

Kalyanaka Ghrtha - A proven chemo-protective and radio-protective formulation from Ayurveda

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Abstract

Radiotherapy and chemotherapy are the major conventional treatments of cancer which will be implemented alone or in combination or along with surgery through which one-half of the cancer patients are benefited worldwide. Radiotherapy uses ionizing radiations capable of generating reactive oxygen species which then react with cellular macromolecules resulting in cellular dysfunction and death. Meanwhile chemotherapy involves the administration of chemotherapeutic agents which cause toxicity to vigorously dividing cells like cancer cells. But due to their non-specificity towards normal tissues and other severe side effects such as immune suppression, breakdown of antioxidant defence system, gastrointestinal toxicity etc., the amount of chemotherapeutic agents or the dose of radiation that can be given against malignant tumours are often limited, but unavoidable in the present scenario. Therefore, the availability of chemoprotective and radioprotective agents which can protect normal tissues from these damaging effects during and after the course of treatment, will improve the outcome and quality of cancer treatment strategies.

The toxicities produced by the chemotherapy and radiation therapy comes are having similar pathophysiology as that of garavisha told in Agadatantra. The Kalyanaka Ghrtha, mentioned in Susrutha Samhitha Kalpasthanam – vishachikitsa prakaranam, is such a formulation which is mainly indicated for visha and gara. The chemoprotective and radioprotective roles of Kalyanaka Ghrtha has been statistically evaluated in Balb/c mice subjected to chemotherapeutic agent, cyclophosphamide (CTX), and radiation exposure respectively. Thus it can be concluded that Kalyanaka Ghrtha can be a favourable lead which can defend against the side effects of chemotherapy and radiotherapy which will provide a new dimension for the present cancer management strategies.

Key words

Chemotherapy, Radiotherapy, Agadatantra, Kalyanaka ghrtha

Introduction

Industrialization, population growth and globalization became the fundamental drivers of pollution and thus human beings are encircled by a vast number of environmental toxins. As we grow up we are exposed to seemingly benign compounds that are even meant to benefit us but have been shown to have long-term negative consequences. For example, fluoride in our drinking water has been linked to osteosarcoma and hypothyroidism. Additionally, vaccinations which undoubtedly prevent disease may contain the mercury compound, Thimerosal, which has been linked to the rise of autism in children. Among all these toxicities, drug induced toxicities are having a major role. The modern medicine is now much more advanced in adopting poison as medicines due to the concept that every drug is potentially toxic. Our body have a variety of mechanisms for dealing with this toxicity, but the current total load and body burden exceeds the body's ability to adapt or remove these toxins. The body will try to deposit these compounds into tissue to minimize their potential damage.

The modern scientific world is drastically searching for effective therapies for managing the cancer. The complete removal of the cancer without damage to the rest of the body is the goal of treatment. Sometimes this can be accomplished by surgery, but the propensity of cancers to invade adjacent tissue or to spread to distant sites by metastasis often limits its

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effectiveness. At present chemotherapy and radiotherapy are the unavoidable treatment modalities in the cancer management. Radical surgical procedure, large field hyper fractionated radiation therapy, high dose chemotherapy and maximum tolerable dose of cytokines are all used in certain settings where 100% of the patients experience toxicity and side effect. When cure of cancer is possible, treatment may be undertaken despite the certainty of severe and perhaps life threatening toxicity.

Toxicity due to chemotherapy

In order to study the toxicity of chemotherapy, cyclophosphamide (an alkylating agent coming under nitrogen mustard group) has been selected. Cyclophosphamide is widely used to treat a variety of malignant and non-malignant disorders. Although it has some tumour selectivity, it also possesses a wide spectrum of toxicities. The requirement of metabolic activation before Cyclophosphamide exerts either its therapeutic or toxic effects is well established, but has not led to effective countermeasures. Clinically, damage to the bladder (haemorrhagic cystitis), immunosuppression (when not desired) and alopecia are the most significant toxicities associated with Cyclophosphamide. Cardiotoxicity is also a possibility when very high doses are given. The crucial factor in the therapeutic and toxic effects of Cyclophosphamide is the requirement for metabolic activation. The active metabolites are generated preferentially in the liver, and to a lesser extent in other tissues. It is generally believed that the chlormethine metabolites (including phosphoramidate mustard and nor-nitrogen mustard) are responsible for the therapeutic effects, and acrolein for the toxic effects of Cyclophosphamide.³

Toxicity due to radiotherapy

As far as radiotherapy is concerned, rapidly dividing cells are more subjected to these damaging effects, the rationale behind this cancer therapy. But, at the same time, the surrounding normal cells and other highly dividing cells, if exposed, will be severely affected leading to major toxicities including immunosuppression, gastrointestinal toxicity, hepatic injury etc. even at low doses. The hematopoietic system is the most sensitive that suffers a decline of precursor bone marrow cells which will be destroyed, as said, thus leading to a depletion of all types of blood cells, especially the nucleated ones and platelets.⁸ Reports also show that radiation can induce the production of pro-inflammatory cytokines such as interleukin 1b (IL-1b) and tumour necrosis factor a (TNF- α) which can modulate undesirable inflammatory responses in various organs. In addition, all these responses to ionizing radiation involve a number of mediators including inflammatory cytokines produced by macrophages, epithelial cells, and fibroblasts. They can mediate intercellular interactions among the effectors of different physiological systems and their mechanism of action is quite complex with varying effects depending on the target cells and tissues.⁹

