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*Review Article*

# Chemistry and Pharmacology of Artocarpin: An Isoprenyl Flavone from *Artocarpus* Species

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## ABSTRACT

Artocarpin is an isoprenyl flavone from *Artocarpus* species (Moraceae). Trees of the genus comprise about 50 species, and are native to tropical and subtropical Asia. First isolated from the root of *A. heterophyllus* (jackfruit), artocarpin has been reported in other *Artocarpus* species such as *A. altilis*, *A. chempeden*, *A. kemando* and *A. maingayi*. Recently, artocarpin has also been isolated from *A. incisus*, *A. chama*, *A. lowii*, *A. anisophyllus*, *A. scortechinii*, *A. odoratissimus* and *A. hirsutus*. It has a molecular formula of $C_{26}H_{28}O_6$ and a 5,7,2',4'-tetrahydroxylated structure with three benzene rings. Ring B has a 2',4'-resorcinol moiety and there is a methoxy group at C-7 of ring A. At C-3 and C-6 of artocarpin are the isoprenyl substituents. Some data on the content of artocarpin in extracts and fractions of different solvents and species of *Artocarpus* have been presented. Other flavones prenylated at C-3 and C-6 include artelasticin, artelastofuran, cudraflavone C and norartocarpin. The inhibition of tyrosinase and melanogenesis are two skin-whitening activities of artocarpin. It protects UVB-induced skin damage. Besides its cosmeceutical activities of skin-whitening and photo protection, artocarpin possesses other pharmacological properties such as cytotoxic, anti-inflammatory, antioxidant, antimicrobial, antiandrogen, antitubercular, antiplasmodial, neuraminidase inhibitory, termiticidal and wound healing activities. In the conclusion, some research studies of interest for the future have been proposed.

**Key words:** *Artocarpus*, Artocarpin, Isoprenyl flavone, Skin whitening, Photo protective, Cytotoxic.

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## INTRODUCTION

In this short review, artocarpin has been selected as the compound with interesting pharmacological properties that can be related to its chemistry. To date, there are no reviews on this compound which has been isolated primarily from trees of *Artocarpus* of the family Moraceae. In our literature search, there is confusion over the names of species used by some authors. For example, *Artocarpus communis* and *Artocarpus incisus* are synonymous to *Artocarpus altilis*, the preferred name for breadfruit. *Artocarpus integer* is the preferred name for chempedak, and *Artocarpus champeden* and *Artocarpus integrifolius* are synonyms.[1] *Artocarpus heterophyllus* is the preferred name for jackfruit and *Artocarpus integrifolia* is synonymous. Leaves and fruits of *A. altilis* (breadfruit) and *A. heterophyllus* (jackfruit) are shown in Figure 1.

Trees of the genus *Artocarpus*, comprise about 50 species, are native to tropical and subtropical Asia.[2] *Artocarpus* species are small to large trees with all plant parts producing white latex.[3] Leaves are spirally arranged, alternate or distichous, simple, entire to pinnate, coriaceous, and glabrous to pubescent. Inflorescences are unisexual (monoecious) with numerous flowers densely packed together. Fruits are syncarps formed by the enlargement of the entire female flower head. Seeds are large without endosperm although some varieties are seedless.

The diversity of secondary metabolites isolated from *Artocarpus* species included classes of compounds such as chalcones, flavonones, flavones, flavan-3-ols, xanthones, stilbenoids and terpenoids.[2] Among the different flavones are prenylflavones which include artocarpin. Among the wide range of pharmacological properties of *Artocarpus* species are biological activities including antibacterial, antitubercular, antiviral, antifungal, antiplatelet, antiarthritic, antityrosinase, antidiabetic, cytotoxic and anti-inflammatory activities.[3]

## CHEMISTRY

Artocarpin was first isolated from the root of *A. heterophyllus*.[4] Later, the prenylated flavone was reported in other *Artocarpus* species such as *A. altilis*, *A. chempeden*, *A. kemando* and *A. maingayi*.[3] Recently, artocarpin has also been isolated from *A. incisus*, *A. chama*, *A. lowii*, *A. anisophyllus*, *A. scortechinii*, *A. odoratissimus* and *A. hirsutus*.

Artocarpin [6-(3-methyl-1-butenyl)-5,2',4'-trihydroxy-3-isoprenyl-7-methoxy flavone] has a molecular formula of $C_{26}H_{28}O_6$ and a 5,7,2',4'-tetrahydroxylated structure with three benzene rings (Figure 2). There is a 2',4'-resorcinol moiety in ring B, and a methoxyl group at C-7.[5] At C-3 and C-6 are isoprenyl substituents of $—H_2CH=C(CH_3)_2$ and $—CH=CHCH(CH_3)_2$, respectively.

