

## CANCER RELATED FATIGUE. POSSIBILITIES OF NUTRITIONAL SUPPLEMENTATION, FROM THE PERSPECTIVE OF TRADITIONAL CHINESE MEDICINE

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**Abstract:** One of the most frequent and persistent symptoms in the oncological process is cancer-related fatigue (CRF). The underlying etiology is still not well understood. The evidence suggests the participation of complex multifactorial processes linked to a variety of molecular/physiological, clinical and psychological factors, which makes its approach very limited and complicated. Validated measurement tools determine that CRF affects the Bio-Psycho-Social spheres of the person. New research approaches, including network pharmacology, open possibilities to the field of Traditional Chinese Medicine (TCM) through acupuncture and phytotherapy, by determining target molecules involved in the development of CRF, both in the signaling pathways of the inflammatory response as well as in the modulation of the gene expression of tumor and angiogenic genes. In Spain, food supplement legislation allows the accessibility of certain formulations to address CRF. Integrative work with qualified TCM personnel is necessary to identify appropriate and individualized supplementation for each person.

**Keywords:** Cancer Related Fatigue, Chinese traditional medicine, Phytotherapy, Cancer Nutrition supplement, Integrative oncology

## INTRODUCTION

Cancer or cancer treatment can cause fatigue, commonly referred to by the medical term CRF, and/or “asthenia.” It manifests itself with a feeling of physical, emotional and mental exhaustion, despite getting enough sleep and rest. It can affect your daily life, lasting months or years after completing treatment, and affects moods and emotions, daily activities, hobbies and other activities, relationships with friends and family, ability to cope. treatment. job performance, hope for the future.<sup>1, 2</sup> As it is a subjective phenomenon, commonly used uni- or multidimensional assessment scales

or questionnaires are required, including the Brief Fatigue Inventory, the European Organization for Research and Treatment of Cancer (EORTC), the Core-30 Quality of Life Questionnaire, the fatigue subscale, the Functional Assessment of Cancer Therapy - Fatigue, the Piper Fatigue Scale. The EORTC has recently developed a questionnaire module that specifically assesses multiple dimensions of FRC (physical, cognitive, emotional).<sup>3,4,5</sup>

## STATISTICS

Among people on active treatment, CRF rates range from 62-85%, of which 9-45% reported moderate to severe CRF. People on maintenance therapy, such as adjuvant endocrine therapy or androgen deprivation therapy (ADT), are more likely to experience CRF. 56% of breast cancer survivors receiving aromatase inhibitors report moderate to severe CRF. Prostate cancer patients currently using ADT or who had used ADT in the past were more likely to report CRF than survivors who never used ADT (38% current vs. 23% past vs. 16% never,  $p < 0.0001$ )<sup>6,7</sup>

## ETIOLOGY

The underlying etiology of CRF is still poorly understood. Evidence suggests the involvement of complex multifactorial processes linked to a variety of molecular/physiological, clinical and psychological factors.<sup>6</sup> Although a recent review found a significant positive correlation between fatigue and circulating levels of inflammatory markers; in particular, the levels of interleukin IL-6, IL-1 and neopterin,<sup>8</sup> Its cause remains unclear. Many patients even present it before starting treatments due to medical tests, surgery, and the emotional stress of facing the diagnosis. Fatigue may worsen during treatment, but it has several different causes:<sup>2,9</sup> Other meta-analyses and reviews include other causes such as deregulation

of the hypothalamic-pituitary-adrenal axis, desynchronization of the circadian rhythm, skeletal muscle wasting, and genetic risk factors (for example: single nucleotide polymorphisms).<sup>10</sup>

- Health changes related to cancer. Fatigue may be a symptom of the cancer itself or that the cancer is growing or spreading.
- Cancer treatments. It is not known why cancer treatments such as surgery, hormone therapy, chemotherapy (short-term of several days), radiation therapy (medium-term of several weeks), and immunotherapy (long-term of months) cause fatigue.
- Pain. Constant pain is exhausting and stressful, and many pain relievers cause drowsiness and fatigue.
- Depression, anxiety and stress. Managing stress and treating depression and anxiety often reduce fatigue.
- Sleep problems (Insomnia). Stress, pain, and worries can affect induction and/or maintenance sleep. Additionally, some medications disrupt normal sleep patterns.
- Poor diet. A poor diet, incorrect or harmful to your process, can worsen FRC. Also if the patient has problems related to taste, loss of appetite, or nausea and vomiting
- Anemia. Treatment for anemia may include supplements, drugs, or blood transfusions.
- Other medical/health conditions such as heart problems, reduced lung and kidney function, hormonal problems, arthritis, nerve problems

