

Review

## Role of Huaier Extract as a Promising Anticancer Drug

Qiang Huo and Qifeng Yang\*

*Department of Breast Surgery, Qilu Hospital, Shandong University School of Medicine, West Wenhua Road No. 107, Ji'nan, Shandong 250012, P. R. China*

**Huaier, which is also called *Trametes robiniophila murr*, has been applied in cancer complementary therapy in mainland China. Many experimental and clinical studies have been conducted to confirm anticancer effect of Huaier extract. Huaier extract could inhibit tumor growth, induce apoptosis and reverse drug-resistance of tumor cells, and performs immunomodulatory and anti-angiogenic functions. Huaier granule, product of Huaier extract, is widely used in the treatment of leukemia, osteosarcoma, malignant lymphoma, breast cancer, lung cancer, rectal cancer, liver cancer, gastric cancer, colon cancer, pancreatic adenocarcinoma and so forth clinically. Multicenter clinical trials are necessary to confirm the clinical uses of Huaier extract for cancer treatment.**

*Key Words:* Huaier, apoptosis, metastasis, angiogenesis

### Introduction

Cancer has already become the leading cause of death worldwide. In 2008, there are 7.6 million cancer deaths (around 13% of all deaths) worldwide, and about 70% happened in low- and middle-income countries. Lung (1.37 million deaths), stomach (736 000 deaths), liver (695 000 deaths), colorectal (608 000 deaths), breast cancer (458 000 deaths) and cervical cancer (275 000 deaths) result in the most cancer deaths each year, while the most frequent types of cancer differ between men and women (44). Among women, breast cancer is the leading cause of cancer death, as well as the most frequently diagnosed malignant tumor. In economically developing countries, cervical cancer is the most cancer death reason previously, while now is breast cancer. In male, lung cancer is the leading cancer, and in developing countries it occupies the similar mortality burden to cervical cancer. Liver cancer in male is the second most frequent cause of cancer death, though it is diagnosed the fifth most frequent cancer worldwide (24).

There are multiple strategies for cancer treatment conventionally, including surgery, radiotherapy, chemotherapy, hormonotherapy, transplantation and

some complementary therapies. However, current anticancer treatments are not able to completely prevent the recurrence and metastasis for cancer patients, therefore new treatment strategies and new drugs are urgently needed for these patients. As for the complementary therapies, traditional Chinese medicine (TCM) has become more and more popular because of its properties and effects for cancer treatment (37).

Traditional Chinese medicine (TCM) has a long history of three millennia and contains a variety of complex compounds of natural origin. The Chinese patent drugs, products of traditional Chinese medicine, develop quickly and have been widely used in clinical anticancer treatment in mainland China. Nowadays tumor has been defined as chronic disease, and long-term complementary treatments are nearly inevitable. Chinese patent drugs are normally much cheaper and easy to use, compared with the conventional antitumor western medicine, which contributes to the popularity of TCM to some extent. Moreover, traditional Chinese medicine emphasizes on adjusting human body functions, enhancing body immunity then activating anti-cancer ability, thus improve the quality of life and prevent tumor metastasis and recurrence after operation, radiotherapy and chemotherapy (33, 64).

Traditional Chinese anti-neoplasms herbs have been widely studied worldwide. For example, Wogonin, derived from the traditional Chinese medicine Huang-Qin (*Scutellaria baicalensis* Georgi), was investigated and showed anticancer effects in human breast cancer (7), human hematopoietic malignancies (1, 28), as well as many other cancers (30). Ginseng was proved to improve the quality of life in breast cancer patients (8), liver cancer and many other gynecological neoplasms (27). Docetaxel could be useful in the treatment of advanced esophagogastric cancer (15), breast cancer (2) and ovarian cancer (48). Huaier (*Trametes robiniophila murr*) is an officinal fungi in China and has been used for approximately 1600 years (32), many experimental and clinical studies

Corresponding author: Dr. Qifeng Yang, Department of Breast Surgery, Qilu Hospital, Shandong University School of Medicine, West Wenhua Road No. 107, Ji'nan, Shandong 250012, P. R. China. Tel.: +86-531-82169268, E-mail: qifengy@gmail.com

Received: March 19, 2012; Revised: May 2, 2012; Accepted: May 7, 2012.

