

Effects of *Xuefu Zhuyu Tang* and Mitomycin C on Liver Tumors in Mice

Jyh-Sheng You, MD, PhD; Hui-Feng Huang¹ MD, PhD; Dou-Mong Hau², PhD

Background: Carcinogenesis, in traditional Chinese medicine, is defined as resulting from the accumulation of stagnant and toxic substances within the human body. *Xuefu zhuyu tang* (*XZT*) represents a group of herbs for 'destagnation'; and mitomycin C (MMC) is currently and widely used for cancer therapy. We investigated the combined effects of *XZT* and MMC on mice bearing liver tumors.

Methods: Mice bearing experimental liver tumors were divided into 4 groups, including tumor control, *XZT*-, MMC-, and combined-treatment groups. Several effects were observed in this study including survival rate, increase of life span, and mean survival time within 60 days after treatment. Survival rates and biosynthesis activities of tumor and liver cells were also evaluated.

Results: Oral administration of *XZT*, an intraperitoneal injection of MMC, and a combination of the two increased the mean survival time of tumor-bearing mice by 12.5, 14.1, and 17.2 days, respectively. These 3 treatments were cytotoxic to sarcoma-180-induced liver tumor cells. The synthesis rates of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and protein by tumor cells were all measurably inhibited by the combined treatment.

Conclusion: *XZT* combined with MMC may be an effective modality in cancer therapy. The detailed mechanisms of these combinations in human liver neoplasms use to be further studied.

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Key words: xuefu zhuyu tang, mitomycin C, experimental liver tumor.

Cancer was the second of the ten leading causes of death in Taiwan from 1972 to 1981, and since 1982, it has been the first.⁽¹⁾ In the past, we evaluated several kinds of combined therapies on malignant tumors, such as photodynamic therapy,^(2,3) chuling with mitomycin C (MMC),⁽⁴⁾ and ginseng with radiation therapy.⁽⁵⁾ However, the drugs we selected for testing were either chemicals or single herbs. Herein, we report on the use of a group of Chinese medicinal herbs (the so-called *xuefu zhuyu tang*,

XZT) combined with MMC on mice bearing liver tumors to estimate their therapeutic effects.

Carcinogenesis in traditional Chinese medicine is defined as the accumulation of stagnant and toxic substances within the human body.⁽⁶⁾ It has generally been treated with multidrug therapy under the collective name of 'destagnation'. The herbal medicines for destagnation are also effective on cardiovascular diseases^(7,8) and in treating various connective tissue diseases.^(9,10) *XZT* represents a group of plants used

From the Chang Gung University School of Traditional Chinese Medicine and Center for Traditional Chinese Medicine, Chang Gung Memorial Hospital, Taoyuan; ¹Chinese Medical Department, China Medical College, Taichung; ²Department of Life Sciences, National Tsing Hua University, Hsinchu.

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Address for reprints: Dr. Jyh-Sheng You, Chang Gung University School of Traditional Chinese Medicine, 259, Wen Hwa 1st Road, Gueishan Shiang, Taoyuan, Taiwan 333, R.O.C. Tel.: 886-3-3283016 ext. 5101; Fax: 886-3-3280097; E-mail: y0606@mail.cgu.edu.tw

in China for 'destagnation'. This group of plants was described in a book called Correction on Errors of Medical Works from the Chin Dynasty.

MMC is an alkylating antibiotic isolated from *Streptomyces caespitosus*. It is widely used in cancer therapies, especially for chemotherapy of gastric and pancreatic cancers.⁽¹¹⁾

In this study, we investigated the combined effects of XZT and MMC against transplanted liver tumors in mice.

METHODS

The herbs used in the current study were supplied in a dry form by the China Medical College Hospital, Taichung, Taiwan. Their identification was authenticated by experts in pharmacognosy.

Preparation of the XZT extract.

Each component of XZT is listed in Table 1.

Fifty grams of the ground material were added to 1000 ml of distilled water under reduced pressure for 6 hours at room temperature. The insoluble residue was further extracted with boiling water under 1 atm for 3 hours. The water-soluble part was

then concentrated to 150 ml by a vacuum pump, lyophilized, and stored as dry powder until use. The final yield of XZT powder was 32.4 g.

