

## ***AYURVEDA* FOR CHEMO-RADIOTHERAPY INDUCED SIDE EFFECTS IN CANCER PATIENTS**

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### **ABSTRACT**

Chemotherapy drugs and radiotherapy are highly toxic and both damage adjacent healthy cells. Side effects may be acute (occurring within few weeks after therapy), intermediate or late (occurring months or years after the therapy). Some important side effects of chemotherapy are: nausea, vomiting, diarrhea, mucositis, alopecia, constipation etc; whereas radiation therapy though administered locally, can produce systemic side effects such as fatigue, anorexia, nausea, vomiting, alteration in the taste, sleep disturbance, headache, anemia, dry skin, constipation etc. Late complications of these therapies also include pharyngitis, esophagitis, laryngitis, persistent dysphagia, fatigue, hepatotoxicity, infertility and cognitive deficits. These arrays of side effects have a devastating effect on the quality of life of cancer survivors.

Due to the inadequacy of most of the radio-protectors and chemo-protectors in controlling the side effects of conventional cancer therapy the complementary and alternative medicines have attracted the view of researchers and medical practitioners more recently. This review aims at providing a comprehensive management protocol of above mentioned chemo-radiotherapy induced side effects based on *Ayurveda*, which is an ancient system of traditional medicine practiced in Indian peninsula since 5000 BC. When the major side effects of chemo-radiotherapy are looked through an *ayurvedic* perspective, it appears that they are the manifestations of aggravated *pitta dosha*, especially under the group of disorders called *Raktapitta* (haemorrhage) or *Raktadushti* (vascular inflammation). Based on comprehensive review of ancient *vedic* literature and modern scientific evidences, *ayurveda* based interventions are put forth. This manuscript should help clinicians and people suffering from cancer to combat serious chemo-radiotherapy related side effects through simple but effective home-based *ayurveda* remedies. The remedies described are commonly available and safe. These simple *ayurveda* based solutions may act as an important adjuvant to chemo-radiotherapy and enhance the quality of life of cancer patients.

**Keywords:** *Ayurveda*, Cancer, Chemotherapy, Radiotherapy, Side Effects

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## INTRODUCTION

Cancer is a major illness and a leading cause of death world over, causing suffering of large population and global economic loss worldwide [1, 2]. There were 12.7 million cancer cases and 7.2 million deaths due to cancer worldwide in the year 2008 [2]. Thus, studies are being conducted globally to prevent cancer or develop nontoxic therapeutic agents which include those using *ayurvedic* herbal medications [3]. In the last few decades though there has been tremendous advancement in the diagnostic modalities and treatment of cancer which has increased cancer survival rates, the long term effects of these treatment modalities on the quality of life of the cancer survivors have attracted the attention [4].

### Conventional Management of Cancer and Its Side Effects

Conventional management of cancer encompasses four major strategies – surgery, radiation therapy (including photodynamic therapy), chemotherapy (including hormonal therapy and molecular targeted therapy) and biologic therapy (including immunotherapy and gene therapy). These modalities are usually given in combination, and they work through different mechanisms to a synergistic effect [5]. Adverse effect of these therapies and drug resistance are two important obstacles in better outcome of treatment and quality of life of the patient respectively. Chemotherapy drugs and radiotherapy are highly toxic and both damage adjacent healthy cells. Most of the patients suffer from adverse effects of chemotherapy and radiation therapy. These side effects may be acute (occurring within few weeks after therapy), intermediate or late (occurring months or years after the therapy) [6]. Some important side effects of chemotherapy are: nausea, vomiting, diarrhea, mucositis, alopecia, constipation etc [5,7]; whereas radiation therapy though administered locally, can produce systemic side effects like fatigue, anorexia, nausea, vomiting, alteration in the taste, sleep disturbance, headache, anemia, dry skin constipation etc. Late complications of these therapies also include pharyngitis, esophagitis, laryngitis, persistent dysphagia, fatigue, hepatotoxicity,

infertility and cognitive deficits [5-7]. There is also a possibility of development of secondary cancer due to chemo-radiotherapy [6]. These arrays of side effects have a devastating effect on the quality of life of cancer survivors.

To manage these, usually three kind of therapeutic agents are used in conventional medicine; first, which are given to prevent tissue damage before the symptoms appear, they are called protectors, second those that are given during or shortly after a course of radiation therapy (mitigators) and third are the treatments given when toxicity develops months to years after therapy [6]. Due to failure of most of the radio-protectors and chemo-protectors in controlling the side effects of conventional cancer therapy completely, the complementary and alternative medicines have attracted the view of researchers and medical practitioners more recently. This review aims at providing a comprehensive management protocol of above mentioned chemo-radiotherapy side effects based on *Ayurveda*, which is the most ancient system of traditional medicine of the world that has been practiced in Indian peninsula since 5000 BC [8]. After an extensive literature survey of both traditional *ayurvedic* texts and modern scientific literature we provide an *ayurveda* based approach and solution to above mentioned problems.

### Ayurveda Based Approaches towards Mitigating Chemo-Radiotherapy Side Effects

*Ayurveda* is a well-documented traditional system of medicine [9]. *Ayurveda* considers human body as an indivisible whole and is based on the principle that health is a state of stability of network of interrelated functions of body, mind and consciousness whereas disease manifests itself as a byproduct of disturbance in the stability of this network [10].

According to *Ayurveda*, *vata*, *pitta* and *kapha* are three basic humors (*doshas*) responsible for all the physiological processes in the body; *vata* causes motion, *pitta* helps metabolism and *kapha* is responsible for structure or stability. Health is identified as balanced functioning of these three *doshas* [11].

