

The Clinical Research on the Anticancer Action of Si-Miao Yong-An Decoction

He Ya Ping, Hou Ming Yan, Wu Yv, Peng Hai Yan *

The Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing, China

Email address:

260615@njucm.edu.cn (Peng Hai Yan)

*Corresponding author

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Abstract: *Background:* Si-Miao Yong-An Decoction is composed of four herbs: honeysuckle, Radix Sophora, Angelica and Licorice. It has the functions of clearing away heat and detoxification, promoting blood circulation and clearing collaterals. It is a famous ancient formula for the treatment of gangrene, and is now widely used in the treatment of multiple diseases in various systems. *Objective:* To explore the anticancer action of Si-Miao Yong-An decoction in the clinical application of the treatment of some kinds of malignant tumors. *Methods:* This paper reviews the sections in classical TCM books and recent report of clinical study of Si-Miao Yong-An Decoction in the treatment of cervical cancer, breast cancer, nasopharyngeal cancer, oral cancer, gastric cancer and etc. *Results:* The composition of the prescription was first recorded in Shen Yi Mi Zhuan in Han dynasty, and also recorded in the book of Shi Shi Mi Lv and Yan Fang Xin Bian, and it was formally named in Journal of TCM in the year of 1958. It was useful in relieving the clinical symptoms and elevating the life quality besides preventing the recurrence and metastasis of cancer. *Conclusion:* Si-Miao Yong-An Decoction is effective in treating various malignant tumors and the related complications of the syndrome of blood stasis and heat-toxin. It is promising to provide a new direction for better exploration of traditional Chinese medicine and its application in the treatment of malignant tumors in the future.

Keywords: Si-Miao Yong-An Decoction, Anticancer, Traditional Chinese Medicine (TCM), Clinical Study

1. Introduction

There are 4 herbs in the formula of Si-Miao Yong-An decoction, including Honeysuckle Flower, radix scrophulariae, Angelica and Licorice [1]. The monarch drug is Honeysuckle Flower, which is sweet in taste and cold in nature and has the function of clearing away heat and detoxification. The minister drug is radix scrophulariae, which is sweet-bitter-salty in taste and mild cold in nature and has the function of clearing heat and cooling blood, nourishing Yin and reducing fire, detoxifying and resolving nodes. The adjuvant is angelica, which is sweet-pungent in taste and warm in nature and has the function of invigorating blood circulation, regulating menstruation and relieving pain, moistening intestines and promoting bowel movement. The conductant drug is licorice, which is sweet in taste and

moderate in nature and has the function of harmonizing various herbs. The whole formula can cure gangrene with its therapeutic effect of clearing heat and detoxification, promoting blood circulation and relieving pain. Recent clinical research showed that applying Si-Miao Yong-An Decoction alone or in combination with other formulas had good therapeutic effect on the blood stasis and heat syndrome of some tumors which was in accord with TCM concept of different treatment for the same disease and the same treatment for different diseases. In order to explore the methods to get better application of this formula, extend its application scope, and study its anticancer mechanism, this paper reviewed the current clinical research on this formula as follows.

Table 1. The different records of Si-Miao Yong-An Decoction in classical books.

NO.	Books names	Published time	honeysuckle	radix scrophulariae	Chinses angelica	licorice	reference
1	Shen Yi Mi Zhuan	Han dynasty	3 Liang	3 Liang	2 Liang	1Liang	2
2	Shi Shi Mi Lv	Year of 1687	8 Liang	1 Liang	2Liang	1Liang	3
3	Yan Fang Xin Bian	Year of 1846	3 Qian	3 Qian	2Liang	1Liang	4
4	Journal of TCM	Year of 1958	4 Liang	4 Liang	2 Liang and 4 Qian	1 Liang and 2 Qian	5

2. Review of Records of Classical Books

Taking a retrospective study of Si-Miao Yong-An Decoction, 4 classical TCM books should be memorized as summarized in table 1.

2.1. The Book of “Secret Biography of Miracle Doctor” (Shen Yi Mi Zhuan)

The formula with the composition of the four herbs was first recorded in the book of “Secret Biography of Miracle Doctor” (Shen Yi Mi Zhuan). This book was written by Hua Tuo, the famous physician in Han dynasty allegedly. There were totally more than 1100 formulas recorded in the book and the formula composed of Honeysuckle Flower, radix scrophulariae, Angelica and Licorice was recorded to treat the symptoms of fester and gangrene of the fingers and toes. The composition of the formula is: 3 Liang (两) of honeysuckle, 3 Liang of radix scrophulariae, 2 Liang of Chinses angelica, 1 Liang of licorice [2].

