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Review Article

Plant Lectins in Therapeutic and Diagnostic Cancer Research

Monira Pervin[1], Yu Koyama[2], Mamoru Isemura[1]* and Yoriyuki Nakamura[1]

[1]*School of Nutritional and Environmental Sciences, University of Shizuoka, Japan*
[2]*Faculty of Health Promotional Sciences, Tokoha University, Japan*

***Corresponding author**
Mamoru Isemura, School of Nutritional and Environmental Sciences, University of Shizuoka, Shizuoka-422-8526, Japan, Tel & Fax: 81-54-264-5822; Email: isemura@u-shizuoka-ken.ac.jp

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Abstract

Lectins are proteins or glycoprotein's of non-immune origin that exhibit specific binding affinity for the carbohydrate moiety of glycol-conjugates. Several plant lectins have been shown to induce cell death in cancer cells, suggesting that these molecules may have applications in cancer treatments. Cancer cells are known to express and/or secrete glycol-conjugates with an aberrant glycan structure. Thus, lectins may detect such changes, leading to their use in cancer diagnosis and cancer-specific treatment. Mistletoe lectins are representative of an anticancer drug target, and lentil lectin has been shown to have diagnostic applications in hepatocellular carcinoma. In this review, we describe recent progress in lectin researches, with special emphasis on the applications of plant lectins in human cancer diagnosis and therapy.

ABBREVIATIONS

AFP: α-fetoprotein; ConA: Concanavalin A; HCC: Hepatocellular Carcinoma; LCA: *Lens culinaris* agglutinin; PNA: *Arachis hypogea* agglutinin; rVAA: ricommbinant *Viscum album* agglutinin; VAA: *Viscum album* agglutinin; VAE*: Viscum album* L. extracts; WFA: *Wisteria floribunda* agglutinin

INTRODUCTION

Lectins are proteins or glycoproteins of non-immune origin with specific binding affinity for the carbohydrate moiety of glycoconjugates [1,2]. Plant lectins exhibit a variety of biological activities, including cell agglutination, mitosis, toxicity, and cell growth inhibition. Several plant lectins have been shown to induce cell death in cancer cells, suggesting that they may have applications in cancer treatments. Cancer cells have been shown to express and/or secrete glycoconjugates with an aberrant glycan structure [3]. Thus, lectins may detect such changes, leading to their use in cancer diagnosis and cancer-specific treatment. Animal lectins have also been identified but plant lectins have attracted specific attention because of their ease of preparation and commercial availability which would make animal experiments feasible. The characteristics of plant lectins have been the subject of several comprehensive review articles [4-10].

In this review, we provide an update of recent progress in lectin researches, with special emphasis on the application of plant lectins in the treatment and diagnosis of human cancer.

The anticancer effects of plant lectins

Plant lectins have attracted attention because of their anticancer properties and potential application as antitumor agents; lectins are expected to be able to bind specifically to cancer cell membranes or receptors, causing cytotoxicity, apoptosis, autophagy [10,11], and inhibition of tumor growth.

Anticancer effects of mistletoe (*Viscum album L.*) extracts (VAE) and *V. album* agglutinins (VAA)

VAE and VAA have been widely studied as potential anticancer therapeutics or adjuvant therapeutic agents [12-14]. For example, patients with sarcoma achieved remission of tumor symptoms when they were subcutaneously administered VAE at an optimal dose of 0.75–1.0 ng/kg body weight twice a week [7].

A recent case report showed complete regression of colon adenoma after intratumoral injection with VAE in a 78-year-old man who had undergone hemicolectomy for stage IIIC colon cancer [13]. In another case, an 88-year-old man showed improvement in symptoms of adenoid cystic carcinoma following treatment with VAE, accompanied by a good quality of life and partial tumor regression [14]. Thus, while more clinical studies are required and the mechanisms are known only partly, VAE could be a promising anticancer agent.

Several studies have shown that VAA is one of the active components of VAE in terms of anticancer effects [15,16]. A clinical study in patients with stratified stage III/IV glioma showed a tendency for prolongation of relapse-free survival

in patients treated with VAA (17.43 ± 8.2 months) versus the control group (10.45 ± 3.9 months) and a statistically significant extension of overall survival for patients treated with VAA (20.05 ± 3.5 months) as compared to the untreated group (9.90 ± 2.1 months) [16].

Schumacher et al. reported that recombinant VAA (rVAA) were successful in treating human ovarian cancer cells transplanted into severe combined immune deficient mice [17]. In an experiment using C57BL6 mice inoculated with B16-BL6 melanoma cells, Korean VAA inhibited tumor growth and metastasis by increasing apoptosis or type I programmed cell death and inhibiting angiogenesis [18].

