Chapter II

Review of Literature
REVIEW OF LITERATURE

All the orthodox systems of Indian Philosophy have one goal in view, the liberation of the soul through perfection. The method is by Yoga.\textsuperscript{20}

The present study analyzed the effectiveness of Pranayama as an intervention to treat cancer related fatigue. It also tested the effect of Pranayama in improving the level of certain enzymatic and non-enzymatic antioxidants in the breast cancer patients and the relationship of cancer related fatigue to the level of antioxidants.

Related research and non-research literature on cancer related fatigue, pranayama and antioxidants are reviewed to broaden the understanding of these concepts. The review of literature is organized under the following headings

1. Prevalence of cancer related fatigue
2. Mechanisms of cancer related fatigue
3. Treatments for cancer related fatigue
4. Yoga and Pranayama
5. Therapeutic effects of Pranayama
6. Yoga and Pranayama as treatments for cancer related fatigue
7. Pranayama and antioxidant status
8. Relationship between Breast Cancer and its Treatments to Antioxidants
9. Glutathione and Oxidative Stress
1. Prevalence of Cancer Related Fatigue

Fatigue is very much common among cancer patients and it has bearing on their lives during disease and treatment. Since the cancer-related fatigue (CRF) experience is personal (subjective) and has got different factors attributed to it, Wu and Mc Sweeney from St. Louis University have explored the meaning of CRF from the individual’s viewpoint using a qualitative study. They found a phenomenological approach, suitable for the study. The study was based on the philosophy of Merleau-Ponty’s embodiment and Gadow’s philosophy of relation between the self and the body. The study was conducted in an outpatient chemo clinic and the patients were selected using criterion sampling i.e., the patients who have experienced fatigue were selected. There were a group of ten cancer patients (women in the age group 30-73 years and were undergoing chemotherapy) who participated in the study. The data were collected by conducting a semi - structured individual interview and a daily fatigue diary. Data was analysed using reduction methodology and specific themes were identified. Cancer patients described fatigue as a different experience; for example, one woman reported it as “It’s so much more than just being tired.” The authors have also found that the women were unable to anticipate the development of cancer related fatigue and they did not have any strategies to fight fatigue. Each of them developed their own ways to combat fatigue and to gain self-control based their personal experience. The author recommended that nurses and other health care providers must help cancer patients to distinguish and manage cancer related fatigue.

Stone et al determined the prevalence of fatigue, its severity and correlating factors of fatigue among both cancer patients and controls. The data were collected using questionnaires on fatigue, psychological symptoms and quality of life. Patients were
recruited from the Royal Marsden NHS Trust (a specialist cancer hospital) and Edenhall Marie Curie Centre (a hospice). Controls were volunteers from the hospital volunteers’ organisations. The number of cancer patients participated in the study was 227 and that of controls were 98. They found that 15% of the recently diagnosed patients of breast cancer reported severe fatigue. The results also showed a statistically significant association between fatigue and the psychological symptoms (anxiety and depression).  

Lavdaniti assessed fatigue and health status among breast cancer patients undergoing radiotherapy in a major oncology center in Athens, Greece. Data were collected with the Revised Piper Fatigue Scale (PFS) and the Short Form-36 (SF-36) Health Survey Scale in the first two days of radiotherapy, during the third week, and during the last week of treatment. Revised Piper fatigue scale had of 22 items measuring fatigue in the following areas. Severity of fatigue, affective meaning of fatigue, sensory and cognitive factor affecting fatigue was captured by the scale. The minimum score of piper fatigue scale was zero and the maximum score was 220. The higher score indicated higher levels of fatigue. As per this, most of the patients experienced low levels of fatigue with a mean fatigue score of 1.96 (± 1.90). Only few patients experienced higher fatigue levels. Approximately 13% of the breast cancer patients only experienced moderate to high levels of fatigue as per the results. Fatigue increased during radiotherapy in patients with breast cancer regardless of stage, type of surgery, or whether they received chemotherapy.  

Lamino, Mota and Pimenta analyzed the prevalence and comorbidity of pain and fatigue in 182 breast cancer patients in all the phases of the disease and treatment. Patients were attending the outpatient follow up clinics in Portugal at the time of data collection.
Fatigue was assessed using the Piper Fatigue Scale, which is a 10 point scale with 22 items assessing the sensorial, affective, cognitive aspects and the intensity of fatigue. If the scores of the fatigue were 0.1-4.9, it was categorised as mild fatigue and if scores were 5-10, it was moderate or intense fatigue. Fatigue was reported by 94 women who were under study. Out of them 44 (46.8%) reported moderate or intense fatigue. Comorbidity of pain and fatigue was observed in 60 (33%) patients.23

Manir et al. assessed the prevalence, course and degree of fatigue among women with breast cancer on adjuvant treatments at Palliative Care Unit of Department of Radiotherapy, Medical College and Hospitals, Kolkata, West Bengal during 2010 -2011. They were stage I to stage III post-mastectomy breast cancer patients. As adjuvant treatment, six cycles of chemotherapy were given using 5-Flurouracil, Doxorubicin, and Cyclophosphamide with a 21-28 days interval. Fatigue was assessed one week before among patients on chemotherapy and a day after chemotherapy. The post-test measurements were repeated two weeks later in every cycle among these patients. Those who had an indication to radiotherapy were treated with external beam radiation with Cobalt 60 machine (50Gy in 25 fractions 5 days a week). Patients undergoing radiation were assessed for fatigue one week before starting radiation and every week during the course of radiation. Fatigue was assessed using Functional Assessment of Chronic Illness Therapy - Fatigue subscale (FACIT-F). The reports showed that 91% of the people receiving chemotherapy and 77% of the people receiving external beam radiation therapy for breast cancer were having fatigue. For patients on external beam radiation therapy, fatigue increased gradually during the course of radiation treatment.24
Bower et al. assessed the occurrence of fatigue among survivors of breast cancer in comparison to that of general population. Breast cancer survivors from Los Angeles, CA, and Washington, DC were assessed for fatigue. The data were collected using standardized scales on quality of life, instruments and scales to measure cancer specific problems, demographic and medical data, and several new questionnaires designed specifically for breast cancer survivors. Low energy levels were exhibited by women (treated with radiation therapy, chemotherapy, or both) at one year after diagnosis (ie, mean energy/fatigue score, 57). Their energy levels increased at two years after diagnosis, and remained relatively stable at 3 years, 4 years, and 5 years after diagnosis. Women treated with surgery alone did not exhibit any fatigue at one year post diagnosis. Fatigue was strongly associated with bodily pain, sleep disturbances, depression and hot flashes and night sweats in menopausal women.25

Biswal, Kumaraswamy and Mukhtar assessed the prevalence of fatigue among patients with cancer undergoing external beam radiation therapy in the Division of Radiotherapy and Oncology of the University Hospital, Sains Malaysia. Thirty three of the patients studied had cancer in the head and neck, 15% had in the breast, 22% had in pelvis, 8% had in brain and spine and 25% had cancer in other sites. Patients were receiving fractionated radiation for five days a week. Fatigue was assessed towards the end of external beam radiation therapy (fractionated course) using Modified Piper Fatigue Scale which assessed the different dimensions of fatigue like severity, affective aspects, and sensory and cognitive mood aspects. In this study, each dimension of fatigue was assessed separately and the sum total was assessed jointly. There were a total of one hundred and fifteen patients who have completed the questionnaire and participated in the study. 43% of them have
reported significant fatigue. Stage of the disease was found to be a significant factor contributing to radiotherapy related fatigue.\textsuperscript{26}

