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Therapeutic Effects of Lignans and Blend Isolated from *Schisandra chinesis* on Hepatic Carcinoma

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1. Introduction

Schisandra chinesis (*S. chinesis*) is widely used as one of the 50 fundamental herbs in traditional Oriental medicine; the species is a member of the *Schisandra* genus of shrub, which grows commonly in the native forests of Northern China, Korea, Japan and Russia. The *Schisandra* are deciduous climbers that thrive in any type of soil, so long as it is moist, shaded, and well-drained (Panossian and Wikman, 2008). The female *S. chinesis* plant can produce the fruit via fertilization with pollen from a male plant (Shilova, 1963). It is harvested in most countries, including Korea, by the cutting of half-matured berries between August and September. The berries of *S. chinesis* are called omija (translated as "five-flavor fruit") in Korea, because this fruit has all five of the basic flavors-salty, sweet, sour, pungent, and bitter (Gutnikova, 1951; Panossian and Wikman, 2008). Generally, its dried fruits have been used for a variety of purposes, including as a therapeutic drug, teas and wines. In many countries, it has been used as a therapeutic drug, and is purported to have liver-protective and immune-modulatory abilities. A variety of key constituents including schizandrin, deoxyschizandrin, gomisin, and pregomisin have been isolated from the seeds of the fruit. Additionally, *S. chinesis* berries have been used in the manufacture of several foods. A wine was using the berries of *S. chinesis* has been produced in China, whereas in Korea, the berries are made into a tea. Meanwhile, in Japan, these berries are referred to as "gomishin", and have been used for medicinal purposes, to treat colds and sea-sickness. In Russia, dozens of tons of berries are used annually in the commercial production of juices, wine, extracts and sweets (Gutnikova, 1951; Agejenko and Komisssarenko, 1960).

A variety of previous pharmacological studies have suggested that *S. chinesis* may exert beneficial biological effects on liver tissue, the central nervous system, the respiratory system, the cardiovascular system and the endocrine system (Table 1) (Panossian and Wikman, 2008). The major and characteristic components of *Schisandraceae* berries have been previously isolated, and are referred to as lignans. The lignans are categorized into the five following classes: dibenzocyclooctadiene lignans (type A), spirobenzofuranoid dibenzocyclooctadiene lignans (type B), 4-aryltetralin lignans (type C), 2,3-dimethyl-1,4-diarylbutane lignans (type D), and 2,5-diaryltetrahydrofuran lignans (type E)(Table 2)(Lu and Chen, 2009). Thus far, a total of 43 lignans have been isolated from *S. chinesis* in various

studies; a list is provided in Table 2. Among these lignans, most of the lignans isolated from *S. chinesis* exhibit a dibenzocyclooctadiene lignan (type A) structure, with the exception of three lignans: pregomisin, meso-dihydroguaiaretic acid and nordihydroguaiaretic acid. The three lignans described in this chapter are of the type A structural group. Additionally, the dibenzocyclooctadiene lignans are further divided into two types based on their stereostructures-S- and R-biphenyl configuration. Structural elucidation studies have shown that the cyclooctene rings of dibenzocyclooctadiene lignans evidence a twist-boat-chair (TBC) or twist-boat (TB) conformation (Lu and Chen, 2009). Approximately half of the lignans from *S. chinesis* evidence an S-biphenyl configuration and the other half exhibit an R-biphenyl configuration. According to the conformation with cyclooctene rings, only four lignans exhibited a TB conformation, but the rest of the lignans had the TBC conformation. Among the three lignins described in this chapter, only gomisin N exhibits an S-biphenyl configuration, whereas tigloylgomisin H and schisandrin A has an R-biphenyl configuration.

Body system	**Regulatory system: stress-system**	**Pharmacological effect: adaptogenic effect**
Cardiovascular system	Central and vegetative nervous system	Stimulating effect
Gastrointestinal system	Endocrine system	Stress-mimetic and stress-protective effect
Respiratory system	Immune system	Stress-protective effect

Table 1. Summary of the pharmacological activities of *S. chinensis* (Panossian and Wikman, 2008).

Compounds	**Structure type**	**Configuration/ conformation**	**References**
Gomisin N	A	S/TBC	Ikeya et al., 1978a
Schizandrin C(wuweizisu C, schisandrin C)	A	S/TBC	Chen and Shu, 1976
(-)-Gomisin K1	A	S/TBC	Ikeya et al., 1980
Gomisin J	A	S/TBC	Ikeya et al., 1978b
(-)-Gomisin L2	A	S/TBC	Ikeya et al., 1982
(-)-Gomisin L1	A	S/TBC	Ikeya et al., 1982
Gomisin S	A	S/TBC	Ikeya et al., 1988
Epigomisin O	A	S/TBC	Ikeya et al., 1991; Ikeya et al., 1979
Tigloylgomisin P	A	S/TBC	Ikeya et al., 1990; Ikeya et al., 1980
Angeloylgomisin P	A	S/TBC	Ikeya et al., 1990; Ikeya et al., 1980
Gomisin D	A	S/TBC	Ikeya et al., 1976
Gomisin E	A	S/TBC	Ikeya et al., 1979
Gomisin O	A	S/TBC	Ikeya et al., 1979
6-o-benzoylgomisin O	A	S/TB	Chen et al., 1994
Angeloylgomisin O	A	S/TB	Ikeya et al., 1982

