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CHEMOTHERAPY IN THE TREATMENT OF CANCER AYURVEDA TREATMENT OF CANCER

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ABSTRACT

Cancer research has made remarkable progress and new discoveries are begining to be made. In this review, we will introduce and describe the latest chemotharapy and Ayurvedic areas of cancer research. This study will lead to further understanding of the mechanism, invasion, and metastasis, as well as the development of cancer detection and therapeutic methods. Chemotharepy are important in understanding the cancer disease. Chemotharepy and Ayurveda are the further treatment in cancer therapy. These study areas may result in the creation of new cancer treatments in the future. This paper study also examines the scope of plant drugs used in the treatment of cancer. A retrospective metanalysis of observations on medicinal plant drugs reported to have an anticancer effect indicate and have significantly greater possibilities of producing anticancer effects.

KEYWORDS: Antimicrobial peptides; Cancer therapies; Clinical trials; Combination therapy; Immunotherapy; Patient survival; Personalized medicine; Targeted drug delivery.

INTRODUCTION

Cancer is a heterogeneous and multifactorial disease in whicha series of genomic/molecular alterations cause the uncontrolled growth and proliferation of the cells, causing a rapid increase in tissue mass in the affected parts of the body. Undernormal conditions, a cell gets signals to die and to supplant the organism with a young and healthier cell. Cancer cells growusing the body's oxygen and supplements, depriving other cells of regular supplements and growth factors. These cells canturn the microenvironment in their favor, deceive the immune system of the body, and can exploit the physiology of othercells to accommodate their needs. Some of the biomarkers which are currently been used to detect cancer including human epididymis protein 4 (HE4), carcinoembryonic antigen (CEA), legumain, mesothelin, osteopontin, and vitamin E- binding plasma protein. A plethora of anti-cancer drugs and natural medicinal compounds have been devised over the years, which can suppress tumor growth through diverse mechanisms. Some of the drugs/compounds work on crucial cellular enzymes, while others may alter cell metabolism. They have also shown the potential to interfere with some critical cellular processes, programmed cell death/ apoptosis, drug resistance, DNA damage, DNA replication, or immune reactions. These drugs have distinct modes of action and selectivity for multiple cancer types; however, sub alteration to their chemical structure could abolish their anti-cancer potency.

The idea of chemotherapy (utilizing toxic compounds and drugs to destroy cancerous cells) came into existence after the reports of mustard gas killing lymphatic tissues and bone marrow and regression of lymphoma tissues. Yale University paved the way for chemicals in treating cancers and developing the field of cancer chemotherapy for treating a variety of cancers. In the early 1900s, the famous German chemist Paul Ehrlich set about developing drugs to treat infectious diseases. He was the one who coined the term ''chemotherapy'' and defined it as the use of chemicals to treat disease. Ehrlich was also interested in drugs to treat cancer, including aniline dyes and the first primitive alkylating agents, but apparently was not optimistic about the chance for success.

Ayurveda adopts a holistic approach and propounds a broad - based understanding of the entities of life, health, and cancer disease. Smith, 1977 in Ayurveda, the cancer disease treatment described in a general model. Arbuda, as described in Ayurveda in a tumor accomponied by local swelling that in not necessarily malignant. Arbudas or tumors that arise in specific organs are named accordingly. Another major disease described in Ayurveda that may be associated with tumors and cancers is Gulma Roga, which refers to a state of chronic enlargement of the abdomen and intra - abdominal structures.

History of Chemotherapy Through The Years

On December 2, 1943 Bari's harbor was bombed by a flight of 105 German bombers. Among the 24 ships of the alliance, one ship named SS John Harvey was carrying a secret cargo of 100 tons of liquid mustard gas. Many seamen on surrounding ships who survived developed blistering of epithelial surfaces, reduced white blood cells and profound lymphoid and myeloid suppression on autopsies. Using this information Goodman and Gilman – two pharmacologists from the Yale School of Medicine - reasoned that this agent could be used to treat lymphoma. Results of Chemotherapy Through The Years (1949-2015) Can cure cancer(even in advanced stages)Germ – cell tumors.

