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# Traditional medicinal plant Phaleriamacrocarpa (Scheff.) Boerl Prove its Worth in Modern Scientific Laboratory: Synergizing Ancient and Scientific Knowledge on Herbal Remedies for Future Clinical Usage.

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**ABSTRACT**

Phaleriama crocarpa(Scheff.) Boerl known as God's crown or Mahkota Dewa is a dense evergreen tree, indigenous to Indonesia and Malaysia. This plant has been frequently used in traditional system of medicine for the treatment of flu, rheumatism, heart diseases and cancer. Various parts of this plant such as the leaves, fruits and seeds were used for the treatment of different ailments in the indigenous system of medicine and were studied for various pharmacological activities in the modern laboratory. In view of the enormous medicinal importance of P. Macro carpa, this review was aimed at compiling all currently available botanical, phytochemical, pharmacological, and toxicological and ethnomedical information on P. macrocarpa including its efficacy as anti-breast cancer agents. Information in the biomedical literature has indicated that the traditional medicinal plant P. macrocarpaprove its worth in modern scientific laboratory which synergizing ancient and scientific knowledge on herbal remedies such as P. macrocarpa. Conclusively, P. macrocarpacan be considered as an ancient remedy to be explored for the development of various novel therapeutic agents, especially as anti-breast cancer agent.

**Keywords:** Medicinal plants; phyto chemicals; anti-cancer; breast cancer; P. macrocarpa

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## INTRODUCTION

Plants of Mother Nature are the greatest pharmacy on Earth which is constantly producing an arsenal of phytochemical with various therapeutic properties. Moreover, the traditional medicinal plants belong to a big plant Kingdome with a great interest to the modern day scientist due to their medicinal properties. Through the man's history, man has evolved with medicinal plants for hundreds of thousands of years by using plants as drugs to treat various ailments. A huge number of traditional medicinal plants are used in folk medicine and have been for more than 3000 years, such as in Indian Traditional Medicine, Chinese Traditional Medicine, etc., most of which perhaps exhibits therapeutic properties and would be recognized as such if they were properly evaluated by Western standards in the modern laboratory. One such traditional medicinal plant which is gaining more interest in the drug discovery field due to its traditional usage is Phaleriamacrocarpa(Scheff.) Boerl. In view of the enormous medicinal importance of P. macrocarpa, this review was aimed at compiling all currently available botanical, phytochemical, pharmacological, and toxicological and ethnomedical information on P. macrocarpa including its efficacy as anti-breast cancer agents. In addition, this review is also attempted to prove the worth of P. macrocarpa potentiality with various modern scientific findings in the modern laboratory and synergizing ancient and scientific knowledge on P. macrocarpa.

## METHODOLOGY

Scientific information on the topic was collected from the literature available in the various databases such as Science Direct, Scopus, Pub Med, Springer, Google and books on medicinal plants. Different combination of keywords i.e., “Phaleriamacrocarpa/medicinal plants”, “Phytochemical/Phaleriamacrocarpa”, “breast cancer/ Phaleriamacrocarpa”,“Plants as anti-cancer agent”, “Toxicity/Phaleriamacrocarpa”, “Plants secondary metabolites/Phaleriamacrocarpa”, “ethnomedical/ Phaleriamacrocarpa” and “Cancer” were applied to gather information available on the topic and P. macrocarpa. The authors also searched key articles from journals like BMC COMPLEMENTARY and ALTERNATIVE MEDICINE, Journal of Ethno pharmacology, INDONESIAN JOURNAL OF PHARMACY, INDONESIAN Journal of CHEMISTRY AND BIOMED RESEARCH INTERNATIONAL to collect as much information as possible which was relevant to the topic and P. macrocarpa. In addition, the references of selected articles were also screened manually for accuracy.

## PLANTS AS POTENTIAL NATURAL PRODUCT

Natural product to be used in medicine is derived from various sources including native plants, microorganisms, marine organisms, terrestrial vertebrates and invertebrates [1].Medicinal plants have played an important role throughout the world in treating and preventing diseases since ancient times. The discovery of pure compounds as active principles in plants was first described at the beginning of the 19th century, and the art of exploiting natural products has become part of the molecular sciences. Plants do not only provide food and shelter but also help in curing human diseases and act as a splendid source of bioactive compounds with anticancer, antioxidant, antimicrobial and anti parasitic activity which has been of recent interest among researchers [2]. The developments of natural products as medicine are due to their pharmacological activities and potential therapeutic uses. Indirectly, natural plant medicine represents a way to rescue valuable aspects of traditional culture. Drugs that are derived from natural products are effective in treating various diseases at specific characteristics with less or no side effects [3]. This is due to the bioactive compounds in natural products which give benefits to the body by improving the immune system. Indirectly, naturally-derived drugs enable patients to withstand higher and more effective dosage of treatments such as chemotherapy without additional side effects [4]. Besides that, patients from low income developing countries claim that natural products medicine are cheaper, effective and have less side effects if compared to synthetic drugs [5].

