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Review Article

Medicinal Plants Commonly Used Against Cancer and Human Immunodeficiency Virus in Malaysia

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Abstract

Human immunodeficiency virus (HIV) and cancer are both considered life-threatening diseases that impose a significant global burden. Despite significant advancements in the treatment and management of both cancer and HIV, challenges persist. However, challenges such as drug resistance, limited accessibility in low-resource settings, and a paucity of cost-effective alternatives persist, underscoring the need for continued research. Chemotherapy frequently results in severe toxicities, including myelosuppression and organ damage, while antiretroviral treatments can lead to long-term adverse effects such as metabolic disorders and liver toxicity. Conversely, natural therapies, encompassing the utilization of plant-derived products in cancer and HIV treatment, have emerged as a potential avenue to mitigate adverse side effects. The utilization of natural products has demonstrated consistent efficacy in the prevention of HIV and cancer. The development of anti-HIV/cancer products has incorporated natural plants and extracts. Indigenous communities have utilized traditional herbal medicine for the treatment of various diseases, including HIV and cancer. A number of Malaysian plants have been identified as having significant anti-HIV/cancer properties, and some of the commonly used plants are described in this review with an account of their compounds and modes of action. However, to date, only a limited number of Malaysian plants have been subjected to bioactivity testing, highlighting the necessity for further research to fully elucidate their medicinal potential and inform the development of novel therapeutic interventions for combating HIV/cancer.

Keywords: *Anti-Cancer, Anti-HIV, Medicinal Plants, Phytotherapy, Traditional Medicine, Natural Compounds.*

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Introduction

Cancer and HIV are the leading causes of death worldwide (Siegel et al., 2016). Despite the implementation of extensive awareness campaigns emphasizing the methods of prevention, treatment, and management of these diseases, they continue to account for a substantial proportion of mortalities in comparison to other diseases. This phenomenon contributes to a decline in overall quality of life and a substantial number of fatalities. While significant advancements have been made in the treatment of both HIV and cancer, the need for alternative sustainable, more accessible, and more affordable methods of prevention and treatment remains paramount to reduce the mortality rate from these diseases. This approach involves the utilization and maintenance of natural methods and therapies derived from indigenous knowledge, encompassing herbs, spices, plants, trees, and vegetables (Mohammed, 2019).

The likelihood of developing cancer is associated with detrimental lifestyle habits, such as sedentary living, a diet high in processed foods, and excessive smoking and alcohol consumption (Waks & Winer, 2019). Additional factors contributing to cancer development include excessive sun exposure and interaction with harmful chemicals. In some cases, the onset of cancer is age-related. Given the wide spectrum of conditions under which cancer can be contracted, it is essential to have measures to proactively prevent infection, while effectively treating and managing the infected parties (Corcoran & Chabner, 2018).

Cancer treatment has historically involved a variety of methodologies, including chemotherapy, immunotherapy, targeted therapy, and hormone therapy, as well as surgical interventions aimed at extirpating cancerous lesions (Anghileri & Robert, 2019). The employment of pharmaceutical agents has been a central tenet of these therapeutic approaches, with the aim of reducing tumor size, eradicating malignancies, or halting their progression. However, the extensive use of pharmaceuticals in cancer treatment has been associated with adverse effects, including toxicity, which can lead to fatalities (Anghileri & Robert, 2019). Consequently, there have been clinical studies and advancements in plant-derived anti-cancer drugs for clinical use. The objective of these studies is to measure the effectiveness of these plant-derived drugs in comparison to existing pharmaceuticals. A key metric of efficacy would be the reduction in mortality rates due to toxicity, as chemotherapy is known to carry a high burden of adverse side effects (Choudhari et al., 2020).

