InaJCC The Indonesian Journal of Cancer Control

Review Article

# Potential of herbal medicines in cancer therapy

*Riki Nova[1], Aida SD Hoemardani[2], Melva Louisa[3*]*



p-ISSN 2797-4189
e-ISSN 2797-457X
DOI : 10.52830/inajcc.v1i1.44

Received: June 15, 2019
Accepted: September 01, 2020

**Authors' affiliations:**
[1] Clinical Pharmacology Study Program, Faculty of Medicine Universitas Indonesia / Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[2] Medical Staff Group of Dermatology and Venereology, Faculty of Medicine Universitas Indonesia / Dharmais National Cancer Hospital. Jakarta, Indonesia
[3] Department of Pharmacology and Therapeutics, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

**Corresponding author:**
Melva Louisa
E-mail: melva.louisa@ui.ac.id

## Abstract

Herbal medicines have long been used for traditional treatment of diseases. Our ancestors used plants empirically as treatment and for the maintenance of health inherited from generation to generation. At present, most of the research and development of drugs is still focused on a single compound as the main compound against the treatment target. It is difficult to get a single compound chemical with high selectivity and potential but low toxicity to the target of the disease. Empiric treatment with medicinal plants is particularly a concern in cancer treatment, where treatment is currently done with chemotherapy, radiotherapy, and surgery. The active compound of herbal plants is one alternative in searching for a new anti-cancer because it is believed to have minimal side effects. Therefore, the design and development of anti-cancer drug candidate from herbal plants are increasingly in demand.

***Keywords:*** *cancer, herbal medicines*

## Abstrak

Obat herbal telah lama dimanfaatkan untuk terapi penyakit secara tradisional. Sejak zaman nenek moyang, masyarakat kita menggunakan tumbuhan sebagai pengobatan maupun untuk pemeliharaan kesehatan yang diwariskan secara turun temurun. Saat ini, sebagian besar penelitian dan pengembangan obat masih berfokus pada bahan senyawa tunggal sebagai senyawa utama terhadap target pengobatan suatu penyakit. Sulit mendapatkan bahan kimia senyawa tunggal dengan selektivitas dan potensi tinggi, namun dengan toksisitas rendah terhadap target suatu penyakit. Hal ini turut menjadi perhatian dalam mengatasi penyakit kanker, dimana penanganan saat ini dilakukan dengan kemoterapi, radioterapi, dan pembedahan. Senyawa aktif tanaman herbal merupakan salah satu alternatif dalam pencarian anti kanker baru karena dipercaya memiliki efek samping minimal. Oleh karena itu, desain dan pengembangan kandidat obat anti kanker dari tanaman herbal semakin diminati.

***Kata kunci:*** *kanker, tanaman herbal*

## Background

Herbal medicine has long been used for traditional therapy. Our society used plants as medicine and health care passed down from generation to generation. Indonesia Basic Health Research (Riskesdas) 2018 shows that the proportion of traditional health services utilization has increased from 30.4% (Riskesdas 2013) to 31.4%.[1] WHO Traditional Medicine Strategy 2014-2023 has agreed to promote and utilize traditional medicine's safety and efficacy, besides giving recommendations on conventional medicine to maintain health, prevent and provide treatment of chronic disease, especially for cancer.[2,3] Thus, the position of herbal plants is crucial in improving public health. Nowadays, plenty of research and drug development still use staple material as the main objects for targeted therapy of disease. It is difficult to obtain single compound chemicals with high selectivity and potency but low toxicity to the target.[4] This is also a concern in overcoming cancer. Active herbal plant compounds are alternative for new anti-cancer due to minimal side effects.

Cancer is a disease caused by abnormal and uncontrolled cell growth and damages or metastasize to other parts of the body.[5] Cancer is still a world health problem which number is estimated to continue to increase. The Global Cancer Statistic (GLOBOCAN) 2018 showed 18.1 million new cases and 9.6 million deaths caused by cancer.[6] Data from Riskesdas 2018 reported that the prevalence of cancer in Indonesia increased from 1.4% (347,792 people) in 2013 to 1.8% (348,809 people).[1,7] In its development, medical cancer treatment now possible in various ways, including operative therapy, chemotherapy, radiation therapy, bone marrow transplantation, immunotherapy, and hormonal therapy.[8] The difficulty in cancer therapy results from cancer cells originating from the body's cells, causing its character to uncontrolled growth.[8] Thus, any treatment aimed at cancer cells will affect normal body cells, which will cause various kinds of side effects.