## TREATMENT

CRF treatments, according to clinical guidelines, involve changes in lifestyle and establishment of certain strategies.:<sup>2,9</sup>

- Physical activity prescribed individually and adapted to the oncological process
- Physiotherapy
- Cognitive-behavioral therapy, hypnosis
- Mind-body strategies. Mindfulness, yoga and acupuncture can reduce fatigue in cancer survivors. Other mind-body strategies that might be helpful, but have not been fully studied by researchers, include the following: Touch therapy, including reiki, music therapy, massage, relaxation, qigong <sup>10,2,11</sup>
- Nutrition by a specialized nutritionist
- Medications and supplements. Some medications such as corticosteroids (Prednisone 20-40 mg/ day), Psychostimulants (Methylphenidate, Modafinil, Armodafinil, Dextroamphetamine)<sup>1</sup> they help people feel more attentive and awake. They are most helpful for people who are currently receiving cancer treatment and people who have advanced cancer. Some treatments can affect hormone production by the thyroid gland or adrenal glands. If these levels are low, you may benefit from medications to restore these hormones. It is necessary to check if there are nutritional deficiencies such as iron, vitamin B12 or vitamin D, and supplement them. Other supplements, such as ginseng,<sup>12</sup> coenzyme Q10, levo-carnitine (L-carnitine), appear to improve CRF. However, it is important to check with your medical team before taking any nutritional or herbal supplements to ensure they do not interact with your cancer treatment. However, this same issue must be extended to food since certain active ingredients present in very com-

mon foods such as spices, fats, meats, fish, vegetables, fibers, dairy products, infusions, wines, alkaline foods, can intercede with the cytochrome P complex. -450 and some of its isoforms and affect medications,<sup>13</sup> resulting in a very complicated task and without quality studies to advise or discourage eating, in fact in the usual practice of oncology it is common to give the patient free rein to eat what they want.

- Other integrative therapies such as TCM, in its different modalities of acupuncture, moxibustion, report in prestigious journals with positive results in effectiveness and safety.<sup>14,8</sup> There is a growing body of evidence for integrative therapies for CRF and a widespread call for clinical trials.<sup>15</sup> A recent meta-analysis of 10 studies conducted primarily among breast and gynecologic cancer survivors, Zhang et al. concluded that acupuncture could be an effective option in the arsenal of FRC interventions.<sup>16</sup> In clinical guidelines on integrative therapies in breast cancer, acupuncture for the treatment of CRF can be considered as an option to improve CRF post-treatment. Many integrative practices are in use, however, they remain unstudied, with insufficient evidence to be definitively recommended or avoided, although there are authors who try to identify their use during or after treatment.<sup>17,15</sup>

Furthermore, we must not ignore the reality revealed by a recent meta-analysis which shows that 74% to 87% of cancer patients use self-management and self-care programs based on the Internet, which are much more beneficial than general medical care. in the management of physical symptoms of cancer patients.<sup>7</sup>

## TCM PERSPECTIVE FOR CRF

In general, in the practice of Western Medicine, the approach to the pathologies that accompany the oncological process is usually symptomatic. But it is necessary to understand the nature that underlies the imbalance in the body behind the symptomatological manifestation. TCM has been in common practice for millennia and they call it syndromes or syndromic patterns (Zheng). The syndrome is an integral and essential part of TCM theory that helps guide the design of individualized treatments.