Figure 2 also shows other flavones prenylated at C-3 and C-6 isolated from *Artocarpus* species. They include artelasticin,[6] artelastofuran,[7] cudraflavone C[8] and norartocarpin.[9] The chemistry and biological activities of isoprenoid-substituted flavonoids from the root and/or bark of *Artocarpus* species have been reviewed.[10]

The content of artocarpin in the diethyl ether and methanol extracts of *A. incisus* heartwood was found to be 45% and 20%, respectively.[11] From the methanol heartwood extract of *A. communis*, the artocarpin content in the dichloromethane fraction was the highest (371 µg/mg) and lowest in the hexane fraction (6.4 µg/mg).[12] The artocarpin content of the fractions decreased in the following order: dichloromethane > methanol > butanol > ethyl acetate > hexane. Recently, the content of artocarpin from different heartwood extracts of *A. heterophyllus* was reported.[13] Both the ethyl acetate and chloroform extracts yielded 22% of artocarpin, while those of methanol and hexane yielded 3.0% and 2.6%, respectively. Norartocarpin and artocarpin have been synthesised from the commercially available 1,3,5-trimethoxybenzene *via* a linear reaction sequence of 9 and 12 steps with overall yields of 14% and 3.5%, respectively.[14] The successful development of this protocol is an important alternative approach to

**Figure 1:** Leaves and fruits of *Artocarpus altilis* or breadfruit (left) and *A. heterophyllus* or jackfruit (right).

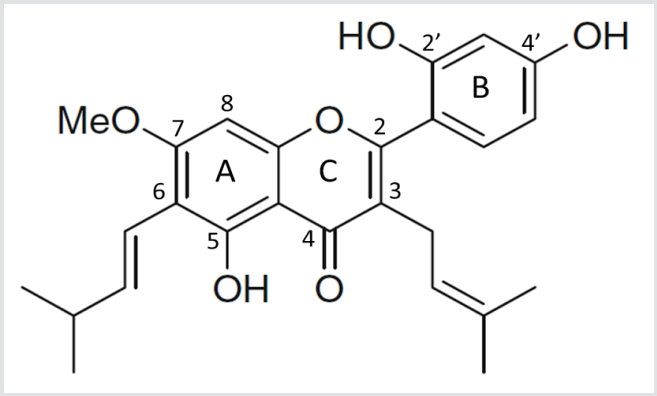



**Figure 2:** Artocarpin and some other C-3 and C-6 prenylated flavones.

address the problem of low content of both these prenylated flavones in the heartwood of *Artocarpus* species.

## PHARMACOLOGY

Studies have shown that artocarpin has multiple pharmacological properties which include skin-whitening, photo protective, cytotoxic, anti-inflammatory, antioxidant, antibacterial, antiandrogen, antitubercular, antiplasmodial, neuraminidase inhibitory, termiticidal and wound healing activities.

### Skin-whitening Activity

Melanogenesis is a process of melanin production in melanocytes, and involves several steps with tyrosinase being the rate-limiting enzyme for melanin synthesis.[15] Alteration of tyrosinase production and activity is a main target for treatment of pigmentation defects. Inhibition of tyrosinase and melanogenesis are two skin-whitening activities of artocarpin. Containing 45% of artocarpin, the diethyl ether extract of *A. incisus* heartwood displayed slightly weaker tyrosinase inhibitory activity ($IC_{50}$ = 10 µg/ml) than that of kojic acid ($IC_{50}$ = 7.9 µg/ml) used as the positive control.[11] At concentrations of 2.0–25 µg/ml, the extract decreased melanin production in B16F1 melanoma cells. The extract did not change the cell morphology but reduced the melanin content by inhibiting melanin synthesis. However, the purified artocarpin caused changes in the cell morphology at 4.5 µg/ml concentration.

An efficient skin-lightening effect was observed following topical application of artocarpin at 250 µM to the UV-induced hyper-pigmented dorsal skins of guinea pigs.[16] Artocarpin, isolated from the heartwood and cortex of *A. altilis*, reduced melanin production in B16 melanoma cells without inhibiting tyrosinase activity.[5] The other isolated compounds, however, inhibited melanin production by strongly suppressing tyrosinase activity. For example, the anti-tyrosinase activity of artocarpin ($IC_{50}$ = 270 µM) was much weaker than that of norartocarpetin ($IC_{50}$ = 0.42 µM). Other studies have also reported no tyrosinase inhibitory activity of artocarpin from *A. incises* [17] or very weak activity ($IC_{50}$ = 315 µg/ml) from *A. lowii*.[18]

Based on structure-activity relationships, the potent anti-tyrosinase activity of norartocarpetin is attributed to the 2',4'-resorcinol moiety in ring B.[5] Although, artocarpin has a similar structure, its isoprenyl substituents at C-3 and C-6, and a methoxy group at C-7 significantly decreased its tyrosinase inhibitory effects. Besides artocarpin, other compounds from *Artocarpus* species that inhibit melanogenesis but lack tyrosinase inhibition have also been reported.[9] The mechanism of these compounds inhibiting melanin production remains unclear. A review of structure-activity relationships of prenyl-substituted polyphenols from *A. heterophyllus* reported that both prenyl and OH groups, as well as the type of substitution pattern, are crucial for the inhibition of melanin production in B16 melanoma cells.

Compared to norartocarpetin, artocarpin has weaker tyrosinase inhibitory activity due to its low polarity substituent groups.[19] However, artocarpin exhibits stronger melanogenesis inhibitory activity in melanoma cells than norartocarpetin even though artocarpin shows lower tyrosinase inhibitory activity, suggesting that it is necessary to consider the expression of melanogenic enzymes as well as tyrosinase activity in melanoma cells.