Huang et al conducted a study among women with breast cancer undergoing endocrine therapy at the Tumour Hospital of Harbin Medical University, Harbin, China. The study assessed the prevalence and severity of cancer-related fatigue and the factors associated with it. All the women who participated in the study were having stage I-IIIA breast cancer and were oestrogen receptor-positive and progesterone receptor-positive or progesterone receptor-negative. Among the 315 women who answered the questionnaire, 54 (17.1%) women had already finished endocrine therapy and 261 (82.9%) women were still undertaking endocrine therapy. Out of 315 patients, 189 (60%) had reported that they have experienced cancer related fatigue while undergoing endocrine therapy. The factors found to be related to cancer related fatigue were body mass index (BMI), clinical stage of the disease, menopausal status of the women and length of endocrine therapy, physical activity, and diet. The factors unrelated were age of the patient, marital status of women, other treatments undergone, drugs used for endocrine therapy, intake of alcohol and history of smoking.\textsuperscript{27}

2. Mechanisms of Cancer Related Fatigue

Ryan et al in the review, mechanisms of cancer related fatigue (CRF) suggested that the etiology of CRF probably involves 5-HT neurotransmitter dysregulation, vagal afferent activation, alterations in muscle and adenosine tri phosphate metabolism, hypothalamo–pituitary–adrenal axis dysfunction, circadian rhythm disruption, and cytokine dysregulation. They have also cautioned in extrapolating this knowledge to cancer related fatigue as these
are results from studies related to chronic fatigue syndrome and fatigue which is exercise-induced.²⁸

Gutstein in the review, the biologic basis of fatigue, has pointed out that symptoms related to energy imbalance and pain treatment may add to the development and progress of fatigue in cancer patients. Further the author explained anemia, stress and mood, cachexia, cancer therapies, infection, para-neoplastic syndromes and metabolic disorders as factors contributing to cancer related fatigue.²⁹

Ahlberg et al in the review “Assessment and management of cancer-related fatigue in adults” have highlighted anaemia, cancer treatments, cachexia (weight loss due to cancer), burden related to tumour, and the discharge of cytokines as physiological factors that contribute to the development of fatigue.³⁰

Portenoy and Itri have pointed out that cancer related fatigue is multi factorial. The factors contributing to cancer related fatigue are summarized as physiologic factors, primary disease and treatment for cancer like chemotherapy, radiation therapy, surgery and biologic response modifiers. It could also be coexisting morbidities like anemia, infection, lung disorders, failure of liver, failure of heart, insufficiency of kidneys, improper nutrition, disorders of the neuromuscular system, water and electrolyte disturbances, disorders of sleep, immobility and lack of exercise, chronic pain and use of centrally acting drugs to treat pain (e.g., opioids). Psychosocial factors like disorders of anxiety, depression, stress-related factors and the environmental reinforcers also may add to the development and progress of fatigue.³¹
Kurzrock in the review article stressed that many factors may contribute to the origin of cancer related fatigue. Those factors may include anemia, loss of weight, pain, fever and infection and medication. The author emphasised the influence of interplay of cytokine levels and their antagonists to these contributing factors of fatigue. High levels of cytokines, such as IL-1 or IL-6 are produced by cancer cells and they initiate a chain of reactions by which other cytokines are formed. In addition to the decreased erythropoietin response, the development of anaemia in cancer patients can also be attributed to some cytokines such as interleukin-, IL-6, tumour necrosis factor-a [TNF-a]), which suppress erythropoiesis. Cancerous cachexia which is a major contributing factor for cancer related fatigue is also associated with cytokines in addition to loss of appetite and poor intake. Cytokines that are known to induce weight loss include tumour necrosis factor, IL-1, IL-6, interferon-g, and leukaemia inhibitory factors.32

Ferreira and Reid in the review highlight the role of reactive oxygen species (ROS) and regulation of thiols in the development of muscle fatigue. Reactive oxygen species are produced within skeletal muscle fibres at multiple sites by various mechanisms like the mitochondrial electron transport chain, phospholipase A2, and arachidonic acid metabolism by the lipoxygenase pathway. Muscles have a intense system of antioxidant enzymes that degrade reactive oxygen species. The antioxidant enzymes in the muscle include Cu-Zn-superoxide dismutase (Cu-Zn-SOD; SOD1), catalase, MnSOD (SOD2) and glutathione peroxidase. Glutathione is the most plentiful non-protein thiol present within the cells. They are present at near milli molar concentrations, and primarily determine the reducing environment of the cells. In the context of muscle fatigue, glutathione is among the most important non-enzymatic antioxidants. At the biochemical level, it is clear that reactive
oxygen species influence components of the muscle during vigorous exercise. The authors assert that thiol oxidation is a change detected after strenuous exercise and oxidation of thiol may be a most sensitive marker of oxidative stress and is most strongly implicated in fatigue.  

Richards, Wang and Jelinek measured malondialdehyde in erythrocytes, reduced glutathione in erythrocytes, 2, 3-diphosphoglycerate and methemoglobin in thirty three patients (10 men and 23 women) with chronic fatigue syndrome and 41 age- and gender-matched controls (18 males and 23 females). 2, 3-DPG, MDA and met Hb were significantly increased in the chronic fatigue syndrome group compared to the control group. The level of reduced glutathione in erythrocytes showed no statistically significant difference. The authors suggest that the normal level of reduced glutathione was probably due to the size of the sample tested. However, regardless of normal levels of erythrocyte reduced glutathione, there were significantly increased levels of MetHb in chronic fatigue syndrome group (mean 5 1.26%) compared to the control group (mean 5 0.55%) which may probably indicate oxidative injury to the haemoglobin molecules. The products like methemoglobin may cause damage to membranes of red cells by oxidation of sulphhydryl groups on the membrane and peroxidation of lipids. Peroxidation of lipids on the red blood cell membrane in chronic fatigue syndrome is strong evidence that free radicals play a part in pathogenesis of this syndrome.  

3. Treatments for Cancer Related Fatigue

Minton et al in their systematic review and meta-analysis of pharmacological treatment of cancer related fatigue identified a few drugs which are helpful in treating cancer
related fatigue. They have reported that methylphenidate (a psychostimulant) was used to treat cancer related fatigue. The results of the meta – analysis of two studies showed that it was superior to placebo. Another analysis showed that erythropoietin was superior to placebo in anaemic cancer patients based on the meta-analysis of ten studies. They recommended further trials in confirming these drugs as pharmacologic treatment of cancer related fatigue.\(^{35}\)

Dimeo in the article ‘Effects of exercise on cancer-related fatigue’ mentioned that patients with cancer often suffer from fatigue and a decrease in ability to perform physically. The author has explained the reasons for development of cancer related fatigue in different contexts, the most important being an alteration in the muscular energetic systems caused by cancer and its treatment. It is further explained that several functional and anatomic changes due to cancer and cancer treatment can affect the oxygen supply to the cells for aerobic respiration. This may include alterations of the bronchial tree, lung and plasma volume, pulmonary perfusion, surface of the alveoli, heart function, red blood cell count, and concentration of oxidative enzymes in the muscle cells. When the energy is not released during aerobic pathway, anaerobic pathway is activated resulting in the release of lactic acid, which may contribute to fatigue. The authors also suggest that increased release of cytokines and anaemia during the course of cancer treatments can contribute to the development of cancer related fatigue. Numerous studies have described that exercise can prevent and reduce the severity of fatigue in cancer patients during and after treatment. Exercise or physical activity is thought to produce positive changes like improvements in muscle mass and volume of plasma, enhanced lung ventilation and perfusion, improved cardiac reserve, and a greater concentration of oxidative enzymes in the muscles. Improvement of physical
performance can increase self-control, individuality, and self-esteem and confidence of patients resulting in better social contacts and a reduction in anxiety and fear. The authors recommended studies on the effects of different exercise forms on the immune system to reduce cancer related fatigue.\textsuperscript{36}

