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REVIEW ARTICLE

A Review: *Melia azedarach* L. as a Potent Anticancer Drug

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ABSTRACT

Chinaberry (*Melia azedarach* L., Meliaceae), a Mahogany family usually used as high quality timber, is native to Asia but now is found in other parts of tropical world continent. The leaves, fruits, bark, seed and root are use in traditional medicine and it has been shown to various pharmacological activities like antifungal, anti-malarial, antibacterial, hepatoprotective, anti-oxidant, anti-fertility, anthelmintic, antipyretic and cytotoxic. A review to its phytochemical and anticancer properties of *M. azedarach* and its sub species or varieties as an effort to analyze the literature on its developing used as anticancer agent. As results of literatures review indicates that fruit, bark, leaves, pulp and seed of *Melia azedarach* L. showed various *in vitro* cytotoxic activities in cancer cell lines, such as human colorectal carcinoma (HT-29), breast cancer (MCF-7, SK-BR-3), cervix hepatoma (HepG-2, SMMC-7721 and Hep3B), kidney epithelial cell (MDBK), human lung adenocarcinoma epithelial cell (A549), non-small cell lung cancer (H460), human lymphoblast lung (U937), human cancer promyelocytic leukemia (HL-60), AZ521 (stomach), human colon cancer (SW480), murine colorectal adenocarcinoma cell (CT26), human oral cancer cell (KB), human prostate cancer (PC3), liver (BEL7404), CNS (SH-SY5Y, U251, SF539), B16F10 mouse melanoma cell line; and showed various *in vivo* to adenocarsinoma mammary in C3H mice and mouse hepatocellular carcinoma H22 cells to BALB/c mice. Previous results suggested that cytotoxic organic compounds of *Melia azedarach* L. were supposed of flavonoids, triterpenoids (tirucallane), limonoids (meliarachin, meliatoxin B1, trichilin H, and toosendanin), steroids, and organic acids content compounds.

Key words: Anticancer, cytotoxic, *Melia azedarach*, *Melia*, triterpenoids, limonoid

INTRODUCTION

Cancer is a generic term for a large group of disease that affects any part of the body. Another definition of cancer is an uncontrolled proliferation of the cells, producing abnormal cells which invade healthy tissue and spread to other organs (malignant) and established secondary lethal tumors (metastases). Cancer is one of the major causes of morbidity and mortality worldwide. There were almost 14 million new cases in 2012, which is predicted to rise about 70% for next two decades. It is the second leading cause of death globally and is responsible for 8.8 million deaths in 2015;18.7% of deaths are caused due to cancer; of which 70% occurs in low- and middle-income countries. Five most common causes of cancer death are lung (39.2%), liver (17.2%), colorectal (16.9%), stomach (16.5%), and breast cancers (12.5%).[1]

Plants play a significant role in the development of anticancer during the last few decades. Ninety out of 121 prescription drugs that are being used today for cancer treatment are plant based as evidenced by the historical use and developing plants for cancer therapy.[2] The first developing natural-derived compound in 1961 was vincristine, a vinca alkaloid class isolated from the dried leaves of periwinkle *Catharanthus roseus*. Vincristine is a chemotherapy medication to cure Hodgkin's disease and some types of leukemia. Etoposide, an epipodophyllotoxin compound class, is another example of natural-derived compound from *Podophyllum peltatum* (the Mandrake Plant) and *Podophyllum emodi* (the Wild Chervil). Etoposide (a topoisomerase II inhibitor class) is effective against testicular cancer and small and non-small cell lung carcinoma, also to malignant lymphomas.[3,4] Etoposide is a topoisomerase II inhibitor, which breaks DNA by stabilizing enzyme–DNA cleavable complexes. An additional number of natural-derived anticancer agents such as camptothecin, paclitaxel, homoharringtonine, and other compounds are shown in Table 1.[5-8]

Chinaberry (*Melia azedarach* L. [MA]) is a plant species belonging to the family *Meliaceae*, a Mahogany family (*Sapindales* order). It is originally from Asia but is now found in parts of North Australia, Africa, North America, tropical South of America, and Southern part of Europe. It named as Paraiso or paradise in South America and as Indian Lilac or White Cedar in the USA. *Melia's* leaves, fruits, bark, and root are used in traditional medicine. The leaves are used for in the traditional medical systems of India (Ayurvedic, Unani-Tibb), China, Japan, and Taiwan as well. The leaves have been used as a natural insecticide, so it has been known highly poisonous if eaten, as a preservative which to keep with stored food. In traditional medicine *Melia* is used for anthelmintic and vermifuge, diuretic, emmenagogue, expectorant, as astringent, to cure leprosy, and scrofula disease. In Japan, it has been used for vermicide, anodyne, and skin disease, while in Traditional Chinese Medicine, it is used as antiparasitic and antifungal agent. Pharmacologically, MA

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Table 1: Plant-derived anticancer agents

Compound	Class of compound	Plants source (Family)	Cancer use
Vincristine	Alkaloid	Leaves of *Catharanthus roseus* (Apocynaceae)	Leukemia, lymphoma, breast, lung, pediatric solid cancers and others
Vinblastine			Breast, lymphoma, germ-cell and renal cancer
Paclitaxel	Taxanes	Bark of Taxus brevifolia, *T. canadensis* (*Taxaceae*)	Ovary, breast, lung, bladder, and head and neck cancer
Docetaxel		Semi synthetic analog from *Taxus baccata*	Breast and lung Cancer
Topotecan	Campothecin derivates	bark and wood of Nyssacea *Camptotheca*	Ovarian, lung and pediatric cancer
Irinotecan	and Topotecan (Hycamtin)	*accuminata* (Nyssaceae)	Colorectal and lung cancer
Flavopiridol	Alkaloid rohitukine	*Amoora rohituka* (leaves and stem) Dysoxylum *Binectariferum* (Maliaceae)	Experimental
Etoposide	Epipodophyllotoxin	*Podophyllum peltatum* and *Podophyllum emodi* (Berberidaceae)	Lung cancer, Malignant lymphomas, Testicular cancer
Acronyciline	Alkaloid	*Acronychia baueri* (Rutaceae)	Experimental
Bruceantin	Alkaloid	*Brucea antidysenterica* (Simaroubaceae)	Experimental
Thalicarpin	Alkaloid	*Thalictrum dasycarpum* (Ranunculaceae)	Experimental
Homoharringtonine	Alkaloid	*Cephalotaxus harringtonia* (Cephalotaxacea)	various leukemias
Elliptinium	Alkaloid	*Bleekeria vitensis* Apocynaceae	breast cancer
4-Ipomeanol	Furan	*Ipomoeca batatas* (Convolvulaceae)	Experimental

