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**Role of traditional Chinese medicine in the management of patients with hepatocellular carcinoma**

Xi SY *et al.* Chinese herbal medicine and HCC

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**Abstract**

Traditional Chinese Medicines (TCMs) has been employed for centuries in the treatment of patients with hepatocellular carcinoma (HCC). Previous reviews of this topic have focused on certain aspects of TCM treatment rather than an overall assessment of their value and mechanisms of action. Both the Chinese and English medical literatures were reviewed to identify where TCM might be of value in the treatment of HCC and the justification for such treatment. TCM treatment corrects the “internal disequilibriums” thought to be responsible for the development, growth and spread of the tumor. It has also been used to manage symptoms associated with HCC and the adverse effects of chemo- and radiation-therapies. Recent research has documented the precise effects of TCM on tumor biology. There are also increasing efforts to identify which of the many components of TCM herbal remedies are primarily responsible for these beneficial effects. This review outlines the benefits of TCM treatment of HCC and the laboratory data describing their anti-tumor properties.

**Key words:** Hepatoma; Herbal medicine; Liver disease; Liver; Cancer

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**Core tip:** Traditional Chinese Medicines (TCMs) are commonly employed by patients with hepatocellular carcinoma (HCC). This review identifies which herbal concoctions are most frequently recommended by TCM authorities. TCMs serve to correct internal imbalances that contribute to HCC. TCMs favorably alter HCC cell biology.

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**INTRODUCTION**

Traditional Chinese Medicine (TCM) is a comprehensive medical system that utilizes herbal remedies, acupuncture, dietary therapy, exercise and massage to prevent, treat and rehabilitate disease states by restoring the internal environments of an individual to a state of equilibrium. It is based on traditional medical theories and the practice experiences of Chinese TCM physicians. The traditional medical theories describe two components of illness: “holism” (the concept of viewing the situation as a whole) and “syndrome differentiation” (the consequences of disrupted holism). Thus, rather than focusing on the tumor *per se*, TCM focuses on correcting the internal disequilibriums responsible for tumor development and progression.

Given the phylogeny of the oncogenic hepatitis B virus (HBV), it can be assumed that hepatocellular carcinoma (HCC) has been prevalent in the Chinese population for centuries[1]. Hence, Chinese TCM physicians have had extensive experience in identifying, developing and refining treatments for this potentially lethal tumor. This longstanding experience and commitment to treating HCC is an important feature of TCM. Specifically, unlike “Western Medicine” where effective treatments are identified by the results of prospective, randomized, placebo-controlled trials, in TCM, the value of a particular herbal concoction is gauged by the number of recommendations it has received by TCM authorities over the course of centuries.

**MOST COMMONLY EMPLOYED TCMS FOR HCC**

TCM physicians have identified various Chinese herbal medicines that represent every category of the Chinese materia medica recognized by International Organization for Standardization (ISO)[2]. The majority of these agents are: Deficiency-supplementing herbs, heat-clearing herbs and blood-quickening stasis-transforming herbs (Table 1).

The 10 most commonly employed individual herbs are provided in Table 2. They are: Poria (Fuling), Rhizoma Atractylodis Macrocephalae (Baizhu), Radix Astragali Mongolici (Huangqi), Herba Hedyotidis (Baihuasheshecao), Radix Glycyrrhizae (Gancao), Radix Bupleuri Chinensis (Chaihu), Radix Codonopsis (Dangshen), Radix Paeoniae Alba (Baishao), Radix Angelicae Sinensis (Danggui) and Carapax Trionycis (Biejia).

Often, combinations of herbs are advocated such as qi-boosting spleen-supplementing herbs being combined with heat-clearing toxin-resolving herbs, blood-quickening stasis-transforming herbs and/or liver-soothing qi-rectifying herbs (qi - the vital life force that is thought to animate the body internally)[3]. The 10 most commonly advocated combinations of herbs are provided in Table 3.

