MIND-BODY THERAPIES AND ITS EFFECT ON THE IMMUNE SYSTEM IN CHRONIC DISEASES: A LITERATURE REVIEW

Gholami SK[1], Santiago C[2], Bhojaraja VS[3], Michael LYS[4], Radhakrishnan AK[5], and Mehta DH[6].
[1]Division of Endocrinology, Diabetes, and Hypertension, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA
[2]Division of Human Biology, School of Medicine, International Medical University, Kuala Lumpur, Malaysia
[3]Department of Anatomy, School of Medicine, Perdana University-Royal College of Surgeons in Ireland School of Medicine, MAEPS Building, 43400 Serdang, Selangor, Malaysia
[4]School of Medicine, International Medical University, Kuala Lumpur, Malaysia
[5]Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia, Bandar Sunway, Malaysia
[6]Benson-Henry Institute for Mind Body Medicine, Massachusetts General Hospital, Boston, MA; Department of Medicine, Massachusetts General Hospital, Boston, MA, USA

Correspondence:
Carolina Santiago,
Division of Human Biology, School of Medicine,
International Medical University,
57000 Kuala Lumpur, Malaysia
Email: carolinasantiago@imu.edu.my

Abstract

Mind-body therapies (MBTs) such as mindfulness, yoga, qigong, tai chi, meditation, and many more have become very popular in the last few decades as useful tools to reduce stress and improve health. These methods are non-invasive and cost-effective. There are several reports that infer MBT can modulate the host immune system in many diseases. Although there are some discrepancies in the reported effects, the majority imply favourable effects of MBTs. This review summarizes the effects of MBTs in various chronic disease including cardiorespiratory conditions, metabolic diseases, cancer, HIV, gastrointestinal diseases, and depression. The results from most studies show that MBT reduced stress and anxiety; whilst improving sleep and overall quality of life. These observations were coupled with a decrease in cortisol level, an increase in glucocorticoid receptors, modulation of the autonomic nervous system, and changes in oxidative stress pathways, which may have resulted in improved immune functions. Furthermore, interactions between different parts of the brain such as the limbic system and hypothalamus upon exposure to MBTs can lead to reduced sympathetic nervous system outflow, which can improve the function of different organ systems resulting in the favourable host immunological responses observed in these studies.

Keywords: Chronic Disease, Immune System, Inflammation, Mind-Body Therapy

Introduction

Mind–body therapies (MBTs) focus on the interactions between the brain, mind, body, and behaviors and on the ways in which emotional, mental, social, spiritual, and behavioral factors can directly affect health (1). Mind–body therapies are used throughout the world in treatment, disease prevention, and health promotion (1-3). The essence of MBT is mindfulness training, which concentrates on the brain, body, and behavior to improve health and alleviate illness. These therapies are commonly delivered by a trained practitioner. Common types of MBTs are yoga, tai chi and qigong (4).

All MBTs aim to achieve physical and mental well-being. However, the approach differs. Certain practices focus more on meditation, whereas some emphasize on physical movements. Details on the methods involved also show that these practices use various tools such as music, images, sounds, and physical movements to aid the meditation process in harboring the therapeutic effects to the practitioners. Despite the differences in the methods involved, most MBTs share one common component, which is the physiological changes that may result in relaxation response. Generally, meditation can be categorized as a means to cultivate attentional skills and the development of a benevolent mental state (5). Further literature review explains that meditation is a practice of visualization of positive images with nature sounds or music. It also can be extended to incorporate elements such as martial arts, laughter, hypnosis, and massage as part of the training (4-6).

MBT and immune system

The immune system is interconnected with the neuroendocrine system (6, 7), and psychological factors can influence the functioning of both systems. Current literature shows that host immune responses can be enhanced or inhibited by behavioral interventions (8). Interactions between the immune and neuroendocrine systems can take place at multiple levels. Psycho-sensorial stimuli can stimulate different parts of the central nervous system (CNS) such as the frontal lobe, limbic system, and hypothalamus (Figure 1). This, in turn, modulates the endocrine and peripheral nervous system (PNS) and eventually the immune response.

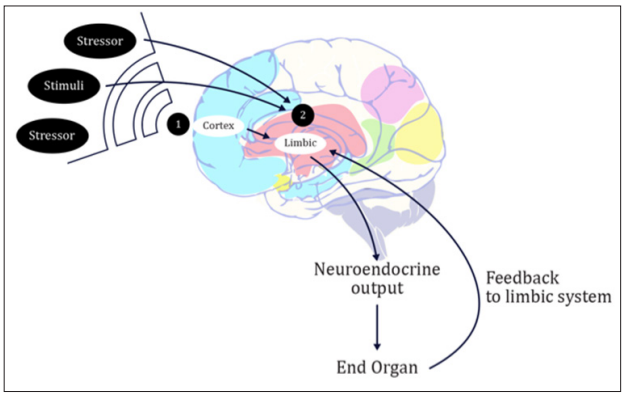

Figure 1: Interactions between exogenous stimuli and different tissues occur via multiple levels in the central nervous system (CNS). Different stimuli can either influence frontal cortex or directly stimulate the limbic system. These changes are then communicated to various tissues through the neuroendocrine system. In addition, changes at the tissue level are conveyed to the CNS via different feedback systems

The normal function of the immune system is to respond to antigenic stimuli. However, the immune system also has some impact on the neuroendocrine and nervous systems (9). These interactions occur via the expression of various receptors on the immune cells. Some immune cells express hormone receptors (e.g. sex hormone receptor, glucocorticoid hormone receptor) (10); neurotransmitters, and neuropeptides (neuropeptide Y, which co-releases with noradrenaline) (11). Besides, the production of cytokines by the immune cells can affect neuroendocrine functions and immune responses.

During an immune response, these interactions can cause functional changes, which occur at the level of the CNS and PNS by endocrine activity (9). Therefore, it has been proposed that behavioral changes induced by MBTs can alter the normal functioning of the immune system which is usually by modulation of NF-κB pathway (12) via 2 mechanisms: 1) through the autonomic nervous system (ANS) by activating the parasympathetic nervous system; or 2) by promoting secretion of hormones that influence the neuroendocrine-immune pathway (9, 13). This indirectly improves one's health by balancing physiological and psychological functions (8, 14).

