RESEARCH ARTICLE

Proliferative and Inhibitory Activity of Siberian ginseng (*Eleutherococcus senticosus*) Extract on Cancer Cell Lines; A-549, XWLC-05, HCT-116, CNE and Beas-2b

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Abstract

Siberian ginseng (*Eleutherococcus senticosus*) is used primarily as an adaptogen herb and also for its immune stimulant properties in Western herbal medicine. Another closely related species used in East Asian medicine systems i.e. Kampo, TCM (Manchuria, Korea, Japan and Ainu of Hokkaido) and also called Siberian ginseng (*Acanthopanax senticosus*) also displays immune-stimulant and anti-cancer properties. These may affect tumour growth and also provide an anti-fatigue effect for cancer patients, in particular for those suffering from lung cancer. There is some evidence that a carbohydrate in Siberian ginseng may possess not only immune stimulatory but also anti-tumour effects and also display other various anti-cancer properties. Our study aimed to determine the inhibitory and also proliferative effects of a methanol plant extract of Siberan ginseng (*E. senticosus*) on various cancer and normal cell lines including: A-549 (small cell lung cancer), XWLC-05 (Yunnan lung cancer cell line), CNE (human nasopharyngeal carcinoma cell line), HCT-116 (human colon cancer) and Beas-2b (human lung epithelial). These cell lines were treated with an extract from *E. senticosus* that was evaporated and re-constituted in DMSO. Treatment of A-549 (small cell lung cancer) cells with *E. senticosus* methanolic extract showed a concentration-dependent inhibitory trend from 12.5 - 50μg/mL, and then a plateau, whereas at 12.5 and 25 μg/mL, there is a slight growth suppression in QBC-939 cells, but then a steady suppression from 50, 100 and 200μg/mL. Further, in XWLC-05 (Yunnan lung cancer cell line), *E. senticosus* methanolic extract displayed an inhibitory effect which plateaued with increasing dosage. Next, in CNE (human nasopharyngeal carcinoma cell line) there was a dose dependent proliferative response, whereas in Beas-2 (human lung epithelial cell line), an inhibitory effect. Finally in colon cancer cell line (HCT-116) we observed an initially weak inhibitory effect and then plateau.

Keywords: *Eleutherococcus senticosus* - A-549 (small cell lung cancer) - XWLC-05 (Yunnan lung cancer cell line)

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Introduction

Diet can play a major role in the development or alleviation of chronic illness such as staple oil type (He et al., 2014), or phytochemicals present in green tea (Cichello et al., 2013). On the other hand, herbs and herbal teas such as ginseng contain a wide array of phytochemicals and the efficacy of their health effect such as anti-cancer effect maybe more difficult to elucidate *in vivo*, and thus *in vitro* investigation is warranted.

It is well established that Korean ginseng (*Panax ginseng*) and its main active phytochemical Ginsenoside Rg1 has been shown to posses' anti-cancer effects *in vitro* (leukemia cells) (Jun Liu et al., 2012; Jing et al., 2014; Zhi-Mei You et al., 2014) and *in vivo* (intestinal carcinogenesis) (Ichihara et al., 2002). Two unrelated genus but with similar therapeutic actions, but also known as 'ginseng', possess similar immune modulating, and adaptogenic properties. The related ginseng's are known as 'Siberian ginseng'. Siberian ginseng comprises of two closely related genus; (*Eleutherococcus senticosus*) and (*Acanthopanax senticosus*). Animal studies and clinical studies have shown various anti-fatigue effects of Siberian ginseng supplementation (cortex) given to mice in a swimming fatigue test, which has been attributed to the phytochemical Eleutheroside B (Li et al., 2008) eleutheroside E, E2 and derivatives (Kimura et al., 2004), eleutheroside E, and also reduced natural killer cell activity and reduced corticosterone hormone elevation during the swimming test (Huang et al., 2011). However, when compared with stress management training (SMT), supplementation with Siberian ginseng was found

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to be non-significant with SMT or their combination (Schaffler et al., 2013), suggesting a physical effect as previously mentioned, rather than mental effect to reduce stress. On the other hand, in the elderly, *E. senticosus* supplementation has been shown to improve aspects of quality of life (Cicero et al., 2004), which may be related to the release of both NPY and Hsp70 via interaction with human neurons (Asea et al., 2013), and also via c-Fos accumulation in both the supraoptic nuclei (SON) and paraventricular nuclei (PVN) of the rat brain (Soya et al., 2008).