Mustian et al. emphasized physical exercise as an integrative non-pharmacologic behavioural intervention in the treatment of acute cancer related fatigue experienced by patients with cancer during and after completion of treatment. Exercise as a strategy has been found to be effective throughout when a patient undergoes cancer care. Its effectiveness has been tested among cancer patients following surgery, following transplant, and during and after radiation therapy, chemotherapy, and/or hormone therapy. It was found that seated exercise with low-intensity was safe and well tolerated even by metastatic breast cancer patients. Progressive resistance training was found to be effective in reducing cancer related fatigue in patients with cancer getting hormone therapy. A meta-analysis by Schmitz and colleagues advocates that even though exercise is consistently shown as an effective therapy for managing cancer related fatigue, different methods and more effective exercise interventions are to be developed. The studies which used exercise as an intervention to treat cancer related fatigue had small sample sizes. Further the type and amounts of exercise to be done to combat fatigue are not specified by these researchers. With such limitations, it is presently not possible to prescribe an exercise regimen tailored to the patient’s needs.\textsuperscript{37}

Next to exercise, the interventions widely used to address cancer related fatigue are psychosocial interventions. These include activities such as individual or group supports, education to manage fatigue, management of stress, training to enhance coping strategies,
and behavioural strategies designed to assist cancer survivors in managing their cancer related fatigue. Cancer survivors for whom exercise is contraindicated will benefit from psychosocial interventions. They can also be used in addition to exercise programs among survivors. It was also found that individual and group psychosocial interventions are equally effective in helping to manage cancer related fatigue. Also it did not matter whether these interventions were administered orally or written and by a licensed professional or a trained non-professional. The effect of these interventions lasted for long times (many months) after the sessions were completed. Too lengthy interventions during the course of cancer treatments were found to worsen cancer related fatigue. There are too many psychosocial interventions tested and most of them lack proper descriptions that confirming an appropriate form or optimal content and mode of delivery of any of these interventions to treat cancer related fatigue is not possible.\textsuperscript{37}

Mindfulness-based stress reduction is another intervention used to reduce cancer related fatigue among many cancer patients undergoing therapy. Here also the evidence is preliminary. The authors recommend that more trials are required using mindfulness-based stress reduction with cancer related fatigue as a primary outcome to confirm it as a modality of treatment for cancer related fatigue.\textsuperscript{37}

Studies have also tested nutritional interventions to treat cancer related fatigue. Cancer and its treatments make the patients prone to the development of malnutrition and other nutrition-related problems. Nausea, vomiting, mucositis, diarrhoea, and malabsorption of food etc may contribute to the development of malnutrition in a cancer patient. Fatigue may be a clinical expression of malnutrition in cancer patients. Studies have shown that
protein supplementation reduces fatigue in cancer patients. Although results from this trial are encouraging further studies are required before confirming the benefits of nutritional therapy on cancer related fatigue.\textsuperscript{37}

Cancer patients with fatigue frequently experience disturbed sleep patterns. Some studies recommend improved sleep hygiene as a solution to the problem. Patients should be encouraged to go to sleep at the same time every night and to get up from bed at the same time every morning. Reducing duration of daytime naps, limiting overall time spent in bed and avoiding stimulants like coffee or tea in the evening might help in falling asleep faster. Again the evidence existing in this area is preliminary because of the lack of adequately powered and controlled studies.\textsuperscript{37}

Polarity therapy is an energy therapy developed by Randolph Stone in 1947. Polarity therapy employs attempts to balance the electrical energy fields of living organisms using gentle human touch. A randomized, controlled pilot study published by Roscoe and colleagues investigated the efficacy of polarity therapy among breast cancer survivors. Participants received one 75-minute session or two 75-minute sessions (a week apart) of polarity therapy during the course of radiation therapy. There were significant reductions in cancer related fatigue among those who receive polarity therapy compared to those receiving radiation therapies alone. This is the only published study available in this area and the sample size for the study was very small (n = 15).\textsuperscript{37}

One aspect of the sensory dimension of cancer related fatigue is decreased capacity of attention or attentional fatigue. Attentional capacity can be regained with restorative therapy. Activities that engage patients attention were includes in restorative therapy. A
randomized controlled trial involving 32 breast cancer patients during the postoperative period has observed improvements in attentional fatigue with restorative therapy. Data in this field is preliminary and further research is needed to establish the efficacy of restorative therapy for the management of cancer related fatigue.37

Yoga combines physical exercise with mindfulness. With the hope of easing side effects like cancer related fatigue, and improving quality of life, more and more cancer patients are turning to yoga. There are not many valid studies done with yoga as an intervention for cancer related fatigue. Most of the evidence remains preliminary. Yoga can be used for the clinical management of cancer related fatigue only after conducting appropriately powered, randomized controlled trials with cancer related fatigue as a primary outcome.37

In the recommendations for future research, the author further stressed that numerous number of studies are still needed in the area of non-pharmacologic behavioural interventions for the clinical management of CRF. The author recommended to focus the future research on aspects like mode, frequency, intensity and duration of physical exercise for treating cancer related fatigue, safety and effectiveness of physical exercise for the various cancers, side effects or negative effects of these exercises, whether they will interfere with the effects of cancer treatments, what is the optimal mode of delivery of exercises and which other non-pharmacologic behavioural interventions, such as yoga, mindfulness based stress reduction, nutrition, sleep, polarity, and restorative therapies, are effective in treating cancer related fatigue.37
Mock in this article emphasized that exercise can be used to manage fatigue in patients with cancer based on the strong evidence from clinical trials. Exercise is tested as an intervention for cancer related fatigue based on the assumption that reduced capacity for physical performance among cancer patients is caused by a decreased level of physical activity and the toxic effects of cancer and its treatment. Exercise is also known to increase blood circulation and may also reduce the amount of circulating cytokines or other toxic substances facilitating cancer related fatigue. Studies done for cancer related fatigue with exercise as an intervention have shown that patients who exercised experienced less fatigue than the control group patients. Most of the studies adopted aerobic exercises and included some walking programs (home-based) or bicycle exercise or treadmill formats. Few studies have also shown that there was reduction in fatigue as a result of resistive strength training. Aerobic exercises have decreased fatigue levels by almost 40%–50%. Most of the studies on exercise as an intervention for cancer related fatigue were conducted on women with breast cancer at different phases of cancer treatment. These patients were selected or recruited for study regardless of their current level of fatigue and the information regarding the effectiveness and acceptability of an exercise program among patients who already suffer from high levels of fatigue is very limited.\textsuperscript{38}

4. Yoga and Pranayama

Man realized very early the need to keep his body healthy, strong and clean in order to follow Dharma and to experience the divinity within himself. In this effort, the Indian Seers compiled the essence of Vedas into Upanishads and Darshanas.
Yoga is the union of the individual self (Jivatma) with the Universal self (Paramatma). The system was first collated and written down by Patanjali in his Yoga Sutras or Aphorisms. The Yoga Sutras consist of 195 aphorisms divided into four chapters. The first deals with the theory of Yoga. The second chapter on the art of yoga initiates the beginner into his practices. The third is concerned with the internal discipline and powers he gains and the fourth chapter about freedom from the bonds of mind as a result of practicing Yoga.

