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Review

A Review of Malaysian Medicinal Plants with Potential Anticancer Activity

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ABSTRACT

The global cancer incidence and its high mortality rate indicate limitations in its current treatment and chemotherapeutic strategies. This sparked a worldwide interest in the demand for chemical diversity in searching for therapeutic drugs derived from natural products. Natural products from medicinal plants, whether as pure compounds or crude extracts, offer inexhaustible sources of new drugs because of their unparalleled chemical diversity. This review aims to disseminate detailed information on the anticancer potential of Malaysian medicinal plants, focusing on the bioactive phytochemicals and mechanisms of action against cancer development in both *in vitro* and *in vivo* studies. A comprehensive search of PubMed, Google Scholar, Scopus, and ScienceDirect databases was conducted to find relevant articles on the anticancer activity of Malaysian medicinal plants. A total of hundred and twenty-two (122) articles on the anticancer activity of Malaysian medicinal plants was identified and reviewed. Eighty-five (85) plants (*in vitro*) and 16 plants (*in vivo*) have been identified to possess anticancer activity. The activity reported was attributed primarily to diverse chemical groups of naturally occurring phytochemicals such as flavonoids, phenolics, glycosides, quercetin, and gallic acid. Henceforth, the findings will hope to aid further research in understanding the underlaying mechanism and the efficiency of the isolation of the bioactive compounds.

Key words: Anticancer, *In vitro*, *In vivo,* Malaysia, medicinal plants

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INTRODUCTION

Cancer is a group of malignant diseases characterized by uncontrolled, abnormal cells (Gurunanselage Don & Yap, 2019). It has been categorized as a disease with a high death rate in human history despite advancements in tools for diagnosis, treatment, and prevention (Mohd-Salleh *et al*., 2020). Although with various treatments and progress in reducing cancer incidence and development in chemotherapeutic strategies, the cases keep increasing and are still a significant public health problem worldwide (Mahmood *et al*., 2020). Global cancer data have recorded that one in every five males and one in every six females are presumably to develop cancer, leading to one in every eight males and one in every ten females death, respectively (Ali *et al*., 2021). This uncontrolled growth of normal cells makes genetics unstable and causes alterations stored within cells and tissues, transforming normal cells into malignant cells (Stadlbauer *et al*., 2019). The instability in genetics includes mutations in DNA repair genes (*p21*, *p22*, *p27*, *p51*, *p53*, & toolbox for DNA), tumor suppressor genes (*p53*, *NF1*, *NF2*, *RB,* & biological breaks), oncogenes (*MYC*, *RAF*, *Bcl-2*, *RAS*, & biological accelerators), and genes works in cell growth metabolism (Jia & Zhao, 2019; Jo *et al*., 2019; Menyhart *et al*., 2019; Mota *et al*., 2020; Negrao *et al*., 2021). The contribution to this instability of genetic causing cancer is due to both internal factors (gene mutation, immune response system, and hormone imbalance) and external factors (external radiation, tobacco smoking, contamination in food, water, air, chemicals & pathogens) (Abdullahi *et al*., 2019). Cancer comes in various types and the most common cancers include breast cancer, colorectal cancer, bladder cancer, kidney cancer, leukemia, non-small cell lung cancer, non-Hodgkin lymphoma, melanoma, and oral and oropharyngeal cancer (Geiger *et al*., 2020).

Malaysia is one of the developing countries in Southeast Asia (Muhammad Nawawi *et al*., 2021), with an estimated 32.7

million population in 2021, growing at a 0.2% annual rate compared to 32.6 million in 2020 (Mahidin, 2021). According to the Malaysian National Cancer Registry Report 2012-2016, breast cancer accounts for 19% of all cancers diagnosed (Bahri *et al*., 2021), with a standardized age rate of 47.4 per 100,000 and over 10,000 unregistered cases each year (Mainasara *et al*., 2021). The second and third-highest cancer in Malaysia were colorectal cancer (CRC) and lung cancer (Azizah *et al*., 2019). CRC is the most common cancer in males, with 16.9% of all cancers diagnosed, and the second most common cancer in females with 10.7% of all cancers diagnosed (Muhammad Nawawi *et al*., 2021). At the same time, lung cancer is the second most common cancer in males, with 14.8% of all cancers diagnosed (Azizah *et al*., 2019). Hence, the cancer disease keeps growing day by day among Malaysian and worldwide.

Plants have been used for a long time in cancer therapy and various plant-derived anticancer drugs that are clinically available, including vincristine, vinblastine, etoposide, camptothecin derivatives, topotecan, irinotecan, paclitaxel which are all isolated from plants (Hussain *et al*., 2019). Malaysia is one of the 12 megadiverse countries globally with the greatest endemism levels (Ahmad Ruzman *et al*., 2021). Besides, Malaysia also features at least 14 major forest ecosystems, such as tropical evergreen lowland rainforest, tropical upper montane rainforest, mangrove forest, peat swamp forest, and many others (Ahmad Ruzman *et al*., 2021). Peninsular Malaysia includes over 8300 species of vascular plants, according to the Flora of Peninsular Malaysia project and the Tree Flora of Sabah and Sarawak project. On the other hand, Sabah and Sarawak have around 12,000 species (Middleton *et al*., 2019). With a wide variety of flora in Malaysia, proper management must be done to benefit from it, such as using them as medicinal plants. According to the World Health Organization, a medicinal plant is any plant that has chemicals that can be used for therapeutic reasons in one or more of its organs (Larki *et al*., 2020). The use of medicinal plants is not something new. It has been used for centuries in the treatment and prevention of disease. It contains various chemical compounds such as flavonoids, phenolics, alkaloids, glycosides, saponins, tannins, resins, oils, and other compounds (Larki *et al*., 2020). Statistics from World Health Organization also reported that medicinal plants, mainly herbal, are curing diseases of an estimated 1.5 billion of the world population (Dutta *et al*., 2020). Around 25% of today's prescribed medicines come from medicinal plants, and in developing countries, about 80% of the population relies on traditional plant-based remedies (Dutta *et al*., 2020). Therefore, this review aims to publicize detailed information on the anticancer potential of Malaysian medicinal plants, focusing on the bioactive phytochemicals and mechanisms of action against cancer development in both *in vitro* and *in vivo* studies.

MATERIALS AND METHODS

The research was performed in the following databases: PubMed, Google Scholar, Scopus, and Science-Direct. These databases were searched for relevant studies which included at least one keyword from each of the following: (i) anticancer, (ii) medicinal plants, (iii) Malaysia, (iv) mechanisms, (v) *in vitro*, (vi) *in vivo*. The limit was placed on the search time frame from 2019 to 2021 to retrieve relevant papers, and the last search was performed on December 31st, 2021. A total of hundred and twenty-two (122) articles including research articles, full articles, proceeding articles, and the references list of articles for additional relevant studies were reviewed.

RESULTS AND DISCUSSION

Cancer treatments currently available include surgery, radiation therapy, and systemic treatment such as chemotherapy, targeted therapy, hormonal therapy, and immunotherapy (Miller *et al*., 2019). The treatments focused on stopping the cell cycle or inducing cell death through the apoptotic or non-apoptotic application (Abroudi *et al*., 2020). The apoptotic or non-apoptotic applications currently available include necrosis, mitotic catastrophe, autophagy, and others (Puñal *et al*., 2019). For example, chemotherapy is essentially founded on the principles of cytotoxic chemicals, which prevent cells from improperly developing (Wadhwa *et al*., 2021). Although the treatment exists, many such drugs come with considerable drawbacks or adverse effects. More specifically, severe allergic reactions, extreme pain, neuronal disintegration, and toxicity (Wadhwa *et al*., 2021). Chemotherapeutic drugs also come with side effects. Despite killing tumor cells, they also cause harm to reproduce normal cells such as in the patient's gastrointestinal tract, hair, and bone marrow, leading to side effects including nausea, vomiting, alopecia, and myelosuppression (Zaidieh *et al*., 2019). Despite advancements in the discovery of new pharmaceuticals, cancer treatment still requires specific and particular drugs to prevent chemotherapeutic side effects (Abroudi *et al*., 2020). Various natural chemicals have demonstrated promising results in the treatment and prevention of cancer, with the added benefit of fewer side effects. Therefore, natural compounds from plants can provide alternative cancer treatment, such as blocking tumors or inducing apoptosis (Intarasam *et al*., 2020).

