Optimizing the health benefit of Indonesian plant medicine for cancer treatment

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Abstract. The increased incidence of cancer is one of the serious health problems related to climate change. The deterioration of the environment becomes one of the risk factors for cancer. In respond to that problem, the Indonesian health system makes a breakthrough to strengthen health resilience by encouraging the use of Indonesian plant medicine in adjunct with standard pharmaceutical therapy for cancer. The study aimed to investigate the potential of Indonesian plant medicine for the development of complementary medicine for cancer. This review is based on the original paper published on the last five years. The search found several Indonesian plant with high potency for anti-cancer activity, based on in vitro and in vivo study. The medicinal plant include Curcuma longa, Annona muricata, Morinda citrifolia, Elephantopus scaber, Zanthoxylum acanthopodium DC, and Caesalpinia sappan.

1. Introduction
Global warming generates climate changes that affect not only sea level, land, water, and crop production, but also human health. The change in the water cycle accounts for many catastrophic events. The increased frequency of floods declines the environment quality. On the other hand, drought in other parts of the world generates hunger and malnutrition. All of those conditions affect the quality of human life. World Health Organization (WHO) predicted that the social and environmental changes as a result of global warming will increase the health burden all over the world. Climate change influences the incidence of both infectious and non-infectious diseases. Flood result in an uncontrolled population of insects which plays a role as a disease vector. Infection spread by biological vectors such as dengue fever and malaria becomes more prevalent. In addition, bad air pollution increase the incidence of respiratory disease such as asthma bronchial and other infection of respiratory system [1].

The incidence of the non-infectious disease is also affected by the environmental condition. The increase in earth’s temperature and high ultraviolet radiation decreases the general quality of human life. Those factors are also related to the incidence of skin cancer. The increased incidence of cancer is one of the serious health problems related to climate change. Although the deterioration of the environment is not straightly initiated the growth of cancer, the quality of the environment becomes one of the risk factors for cancer. Deterioration of environmental quality gives rise to physical and psychological stress which in turn decreases the immune system. The impaired immune surveillance to detect and eliminate the initial changes of abnormal cells play a role in cancer development [2].

The increase in cancer incidence was predicted year by year, and hence it becomes a significant health problem [3]. The incidence of cancer in Indonesia is the second rank among non-infectious
disease [4]. The health problems faced by the Indonesian health system are not only the increasing number of cancer cases but also the dependency on the imported pharmaceutical product. In response to that problem, the Indonesian ministry of Health makes a policy to strengthen health resilience by encouraging the use of Indonesian plant medicine in adjunct with standard pharmaceutical therapy [5]. The biodiversity of Indonesian plant medicine offers potential resources for developing complementary therapy. The use of Indonesian plants with potential therapeutic properties is common in daily consumption among Indonesian. Many people in Indonesian society prefer to choose herbal remedies before taking medicine for alleviating their health problem [6]. The use of the herb in Indonesian daily life can also be seen in the cooking style. The cooking habit of using various herbs native to Indonesian plants is currently recognized as one of the valuable traditions to improve the health status of Indonesian society [7]. This paper will investigate the potential use of Indonesian herb commonly used as part of Indonesian cooking for cancer treatment. This review include Curcuma longa, Annona muricata, Morinda citrifolia, Elephantopus scaber, Zanthoxylum acanthopodium DC, and Caesalpinia sappan.

2. Method
Literature search for this systematic review was conducted on Pubmed and Googlescholar. The literature was restricted to the publication from 2016 until recent. The combination of key word , cancer and Curcuma longa, Cancer and Annona muricata, cancer and Morinda citrifolia, cancer and Elephantopus scaber L, cancer and Zanthoxylum acanthopodium, cancer and Caesalpinia sappan, were used . The search engine was set to exclude patent and citation. The search was also set to show article based on the relevancy. Among other herb search in this study, publication on Curcuma longa, is the most abundance, therefore the inclusion of original paper studying Curcuma longa on anti-cancer activities was restricted for those reporting both in vitro and in vivo studies. Original paper reported in vitro study with the finding of low potency of cancer cell growth inhibitory activities was excluded. Review article and publication in language other than English was also excluded.

3. Result
The literature search for herb commonly used in Indonesia identified potent cancer cell growth inhibition activity on Curcuma longa, Annona muricata, morinda citrifolia, Elephantopus scaber, Zanthoxylum acanthopodium DC, and Caesalpinia sappan. The identification of anti-cancer potency was determined by the IC50 on in vitro study or the mass tumor reduction on in vivo study [6], [7]. Further investigation was made to identify the type of compound for each herb species.

