A Review of Herbal Medicine-Based Phytochemical of Garcinia as Molecular Therapy for Breast Cancer

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Abstract: Data from globocan statistic in 2020 indicate that breast cancer has become highest incidence rate of cancer. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) are known immunohistochemistry (IHC) markers that mediate cell growth and survival signaling. Furthermore, regulator proteins, receptors, and their downstream signaling pathways have emerged as critical components in breast cancer formation and proliferation, and have become well-established therapeutic targets and the core focus of breast cancer therapy research. Garcinia is a big genus in the Clusiaceae family that contains a wide spectrum of biologically active metabolites for the chemical composition of their isolated fruits, stem barks, seeds, leaves, and roots, have resulted including polyisoprenylated benzophenones, polyphenols, bioflavonoids, xanthones, lactones, and triterpenes. This review article aimed to analyze the potential of Garcinia phytochemicals as a molecular therapy of breast cancer. The results showed that phytochemicals of Garcinia (i.e., α-mangostin, Cambogin, Gambogic Acid [GA], Garcinol, Griffipavixanthone, Friedolanostane triterpenoid, Hexane, Neobractatin, 7-Epilusianone, xanthochymol - guttifere E, and isoaxanthochymol - cycloaxanthochymol) have anticancer properties, including apoptosis, inhibition of proliferation, and metastasis. This review is important to provide information regarding phytochemicals of Garcinia as an alternative treatment for breast cancer patients. This article selected 28 article researches based on inclusion criteria with the keyword “Garcinia” and “Breast cancer”, in English, and available in full text and abstract searching on PubMed.

Keywords: breast cancer, Garcinia spp, molecular therapy, Indonesia

Introduction

Data from Globocan showed that the new cases of breast cancer in 2020 were 11.7% and it became the highest incidence rate of cancer for both sexes in all ages.¹ In addition, the International Agency for Research on Cancer (IARC) reported 2.1 million new cases of breast cancer in 2018. Breast cancer is also the top cause of cancer death in women worldwide, with 627,000 fatalities reported in 2018.²

Breast tumor subtyping is traditionally done using immunohistochemistry (IHC) markers such as “estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2).”³⁻⁴ These hormone and growth receptors, which are known to stimulate cell growth and survival signaling, are well-established therapeutic targets for breast cancer treatment and have been the focus of pharmacological research.⁴

Weinberg et al described six cancer hallmarks in 2000:

- maintaining proliferative signals, avoiding growth suppressors, resisting cell death, enabling replicative immortality, initiating angiogenesis, and activating invasion and metastasis.

A wide range of intracellular chemicals have been discovered as causing cancer cells to proliferate uncontrollably. In malignant cells, for example, “cyclin-dependent kinase (CDK)” overexpression and tumor suppressor protein “(p53), BRCA1 and BRCA2, CDK inhibitors, p21, p27, and p57” downregulation have been discovered.⁵⁻⁶ Protein control of pro-apoptotic “Bcl-2 family members, initiator caspase (e.g., caspase 8/9), effector caspase (e.g., caspase 3), and apoptosis” as a barrier to cancer formation.⁷
Several important receptors and signaling pathways have emerged as key players in the development and advancement of breast cancer. “The epidermal growth factor receptor (EGFR), HER2, and Vascular Endothelial Growth factor (VEGF)” are the most prevalent growth factor receptors that are overexpressed in breast cancer cells. These receptors may be activated by the Janus kinases, signal transducer and activator of transcription proteins (JAK/STAT), phosphoinositide 3-kinase (PI3K), protein kinase B (Akt), mammalian target of rapamycin (mTOR), and mitogen-activated protein kinases (MAPK) pathways. Furthermore, tumor cells have been found to exhibit altered expression of many pro-inflammatory transcription factors, including “nuclear factor kpB (NFkpB), activating protein-1 (AP-1), and hypoxia-inducible factor 1 (HIF-1).” Chronic inflammation is thought to play a role in both the start and development of cancer. As a result, addressing the major aberrant proteins and pathways is a promising strategy to breast cancer treatment. 

