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TAI CHI ROLES IN REDUCING FATIGUE, PAIN, AND TNF-α PLASMA LEVEL ON BREAST CANCER PATIENTS: A SYSTEMATIC REVIEW

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ABSTRACT

Tai Chi (TC) has been very popular over the last few decades as useful tools for reducing stress and improving health. Survivors of breast cancer (BC) often experience symptoms that reduce their quality of life during and after treatment, such as cognitive dysfunction, fatigue, sleep disturbances, depression, pain, and weight gain. The proinflammatory biomarkers like TNF-α, IL-1, and IL-6 which are activated through the central nervous system were believed to induce fatigue, pain, and other complications that caused hindrance on life activity. The aim of this study is to identify and evaluate the effect of TC training on inflammatory biomarkers, especially TNF-α, pain, and cancer-related fatigue (CRF) in BC patients. Journal searching processes were performed through five electronic databases (ProQuest, Sciencedirect, PubMed, Google Scholar, and Sage Publications) and restricted from 2012 to 2022. The search strategy on the electronic databases was using terms like 'tai ji', 'tai chi', 'tumor necrosis factor-alpha', 'Interleukin-6', 'fatigue', 'pain', 'breast cancer', 'biomarker', 'TNF', 'TNF-α', and 'TNF-alpha'. Nine journals were chosen to be reviewed and discussed the intervention of Tai Chi, research methodology, and study results using pain, fatigue, and TNF-α biomarker. Tai Chi seems to be effective to reduce pain, cancer-related fatigue, and improves quality of life for breast cancer patients.

Keywords: Tai Chi; breast cancer; TNF-α; Fatigue; Pain

INTRODUCTION

The most frequently diagnosed cancer worldwide according to the International Agency for Research on Cancer (IARC) GLOBOCAN cancer statistics for 2020, especially those found in women, is breast cancer (BC), which is around 2.26 million cases [1]. Careful evaluation and long-term management of side effects is a major challenge from a clinical point of view which is of great importance for BC patients who have undergone chemotherapy and require long-term adjuvant treatment [2].

With early detection and accompanied by advances in the treatment of BC, patients with BC can achieve an increasing percentage of survival and are able to survive longer. With an increase in overall life expectancy, BC survivors who suffer from this disease for a long time are subsequently at risk of accelerated aging, which causes the signs, symptoms of aging and cancer development to overlap. Cancer is also strongly linked with aging [3]. Related to this problem, there have been many epidemiological studies that highlight long-term complications that are closely related, especially with BC treatment. But on the other hand, the underlying molecular mechanisms have not been well elucidated.

Treatment for BC includes surgery, chemotherapy, radiation therapy, and hormone therapy, which can be done alone or in combination. Although survival of patients with BC for at least 5 years after diagnosis ranges from over 90% in high-income countries, to 66% in India and 40% in South Africa, side effects after diagnosis and treatment can be persistently debilitating [4]. It is important to pay attention to other things, not

only from a clinical perspective after cancer treatment, but also the possibility of recurrence and viability, and treatment effect or cancer itself on physical and mental function as well as the welfare of breast cancer patients. Side effects of breast cancer and its treatment include cancer-related fatigue [5,6], sleep disturbances [7], depression, anxiety [8,9], chronic pain [10,11], decreased functional capacity, decreased muscle strength and endurance, and weight gain, which in the end will positively change the quality of life (QOL) [12].

Fatigue, particularly, has a negative effect on quality of life, in breast cancer patients and survivors can last 10 years or more [6]. CRF is described as prolonged discomfort with a feeling exhausted and tired that could interfere with daily activities as the symptoms. Control and monitoring on it is required [13,14]. Even though the CRF pathophysiology is still not well-understood, some mechanisms are proposed to explain the CRF development mechanism, such as dysfunction of inflammation and mitochondria, activation of the immune peripheral, and central mechanism [14,15]. BC patients who sense CRF complaints will find elevated levels of pro-inflammatory cytokines, especially Tumor Necrosis Factor-α (TNF-α), interleukin-1 (IL-1), as well as interleukin-6 (IL-6) [16]. CNS (central nervous system) pathways activated by proinflammatory cytokines, such as interleukin-1beta (IL-1β), IL-6 and TNF-α due to cell stress, cell death, chemotherapy, and tumor microenvironment can induce fatigue, pain and other disturbances [12,16,17]. Due to the limitation on conventional therapies, other methods such as complementary and alternative medicine (CAM) were approached by BC survivors and TC started to gain attention [18,19].

