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LITERARY REVIEW ON AMRUTA GHRITA AGADA (VISHA HARA) PROBABLE ACTION AS ADJUVANT THERAPY DURING CHEMOTHERAPY AND RADIOTHERAPY.

[1]Dr. Ravi Dhaliya, [2]Dr. Harish Babu H. and [3]*Dr. Swathi Sharma

[1]PhD Scholar, Guru Ravidas Ayurved University, Hoshiarpur, Punjab, India.
[2]PhD Scholar, Parul Ayurved University, Gujarat, India.
[3]Assistant Professor, Department of Agada Tantra, Sushrutha Ayurvedic Medical College and Hospital, Karnataka, India.

***Corresponding Author: Dr. Swathi Sharma**

Assistant Professor, Department of Agada Tantra, Sushrutha Ayurvedic Medical College and Hospital, Karnataka, India.

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ABSTRACT

Cancer is the most alarming disease affecting manhood. It has been reported as the second-largest non-communicable disease after ischemic heart disease. Wide research has produced many new healing methods and hundreds of medications for the management of cancer. The clinically useful anti-neoplastic agents are more toxic to the sensitive malignant cells than to the normal cells of the tumor-bearing host. But both treatments such as chemotherapy and radiotherapy have cytotoxic effects and are hazardous to the normal cells of the patient, causing many unnecessary effects. This further leads to complications of the therapy, impaired health, and deterioration of quality of life, resulting in mandatory stoppage of the treatment. The goal of this review is to understand the possible benefits of *amruta ghrita* in cancer care. A review of the ingredients of the formulation might help us understand the scope of the same as an adjuvant.

KEYWORDS: *Agada Tantra, Amruta Ghrita,* Chemotherapy, *Gara visha, Visha Hara.*

INTRODUCTION

Cancer is the most alarming disease affecting manhood. It has been reported as the second- largest non-communicable disease after ischemic heart disease. Extensive research has produced many new healing methods and hundreds of medications for the management of cancer. Radiation therapy is effective in controlling a variety of malignant tumors and is a component in the management of about half of all patients with cancer.[1,2] Second chemotherapy involves the use of cytotoxic drugs and hormones. It also been seen that clinically useful anti-neoplastic agents are more toxic to the sensitive malignant cells than to the normal cells of the tumor-bearing host. But both treatments such as chemotherapy and radiotherapy have cytotoxic effects and are hazardous to the normal cells of the patient, causing many unnecessary effects. This further leads to complications of the therapy, impaired health, and deterioration of quality of life, resulting in mandatory stoppage of the treatment. The health-related quality of life is a multidimensional construct that includes the subjective appraisal of the patient's physical, mental, and social well-being.[3,4] Quality of life outcomes are also the key goals of contemporary cancer management.[5]

The goal of this review is to enhance the awareness for the potential benefits of *Ayurvedic ~ visha hara* formulations as combined treatment for cancer patients undergoing Radiation therapy and chemotherapy which are having ill effects. New approaches to improve tolerance and reduce squeal of cancer chemotherapy are urgently needed and the present Research Topic focuses on this issue and highlights several areas of progress.

Adverse Effect of Chemotherapy & Radiotherapy

Radiation is believed to kill cancer cells by causing the formation of free radicals in tumor tissue, inducing a condition known as oxidative stress that can be enhanced by chemotherapy to achieve better treatment responses. Oxidative stress occurs when the balance between cellular anti- oxidants and pro-oxidants – free radicals and reactive oxygen species – shifts to favor the accumulation of pro-oxidants. If left unchecked, these highly reactive pro-oxidants can damage DNA, proteins, and other biological molecules in the cell and may cause cell death. Acute radiation largely affects cell renewal tissues — skin, oropharynx, mucosa, small intestine, rectum, bladder, and vaginal mucosa. These cell renewal tissues are rapidly proliferating. The anorexia–cachexia syndrome is considered by some authorities to be the most common cause of death in patients with cancer.[6] Radiation therapy can cause anorexia through multiple mechanisms. Decreased **appetite** resulting from altered

taste and smell is a result of cancer or its treatment, and the psychological factors may result in anorexia, diarrhea, nausea, vomiting, and mucocitis. Cancer cachexia includes metabolic, hormonal, and cytokine-related abnormalities that results in progressive **Wasting.**[7] Late effects include necrosis, fibrosis, fistula formation, non-healing ulceration, and damage to specific organs such as spinal cord transaction and blindness.[8]

Radiotherapy frequently causes damage to the normal cells, which is evident in the form of adverse reactions. These adverse effects have been grouped under three classes on the basis of the result. In severe cases, due to overexposure, severe morbidity or death may result. Class II radiation may cause degradation of the quality of life. Class III radiation may cause mild, transient, and reversible reactions. After radiotherapy, acute adverse reactions like nausea, vomiting, skin reaction, mucocitis, and fatigue occur. Among the chronic long-term effects, xerostomia, tastelessness, edema, and damage to other organs may occur.[9]