The heartwood extract of *A. incisus* contained 44.5% of artocarpin which displayed stronger inhibition of melanogenesis ($IC_{50}$ = 30.2 mg/ml) than kojic acid ($IC_{50}$ = 51.4 mg/ml), the positive control.[20] When the extract was topically applied *via* a nano-emulsion onto the UVB-stimulated hyper pigmented dorsal skin of C57BL/6 mice, a visible reduction in hyperpigmentation was observed after six weeks. Depigmentation decreased from 84 to 51 units (39%). The areas applied with the extract returned to their original colour four weeks after treatment.

Depigmentation by melanogenesis inhibitors can be achieved by regulating: i) the transcription and activity of tyrosinase, tyrosinase-related proteins and/or peroxidase; ii) the uptake and distribution of melanosomes in recipient keratinocytes; and iii) the degradation of melanin and melanosome, and turnover of pigmented keratinocytes.[21] Other mechanisms include cytotoxicity to melanocytes, melanosome transfer inhibition and melanocyte-keratinocyte interaction. Recently, the anti-melanogenesis properties of *A. communis* heartwood extract was reported to involve the activation of extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) signalling pathways.[22]

### Photo protective Activity

In another study, the photo protective effect of artocarpin on UVB-induced skin damage was tested in hairless mice.[23] Artocarpin at a topical dose of 0.05% showed significant photo protective effects by decreasing desquamation, epidermal thicken and sunburn cell formation. The effects

were better than those of 0.1% treatment. The topical administration of artocarpin was found to protect against UVB-induced oxidative stress and inflammation in the skin of hairless mice by decreasing ROS-mediated lipid peroxidation, down-regulating tumour necrosis factor (TNF)-α mediated sunburn cell formation, and reducing inflammatory protein expression. The study concluded that with both antioxidant and anti-inflammatory activities, artocarpin has the potential to be developed into a photo protective product for use as medicine and cosmetics.

Another study was conducted to investigate the ability of an artocarpin-enriched extract from the heartwood of *A. altilis* to prevent UVB-induced photo-damage.[24] Human skin fibroblasts and keratinocytes were pre-treated with 50 mg/ml of extract for 24 h and later irradiated with UVB radiation. The treated fibroblasts showed attenuated matrix metalloproteinase (MMP)-1 production but not type-I procollagen production. The treated keratinocytes displayed decreased production of TNF-α and IL-6. Topical application of the extract was shown to suppress epidermal thickening and collagen loss in UVB-exposed skin of hairless mice. A follow-up study reported that the artocarpin-enriched heartwood extract of *A. altilis* protected human skin fibroblasts damaged by UVB-irradiation in fibroblast-embedded collagen lattices.[25] Earlier studies have reported that the artocarpin-enriched extract of *A. altilis* was able to significantly enhance the viability and proliferation of wrinkled-skin fibroblasts,[26] and to reverse the activities of UVA-irradiated fibroblasts and improve collagen deposition in aged and sun-exposed skin tissue.[27]

## Cytotoxic Activity

Artocarpin isolated from the dichloromethane extract of *A. altilis* roots showed moderate cytotoxicity against KB and BC human cancer cells with $IC_{50}$ values of 5.1 and 3.3 μg/ml, respectively.[28] However, it was also moderately cytotoxic to the normal Vero (African green monkey) cells (5.6 μg/ml). The cytotoxicity of artocarpin was among the strongest compared to the other eight prenylated flavones isolated.

Out of 19 compounds isolated from the twigs of *A. heterophyllus* and screened for their cytotoxicity against PC-3 and H460 cancer cells, artocarpin was the most potent with $IC_{50}$ values of 7.9 and 8.3 μM, respectively.[29] Norartocarpin, with an OH group at C-7, exhibited much weaker cytotoxicity with $IC_{50}$ values of 22 and 21 μM, respectively. This suggests that the methoxyl group at C-7 of artocarpin enhances its cytotoxicity.

Of the prenylated flavones isolated from the roots of *Artocarpus chama*, artocarpin was cytotoxic to MCF-7 and MDA-MB-231 breast cancer cells with $IC_{50}$ values of 3.3 and 3.8 μg/ml, respectively.[18] Compared to the other compounds, inhibitory effects of artocarpin were relatively weak but broad-based against the panel of seven cancer cell lines. Similarly, artocarpin from fruits of *A. heterophyllus* can induce apoptosis in SMMC-7721 and SGC-7901 cancer cells.[30] Recently, among five flavones isolated from the ethanol leaf extract of *A. heterophyllus*, artocarpin displayed the strongest cytotoxic activity against PC-3, NCI-H460 and KS49 cancer cells with $IC_{50}$ values of 5.1, 10 and 8.1 μM/ml, respectively.[31]

From the heartwood of *A. heterophyllus*, artocarpin showed potent cytotoxic activity against human T47D breast cancer cells.[32] The compound reduced cell viability, and altered cell and nuclear morphology, indicative of apoptosis. The percentage of sub-G1 phase formation was also elevated dose-dependently. Artocarpin was found to induce the activation of caspases 3, 8 and 10 with negligible changes in the mitochondrial membrane potential. Overall, these results indicated that artocarpin induced apoptosis in T47D cells possibly *via* a mitochondria-independent or extrinsic pathway.