**TCMs FOR THE TREATMENT OF HCC SYMPTOMS**

Anorexia, fatigue, weakness and right upper quadrant discomfort are the most common symptoms of HCC while ascites and jaundice are the most common signs[4]. TCMs are often used in the treatment of these and the other features listed in Table 4. In a recent cluster analysis performed by Liu *et al*[4], Endothelium Coreneum Gigeriae Galli (Jineijin) and Fructus Hordei Germinatus (Maiya) were the most commonly-used herbal medicines for treating anorexia; Radix Astragali Mongolici (Huangqi), fatigue and weakness; Rhizoma Corydalis Yanhusuo (Yanhusuo) and Fructus Toosendan (Chuanlianzi), right upper quadrant discomfort; Pericarpium Arecae (Dafupi), Polyporus (Zhuling) and Poria (Fuling), ascites and Herba Artemisiae Capillaris (Yinchen), jaundice[5]. Other herbal medicines used to treat less common symptoms and signs of HCC are also provided in Table 4.

**TCM FOR IMPROVED QUALITY OF LIFE AND SURVIVAL IN HCC PATIENTS**

The use of TCM to correct disequilibriums in a patient’s internal environment has been associated with improved quality of life for HCC patients. For example, the Jianpi Jiedu decoction has been reported to improve quality of life by attenuating symptoms in 30 patients with advanced HCC[6]. Similar results have been obtained with other combinations[7-10].

Other studies have described improved survival. Specifically, compared to untreated controls, treatment with a Ruanganlidan decoction and Rhizoma Curcumae Longae increased median disease-free survival (DFS) by approximately 12 mo in 78 HCC patients[11]. In another study Qudu Huayu Xiaoji formula not only improved the quality of life in 77 HCC patients after hepatic arterial chemoembolization, but also prolonged survival by 5-9 mo when compared to 76 patients treated with chemoembolization alone[12].

**TCM AND ADVERSE REACTIONS TO CHEMOTHERAPEUTIC AGENTS**

Side effects of chemotherapy are major concerns for cancer patients and often interfere with treatment. Numerous TCM herbs have been identified that reduce the side effects and non-tumor toxicity of chemotherapeutics. For example, Ciji Hua’ai Baosheng Granule Formula (CHBGF), attenuates the decreases in white blood cell and platelet counts of H22 hepatoma transplanted tumor caused by chemotherapy[13]. Combining Rhizoma Zingberis Recens (Shengjiang) and Rhizoma Phragmitis (Lugen) reduces the vomiting caused by chemotherapy in H22 hepatoma carcinoma-bearing mice[14] and Danggui Beimu Kushen attenuates cisplatin toxicity (in the same animal model). Other TCMs such as Panaxan, Fufang Ejiao Jiang, Lianqi Capsule, and the aqueous extract of Fructus Akebiae (Bayuezha) have also been reported to reduce side-effects and improve the efficacy of chemotherapy for HCC in H22 hepatoma bearing mice[15-18]. Compared to chemotherapy alone, Tremella Polysaccharide, extracted from Polyporus (Zhuling), improved quality of life, physical activity and attenuated fatigue, nausea, vomiting, constipation, diarrhea and white blood cell counts during chemotherapy in 50 patients[19]. Jianpi Jiedu Formula minimized hepatic dysfunction following transarterial chemoembolization (TACE) treatment in 16 patients[20]. Similarly, the Zipi Decoction was associated with improved hepatic function following TACE when compared to TACE alone[21]. Jian Pi Li Qi Decoction in 52 patients and Jiedu Granules combined with Cinobufacini in 60 patients alleviated signs and symptoms of the postembolization syndrome following TACE[22]. Finally, it should be noted that on occasion, TCM can adversely affect patient outcome when TCM-chemotherapy drugs interact[23].

**TCM AND HCC TUMOR BIOLOGY**

Recent developments in molecular and cell biology have provided important insights into the pathogenesis and course of HCC. They have also provided investigators with an opportunity to identify the mechanisms whereby TCM might impact on HCC. To date, such research has focused on HCC proliferative activity, apoptosis, metastasis, angiogenesis, immune reactivity and multidrug resistance.

***The effects of TCM on the proliferative activity and growth of malignant hepatocytes and tumors***

A large number of herbs have been reported to inhibit malignant hepatocyte proliferation and tumor growth. In many instances, the precise mechanisms and signaling pathways have also been identified. For example, Akebia trifoliate (Thunb.) and Koidz (Sanyemutong) seed extract inhibited the proliferation of various human HCC cell lines via inducing endoplasmic reticulum stress *in vitro*[24] whereas the ethyl acetate extraction from a Chinese herbal formula, Jiedu Xiaozheng Yin inhibited proliferative activity by suppressing polycomb gene product Bmi1, Wnt/β-catenin signaling and inducing G0/G1 phase arrest *in vitro* and *in vivo*[25,26]. Coptischinensis (Huanglian) restrained HepG2 cell proliferation through activating the NAG-1 gene enzyme *in vitro*[27].