The word ‘Yoga’ means to bind, join, attach or unite. Yoga is practiced to direct the mind to concentrate and become attentive to facilitate meditation. By practicing Yoga, an incoherent mind becomes attentive and reaches a reflective and coherent state.

Patanjali’s Yoga Sutra listed eight stages of Yoga: Yama, Niyama, Asana, Pranayama, Pratyahara, Dharana, Dhyana and Samadhi. Mind in a state of dullness is purified through Yama, Niyama and Asana. Asana and Pranayama bring the restless mind to a state of some stability. The disciplines of Pranayama and Pratyahara make the mind attentive and focus its energy. It is then restrained in this state by Dhyana and Samadhi.

First, Yoga deals with health and strength of the body. Next, it lifts the veil separating the body and the mind. Lastly, it leads to peace and purity.

Thus, Pranayama is the fourth limb of the stages of Yoga. ‘Prana’ means breath, respiration, life, vitality, energy or strength. ‘Ayama’ means stretch, extension, expansion, length, breadth, regulation, prolongation, restraint or control. ‘Pranayama’ thus means the prolongation of breath and its restraint.
Pranayama is an art and has techniques to make the respiratory organs to move and expand intentionally, rhythmically and intensively. It consists of long, sustained subtle flow of inhalation (puraka), exhalation (rechaka) and retention of breath (kumbhaka).

Pranayama is not just automatic habitual breathing to keep body and soul together. Through the abundant intake of oxygen by its disciplined techniques, subtle chemical changes take place in the sadhaka’s body\textsuperscript{17}.

The word \textit{prana} is a combination of two syllables. \textit{Pra} and \textit{na}. Prana denotes constancy; it is a force in constant motion. Prana is the vital life force and pranayama is the process by which internal pranic store is increased. Pranayama is comprised of the words \textit{prana} and \textit{Ayama}, which means ‘pranic capacity or length’. It is not merely breath control, but a technique through which the quantity of prana in the body is activated to a higher frequency.

Pranayama is practiced in order to understand and control the pranic process in the body. Breathing is a direct means of absorbing prana and the manner in which we breathe sets off pranic vibrations which influence our entire being\textsuperscript{39}.

In metaphysics, Prana is the sum total of the energy that is in the universe. It is this Prana by which we breathe and by which the circulation of the blood goes on; it is the energy in the nerves and in the muscles and the thought in the brain. All forces are the different manifestations of the same Prana. The finer movements that are going on inside the body are connected with breathing. If we can get hold of this breathing and manipulate it and control it, we will slowly get to finer and finer motions, and thus enter into the realms of the mind\textsuperscript{20}. 
5. Therapeutic Effects of Pranayama

A study was conducted by van Puymbroeck, Payne and Hsieh among caregivers of patients with Hatha yoga, asanas and Pranayamas as intervention to understand physical fitness and coping changes that may occur as a result of an 8-week program. In this study, caregivers attended yoga for 8 weeks (2.5 hours/week) and performed a variety of asanas and pranayama under the guidance of a certified yoga instructor. Those in the yoga group have reported that they enjoyed the intervention and there was improvement in coping, upper body strength, upper body flexibility, balance and agility and aerobic endurance.40

A study done by Deshpande, Nagendra and Raghuram in Bangalore India has shown that an integrated yoga module that included asanas, pranayama, meditation, notional correction and devotional sessions for one hour daily, six days a week for eight weeks can reduce somatic symptoms (SS), anxiety and insomnia (AI), social dysfunction and severe depression among adults. The authors have also shown that yoga and pranayama has improved global self-esteem, moral, social esteem, family self-esteem, physical appearance and verbal aggressiveness.41,42,43,44

Another study conducted by Jagannathan et al has found that a ten-day group yoga program (satsang, warm-up exercises, yogic asanas and pranayama) developed in a qualitative study reduced the burden and improved coping of caregivers of patients with schizophrenia in India45.

Ebnezar et al conducted a randomized control study on patients with Osteo Arthritis knees at the outpatient department of Dr John's Orthopedic Center, Bangalore. The patients were assigned to a yoga group and a control group. The yoga group performed
shithilikaranavyayama (loosening and strengthening), asanas, relaxation techniques, pranayama and meditation 40 min daily (6 days/week) for 2 weeks whereas the control group performed physiotherapy exercises. The yoga group exhibited significant improvements in quality of life compared to the control group. There were significant improvements in the areas of pain reduction, improvement of general health, social functioning, emotional well-being and energy and fatigue level.

Khemka, Ramarao and Hankey assessed the effect of integral yoga on certain psychological and health variables. 108 healthy volunteers in Bangalore were given an intervention of an integrated approach to yoga therapy module. The module consisted of asanas, kriyas, pranayama, meditation, lectures, yogic games and singing for approximately 45-60 min. Results showed significant improvement in emotional intelligence, attention and general health of the participants.

Ebnezar et al further assessed the effect of integrated yoga on anxiety, pain and morning stiffness in patients with osteoarthritis of knees. Patients were in the age range of 35 to 80 years. There were a total of two hundred and fifty participants with osteoarthritis of knees. The patients were randomly assigned to yoga or control group. The experimental group of patients received 20 min of physiotherapy with transcutaneous electrical stimulation and ultrasound for 15 days. They have also practiced 40 min of integrated yoga therapy after the physiotherapy session. The integrated yoga consisted of muscle loosening and strengthening practices, asanas, relaxation, pranayama and meditation. First post test was done on the 15th day and second post-test on the 90th day. The results showed that integrated yoga was effective in reducing pain and morning stiffness, anxiety, blood pressure and pulse rate in patients with osteo arthritis of the knees.
A study conducted by Acharya et al in Haridwar, India on twenty male junior footballers of Mohun Bagan Athletic Club, Kolkata showed that Pranayama and Yogasanas have caused significant reduction in serum cholesterol, low-density lipoprotein (LDL) cholesterol, serum triglycerides, and very-low-density lipoprotein (VLDL).\textsuperscript{49}

An interventional study conducted by Ankad et al in the Department of physiology of S.N. Medical College, Bagalkot assessed the cardiovascular functions in healthy individuals. The participants received same yoga training for a period of 15 days for 2 hours daily. The participants practiced Vibhagiya Pranayama, Nadishuddi Pranayama, Kapalabathi Kriya, Bahya Pranayama, and Sitali Pranayama. The physiological parameters like the resting pulse rate, mean resting systolic, diastolic and mean arterial blood pressure were reduced significantly after practicing yoga for 15 days. The results showed beneficial effects on cardiovascular function.\textsuperscript{50}

In another study conducted by Tekur et al among patients with chronic low back pain it was observed that yoga and pranayama increased quality of life and spinal flexibility.\textsuperscript{51}

Veerabhadrapa et al assessed the effect of yogic bellows on cardiovascular activity. The study conducted on 50 healthy male volunteers of 18 - 25 years age group has shown that Mukh Bhasrika pranayama performed for 12 weeks resulted in increase in valsalva ratio, reduced basal heart rate, difference in heart rate according to deep breathing and reduced systolic blood pressure on posture variation.\textsuperscript{52}

Sengupta in this review postulates that mind-body exercise such as yoga produces a temporary self-contemplative mental state by sustaining muscular activity with internally
directed focus. It also suppresses sympathetic activity, thus reducing stress and anxiety. Yoga has also shown to improve autonomic and higher neural center functioning and physical health of cancer patients.\textsuperscript{53}

