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# Spleen Function and Anxiety in Chinese Medicine: A Western Medicine Perspective

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#### **Abstract**

This article aims to illustrate the function of the Spleen in Traditional Chinese Medicine (TCM) in the context of modern medicine. TCM has been practiced since ancient times in China for the prevention and/or treatment of diseases. Yet, the complete understanding of its theoretical basis in relation to clinical practice from the modern medicine perspective is still lacking. According to TCM theory, the Spleen, as one of the five Zang (i.e., visceral organs), plays an important role in various physiological functions, including digestion and absorption of nutrients, regulation of water retention and excretion, facilitation of blood perfusion to skeletal muscle and on the optimal functioning of the immune system. Clinical applications of herbal formulations for the treatment of Spleen dysfunction (i.e., Spleen deficiency—a decline in Spleen function) and their pharmacological activities are described. The view point of TCM on how emotions (or Qing Zhi) can influence the body function is introduced. The relationship between anxiety and Spleen function has been analyzed by reviewing relevant research studies in modern medicine. These findings suggest that the cause/consequence relationship between anxiety and Spleen function may be bi-directional.

#### **Keywords**

TCM Theory, Spleen Function, Anxiety

#### 1. Introduction

TCM is a medical practice originating from ancient China through thousand years of experiential use. It still plays an important role in medical care in China and Southeast Asian countries despite the advent of Western medicine. However, the practice of TCM has become increasingly popular in western countries because of its sophisticated and successful treatments for many health conditions and even diseases that are regarded as

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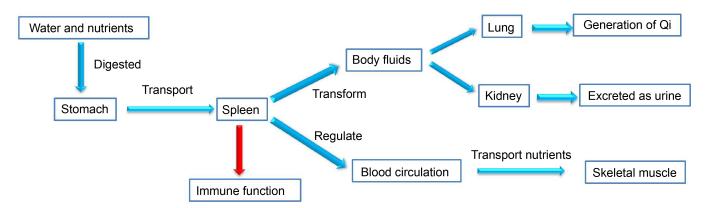
untreatable or incurable by conventional Western medicine. As TCM and Western medicine represent two distinct medical approaches with different origins, both diagnostic strategies and interpretations of symptoms of diseases in TCM are quite different from those of Western medicine. As the mystery goes, TCM provides an "unscientific" but yet "successful" approach to medical practice. It has therefore attracted the efforts of many researchers in deciphering the "science" behind TCM. This will be instrumental in the acceptance and promotion of the practice of TCM in the global arena for the betterment of mankind.

According to TCM theory, the human body consists of five Zang and six Fu (i.e., all visceral organs), which are characterized by the five elements, namely Metal, Wood, Water, Fire and Earth, in the realm of the "Five Element" theory. The five Zang (i.e. visceral organs) are functionally interlinked with each other by generating and restricting mode of action, resulting in an optimally functioning body by maintaining a holistic Yin-Yang balance. Disease will develop when this balance is distorted, as in the cases of over-restricting and counter-restricting (i.e., insulting). Furthermore, the Zang-Fu (i.e. all visceral organs) interplay responds to environmental conditions, and these conditions—referred to as "external evils", can distort the Yin-Yang balance and result in disease.

In this article, we focus on understanding the concept of *dampness*, one of the "external evils" commonly occurring in individuals living in areas with high humidity. According to TCM theory, exposure to humid weather conditions can induce *dampness* in the body. *Water* associated with *dampness* can upset the function of the *Spleen*, one of the *Zang* (*i.e.* visceral organs) with *Earth* characters, as *Water* acts by insulting the *Earth* [1]. Thus, prior to investigating what pathophysiological conditions are influenced by *dampness*, an understanding of the function of the *Spleen* in TCM is essential. The functions of the *Spleen* in relation to TCM theory will first be reviewed. Symptoms of *Spleen* dysfunction (*i.e.*, *Spleen* deficiency—a decline in *Spleen* function) and their treatments by TCM herbal formulations will then be described, with pharmacological activities of the formulations being illustrated in terms of Western medicine. Finally, an interesting concept in TCM concerning how anxiety might impair *Spleen* function will be discussed.