3.1. Curcuma longa
Research for the anti-cancer potential of Curcuma longa was rigorously conducted worldwide. The phenolic compound of Curcuma longa showed high potency of anti-proliferative activity against the growth of various cancer cell lines. Curcuma longa contains many compounds with various ranges of pharmacologic activities. Among other compounds, curcumin was most widely studied for anti-cancer activities [7], [8], [9]. Studies on the subcellular activity of curcumin reveal many molecular targets involved in anti-cancer activities. Table 1 summarizes the anticancer activity of Curcuma longa.

3.2. Annona muricata
Annona muricata is one of Indonesia endemic plants. The use of Annona muricata leaf to treat cancer has become a self-treatment among cancer patients before they seek medical treatment [15]. Although those self-medical practices did not successfully treat cancer patients, the preclinical study showed a promising anti-cancer effect of active compounds extracted from Annona muricata leaf [16], [17], [18], [19]. Table 2 summarizes the result of recent studies on the anti-cancer activity of Annona muricata.

3.3. Morinda citrifolia
Indonesian people have consumed the leaf and fruit of Morinda citrifolia for their health benefit [23]. Various pharmacological properties of Morinda citrifolia have been identified and a formula for a
certain medical purpose has been offered in the market. Investigation on cytotoxic activity of compounds extracted from leaf, stem, fruit, and seed of *Morinda citrifolia* showed its potential for cancer treatment [24]–[27]. Several studies reveal the putative anticancer mechanism of *Morinda citrifolia* against cancer cell growth. Table 3 summarizes the anticancer mechanism of *Morinda citrifolia*.

**Table 1.** Anticancer activities of compound extracted from *Curcuma longa*.

| Compound                          | Molecular target/ Anti-cancer mechanism                  | Reference |
|-----------------------------------|---------------------------------------------------------|-----------|
| Diarylheptanoid Curcumin          | MYC, reduce endogenous level                            | [10]      |
| Curcumin                          | inhibit the TLR4/NF-κB signaling                        | [9]       |
| Curcumin                          | supress AKT phosphorylation                             | [11]      |
| Curcumin                          | supress inflammatory cytokine                           | [12]      |
| Curcumol + Metformin              | supress the Wnt/β-catenin signaling                     | [13]      |
| Curcumin + gemcitabine            | activate PARP/Caspase 3 signalling                      | [14]      |
| Curcumin + docetaxel              |                                                         |           |

**Table 2.** Anticancer activities of compound extracted from *Annona muricata*.

| Compound                          | Molecular target/ Anti-cancer mechanism                  | Reference |
|-----------------------------------|---------------------------------------------------------|-----------|
| Aqueous concentrate               | Increase intracellular ROS                               | [17], [18]|
| Methanolic Extract of twig, seed, and fruit | Induce cell cycle arrest                               |           |
|                                  | Induce intrinsic apoptosis                              |           |
|                                  | Decrease hedgehog signaling                             |           |
| Ethyl acetate bark extract        | Inhibit VEGF                                            | [21]      |
| Silver Nanoparticle of peel aqueous extract | Increase p53 cancer cell                               | [22]      |

**Table 3.** The anticancer activity of *Morinda citrifolia*.

| Compound                          | Molecular target/ Anti-cancer mechanism                  | Reference |
|-----------------------------------|---------------------------------------------------------|-----------|
| aqueous ethanol leaf extract      | upregulating anti-cancer genes: CSF3, IL10,             | [24]      |
|                                  | upregulating anti-inflammatory genes: IL4,              |           |
|                                  | SOCS1,TRP53                                             |           |
| Nordamnacanthal (isolated from root of *Morinda citrifolia*) | downregulated pro-cancer genes: AKT1, BCL2,             | [26]      |
| Morinda citrifolia essential oil of dried seed Fermented noni fruit juice | BCR, BIRC5, CDK1, IL3, JAK2, MAPK2,                    |           |
|                                  | MDM2, mTOR, NF-κB, PTEN, Raf1, STAT3,                    |           |
|                                  | STAT5A, and VEGFA.                                       |           |
| Dammanacanthal                   | Increase T helper, cytotoxic T, and NK cell activity     | [25]      |
| Nordamnacanthal                  | Increase intracellular ROS production                    | [25]      |
|                                  | Increase mitochondrial membrane damage                   |           |
|                                  | decrease anti apoptotic protein (BCL-2) and proliferating gene Ki67, PCNA | [28]      |
|                                  | inhibition of AKT/NF-κB signaling pathway                |           |
|                                  | increase intrinsic apoptotic pathway                    |           |
3.4. *Elephantopus scaber*