TC is a traditional Chinese training in the form of movements that are full of ancient Chinese philosophy and Chinese medicine, such as Confucianism and Taoism. TC is a mind-body exercise that combines breathing exercises, meditation and a series of sequential body movements with coordinated, balance-based postures [20]. TC is often used to improve physical function, strength, balance, and to prevent falls in breast cancer patients [21]. In addition, TC also plays a good role in improving the quality of life (QoL) and improving sleep quality in cancer patients [22–24]. Some possible mechanisms that Tai Chi could relieve fatigue are developing relaxation through slow movement and shifting weight, increasing aerobic capacity, enhancing immune system [13]. The National Comprehensive Cancer Network (NCCN) has proposed a guideline for managing CRF, however the gold standard for CRF has not been decided [13]. Even though several studies show improvement in fatigue and reducing pain as well as reducing TNF-α plasma level, the contrary studies result still remain [13]. Some studies also indicated that no significant changes were made by TC [18,25–28].

Ten randomized controlled trials have investigated the effect of TC on systemic markers inflammation in noncancerous samples. TC reduces circulating TNF-α levels in patients with COVID-19 [29], in patients with ankylosing spondylitis [30], in stroke patients [31,32], COPD patients [33], heart failure patients [34,35]. Few of these studies have focused on breast cancer survivors, and almost none have thoroughly reviewed and assessed the effects of TC on inflammation at the cellular level of proinflammatory cytokines (specifically, TNF-α) regarding the mechanisms of their effect on pain and fatigue in breast cancer patients.

METHODS

a. Methodology

Study design

This study is a systematic review which was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [36]. Literature search, literature selection, data extraction, and critical assessment were performed by the five reviewers independently, and any inconsistencies were resolved by mutual agreement or in consultation with a third experienced reviewer.

Subjects recruitment

The eligibility criteria for this study were as follows: (a) study design: randomized controlled trials (RCTs), and randomized partially blinded trials; (b) participants: adult patients diagnosed with BC who are receiving active treatment (i.e. surgery, radiation therapy, chemotherapy, or antihormonal

therapy); (c) intervention: TC with or without a combination of other interventions; and (d) The control group: other exercise, class meeting, conventional therapy or no treatment at all.
The primary outcome of this study was TNF-α measured with ELISA-kit, and for the second outcomes were pain and fatigue. Other results such as repeated publications, review comments, magazine articles, and other types of research were excluded.

Literature Research
Five electronic databases (ProQuest, Sciencedirect, PubMed Central NCBI, Google Scholar, and Sage Publications) were searched from 2012 to 2022. Search strategy in English electronic database was compiled using the terms The search strategy on the electronic website used terms from 'tai ji', 'tai chi', 'tumor necrosis factor-alpha', 'interleukin-6', 'fatigue', 'pain', 'breast cancer', 'biomarker', 'TNF', 'TNF-α', and 'TNF-alpha'.

b. Material and Procedure
Article searching processes were begun with inserting the keywords to each search engine that was chosen independently by the reviewers to find the literature needed. The next step was excluding the duplications found from the 5 search engines. Title and abstract that qualified the eligibility standard were identified, which next will be assessed by the reviewers. The studies chosen consist of randomized control trials and randomized partially blinded trials with TC exercises that were performed in various times from 20 to 120 minutes per session, with frequency range from once to 5 times a week, over 1-15 months of intervention. These TC practices were under the supervision of experienced TC instructors.

c. Assessment
The reviewers assessed independently by the inclusion criterias and excluded non-representing journals. Then the reviewers analyzed several things from the journal's contents based on the suitability of topics, indexes or journal ratings through the Scimagojr website with journal criteria that met Q1 and Q2 quality, sample size, results from each journal, and limitations that occurred. The journals that met the criterias would proceed for data extraction.

d. Data analysis
Data extraction was performed by five reviewers from selected studies and independently assessed methodological quality. The extracted information included the authors and the year of publication of the journal, the participants, research purposes, intervention characteristics used in the study (the frequency of exercise and the length of time), the outcome being measured, and study results. If any disagreement arises between the five investigators, the discussion would be organized to propose a solution after reaching an agreement. The third party suggestion would be included if the five reviewers could not reach an agreement.

