NUSANTARA BIOSCIENCE
Vol. 2, No. 3, Pp. 146-156
November 2010

ISSN: 2087-3948 (print)
ISSN: 2087-3956 (electronic)
DOI: 10.13057/nusbiosci/n020307

Diversity of secondary metabolites from Genus *Artocarpus* (Moraceae)

ALIEFMAN HAKIM♥
Study Program of Chemistry Education, Faculty of Teacher Training and Education, Universitas Mataram. Jl. Majapahit 62 Mataram, West Nusa Tenggara, Indonesia. Tel./Fax.: +62-370-623873, Fax: +62-370-634918. Email: ♥aliefmanhakim27@gmail.com

Manuscript received: 28 Augustus 2010. Revision accepted: 4 October 2010.

Abstract. *Hakim A. 2010. The diversity of secondary metabolites from Genus* Artocarpus *(Moraceae). Nusantara Bioscience 2:146-156.* Several species of the *Artocarpus* genus (Moraceae) have been investigated their natural product. The secondary metabolites successfully being isolated from *Artocarpus* genus consist of terpenoid, flavonoids, stilbenoid, arylbenzofuran, neolignan, and adduct Diels-Alder. Flavonoid group represents the compound which is the most found from *Artocarpus* plant. The flavonoids compound which is successfully isolated from *Artocarpus* plant consists of the varied frameworks like chalcone, flavanone, flavan-3-ol, simple flavone, prenylflavone, oxepinoflavone, pyranoflavone, dihydrobenzoxanthone, furanodihydrobenzoxanthone, pyranodihydrobenzoxanthone, quinonoxanthone, cyclopentenoxanthone, xanthonolide, dihydroxanthone.

Keywords: *Artocarpus*, Moraceae, flavonoid, Diels-Alder, secondary metabolites.

Abstrak. *Hakim A. 2010. Keanekaragaman metabolit sekunder Genus* Artocarpus *(Moraceae). Nusantara Bioscience 2:146-156.* Beberapa spesies dari genus *Artocarpus* (Moraceae) telah diteliti kandungan bahan alamnya. Metabolit sekunder yang berhasil diisolasi dari genus *Artocarpus* terdiri dari terpenoid, flavonoid, stilbenoid, arilbenzofuran, neolignan, dan adduct Diels-Alder. Kelompok flavonoid merupakan senyawa yang paling banyak ditemukan dari tumbuhan *Artocarpus*. Senyawa flavonoid yang telah berhasil diisolasi dari tumbuhan *Artocarpus* memiliki kerangka yang beragam seperti calkon, flavanon, flavan-3-ol, flavon sederhana, prenilflavon, oksepinoflavon, piranoflavon, dihidrobenzosanton, furanodihidrobenzosanton, piranodihidrobenzosanton, kuinonosanton, siklolopentenosanton, santonolid, dihidrosanton.

Kata kunci: *Artocarpus*, Moraceae, flavonoid, Diels-Alder, metabolit sekunder.

INTRODUCTION

One family of plants in tropical forests that has the potential as a source of bioactive chemicals and the number is relatively large is the Moraceae. Moraceae Family consists of 60 genera and includes 1400 species. The main genus of the Moraceae family is *Artocarpus* which is composed of 50 species and spread from South Asia, Southeast Asia to the Solomon Islands, Pacific Islands, North Australia and Central America (Kochummen 1987; Verheij and Coronel 1992). On the island of Kalimantan, there are 25 species, of which 13 species of them are endemic, but only two species are utilized, namely: *Artocarpus heterophyllus* and *A. integer* (Verheij and Coronel 1992).

In Indonesia, *Artocarpus* is known as the jackfruit that has characterized by a tall tree with white latex in all parts of plants, hardwood, fleshy fruit with lots of seeds. All parts of *Artocarpus* has been used extensively by the community for various purposes such as wooden sticks used for building materials and its fruit as a food ingredient. In addition, *Artocarpus* can also be used as traditional medicine, such as leaves of *A. communis* Frost which is burned and mixed with coconut oil plus turmeric can be used to cure skin diseases. The flowers are used to cure toothache, while its root is used to stop bleeding (Kochummen 1987; Heyne 1987).