The Indonesian name of *Elephantopus scaber* is tapak liman. This plant medicine was studied for many pharmacological activities. Research on its activity to inhibit cancer cell growth suggests its potential use for cancer treatment [30–36]. The anti-cancer activity of this medicinal plant from the currently reported study was summarized in Table 4.

3.5. *Caesalpinia sappan*

*Caesalpinia sappan* is known as Secang for its Indonesian name. The wood of *Caesalpinia sappan* is commonly used as an ingredient of traditional beverages in central Java and some other parts of Indonesia. The pharmacological activity of *Caesalpinia sappan* has been widely investigated including its potential anticancer activities [37], [38]. The anticancer activity of *Caesalpinia sappan* is summarized in Table 4.

**Table 4.** The anticancer activity of *Elephantopus scaber* and *Caesalpinia sappan*.

| Compound                     | molecular target/ Anti-cancer mechanism                                                                 | Reference |
|------------------------------|--------------------------------------------------------------------------------------------------------|-----------|
| *Elephantopus scaber*        |                                                                                                        |           |
| Deoxyelephantopin            | induced apoptosis via ROS production Inhibit vascular permeability                                        | [31,32]  |
| Chloroform fraction          | increased the expressions of caspase-8, caspase9, and caspase3                                         | [33]      |
| Isodeoxyelephantopin         | activation of the JNK signaling pathway Activating protective autophagy                                  | [30,36]  |
| *Caesalpinia sappan*         |                                                                                                        |           |
| Wood and leaf extract        | inhibited lactate production Inhibit phosphorylation of pyruvate dehydrogenase increased mitochondrial ROS levels | [37]      |
| Cassane diterpenoids isolated from the seed of *caesalpinia sappan* | induce apoptosis via the increase of PARP cleavage, p53, and Bax/BCL2                                  | [38]      |

4. **Discussion**

Climate change affects the quality of human health. High carbon dioxide emission accounts for the decline of the quality of the environment. Although direct causative correlation cannot be clearly explained, air pollution and high ultraviolet radiation might play a role in the increase of some cancer cases [2]. In addition, the increase of physical and psychological stress due to the increase in the earth's temperature negatively affects the function of the immune system. Immune surveillance plays a crucial role to prevent the development of cancer. The recognition of cellular changes in the early transformation of a normal cell into a cancer cell by the immune system is required to eliminate cancer cells. The impaired immune system to detect and eliminate the abnormal cell is part of the risk of cancer development [39].

Cancer is a life-threatening disease that contributes to the health burden of Indonesia health system. The expensive cost of cancer treatment put this disease in the group of catastrophic disease. Cancer not only decreases the quality of a patient’s life, but also the quality of their family life. The low survival rate among cancer patients makes cancer a life-threatening disease. Aside from its psychological impact, the cost of cancer treatment becomes one constraint for most cancer patients to seek immediate proper therapy [40]. The economic burden result from cancer therapy affects the behavior in choosing immediate therapy. The use of alternative therapy is quite common among cancer patients. Some cancer patients prefer to choose the use of complementary medicine including herbal medicine for the first-line treatment for the disease [15], [41]. However, the lack of standardized complementary therapy for cancer might lead to failure in cancer therapy. Considering patient preference to choose complementary medicine as the first-line treatment [15], [42], the establishment of standard complementary therapy for...
the cancer patient is urgent. In 2014 committee for cancer prevention as part of the Ministry of Health issued a guideline to encourage the use of Jamu (traditional Indonesian herb) as a remedy complement to standard medicine used to prevent and treat cancer [5].