RESULTS

Reviewers have found 1.557 journals (including duplicates) from five databases. The selection process on several journals were performed according to the relevancy to the title and the article's abstract. In order to check the journals' index, investigations through Scimagojr website were conducted.

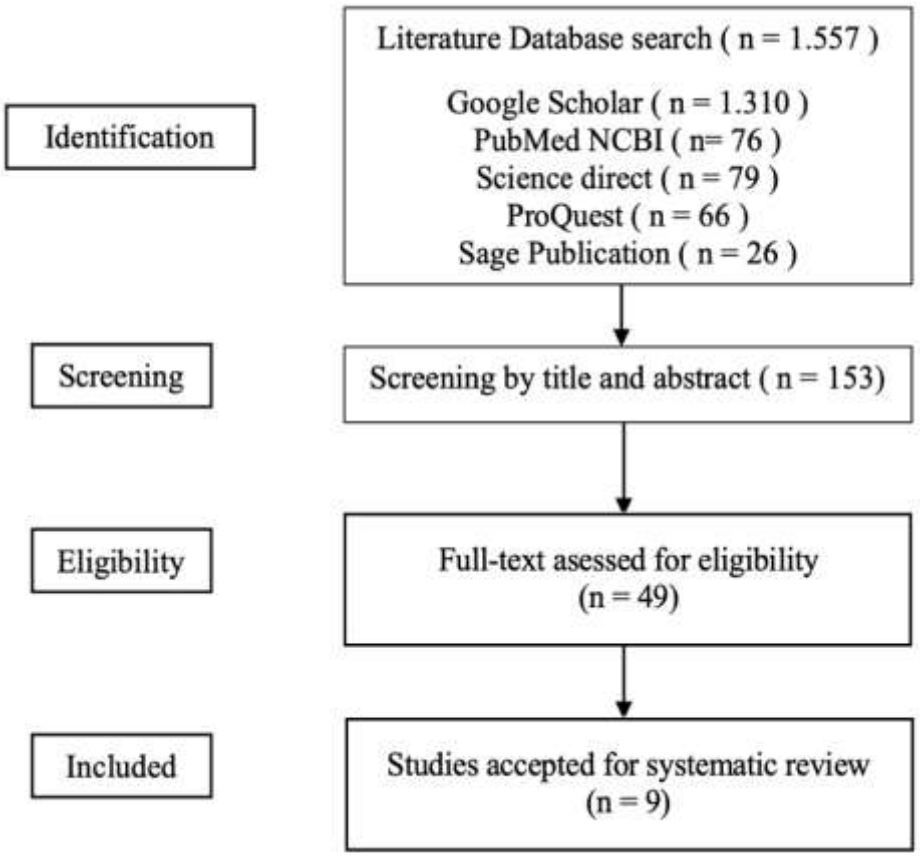

Figure 1. Flowchart of the study selection and identification

Forty-nine journals were selected for this systematic review. At the end, nine journals were chosen to be explored and discussed in more depth because of the appropriateness of the intervention, research methodology and study results using pain, fatigue and TNF-α biomarker. The data extraction of the nine journals is presented in Table 1.