Various other effects of eleutherosides from *E. senticosus* include alleviation of insulin resistance in db/db (obese type 2 diabetic) mice and increased glucose uptake in C2C12 myotubles (Ahn et al., 2013), neuroprotective effects during neural ischemia in rats (Lee et al., 2012), increased endurance capacity and cardiovascular function in athletic training over an 8-week period (Kuo et al., 2010), anti-inflammatory effects on LPS-stimulated macrophages (Soo Kim et al., 2012) and interestingly also cancer (Huang et al., 2005), with glycoproteins from *Acanthopanax senticosus* (glycoproteins (EN-SP) showed anti-tumor effects related to immune-stimulating activities (Ha et al., 2004), further growth inhibition and apoptosis in stomach cancer cells (KATO III cells) (Hibasami et al., 2000), and inhibition of lung cancer metastasis in mice in a dose dependent manner in colon26-M3.1 carcinoma cells (Yoon et al., 2004).

The aim of this study was to observe whether a methanol extract used in the commercial production of OTC herbal extracts conferred the anti-cancer activity, in particular small lung cell, anti-cancer effect and confer with previous author's publications regarding *E. senticosus* and various lung cancer treatment. Moreover, the cell lines used in this study have previously not been investigated, in particular A-549 which is representative of lung cancer.

Further, the study aimed to gain preliminary evidence to proceed with an animal study to confirm either proliferation of tumor growth or that the observed effect is a misrepresentation due to the use of a cell line (i.e. post-absorptive modification of phytochemicals in the *E. senticosu* extract) would render them an immune stimulatory effect rather than tumor proliferative effect.

Materials and Methods

Cell lines, chemicals and bio-chemicals

A-549 (small cell lung cancer), XWLC-05 (Yunnan lung cancer cell line), CNE (human nasopharyngeal carcinoma cell line), HCT-116 (human colorectal carcinoma epithelial cell line) and Beas-2b (human lung [bronchial] epithelial cell line) were kindly donated by Professor Qiao Yao from the Yunnan Tumour Hospital. DMSO, MTT, DMEM/F12, 10% FBS, 100u/ml P/S were purchased from Sigma Aldrich. The assays were performed according to manufacturer's instructions.

Plant material and extraction

The methanol extract of plant material was obtained from a local supplier (BNP Sino, Qingdao, P.R. China). The material is used in the manufacturing of GMP and USFDA herbal supplements of Siberian ginseng as a monomer or as a composite product both in China and abroad. The plant material was sent to Southern Cross University for phytochemical analysis using LC-MS and HPLC.