Garcinia is a Clusiaceae family genus with approximately 450 species found in tropical Asia, South Africa, and America, as well as Madagascar, New Guinea, and Polynesia. For example, the fruits of Garcinia have been used in traditional medicine for a variety of purposes, including antifever infusions in Thai folk medicine, wound healing and treatment of peptic ulcers in Brazilian folk medicine, earache in Thai medicine, and ailments such as heat strokes, infections, and edema in the Ayurvedic system of medicine. “Polyisoprenylated benzophenones, polyphenols, bioflavonoids, xanthones, lactones, and triterpenes” are among the physiologically active metabolites found in the fruits, stem barks, seeds, leaves, and roots of numerous Garcinia species. As a result, Garcinia species have been shown to be abundant in compounds that have medicinal properties. Free-radical scavenging, antiulcer effects, cytotoxicity, nitric oxide synthase inhibition, cancer chemoprevention, induction of apoptosis, anti-HIV, and trypanocidal properties have been associated to these substances. This review aimed to analyze the potential of Garcinia phytochemicals as molecular therapy of breast cancer. This research is important to provide information concerning phytochemicals of Garcinia as an alternative treatment for patients with breast cancer.

Material and Methods
The articles were selected on the basis of inclusion studies published in the PubMed database; articles in English, available in full text and abstract form, consist of the keywords “Garcinia” and “breast cancer.” The sorting processes can be seen in Figure 1.

Results and Discussion
Globocan showed that new cases of breast cancer in 2020 were 2,261,419 (11.7%) and mortality was 684,996 deaths (6.9%), thus, breast cancer has become the highest incidence rate of cancer. Breast tumor subtypes are traditionally classified based on hormonal and growth factor response. In this context, the most clinically important receptors are “ER, PR, and HER2.” Cancer cells deregulate these hormonal and growth signals, allowing them to continue proliferative signaling in a variety of ways. They enhance cell surface receptor expression and accumulate activating mutations, resulting in cell surface receptor or downstream signaling pathway activation that is constant. Some Garcinia metabolites, such as “Garcinol, α-mangostin, Cambogin, and Gambogic acid” (GA) have exhibited anticancer action in vitro and in vivo, causing apoptosis and cellular cycle arrest, suppression of angiogenesis, and gene expression regulation in carcinogenic cells. The general pathways of phytochemicals of Garcinia mechanism in cancer targeted therapy can be seen in Figures 2–4.

α-Mangostin
Garcinia mangostana extracts were found to contain the anticancer phytochemical α-Mangostin. Kurose et al discovered that α-mangostin induced mitochondrial apoptosis. Increased caspase-3, caspase-8, and caspase-9 activity, as well as increased cytochrome c protein release concentration, support this. The expression of CDK - interacting protein 1 (p21cip1) was upregulated, and Checkpoint Kinase 2 (CHEK2) was tended to increase, resulting in a decrease in CDKs and cyclins, as well as G1-phase arrest and inhibition of cell proliferation, followed by decreases in proliferating cell nuclear antigen (PCNA).
When compared to proform-HER2 expression, Kritsanawong et al discovered that α-Mangostin can reduce Phospho-HER2 (p-HER2) at Tyr1221/1222. This results in a decrease in Nuclear Factor NF-κBp 65, c-Rel, and c-Myc expression while increasing IB Kinase Complex Alpha (IKK) expression. However, activation of p38 and c-Jun N-Terminal Kinase 1/2 (JNK1/2) resulted in the expression of C/EBP Homologous Protein and c-Jun. 43

Shibata et al revealed that α-mangostatin promotes mitochondrial apoptosis, G1-phase arrest, and S-phase suppression during the cell cycle. Akt phosphorylation was induced by α-mangostin treatment both in vitro and in vivo, demonstrating that α-mangostin significantly reduces the levels of phospho-Akt-threonine 308 (Thr308); α-Mangostin significantly increased caspase-3, caspase-8, and caspase-9 activity; cytochrome c protein levels in cytosolic fractions were significantly higher in cells treated with α-angostin; and caspase-8-Bid cleavage triggered the mitochondrial pathway. 44

