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Review Article

# Artonin E: A Short Review of its Chemistry, Sources, Anti-Cancer Activities and Other Pharmacological Properties

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ABSTRACT

In this short article, the chemistry, sources, anti-cancer and other medicinal properties of artonin E are reviewed for the first time. Sources of information cited on this prenylated flavonoid were from databases such as Google, Google Scholar, PubMed, Science Direct, J-Stage, Web of Science and PubChem. Artonin E or 5'-hydroxymorusin is a prenylated flavonoid from *Artocarpus* species (Moraceae). Its structure is that of a 3-isoprenyl 2',4',5'-trioxygenated flavone. Artonin E has been reported mostly in the root and bark of 12 *Artocarpus* species. The strong cytotoxic activities of artonin E are well-established and scientists from universities in Indonesia have been using artonin E as positive control when testing the cytotoxicity of compounds isolated from various plant species. The anti-cancer effects and mechanisms of artonin E have been reported in breast, lung, ovarian, colon and gastric cancer cells. Effects include apoptosis, anoikis, anti-proliferation, cell cycle arrest, inhibition of migration and invasion, and overcoming tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) resistance. Mechanisms include activation of caspases, up-regulation of apoptotic proteins and down-regulation of anti-apoptotic proteins. Artonin E is endowed with a wealth of other medicinal properties. A brief account on the medicinal properties and sources of other artonins is provided. Some prospects and further research on artonin E and other artonins are suggested.

***Keywords***: *Artocarpus*, 5'-Hydroxymorusin, Positive control, Apoptosis, Anoikis

## Introduction

Prenylated flavonoids are a sub-class of flavonoids, which combine a flavonoid skeleton with a lipophilic prenyl side chain.[1,2] The side-chain can consist of prenyl, geranyl or lavandulyl moiety. To date, prenylated flavonoids have been identified in 37 of plant genera. More than 1000 prenylated flavonoids have been identified. Most of prenylated flavonoids are found in the families of Cannabaceae, Guttiferae, Leguminosae, Moraceae, Rutaceae and Umbelliferae.

Prenylation usually renders flavonoids with improved bioactivities. The prenyl side chain increases the lipophilicity of flavonoids, which enable them to have greater affinity to cell membranes.[1,3] Depending on the length of prenyl side-chain and flavonoid skeletons, prenylated flavonoids have diverse structures. Pharmacological properties of prenylated flavonoids include antioxidant, antibacterial, antiviral, antifungal, larvicidal, estrogenic, immuno-inhibitory, anti-cancer and anti-inflammatory.[1-3]

The genus *Artocarpus* consists of 50 species that are native to South and Southeast Asia, New Guinea, and the Pacific region.[4] *Artocarpus* species contain flavonoids that include 3-prenylflavones with a 2',4'-dioxygenated or 2',4',5'-trioxygenated pattern of ring B.[5] These 3-prenylflavones are rich in medicinal properties such as antimicrobial, anti-inflammatory and anticancer properties.

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Among the prenylated flavonoids is a group known as artonins. To date, 24 of such compounds (artonins A–Y) have been recorded.[6] Pharmacological properties of artonins include anti-plasmodial, anti-cancer and antibacterial activities.

In this article, the chemistry, sources, anti-cancer and other medicinal properties of artonin E from *Artocarpus* species are reviewed for the first time. A brief account on other artonins is included. Some prospects and future research on artonin E and other artonins are suggested.

