

Revealing Chemopreventive Potential of Active Constituents from Medicinal Herbs Used in Indonesia for Breast Cancer with Particular Molecular Targets

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Abstract

Breast cancer remains as one of the highest causes of cancer-related deaths in the world, including Indonesia. In spite of following the standard protocol therapy, some patients in developing countries consume medicinal herbs as an alternative, complementary, as well as supportive therapies. Several herbs have been recognized to be used for this purpose. Annona muricata, Curcuma longa, Curcuma zanthorrhiza, Curcuma zedoaria, Phyllanthus urinaria, Gynura procumbens, Garcinia mangostana, Morinda citrifolia, and Nigella sativa are some of the plants used as chemopreventive agents with several formulas. Various types of extracts of Annona muricata show anticancer activities in vitro and in vivo. Curcumin, obtained from Curcuma longa and Curcuma zanthorrhiza, acts as p53 regulator and pro-oxidant in MCF-7 cells and also acts as a fatty acid synthase inhibitor in MDA-MB-231 cells. Xanthorrhizol from Curcuma zanthorrhiza has pro-apoptotic activity via modulation of Bcl-2, p53, and PARP-1 protein levels. Curcuma zedoaria contains curcumenone, curcumenol and curdion, which show pro-apoptotic activity in various cell lines and a cancer-induced mouse model. Corilagin and geraniin from Phyllanthus urinaria have different pro-apoptotic effects, in which, the corilagin-caused apoptotic effect is mediated by extrinsic and mitochondrial pathways, whereas geraniin induces apoptosis via ROS-mediated stimulation, both in MCF-7 cells. Thymoquinone from Nigella sativa has been extensively studied for its anticancer activities in recent years. Plants are cultivated, collected and mixed depending on the use as herbal medicines. Active compounds might be formulated if deemed possible. The development of more potential derivatives is also necessary to produce more optimum anti-cancer agents. In conclusion, Indonesian plants and their active constituents show potential activities to be developed as chemopreventive agents.

Keywords: Indonesian medicinal herbs, breast cancer, active constituents, molecular targets

INTRODUCTION

Breast cancer (BC) is still the most frequent cancer among women and on the molecular level, it is a heterogenous disease (Harbeck, *et al.*, 2019). The disease affects 2.1 million women each year,

in which also causes the highest cancer-related deaths among women (Bray, et al., 2018). The BC

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mortality is usually higher in low- and middle-income countries, such as Indonesia, with the mortality rate of 16.6/100,000, a number which is higher than the rest of the world rate: 12.9/100,000 (Youlden, *et al.*, 2014; Coleman, *et al.*, 2008).

of medication's case decision, histological and molecular characteristics of BC are mainly influenced. All BCs begin in the terminal duct lobular units of the collecting duct. Based on the histological subtypes, there are preinvasive (ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS) and invasive (ductal carcinoma no special type (NST) and lobular carcinoma) types of BC (Harbeck, et al., 2019). There are several types of BC based on its intrinsic subtypes based on the signature of 50-gene expression (PAM50), which are luminal A and luminal B (expressing estrogen receptor, ER), basal-like and human epidermal growth factor receptor 2 (HER-2)-enriched (without ER expression) (Perou, et al., 2000; Cheang, et al., 2015).

Different subtypes of BC display distinct tropism in metastatic patterns (Kennecke, *et al.*, 2010; Dent, *et al.*, 2009). Liver, lung, brain and bone are the common target organs for BC metastasis. The ER+ tumours have the best prognosis while triple negative (TN) tumours display the worst prognosis (Dent, *et al.*, 2009). The HER2+ tumour is also considered aggressive, however, since there are anti-HER2 therapy, the prognosis has been improving and the patients' lifespan is significantly prolonged (Jin and Mu, 2015). Despite of increasing knowledge regarding BC, global prevalence does not come down easily, including in Indonesia (Harbeck, *et al.*, 2019).

The prevalence of BC tends to increase despite of the availability of more advanced medicines. Patients are often diagnosed at a later stage and are associated with poor prognosis. In spite of being malignant, the early stage of BC is considered curable in ~70-80% of the patients, whereas the advanced (metastatic) is not considered curable using currently available medications

(Harbeck, *et al.*, 2019). It is still considered curable, though, if the aim of the medication is to prolong survival and control symptoms with low treatment-associated toxicity to maintain or improve quality of life.

In Indonesia, the patients suffering from cancer are 35 years of age or older, and they come from various backgrounds. While detecting the cancer early on is extremely important and necessary, most of the patients come to the hospital are already at advanced stage of the disease. This makes the prognosis and treatment outcomes less improving (Lauver, et al., 1987; McPherson, et al., 2000). Breast cancer in particular, is the most predominant cancer among Indonesian women (Dewi, et al., 2019), with \sim 70% of BC patients come in at a late stage of the disease (Oemiyati, et al., 2011; Ng, et al., 2011). Empowering Indonesian women to selfexamine their own breast is an extremely important step to positively affecting survival rates (Khokhar, et al., 2013).

The BC, like the other cancers, takes time from being initiated to be invasive, therefore we still have time to prevent the malignancy from going further, through cancer chemoprevention. This effort aims to prevent or delay, inhibit, and/or reverse cancer progression (Steward, et al., 2013; Zubair, et al., 2017). According to Zubair, et al. (2017), there are three aims of cancer prevention, which are primary, secondary and tertiary. The natural products, particularly phytochemicals, have been demonstrating the cancer chemoprevention activities (Janakiram, et al., 2016; Chih, et al., 2013). There are several known substances which are producing multi-effect on BC.