Furthermore, HIV is an acquired viral disease that attacks the human immune system, weakening CD4 cells, which are useful for fighting infections in the body, thereby rendering the body incompetent in warding off infections and cancers (Chinsembu, 2016). HIV is most treated through diverse drug regimens, which are uniformly called antiretroviral therapy (ART). This therapy consists of taking multiple tablets daily, which prevents the viral load from multiplying. A reduced viral load leads to a less aggressive progression of HIV to AIDS, thereby enhancing the health and lifespan of infected individuals (Abdel-Kader et al., 2018). The efficacy of ART is contingent on its daily and precise administration. Inconsistent adherence to ART has been observed to result in viral load multiplication. This has led to challenges in low- and middle-income countries, where the health delivery system often lacks the capacity to meet the demand for HIV medications (Akram et al., 2018). Consequently, there has been a growing interest in exploring natural and plant-based remedies for HIV prevention and treatment. These methods of treatment are considered more favourable due to their sustainability and the reduced adverse effects they impose on infected patients. Consequently, this has contributed to the accelerated development and clinical implementation of anti-HIV drugs derived from plants (Adana et al., 2018).

It has been noted that both cancer and HIV present challenges in treatment that are analogous, including drug resistance, adverse side effects from existing therapies, and disparities in healthcare access. Furthermore, the growing interest in plant-derived compounds for both diseases highlights a shared opportunity to explore sustainable and less toxic alternatives that address these gaps.

Medicinal plants play a pivotal role in communities' treatment of diseases due to their accessibility, which facilitates prompt provision of necessary medicine to patients within the vicinity. While medicinal plants may possess reduced potency, they exhibit reduced toxicity, thereby minimizing the likelihood of adverse side effects in patients (Mohammed, 2019). Compared to synthetic counterparts, natural medicines have demonstrated enhanced efficacy in treating diseases. Furthermore, the affordability of medicinal plants ensures enhanced accessibility, thereby expanding treatment options to a greater number of individuals compared to synthetic medicine, which is often more expensive. These characteristics position the utilization of plants in medicine as a beneficial, effective, and holistic approach to healthcare (Nisar et al., 2018).

Malaysia is distinguished by its extensive biodiversity, as evidenced by its habitat for over 23,000 plant species. This substantial reserve of flora offers a valuable resource for investigating the medicinal properties of these organisms (Zaki et al., 2019). The objective of this review is to examine the anti-cancer and anti-HIV properties of select Malaysian plants.

Plant-Derived Anti-Cancer Agents in Clinical Use

The anticancer properties of plants have been recognized in clinical procedures for years, with approximately two-thirds of anti-cancer drugs originating from plants (Sak, 2012). Anti-cancer agents are described as chemicals that weaken cancer cells by either killing them or reducing their multiplication. There are several plant-derived anti-cancer agents that have been successfully implemented in clinical use due to their chemoprotective effects. The National Cancer Institute (NCI) has conducted extensive research, examining over 35,000 plants and identifying potential anti-cancer properties in approximately 3,000 of them (Shalabi et al., 2015). **Figure 1** illustrates some of the anti-cancer drugs derived from plants (Kuruppu et al., 2019).The World Health Organization acknowledges plants as a vital contributor to achieving global healthcare objectives. Herbs and plants have been recognized for their medicinal value and have been used in Europe and the Middle East. Studies in these regions have influenced other parts of the world, prompting the strong consideration of plant-derived agents for the prevention and cure of cancer (Bahadur et al., 2020).