*Chemistry of Artonin E*

Artonin E or 5'-hydroxymorusin from *Artocarpus* species (Moraceae) is a prenylated flavonoid with a molecular formula of $C_{25}H_{24}O_7$ and molecular weight of 436.5 g/mol.[6,7] The molecular structure of artonin E has three aromatic rings (A–C) with three OH groups at C2', C4' and C5' of ring B, and one OH group at C5 of ring A (Figure 1). There are two prenyl units, one isoprenoid substituent at C3 of oxygenated ring C and one forming a dimethylpyrane ring D at C7 and C8. The presence of a double bond between C2 and C3, and a carbonyl group at C4 are essential for the bioactivities of artonin E. Morusin has a similar molecular structure as artonin E except that it lacks the OH group at C5'. For this reason, artonin E is sometimes called 5'-hydroxymorusin.[6]

The structure of artonin E is a 3-isoprenyl 2',4',5'-trioxygenated flavone.[5,7] Other compounds with the same structural type are artoindonesianins L and U. Prenylated flavonoids also include 3-isoprenyl 2',4'-dioxygenated flavones such as artocarpin[8] and morusin.[9]

*Sources of Artonin E*

Artonin E was first isolated from the bark *Artocarpus altilis* (syn. *A. communis*)[10] (Figure 2). Subsequently, artonin E was reported in other *Artocarpus* species that include *A. chama*, *A. elasticus*, *A. gomezianus*, *A. kemando*, *A. lanceifolius*, *A. lowii*, *A. nobilis*, *A. rigida*, *A. rigidus* (syn. *A. rotunda*), *A. scortechnii* and *A. teysmannii* (Table 1). Plant part most reported are the root and bark, with no reports on the leaf.

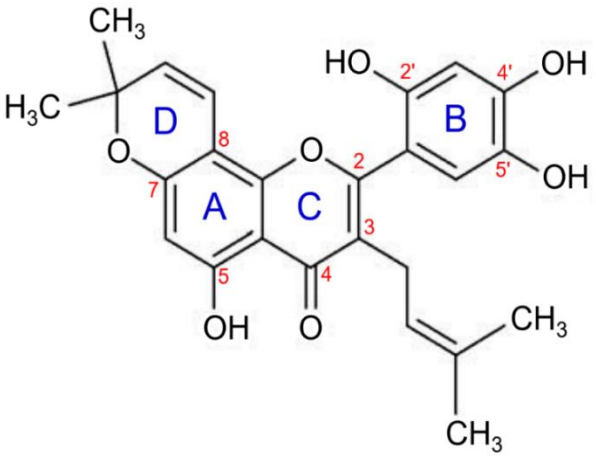


**Figure 1:** Chemical structure of artonin E.

**Figure 2:** (L−R) Leaves, bark and fruits of *Artocarpus altilis* (breadfruit).

*Anti-Cancer Activities of Artonin E*

The cytotoxicity of artonin E towards cancer cells are well established. Against a panel of A549 lung, MCF-7 breast, MDA-MB-231 breast, 1A9 ovarian, HCT-8 ileocecal, CAKI-1 kidney, SK-MEL-2 skin, 87-MG brain, PC-3 prostate and KB nasopharynx cancer cells, artonin E was cytotoxic all cell lines with $ED_{50}$ values of 8.5, 2.2, <1.3, 3.3, 9.7, 4.3, 6.4, 6.9, 3.0 and 6.5 µg/mL, respectively.[12]

Artonin E inhibited the growth of KB oral carcinoma cells, BC breast cancer cells and Vero normal African green monkey kidney cells with $IC_{50}$ values of 9.8, 3.5 and 6.1 µg/mL, respectively.[11] Against murine P388 leukemia cells, inhibition by artonin E was very strong with $IC_{50}$ value was 0.06 µg/mL.[34,37] Inhibition by artonin E acetate ($IC_{50}$ = 2.79 µg/mL) was not as strong but was more stable than artonin E during storage.[38] Against MCF-7 breast, MDA-MB-231 breast, HepG2 liver and WRL68 liver cancer cells, inhibition by artonin E was 2.6, 13.5, 33.8 and 29.6 µg/mL.[19]

A recent study reported that artonin E inhibited the growth of SKOV-3 ovarian cancer cells in 2D and 3D cultures, with $IC_{50}$ values of 6 and 25 µg/mL at 72 h, respectively. Treatment in 3D culture was therefore more than four times higher than that in 2D culture. Against T1074 normal ovarian lines, cytotoxicity of artonin E at 72 h was much weaker with $IC_{50}$ values of 28 µg/mL in 2D culture and 85 µg/mL in 3D culture, respectively.[22]