The active compound of herbal plants is an alternative as a substitute for medical treatment. This alternative therapy is assumed to treat using simple treatment methods and minimal side effects. For the community to receive truly beneficial treatment, it is necessary to carry out structured and measured methods such as clinical trials. The clinical trials could provide evidence that the same treatment will achieve the same results wherever treatment is established. Several herbal plants have currently been proven as anti-cancer.[3] The literature searching on several herbal plants and compounds that have anti-cancer properties is discussed below.

## Rosella (*Hibiscus sabdariffa*; Malvaceae family)

Rosella, roselle, brackish acid, beetle acid, and tamarind or *Hibiscus sabdariffa* are flower species originating from the African continent. The petals, also known as *natal sorrel,* are often used as jelly, jam, juice, syrup, gelatin, pudding, cake, ice cream, and flavor. Its bright red color and unique taste make it becomes a valuable food product. The juice of the flowers is used as a health-enhancing drink due to its high antioxidant content, for instance, vitamin C and anthocyanins. The most nutritious part of the plant is the flower. Steeping rosella flowers has the effect of facilitating bowel movements.[9]

The main bioactive contents of Rosella related to its pharmacological effects consist of organic acids, anthocyanins, polysaccharides, and flavonoids. Rosella extract contains high organic acid compounds, namely citric acid, hydroxy-citric acid, hibiscus acid, malic acid, tartaric acid, oxalic acid, and ascorbic acid.[10]

Rosella is rich in phenolic compounds, such as protocatechuic acid. *In vitro* studies of Rosella in hepatocytes demonstrated an inhibitory effect on free radicals. Rosella also showed protective effects against the cytotoxic and genotoxic effects of tert-butyl-hydroperoxide (t-BHP), inhibiting DNA synthesis. Rosella also inhibited the formation of skin tumors induced by 12-O-tetradecane-olyphorbol-13-acetate (TPA) through experiments on mice and inhibited the growth of the promyelocytic leukemia cancer cell line, HL60. The anti-cancer mechanism of rosella is thought to reduce oxidative stress, DNA fragmentation and increase apoptosis in G1. Apoptotic activity is associated with phosphorylation and degradation of RB also suppression of Bcl-2 protein. A similar effect was observed in gastric cell carcinoma, where the apoptotic effect was mediated via p53 signaling and the MAPK/FasL pAP cascade pathway. The anthocyanin in roselle, delphinidin-3-sambubioside, is known to induce apoptosis against human leukemia cells through the p38-FasL and Bid pathways. Anthocyanin also induced mitochondrial dysfunction pathway, mediated by ROS and the pathway to smooth muscle cells (SMC) via the p38 and p53 pathways. In vitro and *in vivo* demonstrated the

antiapoptotic effect of roselle leaf extract on human prostate cancer cells, which were mediated by both intrinsic (Bax / cytochrome c-mediated 9) and extrinsic (caspase 8/t-Bid mediated by Fas) pathways. *In vivo*, rosella leaf extract inhibited the growth of prostate xenograft in mice.[10]

Rosella flowers are also widely used as antioxidants because of their polyphenol content, namely anthocyanins.[11]

