



Native Indonesian Herbs: Challenges in The Future for Anti-Cancer Drugs

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ABSTRACT

Indonesia has undoubtedly enormous biodiversity with great potential for drug discovery; however, its utilization is still very limited. Current available cancer treatments are still not really effective since they are rather invasive, has side effects, expensive, and not really specific. Researches start to focus on the natural-based anti-cancer drugs and lots of native Indonesian herbs have been scientifically identified to have anti-cancer properties. White turmeric, clove, ant plant, and rodent tuber plant are some of native Indonesian herbs that have been proven to have anti-cancer properties. This review is to demonstrate the anti-cancer properties of these potential native Indonesian herbs to be the future natural anti-cancer drugs and also to inspire the utilization of rich Indonesian biodiversity.

Keywords: Anti-cancer, cancer, *Curcuma zedoaria*, Indonesian biodiversity, *Myrmecodia pendens*, *Syzygium aromaticum*, *Typhonium flagelliforme*

ABSTRAK

Indonesia memiliki keanekaragaman hayati yang sangat melimpah dan berpotensi sangat besar untuk penemuan obat baru, namun pemanfaatannya masih sangat terbatas. Pengobatan kanker saat ini belum cukup efektif karena bersifat invasif, memiliki efek samping, mahal, dan tidak terlalu spesifik. Penelitian-penelitian mulai berfokus kepada obat anti-kanker alami sehingga pemanfaatan keanekaragaman hayati Indonesia menjadi sangat sesuai karena banyaknya tanaman herbal asli Indonesia yang telah teridentifikasi secara ilmiah memiliki kandungan anti-kanker. Kunyit putih, cengkeh, sarang semut, dan keladi tikus adalah beberapa tumbuhan herbal asli Indonesia yang telah terbukti memiliki kandungan anti-kanker. Tinjauan pustaka ini bertujuan untuk mendemonstrasikan potensi kandungan anti-kanker tumbuh-tumbuhan tersebut di masa depan dan juga untuk menginspirasi pemanfaatan keanekaragaman hayati Indonesia. **Dias Rima Sutiono, Malvel Mario Gabriel Reinald Salim, Nadya, Oniko Liani, Sylvania Susanto. Tanaman Obat Indonesia: Potensi untuk Obat Anti-Kanker**

Kata kunci: Anti-kanker, *Curcuma zedoaria*, kanker, *Myrmecodia pendens*, sumber daya alam Indonesia, *Syzygium aromaticum*, *Typhonium flagelliforme*

INTRODUCTION

Indonesia, with more than 17,000 islands, is undeniably rich in both land and marine biodiversity as approximately 15% of world's species live in its various rainforest and marine ecosystems.¹ Nonetheless, as estimated by Indonesian Ministry of Environments, more than half of the total Indonesian species are still unidentified and unrecorded.² Whereas Indonesian biodiversity has a great potential for drug discovery, especially for diseases that have no known cure.

Cancer is one of the diseases that needs to be urgently solved, as cancer cases keep on increasing. World Health Organization (WHO) has predicted that cancer cases will escalate rapidly within the next 2 decades, from 14 million in 2012 to 23.6 million of new cases

worldwide in 2030, which means there will be approximately 68% more cases emerging in 2030 compared to 2012, if the effective cure is not yet discovered.³

Currently, surgery, chemotherapy, and radiation therapy are the most common treatments used nowadays.⁴ Nonetheless; these three treatments involve a rather invasive approach and often causes side effects. There is other alternative treatment available that are safer and much more effective, which is precision medicine.⁵ It is designed to only specifically target affected cells; therefore, possible side effects can be greatly reduced. But this treatment is still very rare and only opulent individuals can afford this treatment due to its high cost.⁵

People also focus on the discovery and utilization of natural-derived anti-cancer drugs because it has fewer side effects and more affordable.⁶ Indonesian herbs have been scientifically studied by scientists and they display anti-cancer properties.⁶ These observation and determination of anti-cancer properties in Indonesian biodiversity are one of the small steps to find natural anti-cancer drugs.