Medicinal plants have long been utilized to make indigenous remedies, and different medicinal plants are also used to formulate medicines with anticancer effects (Jeba Malar *et al*., 2020). Over 10% of vascular plants have been used as medicinal plants (Salmerón-Manzano *et al*., 2020). Initially, the trial and error method was employed to treat ailments or merely to feel better, and in this way, valuable plants with beneficial effects were identified (Salmerón-Manzano *et al*., 2020). Nowadays, medicines generated from medicinal plants are now utilized to treat various disorders, which was not the case in the past (Jeba Malar *et al*., 2020). Plants' therapeutic properties led to the development of pharmaceutical medications derived from certain plants that provide these advantages (Salmerón-Manzano *et al*., 2020). The majority of phytochemicals derived from plants, such as phenolics and flavonoids, have been shown to improve health and cancer prevention (Larki *et al*., 2020).

The evaluation of anticancer activities from medicinal plants consists of several steps and procedures, including collecting plant material, preparing chemicals and reagents, extracting and isolating the plant, culturing cells, and evaluating cytotoxicity and cell proliferation rate against cancerous cells *in vitro* or *in vivo*, using bioassays or cancer cell-induced laboratory animals (Nugraheni *et al*., 2021). In this review, the anticancer effect

evaluation focused on the cytotoxic effect. The most frequently used screening technique for *in vitro* cytotoxicity evaluation against cancer cells for plant extract is the 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assay (Rekha & Anila, 2019; Madankumar *et al*., 2020). The MTT assay relies on the insoluble purple formazan product reduced from yellow soluble MTT by mitochondrial dehydrogenase (Madankumar *et al*., 2020). Because of the insoluble product, this assay necessitates the use of a solvent for example dimethyl sulfoxide (DMSO), dimethylformamide (DMF), and sodium dodecyl sulfate (SDS) to completely dissolve formazan crystals so that a clear solution of formazan may be obtained and the absorbance measured at 550–600 nm wavelength (Nga *et al*., 2020). This colorimetric methods assay was popularly used in quantifying cell densities due to its safety, simple, economical, convenient with lower technical requirements, and also compatible with various animal cell lines (Damiani *et al*., 2019; Nga *et al*., 2020). Furthermore, this method was developed by Mosmann, 1983 where the MTT assay comes with promised benefits compared to other existing technologies of cell counting and radio-labeling of nucleotides (Damiani *et al*., 2019). Later then, the MTT assay was modified for high throughput screening (HTS) followed by another colorimetric and fluorometric assay including the Alamar Blue (resazurin reduction), XTT (tetrazolium salt reduction), acid phosphatase (*p*-nitrophenol phosphate hydrolysis), and SRB (sulforhodamine B amino acid complexation) where it comes with their advantages and limitations (Damiani *et al*., 2019). The cytotoxic activity was evaluated and studies based on 50% inhibition concentration (IC_{50}) values, which specified that: IC_{50} ≤20 µg/mL highly active, IC_{50} 21–200 µg/mL moderately active, IC_{50} 201–500 µg/mL weakly active, and IC_{50} > 501 µg/mL inactive, which is by the American National Cancer Institute protocol (Al-Yousef *et al*., 2020).

The medicinal plant's phytochemicals and their derived analogs are present in various plant parts, including flower, stem, pericarp, sprouts, fruits, seeds, roots, rhizomes, leaf, bark, and galls, and perform several pharmacological activities. Several plant products also being identified such as phenolics, alkaloids, flavonoids, saponins, terpenes, xanthones, vitamins, minerals, glycosides, oils, and other primary and secondary metabolites, are the major compounds in providing anticancer effects such as by inhibiting the growth of cancer cell, exhibit proliferative effect, causing cytotoxic effect against the cancer cell and others (Al-Yousef *et al*., 2020; Aoussar *et al*., 2020; Okoro *et al*., 2021). The Malaysian medicinal plants exhibiting anticancer activity are shown in Tables 1 and 2 for *in vitro* and *in vivo* studies, respectively.

Anticancer activity of Malaysian Medicinal Plants (*in vitro*)

Based on Table 1 (*in vitro* study) 85 plants have been identified and studied previously for their anticancer properties. As a result, three plants have been reported to exhibit high anticancer properties with IC_{50} <1.5 µg/mL, which were, *Ardisia crispa* known as Akar beluloh (1.09±0.18 µg/mL)*, Morinda citrifolia* known as Mengkudu (0.39 µg/mL) and *Senna alata* known as Gelenggang (0.013 µg/mL) (Chahardehi *et al*., 2021). The moderate cytotoxic effect between 23 µg/mL to 132 µg/mL also have been reported by several plants such as *Aquilaria subintegra* known as Gaharu (23 µg/mL), *Citrus macroptera* known as Limau purut (132.081±26.112 µg/mL), *Clausena lansium* known as Daun kari (50 µg/mL) and *Etlingera fimbriobracteata* known as Halia (106.21 µg/mL) (Shahid-Ud-Daula *et al*., 2019). Meanwhile, *Ananas comosus* known as Nanas (250±30 µg/mL), and *Momordica cochinchinensis* known as Teruah (490 µg/mL) is reported as having weak cytotoxicity (Aoussar *et al*., 2020; Nallappan *et al*., 2021). Finally, a plant with an inactive cytotoxic effect is *Coix lacryma* known as Jelai (580.2 µg/mL) (Son *et al*. 2019).

Senna alata from the family Fabaceae also known as Gelenggang in Malay is composed of flavonoids, triterpenoids, alkaloids, glycosides, and saponins (Chahardehi *et al*., 2021). The anticancer properties of flavonoids and triterpenoids are consistent with their antioxidant properties, as they can scavenge free radicals, inhibit the production of radical oxygen species (ROS), and enzymes, and inhibit the oxidation of cells and extracellular compounds (Chahardehi *et al*., 2021). Additionally, it has been demonstrated that flavonoid compounds can inhibit tumor proliferation and slow tumor growth (Chahardehi *et al*., 2021). Next, is *Morinda citrifolia* from the family Rubiaceae also known as Mengkudu in Malay, which contains stigmas-7-ene-3-ol (M1), 28-hydroxy-3β-acetoxy-9-dehydrogramisterol (M2), 3β-acetoxy-taraxast-20(30)-ene-21- ol (M3), 22-dehydroclerosterol (M4)and 22-dehydroclerosterol-3-O-β-D-glucopyranoside (M5), quercetin (M6), hesperidin (M7), naringin (M9) and gallic acid (M8) (Ezzat *et al*., 2021). The compound 28-hydroxy-3β-acetoxy-9-dehydrogramisterol (M2), 3β-acetoxy-taraxast-20(30)-ene-21- ol (M3), and quercetin (M6) function by decreasing the production of TNF-α, IL-1β, IL-6, and IL-10in THP-1 stimulated by LPS (Ezzat *et al*., 2021). Quercetin's (QC) anticancer works by stopping the cell cycle during the G1/S transition or G2/M phases and its main molecular targets are p21, p27, topoisomerase II, and cyclin B (Lakshmi & Kim, 2019). Meanwhile, hesperidin (M7) (HES) is a flavanone glycoside that exhibited an anticancer effect against human pancreatic cells and non-small-cell lung cancer (NSCLC). By inhibiting cell cycle progression, it contributes to the intracellular antioxidant defense system, acting as an agent against superoxide, singlet oxygen, and hydroxyl radicals (El-Sisi *et al*., 2020). Naringin (M9) compounds can exhibit antiproliferative activity and enhance cell death in tumor cells, preventing tumor growth while having a negligible effect on normal cells even at higher concentrations (Lin *et al*., 2020). Naringin also negates the β-catenin signaling pathway, arresting the cell cycle at a G0/G1 phase (Lin *et al*., 2020).