In cancer patients treated annually with radiation therapy and chemotherapy, possibly 20% are cured and an additional 20% may experience significant prolongation of life. The remaining 60% have minimal or no benefit from cytostatic treatment and suffer from its toxic adverse reactions.[10] Rapidly dividing cells found in the bone marrow, mouth, stomach, intestines, and hair follicles bear the brunt of the damage. Sores in the mouth and mucocitis are also common adverse effects of chemotherapy. In the last few years, after vigorous researches regarding safety, the efficacy profiles of radiotherapy and chemotherapy have improved significantly. However, these therapies still produce severe undesired adverse effects. These adverse effects force the patients to discontinue the treatment and make their life miserable and pitiful.

Agada Tantra

Agada tantra is a one branch of *Ayurveda* which deals with ill effects of different kinds of poisons (*visha*) which were used in ancient times. The management and the formulations which are mentioned under *visha hara* (anti-toxic therapy) are found to be effective through many preclinical and clinical studies. ***Amruta ghrita*** is one formulation which is mentioned to be used in all poisonous conditions.[11]

Amrutha Ghrita

Amrutha ghrita is formulation which is explained while explaining *Agada:s (Anti-toxic)* in the context of *–Sarvavisha"* (all kind of poisonous conditions). Amrutha here means –nectar| & is said that it is capable of bringing back an apparently dead man to life. This special formulation is been explained by *Suruta acharya* in *Dundhubhisvaniya adhyaya* (chapter) for all *Visha (poisonous)* condition.[11]

Ingredients

Table 1: Showing the ingredients of Amrutha ghrita agada.[11]

Sr. No.	Drug	Latin Name	Family	Part Used
1	Apamarga	Achyranthus aspera	Amaranthaceae	Beeja (seeds)
2	Shirisha	Albizia lebbek,	Mimosoideae	Beeja (seeds)
3	Aparajitha	Clitorea ternatea,	Fabaceae	Panchanga (all parts)
4	Kakamachi	Solanum nigrum,	Solnaceae	Beeja (seeds)
5	Go mutra	Cow's urine		
6	Go ghritha	Clarified butter		

Method of Preparation

Equal quantity of fine powder of above mentioned drugs should be taken & mardana (pasted) should be done by adding Gomutra (cow's urine), this *kalka dravya* is added to adequate amount of *Ghrita* and heated on mild flame until it attains *Samyak Ghrita paka lakshana* i.e., *phena shanthisthu sarpisha.*[12]

Pharmacological Properties and Its Action

Table no. 2: Showing *Ayurvedic* pharmacological properties.[13]

Drug	*Rasa*	*Guna*	*Veerya*	*Vipaka*	*Dosha*
Apamarga	*Katu, tikta*	*Laghu, ruksha, tikshna*	*Ushna*	*Katu*	*Kapha-Vata hara*
Shirisha	*Kashaya, tikta, madhura*	*Laghu, Ruksha, Tikshna*	*Ushna(Anushna)*	*Katu*	*Tridoshahara*
Aparajitha	*Katu, tikta, kashaya*	*Laghu,ruksha*	*Shita*	*Katu*	*Tridoshahara*
Kakamachi	*Tikta*	*Laghu,snighda*	*Anushna*	*Katu*	*Tridosha*
Go mutra	*Katu,kshara*	*Laghu,ruksha,tikshna*	*Ushna*	*Katu*	*Kapha hara*
Go ghritha	*Kashaya, madhura*	*Laghu,snigdha*	*Shita*	*madhura*	*Tridoshahara*

Table no. 3: Showing Pharmacological action.[13]

Drug	*Karmukta*	Indications	Chemical constituents
Apamarga	*Shirovirechana, depana, pachana, medohara*	*Shula, udara, krimi, mutrakruchra*	Betaine,Achyranthine, Echysterone, Achyranthes, Saponins
Shirisha	***Vishaghna,*** *vranaropana, vedanasthapana, shothahara*	*Shota, vrana, visarpa,* ***visharoga***	Albegenin, Saponins, Albegenic acid,seeds:- proteins,aminoacids
Aparajitha	*Tridoshahara ,medhya,* ***vishaghna****, chakshushya*	*Kushta, shota, unmada, vrana, shula*	Aparajitn, kaempferol, terantins, guercetin
Kakamachi	*Vrshya, Rasayana*	*Shota, jvara, netraroga, kushta*	Leaves: solasonine, solamargin, steroidal alkaloids
Go mutra	*Bedhana*	*Gulma, pandu, mutrakrichra,*	
Go ghritha	*Depana,vrshya,rasayana,vishaghna*	*Agnimandya, visha rog*	

Therapeutic Potential of Amrutha Ghruta

Table 4: Showing Anticancer property.