α-mangostin also activated caspases-8, −9, and −7, elevated Bax, p53, and cytosolic cytochrome c protein levels, and stimulated Poly (ADP-Ribose) Polymerase (PARP) cleavage while lowering Bid and Bcl-2 protein expression, according to Won et al. Furthermore, apoptosis-inducing factor (AIF) was transferred from the mitochondria to the cytosol and promoted apoptosis in E2-stimulated cells in parallel with non-stimulated cells, lowering the expression of ERα and pS2, an estrogen-responsive gene. 45 According to Doi et al, isolated panaxanthone from G. mangostana dramatically boosted caspase-3, caspase-9, and caspase-8 activities, triggered the G1-phase, and lowered the number of cells in both the S- and

**Figure 1** Prisma chart.

Notes: Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71. 46 Creative Commons Attribution (CC BY 4.0) license (https://creativecommons.org/licenses/by/4.0/legalcode).
Figure 2 Cell cycle, mechanism phytochemical of Garcinia inhibit cyclin E in G1 phase arrest to S phase, Cdk1 in G2/M phase transition, and increase activity p21 leads to decreases in CDKs and cyclins.

Figure 3 Apoptosis, the phytochemical of the Garcinia mechanism of apoptosis and the dysregulation of apoptosis modulators involved in the extrinsic and intrinsic apoptotic pathway until cleaved PARP to stop repairing DNA damage in cancer cells.
α-mangostin reduced 12-O-tetradecanoylphorbol-13-acetate (TPA)-induced MMP-2 and MMP-9 production, as well as cell invasion and migration (Figure 5), according to Lee et al.⁴⁷

**Cambogin**

Cambogin compounds (Figure 6) can be found in the branches of *Garcinia esculenta*. Shen et al reported that cambogin treatment via the NOX enzyme is activated by enhancing p22phox and NADPH Oxidase 1 (NOX1) interaction. The dissociation of Thioredoxin 1 (Trx1) from the activation of the Apoptosis Signal-Regulating Kinase 1 (ASK1) pathway and the induction of mitochondrial network abnormalities resulted from an increase in intracellular and mitochondrial levels of Oxide (O2-) and Hydrogen Peroxide (H2O2), resulting in the dissociation of Thioredoxin 1 (Trx1) from the activation of the Apoptosis.⁴⁸ According to Shen et al, activation of ASK-1, SAPK/Erk Kinase (SEK1/MKK4), MKK7,
and Jun Amino-Terminal Kinases/Stress-Activated Protein Kinase (JNK/SAPK) is necessary for cambogin-induced Reactive Oxygen Species (ROS). Cambogin stimulated the caspase-independent mitochondrial apoptotic pathway, as evidenced by an increase in the ratio of B-Cell Lymphoma Protein 2, Associated X (Bax/Bcl-2), and nuclear translocation of AIF. JNK/SAPK or p38 MAPK activation phosphorylated Activating Transcription Factor 2 (ATF-2) and increased histone H3K9 trimethylation in the Bcl-2 gene promoter’s activator protein 1 (AP-1) binding region.\(^48\)

**Gambogenic Acid**

The compound GA is abundant in *Garcinia hanburyi* (Figure 7). According to Wang et al, TNF-Related Apoptosis-Inducing Ligand (TRAIL) and GA increased apoptosis in TRAIL-resistant cells and play a critical role in inducing apoptosis.

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**Figure 6** Cambogin chemical structure.


**Figure 7** GA chemical structure.

apoptosis and reducing levels of anti-apoptotic Bcl-2 protein, boosting the interplay of extrinsic and intrinsic apoptosis signaling. GA induces apoptosis, according to Zhou et al, who looked at changes in the expression levels of apoptosis-regulating proteins such as cleaved caspase-3, caspase–8, and caspase–9, as well as Bax, while Bcl-2 was decreased and Fas and Fas ligand (FasL) were increased. GA depolymerized microtubules and increased JNK1 and p38 phosphorylation, causing G2/M cell-cycle arrest and apoptosis, according to Chen et al.