Structure-cytotoxicity investigations of flavonoids isolated from *A. heterophyllus* on B16 melanoma cells showed that the prenyl-substituted moieties enhanced cytotoxicity of the flavonoids.[33] The attached position and number of prenyl-substituted moieties per molecule influence their cytotoxicity.

A study showed that artocarpin induced apoptosis in HSC-1 human cutaneous squamous carcinoma cells by increasing caspase 3 or 7 activity through modulation of mitogen-activated protein kinase (MAPK) and Akt/mTOR pathways.[34] the effects were more pronounced at low foetal bovine serum (FBS) concentration. At high concentration, the binding of artocarpin to proteins in the FBS inhibited cellular uptake and reduced the cytotoxic activity of artocarpin on HSC-1 cells.

The anti-hepatoma activity of the methanol extract and fractions of *A. communis* heartwood toward HepG2 and PLC/PRF/5 human liver cancer cells has been reported.[12] The extract and fractions did not induce apoptosis but triggered autophagy cell death in a dose-dependent manner. The anti-hepatoma activity was attributed to artocarpin as the fractions with the highest artocarpin content had the highest activity. The order of activity was as follows: dichloromethane fraction > methanol extract > ethyl acetate fraction > butanol fraction > hexane fraction. Another related study reported that the anticancer effect of artocarpin from the heartwood of *A. communis* on HepG2 and PLC/PRF/5 hepatoma cells was mediated through autophagy cell death.[35] Its autophagy activity was enhanced by improving its solubility using a novel nanoparticle delivery system. This system in part resolved the poor water solubility of artocarpin, a drawback which has restricted its clinical application and bioavailability.

More recent studies reported that artocarpin induces p53-dependent or independent apoptosis *via* ROS-mediated MAPKs and Akt activation in non-small cell lung cancer cells,[36] and is a promising colorectal anti-cancer agent by targeting Akt 1 and 2 kinase activity.[37]

## Anti-inflammatory Properties

Prenylated flavonoids isolated from the heartwood of *A. communis* showed potent anti-inflammatory properties when tested for their inhibitory activity on nitric oxide production in RAW264.7 LPS-activated mouse macrophage cells.[38] The $IC_{50}$ value of artocarpin was 18.7 μM with strongest properties displayed by isobacachalcone (6.4 μM) and gemichalcone B (9.3 μM).

## Antioxidant Properties

A study on the antioxidant properties of flavonoids showed that artocarpin displayed the strongest radical scavenging efficiency, followed by dalspinosin, cycloartocarpin and dalspinin.[39] Values were however lower than quercetin, morin and trolox used as positive controls. Recently, the DPPH radical scavenging activity of artocarpin from leaves and the heartwood of *A. anisophyllus* has been reported.[40] The $IC_{50}$ value of artocarpin (140 μg/ml) was however lower than those of the dichloromethane extract (80 μg/ml) and the ethyl acetate extract (40 μg/ml).

## Antimicrobial Activity

A study reported that artocarpin isolated from the heartwood of *A. heterophyllus* showed inhibitory activity against cariogenic bacteria.[41] The compound inhibited the growth of *Streptococcus mutans* and related species including plaque-forming streptococci in the concentration range of 6.25–12.5 μg/ml. The growth of *Actinomyces* species was inhibited at 3.13–12.5 μg/ml and that of *Lactobacillus* species at 12.5 μg/ml.

The antimicrobial activity of flavonoids from leaves and heartwood of *A. anisophyllus* and *A. lowii* was evaluated against Gram-positive bacteria of *Bacillus cereus* and *Staphylococcus aureus*, Gram-negative bacteria of *Pseudomonas putida* and *Escherichia coli*, and fungi of *Candida albicans* and *C. glabrata*.[42] Artocarpin showed strong antimicrobial activity towards all bacteria and fungi. Against the bacteria, diameter of inhibition zone (DIZ) was more than 11 mm and minimum inhibitory concentration

(MIC) was 0.45 mg/ml. Against the fungi, DIZ was more than 9.5 mm and MIC was 1.8 mg/ml. The strong antimicrobial activity of artocarpin was attributed to the two hydroxyl groups at position C-2' and C-4', and two lipophilic isoprenyl groups at positions C-3 and C-6.

Artocarpin from the roots of *A. integer* displayed antibacterial properties.[43] It inhibited the growth of *Staphylococcus epidermidis*, *S. aureus* and *Propionibacterium acnes* with MIC of 4, 2 and 2 μg/ml, respectively. In another study, artocarpin inhibited methicillin-resistant *S. aureus* (MRSA) and *E. coli* (both MIC = 62.5 mg/ml), and against *Pseudomonas aeruginosa* (MIC = 250 mg/ml).[44] When tested for synergistic effects with ampicillin, norfloxacin and tetracycline, results indicated that artocarpin enhanced the antimicrobial activities of the tested antibiotics against MRSA, *P. aeruginosa* and *E. coli*. Artocarpin produced synergistic effect with norfloxacin against MRSA, *P. aeruginosa* and *E. coli*. With tetracycline, synergistic effect was observed against MRSA and *P. aeruginosa*, and with ampicillin, synergistic effect was observed against MRSA.