Table 1. Data Extraction of Literature Review Results

No	Author, Year of Research	Participant/ Research Groups	Outcomes	Intervention and Research Purpose	Duration (weeks or months)	Frequency	Research Methods	Research Result
1.	Robins et al., 2013 [25]	A total of 109 participants	Psychosocial instruments and immunological by proinflammatory cytokines in the acute phase (TNF-α, IL-1, and IL-6)	Spiritual growth group and TC Research purpose: to evaluate quality of life, psychosocial functioning, and biological markers thought to reflect cancer-specific mechanisms and treatment	10 weeks	90 minutes per session each week	Randomized control trial	Psychosocial interventions such as TC or spiritual growth groups may not have a significant enough effect to overcome the physiological or psychosocial stress experienced by BC patients during the treatment period who generally experience side effects such as gastrointestinal disturbances, and fatigue. There was a better recovery in the production of proinflammatory cytokines (TNF-α, IL-1, and IL-6) as indicated by an elevation in IFN-□ levels
2.	Cheng et al., 2021 [37]	120 cancer patients aged 55 years or older; diagnosed with lung, stomach and breast cancer histopathologically ; had received 2-4 courses of chemotherapy and/or with additional radiation therapy and with a Brief Fatigue Inventory (BFI) examination showed complaints of CRF.	CRF	Resistance training and TC Research purpose: Learning impact of TC and RT on CRF and QoL in patients diagnosed with BC, lung, and stomach cancer.	12 weeks	Duration 40 minutes per day 3 times per week.	Randomized controlled trial	The study showed a significant improvement on CRF of cancer patients in both groups (RT and TC) in 12 weeks after intervention, better than pre-treatment ($P<0.05$).

3.	Tsang et al., 2015 [28]	105 breast cancer patients aged 32–42 years that underwent mastectomy for invasive ductal carcinoma and completed 4 cycles of FEC 50 healthy female participants, aged 26–36 years.	white blood cell (WBC), red blood cell (RBC) count and cytokine levels (IL-2, IL-4, IL-6, IFN-c and TNF-α)	Tai Chi Chuan Research Purpose : explore Tai Chi chuan effects on biological marker and psychological aspect of patients diagnosed with advanced invasive ductal carcinoma	12 weeks	90 minutes 3 times per week	Randomized-controlled trial	No significant changes on cytokines (IL-2, IL4, IL6, IFN-c and TNF-α) level between patients and healthy groups after 12 months of Tai Chi Chuan.
4.	Larkey et al., 2016 [38]	250 fatigued, post-menopausal women aged 45 - 75 years, diagnosed with breast cancer (stage 0-III), between 6 months and 5 years past primary treatment. post-menopausal status; and 5) current	Anxiety, fatigue, depression, cognitive function, sleep quality, physical activity Biomarker of HPA axis dysregulation (diurnal cortisol) Inflammation biomarkers (IL-1 Ra, IL-6, TNF-α and INF_{γ})	Qigong/Tai Chi Easy (QG/TCE), educational support (ES) group, and Qigong group (SQG) Research purpose : Finding Qigong/Tai Chi Easy effects on reducing CRF in BC patients and the following biochemical mechanism	12 weeks	Weekly for 1 hour	Three-armed randomized controlled trial Pre - post intervention	No significant differences pre and post intervention on cortisol and inflammation biomarkers.
5.	Irwin et al., 2015 [39]	123 breast cancer adult older than 55 years who met the criteria for primary insomnia in the DSM-IV	Systemic (CRP values), Cellular (TNF-α, TLR-4 activation, and IL-6), Genomic (gene expression)	Cognitive-Behavioral Therapy for Insomnia (CBT-I), Tai Chi Chih intervention (TCC), and Sleep seminar education active control condition.	4 months and followed up in the 7th and 16th month	20 minutes class time done every week	Randomized control trial	This study declared that CBT-I improved sleep behavior and reduced CBT-I-induced systemic inflammation. Tai Chi Chih, induced reduction of cellular inflammation, suggesting that this change was independent of sleep quality improvement.