©2012 by The Society of Adaptive Science in Taiwan and Airiti Press Inc. ISSN : 2076-944X. <http://www.sast.org.tw>

**Table 1. The chemical composition of proteoglycan extracted from Huaier**

A.A.	Composition of Amino Acid		Composition of Polysaccharide		
	percent	A.A.	percent	monosaccharide	molar ratio
Asp	1.418	Met	0.120	L-fucose	0.51
Thr	0.731	Ile	0.398	L-arabinose	1.15
Ser	0.626	Leu	0.569	D-xylose	1.48
Glu	3.525	Tyr	0.249	D-mannos	1.39
Pro	0.740	Phe	0.347	D-galactos	1
Gly	1.073	Lys	0.689	D-glucose	3.24
Ala	0.6624	His	0.267		
Cys	0.160	Try	0.097		
Val	0.652	Arg	0.645		

have been conducted to confirm anticancer effect of Huaier extract.

### Huaier and Its Main Components

The effective ingredient of Huaier extract was proteoglycan, which consists of 41.53% polysaccharides, 12.93% amino acids and 8.72% water (19, 20) (Table 1). The proteoglycan is the most effective anticancer element among all of the isolated ingredients of Huaier extract, which was confirmed on breast cancer MCF-7, liver cancer H22, lung cancer Lewis and sarcoma murine S180 cells (unpublished data). However, the inhibitory effect of proteoglycan was less effective than the Huaier extract (19, 20), indicating that the anticancer activity of Huaier extract is associated with the synergistic or additive effect of these fractions. Here we focused on Huaier extract but not the main ingredient, since the components in herbs probably works together, though the ingredient is important for research as well.

Experimental and clinical studies have revealed various anticancer activities of Huaier extract including apoptotic induction, antiangiogenesis, anti-metastasis, drug resistance reversal and systemic immune activation (25, 32).

### Apoptotic Induction

Apoptosis induced by Huaier extract has been studied in human breast cancer cells (59, 61), pancreatic adenocarcinoma cells (68), ovarian cells (54), hepatocellular carcinoma cells (38, 53), gastric carcinoma cells (51), leukemia cells (47) and so forth. Meanwhile the G<sub>0</sub>/G<sub>1</sub> phase cell-cycle arrest induced by Huaier extract was widely observed (47, 54, 61, 68). We have confirmed that Huaier extract arrests the cell cycle at the G<sub>0</sub>/G<sub>1</sub> phase and induces apoptosis through p53 accumulation and activation in ER-positive MCF-7 breast cancer cells, which express wild-type p53,

leading mitochondrial-mediated apoptosis (61). However, in ER-negative MDA-MB-231 breast cancer cells (mutant-type p53), the p53 expression does not increase, and Huaier cannot induce G<sub>0</sub>/G<sub>1</sub> phase cell-cycle arrest, probably because the p53 in this cell line is in mutant form and dysfunctional (61). Meanwhile, we found that Huaier extract inhibits cell viability and mobility in both ER-positive and ER-negative cell lines (61). Ren *et al.* reported that after the treatment of Huaier extract, the apoptosis of Hep-G2 cells, a human hepatocellular carcinoma (HCC) cell line, is enhanced in a concentration- and time-dependent manner (38). Their study presents that the expressions of p53 and Bcl-2 are significantly decreased and Bax expression is increased after the treatment of Huaier, suggesting that Huaier extract can induce apoptosis of tumor cells by decreasing the p53 and Bcl-2 expressions and enhancing the Bax expression (38). Xu *et al.* also have reported that Huaier can protect liver from chemical injury and furthermore HCC development, possibly associated with the down-regulation of p53 (53).

Another important element, Caspase-3, plays a central role in the execution-phase of cell apoptosis, and Huaier-induced activation of caspase-3 in cancer cells has been observed (61, 68). Wu and his colleagues (51) found that Huaier extract inhibits the expression of surviving mRNA in human gastric carcinoma cells in a concentration-dependent manner, and may result in the up-regulation of caspase-3, since survivin can inhibit the activity of caspase-3 in direct and indirect ways (39, 60).