DRUG	ACTION
Apamarga	Methanolic extract of Achyranthes aspera contains potent anti-proliferative compound with specific activity against pancreatic cancer.[14] Ethanolic plant root extract of Achyranthes aspera L. showed in-vitro anticancer activity against different human cancer cell lines such as liver and colon.[15]
Shirisha	Saponin rich fraction of *A. lebbeck* showed antiproliferative, antiangiogenic and apoptogenic potential using various in-vitro models. It also found to increase chromosomal aberration and thereby may affect cell cycle.[16]
Aparajitha	Treatment with methanol extract of Clitoria ternatea (MECT) led to a decrease in tumour volume, packed cell volume and viable count. It also increased the non-viable cell count and mean survival time, thereby increasing the life span of EAC bearing mice in anticancer activity of Clitoria ternatea in Dalton's lymphoma(DLA) bearing mice.[17]

Table 5: Showing anti-inflammatory activity.

DRUG	ACTION
Shirish	*Albizia lebbeck* Benth. is used both in Indian traditional system and folk medicine to treat several inflammatory pathologies such as asthma, arthritis and burns. The aim of the present study was to evaluate the scientific basis of anti- inflammatory activity of different organic solvent extracts of *Albizia lebbeck.*[18]

Table 6: Showing immunomodulatory activity.

DRUG	ACTION
Apamarga	The extract of Achyranthes aspera Linn. (Amaranthaceae) was found to enhance the induction of ovalbumin (OVA)- specific humoral antibody response in mice. A significant elevation of IgM, IgG 1 and IgG 3 antibodies was observed ($p < 0.01$).[19]
Shirish	Albizzia lebbeck (Sirisha) was evaluated by studying humoral and cell mediated immune responses. The hot aqueous extract and its butanolic fraction were administered once daily for one week in mice, immunised previously with sheep red blood cells (SRBC). Delayed type hypersensitivity response was suppressed in SRBC and macrophage migration index remained unaltered in both mice and rats.[20]
Aparajitha	Root extracts of *Aparajitha (*Clitorea ternatea) showed significant immunosupressive effects as evident from significant decrease in primary and secondary antibody titers in SRBCs-sensitized rats, paw thickness in DTH response, and neutrophil adhesion and In vitro Phagocytosis. The immunomodulatory effects of C. ternatea on humoral, cell mediated and non-specific immune response could be attributed to decreased immune cell sensitization, immune cell presentation and phagocytosis.[21]

Table 7: Showing healing property.

DRUG	ACTION
Apamarga :	The methanolic extract of leaves of Achyranthes aspera was examined for wound healing activity in the form of ointment on albino mice. The
	extract showed considerable response in all the wound models as comparable to those of a standard drug Povidine iodine in terms of wound contracting ability, wound closure time, tensile strength and dry granuloma weight. Histological analysis was also consistent with the proposal that Achyranthes aspera leaves extract exhibits significant wound healing activity.[22]

Table 8: Showing organ protective activity.

DRUG	ACTION
Kakamachi	The ethanol extract showed remarkable **Hepatoprotective** activity. The activity was evaluated using biochemical parameters such as serum aspartate amino transferase (AST), alanine amino transferase (ALT), alkaline phosphatase (ALP) and total bilirubin. The histopathological changes of liver sample in treated animals were compared with respect to control.[23]
Kakamachi	***Gastroprotective*** *activity: Solanum nigrum* showed concomitant attenuation of gastric secretory volume, acidity and pepsin secretion in ulcerated rats. significantly inhibits H^+K^+ATPase activity and decreases the gastrin secretion in EtOH-induced ulcer model.[24]
:	

Table 9: Showing antioxidant activity.

DRUG	ACTION
Aparajitha	The ethanolic extract possess significant anticancer and antioxidant activities studied by *in vitro* models. The presence of flavonoids and related phyto-constituents may be responsible for the activity.[25]

Table 10: Showing antiemetics activity.

DRUG	ACTION
Aparajitha	It is an antiemetic, anti-dyspeptic mild-laxative and cholagogue.[26]

DISCUSSION

According to Ayurveda the reason for cancer lies in imbalance of *tridoshas - vata, pitta* and *kapha*, operating within the body and regulating all cellular functions. According *ayurveda's understands* cancer is a disease of total imbalance and uncoordination of *tridosha*s at the cellular level. Which damage the cells structurally, functionally, physiologically, and emotionally and degrades its behavior, resulting its destruction in whole body.