Against MCF-7 breast cancer cells over 24, 48 and 72 h, inhibition based on $IC_{50}$ values of artonin E were 6.9, 5.1 and 3.8 µM.[41-43] Inhibition was more potent than tamoxifen used as positive control. Values of tamoxifen were 24, 21 and 19 µM. Against MDA-MB 231 breast cancer cells, inhibition was 14, 14 and 9.8 µM at 24, 48 and 72 h, respectively.[44]

The strong cytotoxic activities of artonin E are well-established. Scientists from universities in Indonesia, have been using artonin E as positive control when testing the cytotoxicity of compounds isolated from various plant species. The species included *Macaranga gigantea*,[45] *Macaranga gigantifolia*,[46] *Corypha utan*,[47] *Melicope glabra*,[48] *Macaranga trichocarpa*,[49] *Acronychia pedunculata*,[50] *Calophyllum soulattri*,[51] *Willughbeia coriacea*[52] and *Calotropis gigantea*.[53]

**Table 1:** Isolation of artonin E from *Artocarpus* species and their plant parts

| Species | Plant part | Reference | Species | Plant part | Reference |
|---|---|---|---|---|---|
| *A. altilis* | Root | 11 | | Stem bark | 27 |
| *A. chama* | Root | 12 | *A. lanceifolius* | Heartwood | 28,29 |
| *A. communis** | Bark | 10,13,14 | *A. lowii* | Bark | 30 |
| | Root | 15 | *A. nobilis* | Root bark | 31 |
| | Stem bark | 16-18 | | Stem bark | 32 |
| *A. elasticus* | Bark | 19 | *A. rigida* | Root bark | 33 |
| | Root bark | 20 | *A. rigidus* | Bark | 34 |
| | Stem bark | 21,22 | | Stem bark | 35 |
| *A. gomezianus* | Bark | 23,24 | *A. rotunda** | Root bark | 36-38 |
| | Stem bark | 25 | *A. scortechnii* | Bark | 30,39 |
| *A. kemando* | Root bark | 26 | *A. teysmannii* | Bark | 30,40 |

**Artocarpus communis* and **A. rotunda* are synonyms of *A. altilis* and *A. rigidus*, respectively.

The anti-cancer effects and mechanisms of artonin E have been reported in breast, lung, ovarian, colon and gastric cancer cells (Table 2). Effects include apoptosis, anoikis, anti-proliferation, cell cycle arrest, inhibition of migration and invasion, and overcoming tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) resistance. Broadly, mechanisms include activation of caspases, up-regulation of apoptotic proteins and down-regulation of anti-apoptotic proteins.

Anoikis is a programmed cell death (apoptosis) induced by cell detachment from the extra-cellular matrix.[54] The process is caused by the activation of caspases, DNA fragmentation, and finally by cell death. Anoikis resistance *via* increase of anti-apoptotic proteins or decrease in pro-apoptotic proteins has been detected in some lung cancer cells.[23]

*Other Bioactivities of Artonin E*

Other bioactivities of artonin E include 5-lipoxygenase (5-LOX) inhibitory, anti-nephritis, DNA strand-scission, anti-plasmodial, anti-platelet aggregation, antioxidant, antibacterial, anti-human leukocyte antigen (HLA)-F adjacent transcript 10 (FAT10), inhibitory of prostaglandin 5-lipoxygenese ($PGE_2$) and anti-tyrosinase activities (Table 3).