showed various activities such as antifungal, antibacterial, antimalarial, hepatoprotective, antioxidant, antifertility, anthelminthic, antipyretic, and cytotoxic.[9] The purpose of this article is to review phytochemical and anticancer properties of MA as an effort to give a detailed survey of the literature on its potential developing used as natural-derived anticancer source compounds. The literature reviews was carried out by analyzing journal and peer reviewed concerning of MA and *Melia* sp. Peer-reviewed articles were indexed by databases such as Scopus, PubMed, Google Scholar, and Research Gate. Data selection criteria in this review are based on *in vivo* and *in vitro* cytotoxic and anticancer of *Melia* spp. The keywords used for search the literature in the databases: *Melia* cytotoxic, plants anticancer.

BOTANICAL VIEW AND ETHNOMEDICINAL USE OF *MELIA AZEDARACH* L.

MA belongs to *Meliaceae*, the mahogany family of flowering plants order of *Sapindales*. *Meliaceae* comprises 51 genera and about 575 species of trees and (rarely) shrubs or sometimes shrublets, monopodial or sympodial, usually deciduous, less often monoecious or polygamodioecious, native to tropical and subtropical regions. Most members of the family have more leaves, with the leaflets arranged in the form of a feather, and branched flower clusters. The fruit is fleshy and colored or a leathery capsule. Genera of member of the family are differentiated according to its fruit shape and leave rearrangement of the plants. *Melia* is a genus with the winged seed fruit and leaves bipinnate; margin dentate leaflet blades, crenate, or rarely entire. MA is quite a different genus to the *Azadirachta* tree but are in the same family.[9-11]

According to Mabberley,[10] *Melia* divided into some classes: (1) wild type, (2) Chinese cultivars, and (3) Indian cultivars. The classes are based on the plants type and the regions where *Melia* grows. The wild *Melia* type is a tall forest tree of about 40 m; while Indian and Chinese cultivars are small trees. The wild plants name including *Melia composite* Willd., *Melia dubia* Cav., Dissert, *Melia superba* Roxb., *Melia robusta* Roxb., *Melia australis* Sweet., *Melia candollei* A. Juss, *Melia australasica* A Juss, *Melia birmanica* Kurz., MA var javanica Koord. and Val, *Melia bogoriensis* Koord. and Val., MA var. glandulosa Pierre, *M. composite* var *cochinchinensis* Pierre, which named based on the material collected from. MA cultivars in China with varieties and subvarieties consist of *Melia japonica* G. Don. f., *Melia toosendan* Sieb. and Zucc., *Melia chinensis* Sieb ex Miq., *M. japonica* G. Don var. semperflorens Mak., and MA f. albiflora. MA subvar. intermedia is a subvariety between *japonica* and *toosendan*. In India, MA var. sempervirens L., *Melia commelini* Medik., *Melia arguta* DC., *Melia sambucina* Bl., *Melia angustifolia* Schum. and Thonn., *Melia guineensis* G. Don. F., *Melia bukayun* Royle, MA var subtripinnata Miq., Melia composite var cochinchinensis Pierre.

MA is well known as ecological and ethnomedicinal tree used in India, Japan, and China. It is used mostly as timber and natural insecticide and in the traditional medicine is also well documented. The fruit, the root, and the seed are bitter and poisonous. All parts (the bark, stem, the root and the root bark, the leaves and fruit, the flower including flower oil, the seed, and the seed oil) of MA are used as a traditional medicine and was shown *in vitro* and *in vivo* various pharmacological properties. Among all parts of the plants, its leaves used most. The leave is used for control insect, mite and nematode pests, for skin disease, for gingivitis mouthwash, to treat diabetes, malaria, fever, and stomachache. Sharma and Paul[11] described ethnomedicinal and pharmacological review of MA. Some ethnomedicinal use was supported by pharmacology research result, but some has supposed of empirical base experience. Among pharmacological test, it was known that insecticidal activities were observed most compared to other pharmacological activities of the plants. The most used parts of the plants were the seed and the leaf of the MA. Insecticidal mechanism activities of the plants include antifeedant, anti-oviposition, phagoinhibitor, antimolting, larvicidal, adulticidal, and anticholinesterase. Azadirachtin and tetranortriterpenoids were supposed compound related to these primary insecticidal activities. Azadirachtin, a toxic constituent of MA, is been commercially product of neem oil.[12] Furthermore, Tariq *et al.*[2] was review of seventy eight families plants, which ethnomedicinally use as anticancer in some regions. MA was one of four *Meliaceae* families (MA, *Azadirachta indica* A. Juss., *Trichilia emetica* Vahl., and *Swietenia mahagoni* Jacq.). Among those of four *Meliacea's* anticancer plants, *A. indica* was more exposed to *in vitro* and *in vivo* anticancer activities potency.[2,13]

PHYTOCHEMICAL CONTENT OF *MELIA AZEDARACH* L.

A variety use in solvents extraction revealed the organic compound of MA. Some researchers used methanol and ethanol by reflux or by percolation. In general, organic molecule compounds of MA contain

flavonoids, terpenoids, steroids, organic acids and anthraquinones, alkaloids, saponins, and tannins.[12,14,15] The most secondary metabolite contents in the parts of the plants are terpenoids and limonoid (tetranortriterpenoid), followed by steroid and flavonoids. The organic molecules are in glycoside or aglycone form, so some results confirm saponin (glycoside of triterpene or steroid).