### Antiangiogenesis and Inhibition of Invasion and Metastasis

Cancer angiogenesis plays an important role in the development of cancer, and angiogenesis inhibition is a promising strategy for the treatment of cancer (14). Much preclinical evidence indicates that com-

binning antiangiogenic agents with cytotoxic agents results in additive or even synergistic antitumor effects (16). Several studies have reported that Huaier extract can inhibit angiogenesis both *in vitro* and *in vivo*. Xu *et al.* found (52) that Huaier extract significantly inhibits the angiogenic properties, including the proliferation and differentiation, in human umbilical vein endothelial cells (HUVEC). Chen *et al.* (4) showed that Huaier apparently reduces the proliferative ability, inhibits motility, adherence ability, and the formation of blood vessels. We and others have revealed that Huaier extract can inhibit the mobility and invasion of cancer cells (61, 63) *in vitro*. Zhang *et al.* revealed that Huaier extract PT-S can regulate the mRNA expression of some angiogenic-related genes in human high-metastatic large cell lung cancer cells, including the upregulation of  $\beta$ -catenin, E-cadherin, TIMP-1, endostatin and MMP-2, and the downregulation of VEGF and CD44V6 (63). These results indicate that Huaier extract may suppress the invasion and metastasis of cancer cell through inhibiting the expression of cell adhesion molecules (CAM) (14).

*In vivo* study has showed that combination treatment with Huaier extract significantly decreases the microvessel density (MVD) and VEGF expression in HCC tumor tissues (38), indicating that Huaier can inhibit the VEGF expression and tumor angiogenesis. In tumor-bearing HCC model (38) and breast cancer model (59), average tumor volume and growth rate of the implanted tumor are significantly decreased, while the necrosis rate increases significantly after Huaier treatment. These results suggest that Huaier can suppress the tumor growth and stimulate the tumor necrosis, which is highly related to the antiangiogenesis properties and apoptosis induction of Huaier extract on tumor cells.

### Drug Resistance Reversal

Drug resistance is one of the main obstacles to successful cancer therapy, and is often associated with multidrug resistance (MDR). Intrinsic or acquired resistance to commonly used therapeutic agents is a major challenge in the treatment of cancer patients, since some cells in cancerous tumors may develop resistance to the drugs used in chemotherapy (21). Many mechanisms are involved in this process, including increased efflux of drug (as by permeability glycoprotein), enzymatic deactivation, decreased permeability, altered binding-sites and alternate metabolic pathways. One of the most studied mechanisms is the up-regulation of multidrug resistance gene-1 (MDR-1) and its product permeability glycoprotein (P-gp), since efflux is a significant contributor for the drug resistance in cancer cells, and cancer

cells often acquire the drug resistance due to up-regulation as observed (17).

It is reported that Huaier extract can increase the sensitivity of cancer cells to chemotherapy drugs. Huang *et al.* (22) found that Huaier extract reverses the cisplatin resistance, and increases cisplatin sensitivity in the chemotherapy of human adenocarcinoma cell A<sub>549</sub><sup>DDP</sup>. Chen *et al.* (6) revealed that Huaier extract dramatically augments the sensitivity of both human hepatic cancer cells to TRAIL (tumor necrosis factor related apoptosis-inducing ligand), but only shows slight cytotoxicity on human hepatocyte strain. Several studies have been made to explore the mechanisms of drug resistance reversal of Huaier extract on tumor cells (54, 62). Zhang *et al.* (62) demonstrated that Huaier extract can increase the sensitivity of human gynecologic cancer cells to chemotherapy drug since it lowers the expression of the drug-resistant gene MDR-1 and then reverses the drug resistance. Xu *et al.* (54) showed that Huaier extract can reverse the tamoxifen-resistance of gynecologic cancer cells *in vitro*, and the mechanism may relate to the down-regulation of Phospho-P44/42 (ERK1/2) in mitogen-activated protein kinase (MAPK) pathway, since the activation of MAPK pathway and its downstream element AP-1 influences the expression of P-gp (11, 18, 49).

### Systemic Immune Activation

Another advantage of Huaier as an anticancer drug is that, it can improve and activate systemic immunity. Normally conventional anticancer therapies rely on killing dividing cells or block cell division, and these therapies have severe effects on normal proliferating cells, so that the treatment causes significant morbidity. Immune responses to cancers may be specific for tumor antigens and will not damage most normal cells, thus immunotherapy has the potential as a promising strategy for cancer treatment (42). The immunity to tumor includes cell-mediated immunity and humoral immunity, and the former plays more important roles than the latter. Immune cells that are capable of killing tumor cells consist of cytotoxic T lymphocytes, natural killer cells, and activated macrophages (3).