Research has shown that MBT practices can improve the health of patients with chronic ailments such as cancer, diabetes mellitus, and HIV (15, 16). These papers deduced that there is a strong possibility that MBT can induce positive effects on patients with chronic illness by relieving the symptoms and promoting a calm state of mind. Insight from the literature further indicates that MBTs benefit both the healthy and diseased individuals state through i) reducing stress ii) reducing pain; iii) enhanced cellular health; iv) favourably regulating the immune system.

i. Reducing stress

Interventions like mindfulness-based stress reduction (MBSR) and soothing music in a clinical setting have been shown to help most of patients with chronic conditions to manage stress effectively; resulting in lower stress levels and improved immune functions (13, 17), therefore promoting mental calmness and alertness (18). At physiological level, the mechanism can be attributed to modulation of the sympathetic-adrenal-medullary (SAM) and hypothalamic-pituitary-adrenal (HPA) axes (19).

ii. Reducing pain

A study on rheumatoid arthritis (RA) patients, revealed that relaxation techniques can reduce joint pain (20). It was suggested that relaxation may decrease sympathetic outflow which in turn reduces the interactions of the sympathetic nervous system (SNS) and sensory afferents at the peripheral level (21). As sympathetic products can directly stimulate sensory nerves, the use of relaxation, which reduces the sympathetic activity can reduce the pro-inflammatory effects. This may result in pain reduction (21-23).

iii. Enhanced cellular health

Other reported benefits of MBTs are enhanced cellular health which can be determined based on telomere length as it is linked to stress and disease. Both telomere length and telomerase - an enzyme responsible for maintenance and length of telomeres are partially regulated by psychological stress and well-being (24-26). Shorter telomeres and reduced telomerase activity can be used as an indicator of an increased risk to the host health as well as poorer prognosis (27, 28). Several studies demonstrated that interventions such as yoga, TC, and meditation increased telomerase activity and reduced DNA damage (24, 29, 30). These findings strongly concur that MBTs can provide benefits to cellular health and prevent the weakening of cellular immunity.

iv. Immune functions

The effects of MBTs on the host immune system is of paramount importance as it directly promotes healing. MBTs can modulate the HPA axis, which is made of a

complex system of psychoneuroimmunological network communicating at the sub-cellular and molecular levels (31, 32). This means that activities which trigger behavioral responses may activate the neuroendocrine and autonomic pathways leading to changes in the immune system (33, 34). Furthermore, there is growing evidence, which shows that MBT interventions can induce changes in the lymphocytes and/or anti-inflammatory cytokines (35, 36). The many benefits of MBTs have driven research groups to investigate the impact of the interventions on patients with chronic disease. The majority have reported changes in the components of the immune system as shown in Table 1.

The next section of this paper discusses immunological changes reported in patients with different chronic diseases including cardiorespiratory conditions, cancer, and HIV following MBTs interventions.

Cardiorespiratory diseases

MBTs reportedly led to favorable results in studies of patients with asthma, cold, pulmonary injury, and heart failure. In the case of asthma patients, when yoga was combined with standard medical care; there was a significant increase in the superoxide dismutase (SOD) level (64). This was coupled with a reduction in total leukocyte count and differential leukocytes in the intervention group compared to the control group. Similarly, the intervention of a relaxation technique resulted in significant differences in the number of neutrophils and basophils compared to the control group (73). Eosinophils are leukocytes implicated in the pathology of asthma and its high level plays a key role in the inflammatory responses in allergic asthma (73). The pathology of asthma also lies in oxidative-anti-oxidative disproportion in the body due to the additional free radicals

Table 1: Summary of immunological changes in diseased state upon MBT interventions

Chronic disease	MBI intervention	Immune changes Observed	References
	Yoga (1 month)	Increase in CD4 compared to control	(37)
	Tai Chi, 10-weeks	Augmented lymphocyte proliferative function	(4)
	Mindfulness-based cognitive therapy 8-weeks	Increase in CD4 counts	(38)
HIV patients	Transcendental meditation (TM), 6 months	Cortisol was lower in TM group at follow-up, and higher in the controls (not significant); smaller change in $CD8^+$ HLA-DR^+ $CD38^+$ freq of $CD8^+$ T-cells for TM group, indicating the possibility for immune activation stabilization.	(39)
	MBSR 8-weeks	Increase NK cell number and activity. Additionally, RANTES significantly increased from pretest–post-intervention, the SDF-1 level remained stable	(40)
	MBSR 8-weeks	No significant changes in $CD4^+$ T-lymphocyte levels	(41)
Breast cancer patients	Hatha yoga, 6 months	Participants, on an average of 56.2 years of age & showed improvement in IL-6, IL-8, TNF-α and CRP levels	(42)
	Hatha yoga, 12 weeks	Participants were on an average of 51.6 years of age. IL-6, TNF-α, and IL-1β were lower for yoga participants compared with the control group. At 3 months post-treatment, increasing yoga practice led to a decrease in IL-6, IL-1β production	(43)
	Yoga, 4 weeks	Mean overall age of control and yoga groups were 49.2 ± 9.6 years. Reduction in NK in the control group but no change in the yoga group, pre- to post-surgery. The NK cell percentage was higher in the yoga group post-chemotherapy compared to the control group. However, there were no significant differences between groups following surgery and radiotherapy.	(44)
	Yoga	Mean overall age of control and yoga groups were 49.2 ± 9.6 years. Reduction in TNF- α, no significant changes in soluble IL-2 receptor (IL-2R), IFN- χ.	(45)
	Yoga, 12-weeks	Improve in percentage of NK cells, but not NK cells count; Significant decrease in 0600 h cortisol in the yoga group.	(46)
	Iyengar yoga, 12-weeks	Participants were on average, 54 years old. Reduced activity of the (NF-κB), increased activity of the anti-inflammatory glucocorticoid receptor, reduced activity of cAMP response element-binding protein (CREB) family transcription. Increase in sTNF-RII	(3)
	Iyengar yoga, 8-weeks	Reduction in cortisol compared to baseline	(47)
	MBSR, 8weeks	Restoration of NKCA and cytokine balance (in MBSR), in MBSR and control (pre-post): reduction in NKCA and IFN-γ production, with an increase in IL-4, IL-6 and IL-10 production. No changes in T cell subtype	(48)
	MBSR	Mean overall age 54.5 ± 10.9 years. NK cell production of IL-10 decreased. T-cell production of IL-4 increased and IFN-γ decreased	(49)

Table 1: Summary of immunological changes in diseased state upon MBT interventions (continued)