## Qualities of the Three Doshas

An ancient *sanskrit ayurvedic* text called *Ashtanga Samgraha* (Ash. Sam.) [12] describes the qualities of three *doshas*. Literal meaning of the word *vata* is “air”. The qualities of *vata* as per *ayurvedic* science include: dryness, cold, lightness, mobility, penetration and roughness. These are responsible for all kinds of movements in the body such as circulation, nerve impulse, respiration etc [Ash. Sam. 19/3 ; ref no. 12].

Qualities of *pitta* mentioned in *ayurvedic* texts include: heat, sourness and moisture together. Bodily functions such as appetite, thirst, digestion, metabolism, body heat, eyesight, softness of the body, lustre, mental calmness, and intelligence are governed by the *pitta dosha*. *Pitta* manifests itself through the processes of digestion, metabolism, oxidation, conjugation, reduction, enzymatic and hormonal activities etc.

The third *dosa* is *kapha*, which has the qualities of moisture, steadiness, coolness, heaviness, softness and stickiness. *Kapha* is responsible for body moisture, stability of the joints, firmness of the body, bulk, strength, weight and endurance [Ash. Sam. 19/3 ; ref no. 12].

## Chemo-Radio Therapy Side Effects As Manifestations of Aggravated Pitta Dosha

When the major side effects of chemo-radiotherapy are looked through an *ayurvedic* perspective, it appears that they are the manifestations of aggravated *pitta dosha* especially under the group of disorders called *Raktapitta* (haemorrhage) or *Raktadushti* (vascular inflammation).

The signs and symptoms of aggravated *pitta* as per ancient *ayurveda* texts are: *dav* (burning sensation), *mukhapaka* (stomatitis), *trushna* (excessive thirst), *osha* (feeling of hot sensation in the body), *galpaka* (pharyngitis), *payupaka* (urethritis), *gudapaka* (proctitis), *davatu* (acid regurgitation), *dava* (burning sensation in the oral cavity), *abhishandha* (conjunctivitis) [Ash. Sam. 20/14; ref no. 12]. *Ayurveda* texts also mention “*atapa sevana*” (excessive exposure to sunlight or radiations) as one

of the cause for increase in the *pitta dosha*. This leads to excess of *pitta* and imbalance in the nature (*prakruthi vikruthi*).

## Aggravated Pitta Dosha As Fundamental Basis for Management of Chemo-Radiotherapy Side Effects

*Ayurveda* principles describe that to reduce *pitta dosha* our lifestyle should be such that it promotes other qualities (qualities of *kapha* and *vata*) and it should oppose the qualities of *pitta*. According to the sage *Charaka*, one of the famous authors of ancient *ayurvedic* texts, “*Virechana*” (therapeutic purgation) is the best treatment for aggravated *pitta dosha*. The line of management is; first – *snehana* (oleation therapy) with pure or medicated ghee (clarified butter), then followed by *virechana* (therapeutic purgation) using *ayurveda* herbal medications such as *draksha* (*vitex venifera* or raisins), *vidarikhanda* (*pueraria tuberosa*), *ikhshuras* (*saccharum officinarum* or sugar cane juice) and *trivrutta* (*operculina turpethum*) and then finally administration of medications (*shamana*) which are having sweet, astringent, bitter taste and are cold in potency for e.g. *draksha*, sugarcane, *kharjura* (*phoenix dactylifera* or dates), *yashtimadhu* (*glycyrrhiza glabra*), *vasa* (*adatoda vasika*), *Chandana* (*santalum album* or sandalwood), *ushir* (*vtiveria zizanioides*) preparation containing rose and honey (*gulkand*), milk and ghee (clarified butter) etc.

Along with this one should adopt a cool atmosphere around [Ash. Sam. 21/4; ref no. 12]. *Vasadi ghrita* (clarified butter medicated with *Adatoda Vasika*), *shatavaryai ghrita* (clarified butter medicated with *asparagus racemosa*) and *kiratatiktadi churna* (*swetia chirata*) are special multidrug preparations recommended by *Charaka* for treatment of diseases born out of aggravated *pitta* as mentioned in an authentic *ayurveda* text called *Charak Samhita Chikitasasthana* (*Cha. Sam.*) [Cha. Sam. 4/76, 4/88, 4/97; ref no. 13].

Figure 1 shows schematic summary of management of aggravated *pitta dosha*.

