Antitumor Substances from Higher Plants in Asian Region

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Abstract - In this review, we summarize the isolation, structural determination, antitumor activity of substances from higher plants which were collected in Asian region.

1. Introduction

To date many kinds of compounds have been obtained from plants kingdom as antineoplastic and anti-cancerous agents. However, there is no special type of compounds for cancer therapy. Various types of substances are effective for various types of cancers and tumors: for instance, alkaloids, lignans, terpenes and steroids etc.[1] First of all, most important components obtained from higher plants are Vinca alkaloids and Podophyllum lignans. Vinca rosea (=Catharanthus roseus) has been used as inhibiting agent for milk secretion, hypotensor, astringent and emetics as folks medicines in Madagascar. Moreover, native people in West Indian Island have been using Vinca spp. as depression agent of blood sugar. When the extract of this plant was given non-orally, leucopenic and indirect inhibiting action of nuclear division of cells were observed. Above 60 kinds of alkaloids have been isolated from Vinca spp. Vinblastine and vincristine are most active substances among of them. The former is effective to Hodgkin disease and the latter to leukemia. Podophyllotoxin is a representative lignan isolated from the rhizomes of Podophyllum peltatum. Podophyllum rhizome had been used as an emetic and an anthelmintic by American Indians traditionally. Because podophyllotoxin was also found to have inhibiting action for cell-division, antineoplastic activity was noticed.

The others, curcumol obtained from Curcuma aromatica was tested and noticed to be effective against cancer of the uterine cervix clinically. Oridonin isolated from Rabdosia ssp.is now investigated for clinical trials in China. Moreover, camptothecine isolated from Camptotheca acuminata is also antineoplastic alkaloid, but is very toxic. Chemical modification has been tried to decrease its toxicity. This compound will be permitted to use as clinical agent later.[2] Colchicine derivatives are also said to have inhibiting action of cell-division. Demecolcine and colchicine have activity against mammary cancer. Harringtonin was investigated as an anticancerous drug in China. Taxol, a compound with a taxane ring isolated from the bark of Taxus brevifolia,

has been demonstrated to have substantial anticancer activity in patients with solid tumors refractory standard chemotherapy. Supply of this drug has severely limited full exploration of its antineoplastic potential. Some efforts are continued in National Cancer Institute (NCI) Washington for surveying various Taxus species for optimal taxol content, improvement in semi-synthesis from baccatin III, improvement in method of extraction, and development of alternative renewable resources.[3] Further, there are many compounds which have been reported as antineoplastic agents.

Development of novel clinical useful anticancer agents would be dependent on the screening system and the sample sources for the bioassay. The search for potential anticancer agents from natural sources mainly has been carried out with the guidance of bioassays confirmed by the NCI,[4-10] because the large number of natural products screened at the NCI program have also been discussed from an overview of the relationship of assessment between experimental animals and clinical patients for drug development, and the screening protocols for each tumor system have been well-established. It is considered that these are "compound-oriented" *in vivo* screenings. These screenings could not lead to develop some new drug for solid cancers.[11-14]

Recently, NCI has established a "disease-oriented" approach to antitumor activity screening[5,15,16] and the biological response modifiers (BRM)[17,18] program from a viewpoint of the diversity and specificity of tumor, and the requirements of novel structure types and novel action-mechanistic types of anticancer agents. These screening system led to isolate many antineoplastic compounds from plants,[19-22] microorganism[23,24] and marine metabolites[4,12] etc. On the other hand, we have screened on higher plants collected in Japan, China, Korea, Southeast Asia and South America[25-27] for antineoplastic activity, which has been done using Sarcoma 180 ascites in mice, P388 lymphocytic leukemia in mice, Chinese hamster lung V-79 cells, P388 cells and nasopharynx carcinoma (KB) cells in our laboratory, as primary screening. In this review we will describe on antitumor and cytotoxic substances of the higher plants selected from above screening tests.

In 1982, it was given a definition for expression of activity, that is, the word cytotoxicity must be used only for *in vitro* activity, the words antineoplastic and antitumor must be used only for *in vivo* test using animal. We should call anticancer, when it shows activity in clinical trials of human.[12]

2. An Antitumor Morphinane Alkaloid, Sinococuline, from Cocculus trilobus and the Related Compounds[28-30]

Cocculus trilobus DC. (Menispermaceae) growing in the mountainous areas of East Asia has been used in folk medicine as a diuretic, analgesic and anti-inflamatory crude drug. When an aqueous solution of the methanolic extract prepared from the stems and rhizomes of C. trilobus was partitioned successively with n-hexane and ethyl acetate, the antitumor activity against Sarcoma 180 ascites in mice was concentrated in the