Chronic disease	MBI intervention	Immune changes Observed	References
	MBSR, 6 weeks	Rapid recovery of functional T, recovery of B and NK cells after completion of cancer treatment independent of stress-reducing interventions.	(50)
	Mindfulness	Not detectable: (IL-10, IL-1β, TGF-β1) TNF-α and IL-6 increased during the follow-up period (between 6 to 12-weeks)	(51)
	MBSR, 8-weeks	Continued reduction in Th1 (pro-inflammatory) cytokines. Systolic blood pressure (SBP) decreased from pre- to post-intervention, and HR was positively associated with self-reported symptoms of stress.	(49)
	MBSR, 8-weeks	Improvements in quality of life were associated with decreases in afternoon cortisol levels, but not with morning or evening levels.	(52)
	Tai Chi Chuan	IL-6 increased in the TC group but decreased slightly in the psychosocial therapy group. Pro-inflammatory cytokines IL-2 and IFN-γ increased in the PST group but decreased in the TC group,	(53)
	Cognitive-behavioural stress management, 10 weeks	Downregulation of proinflammatory cytokine (IL1A, IL1B, IL6), the prostaglandin-synthesis enzyme COX2 (PTGS2), inflammatory chemokines and their receptors Upregulation of genes involved in Type I interferon response (IFIT1, IFIT2, IFIT3, IFI44, IFI44L, ISG15, MX2, OAS2, OAS3), Type II interferon signaling , and interferon signal transduction (STAT1, STAT2).	(54)
Prostate cancer patients	MBSR	Mean overall age - 54.5 ± 10.9 years. NK cell production of IL-10 decreased. T-cell production of IL-4 increased and IFN-γ decreased	(49)
	MBSR, 8-weeks	Improvements in quality of life were associated with decreases in afternoon cortisol levels, but not with morning or evening levels.	(52)
Lung cancer patients	Tai Chi,16-weeks	T1/T2 and Tc1/Tc2 ratios in the control group decreased in the natural course of post-surgical non-small cell lung cancer recovery, no changes were observed in the Tai Chi group. Cortisol level increased in the control group but not in the Tai Chi group.	(55)
Cancer patients	Qigong, 10-weeks	Reduction in CRP after 10 weeks	(56)
	Sudarshan Kriya and Pranayama: Breathing Processes, 6 days	NK cells increased at week 12, and 24 compared to baseline, and at week 24 it was significantly higher than the control group, but no changes in T cell subtype ($CD3^+$, $CD4^+$, $CD8^+$)	(57)
Cancer patients and their caregiver	Mindfulness-based stress reduction, 6 weeks	Both patients and caregivers had decreases in cortisol at Weeks 1 and 3 but not at Week 6. salivary IL-6 levels were lower overall (before/after an MBSR-C session), compared with Week 1 for patients and caregivers.	(58)
Inflammatory bowel disease (IBD) & Inflammatory bowel syndrome (IBS)	Breathing, mindfulness, cognitive skills, problem-solving skills	Patients' age ranges from 18-75 years old In IBS: Changes in TNF, AKT and NF-κB IBD: changes at MAPK, P38 MAPK, inflammation (e.g., VEGF-C, NF-κB) and cell cycle and proliferation (e.g., UBC, APP)	(59)
	Yoga, 8-weeks	Patients' age ranges from 16-60 years old No significant changes were observed in cardiovascular autonomic functions, eosinophilic cationic proteins, or IL-2 soluble receptors.	(60)
Ulcerative colitis (UC)	MBSR, 8 -weeks	Significant differences in both IL-10 and ACTH with control flares over time. It appears that MBSR had a biological impact on IL-10 and ACTH, although not enough to prevent the flare-up	(61)
	Mindfulness, 8 weeks	No significant effect on IL-6 levels	(62)
Rheumatoid arthritis	Tai Chi, 12-weeks	Patients were functional class I or II types. No significant results	(63)
Asthma	Yoga, 6-months	Decrease in TLC and differential leukocytes count in comparison to the control group.	(64)
Male veterans with pulmonary injury due to mustard gas exposure	MBSR, 8-weeks	Increase in the lymphocyte proliferation with phytohemagglutinin and peripheral blood IL-17. However, lymphocyte (CD4+, CD8+, and NK-cell) percentages were not affected significantly.	(2)
Heart failure	Hatha yoga, 8-weeks	Age of control & yoga groups: 50-52 years old. Reductions in serum levels of IL-6 and high-sensitive (hs)-CRP and an increase in EC-SOD	(65)
	Yoga, 8-10 weeks	Decrease in IL-6 & hs-CRP and increase in EC-SOD (dismutase)	(66)

Table 1: Summary of immunological changes in diseased state upon MBT interventions (continued)

Chronic disease	MBI intervention	Immune changes Observed	References
Patients with chronic inflammatory diseases and overweight/ obese subjects	Yoga	Cortisol decreased, b-endorphins increased IL-6, TNF α reduced	(16)
Type 2 diabetes mellitus	Tai Chi Chih, 12-weeks	Reduction in CRP	(67)
Class, I obese	Yoga, 90 days	Single case report -31-year older adult. Increase in the activity of telomerase, levels of ß -endorphins, plasma cortisol, and IL-6, sustained reduction in oxidative stress markers.	(68)
Psychological distress	Yoga, 8-weeks	Participants were all women, mean age of 41 years old. Reduced methylation of the TNF region in the yoga group compared to the waitlist, no change in IL-6, CRP, and their DNA methylation level	(69)
Depression patients	Mindfulness, 4 weeks	IL-6 decreased significantly from baseline at both post-treatment and 3-month follow-up; TNF-α significantly reduced from baseline to post-treatment,	(69)
	Tai Chi, 10-weeks	Decline in CRP	(70)
Bereaved widows	Dan Jeon Breathing and stretching exercises, 10 weeks	No significant changes in immune factors, i.e., Th cells, B-cells, monocyte, and NK cells	(71)
Women with histories of interpersonal trauma	MBSR, 8-weeks	Reduction in IL-6	(72)

with increased oxygen consumption. The elevation of SOD scavenges the excessive free radicals and suppress cellular damage therefore reducing the severity of asthma. Plus, the reduction in leukocytes with the intervention implies a decrease in inflammation.

Besides yoga, MBSR is another type of intervention shown useful in reducing respiratory issues such as the incidence of colds in adults (≥ 50 years) (30) and pulmonary injury (2). The samples collected from Iran-Iraq war veterans injured by mustard gas exposure showed an increased lymphocyte proliferation and levels of IL-17 with MBSR intervention compared to the control group. However, there was no marked difference in their overall lymphocyte ($CD4^+$, $CD8^{+,}$ and NK cells) counts (2).

In addition to asthma, yoga was found to be beneficial in patients with heart failure (65, 66, 74). The development of heart failure is associated with a raise in neuro-hormonal activation by the SNS and renin-angiotensin mechanism (74). Components such as heart rate (HR), blood pressure (BP), and respiratory rate interval are regulated by the ANS and these are often affected in heart failure patients. With yoga, the inclusion of breathing exercise reduces sympathetic activation. Hence, resulting in a decreased ventricular filling and subsequently improved exercise tolerance in the studied patient (65, 66). An increase in SOD was also observed among these patients indicating a rise in oxygen consumption which explains improved exercise capacity. The other reported change was a reduction in CRP and IL-6. During yoga, the parasympathetic part becomes dominant, and this enhances oxygen extraction by peripheral tissues therefore leading to changes observed in patients subjected to this intervention. Whereas the decrease in the inflammatory markers suggest improvement in endothelial function in reducing inflammation and oxidative stress at the vascular level (26).

In summary, MBTs that focus on breathing techniques modulate ANS. This in return improves breathing and regulation of blood pressure in patients with cardiorespiratory disease. The enhanced oxygenation, on the other hand, reduces hypoxia subsequently decreases the inflammatory biomarkers. The combination of these results eventually leads to improvement along the course of the disease.

