中國1號天仙液 對移植性S_{180}肉瘤和肝癌抑制作用的研究

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El estudio de los Efectos Inhibitorios de FRC001 (Líquido Tian Xian China No. 1, para Sarcoma) sobre el Transplante S_{180} y el Hepatocarcinoma

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ABSTRACTO

El Sarcoma S_{180} (por transplante) y el Hepatocarcinoma del ratón son los modelos mas importantes y populares para el estudio de las medicinas antineoplásicas. Este trabajo estudió los efectos inhibitorios del FRC001 en estos dos modelos. Los resultados demostraron que el FRC001 tiene efectos inhibitorios hasta cierto grado sobre el Sarcoma S_{180} y el Hepatocarcinoma. Entre estos encontramos que las tasas de inhibición sobre el S_{180} en dosis altas, medianas y bajas del FRC001 fueron en el orden de 59.73%, 52.57% y 41.33% respectivamente, lo que demuestra efectos obvios dependientes de la dosis. El FRC001 también tuvo efectos sobre focos de Hepatocarcinoma, con una tasa de inhibición de 47.81%. Después del tratamiento con el FRC001, el peso promedio disminuyo y los focos de carcinoma se redujeron aparentemente en comparación con el grupo control ($p<0.05$ o $p<0.01$). El FRC001 es una medicina antineoplásica que utiliza medicinas chinas tradicionales como ingrediente principal.

Palabras clave: FRC001; Tumor por transplante, Sarcoma S_{180}; Efecto inhibidor sobre el carcinoma hepático (Hepatocarcinoma).

INTRODUCCIÓN

Tumores malignos son parte de una serie de enfermedades comunes que hacen daño a los seres humanos. En la actualidad su tratamiento es un problema difícil para el mundo de la medicina. Además de cirugía, radioterapia y quimioterapia, los papeles de las medicinas tradicionales chinas y la combinación de las medicinas China y de Occidente son reconocidas

ampliamente en círculos médicos. El FRC001 se prepara utilizando principalmente medicinas chinas tradicionales que pueden eliminar el factor patogénico y apoyar la energía saludable. Esta energía saludable de apoyo incluye el fortalecimiento del Ki y el enriquecimiento de la sangre, calienta el Yang y alimenta el Yin, La eliminación del factor patogénico incluye la estimulación de la circulación de la sangre para eliminar el estancamiento, elimina el calor y los materiales tóxicos y suavizan y resuelven la masa dura. Estos métodos tienen mejor efecto inhibidor sobre los tumores.

Este trabajo estudia los efectos del FRC001 sobre el carcinoma S_{180} (por transplante) y el Hepatocarcinoma de ratones.

MATERIALES Y MÉTODOS

1. Materiales

    1.1. Droga experimental: FRC001 (extracto liquido de medicinas Chinas).

    1.2. Animales experimentales: Ratones Kunming de pura sangre C57, peso de 18-22 gr., sanos de 2-3 meses, machos y hembras proporcionados por el Centro de Animales Experimentales del Instituto de Investigaciones Profiláctico terapéuticos Tumorales Jiangsu.

    1.3. Variedad de Tumor Experimental: (1) Sarcoma S_{180} (2) Carcinoma Hepático. proporcionados por el Departamento de Investigaciones Medicas del Instituto de Investigaciones Profilactico-Terapéuticas Tumorales Jiangsu.

2. Métodos de Preparación del Patrón Animal

    2.1. Sarcoma S_{180}

Se extrajo liquido ascítico de Sarcoma S_{180} de ratones a los cuales se les había inoculado con el S_{180} 7-9 días antes, diluidos con solución salina normal al 1x108/ml de solución de células de Sarcoma. Al día siguiente, los ratones fueron inoculados por vía subcutánea con 0.2 ml de la solución de células de Sarcoma en la pata derecha delantera usando técnica aséptica; luego fueron agrupadas al azar e incluidas en el experimento. A los ratones se les dio medicamentos tales como FRC001, y otras por vía endogástrica una vez al día durante los siguientes 12 días, y luego disecados el día 13 para obtener el Sarcoma. Los sarcomas fueron pesados exactamente (gm) y se calculó la tasa de inhibición de las medicinas sobre Sarcoma por medio de la siguiente formula.

$$A\% = \frac{X - Y}{X} * 100\%$$

A	Tasa de Inhibición del FRC001 sobre el Sarcoma S_{180}
X	Peso promedio del S_{180} en el grupo control (gm)
Y	Peso promedio del S_{180} en el grupo experimental (gm)