Research on medicinal plants has been supported worldwide. The major target of the research is the identification of the values of active compound in medicinal plants and the pharmacological investigation of the extracts which enhance their safety, effectiveness and constant activity. The World Health Organization (WHO) estimates that 80% of people in developing countries are on traditional medicine for their primary health care needs and about 85% of traditional medicine involves the use of plant extracts as sources of drugs.

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**PHALERIA MACROCARPA (SCHEFF.) BOERL**

**General description**

Phaleriamacrocarpa (Scheff.) Boerl, a plant from Thymelaeceae family was first designated by Scheffer as Drimyspermummacrocarpum according to fruiting specimens collected by Teysmann near Dore, in western New Guinea [6].P. macrocarpa, is commonly known as God's crown or Mahkota Dewa, is one of the Indonesian's native medicinal plants that grow on the island of Papua. It is believed to have the ability to treat various diseases with an abundance of benefits. The plant has also been used traditionally by traditional healers in medical and health treatments [7]. The name "God's crown" given to this fruit implies that it descends from heaven, as a godsend from divine powers to help mankind.

**Botanical description**

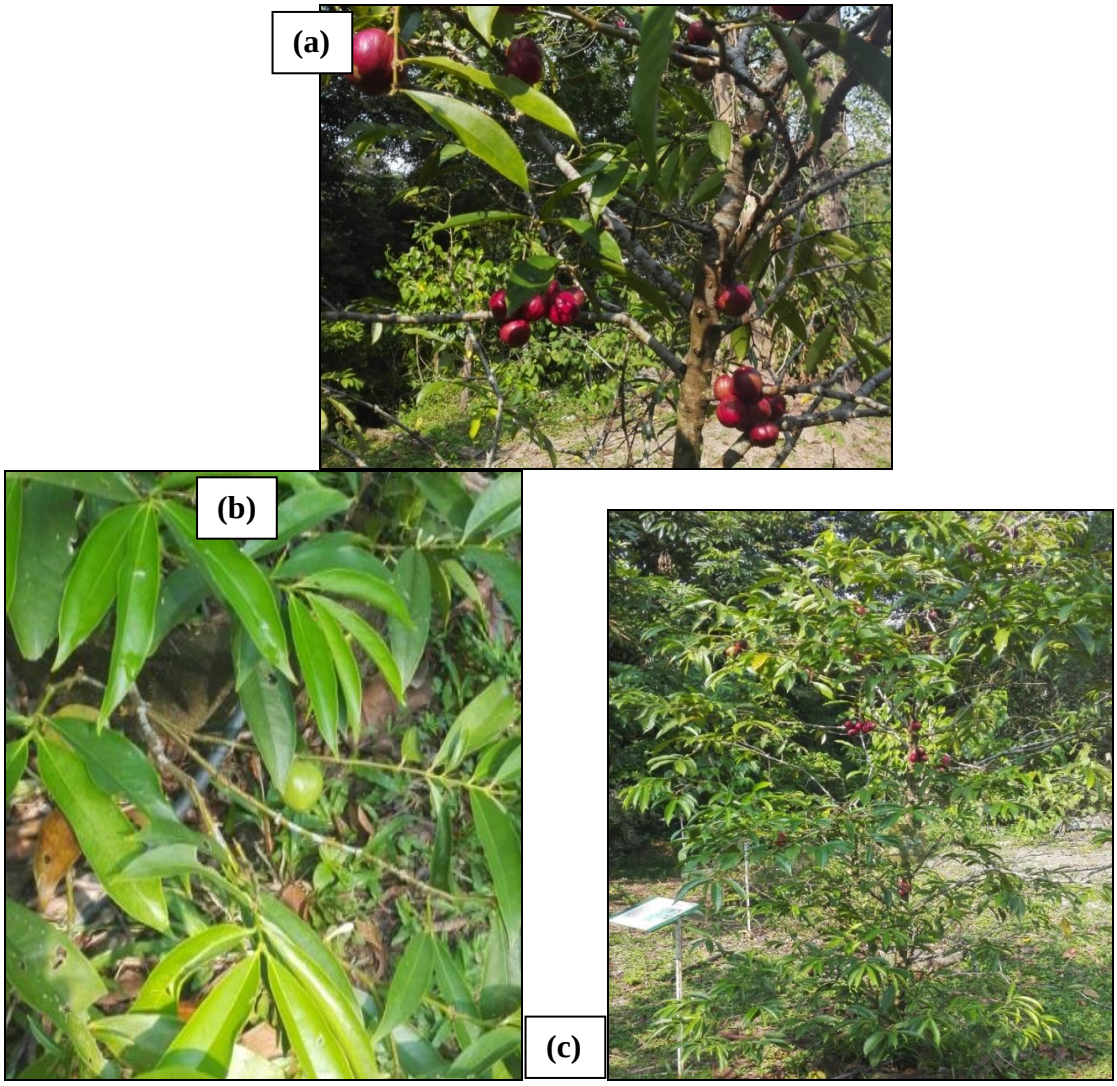


**Figure 1: Phaleriamacrocarpa (A) A bunch of red ripe fruits, (b) Phaleriamacrocarpatree, (c) Green fruit and leaves. The pictures are taken from ECO HUB, PusatRepositoriKearifanTempatan, and UniversitiSains Malaysia.**