2.2. The Book of “Secret Record of Stone Chamber” (Shi Shi Mi Lv)

The formula was also recorded in the book of “Secret Record of Stone Chamber” (Shi Shi Mi Lv) which was written by Chen Shi-Duo, a physician in the end of Ming dynasty and the beginning of Qing dynasty. This book was published in the year of 1687. It was recorded in volume. 1 (volume of ceremony): How to treat lung carbuncle? It could be treated by the prescription of composition of the following herbs: 1 Liang of radix scrophulariae, 1 Liang of raw licorice, 8 Liang of honeysuckle, 2 Liang of Chinses angelica [3].

2.3. The Book of “New Compilation of Proved Recipes” (Yan Fang Xin Bian)

The formula was also recorded in the book of “New Compilation of Proved Recipes” (Yan Fang Xin Bian). This book was written by Bao Xiang-Ao, a physician in Qing dynasty. This book was published in the year of 1846. In the book, it was pointed out the disease of gangrene was commonly seen in fingers or toes and could be treated by applying the powder of licorice externally and administering orally the decoction composed of 3 Qian (钱) of honeysuckle and radix scrophulariae respectively, 2 Liang of Chinses angelica, and 1 Liang of licorice [4].

2.4. Journal of Traditional Chinese Medicine

The name of Si-Miao Yong-An decoction was formally confirmed in the journal of Traditional Chinese Medicine in the year of 1958. The paper was written by TCM department of NO. 1 hospital of He-Bei province Tian-Jin administrative region. The topic of the paper was “report of the treatment of thrombo-angiitis obliterans”. It was recorded that Si-Miao Yong-An decoction was the main effective formula to treat thrombo-angiitis obliterans and the dosage of the herbs was: 4 Liang of radix scrophulariae and honeysuckle respectively, 2 Liang and 4 Qian of Chinses angelica, 1 Liang and 2 Qian of licorice [5].

3. Clinical Study

Si-Miao Yong-An decoction has the effects of clearing heat and detoxification, promoting blood circulation and relieving pain. It could be applied to treat malignant tumors due to blood stasis and heat. The recent research on Si-Miao Yong-An decoction with the application of treating some kinds of cancer was summarized as followings (Table 2).

Table 2. Clinical study of Si-Miao Yong-An Decoction with the application of treating cancers.

Cancer	Cervical cancer	Breast cancer	Nasopharyngeal cancer	Oral cancer	Gastric cancer
Prescription	12 grams of honeysuckle, 15 grams of radix scrophulariae, 12 grams of Chinses angelica	30 grams of honeysuckle and radix scrophulariae respectively, 10 grams of Chinses angelica, 6 grams of licorice	20 grams of honeysuckle, 10 grams of radix scrophulariae and Chinses angelica respectively, 6 grams of licorice	90 grams of honeysuckle and radix scrophulariae respectively, 60 grams of Chinses angelica, 15 grams of licorice	20 grams of Chinses angelica, honeysuckle, and radix scrophulariae respectively, 10 grams of licorice
modification	combined with Wu Ling powder, Chai Hu Shu Gan powder	add radix achyranthis bidentatae, fructus liquidambaris, curcuma zedoary and cassia twig	combined with Qian Jin Wei Jing decoction, Pu Ji Xiao Du decoction	combined with Dan Shen injection	combined with Xi Huang pill
Therapeutic effect	relieving the edema of lower limbs	relieving the edema of the upper arm	relieving the swelling and burning sensation in the face	regulating the levels of TGF- β , IL-6, GSK-3 β and β -catenin	reducing MTDH over expression
Reference	9,10	16,17	21	25	29

3.1. Cervical Cancer

Cervical cancer is the third most common cancer in women worldwide, with concepts and knowledge about its prevention and treatment evolving rapidly [6]. The estimated age-related incidence of cervical cancer was 13.1 per 100,000 women globally and varied widely among countries [7]. Lower extremity edema is a common complication after cervical cancer surgery [8]. It is now considered that its cause is the destruction of lymphatic network during lymph node dissection, resulting in lymphatic stenosis and poor lymph and blood reflux at the distal end of the limb [9]. Professor Liu Long-Min applied Si-Miao Yong-An decoction to treat edema of lower limbs after cervical cancer surgery [10]. He usually applied it with the combination with Wu Ling powder, plantain and motherwort to strengthen the role of promoting diuresis and detumescence. Motherwort is good at clearing heat, promoting blood circulation and promoting diuresis, especially the edema caused by the combination of water, heat, blood stasis and toxin. For those with chronic Qi deficiency, He usually add Astragalus membranaceus, Atractylodes macrocephala, Atractylodes macrocephala and poria cocos to replenish the spleen and stomach.