Radiotherapy can be considered under modified agni karma according to Ayurveda. On exposure to these radiations usna, teekshna and ruksha guna of the agni mahabhuta increases causing vitiation of pitta, vata and rakta both locally and generally. Due to these changes in the body the kapha dosha reduces leading to oja kshaya which in turn leads to dhatupaka and bala haani.[27]

Gara Visha Vs Cancer

According to Gara visha concept, in the present scenario we can compare chemo toxins with *Visha (posion). Visha (*poison*)* possesses *ruksha (dryness)* and *ushna guna* (hot property). These are opposite to that of *Sarera Gunas.* Due to the acute or chronic exposure, *visha* produces increase in *Teekshna* & *ushna guna* in body and destroys *snigdha & sheet gunas.* As a result *teekshna & ushna guna* increases and it alters the balanced state of *tridosha which further damage the normal cells. Visha* mainly vitiates *agni (*metabolism*)* inside the body. Due to the *apāki guna, visha* inconsistent with tissue metabolism And Accumulation of toxins in the body mainly depends upon the digestive capacity.

In such conditions *Visha Hara* drugs (Antitoxic) or formulations are been explained in the management. In view of reducing the dangerous adverse effects of chemotherapy and restoring the damage cells, *Visha-Hara* will be beneficial.

Amrutha Ghruta is having *Laghu, rukshna, teekhna, & vyavayi guna* and Maximum are *Ushna veerya* drugs in it thus it improves the Agni (metabolism) in the body. The formulation is *Tridosha shamaka* & *Sarvavisha hara (Ani-toxic). Amruta ghruta* is a formulation which contains *ghee* as one of the medium.

Ghee in Cancer

According to *Ayurveda*, ghee promotes longevity and protects the body from various diseases.[28] It increases the digestive fire (*agni*) and improves absorption and assimilation. It nourishes *Ojas*, the subtle essence of all the body's tissues (*dhatus*). It improves memory and strengthens the brain and nervous system. It lubricates the connective tissues, thereby rendering the body more flexible. Ghee pacifies *Vata* and *Pitta* and is acceptable for *Kapha* in moderation.[29] *Ghrita* is said to be opposite in property against *Visha* (posion) thus protect the body against its action. It further protects the heart and ultimately protects the *Oja* (essence of life). Ghee is also *dhatuvyapar*[30] (re-establishing homeostatic balance and restoring the physiological process). It thus neutralizes the deleterious effect of chemotherapy and radiotherapy because they both act as *Visha* (poison) to the body. Ghee is also told in the treatment of *dagdha chikitsa. Ghrita* contains essential fatty acids which while carrying medicaments penetrate into all cells through beta oxidation.

Lipids In Cancer

Lipid Oxidative metabolism is a chemical process that occurs in the mitochondria of cells in which oxygen consumption is used to make energy from food sources. Altered oxidative metabolism in cancer cell mitochondria is thought to result in chronic oxidative stress in cancer cells, relative to normal cells. **Ketogenic diets**, which are high in fat and low in protein and carbohydrates, deprive cells of glucose and force them to rely more heavily on mitochondrial oxidative metabolism. Healthy cells don't appear to have the

defects in mitochondrial metabolic pathways that are present in tumor cells. The modulation of cancer by nutritional variables has been a subject of interest and controversy. Carcinogenesis is a complex and protracted multistage process that can be initiated due to damage of cellular macromolecule by an endogenous or exogenous agent. Most of the carcinogens metabolizing enzymes are membrane bound and require a lipid membrane for their activity. Therefore, the oxidative metabolism of carcinogens in the liver endoplasmic reticulum is markedly dependent on the composition of the dietary lipid.[31,32]

These changes in enzymes activities have been associated with alterations in the mutagenicity and carcinogenicity of the pro-carcinogens. Cow's *Ghee* upregulated carcinogen detoxify the activities of **GGTP, UDPGT** and **QR** in liver and **GGTP** and **QR** in mammary tissue, and down regulated the phase I activities of carcinogen activation, CYP1A1, CYP1A2, CYP1B1 and CYP2B1 in liver. These metabolic changes might have contributed to the decrease in DMBA induced incidence of mammary tumours observed in cow *ghee* fed rats.[33]

The review can help others researchers to explore this formulation both clinically and experimentally for further evaluation. It should be of particular interest to explore the ‒visha hara Agada‖ for better, safer and cost-effective drugs can be developed for treating cancer in combination with chemotherapy and radiotherapy.

CONCLUSION

In the present study, we highlight the combination of natural bioactive compounds with chemo- therapeutic drugs may potentiate to reduce side-effects of chemotherapy. Herbal drugs have been contributed to cure different ailments including cancer for thousands of years and their bioactive compounds are play a significant role for prevention cancer activity, but still there are large number of *Ayurvedic* formulations are available in text are not fully phyto-chemically investigated. Agada's are such formulation which should be explored to get new dimension of using such *visha – hara* as an Anti-Toxic Management.

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