It is a tree (Figure 1), including stem, leaves, flowers, fruits and thrives in loose, fertile soil at an altitude of 10 to 1200 m above sea level. The tree height ranges from 1 to 18 m with sap exuding 1 m long root and its bark are brownish green and it has white wood. The leaves are green in colour with the length from 7 to 10 cm and width ranging from 3 to 5 cm. The flowers are typically with 2 to 4 petals of green to

maroon colour. Seeds exist as 1 to 2 seeds per fruit and are brown, ovoid and anatropous. Although the herb is being used in both un-processed and processed form, however, the former can be poisonous and toxic [8]. P. macropcarpa fruit is of eclipse shape with a diameter of 3 cm. Fruits are green when unripe and become red on ripening [9] where the flesh is white, fibrous and watery. It can be propagated by grafting and use of seeds (generative).

**Taxonomical classification**

Table 1 showed the taxonomic classification of P. macrocarpa.

**Table 1: Taxonomic classification of Phaleriamacrocarpa**

| CATEGORY | CLASSIFICATION |
|---|---|
| Kingdom | Planate |
| Subkingdom | Tracheobionta |
| Super division | Spermatophyte |
| Division | Magnoliophyta |
| Class | Magnoliopsida |
| Subclass | Rosidae |
| Order | Myrtales |
| Family | Thymelaeaceae |
| Genus | Phaleria |
| Species | Phaleriamacrocarpa |

**Source:** Angiosperm Phylogeny Group, 2003.

**Common names**

The Javanese referred to this tree as MakutoDewo, Makutorojo, Makuto queen, Makuta god, and 'Pau' [10]. It is also called 'Simalakama' in Sumatra, Depok (West Java), 'Mahkota Dewa' in Malay, Crown of God or God's Crown in English [11].

**Synonyms**

The Latin name of plant is Phaleriamacrocarpa (Scheff.) Boerl and synonyms are PhaleriapapuanaWarb var. Wichanii (Val) Back [12]. Phaleriacalantha Gilg, Phaleriapapuana Warb. Ex K. Schum. Lauterb. and Phaleriawichmannii Valeton.

**Distribution**

P. macrocarpa is an indigenous plant from Papua Island (Irian Jaya) or Papua New Guinea, more specifically in the area of Maprik about 110 km journey from the town of Wewak. A God's Crown tree was found at about nine meters in height bearing fruit on every branch. Centuries ago samples of the Mahkota Dewa tree were transported from the island of Papua by traditional Javanese medicine men and planted in the palace grounds of Solo and Jogjakarta. Its native habitat is terrestrial primary rainforest; it grows well in tropical areas especially in Malaysia and is known as a popular herbal plantation in the South Asian countries.

**Ethnomedicinal uses**

Each part of this plant including fruits, seeds, stems and leaves have their own healing power. The fruits of P. macrocarpa have the ability to treat flu, rheumatism, heart diseases and cancer while the leaves are used to treat dysentery, allergy, tumor and impotency. The stems are beneficial in the treatment of bone cancer [13]. A decoction of the dried fruit is taken orally to control breast cancer, cervix cancer, lung disease, liver, and heart diseases. Seeds are used as external medicine for the treatment of skin problems and mainly for cultivation as a traditional bio-pesticide [14]. These proven findings are advancing current scientific research in developing various herbal formulations to inhibit the growth and spread of breast cancer [15].

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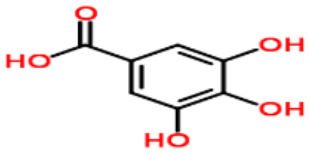
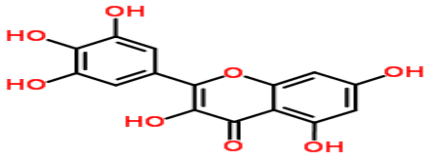
**Phytochemistry**

