(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 5, Issue 3, Page No: 412-419
May-June 2022

IJMSCR

Phytochemical Properties And Anticancer Activity Of Tiliacora Triandra (Colebr.) Diels.

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Type of Publication: Original Research Paper
Conflicts of Interest: Nil

Abstract

Lung Cancer is one of many diseases with a high mortality rate and is difficult to detect until cancer can progress significantly. Its difficulty in detecting the disease has taken a toll on the patient's health. Smoking or being exposed to pollution both indoors and out, radiation exposure, and working in an environment containing hazardous elements are just a few of the many causes of lung cancer identified. Every cancer can cause an uncontrollable growth of a cell because of the ability to evade an induction of apoptosis and can cause nearby cells to mutate and modify a specific characteristic of the cell. Many anticancer substances used in today's world are derived from plants, as they have been known for centuries to possess anticancer properties. After discovering the properties, drugs for small cell lung cancer were developed. Around 3,000 plant species have been shown to exhibit anticancer activity. *T. triandra* is an indigenous Southeast Asian plant folk healer frequently used for anticancer properties. *T. triandra* has been studied and reported to possess anticancer in Numerous parts of the plant, and said components have inhibitory properties against a variety of cancer cell lines. The tests have also shown that *T. triandra* presents an antitumor activity in animals. Using caspase-activation pathways prevented the growth of four human cholangiocarcinoma cell lines. It also showed rapid tumour growth inhibition in cholangiocarcinoma xenografted mice. In conclusion, *T. triandra* has been used for culinary and medicinal purposes for centuries. Numerous studies and publications have been conducted. Apart from its nutritional Tiliacora triandra; anticancer activity; apoptosis; multidrug resistance lung cancerq1q value, studies have revealed that it possesses medicinal and cancer-fighting properties. However, further studies on the mechanisms of *T. triandra* anticancer are necessary.

Keywords: Tiliacora triandra; anticancer activity; apoptosis; multidrug resistance lung cancer

Introduction:

Cancer is a disease which consists of a collection of heterogeneous genetic diseases in which some of the body's cell growth cannot be controlled (1). Various methods have been utilized to treat cancer cells (2, 3). Main alteration that causes untrollable growth is the evasion of apoptosis (4). In addition, two characteristics of cancer which include instability of the genome and mutation tumor-promoting inflammation that have been explained in the hallmarks (5). Coordinated cell actions such as cell proliferation, and apoptosis are modified to produce the altered cell with certain characteristics (6). Plants especially herbs have been a considerable source of new drugs and have been proven useful for the use for cancer treatment (7, 8). Medicines that are made from herbs have been perceived as one of the interesting methods to cure lung cancer as they have proven to be useful and effective in reducing the severity of the side effects (9). *Tiliacora triandra* (F. *Menispermaceae*) is used in various cuisines and is also known for its medicinal potential (10, 11). This review aims to explore its photochemical properties and antiproliferative activity and mechanism of action from the leaves of the plant to cancer.