Angeloyl isogomisin O	A	S/TB	Ikeya et al., 1982
Benzoyl isogomisian O	A	S/TB	Ikeya et al., 1982
Schisandrene	A	S/TBC	Choi et al., 2006
Angeloylgomisin Q	A	S/TBC	Ikeya et al., 1979
Gomisin F	A	S/TBC	Taguchi and Ikeya, 1977
Gomisin G	A	S/TBC	Taguchi and Ikeya, 1977
Schisantherin A(gomisin C, wuweizi ester A)	A	S/TBC	Ikeya et al., 1990; Taguchi and Ikeya, 1977
Schisantherin B(gomisin B, wuweizi ester B)	A	S/TBC	Ikeya et al., 1990; Taguchi and Ikeya, 1977
Schisantherin D	A	S/TBC	Liu et al., 1978; Ikeya et al., 1982
Gomisin R	A	S/TB	Ikeya et al., 1982
Deoxyschizandrin (wuweizisu A, schisandrin A, deoxyschisandrin)	A	R/TBC	Chen and Shu, 1976; Yue et al., 1994
(+)-Gomisin K2	A	R/TBC	Ikeya et al., 1980
Schisanhenol [(+)-gomisin K3]	A	R/TBC	Ikeya et al., 1980; Ikeya et al., 1990
γ-Schizandrin(γ-schisandrin)	A	R/TBC	Liu et al., 1978
Schizandrin B(wuweizisu B, schisandrin B, (±)- γ-schizandrin)	A	R/TBC	Chen and Shu, 1976
(±)-Gomisin M1	A	R/TBC	Ikeya et al., 1982
(+)-Gomisin M2	A	R/TBC	Ikeya et al., 1982
Schizandrin(schisandrol A, schisandrin, wuweizi alcohol A)	A	R/TBC	Chen and Shu, 1976
Gomisin A(schisandrol B, wuweizi alcohol B)	A	R/TBC	Taguchi and Ikeya, 1977
Gomisin H	A	R/TBC	Ikeya et al., 1979
Angeloylgomisin H	A	R/TBC	Ikeya et al., 1979
Tigloylgomisin H	A	R/TBC	Ikeya et al., 1979
Benzoylgomisin H	A	R/TBC	Ikeya et al., 1979
Gomisin T	A	R/TBC	Ikeya et al., 1988
Isoschizandrin	A	R/TBC	Ikeya et al., 1991; Ikeya et al., 1988
Pregomisin	D	/	Ikeya et al., 1978
Meso-dihydroguaiaretic acid	D	/	Ikeya et al., 1979
Nordihydroguaiaretic acid	D	/	Sakurai et al., 1992

Table 2. Lignans isolated from the fruits of *S. chinensis*. A: Dibenzocyclooctadiene lignan; D: 2,3-dimethyl-1,4-diarylbutane lignan; S or R: the configuration of the biphenyl unit; TBC or TB: the conformation of the cyclooctane ring (Lu and Chen, 2009).

Meanwhile, hepatocellular carcinoma is a primary malignancy of the hepatocytes, and generally leads to death within 6-20 months. The disease is the fifth most common cancer in men and the eighth most common cancer in women worldwide (Bosch et al., 2004). Cirrhosis of any etiology is known to be the major risk factor for hepatocellular carcinoma (Adami et al., 2008). Thus far, approximately 80% of patients with newly diagnosed

hepatocellular carcinoma have preexisting cirrhosis in the liver organ, caused mainly by excessive alcohol use, hepatitis C infection and hepatitis B infection (El-Serang and Mason, 2000). Additionally, many therapeutic strategies have been attempted to medically treat hepatocellular carcinoma, including surgical resection and liver transplantation, although the available treatment options depend on the specific characteristics of the tumor (Thomas and Zhu, 2005; Bruix and Sherman, 2005).

There has been some very interesting research conducted to determine whether the lignans isolated from *S. chinensis* may improve and prevent a variety of human diseases, including cardiac disease, respiratory disease, immune disease, endocrine disease and neuronal disease. However, only a few investigations have been conducted to determine the therapeutic effects of lignans isolated from *S. chinensis* on hepatic carcinoma. Therefore, this chapter describes the important results of an experiment using three lignans (gomisin N, tigloylgomisin H (TGH) and schisandrin A) and one blend (KY88 Liver-Livo) which may prove valuable in the development of a therapeutic drug for the treatment of hepatic carcinoma.

2. Therapeutic effects of lignans and blend isolated from *S. chinensis* on hepatic carcinoma

This main section described experimental data regarding the biological effects of three lignans and a blend on hepatic carcinoma, and the potential for the use of those lignins as therapeutic drugs.

2.1 Effects of gomisin N

Gomisin N (Fig. 1) is already well known as a member of the schisandrin B family, and the most abundant lignin in the fruit lignins of *S. chinensis*. Among the various functions of gomisin N, its ability to increase antioxidant capacity and protect against mitochondria decay was initially identified by a biochemical mechanism study (Ko and Lam, 2002). Additionally, gomisin N could induce an increase in heat shock protein, which performed an important function when cells and tissues were affected by a variety of stressful stimuli from the external environment. Recently, a stereoisomer of gomisin N, (-) schisandrin B, was identified and its function in cell protection was investigated. These results demonstrated that schisandrin B and (-) schisandrin B were the most potent in enhancing antioxidant protection. Therefore, these two lignans may be employed for the protection against and reversal of tissue damage induced by environmental hazards, physical exercise, and aging (Chiu et al., 2006). However, we found a new function of gomisin N, particularly its effects against hepatic carcinoma.

