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# Potential of Indonesian Herbal Medicine, *Phaleria macrocarpa* (Scheff.) Boerl, for Targeting Multiple Malignancy Signaling Pathways: An Introductory Overview

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***Authors' contributions***

*This work was carried out in collaboration between all authors. Authors AF, HMBB, LS and DK designed the study and wrote the first draft of the manuscript. Authors AF, MZA and FFW supervise the study and the literature searches. This study was supported by the Academic Leadership Grant (ALG) 1-1-6 Universitas Padjadjaran 2015, Bandung, Indonesia for authors AF, MZA and FFW. All authors read and approved the final manuscript.*

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## ABSTRACT

A wide variety of natural compounds have been recognized for targeting multiple malignancy signaling pathways and inducing apoptosis in various cancer cell lines from different origins. The chemical compositions of those substances present in plants contribute to their significant biological and medicinal value. In this review, we summarized our current findings and knowledge

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of bioactive compounds isolated from the Indonesian medicinal herb, *Phaleria macrocarpa* (Scheff.) Boerl, also known as Mahkota Dewa (MaDe) that originated from Papua province. A growing body of evidence from several countries suggests that the plant possesses potential for cancer therapy and chemoprevention. Exploring its mechanism in targeting multiple malignancy signaling pathways will provide valuable information for possible clinical applications in cancer management.

*Keywords: Indonesian herb medicine; Phaleria macrocarpa; signaling pathways.*

## 1. INTRODUCTION

Indonesian tropical forests are abundant in natural resources; it covers approximately 143 million hectares, and about 80% of the world's medicinal plants are present there [1]. It is the second richest in terms of biodiversity after the Brazilian Amazon forest. It is estimated to harbor approximately 28,000 plant species, which 1,845 of them have been identified as medicinal plants [2]. According to the Indonesian Agency of Drug and Food Control, 283 species of those medicinal plants have been officially registered for their medicinal usage and have been used by the Indonesians as traditional medicines. A total of 180 of these species are from the tropical forests, and 49% of them grow in the low-altitude areas [3].

In recent years, the demand of potent and safer compounds for cancer therapy and chemoprevention has been increasing. Natural bioactive compounds derived from plants and their synthetic derivatives are expected to play an important role in the creation of novel and improved therapies for cancer management, both as monotherapy and in combination with conventional anticancer drugs. *Phaleria macrocarpa* (Scheff.) Boerl or *Phaleria papuana* Warb var. *Wichnannii* (Val) Back, commonly known as Mahkota Dewa (MaDe), is a medicinal plant that originated in Papua (Fig. 1) [4]. It is popular among Indonesians due to its wide array of medicinal properties. *In vitro* and *in vivo* studies have demonstrated that the fruits and leaves extracts of MaDe to have anti-hyperlipidemic [5], anti-hyperglicemic [6,7], anti-oxidant [8], anti-inflammatory [9,10], anti-bacterial and -fungal [11], and anti-artheroscleritic effects [12]. Moreover, its potency as an anticancer agent has been known for generations. Many studies have been conducted about the extraction, isolation, and characterization of MaDe's bioactive constituents (compounds) as potential sources of anticancer agents [13-16].