Finally, *Ardisia crispa* from Primulaceae also known as Mata Ayam in Malay consists of quinone, wogonin, oroxylin A, wogonoside, baicalin, anwulignan, bergenin, β-sitosterol, and viminolol (Blin *et al*., 2021). Compound quinone in general is a cytotoxic agent with selective cytotoxicity against cancer cells (Blin *et al*., 2021). Natural quinones are classified as secondary metabolites of plants based on their aromatic carbon skeleton. They are classified as benzoquinone, naphthoquinone, phenanthrenequinone, and anthraquinone (Tsao *et al*., 2020). Quinone-based drugs, such as doxorubicin and mitomycin C are also used clinically for cancer chemotherapy (Tsao *et al*., 2020). Next is the wogonin compound, also chemically known as 5, 7-dihydroxy-8-methoxy-2-phenyl-4h-1-benzopyran-4-one, which has various therapeutic effects including neuroprotective, anti-inflammatory, and antitumor effects (Yang *et al*., 2020). It also has been proven *in vitro* breast cancer experiments that wogonin induces cell cycle arrest and apoptosis in T47D, SK-BR-3, and MDA-

MB-231 cell lines at high concentrations (Yang *et al*., 2020). Furthermore, wogonin does not cause severe side reactions whereas treatment in nude mice did not lead to a significant change in body weight (Yang *et al*., 2020).

In this study, it was found that the result of anticancer activity of the methanolic extract of the stem bark of *Senna alata* (Gelenggang) varied between previous studies due to different types of cancer cell lines used by both studies: MCF-7 breast cancer cells and PC-3 prostate cancer cell lines which then resulting in two different cytotoxic effects which are moderate and weak with IC_{50} values at 47.11 µg/mL and 427.77 µg/mL, respectively (Madankumar *et al*., 2020; Kamarudin *et al*., 2021). Another study also reported that the different anticancer activity of ethanolic extract of *Morinda citrifolia* (Mengkudu) fruit on different cancer cell lines: THP-1 human monocyte cell and MDA-MB-231 breast cancer cell line resulting in different IC_{50} values at 0.39 µg/mL (highly active) and 49.72 µg/mL (moderately active), respectively (Tsao *et al*., 2020; Vyn *et al*., 2020). Based on these results, it can be concluded that the same extract used on the different cancer cell lines might produce different results.

Anticancer activity of Malaysian Medicinal Plants (*in vivo*)

According to Table 2 (*in vivo* study), 16 plants have been identified and studied for anticancer properties from the previous study. Based on the result, many previous studies used the mouse model to evaluate the anticancer effect. The mouse models provide the most physiological cancer cell microenvironment, allowing for the study to cover various steps of tumorigenesis, including initiation, promotion, and progression (Saito *et al*., 2020). Syngeneic murine tumor cell lines are also used in situations where the preparation of tumor-bearing mice is simple, reproducibility is high, and *in vivo* tumor growth is stable. Another reason for using syngeneic murine tumor cell lines is the scarcity of spontaneous metastasis models that are easily established through the injection of syngeneic cell lines into mice (Saito *et al*., 2020). The significance of using animal models to evaluate anticancer compounds for human cancer treatment must be considered, as tumor heterogeneity and microenvironment play a significant role in tumor development and progression (Phang *et al*., 2021). The mice that have been identified from the previous studies include Swiss albino mice, BALB/c mice, White Wistar rats, Sprague-Dawley (SD) rats, the athymic mouse model, and athymic NCR nude mice. The dosage administered to evaluate anticancer activities also being identified in previous studies where it ranged from 1 to 1000 mg/kg. *Piper methysticum* (1 & 3 mg/kg), *Lignosus tigris* (5 mg/kg), and *Zanthoxylum rhetsa* (25 mg/kg) were identified for *in vivo* anticancer activity and demonstrated an anticancer reaction with lower dosage administered (Bao *et al*., 2019; Manojj *et al*., 2020; Tran *et al*., 2020).

Based on the result obtained, *Piper methysticum* from the Piperaceae family also known as Kava consists of flavokawain C (FKC) that belong to the flavonoid family (Bao *et al*., 2019; Tsao *et al*., 2020). Compound flavokawain C showed no side effects in tested mice (Phang *et al*., 2021). Besides, additional compounds isolated from Kava include flavokawain A (FKA), flavokawain B (FKB), yangonin, kavain, and methysticin, all of which have been shown to have anticancer properties on two human malignant oral keratinocyte cell lines (H400 and BICR56) (Celentano *et al*., 2020). Flavokawain A and flavokawain B compounds performed the same anticancer activity by inducing apoptosis, inhibiting proliferation, blocking metastasis, inhibiting angiogenesis, preventing inflammation, and improving the immune function system on both H400 and BICR56 cancer cell lines (Celentano *et al*., 2020). Next, another study reported that yangonin does inhibit the migration and invasion of oral squamous cell carcinoma (OSCC), resulting in a decrease in malignant signs (Celentano *et al*., 2020). Then, the study concluded that Kava constituents produced a promising outcome for the treatment of oral carcinogenesis and a translation into *in vivo* studies. The next plant is *Lignosus tigris* from also known as Cendawan susu rimau consists of cytotoxic protein including cultivar sclerotia (Ligno TF-K), lectins, a serine protease, RNase Gf29, and 230NA deoxyribonuclease (Kong *et al*., 2020). From all the compounds isolated from *Lignosus tigris*, Ligno TF-K (a high molecular weight (HMW) protein) is the most abandon cytotoxic protein isolated using cold water and also showed a stronger cytotoxic effect with IC_{50} value at 4.23 µg/mL against MCF7 breast cancer cells throughout *in vitro* study (Kong *et al*., 2020). Besides that, in further exploring the mechanisms of cytotoxic of this HMW protein, the 100% saturated ammonium sulfate was used and tested on the MCF7 cell line and found that it effectively inhibited the proliferation of MCF7 cell and was selective with IC_{50} value at 0.76±0.19 µg/mL which was more potent than extract using cold water (Kong *et al*., 2020). The mechanisms of HMW protein showed through in vivo study on Athymic NCR nude mice that it can induce apoptosis where it was hypothesized to be mediated by caspase activation which induces caspase-8 and -9 via the extrinsic and intrinsic apoptotic pathways. At the same time, caspase-3 was absent in the cancerous cell. Both of these pathways will eventually activate by caspase-7, resulting in subsequent cell death (Kong *et al*., 2020). Following that, another novel, the first-time-studied protein was discovered in mushrooms, specifically in Cendawan susu rimau (Kong *et al*., 2020). It was a deoxyribonuclease-like protein. The deoxyribonuclease-like protein encoded by GME1230_g contains a conserved DNase_NucA_NucB domain and was abundantly expressed in Ligno TG-K HMW protein (Kong *et al*., 2020). Although the function of this compound has not been determined, it may act as a deoxyribonuclease due to its conserved domain (Kong *et al*., 2020). Additionally, fungal antitumor proteins with deoxyribonuclease activity have been reported, including those from *Agrocybe aegerita*, *Pholiota nameko* and *Ramaria botrytis* mushrooms (Kong *et al*., 2020). All these mushrooms reported to exhibit potent antiproliferative activity and apoptosis-inducing against several human cancer cells including neuroblastoma (SH-SY5Y), HeLa, MCF7, and A5g49 cell lines (Kong *et al*., 2020). Finally, the ZR3 protein fraction of *Zanthoxylum rhetsa* partially purified protein (*ZR*PPP) found in the *Z. rhetsa* (Hantu duri) plant showed the most potent cytotoxic effect compared to others fraction on HeLa, HCT-116, MDA MB 231, and MCF7, respectively (Parrikar *et al*., 2021). The mechanisms identified via *in vivo* study of this plant concluded that a decrease in the secreted vascular endothelial growth factor (VEGF) as a main role of *ZR*PPP where VEGF function by promoting angiogenesis, thus creating another factor that is prominent in cancer (Parrikar *et al*., 2021).