Other TCM herbs have been reported to inhibit malignant hepatocyte proliferative activity and tumor growth through mechanisms that have yet to be identified. Of these, Bufalin, a component of Venenum Bufonis(Chansu), inhibited both proliferation and invasion of HCC cells *in vitro*[28] and Chaiqiyigan granula enhanced Taxol-induced growth inhibition of HCC xenografts in nude mice[29]. Other herbal medicine extracts that have been reported to possess tumor growth inhibiting properties via yet to be defined mechanisms include Jianpi Huayu Formula which inhibited BEL7402 cell proliferation *in vitro*[30], Compound Recipe Kushen SMMC; 7721 cell proliferation *in vitro*[31], and Fuzheng Yiliu Granule in H22 hepatoma-bearing ICR mice and the HepG2 cell line; PLC tumor growth[32].

***The effects of TCM on apoptosis and autophagy of malignant hepatocytes***

Dysregulation of apoptosis and autophagy are important components of tumor development, often resulting from activation of oncogenes and/or mutations in tumor suppressor genes. Thus, much effort has been expended on identifying TCM herbs that induce malignant hepatocyte apoptosis. Here, Kangai Fuzheng Prescription was found to promote apoptosis and inhibit the growth of human hepatoma SMMZ-7721 cells by downregulating p53 gene expression *in vitro*[33]. TCM matrine, a component of Radix Sophorae Flavescentis (Kushen), induced apoptosis and cell arrest by altering Bcl-2, Bax and miR122a expression in human HepG2 cells and murine HCC cells[34,35]. Quercetin, an extract from multiple herbal medicines, promoted apoptosis in the same HepG2 cells by increasing the transcription of apoptosis-related fas gene[36]. Ligustrumlucidum Aitfruit (Nüzhenzi) extract could induce apoptosis and cell senescence through upregulation of p21 in human HCC cell lines[37]. Finally, modified Yi Guan Jian, a Chinese herbal formula, induced apoptosis in Bel-7402 cells[38] and Rhizoma Panacis Majoria (Zhuzishen) in H22 hepatoma cells[39].

In addition to inducing apoptosis, Baicalein, from Radix Scutellariae Baicalensis (Huangqin), enhanced autophagy via increasing endoplasmic reticulum stress in HCC cells[40]. Similarly, Arenobufagin (Chansu), a natural bufadienolide from toad venom, induced apoptosis and autophagy in human HCC cells but through inhibition of the PI3K/Akt/mTOR pathway in human HCC cells[41].

***The effects of TCM on malignant hepatocyte metastases***

Controlling HCC metastases is an important strategy for preventing tumor recurrence. Various TCM herbs have been reported to possess this property. Specifically, Sini-San inhibited HBx-induced migration and invasiveness of HCC cells by inhibiting multiple signal transduction pathways including ERK/phosphatidylinositol 3-kinase/Akt upstream of NF-κB and AP-1 in human HCC cells[42] while Biejiajian Pill suppressed the invasiveness of HepG2 cells by inhibiting the Wnt/β-catenin pathway in HCC cells[43]. Jinlong Capsule decreased the adhesive ability of highly metastatic MHCC97H cells *in vitro* and thereby, significantly inhibited their movement and invasion[44].

In animal studies, Ginsenoside Rg3 from Ginseng (Renshen) inhibited the growth and metastasis of the highly metastatic human LCI-D20 cells in nude mice. This affect was ascribed to regulating the expression of nm23 and CD44 proteins[45]. By inhibiting SMMC-7721 cell invasion, Radix Salviae Miltiorrhizae (Danshen) decreased intrahepatic and distant metastasis of these cells in nude mice[46]. Another TCM that inhibits malignant hepatocyte metastases is Berberine which inhibited the growth and development of spontaneously developed lung metastases in an orthotopic model of HCC (MHCC-97L) in mice by suppressing Id-1 expression[47].