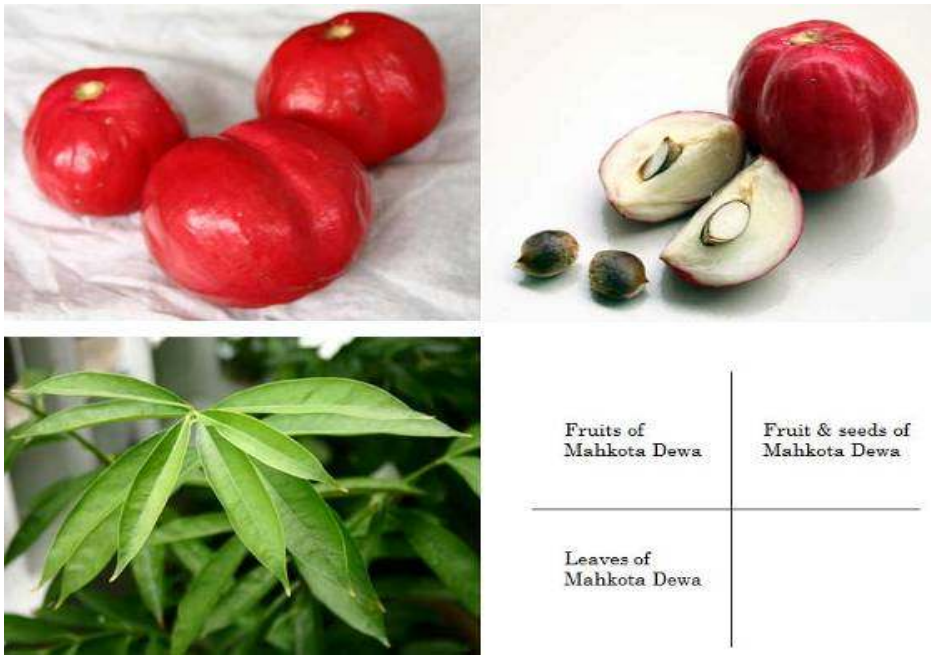



**Fig. 1. Fruits, stems, seeds, and leaves of Mahkota Dewa (MaDe)**

### 1.1 *Phaleria macrocarpa* (Scheff.) Boerl Extract Used as Traditional Medicine

Mahkota Dewa, is a medicinal plant used as an alternative therapy in cases of advanced cancer in Indonesia [17]. A growing body of evidence suggests that fruit extract of MaDe activates cell death extrinsically, and through intrinsic mitochondrial pathways triggers apoptotic cell death, as shown by the expression of poly ADP-ribose polymerase or PARP, the best-known biomarker of apoptosis [18]. Along with that, the extract also disrupts the Bcl-2 family protein (Bax, Bcl-2, and Bcl-xL) balance, activating the apoptosis machinery, which then inhibits cancer development and progression.

### 1.2 Bioactive Compounds Isolated from *Phaleria macrocarpa* (Scheff.) Boerl

In this article, we summarized the bioactive compounds isolated from MaDe, as reported in available literatures (online and offline). Entrez PubMed, ISI Web of Science, and other resources were used to retrieve any online publications available in English and Indonesian, as discussed below:

## 2. PHENOLIC COMPOUNDS

### 2.1 Flavonoids (Polyphenols)

The human diet contains a complex mixture of plant polyphenols. Humans consume as much as one gram of plant phenols per day in their diets [19]. Many studies have shown the cytotoxic effect of plant polyphenols against various types of cells in mediating cell death [20,21].

#### 2.1.1 Flavonols: Kaempferol

A research group in China isolated and identified Kaempferol-3-*O*-β-D-glucoside (Table 2, no. 1) from the fruits of MaDe [22]. Kaempferol was also isolated from *jamu* (traditional Indonesian medicine from plants) and was found to protect H4IIE rat hepatoma cells against oxidative stress [23]. The ability of Kaempferol to inhibit the breakage of DNA strands from oxidative stress supports its role as a protective agent against cancer [23]. Kaempferol increased the number of cells in the $G_2$/M phase and sub-$G_1$ among leukemia cells and enhanced the activation of caspase-3 expression. However, it induced mitochondrial membrane potential loss, which is commonly, if not exclusively, associated with the occurrence of DNA fragmentation during apoptosis [24].

### 2.2 Phenolic Acids

#### 2.2.1 Gallic acids

We and others isolated gallic acid (GA; (Table 2, no. 2) from the fruits of MaDe [14,25-27]. GA selectively induced cancer cell death in various cancer cells, such as human esophageal cancer (TE-2), gastric cancer (MKN-28), colon cancer (HT-29, Colo201, and colon26), breast cancer (MCF-7), cervical cancer (CaSki) [14], and malignant brain tumor (CGNH-89 and CGNH-PM) [24,27]. GA isolated from MaDe demonstrated a significant inhibition of cell proliferation in a series of cancer cells and induction of apoptosis in esophageal cancer cells (TE-2), but not in non-cancerous cells (CHEK-1). Observation of the molecular mechanism of apoptosis showed that GA up-regulated the pro-apoptosis protein, Bax, and induced caspase activity. Synergistically, GA also down-regulated anti-apoptosis proteins, such as Bcl-2 and Xiap (Fig. 2) [14,25,28], and Akt/mTOR survival pathway. In contrast, in non-cancerous cells, we observed delayed expression of pro-apoptosis-related proteins and no reduction of the survival-related protein expression in the non-cancerous CHEK-1 cells. It is tempting to speculate that GA might be less harmful in CHEK-1 cells, as it did not affect the cell cycle profile [14,25,28]. The cell death observed in our study is apoptosis, which we speculate that there are other form that might involve in the process, such as necrosis and/or authophagy. You BR, et al., shown that GA not only induced apoptosis cell death but also necrosis in HeLa cells [27].

The activity of Akt/mTOR pathway is upregulated in many human cancer cells [29-30], including perturbation of the upstream growth factor receptor and PI3K (Fig. 3). By blocking the pathway, the proliferation of tumor cells can be impeded by either inducing or sensitizing tumor cells to undergo death in response to other cytotoxic agents [31]. We and other showed that mTOR signaling has a role in regulating translation of apoptosis protein Bcl-XL through eIF4E, downstream of mTOR. Bcl-XL, an anti-apoptotic protein, inhibits apoptosis by blocking the release of cytochrome c from mitochondria [32,33].