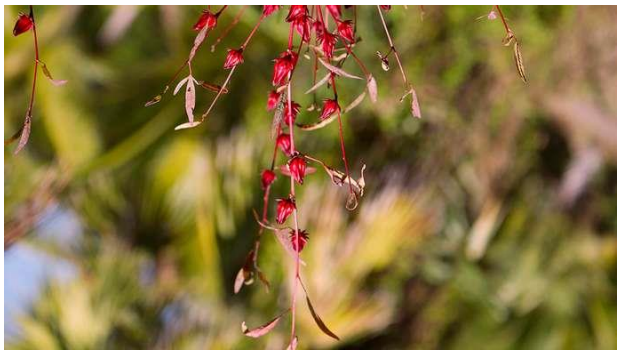

**Figure 1**. Rosella (*Hibiscus sabdariffa*; Malvaceae family).[12]

## Temulawak (*Curcuma xanthorrhiza* Roxb; Zingiberaceae family)

Temulawak, including the Zingiberaceae family, is the rhizome and is a native plant of Indonesia. Temulawak is found commonly in tropical forests. Temulawak is used to treat various stomach complaints and liver disorders (jaundice, gallstones, increased bile flow). The main phytochemical compounds of temulawak are curcumin and xanthorrhizol.[10] Curcumin, as the active compound of temulawak, is known to modulate the growth and cellular responses of various cell types involved in the immune system. Some of the research reports show that curcumin can regulate the proliferation and activation of T lymphocytes. Also, curcumin can increase the number of B lymphocytes. Curcumin in ginger can increase macrophage activity and affect antigen presentation by Antigen Presenting Cells (APC), suppressing costimulatory molecular expression: CD80, CD86, and Major Histocompatibility Complex (MHC) class II but not MHC class I expression. Curcumin also plays a role in dendritic cell regulation by reducing the production of IL-12, IL-1β, IL-6, and TNF-α. In the humoral immune response, temulawak increases IgM production at low doses and inhibits IgG and IgM production at high doses.[13]

Xanthorrhizol is the most active compound isolated from the essential oil of *Curcuma xanthorhizza* Roxb rhizome. Several previous studies found that xanthorrhizol has antimicrobial, anti-inflammatory, antioxidant, antihyperglycemic, antihypertensive, antiplatelet, nephroprotective, and hepatoprotective activities.[8,14] The molecular and cellular mechanisms of the anti-cancer effect of xanthorrhizol are to suppress the potential for carcinogenesis. Xanthorrhizol exerts its anti-cancer mechanism by modulating various rates of cell growth and apoptosis of cancer cells. The morphology of apoptosis is usually characterized by DNA fragmentation, cell shrinkage, elongated lamellipodia, and chromatin condensation. Concurrently, the anti-cancer activity of xanthorrhizol is shown to be closely related to antioxidant and anti-inflammatory effects, induction of apoptosis, and cessation of the cell cycle.[15]

A randomized clinical trial by Rahmayunita et al. in 2018 reported that administering 1% *Curcuma xanthorrhiza* ointment compared to placebo in mild psoriasis patients aged 18-59 years assessed by the Trozak score shown significant results. However, there was no significant difference in the assessment with the expression K6 and PASI (Psoriasis Area Severity Index) of 0.520. Based on the above results, administration of 1% *Curcuma xanthorrhiza* ointment in mild psoriasis is more effective than placebo but requires further research. No side effects emerged during the study.[16]

**Figure 2.** Dried and broken rhizome of Temulawak (*Curcuma xanthorrhiza* Roxb; Zingiberaceae family).[17]

## Garlic (*Allium sativum*; Liliaceae family)

Garlic (*Allium sativum L.*) is one of the plants used for centuries to fight infectious diseases. In ancient times the Egyptians used garlic to treat diarrhea. In Japan and China, people use garlic to treat headaches, flu, sore throats, and fevers. In Africa, especially in

Nigeria, it is used to treat stomach discomfort, diarrhea, otitis media, and respiratory infections. In Europe and India, it is used to treat colds, hay fever, and asthma. Garlic is nicknamed Russian penicillin due to its wide use as a topical and systemic antimicrobial agent.[18]

Garlic consists of 0.1% essential oil. This oil is rich in sulfur but does not contain oxygen. The main constituents of essential oils are diallyl disulfide (60%), diallyl trisulfide (20%), allyl propyl disulfide (6%), small amounts of diethyl disulfide, and possibly diallyl polysulfide. These sulfur compounds contribute to the aroma and taste of garlic. The active properties of garlic are due to this aromatic essential oil. Garlic consists of 84.09% water, 13.38% organic matter, and 1.53% inorganic material. There are 20 types of sulfide compounds in garlic, such as allicin, methyl allyl trisulfide, and diallyl trisulfide. There are seven organosulfur compounds, such as allicin, iso-allicin, methionine, cyclo-allicin, and gamma-l-glutamyl-S-methyl-l-cysteine are also determined in it.[19-21] Allicin is the main ingredient of garlic which is chemically active and provides a therapeutic effect. Allicin is released only by crushing or chewing raw garlic and cannot be formed by heating. Allicin opens a potential channel for transient thermoreceptors (TRPA1) and TRPV1 (Transient receptor potential vanilloid 1), which play a role in the sensation of heat in raw garlic. The non-sulfur compound in garlic, phytoalexin (allicin), can be effective in cancer prevention.[22]