NK cells are considered as a major component of the anticancer immune response and are involved in regulating cancer progression and metastases in animal models (13, 43). Studies have reported that Huaier granule can enhance NK cell activity in gastric cancer patients undergoing postoperative concurrent radiochemotherapy (25) and breast cancer patients received Huaier combined chemotherapy (10). It was noted that CD4<sup>+</sup>/CD8<sup>+</sup> T cells are significantly increased in Huaier groups than control groups, and the

changes may be related to the enhancement of immunity in cancer patients (10, 25). It is widely known that CD4<sup>+</sup> T cells are divided into two subgroups, Th1 and Th2. Th1 cells secrete IFN- $\gamma$ , IL-12, TNF- $\beta$  and others, mediating cell-mediated immunity and anti-tumor activities. Th2 cells can secrete IL-4, IL-5, IL-6, IL-9, IL-10 and IL-13, mediating humoral immunity and immune tolerance. The antitumor effect of CD4<sup>+</sup> T cells mainly relies on some cytokines such as IFN- $\gamma$ , which are secreted by Th1 cells, and the Th1/Th2 balance is quite important for normal intrinsic antitumor activities (12, 40). You *et al.* (57) found that Huaier extract PS-T improves the IFN- $\gamma$  and Th1 cell levels meanwhile decreases the IL-4 and Th2 cell levels, compared to the control group in the patients with non-small cell lung cancer. Wang *et al.* (46) showed that Huaier extract promotes the secretion of Th1-type cytokines IL-2, IL-4, IL-10 and IFN- $\gamma$ , in breast cancer patients. Huaier extract PS-T increases the number of IL-2R<sup>+</sup> cells in liver, strengthens cell-mediated immunity and restrains cancer effectively (35). Another study also revealed that Huaier extract contributes to the Th1/Th2 shift in primary hepatic cancer (PHC) patients after surgical resection (45). All of these studies demonstrate that Huaier extract displays positive anticancer immunomodulatory effect by improving the expression levels of Th1-type cytokines. The results suggest that Huaier extract is hopeful to be a comprehensive therapy to improve the anticancer immunological function in cancer patients.

### Clinical Practice

Huaier granule (trade name: Jinke), the product of Huaier extract, has been widely used in clinic in mainland China and proved to be effective in improving the prognosis and quality of life of patients with various human cancers.

#### *For Lung Cancer Treatment*

Research have showed that Jinke can significantly improve the quality of life, prolong the life time in elderly patients with advanced non-small cell lung cancer (34), and enhance the immunity in patients during chemotherapy (56) or after surgery (66) as an adjuvant.

#### *For Breast Cancer Treatment*

In a cohort of breast cancer patients before operation, Chen *et al.* showed that Huaier granule combined with chemotherapy significantly improves the remission rate in patients with breast cancer compared to control group with chemotherapy alone (5). After

operation, Huaier granule has also been demonstrated to significantly improve the quality of life and prolong the life time in patients with breast cancer (50, 67).

#### *For Liver Cancer Treatment*

Jiang *et al.* reported that Huaier treatment works well in patients with intermediate and late primary liver cancer, and may demonstrate more clinical value in liver cancer patients with a history of hepatitis B (26). Huaier granule can increase the 2-year tumor-free survival rate, restrain the recurrence and metastasis of hepatocellular carcinoma (HCC), and meanwhile does not increase the incidence of immune rejection, in postoperative patients with liver transplantation, suggesting that Huaier treatment is safe and effective for HCC patients with liver transplantation (23, 36).

#### *For Gastric Cancer Treatment*

As an effective adjuvant during the postoperative chemotherapy, Huaier granule improves the chemotherapy endurance, enhances the immunity and prolongs the life time in patients with gastric cancer, (25, 55). Tang *et al.* also found that Huaier Granule obviously relieves the symptoms and improves the quality of life in elderly patients with advanced gastric cancer (41).

#### *For Other Cancer Treatment*

Zhao *et al.* have reported that Huaier shows good efficacy on re-chemotherapy in recurrent non-Hodgkin's lymphoma (NHL) (65). Studies investigated the impact of Huaier granule on several thoracic malignancies including esophageal carcinoma, cardiac carcinoma and adenocarcinoma, and the results revealed that Huaier granule can promote apoptosis of cancer cells (31) and modulate the immunity in these patients (66). Huaier granule significantly enhances the immunity, improves the hematopoietic function and reduces the toxicity when combined with chemotherapy in postoperative patients with colorectal cancer (58).