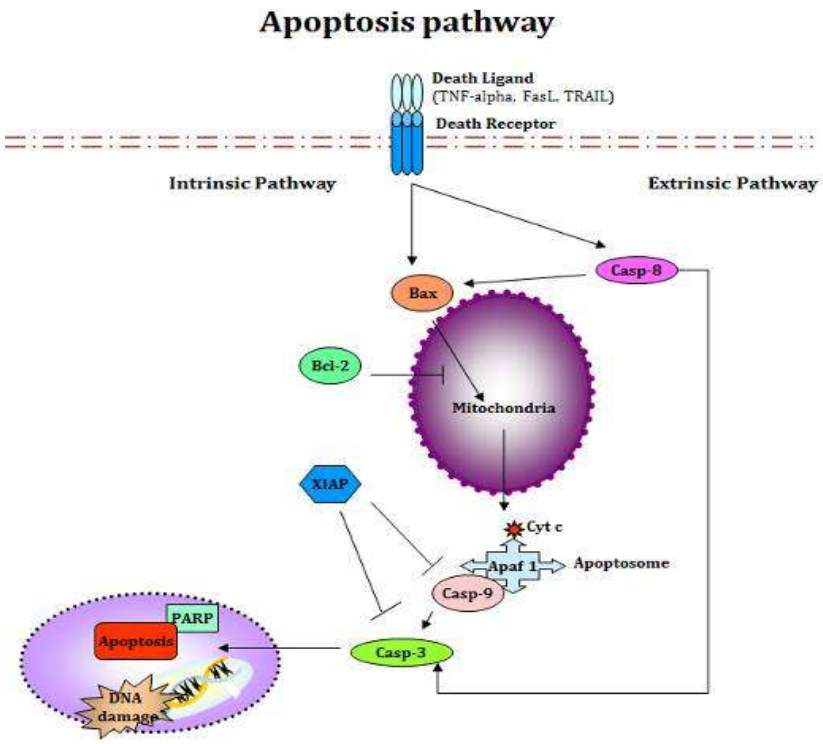



**Fig. 2. Schematic illustration of apoptotic cell death pathways modulated by Gallic acid (GA) isolated from the fruits extracts of Mahkota Dewa (MaDe) in esophageal cancer cell, TE-2 (see text for details)**

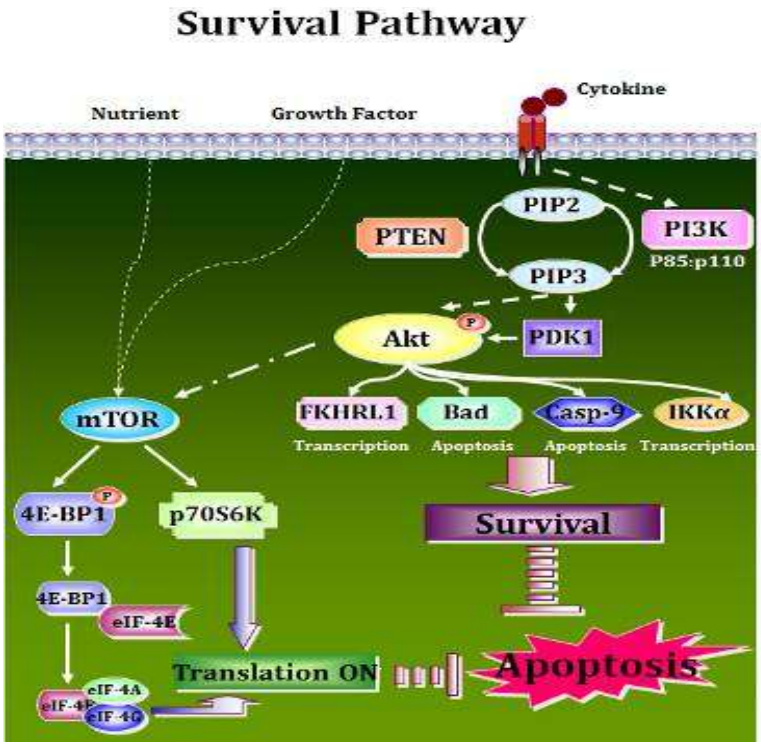



**Fig. 3. Schematic illustration of Akt/mTOR survival pathways**

#### 2.2.2 Tannic acids

(Table 2, no. 3). Large amounts of Tannins are present in the natural kingdom [34]. Fruits and leaves of MaDe have been known to contain Tannin [35], which is closely correlated with the induction of apoptosis and inter-nucleosomal DNA fragmentation in leukemia cells, HL-60 [36].

#### 2.2.3 Lignans

Lignans are compounds present in plants. Plant lignans are polyphenolic substances derived from phenylalanine via dimerization of substituted cinnamic alcohols, known as monolignols, to dibenzylbutane. Plant lignans can be converted by intestinal bacteria into Enterolignans, Enterolactone, and Enterodiol [37]. It has long been assumed that only Secoisolariciresinol and Matairesinol are converted into Enterolignans. In addition, other Enterolignan precursors, i.e., Pinoresinol and Lariciresinol, were discovered [38]. Lignan formation is known to play a role in cancer chemotherapy [39].