Bhavanani, Madanmohan and Sanjay assessed the immediate effect of chandranadi pranayama (left unilateral forced nostril breathing) on cardiovascular parameters in hypertensive patients. This interventional study done on twenty two patients of essential hypertension attending the Yoga out-patient department run by Advanced Centre for Yoga Therapy Education and Research JIPMER, Puducherry, India, has found that chandra nadi pranayama (left unilateral forced nostril breathing) produced an instant decrease in all the cardiovascular parameters like heart rate, pulse pressure and systolic pressure.\textsuperscript{54}

Studies done at Antar Prakash Centre for Yoga, Haridwar, Uttarakhand, India by Malshe have shown that Nisshesha rechaka pranayama which may be described as breath holding at residual volume is the easiest way to produce brief, intermittent hypoxia. Intermittent hypoxia has beneficial effects like increasing the hemoglobin levels through the formation of erythropoietin (EPO), formation of growth factors, such as the vascular endothelial growth factor (VEGF) which prevents oxidative damage and protection of stem cells in the niches of the body and their transfer to the required areas of degeneration.\textsuperscript{55}

In her article “perspectives on yoga inputs in the management of chronic pain” Vallath emphasizes the emotional and physiological benefits of yoga. The author states that yoga influences all aspects of the person: physical, vital, mental, emotional, intellectual and spiritual. Yoga helps to relax, energize, remodel and strengthen body and psyche. The relaxation response caused by asanas and pranayama may be because of the harmony of in
the neuro endocrinal system. This relaxation response causes decrease in the metabolism, quieter breathing, stable blood pressure, reduced muscle tension, lower heart rate and slow brain wave pattern. The internal organs functions in a better way because of relaxation and the person gets deep sleep and as a result the fatigue diminishes. The author concluded that yoga, pranayama and meditation help patients deal with the emotional aspects of chronic pain reduce anxiety and depression considerably and improve the quality of life.\textsuperscript{56}

A study was conducted by Soni et al on 60 diagnosed stable mild-to-moderate chronic obstructive pulmonary disease patients in the age group of 30-60 years (both men and women) in the department of physiology, University College of Medical Sciences (UCMS) and Guru Teg Bahadur (GTB) Hospital, Dilshad Garden, Delhi, India. The COPD patients performed pranayama and asanas for two months. The practice included asanas for 10 min, pranayama for 30-35 min, meditation for 10 min and other life style changes. The patients performed various Pranayamas like Bhasrrika for approximately 5 min, Anulom vilom for approximately 15 min, Kapalbhati for approximately 10 min and Bhramari for approximately 5 min. The asanas included Surya Namaskar, Tadasana, Sukhasana, Paschimotanasana and Shavasana. At the end of the practice the patients observed significant reduction in weight and body mass index. The values of TLCO (Transfer factor of lung for carbon monoxide) showed a statistically significant improvement after two months of yoga training in mild as well as moderate COPD patients.\textsuperscript{57}

Another review by Zope and Zope has reported that Sudarshan Kriya Yoga, a unique yogic breathing practice which involves cyclical breathing patterns, of different speed ranging from slow and calming breaths to rapid and stimulating breathing, can be an aid in
the treatment of stress, anxiety and depression, post-traumatic stress disorder, substance abuse, and rehabilitation of criminal offenders.\textsuperscript{58}

Chaya et al assessed the long term effect of practicing yoga on the basal metabolic rate of healthy individuals. This study conducted at 'sVyas', a residential yoga education and research center near Bangalore City in south India compared the basal metabolic rate of volunteers who performed yoga and who did not perform yoga. One hundred and four participants (39 women and 65 men in the age range of 20–60 years) have enrolled for this study. Asana, pranayama and meditation were practiced by the yoga group for at least 6 months. Techniques practiced by the group were kapalabhathi, shithali and shithkari, vibhagiya pranayama, and nadishuddhi pranayama. The basal metabolic rate of the yoga group was significantly lower (15\%) compared to the group who did not perform yoga.\textsuperscript{59}

Nemati assessed the effect of pranayama on test anxiety and test performance. This study done on 107 MA postgraduate Iranian students has shown that pranayama could reduce test anxiety among them. The number of students with test anxiety was considerably less in the pranayama group. After practicing pranayama, only 33\% of the students in the pranayama group experienced high test anxiety, while there were around 66.7\% of the students in the control group who experienced high test anxiety.\textsuperscript{60}

Saxena and Saxena assessed the effect of various breathing exercises (pranayama) in patients with bronchial asthma. The study was conducted on bronchial asthma patients in the Department of Medicine, Mittal Hospital, Ajmer, India, in collaboration with The Department of Yoga Science, MDS University, Ajmer, India. Fifty patients with bronchial asthma performed deep breathing, Brahmari, and Omkara, etc. for a period of 12 weeks (for
20 minutes twice daily). After 12 weeks, patients had significant improvement in symptoms related to asthma and other lung function parameters like Forced Expiratory Volume, and Peak Expiratory Flow Rate as compared to control group patients.61

A review on yoga and menopausal transition explains that Yoga practices may provide a source of distraction from daily life and enhancement of self-esteem, among women to focus on the simplicity of movement and forget about work responsibility and demands, and thus reduce anxiety as well as depression. Hot flushes and night sweats among menopausal women could be controlled with the practice of yoga and pranayama. The yoga therapy has also shown to improve cognitive functions such as attention and concentration, remote memory and mental balance among these women.62

Nagarathna and Nagendra examined effect of yoga on fifty three patients with asthma. Patients have performed two weeks sessions of a set of yoga exercises, which include yogasana, pranayama, suryanamaskar, breath slowing techniques and dhyana (meditation) in a devotional gathering for 65 minutes daily. The weekly numbers of attacks of asthma have come down among the yoga group. Peak flow rate according to lung function test was also higher among this group.63

A study conducted by Froeliger, Garland and McClernon at the Department of Psychiatry and Behavioral Sciences, and Brain Imaging and Analysis Center, Duke University Medical Center, USA reported that there was significant difference in gray matter volume between yoga meditation practitioners and control group. Gray Matter volume was greater in temporal, occipital, frontal, limbic, and cerebellar regions among the yoga group. The gray matter volume was positively correlated with the duration of yoga practice.64
A study done at the Department of Physiological Nursing, University of California, San Francisco, USA have shown that a 12-week yoga program resulted in improvements in distress related to dyspnea and functional performance (self-reported) in patients with chronic obstructive pulmonary disease.65

Banerjee et al administered assessed the effectiveness of an integrated yoga program on the perceived stress levels, anxiety and depression, and radiation-induced DNA damage among 68 breast cancer patients undergoing radiation therapy. It was observed that there was a significant decrease in the anxiety, depression and stress among the yoga group compared to the control group. There was no significant difference between the two groups with regard to radiation-induced DNA damage. It was significantly elevated in both the groups.66

In a study conducted by Chandwani et al quality of life, sleep disturbances, depressive symptoms, fatigue, benefit finding, intrusive thoughts, and anxiety were assessed before radiotherapy and one week, one month, and 3 months after the completion of radiation therapy among sixty one women with breast cancer. Among the sixty one women, yoga group performed yoga classes once every two weeks during the 6 weeks of radiation therapy and control group received only radiation therapy. There were significant improvements in the scores of general health perception, physical functioning and benefit finding among the yoga group. The groups did not differ significantly with regard to the scores of fatigue, depression, or sleep.67