### Discussion

Traditional Chinese medicine (TCM) has a history of thousands of years, and some Chinese Herb showed favorable anticancer activities with high efficiency and low toxicity (9, 29). Huaier (*Trametes robiniophila murr*) belongs to officinal fungi in China for 1600 years, which is of natural origin. The anticancer properties of Huaier extract have been investigated and applied in complementary therapy for decades (32). Preliminarily experimental studies

indicate that Huaier extract shows effective anticancer activities, including apoptotic induction, antiangiogenesis, anti-metastasis, drug resistance reversal and systemic immune activation (25, 32). Clinical practice also confirms that Huaier treatment is effective and safe for various cancers (32), and the adaptive changes such as altered immunity are also observed after Huaier administration as mentioned above. Traditional Chinese medicine (TCM) is an important player in adaptive medicine, and we believe that Huaier granule is a promising antitumor TCM that contributes to the integrated control of body functions, and will work as an effective adjuvant in complementary anticancer therapy. Intensive studies are expected to investigate the potential active constituents and the anticancer mechanism of Huaier extract, and multicenter studies are necessary to fully explore the clinical value of Huaier treatment for human cancer.

### Conflicts of Interest

The authors declared that no competing interests exist.

### Acknowledgments

Prof. Yang is supported by Program for New Century Excellent Talents in University, Key Project of Chinese Ministry of Education (No. 108080), National Natural Science Foundation of China (No.81072150; No.81172529).