According to a proposed novel concept, the unwanted and underappreciated side effects of chemotherapy or

radiotherapy create a metastasis-receptive microenvironment in bones as well as in other organs of the body (e.g., pelvic cavity).¹⁰ This implies a challenge for modern pharmacology to develop powerful antitoxic compounds that can be combined with standard chemotherapy and radiotherapy protocols or applied as a follow up to these protocols.

Ayurvedic view on toxicity

Visha is defined as the substance which after getting into the body, vitiates rasadi dhatus and hampers health as well as life and also it can define as that substance which by virtue of its ten gunas acts against ojas and thus adversely affects the body and mind.¹² Visha is broadly classified into two types, akrtrima (natural) and krtrima or gara (artificial), in which all types of drug toxicities will come under garavisha.¹³

Garavisha – Mode of action

As per different Acharyas, krithrima visha or gara is a blend of savisha or nirvisha dravyas from animate or inanimate sources which will be always chirakari and rogajanaka in nature.¹² It will not undergo proper digestion and assimilation instead gets accumulated gradually leading to 'srothorodha' and causes agnimandya initially and imbalance of tridoshas later. The impairment of agni due to garavisha can also destroy the normal process of metabolism (dhathu parinama). In normal conditions, the proper dhathu parinama results in sara-kitta vibhajana. The saramsa used in body's development, maintain immunity, health etc and the kittamsa should be expelled out.¹⁷ In gara, the sara-kitta vibhajana gets disturbed due to agnimandya and the kittamsa get increased. These are nothing but the waste products of the body and it has to be expelled out. But due to the srothorodha it cannot be properly expelled out, rather it accumulates. When the rate of entry into the body is more than its rate of elimination, the toxins gradually accumulates in various tissues like kidney, liver, spleen, bone etc. Liver and spleen are the main organs that play a major role in detoxification of the toxins present in the body which are the root of raktavaha srotas also.

Agada – Antitoxic preparation

For managing any type of visha or

poisoning, a variety of formulations have been told in classical text books of Ayurveda which are called as Agadas. The modes of actions of agadas are thought to be through different mechanisms. Some of them may act by denaturing the toxic metabolites or preventing the formation of toxic intermediates. The acceleration of elimination process and activation of channels may be other reasons for the antitoxic property of these drugs. In addition to that there may be an alternate pathway by which the agadas detoxify the body.²²

Kalyanaka Ghrtha

The Agada, Kalyanaka ghrtha is mentioned in Susruta Samhita kalpasthana 6th chapter. Different formulations with the same name are also told by other Acharyas in chapters on unmada. Though all of them are indicated in garavisha, that which comes under Agad Tantra section has been taken for the study.

The drug is a ghrtha preparation and it contains 28 ingredients which are vidanga, triphala, danti, devadaru, harenu, taleesapatra, manjishta, kesara, utpala, padmaka, dadima, malatipushpam, haridradvayam, saribadvayam, sthiradvayam, priyangu, thagara, kushta, brhathidvayam, elavaluka, candana and gavakshi.¹⁸ Among these, thirteen possess vishahara property. It contains rasayana drugs which can repair and rejuvenate damaged cells and can balance the three doshas. Ingredients also contain agnimandya hara, agnivardhaka, amadosha hara, rakthadosha hara, raktha vardhaka, vrnahara and kushta hara properties.¹⁹ Chemoprotection reports of some ingredients of Kalyanaka Ghrtha are available whereas all the ingredients are reported as potent antioxidants. Free radical scavenging property has also been proved in certain drugs. In addition, Malatipushpa shows significant antiulcer property, manjishta, candana and haridra exhibits anticancer property along with chemoprotection and antioxidant property, nagakesaram, triphala, haridra, daruharidra and natha reveals excellent hepatoprotective property also.¹¹

Ghee contains vitamin A & E which are antioxidants and are helpful in reducing ketone bodies and preventing oxidative injury. Ghrtha is considered as one of the best vishaghna dravya. Since most of the toxic substances are lipophilic in nature, they easily conjugate with lipid molecules and the liver can make it water soluble and eliminate easily. Since ghrtha possesses samskarasyanuvartana property it can convey the properties of the drugs used to make formulations. On analyzing the property of the ingredients of Kalyanaka Ghrtha, the drug is predominantly thikta kashaya rasa, laghu rooksha guna, ushna virya, katu vipaka and pittakapha samaka in action. [11]