Table 1. The medicinal plants considered to possess anticancer activity based on *in vitro* studies

Scientific name	Family	Local name	Part/solvent used	Active compounds	Experimental model	IC_{50} (µg/mL)	Mechanisms of action	Ref.
Abrus precatorius	Fabaceae	Akar belimbing or akar saga	Root/ methanol	Abruquinones M, N, O, P, A, E, B, F, I, D, and G	Oral CAL-27, colon (Caco-2), and lung cancer cell lines	Abruquinoes M and N: 6.48 and 5.26 µM	Abruquinones M and N showed cytotoxic activity and inhibited growth against oral CAL-27, colon Caco-2, and lung cancer cells.	(Okoro *et al*., 2021)
Alpinia zerumbet	Zingiberaceae	Lengkuas	Flower/ methyl hydroxide (MeOH)	5,6-dehydrokawain (DK)	Breast carcinoma MCF-7, liver carcinoma Hep-G2, and larynx carcinoma cells HEP-2	3.08, 6.08 and 8.7	DK shows antiproliferative activity against MCF-7, Hep-G2, and HEP-2.	(Zahra *et al*., 2019)
Ananas comosus	Bromeliaceae	Nanas	Fruit/ pineapple vinegar	Gallic acid and caffeic acid	Mouse mammary gland cells 4T1 and human mammary gland cells MDA-MB-231	250±30 and 270±20	The extract showed a weak cytotoxic effect on cancer cell lines.	(Mohamad *et al*., 2019)
Anchusa arvensis	Boraginaceae	Bugloss kecil	Whole plant/ methanol	NA	Human hepatocellular carcinoma cells HepG-2	6.50±0.70	The newly isolated compound demonstrated significant cytotoxicity against HepG-2 cell lines.	(Hussain *et al*., 2019)

Table 1. *Continued...*

Annona muricata	Annonaceae	Durian belanda or durian benggala	Fruit/ionic liquid extract of Graviola fruit (IL-GFE)	Acetogenins	Colon cancer HT29 cell lines	NA	The extract showed an alteration of many metabolic pathways including amino acid metabolism, aerobic glycolysis, urea cycle, and ketone bodies metabolism that contribute to energy metabolism and cancer cell proliferation.	(Daddiouaissa *et al*., 2021)
Aquilaria subintegra	Thymelaeaceae	Gaharu or agarwood	Leaves and branches/ ethane and distilled water	NA	Breast cancer cell	23 and 38	Branch extract with ethanol and distilled water showed a more potent cancer inhibition effect compared to leaf extract.	(Abbas *et al*., 2019)
Ardisia crispa	Primulaceae	Akar beluloh, mata ayam, or mata pelanduk	Root/ hexane (ACRH)	Quinone-rick fraction (QRF), benzoquinonoid (BQ)	VEGF-induced human umbilical vein endothelial cells (HUVECs)	ACRH: 1.09±0.18 QRF: 3.85±0.26 BQ: 1.34±0.16	All extracts showed a high antiproliferative effect on HUVECs cell lines.	(Blin *et al*., 2021)
Artocarpus altilis	Moraceae	Kelur or kulur	Fruit pulp/ methanol	Quercetin	Human lung carcinoma A549 cell line	23.10±0.71	The extract showed an increase of cells at G2/M phases, and it downregulated the expression of the anti-apoptosis gene BCL-2 and upregulated the expression of the pro-apoptosis gene BAX.	(Jalal *et al*., 2019)

Table 1. *Continued...*

Baeckea frutescens	Myrtaceae	Cucor atap, rempah rempah,tuturun atap	Leaves and branches/ ethane, hexane, and water	Phenolic, glycosides, flavonoids, and lipophilic	Hypoxic human breast cancer MCF-7 cell line	23 to 158	All extracts showed a moderate cytotoxic effect against MCF-7 cell lines.	(Shahruzaman *et al.*, 2021)
Barringtonia racemosa	Lecythidaceae	Putat, putat darat, putat ayam	Leaf/water (BLE)	Gallic acid (GA)	Colorectal cancer Caco-2	325.5±12.8 and 10.6±0.6	BLE extract showed a weak cytotoxic effect, while GA extract showed a high cytotoxic effect.	(Ho *et al.*, 2020)
Biophytum petersianum	Oxalidaceae	Rumput kebar	Whole plant/ dichloromethane and methanol	Quercetin, genistein, epigallocatechin gallate, and catechin	Human acute lymphocytic leukemia cell (CCRF-CEM), multidrug resistance human acute leukemia cell (CEM/ ADR5000),	CCRF-CEM: 58.84±15.63 and 69.94±11.85 CEM/ ADR5000: 112±20.84 and 124.83±22.96 HeLa: 76±10.98 and 64.55±11.85	Isolated compounds inhibited the growth of human cancer cells. The extract was found to be moderately cytotoxic to cancer cell lines.	(Darwati *et al.*, 2019)
Blumea balsamifera	Asteraceae	Sambong	Leaves/ethyl acetate	Flavonoids, tannins, and glycosides	NA	25	The extract showed a moderate cytotoxicity effect on cancer cells.	(Ginting *et al.*, 2020)
Blumea lacera	Asteraceae	Malay bumea or sembung	Leaves/ chloroform	Gallic acid, phenolic, quercetin, and flavonoid	HeLa and T-cell line MOLT-4 cell lines	3.46 and 3.29	The extract showed a high cytotoxic effect against both cancer cell lines.	(Khan, 2019)
Boesenbergia rotunda	Zingiberaceae	Temu kunci	Rhizome/ methanol	Panduratins Q-S	Human pancreatic cancer cell PANC-1	6.6	Compound panduratins demonstrated exceptional cytotoxicity against the PANC-1 cancer cell lines.	(Nguyen *et al.*, 2021)

Table 1. *Continued...*

Bouea macrophylla	Anacardiaceae	Kundang, kundang daun besar, or setar	Leaves/ ethanol	Polyphenols, tannins, flavonoids, carbohydrates, steroids, triterpenoids, fixed oils, saponins, and alkaloids	Human cervical cancer HeLa and human colorectal carcinoma HCT116 cell lines	24±0.8 and 28±0.9	Ethanol extract showed a moderate antiproliferation effect on both cancer cell lines.	(Nguyen *et al*., 2020)
Caesalpinia pulcherrima	Fabaceae	Jambul Merak or bunga Merak	Leaves/ petroleum ether, chloroform, ethyl acetate, and methanol	Isobonducellin and 5,7-dimethoxy-3,4-methylenedioxyflavanone	Colon cancer HCT116 cell line	3.8	*C. pulcherrima* (CpAg) silver nanoparticles exhibited a high cytotoxic effect against HCT116 cancer cells.	(Deepika *et al*., 2020)
Carica papaya	Caricaceae	Betik or papaya	Leaves/ methanol and ethanol	Anthraquinone, amino acid, terpenoid, alkaloids, tannins, and saponins	Aedes albopictus clone C6/36 cells	NA	The extract showed a significant anticancer and cytotoxic effect against the tested cell.	(Husin *et al*., 2019)
Cassia siamea	Fabaceae	Bebusok or petai belalang	Stem bark/ methanol (CSME) and aqueous (CSAE)	Serpyllin	MCF-7	CSME: 13.77±5.18 CSAE: 93.51±14.17	The extracts inhibited MCF-7 cell proliferation. CSME exhibits antimetastatic action and induced apoptosis and cell cycle arrest in MCF-7 cells.	(Adebayo *et al*., 2019)