Non – Hodgkin's lymphomas Gestational choriocarcinoma Pediatric tumors (i.e. lymphomas, leukemias neuroblastoma, bone sarcomas) Can achieve considerable prolonged survival (in advanced stages) Breast cancer Ovarian cancer Colorectal cancer Lung cancer Other hematological malignancies (i.e. leukemias, myeloma) Can achieve prolonged progression-free survival (as an adjuvant treatment in non-metastaticdisease) Breast cancer Colorectal Ovarian cancer.

MATHEDOLOGY OF CHEMOTHERAPY

Mechanisms of Resistance to Chemotherapy (I)

Cancer cells may be mutated & develop pathways that are independent of those blocked by cytotoxic drugs. Gene amplification may lead to overproduction of proteins that are blocked by anticancer drugs.

Mechanisms of Resistance to Chemotherapy (II)

Cancer cells may develop mechanism that inactivate anticancer drugs.

They may learn to repair the DNA & protein damages induced by anticancer drugs.

Resistant clones of cancer cells may develop.

Cancer chemotherapy is a modality of cancer therapy that involves the administration of chemical agents to destroy cancer cells.

The aim of cancer chemotherapy is to cure where possible and palliative where cure is impossible

The effective use of chemotherapy needs a deep understanding of the principles of tumor biology, cellular kinetics, pharmacology and drugs resistance.

Alkylating Agents

Busulfan Chlorambucil, Cisplatin, Carboplatin, Oxaliplatin, Cyclophosphamide, Ifosfamide Dacarbazine, Mechlorethamine (Nitrogen Mustard) Melphalan Nitrosoureas Procarbazine Streptozotocin Temozolomide.

Antimetabolites

Mechanism of action: Interfere with DNA synthesis. They are structural analogs or they inhibit several enzymes. S-phase specific, Aracytidine Cytarabin Fludarabine Fluorouracil Leucovorin.

Capecitabine, Gemcitabine Hydroxyurea.

Antitumor Antibiotics

Mechanism of action Cause linkage of double strands of DNA and prevent replication. They are derived from microorganisms. Cell cycle specific drugs. Actinomycin–D Bleomycin Daunorubicin Doxorubicin Doxorubicin Liposomal Epirubicin Idarubicin Mitomycin Mitoxantrone.

Mitotic Spindle Agents

Mechanism of action: Bind to microtubular proteins, thus inhibit microtubule assembly resulting in dissolution of the mitotic assembly structure. M- phase specific drugs. Docetaxel Paclitaxel Paclitaxel Albumin Cabazitaxel Eribulin (Non-taxane tubulin binding agent A marine sponge product)

Topoisomerases Inhibitors

Mechanism of action: DNA Topoisomerases I and II are essential enzymes for transcription, replication and mitosis. The following drugs are able to inhibit these enzymes.

Topoisomerease I inhibitors Irinotecan Topotecan

Miscellaneous Agents Asparaginase Estramustine

Modes of Chemotherapy Administration

Intravenous

Oral

Local Drug Application

Intra-arterial (i.e. hepatic infusion, limb perfusion) Intra-thecal (menengeal metastasis)

Intra-peritoneal (ovarian cancer, peritoneal carcinomatosis) Intra- pleural (pleurisy / pleural metastases)

Intra-pericardial (malignant pericardial effusion)

Principles of Combination Chemotherapy

Use drugs active as a single agent

Use drugs with different mechanisms of action

Use drugs with different mechanisms of resistance

Use drugs with different side-effects

Be aware of drug-drug interactions

Stages of Developmentand Progression

Ayurveda identifies the pattern of develop- ment and progression of a neoplasia by fol- lowing intermediary pathologic lesions occur-ring in a successive manner, for example