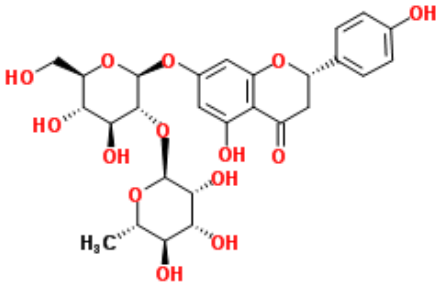
Phytochemical studies of P. macrocarpa have proven that various parts of the plant contain diverse chemical constituents. Mahkoside A (4, 4′ dihydroxy-2-methoxybenzophenone-6-O-β-D-glucopyranoside), magniferin (xanthonoid), kaempferol-3-o-β-D-glucoside, dodecanoic acid, palmitic acid, ethyl stearate, and sucrose were isolated from the seeds [16]. The bark is rich in saponins, alkaloids, polyphenolics, phenols, flavonoid and lignans meanwhile the fruit is rich in tannins, cariside C3, magniferin, gallic acid and phalerin [17]. Phalerin, known as benzophenone glycoside (3, 4, 5, trihydroxy-4-methoxy-benzophenone-3-O-β-D-glucoside) was first isolated from leaves of P. MACROCARPA [18]. The pericarp of fruit contains kaempferol, myricetin, naringin and rutin. Naringin and quercitin are found in mesocarp as well as seeds [9]. Phorboesters, des-acetyl flavicordin-A and 29-norcucurbitacin derivatives have been isolated from seeds [19].Structures of representative secondary metabolites isolated from P. MACROCARPA are shown in Figure 2.

Gallic acid - $C_7H_6O_5$





Myricetin–$C_{15}H_{10}O_8$



Naringin - $C_{27}H_{32}O_{14}$

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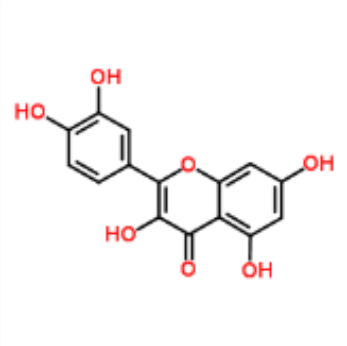
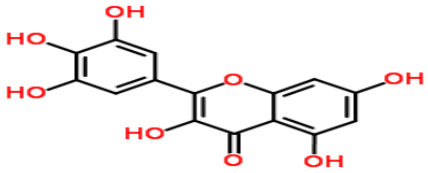
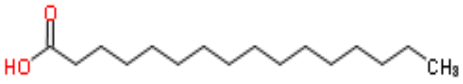


Kaempferol - $C_{15}H_{10}O_6$



Quercetin - $C_{15}H_{10}O_7$



Palmitic acid-$C_{16}H_{32}O_2$

**Figure 2: Chemical structures of some known compounds found in Phaleriamacrocarpa.**

**Source:** http://www.chemspider.com/chemical+structure

**Pharmacological activities**

P. macrocarpa was commonly used for the treatment of various diseases in folk medicine and various pharmacological activities were reported in literature including anticancer, antidiabetic, anti-inflammation, antibacterial, antioxidant, and antifungal effects [20].

**Anticancer activity**

Every part of P. macrocarpa including leaves, bark, stem, seed and fruits are widely used as traditional medicine since ancient time in treating different types of cancer especially against breast cancer [9, 21]. Many studies have been proven scientifically that gallic acid showed significant anticancer activity by inhibiting cell proliferation in different cancer cell lines such as human melanoma cell [22], human hepato cellular carcinoma cell [23], human small lung cancer cell [24] and ovarian cancer cell [25]. For example, Fariedet al. [21] has evaluated the isolated GA from P. macrocarpa which inhibited cancer cell proliferation and induced apoptosis in esophageal cancer cell (TE-2). Besides that, ethyl acetate fraction of P. macrocarpa (PMEAF) was reported to inhibit cell proliferation by inducing cell death in MDA-MB-231 breast cancer cell [13] and also has proven its capability as an anti-proliferative agent and initiates apoptotic cell death in MCF-7 cell which is an estrogen-dependent and fast-growing cell [13].

**Antidiabetic activity**

P. macrocarpa, traditionally known for its anti-diabetic properties and has been found to decrease the post-prandial hyperglycemia in diabetic patients. The bioassay-guided fractions of P. MACROCARPA FRUITwere examined for α-glucosidase and α-amylase activity to discover the anti-diabetic mechanism and potential attenuation action on post-prandial glucose increase. The study revealed that P. MACROCARPA can lower hyperglycaemia in both IN VITRO and IN VIVO experiments by effectively inhibiting carbohydrate-hydrolysing enzymes. The natural compounds from the extract have a therapeutic effect on type 2 diabetes mellitus [26]. Moreover, few studies suggested that the natural compounds from P. macrocarpa fruit extract work as healing treatment for type 2 diabetes mellitus [27]. Another study has reported to decrease the blood glucose due to the presence of magniferin in the most active n-butanol sub-fraction of methanol extract of P. macrocarpa fruit pericarp [28].

**Anti-inflammatory activity**

Latest research are more focused on developing drugs or dietary supplements using secondary metabolites of P. macrocarpa such as phalerin, saponins, and alkaloids which indicated anti-inflammatory properties. Hendra et al. [9] have done anti-inflammatory in vitro assays by using P. macrocarpamethanolic fruit extract treated against macrophage RAW 264.7 cell lines induced by LPS/IFN-γ. The results showed inhibition of inducible nitric oxide synthesis in macrophage and indicating their notable anti-inflammatory potential. Mean while, in vivoanti-inflammatory studies were conducted on animal model; Wistar female rats to determine the effect of dominant compound in P. macrocarpa; hydroxyl benzophenon glucoside. The result showed that the inflammation in rat treated with hydroxyl benzophenon glucoside at 22.5 mg/kg per body weight had decreased two-fold compared to normal drug [29].