Table 1. *Continued...*

Cerbera odollam	Apocynaceae	Buta-buta	Fruit kernel/ methanol	Cerberin (CR)	Breast (MCF-7, MDA-MB-231, MDA-MB-468 and SKBR3), colon (HT-29, HCT-116 and vincristine-resistant-(VR) Ehct-116), pancreatic (PANC-1 and MIA PaCa-2), lung (A549), liver (HepG2) and nasopharyngeal (HK1) carcinomas	NA	Cerberin isolated inhibited cancer cell growth, colony formation, and migration on all cancer cell lines.	(Hossan *et al.*, 2019)
Christia vespertilionis	Fabaceae	Daun rerama	Leaves/ methanolic (CVME)	Tetrahydro-2-methyl-thiophene, phytol, 10-undercenoic acid, 6-methyl heptyl-2-propanoate, 2-(2-benzothiazolylthio)-1-(3,5-dimethylpyrazolyl)-ethanone	Breast cancer cell line MDA-MB-231	37.45±1.05	CVME extract exhibited a weak cytotoxic effect against the MDA-MB-231 cell line by inhibiting proliferation.	(Zahidah Nasuha Mohd Yasin *et al.*, 2020)
Citrus macroptera	Rutaceae	Limau purut, limau hantu, or jeruk purut	Fruit peel/ethyl acetate	Palmitic acid, isoheptadecanoic acid, isostearic acid, linoleic acid, and linolenic acid	A549, MCF-7, and HepG2 cancer cell line	132.081± 26.112, 342.213± 172.361, and 791.873± 42.191	The extract showed low antiproliferative activity against cancer cell lines.	(Gogoi *et al.*, 2021)
Clausena excavata	Rutaceae	Cemama or secerek	Leaf/ethyl acetate, methanol, and chloroform	Phenolic acid, furocoumarin base compound, and 8-geranyloxy psoralen	Non-small-lung cancer NCI-H460 cell line	47.61	Ethyl acetate extract (EACE) showed moderate anticancer activity against the NCI-H460 cell line where the cell undergoes apoptosis where its loss of cell viability, cell shrinkage, and chromatin condensation.	(Albaayit *et al.*, 2021)

Table 1. *Continued...*

Clausena lansium	Rutaceae	Daun kari or wanpee	Fruit and leaf/ethanol	NA	Liver HepG2 cells	50	The extract showed strong antiproliferative activity against HepG2 cells.	(Siew *et al.*, 2019)
Clinacanthus nutans	Acanthaceae	Sabah snake grass or belalai gajah	Leaves/ethanol and aqueous	Choline, creatine, phosphocholine, valine, acetic acid, phenylalanine, leucine, glutamic acid, threonine, uridine, and proline	Rat renal proximal tubular cells (NRK-52E)	NA	Aqueous extract showed the highest potential of nephroprotective effect against cisplatin toxicity on NRK-52E cell lines at 89% viability.	(Mahmod *et al.*, 2020)
Coix lacryma	Poaceae	Jelai	Sprout (CLSE)	NA	Human cervical cancer HeLa cell line	580.2	The CLSE extract showed an inactive cytotoxic effect against the HeLa cell line.	(Son *et al.*, 2019)
Costus speciosus	Costaceae	Halia Malay	Root/ethanol, methanol, and water	Quercetin, caffeic acid, gallic acid, syringic acid, chlorogenic acid, and naringenin	Hepatocellular carcinoma HePG-2 cell line	13.87, 24.06, and 53.69	Ethanolic extract showed good anticancer activity against the HePG-2 cell line compared to other extracts.	(Gheraibia *et al.*, 2020)
Cratoxylum formosum	Hypericaceae	Derum or mempat	Leaves	Zink oxide nanoparticles (ZnO NPs)	Non-melanoma skin cancer cell line A431	83.47	The extract showed anticancer activity, inhibited strong cytotoxicity activity against cancer cells, and altered the number of genes in cancer cell signaling pathways in A431 cells.	(Jevapatarakul *et al.*, 2020)

Table 1. *Continued...*

Crinum amabile	Amaryllidaceae	Bakung labah-labah	Leaves/ chloroform	NA	Breast: MCF-7 and MDA-MB-231 Colon: HCT-116 and HT-29 Leukemia: REH	Breast: 25.61±3.15 and 27.15±1.21 Colon: 40.14±2.53 and 39.53±1.65 Leukemia: 39.53±1.65 and 52.69±8.10	F5 fraction showed the highest cytotoxic among all fractions. It also showed induction of cell apoptosis and inhibited normal cell proliferation.	(Lim *et al*., 2019)
Croton caudatus	Euphorbiaceae	Pokok angguk-angguk	Leaves/ chloroform, ethanol, and aqueous	Crotsparinine, crotoflorine, sparsiflorine, ditriacontamol, bamyrin, and β-sitosterol	Human cervical adenocarcinoma HeLa cell line	80	Ethanol extract showed a decline in cell survival and increased micronuclei and apoptosis induction.	(Shantabi *et al*., 2020)
Cucurma longa	Zingiberaceae	Kunyit	Rhizome/ chloroform	Cucurmin-loaded poly(lactic-co-glycolic acid) (PLGA NPs) nano particles based	Human breast cancer cell MDA-MB-231	4.86	The compound showed a high cytotoxic effect against the MDA-MB-231 cell line.	(Sharma *et al*., 2021)
Cymbopogon citratus	Poaceae	Serai	Leaves/ aqueous	Flavonoid and polyphenol	Cervical cancer cell line SiHa	NA	The extract showed anticancer activity by decreasing cell viability on the SiHa cell lines.	(Pan *et al*., 2021)
Dioscorea bulbifera	Dioscoreaceae	Ubi angin or ubi kemili hutan or ubi kastela	Leaf/methanol, ethyl acetate, and hexane	Acetic acid, n-hexadecanoic acid, acetin, hexadecanoate, 7-tetradecenal, phytol, octadecanoic acid, cholesterol, palmitic acid, and linolenate	MDA-MB-231 cancer cell lines	4.29	*D. bulbifera* showed an apoptosis effect at various stages and a significant decrease in viable cells and improvement after treatment.	(Mainasara, *et al*., 2021)

Table 1. *Continued...*

Elephantopus mollis	Asteraceae	Pokok tutup bumi or tapak leman	Whole plant/ethyl acetate (EM-EA)	NA	Lung cancer cells A549 and leukemia cell HL60	18.66 and 7.45	The extract showed proliferative inhibition and apoptotic induction toward all cancer cell lines.	(Bich Ngoc *et al*., 2020)
Etlingera fimbriobracteata	Zingerberaceae	Halia	Leaves/ methanol	Steroids, cardiac glycosides, saponins,	Human cervical cancer line CasKi	106.21	The extract showed moderate anticancer activity against human cervical cancer cell lines.	(Shahid-Ud-Daula *et al*., 2019)
Eugenia uniflora	Myrtaceae	Cermai belanda	Leaves/ hydroethanolic (HEE) and dichloromethane (DEE)	Quercetin, β-sitosterol, flavonoid, and phenolic	Ovarian cancer cell line OVCAR-3	NA	DEE extract showed antiproliferative activity against OVCAR-3 ovarian cells.	(Gomes *et al*., 2020)
Euphorbia hirta	Euphorbiaceae	Ambin jantan, ara tanah, gelang susu, rumput susu kambing, or susu Fatimah	Whole plant/ethyl acetate (EH-EA)	Quercetin	Lung cancer cells NCI-H460 and liver cancer cells Hep G2	100	The EH-EA extract inhibited the growth of both cancer cell lines.	(Tran *et al*., 2020)
Ficus deltoidea	Moraceae	Mas cotek or ara	Leaf/hexaneethyl acetate, methanol, and water	Polyphenolic and flavonoid	Breast cancer (MCF-7, MDA-MB 231, HCC 1937) and colon cancer (HCT116) cell line	100 to 200	Ethyl acetate extract showed strong antiproliferative activities against breast cancer cells compared to colon cancer cells.	(Abolmaesoomi *et al*., 2019)

