



Anti-proliferative activities on HeLa cancer cell line of Thai medicinal plant recipes selected from MANOSROI II database

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ABSTRACT

Ethnopharmacological relevance: The Thai/Lanna medicinal plant recipe database “MANOSROI II” contained the medicinal plant recipes of all regions in Thailand for the treatment of various diseases including anti-cancer medicinal plant recipes.

Aim of the study: To investigate anti-proliferative activity on HeLa cell lines of medicinal plant recipes selected from the Thai/Lanna medicinal plant recipe database “MANOSROI II”.

Materials and methods: The forty aqueous extracts of Thai/Lanna medicinal plant recipes selected from the Thai/Lanna medicinal plant recipe database “MANOSROI II” were investigated for anti-proliferative activity on HeLa cell line by SRB assay. The apoptosis induction by caspase-3 activity and MMP-2 inhibition activity by zymography on HeLa cell line of the three selected aqueous extracts, which gave the highest anti-proliferative activity were determined. Phytochemicals and anti-oxidative activities including free radical scavenging activity, inhibition of lipid peroxidation and metal chelating inhibition activities were also investigated.

Result: Sixty percentages of the medicinal plant recipes selected from “MANOSROI II” database showed anti-proliferative activity on HeLa cell line. The recipes of N031 (*Albizia chinensis* (Osbeck) Merr, *Cassia fistula* L., and *Dargea volubilis* Benth.ex Hook. etc.), N039 (*Nymphoides indica* L., *Peltophorum pterocarpum* (DC.), and *Polyalthia debilis* Finet et Gagnep etc.) and N040 (*Nymphoides indica* L. Kuntze, *Sida rhombifolia* L., and *Xylinbaria minutiflora* Pierre. etc.) gave higher anti-proliferative activity than the standard anti-cancer drug, cisplatin of 1.25, 1.29 and 30.18 times, respectively. The positive relationship between the anti-proliferative activity and the MMP-2 inhibition activity and metal chelating inhibition activity was observed, but no relationship between the anti-proliferative activity and apoptosis induction, free radical scavenging activity and lipid peroxidation inhibition activity. Phytochemicals found in these extracts were alkaloids, flavonoids, tannins and xanthenes, but not anthraquinones and carotenoids. The recipe N040 exhibited the highest anti-proliferative and MMP-2 inhibition on HeLa cancer cell line at 30 and threefolds of cisplatin, respectively ($p < 0.05$), while recipe N031 gave the highest caspase-3 activity (1.29-folds over the control) ($p < 0.05$).

Conclusion: This study has demonstrated that recipe N040 selected from MANOSROI II database appeared to be a good candidate with high potential for the further development as an anti-cancer agent.

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Introduction

Natural products are one of the most successful sources of pharmacologically active compounds for cancer treatment in humans due to the evidences of long traditional use for many generations. Several medicinal plants are interesting to be investigated and developed as anti-cancer agents including those used

in the Thai–Lanna region. Lanna was an independent country about 700 years ago. It included many cities in Thailand, Myanmar and China. Lanna region had its own wisdoms and cultures. For Thai–Lanna, it was in the northern region of Thailand including eight provinces which were Chiang Mai, Chiang Rai, Phare, Payao, Nan, Lamphun, Lampang and Mae Hong Son. It had its own folklore wisdoms, especially the medicinal plant recipes for treating many diseases including cancer which are now still used by the northern Thais. Only the effective recipes were recorded in mulberry pulp paper, palm leaves or *Streblus asper*, Loir papers. Since 1996, the Thai/Lanna medicinal plant recipe database

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“MANOSROI II” has been developed by Professor Dr. Jiradej Manosroi at the Natural Product Research and Development Center (NPRDC), Science and Technology Research Institute (STRI), Chiang Mai University in Chiang Mai, Thailand. At present, the MANOSROI II database contains the interpreted and translated of 50,000 out of the expected 200,000 recipes with 7467 medicinal plants, and 3613 diseases/symptoms for treating of several diseases and symptoms such as cancer, hypertension, diabetes, fever, pain, wound and abscess. Moreover, the database also included the recipes for cosmetics and food supplements. The MANOSROI II database is a convenient source for searching and ranking of the potential recipes and medicinal plants for further studies.