Tiliacora triandra Diels: Phytochemical constituents

T. triandra also known as *Limacia triandra* (Colebr.) Hook. f. and *Cocculus triandrus* Colebr which belongs to the Menispermaceae family (12). *T. triandra* is a climbing plant with a slender stem and succulent with leaves (13). *T. triandra* is a dioecious plant in which male and female flowers are separated on individual plants (12). Male flowers have 3 or 6 petals and 3 stamens and are yellow in color (12, 14). Female flowers have 6 petals (14). Fruits are drupe in shape and the root surface is grayish-yellow (12, 14). In southeast Asia *T. triandra* are found commonly especially in the northeast of Thailand and Lao PDR (10). Because of the antipyretic and anti cancer properties in the leaves of the plant it is used in Thai medicines and in many traditional cuisines of Thailand (7). A large amount of research reported that the roots of *T.triandra* contain Bisbenzylisoquinoline alkaloids including tiliacorine, tiliacorinine and nor-tiliacorinine (15). Some research has also found Antibacterial, antimalarial, anticancer, anti-inflammation, antioxidant, antipyretic, alcohol detoxification, and acetylcholine esterase (AChE) inhibitory properties in some parts of the plant (16-18). Various chemical components have been reported in the roots, stems and leaves of *T. triandra* (13). The roots and stems have many bisbenzylisoqui noline alkaloids which consist of tiliacorine, tiliacorinine, nortiliacorinine A, tiliacorinine 2'-N-oxide and yanangcorinine which have been reported to be found in both stem and leaves Meanwhile yanangine, dinklacorine, tilianangine, tiliageine, protoquercitol, tilitriandrine, magnoflorine, nortiliacorine A, noryanangine,norisoyanangine and many fatty acids have also been reported only in the stem.An alcoholic extract of *T. triandra* shows the presence of tannins, triterpenes, flavonoids, saponins and alkaloids, alkaloid oxoanolobine, further research also see the presence of polyphenols such as santonin, minecoside, protopseudohypericin, 3-O-methylluteolin glucoside malonylated, monoepoxy-betacarotene, 3-demethoxy-9α-hydroxyligballinol-O-glucoside, p-hydroxybenzoic acid, flavone glycoside cinnamic acids derivative, and flavanone glycoside (11, 19, 20).

Quantification studies have found that *T. triandra* have a High content of phenolic compounds, vitamin E, fatty acids, and essential oils (21). A research of 100 mg water extract revealed that quercetin, cyanidin, gallic acid are found within the extract (12, 22). Chlorophyll, rutin, tannic acid, and isoquercetin, catechin, quercetin and gallic acid are seen in lyophilized leaves juice powder (11). Relatively high levels of vitamin E, phytol and 1-cyclohexenylacetic acid and the other compounds such as oleamide, oleic acid, neophytadiene, palmitic acid, 5-hydroxymethyl-2-furancarboxaldehyde, and 2,6-dimethyl-3-(methoxymethyl)-benzoquinone when doing the GC-MS analyst of the methanolic extract (7, 23). Furthermore, essential oil are yielded by distilling fresh leaves distilling and it is seen that isophytol, linoleic acid, n-hexadecanoic acid are the most abundant components compared to others and by further doing GC-MS analysis of this extract have found another compounds such as linalool, α-terpineol, p-vinylguaiacol, 1-hexanol, β-damascenone, neophytadiene, tetradecanoid acid, 3-hexen-1-ol, sphatulenol, benzeneacetal dehyde, and linalool oxide are found by doing the GC-MS analysis (13, 23). According to the research, *T. triandra* Leaf extract contains many properties including anti-oxidant and anti-inflammatory properties with many active compounds composed of condensed tannin, triterpene, flavonoid, saponin, phyrol and α-tocopherol (20). Polyphenols include p-hydroxybenzoic acid, minecoside, flavones glycoside cinnamic acid derivative, and monoepoxy-betacarotene (18). Thus, *T. triandra* can also be an option in curing diseases involving free radicals and inflammation (11). *T. triandra* leaves also contain oxoanolobine as the main bioactive compound (11, 22). Highest cytotoxic activity against lung cancer (NCI-H187) cell lines are shown with the methanol extract while the water extract exhibited the highest activity against oral cavity cancer (KB) when compared to the other extracts (7, 24, 25).

Anticancer activities of Tiliacora triandra

Plants have been known for centuries to possess anticancer properties. After discovering podophyllotoxin and several other lignans in the common mayapple (*Podophyllum peltatum*), drugs for testicular and small cell lung cancer were developed (26). Around 3,000 plant species have been shown to exhibit anticancer activity (17, 27). Studies about plants' chemoprotective properties have been prevalent (28). *Abrus precatorius*, for example, has anticarcinogenic properties that help