#### 2.2.4 Pinoresinol

An Indonesian researcher in Germany isolated and identified Pinoresinol from wood MeOH-extract of MaDe using semi-preparative HPLC [40]. Pinoresinol has a cytotoxic effect in human cervix carcinoma, the KB cell line (derivative of HeLa) [41]. In parallel with that, other researchers isolated Pinoresinol lignan from the stems of *Helicteres hirsuta* of Indonesian origin [42]. In agreement with the previous finding, Pinoresinol (Table 2, no. 5) was found to be the most cytotoxic among six other isolated compounds from *Helicteres hirsuta* against human lung (Lu1), prostate (LNCap, hormone-dependent), and breast cancer (MCF-7) cells [42].

#### 2.2.5 Lariciresinol

Lariciresinol is a dietary lignan that accounts for a significant portion of the total phytoestrogen intake from Western foods. Lariciresinol is bioavailable as it is found in human serum and urine. When ingested, lariciresinol can be metabolized first to secoisolariciresinol, and then further to enterolignans, *e.g*., enterodiol and enterolactone. Interestingly, all these 3 compounds have been shown to attenuate breast cancer growth in different estrogen-responsive experimental cancer model *in vivo* [43]. Recent epidemiological studies suggest that high dietary intake of lignans and lariciresinol is associated with reduced breast cancer risk [44]. However, no causal relationship between lariciresinol intake and breast cancer development has been established. Lariciresionol (Table 2, no. 6) was also isolated from MaDe with the same method used to isolate Pinoresinol [40].

#### 2.2.6 Matairesinol

Primarily, Matairesinol (Table 2, no. 4) was isolated from the roots and callus extracts of MaDe using HPLC with a C18 column. It was identified by its UV and MS spectra analysis [45]. The roots contain ~0.3-0.5 mg/g dry weight Matairesinol, and the callus, ~0.2 mg/g. Previously, a researcher at the University of Indonesia had isolated a novel compound, cytotoxic lignin, from the fruits extracts of MaDe; this compound is similar to Syringaresinol (Table 2, no. 7) [6]. The anti-proliferation and hormone-decreasing effect of Matairesinol in choriocarcinoma, Jeg-3 cell line, suggested that matairesinol mediates its anticancer effect through an estrogen receptor [46].

## 3. TERPENES (ISOPRENOIDS) COMPOUNDS

### 3.1 Triterpenes

Terpenes are a large and varied class of hydrocarbons; they are produced by a wide range of plants. When terpenes are chemically modified, such as by oxidation or rearrangement of the carbon skeleton, the resulting compounds are commonly referred as terpenoids. Triterpenes belong to a large group of compounds arranged in a four or five ring configuration of 30 carbons with several oxygen attached. Triterpenes are assembled from a C5 isoprene unit through the cytosolic mevalonate pathway to make a C30 compound and are steroidal in nature.

#### 3.1.1 Cucurbitacins: Fevicordin A

The natural Cucurbitacins are a group of tetracyclic triterpenoid derived from the Curcubitacin skeleton and are found primarily in the Cucurbitaceae family. They are well known for their bitterness and toxicity, and their usage in traditional medicine to treat inflammatory diseases and cancers. Twenty-eight or twenty-nine Norcucurbitacin are members of Cucurbitacin family that contain a A-aromatic ring.

A new class of Norcucurbitacins is Fevicordin A and Fevicordin A glucosides [47]. We isolated an active compound from the seeds extracts of MaDe and was identified as Fevicordin A (Table 2, no. 8) [48]. In addition, we isolated and identified other active compounds from the seeds extracts of MaDe, which were: 29-Norcucurbitacin, Deacethyl fevicordin A (Table 2, no. 9), Fevicordin A glucoside (Table 2, no. 10), and Fevicordin D glucoside (Table 2, no. 11) [49; Kurnia D, unpublished data 2006]. We and others found that Cucurbitacins, including the Fevicordin family, have anticancer effects in cancer cells. [48,50,51].

### 3.2 Saponins

Saponins are glycoside groups of steroids, steroid alkaloids (steroids with a nitrogen function), or triterpenes found in plants, especially in plant skins, where they form a waxy protective coating. Saponins are found in the fruits and leaves extracts of MaDe [50,52]. They have been shown to provide protection to humans against cancer [53].

### 3.3 Quinones

Anti-insecticide, such as Toluquinone (Table 2, no. 12), Ethylquinone (Table 2, no. 13), Octanoic acid (Table 2, no. 14), 1-Nonene (Table 2, no. 15), 1-Undecene (Table 2, no. 16), 1-Pentadecene (Table 2, no. 17), 1-Heptadene (Table 2, no. 18) and 6-alkyl-1-4-Naphtoquinone (Table 2, no. 19) have been found in the latex of seeds of MaDe [54]. It has been confirmed that the seeds extracts of MaDe is highly toxic against the larva and adult stage of mosquito, *Aedes aegypti* Linn [55].

## 4. ALKALOIDS COMPOUNDS

The alkaloids are a large family of more than 15,000 nitrogen-containing secondary metabolites found in approximately 20% of the species of vascular plants. The nitrogen atom in these substances is usually part of a heterocyclic ring which contains both nitrogen and carbon atoms. Most alkaloids are alkaline, positively charged, and water soluble. Building block of alkaloids are acetate, amino acids, terpenoids and cholesterol with biological activity for nitrogen storage, detoxification, deterrent and allelochemical. Alkaloids are naturally occurring amines produced by some plants, and they are found in the fruits and leaves extracts of MaDe [50,52]. Alkaloids are strongly suggested to have anticancer activity [56].