Metabolic disease

MBTs were shown to improve cognitive function in obese and overweight people. This group of people was found to have poor control of the neural centers associated with addiction compromising control of food intake. Data shows that the intervention of yoga in these individuals increased cognitive function and brain activity on electroencephalography (75). Moreover, studies found behavioral interventions are beneficial in treating depression and anxiety especially in obese and overweight individuals (76). Depression and anxiety are associated with increased cortisol; and with yoga practice not only cortisol but IL-6 level was found to be decreased. The observation was accompanied by other findings which include an

increase in β-endorphin and improved telomerase activity (68). Similar studies on TC saw a reduction in CRP (67) and hemoglobin A1C (HbA1c) as well as an increase in IL-12 levels and the ratio of T-helper: T-regulatory cells in type 2 diabetes mellitus patients (76, 77). The proposed mechanism for these findings was the improvement of cardiopulmonary fitness and glucose metabolism following the exercise regime. These improvements resulted in lower levels of glycosylated proteins, which can benefit immune regulatory function in diabetic patients (76).

Cancer

Studies of the effects of MBTs in cancer patients predominantly involved breast cancer (BC) patients. The studies vary based on different stages of which the patient is; a survivor, an early stage, waiting to undergo surgery, receiving treatments (adjuvant, chemotherapy, multi-modality treatments), and recovering from treatment. Most research was inclined towards the effects of the mind-body exercises on immune parameters and QOL. General findings concurred that the MBTs such as yoga, qigong, TC, and MBSR improve QOL and reduce distress (44,45, 49, 52, 58, 78), symptom severity, anxiety, depression (44, 49, 52, 79) and improve sleep quality (49, 52, 80) in patients with cancers. MBT interventions are reported to induce a relaxed state of mind, which in return synchronizes their immune system to limit and control tumor growth (58, 81).

Yoga intervention in BC patients that underwent surgery was reported to result in a shortened hospital stay and faster recovery therefore, an improved QOL. These results corresponded to a lower level of TNF-α compared to the non-intervened group (45). Several mechanisms were proposed for the observed changes. The first notion is that relaxation can alter thoughts and emotions and reduce reactivity towards stressors. This minimizes the effects of stress hormone and promotes the body's healing response leading to faster wound recovery. Besides, the breathing exercises (i.e. yoga) may increase oxygen consumption, which aids wound repair, and reduce the risk of pulmonary infections after surgery. Several studies have reported changes in the levels of various cytokines in BC survivors who regularly practiced yoga. Many of these patients had reduced levels of pro-inflammatory markers such as NF-κB (3), TNF-α (43, 45), and IL-6, IL-1β (43). Qigong could also result in a similar effect whereby a decrease in CRP was recorded in patients practicing this exercise (56). In brief, the reduction in inflammatory markers attests to the benefits of MBTs in aiding recovery from cancer ensuring a greater QOL.

Changes in metabolic status upon MBTs intervention was noted in cancer patients. This is important as research implicates that insulin and cytokine pathways in weight gain are linked to the recurrence of BC. Statistics showed that a rise in fasting insulin level is associated with a 2-fold increase in BC recurrence and a 3-fold decrease in survival (82). Both insulin and insulin-like growth factors (IGFs) have been associated with tumor growth as they promote cell proliferation (82). Data on MBT studies, point outs that TC (for example) stabilized insulin levels in BC survivors with a decrease in IL-2 and an increase in IL-6 levels (83). This led to a postulation that inflammatory responses mediated by IL-2, IL-6, TNF-α, and IFN-γ promote abnormal cell proliferation leading to weight gain and recurrence of cancer, and a decrease in these responses' aids in the prevention of recurrence and weight gain. Thus, the ability of MBTs in lowering inflammation is especially useful in BC survivors to sustain a healthy weight and prevent relapse (83).

Study shows MBTs like yoga elicit changes in the activity of T-lymphocytes (CD4+ and CD8+) and NK cells in BC patients undergoing surgery (44). These cells were suppressed in the progression of cancer (50). Thus, improvement in their activities upon MBT is a positive outcome in cancer patients. The increase in cytotoxicity of NK cells and lymphokine-activated killer (LAK) cells following MBT is suggested to be due to the ability of IL-2 and IFN-γ to activate NK cells and convert them to LAK cells (84). Besides that, modulation of B-cells and enhanced T-cells immune responses were observed in BC patients recovering from treatments (e.g. lumpectomy and chemotherapy) upon MBSR intervention (50, 51, 85). Further experiments revealed that these T-cells were found to be more adept to activation by phytohemagglutinin (85). Additionally, there was a shift to the T-helper-1 (Th1) type of immune response in these patients (50), in which the Th1: Th2 ratio was reported to increase (50, 55). Other findings in BC patients were a reduction of IgA level and CD56+ cells in those who practiced yoga (44, 45), which implies that MBTs may affect antibody production in cancer patients. Decrease in stress level and reduction in diurnal cortisol levels was demonstrated in a study (47) on BC survivors who underwent MBT. The authors infer that reduction in stress level and regulation of cortisol may enhance the anti-tumor immune response.

With regards to the relationship between stress levels, lymphocyte activity and cytokine expression, stress hormones, catecholamine, and glucocorticoids can affect the distribution of NK cells in different tissue. Hence, changes in the levels of these hormones following MBTs can influence the NK cells. The NK cells are particularly important in immune response since the high level of these cells correlates with a good prognosis in cancer patients (44). With MBSR, the levels of IL-4, IL-6, and IL-10 were decreased in cancer patients leading to normalization of NK cell and Th1 cytokines (e.g. IFN-γ) activity implying a better chance of recovery. One possibility is MBTs may increase the number of glucocorticoid receptors, thus modulating inflammatory pathways as reflected by NK cells activity (86). The other possibility is the activation of the beta-adrenergic receptor (ßAR). The ßAR activation is crucial since its stimulation can activate NF-κB and increase pro-inflammatory cytokines (87, 88). Exposure to MBT reduces SNS pathways via activation of ßAR as reflected by the drop in the number of cAMP-response element-binding protein (CREB) transcription family (86, 89).

Besides, enhanced oxygenation in cancer patients following MBTs was proposed to reduce the activity of hypoxia-inducible factor 1 (HIF-1); therefore, causing a marked change in the tumor microenvironment (90). Overall, in cancer care, the inclusion of MBTs results in improved breathing in the patients (57). In response, this may activate the parasympathetic nervous system or cause a reduction of cortisol and pro-inflammatory cytokines. Over time, these changes could result in the normalization of immune dysregulation (50). However, it is important to note that the study of MBTs and immune parameters in cancer patients were influenced by factors such as the type of cancer, stage of cancer, type of treatment, patient age (51), baseline health of subjects, or other external factors (49), and duration of MBT training (51). Changes in these factors may affect the immune system. For instance, there was an increase of IL-4 and a decrease in IFN-γ and IL-10 in BC and prostate cancer patients practicing yoga (49). In contrast, interventions like breathing exercise and relaxation did not change the total number of leukocytes when compared to the control group in patients with leukemia or severe aplastic anemia. However, these interventions decreased their depression and anxiety during hospitalization (79).