Based on literature studies, it is known that some species of *Artocarpus* produce many compounds of terpenoid, flavonoids, and stilbenoid classes. The uniqueness of the structure of secondary metabolites in *Artocarpus* produce a broad physiological effects, such as anti-bacterial (Khan et al. 2003), anti-platelets (Weng et al. 2006), anti-fungal (Jayasinghe et al. 2004), anti-malarial (Widyawaruyanti et al . 2007; Boonlaksiri et al. 2000) and cytotoxic (Ko et al. 2005, Judge et al. 2002, Syah et al. 2006), so the research on bioactivity of secondary metabolites anti-malarial from *Artocarpus* can provide benefits in the search for new drugs of the natural material compound, as well as provide a scientific explanation of the use of these plants in traditional medicine.

This information produces the consequences of the need for sustainability investigation of the chemical content of the *Artocarpus* genus. This article provides a review of researches that have been done on *Artocarpus* located in Indonesia.

Extraction, isolation, and purification

The method for extracts making consists of four phases, namely the manufacture of powder, the process of extraction, solvent separation and extract concentration

phase. The dried *Artocarpus* is mashed then is extracted by maceration at room temperature for 24 hours with methanol, then filtered. The extraction process is repeated until the less colorful supernatant is obtained. Solvent separation is performed using a rotary evaporator and then is concentrated in a water bath so a thick extraction is produced.

Then, the obtained extraction underwent TLC (Thin Layer Chromatography) treatment using various eluents. This stage was carried out to determine the chemical components in the extract. Furthermore, the TLC chromatogram was used as a basis for conducting separation/fractionation by vacuum liquid chromatography (VLC).

The main fractions obtained from the VLC then were analyzed again by TLC. Fractions that had same spots (*Rf*) were pooled and analyzed again by TLC. Purification process on main factions was done repeatedly by radial chromatography while were monitored by TLC so pure isolates are obtained. TLC chromatogram is used to test the purity of an isolate, in which the pure isolates must show a single stain on three different eluent systems, besides the purity test can also be done by measuring its melting point.

Structural determination

The structures of pure isolates obtained are determined by spectroscopic methods: (i) Analysis by UV-Vis to determine the presence or absence of double bond conjugation in the structure of these compounds. (ii) Analysis by infrared to know what types of functional groups possessed by these compounds, such as whether the existing O atoms in these molecules exist as clusters of alcohol, ether ketones, aldehydes and so on. (iii) The sample was analyzed by 1H and ^{13}C NMR (Nuclear Magnetic Resonances). (iv) analysis of this structure should be comprehensive of all existing data, to avoid any error in the determination of the structure of a compound.

SECONDARY METABOLITES OF *ARTOCARPUS*

The content of secondary metabolites from Moraceae family has long been studied and in recent years there are many research groups which examine secondary metabolite of *Artocarpus* species (Nomura et al. 1998; Sultanbawa et al. 1989; Hakim et al. (1999, 2006). The researches have found many secondary metabolites belonging to the group of terpenoid, flavonoids, stilbenoid, aril benzofuran, neolignan, and Diels-Alder adducts compounds.

Terpenoid

Terpenoid compounds with a cycloartan frame are succeeded to be isolated from *Artocarpus* plants among others, cycloartenol (1) that have been successfully obtained from *A. champeden* (Achmad et al. 1996) and *A. altilis* (Altman and Zito 1976). Other terpenoid compounds that have been isolated from this same plant are cycloeucalenol (2), 2,4-methylen cycloartenone (3), and cycloartenone (4) (Achmad et al. 1996) which also has been isolated from *A. heterophyllus* (Dayal and Seshadri 1974). Compounds of (24R) and (24S)-9.19-cyclolanost-3-on-24 0.25-diol (5) have been isolated from *A. heterophyllus* (Barik et al. 1997). Glutinol compound (6) is so far the only pentacyclic triterpenoid compound with a glutan frame which is isolated from *Artocarpus* i.e. *A. champeden* (Achmad et al. 1996).