## 5. BENZOPHENON COMPOUNDS

Benzophenones are a class of compounds that can be obtained from natural products or synthetic methods [57]. Benzophenone is the organic compound with the formula $(C_6H_5)_2CO$ and generally abbreviated $Ph_2CO$. Researchers isolated benzophenone glucosides from the fruits extracts of MaDe [58,59]: Makoside A (Table 2, no. 20) [22], 4,5-dihydroxy-4'-metoxy benzophenone-3-*O*-glucoside (Table 2, no. 21), 4'-6-dihydroxy-4-metoxybenzophenone-2-*O*-glucoside (Table 2, no. 22), 3,4,5-trihydroxyl-4'-methoxybenzophenone-3-*O*-β-D-glucoside (Table 2, no. 23) and 2,4′,6-trihydroxyl-4-methoxybenzophenone-2-*O*-β-D-glucoside known as Phalerin (Table 2, no. 24), from the leaves extracts of MaDe [13,60-62]. Benzophenones were proven to exhibit significant anticancer activity both *in vitro* and *in vivo* [61,63,64].

In addition to antioxidant and anticancer compounds, an Oxytocin-like compound was also isolated from the fruits and leaves extracts of MaDe [65]. Moreover, in a recent study from China, Japan, Malaysia and Indonesia there are several compounds that were isolated from the fruits extracts of MaDe. They were Dodecanoic acid (Table 2, no. 25), Palmitic acid (Table 2, no. 26), Ethyl stearate (Table 2, no. 27), Sucrose (Table 2, no. 28) [22], vasorelaxant icariside $C_3$ (Table 2, no. 29) [60], and Mangiferin (Table 2, no. 30) [22,62,66]. One study reported that MaDe shown the potential effect in improving the male fertility [67]. The representative mechanism of the MaDe active compound(s) is summarized in Table 1.

### 5.1 MaDe Function and Therapeutic Implications

Interference with the signaling pathways downstream of receptors, both survival and cell death pathways, may result in the modification of the potential for growth (either by increasing mitosis or altering the level of cell death), and thus, can be targeted for cancer prevention [68[. Some of the major signal transduction pathways in cancer that are commonly up- or down-regulated by the active compound of MaDe are briefly described above, and the imbalance of the malignancy signaling pathways resulting from use of MaDe is illustrated in Fig. 4. All parts of MaDe, such as pericarp, mesocarp and seed

shown to have variable results, but the seed is superior effect as potential anticancer activity above all [69]. Recent study showed that Fevicordin A isolated from the seed acted as human Estrogen Receptor Antagonis (hERα), which make it a good candidate as an anticancer agent [70]. This short review addressed the frequently asked question regarding MaDe's potential by examining the current status of its molecules and the signal transduction targets they modulate. Those active compounds, as summarized in Table 2, and their mechanism of actions exemplify the current and future potential of natural products in drug discovery.

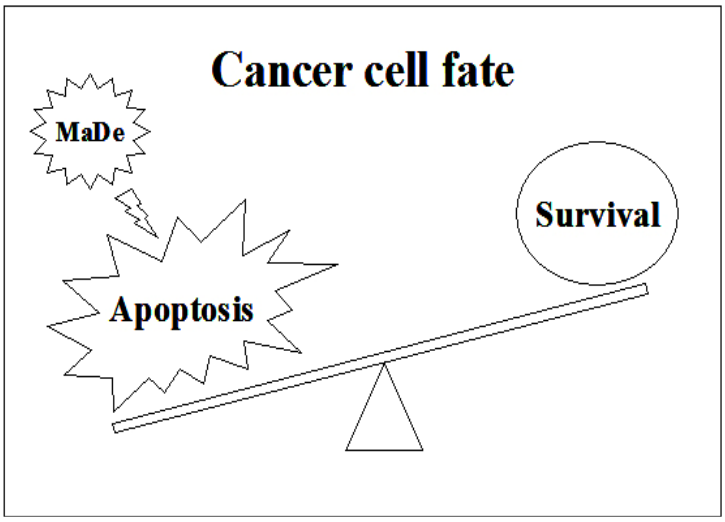


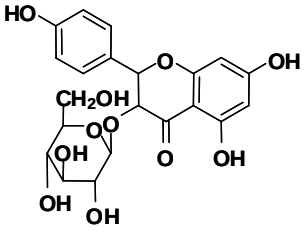

**Fig. 4. Propose model of imbalance interactions of survival and apoptotic cell death induced by active compound(s) from MaDe in cancer cell fate**