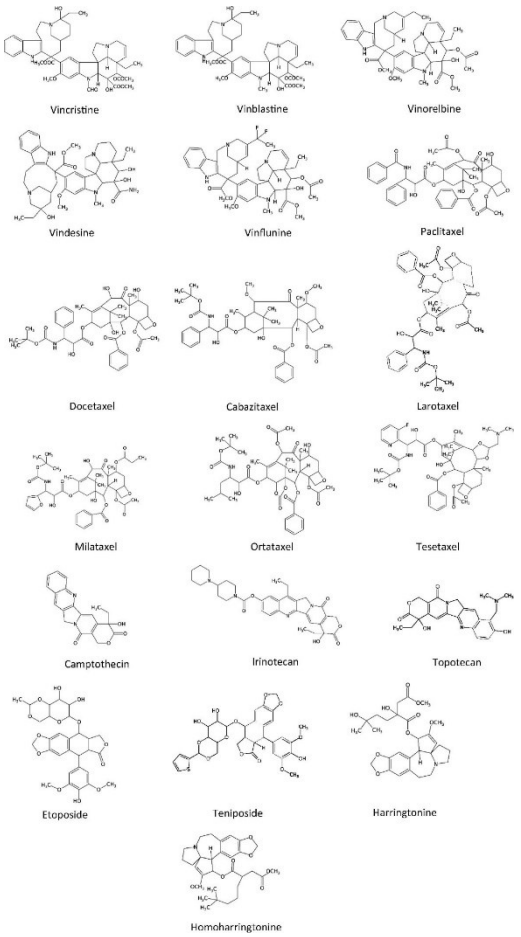

Figure 1. Chemical Structures of Anti-Cancer Drugs Derived from Plants That are in Clinical Use (X. Wang et al., 2018).

The utilization of plants in cancer prevention is driven by the necessity to reverse the adverse effects of chemotherapy and enhance the survival rates of patients' post-surgery. The efficacy of plant-derived cancer agents in impeding cancer cell proliferation in specific bodily regions has been demonstrated (Zaid et al., 2012). For instance, the onion plant Allium cepa L has been found to be effective in inhibiting the growth of breast cancer cells by blocking the accumulation of fatty acids in the adipose tissues (Y. Wang et al., 2012). Another in vitro study also observed the anti-tumor effect of the aloe vera plant in both breast and cervical carcinoma cell lines (HeLa). The study's findings indicated that exposure to aloe vera compounds led to the death of cancerous cells, while having no effect on normal cells (Ahmed & Husain, 2014).

The incorporation of flora, namely plants, herbs, and vegetables, into an individual's dietary regimen has been demonstrated to exert a substantial influence on the probability of contracting cancer, in comparison to an individual with an inadequate diet. Ahmad et al. (2017) posit that in the nascent stages of cancer, it is feasible to arrest its progression, impeding its dissemination to other cells and halting its growth (Ahmad et al., 2017). This assertion is supported by the findings of Aung et al. (2017), who discovered that Calligonum Comosum extracts exert a substantial impact on the latency of hepatocellular carcinoma cells. The use of herbal-based medicines has been proposed as a highly effective cancer prevention strategy due to their potential to mitigate the likelihood of drug interactions, which can compromise the efficacy of combination therapy in addressing cancerous conditions. In comparison to synthetic anti-cancer drugs, natural options are often more cost-effective, readily available, straightforward in formulation, and characterized by a low incidence of adverse side effects (Ahmad et al., 2017).

Malaysian Plants that Have Anti-Cancer Properties

In Malaysia, the primary focus on herbal remedies and plant-based treatments for cancer prevention and treatment is largely driven by the country's abundant rainforests (Mainasara et al., 2018). Local communities have traditionally utilized potent herbs in the treatment of minor malignancies, and at the pharmaceutical level, there has been a growing incorporation of herbal and plant-extract based medications in cancer treatment (Rahman, 2016). While most of the plants identified as having anti-cancer properties have yet to be fully commercialized, they have been effectively used in treating cancer patients with success (Hashim et al., 2016). The combination of plant-derived anti-cancer drugs has been shown to reduce the likelihood of drug

resistance in patients. This is due to the plant extracts' capacity to impede ATP binding cassette (ABC) transporters in conjunction with multidrug resistance proteins (MRP-s), thereby enhancing the efficacy of treatment in patients (Shabani, 2016). A multitude of studies have identified the chemoprotective and anticarcinogenic properties of plants in the treatment of cancer, a subject that will be addressed in the ensuing discussion.

Goniothalamus Umbrosus

The Kenerak plant (G. umbrosus) is a species of plant that is native to Malaysia. It has been utilized in the field of pharmaceuticals for its benefits in maternal health care and general wellbeing. However, research has identified specific species of this plant that contain styryl-lactones and acetogenins, which have been shown to have toxic effects on various forms of cancer, including colon, breast, pancreas, and kidney cancers (Ghazali et al., 2016).

