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Review Article

Cytotoxic Potential of *Mitragyna* speciosa as Anticancer - A Review

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ABSTRACT

Background: Herbal treatment has been proposed and researched as an alternative to cancer treatment. One of the reasons contains compounds that have cytotoxic effects. *Mitragyna speciosa* are known to contain alkaloids and have a cytotoxic effect. **Objective:** This review aimed to provide information about preclinical studies and investigates the cytotoxicity or anticancer activity of *M. speciosa*. **Methods:** Search articles through PubMed, Springer, and Science Direct databases focusing on preclinical trials according to PRISMA guidelines. A database search yielded a total of 206 identifiable studies. Then duplicate removal and feasibility screening were carried out, resulting in 11 studies that were eligible for final analysis. **Results:** The anticancer potentials reviewed in this study include Neuroblastoma, Leukemia, Colon Cancer, Breast Cancer, Kidney & Liver Cytotoxicity, Glutathione Transferases Metabolizing Enzymes, Alkaloid Combination of *M. speciosa* & Cisplatin, Alkaloid Combination of *M. speciosa* & Doxorubicin and Mutagenic-Antimutagenic Activity of *M. speciosa*. Extracts and dominant alkaloids of *M. speciosa* have the potential for anticancer neuroblastoma, leukemia, colon, lung and breast cancer. Based on the safety aspect of the mitragynine compound, there is no mutagenic effect on cells. **Conclusion:** *M. speciosa* contains the dominant active alkaloid compound, mitragynine. Extracts and alkaloids dominant in *M. speciosa* have the potential as an anticancer.

Key words: Alkaloids, Cancer, Cytotoxicity, *M. speciosa*, Mitragynine.

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INTRODUCTION

Cancer is the second leading cause of death worldwide among non-communicable diseases, after coronary disease. Breast cancer is a disease with a high prevalence and a burden on health worldwide. Based on Global Burden of Cancer (GLOBOCAN) 2018, the new case of breast cancer was 2,089 million after lung cancer, which was 2,094 million cases.[1]

The factors that play a role in the emergence of breast cancer include hormonal factors and growth factors. Hormonal factors such as estrogen and progesterone. Growth factors such as the Epidermal Growth Factor Receptor (EGFR). Consequently, some chemotherapy treatments target receptors such as tamoxifen (antiestrogen) and exemestane (aromatase inhibitor). They are both steroid derivatives and trastuzumab (anti-Human Epidermal Growth Factor Receptor-2).[2] However, there are weaknesses in chemotherapy, which are low selectivity that causes side effects at the beginning of therapy like nausea (100%), vomiting (100%), diarrhea (80%), susceptibility to infection (61.5%), neuropathy (50%), and myalgia (90%).[3] In addition, it causes Multi-Drug Resistance (MDR) which results in reduced drug efficacy.[4]

Herbal treatment has been proposed and researched as an alternative to cancer treatment. One of the reasons contains compounds that have cytotoxic effects. Anticancer compounds from nature generally can come from the alkaloid group (such as vincristine and vinblastine)[5] and the steroid group.[6] One of the plants are known to have a cytotoxic effect and contain alkaloids, namely kratom leaf (*Mitragyna speciosa*).

Phytochemical compounds isolated from *M. speciosa* are alkaloids, flavonoids, terpenoid saponins, polyphenols, and glycosides.[7] This plant contains the dominant active alkaloid compound, namely mitragynine. Based on the research of Saidin[8] showed that the pure alkaloid content of mitragynine and kratom leaf extract has cytotoxic activity on SH-SY5Y nerve cells and MCL-5 lymphoblastoid cells. It has a high cytotoxic and antiproliferative effect against erythroleukemia and colon cancer.[9]

M. speciosa has recently become popular as an ethnomedicinal drug in Western countries, especially in the United States (US). Purchase of *M. speciosa* is available online and at other gas stations and specialty stores. *M. speciosa* had different dosage forms, such as tablets, capsules, supplements or powders.[10] Some users reveal that its use is for self-medication of acute/chronic pain, psychiatric disorders, opioid, and substance abuse.[11] There are case reports related to its successful application in reducing pain from COVID-19 disease.[12] Some reasons for several deaths due to Kratom consumption are related to mitragynine toxicity.[13-15] Therefore, the understanding of mitragynine and *M. speciosa* toxicity needs to be investigated.

We will review the cytotoxic potential of *M. speciosa* as anticancer, to provide information about development and application *M. speciosa* of various cancer cells. The articles used are preclinical studies published from January 1st, 2005 onwards, with the intention of offering fresh, up-to-date information.

