Tinospora cordifolia an Augmenting Agent for Quality of Life in Cancer: an Overview

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Abstract

Surgery, chemotherapy and radiotherapy are major approach of cancer treatment and excess reactive oxygen species molecule is generated during chemotherapy. Furthermore, chemotherapy depresses the immunity inviting infection with altered cognitive function. *T. cordifolia* having free radical scavenging capacity, decreases oxidative stress by increasing glutathione & other anti-oxidant enzyme and down regulate the pro-inflammatory cytokines. It stimulates helper T cellular immune, innate immune response and develops antigen specific immunity also increase the acetylcholine which is responsible for enhancing the cognitive function. Additionally, it inhibits cell proliferation, differentiation and induced apoptosis that prevent anti-tumor activity. Thus, we can assume that impaired quality of life due to chemotherapy in cancer will be well-adjusted by *T. cordifolia* and also have anti-tumor activity.

Keywords: *T. cordifolia*, Immunity, Oxidative stress, Inflammation.

Accepted on January 28, 2017

Introduction

Cancer treatment often contains one or more of three possible treatments like surgery, chemotherapy and radiation therapy. Among them chemotherapy is a group of medications act to stop or at least slow down the growth of tumor cells. It is used to kill cancer cell present in body, during chemotherapy normal tissue come in contact of chemotherapeutic agent and resulting in the unwanted side effects. Radiation therapy uses a beam of high energy radiation that targets the tumour while leaving the surrounding tissue less affected. Radiation acts to destroy DNA which can kill the cancer cells. Due to damaging the normal tissues either by chemotherapy or radiotherapy, it leads to numerous side effects like nausea, vomiting, fatigue, anorexia, constipation, hair loss, diarrhoea, sleep disturbance, headache along with these long term toxicity like laryngitis, pharyngitis, esophagitis, stomatitis, dry skin, hepatotoxicity, infertility and cognitive function may also deteriorate the quality of life [1,2]. Quality of life (QoL) perceives life satisfaction i.e. physical health, family, education, employment, wealth, religious beliefs, finance and the environment and has wide range of perspectives, including the fields of international development, healthcare, politics and employment [3,4].

It has been scientifically validated that adjunct treatment with herbo-mineral and metallic ayurvedic drugs appear to have a significant effect on reducing the toxic side effects of chemotherapy drugs in cancer patients [5]. In ayurvedic classics, *chandan* (*Santalum album*), *sariva* (*Hemidesmus indicus*), *manjistha* (*Rubia cordifolia*), *bhumi amalki* (*Phyllanthus niruri*), *kalmegh* (*Andrographis paniculata*), *guduchi* (*Tinospora cordifolia*), *amalaki* (*Emblica officinalis*) etc. has been reported for skin care, hepato-protective as well as cognitive enhancer [6] and protecting unwanted effect of chemotherapy and radiotherapy. Additionally, various herbs are documented for anti-vomiting, anti-pyretic, digestive stimulant etc. that will also helpful in enhancing quality of life. In present review we are trying to explore the pharmacological properties of *T. cordifolia* as quality of life enhancer with scientific facts and figure.

Ayurvedic materia media

Herbs, metals & minerals and animal products are three pillar of ayurvedic material medica. Among them herbs occupy the major seat for treatment of diseases as well as maintenance of health. Herbs have various chemical agents which belong to different classes, such as alkaloids, diterpenoid lactones, glycosides, steroids, sesquiterpenoid, phenolics, aliphatic compounds and polysaccharides. Due to presence of these chemical constitute herbs is responsible for numerous properties as per ancient texts of ayurveda, like *rasayana*, *sangrahi*, *balya*, *agnideepana*, *dahnashaka*, *mehnashaka*, *kasa-swasahara* and *jwarhara* etc. and antipyretic, antispasmodic, anti-inflammatory, antioxidant, anti-allergic, anti-stress, hepato-protective, immuno-modulatory, anti-neoplastic activities etc.

In contemporary sciences [7-9] it has been quoted that *T. cordifola* has *sangrahik*, *vatahar*, *deepaniya*, *shleshma-shonit-vibandh* pacifying properties which may responsible for disease curing as well as improving health [10].

T. Cordifolia as quality of life (qol) enhancer

In ayurvedic science *T. cordifolia* is used in ayurveda to enhance vitality by improves the ability of macrophages, immune system cell. Along with this it is reported as anti-allergic, adaptogen-like properties which protect against DNA damage induced by the environment and radiation therapy. In this way *T. cordifolia* may improve the quality of life even in cancer patients, the possible way of its action is summarized as mentioned.