Furthermore, styryl-lactones from the G. umbrosus species have been identified as effective inducers of apoptosis in mammalian and cancer cells (Arbyn et al., 2020). Ethyl acetate, a compound derived from the G. umbrosus plant, has demonstrated significant potential in the inhibition of cancer growth and spread in breast cancer cells (MCF7) (Arbyn et al., 2020). Following treatment with this compound, a mortality of the cancer cells in the breast was observed. Consequently, there has been a surge in research endeavors exploring the potential of employing plant extracts in the treatment of breast cancer (Ibrahim et al., 2019).

Typhonium Flagelliforme

In Malaysia, the plant is referred to as Keladi Tikus, and it is employed as a derivative drug for the treatment of various forms of cancer. This herbaceous plant, which often grows up to 30 centimeters in height, is utilized as a medicinal agent. The plant's juice is orally administered after the entire plant is crushed (Setiawati et al., 2016). In vitro studies have demonstrated the efficacy of an extract of Typhonium flagelliforme in treating NCI-H23 human lung carcinoma, T-47D human breast carcinoma cell lines, and P388 murine leukemia cells (Setiawati et al., 2016). Moreover, the plant extract has been utilized in Malaysia for the treatment of malignancies.Notwithstanding the plant's anti-cancer properties, clinical trials have been stagnant. The stem and leaves of this tuber plant have been found to contain more potent anti-cancer agents (Sianipar & Purnamaningsih, 2018).

Clinacanthus Nutans

The plant is known in the local context as Sabah snake grass in Malaysia, and it is classified within the family of Acanthaceae (Alam et al., 2016). It is regarded as one of the most ancient native herbs, originating from tropical Asia. It is utilized as a conventional treatment agent in Malaysia, China, and Thailand (Ghantous & Abu Elnaaj, 2017). The plant has been employed to treat various ailments, including animal bites, skin irritations, diabetes, and the Herpes simplex virus (HSV). However, studies have demonstrated that the chloroform extracts from this plant exhibit potent effects in destroying anti-cancer cells in vitro, including HepG2, IMR32, NCL-H23, SNU-1, HeLa, LS-174T, K562, and Raji cells (Ng et al., 2017). Furthermore, the leaves of this plant have been shown to possess significant antiviral and anti-inflammatory properties (Teoh et al., 2017). In addition, they have been identified as effective in inhibiting neutrophil response and the formation of edema. Emerging evidence suggests that C. nutans holds significant anti-tumorigenic effects, which are vital components of anti-cancer growth (Huang et al., 2015). Studies have indicated that the chloroform extract of C. nutans leaves is a potent agent capable of eliminating free radicals and preventing the growth of cancerous cells in culture. Yakop et al. (2018) further suggested that these agents could serve as an effective alternative to chemotherapy for individuals at risk of developing cancer.

Plant-Derived Anti-HIV Agents in Clinical Use

Plants are increasingly being recognized as effective in the development of anti-HIV agents based on their diverse medicinal value. While there are still limited studies to discuss plants that prevent one from being infected with HIV, there is evidence that the inclusion of medicinal herbs and plants help in patients who have drug resistance, toxicity, and other co-morbidities. For example, when an HIV-positive patient eats organic foods, their immune system is strengthened and they have fewer health complications (Prinsloo et al., 2018).

It is common for HIV patients to have liver and kidney toxicity. However, when these patients took herbal medicines and herbs, they were able to get rid of the side effects of toxicity. There was an improvement in their liver and kidney health (Khan, 2017).

Adansonia digitata, Terminalia sericea, Hypoxis Hemerocallidea, and Moringa oleifera have been shown to inhibit HIV-1 reverse transcriptase. HIV patients who used these medicinal plants as a complementary therapy to their HIV treatment regimen were found to have a lower viral load and an increase in their CD4 count (Habibi et al., 2019). However, it is important to note that there has been resistance in several countries to the full adoption of herbal medicine for the treatment of HIV. A common reason for this is that there is still ongoing research into how the medicinal plants would interact with synthetic drugs and whether there would be any side effects (Jayasundar et al., 2019).