METHODS

Search scientific publications about cytotoxicity of *M. speciosa* and mitragynine, using Springer, PubMed, and ScienceDirect. Identification of the

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literature review according to the recommendations of the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) guidelines. Keywords containing a combination of "*Mitragyna speciosa* OR mitragynine" AND "Cancer OR cytotoxicity" were used to search the database for preclinical studies. The exclusion criteria are: (1) non-original publications or research articles that were irrelevant or not potentially related to the purpose; (2) literature reviews, surveys, and comments; (3) Research design that allows biased data; (4) abstract or not available for full text.

Studies included if they met all of the following criteria: the studies are published after January 1st, 2005, research topics about the preclinical studies, in vitro or in vivo, investigating the cytotoxicity or the activity for anticancer potentially related to the review aim, and any preclinical or clinical outcome providing sufficient scientific evidence of kratom, *M. speciosa*, mitragynine, and related or derivative compounds, that would support the traditional medical uses or benefits reported by users.

Articles are analyzed if they met the following inclusion criteria: studies published after January 1st, 2005, research topics regarding in vitro or in vivo preclinical studies, investigating cytotoxicity or anticancer activity, and any preclinical results providing sufficient scientific evidence. Article selection consists of two stages: preliminary screening of relevant titles and abstracts, then the screening of complete papers which are assessed for feasibility. Studies of the anticancer potential of *M. speciosa*, which were selected, are shown in Figure 1.

THE CYTOTOXIC POTENTIAL OF *M. SPECIOSA* AS ANTICANCER

Table 1 summarizes the findings of ten research articles available and their cell line type, test/measures, result, and cytotoxic potential.

The potential for neuroblastoma

Extracts of *M. speciosa* had been reported anticancer properties toward neurobalstoma cell line (SH-SY5Y). Extracts of *M. speciosa* were the more cytotoxic than mitragynine as shown by the IC_{50} value, extracts of *M. speciosa* (11,20-17,00 µg/ml) and extracts of *M. speciosa* resin (2,93 µg/mL) than pure Mitragynine (42,6 µg/mL).[16] Saidin *et al.*[17] reported that mitragynine has IC_{50} 75µM. Mitragynine was examined for the involvement of executioner caspases (caspase 3 and 7) in SH-SY5Y cells and establish significant increases in caspases 3 and 7 at 100 µM and 300 µM of mitragynine tested.

The potential for leukemia

Mitragynine had been reported antitumor properties in leukemia at a high dose and had a potency IC_{50} 25,20±1,53 µM toward K562. Selectivity Mitragynine to colon cancer cells has been evaluated that Mitragynine had high selectivity toward colon cancer cell line (K562) with selective indexes of 1,42 compared to betulinic acid as standard anticancer drug therapy for leukemia which had selective indexes of 3,82.[9]

The potential for colon cancer

Mitragynine had been reported antitumor properties in colon cancer at a high dose > 100 µM. Selectivity Mitragynine to colon cancer cells has been evaluated that Mitragynine had high selectivity toward colon cancer cell line (HCT 116) with respect to CCD18-Co selective indexes of 3,14 compared to 5-Fluorouracil as standard anticancer drug therapy for colon cancer which had selective indexes of 0,60.[9]

The potential for breast cancer

Phenolic compounds isolate from dichloromethane fractions of *M. speciosa* was indicated moderately cytotoxic to T47D breast cancer cells.

