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Cytotoxicity of 114 Mongolian plant extracts on liver, colon, breast and cervix cancer cell lines

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ABSTRACT

A total of 114 Mongolian plant species were subjected to cytotoxicity screening against liver (HepG2), colon (HCT116), breast (MCF7), and cervical (HeLa) cancer cell lines. Among them, ethanolic extracts of *Androsace incana*, *Artemisia rutifolia*, *Saussurea amara*, and *Inula salsoloides* exhibited remarkable cytotoxicity, with IC_{50} values below 1.5 μg/mL against at least 2 tested cell lines when treated for 48 hours. *Erysimum flavum*, *Juniperus sibirica*, and *Stellaria dichotoma* demonstrated selective cytotoxicity against specific cancer cell lines. Extracts from 23 plant species, such as *Artemisia xerophytica*, *Ajania trifida*, *Melandrium brachypetalum*, *Brachanthemum mongolicum*, and *Rhinanthus songaricus*, showed moderate toxicity. Further research on the phytochemicals and biological activities of these species is crucial for a deeper understanding and potential applications. This screening results of the cytotoxic effects of numerous Mongolian plants could establish a foundational dataset for subsequent comprehensive studies on the screened plants.

Keywords: *Medicinal plant, cytotoxicity, cancer cell line, ethanolic extract*

INTRODUCTION

Cancer is one of the leading causes of morbidity and mortality globally. Among men, lung, prostate, colorectal, stomach, and liver cancer are the most prevalent types, whereas breast, colorectal, lung, cervical, and thyroid cancer are frequently diagnosed among women [1]. In Mongolia, liver cancer has the highest mortality rate, and the country ranks second for stomach cancer mortality [2]. Among Mongolian men, the most commonly diagnosed cancers include liver, stomach, lung, esophageal, and colorectal cancers, whereas liver, cervical, stomach, esophageal, and breast cancers are common among Mongolian women [3]. These statistics highlight the urgent need for comprehensive measures to address the burden of cancer in Mongolia and prioritize preventive and treatment strategies for the identified cancer types.

Throughout history, people have developed indigenous drug prescriptions based on the unique flora found in their native habitats [4]. Mongolia is divided into sixteen phytogeographical regions with various vegetation types, namely, alpine steppe, forest, meadow steppe, typical steppe, desert steppe, and desert [5]. Plant species growing in Mongolia synthesize protective compounds to survive the harsh climate, including UV radiation, aridity, winter coldness, and summer heat. In Mongolian ethnomedicine a diverse selection of native plant species was utilized for the treatment of cancer [6]. The identification of powerful anti-cancer drugs like paclitaxel, colchicine, camptothecin derivatives, podophyllotoxin, vincristine, and vinblastine through screening of natural products has inspired scientists to explore the potential anti-proliferative effects of natural herbs against human cancer cells [7]. Despite the discovery of numerous plant-derived compounds as anti-cancer agents and pharmacophores, a vast number of molecules still await discovery or thorough investigation for their anti-tumor activity.

In present study, the anti-proliferative effects of ethanolic extracts from 114 plant species growing in Mongolia were examined employing human liver, stomach, breast, and cervix cancer cell lines. The selection of plant species was based on their traditional use and unexplored biological effects. Liver, stomach, breast, and cervix cancer cell lines were chosen due to their prevalence among the Mongolian population.

EXPERIMENTAL

***Chemicals*:** Analytical grade ethanol was purchased from Xilong Scientific and etoposide and dimethyl sulfoxide (DMSO) were purchased from Sigma-Aldrich.

***Plant material*:** A total of 114 wild plant species were collected from various locations in Mongolia (**Table S1**). Voucher specimens of these species were deposited in the Herbarium of the Laboratory of Bioorganic Chemistry and Pharmacognosy, School of Engineering and Technology, National University of Mongolia. The identification of plant species was carried out by Dr. Chinbat Sanchir, a former taxonomist at the Institute of Botany, Mongolian Academy of Sciences. Prior to extraction, the collected plant materials were dried in the shadow, chopped, and ground.