In search of the potential Indonesian plant medicine, there are some herbs which is already used in daily cooking with a potency as cancer chemo-preventive activity [23]. The available data gathered from publications in the last five years indicate some Indonesian plant medicine with promising potency for inhibiting the growth of cancer. Curcuma longa, Annona muricata, Morinda citrifolia, Elephantopus scaber, and Caesalpinia sappan are highly available in Indonesia [23]. Curcuma longa has been used as part of traditional medicine in Indonesia. Product of herb drink composed of Curcuma longa powdered can be easily found in the market. Consumption of Curcuma longa as cook seasoning, food additive, and herbal drink is common among Indonesian society. The in vitro and in vivo studies investigating the anti-cancer activity of Curcuma longa reveal scientific data to support its use as cancer therapy. Curcuma longa inhibits the Wnt/β-catenin signaling. Wnt/β-catenin signaling is not active in normal conditions. The disruption of Wnt/β-catenin signaling is responsible for the uncontrolled growth of cancer cells, therefore inhibition of this pathway will decrease the cancer cells aggressiveness [13]. Curcumin which is the most widely studied compound of curcuma longa also inhibits the expression of MYC protein. MYC is an oncogenic protein that also plays a part in cancer progression. The inhibition of MYC protein will slow down cancer cell growth [10].

Inflammation becomes one of the targets in cancer therapy. Inflammation in the cancer microenvironment plays role in the maintenance of cancer growth signal. Inflammation is considered an event that exaggerates cancer cell growth. The cancer inflammation pathway involves TLR4/NF-κB signaling. Suppressing this pathway will decrease cancer progression. Tian et al., reported the activity of curcumin to suppress the TLR4/NF-κB signaling [9]. Taken together, the inhibition of the cancer cell proliferation signal and the inflammatory signal will reduce the cancer progression. The biological activity of curcuma longa to potentiate standard chemotherapeutic drugs was also observed. The combination of curcumin with gemcitabine and docetaxel increases the PARP/caspase 3 signaling, thus increase cancer cell death.

The potential anti-cancer activity was also shown by Annona muricata. This plant medicine is widely spread across Indonesia. The investigations of the pharmacological activity of compounds extracted from Annona muricata give promising data for anti-cancer therapy. Compounds extracted from Annona muricata leaf, seed, or bark induce cancer cell death through the increase of intracellular oxidative stress on a cancer cell. Oxidative stress within cancer cell will affect mitochondrial membrane integrity which in turn induce activation of intrinsic programmed cell death [17,18]. Cancer cell death through the increase of intracellular oxidative stress was also shown by the compound extracted from Elephantopus scaber and Caesalpinia sappan [31], [32], [37].

The anti-cancer activity of Annona muricata also includes inhibition of development of new blood vessels through suppression of VEGF [22] and the increase of protein which act as the counterpart of MMP-2 and MMP9. The development of new blood vessel is part of cancer progression, therefore suppression of VEGF which act as a growth factor for new blood vessel development will reduce the cancer progression. Furthermore, the Inhibition of MMP-2 and MMP9 will reduce the cancer aggressiveness to migrate from the primary tumor site [20].

Morinda citrifolia also gives a promising anti-cancer activity. This plant medicine has been used by Indonesian society for many chronic diseases such as hypertension and hyperlipidemia. The anti-cancer activity of Morinda citrifolia was observed on compounds extracted from leaf, root, and fruit. Compounds extracted from the leaf showed suppression activity toward genes related to the cancer progression [24]. The active compound of Morinda citrifolia induces cancer cell death and improves the cytotoxic T cell activity to eliminate cancer cells. The activity of cytotoxic T has become an important target of cancer therapy. The cytotoxic T cell eliminate cancer cells by killing the cancer cells [43].

The above mention data predicted the potential anti-cancer activity of studied plant medicine. However, the inhibiting effect is various among different types of cancer. In addition, the different methods in the preparation of plant extract also result in different anti-cancer effects. Standardization of
compounds for developing herbal medicine for cancer treatment is required. The optimization of the biological compound extracted from plant medicine should improve the bioavailability and selectivity to kill cancer cells. Selectivity is an important issue in developing anti-cancer agents. The increase of bioavailability of the anti-cancer compound should not be harmful to normal cells in the body.

5. Conclusion
The increase of disease prevalence including cancer as an impact of climate change created a health burden for the Indonesian health system. The Indonesian Ministry of Health encourages the use of plant medicine to increase health resilience. Indonesian plant medicine offers a high potential activity to develop an herbal remedy for complementary used to treat cancer. Furthermore, enhancing the use of native Indonesian natural sources will strengthen health independence toward a pharmaceutical product. Further improvement is required to develop a standardized formula to optimize the health benefit of the natural resources widely available in Indonesia.

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