**Antibacterial activity**

Empirically, microorganisms have shown resistance to synthetic antimicrobial agents and this resistance are the current issues in the medical field. Therefore, investigations of alternative medicines from natural products are required to solve those complications. Flavonoids are classified under phenolic groups in plants which have been known to possess antimicrobial activity. The antibacterial assay of P. macrocarpa fruit extracts was carried out by the disc diffusion method and tested against Gram-negative bacteria (Enterobacter aerogenes, Escherichia coli, Klebsiellapneumonie, Pseudomonas aeruginosa) and Gram-positive bacteria (Bacillus cereus, Bacillus subtilis, Micrococcus luteus, and Staphylococcus aureus) [9]. This study elucidated that the flavonoids compounds of P. macrocarpa fruit may possess antimicrobial activities which can be used as an alternative antimicrobial agent in pharmaceutical and cosmetic products [9].

**Antioxidant activity**

Various scientific reports have proven that P. macrocarpa is a rich source of a polyhydroxyphenolic compound known asGA which is a natural antioxidant. Furthermore, phenolics compounds from the extract of P. macrocarpa have also indicated to have biological function as an antioxidant.Lay et al. [30] have examined the antioxidant activity of P. MACROCARPA fruit extract and fractions by determining the DPPH free radical scavenging property using the UV spectrophotometric method. The results revealed that an ethyl acetate fraction of P. MACROCARPA exhibited the highest free radical scavenging activity followed by the methanol extract, hexane fraction, chloroform fraction and water fraction. A recent study was undertaken by treating fructose fed male Sprague-Dawley rats with methanolic extract of P. macrocarpa resulted in the prevention of fructose-induced oxidative stress in rats and decreased endogenous antioxidant activity [31].

**Toxicological Assessment**

Scientific information and evidence on toxicology study is very crucial in terms of safety, quality, and associated toxicity and on the side effects of long term use of the products.A toxicity assessment provides an estimate of how much of a chemical substance is needed to cause harm, in addition to the types of harm it causes. The right dosage differentiates a poison from a remedy [32]. There are different procedures to assess carcinogenic or non-carcinogenic effects which can elucidate the consequence and importance of a toxicity

assessment. Toxicological studies are conducted by exposing animal (in vivo), cells or tissues (in vitro) to chemicals. In addition, intake of medicinal plants without assessing its efficacy and safety can cause unpredicted toxic effects that may damage the organs in the human body. Liver and kidney are the main targets in toxicological evaluation due to the metabolic activity and excretion of chemical components.

Even though P. macrocarpa has been claimed for its abundance of valuable medicinal properties as therapeutic agents, it may show toxicity effect at high concentrations. Due to the possibility of toxicity effect, supportive toxicity study on P. macrocarpa is needed to evaluate the efficacy and safe concentration to produce promising data of P. macrocarpa in curing diseases. Chong et al. [33] reported that P. macrocarpa exhibited fetotoxicity effect in female mice when fed at dose of 27 mg/kg. Besides that, the fresh fruit of P. macrocarpa is taken orally as traditional medicine for treatment of ulcers by the Indonesians [28]. Butanol extracts of ripened fruits of P. macrocarpa is reported to cause mild necrosis of proximal convoluted tubules in mice kidney at a dosage higher than 85 mg/kg [34, 35].Moreover, toxicological assessment will give a very good indication and the confidence to move the research to clinical trials with suggested bioactive compound of P. macrocarpa in future.

**Precautions/Safety for Usage**

Almost all traditional medicinal plants usage is based on knowledge, skills, practices and beliefs of indigenous people of different culture, and is not scientifically validated for its safety and effectiveness. Each drug derived from plants need appropriate scientific knowledge and information about therapy to prescribe and administer accurately. Fundamentally, some important precaution should be taken to ensure the plant parts are not sprayed with weed killer or pesticides. Then the samples are needed to be washed thoroughly or soaked in water to remove unwanted pollutants before being further processed as dietary or supplements.

The bioactive components extracted from natural plant or herbs with therapeutic activity need to be identified and the preparation should be standardized by quantifying chemical constituent through acceptable analytical methods. In order to analyze the causes of adverse effects of the drugs, it needs a specific technical expertise, facilities and suitable analytical laboratories to investigate the products concerned. For example, the WHO guidelines on safety monitoring of herbal medicines in pharmaceutical industries were used to analyze the herbal products [36]. Certain imperative challenges regarding effective observation of natural or herbal derived medicine safety are critically important. Therefore, an adequate protection of public health can be provided by focusing on related regulatory agencies involved in producing material safety data sheet (MSDS) of the herbal products [37].