Plant sample extraction: Plant samples weighing between 50 g and 200 g were extracted three times with 96% ethanol at a ratio of 1:10 (plant sample to ethanol) at room temperature for at least 3 days. The resulting extracts were then filtered and dried under vacuum at 40 °C. The dried extracts were subsequently stored at 4 °C for future use.

Cell culture: HepG2 human hepatocellular carcinoma cell line, HCT116 human colorectal carcinoma cell line, MCF7 human breast adenocarcinoma cell line and HeLa human cervix adenocarcinoma cell line were obtained from American Type Culture Collection (ATCC, Manassas, VA). HepG2 cell line was maintained in Dulbecco's Modified Eagle's Medium (DMEM, Gibco) supplemented with 10% (w/v) fetal bovine serum (FBS, HyClone), 100 U/ml penicillin (HyClone), and 100 µg/ml streptomycin (HyClone). MCF7 cells were cultured in DMEM supplemented with 0.01 mg/mL insulin (Sigma-Aldrich), 10% (w/v) FBS, 100 U/ml penicillin, and 100 µg/ml streptomycin. HCT116 cells were maintained in Minimum Essential Media (MEM, Gibco) supplemented with 10% (w/v) FBS, 100 U/ml penicillin, and 100 µg/ml streptomycin. HeLa cell line was cultured in RPMI 1640 media (Gibco) with 10% (w/v) heat inactivated FBS, 100 U/ml penicillin, and 100 µg/ml streptomycin. All cell lines were maintained at subconfluence in a humidified atmosphere of 95% air and 5% CO_2 at 37 °C.

***Cell viability assay*:** The cytotoxicity of the extracts was evaluated by a cell viability assay as previously described [8, 9]. All cells (1×10^4 cells per well) were plated in 96-well plates and incubated for 24 hrs at 37 °C. Cells were treated with the plant extracts, which was previously stocked in DMSO at 20 mg/mL, at the final dose of 100 µg/mL, then the cells were incubated for additional 24 hrs. The cell viability was measured using the EZ-Cytox cell viability assay kit (Daeil Lab Service, Seoul, Republic of Korea) employing BioTek Microplate Reader (Agilent). Etoposide (100 µM) was included as a positive control in this study due to its known toxicity against the employed cell lines [10].

***Calculation of results*:** The cytotoxicity of the extracts was calculated as a percentage of the negative control value treated with the vehicle (DMSO), which was set as 100%. The cell viability assay was conducted in triplicate for all the extracts, and IC_{50} values were determined for the selected extracts. The data were presented as the mean ± standard deviation (SD).

RESULTS AND DISCUSSION

Numerous libraries containing natural product extracts and fractions have been established to gather information on the cytotoxic effects of plant extracts and fractions on cancer cells worldwide [11]. However, there is currently a lack of screening data regarding the anti-proliferative potential of Mongolian plants on cancer cells. Interestingly, Mongolian nomads have developed their own traditional prescriptions utilizing Mongolian herbs for treating various tumors. Despite this, no comprehensive collection of data regarding the cytotoxicity effects of these plants on cancer cells has been conducted thus far. In this study, we assessed the anti-proliferative effect of extracts derived from 114 Mongolian plant species belonging to 39 families. To evaluate this effect, we employed a cell viability assay conducted on four human cancer cell lines: liver cancer HepG2, colon cancer HCT116, breast cancer MCF7, and cervical cancer HeLa. We utilized the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, which is widely employed as one of the most common methods for screening the anti-proliferative effects of both natural products and synthesized compounds [8]. As a positive control, we selected etoposide, a well-known anti-cancer drug widely prescribed for the treatment of various human cancers. Etoposide exerts its therapeutic effects by targeting topoisomerase II, an enzyme critical for DNA replication, transcription, and repair [10]. This mechanism leads to G2/M cell cycle arrest, nuclear enlargement, and induction of apoptosis [12].

The cytotoxicity of the extracts was categorized as follows: Potent (cell viability below 5.0% for at least 2 cell lines), selective (cell viability below 6.0% for at least 1 cell line), moderate (cell viability below 70.0% for at least 2 cell lines), weak (cell viability below 90.0% for at least 2 cell lines), and without cytotoxicity (cell viability higher than 90.0% for 2 cell lines).