Chemicals

MMC was obtained from Sigma Chemical. Aliquots (2 mg) of MMC were placed with vials, dissolved in normal saline to provide a concentration of 0.37 mg/ml, and kept at 4°C in the dark. Eight grams of NaCl, 0.2 g KCl, 0.2 g KH₂PO₄, and 1.45 g Na₂HPO₄ · 12H₂O were dissolved in 1 L of ion-free water (phosphate-buffered solution). This solution was adjusted to pH 7.2 by the dropwise addition of 1 M HCl. Sodium pentobarbital at 0.25 g was dissolved in 15.5 ml normal saline and kept at 4°C. Trypsin and collagenase were purchased from Sigma Chemical for lysing fibrin. ³H-thymidine (20 Ci/mmol, NEN), ³H-uridine (28.9 Ci/mmol, NEN), and ³H-leucine (53 Ci/mmol, NEN) were added to the medium at a concentration of 50 (Ci/ml and refrigerated. Four grams of PPO (2,5-diphenyloxazole) and 0.5 g POPOP (phenyl-oxazol-phenyl-oxazole) were dissolved in 1 L of toluene (liquid scintillation counting fluid).

Mice and tumors

ICR male mice aged 6-8 weeks and weighing around 25 ± 2 g were obtained from the Animal Center of National Taiwan University Hospital. Mice were kept in an air-conditioned room. Mice were fed with rod lab chow from Fu Show Co. which consisted of protein (23%), fat (5%), fiber (15%), and water (11%). Water and food were supplied ad libitum. The tumor cells we used were sarcoma 180 cells provided by the Biochemical Institute of National Taiwan University and were grown as a monolayer stock culture in Dulbecco's modified Eagle's medium. Cells were incubated at 37°C in a humidified atmosphere composed of 95% air and 5% carbon dioxide. Tumor cells (1 × 10⁷) were implanted into the abdominal cavity of mice on a biweekly basis. Mice with tumors were killed through neck vertebrae dislocation. Ascitic fluid was removed, shaken, and diluted with 0.4% trypan blue. The surviving sarcoma-180 tumor cells were examined microscopically. Live sarcoma-180 tumor cells (1 × 10⁷) were then inoculated into the right lobe of the liver of normal male mice, under anesthesia with 0.1 ml sodium pentobarbital, at a concentration of

Table 1. Composition of the XZT Extract

Constituent herbs	Weight (g)
Radix Angelica Sinensis (Root of <i>Angelica sinensis</i> Oliv. Diels.)	6
Radix Rehmanniae (Root of <i>Rehmannia glutinosa</i> Libosch.)	6
Semen Persicae (Fruit of <i>Prunus persica</i> L. Batsch)	8
Flos Carthami (Flower of <i>Carthamus tinctorius</i> L.)	6
Rhizoma Ligustici Chuanxiong (Root of <i>Ligusticum chuanxiong</i> Hort.)	3
Radix Achyranthis Bidentatae (Root of <i>Achyranthes bidentata</i> BI.)	6
Fructus Aurantii (Fruit of <i>Citrus aurantium</i> L.)	4
Radix Paeoniae Rubra (Root of <i>Paeonia veitchii</i> Lynch)	4
Radix Bupleuri (Whole body of <i>Bupleurum chinense</i> DC.)	2
Radix Platycodi (Root of <i>Platycodon grandiflorum</i> Jacq.A.DC.)	3
Radix Glycyrrhizae (Root of <i>Glycyrrhiza uralensis</i> Fisch.)	2

0.25 g/15.5 ml. One day later, the mice were split into groups and treated.

Treatment

Eighty-six mice bearing experimental liver tumors were divided into 4 groups. Group A served as the tumor control, and no treatment was applied. Group B was given only 0.5 ml of the XZT extract (150 mg/ml) via a feeding tube through the mouth once a day for 10 consecutive days. Group C was given only 0.1 ml of MMC (0.37 mg/ml) intraperitoneal (i.p.) injections once a day on 4 occasions: on days 1, 4, 7, and 10 after tumor cell inoculation. Group D received the combined treatment of XZT and MMC, administered in the same manner and at the same doses as in groups B and C.

The therapeutic effect of each treatment was evaluated using the following criteria: body weight, mortality rate (MR), survival rate, increase in life span (ILS), and mean survival time (MST) within 60 days after treatment.