Indonesia has the second-highest biodiversity in the world after Brazil and this provides more chemopreventive agents based on empirical and scientific data. Furthermore, Indonesia has approximately 40,000 endemic plant species including 6,000 medicinal plants (Nugraha, et al., 2011; Yaman, et al., 2014). Since a long time ago, medicinal plant have been used to



treat maladies including cancer, including by the Indonesian people. Not only in Indonesia, there are medicinal plants that are still being used in the recent days as alternative or combination treatment for breast cancer in Thailand (Poonthananiwatkul, et al., 2015). Numerous plant natural compounds have successfully entered the clinic as cancer chemotheurapetic agents e.g paclitaxel, vinca alkaloids, and homoharringtonine (Martino, et al., 2018; Untch, et al., 2016; Yakhni, et al., 2019).

In this review, we present the potency of the medicinal plants used in Indonesia. We used PubMed search engine to gather the publications with the keywords of each plant combined with "breast cancer" (e.g "Curcuma zedoaria" AND "breast cancer"). We are focusing to collect only the article mentioning these plants related to BC and not with other cancers. The plants are, in a nonalphabetical order: Annona muricata, Curcuma longa, Curcuma zanthorrhiza, Curcuma zedoaria, Gynura procumbens, **Phyllanthus** urinaria, Garcinia mangostana, Morinda citrifolia, and Nigella sativa. We believe that by compiling the information regarding the selected plants, it can help to easen the counseling process to the people who are planning and using those plants and willing to have more understanding concerning the plants they are consuming.

Annona muricata

Annona muricata (Table 1) is used in Nigeria (tropical Africa) Trinidad, Egypt and Jamaica, and the parts used are mainly the leaves, fruit, bark and seeds of the tree (Adewole and Ojewole, 2008; Clement, et al., 2016; Dawood, et al., 2018; Foster, et al., 2017).

There was one case study mentioning that a 66-year old woman with metastatic BC stabilized the disease for five years after the frequent consumption of *Annona muricata* leaves boiled in water and Capecitabine (Hansra, *et al.*, 2014). The ionic liquid extract of the fruit of *Annona muricata* exhibited anticancer activity on MCF-7

cells (estrogen-dependent, ER(+)) with comparable value of IC₅₀ with the standard Taxol, while also reduced the growth of the cell by arresting the cell cycle at G0/G1 phase (Daddiouaissa, et al., 2019). The ethanolic extract from the fruit using solid lipid nanoparticles (SLNs) on MCF-7 cells showed that the particular formulation had better efficacy to kill the cancer cells compared to the free extract (without SLNs) (Sabapati, et al., 2019). Aqueous leaf extract from Annona muricata also showed anticancer effect on triple-negative breast cancer (TNBC) MDA-MB-231 cells and ER(+) MCF-7 cells, however, cell motility and invasiveness decreased only in TNBC cells. The aqueous extract triggered intrinsic apoptotic pathway through reactive oxygen species (ROS) formation in TNBC cells (Kim, et al., 2018). Nineteen samples of Annona muricata leaves from different locations were screened against MCF-7, MDA-MB-231, and 4 T1 cells and the results revealed that the aqueous extract collected from Selangor, Malaysia showed the most potent effect with the lowest IC₅₀ values of 220, 350 and 250 μg/mL for MCF-7, MDA-MB-231, and 4 T1 cell lines, respectively (Najmuddin, et al., 2016). The N-butanolic leaf extract of Annona muricata also showed moderate anticancer effect on another metastatic model MDA-MB-435S cells while exhibiting antioxidant activity (George, et al., 2012). Ethanolic extract of Annona muricata leaves prevented cellular proliferation in BC mice model induced by DMBA and ER(+) T47D cells (Rachmani, et al., 2012; Sulistyoningrum, et al., 2017). Despite showing promising activity in one case mentioned above, more researches are needed to strengthen the base, in particular, finding the responsible compound(s).

Curcuma longa, Curcuma zanthorrhiza, and Curcuma zedoaria

The three species from the genus *Curcuma* (Table 2) have been extensively studied and used in Indonesian medicinal plant formulation. Related to BC studies, *Curcuma longa* has been studied



Table 1. Anti-BC activity of the extracts of Annona muricata.

Extracts	Subjects	Key findings	References
Aqueous	MDA-MB-231 cells, ER(+) MCF-7 cells	↓Cell viability in both cells ↓Cell motility and invasiveness (MDA- MB-231 cells) ROS formation triggered MDA-MB-231 cells intrinsic apoptotic pathway	Kim, et al., 2018
Aqueous (19 extracts from various places in Malaysia)	MCF-7, MDA-MB-231, and 4 T1 cells	$IC_{50}=220,350$ and 250 $\mu g/mL$ (MCF-7, MDA-MB-231 and 4 T1 cell lines, respectively)	Najmuddin, et al., 2016
Aqueous (combined with Capecitabine)	66-year old woman with metastatic BC	Cancer stabilized for 5 years. First report of clinical effect of Annona muricata on metastatic BC patient	Hansra, et al., 2014
Ethanolic	Mouse model induced by DMBA	Improved histological changes of BC-induced DMBA mouse model	Sulistyoningrum, et al., 2017
Ethanolic	T47D cells	IC ₅₀ = 17.149 μ g/mL. ↑Apoptosis induction of fraction F3	Rachmani, et al., 2012
Ethanolic using SLNs formulation	MCF-7 cells	Efficacy: SLNs formulation>free extracts	Sabapati, et al., 2019
Ionic aqueous	MCF-7 cells	IC ₅₀ = 4.75 μg/mL (Taxol = 0.99 μg/mL) ↓Cell cycle in G0/G1 phase	Daddiouaissa, et al., 2019
n-butanolic	MDA-MB-435S cells	Moderate anticancer activity while showing antioxidant activity	George, et al., 2012