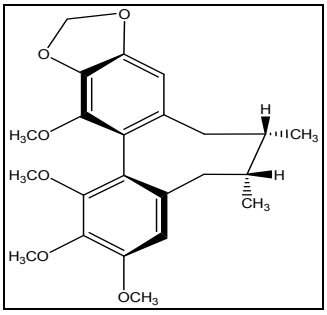

Fig. 1. Chemical structure of gomisin N isolated from *S. chinensis*.

2.1.1 Preparation of gomisin N

The dried fruits of *S. chinensis* (2.5 kg) were ground to a fine powder and were successively extracted at room temperature with *n*-hexane, EtOAc, and MeOH. The hexane extract (308 g) was evaporated under vacuum and chromatographed on a silica gel (40 μm, J.T. Baker, NJ, USA) column (70 x 8.0 cm) with a step gradient of 0%, 5%, 10%, 20%, and 30% EtOAc in hexane (each 1 L). Of these extracts, Fraction 11IA, one of 5 subfraction originated from fraction 11 was further purified by column chromatography on silical gel eluting with $CHCl_3$-acetone (19:1) to give a gomisin N (774 mg)(Yim et al., 2009).

2.1.2 Effects of gomisin N on cell proliferation

The therapeutic effects of gomisin N on hepatic carcinomas was initially suggested by Yim et al. (2009). First, they extracted lignans including gomisin N (Seo et al., 2004), schisandrin (Ikeya et al., 1979a), schisandrin C (Seo et al., 2004) and gomisin A (Ikeya et al., 1979b; Park et al., 2007) from *S. chinensis* via *n*-hexane, EtOAc and MeOH extraction techniques. Their structures were analyzed via LC-MS and NMR analysis for identification. Proliferation activity was screened for all groups that had received one of the four lignans of varying concentrations via an MTT assay to select the lignan with the highest apoptotic effect on hepatic carcinoma. For schisandrin C, the MTT assay demonstrated that this lignan induced cell proliferation rather than cell death in hepatic carcinoma cells in a concentration range of 40 μM to 160 μM, whereas the gomisin A-treated group maintained a stable cell population (Fig. 2). However, the MTT screening also demonstrated that two lignans, gomisin N and schisandrin, significantly induced cell death in relation to other lignans. In the gomisin N-treated group, cell proliferation in the 40 μM-treated groups was slightly increased compared to the vehicle. However, cell proliferation decreased rapidly in a gomisin N concentration range from 80 μM to 320 μM (Fig. 2). Schisandrin also induced cell death at the higher concentrations, but the cell death ratio was lower than that observed with gomisin N (Fig. 2). These results indicated that gomisin N treatment was highly effective in inducing the death of hepatic carcinoma cells at higher concentrations, but not at low concentrations. Yim et al. selected gomisin N as the candidate lignan for further analysis, owing to its anti-proliferation and pro-apoptosis functions.

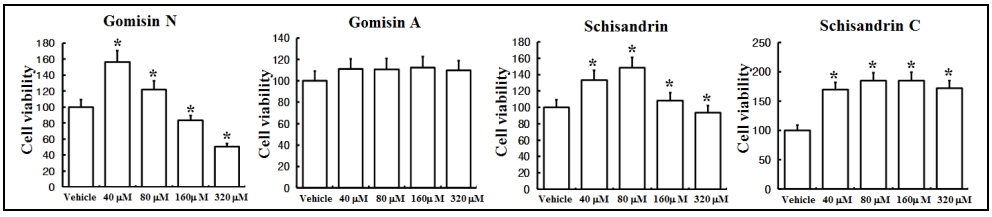

Fig. 2. Anti-proliferative effect of gomisin N, schisandrin, schisandrin C and gomisin A isolated from *S. chinensis* (Yim et al., 2009).

Additionally, phase-contrast microscope analysis was conducted to determine whether the cell death effects observed in the MTT assay were concurrent with the observed cell morphological changes. In the 40 μM-treated group, the number and morphology of hepatic carcinoma evidenced greater crowding than was observed in the vehicle-treated group. The hepatic carcinoma cell line in the 80 μM-treated groups evidenced a pattern similar to that observed with the vehicle-treated group. In the 160 μM-treated group, few dead cells were

observed in the microscopic images of the hepatic carcinoma cell line. The numbers of these cells were increased markedly in the 320 μM-treated groups (Fig. 3). These results demonstrated that the results observed on cell morphology analysis under gomisin N-treated conditions were consistent with the results of an MTT assay under the same conditions (Yim et al., 2009).

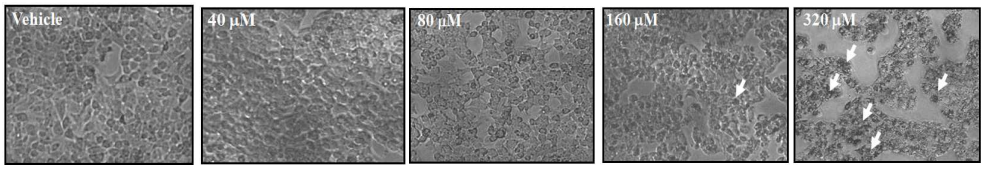

Fig. 3. Microscope images of hepatic carcinoma cell lines after 24 hrs of treatment with gomisin N at various concentrations (Yim et al., 2009).