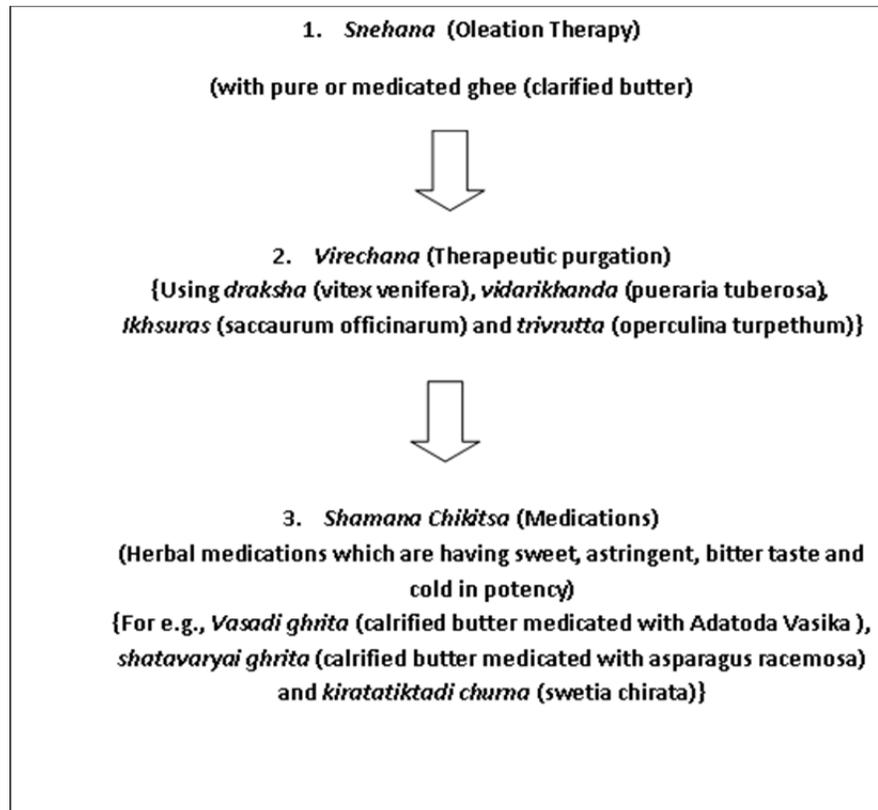


Figure 1. Schematic Representation of Management of Aggravated *Pitta dosha*.

## **AYURVEDA-BASED MANAGEMENT OF COMMON CHEMO-RADIOTHERAPY SIDE EFFECTS IN CANCER PATIENTS**

Following paragraphs in this section of the manuscript describe major side effects of chemo-radiotherapy one by one along with probable *ayurveda* based remedies for the problem on the basis of both ancient *ayurvedic* and modern scientific literature survey:

### **Radio-Protective Effects of *Ayurveda* Polyherbal Preparations**

*Chavanprash avaleha* is a well-known *ayurvedic* poly herbal preparation, which has Indian gooseberry (*embelica officinalis*) as its principal component. In a randomised control study, oral administration of another poly herbal *ayurvedic* preparation called

*Rasyana avaleha* (*embelica officinalis* is the principle ingredient) has shown significantly better effect in controlling the adverse effects of chemotherapy and radiotherapy than the control group [14]. Similarly in an animal study it was observed that *Chavanprash avaleha* has a potential radio-protective effect in the animals which are exposed to gamma radiation [15]. A review describes a polyherbal *ayurvedic* preparation called *Triphala* which contains three ingredients viz. *haritaki* (*Terminala chebula*), *vibhitaki* (*Terminala belerica*) and *amalaki* (*Embilica officinalis*), as useful in cancer as an anti-cancer, chemo-protective and radio-protective agent [16]. Another *ayurvedic* herb – *guduchi* (*Tinospora cardifolia*) has shown its potent radio protective effect in animal experiments. In an animal study it was found that radiation induced testicular injury was significantly ameliorated in the experimental group who consumed *guduchi*, leading to significant increase in the body as well as the tissue weight in

comparison with the control group (which was deprived of the herb) [17].

### Anorexia

Nearly 80% of the cancer patients develop anorexia-cachexia syndrome in advanced stages which is worsened further with the administration of chemotherapy [18]. Anorexia is the commonest chemotherapy side effect and is associated with weight loss, fatigability and decreased appetite which further leads to reduced chances of better outcome and diminished survival [19].

Ayurveda recognizes this condition as *arochak* in which patient feels loss of interest, hunger, and taste in the food. Ancient ayurvedic treatise called *Charak samhita* [13] recommends mouth gargles by the liquid formulations made from the herbs such as *shunthi* (dried ginger) *maricha* (Black pepper), *pippali* (Pepper longum), *lodra* (*Symplocos racemosa*), *teja patra* (*Cinnamomum zeylanicum*) and *yavaksharas* (*Hordeum vulgare*) [Cha. Sam. 26/217; ref no. 13]. As per Sharangdhara Samhita (*Sha. Sam.*) *Lavangadi churna* is another polyherbal preparation indicated for patients suffering from anorexia due to chronic illnesses [Sha. Sam. 6/65-69; ref no. 20], it also improves physical strength. This polyherbal preparation indicated in the diseases of throat tuberculosis, etc. Other important causes of anorexia are oral ulcers and dryness of mouth induced by chemo and radiotherapy. In such cases another multi-herb preparation called *Khadiradi vati* is advised for chewing several times in a day [Cha. Sam. 26/213; ref no. 13].

### Mucositis

Oral mucositis is one of the common and serious complications of chemotherapy. Chemotherapy-induced mucositis is highly painful condition without any definite cure; this condition is an important cause of poor quality of life in cancer patients receiving chemotherapy [21].

As per *Charak Samhita*, the symptoms of mucositis resemble the sign and symptoms of *pittaja mukh roga*, which is basically due to increased *pitta*

*dosha* in the body. Mouth gargles with *kalaka churna* mixed with liquids such as water and honey is indicated for such health problems, it is written in the text that this treatment cures all types of mouth disorders caused by excess of *pitta dosha* (i.e. showing signs of inflammation such as heat, redness and burning sensation) [Cha. Sam. 26/195-199; ref no. 13].

Recent scientific study showed that local application of *Yastimadhu* (*Glycyrrhiza Glabra* or licorice) powder (mixed with honey) in the oral cavity, prior to radiotherapy, reduces radiotherapy induced mucositis [22]. Oral application of honey is considered as a simple remedy for skin and mucosal surface damage as a result of radiotherapy [23]. Another ayurvedic herb called *arka* (*Calotropus procera*) has shown its anti-inflammatory property against chemotherapy induced mucositis [24].