The anti-cancer effect of garlic is associated with stimulating immune effector cells, including T-cells and natural killer cells. Several epidemiological studies, clinical and laboratory studies have shown that garlic has a significant role in preventing gastrointestinal cancer. Population studies show that garlic's regular consumption reduces the risk of cancer of the pharynx, stomach, and colon. This is due to allicin's antioxidant effect in reducing the formation of carcinogenic compounds in the digestive tract. A study in a cohort study in the Netherlands found a significant reduction in gastric cancer development in a population consuming garlic. Garlic can also reduce the risk of prostate cancer. Men with high garlic consumption (equivalent to garlic intake >10.0 g/day) had a lower risk of prostate cancer. An epidemiological study in America analyzed 127 dietary intakes (including 44 vegetables and fruit) in 41,387 women (ages 55-69) was followed for five years for colon cancer incidence. The most striking results found were that garlic was the only food that showed a statistically significant association with a reduced risk of colon cancer. For colon cancer consuming one or more servings of garlic (fresh or powdered) per week resulted in a 35% lower risk of cancer, while distal colon cancer risk was shown to be 50% lower.[21, 23-24]

**Figure 3**. Garlic (*Allium sativum*; Liliaceae family)[25]

## Sambiloto (*Andrographis paniculata*; Acanthaceae family)

Sambiloto (*Andrographis paniculata*) contains the active compound andrographolide, a potential cancer therapy agent. *Andrographis paniculata* plant extract is known to have various pharmacological activities. Andrographolide, the main integral of the extract, has pharmacological activities. Some cellular processes and targets are modulated by andrographolide in cancer cells and immune cells.[26] Andrographolide treatment inhibits the in vitro proliferation of tumor cells in various cancer cell strains. This compound provides direct anti-cancer activity on cancer cells by stopping the cell cycle in the G0 / G1 phase through induction of the p27 cell cycle, impeding protein, and decreasing the expression of cyclin-dependent kinase 4 (CDK4).[27] The immunostimulant activity of andrographolide is shown by an increase in lymphocyte proliferation and production of interleukin-2. Andrographolide also increases tumor necrosis factor (TNF) alpha and CD marker expression, resulting in increased lymphocyte cytotoxic activity against cancer cells, contributing to its anti-cancer activity indirectly. Andrographolide demonstrated anti-cancer activity in melanoma cell lines, B16F0, and HT-29 xenograft models. The results from the study indicate that andrographolide is a potential pharmacotherapeutic agent with have anti-cancer and immunomodulatory effects. Therefore, it has the potential to be developed as a cancer therapeutic agent.[28]

*Andrographis paniculata* is also known to have chemoprotective effects in mice induced with colorectal

cancer. Ethanol extract *A. paniculata* was tested on aberrant crypt foci (ACF) induced with azoxymethane (AOM) *in vivo* and *in vitro*. The treatment group given *A. paniculata* showed a significant reduction in the number of ACF-treated mice. Microscopically, ACF showed highly elongated and stratified cells and thinning of the submucosal glands in the untreated AOM-induced group compared with the treated group. Histologically, the stain shows a mass slightly elevated above the surrounding mucosa with an oval or slit-like opening. Immunohistochemically, *A. paniculata* extract inhibits the expression of proliferating cell nuclear antigen (PCNA) and β-catenin protein. A. paniculata also reducing the levels of malondialdehyde (MDA) and nitric oxide (NO).[29]