The leaf extract contains kaempferol-3-O-β-rutinoside, kaempferol-3-L-rhamno-D-glucoside, rutin, quercetin (flavonoids); stigmasterol, campesterol (phytosterols); β-sitosterol, phytol, squalene, 3-methyldecane, heptadecane (alkane hydrocarbon); hexadecanoic acid, palmitic acid, pentadecanoic acid (n-alkanoic acids); β-carotene, tocopherol (Vitamin E); squalene, 1-eicosanol (triterpene); and 3,5,11,15-tetramethyl-2-hexadecen-1-ol (terpene alcohol). The leaves contain also terpenoids (α-pinene, β-pinene, α-terpinene, α-terpineol) and limonoids (l-cinnamoyl-3-acetyl-11-hydroxy meliacarpin, l-cinnamoyl-3-methacrylyl-l1-hydroxy meliacarpin, deacetyl salannin, 1,3-dicinnamoyl-l1-hydroxy-meliacarpin).[16,17]

The seeds of MA contain terpenoids and limonoid glycosides, viz., 6,11-diacetoxy-7-keto-14 beta-epoxymeliacin (1,5-diene-3-O-β-D-glucopyranoside), 3β,7a-dihydroxy-21,23-epoxy-apotirucalla-14,24-diene-21-one, meldenin and melianol, meliacin, meliacarpin, meliartenin vanillin, vanillin and steroids (β-sitosterol, campesterol, cholesterol, daucosterol, stigmasterol), hydroxy-3-methoxycinnamaldehyde and (±) pinoresinol. The seeds also contain organic acids (linoleic acid, linolenic acid, oleic acid [9-octadecenoic acid], benzoic acid, vanillic acid).[12,16]

Melia's stem contains terpenoids (a-pinene, β-pinene, a-terpinene, a-terpineol) and limonoids (7a-acetoxy-14 β,15β-epoxygedunan-ene-3-O-β-D-glucopyranoside, 12-acetoxyamoorastatin, amoorastatin, fraxinellone, 12-hydroxyamoorastatone, 3-hydroxyeupha-7,24-diene-21,16-olide, kulactone, kulinone, kulolactone, methylkulonate, including melianin-A and melianin-B). They also contain flavonoids (4, 5-dihydroxy flavone-7-O-u-L-rhamnopyranosyl-(1-4)-β-D-glucopyranoside), anthraquinone (1,3,5,8-tetrahydroxy-2-methylanthraquinone; 8-Me-ether, 3-O-α-L-rhamnopyranoside, 1,5-dihydroxy-8-methoxy-2-methyl-anthraquinone-3- O-α-L-rhamnopyranoside, 1,8-dihydroxy-2-methylanthraquinone-3-O-β-D, galactopyranoside).[16]

The roots of *Melia* contain terpenoids and limonoids (6-acetoxy-7a-hydroxy-3-oxo-14β, 15 β-epoxymeliac-l, 5-diene, 6-acetoxy-3β-hydroxy-7-oxo-14 β, 15β- epoxymeliac-l, 5-diene-3-0-β-D-glucopyranoside, azecin-l, azecin-2, azecin-3, azecin-4) and flavonoids (apigenin-5-O-β-D-galactopyranoside); steroids (24-methylenecydoartanol, 24-methylenecydoartanone, 4-stigmastanen-3-one, 4-campestene-3-one β-sitosterol, β-sitosterol-B-D-glucoside); acids (trans-cinnamic acid, vanillic acid [4-hydroxy-3-methoxybenzoic acid]). Root bark contains terpenoids and limonoids (12-O-acetyl azedarachin-A, 12-O-acetyl azedarachin-B, l-acetyl-3-tigloyl-11-methoxy meliacarpinin, 12-O-acetyltrichilin-B, 2α-acetyl-29-deacetyl-29-isobutyrylsendanin, azedarachin-A, azedarachin-C, l-cinnamoyl-3-acetyl-11-methoxy meliacarpinin, l-cinnamoyl-3-hydroxy-11-methoxy meliacarpinin, 1-deoxy-3-methacrylyl-11- methoxy meliacarpinin, 1-deacetylnimbolinin-B, 1,12-diacetyltrichilin-B, 7,12-diacetyltrichilin-B, 29-isobutylsendanin, meliacarpinin E, nimbolidin-B, salannal, salannin, 1-tigloyl-3-acetyl-11-methoxy meliacarpinin, 1-tigloyl-3,20-diacdyl-11-methoxyrneliacarpinin, 3-tigloyl-1,20- diacetyl-11-methoxymeliacar-pinin, trichilin-B, trichilin-D, trichilin-H) and steroids (6-β-hydroxy-4-canpesten-3-one, 6-β-hydroxy-4- stigmasten-3-one, azeclarachol).[12]

Melia's fruits contain terpenoids and limonoids (6-acetoxy-14,15-epoxy-3, 11-dihydroxymeliaca-l, 5-diene-7-one, amoorastatin, amorastatone, azedirachtin-A, l-cinnamoyl-3, 11-dihydroxy-meliacarpinin, l-cinnamoyl melianolone, l-cinnamoyl melianone, compositin, compositolide, 1-O-deacetylohchinolide-B, 29-deacetylsendanin, 1-deacetylnimbolinin-A, 3-deoxymelianone, 21,23:24,25- diepoxy-tirucall-7-ene-21-ol, 3-epimelianol, 3-epimeliantriol, gedunin, 12-a-hydroxyamoorastatin, meliandiol, melianol, melianolone, melianone, melianoninol, meliantriol, meliatoxin-A1, meliatoxin-A2, meliatoxin-B1, meliatoxin-B2, nimbolidin-A, nimbolinin-A, nimbolinin-B, ohchinal, ohchinin, ohchinin acetate, ohchinolal, ohchinolide-A, ohchinolide-B, sendanal, sendandal, sendanin, 3-O-tigloylohchinin, vilasinin, 21-β-acetoxymelianone, methyl kulonate, 3-α-tigloylmelianol. They also contain acids (stearic acid [octadecanoic acid] and trans-cinnamic acid).[12]

In the phytochemistric analysis of MA ethanol extracts, it revealed the presence of triterpenoids and steroids, respectively, and both seeds and leaves also presented alkaloids and condensed tannins, which supposed inhibit the development or insect feeding and ovicidal to insects.[18]

Two new triterpenoid (3a-(2-methylbutyryl)-1,20-diacetyl-11-methoxymeliacarpinin and 3a-tigloyl-17a-20S-21,24-epoxy-apotirucall-14-en-7a, 23a, 25-triol) and a new sterol (2a, 3b-dihydroxyandrostan-16-one 2b, 19-hemiketal), together with six known constituents (1-cinnamoyl-3-acetyl-11-methoxymeliacarpinin, 3-tigloyl-1,20-diacetyl-11-methoxymeliacarpinin, 3S,23R,25-trihydroxytirucall-7-24-one, 2a, 3a, 16b-trihydroxy-5apregnane 20R-metha-crylate, 6-de (acetyloxy)-7-deacetylchisocheton compound E, and toonapubesin C), were isolated from the methanol extract of leaves and twigs of MA.[19]

THE ANTICANCER MECHANISMS OF PHYTOCHEMICAL CONTENT OF *MELIA AZEDARACH* L.