2.2. Carcinoma Hepático

La cepa de carcinoma hepático se diluyo con solución salina normal al 1X108/ml de suspensión de células cancerosas. A los ratones se les inoculo con 0,2 ml de dicha solución en la pata anterior derecha usando técnica aséptica. Al día siguiente fueron agrupados al azar y se les dio medicinas como FRC001 una vez al día por 8 días consecutivos y disecados el día 9. Los ratones y el Hepatocarcinoma fueron pesados exactamente. Se utilizó la siguiente formula para calcular las tasas de inhibición de medicamentos sobre el carcinoma hepático

$$C\% = (1 - \frac{W}{Z}) * 100\%$$

C%	Tasa DE Inhibición del medicamento sobre el carcinoma hepático
W	Peso promedio del Hepatocarcinoma del grupo experimental (gm)
Z	Peso promedio del Hepatocarcinoma del grupo control (gm)

RESULTADOS Y DISCUSIÓN

1. El efecto inhibidor del FRC001 sobre el Sarcoma S_{180} del ratón:

Para los efectos de determinar la dosis optima y estudiar la relación de dosis y efecto del FRC001 sobre S_{180}, usamos tres dosis: alta (6.0 ml/kg. de peso corporal); mediana (3.0 ml/Kg. de peso corporal) y baja (1.5 ml/kg. de peso corporal).

Los resultados se muestran en la Tabla 1 y la Figura 1,2.

Tabla 1. Los efectos del FRC001 sobre el Sarcoma S_{180} Transplantado a Ratones

Grupo	Número (n)	Dosis (ml/kg.pc)	Días del Experimento (d)	Promedio de S_{180}	Peso ($\overline{X}$±SD)	Tasa de Inhibición (%)
Grupo Control	10	0	12	3.75±1.53		-
Dosis Alta	10	6.0	12	1.51±0.43****		59.73
Dosis Mediana	10	10	3.0	1.78±0.58***		52.53

Dosis Baja	10	1.5	12	2.20±0.93**		41.33
Quimioterápia	10	25mg/kg.bw	12	1.96±1.00***		47.73