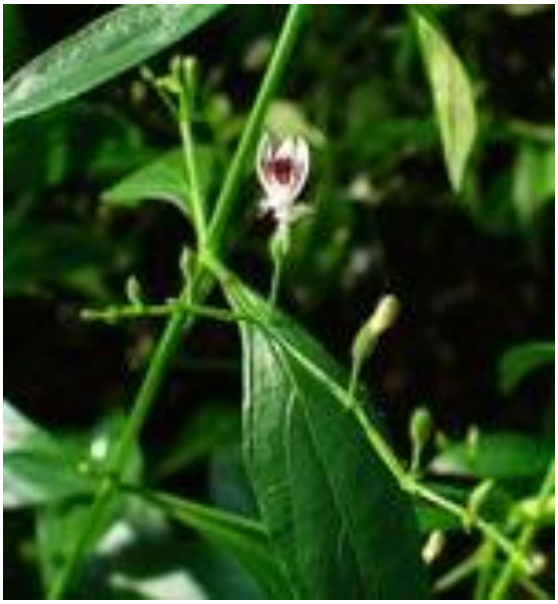

**Figure 4.** Sambiloto (*Andrographis paniculata*; Acanthaceae family)[30]

## Ginseng (*Panax ginseng*; Araliaceae family)

Ginseng extract has been reported to have gastro-protective activity, suppress allergic inflammatory factors such as interleukin (IL)-4 and IL-5, and suppress TNF-α and IL-8 expression lipopolysaccharide-induced HaCaT cells. Saponins isolated from Korean red ginseng were reported to suppress NO production, levels of mRNA NO synthase, interferon-β, COX-2, and inhibit transcription activation of cAMP response element-binding proteins, activate transcription factor 2, and regulate interferon regulation factor-3 in lipopolysaccharide-induced macrophage. *In vivo* anti-cancer research of wild Korean ginseng (joboksansam) shows the cytotoxicity effect of this drug. Ginseng and the compounds found in it, namely compounds K, Rh1, G-F2, G-Rg3, and G-Rp1, have anti-proliferative and anti-cancer properties.[31,32]

A recent study using sun ginseng, with a specific formulation of red ginseng containing the same amount of major ginsenosides (RK1, Rg3, and Rg5), showed a significant increase in cancer death caused by epirubicin or paclitaxel in cervical cancer HeLa cells, adenocarcinoma cells, and colon cancer cells.[32]

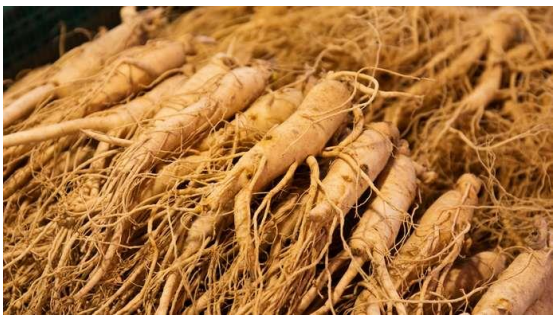

**Figure 5**. Ginseng (*Panax ginseng*; Araliaceae family).[33]

## Pepper (*Piper nigrum*; Piperaceae family)

Ten species of pepper were reported to have anti-cancer effects or cancer-like symptoms. In Mexico, *Piper aduncum L.* is traditionally used to treat urological problems, dermatological conditions, and skin tumors. The dichloromethane extract of *P. aduncum* leaves is cytotoxic against glioma (SF-268), against lung carcinoma (H-460), and breast carcinoma (MCF-7). Piperaduncin A showed inhibitory activity of naso-pharyngeal carcinoma (KB) cell growth (IC50=2.3 µg/ml). Recently, a cytotoxic amide alkaloid compound, 1-[(9E)-10–(3,4-methylenedioxyphenyl)-9-desenoyl] pyrrolidine, was isolated from the whole *Piper boehmeriifolium* plant, showing its effect on cervical cancer cell lines (IC50 = 2.7 µg/ml). Extracts from *Piper aduncum L*, *Piper barbatum Kunth, Piper fragile Benth, Piper jacquemontianum Kunth*, and *Piper pellucidum L*. have high potency at least in cancer cell lines with IC50 values less than 4 µg/ml.[34-36]

Several piper compounds have been studied for their antitumor activity *in vivo*, including Piplartin and flavocawaine B, which showed a significant inhibitory effect on the growth of at least a tumor model *in vivo*, a dose of 15 mg/kg. Piplartine contained in Piper longum fruit is about 0.11%. This compound kills cancer cells in response to oxidative stress as a target. Piplartine induces apoptosis selectively in cells with cancer genotypes by targeting non-

oncogenic co-dependencies obtained through the expression of cancer genotypes to oxidative stress responses. Piplartine can target p38 signaling to cause selective cell death and autophagy. The results showed that the anti-cancer activity of piperine involved inhibiting the ubiquitin-proteasome system at the pre-proteasomal stage and inducing the formation of ROS.[34,37]