2.1.3 Effects of gomisin N on apoptosis

Apoptosis, or programmed cell death, performs a critical role in a variety of physiological processes during fetal development and in adult life. Defects in the apoptotic process lead to the progress of many diseases involving progressive cell accumulation and cancer in most cases. Yim et al. (2009) further investigated the correlation between gomisin N and apoptosis. To achieve this, a hepatic carcinoma cell line treated with various concentrations of gomisin N were stained with FITC Annexin V, and fluorescence activity was determined via flow cytometry. Gomisin N significantly induced the increase in the number of cells undergoing apoptosis, from 15% to 98%, in 24 hrs. However, this reaction was induced even at low gomisin N concentrations, and this level of induction remained at a constant level up to and throughout higher concentrations (Fig. 4). Therefore, these results indicated that gomisin N could induce the apoptosis of hepatic carcinoma cell lines in a dose-independent manner. Specifically, gomisin N may induce the loss of plasma membrane asymmetry, one of the early events in the apoptosis process, for most cells treated at a concentration of 40 μM.

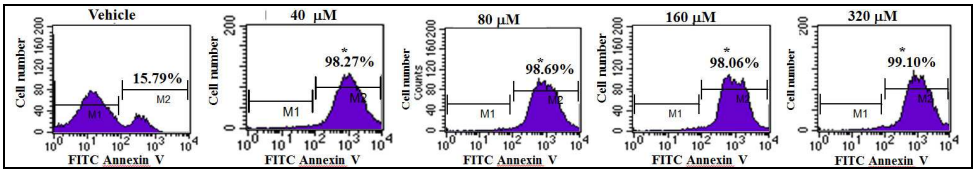

Fig. 4. Identifying apoptotic cells affected with gomisin N treatment. Hepatic carcinoma cells were incubated with gomisin N at various concentrations for 24 hrs, and stained with FITC Annexin V to detect the apoptotic cells (Yim et al., 2009).

Additionally, the apoptosis process involves many families of proteins. Among these proteins, the Bcl-2 proteins are one of the key molecules in inducing the anti-apoptotic process (Apakama et al., 1996). The results of previous studies have shown that this protein was overexpressed in many solid tumors, and that it contributes to chemotherapy resistance and radiation-induced apoptosis (Apakama et al., 1996; Joensuu et al., 1994). Unlike many other known human oncogenes, Bcl-2 exerts its influence by enhancing cell survival rather

than by stimulating cell division (Joensuu et al., 1994). Yim et al. (2009) attempted to determine whether the expression level of Bcl-2 protein would be affected by gomisin N treatment in a hepatic carcinoma cell line. Additionally, Yim et al. (2009) assessed the effects of gomisin N treatment on proteins associated with the apoptosis signaling pathway. To achieve this, the expression levels of Bcl-2 and Bax proteins were determined in the vehicle-treated and gomisin N-treated groups via Western blot analysis. The expression level of Bcl-2 protein did not change in the low concentration range as compared to the vehicle. However, the high concentration range-namely the 160 μM and 320 μM-treated groups-evidenced higher levels of Bcl-2 protein expression than was observed in the low concentration range. In the case of Bax, the expression level of this protein was markedly increased only in the 320 μM treated group compared to the vehicle and the other concentration groups. Furthermore, in order to determine whether the tumor suppressor gene would be affected by gomisin N in the hepatic carcinoma cell line, the expression level of p53 protein was detected in the vehicle and gomisin N-treated groups. The expression level of p53 protein remained unchanged in the four treatment groups and the vehicle (Fig. 5). These results indicate that gomisin N may simultaneously induce an increase in the levels of the proteins associated with the anti-apoptotic and pro-apoptotic processes, but does not alter the level of expression of the tumor suppressor protein, p53.

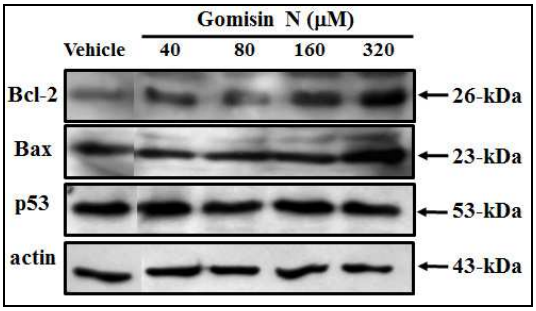

Fig. 5. Effects of gomisin N on Bcl-2, Bax and p53 protein expression to investigate the mechanism underlying apoptosis (Yim et al., 2009).

2.2 Effects of KY88 liver-livo (KY88)

KY88 was one of herbal blends containing *Schizandrae fructus* (Chow et al., 2001). Thus far, three major functions of this drug have been demonstrated; the modulation of the immune system, the induction of apoptosis, and the induction of cytokines by lymphocytes and liver cancer cells (Chow et al., 2004). However, a thorough determination of the therapeutic effects of KY88 against hepatic carcinoma will require further research into its action mechanism.

2.2.1 Preparation of KY88

KY88 is a blend containing the herbal extract of *Schizandrae fructus, Bupleuri radix, Artemisiae capillaris, Desmodii herba, Poria sclerotium, Lithospermi radix, Paeoniae radix, Phellodendri cortex, Scutellariae radix* and *Trichosanthis radix*. Ten grams of each of all ingredients of above herbs were primarily washed and concentrated and purified with the process of extraction. Then,

the essence of the herbal extracts -KY88- was assembled. Also, this capsule had been verified by SGS Hong Kong Ltd (Socie´te´ Ge´ne´rale de Surveillance) to be free of heavy metals and microorganisms. Before the study for inhibition ability, KY88 (50 g) was extracted with three times using MeOH. The solid residue obtained from the crude extract was then dissolved in dimethyl sulphoxide to a concentration of 92 mg/ml and stored at 4°C until use (Loo et al. 2007).