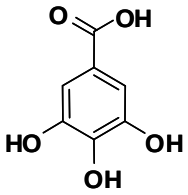
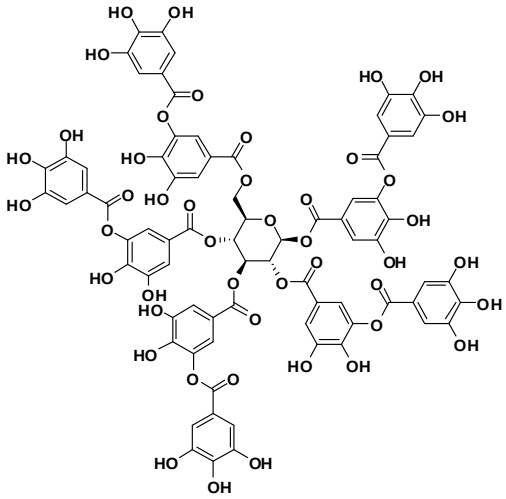
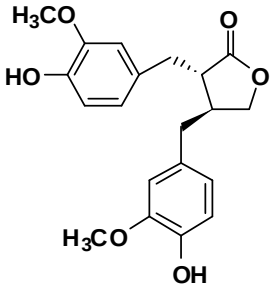
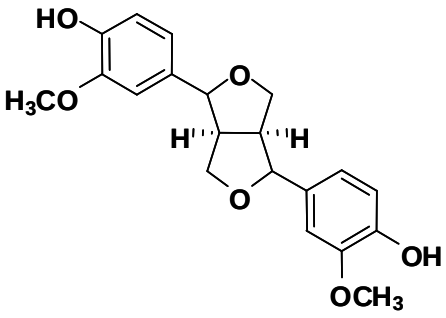
**Table 1. Summary of active compouds in different category of function**

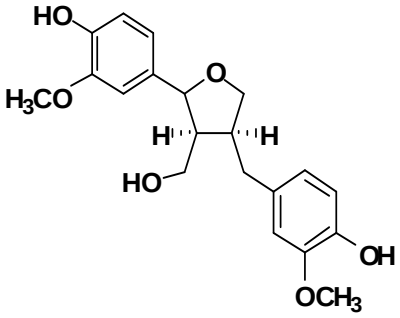
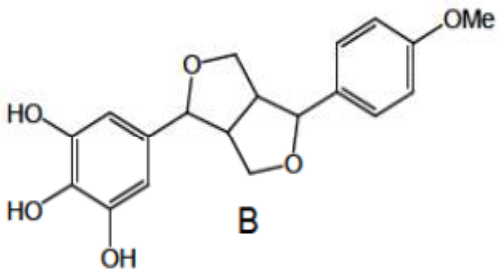
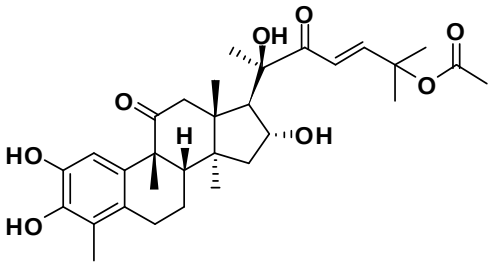
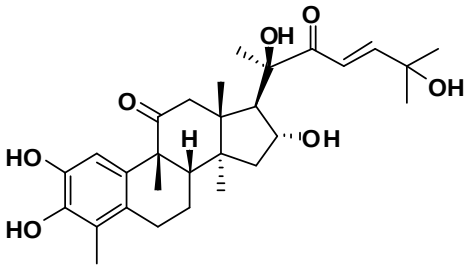
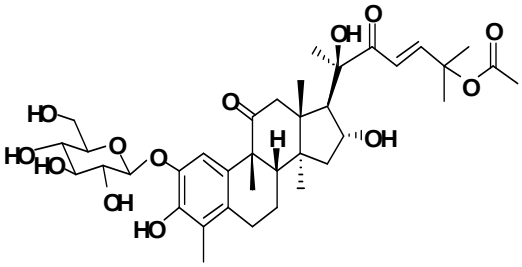
| |
|---|
| a. Antioxidants effect |
| Flavonoids, Polyphenols, and Phenolic compounds |
| b. Anti-inflamatory effects |
| Cox1/2 ihbition: Flavonoids, Polyphenols, and Phenolic compounds |
| c. Immune enhancing effects |
| NK, T cell activity: Flavonoids |
| d. Xenobioyic metabolism and enzyme induction |
| Phase II-GST: Quinone, Flavonoids, and Phenolic compounds |
| e. Induction of apoptosis: |
| Benzophenone, Gallic acid and Fevicordin A |