Plants are also used to treat opportunistic infections that are common in patients infected with HIV/AIDS. The opportunistic infections include cancer, tuberculosis, skin and oral infections, and these are effectively treated with plants and herbs in HIV patients. The Moringa plant is commonly used to treat respiratory infections in HIV patients. It contains a similar structure to nucleoside analogues found in synthetic antiretroviral drugs (Kurapati et al., 2016).

Secondary symptoms of HIV/AIDS are also effectively managed through the consistent use of medicinal plants and herbs. This is seen in the case of tobacco plants, which produce monoclonal antibodies that are essential for supporting the compromised immune system of HIV patients. Since the disease affects and weakens the immune system, the plants used would contain high nutritional and pharmaceutical value (Okay & Sezgin, 2018).

Natural products that have been discovered to contain significant anti-HIV compounds include calanolides (coumarins), ursolic and betulinic acids (triterpenes), baicalin (flavonoid), polycitone A (alkaloid), and lithospermic acid (phenolic compound). However, they are all still in clinical trials and have not yet been commercialized. These plant-derived drugs have been found to have similar structures within the nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) classes (Boukandou Mounanga et al., 2018).

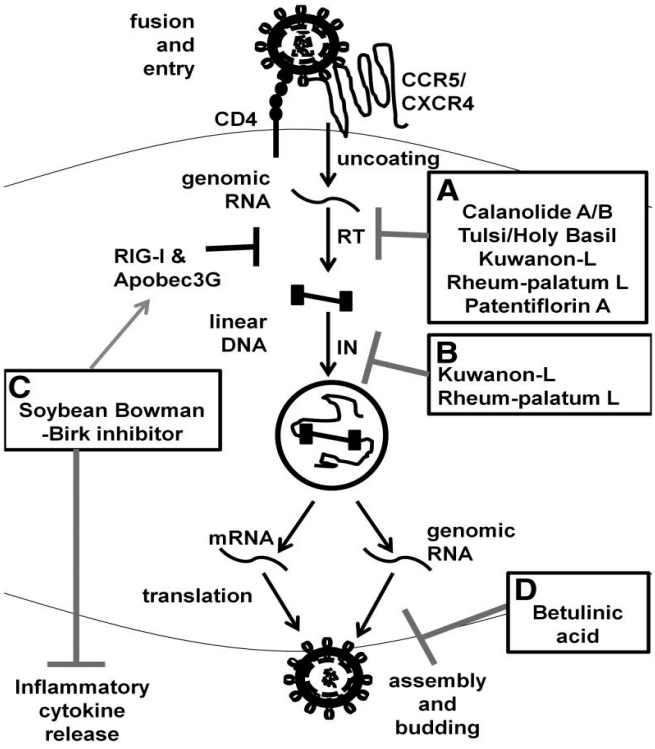

Figure 2. Plants and Compounds Used in HIV Suppression (Cary & Peterlin, 2018)

Figure 2 shows a summary of the plants used to suppress HIV replication. The compounds derived from the plants are also shown, indicating the role they play in the life cycle of the HIV virus. The inclusion of plant-derived anti-HIV agents focuses primarily on the suppression of the virus. These inhibitory agents are effective in targeting mutant cells, suppressing viral replication, and proving to be a cost-effective alternative to ART (Chaturonrutsamee et al., 2018; Okay & Sezgin, 2018).

Malaysian Plants that Have Anti-HIV Properties

Rainforest climates such as Malaysia are typically known for having a wide variety of pharmaceutically useful plants. The following plants have been identified as derivatives for anti-HIV drugs:

Calophyllum

The Calophyllum tree was first discovered in 1987 on the island of Borneo in Malaysia. The National Cancer Institute (NCI) led an expedition to find a cancer cure in the rainforests but instead discovered that the Calophyllum tree had anti-HIV properties. It was discovered that several compounds could be extracted from the tree that were pharmaceutically useful for the purpose of preventing HIV. The part that is harvested is the fruit and the branches from which the compound Calanolide A is derived. The other compounds derived from this plant are dihydrocostatolide and cordatolide A/B, dipyranocoumarins, and soulattrolide. These compounds were found to be able to inhibit the activity of viral infection of T cells in HIV patients (Lim et al., 2016).