The effects of an integrated yoga program with brief supportive therapy were compared by Vadiraja et al among patients with breast cancer undergoing radiation therapy.
There were a total of eighty-eight breast cancer outpatients who were in stage II and III of the disease. Forty-four of them were assigned to receive yoga and the rest forty-four for brief supportive therapy prior to their radiotherapy. 60 min yoga sessions were conducted for the yoga group daily for six weeks while the control group received supportive therapy once every 10 days. At baseline and after six weeks of radiotherapy quality of life and positive and negative affect schedule (PANAS) were assessed. Significant improvements in emotional and cognitive function and positive affect, and decrease in negative affect was observed in the yoga group as compared to control group patients.68

The anxiolytic effects of a yoga program and supportive therapy were compared by Rao et al in breast cancer patients. There were 18 patients in the yoga group and 20 patients in the control group. Yoga group exhibited decrease in both self-reported state anxiety (p<0.001) and trait anxiety (p=0.005).69

Another study was conducted by Rao et al among breast cancer patients undergoing surgery. The effects of yoga intervention on mood, treatment-related symptoms, quality of life and immune outcomes was assessed among ninety-eight breast cancer patients who were in stage II and III. The study also assessed self-reported anxiety, depression, treatment-related distress and quality of life was assessed before surgery and four weeks thereafter. Further counts of subsets of T lymphocytes like CD4 %, CD8 % and natural killer (NK) cell % and serum immunoglobulins (IgG, IgA and IgM) were assessed in the blood samples. Results showed a significant decrease in the state and trait of anxiety, distress, depression, symptom severity, and improvement in quality of life in the yoga group as well as lesser decrease in CD 56% and lower levels of serum IgA in the yoga group.70
Factors predicting adherence to Iyengar yoga in breast cancer survivors was examined among twenty-three breast cancer survivors by Speed-Andrews et al. Objective attendance to the classes was taken as the measure for adherence. Results showed that there was 63.9% adherence to the Iyengar yoga program. Stronger intention to participate in yoga program, better self-efficacy, positive attitude, advanced stage of the disease, experience of yoga in the past year, recurrence of cancer, lower fatigue levels, and greater happiness were the factors related to adherence to the Iyengar yoga program.71

6. Yoga and Pranayama as Treatments for Cancer Related Fatigue

As highlighted by Mock 38 even though fatigue is accepted as the most prevalent symptom reported by patients with cancer, the treatment modalities for fatigue are limited. Mustian 37 et al. in their review claim that many patients achieve promising results and turn to Yoga to alleviate the side effects of cancer treatment such as cancer related fatigue and to improve the quality of life.

Bower, Garet and Sternlieb 72 conducted a pilot study to evaluate the effectiveness of a yoga intervention for cancer related fatigue among fatigued breast cancer survivors based on the Iyengar tradition. The study was conducted in University of California, Los Angeles. Participants’ fatigue was assessed before starting the study and after the 12-week intervention (90 minutes twice a week for 12 weeks). A post-test was also conducted after three months using the vitality subscale of the SF-36. It is a 4-item scale that assesses how much of the time respondents feel “worn out”, “tired”, have “a lot of energy”, and feel “full of pep” over the past 4 weeks. Scores of SF-36 range from 0–100, and scores below 50 indicates disability related to fatigue. Those who scored below 50 on SF-36 were recruited
for this study. The participants performed several yoga poses and breathing exercises regularly for 12 weeks. For the primary outcome, fatigue was assessed using the 14-item Fatigue Symptom Inventory which includes the intensity and duration of fatigue, and interference with daily functioning. On statistical analysis, paired samples $t$-tests showed significant improvement on the Fatigue Symptom Inventory from pre- to post intervention. There were improvements in all aspects of fatigue like reductions in average fatigue (mean change = 3.5, $t$ (10) = 5.7, $P < .001$), most fatigue (mean change = 3.8; $t$ (10) = 4.7, $P = .001$), and number of days fatigued in last week (mean change = 2.4, $t$ (10) = 2.9, $P < .05$).

There was also improvements on the vitality subscale of the SF-36, as indicated by an increase in vitality scores (mean change = 22.7, $t$ (10) = $-4.2$, $P = .002$).

Carson in their pilot study examined a novel, yoga-based palliative intervention, the Yoga of Awareness Program, in a sample of women with Metastatic Breast Cancer (MBC). Volunteers for this study included 21 Metastatic Breast Cancer patients referred by oncologists at the Duke University Medical Center breast oncology unit and affiliate sites. These Metastatic Breast Cancer patients practiced yoga, pranayama, meditation, didactic presentations, and group interchange for eight-weeks. Pain, fatigue, distress, invigoration, acceptance, and relaxation were assessed daily during the two weeks before the intervention and during the final two weeks of the intervention. A total of thirteen women completed the intervention. Results showed significant increases in invigoration and acceptance.\(^\text{13}\)

Bower et al. further conducted a single-center, 2-armed Randomised Controlled Trial at the University of California-Los Angeles (UCLA). Breast cancer survivors with persistent post-treatment fatigue and completed local and/or adjuvant cancer therapy, except hormone
therapy, at least 6 months previously were recruited. Breast cancer survivors (in groups of 4 to 6 women) practiced Iyengar yoga classes for 90 minutes two times a week for 12 weeks. The control group received health education for 120 minutes once in a week for 12 weeks. Outcome measures were obtained at baseline, after two weeks of intervention, and after three months of intervention. Subjective fatigue severity was assessed with the Fatigue Symptom Inventory (FSI) and related outcome “vigor” was assessed using the vigor subscale of the Multidimensional Fatigue Symptom Inventory. Several secondary outcomes also were assessed. It was found that Yoga resulted in statistically significant improvements in fatigue severity and vigor.14

7. Pranayama and Antioxidant Status

Chandwani et al.73 in this review discusses that some studies of yoga intervention have shown beneficial effects on symptoms like fatigue, sleep disturbances, hot flashes, and quality of life. It is further stated that studies conducted on the performance of Yoga and Pranayama by cancer patients as well as cancer survivors indicate that the mechanism by which these therapies act in reducing the adverse effects of cancer treatments is not clearly understood.

A few studies done on normal adults have documented improvement in the antioxidant status and reduction of oxidative stress while performing Yoga and Pranayama. Sinha et al conducted a study in Delhi on healthy male volunteers from the Indian Navy. Sixty personnel from the various branches of Indian Navy were selected initially. There were a drop out of nine volunteers and the final list consisted of 51 volunteers, who were divided into two groups, a yoga group (n = 30) and a control group (n = 21). The mean age
of the experimental group was comparatively higher as the elder people preferred to join the yoga group. Twenty Naval personnel of the Eastern Naval Command got trained from the Kaivalyadhama Institute, Lonavala, Maharashtra, India, for 2 months and these trainers taught theory and practical aspects of yoga to the volunteers. The yoga group performed yogasanas and pranayama for one hour in the morning, five days per week for six months whereas the control group practised routine physical exercises. Pranayama included deep breathing, inhalation-retention exhalation with a ratio of 1:1:2, abdominal (diaphragmatic) breathing, and alternate nostril breathing. Slow running up to four km for about 30 minutes, body-flexibility exercises for about 10 minutes, pull ups for about 5 minutes, and games for about 15 minutes were the exercises practiced by the control group. After completion of six months of training, fasting blood samples were analysed for reduced glutathione (GSH), oxidized glutathione (GSSG), glutathione reductase (GR), activity, and total antioxidant activity (TAS). GSH level increased significantly from the baseline value of 235.3-16.9 nmol/L to 331.7 - 37.6 nmol/L in the yoga group.\textsuperscript{15}

