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Management of Cancer with a Novel Higher Order Medicines in Siddha

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ABSTRACT

Cancer is considered as one of the most common causes of mortality in Worldwide. A boon of Siddha medicine with its nanoparticles in medicine plays an important role in treating cancer and many other degenerating diseases. Siddha medical science is very ancient in origin, as old as the earliest civilization. The exact time of its existence cannot be assessed as it was stated that it was before the spitting out of sand from the stone. Siddha medicine was mainly based on iatrochemistry metals, minerals, animal kingdom, and plants. These were successfully used by spiritual scientists. The process like incineration, calculations of mineral, mercurial products, metals with its high potency of processing miraculous properties of transmitting metals to act as a regenerator for the entire human system. In this review, the authors compile the effect of higher order medicines such as*Chandamaarutha Chendhooram (CMC), Panchamuga Chendhuram (PMC), Veera rasa Padhangam (VP), Gowri Chinthamani Chendhooram (GCC), Rasa Parpam (RP).*

INTRODUCTION

Cancer, a dangerous disease in which no medicine has been found until for complete treatment, even though more research have been validated for cancer. Approximately more than 14 million people suffered from cancer among them 8.2 million people become more victim to cancer death[1].

The main causes of cancer are smoking, tobacco chewing, poor oral health, malnutrition, alcohol, dietary imbalances, HPV infections, obesity, betel quid, hormones and chronic infections leading to chronic inflammation [2].

Siddha medical system provides more information about treating various kinds of threatening diseases such as cancer. The term cancer was explained in Siddha classical literature as *putru* (undetermined growth) with the direct meaning as *Arpudham* (spectacular tumors) and *Vanmeegam*[3] and some considered the symptoms of cancer coincided with the symptoms of *Vippuruthi* 3(multifaceted growth) in their clinical practice[4].

Even though there were many therapeutics have been validated such as surgery, radiotherapy, chemotherapy, immunotherapy, hormonal therapy to treat cancer but there has been noted that there is a limit successful outcome in patients with cancer[5].

Cancer remains as an aggressive killer disease in the World. Cancer demand has been developed in the development of new anticancer drugs with effective action and easily affordable. Thus there is an urgent need for the evaluation of new medicines as an anti-cancer agent from the natural products for the cancer World. Thus the natural products of higher order medicines in Siddha play an important role in the management of cancer.

The aim of medicine is to prevent disease and prolong life; the ideal of medicine is to eliminate the need of a physician. - William James

CLASSIFICATION OF CANCERS:

1) Cancers of Blood and Lymphatic Systems:

a) Hodgkin's disease b) Leukemia’s c) Lymphomas d) Multiple myeloma e) Waldenstrom's disease

2) Skin Cancers:

a) Malignant Melanoma

3) Cancers of Digestive Systems:

a) Esophageal cancer b) Stomach cancer c) Cancer of pancreas d) Liver cancer e) Colon Rectal cancer f) Anal cancer

4) Cancers of the Urinary system:

a) Kidney cancer b) Bladder cancer c) Testis cancer d) Prostate cancer

5) Cancers in women:

a) Breast cancer b) Ovarian cancer c) Gynecological cancer d) Choriocarcinoma

6) Miscellaneous cancers:

a) Bone cancer b) Carcinoid cancer c) Nasopharyngeal cancer[6]

SYMPTOMS:

The symptoms of cancer may depend on the type and location of cancer. For example, lung cancer the symptoms includes coughing, shortness of breath, or chest pain. Colon cancer causes diarrhea, constipation, and blood in the stool. Some cancers don't possess any symptoms. In pancreatic cancer, symptoms proceeds in the advanced stage of cancer. However, the most common symptoms in all types of cancers include chills, Fever, Loss of appetite, Malaise, Night sweats, Weight loss[7].

PREVENTION OF CANCER:

- ❖ Eating a healthy diet
- ❖ Limiting alcohol
- ❖ Not smoking or chewing tobacco
- ❖ Maintaining a healthy weight
- ❖ Exercising regularly

- Minimizing your exposure to radiation and toxic chemicals
- Reducing sun exposure, especially if you burn easily

The screening of Cancer includes mammography, breast examination for breast cancer and colonoscopy for colon cancer, pap smear for cervical cancer, may help to find cancers in early stages. High risk of cancers in patients was advised to take medication to reduce their risk[8].