### 2. Functions of Spleen

TCM theory purports that there are three aspects of *Spleen* function (**Figure 1**). Firstly, the *Spleen* regulates the transport and metabolism of water and nutrients in the body. *Stomach*, the associated *Fu* (*i.e.* organs) of the *Spleen*, works to digest ingested food into various components, which are transported to the *Spleen* for distribution throughout different parts of the body. Water absorbed will be transported upward to the *Lung* for the generation of *Qi* (energy/nutrients), and excessive water and metabolic wastes produced by different regions of the body are transported downward to the *Kidney* for excretion [1]. The accumulation of "humor", as in the case of edema or phlegm formation,



**Figure 1.** The functions of *Spleen* in TCM. The *Spleen* works with the *Stomach* to regulate the transport and metabolism of water and nutrients. Water absorbed is transported upward to the *Lungs* for the generation of *Qi*, and excessive water plus metabolic wastes produced by different regions of the body are transported downward to the *Kidney* for excretion. In addition, the *Spleen* regulates the circulation of blood. The transport of nutrients in blood to skeletal muscle is controlled by the *Spleen*. Therefore, *Spleen* appears to be an important determinant for maintaining a proper functioning of skeletal muscle. The *Spleen* is also related to immune function.

is regarded as a pathological outcome of *Spleen* dysfunction. *Spleen* dysfunction can also lead to a malfunctioning of food digestion and absorption, or even a pathophysiological condition known as "metabolic syndrome" [2]. A study has shown that Glutinous Rice, which is regarded as a functional food for strengthening *Spleen* function, improves digestive function in rats with *Spleen* dysfunction. The beneficial effect of Glutinous Rice on digestive function is associated with increases in levels of salivary amylase and plasma gastrin and motilin, as well as a decrease in plasma level of somatostatin [3]. Experimental findings suggest that the *Spleen* is functionally related to digestive processes in Western medicine. Also, a rat model of *Spleen* dysfunction associated with *dampness-heat* was found to have the over-expression of aquaporin, a water channel commonly found in the lungs, digestive system and kidney, suggesting that the function of the *Spleen* may be related to the functioning of these systems in regulating water content in the body [4].

Secondly, the *Spleen* regulates the circulation of blood. *Spleen* functions to enable the flow of blood within blood vessels in the right direction and then deliver nutrients (*Qt*) throughout the body. Thus, sub-cutaneous bruising and hemorrhage, such as conditions associated with hematuria and excessive menstrual bleeding, are caused by *Spleen* malfunctioning [1]. From the Western medicine point of view, the prevention of internal bruising is regarded as a function of the blood/circulatory system, through the regulation of blood clotting and capillary permeability, with the latter preventing the leakage of red blood cells into the extracellular space. Research has shown that patients with *Spleen* dysfunction generally show an abnormal morphology of blood platelets, leading to a decrease in their ability to aggregate and release clotting factors. Thrombocytes in *Spleen* dysfunction patients have been found to exhibit a shorter lifespan, resulting in a higher likelihood of hemorrhage. *Spleen* dysfunction patients were also found to have an increased capillary fragility, such that that they are more prone to capillary rupture, leading to internal bruising.

In connection with the functions of nutrient metabolism and transport as well blood circulation, the *Spleen* appears to be an important determinant for the maintenance of proper functioning of skeletal muscle. This is because the transport of nutrients in blood to skeletal muscle is controlled by the *Spleen*. This is corroborated by the experimental observations that both the configuration and function of extensor muscle were significantly deteriorated in mice with *Spleen* dysfunction [5], and that *Spleen* dysfunction patients have higher blood lactate levels, as a result of anaerobic glycolysis in skeletal muscles [6]. These observations may well explain why tiredness and muscle pain are commonly observed in patients with *Spleen* dysfunction.