Comparado al grupo control, *P >0.05, **P <0.05, ***P<0.01, ****P<0.001

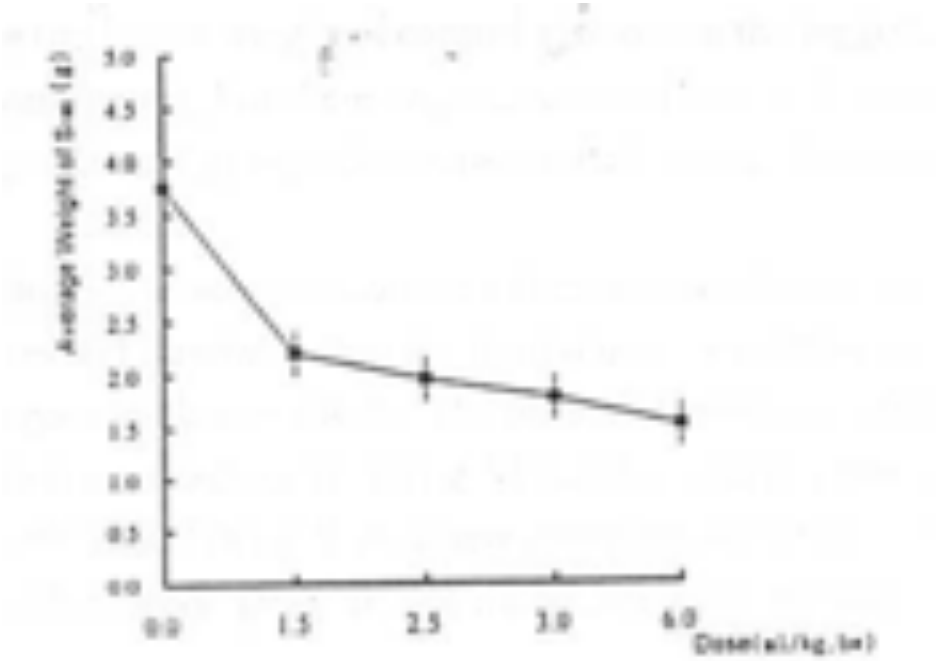

Figura 1 Curva de Dosis-Efecto del FRC001 sobre S_{180}

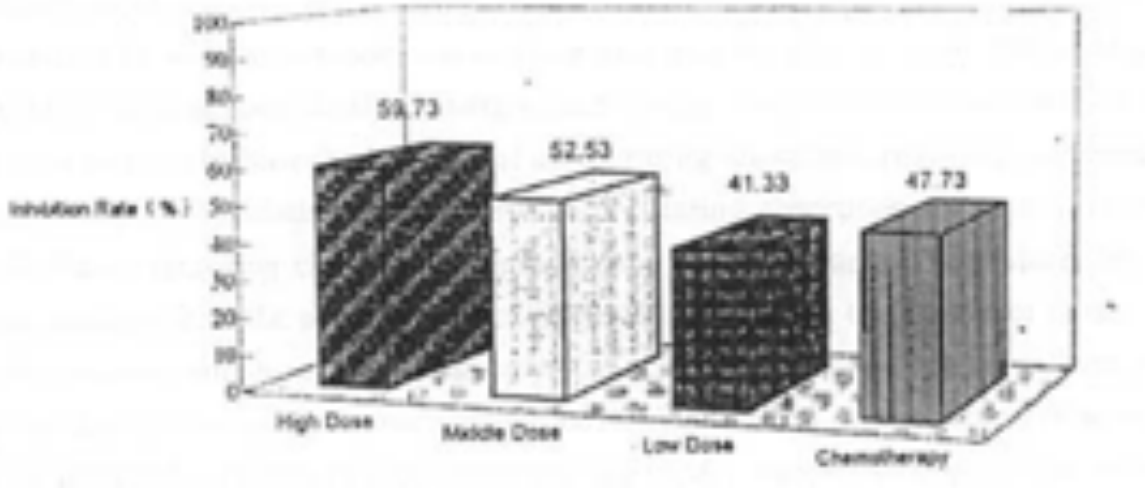

Figura 2. Tasas de Inhibición de Varias Dosis de FRC001 sobre S_{180}

De acuerdo con la Tabla 1 tres dosis de FRC001 tuvieron diferentes efectos de inhibición sobre el Sarcoma S_{180} transplantado al ratón. Los pesos promedio de S_{180} fueron significativamente mas pequeños que los del grupo control (P;0.05 o P;0.01). Estos hallazgos muestran que el FRC001 tuvo un efecto inhibidor sobre el Sarcoma S_{180}.

De acuerdo con la Figura 1, la inhibición del FRC001 sobre el Sarcoma S_{180} transplantado al ratón depende de la dosis, por ejemplo al aumentar la dosis aumentaron los efectos inhibitorios sobre S_{180}, disminuyó el peso del Sarcoma y el tamaño de los focos del tumor.

Basados en las investigaciones de dosis-efecto, fue seleccionada la alta dosis de FRC001 (6.0 ml-kg peso corporal) para estudiar sus efectos sobre el peso corporal, el peso del carcinoma en el animal experimental del carcinoma hepático y la tasa de inhibición, (mostrados en Tabla 2 y Figuras 3 y 4)

De acuerdo con la Tabla 2, estas medicinas tuvieron efectos inhibitorios sobre los focos de carcinoma hepático en los animales experimentales que mostraron una disminución del peso del carcinoma. El peso promedio de carcinomas de Drogas I a vi FUERON 1.41gm, 1.09gm, 1,26gm, 1.49gm, 1.02gm, 0.71gm, respectivamente, disminuyeron 0.65gm, 0.97gm, 0.80gm, 0.59gm, 1.04gm, 1.035gm respectivamente cuando se compara con el grupo control. Comparados con el grupo control, los efectos de droga i y IV no fueron estadísticamente significativos ($P>0.05$), mientras que drogas II,III,V Y VI tuvieron efectos significativos ($P<0.01$ o $P<0.001$)

La figura 3 muestra que el peso del carcinoma del grupo control fue el mayor, los pesos del carcinoma de drogas I-VI disminuyeron en algo, pero hubieron focos de carcinoma en todos los grupos de medicamentos. El orden del peso del carcinoma de todos los grupos fue: Control > droga IV > droga I > droga III > droga II > droga V > droga VI.