Anti-inflammatory activity of *T. cordifolia*

It has been reported that chronic inflammation is moderately associated with lower quality of life (QoL) levels [11]. Most of the cancers are outcome of chronic irritation, inflammation and infection and it assists tumor growth, spread around the body, thus it seems that inflammatory cells are an indispensable sponsor in the neoplastic process, promotion, proliferation, survival and migration. It has been suggested that anti-inflammatory approaches play a big role in cancer prevention and treatment in the future [12,13]. Enormous medicinal plants have been listed in material medica of ayurveda which have potent anti-inflammatory activity such as *patala* (*Stereospermum suaveolens*), *gambhari* (*Gmelina arborea*), *agnimanth* (*Premna integrifolia*), *gokshur* (*Tribulus terrestirs*), *erand* (*Ricinus communis*) and *guduchi* (*T. cordifolia*) etc.[14] Among them *guduchi* occupied significant seat for management of different disorders, it has been reported that compound (1,4)-a-D-glucan (a-D-glucan), derived from *T. cordifolia* activate human lymphocytes with downstream synthesis of the pro-inflammatory cytokines such as tumor necrosis factor (TNF- α), interleukin beta (IL-1b), interleukin (IL-6,) IL-18, interferon's (IFN-c). [12] Among them TNF- α bind with tumor necrosis factor receptor superfamily member 1A /tumor necrosis factor receptor 1 (TNFRSF1A/TNFR1) and tumor necrosis factor receptor superfamily member 1B (TNFRSF1B/TNFBR) receptors, which regulate the biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism and may concern with variety of diseases like cancer, autoimmune diseases etc [15]. Furthermore, TNF- α and IFN- γ, co-expression of IL-18 strongly attenuates IL-12-induced systemic toxicity through a rapid induction of IL-10 [16]. It has been also reported that anti-inflammatory activity of *T. cordifolia* resembles that of non-steroidal anti-inflammatory agents [17] and possess significant antipyretic activity (when given orally) [18,19]. Thus we can assume that *T. cordifolia* diminished pain, fever etc. (common side effect of chemo-radiotherapy) when associated with chemotherapy agent by anti-inflammatory and anti-pyretic activity of *T. cordifolia* and prevent the genesis and growth of cancer.

Immunomodulatory activity of *T. cordifolia*

Cancers inhibit the normal immune response and enabling malignant cells to grow and spread through variety of mechanisms [20,21]. It has been reported that immune system is capable of eliminating tumor cells thus compromised immune system may have an increased incidence of cancer and are more likely to develop malignant tumors [22,23]. It has reported that immunomodulator improves the health-related quality of life [24,25]. So that immunotherapies are expected to become a treatment option for quality of life may be characterized within physical, material, social, emotional wellbeing, development and enhance activity cancer therapy along with the traditional methods such as surgery, radiation and chemotherapy. Used in combination with these three traditional methods, immunotherapies may upsurge the probability of long-term remissions in cancer.

It has been reported that IL 10 decreases immune pathology due to uncontrolled inflammation and inhibits sterile immunity [26] and IL 12 stimulate and maintenance of T helper (Th1) cellular immune responses, including the normal host defense against various intracellular pathogens and Th 1 further activate macrophages which are responsible for cell mediated immunity and phagocyte dependent protective responses. IL 18 increases NK cell activity which is part of innate immune response and develops antigen specific immunity and induces production of IFNγ [27] that directly inhibit viral replication, and shows immune-stimulatory and immune-modulatory effects [28]. Additionally, it executes diverse biological functions like host & anti-bacterial defense, cell cycle, apoptosis [29] and also associated with cytostatic/cytotoxic and anti-tumor functions by activated human T lymphocytes. Alpha-glucan polysaccharide present in *T. cordifolia* activates natural killer (NK) cells, T cells, and B cells and also induces production of interleukin (IL)-1, IL-6, IL-12, IL-18, interferon-gamma [30].

Due to stimulation of IL-12, IL-18, *T. cordifolia* stimulates Th1 cellular immune responses and innate immune response and also develops antigen specific immunity. Additionally *T. cordifolia* have a immunomodulation property through activation of macrophage [31] and increase in the WBC counts and bone marrow cells which stimulate haemopoetic [32,33]. Thus it shows immune stimulatory and immuno-modulatory activity. It has been reported that IL-10 was regarded as an immune suppressive cytokine that hindered anti-tumor immunity [34]. It has been reported that G1-4A obtained from *T. cordifolia* down regulate the IL-10. It has been reported that G1-4A which is a Polysaccharide obtained from *T. cordifolia* down regulate the IL-10 [29].

Thus we can assume that *T. cordifolia* decreases the immune suppression caused by IL 10 i.e. *T. cordifolia* may have immuno-stimulatory properties. Cancer therapy is associated with increased risk of development of tuberculosis [35,36] and it has been reported that combination of G1-4A (compound present in *T. cordifolia*) with Isoniazid (INH) exhibited better protection against MTB compared to that due to INH or G1-4A alone, suggesting its potential as adjunct therapy. Thus, G1-4A might improve the therapeutic efficacy of existing anti-tubercular drugs and provide an attractive strategy for the development of alternative therapies to control tuberculosis [29] in immune-compromised patients.