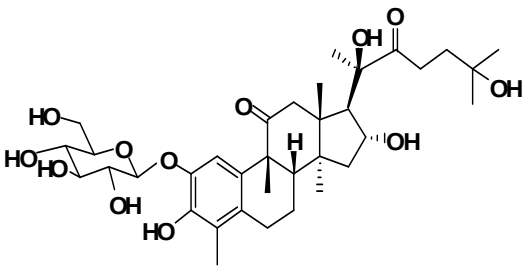
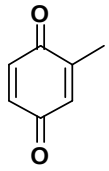
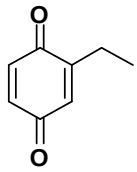
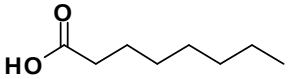
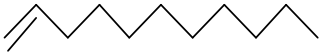
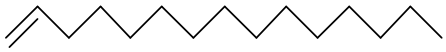
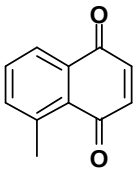
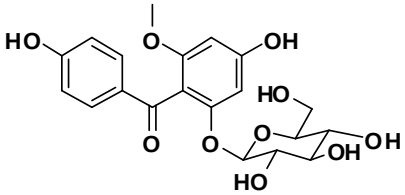
*NK, natural killer; GST, glutathione S-transferases*

**Table 2. Bioactive compounds isolated from *Phaleria macrocarpa* (Scheff.) boerl**

| No | Compounds (reference in text) | Structure | Cited references |
|---|---|---|---|
| 1 | Kaempferol-3-*O*-β-D-glucoside (22) |  | [72] |

| | | | |
|---|---|---|---|
| 2 | Gallic acid (14, 25, 28) |  | [73] |
| 3 | Tannic acid (35) |  | Available at http://www.sigmaaldrich.com |
| 4 | Matairesinol (45) |  | [74] |
| 5 | Pinoresinol (40) |  | [74] |

| | | | |
|---|---|---|---|
| 6 | Lariciresinol (40) |  | [74] |
| 7 | Syringaresinol: 5-4(4-methoxyphenyl-tetrahydrofuro-(3,4-c)furan-1-yl) benzene-1,2,3-triol (40) |  | [75] |
| 8 | Fevicordin A (48) |  | [76] |
| 9 | Deacethyl fevicordin A (Kurnia D, unpublished data 2006) |  | [76] |
| 10 | Fevicordin A glucoside (Kurnia D, unpublished data 2006) |  | [76] |

| | | | |
|---|---|---|---|
| 11 | Fevicordin D glucoside (Kurnia D, unpublished data 2006) |  | [76] |
| 12 | Toluquinone (54) |  | [77] |
| 13 | Ethylquinone (54) |  | [78] |
| 14 | Octanoic acid (54) |  | |
| 15 | 1-Nonene (54) |  | |
| 16 | 1-Undecene (54) |  | |
| 17 | 1-Pentadecene (54) |  | |
| 18 | 1-Heptadene (54) |  | |
| 19 | 6-alkyl-1-4-Naphtoquinone (54) |  | [79] |
| 20 | 4,4′-dihydroxy-2-methoxybenzo-phenone-6-*O*-α-D-glucopyranoside (Makoside A) (22) |  | |

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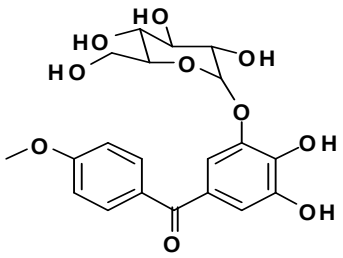
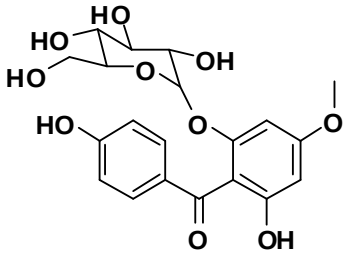
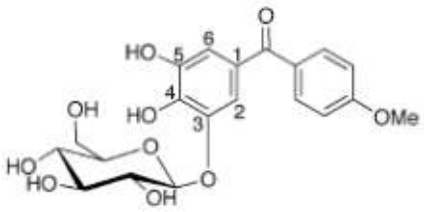
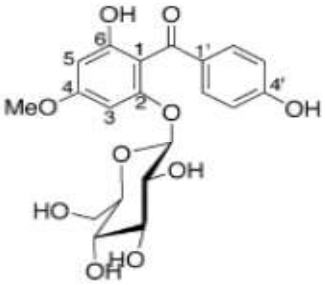
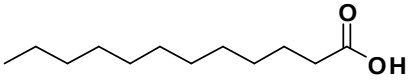
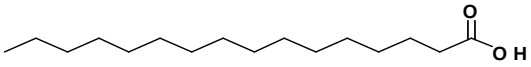
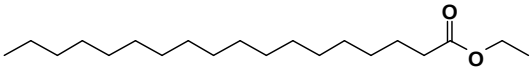
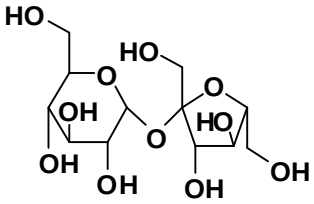
| 21 | 4,5-dihydroxy-4'-metoxybenzo-phenone-3-*O* glucoside [71] |  | |
| 22 | 4'-6-dihydroxy-4-metoxybenzo-phenone-2-*O*-glucoside (60) |  | |
| 23 | 3,4,5-trihydroxy-4'-methoxybenzo-phenone-3-O-β-D-glucoside (Phalerin) (61) |  | |
| 24 | 2,4′,6-trihydroxy-4-methoxybenzopheno ne-2-*O*-β-D-glucoside (Phalerin) (62) |  | [80] |
| 25 | Dodecanoic acid (22) |  | |
| 26 | Palmitic acid (22) |  | |
| 27 | Ethyl stearate (22) |  | |
| 28 | Sucrose (22) |  | |