Table 1. *Continued...*

Garcinia mangostana	Clusiaceae	Manggis	Fruit peel/iron oxide nanoparticles synthesized	Flavonoid: xanthones and epicatechin Benzophenones: maclurin, kolanone, and garcimangosone D Anthocyanin: chrysanthemin and cyanidin-3-O-sophoroside	Colon cancer HCT116 cell line	99.80	The extract showed a moderate cytotoxic effect against HCT116 cell lines.	(Yusefi *et al.*, 2021)
Hibiscus calyphyllus	Malvaceae	Bunga raya	Aerial/ distilled water	N-feruloyltyramine and ascorbic acid	Human colon carcinoma HCT-116 and human lung carcinoma A-549 cell lines	92.9±4.1 and 113±3.4	The extract showed a moderate cytotoxicity effect on both cancer cell lines.	(Al-Yousef *et al.*, 2020)
Hibiscus deflersii	Malvaceae	Bunga raya	Aerial/ distilled water	Butein flavonoid, peonidin dipentoside anthocyanin, oleuropein, and peonidin dependoside	Human lung carcinoma A-549 and human colon carcinoma HCT-116 cell lines	50±5.1 and 96±3.2	The extract showed a moderate cytotoxicity effect on both cancer cell lines.	(Al-Yousef *et al.*, 2020)
Hibiscus micranthus	Malvaceae	Bunga raya	Aerial/ distilled water	Oleuropein, peonidin dependoside, and N-feruloyltyramine	Human colon carcinoma HCT-116 and human lung carcinoma A-549 cell lines	56±1.9 and 60.4±1.7	The extract showed a moderate cytotoxicity effect on both cancer cell lines.	(Al-Yousef *et al.*, 2020)
Kaempferia galanga	Zingiberaceae	Kencur	Rhizome/ trans-ethyl para methoxycinnamate (EPMC)	Phenolics, saponins, phytic acid, alkaloids, tannins, diterpenoids, and oxalate	HeLa and HSC-2 cancer cells	50	The extract showed good antiproliferative and anticancer activities against cancer cell lines.	(Srivastava *et al.*, 2019)

Table 1. *Continued...*

Labisia pumila	Myrsinaceae	Kacip Fatimah	Whole plant/ethanol	Gallic acid and caffeic acid	Uterine leiomyoma cells SK-UT-1	100 to 250	Moderate cytotoxic concentration showed a significantly reduced viable cell while lower cytotoxic concentration showed a significant increase in the late apoptosis effect.	(Zakaria *et al.*, 2020)
Leea indica	Leeaceae	Memali	Leaf/water, ethanol, and methanol	NA	Liver (SNU-182, SNU-449, HepG2), ovarian (PA-1, OVCAR-5, SK-OV-3), cervical (C33A), uterine (MES-SA/Dx5), breast (MDA-MB0231, T47D), colon (HCT116) cancer cells	20 to 50	Leaf extract showed strong or moderately strong anti-proliferative activity against all cancerous cells.	(Siew *et al.*, 2019)
Lignosus tigris	Polyporaceae	Cendawan susu rimau	Mushroom sclerotium/ cold water	Cultivar sclerotia (Ligno TF-K), lectins, a serine protease, RNase Gf29, and 230NA deoxyribonuclease	MCF-7, A549, and PC3 cell lines	28.9 to 95	Cold water extract showed a proliferative inhibition effect against MCF-7, A549, and PC3 cell lines.	(Kong *et al.*, 2020)

Table 1. *Continued...*

Luffa acutangula	Cucurbitaceae	Petola segi	Leaves/ aqueous	1,8 dihydroxy-4-methylanthracene 9,10-dione (DHMA)	Human nonsmall cell lung cancer cell line (NCI-H460) and colon cancer cell line HT29	NA	Compound DHMA showed antiproliferative and anticancer activities against NCI-H460 and H and HT29 cell lines.	(Nallappan *et al*., 2021)
Melaleuca leucadendra	Myrtaceae	Kayu putih or gelam	Leaves/ hexane and methanol	Phenolic, flavonoid, terpenoid, saponin, alkaloid, and glycoside	HepG2 cell line	23.7	Methanol extract showed moderate cytotoxic activity against HepG2 cell lines.	(Vyn *et al*., 2020)
Melastoma malabathricum	Melastomataceae	Senduduk	Leaves/ methanol	Ursolic acid, 2-hydroxyursolic aicd, asiatic acid, gallic acid, quercetin, and rutin	Human colon cancer HT29 cell line	100	The extract showed cytotoxic and antiproliferative activities against HT29 cell lines.	(Kamsani *et al*., 2019)
Mesua ferrea	Calophyllaceae	Nagacuram or nagasari	Whole plant/oleo-gum resin, ethanol extract (RCr), n-hexane (RH), and chloroform (RCF)	α-Amyrin, phthalic acid mono-2-ethylhexyl ester, aromadendrene, 2,4-di-tert-buthylphenol, and betulinic acid (BA)	Human colorectal carcinoma HCT 116	17.38±0.92	Cytotoxic screening showed that RH extract consists the most potent cytotoxic effect on HCT 116 cell lines.	(Asif *et al*., 2019)
Momordica cochinchinensis	Cucurbitaceae	Teruah	Arial/water	NA	Breast cancer (MCF7 and Bt474) and melanoma (MM418C1 and D24) cell lines	490 to 730	The extract showed a weak cytotoxic effect against cancer cell lines. It induces apoptotic and necrotic cell death.	(Wimalasiri *et al*., 2020)

Table 1. *Continued...*

Moringa oleifera	Moringaceae	Daun kelor or daun lemunggain	Leaf/hexane fraction of the seeds (HF-CFE)	NA	Breast cancer MCF-7 and MDA-MB-231	130	Extract HF-CEE showed inhibition in the proliferation of the MCF-7 cell. It also induced apoptosis and cell cycle arrest at the S and G2/M phases of both cancer cells.	(Adebayo *et al*., 2019)
Morinda citrifolia	Rubiaceae	Mengkudu	Fruit/ethanol (EE)	Sterol, glycoside, triterpene, quercetin, hesperidin, naringin, and gallic acid	Human monocyte cell line (THP-1, ATCC TIB-202)	0.39 to 100	The extract showed increased paw edema and decreased production of TNF-α, IL-1β, and IL-6/IL-10.	(Ezzat *et al*., 2021)
Morinda elliptica	Rubiaceae	Mengkudu kecil	Roots/ chloroform	Nordamnacanthal and damnacanthal	T-lymphoblastic leukemia (CEM-SS) cell lines	1.7 and 10	Nordamnacanthal showed a high cytotoxic effect by inducing apoptosis while damnacanthal caused arrest at the G0/G1 phase of the cell cycle.	(Latifah *et al*., 2021)
Nerium olender	Apocynaceae	Bungan Anis or sudu ayah	Flower/ ethanolic (FE)	Chlorogenic acid, caffeoylquinic acid, glycosidic, quercitin, and kaempferolglycostlated	HT29 cell line	11.72±0.02	The extract showed a high cytotoxic effect against HT29 cell lines.	(Ayouaz *et al*., 2021)
Ocimum tenuiflorum	Lamiaceae	Kemangi, ruku-ruku, selasih hitam or tulsi	Leaves/ essential oil (OTEO)	Caryophyllene and α-pinene	Human gastric cancer cell line (AGS)	163.42	OTEO showed a moderate cytotoxic effect on the AGS cell line. It also significantly decreased AGS cell viability, and inhibited cell migration and invasion.	(Boonyanugomol *et al*., 2021)

Table 1. *Continued...*

Oroxylum indicum	Bignoniaceae	Bonglai kayu or kulia	Leaves/ petroleum ether and methanol	Baicalein	HeLa cell line	NA	The extract showed great anticancer activity against HeLa cell lines.	(Rahman *et al*., 2019)
Orthosiphon aristatus	Lamiaceae	Misai kucing	Whole plant/ PBS buffer	Licodiane-synthase and licodione synthase-like, plastocyanin	Carcinomas nasopharyngeal cell line HK-1	NA	Extract from *O. aristatus* showed inhibition towards the HK-1 cell line with cell viability below 80%.	(Hussain *et al*., 2019)
Pereskia bleo	Cactaceae	Duri tujuh or jarum tujuh	Leaf/ methanol	NA	Breast T47D and colon HCT116	2 and 41.6	Methanol extract showed strong or moderately strong anti-proliferative activity against breast and colon cancerous cells.	(Siew *et al*., 2019)
Perilla frustescens	Lamiaceae	Daun Shinso or daun perilla	Leaf/ methanol	Luteolin, rosmarinic acid, and catechin	MCF-& and HepG2	37.92 and 13.43	The extract showed moderate antiproliferative activities against MCF-7 and HepG2 cell lines.	(Wang *et al*., 2021)
Phyllanthus amarus	Phyllanthaceae	Amin buah, dukung anak, or turi hutan	Leaf/ dimethylformamide	N-Hexadecanoic acid, lignans, and polyphenols	Human colorectal adeno carcinoma HCT15 and human breast cancer T47D cell lines	106.7 and 90.3	The extract showed a moderate cytotoxic effect on both cancer cell lines. Anticancer activity was recorded higher in T47D compared to HCT15.	(Sravanthi Pammi & Archana Giri, 2021)
Piper sarmentosum	Piperaceae	Daun kaduk	Whole plant/ PBS buffer	Aspartate minotransferase, cyclophilin, and RuBisCO	Carcinomas nasopharyngeal cell line HK-1	NA	Extract from *P. sarmentosum* showed inhibition towards the HK-1 cell line with cell viability below 80%.	(Hussain *et al*., 2019)