HPLC analysis of phytochemical composition

The standardized extract contains the following

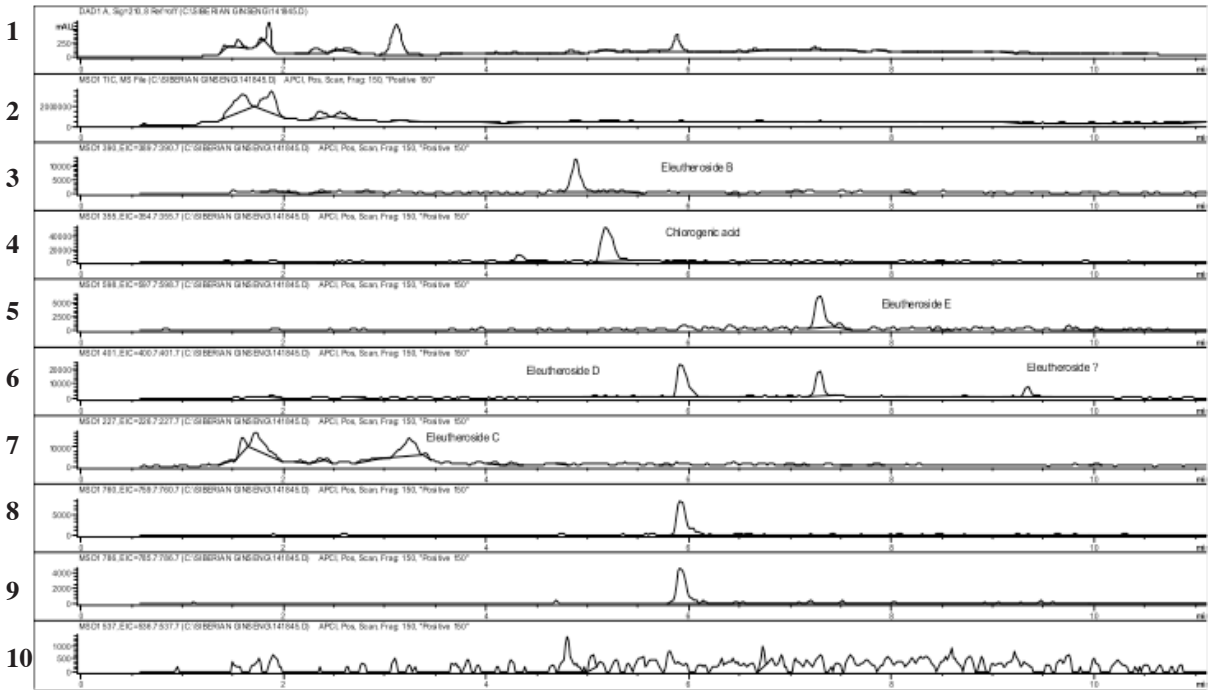

Figure 1. HPLC Trace of an *E. senticosus* (first 2 rows) as Performed by Southern Cross University Showing Eleutherodises B and E, and Chlorogenic Acid Detected. Individual phytochemicals (Eleutherodises B and E, and Chlorogenic acid) references shown in rows 3-10

Table 1. Current Therapeutic Use(s) of Siberian Ginseng (E. senticosus). Part(s) Used/ Active Constituent(s) Present and Indication(s)

Common Name (Latin binomial)	Part Used/ Active Constituent	Main Action (Indication)
Siberian ginseng (*Eleutherococcus senticosus*; Acanthopanax senticosus)	Root Eleutherosides, and triterpenoid saponins and glycans	Adaptogenic properties Immune modulating; indicated in physical stress, fatigue, debility and chronic fatigue (Bone 2007, p. 62)

Figure 2. Aerial Parts of Siberan Ginseng (*Eleutherococcus senticosus; Acanthopanax senticosus*) (Extracted from Herb List 2012)

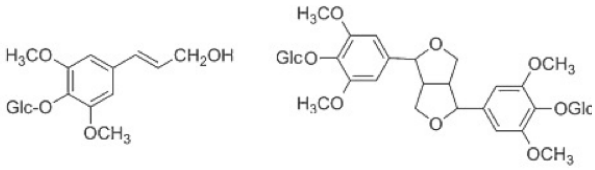

Figure 3. Eleutheroside B (left) and Eleuetheroside E (right); Syringin and Syringaresinol Diglucoside Respectively

identified phytochemicals as determined by LC-MS; Eleutherodises B and E and cholorogenic acid.

Determination of eleutheroside B-E content in Siberian ginseng extract

The chromatographic column used was Supelco LC-18-db 15cm*4.6mm 5um. The flow rate was set at 1ml/min at a detection wavelength of 220nm at a column temperature of 25°C. The injection volume used was 5ul, with a running time of 40min. The mobile phase used was 8% Acetonitrile B: 20% Acetonitrile.

A reference solution weighing 1.5mg of either Eleutheroside B, & Eleutheroside E or *E. senticosus* extract was placed into a 50ml bottle container, with 80% methanol solution constant volume. To determine the Eleutheroside B & Eleutheroside E content, 20mL of either reference standard or herbal extract sample were added into a 25ml bottle. A small amount of methanol was added and the solution was shaken. Then 15 ml 80% methanol, was added and then placed at room temperature for 20 minutes. A further volume of 15ml 80% methanol solution was added and the solution shaken for another 20min.

Determination of the proliferation or inhibitory effects of E. senticosus extract on cells

The *E. senticosus* extract was applied to A-549, XWLC-05, HCT-116, CNE, and Beas-2b cells to determine either an inhibitory or proliferative activity. The *E. senticosus* blend extract was prepared at either a dosage of 12.5, 25, 50, 100, or 200μg/ml dissolved in DMSO. A 10-ml volume of growth media was added to the herbal extract dosage, and the cell suspension was centrifuged at 3000 rpm for 10 min. The supernatant was poured off and re-suspended in 10 ml of media. Cells were counted on a hemacytometer and diluted accordingly, based on the number of cells needed for the assay. Cells were seeded at 30,000 cells per well. 24h later following cell seeding in 96-well plate, the medium was removed from the well, and 0.2ml of new medium was added (DMEM/F12, 10% FBS, 100u/ml P/S). The plate was incubated for a further 72h, and then the media was removed from the well, and another 0.2ml of new medium containing 10% MTT (5mg/ml) was added (cell staining). The plate was incubated for another 4h, and then the MTT was removed and 0.2ml DMSO was added. The plate was shaken in the dark for 10 minutes and then the OD value was recorded using a reader at 490nm. Controls for the assay included DMSO, cells alone, DPP alone. The cell growth was plotted against *E. senticosus*, and compared with the cell growth in doxorubicin alone.