Thirdly, the *Spleen* is related to immune function. TCM theory states that one will not be influenced by "external evils" if the *Spleen* is functioning optimally. The *Spleen*, being endowed with the *Earth* nature, is thought to be the center of other elements. If the *Spleen* functions well, other Zang (*i.e.* visceral organs) will also be better off [1]. Results from a number of studies have established the functional relationship between the *Spleen* and the immune system. Patients with Type 2 Diabetes Mellitus with *Spleen* dysfunction showed an obvious immune dysfunction (*i.e.*, either hypo- or hyper-activity of immune cells [7]. Patients suffering from ulcerative colitis with *Spleen/Kidney Yang* deficiency showed a reduction of serum Treg and TGF $\beta$ 1 levels, indicative of an impairment in immune tolerance [8]. *Cang Zhu* (Atractylodis Chinensis Rhizoma), a *Spleen*-invigorating herb, has been found to improve the immune function of rats with *Spleen* dysfunction as well as protect and repair damaged mucosal tissues [9].

# 3. TCM Approach to the Treatment of Spleen Deficiency

The effectiveness of various TCM herbal formulations for the treatment of various patterns of *Spleen* dysfunction has been well established [10], but the underlying pharmacological mechanisms are relatively unclear. *Gui Pi Tang* (Restore the *Spleen* Decoction) and *Huang Tu Tang* (Yellow Earth Decoction), which are two commonly prescribed preparations for the treatment of *Spleen* dysfunction, have been investigated for their pharmacological properties [11].

Herbal components in the two formulations act mainly on the digestive system. The main constituent herb in *Gui Pi Tang* (Restore the *Spleen* Decoction) namely *Huang Qi* (Astragali Sinesis Radix), has been found to reduce the secretion of gastric juice and suppress the activity of pepsin by reducing the secretion of gastrin, thereby preventing the development of ulcers [12]. *Bai Zhu* (Atractylodes Macrocephala Rhizoma) protects gastric mucosa against gastric acid-induced injury, and it also suppresses abnormal peristaltic motion in the small intestine [13] [14]. *Gan Cao* (Glycyrrhiza Uralensis Radix) suppresses the secretion of gastric juice and reduces the acidity of gastric juice by neutralizing the hydrochloric acid [15]-[17]. The main herbal constituent of *Huang Tu Tang* (Yellow Earth Decoction), namely, *Zao Xin Tu / Fu Long Gan* (Ignited Yellow Earth; Terra Flava Usta), is rich in aluminum oxide, which protects the gastric mucosa by neutralizing acidic gastric juice [18]-[20]. *Zhi Fu Zi* (Aconiti Lateralis Preparata Radix) in *Huang Tu Tang* (Yellow Earth Decoction) was found to suppress gastric emp-

tying, and protect against gastric ulceration [21]-[23]. *Bai Zhu* and *Gan Cao* in the preparation also produced significant protection to the digestive system [13]-[17].