(1) Sopha - swelling/inflammation
(2) Granthi – glandular swelling
(3) Arbuda - tumor
(4) Karkata rbuda - malignant tumor
(5) Adhyarbuda – metastasis in primary sites

RESULTS AND DISCUSSION

What kind of plant drugs of Ayurveda could produce antitumor/anticancer effects? This has long been debated. In a collaborative study, it was proposed that, in view of the *Samprapti* model described above, it

could be tentatively presumed that the drugs having *Katu, Tikta, Kasaya Rasa* (tastes), and *Usna Guna* (p roperty) and *Usna Veerya* (potency) could *be* researched for thispurpose. Based on the *Samprapti* model, the selection criteria for plant drugs were formed. Accordingly, a series of plants were collected from India and Nepal for study (Smit et al., 1995). The dried materials of selected plants were extracted in 70% ethyl alcohol and tested for their cytotoxicity against *Colo* 320 tumor Diotherapy or surgical removal of a tumor are all nothing but anti-*Kapha* measures according to Ayurveda. Because *Srotavarodha (i.e.,* obstruction of channels of the body) is the primary event in the pathogenesis of this disease, one has to plan a suitable *Samśodhána* or biopurificatory treatment in these patients utilizing appropriate *Panca Karma* therapy measures. As also found in Western medicine, cancer is often associated with immune dysfunction; an important com- ponent of the therapy has to be through im- munomodulation. Use of appropriate *Rasayana* (adaptogen and immunopotentiating) remedies of Ayurveda such as *Amalaki, Guduci, Pippali, Cyavanapraśa, Amrta* and *Bhallataka* are indi- cated. Many patients with cancer are emotionally distraught and as such they need supportive psychotherapy, *Sattvavajaya* or Ayurvedic psychotherapy, *Yoga*, meditation, and regular exercise and relaxation in addition to suitably planned nutrition and *Pathyapathya* (dietary intervention).

Table 01: Common Combination Chemotherapy Regimens.

Cancer Type	Drugs	Acronym
Breast Cancer	Cyclophosphamide, methotrexate, 5-FU Doxorubicin (Adriamycin), cyclophosphamideDoxorubicin (Adriamycin), Paclitaxel (Taxol)	CMFAC AT
Hodgkin's disease	Mustine, Vincristine (Oncovin), Procarbazine, Prednisone Doxorubicin (Adria), bleomycin, vinblastine, dacarbazine	MOPP ABVD
Non-Hodgkin'slymphoma	Cyclophosphamide, doxorubicin, vincristine, prednisone	CHOP
Germ cell tumor	Bleomycin, etoposide, cisplatin	BEP
Stomach cancer	Epirubicin, cisplatin, 5-FU	ECF
Bladder cancer	Methotrexate, vincristine, doxorubicin, cisplatin	MVAC
Colorectal cancer	5-FU, folinic acid, oxaliplatin	FOLFOX

Table 2: Botanical Name of Anticancer Plants.

Name (Botanical Name)	Part Used	IC 50 mg/ml
Vaca(A. calamus L.)	Rhizome	100
Arka (Calotropis procera (A.t.) R. Br.)	Flowers	10
Karcura (Curcuma zedoaria Rosc.)	Rhizome	100
Dhattura (Daturra metal L.)	Fruits	100
Kampillaka (M. philippinensis)	Glandula	10-100
Mahanimba (M. azadarach L.)	Fruits	10-100
S´igru (M. oleifera Lam.)	Cotex	100
Citraka (P. zeylanica L.)	Branches	100
Gajapippali (S. officinalis Schott)	Fruits	10-100
Bhallataka (Seme carpus anacardium L.f.)	Fruits	10
Brhati (Solanum indicum L.)	Fruits	100
Kantakari (S. xanthocarpum S and W)	Fruits	10-100
Munditaka (S. indicus L.)	Flower	10-100
Nirgundi (Vitex negundo L.)	Leaves	100

Table 03: Classical Treatment Protocols for Various Tumours in Ayurveda.