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rodents tumor cells that are in their bodies do not become cancerous (1, 7). *T. triandra* is a plant that folk healers frequently use in anticancer formulations and cancer prevention (14, 28). Numerous components of *T. triandra* have been studied and reported to possess anticancer properties to a variety of cancer cell lines (1, 7). The ethanolic root extract was found to be cytotoxic to a variety of lung cancer cell lines, including KB, Hep2, A549, COR-L23, and NCI-H226 (12, 29). The ethanolic stem extract was cytotoxic to HepG2 cells (7, 22). The methanolic leaves extract was cytotoxic to the human colon cancer cell line (HT-29) (17, 30). In another study, ethyl acetate, methanolic, and water extracts were found to be cytotoxic against oral cavity cancer (KB) and lung cancer (NCI-H187) cell lines, and oxonanolobine, a major active compound isolated from the methanolic extract, exhibited activity against NCI-H187 (7, 12). Additionally, against lung cancer cells and multidrug-resistant lung cancer cells were tested with different extracts of the leaf (7). With IC_{50} values of 22.0 and 48.5 g/ml, the dichloromethane extract was the most cytotoxic to both normal and resistant cells (31). On the other hand, the hexane extract was ineffective; however, a mixture of fatty acids isolated from the hexane extract exhibited multidrug resistance reversing activity in the A549RT-eto cell line by enhancing P-glycoprotein function, which was previously reported (18). Tiliacorinine, an alkaloid isolated from the roots and stems, inhibits the proliferation of cholangiocarcinoma cell lines and presents an antitumor activity in an animal (4, 28). Using caspase-activation pathways prevented the growth of four human cholangiocarcinoma cell lines (4, 32). It also showed rapid tumor growth inhibition in cholangiocarcinoma xenografted mice (7).

Tiliacora triandra Diels and Multidrug resistance lung cancer

Because it is difficult to detect until the disease has progressed significantly, lung cancer is currently the malignant tumour with the highest incidence and mortality rate globally (33). This is often because the disease has progressed significantly and compromised the patient's health (34). Smoking, passive smoking, using pipes and cigars, being exposed to pollution both indoors and out, radiation exposure, and working in an environment that contained hazardous materials like asbestos, nickel, chromium, and arsenic are just a few of the many causes of lung cancer that have been identified. Smoking is the leading risk factor (1, 35). NSCLC, which includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma, accounts for approximately 80% of all lung cancer cases, while small cell lung carcinoma (SCLC) accounts for 20% (27, 36). The recent publication of a new classification system for lung cancer defined "molecular subtypes" based on specific, actionable genetic aberrations (37). It has been looked into whether blocking the STAT3 pathway, halting the cell cycle, hTERT silencing, changing miRNA, blocking angiotensin receptors, TGF-beta antagonism, blocking VEGFR-2/EGFR inhibition, and activating Nrf2 could be good ways to fight lung cancer (36, 38-40). Specific strategies have been shown to be effective in human trials, including a phase 1 study of ceritinib, a novel ALK (anaplastic lymphoma kinase gene) blocker, in patients with advanced lung cancers harbouring ALK genetic mutations (35, 41).

Numerous molecular mechanisms underlying the development, progression, and prognosis of lung cancer have been identified, enabling the development of new targeted therapies (27, 42). Tumour-associated biomarker research is also becoming increasingly important in reducing lung cancer mortality by detecting and diagnosing the disease early. Another strategy being investigated is using the cancer stem cell model, which sheds new light on the limitations of current cancer therapies (6). Clinical evidence supports VEGF and EGF signalling pathways in treating advanced non-small cell lung cancer (NSCLC) (3, 43).

MDR in cancer cells is a term that refers to the ability of anticancer agents to resist cell apoptosis through the use of multiple structures within the same cells/tissue (17, 30). When the mdr1 (multidrug resistance 1) gene overexpresses P-glycoprotein (P-gp), a 170 kDa plasma membrane protein, this indicates MDR (9, 44, 45). Doxorubicin, vinblastine, vincristine, etoposide, and paclitaxel are chemotherapeutic drugs conveyed by P-gp across the plasma membrane and out of the cell (8, 9). P-gp is a membrane efflux pump whose activity is energy-dependent (9). Due to the ability of P-gp to remove chemotherapy drugs from cancer cells, inhibiting their activity may increase the efficiency of

