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CALCIUM SIGNAL MODULATION FOR CANCER CELL APOPTOSIS – A SIDDHA NANOTHERAPEUTIC APPROACH

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Abstract: ***In recent days, Siddha system of medicine has emerged as an arena for researches especially in the management of cancer. Nearly 14.5 lakhs estimated number of people are being reported to be affected with cancer in India every year. Researches on cancer biology have concluded that alteration in calcium channel pump is a main characteristic feature of cancers and Calcium has ability to regulate both cell death and proliferation. To eliminate cancer cell from the human body is one of the most important challenges for immune system. Thus, the therapy that have the ability to modulate calcium signaling in the cancer cells to regulate proliferation and apoptosis can be beneficial to have target action on cancer cells. The drug with Calcium helps to prevent, suppress or reverse the process of carcinogenesis before development of malignancy. This article deals with intervention of Calcium in promoting cancer cell apoptosis and validation of Calcium rich siddha therapy such as Man kombu parpam, Anda vodu parpam, Nandu odu parpam, Aamai odu parpam, Sangu parpam, Anda chunnam which has anticancer activity. This review critically explores the novelty behind the traditional use of siddha medicine for the effective management of cancer.***

Keywords: Calcium, Cancer, Man kombu parpam, Anda vodu parpam, Nandu odu parpam, Aamai odu parpam, Sangu parpam, Anda chunnam.

1. INTRODUCTION

Immune system plays an important role in killing cancer cells. Ca involves in both activation of immune system and apoptosis of cancer cells. Ca has the potential to modulate proliferation and cancer cell apoptosis. Thus, the increased intracellular calcium involves in elevating the immune response as it is most likely Ca dependent which tends to kill cancer cells. Nanoparticles can easily enter into the cells in different ways such as penetration, endocytosis and semi endocytosis. Nanoparticle have to cross the cell membrane to enter into the cells. Unique feature of siddha medicine is vast. Preparation of Siddha system of medicine such as *parpam*, *chenduram*, *chunnam*, *kattu* and *pathangam* are the lifesaving miraculous Nano medicine, which were used by Siddhars on the basis of nanotechnology. Recent scientific researches where explored that this nanoparticle plays a major role in treating various diseases such as cancer. Siddha medical system has the theoretical references

and practical application of nanoparticle from many centuries. This article explains how Siddha system of medicine which are in nanoparticle size and rich in Ca helps to kill the cancer cells and thereby treating cancer in natural way.

Entry of nanoparticle into the cell

To enter into the cell, the nanoparticle have to cross the cell membrane. There are 3 ways with which nanoparticle may enter into cells. They are penetration endocytosis and semi endocytosis.

When the membrane starts wrapping up the nanoparticle, endocytosis occur. This endocytosis occurs with the help of components called receptors. With the help of receptor, nanoparticle is completely wrapped in cell membrane known as vesicle. In semiendocytosis, the nanoparticle is wrapped up slowly not fully.

Penetration

When a particle is too small, it can easily enters through the cell membrane. This process is known as penetration.

Nanoparticle in Siddha medicine

In modern nanotechnology, various techniques are used to synthesize nanoparticles like attrition, pyrolysis, inert gas condensation, radiation chemistry, hydrolysis, polycondensation etc. In siddha medical system, Nano medicines were prepared by triturating the raw drug with herbal juice then subjected to incineration in earthen pot for certain hours, coded and again triturated [1].

Many siddha Nano medicine are already in a clinical practice and it is very effective and potential. According to current nanoscience, nanotechnology is in relation to width of human hair about 60-80,000 nanometer wide. This concept is very old which was already explained in thirumandhiram and thirukural. Nanoparticle having several properties such as ultra-small size, greater surface area per unit weight and larger particle with high reactivity. They can deliver drug at cellular and nuclear level. Nanoparticle can be delivered through different routes. Thus, the Nano medicine preparation is economic and highly therapeutic when executed with intense knowledge[2].