Piplartine can reduce Epstein-Barr virus-encoded membrane protein 1 (EBV-encoded LMP1), cellular myelocytomatosis oncogene (myc), NF-kB activity, and several LMP1-Myc-NF-kb, which are regulated by target genes, while LMP1-NF-kB-Myc plays a role in B-lineage neoplasia. Piplartin-dependent cytotoxicity is influenced in part by reduced NF-kB and myc activity. Piplartin induces a rapid decrease in androgen receptors on prostate cancer cells. As a result, piperine provides new opportunities for the prevention and treatment of prostate cancer malignancies. Piperine can act on the mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) pathway that causes colon cancer cell death.[34,37]

Piperine is the main component of black pepper (*Piper nigrum* and *Piper longum*). The piperine content in black pepper varies between 5% and 9%. Piperin can inhibit the expression of fibrosarcoma cells (HT-1080) from matrix metalloproteinase (MMP)-9, thereby interfering with tumor cell migration and invasion. It inhibits overexpression of the HER2 gene at the transcription level, which can prevent and treat breast cancer. Piperine-induced cytotoxicity against rectal tumor cells (HRT)-18 was done partly via ROS. Piperine also exerts an anti-proliferative effect on prostate cancer cells by inducing autophagy.[34-36]

Kava (*Piper methysticum* Forst.) is an annual plant grown in the Pacific islands. Some data show that the more kava consumed by a population, the lower the incidence of cancer in that population. Flavocawain B, containing 0.015% kava extract, can be a remarkable anti-proliferative agent against various cancer cells. Flavocawain B is known to induce apoptosis through mitochondrial pathways and receptor death. Flavocawain B also has a pro-apoptotic effect on the synovial sarcoma cell line. Flavocawaine B also induces apoptosis of non-small cell lung cancer H-460 via Bax-initiating mitochondria and c-Jun N-terminal kinase (JNK). In osteosarcoma cell lines, flavocawain B induces apoptosis involving extrinsic and intrinsic pathways. Flavocawain B also causes cell cycle arrest of the G2 / M phase.[34]

**Figure 6**. Black pepper (*Piper nigrum*; Piperaceae family) [38]

## Black Cumin (*Nigella sativa* L; Ranunculaceae Family)

*Nigella sativa* (NS), or black cumin, is a plant from the Ranunculaceae family native to the Mediterranean and neighboring countries of Pakistan and India. In the Middle East, NS is included in the daily diet as a spice and preservative. Black cumin has been widely used for thousands of years to treat ailments, including asthma, high blood pressure, diabetes, inflammation, coughs, headaches, eczema, fever, dizziness, and influenza. Over the last five decades, many scientific studies have looked for the pharmacological effects of *Nigella sativa* as an anti-cancer.[39] Research by Agbaria et al. (2015) showed an anti-proliferative effect of *Nigella sativa* extract on mouse colon carcinoma cells (MC38). The results obtained were *Nigella sativa* seeds, which were processed by heating at high temperature, had a potent anti-proliferative effect. NS oil from heated seeds can inhibit transcription expression of NF-κB, which unheated seeds produce half the inhibition.[40]

Another study by Salim (2010) looked for the chemo-protective potential of *Nigella sativa* crude oil in mice with multi-organ carcinoma. In experiments on male Wistarjian rats given 1000 or 4000 ppm NS oil for 30 weeks, there was a significant reduction in the size of malignant and benign colon tumors, incidence, and their reproduction. This also occurs in the proliferation of tumor cells in the lungs, esophagus, and forestomach. The mechanism of tumor cell inhibition is probably related to the suppression of tumor cell proliferation.[41]

Meta-analysis on NS by Mollazadeh H et al. (2017) found that NS, which has levels of thymoquinone as its main bioactive element (about 50%), exerts an anti-cancer effect through the cell apoptosis mechanism. This causes upregulation of tumor suppressor proteins, namely p21 and p53, followed by Bcl-2 inhibition, caspase-3, -8, -9 activation, and increased Bax / Bcl-2 ratio.[42]