Anti-oxidant activity of *T. cordifolia*

Anti-cancerous agent kills the cancer cells (ionizing radiation, most chemotherapeutic agents and some targeted therapies) either directly or indirectly generating reactive oxygen species that block key steps in the cell cycle. And increasing concentration of exogenous oxidants modifies vital proteins, leading to cardiac muscle dysfunction and causes muscle weakness [37]. Reactive oxygen species (ROS) damages macromolecules, especially DNA, which undergoes strand breakage, change and release of bases as well as modification of sugar moieties [38,39]. Thus promoting a series of pathological event viz. cancer and aging. Furthermore,

chemotherapy drugs cause oxidative stress in noncancerous tissues which is negatively correlated with QoL. Moreover, oxidative stress leads to destabilization and disintegration of the cell membrane [40,41]. Additionally high ROS levels causes oxidation of protein which in turn induce oxidative stress and also decrease in the tissue glycoprotein, a potential mediator of pathogenic conditions [42]. It has been reported that antioxidants provide relief in cancer patients from debilitating muscle weakness, leading to improved quality of life. ROS are scavenged by cellular enzymatic and non-enzymatic antioxidants, which protect from oxidative stress. Glutathione (GSH) is an important non enzymatic antioxidant scavenging of free radicals and used to assess oxidative stress and chemo-preventive ability [43]. In previous research, antioxidant supplementation with chemotherapy and radiotherapy apparently decreased oxidative stress, maintained hemoglobin levels, and improved QoL [44]. *T. cordifolia* increases level of GSH as well as glutathione peroxidase (GPx) glutathione-S-transferase (GST), catalase (CAT) and superoxide dismutase (SOD) that protects harmful effects of lipid peroxidation and act as chemo-protective agent [45]. It has been reported that *T. cordifolia* increased the tissue glycoprotein and reduces oxidative stress [46] which protect from destabilization and disintegration of the membrane and improve quality of life.

Cognition function

Chemotherapy agents commonly produce cognitive impairment and can persist for 1 and 2 years after the completion of chemotherapy [47,48] and lasting between 4 and 10 years after chemotherapy [49,50] anticancer treatment regarding attention deficits, memory loss and thought processes and receiving increasing attention after long term and during & shortly after chemotherapy and for cancer. It is found that cognitive difficulties persist in 70% of cancer patients [51-53] and also reported that standardized neuropsychological treatment shows mild to moderate effects on cognitive performance in 15-50% patients [54,55]. The anti-cancerous drug (cyclosporine) produced impairment of learning and memory may be associated with degeneration of hippocampal neurons. *T. cordifolia* enhances cognition (learning and memory) by immune stimulation and increasing the synthesis of acetylcholine that is important neurotransmitter [56]. In ayurvedic literature, *T. cordifolia* is quoted as best medhya rasayana (learning and memory enhancer) [57] and useful for treatment of Bhrama (Vertigo), anti-stress activity [58] with moderate degree of behaviour disorders and mental deficit, along with improvement in IQ levels [59]. It has been reported that cognitive stimulation therapy (CST) will be effective to improve their cognitive functioning as well as QoL [60]. *T. cordifolia* has also been shown to enhance cognition (learning and memory) and reverse cyclosporine induced memory deficit. Along with its radio and chemo-protective effects, *T. cordifolia* has also been reported for neuro-protective potential by modulating anti-oxidant enzyme system of brain tissue, thus *T. cordifolia* may improve QoL.

Anti-tumor activity of *T. cordifolia*

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [61]. It is the disease of tissue growth regulation and normal cell to transform into a cancer cell, the genes that regulate cell growth and differentiation must be altered. Characteristic abilities developed by cancers are divided into categories, specifically evasion of apoptosis, self-sufficiency in growth signals, insensitivity to anti-growth signals, sustained angiogenesis, limitless replicative potential, metastasis, reprogramming of energy metabolism and evasion of immune destruction [62,63]. The term apoptosis is often used interchangeably with programmed cell death. In the strictest sense, programmed cell death may be applied to other forms of cell death that require gene expression without fulfilling some, or all, of the morphological criteria of apoptosis [64]. Naturally occurring phytochemicals display an active cancer preventive strategy to inhibit, delay, or reverse human carcinogenesis. It has been reported that 13-n-octyl-palmatine (4d) displayed potent cytotoxic activity against seven cancer cells and also improve the anti-proliferative activity, improve the anti-proliferative activity and exhibit significant antitumor activity against HL-60 leukemic cells [65]. It has been reported that *T. cordifolia* inhibit cell proliferation, differentiation and tumor-associated macrophages (TAM) [66] and induced cell death and also act as chemo-preventive agents through the induction of apoptosis [67]. Also, *T. cordifolia* extracts has anti-neoplastic as comparable as or better than doxorubicin treatment [68]. It is found that palmatine, yellow color compound is active constituents of a number of plants, such as *T. cordifolia* [69,70]. Thus *T. cordifolia* helpful in treatment of cancer by the presence of palmatine as active compound. The polysaccharide fraction from *T. cordifolia* is effective in reducing the metastatic potential of B16-F10 melanoma cells.

Conclusion

Hazardous effect of chemotherapy such as immunosuppression, impairment of cognition, generation of reactive oxygen species which hamper the quality of life will be well adjusted by *T. cordifolia* by its pharmacological properties like immuno-stimulant, cognitive enhancer and decreasing oxidative stress. Likewise, it also acts has antitumor activity. Thus *T. cordifolia* improve the quality of life in cancer patient and it may be beneficial if used with chemotherapeutic agent.

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