Table 1. *Continued...*

Plectranthus amboinicus	Lamiaceae	Daun bangun-bangun	Aerial/ dimethyl sulfoxide	Carvacrol	Human breast cancer (MCF-7 and MDA-MB-231) and human prostate carcinoma (22Rvl) cell lines	29.1, 41.5, and 29.6	The extract showed the highest cytotoxicity effect on the 22Rvl cell line. The antiproliferative effect is due to attributes of compound carvacrol.	(Monzote *et al*., 2020)
Polygonum minus	Polygonaceae	Kesum or daun laksa	Leaves/ethyl acetate, ethanol, methanol	Phenol	Colon cancer cell lines HCT-116, and CT-26, HT-29	7±0.06, 7±0.03, and 24±0.01	Ethyl acetate extract showed higher cytotoxic activity against all colon cancer cell lines.	(Rohin *et al*., 2020)
Psidium guajava	Myrtaceae	Jambu batu or guava	Fruit peel and pulp/ distilled water	Phenolic, flavonoid, and vitamin C	Leukemia cell line	NA	The extract showed decreased cell viability and exhibited a cytotoxic effect against cancer cells.	(Suwanwong & Boonpangrak, 2021)
Pyrrosia piloselloides	Polupodiaceae	Daun seberneh panjang	Whole plant/ methanol and water	5-hydroxymethylfurfural, allopurinol, 3,5-dihydroxy-6-methyl-2,3-dihydropyran-4-one, sulfolan-3-ol, linoleic acid, and β-sitosterol acetate	HeLa cell line	16.25	Methanol extract showed antiproliferative activities on the HeLa cell line and does not show apoptosis.	(Sul'ain *et al*., 2019)

Table 1. *Continued...*

Quercus infectoria	Fagaceae	Manjakani	Galls/ methanol	Gallotannin and F4 fraction	Human GBM cancer cell line DBTRG-05MG	15	The extract of F4 showed better suppression of GBM cell growth compared to pure synthetic gallotannin.	(Kamarudin *et al.*, 2021)
Rhizophora mucronata	Rhizophoraceae	Bakau or bakau belukap	Whole plant/ methanol	Epi-catechin, 4-O-caffeoyl quinic acid, 5-O-quinic acid, and procyanidin B2	Breast T47D, colorectal HT29, and ovarian A780, SKOV3 cancer cell lines	16.77±0.58 to 28.28±0.89	All compounds isolated showed a strong to moderate anticancer effect on all cancer cell lines.	(Yunos *et al.*, 2021)
Rhodomytus tomentosa	Myrtaceae	Kemunting	Leaves/ hexane and methanol	Phenolic, flavonoid, terpenoid, saponin, alkaloid, and glycoside	HepG2 cell line	28	Methanol extract showed moderate cytotoxic activity against HepG2 cell lines.	(Vyn *et al.*, 2020)
Sandoricum koetjape	Meliaceae	Sentul	NA	Koetjapic acid (KA) and potassium koetjapate (KKA)	Human endothelial cells EA.hy926	18.4±4.2 µM	KKA showed significantly suppressed sprouting of microvessels in rat aorta and inhibited major endothelial functions such as migration, differentiation, and VEGF expression in endothelial cells.	(Jafari *et al.*, 2020)

Table 1. *Continued...*

Senna alata	Fabaceae	Gelenggang	Leaves/ n-hexane, dichloromethane, and chloroform	Flavonoids, triterpenoids, alkaloids, glycosides, and saponins	Breast cancer MCF-7	0.013, 47.11, and 57.61	n-hexane extract showed the highest cytotoxic effects against the MCF-7 cell line compared to dichloromethane and chloroform extract.	(Chahardehi *et al.*, 2021)
Solanum nigrum	Solanaceae	Terung meranti or terung para cicit	Whole plant/ aqueous (AESN)	NA	Breast cancer luminal A sub-type cell line MCF-7	5 and 10	Extract with higher concentration showed a higher cytotoxicity effect toward MCF-7 cell lines.	(Ling *et al.*, 2019)
Strobilanthes crispus	Acanthaceae	Pecah kaca, pecah batu, or jin batu	Leaves and stems/ stem hexane extract (SH)	Stigmasterol and β-sitosterol	HepG-2	38.8	SH extract exhibited the highest cytotoxic effects against HepG-2.	(Baraya *et al.*, 2021)
Swietenia macrophylla	Meliaceae	Tunjuk langit	Seed/ethyl acetate fraction (SMEAF)	Limonoids, swietenioides, methyl angolensate, and deacetyl swietenioides	HCT-166 human colon cancer cell	12.5	The extract showed a reduction in cell viability. It also exhibited significant anticancer activity against cancer cells.	(Low *et al.*, 2021)

Table 1. *Continued...*

Syzygium polyanthun	Myrtaceae	Daun salam	Leaf/hydromethanolic	NA	MCF-7	126.05±50.89	The extract showed a moderate cytotoxic effect against MCF-7 cancer cells.	(Nordin *et al*., 2019)
Tabebula chrysantha	Bignoniaceae	Pokok Trompet Mawar or Tecoma	Stem/ methanol (METC)	Naphthaquinones and polyphenol	Ehrlich Ascites Carcinoma EAC	NA	The extract showed a direct cytotoxic effect on EAC cell lines.	(Panda *et al*., 2019)
Tarenna asiatica	Rubiaceae	River tarenna	Whole plant/ethanol	Phenolic and flavonoids	Lung cancer cell line A549	NA	The extract showed high anticancer activity range between 60-67% on lung cancer cell lines.	(Manojj *et al*., 2020)
Terminalia catappa	Combretaceae	Ketapang	Leaves/ hexane and methanol	Phenolic, flavonoid, terpenoid, saponin, alkaloid, and glycoside	HepG2 cell line	26.6	Methanol extract showed moderate cytotoxic activity against the HepG2 cell line.	(Vyn *et al*., 2020)
Urgenia grandiflora	Annonaceae	Akar larak or akar mempisang	Bulb/ chloroform and methanol	Cardiac glycosides, flavonoids, tannin, alkaloids, saponins, terpenes, and sterol	Invasive breast cancer MCF-7, colorectal carcinoma HCT116, and human hormone resistance breast cancer MDA-MB-231 cell lines	10.91 and 50	The extract showed a high cytotoxic effect against the MCF-7 cell line. The extract also showed a moderate cytotoxic effect against HCT116 and MDA-MB-231 cell lines.	(Bashir *et al*., 2019)

Table 1. *Continued...*

Vernonia amygdalina	Acanthaceae	Pokok afrika or bitter leaf	Leaf/ Methanol	NA	Uterine (MES-SA/Dx5) cell line	269.2± 32.7	The extract showed a weak antiproliferative activity against uterine cancer cell lines.	(Siew *et al*., 2019)
Vitex trifolia	Lamiaceae	Halban or legundi	Leaf/ methanol, ethanol, and water	NA	Liver (SNU-182, SNU-449. HepG2), ovarian (PA-1, OVCAR-5), cervical (C33A), breast (MDA-MB0231, T47D)	20 to 50	The extract showed strong or moderately strong antiproliferative activity against all cancerous cell lines.	(Siew *et al*., 2019)
Xylocarpus granatum	Meliaceae	Nyireh or nyireh bunga	Leaves/ethyl acetate	Succinic acid, acetic acid, flavonoids, and phenolic	HT-29, HeLa, and T47D cancer cell lines	23.12	The extract with fraction 5 showed a moderate cytotoxic effect against HT-29 cell lines.	(Darmadi *et al*., 2021)