2.2.2 Effects of KY88 on cell proliferation and HBeAg/HBsAg secretion

Loo et al. (2007) was the first to investigate whether KY88 has an ability to inhibit hepatocellular carcinoma cell proliferation and the secretion ability of HBsAg (hepatitis B virus surface antigen) and HBeAg (hepatitis B virus core antigen). For this assessment, KY88 was applied to the HB-8064 hepatocellular carcinoma cell line, and the cell proliferation rate and HBsAg/HBeAg secretion were measured on days 1, 3, 5 and 7. The MTT assay showed that the treatment of 0.1, 0.5 and 1 mg/ml KY88 for 7 days induced the significant suppression of hepatic carcinoma. Additionally, the cell proliferation rate of all KY88-treated cells was significantly lower than that of the control-treated group (Fig. 6). In particular, a remarkable suppression of cell proliferation was detected at three concentrations from day 5. Therefore, these data demonstrated that KY88 may potentially exert an effect in inhibiting the cellular proliferation of hepatocellular carcinoma.

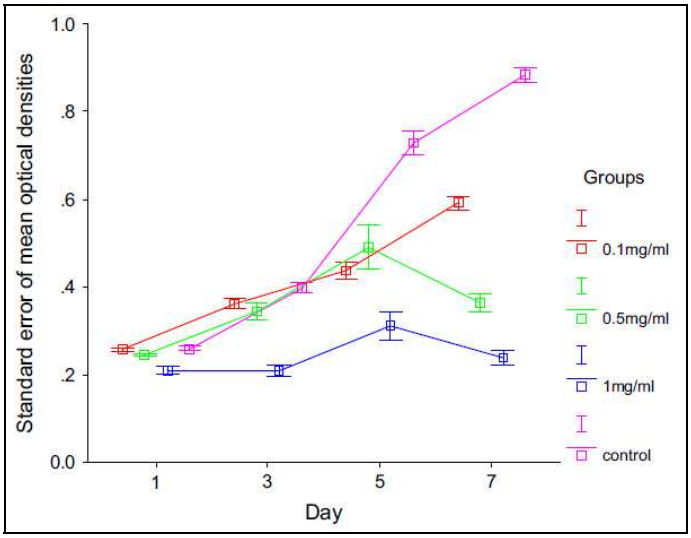

Fig. 6. Dose-dependent inhibition of cell proliferation at three concentrations of KY88 (Loo et al., 2007).

Furthermore, the secretions of HBsAg and HBeAg from the hepatocellular carcinoma cell line were dramatically inhibited by KY88 treatment (Fig. 7). The observation of HBsAg and HBeAg reflected the cell's infection with hepatitis B virus and their replication activity (Loo et al., 2007). This data indicated that KY88 may potentially have the ability to inhibit the proliferation of hepatocellular carcinoma cells, as well as the reduced secretions of HBsAg and HBeAg to restrict tumor growth.

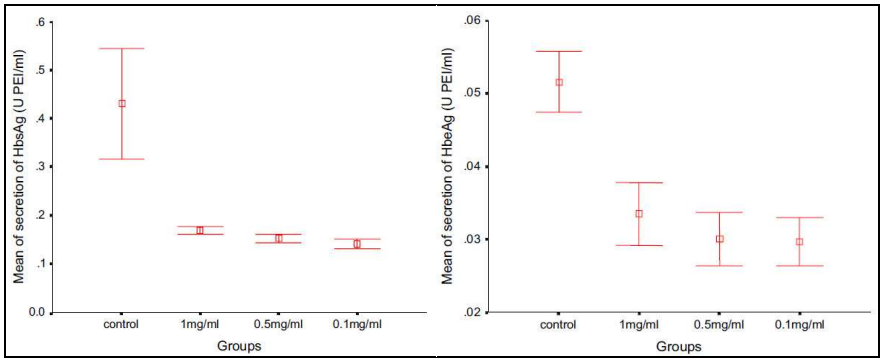

Fig. 7. Secretion level of HBsAg and HBeAg from hepatocellular carcinoma cell line after KY88 treatment (Loo et al., 2007).

2.2.3 Effects of KY88 on apoptosis and cytokine secretion

Chow et al. (2004) previously evaluated the effects and action mechanism of KY88 on liver cancer cells using methanol extracts of KY88 to develop a novel therapeutic drug for the treatment of hepatoma. After methanol extracts of KY88 were applied to a hepatocellular carcinoma cell line, the cell proliferation, DNA laddering and cytokine secretion were detected in these cells. KY88 induced a significant inhibition of cell proliferation and an increase in the DNA ladder pattern, which is a marker that indicates apoptosis in hepatocellular carcinoma cells (Fig. 8).

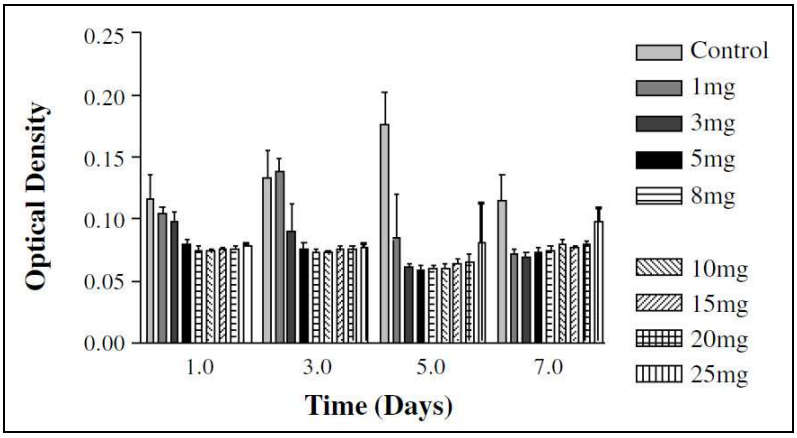

Fig. 8. Inhibition effect of KY88 methanol extracts on hepatocellular carcinoma cell (Chow et al., 2004).