***The effects of TCM on HCC angiogenesis***

HCC survival, growth and metastases are dependent on new blood vessel growth or angiogenesis (Figure 1). TCM herbs that inhibit HCC angiogenesis include the alkaloids of Rubusalceifolius Poir (Cuyexuangouzi) and Livistonachinensis seeds (Pukuizi) which interfere with Notch signaling in a mouse model of HCC[48,49]. Resveratrol [typically extracted from Rhizoma Polygoni Cuspidati (Huzhang) or Fructus Mori (Sangshen)] decreases microvessel density (MVD) of transplanted hepatic tumors in nude mice and inhibits tumor growth[50]. By significantly reducing vascular endothelial growth factor (VEGF) expression, Celastrusorbiculatus Thunb (Nansheteng) inhibited Hep-G2 induced tumor growth in orthotopic nude mice[51]. Finally, Qinggan Huayu Formula has been reported to inhibit tumor development and growth by reducing VEGF and TGF-β1 protein expression and neovascularization in HCC rats[52].

***The effects of TCM on the immunologic response to HCC***

In the absence or setting of a suboptimal immune response, tumor cell growth, metastasis and rates of recurrence are enhanced. Thus, the status of natural killer cells, T lymphocyte subpopulations such as CD3+, CD4+ and CD8+, and pro- as well as anti-inflammatory cytokines are important and the ability of TCM to enhance the immune response to HCC would be of therapeutic value. Ganodermalucidum polysaccharides (GLPS) is an extract from Ganoderma Lucidum (Lingzhi) that significantly increases the ratio of T effector (Teff) to regulatory T cells (Treg) and suppresses tumor growth in HCC-bearing mice[53]. Moreover, GLPS eliminates Treg suppression of Teff proliferation resulting in increased pro-inflammatory IL-2 secretion. GLPS has also been reported to inhibit T cell Notch1 and FoxP3 expression by increasing miR-125b expression in hepatoma-bearing mice[53]. Another TCM with immuno-modulant properties is Radix Astragali Mongolici(Huangqi), a polysaccharide which inhibits the growth of mouse HCC HepA by promoting pro-inflammatory TNF-α and IFN-γ production[54]. Combining Jiedu Xiaozheng Yin and Fuzheng Yiliu Formula improved the immune function of mice with H22 HCC by increasing CD3+ and CD3+/CD4+[55]. Shaoyao Ruangan Recipe, Biejiajian Pill, Ganoderma spore oil soft capsule, Ginsenoside Rg3, flavonoids extracts from Semen Astragail Complanati (Shayuanzi), Fructus Lycii (Gouqizi) polysaccharide, and Fructus Schisandrae Chinensis (Wuweizi) polysaccharides are other herbal medications that have been reported to inhibit HCC by enhancing the host’s immune responsiveness in HCC-bearing mice[56-62].

***The effects of TCM on the multidrug resistance of malignant hepatocytes***

Increased expression of multidrug resistance (MDR) protein activity, the family of transporters responsible for exporting xenobiotics from within cells, is considered the principal explanation for the failure of chemotherapy in HCC treatment. Many TCM herbs have been reported to reverse MDR expression and/or activity. For example, Tetramethylpyrazine, a bioactive constituent isolated from the root of Ligusticum chuanxiong Hort (Chuanxiong) down-regulated P-gp, MRP2, MRP3 and MRP5 expression in HCC BEL-7402/ADM cells[63]. Bufalin, extracted from Venenum Bufonis (Chansu), achieved the same effect in BEL-7402/5-FU cells[64] and Hedyoticdiffusa (Baihuasheshecao) injection, Hirudo (Shuizhi) extract, Qizhu Decoction, Shehuang Xiaoliu Decoction, Jianpi Huayu Formula and Quercetin all reversed MDR activity in HCC tissues[65-70].

**CONCLUSION**

Although much progress has been made in our utilization and understanding of TCMs for the treatment of HCC, additional experimentation and research is still required. Clearly, no single herbal medicine, active component or compound recipe has been identified to be curative. Moreover, the mechanism(s) involved in achieving the benefits described are multiple and complex. None-the-less, empiric and experimental data suggest that TCM is effective in limiting symptoms, reducing treatment associated side effects, inhibiting tumor growth and altering key intracellular signaling pathways. While a combination of TCM and Western medicine may evolve as the optimal approach to treating HCC, certain challenges remain. Principal amongst these is the need for Western Medicine physicians to consider and where appropriate, accept the concept of “holism” for cancer treatment. These physicians must also be willing to consider empiric findings, albeit of centurys’ duration, as an additional measure of efficacy, particularly for compounds such as TCM herbs that due to their unique fragrance, do not always lend themselves to testing in placebo-controlled clinical trials.