Infection with the human immunodeficiency virus

In infections, MBTs not only increase virus-specific or cell-mediated immunity at rest; but also work in response to vaccinations (34). Reports showed yoga and TC intervention produced desirable outcomes in patients with human immunodeficiency virus (HIV). The outcomes include a decrease in depression and anxiety eventually a better QOL (4, 37). It was noted that exposure to TC and Transcendental Meditation had a minor effect on cortisol level in the HIV patients (4). However, yoga and mindfulness-based cognitive therapy (MBCT) was shown to have better effects such as an increase in the level of $CD4^+$ T-lymphocytes and NK cell activity (4, 37, 38, 40). 2 mechanisms have been proposed to explain the effect of MBSR on $CD4^+$ T-lymphocytes in the HIV patients; i) through its impact on hematopoiesis, T-cell redistribution dynamics, or T- cell turnover in lymphoid tissues and ii) by decreasing the HIV RNA levels (41).

Mindfulness also promotes behavioral changes in smoking habits, diet, and adherence to combined antiretroviral treatment (cART). On top of reducing the impact of depression or anxiety, these changes also led to a positive effect on CD4+ T-cell count (38). The same research also observed that there were no changes in the expression of CD38 and HLA-DR on the $CD4^+$ or $CD8^+$ T-cells in these HIV patients (4, 41), which is debatable.

Gastrointestinal diseases

MBT has been shown advantageous in certain conditions associated with gastrointestinal (GI) diseases, and its effect depends on the severity of the disease (61, 91). For instance, yoga practice could improve anxiety scores in patients with ulcerative colitis (UC) (60). However, the same was not observed in patients with Crohn's disease (CD) (60). These differences could be attributed to the higher anxiety levels in patients with CD. Therefore, it has been proposed that CD patients may require a longer duration of yoga to achieve similar effects as observed in UC patients (60). In inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS), MBT intervention lessens the anxiety and pain catastrophizing scores (91). The study showed that relaxation response-based group mind-body intervention (RR-MBI) targets various signaling proteins in the NF-κB pathway (12, 59) (e.g. MAPK, P38 MAPK, MAPK8) by counteracting the effects of stress in IBD and IBS through modulation of stress (59). Studies on ulcerative colitis (UC) patients, revealed that MBSR affected the levels of IL-10 and adrenocorticotropic hormone (ACTH), but the impact was not significant enough to prevent flare-ups in these patients. Several factors can cause a flare-up in UC and it should be noted that stress is not the primary trigger. Therefore, MBT, which targets stress, may not be completely effective in reducing the flare. However, this intervention may help to minimize the impact of stress on the inflammatory cascades, and it may be beneficial for individuals with heightened physiological responses to stress (61).

Depression

MBSR interventions were reported to decrease stress in a group of women with low-income, exposure to trauma, and depressive symptoms (13). These interventions helped these patients to enhance their psychosocial functioning and result in better QOL. Investigation of immune markers showed that MBSR interventions or mindfulness training improved NK cell activity and reduced pro-inflammatory cytokines such as IL-6 and TNF-α (13, 72, 92). In addition, a reduction of CRP was reported in the elderly patient with depression upon TC intervention (70).

A study on the molecular impact on markers of immune function revealed that brief yoga practice decreased DNA methylation of the *TNF* genes in chronically depressed women (69). DNA methylation is linked to a higher level of inflammation and poor health status (93). In addition, changes in the epigenetics profile of these women were also noted.

Conclusion

Psychosocial and physiological stress lead to changes in the immune system. These occur via different pathways. It can be through a metabolic pathway increasing reactive oxygen species (ROS), and activation of the NF-κB signaling pathways. An increase in ROS and oxidative stress can enhance the production of pro-inflammatory cytokines; and if this turns into a chronic condition, it might weaken the host immune system. On the other side, stressors can dysregulate the ANS and HPA axis, which increases catecholamines and cortisol as well as reduce glucocorticoid receptors in the long run. These changes can trigger systemic shifts such as dysregulation of breathing, HR, and BP. Activation of the HPA axis, increase in CRH,

and cortisol can also enhance the generation of ROS and inflammatory responses, increase in pro-inflammatory cytokines, and cause dysregulation of immune cells. In addition, different immune cells have receptors of SNS; therefore, SNS can directly impact the immune system.

MBTs intervention reduces stress and anxiety as well as improves QOL and sleep. MBT-related breathing modulates ANS, which consequently affects the suprachiasmatic nucleus (SCN) that regulates the sleep-wake cycle (94). Reduction in cortisol levels upon MBT intervention has been reported in different diseases as the main reason for the observed beneficial effects. Lessening distress and buffering stress hormones facilitate the recruitment of inflammatory cells at the wound site, therefore, sustaining pro-inflammatory cytokines to decrease infection rates. Other benefits are better oxygen consumption and improved endothelial functions which aid in healing physiologically (45, 59).

It is worthy to note that there are also discrepancies on the reported effects of MBT, which could be attributed to several factors (e.g. disease status, medications, type of diet), and are not generally considered in these studies. Moreover, different studies used different control groups; a group with similar health conditions without any intervention, health education control, wait-list control, and so on. Furthermore, assessment of the effects of the interventions may have occurred at a different time point, from immediately before and after the intervention, or up to 6 months following the intervention. The duration of the intervention also varied, as it could be as short as 1 day or up to a few months. All of these could affect the results, hence some inferred beneficial impact whereas others reported no effect.

Conflict of Interests

The authors declare no conflict of interest. There is no financial support to disclose.