### References

- Baumann, S., Fas, S.C., Giaisi, M., Muller, W.W., Merling, A., Gulow, K., Edler, L., Krammer, P.H. and Li-Weber, M. Wogonin preferentially kills malignant lymphocytes and suppresses T-cell tumor growth by inducing PLCgamma1- and Ca<sup>2+</sup>-dependent apoptosis. *Blood* 111: 2354-2363, 2008.
- Bergh, J., Mariani, G., Cardoso, F., Liljegren, A., Awada, A., Viganò, L., Huang, X., Verkh, L., Kern, K.A., Giorgetti, C. and Gianni, L. Clinical and pharmacokinetic study of sunitinib and docetaxel in women with advanced breast cancer. *Breast*, 2012. (In Press)
- Bookman, M.A. Biological therapy of ovarian cancer: current directions. *Semin. Oncol.* 25: 381-396, 1998.
- Chen, D., Chen, X. and Zhang, W. Experimental research of the Fungi of Huaier in treating liver cancer. *Chinese J. Gen. Surg.* 13: 578-582, 2004.
- Chen, Q., Lai, X., Situ, H. and Liu, P. Clinical effect of Huaier Granule with combination chemotherapy preoperation in breast cancer. *China Cancer* 13: 330-331, 2004.
- Chen, X., He, S., Zhao, X., Huang, Z. and Li, C. Chinese medicine Extractum trametes robiniophila murr augment tumor necrosis factor related apoptosis-inducing ligand induced apoptosis in human hepatic cancer cell lines. *Chinese J. Surg.* 43: 1524-1527, 2005.
- Chung, H., Jung, Y.M., Shin, D.H., Lee, J.Y., Oh, M.Y., Kim, H.J., Jang, K.S., Jeon, S.J., Son, K.H. and Kong, G. Anticancer effects of wogonin in both estrogen receptor-positive and -negative human breast cancer cell lines *in vitro* and in nude mice xenografts. *Int. J. Cancer* 122: 816-822, 2008.
- Cui, Y., Shu, X.O., Gao, Y.T., Cai, H., Tao, M.H. and Zheng, W. Association of ginseng use with survival and quality of life among breast cancer patients. *Am. J. Epidemiol.* 163: 645-653, 2006.
- da Rocha, A.B., Lopes, R.M. and Schwartzmann, G. Natural products in anticancer therapy. *Curr. Opin. Pharmacol.* 1: 364-369, 2001.
- Dai, Y. and Cun, Y. Effect of Huaier Granule combined with chemotherapy on the cellular immune function in breast cancer patients. *Modern Oncol.* 15: 1438-1439, 2007.
- Daschner, P.J., Ciolino, H.P., Plouzek, C.A. and Yeh, G.C. Increased AP-1 activity in drug resistant human breast cancer MCF-7 cells. *Breast Cancer Res. Treat.* 53: 229-240, 1999.
- De Giovanni, C., Nanni, P. and Forni, G. The prospects for cancer gene therapy. *Int. J. Immunopharmacol.* 22: 1025-1032, 2000.
- Dewan, M.Z., Terunuma, H., Takada, M., Tanaka, Y., Abe, H., Sata, T., Toi, M. and Yamamoto, N. Role of natural killer cells in hormone-independent rapid tumor formation and spontaneous metastasis of breast cancer cells *in vivo*. *Breast Cancer Res. Treat.* 104: 267-275, 2007.
- Ferrara, N. and Kerbel, R.S. Angiogenesis as a therapeutic target. *Nature* 438: 967-974, 2005.
- Font, A., Salazar, R., Maurel, J., Taron, M., Ramirez, J.L., Tabernero, J., Gallego, R., Casado, E., Manzano, J.L., Carcereny, E., Guix, M., Fernandez-Llamazares, J. and Rosell, R. Cisplatin plus weekly CPT-11/docetaxel in advanced esophagogastric cancer: a phase I study with pharmacogenetic assessment of XPD, XRCC3 and UGT1A1 polymorphisms. *Cancer Chemother. Pharmacol.* 62: 1075-1083, 2008.
- Gasparini, G., Longo, R., Fanelli, M. and Teicher, B.A. Combination of antiangiogenic therapy with other anticancer therapies: results, challenges, and open questions. *J. Clin. Oncol.* 23: 1295-1311, 2005.
- Gottesman, M.M., Fojo, T. and Bates, S.E. Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat. Rev. Cancer* 2: 48-58, 2002.
- Guo, X., Ma, N., Wang, J., Song, J., Bu, X., Cheng, Y., Sun, K., Xiong, H., Jiang, G., Zhang, B., Wu, M. and Wei, L. Increased p38-MAPK is responsible for chemotherapy resistance in human gastric cancer cells. *B.M.C. Cancer* 8: 375, 2008.
- Guo, Y., Cheng, P., Chen, Y., Zhou, X., Yu, P., Li, Y. and Zhuang, Y. Studies on the constituents of polysaccharide from the hyphae of *Trametes Robiniophila*(II)—identification of polysaccharide from the hyphae of *Trametes Robiniophila* and determination of its molar ratio. *J. Chinese Pharm. U.* 23: 155-157, 1992.
- Guo, Y., Cheng, P., Chen, Y., Zhou, X., Yu, H., Li, Y. and Zhuang, Y. Isolation and analysis of the polysaccharide of Huaier mycelium. *Chinese J. Biochem. Pharm.* 63: 56-59, 1993.
- Hait, W.N. and Yang, J.M. Clinical management of recurrent breast cancer: development of multidrug resistance (MDR) and strategies to circumvent it. *Semin. Oncol.* 32: S16-S21, 2005.
- Huang, T., Kong, Q., Lu, H. and Dai, G. Reversion of PS-T on cisplatin resistance of human lung adenocarcinoma cell line A549DDP *in vitro*. *China Pharmacist* 5: 517-521, 2002.
- Huang, W., Yan, L., Wu, H., Yang, J., Wang, W. and Xu, M. Retrospective cohort study on clinical value of Huaier Granule in postoperative patients with liver transplantation for hepatocellular carcinoma. *Chinese J. Bases Chinese General Surg.* 17: 547-551, 2010.
- Jemal, A., Bray, F., Melissa, M., Ferlay, J., Ward, E. and Forman, D. Global cancer statistics. *C.A. Cancer J. Clin.* 61: 69-90, 2011.
- Ji, D. and Mai, D. Effect of Huaier Granule on immunity and quality of life in patients with gastric cancer undergoing postoperative concurrent radiochemotherapy. *China Cancer* 19: 73-76, 2010.
- Jiang, M. and Zhou, D. "Huaier Granule" for intermediate and late primary liver cancer in 98 cases. *Shanghai J. Tradit. Chinese Med.* 38: 21-22, 2004.
- Kim, J.H., Park, C.Y. and Lee, S.J. Effects of sun ginseng on subjective quality of life in cancer patients: a double-blind, placebo-