Previously, several works have published from this database. But, by that time, the name MANOSROI II has not established yet. However, there is many researches have also reported the anti-proliferative activity of several medicinal recipes and single plants found in the MANOSROI II database. The extracts from recipes S016 and S015 selected from this database gave anti-proliferative activity on HeLa and KB cell lines with the potency of 0.38- and 0.17-fold of cisplatin respectively (Sainakham et al., 2011). The extracts from recipes NE028, S003 and N036 which exhibited the high potential anti-proliferative activity on KB, HT-29 and HepG2 cell lines (Boonpisuttinant et al., 2012). The chloroform extract from leaves of *G. speciosa* inhibited cancer cell growth with the GI_{50} of 4, 6.6, and 3.7 $\mu\text{g/ml}$ in HeLa, KB, and $B_{16}F_{10}$ cell lines, which were 13-, 20- and 142-fold less potent than doxorubicin, respectively (Manosroi et al., 2007). The oil of Guava (*Psidium guajava* L.) leaf showed the highest anti-proliferative activity on KB cell lines with the IC_{50} value of 0.0379 mg/ml, whereas Sweet Basil (*Ocimum basilicum* L.) oil gave the highest anti-proliferative activity with the IC_{50} value of 0.0362 mg/ml in P388 cell line (Manosroi et al., 2006). The extracts from recipes NE028 and S003 gave the highest anti-proliferative activity on KB and HT29 with the IC_{50} values of 2.48 ± 0.24 and 6.92 ± 0.49 $\mu\text{g/ml}$, respectively (Manosroi et al., 2012). The extract of *Garcinia mangostana* L. showed anti-proliferative activity on SKBR3 human breast cancer cell line (Moongkarndi et al., 2004). The extract of *Coscinium fenestratum* (Gaertn.) Colebr., gave selective activity against lung carcinoma and/or lung metastatic cell lines, A549, LLC and B16-BL6. The extract of *Jatropha curcas* L. gave anti-colon cancer property (Saetae et al., 2011). The extracts from *Hydnophytum formicarum* Jack. and *Streptocaulon juvenas* (Lour.) Merr. indicated selective activity against human tumor cell lines, HeLa and A549 (Ueda et al., 2002). *Gardenia turgida* Roxb. and *Psophocarpus tetragonolobus* DC., *Senna alata* (L.) Roxb. demonstrated anti-tumor activity (Morris, 1999).

Cervical cancer is one of many malignant tumors threatening womens' lives. In the recent year, the death rate from cervical cancer has increased worldwide dramatically (Wang et al., 2004). The current cancer therapeutic approaches include surgery, chemotherapy and radiotherapy. The major disadvantage of the application of chemical anti-cancer drugs is several severe side effects including hair loss, fever, diarrhea, nausea, joint pain, anemia, cardiotoxicity, fertility and sexuality problems and dry skin (Ambrose and Roe, 1996; Haskell, 1985). The development of the less side effects with better therapeutic efficacy of the anti-cancer drugs remains one of the most challenging area in cancer treatment. The Thai–Lanna medicinal plant recipes have been used for the treatment cancer patients for many generations with efficiency and safety. However, there is no scientific reports to confirm the anti-cervical cancer and anti-oxidative activities of these recipes. The anti-proliferative activity by the sulforhodamine B (SRB) assay, apoptosis induction by caspase-3 activity and acridine orange/ethidium bromide (AO/EB) staining, and inhibition of matrix metalloproteinase-2 (MMP-2) are the popular

methods for the evaluation of anti-cancer activity of the natural extracts.

In this study, anti-proliferative activity on human cervical carcinoma (HeLa) cell lines of the aqueous hot extracts of the 40 Thai/Lanna anti-cancer medicinal plant recipes selected from the Thai medicinal plant recipe database MANOSROI II was investigated. The top three extracts showing the highest anti-proliferative activity were selected to test for apoptosis induction and inhibition of MMP-2 on HeLa cancer cell line as well as the phytochemical investigation and anti-oxidative activities in order to evaluate for their potential to develop as a novel anti-cancer drug.

Methodology

Plant Authentication and extraction

Authentication: Two hundred twenty one Thai anti-cancer medicinal plant recipes were selected from the “MANOSROI II” database by using the Thai keywords of Ma-Reng or San, which mean mass or cancer. The recipes were ranked for the priority of further investigation by the highest frequency of single plants appeared in the recipes. The top 40 recipes were further extracted and investigated for anti-proliferative activity using SRB assay. The medicinal plants in the recipes were collected from Chiang Mai province in Thailand during January to March, 2009. The plant specimens were authenticated by a botanist at the Faculty of Pharmacy, Chiang Mai University in Thailand. The voucher specimens were kept at Natural Product Research and Development Center (NPRDC), Science and Technology Research Institute (STRI), Chiang Mai University, Chiang Mai in Thailand. Parts of the medicinal plants were collected and cut with a sharp knife or machete. The plant materials were dried at 50 °C in hot air oven and ground into powder using a stainless steel grinder.

Extraction: The extract of 40 recipes was prepared by the traditional method according to the instruction in recipes, which were used for the extraction by boiling in hot water. Briefly, 40 g mixed dried powder of the medicinal plants in each recipe were dispersed in 800 ml distilled water and boiled for 1 h. After cooling, the extract was filtered through Whatman filter paper No.1 and centrifuged at 1032g, room temperature (26 °C) for 2 min. The filtrate was concentrated by a rotary evaporator (R-124 Buchi, Switzerland) and lyophilized by a freeze dryer (Christ Beta 1–8 K, Germany). The lyophilized extract was kept in glass bottles and stored at 4 °C until use.

Cancer cell culture

Human cervical carcinoma cell line (HeLa) was obtained from National Cancer Institute in Bangkok, Thailand. The cells were cultured under the standard conditions in the DMEM (Sigma–Aldrich Biotechnology, St. Louis, MO, USA) supplemented with 10% fetal bovine serum (FBS) (Sigma–Aldrich Corporation, St. Louis, MO, USA), 100 IU/ml of penicillin and 100 mg/ml of streptomycin (Gibco BRL, Gaithersburg, USA). The cells were incubated at 37 °C under 5% CO_2 for 24 h.

Anti-cancer activity

Anti-proliferative activity

Fourty aqueous hot extracts of the Thai–Lanna anti-cancer medicinal plant recipes selected from the MANOSROI II database were investigated for anti-proliferative activity on HeLa cell line by sulforhodamine B (SRB) assay as previous described (Manosroi et al., 2007). After the 1×10^4 cells were seeded into a 96-well

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