This review aimed to summarize the findings of several Indonesian native herbs, which are white turmeric, clove, ant plant, and rodent tuber plants, that have been proven to have anti-cancer property as promising candidate for anti-cancer drugs and also to encourage the utilization of Indonesian biodiversity.



White Turmeric

White turmeric, scientifically identified as *Curcuma zedoaria*, or more commonly known as *kunyit putih* in Indonesia, is among one of the native Indonesian herbs that is known to possess anti-cancer property.¹¹ It is often used as food flavorings in Indonesian dishes such as in curry. White turmeric is also produces a bright yellow orange color and used as a natural food coloring agent. The health benefits of white turmeric had been known for ages and is passed down from generation to generation; according to traditional belief, white turmeric is known to be effective in treating diarrhea, allergies, menstrual disorders, vomiting, dyspepsia, and cancer.¹²

For the past few years, white turmeric is garnering interest due to its so-called anti-cancer properties. In 2007, a group of scientist in America conducted research to find out whether this particular herb possesses the ability to prevent cancer spread. The study was conducted in mice infected with breast cancer, it is discovered that white turmeric indeed stops the spread of breast cancer cells.⁷ Another group of scientist conducting a similar research, conclude that action was due to the anti-proliferative effect of white turmeric, which can prevent metastasis.⁸

Lakshmi, *et al*, conducted a similar study on the inhibition of cancer cell growth using white turmeric on multiple cell lines, including Dalton's lymphoma ascites (DLA), adenocarcinomic human alveolar basal epithelial cells (A549), myelogenous leukemia line (K-562) and subline of the ubiquitous KERATIN-forming tumor cell line HeLa (KB cells). This is done to determine the sensitivity of white turmeric on each cell lines and to identify the effectivity on each individual cells. The extract used here was the CZ-PC (*Curcuma zedoaria* Purified compound), isocurcumenol. The outcome shows that white turmeric treatment is more effective in treating DLA, A549, and K562 cells compared to KB cells. KB cells appear to have the highest IC50 values, which is 142.2 $\mu\text{g}/\text{mL}$. While the IC50 values for DLA, A549, and K562 are 75.3, 75.7, and 45.83 $\mu\text{g}/\text{mL}$ respectively.¹³

Another study is also conducted, involves the use of white turmeric in conjunction with chemotherapy to treat bowel cancer cells; the combined treatment appears to be more

effective in killing cancer cells compared to chemotherapy alone.⁷ Staeger, *et al*, conducted a similar study to identify the synergistic effect between white turmeric and chemotherapy; HL cells were used and subjected to two different treatments. Cisplatin was used as the chemotherapy drugs. A low dose of 1.25 μM of curcumin extract, one of the active compound found in white turmeric, was used with varying concentration of cisplatin.⁹ The combined treatment between curcumin extract and cisplatin, appears to demonstrate a stronger cytotoxic effect towards the cell compared to the chemotherapy alone. There is a significant drop in the percentage of cell viability of combined treatment (Figure 1).

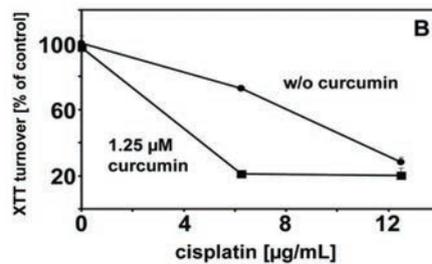


Figure 1. Curcumin inhibits growth of HL cells³

Similar studies are also conducted on different cell lines. Seo, *et al*, conducted an *in vitro* study to investigate the inhibitory effect of white turmeric water extract in preventing pulmonary metastasis on the B16 melanoma cells. In the study, B16 melanoma cells are treated with the water extract for duration of 42 days. After the treatment period was over, the number of metastatic surface nodules in the lung showed a significant decrease.¹⁰ In addition to that, they also found that the water extract of white turmeric possesses an anti-migratory effect, which leads to the significant decrease of metastatic surface nodules in the lung.¹⁰ The outcome seems to provide a solid evidence that white turmeric may indeed possess anti-cancer properties that might be the key to new novel treatments.

