Substantial clinical effect in the treatment of various tumors. Moreover, experimental and clinical data indicate that elemene has fewer side effects, especially no myelosuppression. These characteristics are significantly different from those of the conventional chemotherapeutic drugs.

Chemistry

Elemene is a naturally occurring compound that can be isolated from the traditional Chinese medicinal herb *Rhizoma zedoariae* native to south China, which was used to treat tumors in Chinese folk medicine (2). Elemene exists as a mixture of α-, β-, γ- and δ-isomers. Pure isomers of elemene have been isolated and purified from the mixture. It has been demonstrated that the main antitumor active component of elemene is the β-isomer. Accordingly, elemene used in experimental and clinical investigations is also mainly composed of the β-isomer (3).

Antitumor Activity

Experimental studies have shown that elemene exerts obvious antitumor activity *in vitro* and *in vivo*. The cytotoxicity of elemene has been determined in various tumor cell lines *in vitro* (3-9). As shown in Table I, elemene inhibits the growth of uterocervical carcinoma HeLa cells, promyelocytic leukemia HL-60 cells, erythroleukemia K562 cells and drug-sensitive and doxorubicin-resistant hepatoma BEL-7402 cells. In addition, the growth of other tumor cells such as several pulmonary carcinoma cell lines (Lax, Anip-937, SPC-A1, H128, SPC) was also inhibited by the agent. However, the IC_{50} of elemene for normal human peripheral blood leukocytes is 254.3 mg/l. Based on the comparison of the IC_{50} between tumor cells and normal leukocytes, it appears that the growth inhibitory effect of elemene on tumor cells is much stronger than on normal cells. When elemene was used in combination with adriamycin or cisplatin *in vitro*, a synergistic inhibition of the growth of gastroadenoacarcinoma SGC-7901 cells was found (10).

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Elemene was given i.p. to mice bearing Ehrlich ascites carcinoma (EAC) and ascertes sarcoma 180; the antitumor activities were significant (Table II). The drug also exhibited antitumor activities for other mouse ascites tumors such as sarcoma 37, leukemia L1210, leukemia P388, reticulosarcoma ARS, and rat ascites tumors such as Yoshida sarcoma. Antitumor activities of elemene were also found in several subcutaneously implanted solid tumors such as mouse Lewis lung carcinoma and rat Walker 256 sarcoma (Table III) (11).

Mechanism of Action

It has been shown that the mechanism of action of elemene involves direct cytotoxic activities as well as indirect immunostimulatory effects.

Direct cytotoxic activities

It was found by electron microscope technique that elemene selectively decreased microvilli of the surface of tumor cells, suggesting that the drug may affect some characteristics of tumor cell membrane. Further studies indicated that elemene suppressed DNA, RNA and protein syntheses in EAC cells and several lung cancer cells, which may also contribute to its cytotoxic effect (11). The effect of elemene on the cell-cycle progression of tumor cells was studied in vitro by using flow cytometry technique. When HL-60 cells were treated with 20 mg/l of elemene, cell proportion at the G2M phase was decreased and at the S stage was increased (Table IV). These results suggest that the inhibitory effects of elemene on tumor cell growth are related to cell cycle arrest from S to G2M phase transition, consequently inhibiting the mitosis of tumor cells (8).

Although targeting of apoptosis is a relatively novel concept, there is sufficient evidence to indicate that induction of apoptosis could provide a highly specific means of attacking malignant cells (12, 13). Induction of tumor cell apoptosis by elemene has recently been confirmed (8). When HL-60 cells were treated with 20 mg/l elemene, flow cytometry analysis showed that the histogram exhibited the distinct apoptotic feature of sub-G1 peak (apoptosis peak). The percentages of apoptotic cells with elemene treatment of 4, 24 and 48 h were 41.5, 35.3 and 47.7%, respectively. An important hallmark of apoptotic cell death is the fragmentation of genomic DNA into integer multiples of 180 bp units producing a characteristic ladder on agarose gel electrophoresis. To characterize elemene-inducing apoptotic cell death in HL-60 cells, internucleosomal DNA fragmentation was analyzed after the cells were exposed to different concentrations of elemene from 2-24 h. The distinct internucleosomal DNA fragmentation ladder was observed in HL-60 cells treated for 2 h. Moreover, in comparison with 2-h treatment, the concentration of elemene for triggering DNA fragmentation was much lower than that for 24-h treatment. When morphological changes in elemene-treated HL-60 cells...
Elemene administered by intercavernous injection also stimulated LAK activity of effusion-associated lymphocytes (EAL) in malignant pleural effusion. Moreover, elemene increased leukocytes and lymphocytes counts, as well as red cell membrane complement 3 receptors in peripheral blood of patients treated with other chemotherapeutic drugs (Table VI) (11).

### Pharmacokinetics

The preliminary studies on absorption, distribution and excretion of elemene have been performed in mice using [3H]-elemene (11). The blood concentration-time curve of the drug was shown to fit a two-compartment open model. Its half-life ($t_{1/2}$) was as follows: $t_{1/2}^\alpha = 11.2$ min, $t_{1/2}^\beta = 10.5$ h. Low absorption after oral administration was observed; the bioavailability was only 18.8%. Peak blood levels were reached at about 6 h after oral administration. After i.v. administration, high concentrations were found in the lungs, spleen, liver and lymph glands, and concentrations were highest in the lungs. Elemene also penetrated the brain through the blood-brain barrier after i.v. or oral administration. In addition, it was distributed into tumor tissues.