- controlled pilot trial. *J. Clin. Pharm. Ther.* 31: 331-334, 2006.
28. Kumagai, T., Muller, C.I., Desmond, J.C., Imai, Y., Heber, D. and Koeffler, H.P. Scutellaria baicalensis, a herbal medicine: anti-proliferative and apoptotic activity against acute lymphocytic leukemia, lymphoma and myeloma cell lines. *Leuk. Res.* 31: 523-530, 2007.
  29. Lee, K.H. Anticancer drug design based on plant-derived natural products. *J. Biomed. Sci.* 6: 236-250, 1999.
  30. Li-Weber, M. New therapeutic aspects of flavones: the anticancer properties of Scutellaria and its main active constituents Wogonin, Baicalein and Baicalin. *Cancer Treat Rev.* 35: 57-68, 2009.
  31. Li, B., Li, Y., Wang, Q., Liu, J. and Wang, F. The impact of Huaier Granule on apoptosis and the immunity in patients with esophageal carcinoma. *China Cancer* 12: 752-753, 2003.
  32. Li, L., Ye, S., Wang, Y. and Tang, Z. Progress on experimental research and clinical application of trametes robiniophila. *China Cancer* 16: 110-113, 2007.
  33. Li, P. Application of traditional Chinese patent drugs in cancer treatment. *Chinese J. Oncol.* 33: 400, 2011.
  34. Liu, L., Li, Q., Gao, D. and Liu, C. Influence of Huaier Granule on quality of life in elderly advanced non-small cell lung cancer. *J. Oncol.* 12: 70-71, 2005.
  35. Lu, P., Chen, L. and Lu, Z. Effect of PS-T and IL-2 on PTEN and IL-2R positive cells in experimental hepatic carcinoma. *Modern J. Integ. Tradit. Chinese Western Med.* 13: 1982-1985, 2004.
  36. Mo, B., Yang, J., Yan, L., Xu, M. and Wang, W. Clinical study of Huaier Granule in postoperative patients with liver transplantation for hepatocellular carcinoma. *J. Sichuan Univ. (Med. Sci. Ed.)* 42: 739-741, 2011.
  37. Pu, C.Y., Lan, V.M., Lan, C.F. and Lang, H.C. The determinants of traditional Chinese medicine and acupuncture utilization for cancer patients with simultaneous conventional treatment. *Eur. J. Cancer Care (Engl.)* 17: 340-349, 2008.
  38. Ren, J., Zheng, C., Feng, G., Liang, H., Xia, X., Fang, J., Duan, X. and Zhao, H. Inhibitory effect of extract of fungi of Huaier on hepatocellular carcinoma cells. *J. Huazhong Univ. Sci. Technol. Med. Sci.* 29: 198-201, 2009.
  39. Sah, N.K., Khan, Z., Khan, G.J. and Bisen, P.S. Structural, functional and therapeutic biology of survivin. *Cancer Lett.* 244: 164-171, 2006.
  40. Seo, N. and Tokura, Y. Downregulation of innate and acquired antitumor immunity by bystander gammadelta and alphabeta T lymphocytes with Th2 or Tr1 cytokine profiles. *J. Interferon Cytokine Res.* 19: 555-561, 1999.
  41. Tang, Q., Zhan, X., Liu, J., Hu, G. and Hu, S. Effect of Huaier Granule in treatment for advanced gastric cancer in 47 elderly cases. *China Cancer* 15: 137-138, 2006.
  42. Topalian, S.L., Weiner, G.J. and Pardoll, D.M. Cancer immunotherapy comes of age. *J. Clin. Oncol.* 29: 4828-4836, 2011.
  43. Trinchieri, G. Biology of natural killer cells. *Adv. Immunol.* 47: 187-376, 1989.
  44. W.H.O. *Programmes and projects: Media centre: Fact sheet N°297 (February 2012)*. . 2012 [cited 2012 February 17]; Available from: <http://www.who.int/mediacentre/factsheets/fs297/en/>
  45. Wang, X., Yang, L., Qiu, F., Wu, L. and Lu, Y. The impact of Huaier Granule to Th1/Th2 shift on patients with primary hepatic cancer after surgical resection. *Chinese J. Mod. Drug Appl.* 2: 7-9, 2008.
  46. Wang, X., Zhang, C. and Zhang, J. Effect of Huaier extract on the PBMC-secreted cytokines in breast cancer patients. *Chinese J. Gen. Surg.* 26: 436-437, 2011.
  47. Wang, Y. and Wu, Z. Effects of extractum trametes robiniophila murr on K562 cells *in vitro*. *J. China Pediatr. Blood Cancer* 11: 104-107, 2008.
  48. Watari, H., Hosaka, M., Mitamura, T., Moriwaki, M., Ohba, Y., Todo, Y., Takeda, M., Ebina, Y. and Sakuragi, N. Weekly paclitaxel/5-fluorouracil followed by platinum retreatment for patients with recurrent ovarian cancer: a single institution experience. *Eur. J. Gynaecol. Oncol.* 29: 573-577, 2008.