Estos resultados muestran que como un agente antineoplásico, FRC001 tuvo efectos sobre Sarcoma S_{180} y Hepatocarcinoma. Los mecanismos pueden ser:

(1) FRC001 es una preparación compleja de medicamentos Chinos y Occidentales, que puede estimular la circulación sanguínea para eliminar el estancamiento de la sangre, eliminar el calor y materias tóxicas, ablandar y resolver masas duras, estimular el Ki, enriquecer la sangre, calentar el Yang y nutrir el Yin, para ayudar al cuerpo a eliminar el factor patogénico y apoyar energía saludable, eliminar materias tóxicas y resistir tumores, (2) Los componentes en el Edfrann podrían tener la función de vitalizar el Ki, el bazo, resolver la humedad, aliviar el hígado y regular la circulación del Ki, digestivo, regula absorción, elimina el desbalance del metabolismo de sustancias, facilitando circulación, hemopoyesis, inmunidad y pueden regular las funciones neuronales, endocrinas, de electrolitos y nucleósidos cíclicos, etc. (3) FRC001 puede inhibir el crecimiento del tumor por medio de la regulación de las funciones inmunológicas, favoreciendo la función fagocítica del sistema retículo endotelial . (4) Quizás el

FRC001 tiene la función de inhibir el metabolismo del ADN y ARN de la célula cancerosa para de esta manera matar la célula cancerosa o inhibir su crecimiento. (5) Quizás el FRC001 tenga la función de eliminar los radicales libres, ya que los radicales libres juegan un papel importante en la mutagenesis y carcinogenesis. FRC001 elimina macromoléculas y macromoléculas. Por supuesto que el crecimiento , desarrollo o inhibición es un curso biológico complicado, los efectos y mecanismos exactos del FRC001 requieren mas estudios todavía.

The Study on the Inhibition Effects of FRC001(China No.1 Tian Xian Liquid) on Tansplatation Sarcoma S180 and Hepatocarcinoma

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ABSTRACT

The transplatation sarcoma S_{180} and hepatic carcinoma of mouse are the most popular and important models in the screening of antineoplastic drugs. This paper studied the inhibition effects of FRC001 on these two models. The results showed that on FRC001 had inhibition effects, to some extent, sarcoma S_{180} and hepatic carcinoma. Among then, the inhibition rate of high, middle and low dose of FRC001 on S_{180} were 50.73%, 32.57%, 41.30%, respectively which showed obvious dose-dependent effects; FRC001 also had some effects on hepatic carcinoma foci, and the inhibition arte was 47.81%;after the treatment of FRC001, the average weight decreased and the carcinoma foci shrinked apparently compared with the control group ($P<0.05$ or $P<0.01$) . FRC001 is an antineoplastic using traditional Chinese medicine as the main ingredient.

Key Words: FRC001; Transplatation tumor; Sarcoma S_{180}; Inhibition effect on hepatic carcinoma

BACKGROUND

Malignant tumor is a series of commonly encountered diseases which harm the human. The treatment of it is a difficult problem of today's world medical science. Besides operation, radiotherapy, chemotherapy, the roles of TCM and the combination of Chinese and Western medicine are widely noted by medical circles. FRC001 is prepared mainly using traditional Chinese drugs which can eliminate the pathogenic factor and support healthy energy. The supporting healthy energy includes invigorating Qi and enriching the blood, warming Yang and nourishing Yin; the eliminating the pathogenic factor includes promoting blood circulation to remove stasis, clearing away heat and toxic material and softening and resolving hard mass. These methods have better inhibition effect on tumors.

This paper studied the effects of FRC001 on transplatation carcinoma S_{180} and hepatic carcinoma of mice.

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MATERIALS AND METHODS

1.Materials

1.1 Test Drug: FRC001（1iquid extract of Chinese drugs）, provided by China-Japan Feida Union Co.LTD.

1.2 Experimental Animal: mouse, pure kunming bred C_{57},18-22g, healthy, 2-3 months, male and female, provided by Experimental Animal Center of Jiangsu Tumor Prophylactico-therapeutic Research Institution.

1.3 Test Tumor Strain: ①Sarcoma S_{180} strain; ②Hepatic carcinoma strain, provided by Medicine Research Department of Jiangsu Tumor Prophylactico-therapeutic Research Institution.

2.Methods of Preparing Animal Pattern

2.1 Sarcoma S_{180}

Asciter S_{180} sarcoma were drawn from mice in which S_{180} had been inoculated 7-9 days ago, diluted by normal saline to be 1×10^6/ml sarcoma cell solution. The next day, mice were inoculated the sarcoma cell solution 0.2 ml subcutaneously in their right forefeet by aseptic manipulation; then were randomly grouped and put into experiment. The mice were endogastricly given drugs such as FRC001, etc, one time daily for successive 12 days, and dissected to get sarcoma on the 13th day. The sarcoma were weighted precisely（g）, and calculate the inhibition rates of drugs on sarcoma by following formula

$$A\% = \frac{X-Y}{X}\times 100\%$$

A——Inhibition rate of FRC001 on sarcoma S_{180};

X——The average S_{180} weight of control group（g）;

Y——The average S_{180} weight of experimental group.