SCREENING OF DRUGS IN ANTICANCER:

***IN VITRO* METHODS:**

- Ideal characteristics of an in Vitro screening method
- Tetrazolium Salt Assay (Microculture Tetrazolium Test or MTT)
- Sulphorhodamine B Assay.
- H-thymidine Update Assay
- Fluorescence
- Dye Exclusion test
- Clonogenic Assay
- Cell Counting Assay
- 3D Tumor Models
- 4D Tumor Models
- National Cancer Institute's in vitro Screening Program.

***IN VIVO* METHODS:**

- Chemically induced tumor models
- National Cancer Institute's invivo Screening Program.
- DMBA-induced Mouse Papillomas

- N-methyl, N- nitrosourea (MNU)- induced Rat Mammary Gland Carcinogenesis
- DMBA-induced Rat Mammary Gland Carcinogenesis
- N-methyl, N- nitrosourea (MNU)- induced Tracheal Squamous Cell Carcinoma in Hamster.
- N-methyl, N- nitrosourea (MNU)- induced Prostate cancer in Gerbils
- N, N-diethylnitrosamine (DEN)- induced Lung adenocarcinoma in hamster
- 1,2 – Dimethylhydrazine (DMH) – induced Colorectal adenocarcinoma in Rat
- Azoxymethane (AOM) – induced Aberrant Crypt foci in rats
- OH-BBN induced bladder cancer in mouse
- DMBA – induced oral cancer in Hamster
- DMBA sustained release suture technique
- 3 Methylcholanthrene – induced fibrosarcoma tumors in mouse
- 3 Methylcholanthrene – induced skin tumors in mouse
- Benzopyrene –induced forestomach tumors in mouse
- High-fat diet-induced NAFLD/ NASH models in mouse
- Angiogenesis Assay[9]

TABLE NO: 1 HIGHER ORDER MEDICINES IN THE TREATMENT OF CANCER:

Sr. No.	SIDDHA FORMULATIONs	CELL LINES AND ASSAY	CANCER
1.	*Chandamaarutha Chendhooram (CMC)*	MCF7 cell line in MTT assay	Breast Cancer
2.	*Panchamuga Chendhuram (PMC)*	MCF7 cell line in MTT assay	Breast Cancer
3.	*Veera rasa Padhangam(VP)*	MCF7 cell line in MTT assay	Breast Cancer
4.	*Gowri Chinthamani Chendhooram(GCC)*	*HeLa* cell line in MTT assay	Cervical Cancer
5.	*Rasa Parpam(RP)*	*HeLa* cell line in MTT assay	Cervical Cancer

IMPORTANCE OF HIGHER ORDER MEDICINES:

- ❖ Effective even in the minimal dose of the drug.
- ❖ Challenges in treating incurable diseases.
- ❖ Increased bioavailability.
- ❖ Shelf life is higher when compared to the plant products.
- ❖ Therapeutic efficacy is high.
- ❖ Quick remedy even in small doses.
- ❖ The great specialty of higher order formulation is adoptogenicity. (ie) the same drug can be successfully used for various diseases[10].

HIGHER ORDER DRUGS IN THE MANAGEMENT OF CANCER:

1. CHANDAMAARUTHA CHENDHOORAM (CMC):

The ingredients of "*Chandamaarutha Chendhooram*" are 1.Purified Mercuric sulfide, 2. Purified Mercurous chloride, 3. Purified Elemental Sulphur, 4. Purified Red Sulphide of Mercury, 5. Mercury chloride, 6. Egg white as mentioned in *Anubogavaidhiya navaneedham* (part 4).

Procedure:

The ingredients were powdered in a stone mortar. Then it was ground for about 6 hrs by adding egg white little by little and made into pellets, let dry. Water was taken in a new pot and boiled. Now, the pellets were introduced into the boiling water. The boiled pellets were dried and collected. Then raw rice and bottle guard was placed in the pot and boiled as said before.1-2 mins later the pellets were added into the pot and were taken immediately. It was then washed with cold water and dried in the sunlight.