A number of cellular experiments have indicated that VAA inhibit cell growth [5,6]. Janssen et al. demonstrated that purified VAE and VAA inhibited the growth of a variety of tumor cell lines, including B cell hybridomas and P815, EL-4, Ke37, MOLT-4, and U937 cells. The mechanism of growth arrest was shown to involve the induction of apoptosis [19]. European mistletoe lectin, VAA-I, was shown to accelerate apoptosis by shutting down the synthesis of proteins, including the anti-apoptotic protein Mcl-1 [20].

Japanese VAA also induced apoptosis in cancer cells. The lectin lead U937 cells to chromatin condensation and nucleosomal fragmentation which was blocked by a caspase inhibitor drug [21], similar to the findings with European VAA [22] (Figure 1). Therefore, one of the major causes of the anticancer effects of VAA is thought to be their ability to induce apoptosis. A mechanism involving autophagy has also been proposed [6,11] (Figure 1).

Another possible mechanism through which VAA exhibits anticancer activity may be associated with their immunomodulatory activities [12]. Hajto et al. demonstrated that 10 ng/mL VAA-I or 50 ng/mL rVAA induced a significant increase in the secretion of interleukin-12 in cultured human peripheral blood mononuclear cells. A single intravenous injection of 0.5–1 ng/kg of VAA-I into Wistar rats doubled the natural killer cell cytotoxicity of splenocytes against YAC-1 targets as compared to control animals. These results suggested that VAA augmented the secretion of the active form of interleukin-12 and potentiated cytokine-induced NK activation [23]. ML-J strongly enhanced the gene expression of certain pro-inflammatory cytokines in Caco-2 human colon carcinoma cells and in the mouse duodenum [2].

Future studies should examine the specific mechanisms through which VAE and VAA modulate the immune system *in vivo* in animal and human experiments.

RICIN

Ricin is a lectin found in the castor bean *Ricinus communus*, and ricin A-chain has RNA *N*-glycosidase activity, which inactivates eukaryotic ribosomes, thereby causing cytotoxicity [24]. Conjugates of ricin A-chain with antibodies against cancer cells have been developed as a therapeutic agent [25]. The results of a phase III study in 157 randomized patients with B-cell lymphoma showed that anti-B4-blocked ricin therapy tended to improve survival, although no significant differences were found in event-free survival and overall survival as compared with control observations [26].

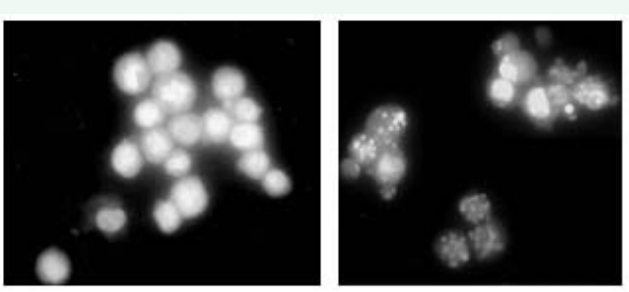

Figure 1 Japanese VAA-induced chromatin condensation.
U937 cells were incubated with (right) or without (left) the lectin at 5 µl/mL at 37°C for 8 h. Hoechst 33342 stain. Reproduced from [21] by permission.

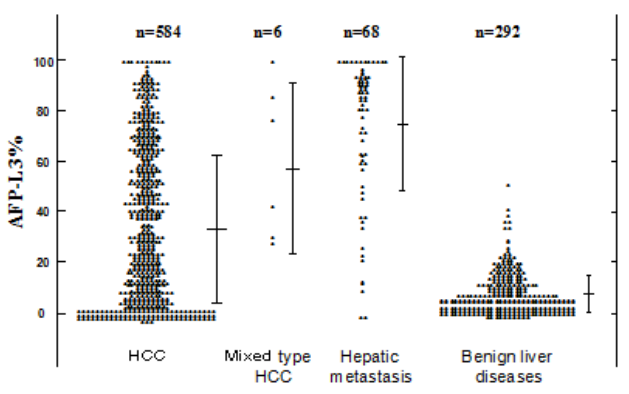

Figure 2 AFP-L3% values for patients with HCC, mixed type HCC, and hepatic metastasis, and benign liver disease. n, number of patients examined [54].

Haraand Seon found that treatment with immunotoxins containing ricin A-chain completely or partially suppressed solid tumor growth in nude mice inoculated with MOLT-4 human T-cell leukemia cells [27]. Future studies are required to determine the applicability of ricin and its derivatives as anticancer drugs.