Rectal mucosal damage is also a common complication of radiotherapy in ano-rectal carcinoma. In one study, oral administration of *triphala* prior to the radiotherapy, daily for consecutive five days, significantly reduced the mucosal damage associated with radiotherapy [25].

### Nausea and Vomiting

They are the most common occurrence during chemo-radiotherapy. In spite of use of anti-emetic drugs, 70% of patients show persistent symptoms [26]. Ayurveda recognizes this condition as *Chardi*. Nausea and vomiting induced by chemo-radiotherapy can well correlate with *pittaja chhardi* (*pitta dosha* dominant). The treatment mentioned for the same in ayurveda is as follows: Powder of *haritaki* (terminal chebula) mixed with honey or the Juice of resins or cold water processed with tender leaves of mango (*Mangifera indica*) and *jamun* (*Syzygium Cumini*) are all indicated for nausea and vomiting [27]. Multidrug preparations like *Kalyanaka Grita*, *Jivaneeya Ghritha* are also useful in the treatment of vomiting. *Khandkushmandavaleha* a poly-herbal preparation is indicated in various conditions like vomiting, hoarseness of the voice, fatigue, debility, burning sensation and cough [27]. *Eladi churna* is another multi-drug preparation which has potential of curing any kind of vomiting [Sha. Sam. 6/65-69; ref no. 20].

One scientific study has shown that ginger (*Zingiber officinalis*) supplementation at daily dose of 0.5g-1.0g significantly aids in reduction of the severity of acute chemotherapy-induced nausea in adult cancer patients [26].

## Anemia

Anemia is another common condition in cancer patients receiving chemotherapy. It significantly hampers the quality of life and is an important cause for blood transfusion in cancer patients [28].

*Ayurveda* mentions anemia under the heading of *pandu roga*. The treatment of *pandu roga* includes systemic purificatory therapy (*Panchakarma*), oleation therapy (internal and external application of medicated oil or ghee) followed by purgation, dietary modifications and oral medications. *Charak samhita* advocates use of cow's urine with other formulations for anemia. Cow's urine with *haritaki* or with *triphala* decoction or cow's milk is also indicated in case of anemia [Cha. Sam. 16/64; ref no. 13]. *Dhatriavaleha* is one of the best multidrug preparations for *panduroga* mentioned in ayurveda texts [Cha. Sam. 16/16; ref no. 13].

In a recent scientific study *Dhatriavaleha* was found as a good adjuvant in the management of thalassemia by reducing symptoms of fatigue, abdomen pain, pallor and joint pain in thalassemia patients [29].

## Diarrhoea

Fifty to eighty percent of patients receiving chemotherapy suffer from diarrhea which is contributor to poor quality of life and reduced treatment output [30]. *Ayurveda* identifies this condition as *atisara*. *pittaja atisara* is a type of *atisara* which is characterized by symptoms of excessive thirst, burning sensation and fainting. These symptoms are commonly found in diarrhea associated with chemo-radiotherapy. Treatment remedy mentioned in *ayurveda* is pepper powder with honey or butter milk with powder of *chitraka*. It has potential to cure all kind of diarrheas [Cha. Sam. 29/79; ref no. 13]. *Pippalyadi yoga* and *dadimastaka*

*churna* are also few of the multi-drug preparations indicated in diarrhea [Cha. Sam. 29/113; ref no. 13, Sha. Sam. 6/65-69; ref no. 20].

*Brahmi* (*Boswellia serrate*) [31] and *Jatiphala* (*Myristica fragrans*) [32] are other herbs with proven anti-diarrheal properties.

## Sleep Disturbances

Disturbed sleep is a major problem in patients receiving radiotherapy [33]. *Ayurveda* considers sleep as one of the important components of health. As per *ayurveda*, disturbed sleep leads to anxiety, worry, stress and vomiting [Cha. Sam. 21/55-56; ref no. 13]. *Ayurvedic* management of disturbed sleep includes whole body massage, bath, food items such as rice with curd or milk or ghee etc., meat soup of aquatic or forest animals, listening to soft and pleasant music, taking pleasant smell, sleeping in soft and comfortable bed [Cha. Sam. 21/52-54; ref no. 13]. *Kshirbala* oil and *mahamasha* oil are considered good for body massage.

The herbs *Shweta Musli* (*borivilianum*) and *Atmagupta* (Velvet bean) have significantly increased sleep quality in a scientific study [34]. Methionic extract of another herb called *Mundi* (*S. Indicus*) has shown its sedative property [35].

## Constipation

Constipation is another major problem in patients receiving specific chemotherapeutic agents such as cisplatin [36]. According to *ayurveda*, increased *pitta* aggravates *vata*, which leads to drying up of the colon and causes constipation [37].

*Erand* tail (caser oil) with the decoction of *triphala* or milk or with meat soup is indicated in constipation caused by increased *pitta* and *vata dosha* [Cha. Sam. 26/27-28; ref no. 13]. *Triphala* powder 2-6 gms with warm water and ghee is considered as good remedy for constipation [Cha. Sam. 26/27-28; ref no. 13].

In a scientific study a polyherbal preparation, which contains *ayurvedic* herbs such as Isabgol husk, senna extract and *triphala*, has shown its efficacy and

safety in the management of functional constipation [38].