**Table 2:** Anti-cancer activities of artonin E (AE) from *Artocarpus* species.

| Cancer cell (type) | Effect and mechanism | Reference |
|---|---|---|
| MCF-7 (breast) | AE significantly inhibited 4T1-induced mammary gland tumor in mice, inhibition included secondary tumors formed by metastasis. | 20 |
| MCF-7 (breast) | Molecular modeling showed that AE could interact directly with hERα expressed by breast cancer cells, forming more stable complexes than other analogs of AE. | 42 |
| MCF-7 (breast) | AE induced apoptosis of cancer cells by significant up-regulation of cytochrome c, Bax, caspase-7, caspase-9 and p21, and down-regulation of MAPK and cyclin D. | 43 |
| MDA-MB 231 (breast) | AE induced G1 cell cycle arrest and apoptosis in cancer cells by repressing livin protein, up-regulating p21 and activating ROS production. | 45 |
| H460, A549 & H292 (lung) | AE induced detachment apoptosis of cancer cells (anoikis) by down-regulating the expression of anti-apoptotic MCL1 protein. | 23 |
| H460 & A549 (lung) | AE inhibited the migration and invasion of cancer cells by suppressing the expression of FAK, AKT and CDC42. | 24 |
| SKOV-3 (ovarian) | AE induced anti-proliferation of cancer cells by triggering cell cycle arrest at S phase and induced apoptosis in cancer cells through dysregulation of mitochondrial pathways. | 21 |
| SKOV-3 (ovarian) | AE induced apoptosis of cancer cells *via* elevated levels of caspase-3, caspase-9, and bax, and decreased levels of bcl-2, Hsp70 and survivin. | 22 |
| LoVo (colon) | AE induced TRAIL-induced apoptosis of cancer cells by up-regulating DR5 and down-regulating cFLIP. | 55 |
| HCT116 (colon) | AE induced apoptosis of cancer cells through the up-regulation of caspase-7, PARP and p-ERK1/2 expression. | 56 |
| LoVo & HCT116 (colon) | AE induced apoptosis of cancer cells *via* caspase activation and up-regulation of the MAPK pathway. | 57 |
| AGS (gastric) | AE induced apoptosis of cancer cells by up-regulating ROS and DR5 expression, and by overcoming TRAIL-resistance. | 15 |
| A431 (skin) | AE induced anti-proliferation and apoptosis of cancer cells by activating caspase 7 and PARP. | 58 |

Abbreviations: AKT = protein kinase B, CDC42 = cell division cycle 42, cFLIP = cellular FLICE-inhibitory protein, DR5 = death receptor 5, FAK = focal adhesion kinase, hERα = human estrogen receptor α, MAPK = mitogen-activated protein kinase, MCL1 = myeloid leukemia cell sequence-1, PARP = poly (ADP-ribose) polymerase, ROS = reactive oxygen species and TRAIL = (TNF)-related apoptosis-inducing ligand.

**Table 3:** Other medicinal properties of artonin E (AE) from *Artocarpus* species

| Bioactivity | Description | Reference |
|---|---|---|
| 5-LOX inhibitory | AE inhibited 5-LOX purified from porcine leukocytes more strongly than cirsiliol (a 5-LOX inhibitor) with $IC_{50}$ values of 0.36 and 1.3 μM, respectively. | 13 |
| | AE showed marked inhibitory activity against 5-LOX in LPS-stimulated microglia cells with $IC_{50}$ value of 56 μg/mL. | 32 |