## Antiandrogen Activity

Antiandrogen activity *via* inhibition of 5α-reductase is critical for male sexual differentiation and its deficiency may be involved in the development of prostate cancer.[45] From the heartwood of *A. incisus, artocarpin* inhibited 5α-reductase ($IC_{50}$ = 85 μM).[46] Structure-activity investigations of the isolated compounds suggested that the presence of an isoprene substituent (prenyl and geranyl) would enhance 5α-reductase inhibitory effects. Although artocarpin possesses potent 5α-reductase inhibitory effect, it has to penetrate the skin to reach the androgen receptors. A technique using alginate/chitosan microparticles for targeted transfollicular delivery of artocarpin has been developed.[47]

## Antitubercular and Antiplasmodial Activities

Out of nine prenylated flavones isolated from the dichloromethane extract of *A. altilis* roots, artocarpin exhibited the potent antitubercular activity against *Mycobacterium tuberculosis* (MIC = 3.1 μg/ml) and antiplasmodial activity against K1 strain of *Plasmodium falciparum* ($IC_{50}$ = 3.0 μg/ml).[28] Chaplashin showed similar antitubercular activity (MIC = 3.1 μg/ml) but stronger antiplasmodial activity was observed in morusin ($IC_{50}$ = 1.9 μg/ml).

## Neuraminidase Inhibition

Inhibition of neuraminidase (NA) has become an established target for the treatment of influenza. Among the flavonoids, artocarpin from *Artocarpus* has been reported to be a remarkable NA inhibitor.[48] The compound inhibited NA of oseltamivir-sensitive influenza strains (PR/8/34, Jena/5528/09 and Jena/5555/09) with $IC_{50}$ values of 0.18, 0.23 and 0.30 μM, respectively, and oseltamivir-resistant strain (342/09) with $IC_{50}$ value of 0.55 μM.

The NA inhibitory activity of artocarpin (180–300 nM) was ten-fold stronger than katsumadain A used as positive control. Artocarpin also inhibited the growth of *Streptococcus pneumoniae* and biofilm formation.[49] This rendered artocarpin a promising natural anti-influenza product as *S. pneumoniae* is a major cause of pneumonia during influenza epidemics and neuraminidase is a virulence factor of pneumococci and influenza viruses. A related study further explored the potential of using artocarpin in combination with katsumadain A as remedy for pneumonia and influenza.[50] Results showed that both compounds synergistically inhibited NA, NanA, including the recombinants rNanA and rNanB. Recently, the discovery of prenylated flavonoids from the root bark of *Morus alba* (mulberry) with similar dual activity against influenza virus and *S. pneumoniae* has been reported.[51]

## Termiticidal Activity

Artocarpin, a major component in the heartwood extract of *A. heterophyllus*, elicited the highest termiticidal activity against both *Coptotermes formosanus* and *Reticulitermes speratus*.[52] Similarly, another related study reported that artocarpin from jackfruit displayed moderate anti-feed ant activity against the cutworm *Spodoptera litura* and had lethal effects on the termite *R. speratus* at a dose of 10 μg/disc.[53]

## Wound Healing Activity

A study conducted showed that artocarpin promotes wound healing through multiple mechanisms.[54] The compound accelerates the inflammatory phase, and enhances the differentiation, proliferation and migration of fibroblasts and keratinocytes, collagen deposition, re-epithelialization, wound contraction, and angiogenesis.

# CONCLUSION

Artocarpin, an isoprenyl flavone, was first isolated from the root of *A. heterophyllus* (jackfruit). The compound has a molecular formula of $C_{26}H_{28}O_6$ and a 5,7,2',4'-tetrahydroxylated structure with three benzene rings. Ring B has a 2',4'-resorcinol moiety and there is a methoxy group at C-7 of ring A. At C-3 and C-6 are the isoprenyl substituents. Besides its cosmeceutical activities of skin-whitening and photo protection, artocarpin possesses other pharmacological properties which include cytotoxic, anti-inflammatory, antioxidant, antimicrobial, antiandrogen, antitubercular, antiplasmodial, neuraminidase inhibitory, termiticidal and wound healing activities. Comparisons between artocarpin and other flavones with and without isoprenyl substituents would be interesting research in the future. Bioactivities of artocarpin and their synergies with other flavonoids (if any) would be equally exciting.

# CONFLICT OF INTEREST

The authors do not have any conflict of interest to declare.

# ABBREVIATION USED

**DIZ:** diameter of inhibition zone; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; **ERK:** extracellular signal-regulated kinase; **FBS:** foetal bovine serum; **FRC:** Forest Research Centre; **ISME:** International Society for Mangrove Ecosystems; **JNK:** c-Jun N-terminal kinase; **MAPK:** mitogen-activated protein kinase; **MIC:** minimum inhibitory concentration; **MMP:** matrix metalloproteinase; **MRSA:** methicillin-resistant *Staphylococcus aureus*; **NA:** neuraminidase; **ROS:** reactive oxygen species; **SFD:** Sabah Forestry Department; **TNF:** tumour necrosis factor; **UVA:** ultraviolet A; **UVB:** ultraviolet B.