Flavonoids

The content of flavonoid compounds with a variety of frameworks such as chalkon derivatives, flavanones, flavan-3ol, simple flavone, prenylflavone, oxepinoflavone, pyranoflavone, dihydrobenzoxanthone, furanodihydro-benzoxanthone, pyranodihydrobenzoxanthone, quinonoxanthone, cyclopentenoxanthone, xanthonolide, dihydroxanthone, and cyclopentenoxanthone have been isolated from *Artocapus* plants.

Chalcone

Chalcone compounds are found as chalcone and dihydrochalcone. Prenylation of chalcone by isoprenoid groups and geranyl can be found in ring A or B but can not be found on Cα which is comparable to C3 on flavone. Some Diels-Alder adduct compounds also come from chalcone. It is noted that most chalcone compounds found are derived from the leaf. Canzonol compound C (7) and artoindonesianin J (8) was isolated by Ersam (2001) from the stem bark of *A. bracteata*.

Another class of chalkon compounds is dihydrochalcone. These compounds have some cytotoxic activities. Some dihydrochalcone compounds are successfully isolated by Wang et al. (2007) from *Artocarpus altilis*, namely 1-(2,4-dihydroxyfenyl)-3-(8-hydroxy-2-methyl-2-(4-methyl-3-pentenyl)-2H-1-yl-5-benzopyran)-1-propanone (9), 1-(2,4-dihydroxyfenyl)-3-{4-hydroxy-6 ,6,9-trimethyl-6a, 7,8,10 a-tetrahydro-6H-dibenzo (b, d) pyran-5-il}-1-propanone (10), 2-geranyl-2 ', 3,4,4'-tetrahydroxydihydrochalcone (11).

Flavanones

Flavanones compounds are found in all parts of *Artocarpus*. Several compounds have been isolated, among others, by Djakaria (1999) that is artocarpanone (12) from the root timber of *A. champeden*. Judge et al. (2002) isolates artoindonesianin E (13) and heteroflavanone A. (14) from the stem bark of *A. champeden*, compound 14 also been isolated from the root bark of *A. champeden* by Nomura et al. (1998), while Jayasinghe et al. (2006) from the fruit of *A. nobilis* isolates 8-geranyl-4 '0.7-dihydroxyflavanon (15), 3'-geranyl-4',5,7-trihydroxy-flavanon (16) and isonimfaeol-B (17). Compounds 15 and 17 are reported to have strong antioxidant activity. Compounds flavanones have oxygenation pattern in ring B is unique is there monohydroxide at position 4 '; dioxygenation 2', 4 ', 3', 4 'or trioxygenation 2', 4 ', 6'.

Flavan-3-ol

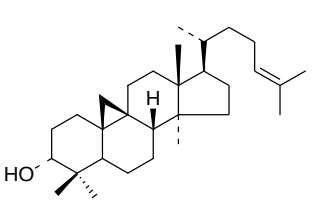
Compounds with a flavan-3-ol framework found are not prenylated. The three compounds of flavan-3-ol are afzelecin (18) and catechin (19) from the root bark of *A. reticulatus* (Udjiana 1997), where compound 19 had

previously been isolated from *A. integra* by Yamazaki et al. (1987), and afzelecin ramnoside (20) which is isolated from the bark of *A. reticulatus* by Murniana (1995). By considering the structure of these compounds (18, 19, 20), significant differences in oxygenation patterns are found if they are compared with the structure of simple flavonoids. In the flavan-3-ol oxidation in ring B is monohydroxy or 3', 4"dihydroxy.