Type of Tumour	Tumour Subtypes	Classical Treatment Procedures
Granthi	*Vatika granthi*	Helloborus niger, Tinospora cordifolia, Clerodendron serratum, Aegle marmelos, Hoya viridiflora, Elephantopus scaber, Soymida febrifuga and Gynandropis pentaphyllawere applied locally.
	Paittika granthi	Terminalia chebula powder with either grape or sugarcane juice were used orally. The paste of Glycyrrhiza glabra, Eugenia jambolana, Terminalia arjuna or Calamus rotang were used of external application.
	Kapaja granthi	Paste of Capparis spinosa, Capparis sepiaria, Agati grandiflora, Lagenaria vulgaris, Premna herbacea, Pongamia glabra, Musa sapientum and Randia dumetorum used in local application.
Arbuda	*Classical procedures*	Fomentations, cauterisation, scraping, blood letting, medicated enemata and other surgical procedures.

	Traditional treatment	Habitual intake of Basella rubra or application of alkali preparation of Musa paradisiaca, Conch shell ash, Elaeocarpus tuberculatus, Sulphur, Potassium carbonate, Embelia ribes and ginger were used to cure arbuda.
	Vataja arbuda	Paste of Benincasa cerifera, Cucumis memordica, Cocos nucifera, and Eranda
	Pittaja arbuda	beeja, Ricinus communis along with butter or milk were applied.
	Kaphaja arbuda	Tumours were treated with leaves of Ficus glomerata, Tectona grandis, and Elephantopus scaber repeatedly and then with a honey mixed fine paste of Aglaja roxburghiana, Caesalpinia sappa, Symplocos racemosa, Terminalia arjuna, Xanthium strumarium was applied.
	Medoja arbuda	After surgical removal of tumour, a drug that remove doshas from both the ends (vomiting and purgation) were employed. Then for purification, a decoction of Clitoria ternatea, Jasminum grandiflorum and Nerium odorum leaves was used. For the postoperative care, oil cooked with Premna herbacea, Embelia ribes, Cissampelos pareira was applied Curcuma domestica, Triticum sativum, Symplocos racemosa, etc. were made into a powder and applied externally by mixing them with honey. Oil from Pongamia glabra were used of internal administration.

Table 04: List of herbs commonly used in ayurvedic anticancer treatment.

Name of the herb	Method and use
Vitis vinifera	The mixture of Terminalia chebula, grape juice and sugar cane juice has been used. Resveratrol, a natural product derivative from grape juice has been proved to possess cancer chemopreventive activity.
Baliospermum montanum	The paste comprising of Baliospermum montanum, Plumbago zeylanica, Euphorbia neriifolia, Calotropis procera, jaggery, Semecarpus anacardium applied over the tumours.
Madhuca indica	This paste is prepared from the barks of Madhuca indica, Syzygium cumini, arjuna Terminalia arjuna and Salix caprea and prescribed for local application.
Pandanus odoratissimum	A paste of Pandanus odoratissimum with sugar was applied externally.
Pterospermum acerifolium	The flowers of Pterospermum acerifolium mixed with sugar to be applied locally.
Raphanus sativus	Local application of Raphanus sativus powder paste with the radish ash was considered effective against kaphaja arbuda.
Barleria prionitis	The Barleria prionitis oil prepared with whole plant is indicated for external application during acute stages of cyst in blood vessels.
Prosopis cineraria	This paste made up of Prosopis cineraria seeds, Raphanus sativa, Moringa oleifera, barley and mustard with sour buttermilk was applied locally for disintegrating cysts.
Amorphopallus campanulatus	The mature tuber is first burnt and then mixed with butter and jaggery and applied for tumour destruction.
Oxoxylum indicum	The drug Oxoxylum indicum prescribed in treatment of granthi.
Basella rubra	The plant and leaves are ground with sour buttermilk with salt for preparing a poultice and indicated for arbuda
Flacourtia romantchi	The paste of Flacourtia romantchi, Cassia fistula, Capparis sepiaria, is recommended for kaphaja tumours.
Moringa oleifera	The paste of Moringa oleifera seeds, Solanum xanthocarpum, Sinapis dichotoma, Holarrhena antidysenterica and Nerium odorum roots prepared with buttermilk is used for arbuda tumours.
Ficus bengalensis	Application of mixture of Ficus bengalensis and Saussurea lappa pacify tumour growth on bone.
Curcuma domestica	The Curcuma domestica powder in combination with Symplocos racemosa, Soymida febrifuga, is mixed with honey and this is used as an external remedy