ILS = [(T-C)/C] × 100; where T is the mean survival time of treated mice, and C is the mean survival time of untreated mice.

$$\text{Survival rate} = \frac{\text{number of surviving mice}}{\text{total number of mice}} \text{ in each group} \times 100\%.$$

Effect of the drugs on the survival rate of tumor and liver cells.

Fifty mice bearing liver tumors were divided into 5 groups, with 10 mice per group. One group served as a tumor control group and received no treatment; 2 other groups received 0.5 ml of the XZT extract once a day for either 5 or 10 days, respectively; another group received 0.1 ml of MMC; and the other group received combined treatment with XZT and MMC. After treatment, the animals were sacrificed, and liver tissue and tumors were excised. Following excision, the liver tissue and tumors were washed with phosphate-buffered solution (PBS) at 4°C, dissected with crossed scalpels, and weighed. After being washed with PBS, the resulting fragments were disaggregated by gentle agitation for 30 min in an enzyme cocktail of trypsin (0.2%) and collagenase (0.05%). The resulting cell suspension was filtered through a polyester mesh (50-µm pore size) and centrifuged, and the cell pellet was resuspended in medium for sorting. Cell suspensions were rou-

tinely counted on a hemocytometer with trypan blue, enabling the tumor cell yield to be ascertained. The mean cell yield for tumors was 2.4×10^4 /g of tissue (SD, 1.1×10^4) and that for liver was 1.9×10^4 of tissue (SD, 8×10^3). The percentage of surviving tumor cells was determined from the relation:

$$\text{Percentage of surviving tumor cells} = (\text{counts of live tumor or liver cells} / \text{counts of total tumor or liver cells}) \times 100\%.$$

Effects of the drugs on protein, RNA, and DNA synthesis rates.

Aliquots of the aforementioned cells in single cell suspensions (3×10^6 cells in a 96-well microtiter plate in each group) were labeled by adding 200 µl ³H-thymidine (20 Ci/mmol), ³H-uridine (28.9 Ci/mmol), and ³H-leucine (53 Ci/mmol) and then were placed in an incubator. After 18 hours, cells were collected on filter paper disks. Each disk was placed in a counting vial, and 5 ml of scintillation mixture was added (0.47% diphenyloxazole (PPO) and 0.01% phenyl-oxazolyl-phenyl-oxazolyl-phenyl (POPOP) in 100% toluene). The sample was counted in a liquid scintillation counter (Nuclear-Chicago Mark 1).

The count per minute (CPM) was determined by the following formula:

$$\Delta \text{CPM of control (\%)} = \frac{\text{counts of treated tumor or liver cells}}{\text{counts of untreated tumor or liver cells}} \times 100\%$$

Data analysis

Data were expressed as the mean ± SEM. For statistical analysis of the data, group means were compared by one-way ANOVA, and Bonferroni's test was used to identify differences between groups. Statistical significance was defined as $p \leq 0.05$.

RESULTS

Body weight

The body weights of the mice in each group are listed in Table 2. The body weight of the untreated control group showed no significant change during 60 days. However, the body weight of the tumor control group increased quickly after inoculation with tumor cells compared with the other treated groups ($p < 0.05$). Such effects might have been due to tumor growth and ascites formation in the tumor control group.

Table 2. Effects of XZT and/or Mitomycin C on Body Weight (g) of Mice Bearing Liver Cancer Induced by Tumor Cells

Group	Treatment conditions	Dose	Time after beginning of treatment (day)				
			0	10	20	40	60
	Normal control		24.8±3.2 (20)	24.9 ±2.3 (20)	25.2 ± 3.0 (20)	24.7 ±2.5 (20)	25.0 ±2.3 (20)
A	Tumor control		25.2±3.8 (26)	30.6 ±5.6 (26)	41.8 ±10.2 (8)	#	#
B	XZT	10	25.2±3.3 (19)	26.8*±4.5 (15)	32.4*± 6.0 (11)	34.7 ±2.9 (5)	37.2 ±3.6 (5)
C	MMC	4	24.3±2.4 (26)	25.7*±2.0 (26)	32.0*± 5.5 (23)	30.4*±4.7 (6)	32.8*±2.9 (3)
D	MMC	4	21.7±2.1 (15)	22.1*±2.3 (12)	23.3+± 2.5 (8)	24.1+±2.3 (7)	24.8 ⁺ ±2.4 (5)
	+XZT	10					

Abbreviations: XZT, Xuefu zhuyu tang; MMC, mitomycin C.