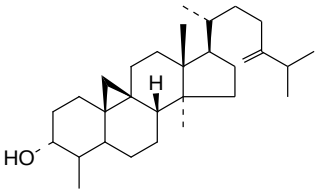
Simple flavone

There are only a few simple flavonoids which are not prenylated, two of them are artocarpetin (21) and norartocarpetin (22) which were isolated from the root wood of *A.heterophyllus* by Lin et al. (1995). Compound 21 is also successfully obtained from *A. hirsutus* (Venkataraman 1972) and *A. integrifolia* (Dave et al. 1962), while compound 22 is successfully isolated from the bark of *A. scortechinii* by Ferlinahayati (1999). This compound is believed to be a precursor for the biosynthesis of prenylated flavonoids.

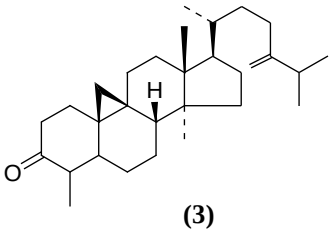
These simple flavonoids have characteristic of ring B oxygenation patterns in position of dihydroxy 2 ', 4'. This fact is interesting because some prenylated flavones that are found have patterns of monooxygenation at C4' and trioxygenation at C2', C4 'and C6'.



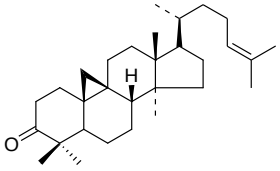
(1)



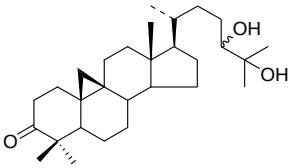
(2)



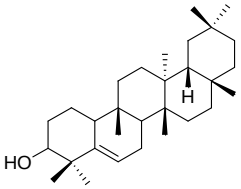
(3)



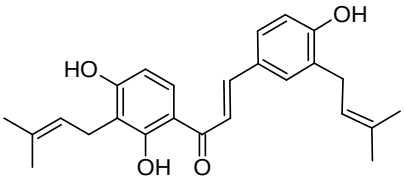
(4)



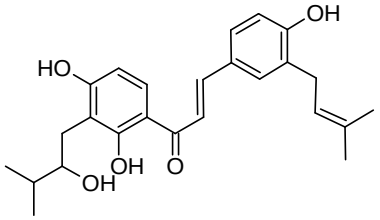
(5)



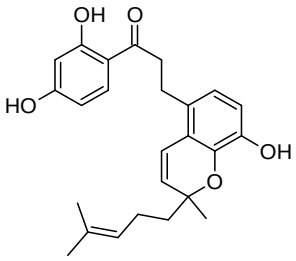
(6)



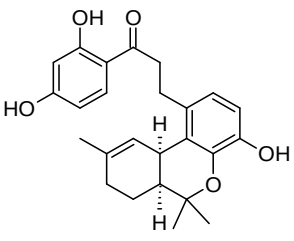
(7)



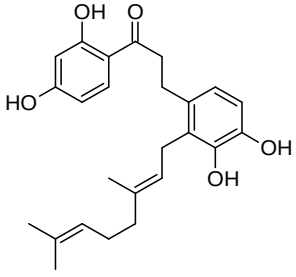
(8)



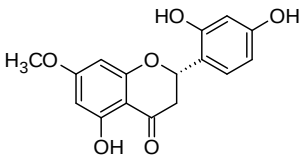
(9)



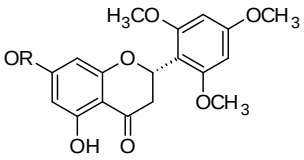
(10)



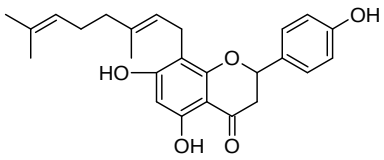
(11)