Additionally, cytokine ELISA assay results demonstrated that IL-4 and TNF-α concentrations were increased significantly by KY88 treatment when compared against the control group at 24 hrs. However, IL-2, IL-6 and INF-γ concentrations were maintained at constant levels (Fig. 9). Therefore, this data indicates that the methanol extracts of KY88 may induce apoptosis via the regulation of IL-4 and TNF-α secretion.

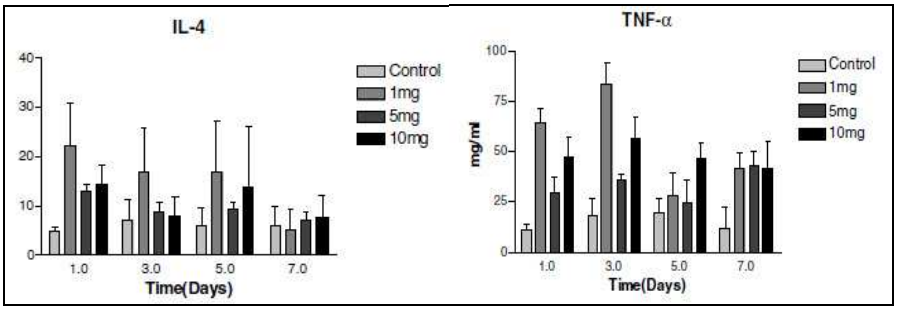

Fig. 9. Significant change of IL-4 and TNF-α level in hepatocellular carcinoma cell after KY88 treatment (Chow et al., 2004).

2.3 Effects of schizandrin A

Schizandrin A is referred to by several other names, including deoxyschizandrin, wuweizisu A, and deoxyschisandrin (Lu and Chen, 2009), and is one of the most effective lignins isolated from *S. chinensis* (Fig. 10). Previous studies have also demonstrated that schizandrin A may have the hepatoprotective, antioxidative, neurobiological performance-improving and anti-tumor activities (Deng et al., 2008; Huang et al., 2008). For the first time, the function of schizandrin A was found to protect against liver injuries, activate liver regeneration and supress liver carcinogenesis (Zheng et al., 1997). Additionally, this lignan was partially used as a Ca^{2+} modulator which induced the synchronization of Ca^{2+} oscillation via the influx inhibition of extracellular Ca^{2+} and the initiation of action potential (Fu et al., 2008). However, only a small amount of research has been conducted regarding the possible inhibitory effects of schizandrin A on hepatocellular carcinoma. This chapter also describes recent key results regarding the possible anti-liver cancer effects of schizandrin A.

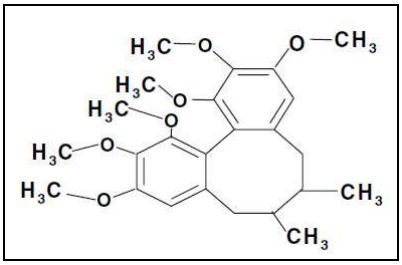

Fig. 10. Chemical structure of schizandrin A isolated from *S. chinensis*.

2.3.1 Preparation of schizandrin A

Generally, schizandrin A was prepared with a methods suggested by Chen et al. (1976) and Yue et al. (1994). Firstly, *S. chinensis* Baill (10 kg) was extracted with 50 L of hexane for 1.5 hr and the obtained extract was dried under a reduced pressure. The 978.8 g of hexane extract were dissolved in 9.8 L of hexane and sequentially extracted two times with 9.8 L of 60% (v/v) MeOH. The mixture obtained from above extraction was dried under a reduced pressure and finally 112.2 g of a fraction having a high lignan content were obtained. These fraction having a high lignan content was subjected to the fractionation high-speed liquid chromatography

[column: Kiesel Gel 60 (230 to 400 mesh) supplied by Merk, diameter=10 cm, length=100 cm, moving phase: n-hexane/ethyl acetate (7/3), flow rate: 200 ml/min, apparatus: Waters Prep LC/System 500A]. Fractions eluted at 63 to 70 minutes in the fractionation high-speed liquid chromatography were combined and dried under a reduced pressure. The obtained residue (schizandrin A) was recrystallized from methanol to obtain 1.05 g of a colorless prism crystal.

2.3.2 Effects of schizandrin A and LCC (five schizandrins and crud extract from *Fructus shizandrae*) on human hepatocellular carcinoma

Huang et al. (2008) evaluated the reversal effects of five schizandrins (schizandrin A, schizandrin B, schizandrin C, schizandrol A and schizandrol B) and LCC on multidrug resistance (MDR) in several cancer cells, including hepatocellular carcinoma and epidermal carcinoma *in vitro* and *in vivo*. After treatment with various concentrations of five schizandrins and LCC into cancer cell lines, drug sensitivity, apoptosis, doxorubicin (Dox) accumulation and protein kinas C (PKC) expression were measured in cancer cell lines. Various levels of MDR reversal activity were noted at a 25 μM concentration of the five tested compounds. The most potent compound found was schizandrin A. The reversal activity of MDR was also induced by 25 μg/ml of LCC in KBV200, MCF-7/Dox cells, and human hepatic cellular carcinoma Bel7402 cells. The flow cytometry analysis results demonstrated that both schizandrin A and LCC treatment induced an increase in apoptosis in human hepatocellular carcinoma cells. As shown in Fig. 11, the sub-G1 peak, which is one of the characteristics of apoptosis, was increased significantly from 1.8% in the Bel7402 cells treated with Dox only to 10-14% in the schizandrin A + Dox-treated cells or the LCC + Dox-treated cells. Additionally, chromatin condensation, another marker of apoptosis, was enhanced in cells treated with schizandrin A + Dox or with LCC + Dox. Furthermore, downregulations of PKC and P-glycoprotein expression were noted in cells treated with schizandrin A + Dox or LCC + Dox (Fig. 11). These data showed that schizandrin A and LCC may induce a reversal of MDR in cancer cells via the inhibition of P-glycoprotein and PKC expression.