**CANCER**

Cancer is currently the second leading cause of death after heart diseases worldwide [36]. In Malaysia, cancer is a major cause of morbidity and mortality among Malaysian population. According to National Cancer Registry Data, it was estimated that there are nearly 40,000 new cases per year and a cumulative lifetime risk of about 1:4. In addition, reports from the National Cancer Society of Malaysia (NCSM) projects presented that one in every four Malaysians is likely to develop cancer by the age of 75 years.

There are plenty of known cancer types characterized by its origin such as breast cancer, bladder cancer, lung cancer, brain cancer, melanoma, non-Hodgkin lymphoma, cervical cancer, ovarian cancer, colorectal cancer, pancreatic cancer, oesophageal cancer, prostate cancer, skin cancer etc. Typically, cancer can be initiated through genetic disorders when a defective gene in a particular chromosome is passed to the next generation or when imperfections in DNA replication are found in inherited genes [38, 39]. An increase in the ageing population, obesity, physical inactivity, nutrition intake and environmental risks such as the annual haze in Malaysia are some of the additional factors. Several cancers are associated with infectious virus and bacteria such as hepatitis B virus (HBV), human papillomavirus (HPV), human immunodeficiency virus (HIV), and Helicobacter pylori (bacteria).

Cancer is the abnormal cell growth that forms tumours and these tumours can be divided into ‘benign’ (non-cancerous cells) and ‘malignant’ (cancerous cells) that invade and destroy healthy tissue in a process called invasion. In recent years, there is advancement in cancer treatments where more than cures, scientists are enthusiastically finding possibility of early detection and prevention of cancer [40]. Since, cancer

requires a long time to develop; therefore, there are opportunities to prevent cell proliferation, mutation and cancer progression at an early stage. The most common type of cancer treatment is surgery which implies the primary treatment option for most types of cancer is to remove solid tumours. In addition, another two common treatments are radiotherapy that uses high-energy X-rays and chemotherapy that uses powerful cancer-killing medications. Although modern treatments aim to eliminate the cancer cells but side effects still arise with the use of synthetic drugs in cancer treatment [41].

**Breast cancer**

Breast cancer affects women worldwide and it is the leading cause of fatality in Asia but it occurs less frequently in men. Originally, breast cancer cells are formed in the tissues of the breast and divide at an abnormally faster rate to form a lump. There are two types of breast cancer namely ductal carcinomas beginning in the tubes (ducts) and lobular carcinoma in the parts of the breast (lobules). Breast cancer rates are increasing with age of most women above 50's and treatments vary depending on stage (Stage I, II, III and IV) of cancer [42]. The stages of breast cancer are crucial factors in determining prognosis before treatment starts. Staging involves clinical examination, mammogram, biopsy, and certain imaging investigation such as chest radiograph (CXR), liver ultrasound (LUS), bone scan (BS), computed tomography scan (CT scan) and magnetic resonance imaging (MRI) [43].

Surgery to remove cancerous tissue is known as 'lumpectomy' (remove the cancer and leave the healthy tissue behind) and 'mastectomy' (removal of all the breast gland tissue). Subsequently, chemotherapy treatments are given through injection of 'chemo' medicine such as docetaxel, paclitaxel, vinorelbine, capecitabine, liposomal doxorubicin, gemcitabine, and mitoxantrone to kill cancer cells. Radiation therapy, which involves a high-dose of radioactive substance (brachytherapy) that injected into blood to destroy cancerous tissue. Final follow up with hormone therapy medicine for breast cancer such as tamoxifen, toremifene, and fulvestrant as an oral intake for long period of time with a minimum 5 years [44]. It is a preventive measure to prevent gene alteration in cancer cells which blocks specific hormones that stimulate cancer development. Hormone medicine namely Tamoxifen, is specifically endorsed for women of breast cancer with hormone receptor-positive (ER- positive) breast cancers, but there is no effective medicine for women with hormone receptor-negative (both ER- negative). Example of ER positive breast cancer cell lines such as MCF-7, T-47D, BT-474,BT-483, and 600MPE while ER negative breast cancer cell lines are MDA-MB-231, SkBr3, Hs578T, Evsa-T, BT-549, BT-20, and AU565 [45].

Unfortunately, most of the treatments cause side effect, different treatment dose response and resistance after prolonged exposure to the treatments. The synthetic drugs applied in chemotherapy and radiation treatment not only kill the cancer cells but also affect the healthy cells by causing side effect such as nausea, anaemia, vomiting, weakening of the immune system, diarrhoea and hair loss. Studies have proven that cancer cells have the ability to change and develop resistance towards chemotherapeutic drugs due to the prolonged intake [46]. Therefore current studies focus more on finding novel therapeutic agents derived from natural products/plants as anticancer agents which effectively treat cancer with less/no side effects.

## PLANT AS ANTICANCER AGENTS

Since ancient time, plants possess medical history in the treatment of cancer according to Hartwell [47], where it has been acknowledged that more than 3000 plant species were discovered as a favourable natural medicine in treatment of cancer but some of this plant species were used without proper references.