Table 05: Pharmacological details of Ayurvedic Anticancer Herbs.

Name of the Herb	Therapeutic Dose	Safety/Duration/Toxic Dose	Side Effects/ Contraindications	Interactions with other Herbs/Drugs
Alstonia scholaris	powder: 0.05–0.2 g Liquid extract: 4–8 ml	therapy Insufficient information	aggravate ulcers, haemorrhoids Lethargy, Nasal	cardiac glycosides and diuretics Interact with St. John's
Amorphopallus	0.3–0.6 g	available Likely safe	congestion, allergy None reported	wort, general anaesthetics None known

campanulatus Anacardium occidentale	No typical dosage	Safe	None reported	None known
Bacopa monniera	5–10 g (0.4–0.5 g 8×)	Safe	Rarely cause dermatitis	None known
Berberis aristata Boswellia serrata	Powder: 1–3 g 0.4 g/2–3 times a day,	May be toxic at higher dosage Safe	May cause lethargy, nose bleeds, nausea, vomiting, diarrhoea No adverse effects	May interfere with Vitamin B assimilation None known
Curcuma longa	1.5–3.0 g	Safe, non-toxic	bradycadia Contraindicated in	cardioactive herbs and horsetail No interactions reported
Datura stramonium	0.05–0.1 g	Likely unsafe	gastric ulcers Vomiting, hypertension,	May interact with
Erythrina suberosa	28–32 g	Insufficient information	loss of consciousness. May lead to coma Insufficient information	anti-cholinergic drugs Insufficient information
Euphorbia hirta	Powder: 0.12–0.3 g,	available No information about	available Nausea, vomiting,	available No interactions known to
Gynandropis pentaphylla	liquid extract: 60–120 ml 2 g	dosage Insufficient information	catharsis/allergies Insufficient information	Insufficient information
Hygrophila spinosa	Seed powder: 2–8 g,	available Insufficient information	available Insufficient information	available Insufficient information
Melia azedarach	Liquid extract: 15–30 ml	Insufficient information	Insufficient information	occur Insufficient information
Nerium indicum	0.25–0.4 g	available Likely unsafe	available Nausea, vomiting,	available None known
Nigella sativa	1–3 g	Safe	diarrhoea No adverse effects reported	No interactions known

CONCLUSION

The clinical efficacy and extent of toxicity of numerous anticancer agents are unknown and uncertain. For example,research on majority of ayurvedic drugs is in the pre-clinicalphase or is not being actively pursued. Future research on this topic would help to identify safe and effective anti- cancer drugs and will further the exploration of their mech- anism of action. Ayurvedic practitioners and researchers in medical sciences can help to improve this medicine by in- creasing their involvement and contribution. Case study is the research design, which can form basis for future re- search directions and can provide valuable contributions to the medical field with minimal cost budgets. Case studies have also been suggested by the NCCAM (National Cen- ter for Complementary and Alternative Medicine, Bethesda, USA) as a means to determine whether a complementary anticancer therapy demonstrates potential efficacy against particular cancer and whether clinical development of the therapy should continue. It is no longer an optionto ignore ayurvedic drugs or treat them as something un- conventional from regular medical practices. The challenge put before this medicine is to move forward carefully, using both reasoning and wisdom.

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