3.2. Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women and ranks second among causes for cancer related death in women [11]. Evidence in literature has shown that the past and ongoing research has an enormous implication in improving the clinical outcome in breast cancer [12]. Surgical treatment is still the first choice for breast cancer patients [13]. Edema on the affected side is one of the common complications after axillary lymph node dissection for breast cancer [14]. The upper limb dysfunction caused by upper extremity edema, repeated infection and abnormal appearance bring great physical pain and psychological burden to patients, which seriously affects the quality of life of patients [15]. Diuretics are generally used in clinic which can relieve the edema temporarily, but it can cause side effects probably [16]. Huang Xiao-Na et al. applied Si-Miao Yong-An decoction to treat upper limb edema after breast cancer operation with satisfied therapeutic effect and without any side effect [17]. The results showed that the therapeutic effect was better in the patients with the symptoms of red in color, swelling, hot sensation and pain in the local position.

3.3. Nasopharyngeal Cancer

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma arising from the epithelial lining of the nasopharynx [18]. It is thought that disparities in dietary habits, lifestyle, and exposures to harmful environmental factors are likely the root cause of NPC incidence rates to differ geographically [19]. Most of nasopharyngeal carcinoma have moderate sensitivity to radiotherapy. Radiotherapy is the first choice for nasopharyngeal carcinoma. Oropharyngeal mucosal reaction is the most

common adverse reaction of radiotherapy [20]. According to TCM theory, radiation belongs to the evil of heat toxin which can further cause blood stasis and consume blood and body fluid. Lu Wei et al. applied Si-Miao Yong-An decoction to treat radiation related Oropharyngeal mucosal reaction of the patients of NPC [21]. He usually added Forsythia suspensa, Scutellaria baicalensis, Hedyotis diffusa to strengthen the action of clearing away heat and detoxification, and added Adenophora stricta and Ophiopogon japonicus to nourish Yin and body fluid.

3.4. Oral Cancer

Oral cancer is the general name of malignant tumors in the oral cavity. Most of them belong to squamous cell carcinoma, that is, the so-called mucosal variation [22]. The management of oral cancer is a multidisciplinary endeavor, as each patient presents the treating clinicians with a unique set of challenges the management of which impacts on both survival and quality of life [23]. The clinical manifestations of oral cancer and effects of treatment can lead to negative effects on the quality of life of the patient [24]. Patients may experience significant dysfunction in talking, swallowing, with alteration of cosmetic appearance, and sensory impairment, as well as chronic pain. All these factors when compounded lead to poor mental health. TCM treatment with its regulation through multiple targets and pathways can play a beneficial role in prohibiting the development and recurrence of oral cancer. Xiao Yan-Bo et al. applied Si-Miao Yong-An decoction to treat oral submucous fibrosis (OSF) with an effective result in regulating the levels of TGF- β , IL-6, GSK-3 β and β -catenin [25]. He administered Si-Miao Yong-An decoction to the patients orally and combined with Dan Shen injection intravenously with a good result in relieving pain and elevating life quality of the patients clinically.

3.5. Gastric Cancer

Gastric cancer is a malignant tumor originating from gastric mucosal epithelium, and it is the fifth most common and the third most lethal cancer worldwide [26]. Surgery is the only chance of cure, but recurrence is common, even with complete resection [27]. The management of gastric cancer is a challenge requiring a multidisciplinary approach for optimal treatment [28]. TCM treatment plays an important role in multidisciplinary scheme for gastric cancer with its beneficial effect in tonifying body constituent and improving life quality. Jiang Lin hold that ulcerate type of gastric cancer had a long duration and the pathogenesis was the mixture of blood stasis and toxin [29]. She advocated the treatment methods of clearing away heat and detoxification and applied Si-Miao Yong-An decoction combined with Xi Huang pill for the patients of ulcerate type of gastric cancer. The results showed that the symptoms of pain in the stomach region, hot sensation in the five centers, abdominal distension, and dry and tarry stool of the patients of the treatment group were

relieved obviously, and the overexpression of Metadherin (MTDH) was also decreased.