The plant extracts with potent, selective, and moderate cytotoxicity were presented in Table 1, while extracts with weak and no cytotoxic effects were demonstrated in **Table S2**.

Furthermore, 12 extracts exhibiting potent, selective and moderate cytotoxicity against the cancer cell lines

Table 1. The plant extracts with potent, selective and moderate cytotoxicity against four cancer cell lines at 100 µg/mL (n=3)

	Species	Cell viability (%)			
		HCT116	MCF7	HepG2	HeLa
	Potent cytotoxicity				
1	*Androsace incana* Lam.	3.04±0.95	1.36±0.76	1.34±1.40	16.75±5.41
2	*Artemisia rutifolia* Steph. Ex Spreng.	3.87±0.26	19.04±5.23	2.06±3.03	10.67±1.39
3	*Inula salsoloides* (Turcz.) Ostenf.	1.29±0.76	1.57±4.63	3.87±5.55	1.31±2.26
4	*Saussurea amara* DC.	2.73±1.58	5.81±1.06	1.84±2.62	9.73±3.13
	Selective cytotoxicity				
5	*Erysimum flavum* (Georgi) Bobr.	45.62±1.15	5.38±0.83	38.66±5.91	44.56±7.34
6	*Juniperus sibirica* Burgsd.	1.45±0.29	8.98±1.58	41.41±17.99	18.67±1.22
7	*Stellaria dichotoma* L.	5.66±2.09	18.76±0.63	81.79±5.82	41.01±2.11
	Moderate cytotoxicity				
8	*Allium bidentatum* Fisch. ex Prokh.	75.18±3.25	65.18±3.53	70.43±9.42	62.94±0.26
9	*Ajania trifida* (Turcz.) Tzvel.	24.80±0.59	43.54±0.33	26.48±13.67	39.00±3.87
10	*Artemisia annua* L.	85.92±5.74	67.93±9.55	52.00±2.13	69.51±1.69
11	*Artemisia demissa* Krasch.	100<	86.61±0.77	65.16±8.67	57.67±3.07
12	*Artemisia xerophytica* Krasch.	23.31±1.74	38.91±0.92	35.98±7.40	32.33±2.76
13	*Brachanthemum mongolicum* Krasch.	55.85±2.64	50.35±2.10	46.12±1.09	59.60±0.97
14	*Brachanthemum gobicum* Krasch.	100<	68.02±4.00	55.03±8.62	61.58±4.88
15	*Bupleurum bicaule* Helm.	77.42±5.64	64.78±1.72	29.00±2.40	52.36±1.24
16	*Bupleurum multinerve* DC.	74.86±5.64	62.81±2.72	46.24±12.42	42.13±2.54
17	*Caragana pygmaea* (L.) DC.	77.89±2.99	66.05±2.15	66.49±7.60	50.51±1.61
18	*Cirsium arvense* (L.) Scop.	98.91±1.45	64.78±7.49	68.85±3.89	71.85±1.82
19	*Delphinium pumilum* W.T.Wang	76.49±3.96	67.73±4.59	54.44±1.44	64.77±3.88
20	*Geranium pratense* L.	81.20±3.71	65.57±1.83	84.64±7.54	59.35±2.20
21	*Goniolimon speciosum* (L.) Boiss.	93.44±4.69	93.93±2.57	58.43±13.82	57.44±1.87
22	*Haplophyllum dauricum* (L.) G. Don	77.62±7.34	78.65±2.26	44.29±8.14	55.51±7.27
23	*Heracleum dissectum* Ldb.	92.58±3.56	68.63±4.93	71.51±4.91	48.86±0.99
24	*Melandrium brachypetalum* (Hornem.) Fenzl	16.79±2.04	80.20±1.41	23.27±0.19	69.38±7.59
25	*Polygonum sericeum* Pall. ex Georgi	66.80±1.77	77.61±3.42	49.14±6.28	63.62±4.51
26	*Potentilla strigosa* Pall. ex Pursh.	91.34±2.95	84.00±2.37	65.54±6.36	60.15±2.65
27	*Potentilla viscosa* G. Don	78.02±1.49	82.19±1.20	61.47±1.48	55.69±3.74
28	*Rhinanthus songaricus* (Sterneck) B. Fedtsch	40.80±2.00	49.17±5.14	58.43±4.05	32.07±0.39
29	*Sphallerocarpus gracilis* (Bess. ex Trev.) K. -Pol.	73.59±3.54	60.66±0.98	57.41±4.63	69.79±1.55
30	*Urtica angustifolia* Fisch. ex Hornem	67.84±1.59	66.94±3.81	70.89±11.51	61.87±1.04
	Positive control				
31	Etoposide	71.05±2.95	72.72±4.80	37.36±2.33	33.62±2.14