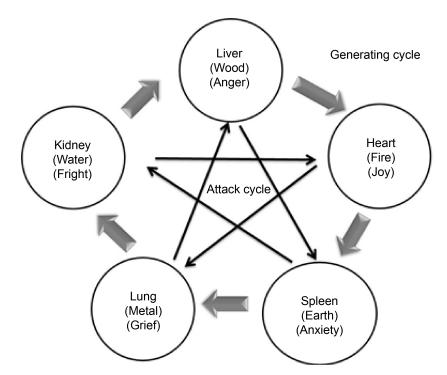
Gui Pi Tang (Restore the Spleen Decoction) and Huang Tu Tang (Yellow Earth Decoction) contain medicinal herbs that can suppress hemorrhage and facilitate blood flow. Huang Qi in Gui Pi Tang was found to prevent thrombus formation in blood vessels by inhibiting the action of phosphodiesterase. Huang Qi also improves the microcirculation and reduces the viscosity of blood [24]. Huang Qi and the "assistant" herb, Ginseng (Panax Ginseng Radix), can dilate blood vessels and promote a smooth flow of blood. Ginsenoside Rg1 and Rg3 in Ginseng were found to decrease blood viscosity and prevent the aggregation of thrombocytes [25] [26]. Zao Xin Tu (Terra Flava Usta) in Huang Tu Tang (Yellow Earth Decoction) is calcium-rich, and its "assistant" herb, Donkey-hide Gelatin (Er Jiao; Corii Asini Colla), is rich in glycine that can promote the uptake of calcium, an essential factor in blood clotting (i.e., preventing internal bleeding). Donkey-hide Gelatin also reduces blood clotting time, and increases the number of plasma thrombocytes [27]. Zhi Fu Zi in Huang Tu Tang also promotes the agglutination of thrombocytes [21]-[23]. It was observed that opposing pharmacological actions are produced by Gui Pi Tang (Restore the Spleen Decoction) and Huang Tu Tang (Yellow Earth Decoction), with the former reducing blood clot formation and thus smoothening blood flow, and the latter facilitating blood clot formation and preventing internal bleeding. Yet, both formulations are effective in treating Spleen dysfunction [11] [21].

With respect to the enhancement of immune function, Huang Qi in Gui Pi Tang (Restore the Spleen Decoction) contains Astragalus polysaccharides that can boost immunity by inhibiting the action of suppressive T-cells and thereby increase the activities of other types of T-cells, as well as stimulating the growth of plasma cells for the production of antibodies. Various herbal components in the formulation regulate the production of immunoglobulins and increase the activity of natural killer cells. Huang Qi has been found to induce the  $\gamma$ -interferons and thereby boost the activity of natural killer cells [28]. Ginsenosides from Ginseng increases the concentration of IgG, IgA, IgM and IL-2 in plasma, and stimulates the activity of natural killer cells and other types of white blood cells [25] [26] [29]. Guang Pi Tang (Restore the Spleen Decoction) was found to be effective in suppressing the production of autoantibodies in patients with chronic immune thrombocytopenic purpura, an autoimmune disease characterized by a reduction in the number of thrombocytes [30]. Donkey-hide Gelatin in Huang Tu Tang (Yellow Earth Decoction) was found to increase the phagocytotic activity of monocytes and the activity of natural killer cells. Bai Zhu stimulates the production of antibodies and the activity of phagocytes by increasing the production of IL-1 and IL-2 from lymphocytes. Baicalin in *Huang Qin* (Scutellariae Baicalensis Radix) increases the amount of cAMP in monocytes, thereby promoting the differentiation of lymphocytes. Gan Cao can induce the production of interferons that can activate natural killer cells. Gan Cao suppresses the immune response by decreasing the concentration of antigens, and glycyrrhinic acid in Gan Cao was found to enhance the production of IL-1 and immunoglobulins [31] [32]. Taken together, herbal formulations for treating *Spleen* dysfunction also possess immunomodulatory activity.

# 4. Anxiety and Spleen Function

The practice of TCM adopts a holistic approach in making diagnosis of diseases, with the categorization of symptoms into various patterns of *Zang-fu* (*i.e.* visceral organs) disorders. Furthermore, TCM views that various emotions, or *Qing Zhi*, do influence an individual's physiological functions.

In TCM theory, there are seven *Qing*—five of which are collectively called *Zhi*. The five *Zhi*, namely, joy, anger, grief, anxiety and fright, are characterized by *five elements*, namely, *Fire*, *Wood*, *Metal*, *Earth* and *Water*, respectively. As *Zang-fu* (*i.e.* all visceral organs) are linked to these *five elements*, the over-expression of each *Zhi* can affect the function of its respective *Zang-fu* (*i.e.* all visceral organs). In light of the *Five Element* theory, all *Zhi* are related by generating, restricting, over-restricting and reverse-restricting one another (**Figure 2**). Thus, balancing the expression of the five *Zhi* is thought to be crucial in maintaining psychological and physical health [33].