## Fatigue

Deterioration of the general physical health with reduced exercise tolerance and muscle strength and fatigue are common manifestations of chemotherapy related side effects [39]. *Ayurveda* recognizes fatigue as *krish* or *dourbalya* and advocates use of drugs which are having the property of promoting strength (*Balya*). *Ashwagandha* (*Withania Somnifera*) and *Shatavari* (*Asparagus Racemosus*) are the famous drugs which are mentioned in this category [*Cha. Sam. Sutra* 4/7; ref no. 13].

In a randomized control trial, consumption of medicated ghee called *Ashwagandha ghrita* lead to significant improvement in shoulder stretch and weight bearing capacity. It indicates that this formulation may help in the patient suffering from fatigue [40].

Also in many studies anti-tumor activity of *Ashwagandha* has been reported. In one of them *ashwagandha* has shown anti-tumor property on chinese hamster ovary (CHO) cells carcinoma, hence it can synergize with conventional therapies of cancer [41].

## Cognitive Deficits

Nearly 61% of the patients receiving chemotherapy have cognitive declines in learning, attention and processing speed and cognitive difficulties in the domains of executive function, memory, psychomotor speed, and attention [42].

*Ayurveda* uses terms like *dhriti*, *medha*, *smriti* etc., which are different facets of cognition. There several drugs mentioned under the heading of *Medhya rasayana* which improve these facets of cognition [*Cha. Sam. chi* 1/73; ref no. 13]. Multi-drug formulations like *shankhapushpa* (*Convolvulus pluricaulis*), *Brahmi* (*Bacopa monniera*), *Mandukaparni* (*Centella asiatica*), *Vacha* etc. are considered as *medhya rasayana* [*Cha. Sam. chi* 1/73; ref no. 13]. *Chavanprash* is one of the *rasayana* which has vast use as per *ayurveda*, in relation to

cognition, it improves memory and intellect. It also helps in relieving excessive thirst and fatigue which is commonly seen during cancer treatment [*Cha. Sam. chi* 1/73; ref no. 13].

In recent study, *Chavanprash* has shown its protective effect against memory impairment along with decreased free radical generation and increased scavenging of free radicals [43]. In another animal experimental study *ayurvedic* herb *Brahmi* (*Bacopa monniera*) which is considered as one of the best *medhya rasayanas* ( which enhances the intellect and memory) has shown its effect improving the special learning performance and enhancing the memory retention [44].

Another herb *Ashwaganda* (*Withania Somnifera*) has a cognition promoting effect and was found useful in children with memory deficit and in old age people loss of memory [45]. *Ashwaganda* also been shown to have anti-tumor property in an animal study where it reduced cell proliferation and increased apoptosis [46].

In another animal experiment, a poly herbal preparation containing *Withania somnifera* (*Ashwagandha*), *Nardostachys jatamansi* (*Jatamansi*), *Rauwolfia serpentina* (*Sarpagandha*), *Evolvulus alsinoides* (*Shankhpushpi*), *Asparagus racemosus* (*Shatavari*), *Emblica officinalis* (*Amalki*), *Mucuna pruriens* (*Kauch bij extract*), *Hyoscyamus niger* (*Khurasani Ajmo*), *Mineral resin* (*Shilajit*), *Pearl* (*Mukta Shukhti Pishti*), and coral calcium (*Praval pishti*) has shown significant improvement in learning and memory retrieval [47].

## Pharyngitis

Pharyngitis is another common problem in patients receiving chemo-radiotherapy. A spray prepared from five aromatic essential oils (*Eucalyptus citriodora*, *Eucalyptus globulus*, *Mentha piperita*, *Origanum syriacum*, and *Rosmarinus officinalis*) has shown better immediate relief from the symptoms of sore throat than placebo control group [48].

## Skin Toxicity

Cutaneous adverse effects are among the more common adverse effects of newer antitumor drugs, they occur in up to 34% of patients receiving multikinase inhibitors, up to 90% of those receiving selective tyrosine kinase inhibitors (such as EGFR or mutant BRAF inhibitors) and up to 68% of those receiving immunotherapeutic agents (such as CTLA4 inhibitors) [49]. Commonly found cutaneous conditions side effects are - seborrhea, epidermal atrophy, xerosis cutis, itching, dry eczema and vulnerability of the skin to fissures - especially on the fingers, toes, and heels [49].

The above mentioned symptoms of the skin toxicity due to chemotherapy or radiotherapy are similar to skin disease due to increased *vata dosha* as mentioned in the *Charaka samhita*. While describing the treatment of these conditions *Charaka* mentioned *Abhyanga* (massage) and *swedana karma* (sudation therapy) and *basti* (enema) for *vata* related disorders [*Cha. Sam. chi* 28/30; ref no. 13]. *Bala taila* is mentioned in the context of treatment of *vata* related disorders. This oil can be used for massage, enema or internal use also. So body massage with *bala taila* may help to overcome skin related problems due to chemotherapy or radiotherapy [*Cha. Sam. Chi* 28/148-154; ref no. 13].

## Infertility

Cancer treatment affects fertility through both psychological as well as physiological effects; infertility could cause long-term distress [50].

*Ayurveda* has explained in detail about male infertility under the heading *klaibya* and female infertility under *vandhya*. Regarding the treatment in both male and female infertility Sage *Charaka* prescribed all the therapeutic cleansing procedures. These procedures are *vamana* (emesis therapy), *virechana* (therapeutic purgation), *basti* (enema with medicated decoctions or oils) etc. Once cleansing is over one should follow the prescribed dietary regimens [*Cha. Sam. chi* 30/45, 30/196; ref no. 13].