Anticancer drugs' mechanism of action can be classified into six classes which are DNA-interactive agents, antimetabolites, molecular targeting agents, antitubulin agents, hormones, monoclonal antibodies, and other biological agents.[20,21] Most derived anticancer plants are altered the three-dimensional structure of DNA by cleaving or rejoining reactions. This is abrupt process on DNA replication, transcription, and results on chromatid segregation. Development of tumor/cancer is mostly associated with apoptosis process. Bcl-2 (antiapoptosis agent of the cell) is a membrane protein found in different cell organelles such as mitochondria, endoplasmic reticulum, and nuclear membrane.[22] These agents regulate calcium ion fluxes through endoplasmic reticulum and inhibit apoptosis. If some cells suffer from permanent gene mutation, they become more susceptible to overexpression effects of Bcl-2. Their overexpression causes mutated genes to divide normally rather than their apoptosis. On the other hand, Bax is an apoptosis-inducing agent. These are normally attached to different membranes or present in cytosol.[23] Proportion of Bcl-2 and Bax decides about the life or death of tumor cell.[24]

A study by Tariq *et al.*[2] showed that a total of 29 compounds belonging to eight classes of secondary metabolites were reported to be checked against different types of cancer. Among 29 reportedly isolated compounds, most of them were phenolic compounds (16), followed by terpenoids (6), glycosides (2), and alcohol, alkaloid, alkyne, carotene, and hydrazine (1 each). Three secondary metabolites were reported to be used in animal model studies, and the rest of compounds were checked *in-vitro* methods. Anticancer mechanisms of phenolic compounds are due to their chemopreventive structure which can regulate ontogenesis expression and carcinogen metabolism. They are natural antioxidants, have the ability to arrest cell cycle, inhibit DNA binding and cell proliferation, so have effect on inhibit carcinogenesis and mutagenesis.

These may be hydroxyl cinnamic acid derivatives, phenols or phenolic acid, tannins, lignins, coumarins, quinones, stilbenes, etc.[25]

Huang *et al.*[26] presented a comprehensive review about terpenoids and their potential effects against cancer. A variety of terpenoids have been identified that are effective against proliferation of cancer cell. Anticancer terpenoids include sesquiterpenoids, monoterpenoid, diterpenoid, and triterpenoid or tetraterpenoids. It was triterpenoids which most extensively studied as anticancer research. The mechanism of terpenoid as anticancer cell molecular target remains unclear. The proposed mechanism action of monoterpene D-limonene might inhibit 3-hydroxy-3-methylglutanyl coenzyme reductase, which leads to obstructing p21, and its membrane localization by inhibiting small G proteins isoprenylation. This mechanism is believed in contributing to the chemoprevention on the cancer therapy. P21 is a cyclin-dependent kinase inhibitor protein, has functions in cell cycle regulator (progression at G_1 and S phase), but does not appear to be applicable to all cancer types. Other findings suggest that D-limonene is primarily involved the mitochondrial death pathway by apoptosis-upregulated Bax protein expression, by the mitochondria release of cytochrome c, and by the cleavage of caspase-3 and -9 but not caspase-8.

Terpenoid is mostly produced in vegetative parts of plants, flowers, but occasionally in roots.[27] These anticancer compounds are isolated from a very limited number of plants, while still large numbers of reported plants are phytochemical unexplored.[2]

Kim *et al.*[28] isolated a limonoid compound, 28-deacetylsendanin, from the fruit of *M. toosendan* Sieb. et Zucc. and examined on anticancer activity against eight human cancer cells from six organs lines and SRB assay as compared to adriamycin. The most sensitive cell of 28-deacetylsendanin (dose–response) was against SF-539 (central nervous system [CNS]) and PC-3 (prostate). All the cell lines responded similarly to adriamycin to give rise to nearly identical dose-response profiles. This result showed that 28-deacetylsendanin had more sensitive and selective inhibitory effects on *in vitro* growth of human cancer cell lines in a comparison with adriamycin.

Other two new limonoid compounds (toosendanal and 12-O-methyl volkensin), along with three known limonoids (meliatoxin B1, trichilin H, and toosendanin [TSN]), were isolated from the fruits of *M. toosendan* Sieb. et Zucc. Trichilin H and TSN were highly cytotoxic against KB cells *in vitro*, while 12-O-methyl volkensin, toosendanal, and meliatoxin B1 did not show any significant level of toxicity. Limonoid meliatoxin B1 and TSN showed cytotoxic activity against KB cells (IC_{50} 10 µg/ mL and 3.82 µg/ mL). results also suggesting structure- cytotoxic activity relationship of C-14/C-15-epoxide and C-15-keto structures against KB cells (cytotoxic requires the C-14/C-15-epoxide structure such structure of trichilin H and TSN compared to C-15-keto structures of toosendanal and meliatoxin B1).[29]

Wu *et al.*[30] isolated 6 steroids from the leaves of MA. The compounds were elucidated and tested to A549, H460, U251 cell line. The result obtained 3 compounds have cytotoxic effect (IC50 12.0-30.1 µg/ mL). Ntalli *et al.*[31] isolated three known tirucallanes and a new tirucallane triterpenoid, 3-α-tigloylmelianol, from the dichrolomethane-soluble part of the methanol extract obtained from the fruits of MA 21β-acetoxymelianone, 3α-tigloylmelianol, and melianone were cytotoxic while 21-β-acetoxymelianone and 3-α-tigloylmelianol showed an additional moderate antiproliferative effect against the A549 (human lung adenocarcinoma epithelial) cell line. The structure of tirucallane triterpenoid and limonoid is shown in Figure 1.