were selected and evaluated for their IC_{50} values (Table 2).

The extract of *Androsace incana* (*AI*) exhibited strong cytotoxicity against all cell lines, except for HeLa. In Mongolian traditional medicine, *AI* is commonly used for its anti-swelling, wound healing, detoxifying, body strengthening, and dehydrating properties [6]. In previous studies, other members of the Androsace genus, namely *Androsace umbellate* and *Androsace integra*, were investigated for their cytotoxic effects [13-15]. Triterpenoid saponins, including saxifragifolin A, saxifragifolin B, saxifragifolin C, and saxifragifolin D, isolated from *Androsace umbellate*, demonstrated apoptotic effects on RAW 264.7 cells and exhibited cytotoxicity against various multidrug resistance and non-multidrug resistance human tumor cell lines [13]. In HepG2 cells, saxifragifolin B induced apoptosis through the accumulation of sub-G1 population, mitochondrial membrane depolarization, cytochrome c

Table 2. IC_{50} values of some selected plant extracts (μg/mL)

	Species	Treatment time: 24 hrs			Treatment time: 48 hrs		
		MCF7	HepG2	HCT116	MCF7	HepG2	HCT116
	Potent toxicity						
1	*Androsace incana* Lam.	3.96±5.29	7.13±4.97	9.27±5.90	1.5>	1.5>	3.62±4.41
2	*Artemisia rutifolia* Steph. Ex Spreng.	35.85±5.24	7.53±4.27	10.21±6.3	12.54±4.47	1.5>	1.5>
3	*Inula salsoloides* (Turcz.) Ostenf.	9.67±8.63	6.04±4.52	6.25±3.68	1.5>	1.5>	1.5>
4	*Saussurea amara* DC.	17.88±6.06	7.34±9.55	7.26±8.10	1.5>	1.5>	1.5>
	Selective toxicity						
5	*Erysimum flavum* (Georgi) Bobr.	9.22±4.52	47.61±8.70	200<	1.5>	20.77±6.10	200<
6	*Juniperus sibirica* Burgsd.	32.07±8.40	65.88±8.41	16.65±08	9.09±6.56	41.50±6.25	1.5>
7	*Stellaria dichotoma* L.	42.60±6.30	96.97±8.25	27±8.1	29.3±5.29	74.84±8.63	18.0±6.9
	Moderate toxicity						
8	*Ajania trifida* (Turcz.) Tzvel.	121.30±9.53	46.51±13.70	200<	74.6±8.6	19.6±6.4	200<
9	*Artemisia xerophytica* Krasch.	68.15±8.92	64.56±7.74	200<	31.21±9.65	21.10±6.52	200<
10	*Brachanthemum mongolicum* Krasch.	104.09±10.32	72.68±8.47	200<	48.32±9.20	25.84±12.19	200<
11	*Melandrium brachypetalum* (Hornem.) Fenzl	143.71±14.44	33.09±9.31	25.53±6.68	96.94±12.23	13.7±6.1	8.1±6.4
12	*Rhinanthus songaricus* (Sterneck) B. Fedtsch	69.28±8.35	82.71±6.41	200<	45.06±9.91	65.30±6.82	200<
	Positive control						
13	Etoposide*	72.79±4.80	37.36±2.33	200<	47.11±5.25	12.68±3.55	200<

*IC_{50} values of etoposide were expressed as μM.