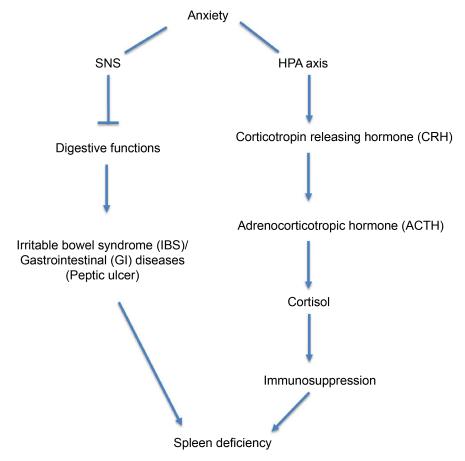
**Figure 2.** Relationship between Zang-fu and Five Zhi in TCM. Five Zhi, namely, joy, anger, grief, anxiety and fright, are characterized by *five elements*, namely, *Fire, Wood, Metal, Earth* and *Water*, respectively. As Zang-fu are linked to the *five elements*, the over-expression of each Zhi can affect the function of its respective Zang-fu. In addition, there is a generating cycle and restricting (or attack) cycle in which the five Zang-fu interact. The generating cycle describes the ways in which each element, serving as a mother, promotes the growth and development of the following child element. The restricting cycle provides for a check and balance system among all of the elements. The third form of interaction, namely insulting (not shown in the figure), describes the triggering of the attack. Thus, the direction of the insulting is the reverse of the restricting cycle.

Both *Spleen* and anxiety belong to the *Earth*, giving rise to a TCM theory stating that "Anxiety impairs *Spleen*". According to TCM theory, over-focusing or over-thinking on one subject will lead to anxiety, with resultant dysfunction in the transport of water and nutrients around the body and the stagnation of *Qi* (energy/ nutrients), indicative of a poorly functioning of the *Spleen*. *Zhi* arises as a phenotype of an outcome from one's thoughts, and prolonged anxiety can worsen the functions of other *Zang* (*i.e.* visceral organs), which is consistent with the inter-functional relationship among various *Zang* (*i.e.* visceral organs) [33]. Interestingly, anger can be used to alleviate anxiety. Anger belongs to *Wood*, which restricts the *Earth* according to the *Five Element* theory. Thus, by inducing a state of rage, the effects of anger can effectively alleviate a state of anxiety [33]. Although such psychotherapy is theoretically sound, little is currently known about the scientific basis of such treatment.

It is worth noting the difference between stress and anxiety. Stress can be defined as a short-term psychological pressure when only limited resources are available to finish a task, whereas anxiety can be defined as a long-term worry about something uncertain in the future. Yet, a prolonged state of stress can also lead to anxiety. Modern biomedical research has shown a causal relationship between anxiety and Spleen-regulated function, but the physiological characteristic of anxiety should first be defined prior to achieving an understanding of such an interrelationship. Studies have shown that General Anxiety Disorder (GAD) can be characterized by an asymmetrical expression of the Sympathetic Nervous System (SNS) and the Hypothalamic-Pituitary-Adrenal (HPA) axis [34]. Based on this observation, it can be deduced that the influence of anxiety on Spleen function is likely mediated by both nervous and endocrine factors. The SNS, a component of the autonomic nervous system, serves to inhibit digestive functions (including peristalsis) and the enteric nervous system, an intrinsic nervous system in the digestive process. The HPA axis regulates a series of endocrine glands, wherein the hypothalamus secretes Corticotropin Releasing Hormone (CRH) that stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), and ACTH in turn stimulates the secretion of cortisol from the adrenal cortex (Figure 3).