3.6. Others

TCM Botanic physician Zhang Pei-Yv applied Si-Miao Yong-An decoction for the patients of syndrome of excessive heat and toxin with the side effect of red swelling and burning pain after radio-therapy. The composition of the formula was: 18 grams of honeysuckle, radix scrophulariae and licorice respectively, 12 grams of Chinses angelica [30]. Lu Wei applied modified Si-Miao Yong-An decoction for a patient of lung cancer with facial erythema and scattered rash all over the body. After taking the decoction for 7 days, the patient's erythema and rash subsided gradually and the itching relieved [21]. Professor Shu Qi-Jin treated a patient of postoperative lung cancer with oral ulcer by giving him the gargle of Si-Miao Yong-An decoction [31]. He put forward that administering Si-Miao Yong-An decoction externally could perform the action of clearing away heat and detoxification without the side effect of impairing stomach-Qi.

4. Conclusions and Perspectives

The clinical application of Si-Miao Yong-An decoction has a long history. The main action of it is clearing away heat and detoxification. It is usually used to treat gangrene, fester, pustule, sore, and so on. Recent clinical study of Si-Miao Yong-An decoction in the treatment of several kinds of cancers shows that it is also effective in the syndrome of blood stasis and heat-toxin of cancers. The above results of clinical studies show that Si-Miao Yong-An decoction has good curative effect on the syndrome of heat toxin and blood stasis of cancers. With its action of clearing away heat and detoxification, It can both reduce the symptoms caused by blood stasis blockage, prevent tumor recurrence and metastasis, and relieve the local edema caused by blood stasis blockage in the limbs. As to some tumors treated with radiation therapy, the syndrome is very easily to transform into heat toxin and blood stasis in the course of disease and lead to the symptoms of red in color, swelling, hot sensation and pain in the local position. Combined with the application of Si-Miao Yong-An decoction, TCM treatment can perform the action of protecting mucosal tissue and relieving patients' clinical symptoms effectively.

The occurrence of some tumors is related to the persistence of chronic inflammation. According to TCM theory, the cause is pathogenic factors accumulating and changing into heat-fire which then producing cancerous toxin consequently. With its strong pathogenicity, cancerous toxin can promote tumor growth and enlargement on one hand, and do harm to the healthy qi of human body on the other hand. In the clinic, the syndrome of deficiency of healthy qi mixed with heat toxin and blood stasis is very common and it is the reason why the treatment discipline of strengthening vital qi combined with expelling pathogens is advocated. Study on the herbal collocation in the formula of Si-Miao Yong-An

decoction shows as the following: Honeysuckle Flower is good at clearing away heat and detoxification so as to relieving inflammation and swelling. Radix scrophulariae can nourish Yin and cool blood, subdue fire, detoxicate and resolve nodes so as to protect healthy qi and dissipate the pathogen of heat and toxin. Angelica can nourish blood and promote blood circulation so as to keep the smooth flow of blood throughout the whole body. Licorice can strengthen spleen qi and detoxicate besides harmonize herbs. The collocation of Honeysuckle Flower and Radix scrophulariae can perform the action of clearing away heat and detoxification and inhibit the heat-toxin pathogen. The collocation of Radix scrophulariae and Angelica can perform the action of nourishing Yin and blood so to protect and replenish healthy qi. With the decrease of heat-toxin pathogen and increase of Yin and blood, the circulation of blood and qi can be kept in a smooth status and the whole body can be nourished properly and the viscera can perform their physical function normally and the occurrence and development of cancers can be inhibited.

On the basis of existing study, we realized that Si-Miao Yong-An decoction had confirmed curative effect on the combined syndrome of blood stasis and heat, and we believed that it can be used alone or in combination with other formulas for the treatment of a variety of tumors and their complications. The exact therapeutic effect rate and its action mechanism are both worthy of further observation and research. We speculated that there were various actional pathways and targets of Si-Miao Yong-An Decoction including anti-inflammation, changing tumor microenvironment, intervening hypercoagulable state of malignant tumor, anti-tumor angiogenesis, and etc.

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