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chemotherapy (45, 46). Numerous natural compounds have been extensively explored and investigated in recent years for their ability to reverse cellular MDR (9, 30, 45). To enhance chemotherapy drug uptake and thus reduce systemic or targeted drug dose, natural substances that repress P-gp-mediated drug efflux should be administered concurrently with chemotherapy drugs (17). These compounds, also known as MDR-reversing agents, chemosensitizers, or modulators, have various chemical structures (46). Thailand is naturally densely forested with *T. triandra*, an angiosperm native to mainland Southeast Asia (26). The roots of this plant are believed to contain alkaloid compounds, most notably the bisbenzylisoquinoline alkaloids tiliacorinine, tiliacorine, and nortiliacorinine, which have been widely used medicinally (15, 17, 47). Numerous biological activities have been reported, including cytotoxic activity against cholangiocarcinoma cell lines, antimycobacterial activity against the multidrug-resistant *Mycobacterium tuberculosis* strain, and antimalarial activity (4, 47, 48). Additionally, the leaves of *T. triandra* have been shown to be a natural source of antioxidants due to their high beta-carotene, condensed tannins, triterpenes, flavonoids, and saponins content, as well as minerals like calcium and iron (32, 49). Antioxidant and antimutagenic properties of these compounds lend additional support to their anticancer potential (14, 16, 20).

Antitumor Activity of Tiliacorinine in Human Cholangiocarcinoma

Cholangiocarcinoma (CCA) is a terminal disease with a dismal prognosis (3). The prognosis for conventional chemotherapy is bleak (9, 33). Substances derived from plants are gaining attention because they may be used to treat cancer, particularly resistant cancers (35, 46). Tiliacorinine, the major alkaloid isolated from the medicinal plant Tiliacora triandra, has exhibited antimalarial and antimycobacterial activity (47, 50). Tiliacorinine inhibited CCA cell proliferation effectively by inducing apoptosis and significantly reduced tumour growth in mice with CCA xenografts (4, 17, 32). Tiliacorinine inhibited the growth of four human CCA cell lines at concentrations ranging from 4.5 to 7.0 M (13). When compared to other natural compounds, tiliacorinine appears to be more effective than tannic acid (11). In contrast, sesquiterpenes appear to be less effective than caged xanthones (25, 51). Tiliacorinine inhibited CCA cell growth by inducing apoptosis, as evidenced by the results of three separate essays (39). To begin, tiliacorinine treatment increased in apoptotic cells (32). Second, in cells treated with tiliacorinine, DNA ladder formation was observed (4, 52). Third, as determined by flow cytometry, tiliacorinine treatment significantly increased the number of apoptotic cells in the sub G1 peak (4, 5). Anticancer drugs are thought to work primarily through the induction of apoptosis (34, 53). Tiliacorinine induced apoptosis through caspase-3,-9 activation and subsequent PARP cleavage (4, 43). Tiliacorinine also elevated BAX, a proapoptotic protein, and lessened XIAP and BclxL expression in human CCA cells (28, 32). For years, scientists searched for new agents that could stop CCA cells from multiplying and spreading, but most of these agents have only been tested *in vitro*, such as diethyldithiocarbamate and histone deacetylase inhibitors (7). The antitumor activity of tiliacorinine has been demonstrated in CCA cell lines, and mice xenografted with CCA (17, 32). When comparing the tiliacorinine-treated group to the control group, it was found that tumor volumes and weights were reduced by a factor of two (9, 44). Tiliacorinine appeared to have an immediate antitumor effect, as it was given three consecutive days after CCA cell injection and significantly reduced tumour volume (36, 44, 54). This is the first time that the antitumor activity of tiliacorinine has been reported (55). Tiliacorinine's pharmacokinetics, drug safety, and efficacy should be investigated further (56, 57).