References

1. Wahbeh H, Elsas SM, Oken BS. Mind-body interventions: applications in neurology. Neurology. 2008;70(24):2321-8.
2. Arefnasab Z, Babamahmoodi A, Babamahmoodi F, Noorbala AA, Alipour A, Panahi Y, *et al*. Mindfulness-based stress reduction (MBSR) and its effects on psychoimmunological factors of chemically pulmonary injured veterans. Iran J Allergy Asthma Immunol. 2016;15(6):476-86.
3. Bower JE, Greendale G, Crosswell AD, Garet D, Sternlieb B, Ganz PA, *et al*. Yoga reduces inflammatory signaling in fatigued breast cancer survivors: a randomized controlled trial. Psychoneuroendocrinology. 2014;43:20-9.
4. McCain NL, Gray DP, Elswick RK, Robins JW, Tuck I, Walter JM, *et al*. A randomized clinical trial of alternative stress management interventions in persons with HIV infection. J Consult Clin Psychol. 2008;76(3):431-41.
5. Jacobs TL, Epel ES, Lin J, Blackburn EH, Wolkowitz OM, Bridwell DA, *et al*. Intensive meditation training, immune cell telomerase activity, and psychological mediators. Psychoneuroendocrinology. 2011;36(5):664-81.
6. Besedovsky HO, del Rey A. Regulating inflammation by glucocorticoids. Nat Immunol. 2006;7(6):537.
7. Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol. 2006;6(4):318-28.
8. Lee MS, Huh HJ, Jeong SM, Lee HS, Ryu H, Park JH, *et al*. Effects of Qigong on immune cells. Am J Chin Med. 2003;31(2):327-35.
9. Besedovsky HO & Rey AD. Physiology of psychoneuroimmunology: a personal view. Brain Behav Immun. 2007;21(1):34-44.
10. Bereshchenko O, Bruscoli S, Riccardi C. Glucocorticoids, Sex Hormones, and Immunity. Front Immunol. 2018;9:1332.
11. Farzi A, Reichmann F, Holzer P. The homeostatic role of neuropeptide Y in immune function and its impact on mood and behaviour. Acta Physiol (Oxf). 2015;213(3):603-27.
12. Niles H, Mehta DH, Corrigan AA, Bhasin MK, Denninger JW. Functional genomics in the study of mind-body therapies. Ochsner J. 2014;14(4):681-95.
13. Fang CY, Reibel DK, Longacre ML, Rosenzweig S, Campbell DE, Douglas SD. Enhanced psychosocial well-being following participation in a mindfulness-based stress reduction program is associated with increased natural killer cell activity. J Altern Complement Med. 2010;16(5):531-8.
14. Manzaneque JM, Vera FM, Maldonado EF, Carranque G, Cubero VM, Morell M, *et al*. Assessment of immunological parameters following a qigong training program. Med Sci Monit. 2004;10(6):CR264-70.
15. Chen N, Xia X, Qin L, Luo L, Han S, Wang G, *et al*. Effects of 8-Week Hatha Yoga Training on Metabolic and Inflammatory Markers in Healthy, Female Chinese Subjects: A Randomized Clinical Trial. Biomed Res Int. 2016;2016:5387258.
16. Yadav RK, Magan D, Mehta N, Sharma R, Mahapatra SC. Efficacy of a short-term yoga-based lifestyle intervention in reducing stress and inflammation: preliminary results. J Altern Complement Med. 2012;18(7):662-7.
17. Núñez MJ, Mañá P, Liñares D, Riveiro MP, Balboa J, Suárez-Quintanilla J, *et al*. Music, immunity and cancer. Life Sci. 2002;71(9):1047-57.
18. Eda N, Shimizu K, Suzuki S, Tanabe Y, Lee E, Akama T. Effects of yoga exercise on salivary beta-defensin 2. Eur J Appl Physiol. 2013;113(10):2621-7.
19. Creswell JD, Pacilio LE, Lindsay EK, Brown KW. Brief mindfulness meditation training alters psychological and neuroendocrine responses to social evaluative stress. Psychoneuroendocrinology. 2014;44:1-12.

20. Ishigami S, Nakajima A, Tanno M, Matsuzaki T, Suzuki H, Yoshino S. Effects of mirthful laughter on growth hormone, IGF-1 and substance P in patients with rheumatoid arthritis. Clin Exp Rheumatol. 2005;23(5):651-7.
21. Lutgendorf S, Logan H, Kirchner HL, Rothrock N, Svengalis S, Iverson K, *et al*. Effects of relaxation and stress on the capsaicin-induced local inflammatory response. Psychosom Med. 2000;62(4):524-34.
22. Janssen SA, Arntz A, Bouts S. Anxiety and pain: epinephrine-induced hyperalgesia and attentional influences. Pain. 1998;76(3):309-16.
23. Wallace RK, Benson H, Wilson AF. A wakeful hypometabolic physiologic state. Am J Physiol. 1971;221(3):795-9.
24. Epel ES. Telomeres in a Life-Span Perspective: A New "Psychobiomarker"?. Curr Dir Psychol Sci. 2009;18(1):6-10.
25. Epel ES, Blackburn EH, Lin J, Dhabhar FS, Adler NE, Morrow JD, *et al*. Accelerated telomere shortening in response to life stress. Proc Natl Acad Sci USA. 2004;101(49):17312-5.
26. Ornish D, Lin J, Daubenmier J, Weidner G, Epel E, Kemp C, *et al*. Increased telomerase activity and comprehensive lifestyle changes: a pilot study. Lancet Oncol. 2008;9(11):1048-57.
27. Blackburn EH. Structure and function of telomeres. Nature. 1991;350(6319):569-73.
28. Blackburn EH, Chan S, Chang J, Fulton TB, Krauskopf A, McEachern M, *et al*. Molecular manifestations and molecular determinants of telomere capping. Cold Spring Harb Symp Quant Biol. 2000;65:253-63.
29. Goon JA, Noor Aini AH, Musalmah M, Yasmin Anum MY, Wan Ngah WZ. Long term Tai Chi exercise reduced DNA damage and increased lymphocyte apoptosis and proliferation in older adults. Med J Malaysia. 2008;63(4):319-24.
30. Vijayaraghava A, Doreswamy V, Narasipur OS, Kunnavil R, Srinivasamurthy N. Effect of Yoga Practice on Levels of Inflammatory Markers After Moderate and Strenuous Exercise. J Clin Diagn Res. 2015;9(6):CC08-12.
31. Booth RJ. The psychoneuroimmune network: expanding our understanding of immunity and disease. NZ Med J. 1990;103(893):314-6.
32. Glaser R, Kiecolt-Glaser JK. Stress-induced immune dysfunction: implications for health. Nat Rev Immunol. 2005;5(3):243-51.
33. Buric I, Farias M, Jong J, Mee C, Brazil IA. What is the molecular signature of mind-body interventions? A systematic review of gene expression changes induced by meditation and related practices. Front Immunol. 2017;8:670.
34. Morgan N, Irwin MR, Chung M, Wang C. The effects of mind-body therapies on the immune system: meta-analysis. PLoS One. 2014;9(7):e100903.
35. Li H, Geib RW. Exploring the use of five color flow cytometry to examine the effect of acute tai chi practice on pro inflammatory monocyte subtypes - biomed 2013. Biomed Sci Instrum. 2013;49:209-15.
36. Wood GJ, Bughi S, Morrison J, Tanavoli S, Tanavoli S, Zadeh HH. Hypnosis, differential expression of cytokines by T-cell subsets, and the hypothalamo-pituitary-adrenal axis. Am J Clin Hypn. 2003;45(3):179-96.
37. Naoroibam R, Metri KG, Bhargav H, Nagaratna R, Nagendra HR. Effect of Integrated Yoga (IY) on psychological states and CD4 counts of HIV-1 infected patients: A randomized controlled pilot study. Int J Yoga. 2016;9(1):57-61.
38. Gonzalez-Garcia M, Ferrer MJ, Borras X, Muñoz-Moreno JA, Miranda C, Puig J, *et al*. Effectiveness of mindfulness-based cognitive therapy on the quality of life, emotional status, and CD4 cell count of patients aging with HIV infection. AIDS Behav. 2014;18(4):676-85.
39. Chhatre S, Metzger DS, Frank I, Boyer J, Thompson E, Nidich S, *et al*. Effects of behavioral stress reduction Transcendental Meditation intervention in persons with HIV. AIDS Care. 2013;25(10):1291-7.
40. Robinson FP, HL Mathews, L Witek-Janusek. Psycho-endocrine-immune response to mindfulness-based stress reduction in individuals infected with the human immunodeficiency virus: A quasiexperimental study. J Altern Complement Med. 2003;9(5):683-94.
41. Creswell JD, Myers HF, Cole SW, Irwin MR. Mindfulness meditation training effects on CD4+ T lymphocytes in HIV-1 infected adults: a small randomized controlled trial. Brain Behav Immun. 2009;23(2):184-8.
42. Long Parma D, Hughes DC, Ghosh S, Li R, Treviño-Whitaker RA, Ogden SM, *et al*. Effects of six months of Yoga on inflammatory serum markers prognostic of recurrence risk in breast cancer survivors. Springerplus. 2015;4:143.
43. Kiecolt-Glaser JK, Bennett JM, Andridge R, Peng J, Shapiro CL, Malarkey WB, *et al*. Yoga's impact on inflammation, mood, and fatigue in breast cancer survivors: a randomized controlled trial. J Clin Oncol. 2014;32(10):1040-9.
44. Rao RM, Nagendra HR, Raghuram N, Vinay C, Chandrashekara S, Gopinath KS, *et al*. Influence of yoga on mood states, distress, quality of life and immune outcomes in early stage breast cancer patients undergoing surgery. Int J Yoga. 2008;1(1):11-20.
45. Rao RM, Nagendra HR, Raghuram N, Vinay C, Chandrashekara S, Gopinath KS, *et al.* Influence of yoga on postoperative outcomes and wound healing in early operable breast cancer patients undergoing surgery. Int J Yoga. 2008;1(1):33-41.
46. Rao RM, Vadiraja HS, Nagaratna R, Gopinath KS, Patil S, Diwakar RB, *et al*. Effect of yoga on sleep quality and neuroendocrine immune response in metastatic breast cancer patients. Indian J Palliat Care. 2017;23(3):253-60.
47. Banasik J, Williams H, Haberman M, Blank SE, Bendel R. Effect of Iyengar yoga practice on fatigue