Intervention of Ca in killing cancer cells

Immune system plays a significant role in inhibiting the transformation of normal cell to cancer cell. Recent researcher have concluded that calcium has the potential to modulate the proliferation and involves in the apoptosis of cancer cells.

Raise of intracellular calcium concentration is required for efficient CTL (Cytotoxic T-Lymphocyte) and NK(Natural Killer) cell function and thus for killing the target in case of cancer.

Dendric cell scan the human body and phagocytose the foreign antigens through cytotoxic T-lymphocyte. Natural killer cells are enriched in sinusoidal region of liver and in red pulp of spleen under resting condition. During infection they proliferate and mature from resting to an effector state, which increase their responsiveness and killer effectiveness. CTL cannot kill because they do not express perforin. But the combination of CTL and NK cells effectively attack the cancer cell because they complement each other.

When the calcium is given intracellularly, the role of calcium influx magnitude through ORAI channels for efficient target killing. When calcium entry is elevated the number of lytic granules are released upon the target cell, assuring the killing of cancer cells.

Thus, the raise of intracellular Ca is in the form of nanoparticle which involves the activation of CTL and NK cells to form immune synapse with cancer cells. This results in the release of lytic granules filled with perforin. FAS ligand receptor called as death receptor is activated which results in CTL involves in reacting on MHC antigen present on the target cell and NK cell involves in killing of cancer cells[3].

Immunotherapy

- In modern system of medicine to cure cancer in an effective manner, immunotherapy is being conducted.
- Immunotherapy is also called as biologic therapy which helps to boost the body's natural defence to fight against cancer. In this method, substance made by the body or laboratory is used to improve the immune system function [4].
- There are several type of immunotherapy includes,
    - Monoclonal antibodies
    - Non-specific immunotherapy.
    - Oncolytic virus therapy
    - T cell therapy
    - Cancer vaccine

i) Monoclonal antibodies

Any harm or entry of foreign agents into the body, the immune system responds by releasing the antibody. These antibodies are protein which flight against infection. Monoclonal antibodies are a specific type of therapy made in laboratory and it can be used in various ways. These monoclonal antibodies helps in blocking the abnormal protein in cancer cells. Some antibodies work by releasing the brakes on the immune system so it can destroy cancer growth. This pathway is known as "Immune checkpoints". Many cancer cells escapes through this pathway[5]. Immune system involves in killing the cancer cells by blocking this pathway with specific antibodies known as immune checkpoint inhibitors[6]. Some of the examples of immune checkpoint inhibitors are

- Ipilimumab(yervoy)
- Nivolumab(Opdivo)
- Avelumab(Bavencio)
- Durvalumas(Imfinzi)

ii) Non-specific immunotherapies

Non-specific immunotherapies helps in elevating the immune system to kill the cancer cells. It is given after specific cancer treatment such as chemotherapy, radiotherapy etc. Some non-specific immunotherapy are given as main cancer treatment[7]. Common non-specific immunotherapy are,

a) Interferon

Interferon enhances the immune system to fight against cancer and slows down the cancer growth. Interferons which are made in laboratory are called interferon alpha such as Referon-A [2a], Intron-A[2b], Alferon[2A]. It is the most common type used in cancer treatment. Side effects of interferon are flu, infection, rashes and thinning of hair.

b) Interleukins

It also helps the immune system to destroy the cancer cells. Interleukin-2, 1L-2 or aldesleukin (proleukin). It involves in treating kidney cancer, skin cancer and also melanoma. Side effects are weight gain and low blood pressure.

iii) Oncolytic virus therapy

In oncolytic virus therapy, genetically modified and engineered virus are infected to kill the cancer cells. Primarily, the virus is infected into tumor and it copies itself then the cell burst and die. While killing the cell, it releases specific substance called antigen. This antigen enhances the immune system and helps in killing the cancer cell. This virus does not enter healthy cells. Side effects of this treatment are fatigue, fever, chills, nausea, flu and pain at injection site [8].