A TCM syndrome, in essence, is a characteristic profile of all the clinical manifestations in a patient that a TCM doctor can easily identify.<sup>18</sup>

The evolution of the need to integrate the possibilities offered by both ways of doing medicine has led to studying for years, including the cellular, genomic and molecular bases to translate or interpret them into syndromic patterns, in many cases specifically tumor diseases such as lung, liver, gastric, mammary, colorectal and pancreatic, identifying common syndromes such as Qi stagnation (Qi Yu), blood stagnation (Xue Yu), humidity-heat (Shi Re), Yin deficiency (Yin Xu) and deficiency of spleen (*Pi Xu*).<sup>19</sup>

Systematic reviews regarding the “translation” of the term CRF in patients with breast cancer, to syndromic patterns of TCM, allow us to open new therapeutic windows of CRF, concluding that CRF and poorer quality of life are related to the concept of Qi deficiency deficiency (氣虛 Qi Xü) by 69.6%, Yin deficiency (陰虛 Yin) 39.1% and blood deficiency (血虛 Xue Xu) 34.8%. Therefore, this identification allows us to propose that the improvement in quality of life and CRF be with methods to tone the Qi (氣) and Yin (陰) apart from the Yang (陽) and blood (血)<sup>20</sup>

Even the latest molecular, immunological and inflammatory etiopathogenic conclusions

in CRF, with elevation of proinflammatory cytokines interleukin IL-6, IL-1 and neopterin,<sup>8</sup> are represented in Heat-Humidity (Shi Re) syndromic patterns in pancreatic cancer, proposing that tumors with the Shi-Re Zheng pattern exhibited altered proliferative activities of cancer-associated myofibroblasts (CAFs) and infiltration of tumor-associated macrophages (TAM), which led to altered levels of secreted cytokines derived from CAF and TAM (such as SDF -1, VEGF, TGF-1 $\beta$ , IL-6, CCL3, CCL4, CCL5, TNF- $\alpha$ , IL-8 and bFGF). The presence of Shi-Re syndrome has an impact on tumor growth. Chinese Herbs for Qing-Re-Hua-Shi (Heat and Moisture Removal) Inhibited In Vivo Proliferation, Invasion, and Metastasis of Cancer Cells by Modifying the Tumor Microenvironment.<sup>19</sup>

The American Society of Clinical Oncology (ASCO) defines the term CRF or asthenia as the “feeling of physical, emotional, and mental exhaustion, despite sufficient sleep and rest.”<sup>2</sup> In this sense, TCM does frame it within certain terms and each of them can be developed by different syndromic patterns.,<sup>21</sup> Therefore, the therapy of each term will be individualized to the syndromic pattern expressed by the patient.:

- Asthenia (*Pí Fà*): Also called fatigue (*Pí Juàn*), or fatigue and weakness (*Pi Juàn Fá Li*) and refers to weakness of the extremities accompanied by mental fatigue. This can develop from 13 different types of syndromes that trigger one of Qi insufficiency. (氣虛 Qi Xü)
- Consumption-exhaustion (*Xü Lao*) and Chronic Fatigue Syndrome (*Màn xìng pí láo zòng hé zhěng*): Extreme fatigue defined as a set of neurological, neuromuscular, and immunological abnormalities, combined with cognitive alterations, disabling fatigue, frequent colds, myalgias, erratic arthralgias, sleep disturbances, headaches, cognitive



alterations, emotional lability, digestive alterations. It can be caused by 12 types of syndromes that are all included, in states of insufficiency of both Qi, Yin, Blood and Yang, exactly coinciding with the results of current studies such as that of Chien & al in 2012.<sup>20</sup>

- Body heaviness (Shěn Zhòng): Accompanied by difficulty moving the extremities. It can be generated from 5 syndromes, but mainly due to sinking of Spleen Qi and emptiness or insufficiency of Kidney Yang.
- Mental Weakness (Chǐ Dǎi): Defined as a state of mental confusion, brain fog, bradypsychia, mild amnesia, decreased stimulation, etc., and can develop from various syndromes such as Heat-Dampness (Shi Re), Qi insufficiencies, of Yin, etc.