Carvalho, *et al*, revealed that white turmeric contains three known active curcuminoids, which are curcumin, demethoxycurcumin, and bisdemethoxycurcumin.¹¹ These three components are suspected to be responsible for anti-cancer properties in white turmeric. Curcumin, a yellow odorless pigment, which are commonly found in most turmeric species, is among one of the widely studied

chemopreventive phytochemicals. This particular substance is capable of preventing cancer metastasis by arresting cancer cells proliferation in various cell cycle that eventually leads to apoptosis of the cancer cells.¹¹ In addition to that, several studies conducted on various *in vivo* studies have also shown that this substance is not only capable of preventing metastasis, it is also capable of suppressing angiogenesis in animal tumor models.¹¹

Clove

Clove is an aromatic flower bud from a tree called *Syzygium aromaticum*. The tree is widely found in Maluku Islands, Indonesia. This aromatic flower is often used as a spice in foods for its unique aroma and flavor.

Studies have shown that clove is potentially able to treat different types of cancers.¹⁸ The research on clove and its anti-cancer properties has long been done in the 90s.¹⁸ GuoQiang Zheng, *et al*, conducted an experiment for the compounds in clove essential oil and its activity towards an enzyme called Glutathione-S-transferase (GST). This major enzyme is responsible for detoxification of toxic xenobiotics including carcinogens.¹⁴ They reported that a compound called eugenol is able to induce the enzyme activity of GST in the liver by 26% higher than the control.¹⁴ Additionally, four more compounds in the clove essential oil are able to increase the GST activity in the liver at least 2 times more than control.¹⁴ These results indicate that clove essential oil has the potential as a natural anti carcinogenic agents.

Chaieb, *et al*, made a short review on the chemical composition and biological activity of clove essential oil. They reported that clove essential oil has cytotoxic action towards prostate cancer cells and human liver cancer cells;¹⁵ a study by Zheng¹⁴ shows that eugenol induces apoptosis of human cancer cells. It is also known that clove oils have anti mutagenic compound which are dehydrodieugenol and cinnamaldehyde.¹⁵ Other than the induction of apoptosis, Carrasco, *et al*, reported that clove essential oil increases the total white blood cell and enhance the delayed-type hypersensitivity (DTH) response in mice.¹⁶ The highest response of DTH are observed in 200 and 400 mg/kg of clove essential oil.¹⁶ Clove essential oil is also able to restore



cellular and humoral immune responses in cyclophosphamide-immunosuppressed mice.¹⁶

Kumar, *et al*, did another experiment to determine anti-cancer potential of clove in human breast cancer cells (MCF-7). They used MTT assay to evaluate the cytotoxic activity of clove on MCF-7 cancer cells. The water extract cloves showed no cytotoxic activity towards the MCF-7 cancer cells.¹⁷ The ethanol extract, however, showed a promising result after 24 and 48 hours of incubation. It showed that 24 hours of incubation has higher IC₅₀ of 61.29 µg/mL compared to 48 hours of incubation with IC₅₀ of 16.71 µg/mL.¹⁷ The highest potential as an anti-cancer source is obtained in clove essential oil with its lowest IC₅₀ concentration, compared to water and ethanol extract of cloves, in both 24 and 48 hours of incubation which are 36.43 µg/mL and 17.6 µg/mL respectively.¹⁷

An experiment in India shows positive results of clove oil extract to four different types of cancer including breast cancer, cervical cancer, prostate cancer, and most effective towards esophageal cancer.¹⁸ They suggested clove can be made into an essential oil or packed into food supplements as esophageal cells are the first one to interact with the extract after ingestion. This is easier, rather than doing chemotherapy and other treatments. As a conclusion, clove essential oil is a natural resource for anti-carcinogenic agent. Its mode of action towards cancer cells are the induction of apoptosis, increase the production of white blood cells, and restoration of cellular and humoral immune responses.²⁸ Further research of clove against the other cancer cell types is still needed to determine the maximum potential of clove as an alternative cure for cancer.