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**Figure 1 Solid tumor’s occurrence and angiogenesis.**

**Table 1 Types of Herbal medicines and frequency of use in the treatment of patients with hepatocellular carcinoma**

|  |  |  |  |
| --- | --- | --- | --- |
| Category | Relative frequency | Category | Relative frequency |
| Herbs that supplement deficiency: Baizhu, Huangqi, Dangshen,Danggui, Shanyao, Gancao, Baishao, Biejia | 27.70% | Herbs that drain downwards: Dahuang, Yuanhua | 1.37% |
| Herbs that clear the heat: Baihuasheshecao, Banzhilian, Shengdihuang, Zhizi, Huangqin, Qinghao | 19.26% | Herbs that astringe: Wuweizi, Shanzhuyu | 1.01% |
| Herbs that invigorate blood and dissolve stasis: Ezhu, Danshen, Yujin, Tubiechong | 13.67% | Herbs that counteract toxins, kill parasites and relieve itching: Fengfang | 0.68% |
| Herbs that promote urination and percolate dampness: Fuling, Yiyiren, Yinchen, Cheqianzi, Yumixu | 12.04% | Herbs that warm the interior: Wuyao | 0.54% |
| Herbs that rectify qi: Zhiqiao, Chenpi | 8.39% | Herbs that expel wind and damp: Sangjisheng, Qinjiao | 0.46% |
| Herbs that release the exterior: Chaihu, Guizhi | 4.14% | Herbs that calm the mind: Suanzaoren, Longgu | 0.42% |
| Herbs that promote digestion: Jineijin | 3.18% | Herbs that calm the liver and extinguish wind: Muli, Wugong | 0.25% |
| Herbs that relieve cough, dissolve phlegm and calm panting: Banxia, Tinglizi, Walengzi | 2.94% | Herbs that open the orifices: Shexiang | 0.11% |
| Herbs that stanch bleeding: Sanqi, Xianhecao, Baimaogen | 1.91% | Herbs that expel parasites: Binglang | 0.08% |
| Herbs that transform dampness: Houpo | 1.86% | Herbs that induce vomit: Changshan | 0.02% |

**Table 2 The most frequently prescribed Herbal medicines used in the treatment of patients with hepatocellular carcinoma**

|  |  |  |  |
| --- | --- | --- | --- |
| Herb name | Relative frequency | Herb name | Relative frequency |
| Poria (Fuling) | 5.20% | Radix Angelicae Sinensis (Danggui) | 2.35% |
| Rhizoma Atractylodis Macrocephalae (Baizhu) | 5.20% | Carapax Trionycis (Biejia) | 2.22% |
| Radix Astragali Mongolici (Huangqi) | 4.07% | Radix Bupleuri Chinensis (Chaihu) | 3.66% |
| Herba Hedyotidis (Baihuasheshecao) | 3.75% | Radix Codonopsis (Dangshen) | 3.26% |
| Radix Glycyrrhizae (Gancao) | 3.71% | Radix Paeoniae Alba (Baishao) | 3.03% |

**Table 3 Descending frequency of Herbal medicine combinations used in the treatment of patients with hepatocellular carcinoma**

|  |  |
| --- | --- |
| Precedence | Herbal medicine combinations |
| 1 | Rhizoma Atractylodis Macrocephalae (Baizhu) and Poria (Fuling) |
| 2 | Radix Astragali Mongolici (Huangqi) and Rhizoma Atractylodis Macrocephalae Baizhu) |
| 3 | Radix Astragali Mongolici (Huangqi) and Radix Codonopsis (Dangshen) |
| 4 | Radix Astragali Mongolici (Huangqi) andRadix Angelicae Sinensis (Danggui) |
| 5 | Radix Astragali Mongolici (Huangqi) and Poria (Fuling) |
| 6 | Rhizoma Atractylodis Macrocephalae (Baizhu) and Radix Curcumae Wenyujin (Yujin) |
| 7 | Rhizoma Atractylodis Macrocephalae (Baizhu) andRadix Bupleuri Chinensis (Chaihu) |
| 8 | Rhizoma Atractylodis Macrocephalae (Baizhu) and Radix Glycyrrhizae (Gancao) |
| 9 | Rhizoma Atractylodis Macrocephalae (Baizhu) and Pericarpium Citri Reticulatae (Chenpi) |
| 10 | Rhizoma Atractylodis Macrocephalae (Baizhu) and Radix Codonopsis (Dangshen) |