 \downarrow / 1: indication of down/up-regulation or activation/suppression or induction/inhibition of a protein and/or pathway.

more extensively than the others, mainly because the curcumin compounds found mainly in *Curcuma longa*. There are more than 400 publications documented in PubMed with the term "curcumin" in the title combined with "breast cancer", as per this manuscript was prepared.

As for BC studies, there are several findings in the recent years regarding *Curcuma longa*, mainly its main constituent curcumin and its derivatives. The extract from *Curcuma longa* root showed anti-metastatic activity through regulating the expression of metastasis markers including C-C Chemokine receptor type 7, matrix metalloproteinase 9 and the protooncogenes c-fos and c-jun (Kaya, *et al.*, 2019). Curcumin inhibited the migratory activity of MDA-MB-231 cells through down-regulating the protein expression of NF-κBp65 and reversed doxorubicin resistance in MCF-7 and MDA-MB-231 cells by inhibiting the ATPase activity of ABCB4 (Chiu, *et al.*, 2009; Wen, *et al.*, 2019). Curcumin derivatives (Z)-3-

hydroxy-1-(2-hydroxyphenyl)-3-phenylprop-2en-1-one (DK1) and pentagamavunon-1 (PGV-1) exhibited anticancer activities by preventing cell proliferation and promoting apoptosis in vitro and in vivo (Ali, et al., 2017; Lestari, et al., 2019). Curcumin directly targets dual-specificity tyrosineregulated kinase 2 (DYRK2), leading to impaired cancer cell proliferation, has been suggested to interact with CYP17A1, CYP19A1, fatty acid synthase (FAS), and α6β4 integrin, resulting in cancer cell weakening, thus more prone to the medication (Banerjee, et al., 2018; Castaño, et al., 2019; Fan, et al., 2016; Kim, et al., 2008). Curcumin was suggested to inhibit amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP)-induced DNA adduct formation and DNA double strand breaks with associated decrease in ROS production. The PhIP-DNA formation may cause mutations which in turn leads to DNA damage, chromosome aberrations, and BC (Jain, et al., 2015; Gooderham, et al., 2002; Otsuka, et al., 1996; Wu, et al., 1997;



Table 2. Anti-BC activity of the constituents of *Curcuma longa*, *Curcuma zanthorrhiza*, and *Curcuma zedoaria*.

Extracts/compounds	Subjects	Key findings	References
ADQ formula	MDA-MB-231 cells,	↓Caveolin-I	Wang, et al., 2018
Aromatic turmerone	MCF-7 cells MDA-MB-231 cells	↓TPA-induced up-regulation of MMP-9 and COX-2 ↓NF-kB, PI3K/Akt, and ERK1/2 signaling	Park, 2012
Curcumenone and Curcumenol	MCF-7 cells	Curcumenon IC ₅₀ = $8.3\pm1.0 \mu g/mL$ Curcumenol IC ₅₀ = $9.3\pm0.3 \mu g/mL$	Hamdi, et al., 2014
Curcumin	MDA-MB-231	↑Apoptosis induction Targets DYRK2 → reduced proteasome activity and	Banerjee, et al., 2018
Curcumin	cells NCI-H295R cells, JEG3 cells	impaired cell proliferation. ↓CYPI7AI ↓CYPI9AI	Castaño, et al., 2019
Curcumin	MDA-MB-231 cells	↓Fatty acid synthase	Fan, et al., 2016
Curcumin	MDA-MB-231 cells	↓α ₆ β₄ integrin	Kim, et al., 2008
Curcumin	MCF-10A SK-BR-3 cells,	↓PhIP-induced cytotoxicityin	Jain, et al., 2015
Curcumin	MDA-MB-231 cells, MDA-MB- 468 cells	↓Metastatic potential of both cells	Palange, et al., 2012
Curcumin	T47D cells	↓Autocrine GH-mediated miR-182-96-183 cluster expression stimulation. ↓Autocrine GH-triggered invasion-metastasis ↓EMT activation through inhibiting NF-κB signaling and miR-182-96-183 cluster expression ↑Induced apoptotic cell death by modulating Bcl-2 family members	Coker-Gurkan, 2019
Curcumin	MDA-MB-231 cells	↑miR-34a	Gallardo, 2020
Curcumin	MCF-7 cells	↓TPA ↑MMP-9	Kim, et al., 2012
Curcumin	CML-derived leukemic cells in a xenograft model and <i>in vitro</i> culture system	↑ROS	Larasati, et al., 2018
Curcumin	Mice model of BC	Treatment with dendrosomal curcumin (DNC): †STAT4 †IL-12 \$STAT3 ↓IL-10 ↓arginase I	Shiri, et <i>al</i> , 2015
Curcumin	MDA-MB-231 cells	↓EFGR pathway	Sun, et al., 2012
Curcumin	MDA-MB-231 cells, MD-MB-468	↓FABP5 ↓PPARβ/δ	Thulasiraman, et al., 2014
Curcumin	cells MCF-7 cells	↑Urokinase-type plasminogen activator	Zong, et al., 2012
Curcumin + Doxorubicin	MCF-7 cells, MDA-MB-231 cells	↑Doxorubicin anticancer activity ↓Doxorubicin efflux ↓ATPase of ABCB4 ↓ALDOA ↓ENO2	Wen, et al., 2019
Curcumin + Electrical pulse	MDA-MB-231 cells	↓LDHA ↓LDHB ↓PFKP ↓PGMI ↓PGAMI ↓PGKI	Mittal, et al., 2020