In the case of i.v. or oral administration, 26.1% of total dose administered was excreted from urine, 2.2% via feces and 38.5% via bile within 24 h. As a volatile oil, elemene has more distribution in the lungs, so the respiratory system is its main route of excretion. Such pharmacokinetic characteristics should be taken into consideration for the clinical use of this compound.

### Toxicity

Acute lethal doses (LD$_{50}$) of elemene are 270 mg/kg i.v. and more than 5 g/kg i.g. (11). Elemene had slight suppressive effects on the central nervous system, but no effects on cardiovascular and respiratory systems were observed. The hereditary tests also did not show any

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**Table IV: Effect of elemene on cell cycle progression of HL-60 cells.**

<table>
<thead>
<tr>
<th>Concentration (mg/l)</th>
<th>Time (h)$^a$</th>
<th>$G_1$</th>
<th>S</th>
<th>$G_M$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4</td>
<td>35.7$^b$</td>
<td>50.4</td>
<td>13.9</td>
</tr>
<tr>
<td>20</td>
<td>4</td>
<td>26.8</td>
<td>59.0</td>
<td>14.2</td>
</tr>
<tr>
<td>0</td>
<td>24</td>
<td>36.8</td>
<td>50.8</td>
<td>12.4</td>
</tr>
<tr>
<td>20</td>
<td>24</td>
<td>21.8</td>
<td>74.8</td>
<td>3.4</td>
</tr>
<tr>
<td>0</td>
<td>48</td>
<td>40.7</td>
<td>46.0</td>
<td>13.3</td>
</tr>
<tr>
<td>20</td>
<td>48</td>
<td>47.2</td>
<td>48.9</td>
<td>3.9</td>
</tr>
</tbody>
</table>

$^a$ Hour after elemene administration. $^b$ Percent.

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**Table V: Effect of elemene on peripheral blood T-cell subset count and LAK activity of effusion-associated lymphocytes in malignant pleural effusion in patients with various tumors.**

<table>
<thead>
<tr>
<th>Group</th>
<th>T3 (%)</th>
<th>T4 (%)</th>
<th>T8 (%)</th>
<th>T4/T8</th>
<th>LAK activity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal donors</td>
<td>47.8</td>
<td>37.4</td>
<td>24.1</td>
<td>1.51</td>
<td>-</td>
</tr>
<tr>
<td>Patients with tumors</td>
<td>37.9</td>
<td>32.4</td>
<td>18.9</td>
<td>1.79</td>
<td>10.5</td>
</tr>
<tr>
<td>Elemene</td>
<td>40.9</td>
<td>34.1</td>
<td>21.2</td>
<td>1.55</td>
<td>35.1</td>
</tr>
</tbody>
</table>

---

**Table VI: Effect of elemene on chemotherapy-inhibited immune functions in patients with tumors.**

<table>
<thead>
<tr>
<th>Group</th>
<th>Leukocytes (x 10$^9$ cells/l) Without C With C</th>
<th>Leukocytes (x 10$^9$ cells/l) Without C With C</th>
<th>C3 receptors Without C With C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.3</td>
<td>1.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Elemene</td>
<td>5.9</td>
<td>1.9</td>
<td>9.4</td>
</tr>
</tbody>
</table>

C: chemotherapy.
were 77.6% in patients with malignant pleural effusion and 66.1% in patients with malignant peritoneal effusion. It was concluded that elemene administered by local injection is an active agent in the management of malignant effusions.

Elemene was also effective by hepatic artery injection for primary hepatocarcinoma (PHC) (20). In 71 patients with PHC, 2 CRs and 38 PRs were observed. Elemene administered intravenously has also been recommended for clinical treatment of advanced lung cancer with 32.1% total response rate (Table IX). It was also effective for advanced lung cancer by bronchial artery injection or pulmonary artery injection (21, 22). It is known that elemene penetrates the blood-brain barrier. Therefore, the agent was also used for the treatment of brain cancers by intracarotid artery infusion; a 63.3% response rate (8 CRs and 11 PRs in 30 patients) was reported (11).

Elemene was effective by local infiltration for superficial cancers with a 63.5% total response rate (Table X). Combination drug treatment in tumor therapy is becoming more and more important. When elemene was combined with other chemotherapeutic drugs, radiotherapy or immunotherapy, a synergistic inhibition of tumor growth was found in patients with various tumors. In addition, elemene has also been used for treating other tumors such as dermatocarcinoma, osteosarcoma, multiple myeloma and leukemia, with favorable results reported in some patients (11).

**Conclusions**

Elemene, a new natural product isolated from Chinese medicinal herb, exhibited broad antitumor
activity. However, the sensitivity of various tumors to the drug may differ. It is also noteworthy that methods of therapeutic use and pharmacokinetics characteristics may influence the efficacy of elemene therapy. Therefore, close attention should be paid to these factors in cancer treatment with the drug.

Conventional tumor chemotherapy has a low degree of specificity, indicating that resulting side effects have limited its efficacy. Therefore, it is important to develop cancer-specific agents with greater selectivity (13). Although elemene does not produce a significantly better chemotherapeutic effect than those drugs already in use, fewer side effects were reported in clinical trials with the compound. Elemene may not rapidly kill proliferating non-malignant cells such as bone marrow stem cells. No overt signs of drug-induced toxicity on liver and kidney function, and no myelosuppression were observed. Moreover, it has been demonstrated that elemene exhibits immunostimulatory activities. These data suggest that elemene has the potential to be developed as a new antitumor drug with high specificity.

Source

Dalian Jin Gang Pharmaceutical Co., Ltd. (P.R. China).

References