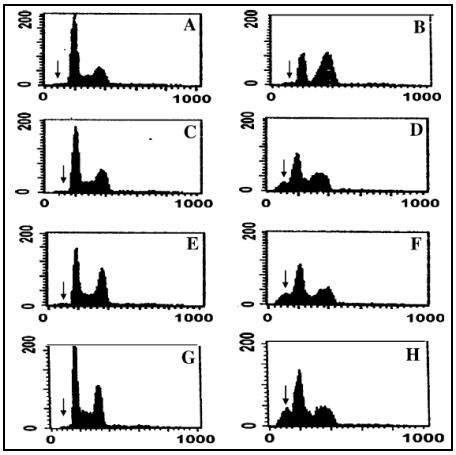

Fig. 11. Enhancing effects of schizandrin A and LCC on apoptosis in human hepatocellular carcinoma cells. **A** Control, **B** Dox 1,250 ng/ml, **C** Verapamil (VPL) 20 μM, **D** Dox 1,250 ng/ml + VPL 20 μM, **E** Schizandrin A 25 μM, **F** Dox 1,250 ng/ml + Schizandrin A 25 μM, **G** LCC 25 μg/ml, **H** Dox 1,250 ng/ml + LCC 25 μg/ml (Huang et al., 2008).

2.3.3 Effects of LCC on the tumor growth of mice

In order to confirm the MDR-reversing effects of LCC and schizandrin A detected *in vitro*, tumor growth was measured in nude mice bearing KBv200 xenografts. Following 10 days of vincristine injection, tumor growth was inhibited significantly-by approximately 12%-when tumor size was compared to that of the control group (Huang et al., 2008). Furthermore, co-treatment with LCC and vincristine at 100, 200 and 300 mg/kg BW increased the anti-tumor activity induced by vincristine in a dose-dependent manner (Fig. 12). In particular, LCC 300 mg/kg BW co-treatment for 15 days resulted in dramatic differences-most notably, a 41.9% inhibition of tumor size (Huang et al., 2008). These results indicate that LCC has potential for use in the development of a therapeutic drug for hepatoma *in vivo*.

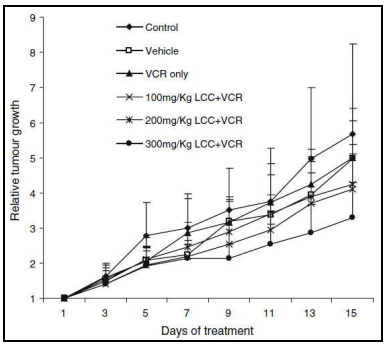

Fig. 12. Inhibition effects of LCC on vincristine-induced anti-tumor activity in nude mice bearing the KBv200 xenograft (Huang et al., 2008).

2.4 Effects of TGH

The structure of TGH (Fig. 13) was firstly assessed by Ikeya et al. (1978a). In Korea, this lignin was initially identified via gas chromatography/mass spectrometry (GC/MS) from *S. chinensis* harvested in Muju, Korea (Sohn and Bock, 1989). However, many things remain unknown regarding the functions of this lignan. Recently, several important study results suggesting a possible function of TGH in cancer therapy have caused an increase in interest in the compound.

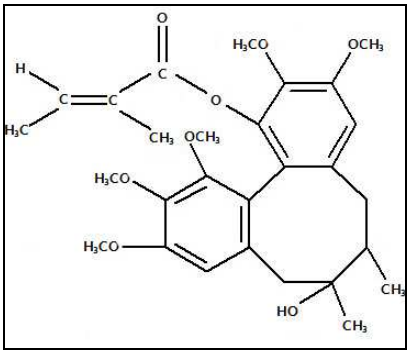

Fig. 13. Chemical structure of TGH isolated from *S. chinensis*.

2.4.1 Preparation of TGH

In order to prepare TGH, the fruit of *S. chinensis* (250 g) was firstly extracted three times using 500 mL of MeOH with sonication for 1 hr. The dried MeOH extract was collected from filtered solution with dryness under reduced pressure. Then, MeOH extract (50 g) was suspended in water and sequentially fractionated with *n*-hexane and CH_2Cl_2. The purified *n*-hexane fraction (10 g) was subjected to chromatography on an RP-18 column (4.5 x 20 cm, 5:5 - 9:1 MeOH:water, v/v) to yield fractions 1-8. Furthermore, fraction 4 (650 mg) was dissolved in MeOH and subjected to isocratic semi-preparative HPLC using an YMC J-sphere ODS column (20 x 250 mm, 4 μm; YMC). TGH was separated with MeCN-0.1% TFA in H2O (50:50 in 50 min, 10 mL/min, 254 nm) to yield 62.0 mg of compound 4 (93.65%). The identity of TGH was confirmed by 1H- and 13C-NMR spectroscopy (Lee et al., 2009).