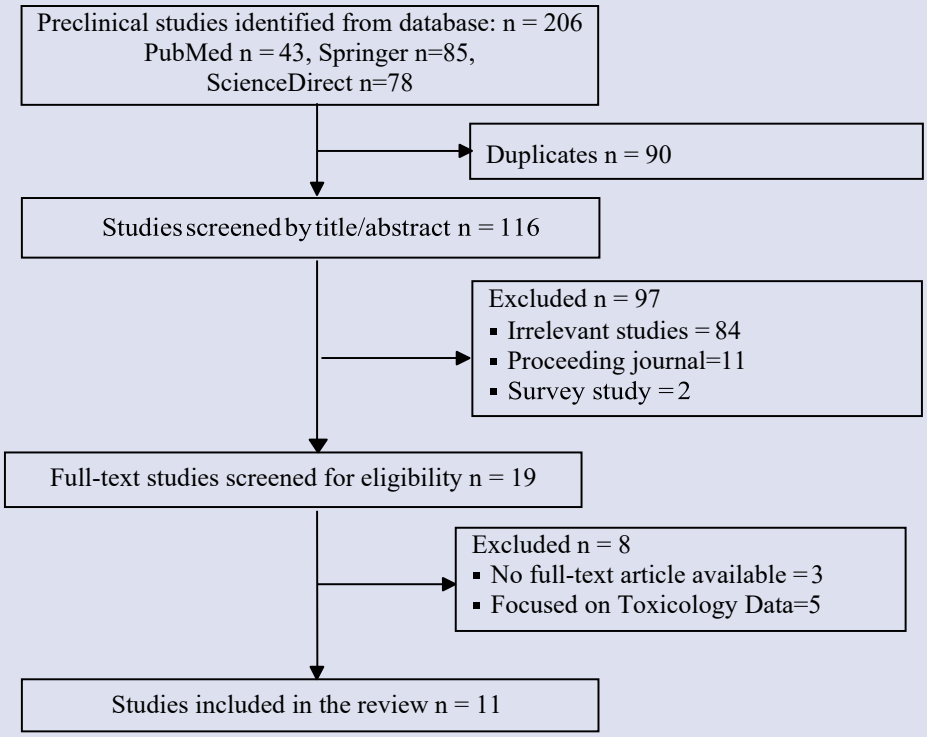

Figure 1: Study selection: The cytotoxic potential of *M. speciosa* as anticancer.

Table 1: The cytotoxic potential of *M. speciosa* as anticancer.