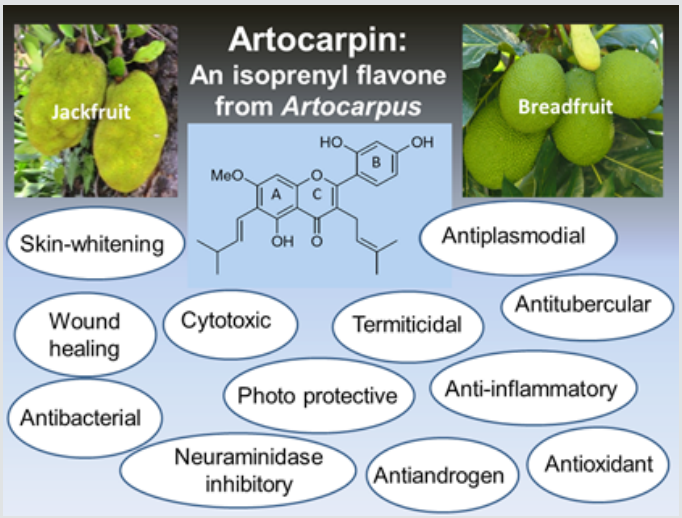
# REFERENCES


1. The Plant List, *Artocarpus. 2013.* Database available online at http://www.theplantlist.org/ tpl1.1/search?q=*Artocarpus* [Accessed in Oct 2017]
2. Hakim A. Diversity of secondary metabolites from genus *Artocarpus* (Moraceae). Nusantara Biosci. 2010;2(3):146-56.
3. Jagtap UB, Bapat VA. *Artocarpus*: A review of its traditional uses, phytochemistry and pharmacology. J Ethnopharmacol. 2010;129(2):142-66.
4. Lin CN, Lu CM, Huang PL. Flavonoids from *Artocarpus heterophyllus*. Phytochemistry. 1995;39(6):1447-51.
5. Lan WC, Tzeng CW, Lin CC, Yen FL, Ko HH. Prenylated flavonoids from *Artocarpus altilis*: Antioxidant activities and inhibitory effects on melanin production. Phytochemistry. 2013;89:78-88.
6. Kijjoa A, Cidade HM, Pinto MMM, Gonzalez MJG, Anantachoke C, Gedris TE, *et al.* Prenyl-flavonoids from *Artocarpus elasticus*. Phytochemistry. 1996;43(3):691-4.
7. Kijjoa A, Cidade HM, Gonzalez MJG, Afonso CM, Silva AMS, Herzt W. Further