According to Wang et al, GA also increase the expression of apoptosis-related proteins FasL, caspase-3, caspase-8, caspase-9, and Bax while suppressing the anti-apoptotic protein Bcl-2. GA also caused PARP cleavage, caspase-3, caspase-8, and caspase-9 activation, and an increase in the Bax/Bcl-2 ratio, according to Li et al. Furthermore, GA caused apoptosis via the buildup of ROS and mitochondrial apoptotic pathway, as shown by AIF translocation and cytochrome c (Cyt c) release from mitochondria. By decreasing Akt/mTOR signaling, GA also reduced cell survival. GA also prevented tumor invasion and metastasis by reducing MMP-2 and MMP-9 activity, according to Qi et al.

Garcinol
Garcinol (Figure 8) compound can be found in *Garcinia morella* and *Garcinia indica*. Choudhury et al reported that Garcinol inhibited the complex polysaccharides like Lipopolysaccharide (LPS) induced increase in cytokine secretion such as Tumor Necrosis Factor Alpha (TNF-α), Interleukin 1 Beta (IL-1β) by macrophages as inflammatory agent. Ahmad et al showed that garcinol causes Mesenchymal-Epithelial Transition (MET) in aggressive breast cancer cells through apoptosis mediated by downregulation of the NF-kB signaling pathway. This is in line with the mesenchymal markers vimentin, ZEB1, and ZEB being downregulated and the epithelial marker E-cadherin being increased, as well as the miRNAs, miR-200, and let-7 families being implicated in the maintenance and control of EMT to MET. The results also show that garcinol has an effect on the Wnt signaling pathway, causing β-catenin to translocate to the nucleus. There is crosstalk between the NF-kB and Wnt signaling pathways when the phosphorylated form of β-catenin increases. GSK-3, the phosphorylation factor for β-catenin, was discovered to be increased, causing β-catenin nuclear translocation to be inhibited and, as a result, Wnt signaling pathways to be inhibited.

Garcinol increased Taxol-induced antimitotic activity, reduced caspase-3/iPLA2-stimulated cell repopulation and prevented NF-kB/Twist1-derived pro-inflammatory signaling and pro-metastatic properties, according to Tu et al. Chen et al discovered that Garcinol-induced 9-nAChR downregulation may have a direct impact on cyclin D3 gene expression transcriptional regulation. Garcinol inhibits the progression of the cell cycle in human breast cancer cells through regulating the cyclin D3 gene. According to Ahmad et al, garcinol suppressed IL-6-induced STAT-3

![Figure 8 Garcinol chemical structure.](image-url)
phosphorylation as well as the synthesis of urokinase-type plasminogen activator (uPA), VEGF, and matrix metalloproteinase-9 (MMP-9) activator, reducing cell invasion and aggressiveness.\textsuperscript{57} Garcinol inhibited IL-6-induced STAT-3 phosphorylation and production of urokinase-type plasminogen activator (uPA), VEGF, and matrix metalloproteinase-9 (MMP-9) activator, which reduced cell invasion and aggressiveness, according to Ahmad et al.\textsuperscript{58} Induction of caspase-mediated apoptosis (Caspase 3, Caspase 9) was also added by Ahmad et al, as evidenced by PARP cleavage. Apoptosis is induced by inactivation of NF-κB signaling and downregulation of its target genes.\textsuperscript{59}

According to Ye et al, garcinol suppressed 17-Estradiol (E2), which elevated ac-H3, ac-H4, and NF-κB/ac-p65 levels. Nuclear translocation of NF-κB/p65, as well as cyclin D1, Bcl-2, and Bcl-xl mRNA and protein expression levels, were decreased in E2-treated cells. In the NF-κB pathway, reduced ac-p65 protein expression is hypothesized to be connected to downregulation of cyclin D1, Bcl-2, and Bcl-xl expression.\textsuperscript{60}

**Griffipavixanthone (GPX)**

Griffipavixanthone (GPX) is found in Garcinia oblongifolia (Figure 9). According to Ma et al, GPX cleaves caspase-8/9, and PARP GPX increased the mRNA level of the p53 gene and its target genes, and changed Bax expression while Bcl-2 decreased in mitochondria by releasing cytochrome c.\textsuperscript{40}

**Friedolanostane Triterpenoid**

*Garcinia celebica* fruits contain the triterpenoid compound friedolanostane (Figure 10). Subarnas et al discovered that a compound inhibited the oncogenic protein Akt, resulting in an increase in PARP.\textsuperscript{61}

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**Figure 9** Griffipavixanthone chemical structure.