2.2 Hepatic Carcinoma:

Hepatic carcinoma strain was diluted to 1×10^6/ml carcinoma cell suspention solution by normal saline. The mice were inoculated above carcinoma solution 0. 2ml in their right forefeet by aseptic manipulation. The next day, they were randomly grouped and given drug such as FRC001, etc/one time daily for successive 8 days, and dissected on the 9th day. The body weight and hepatocarcinoma weight were got accurately. To calculate the inhibition rates of drugs on hepatic carcinoma by following formula:

$$C\% = \left(1-\frac{W}{Z}\right)\times 100\%$$

C%——Inhibition rate of drug on hepatic carcinoma;

W——Average hepatocarcinoma weight of experimental group（g）

Z——Average hepatocarcinoma weight of control group（g）

RESULTS AND DISCUSSION

1.The inhibition effect of FRC001 on transplatation Sarcoma S_{180} of mice:

To explore the dose-effect of FRC001 on S_{180} and find the optimal dose, we tested three doses,i.e. high dose（6.0ml/kg.bw）, middle dose（3.0ml/kg.bw）and low dose（1.5ml/kg.bw）of FRC001 on

Table 1 . The Effects of FRC001 on Transplatation Sarcoma S_{180} of Mice

Group	Number (n)	Dosage (ml/kg.bw)	Experiment Days (d)	Average of S_{180}	Weight (X±SD)	Inhibition Rate (%)
Control Group	10	0	12	3.75±1.53		—
High Dose	10	6.0	12	1.51±0.43****		59.73
Middle Dose	10	3.0	12	1.78±0.58***		52.53
Low Dose	10	1.5	12	2.20±0.93**		41.33
Chemotherapy	10	25mg/kg.bw	12	1.96±1.00***		47.73