Studied Compound	Cells Line	IC_{50}	Test/Measures	Results	References
Mitragynine	K 562 HCT 116	25.20±1.53 µM 47.10±3.47 µM	MTT cell and antiproliferation Assay	Profound antiproliferative efficacy at concentration > 100 µM towards erythroid leukaemic K 562 and colon carcinoma HCT 116 cells.	Goh *et al.*[9]
Kratom leaves extract Mitragynine	HEK-293 CCL-13 HEK-293 CCL-13	>500 µg/ml 153.75 - 500 µg/ml 112.30±17.59 µM 210.04±0.80 µM	MTT cell Viability Assay	Kratom leaf extract is non-cytotoxic towards Human embryonic kidney HEK-293 and HeLa Chang liver CCL-13 cells.	Goh *et al.*[20]
Kratom leaves extracts Mitragynine	Caco-2 SH-SY5Y Caco-2 SH-SY5Y	9.43 - 49.0 µg/ml 2.93-17.0 µg/ml 42.5 µM 42.6 µM	Cell viability assay and Genotoxicity assay	Kratom induced cytotoxic in human neuronal SH-SY5Y cells and Caco-2 intestinal cells. Kratom leaves extracts were significantly more cytotoxic than pure Mitragynine. Significant DNA damage in Caco2 cells exposed to these extracts but not to Mitragynine.	Oliveira *et al.*[16]
Methanol-chloroform extract Mitragynine	HepG2 MCL-5 HEK-293 SH-SY5Y HEK-293 SH-SY5Y	230.8 µg/ml 410.3 µg/ml 282.1 µg/ml 91.2 µg/ml 240 µM 75 µM	Cytotoxicity, clonogenicity assay, morphological examinations, and biochemical assessments	Methanol-chloroform extract and mitragynine have cytotoxicity effects at high doses. They inhibit Colony-forming from embryonic kidney HEK 293 cells and neuroblastoma SH-SY5Y cells. Cell death is induced by this extract in which SH-SY5Y cells via apoptosis mechanism while HEK 293 cells and lymphoblastoid MCL-5 cells via necrosis. This extract induced cell death independent of the p53 or caspases pathway, mitragynine cell death appeared associated with p53 and caspases pathway.	Saidin[8]
Mitragynine	SH-SY5Y HEK 293 MCL-5	75 µM 240 µM 80 µM	Cell viability, Flow cytometry analysis, Immunoblot analysis, and The L5178Y TK+/– mouse lymphoma cell assay	Mitragynine showed inhibition of cell proliferation. SH-SY5Y and MCL-5 cells were more sensitive than HEK 293. It was not genotoxic at the TK locus. It shows apoptosis activity of executioner caspases 3/7. CYP 2E1 and 2A6 were involved in cytotoxicity. Cytotoxicity did by cell cycle arrest in G1 and S phases.	Saidin *et al.*[17]
Methanol extract Dichloromethane Hexane Methanol Ethyl acetate (fractions of kratom)	T47D T47D T47D T47D T47D	275.10 µg/ml 238.34 µg/ml 442.18 µg/ml 274.72 µg/ml 179.46 µg/ml	MTT cell	Fractions of dichloromethane and isolate FD4.4 was indicated moderately cytotoxic to T47D breast cancer cells.	Suryandari *et al.*[18]
Methanol extract Dichloromethane Hexane Methanol Ethyl acetate (fractions of kratom)	T47D T47D T47D T47D T47D	275.10 µg/ml 238.34 µg/ml 442.18 µg/ml 274.72 µg/ml 179.46 µg/ml	MTT cell	Quercetin-3-O-β-glucopyranoside isolated from ethyl acetate was indicated moderately cytotoxic to T47D breast cancer cells with IC_{50} 161,67 µg/mL.	Ikhwan *et al.*[19]
Methanol, aqueous and total alkaloid of *M. Speciosa*	Rat liver cytosolic fraction	Not determined	Inhibition of GSTs specific activity	The highest GSTs specific activity inhibition (61%) showed by methanolic extract, followed by aqueous (50%) and total alkaloid extract (43%). Only aqueous extract with a dosage of 100 mg/kg showed significant results of 129% compared to control.	Azizi *et al.*[22]
Aqueous extract of *M. speciosa*	Salmonella *typhimurium* strain TA 98 strain TA 100	Not determined	Antimutagenicity test with and without exogenous metabolic activation S9 system	The extracts didn't inhibit the mutagenic activity in the absence of metabolic activation S9 mix. However, in the presence of a metabolic activation mix, all concentrations of *M. speciosa* induced strong antimutagenic activity.	Ghazali *et al.*[24]
Methanol extract Alkaloid extract Cisplatin Cisplatin-Mitragynine Cisplatin-Speciociliatine Cisplatin-Paynantheine Cisplatin Cisplatin-Mitragynine Cisplatin-Speciociliatine Cisplatin-Paynantheine	NPC/HK1 NPC/HK1 NPC/HK1 NPC/HK1 NPC/HK1 NPC/HK1 C666-1 C666-1 C666-1 C666-1	133.71±0.72 µg/ml 32.16±0.94 µg/ml 9.7 - 10.5 µM 2.3 - 4.5 µM 2.2 - 6.6 µM 4.6 - 8.5 µM 13.9 - 14.8 µM 2.6 - 7.6 µM 2.5 - 8.6 µM 2.5 - 8.1 µM	Cell viability assays and sensitization of the NPC cell lines to cisplatin by the *M. speciosa* alkaloids	Methanolic and alkaloid extracts showed mild to moderate cytotoxicity. Both NPC cell lines were insensitive to single-agent & combination treatments of the *M. speciosa* alkaloids. Mitragynine and speciociliatine sensitized the NPC/HK1 and C666-1 cells to cisplatin at 4-5-fold. The combination of mitragynine and cisplatin significantly inhibited cell migration of NPC cell lines.	Domnic *et al.*[23]
Alkaloid extracts-doxorubicin	A549	48–55 ppm	Cytotoxic Assays Apoptosis Assays	Alkaloid extract and doxorubicin combined sensitized A549 lung cancer cells to the drug by 2.6 to 3.4 times, suggesting that the two agents could work in concert to lower the dosage of doxorubicin used in chemotherapy.	Bayu *et al.*[25]

Suryandari *et al.*[18] reported with IC_{50} value from phenolic compounds isolate IC_{50} 159,66 µg/mL lower than fractions of dichloromethane IC_{50} 238,34 µg/mL. Ikhwan *et al.*[19] reported Quercetin-3-O-β-glucopyranoside isolated from ethyl acetate fraction was indicated moderately cytotoxic to T47D breast cancer cells with IC_{50} 161,67 µg/mL lower than ethyl acetate fraction IC_{50} 179,46 µg/mL.

Cytotoxicity for kidney & liver

Methanol-chloroform extract of *M. speciosa* (MSE) and mitragynine caused inhibition of cell proliferation from HEK 293 cells at doses equivalent / higher than 113 µg/ml with IC_{50} 282 µg/ml for MSE and at doses equivalent or higher than $3{,}33x10^{-3}$-$3{,}33x10^{-4}$ M with IC_{50} 2,4 x 10^{-4}M for mitragynine.[8] Goh *et al.*[20] reported that the accelerated solvent extraction of aqueous, MEOH, EtOAc and EtOH kratom leaf extracts showed higher IC_{50} values against HEK-293 kidney with IC_{50} >500 µg/mL. However, the mitragynine had lower IC_{50} value against HEK293 kidney cell with IC_{50} 112,30 ± 17,59 µM.