Functional group analysis shows the presence of primary and secondary alcohol, phenols, alkanes, α –β unsaturated aldehydes, ketones, alcohol, alkyl halides in "*Chandamaarutha Chendhooram*"[11].

Preparation of CMC for anticancer activity:

Stock Solution of CMC was prepared by the concentration of 10mg/ml by using DMSO at various concentrations 5, 10, 20, 40, 80 and 100µg/ml. The diluted sample CMC was then transferred to the culture plate. 500 µl of MCF7 cell at the 1x104 cells/well. MCF7 breast cancer cell line was obtained from National Centre for Cell Sciences (NCCS), Pune. They were cultured with the Minimal Essential medium (MEM) with 10% FBS, Trypsin, EDTA, Glucose, 1% streptomycin, penicillin G and amphotericin B under a fully humidified atmosphere 5% CO2 at 370C. The effect of test drug CMC on the cell viability in the breast cell line MCF7 was determined by MTT(3-[4,5-dimethyl thiozole-2-yl]-2-5-diphenyl tetrazolium bromide) assay.

Anticancer effect:

In this study, the results show that there is a decrease in the viability of cells in MCF7 cell line with an increase in the concentration of the test sample CMC. The inhibitory concentration of IC50 value was seen in 25.26 ± 9.00 µg/ml. The cell viability with lowest concentrations are seen in the concentration of 100µg/ml as 8.33 ±0.46%, followed by 80µg/ml shows 13.84 ± 0.92%, 40,20,10 and 5 µg/ml shows 24.29 ± 2.23, 31.98 ±2.32, 37.52 ± 2.81 and 44.28 ± 1.84 % cell viability in MTT assay. Thus the Siddha formulation CMC shows a potent anticancer effect in MCF7 cell line determined by MTT assay[12].

2. PANCHAMUGA CHENDHURAM (PMC):

The ingredients of *PMC* includes Purified *Rasam* (Hydragyrum)-100g, Purified *Gandhagam* (Sulphur)-100g, Purified *Thalagam* (Arsenic trisulphide)-100g, Purified *Lingam* (Mercury II sulfide)-100g, Purified *Veeram* (Mercuric chloride)-100g, *Piper betel* leaf juice Q.S.

Procedure:

All the ingredients were ground well for 1 day and made into (*villais*) pellets. The pellets were allowed to dry, then it is ignited for the small flame (*Deepaagni*)- 6 hrs, moderate flame *(Kamalaagni)*-6hrs, high flame (*Kaadaagni)*-9hrs. After self-cooling, the product was again subjected to grinding for 1 day. The final product (PMC) was weighed and stored in an airtight container.

Preparation of PMC for anticancer activity:

The stock solution was prepared by the test drug PMC in the concentration of 0–50 µg/mL, dissolved in DMSO (Sigma-Aldrich). Human breast cancer cells MCF-7 were obtained from National Center for Cell Science (NCCS), Pune, India. Then the cells were maintained in the medium of Dulbecco's Modified Eagle Medium (DMEM) supplemented with the10% Fetal Bovine Serum (FBS) (Sigma-Aldrich, St.Louis, Mo, USA), with 100 U/mL penicillin and 100 µg/mL streptomycin was used as a antibiotics (Himedia, Mumbai, India) in a humidified atmosphere of 5% CO2 and 95% air in a CO2 incubator (Heraeus, Germany). The effect of test drug PMC on the cell viability in the breast cell line MCF7 was determined by MTT (3-[4,5-dimethyl thiozole-2-yl]-2-5-diphenyl tetrazolium bromide) assay.

Anticancer effect:

In vitro studies showed that after 24 hrs and 48 hrs of incubation, the IC 50 values of *PMC* were found of 65.03 ± 0.05 µg/ml, 70.51±0.01 µg/ml in compared with the standard drug taxol 72±2.4, 75±3.2 µg/ml. Thus the Siddha formulation PMC shows a potent anticancer effect in MCF7 cell line determined by MTT assay[13].

3. VEERARASA PADHANGAM (VRP):

Procedure:

Veeram (Mercuric chloride) - 100 g and *Urukku* (Steel)-100 g were ground in a stone mortar, mercury was expelled out from the mixture. The mixture was subjected to the process of sublimation for 12 hrs. After self-cooling, the sublimated product was again subjected to sublimation for 12 hrs. The final product was weighed and stored in a glass vessel.