Nikam et al conducted a study in Belgau, Karnataka, India to assess the effect of Pranayama practicing on lipid peroxidation and antioxidants in coronary artery disease (CAD). There were a total of 60 coronary artery disease patients in age group 40-60 years. Out of these, 30 patients were practicing Bhashrika Pranayama, Kapalbhati Pranayama, Bhya Pranayama, Anulom-vilom Pranayama and Brahmari Pranayama and the other 30 were kept on drug therapy. Age and sex matched 60 normal healthy subjects from Anand Yoga Center, Nipani and Belgau was used as controls. Thirty patients who practised did it regularly one hour at early morning 5.00 am to 6.00 am and one hour at evening 6.00 pm to 7.00 pm in fresh air. Bhashrika breathing was practised for 10 min, Kapalbhati Pranayama for 40 min,
Anulom-Vilom Pranayama for 30 min and Bhya Pranayama and Brahmari were practiced for seven times. The fasting venous blood samples obtained from these subjects were analysed for the activity of enzymatic antioxidants superoxide dismutase [SOD], glutathione peroxidase [GPx] and catalase before starting the practise and at the end of 4, 6 and 8 weeks of practicing pranayama. In patients suffering from coronary artery disease there was significantly decreased activity of catalase and GPx and Superoxide dismutase in the beginning. This lowered activity of SOD, GPx and catalase were significantly raised after practicing 4 and 6 weeks of these five pranayama and it became within normal range after 8 weeks.¹⁶

8. Relationship Between Breast Cancer and its Treatments to Antioxidants

As mentioned by Pala and Gurkan⁷⁴, cancer and its treatments can lead to an important phenomenon called oxidative stress. Oxidative stress is caused by an intracellular excess of reactive oxygen (ROS) free radical species over intracellular antioxidants. Excess of reactive oxygen species results in oxidation of cellular structures, such as membrane lipids and proteins; it also causes mutation of mitochondrial and nuclear DNA. Apart from DNA damage, lipid peroxidation process also plays a role in carcinogenesis.

Sivakumar and Devaraj⁷⁵ compared the antioxidant status in breast cancer patients and normal subjects. This study was conducted in Government Arginar Anna Memorial Cancer Hospital, Karapettai, Kanchipuram, Tamilnadu in 2011. There were fifty histopathologically proven breast cancer patients and fifty age matched controls. Blood samples from both the groups were drawn and assessed for enzymatic antioxidants like
Superoxide dismutase (SOD), Catalase (CAT), Glutathione peroxidase (GPx), and Glutathione-S-transferase (GST) in Erythrocytes and and non-enzymatic antioxidants like Vitamin C, Vitamin E and Reduced glutathione (GSH) in plasma. The levels of enzymatic and non-enzymatic antioxidants were much lower among patients than the normal subjects. The study also reported that the difference in the level of antioxidants between patients and normal subjects were statistically significant.

Abdel-Salam et al\textsuperscript{76} noticed reduced total serum antioxidant capacity and increased oxidative stress in breast cancer patients undergoing chemotherapy as well.

KASAPOV\'IĆ \textsuperscript{77,78} investigated the effects of breast cancer radiotherapy on the antioxidant (AO) enzyme activities of copper, zinc superoxide dismutase (CuZnSOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR), as well as on the concentration of reduced glutathione (GSH) and lipid peroxides (LP) in blood of patients aged 45-58 years and older than 60 years. Pre-test values of the level of glutathione was very low among patients older than 60 years (6.04 ± 0.62 nmol/mg of prot) and in patients aged 45-58 years (5.67±0.58 nmol/mg of prot).

Hall and Giaccia\textsuperscript{79} have highlighted the fact that radiation therapy causes DNA strand breakage in cells by the generation of free radicals. Radiation therapy aims to prevent the local recurrence of cancer and controls the growth of tumor locally by causing direct DNA strand breakage or by the liberation of free radicals. However when reactive oxygen species are in excess of cellular antioxidants, oxidative damage can occur to surrounding cellular structures.
Unsal et al conducted a study\textsuperscript{80} at the outpatients Radiation Oncology Department of Gazi University Faculty of Medicine, Ankara and evaluated the effect of radiotherapy on lipid peroxidation, total sulfhydryl groups (RSH) and nitric oxide (NO\textsuperscript{-}) levels in plasma of patients with cancer treated on different anatomic sites, and compared the results with control group. 89 patients with stage II–III cancers and 33 healthy control subjects were recruited for the study. Patients who had distant metastasis were excluded. All patients were above 18 years of age and with a Karnofsky Performance Status of 70\%. Patients with a history of previous radiation therapy to the same region were not included. There were five groups of patients according to their irradiated sites: group 1 (n = 12) head and neck RT, group 2 (n = 13) thoracic RT, group 3 (n = 32) breast RT, group 4 (n = 17) abdominal RT and group 5 (n = 15) pelvic RT. The maximum number of patients (n = 32) were having breast cancer. There were a total of 46 women and 43 men among the study group and 17 women and 16 men in the control group. All patients received 50 Gy in 25 fractions of external beam radiation therapy. Blood samples were collected before the start of radiotherapy and after completion of the fifth week of radiation therapy and assessed for plasma levels of malondialdehyde (MDA), nitric oxide (NO) and total sulfhydryl groups (SH). Plasma levels of malondialdehyde (MDA) and NO\textsuperscript{-} of cancer patients before irradiation were found higher than those in control subjects. After irradiation, a marked lipid peroxidation increase was demonstrated as well as the significant decrease of plasma RSH level. The authors concluded that the alterations of the parameters are suggestive of enhanced oxidant stress and point to the necessity of antioxidant prophylaxis.

Nair et al in this article\textsuperscript{81} explain that ionizing radiation causes damage to the living tissues through a series of actions mainly because of the generation of free radicals. The free radicals generated by the action of radiation on water react with cellular macromolecules,
such as DNA, RNA, proteins, membrane, etc., and cause cell dysfunction and mortality. These reactions take place in tumour as well as normal cells when exposed to radiation.

Shariff et al.\textsuperscript{82} conducted a study in Karad, Maharashtra, India to assess the variations in the serum levels of malondialdehyde and total antioxidant status, in head and neck malignancies with different stages, before and after radiotherapy. There were 96 head and neck malignancy patients who were previously untreated and with early (I and II) and late (III and IV) stages of the disease. All patients were treated with standard dose of radiations (60-66 Gy / 30-33 fractions for 6-7 weeks). Out of these 96 patients, 30 patients were randomised into group 1 and supplemented with oral antioxidant supplementation for 35-40 days along with radiotherapy and the rest 66 patients were randomised into group 2 who received only the standard radiation therapy. In group 2, the level of serum malondialdehyde (MDA) was significantly elevated and the level of total antioxidants significantly reduced at the end of therapy indicating oxidative stress.

A link between oxidative stress and fatigue and fatiguinging illnesses is proposed by Michael Maes.\textsuperscript{83,84} Fatiguuing illnesses are associated with increased production of free radicals, decrease in the level of antioxidants and the damage caused by oxidative stress.