Statistical analysis

Once the data was collected and processed, the data sets were tested with ANOVA using SPSS 12.0 for Windows software. to a p-value of 0.05. Results were calculated as the mean±S.E.M., using n=5, and then converted into either % proliferation or inhibition of the DMSO control. Student's t-test was used for statistical analyses.

Results

The methanol extract of *E. senticosus* was found to contain a number of phytochemicals; eleutherodises B and E and cholorogenic acid. Treatment of A-549 (small cell lung cancer) cells with the *E. senticosus* methanolic extract showed a concentration-dependent trend from 12.5 - 50μg/mL, and then plateaus (see Table 1), whereas at 12.5 and 25 μg/mL, there is a slight growth suppression in QBC-939 cells, but then a steady suppression from 50, 100 and 200μg/mL (Figure 2). Further, in XWLC-05 (Yunnan lung cancer cell line), *E. senticosus* methanolic extract displayed an inhibitory effect but plateaued with increasing dosage. Next, in CNE (human nasopharyngeal carcinoma cell line) there was a dose dependent proliferative response, whereas in Beas-2 (human lung epithelial cell line), an inhibitory effect. Finally in colon cancer cell line (HCT-116) we observed an initially weak inhibitory effect and then plateau.

Discussion

In the current study, the methanolic extract of

Table 2. IR%-Inhibitory Ratio (%) of the Siberian Ginseng Extract in Various Cancer Cell Lines (N.B. -ve Number Denotes Proliferative Effect)

Cell Line	DMSO	12.5μg/ml	25μg/ml	50μg/ml	100μg/ml	200μg/ml
A-549	0%	23.3±0.23%#	24.93±0.21%	22.86±0.20%	27.16±0.24%#	32.12±0.08%#
XWLC-05	0%	15.11±0.06%#	16.39±0.10%	16.11±0.02%	15.09±0.10%	16.37±0.04%
CNE	0%	6.34±0.11%#	5.27±0.08%	-1.45±0.03%*	-7.14±0.11%*	-14.27±0.25%*
Beas-2b	0%	-1.05±0.06%#	2.96±0.13%	1.22±0.06%	5.34±0.24%	15.57±0.63%*
HCT-116	0%	-10.47±0.40%#	9.95±0.23%	7.85±0.17%	13.35±0.23%#	10.75±0.14%

E. senticosus was found to contain a number of phytochemicals; eleutherosides B and E and cholorogenic acid. Further, in this study, a methanolic extract of Siberian ginseng conferred grow inhibitory effects against a number of lung and colon cancer cell lines *in vitro*. In particular, eleutherosides have been shown to activate natural killer cells and thus enhance immune function (Bohn et al 1987; Kimura et al., 2004), as they are suppressed in cancer patients as tested with A-549 cells and using the immunopotentiator, OK-432 (Sasanami et al 1982). The extract conferred an inhibitory effect against the A-549, XWLC-05, HCT-116 cell lines with increasing concentration displaying a non-linear inhibition in cancer call differentiation from 12.5 μg/ml to 200 μg/ml. On the other hand, in the Beas-2b (human lung [bronchial] epithelial cell line), at a dosage of above 50 μg/ml, the extract confers a cytotoxic effect, and thus maybe toxic to all bronchial epithelial cells after this dosage. Interestingly, the extract also showed a slight proliferative effect in human nasopharyngeal carcinoma cell line, an unreported finding to date. Extrapolation of the mechanisms requires further mechanistic analysis. In addition to Beas-2b and other cell lines mentioned, specific phytochemicals responsible for cytotoxicity and also cellular mechanisms of apoptosis are required to be measured to further explain these observations.