Preparation of VRP for anticancer activity:

The stock solution was prepared by the test drug VRP in the concentration of 0–50 µg/mL, dissolved in DMSO (Sigma-Aldrich). Human breast cancer cells MCF-7 were obtained from National Center for Cell Science (NCCS), Pune, India. Then the cells were maintained in the medium of Dulbecco's Modified Eagle Medium (DMEM) supplemented with the10% Fetal Bovine Serum (FBS) (Sigma-Aldrich, St.Louis, Mo, USA), with 100 U/mL penicillin and 100 µg/mL streptomycin was used as a antibiotics (Himedia, Mumbai, India) in a humidified atmosphere of 5% CO2 and 95% air in a CO2 incubator (Heraeus, Germany). The effect of

test drug VRP on the cell viability in the breast cell line MCF7 was determined by MTT(3-[4,5-dimethyl thiozole-2-yl]-2-5-diphenyl tetrazolium bromide) assay.

Anticancer effect:

In vitro studies showed that after 24 hrs and 48 hrs of incubation, the IC 50 values of *VRP* were found of 63.62±0.03 µg/ml, 90.16±0.02 µg/ml compared with the standard drug taxol 72±2.4, 75±3.2 µg/ml. Thus the Siddha formulation VRP shows a potent anticancer effect in MCF7 cell line determined by MTT assay[13].

4. GOWRI CHINTHAMANI CHENDHOORAM (GCC):

Procedure

The raw drugs were purified as per the methods quoted in the book „Sigichaarathna DeepamEnnuum Vaidhya Nool‟ written by Vaidhya Ratnam C. Kannusami Pillai. Purified Mercury and purified Sulphur were ground together in a mortar to attain the state of kajali which means thick black color compound. Then purified Borax was added with the above mixture and ground firmly. The whole mixture was separated into small equal parts. Each part is kept in a piece of tough cotton cloth and tied by thread carefully. Place the mixture filled pouches into the mud pot which was contained sand. This set up was sealed with proper midpalate. And the junction of two was sealed with clay smeared cotton ribbon for 7 times. Allow it to dry. The whole apparatus was kept into a pit which was already prepared as per the literature. Fill the pit with cow dung cakes and furnace. This is known as sand both incineration. After incineration allows to cool. Then the product was collected carefully and powdered in a mortar. The prepared medicine was stored in an airtight container and labeled as GCC. The trial drug underwent some special Siddha techniques to prove its perfection.

Preparation of GCC for anticancer activity:

Stock Solution of GCC was prepared by using DMSO at various concentrations 7.8, 15.6, 31.2, 62.5, 125, 250, 500 and 1000µg/ml. *HeLa* cell lines were obtained from the National center for cell sciences Pune (NCCS). The cells were maintained in Minimal Essential Medium supplemented with 10% FBS, penicillin (100U/ml), and streptomycin (100 µg/ml) in a humidified atmosphere of 50 µg/ml CO2 at 37 °C. The effect of test drug GCC on the cell

viability in the *HeLa* cell lines was determined by MTT(3-[4,5-dimethyl thiozole-2-yl]-2-5-diphenyl tetrazolium bromide) assay.

Anticancer effect:

The inhibitory effect of GCC against HeLa cell lines with different concentrations was carried out. It shows the anticancer effect by increasing the concentration of the test drug, there was an increase in cell growth inhibition. The inhibitory concentration (IC50) of the test drug value was found at the concentration of 31.2µg/ml as 48.21µg/ml, followed by 62.5µg/ml as 52.85µg/ml, 125µg/ml as 37.5µg/ml, 250 µg/ml as 32.14µg/ml, 500 µg/ml as 23.21µg/ml, 1000µg/ml as 16.07µg/ml. The lowest cell viability in the concentration was 1000µg/ml as 16.07µg/ml. Thus the Siddha formulation GCC shows a potent anticancer effect in *HeLa* cell line determined by MTT assay[14].

