RECENT ADVANCES IN PHARMACOLOGIC STUDY OF NATURAL ANTICANCER AGENTS IN CHINA

XU Bin

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 319 Yue-yang Road, Shanghai 200031, China

In this paper a number of anticancer agents of natural origin will be presented. Hydroxycamptothecin (HCPT) was found to produce a strong inhibitory action on a variety of animal tumors. It is also effective for treatment of patients with gastric carcinoma, liver carcinoma, tumor of head and neck or leukemia. Pharmacologic studies showed that it could depress S phase of tumor cells significantly and cause formation of cellular chromatid breaks. By means of alkaline elution and nick translation methods it has been proved that HCPT induced DNA single strand breaks remarkably.

Homoharringtonine (HHRT) was shown to be effective against acute leukemia. Recent experiments in tumor-bearing mice indicated that (HHRT) could diminish tumor metastasis. Using molecular hybridization technique it was demonstrated that (HHRT) decreased the content of c-myc RNA in the cytoplasm but not in the nuclei. Lycobetaine (LBT) possessed strong inhibitory effects on a number of ascites tumors. In clinical trials it was effective against ovarian and gastric carcinomas. It is able to intercalate into DNA. Oxalysine (OXL) is a new antibiotic and shown to be effective against tumor metastasis. When used in combination with 5-FU, its anticancer action could be enhanced.

Other natural compounds such as indirubin, β-elemene, irisquinone, oridonine, norcantharidin and PSP have been also found to possess antitumor action.

Key words: anticancer agents – hydroxycamptothecin – homoharringtonine – lycobetaine – oxalysine

In contemporary cancer chemotherapy the natural anticancer substances have attracted the attention of many scientists in the world. China has a long history of traditional herb medicine and is rich in plant and animal resources. Anticancer screening data reported in Chinese literature in the past 30 years showed that several hundred plants were found to have antitumor activity. Several dozen of active compounds have been tested clinically (Xu, 1980). In this paper a number of anticancer agents of natural origin will be reviewed, with special reference to hydroxycamptothecin, homoharringtonine, lycobetaine and oxalysine.

Hydroxycamptothecin (HCPT) and analogues. HCPT was found in a popular Chinese tree Camptotheca acuminata Decaisne. Our experiments showed that HCPT could induce a strong inhibitory action on a variety of animal tumors (Xu et al., 1985). In clinical trials it exerted therapeutic effects against gastric carcinoma, liver carcinoma, tumor of head and neck as well as leukemia. Pharmacologic studies demonstrated that HCPT depressed significantly S phase of tumor cells, delaying the cell transit from G1 to S phase. It caused formation of cellular chromatid breaks and damaged nuclear membrane and other membrane structures including mitochondria. By means of alkaline elution and nick translation methods it has been proved that HCPT could cause DNA single strand breaks. It inhibited strongly DNA polymerase α. After removing the drug this action was reversible. Summarizing our experimental results, the schematic mode of action of HCPT may be shown in figure 1 (Fig. 1). Its analogue camptothecin (CPT) was shown to have the similar action as HCPT, but more toxic. It has been reported that CPT could inhibit the activity of topoisomerase.
**Homoharringtonine (HHRT)** — HHRT is one of the alkaloids obtained from *Cephalotaxus fortunei* Hook F. After pharmacologic and clinical studies HHRT and its analogue harringtonine (HT) were proved to be effective in the treatment of acute leukemia patients. When used in combination with other antitumor drugs, it could be also useful for treating some solid tumors such as mammary carcinoma.

Recent experiments in tumor-bearing mice indicated that HHRT could diminish tumor metastasis. Sodium phenobarbital was found to be able to reduce the toxicity of HHRT. The drug markedly inhibited protein and nucleic acid syntheses. Using molecular hybridization technique it was proved that HHRT decreased the content of c-myc RNA in the cytoplasm but not in the nuclei. HHRT accelerated the degradation of oncogene mRNA in cytoplasm. The change of c-myc mRNA occurred earlier than that of morphology or DNA and protein biosynthesis (Fig. 2). It is considered to be the primary effect of HHRT.

**Lycobetaine (LBT)** — LBT was derived from lycorine which is the main component isolated from *Lycoris radiata* L'Herit. Herb. LBT was also called ungeremine. This compound possessed a strong inhibitory action on a number of ascites tumors and damaged cell membrane structures greatly. In clinical trials it was shown to have therapeutic effect in patients with ovarian carcinoma and gastric carcinoma. Experiments with dichroism and nick translation methods showed that LBT was able to intercalate into DNA. LBT could also decrease the sensitivity of c-myc and N-ras oncogene to DNase I (Fig. 3). It might be classified as a new DNA intercalator of natural origin.

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**Fig. 1**: The mode of action of hydroxycamptothecin (HCPT).

**Fig. 2**: Effects of homoharringtonine 40 nmol/L on incorporation of [3H]TdR or [3H]Leu and content of c-myc mRNA in cytoplasm of HL-60 cells.
**Fig. 3**: schematic mode of action of lycobetaine (LBT).

**Oxalysine (OXL)** — OXL was isolated from *Streptomyces roseoviridofuscus* n. sp. as a new antibiotic. Our experimental results revealed that it had a significant antitumor action on a number of solid animal tumors such as brain tumor B22, S37, Lewis lung carcinoma etc. This compound reduced tumor metastasis remarkably. Its antimetastatic action was found to be related to blood fibrinogen which was decreased significantly during OXL treatment (Fig. 4). It had no noticeable depressive effect on body immunity. When used in combination with 5FU, the anticancer action could be enhanced. In liver carcinoma patients OXL was discovered to reduce the serum glutamic-pyruvate transaminase (SGPT) level apparently and exhibited some efficacy. Thereafter it was tried for the treatment of both cancer and hepatitis patients.

**Fig. 4**: schematic explanation of inhibitory action of oxalysine (OXL) on tumor growth and metastasis.

**Other antitumor agents** — Several antitumor compounds of natural origin have also been shown to be quite promising. Indirubin isolated from *Indigo naturalis* has been demonstrated as an active principle for the treatment of chronic
myelocytic leukemia. From *Curcuma aromatica* the principle β-elemene was found to be effective for cervical carcinoma. Irisquinone was extracted from the seeds of *Iris palasii* can be used as radio-sensitizer clinically. *Rabdoscia rubesens* has been used in folk medicine in China for treatment of esophageal carcinoma. The active principle of this plant was thought to be oridonine. PSP, an analogue of PSk, isolated from *Coriolus versicolor* in Shanghai has been reported to have antitumor and immunomodulating activities (Zhou et al., 1988). Norcantharidin is derived from cantharidin which was isolated from *Mylabris phalerata*, a kind of bettle. Results indicated that it has antitumor activity in hepatoma patients.

From above-mentioned data it can be seen that the anticancer agents of natural origin developed in China have great potential for further development of better drugs in the treatment of malignancies.

REFERENCES