  49. Whitmarsh, A.J. and Davis, R.J. Transcription factor AP-1 regulation by mitogen-activated protein kinase signal transduction pathways. *J. Mol. Med. (Berl.)* 74: 589-607, 1996.
  50. Wu, Y. The effect of Huaier Granule in the treatment for 24 cases of breast cancer stage IV. *Jiangxi J. Tradit. Chinese Med.* 40: 50-51, 2009.
  51. Wu, Z., Jiang, J., Cao, M., Chen, T., Zhang, X. and Wu, F. Experimental study on apoptosis of human gastric carcinoma SGC-7901 cells induced by Trametes robiniophila. *J. Shanghai Jiaotong Univ. (Med. Sci.)* 29: 370-373, 2009.
  52. Xu, G., Jia, W., Ma, J. and Yu, J. Experimental study of extract of funji of Huaier on angiogenesis *in vitro*. *Chin. Pharmacol. Bull.* 19: 1410-1412, 2003.
  53. Xu, X., Wei, Q., Wang, K., Ling, Q., Xie, H., Zhou, L. and Zheng, S. Anticancer effects of Huaier are associated with down-regulation of P53. *Asian Pac. J. Cancer Prev.* 12: 2251-2254, 2011.
  54. Xue, D., Ling, L., Zhao, Y., Liu, X., Wang, S. and Cha, X. Experimental study on reversal of drug-resistance of human breast cancer cell line MCF-7 by Huaier fungi extract *in vitro*. *Chinese J. Exp. Surg.* 27: 1663-1665, 2010.
  55. Yao, J., Han, S., Zhu, G., Zhou, H. and Chen, Z. Effect of post-operative adjuvant chemotherapy combined with Huaier Granule for stage III gastric cancer. *China Cancer* 12: 606-608, 2003.
  56. Yao, Y., Ma, Z. and Zhao, Y. Clinical study on treatment with JinKe Granule combined chemotherapy for non-small cell lung cancer in 41 cases. *China Cancer* 10: 184-185, 2001.
  57. You, J., Hu, C., Gu, Q. and Yang, H. Th1/Th2 cells immunomodulatory effect of EGCG and PS-T on non-small cell lung cancer. *Chinese J. Lung Cancer* 12: 543-548, 2009.
  58. Yuan, M., Huang, G., Li, Z. and Ding, W. Effect of combined Huaier Granule and chemotherapy on immunity in patients with colorectal carcinoma postoperation. *China Cancer* 14: 487-488, 2005.
  59. Yuan, P., Huang, T.C., Tian, Y., Song, H., Li, Z. and Song, Q. Influence of JINKE on cells growth and apoptosis in nude mice breast cancer transplanted model. *China Cancer* 16: 348-350, 2007.
  60. Zaffaroni, N., Pennati, M. and Daidone, M.G. Survivin as a target for new anticancer interventions. *J. Cell. Mol. Med.* 9: 360-372, 2005.
  61. Zhang, N., Kong, X., Yan, S., Yuan, C. and Yang, Q. Huaier aqueous extract inhibits proliferation of breast cancer cells by inducing apoptosis. *Cancer Sci.* 101: 2375-2383, 2010.
  62. Zhang, Y., Zhang, G., Wang, J. and Zhang, Q. Function and clinical application of Huaier plaster in comprehensive therapy of breast cancer. *Chinese J. Clin. Oncol. Rehabil.* 11: 512-515, 2004.
  63. Zhang, Z., Fan, Y., Zhou, Q., Wang, Y., Ma, L., Chen, X., Zhu, W., Yang, X. and Zhao, Y. Effects of polysaccharid on expression of angiogenic-related genes in human high-metastatic large cell lung cancer cell line L9981. *Chinese J. Lung Cancer* 9: 137-142, 2006.
  64. Zhao, F. and Liu, P. Progress of study on action mechanisms of TCM in antitumor and preventing metastasis of tumor. *Chinese J. Integ. Tradit. Western Med.* 27: 178-181, 2007.
  65. Zhao, W. The effect of Jinke based combination chemotherapy in the treatment of non-Hodgkins lymphoma. *China Cancer* 8: 237-238, 1999.
  66. Zheng, M., Zhou, N., Liang, C., Liu, X., Wang, Y. and Deng, X. The impact of Trametes Robiniophila Murr granulated powder on postoperative immunity in patients with thoracic malignancies. *China Cancer* 12: 111-113, 2003.
  67. Zhong, S., Jiang, H., Liu, X., Liu, X. and Situ, H. The effect of Huaier Granule in the treatment for breast cancer stage IV. *China Cancer* 12: 754-755, 2003.
  68. Zhou, J., Li, D. and Kuang, Y. Experimental study of growth and metastasis inhibition induced by Jinke in human pancreatic adnocrinoma cell line Panc-1. *Suzhou Univ. J. Med. Sci.* 25, 2005.