CONCANAVALIN A (CONA) AND OTHER LECTINS

ConA induces apoptotic morphology in cultured MCF-7 human breast carcinoma cells. When nude mice bearing MCF-7 cell-derived tumors were injected intraperitoneally with ConA (40 mg/kg) daily for 14 days, tumor volumes and weights decreased [28]. ConA induced apoptosis and autophagic death in HeLa cells through suppression of the phosphoinositol 3-kinase/Akt/mammalian target of rapamycin pathway and promoted both autophagic and apoptotic cell death through reactive oxygen species generation in HeLa*cells [29]*.The potential of ConA as an anticancer agent with apoptotic, autophagic, and anti-angiogenic effects in cancer therapy has been described in a comprehensive review [30].

Similarly, several animal studies have suggested the potential usefulness of various lectins as therapeutic agents. A study on intraperitoneally administered *Pisum sativum* lectin at 2.8 mg/kg body weight showed reduced growth of Ehrlich ascites carcinoma, accompanied by increased red blood cell numbers and normal

white blood cell numbers in mice, suggesting the usefulness of this lectin for cancer therapy. The mechanism of inhibition of tumor growth in mice was shown to involve apoptosis by cell cycle arrest at G_2/M phase via increased expression of pro-apoptotic *Bax* and reduced expression of anti-apoptotic *Bcl-2* and *Bcl-X*$_L$ [31]. In another study, administration of 100 mg/kg body weight *Lycoris aurea* agglutinin reduced the volume and weight of subcutaneous tumors derived from A549 cells in nude mice via an apoptotic pathway [32].

Recent animal studies have demonstrated the anti-tumor effects of several lectins as exemplified below. *Abrus precatorius* agglutinin, a ribosome inactivating lectin inhibited the tumor growth in nude mice bearing xenografts of human hepatoma HepG_2 cells [33]. *In vivo* administration of *Arachis hypogea* agglutinin (PNA) reduced tumor cell proliferation in mice bearing Dalton's lymphoma with increase in autophagic and apoptotic characteristics [34]. Similarly *Glycin max* lectin inhibited tumor cell proliferation in mice bearing Dalton's lymphoma [35]. D-galactose-specific *Momordica charantia* lectin showed dose-dependent inhibition of growth of Ehrlich ascites carcinoma cells in mice when administered intraperitoneally [36]. Experimental therapy *in vivo* showed that *Pinella ternate* lectin inhibited proliferation of transplanted Sarcoma 180 cells in mice [37]. Flow cytometric analysis demonstrated that the inhibition mechanism involved induction of G0/G1 cell cycle arrest.

In addition, a number of experiments have used cultured human cell lines to determine a mechanism through which lectins exhibit anticancer activity. For example, soybean lectin was found to induce both apoptotic and autophagic cell death in HeLa cells by a pathway mediated by reactive oxygen species-dependent caspase activation [35]. Several other recent cellular experiments are listed in (Table 1) [38-50].

LECTIN-BASED CANCER DIAGNOSIS

Lens culinaris agglutinin (LCA)

The most successful application of lectins is the use of lentil lectin, LCA, for diagnosis of hepatocellular carcinoma (HCC) [4,51]. Although the serum concentration of α-fetoprotein (AFP) may be a marker for HCC, its levels also increase in non-neoplastic liver diseases, such as hepatic cirrhosis and fulminant hepatitis. In early studies, it was shown that measurement of serum AFP using LCA was useful to distinguish HCC from other hepaticdiseases. For example, the results of immuno-affinoelectrophoresis with LCA showed that the percentage of LCA-reactive species of AFP in the HCC group (45% ± 33%, n=83) was significantly higher than that in the benign liver disease group (3% ± 5%, n=51) [52]. An additional study, in which AFP-L3was defined as AFP reactive strongly with LCA [53], confirmed that the AFP-L3% value was useful to distinguish HCC from benign liver diseases and suggested that the value is also useful to mixed type HCC and hepatoma metastatic from benign liver diseases [54] (Figure 2).

Accumulated data have indicated that LCA can be used to detect the onset of HCC from chronic hepatic cirrhosis during follow-up of a patient [4,51]. The molecular basis of this detection was cancer-associated changes in the glycan structure of AFP, which had undergone α-1,6-fucosylation of the innermost *N*-acetylglucosaminyl residue owing to enhanced activity of α-1,6-fucosyltransferase [4].

A clinical kit for the determination of AFP-L3% was later developed [55] and then became available commercially. The results of a recent meta-analysis indicated that the AFP-L3% value is complementary to the total AFP value as a serum marker for HCC [51]. Since 1996, measurement of the AFP-L3% has been covered by the health insurance of the Japanese Medical Service, reducing the burden of medical expenses for patients.

Table 1: Effect of lectins on cell death of human cancer cells.