leakage, and activation of poly (ADP-ribose) polymerase (PARP) and caspase cascades [14]. Additionally, another triterpenoid saponin called ardisiacrispin A from *Androsace integra* exhibited cytotoxicity against HepG2 cells [15]. Based on these previous reports, it is plausible to hypothesize that *AI* may also contain cytotoxic triterpenoid saponins similar to those found in other Androsace species. However, further research is needed to explore the chemical constituents and biological activities of *AI.*

The ethanol extract of *Artemisia rutifolia* (*AR*) exhibited potent inhibition of cell growth in both the HepG2 and HCT116 cell lines, with IC_{50} values of less than 1.5 μg/mL after 48 hours of treatment. However, the extract demonstrated moderate toxicity in other cell lines. *AR* has limited data available regarding its use in traditional folk medicine. Few reports have focused on its specific sesquiterpene lactone content, revealing the presence of several guaianolides, seco-guaianolides, germacranolide, and eudesmane derivatives in the aerial parts of *AR* along with its *in vitro* cytotoxic properties [16,17]. Artemisia (Asteraceae) is a diverse genus comprising 200-400 species, known for its rich reservoir of active biological compounds. Within the phytochemicals isolated from Artemisia species, terpenoids, particularly sesquiterpenoids, as well as flavonoids, coumarins, and lignans, have exhibited noteworthy anti-proliferative activity against cancer cells. Notably, sesquiterpenoids like artemisinin, artesunate, artemether, dihydroartemisinin, and arteether derived from *Artemisia annua*, along with flavonoids such as eupatilin, jaceosidin, cirsilineol, and 6-methoxytricin from *Artemisia asiatica*, have been reported for their cytotoxic effects against cancer cells [18]. *Inula salsoloides* (*IS*) exhibited significant cytotoxicity against all cell lines tested. Inula species are famous

for their anti-tumor effects in the folk medicine of China, Mongolia, and Korea [6]. Sesquiterpene lactones are considered the active components in Inula plants, displaying anti-cancer activity against various human cancer cell lines. Inula sesquiterpene lactones exert their anti-tumor effects through cell cycle arrest induction, inhibition of neoangiogenesis, and stimulation of apoptosis signaling pathways [19]. However, there are limited reports regarding the chemical constituents with cytotoxic activity of *IS*, except for the cytotoxicity demonstrated by sesquiterpene lactones inulasalsolin and eupatolide, against human cancer P-388 and KB3 cell lines [20].

The extract of *Saussurea amara* (*SA*) demonstrated remarkable toxicity against all cell lines utilized in this study. In Mongolian traditional medicine, *SA* is commonly employed for treating bacterial, protozoal, and viral infections, intoxication, jaundice, and tumors [6]. *SA* contains several flavonoids, including apigenin, luteolin, genkwanin, quercitrin, and apigenin-7-O-glucoside, as well as terpenoids such as taraxasterol, taraxasterol-acetate, cynaropicrin, and desacylcynaropicrin [21]. Although the biological activity of *SA* has not been extensively studied, it has shown choleretic effects in isolated perfused rat liver [22]. Other Saussurea species have exhibited cytotoxic potential against various human cancer cells. Sesquiterpene lactones, particularly guaiane-type sesquiterpene lactones from *Saussurea deltoidea* and *Saussurea calcicola* have demonstrated strong toxicity against cancer cell lines [23, 24]. Cynaropicrin, a guaiane sesquiterpene lactone identified in *Saussurea calcicola, Saussurea pulchella,* and *Saussurea salicifolia*, exhibited cytotoxic potential against skin melanoma SK-MEL-2, ovary malignant ascites SK-OV-3 [25], non-small cell lung adenocarcinoma A549, skin melanoma SK-MEL-2, human CNS solid tumor XF498, colon adenocarcinoma HCT15 [24], gastric adenocarcinoma AGS cells, and murine hepatoma Hepa1c1c7 cells [26]. Dehydrocostus lactone and costunolide, which are sesquiterpene lactones isolated from *Saussurea lappa*, exhibited potent cytotoxicity against ovarian carcinoma OVCAR-3, hepatoma HepG2, and cervical adenocarcinoma HeLa cell lines [27] and induced apoptosis in neuroblastoma IMR-32, NB-39, SK-N-SH, and LA-N-1 cell lines by activating caspase-7 and cleaving PARP [28]. Therefore, the cytotoxicity observed in the extract from *SA* may be attributed to its constituents of sesquiterpene lactones.