6.	Irwin et al., 2017 [40]	145 BC survivors	Improve insomnia, boost good quality of sleep, reduce fatigue, and depression.	Tai Chi Chih and CBT-I Research purpose: Sleep Quality Index to evaluate insomnia treatment response and fatigue	3-15 months	120 minutes per sessions One times per week	Randomized partially blinded trial	The study conducted with this non-inferiority test showed that TCC was not lower than CBT-I at 3 months, which was indicated by the absence of significant differences between the two groups.
7.	Sprod et al., 2012 [41]	35 BC survivors	Cortisol, insulin, glucose, IL-6, IGF-1, IL-8, insulin-like growth factor-binding protein (IGFBP)-1, and IGFBP-3. Quality of life (includes physical and emotional capacity limitations, mental health, social and physical well-being, pain, energy, and general health responses).	Standard support therapy (SST) and Tai Chi Chuan Research purpose: To examine the impact of TCC based on health-related QoL, Inflammatory biomarkers and other biomarkers associated with aftereffects of disease and treatment in BC.	12 weeks	60 minutes, 3 times per week	Randomized controlled trial	No significant differences in IL-6, IGF-1, and Body Mass Index. Physical capacity limitations, social well-being, mental health, energy, significantly better in the TCC group. No significant change in pain, emotional limitations, and general health responses in both groups, SST and TCC.
8.	Campo et al., 2015 [42]	63 women with cancer (aged 55 – 84 years) who have limited physical function (physical role 72 or SF-12 physical function 80)	Salivary cortisol, BP, anti-inflammatory cytokines (IL-12, IL-4, IL-6, IL-10, and TNF-α)	Intervention: Tai Chi and Health Education. Research purpose: to examine TC as a mental and physical exercise that is associated with reduced risk factors for chronic illness.	5 to 12 weeks	45 minutes - 2 hours per session 2 - 5 times a week	Randomized controlled trial	The results showed no significant difference between post-intervention pro-inflammatory and anti-inflammatory cytokines. No interventional effect was seen on the levels of inflammatory cytokines, this is consistent with the results reported in a previous TC study conducted in a group of healthy elderly and elderly with breast cancer.

9.	Irwin et al., 2014 [43]	90 insomnia - breast cancer survivors.	IL-6 and TNF-α	Intervention: Tai Chi Research purpose: This study assumed that Tai Chi (TCC) reduced systemic, cellular, and genomic markers of inflammation compared to cognitive-behavioral therapy (CBT-I) for insomnia in breast cancer survivors.	3 months	2-hour sessions weekly.	Randomized controlled trial	This study highlights Tai Chi and other mind-body therapy may play a role in the regulation of the immune system, consistent with other findings that psychosomatic therapy and CBSM (cognitive behavioral stress management, help reduce inflammation, including in cancer patients Post-treatment assessments showed reduced TLR4-activated monocyte production of IL6 and TNF-α in cancer survivors treated with TCC.

DISCUSSION

This systematic review describes the procedures and methodology of a ten-year randomized controlled trial, housed in various locations, which will investigate the effectiveness of TC exercise on fatigue, pain and its effect on TNF-α biomarkers in breast cancer patients.

Several trials were included in this review, and there was a high risk of bias in the blinding. This literature review analysis was carried out according to the types of TC exercises with different intensities, consisting of 12 weeks with a frequency of 1-3 times per week with a duration of 40 minutes [37], 60 minutes [38,41], 90 minutes [28], 10 weeks with a duration of 90 minutes per session each week [25], 4 months with a duration of 20 minutes class time done every week [39], 3 months for 120 minutes per session each week [43], 3-15 months [40], 5-12 weeks with a duration of 45 minutes - 2 hours per session and frequency 2 - 5 times a week [42], 120 minutes per session each week for 3 until 15 months [40].

From existing studies, TC intensity has been shown to have an effect on IL-6 and TNF-α, which results show that high-intensity TC significantly reduces TNF-α [29].

TC has steadily grown in recent decades. It has been shown that this intervention approach to reduce aging symptoms and improve quality is valid. And several recent studies have begun to look for evidence of the influence of TC on biological processes of the body (including the inflammatory response including cellular, circulatory, and genomic marker responses of inflammation), that quantitatively assess the effect of TC on inflammatory markers such as IL-6, TNF-α, CRP, and stimulated cytokine production [27].

Irwin et al emphasizes that TC and other mind-body therapy may play a role in the regulation of the immune system. This is consistent with other findings that psychosomatic therapy and CBSM (cognitive behavioral stress management, help reduce inflammation, including in cancer patients [43].