Source of lectin	Cancer cell type	Cell growth inhibition/apoptosis/autophagic cell death	Reference
*Abelmoschus esculentus*L.	Breastcarcinoma MCF7	Apoptosis	[38]
*Astragalus membranaceus*L.	Leukemia CML K562	Apoptosis	[39]
Bauhinia ungulata L.	Colon adenocarcinoma HT-29	Cell growth inhibition	[40]
Bauhinia forficata	Breastcarcinoma MCF7	Cell growth inhibition	[41]
Canavalia ensiformis, Canavalia brasiliensis	Leukemia MOLT4, HL-60	Apoptosis	[42]
Dioscorea opposite	Breast cancer MCF7, hepatoma HepG2, nasopharyngeal carcinoma CNE2	Apoptosis	[43]
Lotus corniculatus	Leukemia THP1, lung cancer HOP62, colon cancer HCT116	Cell growth inhibition, apoptosis	[44]
Morus alba L.	Breast cancer MCF7, colon cancer HCT15	Apoptosis	[45]
Phaseolus vulgaris cv.	Breast cancer MCF7, hepatoma HepG2, nasopharyngeal carcinoma CNE1 and CNE2	Cell growth inhibition	[46]
Phaseolus vulgaris cv.	Breast cancer MCF7	Cell growth inhibition	[47]
*Phaseolus vulgaris*cv.	Breast cancer MCF7, nasopharyngeal carcinoma, HONE1	Cell growth inhibition	[48]
Polygonatum odoratum	breast cancer MCF7	Apoptosis, autophagic cell death	[49]
Sophora alopecuroides	Cervical cancer HeLa, esophageal cancer Eca109	Cell growth inhibition	[50]

Con A

Con A was shown to be of diagnostic value for certain hepatic diseases [4,53]. The percentage of serum Con A-reactive species of AFP in patients with liver metastases was much lower than that in patients with HCC and benign liver diseases [52]. The serum concentration of Con A-binding procathespsin D was found to be significantly increased in patients with HCC [56]. Analysis of procathespsin D protein expression by western blotting in HCC revealed 4.3- and 2.3-fold increases as compared with those in non-cirrhotic and cirrhotic controls, respectively. HCC tissues underwent differential staining with Con A from normal tissues [57]. Recent approaches using Con A-magnetic particles may lead to the discovery of additional HCC-specific biomarkers [58].

Wisteria floribunda agglutinin (WFA)

The combination assay of WFA-reactive L1 cell adhesion molecule and WFA-reactive sialylated tumor-associated mucin 1 may become a reliable serological test for cholangiocarcinoma [45]. Moreover, because WFA-reactive ceruloplasmin levels increase in as cites fluids from patients with epithelial ovarian cancer compared with those in benign tissues, this protein could be a good biomarker for ovarian cancer, including clear cell carcinoma [59].

Other lectins

Erythro agglutinating *Phaseolous vulgaris* agglutinin may allow for discrimination between HCC and benign liver disease [4]. Additionally, *Sambucus nigra* agglutinin could be used to detect cancer-associated sialyl Tn-antigen in serum [60] and circulating cancer-associated sialylated glycoproteins at a very low abundance [61]. PNA [62,63] may be useful to detect Thomsen-Friedenreich antigen, agalactosyl-β-(1, 3)-*N*-acetyl-D-galactosamine structure that is expressed in colorectal cancer and other types of cancer.

Cancer tissues exhibit differential staining for various lectin probes, including PNA in colorectal cancer [64], *Artocarpus incisa* lectin in prostate cancer [65], *Agaricus bisporus* agglutinin in colorectal cancer [66], and *Maackia amurensis* lectin for distal colorectal cancer [67]. Cultured cancer cells may exhibit differential staining for lectins from nonmalignant cells, as exemplified by leukemic K562 cells stained with jacalin [68], EBC-1 and HEK293 cells stained with *Wisteria japonica* lectin [69], and U937 and MKN45 cells stained with *Datura strasmonium* agglutinin [70].

Additional studies are needed to develop non-invasive applications for the above-described lectins with cancer tissue-specific and/or cancer cell-specific reactivities.

CONCLUDING REMARKS

As addressed in this review, lectins appear to be promising targets for therapeutic and diagnostic cancer research. Administration of lectins has not been shown to cause deleterious effects in general. For example, when VAE were injected subcutaneously in healthy male volunteers, VAA was detected in serum, and no serious adverse effects were detected [71]. Although high doses of rVAA has been shown to result in reversible hepatotoxicity in some cases, administration of rVAA in humans was not accompanied by immune-suppression and had a low risk of adverse effects overall [12].

On the other hand, ConA has been shown to induce hepatitis in murine models [72]. Dietary LCA was shown to upregulate cancer-associated gene expression in the mouse duodenum, suggesting that the lectin may promotecolorectal cancer [73]. Therefore, clinical application of lectins should be monitored carefully by clinicians, and more studies on the adverse effects of lectins, including carcinogenesis induced by plant lectins, are needed.

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