Ant Plant

Ant plant or *Sarang semut* plant is a plant that is native to Papua Island, Eastern Indonesia, lives as epiphyte on other independent plants, especially *Casuarina*, *Castanopsis*, *Melaleuca*, and *Nothophagus* genus.¹⁹ It is a member of Rubiaceae family with the scientific name of *Myrmecodia pendens*. This plant is usually called *Sarang semut* (ant nest) because the hypocotyl inner part of this plant is usually used as a nest by *Ochetellus sp.* ants. The locals have been long believed that this plant is able

to cure diseases and abnormalities, such as allergy, backache, nosebleed, heart problem, stroke, tuberculosis, and even cancer.²⁰

The anti-cancer property of *sarang semut* plant has been proven by various studies. A study in Indonesia²³ published by Pakistan Journal of Biological Sciences in 2010 has found out that this plant extracts possess inhibitory activities against human cervical cancer cells (HeLa cells).¹⁻¹⁵ All of the extracts of *sarang semut* plant tested in this study, which are water, ethyl acetate, and n-butanol extract, have positively shown inhibitory activity against HeLa cells with the IC₅₀ of 29.36, 48.13, and 42.33 ppm, respectively. The study has also figured out that 30 ppm concentration of each of *sarang semut* plant extracts is equal to 5 ppm doxorubicin, which is a drug in cancer chemotherapy.

Other studies are looking through its bioactive compound. The ethyl acetate, ethanol, hexane, and water fraction of *sarang semut* plant flavonoid has resulted in the IC₅₀ of

452.06, 937.56, 2691.5, and 12302.69 µg/mL, respectively against SP-C1 tongue cancer cells.²¹ This study also discovered that the expression of VEGF, angiogenesis growth factor, and interleukin-8 (IL-8) were decreased compared to control after treated with ethanol and ethyl acetate fraction (Figure 2), which clearly indicates the inhibition of angiogenesis in tongue cancer cells.²¹ Furthermore, a study by Hasanuddin, *et al*, has also revealed that terpenoid bioactive compound of *sarang semut* plant has the capability to inhibit ovarian cancer (SKOV-3 cell lines) growth.²² Study on terpenoid in ethyl acetate solvent has produced the IC₅₀ of 481 ppm for 48 hours and 463 ppm for 72 hours against SKOV-3 ovarian cancer cell lines.¹⁸ Besides, the apoptotic index has been observed with the maximum of 37% at 72 hours with 600 µg/mL concentration.¹⁸

Flavonoid compound inhibits the cancer growth by tyrosine kinase and angiogenesis inhibition, which are very important elements for cancer proliferation.²³ This capability is also applied to flavonoid compounds in