5. RASA PARPAM (RP):

Ingredients

Vaalai Rasam (Purified Elemental Mercury) 35gms, *Gandhagam* (Sulphur) 35gms, *Kattuulli* – Indian squill (*Urginea indica*) 35gms

Procedure:

Indian squill and Sulphur – each 35gms were taken and placed in a stone mortar and ground well to get a paste. This is made as a pellet. The pellet was kept in an earthen pot and medicated oil was obtained by calcination method using the equipment – *Kuzhi pudaKaruvi*.This oil got by *Pudam* (*Kuzhi puda thylam*) was added to *Vaala Rasam* and kept exposed to sunlight for one day. And the substance was dried. This was ground with the above oil and made as a pellet. Bricks were taken and crushed into pieces to the size of betel nut. Half of the brick pieces were spread in a round bottom earthen pot. 1*padi* (1.3lit) of salt was layered above the brick pieces and the pellets kept over the salt. The pot was covered with the earthen dish and sealed with 8 layers of mud pasted cloth and heated using fire woods through a high flame (*Kaadakkini*). After that, the covering dish was removed. The sublimate was obtained in the upper earthen dish. Finally, *Parpam* has collected a ground well. The *Rasaparpam*was collected and kept in an airtight container. The *Rasaparpam* was

labeled as RP. *Panavedai alavu* (488 mg) Adjuvant: Palm jaggery.Indications: Tumor, Cervical cancer, Inguinal bubo, Abscess.

Preparation of RP for anticancer activity:

The stock solution of RP was prepared by 1 mg of sample/compound was added to 1ml of DMEM and dissolved completely by cyclomixer in the concentration of 7.8, 15.6, 31.2, 62.5, 125, 250, 500 and 1000µg/ml. After that, the solution was filtered through a 0.22 µm Millipore syringe filter to ensure the sterility.HeLa (cervical cancer cells) was initially procured from National Centre for Cell Sciences (NCCS), Pune, India. The HeLa cell line was cultured in 25 cm2 tissue culture flask with DMEM supplemented with 10% FBS L-glutamine, sodium bicarbonate and an antibiotic solution containing: Penicillin (100U/ml), Streptomycin (100µg/ml), and Amphotericin B (2.5µg/ml). Cultured cell lines were kept at 37ºC in a humidified 5% CO2 incubator (NBS Eppendorf, Germany). Cells seeding in 96 well plates: Two days old confluent monolayer of cells were trypsinized and the cells were suspended in 10% growth medium, 100µl cell suspension (5x104 cells/well) was seeded in 96 well tissue culture plate and incubated at 37ºC in a humidified 5% CO2 incubator. The effect of test drug RP on the cell viability in the *HeLa* cell lines was determined by MTT (3-[4,5-dimethyl thiozole-2-yl]-2-5-diphenyl tetrazolium bromide) assay.

Anticancer effect:

The inhibitory effect of RP against HeLa cell lines with different concentrations was carried out. It shows the anticancer effect by increasing the concentration of the test drug, there was an increase in cell growth inhibition. The inhibitory concentration (IC50) of the test drug value was found at the concentration of 125 µg/ml as 53.86 µg/ml, followed by 250 µg/ml as 46.34µg/ml, 500 µg/ml as 41.03 µg/ml, 1000 µg/ml as 34.13 µg/ml. The lowest cell viability in the concentration was 1000 µg/ml as 34.13 µg/ml. Thus the Siddha formulation RP shows a potent anticancer effect in *HeLa* cell line determined by MTT assay[15].

LATERAL RESEARCH REGARDING CANCER IN ABOVE MENTIONING INGREDIENTS OF HIGHER ORDER MEDICINE:

1. MERCURY:

The drug Arkashara Rasa showed potent activity against pancreatic cancer cells (MIA-PaCa-2). LDH activity confirmed that AR was active against pancreatic Cancercells[16].

2. SULFUR:

❖ The growth inhibitory and apoptosis-related effects of a newly developed highly purified sulfur (HPS) on immortalized human oral keratinocytes (IHOKs) and on oral cancer cells representing two stages of oral cancer (HN4, HN12) based on a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, Western blotting, cell cycle analysis, and nuclear staining[17].

❖ Both diol-containing compounds, 2a and 3, were the most cytotoxic of the sulfide series against V-79 cells in vitro (IC(90) = 2.1 microM and 1.9microM, respectively). A preliminary anticancer screening against P388leukemia showed that 2a is highly active in vivo as well[18].