prenyl-flavonoids from *Artocarpus elasticus*. Phytochemistry. 1998;47(5):875-8.
8. Syah YM, Juliawaty LD, Achmad SA, Hakim EH, Ghisalberti EL. Cytotoxic prenylated flavones from *Artocarpus champeden*. J Nat Med. 2006;60(4):308-12.
9. Arung ET, Shimizu K, Kondo R. Structure-activity relationship of prenyl-substituted polyphenols from *Artocarpus heterophyllus* as inhibitors of melanin biosynthesis in cultured melanoma cells. Chem Biodiver. 2007;4(9):2166-71.
10. Nomura T, Hano Y, Aida M. Isoprenoid-substituted flavonoids from *Artocarpus* plants (Moraceae). Heterocycles. 1998;2(47):1179-205.
11. Donsing P, Limpeanchob N, Viyoch J. Evaluation of the effect of Thai breadfruit's heartwood extract on melanogenesis-inhibitory and antioxidation activities. J Cosmet Sci. 2008;59(1):41-58.
12. Tzeng CW, Yen FL, Lin LT, Lee CW, Yen MH, Tzeng WS, *et al.* Anti-hepatoma activity of *Artocarpus communis* is higher in fractions with high artocarpin content. Sci World J. 2014;8. Article ID 978525.
13. Septama AW, Panichayupakaranant P. Simultaneous HPLC analysis of three flavonoids in the extracts of *Artocarpus heterophyllus* heartwoods. Nat Prod. Sci. 2016;22(2):77-81.
14. Zhang WJ, Wu JF, Zhou PF, Wang Y, Hou AJ. Total syntheses of norartocarpin and artocarpin. Tetrahedron. 2013;69(29):5850-8.
15. Luangpraditkun K, Viyoch J. Potential uses of *Artocarpus altilis* heartwood extract in cosmeceuticals. Naresuan Univ J (Sci Technol). 2017;25(4):1-8.
16. Shimizu K, Kondo R, Sakai K, Takeda N, Nagahata T. The skin-lightening effects of artocarpin on UVB-induced pigmentation. Planta Med. 2002;68(1):79-81.
17. Shimizu K, Kondo R, Sakai K, Lee SH, Sato H. The inhibitory components from *Artocarpus incisus* on melanin biosynthesis. Planta Med. 1998;64(5):408-12.
18. Wang YH, Hou AJ, Chen L, Chen DF, Sun HD, Zhao QS, *et al.* New isoprenylated flavones, artochamins A-E, and cytotoxic principles from *Artocarpus chama*. J Nat Prod. 2004;67(5):757-61.
19. Mitsunaga T, Yamauchi K. Effect of quercetin derivatives on melanogenesis stimulation of melanoma cells. J Wood Sci. 2015;61(4):351-63.
20. Buranajaree S, Donsing P, Jeenapongsa R, Viyoch J. Depigmenting action of a nanoemulsion containing heartwood extract of *Artocarpus incisus* on UVB-induced hyper-pigmentation in C57BL/6 mice. J Cosmet Sci. 2011;62(1):1-14.
21. Donsing P, Viyoch J. Thai breadfruit's heartwood extract: A new approach to skin whitening. Srinakharinwirot Sci J. 2008;24(1):9-23.
22. Fu YT, Lee CW, Ko HH, Yen FL. Extracts of *Artocarpus communis* decrease α-melanocyte stimulating hormone-induced melanogenesis through activation of ERK and JNK signalling pathways. Sci World J. 2014;8. Article ID 724314.
23. Lee CW, Ko HH, Lin CC, Chai CY, Chen WT, Yen FL. Artocarpin attenuates ultraviolet B-induced skin damage in hairless mice by antioxidant and anti-inflammatory effect. Food Chem Toxicol. 2013;60:123-9.
24. Tiraravesit N, Yakaew S, Rukchay R, Luangbudnark W, Viennet C, Humbert P, *et al.* *Artocarpus altilis* heart wood extract protects skin against UVB *in vitro* and *in vivo*. J Ethnopharmacol. 2015;175:153-62.
25. Tiraravesit N, Humbert P, Robin S, Tissot M, Viennet C, Viyoch J. Artocarpin-enriched (*Artocarpus altilis*) heartwood extract protects against UVB-induced mechanical damage in dermal fibroblasts. Photochem Photobiol. 2017;93(5):1232-9.
26. Viyoch J, Buranajaree S, Grandmottet F, Robin S, Binda D, Viennet C, *et al.* Evaluation of the effect of Thai breadfruit's heartwood extract on the biological functions of fibroblasts from wrinkles. J Cosmet Sci. 2010;32(6):473.
27. Itsarasook K, Ingkaninan K, Viyoch J. Artocarpin-enriched extract reverses collagen metabolism in UV-exposed fibroblasts. Biologia. 2014;69(7):943-51.
28. Boonphong S, Baramee A, Kittakoop P, Puangsombat P. Antitubercular and antiplasmodial prenylated flavones from the roots of *Artocarpus altilis*. Chiang Mai J Sci. 2007;34(3):339-44.
29. Di X, Wang S, Wang B, Liu Y, Yuan H, Lou H, *et al.* New phenolic compounds from the twigs of *Artocarpus heterophyllus*. Drug Discov Ther. 2013;7(1):24-8.
30. Yang YL, Hou AJ, Zhang HQ, Shen H, Li QS, Zhang CC, *et al.* Effects of cycloartocarpin A and artocarpin extracted from Fructus Artocarpin Heterophylli on apoptosis of SMMC-7721 and SGC-7901 cells. J Integr Med. 2010;8(1):61-6.
31. Wang XL, Di XX T, Shen T, Wang SQ, Wang XN. New phenolic compounds from the leaves of *Artocarpus heterophyllus*. Chin Chem Lett. 2017;28(1):37-40.
32. Arung ET, Wicaksono BD, Handoko YA, Kusuma IW, Shimizu K, Yulia D, *et al.* Cytotoxic effect of artocarpin on T47D cells. J Nat Med. 2010;64(4):423-9.
33. Arung ET, Yoshikawa K, Shimizu K, Ryuichiro K. Isoprenoid-substituted flavonoids from wood of *Artocarpus heterophyllus* on B16 melanoma cells: Cytotoxicity and structural criteria. Fitoterapia. 2010;81(2):120-3.
34. Hu SCS, Lin CL, Cheng HM, Chen GS, Lee CW, Yen FL. Artocarpin induces apoptosis in human cutaneous squamous cell carcinoma HSC-1 cells and its cytotoxic activity is dependent on protein-nutrient concentration. Evid-based Complement Altern Med. 2015;8. Article ID 236159.
35. Tzeng CW, Tzeng WS, Lin LT, Lee CW, Yen FL, Lin CC. Enhanced autophagic activity of artocarpin in human hepatocellular carcinoma cells through improving its solubility by a nanoparticle system. Phytomedicine. 2016;23(5):528-40.
36. Tsai MH, Liu JF, Chiang YC, Hu SC, Hsu LF, Lin YC, *et al.* Artocarpin, an isoprenyl flavonoid, induces p53-dependent or independent apoptosis *via* ROS-mediated MAPKs and Akt activation in non-small cell lung cancer cells. Oncotarget. 2017;8(17):28342.
37. Sun G, Zheng Z, Lee MH, Xu Y, Kang S, Dong Z, *et al.* Chemoprevention of colorectal cancer by artocarpin, a dietary phytochemical from *Artocarpus heterophyllus*. J Agric Food Chem. 2017;65(17):3474-80.
38. Han AR, Kang YJ, Windono T, Lee SK, Seo EK. Prenylated flavonoids from the heartwood of *Artocarpus communis* with inhibitory activity on lipopolysaccharide-induced nitric oxide production. J Nat Prod. 2006;69(4):719-21.
39. Rajendran M, Manisankar P, Gandhidasan R, Murugesan R. Free radicals scavenging efficiency of a few naturally occurring flavonoids: A comparative study. J Agric Food Chem. 2004;52(24):7389-94.
40. Abdul Lathiff SM, Jemaon N, Abdullah SA, Jamil S. Flavonoids from *Artocarpus anisophyllus* and their bioactivities. Nat Prod Commun. 2015;10(3):393-6.
41. Sato M, Fujiwara S, Tsuchiya H, Fujii T, Iinuma M, Tosa H, *et al.* Flavones with antibacterial activity against cariogenic bacteria. J Ethnopharmacol. 1996;54(2-3):171-6.
42. Jamil S, Abdul Lathiff SM, Abdullah SA, Jemaon N, Sirat HM. Antimicrobial flavonoids from *Artocarpus anisophyllus* Miq. And *Artocarpus lowii* King. J Technol (Sci Eng). 2014;71:95-9.
43. Dej-Adisai S, Meechai I, Puripattanavong J, Kummee S. Antityrosinase and antimicrobial activities from Thai medicinal plants. Arch Pharm Res. 2014;37(4):473-83.
44. Septama AW, Panichayupakaranant P. Synergistic effect of artocarpin on antibacterial activity of some antibiotics against methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. Pharm Biol. 2016;54(4):686-91.
45. Hiipakka RA, Zhang HZ, Dai W, Dai Q, Liao S. Structure-activity relationships for inhibition of human 5α-reductases by polyphenols. Biochem Pharmacol. 2002;63(6):1165-76.
46. Shimizu K, Fukuda M, Kondo R, Sakai K. The 5α-reductase inhibitory components from heartwood of *Artocarpus incisus*: Structure-activity investigations. Planta Med. 2000;66(1):16-9.
47. Pitaksuteepong T, Somsiri A, Waranuch N. Targeted transfollicular delivery of artocarpin extract from *Artocarpus incisus* by means of microparticles. Eur J Pharm Biopharm. 2007;67(3):639-45.
48. Kirchmair J, Rollinger JM, Liedl KR, Seidel N, Krumbholz A, Schmidtke M. Novel neuraminidase inhibitors: Identification, biological evaluation and investigations of the binding mode. Future Med Chem. 2011;3(4):437-50.
49. Walther E, Richter M, Xu Z, Kramer C, Von Grafenstein S, Kirchmair J, *et al.* Anti-pneumococcal activity of neuraminidase inhibiting artocarpin. Int J Med Microbiol. 2015;305(3):289-97.
50. Walther E, Xu Z, Richter M, Kirchmair J, Grienke U, Rollinger JM, *et al.* Dual acting neuraminidase inhibitors open new opportunities to disrupt the lethal synergism between *Streptococcus pneumoniae* and influenza virus. Front Microbiol. 2016;7:357.
51. Grienke U, Richter M, Walther E, Hoffmann A, Kirchmair J, Makarov V, *et al.* Discovery of prenylated flavonoids with dual activity against influenza virus and *Streptococcus pneumoniae*. Sci Rep. 2016;6:27156.