Compared to control group, *P>0.05; **P<0.05; ***P<0.01; ****P<0.001

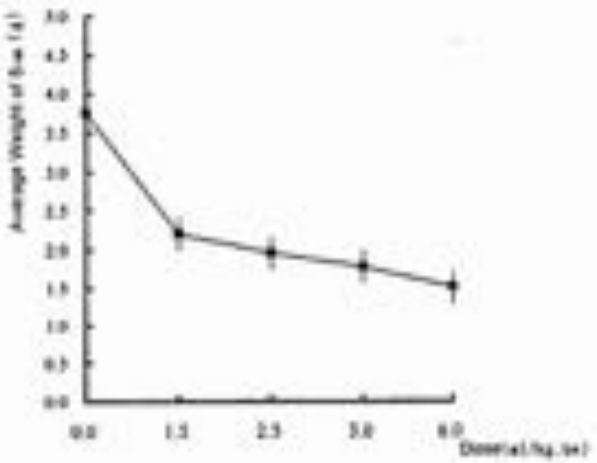

Figure 1 . Dose-effect Curve of FRC001 on S_{180}

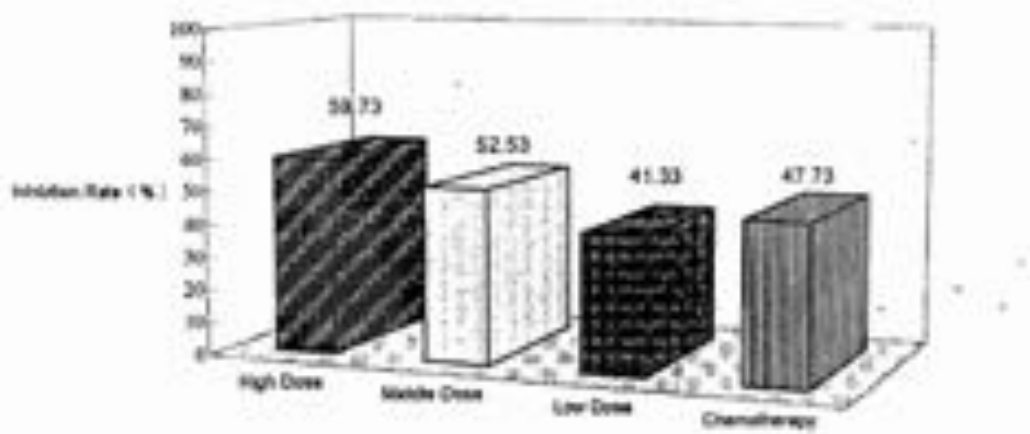

Figure 2 . Inhibition rates of Different Doses of FRC001 on S_{180}

transplatation sarcoma S_{180} of mice（results showed in Table 1 and Figure 1,2）

According to Table 1, three doses of FRC001 had different inhibition effects on transplatation Sarcoma S_{180} of mouse. The average weights of S_{180} of the three doses were significantly smaller than that of control group（P<0.05 or P<0.01）. These findings showed that FRC001 had some inhibition effect on sarcoma S_{180}.

According to Figure 1, the inhibition of FRC001 on transplatation sarcoma S_{180} of mouse were dose-dependent, i.e. as the increasing of the dose of FRC001, the inhibition effects on S_{180} enhanced, the weight of sarcoma decreased and the foci shrinked.

On the basis of the dose-effect research, high dose of FRC001 (6.0ml/kg bw) was chosen to test and its effects on the body weight, carcinma weight of experimental animal of hepatic carcinoma and the inhibition rate were investigated (showed in Table 2 and Figure 3,4).

According to Table 2, these drugs had some inhibiton effects on hepatic carcinoma foci of experimental animals which showed in the decrease of carcinoma weights. The average carcinoma weights of drug Ⅰ-Ⅵ were 1.41g,1.09g,1.26g,1.49g,1.02g,0.71g,respectively, decreased 0.65g,0.97g,0.80g,0.59g,1.04g,1.35g,respectively compared with control group. Compared to the control group, the effects of drug Ⅰ, Ⅳwere not significant statistically (P>0.05), whereas drug Ⅱ,Ⅲ,Ⅴ,Ⅵ had significant effects (P<0.01 or P<0.001).

Figure 3 showed that the carcinoma weight of control group was the biggest, the carcinoma weights of drug Ⅰ-Ⅵ decreased to some extent, but there were carcinoma foci in all drug groups. The orders of carcinoma weights of all experimental groups:Control>drug Ⅳ>drug Ⅰ>drug Ⅲ>drug Ⅱ>drug Ⅴ>drug Ⅵ.

Figure 4 showed these drugs had some inhibition effects on carcinoma foci. According to the antineoplastic screening procedures and standards that the inhibition rate must be up to 30%,except for drug Ⅳ (27.67%), all drugs had good inhibition effects. The orders of inhibition rates of drug Ⅰ-Ⅵ:drug Ⅵ>drug Ⅴ>drug Ⅱ>drug Ⅲ>drug Ⅰ>drug Ⅳ. Drug Ⅵ is 5-Fu which is one of the chemotherapeutic drugs having good antieoplastic effect. Drug Ⅴ is a new complex preparation of Chinese and Western drugs which is being screened by author. Drug Ⅱ is a marketing antineoplastic, and its effect is weaker than drug Ⅵ and Ⅴ.

These results showed that, as a antineoplastic, FRC001 had some effects on sarcoma S_{180} and hepatocarcinoma. The mechanisms may be:①FRC001 is a complex preparation of Chinese and Western drugs, can promote blood circulation to remove stasis, clear away heat and toxic material, soften and resolve hard mass, invigorate Qi, enrich the blood, warm Yang and nourish Yin, so it can help body to eliminate the pathogenic factor and support healthy energy, clear away toxic material and resist tumors;②The components in Edfrann maybe have the function of invigorating Qi, spleen, resolving dampness, soothing the liver and regulating the circulation of Qi, digestant, regulating absorption, eliminating disturbance of substance metabolism, enhancing circulation, hemopoiesis, immunity, and can regulate the function of nerve, endocrine, electrolyte, cyclic nucleoside, etc;③FRC001 can inhibit the growth of tumor by regulating immunologic function, enhancing the phagocytic function of reticuloendothelial system; ④ FRC001 maybe has the function of inhibiting the metabolism of RNA and DNA of carcinoma cell so as to kill the carcinoma cell or inhibit the growth of carcinoma cell;⑤FRC001 maybe has the function of eliminating free radicals, as the free radicals play an important role in mutagenesis and carcinogenesis. FRC001 contains macromolecule and micromolecule radical scavenge. Of course, the growth, development or inhibition is a complicated biologic course, the effects and accurate mechanism of FRC001 on tumor are awaited to further study.

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