Calanolide A

This compound is extracted from Calophyllum lanigerum var austrocoriaceum, an unusual member of the Guttiferae or mangosteen family (Wu et al., 2017). In vitro studies have shown that calanolide A, a non-nucleoside reverse transcriptase inhibitor, may be useful in HIV prevention. It was found to be effective in inhibiting cells from being infected by the virus, even those strains that had failed other drugs such as zidovudine (AZT) and nevirapine. The studies showed that the drug would work optimally when combined with other inhibitors such as AZT, didanosine, nevirapine and carbovir. This compound works by crossing the blood-brain barrier and accumulating in the lymph nodes. A modified and more potent structure of calanolide, F18, was discovered in 2017 (Pawar & Patil, 2019).

Calophyllum Teysmannii Var. Inophylloide

This plant, also discovered in the Borneo Islands of Malaysia, has been shown to have anti-HIV properties. The latex of this tree produces the compound

costatolide, also called calanolide B, which also shows activity against HIV. Both compounds are classified as non-nucleoside reverse transcriptase inhibitors (NNRTIs). These drugs protect and prevent the healthy T-cells in the body from being infected by the HIV virus (Kainuma et al., 2016). When comparing the two plants from Malaysia, it was found that even the latex of Calophyllum teysmanii produces (-)-calanolide B (70), which is less potent than the (+)-calanolide A of Calophyllum lanigerum, but it is a more sustainable option as it is derived from the latex of the tree, eliminating the need to cut down the tree (Jain et al., 2018).

The processing of these drugs has been spearheaded by Sarawak Medichem Pharmaceuticals, a collaboration between the Sarawak state government and Medichem Research, Inc. However, the commercialization of these drugs has been a slow process to date, although the efficacy of the drugs has been authenticated by several pharmaceutical bodies.

The compound Calanolide A was synthesized by Medichem chemists. The compound has demonstrated significant efficacy and a safe pharmacokinetic profile in HIV-negative healthy subjects. Calanolide B is still in preclinical development (Gupta & Gupta, 2020).

Phyllanthus Pulcher

This plant belongs to the Euphorbiaceae family and is native to Malaysia. The dried root powder of this plant has been commonly used for the treatment of gastric infections and ulcers (Salehi et al., 2018). However, due to the potency of the methanol extracts of this plant, it was tested for anti-HIV-1 reverse transcriptase (RT). This test was to be done through HIV-RT assay by inhibiting the HIV-1 RT enzyme based on their IC50 values. Azido-deoxythymidine triphosphate (AZT151TP) was used as a control in the assay. The results of this test indicated that the extracts of this plant contained anti-HIV properties that would be pharmaceutically useful in inhibiting HIV-1 virus from spreading to healthy T-cells (Cary & Peterlin, 2018).

Conclusions

In summary, it is clear that the use of plant-derived drugs is effective in the prevention of HIV and cancer. However, it is concerning that despite the early discovery of these compounds, their commercialization has been quite slow. This delay can be attributed to regulatory hurdles, such as the rigorous testing required to meet international safety standards, and financial barriers, including the high cost of clinical trials and limited funding for natural product research. Overcoming these challenges will be critical to accelerating the availability of plant-based medicines for widespread clinical use. Another growing concern is the potential extinction of plants in which anti-cancer and anti-HIV compounds have been found. The extinction of these plants would mean that the medicinal value of these discoveries would be lost, with possibly no chance of recovery, as was the case with the early discoveries of the anti-HIV plant Callophylum in the Borneo Islands, Malaysia. There is also a need to investigate how to accelerate the use of plant-derived anti-cancer and anti-HIV agents to intervene in cases where patients have adverse reactions or resistance to synthetic drugs and alternative treatment methods. Future research should focus on sustainable harvesting methods to conserve the biodiversity of medicinal plants, especially those at risk of extinction. In addition, overcoming bioavailability challenges, such as poor absorption and rapid metabolism of plant-derived compounds, will be critical. Advances in nanotechnology and drug delivery systems could play a key role in improving the therapeutic efficacy of these compounds.

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