The number in parentheses indicates the number of surviving mice; # is the number of mice which died.

Dose: times for treatment.

* and ⁺ $p \leq 0.05$ compared with all other groups.

Table 3. Therapeutic Effects of XZT and/or Mitomycin C on Mice Bearing Liver Cancer Induced by Tumor Cells

Group	Treatment conditions	Dose	No. of mice	MR ₆₀	MST ₆₀	ILS ₆₀
				(%)	(day)	(%)
A	Tumor control		26	100.0	20.1 ± 3.9	
B	XZT	10	19	71.4	32.6±20.0*	62.2
C	MMC	4	26	88.5	34.2±13.6*	70.1
D	MMC	4	15	66.6	37.3±20.9 ⁺	85.6
	+XZT	10				

Abbreviations: MR₆₀, mortality rate within 60 days after treatment; MST₆₀, mean survival time within 60 days after treatment; ILS₆₀, increase in life span within 60 days after treatment.

Dose: times for treatment.

* and ⁺ $p \leq 0.05$ compared with all other groups.

Therapeutic effects

The MR and MST of the tumor control group were 100% and 20.1 days, respectively. Meanwhile, the MR, MST, and ILS of the XZT-treated group were 71.4%, 32.6 days, and 62.2%, respectively. In the MMC-treated group, they were 88.5%, 34.2 days, and 70.1%, respectively. The best therapeutic effect was found in the group treated with a combination of XZT and MMC: the MR was 66.6%, MST was 37.3 days, and ILS was 85.6% (Table 3).

Effects of XZT and/or MMC on the survival rates of tumor and liver cells

Survival rates of tumor cells in the XZT groups treated for 5 and 10 days were 73.7% and 68.5%, respectively (200 and 400 mg). In the MMC-treated group, it was 66.8%. The most-marked inhibitory effect was found in the combined treatment group for which the survival rate of tumor cells was 63.7% (Table 4).

Table 4. Effects of XZT and/or MMC on the Survival Rate of Tumor Cells

Group	Treatment conditions	Dose	No. of mice	Tumor cell survival rate (%)
A	Tumor control		10	78.5±4.1
B	XZT	5	10	73.7±3.7*
C	XZT	10	10	68.5±3.9*
D	MMC	4	10	66.8±8.7*
E	MMC	4		
	+XZT	10	10	63.7±6.7 ⁺

Abbreviations and designations are the same as those in Table 2.

* and ⁺ $p \leq 0.05$ compared with all other groups.

The survival rates of liver cells in the XZT groups treated for 5 and 10 days were 81.5% and 80.1%, respectively (200 and 400 mg). They showed no significant differences compared with the tumor control group (82.1%). In the MMC-treated group it was 69.9%, and in the combined treatment group was 68.3% (Table 5).

Table 5. Effects of XZT and/or MMC on the Survival Rate of Liver Cells

Group	Treatment conditions		No. of mice	Liver cell survival rate (%)
		Dose		
A	Tumor control		10	82.1±6.2
B	XZT	5	10	81.5±7.4
C	XZT	10	10	80.1±8.3
D	MMC	4	10	69.9±8.1*
E	MMC +XZT	4	10	68.3±5.7*

Abbreviations and designations are the same as those in Table 2.

* $p \leq 0.05$ compared with the tumor control and XZT groups.

Effects of XZT and/or MMC on the synthesis of DNA, RNA, and protein by tumor and liver cells

Figure 1 shows that XZT (200 mg) inhibited the synthesis rates of RNA by 21%, DNA by 22%, and protein by 15% in tumor cells compared with the control group; while XZT (400 mg) inhibited synthesis of RNA by 41%, DNA by 51%, and protein by 32%. MMC inhibited the synthesis of RNA, DNA, and protein by 28%, 65%, and 41%, respectively. In the combined group, RNA synthesis was inhibited by