 $[\]downarrow$ / 1: indication of down/up-regulation or activation/suppression or induction/inhibition of a protein and/or pathway.



Lauber, et al., 2007). Curcumin is suggested to limit the metastatic potential of adenocarcinoma cell lines SK-BR-3, MDA-MB-231, MDA-MB-468, possibly by altering the expression of adhesion molecules, and the organization and stiffness of the cell cytoskeleton (Palange, et al., 2012). Curcumin also showed to acting on several pathways to directly or indirectly inhibit BC progression in vitro (Coker-Gurkan, et al., 2019; Gallardo, et al., 2020; Kim, et al., 2012; Larasati, et al., 2018; Shiri, et al., 2015; Sun, et al., 2012; Thulasiraman, et al., 2014; Zhou, et al., 2017; Zong, et al., 2012). The antiproliferative effect of curcumin was seen when combined with other anticancer drugs such as paclitaxel, tamoxifen and docetaxel in vitro (Calaf, et al., 2018; Jiang, et al., 2013; Quispe-Soto, et al., 2016). Several unique preparations of curcumin, such as β-cyclodextrin-curcumin inclusion complex and electric pulses, helped to enhance curcumin delivery in T47D cells and MDA-MB-231 cells, respectively, thus increased its antiproliverative ability (Kazemi-Lomedasht, et al., 2013; Mittal, et al., 2020). Another less popular compound in Curcuma longa is aromatic turmeron which has been shown to suppress TPA-induced up-regulation of MMP-9 and COX-2 expression by blocking NFkB, PI3K/Akt, and ERK1/2 signaling in human breast cancer cells (Park, et al., 2012). Aside from the basic research, clinical studies showed that curcumin also had a promising future (Martinez, et al., 2018; Saghatelyan, et al., 2020).

Curcuma zanthorrhiza is also known locally in some part of Indonesia as "temulawak". Xanthorrhizol is the most active and abundant compound isolated from the essential oil of its rhizomes (Jantan, et al., 2012). To our knowledge, xanthorrhizol is also the only compound tested in the studies conducted on BC in vitro. It is been reported that the compound exerted anticancer activities on MCF-7 cells, YMB-1 cells and MDA-MB-231 cells (Anggakusuma, et al., 2009; Cheah, et al., 2006; Cheah, et al., 2008; Udin 2013). When it was combined with curcumin, xanthorrhizol

showed synergistic inhibitory growth inhibitory effect to MDA-MB-231 cells (Cheah, *et al.*, 2009). To our knowledge, based on the specific keywords on PubMed (either "xanthorrhizol", "*Curcuma xanthorrhiza*", "*Curcuma zanthorrhiza*", combined with "breast cancer"), as this manuscript was being written, there has been no new publications in past 5 years.

Curcuma zedoaria is also known as white turmeric or "temu putih" in Indonesia. The plant has been used since long time ago, even it is featured in Ayurveda and has been used traditionally to treat dyspepsia, menstrual disorders, vomiting and cancer (Lobo, et al., 2009). Ether extract of Curcuma zedoaria inhibited progression of MDA-MB-231 cells by arresting G0/G1 phase of cell cycle (Gao, et al., 2014). Hamdi (2014) tested the hexane, dichloromethane, ethyl acetate, methanol, and the methanol-Soxhlet extracts of Curcuma zedoaria rhizomes and found that curcumenone and curcumenol showed strong anticancer activity on MCF-7 cells. Curdione, one of the main constituents in Curcuma zedoaria, was reported to inhibit proliferation of BC cells in vivo and in vitro, possibly by inducing apoptosis via increased expression of cleaved caspase-3, caspase-9 and Bax (Li, et al., 2014). Apart from India, where the traditional use of Curcuma zedoaria is well documented (Lobo, et al., 2009), the plant is also used in China as part of traditional Chinese medicine (TCM). One of the TCM formulas containing Curcuma zedoaria is Ai Du Qing (ADQ), which consist of *Hedyotis diffusa*, Curcuma zedoaria, Astragalus membranaceus, and Glycyrrhiza uralensis. The ADQ was reported to improve chemosensitization of BC in vitro via the suggested caveolin-1 targeting (Wang, et al., 2018).

Gynura procumbens and Phyllanthus urinaria

Gynura procumbens and Phyllanthus urinaria (Table 3) have not been caught much attention like Curcuma, regarding their activity as anticancer agent. To our knowledge, there is



Table 3. Anti-BC activity of the constituents of Gynura procumbens and Phyllanthus urinaria.