52. Shibutani S, Yusuf S, Doi S. Anti-termite (Isoptera) component from *Artocarpus heterophyllus* heartwood. *Sociobiology.* 2006;47(3):711-20.
53. Morimoto M, Ohta Y, Ihara T, Arima K, Fukumoto H, Chavasiri W, *et al.* Insect anti-feedant in Thailand plant extracts against common cutworm, *Spodoptera litura*, and a subterranean termite, *Reticulitermes speratus*. Japan J Environ Entomol Zool. 2006;70(8):1864-8.
54. Yeh CJ, Chen CC, Leu YL, Lin MW, Chiu MM, Wang SH. The effects of artocarpin on wound healing: *in vitro* and *in vivo* studies. Sci Rep. 2017;7(1):15599.

## GRAPHICAL ABSTRACT




## SUMMARY

- Artocarpin is an isoprenyl flavone from *Artocarpus* species (Moraceae). The compound was first isolated from the root of *Artocarpus heterophyllus* (jackfruit).
- With a molecular formula of $C_{26}H_{28}O_6$ , artocarpin has a 5,7,2′,4′-tetrahydroxylated structure with three benzene rings. Ring B has a 2′,4′-resorcinol moiety and there is a methoxy group at C-7 of ring A. Attached to C-3 and C-6 are the isoprenyl substituents.
- The inhibition of tyrosinase and melanogenesis are two skin-whitening activities of artocarpin. It protects UVB-induced skin damage. Besides its cosmeceutical activities of skin-whitening and photoprotection, artocarpin possesses other pharmacological properties such as cytotoxic, anti-inflammatory, antioxidant, antimicrobial, antiandrogen, antitubercular, antiplasmodial, neuraminidase inhibitory, termiticidal and wound healing activities.

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