In all of them, even for Western medicine, there is a lack of energy (Qi insufficiency or deficiency for TCM). From this perspective, TCM through Chinese herbal medicine can provide interesting therapeutic opportunities for each of the syndromes that are present in the oncological process, understanding that the therapeutic principles will change according to the evolutionary stage of the syndrome, adjusting to the patient in an individualized, personalized and without protocols. Thus, in general, and according to Spanish legislation, with commercial limitations, the phytotherapy formulation options, such as dietary supplements, closest to the FRC would be, for example:<sup>22, 23, 24</sup>

- Tonify Qi
- Si Jun Zi Wan (SJZ) (Due to Spleen/Stomach Qi deficiency)
- Yu Ping Peng Wan (YPP) (for Lung Qi deficiency)
- Yi Qi Cong Ming Wan (YQCM)
- Bu Zhong Yi Qi Wan (BZYQ)
- Nourish Blood: Si Wu Wan (SW) (for

Liver Blood deficiency)

- Tonify Qi-Xue: Gui Pi Wan (GP) (For Heart Qi deficiency) or Ba Zhen Wan (BZ = SJZ + SW)
- Nourish Yin: Liu Wei Di Huang Wan (LWDH) (for Liver and Kidney Yin deficiency)
- Tonify Qi – Nourish Yin: Huang Qi Sheng Mai Wan (HQSM)
- Strengthen Yang: Er Xian Wan (EX)
- Eliminate Heat-Dampness (inflammation): Er Chen Wan (EC)

As we can see, the therapeutic possibilities of CRF with Chinese herbal medicine are as broad as the root that causes CRF is different. Providing solutions apart from the current corticosteroids, and psychostimulants and some supplements indicated by oncological institutions such as ASCO.<sup>1, 2, 9</sup>

Taking into consideration, the identification of syndromic patterns present in CRF identified by Chien 2012, the improvement of quality of life and CRF must be treated with formulas and procedures with a therapeutic principle to tonify the Qi. (氣) and nourish Yin (陰), Yang(陽) y Sangre (血).<sup>20</sup>

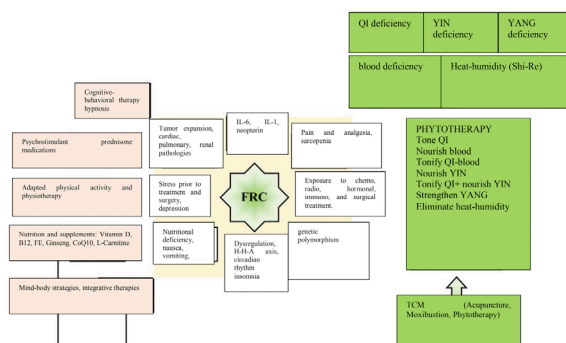


Figure 1. Diagram of the etiopathogenesis of CRF and proposal for an integrative approach with nutritional supplementation from the perspective of TCM.

Of the majority of formulas described above, there are 2 plant drugs whose nature is Tonify the Qi. (*Radix Astragali-Huang Qi (HQ)* y *Rhizoma Atractylodis Macrocephalae-*

*Bai Zhu (BZ)*). Using mouse animal models, twenty-four randomized controlled trials (RCTs) with 1865 patients showed that TCM produced more positive effects on CRF than standard therapy alone. HQ and BZ can be considered as the main plant drugs for the treatment of FRC, since they improve the physical condition of mice, reduce abdominal circumference, reduce the levels of inflammatory factors and reduce tumor weight and regulate body weight and sugar in the blood. Network pharmacology analysis showed that the mechanism of action of HQ and BZ in CRF mainly involves compounds, such as quercetin, kaempferol and luteolin, which act through multiple targets, such as protein kinase B  $\alpha$  (AKT1), TNF and IL -6. These molecules regulate cytokines, cancer signaling and metabolic pathways and confer an anti-fatigue effect.<sup>25</sup>

### **EFFICACY AND SAFETY OF PHYTOTHERAPY FORMULATIONS IN CRF**

Phytotherapy formulas have also been the subject of recent meta-analyses and reviews on fatigue, with 25 studies including 1,777 subjects with cancer-related symptoms and reporting that Chinese herbal medicines had significantly greater efficacy in treating ulcers and related wounds. with cancer, fatigue (OR, 2.81; 95% CI, 1.78-4.41,  $P < 0.001$ ), and efficacy in treating constipation (OR, 2.59; 95% CI, 1.57-4.25,  $P < 0.001$ ) compared to control in subjects with cancer-related symptoms.<sup>26</sup> Another meta-analysis and review on 14 RCTs and 878 patients showed the comparison of the combination of chemotherapy (epirubicin plus taxol) and Fu-zheng decoction with chemotherapy alone in patients with breast cancer. After 9 weeks of treatment, the combination treatment group showed a significantly lower fatigue symptom inventory score than the chemotherapy