In vitro research on anticancer activity of the extract and some compounds being isolated from MA showed the promising results. Jafari *et al.*[32] reported that extract from *Melia's* seed kernel produced IC_{50} range of 8.18–60.10 µg/mL, as the highest cytotoxic activity and selectivity to cancer cell lines by MTT assay compared to *A. indica*. At the study, the leaves, pulps, and seeds as well as three main fractions of the leaf extracts were determined against five cell line (HT-29, A-549, MCF-7, HepG-2, and MDBK). Four flavonol 3-O-glycosides (rutin, kaempferol-3-O-robinobioside, kaempferol-3-O-rutinoside, and isoquercetin), purine nucleoside, and β-adenosine were isolated in phytochemical analysis. The leaves of MA have plenty content of flavonols, well-known secondary compounds which supposed to be accountable for many medicinal uses in the traditional exploited. The results also showed that in terms of cytotoxicity methanol leaf fraction of MA to be safer compared to other solvent fractions.

Flavonoids as phenolic compounds have important effects on cancer chemoprevention and chemotherapy. In many molecular mechanisms of chemoprevention, they play a major role by interacting between different types of genes and enzymes. Many mechanisms of action have been identified, including antioxidation, carcinogen inactivation, antiproliferation, cell cycle arrest, apoptosis induction, angiogenesis inhibition, and reversal of multidrug resistance or a combination of these mechanisms.[33-35] Proposed mechanism of inhibition carcinogenesis of flavonoid is shown in Figure 2.[35]

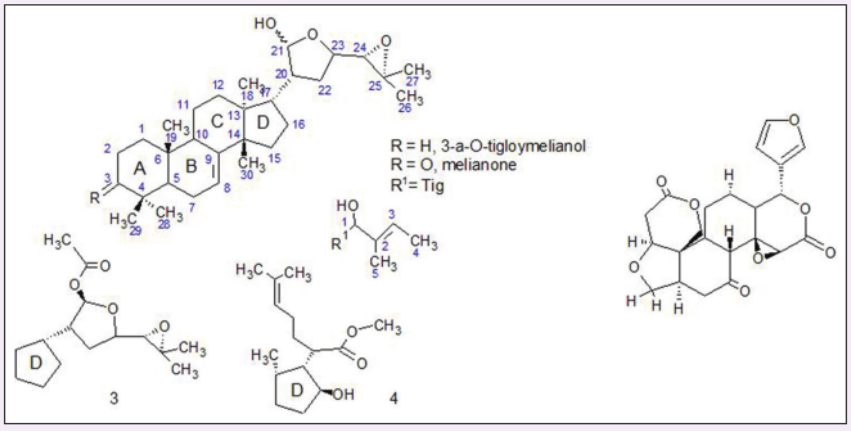

Figure 1: Molecular structure of triterpenoid (a) (3. methyl kulonate, 4. 3-α-tigloylmelianol) and limonoid (b) content in *Melia azedarach* L.

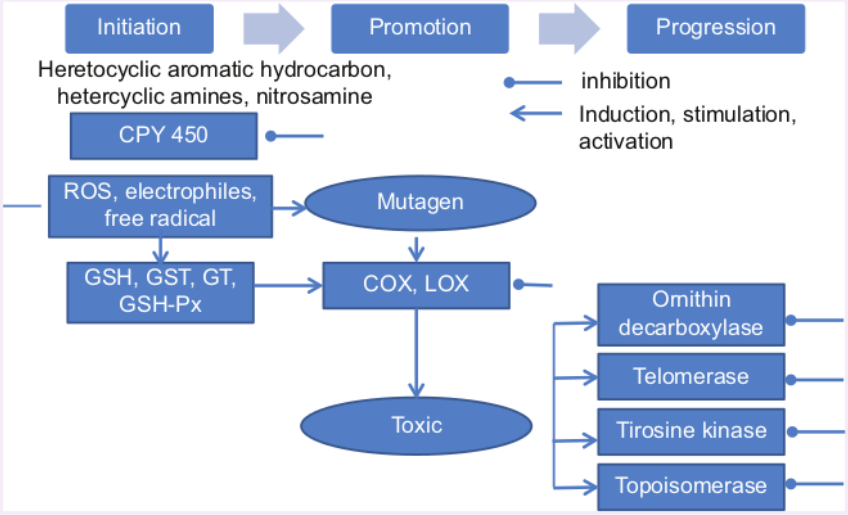

Figure 2: Hypothesis of carcinogenesis by flavonoid, COX2 cyclooxygenase. LOX: Lipooxygenase, ROS: Reactive oxygen species, GSH: Glutathione, GST: Glutathione S-transferase, Px: Peroxidase, NSAID: Nonsteroid anti-inflammatory drug

He *et al.*[36] tested *in vivo* and *in vitro* of TSN, a triterpenoid derivative isolated from *M. toosendan* Sieb. et Zucc. in the *in vitro* experiment by means of TSN (0.1–0.9 μM) to human hepatocellular carcinoma cell lines (SMMC-7721 [a p53+] and Hep3B [a p53−]). Dose- and time-dependent manner of antiproliferation effects was observed. The IC_{50} of TSN against SMMC-7721 and Hep3B cells was 0.5 μM and 0.9 μM, respectively (after treated 72 h). Caspase activity was also shown from annexin V staining (morphological observation). Ratio of Bcl-2/Bax and Fas was associated with the induction of apoptosis via the mitochondria-dependent pathway in p53− and p53 + hepatocellular carcinoma cell. *In vivo* experiment used BALB/c mice which were subcutaneous inoculated with mouse hepatocellular carcinoma H (22) cells. The intraperitoneal high dose (0.69 mg/kg) and low dose (0.173 mg/kg) resulted in strongly suppressive effects on the tumorigenicity and apoptotic response. Results from the immunohistochemistry for Bcl-2, Bax, as well as Fas, showed that the anticancer effects of TSN were induced via apoptosis in a mitochondria-dependent manner. *In vitro–in vivo* confirmed results of TSN have induced mitochondria-dependent apoptosis in hepatocellular carcinoma cells.

Tang *et al.*[37] evaluated *in vitro* and *in vivo* of *M. toosendan* fruit ethanolic extract of (EMTF) against human colon cancer (SW480) and murine colorectal adenocarcinoma cells (CT26). Chromatin condensation and DNA fragmentation of EMTF treated were proved that cell proliferation of SW480 and CT26 was inhibited by EMTF. Apoptosis of the tumor cells is resulted by increasing mitochondrial membrane permeability and cytochrome c release from mitochondria. EMTF induced caspase-9 activity which further activated caspase-3 and poly-(ADP-ribose) polymerase cleavage. EMTF also confirmed *in vivo* result of tumor volume reduction and apoptotic effects, while EMTF did not induce the side effects. All results suggested that EMTF may be a chemotherapeutic agent effective to treat colon cancer.