iv) T-cell therapy

T-cell plays a major role in immune system to fight against infection. In this therapy, T-cells of the patient are removed and engineered laboratory. This engineered T-cells have the receptors. This receptor have the tendency to recognize the cancer cells. Thus, this engineered T-cells are grown in large number in laboratory and injected into patient. It has the tendency in recognizing and killing the cancer cells. This type of treatment is known as chimeric antigen receptor [CAR] T-cell therapy.This therapy is widely tested for prostate cancer [9].

v) Cancer vaccine

Vaccine helps in triggering the immune system to recognize and destroy the antigen. Continued vaccination increases the probability of high antibody response associated with better survival[10]."Cancer vaccine are of two types, they are,

- Prevention vaccine
- Treatment vaccine

Presence of Calcium in Siddha therapeutics

Ca signaling in tumor cells and in T-cells depends upon the activity of Ca channel. When normal cells are changed into cancer cells, they are usually attacked by immune system. Ca plays a major role in elevating the immune response against cancer. Calcium has the efficiency of finding cancer cells, for example during immune cell migration, chemotaxis and adherence to target cells. Thus, the researcher have concluded that calcium has the potential to modulate proliferation and apoptosis of cancer. Siddha system of medicine consists of several formulation such as parpam, chunnam that can deliver Ca in the form of nanoparticle. Thus when the Ca is given intracellularly as a nanoparticle, it involves in activation of CTL(Cytotoxic Tlymphocytes) and NK(Natural Killer) cell function and thus kills cancer cells. Certain siddha medicines which helps in treating the cancer are Nandu odu(Crab shell) parpam, Anda odu(Egg shell) parpam, Anda odu chunnam, Aamai Odu(Turtle shell) parpam. Amount of calcium present in crab shell is 40-70% [11],conch shell is 33-40% [12],egg shell is 95% [13]]turtle shell is 40-50% [14].Amount of calcium with reference is given in the below table,

Advantage of Siddha therapeutics

- Nanoparticle easily absorbed by cells
- Increased life span
- Cost efficiency compared to immunotherapy

i) Nanoparticle easily absorbed by cells

Nanoparticle having various properties such as ultra-small size, greater surface area per unit weight than large particle and high reactivity. Stability of nano

particle after the possibility of oral administrated. They ensure greater degree of cell specificity improves efficacy and minimize adverse effect.

ii) Increased life span

When they are in dangerous condition, without any awareness and knowledge people taking chemotherapy and radiotherapy. However it gives a temporary relief but it reduce their life span. But if we treat this in natural way by elevating the immune system, it involves in apoptosis of cancer cells and thus probably we can increase the life span.

iii) Cost efficiency compared to immunotherapy

Oncology drug prices are increasing day by day. It also cures the cancer in natural way by enhancing the immune system. But the drawback behind it is only rich people can take this remedy as it costs almost in crores. At present, oncology drug prices elevated from $12,500 to $13,100. Others who are not sufficient to do this are taking radiotherapy and chemotherapy and reducing their life span without any awareness. In our siddha system, we are doing the same concept which kills the cancer cells by elevating immune system that too with cost efficiency[15].

2. CONCLUSION

To eliminate the cancer cells from human body is most important challenge for immune system. Thus, the siddha drug with Ca helps to strengthen the immune system and prevent, suppress or reverse the process of carcinogenesis. I have expressed my opinion regarding the supremacy of siddha medicine over all other medicinal system. For instance all other modes of treating cancer is very costly and hindering the human system .siddha medicine is affordable and has access to the cancer cells there by curing the disease to the core. Siddha speeds up the recovery process of cancer cells increasing the life span of the diseased people. On the contrary, other medicinal methods are tedious troubling the patient who are already suffering a lot. Siddha medicine uses nano therapy to increase the immune system of the patient by easily reacts with the body and treats the disease in natural way. Considering the pros and cons of all system siddha system stands out as it has minimum side effects. Identifying the root cause of the disease is the distinction of this medicine over other methods.

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