| | | |
|---|---|---|
| Anti-nephritis | AE reduced the amount of urinary protein excretion by 35% compared to nephritic mice, after 10 days of oral administration (30 mg/kg/day). | 59 |
| DNA strand-scission | AE exhibited significant DNA strand-scission activity with 93% relaxation at 2.5 µg/mL. | 27 |
| Anti-plasmodial | AE inhibited the growth of K1 strain of *Plasmodium falciparum* with $IC_{50}$ value of 2.8 µg/mL. | 11 |
| | AE strongly inhibited K1 strain ($IC_{50}$ = 0.1 mg/mL) and 3D7 strain ($IC_{50}$ = 0.3 mg/mL) of *P. falciparum*. | 60 |
| Anti-platelet aggregation | AE at 100 µg/mL inhibited AA-induced and ADP-induced platelet aggregation in human blood with $IC_{50}$ values of 19% and 55%, respectively. | 30 |
| Antioxidant | The free radical scavenging and NO inhibitory activity of AE in $IC_{50}$ values were 13.5 and 16.3 µM, respectively. | 25 |
| Antibacterial | AE inhibited the growth of *Pseudomonas aeruginosa*, *Salmonella typhi* and *Escherichia coli* with both MMC and MIC of 32, 64 and 64 µg/mL, respectively. | 16 |
| | AE inhibited the growth of *Staphylococcus aureus* ATCC 25923 and ATCC BAA-1720 with comparable inhibition diameters of 13.7 and 13.3 mm, respectively. | 17 |
| Anti-FAT10 | Docking analysis revealed that AE was found to have close affinity for FAT10 protein and may suggest its inhibitory effect towards hepatic carcinoma. | 61 |
| Inhibitory of $PGE_2$ | AE inhibited the production of $PGE_2$ in LPS-induced human plasma with $IC_{50}$ value of 3.9 µg/mL. | 62 |
| Anti-tyrosinase | AE showed marked inhibitory activity against tyrosinase in LPS-stimulated microglia cells with $IC_{50}$ value of 61 µg/mL. | 32 |

Abbreviations: AA = arachidonic acid, ADP = adenosine diphosphate, DNA = deoxyribonucleic acid, FAT10 = human leukocyte antigen (HLA)-F adjacent transcript 10, MIC = minimal inhibitory concentration, 5-LOX = 5-lipoxygenase, LPS = lipopolysaccharide, MMC = minimal microbicidal concentration, NO = nitric oxide and $PGE_2$ = prostaglandin.

*Bioactivities of Other Artonins*

Bioactivities of other artonins (A, B, F, M & O) from *Artocarpus* include anti-cancer, anti-plasmodial, antibacterial, anti-trypanocidal, antioxidant and cathepsin (CatK) inhibitory activities (Table 4).

A review of prenylated flavonoids and related compounds of *Artocarpus* species in Indonesia reported that the sources of artonins A & B (*A. champeden*), artonin J (*A. teysmanii*), and artonins M & O (*A. rigidus*).[5] In contrast, artonin E is found in *A. altilis*, *A. rigidus* and *A. scortechinii*. Artonins from the bark and root bark of *Artocarpus* species have been isolated and identified by a group of scientists from the Faculty of Pharmaceutical Sciences in Toho University, Chiba, Japan. Artonins A & B,[73] artonins C & D,[74] artonins J–L,[75] artonins Q–U,[76] and artonins X & Y[77,78] were isolated from *A. heterophyllus*. Artonins E & F[70] were isolated from *A. altilis*, and artonins G & H,[80] artonins M–P[81] and artonin V[82] were isolated from *A. rigida*. Unfortunately, these studies on artonins were on phytochemistry and not on pharmacology.

## Conclusion

Artonin E was first isolated from the bark *A. altilis* (syn. *A. communis*). The prenylated flavonoid was reported in 12 *Artocarpus* species. Mostly from the root and bark, all plant parts have been reported except the leaf. The other artonins were reported in *A. heterophyllus* and *A. rigida*. In view of the strong cytotoxic activities, artonin E has been used by scientists from universities in Indonesia as a positive control when testing the cytotoxicity of phytocompounds. Currently, artonin E is not commercially available and studies on this compound would require its isolation from *Artocarpus* species such as *A. altilis*, *A. elasticus* and *A. rigidus*. Logically, efforts into developing extraction and purification protocols of artonin E would be recommended. Research on the medicinal properties of artonin E lacked *in vivo* studies using animal models, structure-activity relationships, clinical trials and safety evaluation. Its chemo-preventive efficacy when used alone or in combination with other chemotherapy agents, its ability to reverse multi-drug resistance in cancer cells, and its structural modifications to synthesis novel derivatives or analogues with enhanced anti-cancer properties are worth exploring. Finally, information on the pharmacokinetics, bioavailability, biotransformation, synergism, dose-response and side-effects of artonin E are warranted. Suggestions for further research also apply for other artonins.