alone group (MD: -18.62, 95% CI: -24.08 to -13.16)<sup>27</sup>. Another recent meta-analysis on CRF that included a total of 23 trials with 1832 participants showed that 20 trials reported a beneficial effect of TCM on CRF. By combining the data from treatment with Chinese herbal medicines and treatment with acupuncture or moxibustion, respectively, significant differences were found between the experimental groups and the control groups. Fatigue improvement rates showed significant differences between TCM and control groups (OR, 7.62; 95% confidence interval (CI), 3.75-15.49;  $P < 0.000 01$ ); and (OR, 3.78; 95% CI, 2.29-6.23;  $P < 0.000 01$ ). Fatigue change scores also showed significant differences between the two groups (mean difference, -0.91; 95% CI, -0.16 to -0.65;  $P < 0.000 01$ ). Eleven trials demonstrated that TCM improved the quality of life of cancer patients. No serious adverse effects occurred in the traditional Chinese medical therapy groups and it is considered significantly safe.<sup>28</sup>

In gastric cancer, as in lung cancer, the CRF is usually very intense. A meta-analysis of a total of 13 studies that included 986 patients was studied with the FRC score with dichotomous variables, the study being quite homogeneous ( $I^2=0\%$ ), resulting in a significant clinical efficacy of 100% of the phytotherapy group compared to the control (OR = 4.22; 95%CI 1.67 to 10.68; In the Piper Fatigue affective subscale with a heterogeneity index ( $I^2=34\%$ ), the phytotherapy group showed a significantly better score of 100% compared to the control group (MD = -0.79; 95%CI -0.92 to -0.65;  $p < 0.00001$ ). The same occurs as Quality of Life Questionnaire Core 30 (QLQ-C30) (MD = 10.53, 95% CI: 8.26 to 12.80;  $p < 0.00001$ ) and the Karnofsky Performance Status (KPS) scale (MD = 5.18, 95% CI 2.60 to 7.76;  $p < 0.0001$ ). In addition, the phytotherapy group combined with Western medicine achieved greater effectiveness in controlling CRF and

had milder adverse effects than the Western medicine group alone, showing itself to be safe for CRF in patients with gastric cancer.<sup>29</sup> In 12 RCTs and 861 patients with lung cancer, the results showed with a CI=95% that herbal medicine combined with Western medicine, compared to Western medicine alone, significantly improved the level of fatigue, quality of life and activities. of daily living (ADL). As monotherapy, herbal medicine significantly improved ADLs compared to Megestrol. No serious adverse events related to phytotherapy were reported.<sup>30</sup>

Regarding the formula (SJZ) that tonifies the Qi, an RCT on 94 breast cancer patients diagnosed with syndromic patterns of Spleen/Stomach Qi insufficiency to assess its effectiveness in CRF. The experimental group of 47 women received a 21-day cycle of chemotherapy and SJZ. It was observed an improvement in CRF measured on the modified Piper scale, improvement in emotional and cognitive fatigue ( $p < 0.001$ ) and a response rate of 89.4%. Additionally, the active ingredients of the formula plants and their molecular and genetic objectives were studied to find out the therapeutic targets in CRF. Identifying 250 targets for SJZ, 2653 CRF-related genes, 15,329 breast cancer-related genes and 161 targets. The molecular docking study showed a high affinity for the oncogenes AKT1, CASP3 and the cytokine IL6, transcription factor JUN and vascular endothelial growth factor VEGFA. SJZ improves CRF symptoms possibly by regulating multiple signaling pathways, including PI3K-Akt through AKT1.<sup>31</sup> Another meta-analysis on SJZ combined with enteral nutrition in 688 patients with gastric cancer showed efficacy in significant terms in reducing flatulence, hospital stay time, fewer postsurgical complications, improvement in albumin, prealbumin, transferrin, IgG, IgA, IgM, and lymphocyte levels. CD3+, CD4+,