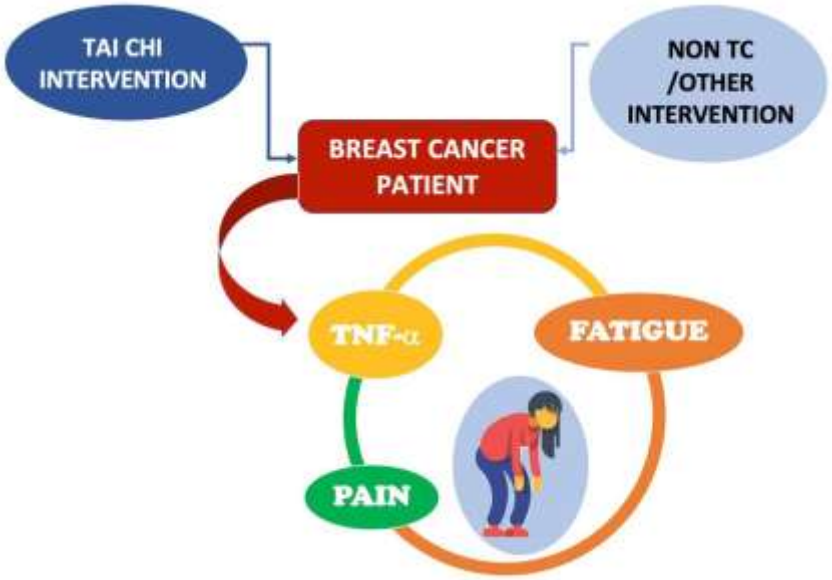

Figure 2. Hypothesis Of Tai Chi Roles In Reducing Fatigue, Pain, And TNF-α Plasma Level On Breast Cancer Patients

a. Tai Chi And Fatigue In Breast Cancer

Cancer-related fatigue (CRF) is defined as the most common side effect experienced by cancer patients in the form of persistent emotional, physical, and/or cognitive fatigue associated with cancer itself or cancer treatment that can interfere with function and quality of life. Guidelines on fatigue screening and

recommendations for intervention based on treatment stage can be studied further in the NCCN Guidelines for Clinical Practice in Oncology. Interventions include counseling and education, common strategies for fatigue management, specific pharmacological and non-pharmacological interventions. Thus, routine screening for identifying CRF is important to ameliorate the quality of life of cancer patients [6,44,45].

Fatigue is a complication that is often underreported, but is considered to be majorly responsible for the decline in quality of life. This CRF has been shown to be a consequence of active treatment, and can be felt until after treatment [44]. Many women with breast cancer report markedly increased fatigue in intensive care patients. Biering et al (2020), conducted a study to describe the process of fatigue in women with breast cancer [46]. The pathophysiological background of fatigue is unknown and its correlation with various biomarkers is weak and still not consistent [47].

The development of CRF is thought to be related to serotonin, adenosine triphosphate and HPA (hypothalamic-pituitary-adrenocortical) axis dysregulation, skeletal muscle shrinkage, desynchronization of circadian rhythms, and cytokines level (especially proinflammatory cytokines). Immune system activation by body injury, trauma, and infection causes proinflammatory cytokine release and other immune factors. These immune factors include soluble receptors, receptor antagonists, and cellular activation products, one of which is TNF-α. These inflammatory cytokines then control local and systemic immune responses. This regulation will mediate neurologic symptoms i.e. fatigue [47].

Therefore, the CRF deserves special review, firstly, because of the demographic relevance of the issue. Fatigue has been considered, not only the most common, but also the most damaging, symptom after treatment for breast cancer patients [45].