MSE and mitragynine caused inhibition of cell proliferation from HepG2 cells at doses higher than 1,13 µg/ml with IC_{50} 230,8 µg/ml.[8] *Goh et al.*[20] reported that the accelerated solvent extraction of aqueous, MEOH and EtOH kratom leaf extracts showed higher IC_{50} values against HeLa Chang Liver Cells with IC_{50} >500 µg/mL and EtOH kratom leaf extracts with IC_{50} >153,75± 31,75 µg/mL. However, the mitragynine had lower IC_{50} value against HeLa Chang Liver Cells with IC_{50} 210,04 ± 0,80 µM.

Metabolizing Enzymes Glutathione Transferases

GSTs have appeared as an optimistic therapeutic target of tumors and other diseases.[21] GSTs activities have been reported to be inhibition by methanolic, aqueous, and total alkaloid of *M. speciosa*. Only these aqueous extract with a dosage of 100 mg/kg showed significant results 129% compared to control.[22]

Combination of M. speciosa alkaloids and drug

Domnic *et al.*[23] reported that *M. speciosa* alkaloids from mitragynine and speciociliatine could be potential chemosensitizers for cisplatin with available sensitized the NPC/HK1 and C666-1 cells to cisplatin at 4-5-fold. Combination of mitragynine and cisplatin significantly inhibited cell migration of the nasopharyngeal cancer cell lines. Doxorubicin sensitized A549 lung cancer cells by 2.6 to 3.4 times when combined with alkaloid extracts. The potential for a synergistic combination to lower the dose level of doxorubicin used in chemotherapy was indicated by the calculated combination index (CI) of 0.3 for doxorubicin and alkaloid extract. The alkaloid extract was found to inhibit A549 cancer cells by apoptosis, as indicated by the greater relative fluorescence intensity with Annexin compared to propidium iodide (PI).[25]

Mutagenic and Antimutagenic Activities of M. speciosa

Aqueous extract of *M. speciosa* has strong antimutagenic potential and didn't show any mutagenic activities from the studies using the Ames test (Salmonella mutagenicity assay). Ames test using *Salmonella typhimurium* TA 98 and TA 100 bacterial strains against pre-incubation assay. The absence of a mutagenic response by *M. speciosa* against strains of *S. typhimurium* is a positive thing in determining the safety of using this plant in traditional medicine.[24] Saidin *et al.*[17] investigated the ability of mitragynine to damage DNA and induce mutation using the mouse lymphoma TK assay. Mitragynine was not considered to be mutagenic, even at doses that were highly cytotoxic. DNA damage in Caco2 cells exposed to these extracts but not to pure mitragynine.[16]

DISCUSSION

Pure mitragynine produced lower cytotoxicity than extracts of *M. speciosa* toward the neuroblastoma cell line. These observed cytotoxic effects are produced by Mitragynine and other constituents in Kratom or by interactions between them.[16] Mitragynine applied in SH-SY5Y cells appeared to be resistant to cell cycle effects where there was evidence for a G1 arrest. Mitragynine examined the involvement of executioner caspases (caspase 3 and 7) in SH-SY5Y cells.[17]

Selectively induced apoptosis in leukemia and colon cancer of mitragynine suggests an active compound for cancer therapies development. Apoptosis is a better method than the necrotic to kill damaged cells and is a desirable strategy for cancer treatment.[9]

Evaluated *M. speciosa* had cytotoxicity in the kidney. Cell cycle analysis performed using HEK 293 cells shows that indicated that cell cycle arrest at S and G2/M phases were observable at concentrations of ≥ 100 µg/ml of methanol-chloroform extract (MSE) with concurrent increased subG1 population.[8] Accelerated solvent extraction (ASE) of aqueous, MeOH, EtOAc and EtOH kratom leaf extracts are generality non-cytotoxic towards HeLa Chang liver and HEK-293 cell lines. The results indicate that the synergistic interactions between active phytochemicals in the *M. speciosa* leaf extracts could decrease the toxic effect of alkaloids.[26] A high content of phenolics in extracts could help and increase cell survival in the HEK-293 cell line.[20]