Extracts /compounds	Subjects	Key findings	References
Active protein fraction SN-FII/I2	MDA-MB-231 cells	↓Cell growth (EC50 of 3.8 mg/mL) ↓Ki67 ↓PCNA ↓CCL2	Hew, et al., 2013
Aqueous extract, methanolic extract	MCF-7 cells	↑Apoptosis induction ↑Caspase-3 ↑Caspase-7 Presence of DNA-fragmentation	Lee, et al., 2011
Aqueous extract, methanolic extract	MCF-7 cells	↑Apoptosis induction ↓Metastasis ↓MMP-2 ↓MMP-9 ↓ERK pathway ↓Hypoxia-inducible factor I-a	Lee, et al., 2016
Canilaria	MCF-7 cells	↑Apoptosis induction ↑Autophagy ↑Caspase-8 ↑Cleaved PARP ↑Caspase-9 ↑Bax ↑ROS generation	Tong, et <i>al.</i> , 2018
Corilagin	MCF-7 cells	↓Procaspase-8 ↓Procaspase-3 ↓PARP ↓Bcl-2 ↓Procaspase-9	Tong, et al., 2010
		↓Akt/mTOR/p70S6K pathway IC ₅₀ = 9.94, 17.98 and 42.32 mM (72-, 48- and 24-h treatment, respectively) ↓S phase arrest Disruption of mitochondrial membrane potential	
Geraniin	MCF-7 cells	†Apoptosis induction †Phosphorylation of Bcl-2 †Cleaved PARP †Caspase-3 †p38 MAPK †ROS generation	Zhai, et al., 2016

1: indication of down/up-regulation or activation/suppression or induction/inhibition of a protein and/or pathway. The first four and the last four constituent names were from *Gynura procumbens* and *Phyllanthus urinaria*, respectively.

only one BC-related study mentioning *Gynura* procumbens (Hew, 2013), reporting that the leaves contained defense proteins such as peroxidase, thaumatin-like proteins and miraculin. The active protein fraction SN-F11/12 was reported to inhibit the growth breast cancer in vitro. Phyllanthus urinaria, along with other Phyllanthus (Phyllanthus niruri, Phyllanthus watsonii, and Phyllanthus amarus) was reported to induce apoptosis in concomitant with antimetastatic action with the indication that ERK and hypoxia pathways were

the targets (Lee, et al., 2011; Lee, et al., 2016). Corilagin is polyphenol tannic acid obtained from *Phyllanthus urinaria* selectively induced apoptosis and autophagy in cancer cells but not in healthy cells (Tong, et al., 2018). Geraniin, also present in *Phyllanthus urinaria*, has been shown to induce apoptosis on BC in vitro by stimulation of ROS via p38 MAPK signaling (Zhai, et al., 2016). The table below consisted of all publications found in PubMed using either "Gynura procumbens" or "Phyllanthus urinaria" combined with "breast cancer" keywords



and all of them showed anticancer activity *in vitro*. Therefore, to our knowledge, no clinical trial has been performed.

Garcinia mangostana

Garcinia mangostana (mangosteen; Table 4) is known locally in most part of Indonesia as "manggis". The seeds and the pericarps of the fruit have been used as traditional medicine since a long time ago (Ovalle-Magellanes, et al., 2017). There are many reports regarding pharmacological activity of this plant and more than 50 secondary metabolites found in Garcinia mangostana, from which the major bioactive ones are the xanthones (α -mangostin and γ -mangostin are the most abundant ones) (Obolskiy, et al., 2009). Nauman, et al. (2020) screened 9 xanthone constituents from the fruit of mangosteen and reported that γ-mangostin and α-mangostin were the most potent compound on BC cell line MDA-MB-231 by inhibiting CDK2/ CyclinE1 activity. Panaxanthone, a mixture of ~80% α -mangostin and ~20% γ -mangostin, has been reported to induce apoptosis, to suppress tumor growth and metastasis in vivo and in vitro (Doi, et al., 2009). The compound α -mangostin was suggested to exhibit anticancer activites in vivo and in vitro (Kritsanawong, et al., 2016; Kurose, et al., 2012; Moongkarndi, et al., 2014; Scolamiero, et al., 2018; Shibata, et al., 2011; Suksamrarn, et al., 2006; Taokaew, et al., 2014). The γ-mangostin was reported to inhibit BC cell growth by increasing α-tubulin acetylation (Yeong, et al., 2020). There are several clinical trials indexed by PubMed with the specific keywords ["Garcinia mangostana" or "mangostin" AND "clinical trial"], however, none of them are related to BC.

Morinda citrifolia

Morinda citrifolia (noni) is known as "mengkudu" in Indonesia, or "pace" in particular region of Central Java. Almost all parts of the plants have been used as traditional medicine and it is well known for the matured fruit's unpleasant butyric acid smell (Torres, et al., 2017). Noni juice has been

sold all over the world and were reported to contain antiproliverative effect on BC in vivo and in vitro (Clafshenkel, et al., 2012; Taşkin, et al., 2009). Noni oil from the fruit was also reported to contain six compounds, mainly caprylic acid and hexanoid acid, and to have antiproliferative effect in vitro (Piaru, et al., 2012). The methanolic, ethyl acetate and water-ethyl acetate extracts were also found to have anticancer activity on MCF-7 cells and MDA-MB-231 cells (Sharma, et al., 2016; Huang, et al., 2016). Two anthraquinones, nordamnacanthal and damnacanthal, were also reported to inhibit BC progression in vivo and in vitro (Abu, et al., 2018; Aziz, et al., 2014; Aziz, et al., 2016). The search in PubMed using the combination keywords ["Morinda citrifolia" AND "clinical trial"] yielded in less than 10 publications, however, only one is related to BC and it's not a clinical trial (Marchiori and Zanello, 2017).