## Conflict of Interest

The author declares no conflict of interest.

**Table 4:** Medicinal properties of other artonins from *Artocarpus* species

| Bioactivity | Effect and mechanism | Reference |
|---|---|---|
| Anti-cancer | From *A. kemando*, artonin O displayed stronger cytotoxicity than artonin E against P388 murine leukemia cells with $IC_{50}$ values of 0.5 and 3.0 µg/mL, respectively. | 27 |
| | Artonins M & O from *A. rigidus* showed significant cytotoxicity against P388 murine leukemia cells with $IC_{50}$ values of 7.9 and 0.9 µg/mL, respectively. | 37 |
| | Artonin B from *A. heterophyllus* inhibited CCRF-CEM acute leukemia cells mediated through down-regulation of Bcl-2 expression, up-regulation of Bax and Bak expression, and activation of caspase-3. | 63 |
| | Artonin F from *A. rigidus* inhibited NCI-H187 lung cancer cells with $IC_{50}$ value of 1.3 µg/mL. | 64 |
| | Artonin B from *A. champeden* showed weak cytotoxicity against P388 murine leukemia cells with $IC_{50}$ value of 46 µM. | 65 |
| | Against KB oral epidermal carcinoma cells, artonin B from *A. styracifolius* displayed activity with $IC_{50}$ value of 11.3 µM. | 66 |
| | Artonin F from *A. gomezianus* was significantly cytotoxic towards A549 and H292 lung cancer cells at 20-50 µM, and towards H460 lung cancer cells at 40-50 µM. Apoptosis was induced *via* the down-regulation of c-Met by enhancing ubiquitin proteasomal degradation and by decreasing Akt-mTOR signaling. | 67 |
| Anti-plasmodial | Artonin F from *A. rigidus* inhibited *Plasmodium falciparum* with $IC_{50}$ value of 2.4 µg/mL. | 64 |
| | Artonins A, B & F displayed inhibitory activity with $IC_{50}$ values of 4.9, 1.6 & 2.2 µM against FcB1 *P. falciparum*. | 66 |
| | Artonin A from *A. champeden* inhibited *P. falciparum* with $IC_{50}$ value of 0.5 µmol/L. | 68 |
| | Artonin M from *A. kemando* exhibited strong inhibition towards *P. falciparum* with $IC_{50}$ value of 0.3 µg/mL. | 69 |
| Antibacterial | Artonin F from *A. rigidus* inhibited *Mycobacterium tuberculosis* with $IC_{50}$ value of 6.2 µg/mL. | 64 |
| | Artonin O from *A. rigida* inhibited *Bacillus subtilis* with 8.5 mm diameter of inhibitory zone at 0.5 mg/disc. | 70 |
| Anti-trypanocidal | Against KB oral epidermal carcinoma cells, only artonin B displayed activity with $IC_{50}$ value of 11.3 µM. Only artonin B displayed anti-trypanocidal activity *Trypanosome brucei* with $IC_{50}$ value of 8.8 µM. | 66 |
| Antioxidant | Artonins A & B from *A. heterophyllus* displayed antioxidant activity *via* DPPH free radical scavenging, lipid peroxidation and inhibition of LDL. | 71 |
| CatK inhibitory | Artonin A from *A. heterophyllus* strongly inhibited CatK with $IC_{50}$ value of 1.9 µM while artonin B was 4.7 times weaker. | 72 |

Abbreviations: Bax = bcl-2 associated X protein, CatK = cathepsin, DPPH = 2,2-diphenyl-1-picrylhydrazyl, LDL = low-density lipoprotein and mTOR = mammalian target of rapamycin

## Author's Declaration

The sole author hereby declares that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by him.

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