Currently there are many experiments being carried out to isolate the bioactive components as anti-cancer agents. The potential new anticancer drugs which are undergoing pre-clinical trial are selected based on molecular targets and are comparable or even have better outcomes than synthetic drugs. There are several plant-derived anticancer drugs that are successfully used namely; vincristine, the camptothecin derivatives, topotecan and irinotecan, etoposide, derived from epipodophyllotoxin, and paclitaxel [48].

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**P. MACROCARPA PROVE ITS VALUE CLAIMS TRADITIONALLY AS AN ANTICANCER AGENT IN MODERN SCIENTIFIC LABORATORY**

Traditional medicinal plant P. macrocarpais still prominent and is considered an important medicinal plant particularly in developing countries. Despite its well-known traditional benefits as an anticancer agent, P.macrocarpa is still proved its value claims as an anticancer agent through various modern sophisticated techniquesin the modern scientific laboratory (Figure 3). Numerous studies showed cytotoxicity and anticancer activities of P. macrocarpa various parts crude extract or isolated compounds against various human cancer cell lines through the induction of cell cytotoxicity, induction of apoptotic cell death, cell cycle arrest and induction of apoptotic protein [9, 13, 21, 49-66].Beside their anticancer activity against various cancer cells, P. macrocarpa also exhibited good anticancer activity against human breast cancer cell line such as MDA-MB231 cell, MCF-7 cell and T-47D cell [9, 13, 52-55, 58, 61, 63].

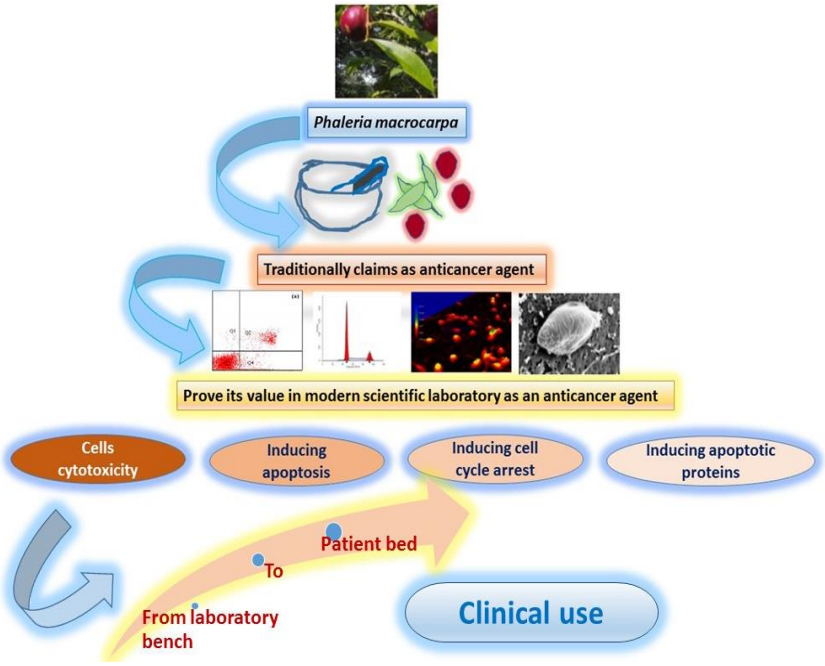


**Figure 3: Anticancer potentials of tradition medicinal plants of Phaleriamacrocarpa**

Recently, Kavitha et al. [53] reported the P. macrocarpafruit ethyl acetate fraction (PMEAF) anticancer activity and the underlying molecular mechanism of cell death in the MDA-MB231 cell. Their findings showed that the AO/PI staining and flow cytometric analysis of MDA-MB-231 cells treated with PMEAF were exhibited apoptotic cell death. The cell cycle analysis by flow cytometry analysis revealed that the accumulation of PMEAF treated MDA-MB-231 cells in G0/G1 and G2/M-phase of the cell cycle. Furthermore, the PMEAF exert cytotoxicity by increased the ROS production in MDA-MB-231 cells consistently stimulated the loss of mitochondrial membrane potential (ΔΨm) and induced apoptosis cell death by activation of numerous signalling proteins. The results from apoptosis protein profiling array evidenced that PMEAF stimulated the expression of 9 pro-apoptotic proteins (Bax, Bid, caspase 3, caspase 8, cytochrome c, p21, p27, p53 and SMAC) and suppressed the 4 anti-apoptotic proteins (Bcl-2, Bcl-w, XIAP and survivin) in MDA-MB-231 cells. Conclusion The results indicated that PMEAF treatment induced apoptosis in MDA-MB-231 cells through the intrinsic mitochondrial related pathway with the participation of pro and anti-apoptotic proteins, caspases, G0/G1 and G2/M-phases cell cycle arrest by p53-mediated mechanism. These findings were further proved by Kavitha et al. [52] by various conventional and modern in situ microscopies techniques such as light microscopy, holographic microscopy, transmission (TEM) and scanning (SEM) electron microscope by the observation of morphological changes in PMEAF treated MDA-MB-231cells for 24 h. The characteristic of apoptotic cell death includes cell shrinkage, membrane blebs, chromatin condensation and the formation of apoptotic bodies were observed via these various in situ microscopies techniques.