and diurnal salivary cortisol concentration in breast cancer survivors. J Am Acad Nurse Pract. 2011;23(3):135-42.
48. Witek-Janusek L, Albuquerque K, Chroniak KR, Chroniak C, Durazo-Arvizu R, Mathews HL. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. Brain Behav Immun. 2008;22(6):969-81.
49. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress, and immune parameters in breast and prostate cancer outpatients. Psychosom Med. 2003;65(4):571-81.
50. Lengacher CA, Kip KE, Post-White J, Fitzgerald S, Newton C, Barta M, *et al*. Lymphocyte recovery after breast cancer treatment and mindfulness-based stress reduction (MBSR) therapy. Biol Res Nurs. 2013;15(1):37-47.
51. Reich RR, Lengacher CA, Klein TW, Newton C, Shivers S, Ramesar S, *et al*. A Randomized Controlled Trial of the Effects of Mindfulness-Based Stress Reduction (MBSR[BC]) on Levels of Inflammatory Biomarkers Among Recovering Breast Cancer Survivors. Biol Res Nurs. 2017;19(4):456-64.
52. Carlson LE, Speca M, Patel KD, Goodey E. Mindfulness-based stress reduction in relation to quality of life, mood, symptoms of stress and levels of cortisol, dehydroepiandrosterone sulfate (DHEAS) and melatonin in breast and prostate cancer outpatients. Psychoneuroendocrinology. 2004;29(4):448-74.
53. Janelsins MC, Davis PG, Wideman L, Katula JA, Sprod LK, Peppone LJ, *et al*. Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. Clin Breast Cancer. 2011;11(3):161-70.
54. Antoni MH, Lutgendorf SK, Blomberg B, Carver CS, Lechner S, Diaz A, *et al*. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol Psychiatry. 2012;71(4):366-72.
55. Wang R, Liu J, Chen P, Yu D. Regular tai chi exercise decreases the percentage of type 2 cytokine-producing cells in postsurgical non-small cell lung cancer survivors. Cancer Nurs. 2013;36(4):E27-34.
56. Oh B, Butow P, Mullan B, Hale A, Lee MS, Guo X, *et al*. A critical review of the effects of medical Qigong on quality of life, immune function, and survival in cancer patients. Integr Cancer Ther. 2012;11(2):101-10.
57. Kochupillai V, Kumar P, Singh D, Aggarwal D, Bhardwaj N, Bhutani M, *et al*. Effect of rhythmic breathing (Sudarshan Kriya and Pranayam) on immune functions and tobacco addiction. Ann N Y Acad Sci. 2005;1056:242-52.
58. Lengacher CA, Kip KE, Barta M, Post-White J, Jacobsen PB, Groer M, *et al*. A pilot study evaluating the effect of mindfulness-based stress reduction on psychological status, physical status, salivary cortisol, and interleukin-6 among advanced-stage cancer patients and their caregivers. J Holist Nurs. 2012;30(3):170-85.
59. Kuo B, Bhasin M, Jacquart J, Scult MA, Slipp L, Riklin EI, *et al.* Genomic and clinical effects associated with a relaxation response mind-body intervention in patients with irritable bowel syndrome and inflammatory bowel disease. PLoS One. 2015;10(4):e0123861.
60. Sharma P, Poojary G, Dwivedi SN, Deepak KK. Effect of Yoga-Based Intervention in Patients with Inflammatory Bowel Disease. Int J Yoga Therap. 2015;25(1):101-12.
61. Jedel S, Hoffman A, Merriman P, Swanson B, Voigt R, Rajan KB, *et al.* A randomized controlled trial of mindfulness-based stress reduction to prevent flare-up in patients with inactive ulcerative colitis. Digestion. 2014;89(2):142-55.
62. Zautra AJ, Davis MC, Reich JW, Nicassario P, Tennen H, Finan P, *et al*. Comparison of cognitive behavioral and mindfulness meditation interventions on adaptation to rheumatoid arthritis for patients with and without history of recurrent depression. J Consult Clin Psychol. 2008;76(3):408-21.
63. Wang C, Roubenoff R, Lau J, Kalish R, Schmid CH, Tighiouart H, *et al.* Effect of Tai Chi in adults with rheumatoid arthritis. Rheumatology. 2005;44(5):685-7.
64. Agnihotri S, Kant S, Kumar S, Mishra RK, Mishra SK. Impact of yoga on biochemical profile of asthmatics: A randomized controlled study. Int J Yoga. 2014;7(1):17-21.
65. Pullen PR, Nagamia SH, Mehta PK, Thompson WR, Benardot D, Hammoud R, *et al*. Effects of yoga on inflammation and exercise capacity in patients with chronic heart failure. J Card Fail. 2008;14(5):407-13.
66. Pullen PR, Thompson WR, Benardot D, Brandon LJ, Mehta PK, Rifai L, *et al*. Benefits of yoga for African American heart failure patients. Med Sci Sports Exerc. 2010;42(4):651-7.
67. Chen SC, Ueng KC, Lee SH, Sun KT, Lee MC. Effect of t'ai chi exercise on biochemical profiles and oxidative stress indicators in obese patients with type 2 diabetes. J Altern Complement Med. 2010;16(11):1153-9.
68. Kumar SB, Yadav R, Yadav RK, Tolahunase M, Dada R. Telomerase activity and cellular aging might be positively modified by a yoga-based lifestyle intervention. J Altern Complement Med. 2015;21(6):370-2.
69. Harkess KN, Ryan J, Delfabbro PH, Cohen-Woods S. Preliminary indications of the effect of a brief yoga intervention on markers of inflammation and DNA methylation in chronically stressed women. Transl Psychiatry. 2016;6(11):e965.
70. Lavretsky H, Alstein LL, Olmstead RE, Ercoli LM, Riparetti-Brown M, Cyr NS, *et al.* Complementary use of tai chi chih augments escitalopram treatment of