Several plant extracts demonstrated selective toxicity towards specific cell lines in this study. *Erysimum flavum, Juniperus sibirica*, and *Stellaria dichotoma* exhibited cytotoxic effects on certain cancer cell lines.

The ethanol extract of *Erysimum flavum* (*EF*) exhibited selective cytotoxicity against the breast cancer cell line MCF7, while the extract demonstrated only a moderate cytotoxic effect on other cell lines (Table 1). In Mongolian traditional medicine, this plant is utilized for the treatment of heart disorders, indigestion, and swellings [29]. However, the phytochemical composition and biological activities of *EF* have not been investigated to date. Similarly, limited research has been conducted on the chemical composition and biological activities of other Erysimum species. For example, a study focused on assessing the *in vitro* cytotoxicity of *Erysimum corinthium* seeds against colorectal, hepatic, and Hela cell lines [30]. Therefore, there is a need for future studies aimed at identifying and evaluating phytochemicals of *EF* that possess potential anti-proliferative effects.

Juniperus sibirica (*JS*) exhibited selective cytotoxicity against colorectal carcinoma HCT116 cells. In Mongolian culture, *JS* is commonly utilized as an air fragrance by smoking and fuming the dried needles. *JS* has been traditionally employed in Mongolian oriental medicine for the treatment of kidney diseases and bladder inflammation through oral administration and for wound healing and rheumatism treatment through immersion methods [29]. While the phytochemical constituents with cytotoxic effect of *JS* have not been investigated yet, it is worth noting that the Juniperus family is known for its cytotoxic lignan constituents, such as podophyllotoxin and deoxypodophyllotoxin, which hold significant pharmaceutical potential for cancer chemotherapy [31]. In addition, chemical composition and cytoxicity of essential oil from *JS* against MCF7 human breast cancer cell line was reported previously [32]. Therefore, it can be suggested that the presence of lignans and volatile components in the extract of *JS* may be responsible for its toxic effects on cancer cell lines.

The extract of *Stellaria dichotoma* (*SD*) demonstrated cytotoxic effects on HCT116 and MCF7 cells (Table 1, 2). Two alkaloids dichotomine B and glucodichotomine B isolated from this plant displayed moderate toxicity towards colon carcinoma HCT116 and hepatocarcinoma SMMC7721 cells [33]. Despite this finding, the cytotoxic effect of *SD* has not been extensively documented up until now.

Moderate cytotoxicity was exhibited in the extracts of 23 plant species including previously unexplored ones such as *Artemisia xerophytica, Melandrium brachypetalum, Brachanthemum mongolicum*, and *Rhinanthus songaricus* (Table 1). Conversely, weak cytotoxicity was observed in the extracts of 47 plant species, while no cytotoxicity was detected in the extracts of 36 plant species. (**Table S2**).

CONCLUSIONS

The cytotoxic effects of ethanolic extracts from a total of 114 Mongolian plant species were evaluated against human liver (HepG2), colon (HCT116), breast (MCF7), and cervix (HeLa) cancer cell lines. Notably, Androsace incana, *Artemisia rutifolia, Saussurea amara*, and *Inula salsoloides* exhibited the most potent cytotoxic effects against all tested cell lines with IC_{50} values below 1.5 µg/mL against at least 2 tested cell lines when treated for 48 hours. *Juniperus sibirica, Stellaria dichotoma*, and *Erysimum flavum* demonstrated cytotoxic effects against specific cancer cell lines. On the other hand, moderate cytotoxicity was observed in the extracts of 23 plant species, while weak cytotoxicity was observed

in the extracts of 47 plant species. It is essential to further investigate the chemical constituents and biological activities of these plants exhibiting cytotoxic effects. This first comprehensive screening results of the cytotoxic effects of a great number of Mongolian plants could provide the basis for subsequent in-depth studies on the screened plants.

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