**Figure 7**. Black Cumin (*Nigella sativa* L; Ranunculaceae Family)[43]

## Soybean (*Glycine max* (L.) Merr; Fabaceae family)

Soybean or *Glycine max*. (GM) is included in the Leguminosae family, contains isoflavones as anti-oxidants. A study by Pratama et al. (2015) looking for the antimitotic effect of hydrolyzed GM extracts. The extract was obtained from the maceration process of soybeans using ethanol, followed by a hydration process using hydrochloric acid. The results of this soybean hydrolysis extract were then tested against sea urchin zygote cells (*Tripneustes gratilla* Linn) *in vitro*. They found cytotoxic, teratogenic, and anti-neoplastic activities. This study describes how GM can be a prototype to be developed as an anti-cancer.[44]

Research by Wang et al. (2018) found the inhibitory effect of human breast cancer cell lines after GM administration. This study used two human breast cancer cell lines, MCF-7 and MDA-MB-231, administered with soybean extract. The results showed that soybean extract had a significant effect on suppressing the growth of MCF-7 and MDA-MB-231 ($P < 0.05$) depending on the dose.[45]

**Figure 8.** Soybean (*Glycine max* (L.) Merr; Fabaceae family)[46]

## *Keladi tikus* (*Typhonium flagelliforme*; Arecaceae family)

*Typhonium flagelliforme* (Lodd.) Blume (Araceae) is a plant from Malaysia often used to treat cancer. Bioactivity studies were done to evaluate the anti-proliferative activity of the plant and identify active chemical constituents. The active extract of *Typhonium flagelliforme* was fractionated using chromatography. Each fraction assessed for its anti-proliferative activity using the MTT assay. The apoptotic effect of this active fraction was studied microscopically and evaluated using the TUNEL colorimetric test.[47]

Several hexanes and dichloromethane extract fractions were found to inhibit the growth of NCI-H23 pulmonary carcinoma cells significantly. However, most of these fractions were also found to inhibit the growth of BALB/c 3T3 rat non-tumorigenic fibroblast cell lines, except for fraction 21 of dichloromethane extract (D/F21). This fraction and being less cytotoxic against non-tumorigenic cells, with strong IC50 values and can induce apoptosis in the cancer cell line. GC-MS analysis revealed that D/F21 contained hexadecanoic acid, 1-hexadecane phytol, and phytol derivatives. Unsaturated fatty acids were also found in this fraction and were confirmed by nuclear magnetic resonance spectroscopy. So that D/F21 functions as a specific and active *Typhonium flagelliforme* fraction on cancer cells.[47]

Another study showcased the use of *Typhonium flagelliforme* plant extracts. The extracts were able to significantly reduce telomerase expression in cancerous Raji cells and Vero cells. This showed that the *keladi tikus* extract (*Typhonium flagelliforme* Lodd) could reduce telomerase expression in Raji cells. All parts of the *keladi tikus* can be used to treat disease. This plant should be used fresh, processed into juice (plant extract), and drunk immediately after processing.[48]

**Figure 9.** *Keladi tikus* (*Typhonium flagelliforme*; Arecaceae family)[49]

## Green Betel (*Piper betle*; Piperaceae family)

*Piper betle* is a medicinal plant with many known biological activities. However, not much data is available on the anti-cancer effects of breast cancer. Abrahim et al. (2012) studied the antioxidant activity of *P. betle* leaves and their inhibitory effect on the proliferation of breast cancer cell line, MCF-7. The leaves of *P. betle* were extracted with various solvents (water, methanol, ethyl acetate, and hexane), then their phenolic and flavonoid contents were measured using a colorimetric test. The phenolic composition was then depicted using HPLC. Antioxidant activity was measured using FRAP, DPPH, superoxide anion, nitric oxide, and hydroxyl radical scavenging assays. The biological activity of this extract was then analyzed using the MTT and antioxidative assays in MCF-7 cells. Overall, the ethyl acetate extract showed Fe3+ reduction activity and free radical scavenging activity against DPPH, superoxide anions, and nitric oxide radicals. This extract also contains the highest phenolic content, making a potential contribution of phenolics to antioxidant activity. HPLC analysis revealed the presence of catechins, morin, and quercetin in the leaves. Ethyl acetate extract also showed the highest inhibitory effect on MCF-7 cell proliferation (IC50 = 65 µg/ml). Treatment of MCF-7 cells with this plant extract increased catalase and superoxide dismutase activity. These results concluded ethyl acetate extract from the *Piper betle* plant is a high potential source of natural antioxidants and can be developed into cancer therapy agents.[50]