Cortisol primarily activates gluconeogenesis and the metabolism of fat, protein and carbohydrate in cells. However, the effect of immunosuppression by cortisol explains the functional relationship between HPA axis and the *Spleen*, with the latter being a regulator of immune function. The secretion of cortisol, which is stimulated by cytokines, can inhibit the further production of cytokines by immunosuppression, and this negative feedback loop of regulation is primarily used to prevent the over-activation of the immune system [35]. However, cortisol, as a "stress" hormone, has been found to be strongly associated with anxiety. The overproduction of cortisol under conditions of anxiety leads to immunosuppression, a symptom of *Spleen* dysfunction in TCM. Other studies have found that GAD patients have a lower level of peripheral benzodiazepine receptors on their T lymphocytes [36], suggesting that benzodiazepines (which are antianxiety drugs) may also exert a regulatory effect on immune function [37].

The correlation between anxiety and gastrointestinal (GI) diseases has been studied.



**Figure 3.** Anxiety and *Spleen* deficiency. In Western medicine, general anxiety disorder (GAD) can be characterized by the asymmetrical expression between the sympathetic nervous system (SNS) and the hypothalamal-pituitary-adrenal (HPA) axis. The SNS serves to inhibit digestive functions. The over-stimulation or under-stimulation of the digestive system by SNS, leads to contradicting irritable bowel (IBS) symptoms and gastrointestinal (GI) diseases, which are associated with *Spleen* dysfuction in TCM. On the other hand, the HPA axis regulates a series of endocrine glands, wherein the hypothalamus secretes corticotropin releasing hormone (CRH) that stimulates the pituitary gland to secrete adrenocorticotropic hormone (ACTH), and ACTH in turn stimulates the secretion of cortisol from the adrenal cortex, with resultant immunosuppression and thus *Spleen* dysfuction. The secretion of cortisol, which is also stimulated by cytokines, can inhibit the further production of cytokines. This negative feedback loop of regulation is primarily used to prevent the over-activation of the immune system.

It was found that Irritable Bowel Syndrome (IBS) was closely associated with anxiety [38]. IBS is a collection of patterns of altered bowel movement in the absence of any damage in GI tract [39]. This may be explained by the over-stimulation or under-stimulation of the digestive system by the SNS, leading to contradicting IBS symptoms such as constipation and diarrhea. A study also shows that stressors can disrupt the function of GI microbiota by inducing a neural response, which increases the risk of mucosal infection and inflammation. Stress on the GI mucosal immune system can lead to the translocation of pathogenic microbes from the GI tract to the interior of the body, with the resultant infection and the associated inflammatory response [40]. Se-

vere and sustained anxiety can induce peptic ulceration. Symptoms of peptic ulcer, including digestive discomfort and bleeding along the digestive tract, can be related with *Spleen* dysfunction, in which the *Spleen* fails to sustain the function of the digestive system and regulate the circulation of blood.

A causal relationship between anxiety and peptic ulceration is supported by clinical and experimental observations. It has been shown, for example, that stress, which is correlated to anxiety, can cause peptic ulcer in absence of *Helicobacter pylori* [40]. An increase in the number of patients with peptic ulcers that are not caused by bacteria or non-steroidal anti-inflammatory drugs was observed after the traumatic earthquake in East Japan on 11 March, 2011, suggesting that psychological stress arising from this natural disaster can be a significant factor in causing peptic ulcers [41]. "Executive monkey" studies have also shown that animals that had been exposed to stressors were more prone to developing gastric ulcers [42].