Nigella sativa

Nigella sativa from the family of Ranunculaceae, is ordained as one of super herbs and amazing medicinal plant. It is rich in religious and historical background since hundreds of years ago (Sahak, et al., 2016; Goreja, 2003). Not only historical, there are many scientific reports showing various effects of Nigella sativa including as anti-BC activity. The methanolic extract and the unique formulations induced apoptosis on BC in vitro (Alhazmi, et al., 2014; Periasamy, et al., 2016; Rohini, et al., 2019). Thymoquinone, an active compound from Nigella sativa, has been shown to exert anticancer activity in vivo and in vitro, either when it worked alone or combined, with several cell signaling cascades involved (Kabil, et al., 2018; Linjawi, et al., 2015; Rajput, et al., 2013; Shanmugam, et al., 2018; Sutton, et al., 2014; Woo, et al., 2011; Woo, et al., 2013). There are more than 50 publications related to the combination of keywords ["Nigella sativa" AND "clinical trial"] and at least 2 clinical trials were performed in the past 5 years with promising results related to BC (Rafati, et al., 2019; Huseini, et al., 2016).



Table 4. Anti-BC activity of the constituents of Garcinia mangostana constituent.

Extracts /compounds	Subjects	K ey findings	References
		↓Cell proliferation	
		↑DNA fragmentation	
		Nuclear condensation	
		↑Cleaved caspase-3	
		↑Cleaved caspase-9	
		Bcl-2	
		McI-I	
lpha-mangostin	T47D cells	LERα	Kritsanawong, et al., 2016
		HER2	
		↓PI3K	
		↓Akt	
		JERK 1/2	
		*	
		↑p-JNK1/2	
		↑p-p38	
		†Mitochondria-mediated apoptosis induction	
		↑GI phase arrest	
		↑p21cip1	
α -mangostin	MDA-MB-231 cells	↓Cyclins	Kurose, et al., 2011
		↓cdc(s)	
		↓CDKs	
		↓PCNA	
	MDA-MB-231 cells,	†apoptosis induction	
α -mangostin		↓cell viability	Scolamiero, et al., 2018
•	MCF-7 cells	cell adhesion	
		†survivability rate in vivo	
	Breast cancer BALB/c mice model inducted with	apoptosis induction in vivo	
		↑caspase-3	
		↑caspase-9	
		tumor volume in vivo	
α -mangostin	BJMC3879luc2 cells,	Jlymph node metastasis in vivo	Shibata, et al., 2011
	MDA-MB-231 cells	†mitochondria-mediated apoptosis induction in	
		vitro	
		↑GI-phase and S-phase suppression in vitro	
		Thr308 in vivo and in vitro	
cy mangastin	BC-I cells	•	Suksamrarn et al. 2006
α -mangostin	BC-1 cells	IC ₅₀ = 0.92 μg/mL	Suksamrarn, et al., 2006
	MD 4 MD 221 II	Discovery and identification of γ-mangostin as	
γ-mangostin	MDA-MB-231 cells,	potent and selective SIRT2 inhibitor	Yeong, et al., 2020
7	MCF-7 cells	↑a-tubulin acetylation on both cells	
		↓Cell proliferation	
lpha-mangostin (bacterial		↓Cell viability	
cellulose films containing	MCF-7 cells	Cell survival rate	Taokaew, et al., 2014
ethanolic extract of the	Tici-7 cells	Cell morphological change	Taokaew, et ul., 2014
peel)		Cell morphological change	
α -mangostin and γ -	MDA MD 221II-	¢cell viability in dose-dependent manner	Name at al. 2020
mangostin	MDA-MB-231 cells	CDK2/CyclinEI	Nauman, et al., 2020
		†Apoptosis induction	
		Tumor suppression	
Panaxanthone, (~80% α -	BC BALB/c mice model	↓Metastasis to lung	
mangostin + ~20% γ-	inducted with BJMC3879	↓Metastasis to lymph node	Doi, et al., 2009
mangostin)	cells	↓PCNA	
		↓ Angiogenenesis	
		1 VII Sin Sei i ei i ezi z	

 \downarrow / 1: indication of down/up-regulation or activation/suppression or induction/inhibition of a protein and/or pathway. ¹The ED₅₀ (median effective dose) is the dose of a medication that produces a specific effect in 50% of the population that takes that dose (Kenny and McPhee, 2020).

DISCUSSION

Nine Indonesian medicinal plants used in complementary therapy against breast cancer have shown scientifically that they exert anticancer and chemopreventive activities. Of course, some of the plants were not originated from South East Asia region, let alone Indonesia. However, along with the spread of human population and technological advances, those plants were able to reach Indonesia,



Table 5. Anti-BC activity of the constituents of Morinda citrifolia.