9. Glutathione and Oxidative Stress

As highlighted by Kidd\textsuperscript{85} the antioxidant defence systems guard the body against oxidative stress by scavenging the free radicals and donating hydrogen atom. The endogenous cellular antioxidant defences are maintained by the glutathione system. GSH (reduced glutathione) is an important cell protectant because of its reducing power. GSH works along with its redox system enzymes, glutathione peroxidase and reductase and is a
primary protectant of skin, lens, cornea, and retina against radiation damage, and the biochemical foundation of P450 detoxication in the liver, kidneys, lungs, intestinal epithelia, and other organs.

Harlan et al\(^{86}\) identifies the major role Glutathione plays in the physiological balance between pro-oxidants and antioxidants. Glutathione and its redox system enzymes, glutathione peroxidase and reductase, help in providing a widespread protection system from oxidative damage. Normal or increased levels of glutathione play an important role in the cellular defence against radiation.

Glutathione plays important roles in antioxidant defense, nutrient metabolism, and regulation of cellular events (including gene expression, DNA and protein synthesis, cell proliferation and apoptosis, signal transduction, cytokine production and immune response, and protein glutathionylation). Glutathione deficiency contributes to oxidative stress, which plays a key role in aging and the pathogenesis of many diseases like cancer.\(^{87}\)

Glutathione peroxidase plays a crucial role in protecting cells from damage by free radicals. Free radicals are formed by the decomposition of peroxides. Glutathione peroxidase detoxifies peroxides in living cells. Peroxidation occurs with lipid components of the cell as lipids are especially susceptible to reactions with free radicals, resulting in lipid peroxidation. Peroxides are reduced to alcohols by glutathione peroxidase enzymes with the help of glutathione and thereby prevent the formation of free radicals. GPx enzymes will catalyze the reduction of hydrogen peroxide (H\(_{2}\)O\(_2\)) and a wide variety of organic peroxides (R-OOH) to the corresponding stable alcohols (R-OH) and water using cellular glutathione as the reducing reagent.\(^{88,89}\)
Glutathione acts as an electron donor and reduces disulfide bonds formed within the cytoplasmic protein. In the process glutathione gets converted to its oxidized form glutathione disulfide (GSSG). Glutathione reductase is another enzyme in the glutathione redox systems. Glutathione reductase catalyses the reduction of glutathione (GSSG) in the presence of NADPH, which is oxidised to NADP+.\(^9^0\)

The human GST is a family of multifunctional enzymes that catalyzes the conjugation reaction between reduced glutathione and a variety of electrophiles. It catalyzes the conjugation of reduced glutathione (GSH) to various substrates. The GSTs are divided into four classes: alpha, mu, pi and theta based on amino acid sequence similarity and antibody cross-reactivity.\(^9^1\)

Sergentanis and Economopoulos have done a meta-analysis to examine whether polymorphisms of glutathione transferase enzymes, GSTT1 and GSTP1 are associated with breast cancer risk. The pooled analysis showed that the null GSTT1 genotype was associated with elevated breast cancer risk (pooled OR = 1.114, 95% CI: 1.035-1.199, random effects) among non-Chinese populations (33 studies, pooled OR = 1.128, 95% CI: 1.042-1.221, random effects). On the other hand, the GG genotype was associated with increased breast cancer risk in Chinese populations (five studies, pooled OR = 1.297, 95% CI: 1.023-1.645, fixed effects); accordingly, the recessive model yielded statistically significant results (pooled OR = 1.273, 95% CI: 1.006-1.610, fixed effects). Authors concluded that polymorphisms of both GSTT1 and GSTP1 genes seem associated with elevated breast cancer risk in a race-specific manner.\(^9^2\)
Nakayama, Alladin, Igbokwe and White reviewed the risk-benefit ratio for concurrent use of dietary antioxidants with chemotherapy or radiation therapy with the help of published literature. Out of the 56 studies reviewed, 26 studies were about combination of GSH and chemotherapy or radiation therapy. 65% of the studies were single arm, 20% randomized controlled trials and 15% double blind placebo controlled randomized trials. Mostly it was studied in ovarian cancer. Intravenous glutathione was usually administered 15-30 min before radiation therapy or chemotherapy because of its short half-life. Regarding symptom management different studies have found that administering glutathione along with chemotherapy reduced nephrotoxicity, neurotoxicity and neuropathy among ovarian cancer patients. The authors concluded that mechanistic studies on the interaction between antioxidants and conventional cancer therapy could lead to novel biomarkers for assessing dose adequacy.93

With respect to cancer, glutathione metabolism is able to play both protective and pathogenic roles. It is crucial in the removal and detoxification of carcinogens, and alterations in this pathway, can have a profound effect on cell survival. However, by conferring resistance to a number of chemotherapeutic drugs, elevated levels of glutathione in tumour cells are able to protect such cells in bone marrow, breast, colon, larynx and lung cancers and may impede the effectiveness of these treatment measures.94,95

Jadhav et al monitored changes in tumor/blood glutathione (GSH) levels after one fraction of radiotherapy and correlated it with the treatment response in patients with carcinoma of the uterine cervix. 17 patients with FIGO stage IIB of cancer cervix was given 35 Gy of cobalt-60 external radiotherapy (RT) in 16 fractions over 4 weeks with a
concurrent high-dose-rate intracavitary dose of 8.5 Gy once a week. 28 patients with FIGO stage III B were given 45 Gy of RT in 20 fractions over 5 weeks, followed by two doses of intracavitary therapy once a week. GSH was estimated in blood and tumor samples before and after one dose of radiation therapy. Tumor response was assessed clinically after one month. Results showed that there was a significant decrease in the level of glutathione in both blood and tumor. Seven stage IIB patients and eight stage IIIB patients had complete tumor response and they showed more than or equal to 70% decrease in both tumor and blood GSH. The authors concluded that the changes in GSH levels after one fraction of RT could serve as an index of tumor response to therapy and may help in identifying radioresistant tumors, at least in the case of cervix carcinoma.

Vidyasagar et al assessed the predictive significance of serum glutathione (GSH) and tumor tissue DNA damage in the treatment of cervical cancer patients undergoing chemoradiotherapy. Study included both women with normal cervical tissue who have undergone hysterectomy and patients with cervical cancer. Cervical cancer patients have undergone chemotherapy with cisplatin once per week for 5 weeks with concurrent external radiotherapy of 2 Gy per fraction for 5 weeks, followed by two applications of intracavitary brachytherapy once per week after 2 weeks' rest. Serum for total GSH content and tissues were processed for single-cell gel electrophoresis (SCGE) assay for DNA damage analysis. Tumor radioresponse was assessed clinically 2 months after the completion of treatment. Results showed that Serum GSH content depleted significantly after a total dose of 4 Gy and 10 Gy of radiotherapy with a single dose of cisplatin. Olive Tail Moment, the index of DNA damage, indicated significantly higher values in the fifth fraction of radiotherapy (5-RT) than in pretreatment. The authors concluded that Serum GSH analysis and tumor tissue
SCGE assay found to be useful parameters for predicting chemoradioresponse prior to and also at an early stage of treatment of cervical cancers.  

**Summary**

Research and non-research literature related to the present study has been reviewed. Extensive literature review was done and was organized and discussed as Prevalence of cancer related fatigue, Mechanisms of cancer related fatigue, Treatments for cancer related fatigue, Yoga and Pranayama, Therapeutic effects of Pranayama, Yoga and Pranayama as treatments for cancer related fatigue, Pranayama and antioxidant status, Relationship between Breast Cancer and its Treatments to Antioxidants and Glutathione and Oxidative Stress. The review was helpful in developing the data collection instruments and to compare the results of the present study findings.