent cells, most often presenting in the testicle or the ovary (seminoma and dysgerminoma, respectively).

Blastoma: Cancers derived from immature "precursor" cells or embryonic tissue.

Cancers are usually named using *-carcinoma*, *-sarcoma* or *-blastoma* as a suffix, with the Latin or Greek word for the organ or tissue of origin as the root.

Prevention

Cancer prevention is defined as active measures to decrease cancer risk.[38] The vast majority of cancer cases are due to environmental risk factors. Many of these environmental factors are controllable lifestyle choices. Thus, cancer is generally preventable.[39] Between 70% and 90% of common cancers are due to environmental factors and therefore potentially preventable.[40]

Greater than 30% of cancer deaths could be prevented by avoiding risk factors including: tobacco, excess weight/obesity, poor diet, physical inactivity, alcohol, sexually transmitted infections and air pollution.[41] Not all environmental causes are controllable, such as naturally occurring background radiation and cancers caused through hereditary genetic disorders and thus are not preventable via personal behavior.

Screening

Unlike diagnostic efforts prompted by symptoms and medical signs, cancer screening involves efforts to detect cancer after it has formed, but before any noticeable symptoms appear.[42] This may involve physical examination, blood or urine tests or medical imaging.[42]

Cancer screening is not available for many types of cancers. Even when tests are available, they may not be recommended for everyone. *Universal screening* or *mass screening* involves screening everyone.[43] *Selective screening* identifies people who are at higher risk, such as people with a family history.[43] Several factors are considered to determine whether the benefits of screening outweigh the risks and the costs of screening.[42]

Chemotherapy

All chemotherapy regimens require that the recipient be capable of undergoing the treatment. Performance status of often used as a measure to determine whether a person can receive chemotherapy, or whether dose reduction is required. Because only a fraction of the cell in a tumor die with each treatment (fractional kill), repeated doses must be administered to continue to reduce the size of the tumor in cancer.

1. Chemotherapy (often abbreviated to **chemo** and sometimes **CTX** or **CTx**) is a type of cancer treatment that uses one or more anti-cancer drugs (chemotherapeutic agents) as part of a standardised chemotherapy regimen. Chemotherapy may be given with a curative intent (which almost always involves combinations of drugs), or it may aim to

prolong life or to reduce symptoms(palliative chemotherapy). Chemotherapy is one of the major categories of the medical discipline specifically devoted to pharmacotherapy for cancer, which is called *medical oncology*.

2. The term *chemotherapy* has come to connote non-specific usage of intracellular poisons to inhibit mitosis, cell division. The connotation excludes more selective agents that block extracellular signals (signal transduction). The development of therapies with specific molecular or genetic targets, which inhibit growth-promoting signals from classic endocrine hormones (primarily estrogens for breast cancer and androgens for prostate cancer) are now called hormonal therapies. By contrast, other inhibitions of growth-signals like those associated with receptor tyrosine kinases are referred to as targeted therapy.
3. Importantly, the use of drugs (whether chemotherapy, hormonal therapy or targeted therapy) constitutes *systemic therapy* for cancer in that they are introduced into the blood stream and are therefore in principle able to address cancer at any anatomic location in the body. Systemic therapy is often used in conjunction with other modalities that constitute *local therapy* (i.e. treatments whose efficacy is confined to the anatomic area where they are applied) for cancer such as radiation therapy, surgery or hyperthermia therapy.
4. Traditional chemotherapeutic agents are cytotoxic by means of interfering with cell division (mitosis) but cancer cells vary widely in their susceptibility to these agents. To a large extent, chemotherapy can be thought of as a way to damage or stress cells, which may then lead to cell death if apoptosis is initiated. Many of the side effects of chemotherapy can be traced to damage to normal cells that divide rapidly and are thus sensitive to anti-mitotic drugs: cells in the bone marrow, digestive tract and hair follicles. This results in the most common side-effects of chemotherapy: myelosuppression (decreased production of blood cells, hence also immunosuppression), mucositis (inflammation of the lining of the digestive tract), and alopecia (hair loss). Because of the effect on immune cells (especially lymphocytes), chemotherapy drugs often find use in a host of diseases that result from harmful over activity of the immune system against self (so-called autoimmunity). These include rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, vasculitis and many others.

Anticarcinogenic activity of plant extract (Centella asiatica)

The asiatic acid has shown cytotoxic activity on fibroblast cells and induces apoptosis in different sorts of cancer.

C. asiatica extract showed an obvious dose dependent inhibition of cell proliferation in breast cancer cells, MCF-7. In MCF-7cells, a concentration dependent decrease in cell viability (by MTT assay) on treatment with different concentrations of *C. asiatica* extract. However, in other cell lines such as HeLa, HepG2 and SW 480 we did not observe a concentration dependent decrease in cell viability. We observed a higher LD50 for MECA that may be due to the synergistic action of both cytotoxic and cytoprotective components present in the extract. Study showed nuclear condensation, a characteristic apoptotic feature visualized by Ethidium Bromide/Acridine Orange staining upon treatment with MECA. The binding of Annexin V to the phosphatidyl serine of the cell membrane emphasize the ability of the extract to initiate apoptosis. The observed loss of mitochondrial membrane potential suggests the involvement of an intrinsic pathway of apoptotic induction by MECA. DNA strand breaks induced by MECA, a characteristic feature in programmed cell death was also observed. Even though we have observed a higher LD50 value with MECA, asiatic acid (10 μM), one of the active components of MECA killed ~95% cells. The individual components of the extract may show opposing roles and it may be important in making the crude drug less effective than the isolated component. In this connection the increased cell death by means of Asiatic acid may due to ROS generation (Park et al., 2005; Yoshida et al., 2005). In contrast, methanolic extract of the same plant is known to have antioxidant properties (Jayashree et al., 2003).

CONCLUSION

This is very much a proof by the study and tests on cells and tissue, the plant shows the anticarcinogenic effect where the crude extract was found to be curing the ehrlich ascites tumor in mice and Asiatic acid helps in the treatment of skin cancer. The extract showed an obvious dose dependent inhibition of cell proliferation in breast cancer cells, MCF-7. In MCF-7cells, a concentration dependent decrease in cell viability (by MTT assay) on treatment with different concentrations of *C. asiatica* extract.

The extract of centella asiatica containing Asiatic acid showed the anticarcinogenic effect but the individual components of the extract may show opposing roles and it may be important in making the crude drug less effective than the isolated component. In this connection the

increased cell death by means of Asiatic acid may due to ROS generation (Park et al., 2005; Yoshida et al., 2005). In contrast, methanolic extract of the same plant is known to have antioxidant properties (Jayashree et al., 2003).

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