## Male Infertility and Ayurveda

This condition is called *klaibya* in *ayurveda*. The therapy which is given to maintain or regain the fertility in order to have good progeny is called *vajikarana*. *Bhavprakash (Bha. Pra.)* is another *ayurveda* text which describes that one should avoid everything which is the cause of the infertility [Bha. Pra. 72/22; ref no. 51]; stress anxiety are given as the common factors which contribute to infertility along with chemotherapy. These factors can be removed by the help *yoga brahatahatavari grita*, which is polyherbal preparation indicated for problems related to reproductive system both in male and female [Bha. Pra. 26/30; ref no. 51]. Several single drugs and polyherbal preparations are mentioned in *ayurveda* texts for infertility. Wheat powder cooked with milk along with cow ghee [Bha. Pra. 72/39; ref no. 51] or milk preparation with powder of wheat mixed with powder of *kapikachhu* (*Mucuna pruriens*) should be taken first then one should drink the milk which is also good aphrodisiac [Bha. Pra. 72/39; ref no. 51]. Several multidrug preparations like *gorakshadi modak*, *amrapaka*, *vanari vati* are also considered as few of the best aphrodisiac agents [Bha. Pra. 25/27; ref no. 51].

In a recent clinical study on the *Ayurvedic* herb *Mucuna pruriens (Kapikachhu)*, which is considered as a best among the Aphrodisiac, has significantly reduced psychological stress and seminal plasma lipid peroxide levels along with significant improvement in the sperm count and motility at the end of three months [52]. In an animal experiment, herb *Tribulus terrestris* also mentioned as *Gokshura* in the *Ayurvedic* text, has shown its aphrodisiac property by increasing mount frequency, intromission frequency, and penile erection index, as well as a decrease in mount latency and intromission latency along with increase in the serum testosterone levels [53].

## Female Infertility

Infertility is common in women receiving chemotherapy [54]. *Vandhya* is the term used to denote this condition in females in *Ayurveda*. Like in male infertility female also should undergo systemic cleansing procedures and then oral medication.

Following are the few remedies told in the *Ayurveda* - as the first and for most line of treatment, the women should avoid all foods and lifestyles that aggravate this problem. The herb of choice for female infertility is *ashoka* (*Saraca asoca* Roxb De Wilde) – by its astringent taste and cold potency, it strengthens the uterus. It stops bleeding by contracting the uterine blood vessels and promoting uterine muscular contraction. It stimulates uterine function by stimulating the decidual and ovarian functions. *Kumari* (Aloe vera) is another herb that improves blood flow to the decidual membrane and it stimulates uterine musculature to contract. It thus improves the menstrual flow. It should not be given during pregnancy as it may cause abortion [55]. It is useful in inducing ovulation. *Shatavari* (*Asperagus recemosus*) also nourishes the uterus and gives strength to the muscles. It induces ovulation and it also prevents abortion or miscarriage. *Ashokarista* (fermented medicine which is prepared by using *Saraca asoca* and other herbs) is most commonly used to regulate the menstrual cycle, improve endometrium and to stimulate ovulation. From the 4th day of the menstruation, *Ashokarista*, in combination with *Kumaryasava* (fermented medicine which is made by using Aloe vera and other herbs) should be given. It is usually combined with Aloes compound [a tablet which is made by using Aloe vera, *Manjista* (*Rubia cardifolia*), etc], *Rajapravrtinivati* (asafoetida, etc) to induce ovulation [55].

### Ayurvedic anti-oxidants

Psychological stress due to cancer diagnosis and cancer treatment itself can be cause for deficiency of anti-oxidants. Deficiency of anti-oxidants may have impact on tolerance of normal tissue to antitumor treatment and anti-oxidant supplements may lead to dose reductions and compromised treatment outcome [56].

Recently, studies have been conducted on the *Ayurvedic* medicinal herbs and many of them are found to be rich in antioxidants. *Amalaki Rasayana* (AR) is one among them. AR is a polyherbal preparation mentioned in the *Charaka Samhita*, it revitalizes and rejuvenates the cells to work against age-related deterioration. In one of the in-vitro studies

on methanoic extract of AR, its antioxidant property and free radicals scavenging activity have been demonstrated [57]. *Selagenella bryopteris* is another *ayurvedic* herb with proven anti-cancer, anti-oxidant, anti-inflammatory and chemo protective activity [58]. Other drugs such as *vyaghra nakhi* (*Capparis zeylanica*), *amalaki* (*Amlica officinalis*), *bhunimba* (*Andrographis paniculata*), Mango (*Mongefera indica*), *haritaki* (*Terminalia chebula*), *Brahmi* (*Bopa monniera*) etc. are other powerful anti-oxidants [59-61]. One of the most well-known preparations called *Triphala* is a polyherbal *ayurvedic* compound which contains three ingredients viz. *Haritaki* (*Terminalia chebula*), *vibhitaki* (*Terminalia belerica*) and *Amalaki* (*Embilica officinalis*). It is a potent anti-oxidant and laxative. Experimental studies on *triphala* have emphasized its importance as an anti-cancer, chemo-protective and radio-protective agent, especially *Haritaki* have been shown to reduce lipid peroxidation by increasing the glutathione levels [62-63].

### Hepatotoxicity

Many of the chemotherapeutic agents are hepatotoxic and they commonly cause hepatic injury in the patients [64].

*Ayurveda* identifies abnormalities related to liver by the term *yakrittodar*. It is associated with symptoms of fatigue, anorexia, constipation, nausea, vomiting, excessive thirst, emaciation, mild fever, loss of taste, abdominal distension, indigestion, prominent veins on the abdomen fainting, dyspnoea and cough [*Cha. Sam. Chi.* 13/38, ref no. 13].