Chemoprotective and radioprotective effects of Kalyanaka Ghrtha

Toxicity due to chemotherapy and radiotherapy mainly affects the fast proliferative cells i.e. bone marrow and thereby erythrocytes and leucocytes, intestinal mucosal cells etc. These are discussed on the basis of experimental studies on chemoprotective and radioprotective effects of Kalyanaka Ghrtha in Cyclophosphamide

and radiation induced toxicity in mice. The hematological parameters (Hb, total count and differential count), biochemical parameters (AST, ALT and ALP of liver, serum urea and creatinine of kidney), antioxidant enzymes (SOD, catalase, GPx, GSH activity), oxidative stress marker (lipid peroxidation), bone marrow cellularity, histopathological changes of liver, kidney and intestine, changes in body weight and organ weight were analyzed.^{11,20}

Oxidative stress

Oxidative stress can be estimated by analyzing the lipid peroxidation, and the antioxidants SOD (Superoxide dismutase), CAT (Catalase), GPx (glutathione peroxidase) and GSH (Glutathione) levels. In this study the Cyclophosphamide group showed significant reduction in SOD, Catalase, GSH and GPx level. In Kalyanaka Ghrtha treated group, antioxidant enzyme and GSH level seems to be increased and lipid peroxidation level reduced significantly ($P < 0.001$). This protective effect may be due to the inhibition of the activity of cytochrome P-450, thereby reducing the production of ROS (Reactive oxygen species). Presence of Vitamin A and E, antioxidant and free radical scavenging property of the ingredients of Kalyanaka Ghrtha may be the reason for increased antioxidant and GSH levels and decreased lipid peroxidation. [11, 20]

Bone Marrow Suppression

On analysis, Kalyanaka Ghrtha seems to be highly effective to increase bone marrow cellularity and thereby the hematological parameters - hemoglobin level, total WBC count and differential count of leucocytes. It significantly increased bone marrow cells, leucocytes count and hemoglobin content ($P < 0.001$) Proportional increase was also seen in between granulocytes and agranulocytes. Amalaki, Manjishta, Kesaram, Dadimam, Ulpalam, Sariba, Priyangu, Candana etc. are excellent raktha dosha hara and raktha vardhaka drugs. Results indicate that the active ingredients of the drug may help to reduce myelosuppression and promotes cell growth. Enhanced numbers of bone marrow and α -esterase positive cells clearly indicated the effect of Kalyanaka Ghrtha on stem cell proliferation in irradiated mice

and its protective activity against radiation-induced hemopoietic syndrome. [11, 20]

Liver, Urinary Bladder and Intestine Injuries

Kalyanaka Ghrtha was found to be highly significant in the protection of organs from the toxicity caused by Cyclophosphamide. Both groups treated with Kalyanaka Ghrtha significantly reduced the hepatotoxicity and nephrotoxicity. ALP, AST, ALT serum urea and serum creatinine levels were observed to be decreased upto that of normal value ($p < 0.001$). Enhanced levels of GSH could prevent tissue damage in intestine. It will scavenge reactive oxygen species thereby preventing further peroxidation of membrane lipids. In Kalyanaka Ghrtha treated group, GSH level seems to be increased and lipid peroxidation level was reduced significantly ($P < 0.001$). [11, 20] Histopathological reports also agreed with the findings of the study that the organs of Kalyanaka Ghrtha treated groups showed no significant structural damage when compared to Cyclophosphamide and radiation alone treated group. Biochemically, cell membrane is composed of complex mixture of lipids, proteins and carbohydrates. Since the drug is a lipid preparation, they have a major role to maintain and repair the cell membrane. Ghrtha is also used as a carrier media in certain medicines to facilitate the transport of active principles across the cell membrane. All these may protect and repair the damaged cells. A significant reduction in body weight was also observed, whereas no significant change was noted for organ weight. [11, 20]

As per the statistical evaluation, among all the parameters except body weight and organ weight, Kalyanaka Ghrtha showed significant effect to protect from chemotoxicity and radiotoxicity. [11, 20]

Conclusion

Thirteen ingredients of Kalyanaka Ghrtha possess vishahara property. Vishahara drugs act either by denaturing the toxic substance or by accelerating the elimination process. In addition to that, ghrtha is mentioned as a dēpana dravya. It can promote the digestive power in all the agni level. So the chance for agnimandya and thereby srothorodha will be reduced and thus the cumulative property of the toxins get reduced. This also might be the reason for the protective action of the drug. Another thing to be considered is that, due to the dēpana and pachana property, the drug may help to speed up the metabolism, accelerate the elimination process and activation of elimination channels. Since the Kalyanaka ghrtha is having proved chemoprotective and radioprotective action its anti-metastatic property can also be studied in various cell lines which may add on the effective cancer therapy. As mentioned earlier, these toxicities are just a part of the various environmental toxicities. We are encircled with many types of such toxins which increase the relevance of more anti-toxic preparations or agadas. A variety of agadas are being told in Agadatantra which can be studied for various toxicities.

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