Apoptosis, the programmed cell death of tumour cells, is a goal of nearly every anticancer drug in clinical trials (28, 53). It has been shown in numerous studies that defects in apoptotic pathways play an essential role in many types of cancer and that numerous new apoptotic-targeting therapeutic strategies can be effective in treating these diseases (42, 46). Tiliacorinine inhibited human CCA cell growth and slowed the growth of tumours in mice that had been injected with CCA (12). This suggests that this alkaloid is a good treatment for CCA (12, 17). Nevertheless, extensive research into tiliacorinine's safety and efficacy is strongly recommended (12). The combination of tiliacorinine and other cancer-fighting agents should be studied further to achieve synergistic therapeutic potential,

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minimize toxicity, and minimize the development of resistance to treatment (8, 17, 28, 57).

Conclusion:

T. triandra is an indigenous Southeast Asian plant that has been used for centuries for culinary and medicinal purposes. Numerous studies and publications have been conducted, most notably in Thailand. The statistics, on the other hand, are dispersed. Apart from its nutritional value, studies have revealed that it possesses medicinal and cancer-fighting properties. These properties may result from the presence of a variety of bioactive compounds throughout this plant. *T. triandra* possesses a variety of pharmacological properties. However, further studies on *T. triandra*'s anticancer mechanisms is necessary.

References:

1. Laconi E, Marongiu F, DeGregori J. Cancer as a disease of old age: changing mutational and microenvironmental landscapes. British journal of cancer. 2020;122(7):943-52.

2. Negoita S, Feuer EJ, Mariotto A, Cronin KA, Petkov VI, Hussey SK, et al. Annual report to the nation on the status of cancer, part II: recent changes in prostate cancer trends and disease characteristics. Cancer. 2018;124(13):2801-14.

3. Chen Y, Ma G, Su C, Wu P, Wang H, Song X, et al. Apatinib reverses alectinib resistance by targeting vascular endothelial growth factor receptor 2 and attenuating the oncogenic signaling pathway in echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase fusion gene-positive lung cancer cell lines. Anti-Cancer Drugs. 2018;29(10):935-43.

4. Pal A, Sengupta S, Kundu R. Tiliacora racemosa leaves induce oxidative stress mediated DNA damage leading to G2/M phase arrest and apoptosis in cervical cancer cells SiHa. Journal of Ethnopharmacology. 2021;269:113686.

5. Kim B-G, Malek E, Choi SH, Ignatz-Hoover JJ, Driscoll JJ. Novel therapies emerging in oncology to target the TGF-β pathway. Journal of Hematology & Oncology. 2021;14(1):1-20.

6. Guterres AN, Villanueva J. Targeting telomerase for cancer therapy. Oncogene. 2020;39(36):5811-24.

7. Maki P, Itharat A, Thongdeeying P, Tuy-On T, Kuropakornpong P, Pipatrattanaseree W, et al. Ethnopharmacological nexus between the traditional Thai medicine theory and biologically based cancer treatment. Journal of Ethnopharmacology. 2022;287:114932.

8. Jiso A, Khemawoot P, Techapichetvanich P, Soopairin S, Phoemsap K, Damrongsakul P, et al. Drug-Herb Interactions among Thai Herbs and Anticancer Drugs: A Scoping Review. Pharmaceuticals. 2022;15(2):146.

9. De Vera AA, Gupta P, Lei Z, Liao D, Narayanan S, Teng Q, et al. Immuno-oncology agent IPI-549 is a modulator of P-glycoprotein (P-gp, MDR1, ABCB1)-mediated multidrug resistance (MDR) in cancer: In vitro and in vivo. Cancer letters. 2019;442:91-103.

10. Makinde EA, Ovatlarnporn C, Adekoya AE, Nwabor OF, Olatunji OJ. Antidiabetic, antioxidant and antimicrobial activity of the aerial part of Tiliacora triandra. South african journal of botany. 2019;125:337-43.

11. Weerawatanakorn M, Rojsuntornkitti K, Pan M-H, Wongwaiwech D. Some phytochemicals and anti-inflammation effect of juice from Tiliacora triandra leaves. J Food Nutr Res. 2018;6:32-8.