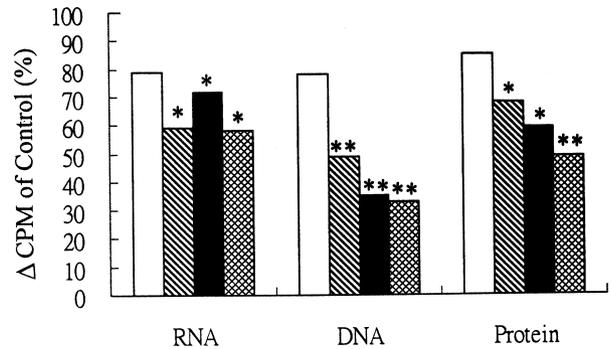


Fig. 1 Effects of XZT and/or MMC on the protein, RNA, and DNA synthesis rates of tumor cells. Mice bearing liver tumors, either treated or untreated, were excised. Tumor cell suspensions (3×10^6 cells) were labeled by adding 200 μ l (50 μ Ci/ml) 3 H-thymidine, 3 H-uridine, and 3 H-leucine. Cells were collected on filter paper disks, and scintillation mixture was added. Samples were counted in a liquid scintillation counter. Values are Δ CPM of the control (%). \square 200 mg XZT only, diagonal lines 400 mg XZT only, \blacksquare 0.148 mg MMC only, and cross-hatched 400 mg XZT plus 0.148 mg MMC. * $p \leq 0.05$, ** $p \leq 0.01$.

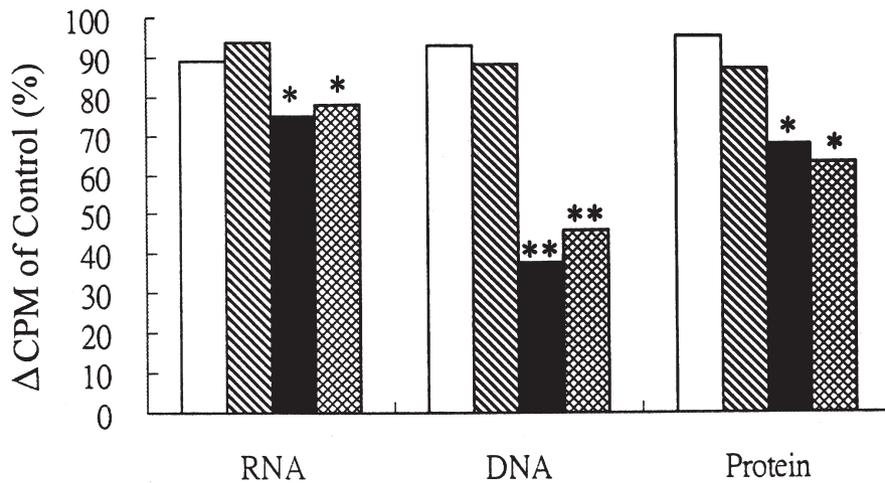


Fig. 2 Effects of XZT and/or MMC on the protein, RNA, and DNA synthesis rates of liver cells. Mice bearing liver tumors, either treated or untreated, were excised. Liver cell suspensions (3×10^6 cells) were labeled by adding 200 μ l 3 H-thymidine, 3 H-uridine, and 3 H-leucine (50 μ Ci/ml). Cells were collected on filter paper disks, and scintillation mixture was added. Samples were counted in a liquid scintillation counter.

Values are Δ CPM of the control (%). \square 200 mg XZT only; diagonal lines 400 mg XZT only; \blacksquare 0.148 mg MMC only; and cross-hatched 400 mg XZT plus 0.148 mg MMC. * $p \leq 0.05$, ** $p \leq 0.01$.

42%, DNA synthesis by 67%, and protein synthesis by 51%. Figure 2 shows that 200 mg *XZT* inhibited the synthesis rates of RNA by 11%, DNA by 7%, and protein by 5% in liver cells compared with the control group; while 400 mg *XZT* inhibited RNA by 6%, DNA by 12%, and protein by 13%. MMC inhibited RNA synthesis by 25%, DNA synthesis by 62%, and protein synthesis by 32%. The combined group inhibited RNA synthesis by 22%, DNA synthesis by 54%, and protein synthesis by 37%. Inhibition of the synthesis of RNA, DNA, and protein showed no significant differences from the MMC group.