Cytotoxic compounds from the fraction of dichloromethane and ethyl acetate leaf kratom were evaluated on breast cancer cells T47D. The dichloromethane and ethyl acetate fractions of *M. speciosa* are indicated to be cytotoxic to T47D breast cancer cells.[18,19] One of the alkaloid content of the leaves of *M. speciosa*, mitraphylline, has been reported to have anticancer activity in breast cancer cells. Mitraphylline can provide growth inhibition in MT-3 human breast cancer cells with an IC_{50} of 11.80 ± 1.03 µM, better than the control of cyclophosphamide IC_{50} 38.01 ± 2.21 µM and vincristine IC_{50} 44.66 ± 2.72 µM.[27] The chemical content of Mitragynine is an indole alkaloid monoterpene of the corynanthe type.[28] One of the corynanthe type indole alkaloid monoterpenes, strychnine, has been reported to have anti-cancer activity and anti-angiogenic effects on human breast tumor cell lines (MCF-7). Strychnine can potentiate cell death induced by anti-VEGF antibodies. Strychnine has a pro-apoptotic effect that can increase the activity of caspases-3 and -9.[29] According to the chemical class, in silico studies have shown that indole alkaloids present in kratom leaves can inhibit estrogen receptor alpha and trigger apoptosis. In order to accomplish this, the relationship between p53 and MDM2 is broken, and p53 activity is then restored.[30]

Glutathione transferases (GSTs) are multifunctional enzymes that catalyze the conjugation reactions of glutathione (GSH) and electrophilic compounds (EC). EC lack paired electrons and contributes to several diseases (including cancer and neurodegenerative disorders) by capturing electrons from macromolecules such as DNA, lipids, and proteins.[31] GSTs have appeared as an optimistic therapeutic target because specific isozymes are overexpressed in many wild tumors and other diseases.[21] GSTs activities have been reported to be inhibition by methanolic, aqueous, and total alkaloid of *M. speciosa*.[22]

Most cancer chemotherapies use a combination of several drugs. This combination of therapeutic agents expected to provide a synergistic effect in inhibiting the growth of cancer cells with a toxicity profile still be tolerated. Chemotherapy agents can be combined with chemopreventive agents from natural ingredients. Mutiah *et al.*[32] reported that using a combination of *Calotropic gigantea* leaf extract (EDCG) with the chemotherapy drug of 5-Fluorouracil (5-FU) provides a synergistic effect and produces more effective activity than the single chemotherapy drug. Sukardiman *et al.*[33] also reported that the combination of the ethyl acetate fraction of *A. paniculata* and doxorubicin could increase apoptosis and decrease VEGF protein expression in rat fibrosarcoma cells which can inhibit tumor growth. The mechanism of action of the alkaloid mitragynine in combination

with cisplatin is related to the expression of Cyclooxygenase-2 (COX-2). High COX-2 expression is associated with the resistance of NPC cells to cisplatin.[34] Application of cisplatin with compounds that downregulate COX-2 can resensitize NPC cells to cisplatin. For example, mitragynine was reported to inhibit COX-2 mRNA.[35] A combination of mitragynine and cisplatin can inhibit the cell migration of nasopharyngeal cancer.[23] Combination alkaloid extracts and doxorubicin sensitized A549 lung cancer cells by 2.6 to 3.4 times.[25]

The antimutagenic properties of the species have good prospects for health development. Recently, herbal medicines with antimutagenic properties are being developed to counter electrophilic attacks (eg. free radicals) on DNA, or more broadly in aging and cancer. Determination of chemopreventive or chemoprophylactic compounds is important to reduce cancer risk.[36] Mitragynine is not considered mutagenic even at highly cytotoxic doses,[17] but *M. speciosa* extract induced DNA damage in Caco2 cells exposed to this extract.[16] Herbal extracts consist of various phytochemicals. Tannins and flavonoids are related to mutagenesis and carcinogenesis caused by popular plant extracts.[37] These two phytochemicals were present in the extract of *M. speciosa*. However, Kratom products can cause DNA damage, thus raising concerns about their use.[16]

CONCLUSION

M. speciosa contains the dominant active alkaloid compound, mitragynine. Extracts and alkaloids dominant in *M. speciosa* have the potential for anticancer neuroblastoma, leukemia, colon cancer, and breast cancer. Further research is needed on other types of cancer because the cytotoxic potential is suitable as an anticancer. Based on the safety aspect of the mitragynine compound, there is no mutagenic effect on cells. Alkaloid of *M. speciosa* combined with cisplatin and doxorubicin provides good potential prospects for inhibiting cancer cell migration. Therefore, further studies are needed regarding in vivo mechanism and activity studies to determine the dose of *M. speciosa* as an anticancer.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this research.

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