12. Nutmakul T. Phytochemical and pharmacological activity of Tiliacora triandra (Colebr.) Diels. Songklanakarin Journal of Science & Technology. 2021;43(5).

13. Makinde EA. Chemical Constituents and Antidiabetic Activities of The Aerial Parts Of Tiliacora triandra. 2019.

14. Nema V, Dhas Y, Banerjee J, Mishra N. Phytochemicals: An Alternate Approach Towards Various Disease Management. Functional Food and Human Health: Springer; 2018. p. 623-53.

15. Tiam ER, Ngono Bikobo DS, Abouem A Zintchem A, Mbabi Nyemeck N, Moni Ndedi EDF, Betote Diboué PH, et al. Secondary metabolites from Triclisia gilletii (De Wild) Staner (Menispermaceae) with antimycobacterial activity against Mycobacterium tuberculosis. Natural product research. 2019;33(5):642-50.

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16. Thong-Asa W, Bullangpoti V. Neuroprotective effects of Tiliacora triandra leaf extract in a mice model of cerebral ischemia reperfusion. Avicenna Journal of Phytomedicine. 2020;10(2):202.

17. Qing Z-X, Huang J-L, Yang X-Y, Liu J-H, Cao H-L, Xiang F, et al. Anticancer and reversing multidrug resistance activities of natural isoquinoline alkaloids and their structure-activity relationship. Current medicinal chemistry. 2018;25(38):5088-114.

18. Wachiryah T-a, Hathaipat L. Enhancing effect of Tiliacora triandra leaves extract on spatial learning, memory and learning flexibility as well as hippocampal choline acetyltransferase activity in mice. Avicenna Journal of Phytomedicine. 2018;8(4):380.

19. Nayak T, Jena L, Waghmare P, Harinath BC. Identification of potential inhibitors for mycobacterial uridine diphosphogalactofuranose-galactopyranose mutase enzyme: A novel drug target through in silico approach. International Journal of Mycobacteriology. 2018;7(1):61.

20. Nanasombat S, Yansodthee K, Jongjaited I. Evaluation of antidiabetic, antioxidant and other phytochemical properties of Thai fruits, vegetables and some local food plants. Walailak Journal of Science and Technology (WJST). 2019;16(11):851-66.

21. Morais RMSC, Morais AMMB, Dammak I, Bonilla J, Sobral PJA, Laguerre JC, et al. Functional dehydrated foods for health preservation. Journal of Food Quality. 2018;2018.

22. Pasachan T, Duangjai A, Ontawong A, Amornlerdpison D, Jinakote M, Phatsara M, et al. Tiliacora triandra (Colebr.) diels leaf aqueous extract inhibits hepatic glucose production in HepG2 cells and type 2 diabetic rats. Molecules. 2021;26(5):1239.

23. Makinde EA, Radenahmad N, Adekoya AE, Olatunji OJ. Tiliacora triandra extract possesses antidiabetic effects in high fat diet/streptozotocin-induced diabetes in rats. Journal of food biochemistry. 2020;44(6):e13239.

24. Ruangnoo S, Rattarom R, Itharat A. Cytotoxic activity of local Thai vegetables against breast and prostate cancer cells. Thammasat Medical Journal. 2019;19(1):70-8.

25. Li S-J, Zhang X, Wang X-H, Zhao C-Q. Novel natural compounds from endophytic fungi with anticancer activity. European Journal of Medicinal Chemistry. 2018;156:316-43.

26. Uzma F, Mohan CD, Siddaiah CN, Chowdappa S. Endophytic fungi: promising source of novel bioactive compounds. Advances in endophytic fungal research: Springer; 2019. p. 243-65.

27. James N, Shanthi V, Ramanathan K. Discovery of novel anaplastic lymphoma kinase inhibitors: Structure and energy-based pharmacophore strategy. Journal of Theoretical and Computational Chemistry. 2019;18(03):1950014.

28. Farooqi AA, Naureen H, Zahid R, Youssef L, Attar R, Xu B. Cancer chemopreventive role of fisetin: Regulation of cell signaling pathways in different cancers. Pharmacological Research. 2021;172:105784.