Extracts /compounds	Subjects	K ey findings	References
		↓Cell proliferation (72h treatment)	
		\downarrow Cell growth (72h treatment; IC ₅₀ = 8.2 \propto g/mL)	
		↑G1 checkpoint phase arrest	
Damnachantal	M CF-7 cells	†Apoptosis induction	Aziz, et al., 2014
	TTCT 7 CCIIS	↑p21 activation	7 (212, Ct 01., 2011
		↑p53	
		↑Bax	
		↑Caspase-7	
		Apoptosis induction	
		↑p21	
		↑BAX	
_		↑Caspase-3	
Damnachantal +	MCF-7 cells	↑Caspase-7	Aziz, et al., 2016
doxorubicin		↑p53	, 12.2, 60 d, 20.0
		↓Bcl-2	
		↓XIAP	
		↓ER-alpha	
		$IC_{50} = 25$ and 35 mM (MCF-7 and MDA-MB-231	
		cells, respectively)	
	MCF-7 cells,	↓Cell proliferation	
Ethyl acetate extract	MDA-MB-231	↑Apoptosis induction	Sharma, et al., 2016
,	cells	↑GI/S and G0/GI phase arrest (MCF-7 and	
	Cells	MDA-MB-231, respectively)	
		↓Intracellular ROS generation	
		↓Mitochondrial membrane potential	
	60 BC survivor		
Fruit extract + N-	(women) with	†Efficacy in NDM + antibiotics group, compared	Marchiori and
acetylcysteine + D-	recurrent cystitis,	to antibiotics only group (in reducing reducing	Zanello, 2017
mannose (NDM)	a retrospective	urinary tract infections and urinary discomfort)	Zanello, 2017
, ,	study		
	,	NJ did not affect mammary tumor latency,	
	MMTV-neu	incidence, multiplicity and metastatic incidence.	Clafshenkel, et al.,
Noni juice	transgenic mice	Tumor weight and volume	2012
		↓Tumor doubling times	
	Breast cancer	· -	
	BALB/c mice	↓Tumor size	
Noni juice	model inducted	↓Tumor proliferation	Taşkin, et al., 2009
Non juice	with Ehrlich	†Apoptosis induction	1 aşkiii, et ul., 2007
	ascites	↑Caspase-cleaved cytokeratin 18	
	ascites	First was not warned to a the consensation of ward	
		First report regarding the composition of noni	
Noni oil	MCF-7 cells	fruit oil, with caprylic acid and hexanoid acid as	Piaru, et al., 2012
		main constituent.	,,
		Noni oil $IC_{50} = 78.15 \infty\text{g/mL}$	
	MDA-MB-231		
	cells,	↑Apoptosis induction in vitro	
Nordamnachantal	MCF-7 cells, 4TI	↑Tumor immunity in vivo	Abu, et al., 2018
	cells-challenged	Delayed tumor progression in vivo	
	mice		
		The extract contained chrysin as the most	
		predominant compound in it	
		Chrysin + apigenin (72 – 96h treatment):	
		↓Cell viability	
		†Apoptosis induction	
Water-ethyl acetate	MDA-MB-231	↓Skp2	
		↓LRP6	Huang, et al., 2016
extract	cells		i lualig, et ul., 2016
		Chrysin + apigenin (36h treatment):	
		Cell motility but not cell viability	
		↓MMP2	
		↓MMP9	
		↓Fibronectin	
		Snail	

 \downarrow / 1: indication of down/up-regulation or activation/suppression or induction/inhibition of a protein and/or pathway.

and were able to be used as traditional medicine in particular. Some of the plants have been more extensively studied than the others (Table 1-6). The plant *Curcuma longa*, *Curcuma zanthorrhiza*, *Garcinia mangostana*, and *Nigella sativa* have been known to contain active constituent curcumin,

xanthorrhizol, α-mangostin, and thymoquinone, respectively, as they have been extensively studied *in vivo* and *in vitro*, not only in BC study but also other fields.

For the most part, the selected plants have shown that they induced apoptosis through various



Table 6. Anti-BC activity of the constituents of Nigella sativa.