Moreover, Tjandrawinata et al. [13] also reported a similar anticancer study on DLBS1425, a standardized extract of flesh fruit of P. macrocarpa against MDA-MB-231 and MCF-7 cells. DLBS1425 showed

an inhibition of proliferation in both cell lines in their study. Induction of apoptosis was shown by DNA fragmentation, activation of caspase 9, and regulation of Bax and Bcl-2 at the mRNA level. DLBS1425 down regulated COX-2, cPLA2, and VEGF-C mRNA expressions. DLBS1425 also down-regulated c-fos and HER-2/neu mRNA expression in TPA- or fatty acid-induced MDA-MB-231 cells. Fevicordin-A (FevA) isolated from P. macrocarpaseeds was evaluated for its potential anticancer activity against MCF-7 and T-47D human breast cancer cell lines. Cytotoxicity studies conducted by Muchtaridi et al. [58] indicated that FevA was selective against cell lines of human breast adenocarcinoma (MCF-7) with an $IC_{50}$ value of 6.4 µM. At 11.2 µM, FevA resulted in 76.8% cell death of T-47D human breast cancer cell lines.

The most recent studies by Kavitha et al. [67] have demonstrated a potent anticancer potential of P. MACROCARPA, especially against HeLa cell by the regulation of MIRNAS in MDA-MB-231 cells treated with P. MACROCARPA ethyl acetate fraction. They reported that P. MACROCARPA ethyl acetate fraction treatment against MDA-MB-231 cells identified 10 up regulated and 10 down regulated MIRNAS. A set of 606 target genes of 10 up regulated MIR NAs and 517 target genes of 10 down regulated MIRNAS were predicted based on computational and validated databases by using MIR Gate DB Query by this group. Meanwhile, their results from DAVID Bioinformatics Resources 6.8 specified the functional annotation of the up regulated MIRNAS involvement in cancer pathway by suppressing the on cogenes and down regulating MIRNAS by expressing the tumor suppressor genes in the regulation of apoptosis pathway.

## SUGGESTION FOR FUTURE CLINICAL USAGE OF P. MACROCARPA

The potential advantage of P. macrocarpaas an anticancer agent as claims traditionally is of interest since cancer can be deadly and it is an important health issue in many countries [68].Although there are numerous reports on the anticancer effect of P. macrocarpa, the in vitro cell studies, in vivo and preclinicalfindings should move from laboratory bench to patient bed at clinical level to translate the bench results to the bedside of herbal products [69]. Toxicity problem of administration of P. macrocarpa herbal preparation in humans is an important issue. Therefore, additional detail studies have to be carried out in order to establish the toxicity effect of the extracts from the various part of P. macrocarpa in the translational processes of moving the laboratory bench results to the patient bedside. In addition, the bioavailability and therapeutic efficacy of P. macrocarpa in human may also limit by the various factors such as the poor absorption, rapid metabolism, and ultimately poor oral bioavailability of P. macrocarpa herbal preparation in the clinical usage. However, current advances in the nanotechnology-based drug delivery is an available approach to solving these issues and more future research should be conducted in this direction on nanotechnology-based applications and developments on P. macrocarpa herbal preparation based delivery systems [70, 71].

Besides that, P. macrocarpa herbal preparation also can be consumed in a range of methods such as by drinking as teas, capsules and tinctures as a supplement or functional food by the patient. Some herbal preparation may necessitate precise preparation approaches to yield the desired and most effective results for a particular condition. In such cases, different preparations of herbal medicines such as infusions (hot teas), decoctions (boiled teas), tinctures (alcohol and water extracts), and macerations (cold-soaking) method can be used to prepare the herbal remedies to achieve the desired and most effective results. The selection of appropriate preparation method is important since different methods facilitate the extraction of different type of phytochemical into the herbal remedy that is being prepared [72].

## CONCLUSION

Traditional medicinal plants such as P. macrocarpaare gaining more interest in the drug discovery field due to its traditional usage and the fact that they are rich in valuable phytochemical which can be extracted to treat various diseases at clinical stage. This is a detailed review of the botanical, Ethnomedicinal usage, phytochemistry, pharmacological and toxicological information on the medicinal plant P. macrocarpawhich have been widely used in folk medicine and attracted the attention of world researchers and scientist. Collectively, all the experimental results indicated that P. macrocarpa has potential as a candidate for an anticancer agent, which is worth promoting for further preclinical and clinical evaluation, especially against breast cancer. In summary, this review proved the worth of P. macrocarpa potentiality with various modern scientific findings in the modern laboratory and synergizing traditional and scientific knowledge on P. macrocarpa for the betterment of human race.

## CONFLICT OF INTEREST

Authors declare no conflict of interest in the present work.

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