*Ayurveda* recommends systemic purificatory therapy (*panchakarma*) depending on dominancy of the *dosha* (considering the strength of the patient). Massage, medicated enemas and intake of milk are strongly recommended. Oral administration of different poly-herbal preparations is also given for long term [*Cha. Sam. Chi.* 13/67; ref no. 13].

The multi-drug preparations such as *rohitaka ghrita*, *panchakola ghrita*, *pippalyadi churna panchgavya ghrita* etc. are recommended in such conditions associated with liver and abdominal diseases [*Cha. Sam. chi* 13/83-85, 13/149, 13/79; ref no. 13].

In a recent animal study where albino rats were exposed to gamma radiations, the rats treated with *Ashwagandha* (*Withenia somnifera*) showed significant reduction in serum hepatic enzymes, DNA damage, malondialdehyde (MDA levels), hepatic nitrates and significant increase in heme-oxygenase, super oxide dismutase and glutathione peroxidase activity respectively, as compared to the controls. This suggests its hepato-protective and anti-oxidant enhancing effect against radiation induced hepatotoxicity [65]. In another animal study, root extract of *ayurveda* herb *Himsra* (*Capparis sepiaria* L) was found to have significant hepato-protective property

against acetaminophen induced hepatotoxicity [66]. Similarly, *ayurvedic* polyherbal formulation called *Punarnavastaka kwath* has also been demonstrated to have hepato-protective property against CCL-4 induced hepatotoxicity [67]. Liv 52 is another multi-herb preparation proven to have hepato-protective effects against CCL-4 induced liver toxicity [68]. *Kumaryasava* is another important polyherbal compound shown to reduce liver weight that is increased due to CCL-4 induced hepatotoxicity [68]. Table 1 summarizes all major chem.-radiotherapy related side effects and *ayurveda* based remedies for them.

**Table 1. Summary of Chemo-radiotherapy side effects and *Ayurveda* based remedies**

| S. No. | Side effects of chemo-radiotherapy | <i>Ayurvedic</i> remedy   |   |
|--------|------------------------------------|---|---|
|        |                                    | Classical   | Research based  |
| 1      | Mucositis                          | <i>Khadiradi vati</i> for chewing<br>Mouth gargles with <i>kala churna</i> [ <i>Cha. Sam.</i> 26/195-199; ref no. 13]   | Oral application of <i>Yestimadhu</i> powder with honey [22]<br><i>Triphala</i> administration for five day prior to chemo [23]   |
| 2      | Nausea and Vomiting                | powder of <i>Haritaki</i> with honey or <i>Khandkushmandavaleha</i> [28]<br><i>Eladi churna</i> [29]  | Gut-Gard a extract from the <i>ayurvedic</i> herb <i>Yestimadhu</i> ( <i>glycrrhiza glabra</i> ) [Kadur Ramamurthy Raveendra et al] 2012<br>Ginger supplementation [26] |
| 3      | Anaemia                            | Oliation, purgation, oral intake cows urine with milk or<br>Cow's urine with decoction of <i>triphala</i> for 7 days [ <i>Cha. Sam.</i> 16/64; ref no. 13]  | <i>Dhatriavaleha</i> [29]   |
| 4      | Diarrhoea                          | <i>Pippali</i> powder with honey then butter milk with powder of <i>chitraka</i> or <i>Pippalyadi yoga</i> [ <i>Cha. Sam.</i> 29/79; ref no. 13]<br><i>Dadimashtaka churna</i> [ <i>Cha. Sam.</i> 29/113; ref no. 13, <i>Sha. Sam.</i> 6/65-69; ref no. 20] | Extract from herb <i>Brahmi</i> [31] and <i>Jatiphala</i> [32]  |
| 5      | Constipation                       | <i>Triphala</i> with warm water and ghee(evidence based) [ <i>Cha. Sam.</i> 26/27-28; ref no. 13]<br>Constipation caused by <i>vata</i> and <i>pitta</i> castor oil ( <i>Erand taila</i> ) with decoction of <i>triphala</i> or milk or meat soup. [56,47]  | <i>Isab</i> husk, senna extract and <i>Triphala</i> . TLPL/AY/01/2008 [ <i>Cha. Sam.</i> 26/27-28; ref no. 13]  |
| 6      | Pharyngitis                        | <i>Khadiradi vati</i> for chewing   | Spray of five aromatic plant oils [48]  |
| 7      | Sleep problem                      | Whole body massage, bath, rice with curd or ghee or milk etc. music, comfortable bed, cuddling before sleeping. [ <i>Cha. Sam.</i> 21/52-54; ref no. 13]  | Methoinic extract of <i>Mundi</i> ( <i>Sphaeranthus indicus</i> ) has sedative effect [35]<br>dietary supplement of <i>Shweta musli</i> and <i>atmagupta</i> [43]       |
| 8      | Hepatotoxicity                     | <i>Panchakola ghrita</i><br><i>Rohitaka ghrita</i><br>[ <i>Cha. Sam. chi</i> 13/83-85, 13/149, 13/79; ref no. 13].  | <i>Punarnavashtaka kwath</i> [65]<br>Syr Liv 52 [68]<br>Syr <i>Kumaryasav</i> [68]  |