Kim and Kang[38] studied toxicity and anticancer activity of the hexane layer of MA var. *japonica* Makino's bark extract by hollow fiber (HF) assay and 28-day repeated toxicity. As a result, highest cytotoxicity was observed at 200 mg/kg body weight of hexane layer with 4 mg/kg body weight of cisplatin treated group. The toxicity results showed no significant changes in body weight gain and general behavior, while cisplatin-treated group showed significantly decreased compared to the control group but regained weight with hexane layer treated (100 and 200 mg/kg body weight). The biochemical parameters (alanine aminotransferase, total bilirubin, aspartate aminotransferase, creatinine, and blood urea nitrogen) showed significant increase in cisplatin-treated groups; however, in the group cotreatment of hexane layer (200 mg/kg b.w), these parameters decreased. In white blood cells and neutrophils analysis, cisplatin was reduction, but co-treatment with hexane layer improved these toxicities caused by cisplatin. The eosinophil foci cell in the central vein and portal triad of the liver showed in cisplatin-treated mice. These results showed that hexane layer of MA might have anticancer activity and improve the toxicity effect of cisplatin anticancer drug.

Akihisa *et al.*[39] isolated limonoid and triterpenoid from the fruits of MA (*Meliaceae*). All isolated compounds (31 limonoids and one tirucallane-type triterpenoid) examined the cytotoxic activities against HL60, A549, AZ521, and SK-BR-3 human cancer cell lines. The results showed that meliarachin C (IC_{50} 0.65 lM) and 3-O-deacetyl-40-demethyl-28-oxosalannin (IC_{50} 2.8 lM) produced highest cytotoxic activity and exhibited high selective toxicity against HL60 cells (leukemia). This was demonstrated mostly due to the induction of apoptosis via the mitochondrial and death receptor-mediated pathways.[35] Apoptosis-inducing activity was measured by flow-cytometry (annexin V–propidium iodide (PI), while western blot analysis to obtain apoptotic mechanism (evaluate activation of caspases -8, and -9 by which compounds induce apoptotic cell death). One of the earliest markers of apoptotic cell death is exposure of the membrane phospholipid phosphatidylserine to the external cellular environment.[40] Annexin V is a protein calcium-dependent phospholipid binding. It has high affinity for phosphatidylserine, which locates on the cell surface. PI does not enter intact membranes cells. By observing annexin V and PI result, apoptotic processes mechanism can be determined. Annexin V positive and PI negative are observed at early apoptotic process, annexin V and PI double-positive are observed at late apoptotic, while annexin V negative and PI positive will be observed on necrotic of cell death. The

levels of procaspases-8, -9, and -3 reduced (almost in a time-dependent manner).[41] Caspases are known to mediate the apoptotic pathway.[42,43] Initiator caspases including caspases-8 and -9 seem as apical caspases will be activated in death receptor and apoptotic cell death by mitochondrial stress-induced mechanism. These initiator caspases are accountable (directly or indirectly) for activating various effector caspases including caspases-3, -6, and -7, which have short prodomains). Many of the apoptotic features, which are nuclear and cytoplasmic condensation, DNA fragmentation, cell membrane decomposition, and others, are directly responsible by effector caspases cleave and a number of structural and regulatory proteins.[44]

Furthermore, potential antitumor-promoting effects for 25 compounds were further examined by inhibitory effects on the induction of Epstein–Barr virus early antigen (EBV-EA) by TPA induced. All compounds tested exhibited moderate inhibitory effects (IC_{50} 347–530 mol ratio/32 pmol TPA) with preservation of high viability (60%) of Raji cells. Among the compounds tested, three compounds, 1 meliarachin C, 12-dehydro-29-exo-neoazedarachin D, and mesendanin E, exhibited more potent than or almost equivalent inhibitory effects (IC_{50} 347–401 mol ratio/32 pmol TPA) with the reference compound, compared to β-carotene (IC50 397 mol ratio/32 pmol TPA), a vitamin A precursor studied widely in cancer chemoprevention animal models. Since the inhibitory effects against EBV-EA activation have been demonstrated to closely parallel to those against tumor promotion *in vivo*, compounds meliarachin C, 12-dehydro-29-exo-neoazedarachin D, and mesendanin E (nimbin type limonoid) could be valuable antitumor promoters.[39]

Acetylazedarachin B as induced apoptotic cell compound, activates caspases-3, -8, and -9 w, cleaved caspases-3, -8, and -9 of HL-60 for 12, 24, and 36 h, respectively. It would decrease the level of Bid and increase of tBid in a time-dependent manner, in which could activate the mitochondrial pathway. It would also decrease the level of Bcl-2 and increased the level of Bax. The Bax/Bcl-2 ratio is one of the intrinsic mechanisms of apoptosis in mitochondria. These results involved Bax/Bcl-2 signal transduction death in leukemia cells both by the mitochondrial and death receptor-mediated pathways.

TSN, a triterpenoid derivative isolated from the barks of *M. toosendan* Sieb et Zucc, was shown stronger cytotoxicity on U937 cells than VP-16 (etoposide), a clinical anticancer drug. The apoptosis activity of TSN was subsequently associated as evidenced by the typical condensed and fragmented nuclei, DNA and exposure of phosphatidylserine on the outer leaflet of plasma membrane of the cells.[41]