**Table 4 Herbal medicines and the frequency of their use in treating symptoms and signs associated with hepatocellular carcinoma**

|  |  |
| --- | --- |
| Symptoms and signs | Herb and frequency of use (*n*) |
| Anorexia | Endothelium Coreneum Gigeriae Galli (Jineijin) (18), Fructus Hordei Germinatus (Maiya) (12), Fructus Amomi (Sharen) (9), stir-baking Fructus Hordei Germinatus et Massa Fer-mentata Medicinalis (Jiaosanxian) (7), Fructus Setariae Germinatus (Guya) (6), Massa Medicata Fermentata (Shenqu) (5) and Fructus Crataegi Pinnatifidae (Shanzha) (5) |
| Fatigue | Radix Astragali Mongolici (Huangqi) (23) and Radix Codonopsis (Dangshen) (14) |
| Discomfort | Rhizoma Corydalis Yanhusuo (Yanhusuo) (15), Fructus Toosendan (Chuanlianzi) (13), Radix Curcumae Wenyujin (Yujin) (10), Olibanum (Ruxiang) (9), Myrrha (Moyao) (7), Fructus Citri Sarcodactylis (Foshou) (7), Radix Aucklandiae (Muxiang) (5) andRhizoma Cyperi (Xiangfu) (5) |
| Ascites | Pericarpium Arecae (Dafupi) (30), Polyporus (Zhuling) (22), Poria (Fuling) (18), Rhizoma Alismatis (Zexie) (13), Semen Plantaginis (Cheqianzi) (8) and Cortex Magnoliae Officinalis (Houpo) (5) |
| Jaundice | Herba Artemisiae Capillaris (Yinchen) (37), Rhizoma Polygoni Cuspidati (Huzhang) (13), Radix et Rhizoma Rhei Palmati (Dahuang) (11), Herba Hyperici Japonici (Tianjihuang) (8), Fructus Gradeniae (Zhizi) (8), Herba Lysimachiae(Jinqiancao) (7), Radix Paeoniae Rubra (Chishao) (6) and Radix Scutellariae Baicalensis (Huangqin) (6) |
| Abdominal distention | Fructus Aurantii Submaturus (Zhiqiao) (11), Cortex Magnoliae Officinalis (Houpo) (8), Semen Raphani Sativi (Laifuzi) (7), Pericarpium Citri Reticulatae Viride (Qingpi) (6), Radix Aucklandiae (Muxiang) (6), Fructus Amomi (Sharen) (5) and Fructus Aurantii Immaturus (Zhishi) (5) |
| Nausea and vomiting | Caulis Bambusae in Taeniam (Zhuru) (27), Rhizoma Pinelliae (Banxia) (19), Flos Inulae (Xuanfuhua) (17), Fructus Amomi (Sharen) (10), Ochra Haematitum (Daizheshi) (7) and Pericarpium Citri Reticulatae (Jupi) (6) |
| Fever | Gypsum Fibrosum (Shigao) (9), Cortex Moutan Radicis (Mudanpi) (8), Radix Bupleuri Chinensis(Chaihu) (8), Herba Artemisiae Annuae (Qinghao) (6), Rhizoma Anemarrhenae (Zhimu) (6) and Fructus Gradeniae (Zhizi) (6) |
| Diarrhea | Poria (Fuling) (7), Rhizoma Alismatis (Zexie) (7), Semen Euryales (Qianshi) (6) and Fructus Schisandrae Chinensis (Wuweizi) (5) |
| Constipation | Radix et Rhizoma Rhei Palmati (Dahuang) (12), Fructus et Semen Trichosanthis Kirilowii (Gualou) (6), Semen Pruni Japonicae (Yuliren) (5) and Fructus Cannabis(Huomaren) (5) |