geriatric depression: a randomized controlled trial. Am J Geriatr Psychiatry. 2011;19(10):839-50.
71. Kang HY, Yoo YS. Effects of a bereavement intervention program in middle-aged widows in Korea. Arch Psychiatr Nurs. 2007;21(3):132-40.
72. Gallegos AM, Lytle MC, Moynihan JA, Talbot NL. Mindfulness-based stress reduction to enhance psychological functioning and improve inflammatory biomarkers in trauma-exposed women: A pilot study. Psychol Trauma. 2015;7(6):525-32.
73. Kern-Buell CL, McGrady AV, Conran PB, Nelson LA. Asthma severity, psychophysiological indicators of arousal, and immune function in asthma patients undergoing biofeedback-assisted relaxation. Appl Psychophysiol Biofeedback. 2000;25(2):79-91.
74. Hartupee J, Mann DL. Neurohormonal activation in heart failure with reduced ejection fraction. Nat Rev Cardiol. 2017;14(1):30-8.
75. Magan D, Yadav RK, Mehta M. Efficacy of a Short-Term Yoga-Based Lifestyle Intervention in Improving Cognition in Overweight/Obese Subjects. IJCEP. 2017;4(4):202-6.
76. Yeh SH, Chuang H, Lin LW, Hsiao CY, Eng HL. Regular tai chi chuan exercise enhances functional mobility and CD4CD25 regulatory T cells. Br J Sports Med. 2006;40(3):239-43.
77. Yeh SH, Chuang H, Lin LW, Hsiao CY, Wang PW, Liu RT, *et al*. Regular Tai Chi Chuan exercise improves T cell helper function of patients with type 2 diabetes mellitus with an increase in T-bet transcription factor and IL-12 production. Br J Sports Med. 2009;43(11):845-50.
78. Oh B, Butow P, Mullan B, Clarke S, Beale P, Pavlakis N, *et al.* Impact of medical Qigong on quality of life, fatigue, mood and inflammation in cancer patients: a randomized controlled trial. Ann Oncol. 2010;21(3):608-14.
79. Kim SD, Kim HS. Effects of a relaxation breathing exercise on anxiety, depression, and leukocyte in hemopoietic stem cell transplantation patients. Cancer Nurs. 2005;28(1):79-83.
80. Chandwani KD, Perkins G, Nagendra HR, Raghuram NV, Spelman A, Nagarathna R, *et al*. Randomized, controlled trial of yoga in women with breast cancer undergoing radiotherapy. J Clin Oncol. 2014;32(10):1058-65.
81. Grossman P, Niemann L, Schmidt S, Walach H. Mindfulness-based stress reduction and health benefits. A meta-analysis. J Psychosom Res. 2004;57(1):35-43.
82. Kleinberg DL, Wood TL, Furth PA, Lee AV. Growth hormone and insulin-like growth factor-I in the transition from normal mammary development to preneoplastic mammary lesions. Endocr Rev. 2009;30(1):51-74.
83. Sanada K, Alda Díez M, Salas Valero M, Pérez-Yus MC, Demarzo MM, Montero-Marín J, *et al*. Effects of mindfulness-based interventions on biomarkers in healthy and cancer populations: a systematic review. BMC Complement Altern Med. 2017;17(1):125.
84. Lengacher CA, Bennett MP, Gonzalez L, Gilvary D, Cox CE, Cantor A, *et al.* Immune responses to guided imagery during breast cancer treatment. Biol Res Nurs. 2008;9(3):205-14.
85. Danhauer SC, Addington EL, Sohl SJ, Chaoul A, Cohen L. Review of yoga therapy during cancer treatment. Support Care Cancer. 2017;25(4):1357-72.
86. Cruz-Topete D, Cidlowski JA. One Hormone, Two Actions: Anti- and Pro-Inflammatory Effects of Glucocorticoids. Neuroimmunomodulation. 2015;22(1-2):20-32.
87. Irwin MR, Cole SW. Reciprocal regulation of the neural and innate immune systems. Nat Rev Immunol. 2011;11(9):625-32.
88. Sanders VM and RH Straub. Norepinephrine, the beta-adrenergic receptor, and immunity. Brain Behav Immun. 2002;16(4):290-332.
89. Bremner M, B Blake, C Stiles. The experiences of persons living with HIV who participate in mind-body and energy therapies: A systematic review protocol of qualitative evidence. JBI database System Rev Implement Rep. 2015;13(10):41-9.
90. Bhargav H, Metri K, Raghuram N, Ramarao NH, Koka PS. Enhancement of cancer stem cell susceptibility to conventional treatments through complementary yoga therapy: possible cellular and molecular mechanisms. J Stem Cells. 2012;7(4):261-7.
91. Aucoin M, MJ Lalonde-Parsi, K Cooley. Mindfulness-based therapies in the treatment of functional gastrointestinal disorders: a meta-analysis. Evid Based Complement. Alternat Med. 2014;2014:140724.
92. Walsh E, T Eisenlohr-Moul, R Baer. Brief mindfulness training reduces salivary IL-6 and TNF-alpha in young women with depressive symptomatology. J Consult Clin Psychol. 2016;84(10):887-97.
93. Myte R, Sundkvist A, Van Guelpen B, Harlid S. Circulating levels of inflammatory markers and DNA methylation, an analysis of repeated samples from a population based cohort. Epigenetics. 2019;14(7):649-59.
94. Nopitasari D, Rahayu RSR. Analysis of the effect of hatha yoga on the quality of sleep and immune system among the students in public health postgraduate program at UNNES. Public Health Perspective J. 2018;3(1):1-6.