29. Juckmeta T, Pipatrattanaseree W, Jaidee W, Dechayont B, Chunthorng-Orn J, Andersen RJ, et al. Cytotoxicity to five cancer cell lines of the respiratory tract system and anti-inflammatory activity of Thai traditional remedy. Natural Product Communications. 2019;14(5):1934578X19845815.

30. Erin N, Grahovac J, Brozovic A, Efferth T. Tumor microenvironment and epithelial mesenchymal transition as targets to overcome tumor multidrug resistance. Drug Resistance Updates. 2020;53:100715.

31. Nutmakul T, Pattanapanyasat K, Soonthornchareonnon N, Shiomi K, Mori M, Prathanturarug S. Speed of action and stage specificity of Bencha-loga-wichian, a Thai traditional antipyretic formulation, against Plasmodium falciparum and the chloroquine-potentiating activity of its active compounds, tiliacorinine and yanangcorinine. Journal of Ethnopharmacology. 2020;258:112909.

32. Kismali G, Ceylan A, Meral O, Alpay M, Kosova F, Cakir DU, et al. Piperlongumine inhibits cell growth and enhances TRAIL-induced apoptosis in prostate cancer cells. Asian Pacific Journal of Tropical Biomedicine. 2020;10(5):216.

33. Sharifi-Rad J, Salehi B, Stojanović-Radić ZZ, Fokou PVT, Sharifi-Rad M, Mahady GB, et al. Medicinal plants used in the treatment of

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tuberculosis-Ethnobotanical and ethnopharmacological approaches. Biotechnology advances. 2020;44:107629.

34. Zhang X, Peng X, Wang C, Olatunji OJ, Famurewa A. Tiliacora triandra attenuates cisplatin triggered hepatorenal and testicular toxicity in rats by modulating oxidative inflammation, apoptosis and endocrine deficit. Frontiers in Bioscience (Landmark Edition). 2022;27(2):44-.

35. Hirota T, Muraki S, Ieiri I. Clinical pharmacokinetics of anaplastic lymphoma kinase inhibitors in non-small-cell lung cancer. Clinical Pharmacokinetics. 2019;58(4):403-20.

36. Shen M, Xu Z, Xu W, Jiang K, Zhang F, Ding Q, et al. Inhibition of ATM reverses EMT and decreases metastatic potential of cisplatin-resistant lung cancer cells through JAK/STAT3/PD-L1 pathway. Journal of Experimental & Clinical Cancer Research. 2019;38(1):1-14.

37. Jain S, Chalif EJ, Aghi MK. Interactions Between Anti-Angiogenic Therapy and Immunotherapy in Glioblastoma. Frontiers in Oncology. 2022:5702.

38. Mohrherr J, Uras IZ, Moll HP, Casanova E. STAT3: versatile functions in non-small cell lung cancer. Cancers. 2020;12(5):1107.

39. Fan J, Xu G, Chang Z, Zhu L, Yao J. miR-210 transferred by lung cancer cell-derived exosomes may act as proangiogenic factor in cancer-associated fibroblasts by modulating JAK2/STAT3 pathway. Clinical Science. 2020;134(7):807-25.

40. Shi J, Li J, Yang S, Hu X, Chen J, Feng J, et al. LncRNA SNHG3 is activated by E2F1 and promotes proliferation and migration of non-small-cell lung cancer cells through activating TGF-β pathway and IL-6/JAK2/STAT3 pathway. Journal of cellular physiology. 2020;235(3):2891-900.

41. Liu D, Xu X, Wen J, Zhang C, Fan M. Identification of a EML4-ALK exon 19 fusion variant in lung adenocarcinoma and alectinib resistance. Lung Cancer. 2021;160:32-5.

42. Naghizadeh S, Mohammadi A, Baradaran B, Mansoori B. Overcoming multiple drug resistance in lung cancer using siRNA targeted therapy. Gene. 2019;714:143972.