The relationship between TC and fatigue was discussed in several literature reviews. Research conducted by Cheng Duan et al (2021) showed that CRF in BC patients improved better than the control group with a TC exercise intervention of 60 minutes per session for 12 weeks [37]. According to Irwin et al (2017) TC exercises provide a significant change in fatigue in breast cancer patients [40]. The same thing is also shown in research conducted by Lisa Sprod and Linda Larkey [38,41]. Whereas in other literature does not show significant changes [25].

b. Tai Chi And Pain In Breast Cancer

Chronic pain is a common complaint in breast cancer patients and is connected with the release of inflammatory mediators from the tumor, tissue injury, and nerve involvement. This mechanism is the outcome of a network generated by pro-inflammatory cytokines, inflammatory pathway genes and cytokine gene polymorphisms. Breast cancer patients, especially in pre menopausal phase, usually has lower estrogen levels that linked to increased pain as well as impairment of descending pain inhibitory pathways, which may be a risk for developing chronic pain and symptoms such as discomfort and stiffness [48]. According to Sprod et al (2012) in their study that assessing pain as one of the pathological parameters, showed not much improvement-related to BC [41].

There is an explorative study that investigates the effect of TC on β-endorphin, describes that pain and stress may have increased basal β-endorphin and by doing TC could reduce the levels, implying that TC and other physical exercise may increase the capacity of endogenous opioid. But this study also found no significant influence of TC or modest physical activity on inflammatory markers, especially on older adults who suffer from chronic pain [26].

c. Tai Chi And TNF-α Plasma Level In Breast Cancer

The study conducted by Campo et al showed that the study group had no significant difference between post-intervention pro-inflammatory and anti-inflammatory cytokines [42]. No interventional effect on inflammatory cytokine levels was seen consistent with cytokine results reported in previous TC studies conducted in healthy elderly and breast cancer survivors [49]. The speculation about the finding of nulls is that due to the complex interaction of age-related factors (chronic mild inflammation), the presence of comorbidities, and the late impairment of cancer treatment, TC have older cancer survival. It has a limited effect on a person's inflammatory cytokines. This can lead to immunodeficiency dysregulation [50].

The same result also obtained from the Linda et al and William Tsang et al studies showing that no significant differences caused by TC intervention between pre-post intervention to TNF-α and other biomarkers [28,38]. The same thing is also shown in research conducted by Rebecca Campo [42]. However, a contrary post-treatment assessments by Irwin et al showed reduced TLR4-activated monocyte production of IL-6 and TNF-α in cancer survivors treated with TC Chih [39,43].

Cancer patients have proinflammatory tendencies which could activate the immune system, including releasing inflammatory cytokines (IL-1β, IL-6, IL-8, TNF-α and CRP) but the mechanism of physical exercise in decreasing inflammatory biomarkers is still not clearly understood [51]. Several studies showed inflammatory gene expression was decreased due to MBT (Tai Chi and Yoga) and that statement was supported by the trial results that identified changes in molecular signaling pathway even on trials that showed no significant differences [27]. In spite of that, further studies are required to deeply understand the benefit of TC in downregulation of inflammatory biomarkers.

CONCLUSION

Survivors as well as breast cancer patients, during and after treatment, often experience complaints of fatigue, pain, depression, sleep disturbances, and cognitive dysfunction. There is an increased interest among breast cancer patients and survivors to use mental and physical practices, including Tai Chi, Qigong, Yoga, and other practices. TC is still under-researched but seems promising to increase the ability of physical activity, which adds meditative benefits to cancer survivors and thereby improves survival outcomes.

In this systematic review, there are three studies showing that TC had no significant impact on TNF-α plasma levels in breast cancer patients. However, two other studies showed significant impact in reducing TNF-α plasma levels in BC patients. One study showed that TC had no significant impact on pain in breast cancer patients. Two studies showed that TC had a significant impact on fatigue in breast cancer patients, yet one study stated otherwise.

These contrary results might be caused by age-related multifactorial condition interactions that impaired inflammatory cytokines function. These conditions possibly lead to no improvement on fatigue and pain. Based on published research, it is still difficult to determine inflammatory biomarkers that are influenced by the frequency, duration and intensity of TC exercise. A clearer comprehension is required of the biological pathways through which TC design was capable of developing a powerful TC intervention to decrease the symptom of breast cancer survivors.

This conclusion should be interpreted with more caution because the included journal is limited. Additional randomized controlled trials with more rigorous and precise methodologies accompanied by a lower risk of bias in each study, are needed to provide more accurate evidence. Furthermore, more research is needed in all areas of cancer survival and TC.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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