Another study evaluated the methanol extract of *Piper betle* leaf (MPBL) and the effect of its organic fraction on Ehrlich ascites carcinoma (EAC) in Swiss albino rats. The extract was administered at 25, 50, and 100 mg/kg body weight of the mice for nine consecutive days to the subjected mouse. The antitumor effect of the extract was then assessed according to the tumor volume, the number of cells grafted, the number of viable and non-viable tumor cells, the survival time, and the life span of the mice containing EAC. The researcher then assessed the hematological profile, serum biochemical parameters, and antioxidant properties. The methanol extract of *Piper betle* leaves (MPBL) and the ethyl acetate fraction of *Piper betle* leaves (EPBL) at a dose of 100 mg/kg induced a significant reduction in tumor volume, the number of inoculated cells and the number of living cells, and an increase in the life span of mice containing EAC. The hematological and biochemical profiles of serum were able to return to normal values in extract-treated mice compared to EAC control mice. Administration of MPBL and EPBL significantly decreased lipid peroxidation, bringing GSH, SOD, and CAT levels closer to normal than EAC controls. These results indicate that the *Piper betle* extract showed significant antitumor activity.[51]

**Figure 10.** Green Betel (*Piper betle*; Piperaceae family)[52]

## Myrmecodia (*Myrmecodia pendens, Myrmecodia tuberosum, and Hydnophytum formicarum* Jack; Rubiaceae family)

Achmad et al. (2014) studied the effects of flavonoids from the Myrmecodia pendens fraction as anti-cancer through Akt signaling and inhibiting NF-KB in SP-C1 tongue cancer cells. The results showed that the cytotoxicity test had the highest concentration of 1000 µg/ml to the lowest concentration of 7.8125 µg/ml in the ethyl acetate, ethanol, hexane, and water fractions, which resulted in a significant percentage of SP-C1 tongue cancer cell death. The concentration of 1000 µg/ml ethyl acetate flavonoid fraction caused a cell death percentage of 64.60%. The lowest concentration of 7.8125 µg/ml caused cell death as much as 15.80%. The LC50 values of ethyl acetate fraction, ethanol fraction, hexane fraction and water fraction were 452.059 µg/ml respectively; 937,562 µg/ml; 2691,535 ug / ml; 12302.69 ug / ml. Analysis of the anti-proliferative flavonoid fraction and ethanol-based ethyl acetate fraction on the concentration and incubation time to absorb the powerful SP-C1 cells. These results indicate that the flavonoid fraction from myrmecodia has the potential to be anti-cancer in tongue cancer cells (SP-C1), a type of squamous cell carcinoma.[53]

Another study on myrmecodia plants by Soeksmanto et al. (2010) found that the anti-cancer activity of methanol extract (ethyl acetate, n-butanol, and water partition) and water extract. The extract tested for its activity in several cancer cells (HeLa and MCM-B2). The results showed that the water extract of this plant had superior anti-cancer activity than other extracts. The IC50 values of water extract A were 27.61 ppm (HeLa) and 54.57 ppm (MCM-B2), while water extract B was 29.36 ppm (HeLa) and 74.20 ppm (MCM-B2). Our study concluded that polar (water) extracts had higher anti-cancer activity than non-polar extracts (ethyl acetate and n-butanol).[54]

**Figure 11. Myrmecodia** (*Myrmecodia pendens*; Rubiaceae family)[55]

## Conclusion

In the existing new drugs rapid research development, herbal plants emerged as an option in cancer treatment. Several studies in this field have proven that herbal plants have various specific anti-cancer mechanisms. Some examples are rosella, ginger, garlic, sambiloto, ginseng, pepper, black cumin, soybean, taro rods, green betel, and myrmecodia. However, to this day, research on various herbal plants above is still limited to *in vitro* and *in vivo* tests. Randomized controlled clinical trials are needed to confidently prove the efficacy and benefits of numerous herbs in cancer therapy.

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