43. Li B, Ding C-M, Li Y-X, Peng J-C, Geng N, Qin W-W. Over-regulation of microRNA-133b inhibits cell proliferation of cisplatin-induced non-small cell lung cancer cells through PI3K/Akt and JAK2/STAT3 signaling pathway by targeting EGFR. Oncology reports. 2018;39(3):1227-34.

44. Chen Q, Liu X, Luo Z, Wang S, Lin J, Xie Z, et al. Chloride channel-3 mediates multidrug resistance of cancer by upregulating P-glycoprotein expression. Journal of Cellular Physiology. 2019;234(5):6611-23.

45. Ganesan M, Kanimozhi G, Pradhapsingh B, Khan HA, Alhomida AS, Ekhzaimy A, et al. Phytochemicals reverse P-glycoprotein mediated multidrug resistance via signal transduction pathways. Biomedicine & Pharmacotherapy. 2021;139:111632.

46. Cheng Q, Liao M, Hu H, Li H, Wu L. Asiatic acid (AA) sensitizes multidrug-resistant human lung adenocarcinoma A549/DDP cells to cisplatin (DDP) via downregulation of P-glycoprotein (MDR1) and its targets. Cellular Physiology and Biochemistry. 2018;47(1):279-92.

47. Swain SS, Pati S, Hussain T. Quinoline heterocyclic containing plant and marine candidates against drug-resistant Mycobacterium tuberculosis: A systematic drug-ability investigation. European Journal of Medicinal Chemistry. 2022;232:114173.

48. Somwong P, Chuchote C. Determination of lupeol, a cytotoxic compound against SW620 cells in the extracts of Ha-Rak recipe. Pharmacognosy Journal. 2021;13(1).

49. Suriyapha C, Ampapon T, Viennasay B, Matra M, Wann C, Wanapat M. Manipulating rumen fermentation, microbial protein synthesis, and mitigating methane production using bamboo grass pellet in swamp buffaloes. Tropical Animal Health and Production. 2020;52(4):1609-15.

50. Obakiro SB, Kiprop A, Kowino I, Kigondu E, Odero MP, Omara T, et al. Ethnobotany, ethnopharmacology, and phytochemistry of traditional medicinal plants used in the management of symptoms of tuberculosis in East Africa: a systematic review. Tropical Medicine and Health. 2020;48(1):1-21.

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51. Faustino C, Andrade JM, Ferreira IM, Almeida JF, Rijo P. Lead molecules from natural products: insight into tubercular targets. Studies in Natural Products Chemistry. 2020;65:41-84.

52. Bose P, Harit AK, Das R, Sau S, Iyer AK, Kashaw SK. Tuberculosis: current scenario, drug targets, and future prospects. Medicinal Chemistry Research. 2021;30(4):807-33.

53. Kuo Y-C, Rajesh R. Functionalized drug-gene delivery materials to transport inhibitor of apoptosis protein antagonists for tumor malignancy management. Journal of the Taiwan Institute of Chemical Engineers. 2022;133:104283.

54. Ludlow AT, Wong MS, Robin JD, Batten K, Yuan L, Lai T-P, et al. NOVA1 regulates hTERT splicing and cell growth in non-small cell lung cancer. Nature communications. 2018;9(1):1-15.

55. Panthiya L, Pantan R, Tocharus J, Nakaew A, Suksamrarn A, Tocharus C. Endothelium-dependent and endothelium-independent vasorelaxant effects of tiliacorinine 12′-O-acetate and mechanisms on isolated rat aorta. Biomedicine & Pharmacotherapy. 2019;109:2090-9.

56. Kongkham B, Prabakaran D, Puttaswamy H. Opportunities and challenges in managing antibiotic resistance in bacteria using plant secondary metabolites. Fitoterapia. 2020;147:104762.

57. Halder SK, Elma F. In silico identification of novel chemical compounds with antituberculosis activity for the inhibition of InhA and EthR proteins from Mycobacterium tuberculosis. Journal of Clinical Tuberculosis and Other Mycobacterial Diseases. 2021;24:100246.

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