Furthermore, Zhang *et al.*[19] isolated 12-O-acetylazedarachin B from the fruit extract from MeOH extract of defatted MA fruit by silica gel column chromatography and RP preparative HPLC. Kikuchi *et al.*[45] tested the cytotoxic activity of compound 1 and two anticancer drugs, cisplatin and 5-fluorouracil (5-FU), against four human cancer cell lines, HL-60 (leukemia), AZ521 (stomach), A549 (lung), and SK-BR-3 (breast), with MTT assay. The result showed potent cytotoxicity of the extract against leukemia (HL-60) (IC_{50} 0.016 μm) and stomach (AZ521) (IC_{50} 0.035 μm) cancer cell lines; and 100 times higher than those of cisplatin (IC50 4.2 μm [HL-60] and 9.5 μm [AZ521]). 12-O-acetylazedarachin B, however, did not show cytotoxicity against SK-BR-3 cells. The potent cytotoxicity of 1 against HL-60 and AZ521 and nonactivity against SK-BR-3 might be due to the presence of a cell-specific receptor that differentiates one tumor type from another or receptor activated the antiapoptotic signaling pathway. 12-O-acetylazedarachin B exhibited induction of apoptosis detected by the observation of membrane phospholipid exposure and DNA fragmentation in flow-cytometry and western blot analysis showed that compound markedly reduced the levels of procaspases-3, -8, and -9; while the levels of cleaved caspases-3, -8, and -9 are increased. 12-O-acetylazedarachin B increased significantly the Bax/Bcl-2 ratio. These results suggested that compound 1 induced apoptotic cell death in HL-60 via both mitochondrial-mediated and death receptor-signal transduction-mediated pathways. It was also reported that Fas receptor, a known death receptor which induces apoptosis, can activate the necrotic pathway. The necrotic cell death of AZ521 by compound 1 was, therefore, supposed to be induced by the participation of Fas receptor signaling although it is not certain whether caspase-8 is activated by Fas receptor. Therefore, 12-O-acetylazedarachin B may be a promising lead compound for developing an effective drug for the treatment of leukemia. Flow-cytometric analysis suggested that the cytotoxicity of compound 1 against AZ521 is due to inducing apoptosis as well as necrosis and may be a promising lead compound for developing an effective drug for leukemia.

Yao *et al.*[46] tested of 70% ethanol extract of MA on melanogenesis of mouse melanoma cell line (B16F10). The melanin content increased after treatment of the cells with the MA extract (10, 20, and 40 μg/ml in a concentration dependent manner without cytotoxicity at 24 h) while did not influence tyrosinase activity and the protein level of tyrosinase and tyrosinase-related protein-2 (TRP-2). In conclusion, that the MA extract increases melanogenesis via upregulating of TRP-1 posttranscriptional control protein expression in B16F10 cells and supposed MA extract acts as melanogenesis rapid inducer. This result showed that MA extract has potential treat the hypopigmentation diseases.

Sumarawati *et al.*[47] showed a significant decrease in tumor volume of adenocarcinoma mammary in C3H mice of combination group of MA extract, doxorubicin, cyclophosphamide. The mechanism supposed via increasing BAX expression and decreasing AgNOR expression. Liu *et al.*[48] also tested an alcohol-chloroform extraction of the bark of *M. toosendan* Sieb. et Zucc *in vitro* against human hepatocellular carcinoma cell lines (SMMC-7721) and Hep3B and *in vivo* by inoculated subcutaneous H22 cells (mouse hepatocellular carcinoma) to BALB/c mice. As the results showed that TSN has potent anti-cancer effects, supposed through suppressing proliferation and inducing apoptosis of cancer cells *in vivo* and *in vitro*. The mechanism anticancer of MA via apoptosis emphasized also involves in mitochondrial and death receptor pathway. The summary of *in vitro–in vivo* anticancer research, including cytotoxic isolated compounds such as limonoid, triterpenoid, and steroid derivatives of *Melia* spp., is depicted in Table 2.

Accumulating results and evidence indicate that the anticancer potency effects of neem extracts are mediated by free radical scavenging, by DNA repair and cell cycle alteration, by programmed cell death (apoptosis) and autophagy, by increasing immune surveillance, anti-inflammatory, anti-angiogenic, anti-invasive and anti-metastatic activities as well as its ability to modulate several dysregulated oncogenic signaling pathways. Neem and its constituents including limonoids that target multiple signaling pathways aberrant in cancer are promising candidates for anticancer drug development.[49] Recent developing research trends are optimizing cytotoxicity of the plant extracts by developing it to nanoparticle form. Sukirtha *et al.*[50] and Kathiravan *et al.*[51] provided green route synthesis of silver nanoparticles of Melia dubia leaf extract. The results of Kathiravan showed that the silver nanoparticle (7.3 nm) of leaf extract of the plants active against KB cell.

CONCLUSION

Review of literature indicates that fruit, bark, leaves, pulp, and seed of MA showed various *in vitro* cytotoxic activities in cancer cell lines, such as human colorectal carcinoma (HT-29), breast cancer (MCF-7, SK-BR-3), cervix hepatoma (HepG-2, SMMC-7721 and Hep3B), kidney epithelial cell (MDBK cell lines), human lung adenocarcinoma epithelial (A549),

nonsmall cell lung cancer (H460), human lymphoblast lung (U937), human cancer promyelocytic leukemia (HL-60), AZ521 (stomach), human colon cancer (SW480), murine colorectal adenocarcinoma cell (CT26), human oral cancer cell (KB), human prostate cancer cell (PC3), liver (BEL7404), CNS (SH-SY5Y, U251, SF539), and B16F10 mouse melanoma cell line and showed various *in vivo* to to adenocarsinoma mammary in C3H mice and mouse hepatocellular carcinoma H22 cells in BALB/c mice.