Table 1. *Continued...*

Xylopia aromatica	Annonaceae	Jambar surai, jangkang, or kayu tapis	Leaves/ hexane (XaHF)	Phenolic acid, flavonoids, and alkaloids	Ehrlich ascites carcinoma cells lines (EAC)	NA	The XaHF extract showed weak cytotoxic properties on EAC cell lines.	(Mainasara *et al.*, 2021)
Zanthoxylum rhetsa	Rutaceae	Kayu lemah	Pericarp/ phosphate buffer saline	NA	MCF-7, MDA-MB-231, HeLa, and HCT116	21.5	Fraction 3 of *Z. rhetsa* showed a moderate cytotoxic effect against MCF-7 cells.	(Parrikar *et al.*, 2021)
Zea mays	Poaceae	Jagung	Corn/ Ethanol	Tannins, saponins, flavonoids, glycosides, and steroids	SK-MEL-28 cell line	100	The extract showed a cytotoxicity effect against SK-MEL-28 cell lines.	(Abirami *et al.*, 2021)
Zingiber zerumbet	Zingiberaceae	Lempoyang or lampunyang	Rhizomes/dimethyl sulfoxide (DMSO)	Zerumbone (ZER)	Anti-human Burkitt's lymphoma (Raji) cell	5.1	ZER showed an antiproliferative effect against the Raji cell and causes late apoptosis.	(Albaayit, Khan, & Abdullah, 2021)

Table 2. The medicinal plants considered to possess anticancer activity based on *in vivo* studies

Scientific name	Family	Local name	Part/solvent used	Dose of extract (mg/kg)	Experimental animal	Results	Ref.
Alpinia zerumbet	Zingiberaceae	Lengkuas	Flower/methyl hydroxide (MeOH) and dichloromethane (CH_2Cl_2)	250	Adult female Swiss albino mice	*A. zerumbet* extracts with MeOH and (CH_2Cl_2) exhibited significant inhibitory activity towards tumor volume (TV).	(Zahra *et al*., 2019)
Ananas comosus	Bromeliaceae	Nanas	Fruit/pineapple vinegar	0.08 to 2 ml/kg	BALB/c mice	The extract showed a reduction of tumor weight and volume by 45%. It also downregulates the inflammation-related gene, metastasis-related gene, and angiogenesis-related genes.	(Mohamad *et al*., 2019)
Ardisia crispa	Primulaceae	Mata ayam or mata itik	Root/hexane (ACRH)	10 µg/mL	Human umbilical vein endothelial cells (HUVECs)	ARCH extract showed antiproliferative at higher concentrations, inducing apoptosis, migration, invasion, and differentiation in cancer cells.	(Wen Jun *et al*., 2019)
Clinacanthus nutans	Acanthaceae	Sabah snake grass or belalai gajah	Leaves/methanol	200 and 1000	4T1 tumor-bearing mice or BALB/c mice	Extract of 1000 mg/kg showed a significant decrease in the number of mitotic cells, tumor weight, and tumor volume.	(Nik Abd Rahman *et al*., 2019)
Cucurma zedoaria	Zingiberaceae	Kunyit putih	Rhizome/ethanol	100, 200, and 300	White Wistar rats	All doses administered showed a decreased in the mitosis count.	(Xavier *et al*., 2019)
Eurycoma longifolia	Simaroubaceae	Herbal tea (Tongkat Ali tea)	Stem/ethanol (EL)	100, 200, and 400	Sprague-Dawley (SD) rats	Extract of all doses showed significantly reduced serum and plasma uric acid levels in rats, increased uric acid and creatinine clearance rate, and improved renal pathological injury.	(Bao *et al*., 2019)

Table 2. *Continued...*

Labisia pumila	Myrsinaceae	Kacip Fatimah	Whole plant/ethanol	200 and 400	Athymic mouse model	Both doses administered showed a significant reduction in tumor volume. No significant reduction in the body weight of mice was recorded.	(Zakaria *et al*., 2020)
Lignosus tigris	Polyporaceae	Cendawan susu rimau	Mushroom sclerotium/ cold water	5	Athymic NCR nude mice	The dose administered showed expression of caspase-8 and -9 enzymes, and pro-apoptotic Bax protein while inhibiting expression of tumor survival protein, Bcl-2. It also induces tumor-cell apoptosis and suppresses the growth of tumors in mice.	(Kong *et al*., 2020)
Mesua ferrea	Calophyllaceae	Nagacuram or nagasari	Whole plant/ n-hexane (RH)	100 and 200	Athymic NCR nu/nu nude mice	A dose of 200 mg/kg showed a more potent antitumor effect on cancer cells than a dose of 100 mg/kg. Resulting in a reduction in viable tumor cells and several intratumor blood vessels.	(Asif *et al*., 2019)
Morus latifolia	Moraceae	Buah mulberi or kertau or bebesaran	Leaf and bark/ Methanol	50, 100, and 200	Swiss albino mice with EAC cells	Dose extract from the leaf showed higher inhibition of EAC cell growth than dose extract from the bark.	(Islam *et al*., 2020)
Orthosiphon aristatus	Lamiaceae	Misai kucing	Whole plant/ethanol	200 and 400	Athymic nude mice	The extract showed a reduction in cell cancer cell growth.	(Yehya *et al*., 2019)
Piper methysticum	Piperaceae	Kava	NA	1 and 3	HCT 166 cell line bearing BALB/c nude mice	The flavokawain C (FKC) extracted from the plant showed a reduction in tumor growth rate.	(Phang *et al*., 2021)
Strobilanthes crispus	Acanthaceae	Pecah kaca, pecah batu, or jin batu	Leaves and stems/ stem hexane extract (SH)	100	Balb/c tumor-bearing mice	The doses administered showed a significant reduction of physical tumor growth in tumor-bearing mice.	(Baraya *et al*., 2021)

Table 2. *Continued...*

Tabebula chrysantha	Bignoniaceae	Pokok Trompet Mawar or Tecoma	Stem/ methanol (METC)	300	Swiss albino mice	The EAC-treated mice showed a decrease in tumor volume, tumor weight, and viable cell count.	(Panda *et al*., 2019)
Xylopia aromatica	Annonaceae	Jambar surai, jangkang, or kayu tapis	Leaves/ hexane (XaHF)	32.2	Swiss mice	XaFH extract showed a growth suppression with a significant decrease of 46% in tumor volume.	(Mainasara *et al*., 2021)
Zanthoxylum rhetsa	Rutaceae	Hantu duri	Pericarp/ phosphate buffer saline	25	Swiss albino mice	The dose administered showed a decrease in tumor weight. It also blocks the cell in the G2/M phase of the cell cycle.	(Parrikar *et al*., 2021)

CONCLUSION

Previous studies provided detailed information about the plant, such as phytochemical or active constituents, pharmacological properties, and their mechanisms of action as anticancer agents. This review demonstrates the potential of Malaysia medicinal plants as anticancer agents in which, *Senna alata* (Gelenggang), *Morinda citrifolia* (Mengkudu), and *Ardisia crispa* (Mata Ayam) exhibited potent cytotoxicity *in vitro*. On the other hand, *Piper methysticum* (Kava), *Lignosus tigris* (Cendawan susu rimau), and *Zanthoxylum rhetsa* (Hantu duri) were found to possess anticancer activity *in vivo* against several experimental animal models with minimal adverse effects. Phytochemical and pharmacological studies revealed that the diverse chemical groups of naturally occurring substances in plants show promising anticancer activity. Therefore, this review suggests further research need to be carried out on the bioactive compounds present in Malaysian medicinal plants which have not been analyzed for their potential to treat cancer and the underlying mechanisms of anticancer.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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