![Griffipavixanthone chemical structure](https://Example.com/Griffipavixanthone.png)

**Figure 10** Friedolanostane triterpenoid chemical structure.

Hexane

The fruits of *Garcinia quaesita* consist of Hexane (Figure 11). Pathiranage et al reported that the compound increased the activity of caspase 3/7, increased Bax, and decreased Baculoviral Inhibitor of Apoptosis Repeat Containing 5 (BIRC-5).⁶²

Neobractatin (NBT)

Neobractatin (NBT) was found in *Garcinia bracteata* extract (Figure 12), which inhibited metastasis by decreasing the expressions of pAKT, the EMT markers vimentin and cofilin, and Matrix Metalloproteinase 2 (MMP2).⁶³
7-Epiclusianone (7-Epi)
The extract of *Garcinia gardneriana* fruits contains 7-Epiclusianone (7-Epi), which enhances the BAX/BCL-2 ratio when cells accumulate in the G0/G1 phase (Figure 13). 7-Epi reduced the expression of CDK Inhibitor 1A (CDKN1A (p21)) and cyclin E in both cell lines, while decreasing the expression of cyclin D1 and p-ERK in the MCF-7 cell line.64

S1 (the Regioisomeric Mixture of Xanthochymol and Guttiferone E) and S2 (the Regioisomeric Mixture of Isoxanthochymol and Cycloxanthochymol)
These compounds are found in *Garcinia xanthochymus* (Figure 14). According to Xu et al, S1 and S2 reduced the phosphorylation of STAT3’s upstream kinases, Janus Kinase 2 (JAK2) and Src, as well as the expression of various STAT3-regulated genes, including anti-apoptotic (Bcl-XL, Mcl-1, and survivin), proliferative (cyclin D1), and angiogenic (VEGF) genes.65

The result of this review showed several pieces of research that reported the use of *Garcinia* phytochemicals as molecular therapy for breast cancer, as seen in Table 1.
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<th>Plant Species</th>
<th>Part Used</th>
<th>Phyto-Chemicals</th>
<th>Cell Lines</th>
<th>Study Type</th>
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<td>in vitro</td>
<td>$\alpha$-mangostin induce apoptosis.</td>
<td>Caspase 8, 9.7, Bax/Bcl-2, p53, AIF, E2</td>
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<td>Doi et al, 2009</td>
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<td>in vitro and in vivo BALB/c female nude mice</td>
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<td>Induce apoptosis.</td>
<td>TNF-related apoptosis-inducing ligand (TRAIL)</td>
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<td>in vitro</td>
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<td><em>Garcinia xanthochymus</em></td>
<td>S1 (the regioisomeric mixture of xanthochymol and guttiferone E) and S2 (the regioisomeric mixture of isoxanthochymol and cycloxanthochymol)</td>
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<td>in vitro</td>
<td>Apoptotic activity by inducing cell cycle arrest at G1/S transition</td>
<td>STAT3</td>
<td>Xu et al, 2020</td>
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Conclusion
On the basis of this review, it can be concluded that *Garcinia* phytochemical compounds are potential as molecular therapy for breast cancer and have low toxicity to normal cells. This result can be used as an alternative for minimally invasive therapy for patients with breast cancer, since chemotherapy agents have many adverse side effects on healthy cells. The result confirms α-mangostin, Cambogin, GA, Garcinol, Griffinivixanthone, Friedolanostane triterpenoid, Hexane, Neobractatin, 7-Epiclusianone, xanthochymol - guttiferone E, and isoxanthochymol - cycloxanthochymol have anticancer properties including apoptosis, inhibition of proliferation and, metastasis. These phytochemicals can be used as candidates for molecular therapy to improve the health and life expectancy of patients with breast cancer.

Disclosure
The authors report no conflicts of interest in this work.

References