The extract has be shown as per Figure 1., to contain two main phytochemicals, eleutheroside B and E, usually present at 0.6-0.9% of plant dry weight. In this sample, being a 10:1 methanolic extract, eleutherosides would comprise up to 10% of the sample. Proteins, and other isolates from the cortex of *A. senticosus* a related genus to *E. senticosus* to have been shown to confer an anti-tumor effect and increase the survival time in mice (Shan et al., 2004), which may include eleutherosides. The anti-cancer effect of various Siberian ginseng extracts both *E. senticosus* and *A. senticosus* have been investigated in a number of studies such as using an aqueous extract of *E. senticosus* and combining it with either cytarabine or N6-(delta 2-isopentenyl)-adenosine potentiated the anti-proliferative effects against L1210 murine leukemia at 75 μg/mL (ED50) (Hacker et al., 1984). Other than eleutherosides, there are a number of other compounds in *E. senticosus* and the related species *A. senticosus* that confer anti-cancer effect. A major coumarin (isofraxidin) isolated from the stem of *A. senticosus* was found to display anti-tumor effects against human hepatoma cell lines HuH-7 and HepG2 via inhibition of 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced matrix metalloproteinase-7 (MMP-7) in hepatoma cells. Further, another compound isolated from the bark of *A. senticosus*; (+)- Syringaresinol-di-O-beta-D-glucoside (SR), syringin, and also isofraxidin confer anti-inflammatory response in SW982 human synovial sarcoma cell system (i.e. especially SR suppressed IL-6 production, as well as IL-1β, IL-6, cyclooxygenase (COX)-2 and matrix metalloproteinases (MMP)-1 mRNA, thus able to modulate inflammatory processes *in vitro* (Yamazaki et al., 2007). Altered immune and inflammatory response was also seen in an aqueous extract of *A. senticosus* termed GF100. The anti-tumor and immune-modulatory activities induced lung metastasis of colon26-M3.1 carcinoma cells implanted in mice in a dose dependent manner. This observation was not seen in an *in vitro* cytotoxicity analysis, (UL 1000 μg/ml) did not alter the growth of colon26-M3.1 cells but did improve the responsiveness of splenocytes to the mitogen; concanavalin A (ConA). However, peritoneal macrophages obtained from mice stimulated with GF100 (500μg) produced an array of cytokines including; IL-1β, TNF-α, IL-12 and IFN-γ in an *in vitro* experiment (i.e. higher tumoricidal activity against tumor cells than that of the untreated macrophages) as well as natural killer cell activiation (Yoon et al., 2004).

Other mechanisms include potentiating immune response and direct cellular membrane dysfunction caused by polysaccharides present in *A. senticosus*. *A. senticosus* polysaccharides (ASPS) have shown inhibitory action against the animal tumor growth, via enhanced immune function. In particular, the reduced cell proliferation in mice sarcoma (ascitic type) S180 and human chronic myelogenous leukemia K562 cells with IC50 ASPS being 0.38 mg/ml (S180 cells) and 0.28mg/ml (K562 cells) respectively. Mechanistically, ASPS also increase sialic acid and reduced phospholipid in the S180 cell membrane (Tong et al 1994). Further, *Ha et al* fractionated glycoproteins (EN-SP) from the soluble protein layer (GF-AS) of *A. senticosus* conferred anti-tumor (anti-metastatic) and immune-stimulating activities via intravenous administration of mice implanted with colon26-M3.1 carcinoma cells to the lung. The mechanism revealed an enhanced *in vitro* proliferation of splenocytes, stimulation of peritoneal macrophage and associated cytokines i.e. IL-1β, TNF-α, IL-12 and IFN-γ.

In animal studies, rat nervous tissue tumor's a preparation of *E. senticosus* root extract provided orally, conferred a reduction in the occurrence rate of tumor's and extended survival time (Bespalov et al., 1992). The anti-carcinogenic, anti-inflammatory, and anti-oxidant activity of *E. senticosus* and *A. senticosus* seen in cell cultures and animal studies has also been seen in humans. In a clinical study, the injection of *Acanthopanax senticosus* in 39 cancer patients injected for 21 days showed a comparable level of TNF-α as per the control group with higher

activity of TNF-β and also plasma immunoglobulin (Ig); IgA, IgG and IgM levels as well as natural killer cells (NKC) thus facilitating potentiating cellular immunity (Guo et al., 2014).

In conclusion, further research is required to isolate and test specific fractions or phytochemicals present in *E. senticosus* and confirm in isolate or combination which phytochemicals confer an *in vitro* inhibitory effect and whether this can be shown *in vivo*.

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