DISCUSSION

The mode of action of *XZT* is believed to be mainly through the removal of blood stasis, a decrease in the microcirculation barrier, promotion of circulation in tissues and organs, and an increase oxygen-blood perfusion.⁽¹²⁾ It has been clinically applied for cases of amenorrhea and dysmenorrhea due to blood stasis. It is also applied in cases of chest contusion, rheumatic heart disease, and coronary heart diseases with chest pain which are attributed to retention of blood in the chest or obstruction of blood stasis with consequent stagnation of vital energy.^(13,14)

XZT markedly increased the mean survival time and life span of mice bearing experimental liver tumors as compared with the control group. It also showed toxicity to tumor cells and inhibition of synthesis rates of DNA, RNA, and protein as the dosage was gradually increased, indicating the antitumor activity of *XZT*. Its antitumor activity might be due to the synergism of some ingredients: *Angelica sinensis* and *Rehmanniae* nourish the blood and activate the immune system. *Persicae* and *Carthami* are known to have antitumor activity, to activate the blood circulation, and reduce blood stasis.⁽¹⁵⁾ However, the dosage and the quantitative analysis of active ingredients in *XZT* have not been clearly elucidated. Further study is needed to identify the active ingredients.

MMC has potent antitumor activity and has been used in the treatment of gastrointestinal cancer. It interferes with replication of DNA in cancer cells and inhibits division, thus leading to the death of cancer cells.^(16,17)

Our results showed that MMC killed the experimental liver tumor cells and liver cells mainly due to inhibition of the biosynthesis of DNA. This corresponds to Dorr's observation.⁽¹⁸⁾

The antitumor effect of MMC on the experimental liver tumors was enhanced by the simultaneous administration of *XZT*. This may have been due to promotion of the microcirculation in the tumor by *XZT*, which may have enhanced the killing effect of MMC. The pharmacological interactions between *XZT* and MMC are very complicated. The exact mechanism of the antitumor effect of the combination is not clear and, therefore, needs further investigation.

The radioactive tracer method (the thymidine, uridine, and leucine incorporation assay) indicated that DNA, RNA, and protein synthesis rates of tumor cells were inhibited by *XZT* and MMC, which reflects their cytotoxic properties. However, *XZT* alone had no significant inhibition on biosynthesis of liver cells compared to the control group. This phenomenon cannot be explained by our present pharmacological knowledge of *XZT*. The mechanisms of action of *XZT* acts on tumor and liver cells need further research. When *XZT* was combined with MMC, biosynthesis of tumor cells showed marked inhibition, especially with respect to DNA synthesis,⁽¹⁹⁾ but this was not greater than that seen with MMC alone. In summary, Chinese medicinal herbs in combination with chemotherapy might be an effective modality for cancer therapy on various cancers. More work is needed to evaluate the usefulness of these combinations against human neoplasms.

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血府逐瘀湯與絲裂黴素對鼯鼠肝腫瘤的效應研究

游智勝 黃蕙棻¹ 郝道猛²

背景：中醫認為腫瘤的形成是由於“氣滯血瘀”，氣血瘀滯以致有毒的物質滯留體內，血府逐瘀湯是“理氣活血”的代表方劑，而絲裂黴素為一廣泛使用的抗腫瘤藥物。本研究即是觀察以上二者對鼯鼠肝腫瘤的治療效應。

方法：以肉瘤180細胞接種在鼯鼠肝臟後，隨機分為四組，包括腫瘤對照組、血府逐瘀湯組、絲裂黴素組，以及血府逐瘀湯與絲裂黴素的合併組。我們觀察了鼯鼠肝腫瘤在治療後60天內的存活率，平均存活時間與延長壽命程度，並且把腫瘤取下後檢測其細胞存活率與生物合成速率。

結果：血府逐瘀湯組、絲裂黴素組與合併組相較於對照組分別增加鼯鼠存活時間為12.5，14.1，與17.2日。這三組治療對肝腫瘤細胞具有毒殺作用，對生物合成速率亦有抑制作用。其中合併組的療效最佳。

結論：本研究結果顯示，血府逐瘀湯合併絲裂黴素的治療模式，可提供肝腫瘤治療的參考，其機制有待進一步的探討。

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關鍵字：血府逐瘀湯，絲裂黴素，實驗性肝腫瘤。

長庚大學 中醫學系暨長庚紀念醫院 中醫部；¹中國醫藥學院 中醫學系；²清華大學 生命科學院

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