❖ Allyl sulfur compounds from garlic are reported to reduce the incidence of Breast, Colon, Skin, Uterine, and Lung cancers and to depress proliferation of tumor cells.

❖ Allyl sulfur compounds contribute to cell proliferation, although the suppression of Anti-cancer activity[19].

3. MERCURIC CHLORIDE:

❖ Amongst various concentration of drug(VM) tested 500 UG/ml showed maximum absorbance of 0.53 0.01. The *Veera Mezhugu* possess both antioxidant anti-cancer potentials justifying scientifically administration in cancer[20].

❖ *The Kodasuri veeravaippu* possess inhibition of the synthesis of arachidonic acid metabolites via inhibiting COX-2. Kodasuri veeravaippu possess significant anti-inflammatory activity on both acute and chronic inflammation[21].

❖ *Kanakalinga karpura mezhugu*. Mezhugu was investigating with scientific parameters to reveal many ascertained drugs for present-day refractory diseases like cancer, rheumatoid arthritis, thyroid disorders, bronchitis, benign growths, adenitis and swellings[22].

4. THALAGAM:

Low doses of arsenic trioxide can induce complete remissions in patients with APL who have relapsed. The clinical response is associated with incomplete cytodifferentiation and the induction of apoptosis with caspase activation in leukemic cells[23].

5. SODIUM BORATE (*VERGARA M):*

Borax shows potent anti-inflammatory and healing properties. Hence, it has been used as a treatment in chronic tonsillitis in the form of a gargle. To ensure the scientific validity of the efficacy, a comparative study is conducted between Aspirin tablet and borax which was statistically analyzed. In the study, borax showed significant relief from symptoms that were statistically significant[24].

6. CINNABAR (RED MERCURY (II) SULFIDE (HGS) (*LINGAM)*:

The study shows a *Mupoora chendurum* in which cinnabar is one of the ingredients was prepared as per the Siddha textual references, with Sophisticated tests reveals the absence of heavy metals like Arsenic, Lead, Cadmium, and Copper. Mercury was within the permissible limit. The Particle size of the drug was 83.3 nm. In spectra by visual gratitude, there is no significant difference in the characteristic absorption bands but the intensity of certain wavelength do differ from each other especially at the fingerprint region (3584–1035 cm-1). This report is a fingerprint for future references in the analysis of *Mupoora chendurum*, the drug has antibacterial activity against *Bacillus, Streptococcus and Vibrio*[25].

7. MERCUROUS CHLORIDE:

It has Analgesic, Antipyretic and Anti-inflammatory[26].

8. URGINEA INDICA

❖ *U. indica*, an antiproliferative assay with ER-positive breast cancer cell line (MCF-7) and ER-negative **Breast cancer** cell line (BT-549) was performed. The aqueous bulb extract of red variety exhibited 82% of anti-proliferative activity against MCF-7 compared to control,

whereas white variety inhibited 62%. The percent of inhibition of DPPH radical was 16.5, 18.0, 14.0, 11.5% with aqueous extracts of bulb, leaf, stem, and root of white variety respectively, whereas 18, 18, 16, 14% respectively, with red variety at 25 mg/ml. It has **an Anti-oxidant** property[27].

- The extract of the bulb of *Urginea indica Kunth*. were collected by using alcoholic extraction. The **anti-inflammatory** action of the alcoholic Extract of the bulb of the plant *Urginea indica* was evaluated in rats (female) against carrageenan-induced edema i.e., using plethysmographic method[28].

9. BETLE (*PIPER BETLE)*

- Antimicrobial activity, Antidiabetic activity, *Protective and healing activity,* Gastroprotective activity, Immunomodulatory activity, Hepatoprotective activity, Cytotoxicity / Anticancer Potential, Radioprotective activity[29].

CONCLUSION

Cancer is a life-threatening disease which occupies 5th position in the mortality rate in Worldwide. The prevalence of cancer is increased day by day in order to reduce the vigorosity of cancer. I would explore some higher order Siddha formulation to reduce the cost-effectiveness, easily affordable when compared with the other systems. This review will provide much information about natural products in the management of cancer.

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