CD4+/CD8+, apart from showing safety in use and not having serious adverse effects<sup>32</sup>

About the formula (BZYQ), to tonify central Qi and coming from the “treatise of Spleen and Stomach” of Li Gao en 1249 “*Pi Wei Lun* -脾胃論”, (24), (23), (22) whether it has been studied specifically for CRF. Its formulation in strategic proportions contains Astragalus Root (Huang Qi), Atractylodes macrocephala Rhizome (Bai Zhu), Angelica sinensis Root (Dang Gui), Codonopsis pilosula Root (Dang Shen), Bupleurum chinense Root (Chai Hu), Tangerine Pericarp (Chen Pi) and Licorice Root and Rhizome (Gan Cao). Currently, it has been possible to study the effective components of BZYQ against CRF and its objective molecular coupling with the key target genes in CRF. Molecular docking with stable hydrogen bonds showed that, especially quercetin in combination with IL-6 and quercetin in combination with STAT3. Quercetin bound to IL-6 through three hydrogen bonds at sites GLY-1020, ARG-1007, GLU-883. Quercetin bound to STAT3 through five hydrogen bonds at the LEU-959, ARG-1007, ASN-1008 sites. Furthermore, molecular coupling of Saikosaponin to A – mTOR was shown.<sup>33</sup>

## DISCUSSIONS AND CONCLUSIONS

This current situation of limitation of effective therapeutic options against CRF, together with the debilitating nature of the oncological disease and the real demand on the part of the research community to carry out quality trials on integrative therapies based on current evidence, generate the necessary scenario. to delve deeper into the possibilities TCM has to treat CRF cases. To do this, it is necessary to know the theoretical and conceptual framework of TCM and arrive at it.



There are increasing reports of evidence on the possibilities that TCM offers for CRF. The new analytical methods of network pharmacology for the active substances and ingredients of plant drugs allow us to establish the molecular, cellular and genetic targets or objectives involved in pathologies.

There is a vast and vast unknown resource field of TCM possibilities, largely untapped by modern medicine and opening up future avenues of research.<sup>34</sup> To do this, it is necessary to know the theoretical and conceptual framework of TCM and to establish bridges of connection and be able to bidirectionally translate an understanding between both medicines, to adjust them to the scientific language of modern biology and physiology. TCM offers complementary treatments based on personalized interventions, informed by knowledge accumulated from empirical observations gathered over centuries of practice, that address the impact of disease on the entire body. In this context, understanding the mechanisms of action of traditional Chinese medicinal preparations will offer new routes for the discovery and development of new therapies, as well as patented medical recipes, which will largely depend on modern scientific methodologies for their adoption and success.<sup>35</sup>

For the same reasons, at the research level, the selection of patients for clinical trials must be seen and agreed upon in an interdisciplinary manner, due to the very nature of personalized therapeutic principles in phytotherapy, since the syndromic patterns where the pathology manifests must be

identified. of the FRC. It would be a bit wise to establish identical phytotherapy protocols for all patients equally.

More research is required on the capabilities it offers for Western Medicine, Chinese phytotherapy and registered formulations, in addition to promoting clinical trials. The clinical argument that, given the lack of knowledge of the interactions of food supplements (Chinese Phytotherapy) with drugs, is a common, correct and conservative practice. This same position must be extended to food, since there is also a lack of knowledge about it in clinical practice, so recommending eating whatever or whatever the patient undergoing treatment wants is in itself an indication that is not free of risk. In fact, it is known that certain fasting practices or modalities increase the effectiveness of oncological treatments and reduce their toxicity, and could be motivated by the release of the workload of cytochrome P-450 enzyme complexes. Therefore, it is being studied in systematic reviews.<sup>36</sup>

Formulas to tonify Qi (BZYQ, SJZ), those that nourish Yin (LWDHG), those that nourish Qi and Blood (BZ or GP), those that nourish Blood (SW), and those that eliminate heat-humidity or inflammation (EC) may be one of the priorities to improve CRF, and are available in the Spanish market as nutritional supplements

The safety reported in the meta-analyses and reviews of these formulations must give us a vote of confidence to carry out new clinical trials.

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