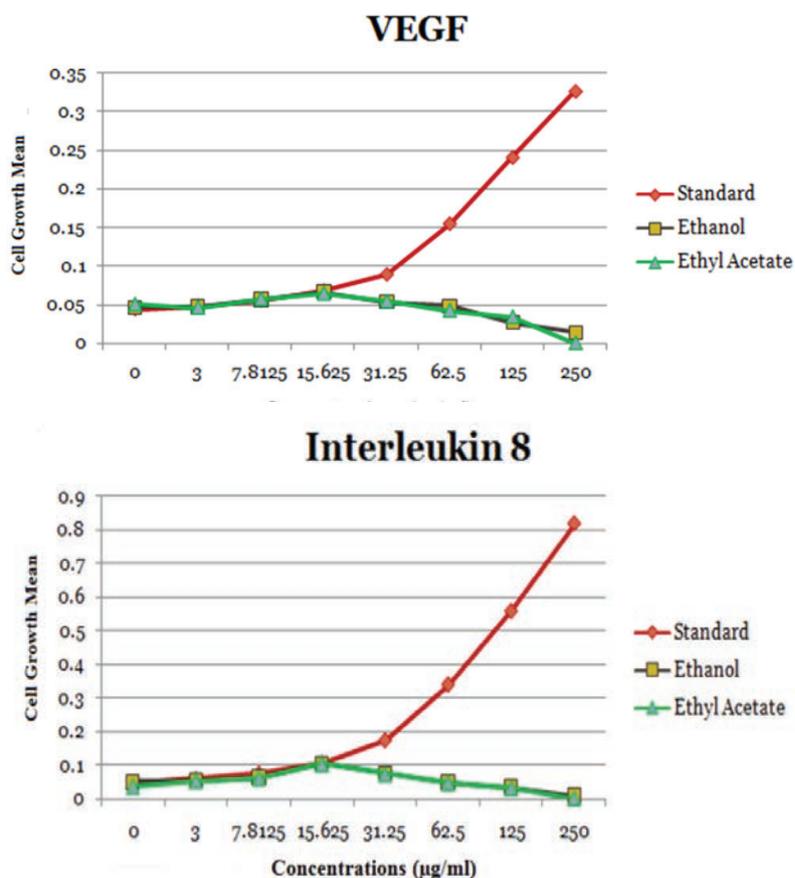


Figure 2. *Sarang semut* inhibits VEGF and IL-8 expression *in vitro*²¹



sarang semut plant. In addition, terpenoid of *sarang semut* plant has the ability to inhibit the proliferation of ovarian cancer cell by the induction of apoptotic effect.²² The underlying mechanisms behind this effect remain unclear, but these facts have shown that the *sarang semut* plant has a potential to be the future of anti-cancer drugs.

Rodent Tuber

Another commonly used herb which is known to possess anti-cancer properties called *Typhonium flagelliforme* or rodent tuber. This plant could grow up to 30 cm, wild in wasteland and is commonly found in Indonesia's lowlands as well as forests.^{24,25} Health benefits from this plant have been shown to be ranging from to soothe swelling, cough, asthma and different types of cancer.^{24,25} It is also known to have antioxidant characteristics, protecting the cells from free radicals, which could result to cancer.²⁶ Farida, *et al*, tested different rodent tuber extracts such as hexane, dichloromethane (DCM), methanol (MeOH), butanol and ethyl acetate for its neoplastic activity, and have shown to be very promising towards the ability of rodent tuber to combat cancerous cells.

Further studies have shown that human lung carcinoma cell line (NCI-H23) to be the most significantly affected by the plant extracts.²⁷ It has also been shown that the

dichloromethane extract has the most effective antineoplastic activity towards NCI-H23 tumor cells compared to the hexane and methanol extract, having the lowest IC-50 value of 15.42 $\mu\text{g}/\text{mL}$ on average.²⁴ One of the DCM extract with the greatest activity towards the NCI-H23 tumor cells showed to be not specific, however, the DCM extract with the second greatest activity towards the NCI-H23 tumor cells was found to have specific ant proliferative action against NCI-H23.²⁴

Another similar study was also conducted. Mohan *et al.* conducted an *in vitro* studies of human lung carcinoma cell line (NCI-H23) as well as human T4 lymphoblastoid (CEMss) using the dichloromethane extract. MTT assay was then used to assess the cellular growth. Consistent results were obtained that the DCM extract of rodent tuber showed cytotoxicity to NCI-H23 tumor cells.²⁷ Moreover, it has been proven that one of the DCM fraction of rodent tuber selectively induce apoptosis to leukemic cells (CEMss), preventing further proliferation.²⁷ Cell death in these cells are characterized by different morphological change including chromatin condensation and oligonucleosomal DNA cleavage which leads to the blebbing of the cell membrane and the shrinkage of the cells.²⁷

Besides ant proliferative action, anti-oxidation tends to be also effective in combating cancer

cells. Antioxidants are substances which inhibits oxidation by preventing free radicals from damaging body cells, which could cause cancer.²⁶ Study in 2014²⁶ have also found out that ethyl acetate extract showed the greatest activity, compared with hexane, methanol, butanol and water, having the smallest IC-50 value of 56.32 $\mu\text{g}/\text{mL}$.

Future Development

These four Indonesian herbs are only a small part of many Indonesian biodiversity. Further research needs to be done to determine the maximum potential of bioactive compound. There are still many known and unknown species that have not been studied further for their anti-cancer properties. Human clinical trials are also needed. Advanced study of these herbs' bioactive compounds that are specifically have anti-cancer properties is necessary in order to be able to formulate effective natural derived anti-cancer drugs.

Conclusion

White turmeric, clove, ant plant, and rodent tuber plant have been proven to possess anti-cancer properties. These herbs can be a promising candidate for anti-cancer drug but further clinical trials are needed. Additional studies to other herbs in Indonesian biodiversity are needed as many species have not been studied for their anti-cancer properties.

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