Table 2: Cytotoxic activity of Melia spp

Melia species	Part of the plant used	Extract	Cytotoxic/AntiCa Method	Result	Ref.
Melia toosendan Sieb. et Zucc	Fruit	-	Eight human cancer cell from six different organs lines and SRB assay compare to adriamycin	28-deacetyl sendanin had more sensitive and selective inhibitory effects on in vitro. The most sensitive cell of 28-deacetyl sendanin (dose-response) was against SF-539 (CNS) and PC-3 (prostate), six cell lines were more sensitive to 28-deacetyl sendanin and two were more resistant	Kim, *et al.*[28]
Melia toosendaan Sieb. et Zucc.	Fruits	Aqueous solution of the methanolic extract was partitioned with diethyl ether and l-butanol	bioassay-guided frac-tionation against KB cells.	IC_{50} (mg/ml) of monoids: Toosendanal >10, 12-O-Methylvolkensin 8.72, Meliatoxin B1 >10, Trichilin H 0.11, Toosendanin 3.82; and Adriamycin HCl 0.066	Tada, *et al.*[29]
Melia azedarch	Leaves	Extract	3 human cancer cell line (A549, [illegible]0, U251) IC_{50} 12.0-30.1 µg/ml	6 steroids	Wu *et al.*[30]
M azedarach L.	Fruit	Dichloromethane-soluble part of the methanol extract	human lung adenocarcinoma epithelial cell line A549	Tirucallane triterpene, 3-α-tigloylmelianol and tirucallanes, melianone, 21-β-acetoxymelianone, [illegible]l methyl kulonate	Ntalli, *et al.*[31]
M azedarach and *A indica*	Leaves, pulps and seeds	MeOH extraction	HT-29, A-549, MCF-7 and HepG-2 and MDBK cell lines; MTT assay	Flavonol 3-O-glycosides including rutin, kaempferol- 3-O-robinobioside, kaempferol-3-O-rutinoside and isoquercetin along with a purin nucleoside, β-adenosine	Jafari *et al.*[32]
Melia toosendan Sieb. et Zucc.	Toosendanin, a triterpenoid derivative isolated from bark		*in vivo* of toosendanin (0.1~0.9 µM) add to SMMC-7721 (p53+) and Hep3B (p53-) (human hepatocellular carcinoma cell lines); *in vivo* to Balb/c mice s.c. inoculated with mouse hepatocellular carcinoma H (22) cells. i.p TSN high-dose (0.69 mg/kg) and low-dose (0.173 mg/kg)	The IC_{50} of TSN treated after 72h for SMMC-7721 and Hep3B cells was 0.5 µM and 0.9 µM, respectively. Morphological observation results show of caspases activity. Ratio of Bcl-2/Bax, and Fas were associated with induction of apoptosis via the mitochondria-dependent pathway in p53- and p53 + hepatocellular. In the *In vivo* experiment, BALB/c mice were resulted in strongly suppressive effects on the tumorigenicity and apoptotic response. Results from the immunohistochemistry for Bcl-2, Bax, as well as for Fas showed that the anticancer effects of toosendanin were induced via apoptosis in a mitochondria-dependent manner. *In vitro- in vivo* confirmed results of anticancer of TSN	He *et al.*[36]
Melia toosendan	Fruit	ethanolic extract (EMTF)	in vitro and *in vivo* against human colon cancer (SW480) and and murine colorectal adenocarcinoma cells CT26.	[illegible] results showed that EMTF inhibited cell proliferation of SW480 and CT26 by promoting apoptosis. The *in vivo* results confirmed [illegible]duction of tumor.	Tang *et al.*[37]
Melia azedarach L. var. japonica Makino's	Bark extract	hexane layer	hollow fiber (HF) assay and 28-day repeated toxicity study to confirm the anti-cancer effect and safety of the hexane layer against A549 carcinoma cells	Hexane layer might have an anti-cancer activity and could improve the toxicity of cisplatin	Kim & Kang[38]
Melia dubia	Extract	Silver nanoparticle	KB cell	Remarkable toxic to KB cell	Kathiravan, *et al.*[51]

Contd...

Table 2: Contd...

Melia species	Part of the plant used	Extract	Cytotoxic/AntiCa Method	Result	Ref.
M azedarach	Fruit	MeOH extract of n-hexane defatted, fractionated and isolated	Cytotoxic activities against HL60, A549, AZ521, and SK-BR-3 human cancer cell lines. Meliarachin C (IC_{50} 0.65 lM) and 3-O-deacetyl-40-demethyl-28-oxosalannin (IC_{50} 2.8 lM) exhibited potent cytotoxic activity against HL60 cells, and was mainly due to the induction apoptosis	Thirty-one limonoids and one tirucallane-type triterpenoid	Akhihiza *et al.*[39]
Melia toosendan Sieb et Zucc	Bark	Ethanolic	Human cancer cell lines, including PC3, BEL7404, SH-SY5Y, U251, HL-60 and U937 was assessed by measuring the number of viable cells *via* a colorimetric MTT assay, Suppressing the cell cycle procession, Inducing cell apoptosism	Toosendanin, a triterpenoid derivative	Zhang *et al.*[41]
Melia azedarach	Mature Fruits	aqueous of MeOH extract of deffated n- hexane extract and partitioned, column chromatograph	Cytotoxicity against leukemia (HL-60) (IC50 µm) and stomach (AZ521) (IC50) cancer cell lines	IC_{50} (µm) HL-60 (leukemia), AZ521 (stomach), A549 (lung), SK-BR-3 (breast) respectively of 12-O-Acetylazedara chin B 0.016, 19.0, 0.035 µm and >100 µm; of Cisplat 4.2 in*b*) 4.2, 9.5, 24.9 and 18.8 µm; and , 5-Fluorouracil (5-FU)*b*) 9.1, 28.7 >100 and >100 µm	Kikuchi, *et al.*[45]
Melia azedarach	extract	70% ethanol extract of MA	Melanogenesis of a B16F10 mouse melanoma cell line	reased melanin content through upregulation of TRP-1 protein expression by post-tran iptional control in B16F10 cells. MA extract did not affect intracellular tyrosinase activity and the protein levels of tyrosinase and tyrosinase-related protein-2 (TRP-2)	Yao *et al.*[46]
Melia azedarach	Seed	Aqueous of EtOH Soxhletation extract	Volume tumor, AgNOR measurement and Bax protein expressionto C3H mice inoculated with adenocarcinoma mammary, axilla i.p.	Tannin, flavonoidsquersetin, saponin. Combination of MA-Dox-Cyclo decrease volume, BAx increase and decrease AgNOR	Sumarawati, *et al.*[47]
Melia toosendan Sieb. et Zucc,	Bark	alcohol-chloroform extraction	*In vivo* and in vitro studies man hepatocellular carcinoma cell lines SMMC-7721 and Hep3B and BALB/c mice inoculated s.c mouse hepatocellular carcinoma H22 cells	Toosendanin extract has potent anti-cancer effects via suppressing proliferation and inducing apoptosis ancer cells *in vivo* and in vitro. The mechanism of apoptosis involves in mitochondrial pathway and death receptor pathway	Liu *et al.*[48]
Melia dubia	extract	Silver nanoparticle	KB cell	Remarkable toxic to KB cell	Kathiravan, *et al.*[51]

Previous results showed that cytotoxic organic compounds of MA were supposed of flavonoids, triterpenoids (tirucallane), limonoids (meliarachin, meliatoxin B1, trichilin H, and TSN), steroids, and organic acids content compounds.

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Conflicts of interest

There are no conflicts of interest.

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