| S. No. | Side effects of chemo-radiotherapy | Ayurvedic remedy  |  |
|--------|------------------------------------|---|--|
|        |                                    | Classical   | Research based                                     |
| 9      | Male Infertility                   | <i>Gokshuradi modaka</i><br>[Bha. Pra. 25/27; ref no. 51].  | <i>Mucuna pruriens</i> [52]                        |
| 10     | Female infertility                 | <i>Brahataшатavari Ghrita</i>   | <i>Ashokarista</i> [55]                            |
| 11     | Fatigue                            | <i>Ashwagandha</i> , <i>Shatavari</i><br>[Cha. Sam. Sutra 4/7; ref no. 13]                                  | <i>Ashwagandha ghrita</i> [41]                     |
| 12     | Skin changes                       | Massage with <i>bala taila</i><br>[Cha. Sam. chi 28/30; ref no. 13]   |  |
| 13     | Cognitive deficit                  | <i>Kalyanaka Grita</i> <i>Charaka chikatsa</i> 9<br><i>Chavanprash</i><br>[Cha. Sam. chi 1/73; ref no. 13]. | <i>Chavanprash</i> [43]<br><i>Ashwagandha</i> [46] |

### **Ayurvedic drugs having anti-cancer property: Scientific Evidences**

In series of animal experiments Wathaferin A, a constituent of *Ashwagandha* (*Withenia somnifera*) has been found effective in reducing mammary tumor size, microscopic tumor area and incidences of pulmonary metastasis [69-70]. It is being shown that *Ashwagandha* selectively kills cancer cells by inducing of ROS-signaling [71]. In another study, *Bhandirah* (*Clerodendrum viscosum*) was shown to have selective bioactivity against cervical cancer cells, its pro-apoptotic, anti-proliferative, and anti-migratory activities were demonstrated in a dose-dependent fashion against cervical cancer cell lines [72]. In one of the studies, *Haridra* (*Curcuma longa*) with an active ingredient of curcumin was shown to bind to cancer cell surface membrane and then infiltrate into cytoplasm to initiate apoptotic process. It was also reported that curcumin induced growth inhibition and cell cycle arrest at G2/M phase in the glioblastoma and medulloblastoma cells. This shows that curcumin has anti-cancer property [73]. *Manjistha* (*Rubia cardifolia*) is another widely used herb. Recent in-vitro study used its methanolic extract to induce apoptosis in HEP-2 (Human laryngeal cell line) as evidenced by cytotoxicity, morphological changes and modification in the levels of pro-oxidants [74]. Another study showed that aqueous extract of *Palash* (*Butea monosperma*) inhibited cell proliferation and accumulation of cells in G1 phase. Also there was a marked reduction in the levels of activated Erk1/2 and SAPK/JNK along with induction of apoptotic cell death [75]. *Triphala* is another useful

ayurveda formulation for treatment and prevention of cancer [76].

### **Ayurveda for Inhibition of Cancer Stem Cells: Hypothesis**

Many studies report association of inflammation and cancer. The identification of transcription factors such as NF- $\kappa$ B, AP-1 and STAT3 and their gene products such as tumor necrosis factor, interleukin-1, interleukin-6, chemokines, cyclooxygenase-2, 5-lipoxygenase, matrix metalloproteases, and vascular endothelial growth factor have provided the molecular basis for the role of inflammation in cancer [77]. These inflammatory pathways may get activated by tobacco, stress, dietary agents, obesity, alcohol, infectious agents, irradiation, and environmental stimuli. These pathways have been implicated in transformation, cancer cell survival, proliferation, invasion, chemo-resistance, and radio-resistance in cancer. The survival and proliferation of most types of cancer cells themselves appear to be dependent on the activation of these inflammatory pathways through their precursors, presumably cancer stem cells [77].

*Ayurveda* works on the fundamental principles of *tridosha* and *panchamahabhuta* (five basic elements of nature). According to *ayurveda* the inflammatory process is manifestation of abnormally increased *pitta dosha*. Most of the above mentioned herbs in the management of chemo-radiotherapy side effects are *pitta dosha* mitigating and thus, these herbs may indirectly inhibit growth of cancer stem cells via reducing inflammation. Further scientific studies are needed in this area. Till now one study on methanolic extract of the whole fruit of bitter melon also called

*karravella* (*Momordica charantia*) has shown dose-dependent reduction in the number and size of colonospheres. The extracts also inhibited cancer stem cells by reducing the expression of DCLK1 and Lgr5, which are markers of quiescent and activated stem cells [78].

*Rasayana* is one among the eight limbs of *ayurvedic* treatment which acts through various ways. The emerging data suggest that the possible mechanisms may be by immune-stimulation, quenching free radicals, enhancing cellular detoxification mechanisms; repair damaged non-proliferating cells, inducing cell proliferation and self-renewal of damaged proliferating tissues, and replenishing them by eliminating damaged or mutated cells with fresh cells [79]. These *rasayana* may also inhibit cancer stem cells; future studies should test the effect of these groups of medications on cancer stem cell survival and growth.

## CONCLUSION

This manuscript highlights a very important area of chemo-radiotherapy induced side effects in cancer patients. All the major and common side effects are covered and based on comprehensive review of ancient *vedic* literature and modern scientific evidences, *ayurveda* based management strategies are put forth. This manuscript should help clinicians and people suffering from cancer to combat serious chemo-radiotherapy related side effects through simple but effective home-based *ayurveda* remedies. The remedies described are commonly available and safe. These simple *ayurveda* based solutions may act as an important adjuvant to chemo-radiotherapy and enhance the quality of life of cancer patients. Future studies should scientifically test these recommendations for various side effects induced by conventional management of cancer.

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