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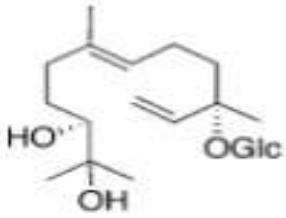
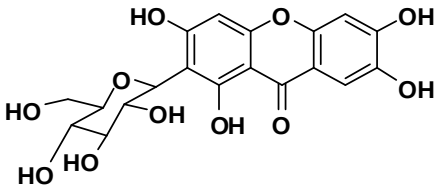
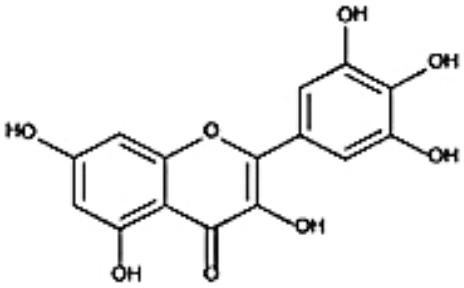
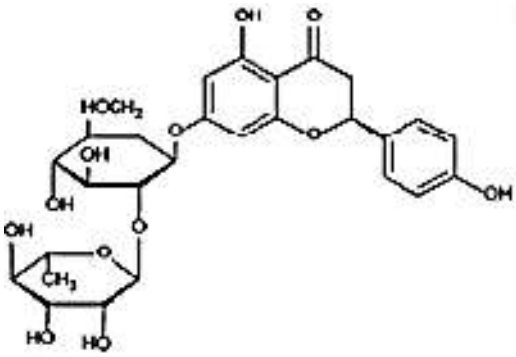
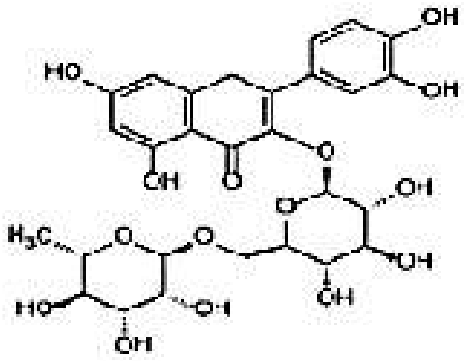
| 29 | Icariside $C_3$ (sesquiterpene glycoside) (62) |  | [81] |
| 30 | Mangiferin (xanthone-C-glycoside) (22,62) |  | [82] |
| 31 | Myricetin (21) |  | |
| 32 | Naringin (21) |  | |
| 33 | Rutin (21) |  | |

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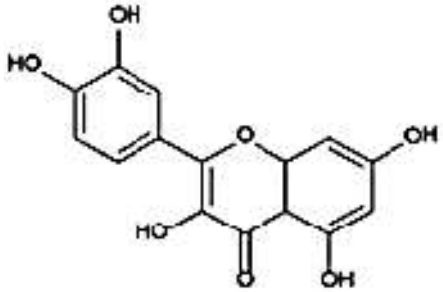
| 34 | Quercitin (21) |  |

The continuing problems caused by malignant cells and the failure of conventional chemotherapy on treating advanced invasive carcinoma indicate that new approaches to control the disease are critically needed. The concept of chemoprevention has become an important and feasible stategy for cancer management. The idea is to control the occurance of cancer cells by slowing, blocking or even reversing the development of the disease by the administration of naturally occuring or synthetic compound(s) from nature.

## 6. CONCLUSIONS

Several bioactive compounds isolated from MaDe have been tested for their potential as anticancer agents against several cancer cell lines. In our preliminary study of the MeOH extract, the active compounds of MaDe were tested using brine shrimp (*Artemia salina* Leach) lethality assay. Based on the findings of the study, it is reasonable to conclude that MaDe has cancer chemoprevention potential, and can be considered as an alternative cancer therapy. Although the advances in molecular biology techniques have greatly helped understanding many aspects of MaDe active compounds and provided new insights in cell signaling on a molecular basis for clinical benefits. Still, exploring new active compounds isolated from MaDe and their biomolecular mechanism in inhibiting cancer cell growth and inducting of cell death remains intriguing and challenging. Moreover, to fully elucidate the precise molecular mechanism of MaDe active compounds, in-depth in vitro and in vivo experiments are needed. Furthermore, the possibility of combining it with conventional anticancer drugs might contribute to the improvement of clinical outcomes in cancer therapy.

In the past few years, the Indonesian Ministry of Health have been attempting to modernize traditional medicines. They have issued policies encouraging, both basic and clinical, studies on the safety and efficacy of traditional medicines. So that in the future, traditional medicine can be integrated into the conventional health care system in Indonesia.

## CONSENT

It is not applicable.

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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