The causal relationship between psychological stress and peptic ulceration can be explained by the adverse effect of the SNS innervation of the mucosa and Gut-Associated Lymphoid Tissue (GALT). Sympathetic nerve fibers enter the alimentary canal along arteries and eventually terminate on blood vessels in the close vicinity of the mucosa. As such, mucus secretoneurone is regulated by inhibitory signals via  $\alpha 2$  adrenergic signaling with noradrenaline as the neurotransmitter. Sympathetic noradrenergic nerve fibers also innervate the interdomal region of the submucosa with T-lymphocytes and plasma cells [43]. While the mechanism by which over-innervation of the SNS can produce an immunomodulatory action remains unclear, a hypothesis concerning the development of peptic ulcers caused by anxiety can be postulated based on the relationship between the SNS and gastrointestinal mucosa. Since anxiety can be characterized by the over-stimulation of the SNS [44], overwhelming signals from the SNS may trigger a higher output of inhibitory signals that suppress the production or release of secretoneurone. This leads to a decreased production of mucus, resulting in erosion of the mucosa and muscle layer of the duodenum by gastric juice.

In TCM, it is believed that anxiety arises from an imbalance of Zang (i.e. visceral organs) functions, wherein different combinations of functional imbalances among Zang (i.e. visceral organs) result in various symptoms. Yet, as the Five Element theory goes, Earth, which is considered as the center of the five elements, will eventually be hindered by the imbalance of other elements. Thus, the treatment of different types of anxiety is primarily focused on invigorating the function of the Spleen [44]. Gui Pi Tang (Restore the Spleen Decoction), which is a commonly used formulation in treating anxiety, not only ameliorates the symptoms of Spleen dysfunction caused by anxiety, but also directly alleviates anxiety. From the perspective of TCM theory, Gui Pi Tang (Restore the Spleen Decoction) mobilizes the stagnant Qi (energy/nutrients) and nourishes shen in the Heart, which is thought to be the master of Qing Zhi. As anxiety is pathologically-related to the stagnation of Qi, a smooth flow of Qi will ease anxiety [44]. The pharmacological properties of Gui Pi Tang (Restore the Spleen Decoction) have been investigated. In treating peptic ulcers, Dang Gui (Angelicae Sinensis Radix) can prevent

bleeding in the alimentary canal caused by peptic ulceration. *Huang Qi* and *Ginseng* were found to be effective in preventing peptic ulcer development [12]-[21]. It was also observed that *Gan Cao* produced an anti-ulcer action by increasing gastric mucosal defensive factors [45]. *Gan Cao* also promotes the proliferation of gastric mucosal cells and protects the mucosa by releasing endogenous prostaglandins that can stimulate mucus production. On the other hand, *Huang Qi*, *Gan Cao* and *Suan Zao Ren* (Zizyphi Spinosae Semen) were found to produce a tranquillizing action [10] [11] [46]-[48].

On the basis of TCM theory, a causal relationship between anxiety and *Spleen* function has been clearly established. However, a recent study has shown that the status of GI microbiota can in turn induce anxiety-like behavior [49]. The complete removal of GI microbiota leads to a decrease in anxiety-like behavior and alteration in the neurochemistry of the central nervous system [50]. Such an interaction, known as the microbiome-gut-brain axis, is poorly understood in molecular and physiological terms, but the finding does suggest the possibility that the correlation between anxiety and *Spleen* function can be bi-directional. In this connection, patients with *Spleen* dysfunction show a higher blood lactate level [6], which is consistent with the symptoms of tiredness and muscle fatigue in *Spleen* dysfunction. While patients with GAD exhibited significantly higher blood lactate levels than those of control subjects after vigorous exercise (indicative of *Spleen* dysfunction), anxiety attacks could be induced by the infusion of lactate into controls, suggesting that *Spleen* dysfunction may also be a cause of anxiety [51].

The practice of TCM remains popular in Asian countries despite the advent of Western medicine. While TCM and Western medicine belong to two distinct treatment systems, the explanation of TCM theory in the context of Western medicine can hopefully bridge the theoretical gap between TCM and Western medicine and thus facilitate the integration of the two therapeutic approaches to the prevention and/or treatment of diseases. In this article, we have endeavored to describe the function of the *Spleen* in TCM using the language of Western medicine. Hopefully, concerted efforts of this type can serve to modernize the theory of TCM which can be comprehended by individuals living in the 21<sup>st</sup> century.

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