Extracts /compounds	Subjects	K ey findings	References
Essential oils nanoemulsion	MCF-7 cells	↓Cell viability ↑Apoptosis induction	Periasamy, et al., 2016
	62 BC patients	Apoptosis induction	
Gel (5%)	undergoing	↓severity of acute radiation dermatitis	Rafati, et al., 2019
Gei (3%)	radiotherapy, a clinical trial	↓onset of moist desquamation	Naiau, et ul., 2017
		↑Apoptosis induction	
Methanolic extract of the		↑Caspase-3	
seed	MCF-7 cells	↑Caspase-8 ↑Caspase-9	Alhazmi, et al., 2014
seed		↑caspase-7 ↑p53	
		IC ₅₀ = 62.8 ∞d/mL	
		pain of active treatment groups compared	
	52 women with cyclic	with the placebo.	
Seed oil	mastalgia, a clinical	No adverse effect observed.	Huseini, et al., 2016
3000 011	trial	Seed oil has clinical effectiveness compared	riddenn, et di., 2010
		to topical diclofenac for the treatment of	
		cyclic mastalgia.	
		Dose-dependent cytotoxicity observed Morphological alterations observed	
Silver nanoparticles from an	MCF-7 cells	Bcl-2	Rohini, et al., 2019
aqueous seed extract		COX-2	
		† ↑Ba×	
		↓eEF-2K in vitro	
		↓Src/FAK in vitro	
	.45.4.15.22.	↓Akt in vitro	
Thomas accionana	MDA-MB-231 cells,	↓NF-kB in vitro	Kabil at al 2019
Thymoquinone	orthotopic xenograft TNBC tumor model	↑miR-603 <i>in vitro</i> ↓Cell growth in vivo	Kabil, et al., 2018
	TABE tullor model	LeEF-2K in vivo	
		↓Cell proliferation in vivo	
		↓Tumor migration/invasion in vivo	
		CXCR4 in vitro	
	MDA-MB-231 cells,	↓NF-kB binding to CXCR4 promoter in vitro	
Thymoquinone	metastasis breast	↓CXCL12-mediated migration and invasion in	Shanmugam, et al., 2018
	cancer mouse model	vitro	
		Multiple lung, brain and bone metastasis	
		↑GI-phase arrest ↑Apoptosis induction	
		↑Bax	
		↑Cytoplasmic cytochrome-c	
		↑Procaspase-3	
		↑PARP cleavage	
Thymoquinone	MDA-MB-468 cells,	↓Bcl-2	Rajput, et al., 2013
,	T47D cells	↓Bcl-xL	,,
		↓Survivin ↓Akt	
		↓ART ↓Phosphorylation of 4E-BPI	
		Phosphorylation of elF4E	
		Phosphorylation of S6R	
		Phosphorylation of p70S6K	
		↓Cell growth	
		↑GI-phase arrest	
		↑Apoptosis induction	
Thymoquinone	MDA-MB-468 cells	↑Cytochrome-c ↑Caspase-9	Sutton, et al., 2015
inymoquinone	1 107-1 10-400 CEIIS	↑Caspase-8	Julion, Et al., 2013
		↑Cleaved PARP	
		∱γH2AX	

1 : indication of down/up-regulation or activation/suppression or induction/inhibition of a protein and/or pathway.

mechanisms involving the modulation of specific molecular targets e.g. Bcl-2, Bcl-xL, caspase-3, caspase-8, caspase-9 and Bax, either *in vivo* and/ or *in vitro*. Some active constituents, like curcumin, induced cell cycle arrest in G2/M phase (Chiu,

et al., 2009; Jiang, et al., 2013), whereas thymoquinone induced cell cycle arrest in G1 phase, thus accumulating the cell cycle at subG1 phase (Rajput, et al., 2013; Sutton, et al., 2015; Woo, et al., 2011). The ROS species plays part in cancer develop-

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ment, however, the findings below menresults. Corilagin, geraniin tioned interesting and thymoquinone showed to increase ROS production in MCF-7 cells (Tong, et al., 2017; Zhai, et al., 2016; Woo, et al., 2013), where in contrast, Garcinia mangostana crude extract, α-mangostin, and Morinda citrifolia fruit extract showed to decrease ROS production (Moongkarndi, et al., 2014; Sharma, et al., 2016). The contradiction showed above suggest that more researches are needed in order to better explain what happens in ROS pathway during the exposure of cancer cells by the selected compounds.

To our knowledge, based on PubMed search we used, only 4 clinical trials related to the reviewed plants and BC. Curcumin (from Curcuma longa) and Nigella sativa extracts were mentioned twice, respectively. (Martinez, et al., 2018; Saghatelyan, et al., 2020; Rafati, et al., 2019; Huseini, et al., 2016). Those trials showed encouraging results from respective plants, opening the possibility to explore the efficacy, safety and toxicity deeper into bigger population. On the other hand, the retrospective clinical study of Morinda citrifolia showed promising results with the combination of the fruit extract with N-acetylcysteine and D-mannose having greater efficacy in reducing urinary tract infections and urinary discomfort compared to antibiotic use only (Marchiori and Zanello, 2017).

There are limitations of our study. Firstly, to our knowledge, the other plants (*Annona muricata*, *Curcuma zedoaria*, *Gynura procumbens*, *Phyllanthus urinaria*, and *Morinda citrifolia*) do not have a single prominent compound unlike the rest of the plants. The latter mentioned's reports are mainly from extracts/fractions/unique formulations on BC *in vivo* and *in vitro*. The least reported one, *Gynura procumbens*, until this manuscript was being finished, has 49 publications in PubMed if we search with a full "*Gynura procumbens*" term with only one study related to BC (Hew, *et al.*, 2013). Secondly, this review focused on reviewing the plants and their constituents in BC-related works solely. Therefore, we did not mention

the other targets/effects exhibited by the mentioned constituents outside our BC-related scope. We believe by creating such environment, it may help the reader to focus on what's inside the manuscript rather than asking what's not mentioned in this review. Nevertheless, there are still a very wide-open opportunities for the scientists to uncover the responsible compound acting in cancer generally and BC particularly.

CONCLUSION

In this review, nine plants *i.e Annona muricata*, *Curcuma longa*, *Curcuma zanthorrhiza*, *Curcuma zedoaria*, *Phyllanthus urinaria*, *Gynura procumbens*, *Garcinia mangostana*, *Morinda citrifolia*, and *Nigella sativa*, have shown to have chemopreventive potential in BC. There are still a lot to understand regarding on how the extracts/compounds work against cancer, therefore more reviews are also needed to reveal their working pattern. Even though most of the plants mentioned here have been extensively inspected, a few of them are not thoroughly traced for their anticancer activity, thus opening a wide opportunity for experimental research and possibly reaching the clinical trial in the future.

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