2.4.2 Effects of TGH on cell survival

Lee et al. (2009) initially investigated the anti-cancer functions and action mechanisms of nine lignans isolated from the fruit of *S. chinensis*. Firstly, nine lignans including schisandrol A, schisandrol A, TGH, angeloylgomisin H (AGH), schisandrin A, schisandrin B, gomisin J, gomisin N and schisandrin C were isolated from *S. chinensis* and the effects of each lignin on the cell survival rate were determined. Among the nine lignans, TGH induced a reduction in cell survival at concentrations ranging from 31.3 μM to 250.0 μM, whereas the AGH samples maintained a steady level in terms of cell survival (Fig. 14). During this period, the quinone reductase activity was dramatically increased in hepatocarcinoma cells and evidenced a high chemoprevention index. Additionally, the mechanism study results demonstrated that the expression of genes mediated by the antioxidant response element (ARE), an important regulatory region in the promoter of the detoxification enzyme gene which is regulated by the nuclear accumulation of Nrf2, was enhanced significantly by TGH. Therefore, all study results appear to indicate that TGH may be considered as a potential liver cancer-preventive compound that specifically induces increases in antioxidant enzyme expression via the formation of the Nrf2-ARE binding complex.

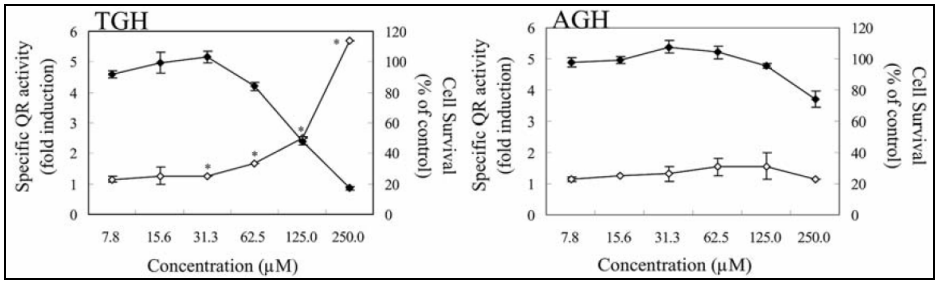

Fig. 14. Effects of TGH treatment on the quinone reductase activity and cell survival (Lee et al., 2009).

3. Conclusion

The development of novel therapeutic drugs for hepatic carcinoma is a very important objective in the field of pharmacological research. Among the variety of approaches thus far pursued to develop novel drugs, identification and screening of natural compounds from

medical herbs has proven a very effective one-not least, because this method saves a great deal of time and cost. Recently, many institutes and companies in advanced countries have focused on an approach to novel drugs for hepatic carcinoma via the use of various lignins isolated from *S. chinensis*. This chapter introduces three lignans and one blend which may prove valuable in efforts to combat hepatic carcinoma. Gomisin A at high concentration was found to significantly induce anti-proliferative and pro-apoptotic effects in hepatic carcinoma. Schizandrin A markedly increased vincristine-induced hepatic carcinoma apoptosis and anti-tumor activity. Additionally, TGH induced the death of hepatic carcinoma cells and inhibited quinone reductase activity. Furthermore, KY88 was a blend composed of 10 herbal extracts and effects a dose-dependent inhibition of hepatocellular carcinoma cellular proliferation (Table 3).

Collectively, the results of these studies demonstrated that these lignins and the blend from *S. chinensis* were regarded as an anti-cancer drug candidate capable of inducing apoptosis and inhibiting the cell proliferation of hepatocellular carcinoma via a variety of mechanisms.

Compounds	**Function on hepatocellular carcinoma**	**References**
Gomisin N	· Induction of hepatic carcinoma apoptosis · Increase of Bcl-2 protein expression	Yim et al., 2009
KY88	·Dose-dependent inhibition of hepatocellular carcinoma proliferation and secretion of HBsAg and HBeAg ·Induction of hepatic carcinoma apoptosis and IL-4/TNF-α secretion	Loo et al., 2007 Chow et al., 2004
Schizandrin A	·Induction of hepatic carcinoma apoptosis and PKC down regulation ·Increase of anti-tumor activity induced by vincristine	Huang et al., 2008
TGH	·Induction of hepatic carcinoma death and inhibition of quinone reductase activity	Lee et al., 2009

Table 3. Summary therapeutic function of three lignins and one blend from *S. chinensis* on hepatocellular carcinoma.

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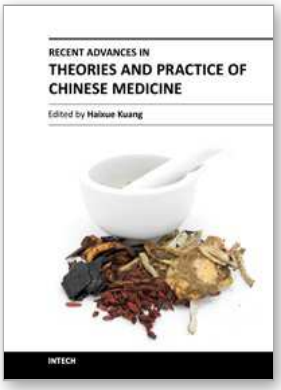

Recent Advances in Theories and Practice of Chinese Medicine

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During the recent years, traditional Chinese medicine (TCM) has attracted the attention of researchers all over the world. It is looked upon not only as a bright pearl, but also a treasure house of ancient Chinese culture. Nowadays, TCM has become a subject area with high potential and the possibility for original innovation. This book titled Recent Advances in Theories and Practice of Chinese Medicine provides an authoritative and cutting-edge insight into TCM research, including its basic theories, diagnostic approach, current clinical applications, latest advances, and more. It discusses many often neglected important issues, such as the theory of TCM property, and how to carry out TCM research in the direction of TCM property theory using modern scientific technology. The authors of this book comprise an international group of recognized researchers who possess abundant clinical knowledge and research background due to their years of practicing TCM. Hopefully, this book will help our readers gain a deeper understanding of the unique characteristics of Chinese medicine.

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