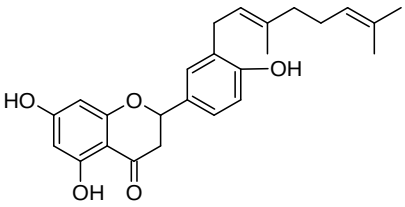
(12)



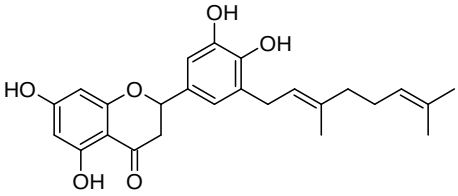
(13) R=H
(**14**) R=CH_3



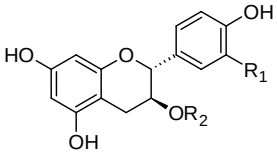
(15)



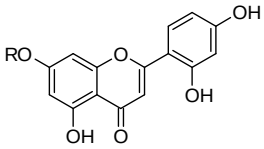
(16)



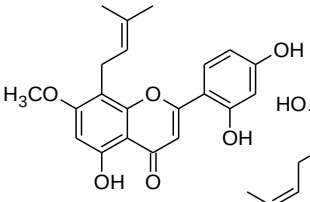
(17)



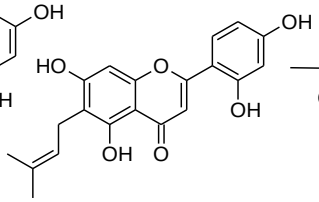
(**18**) R_1=H; R_2= H
(**19**) R_1=H; R_2=ramnosid
(**20**) R_1=OH; R_2=H



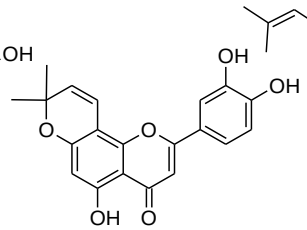
(21) R=CH_3
(22) R=H



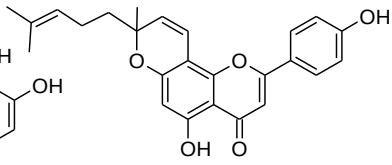
(23)



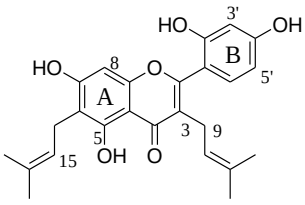
(24)



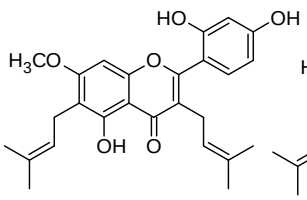
(25)



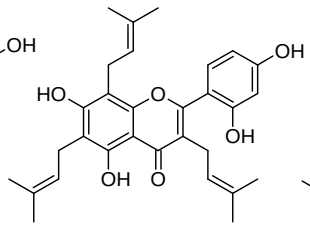
(26)



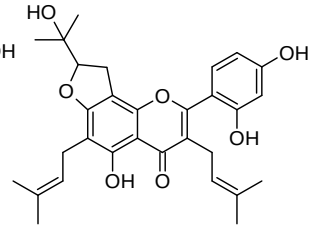
(27)



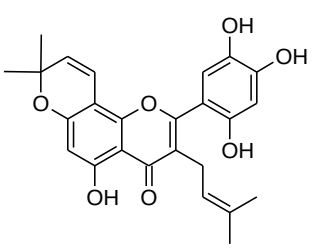
(28)



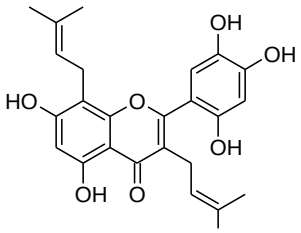
(29)



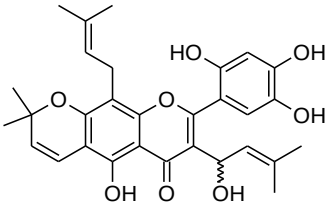
(30)



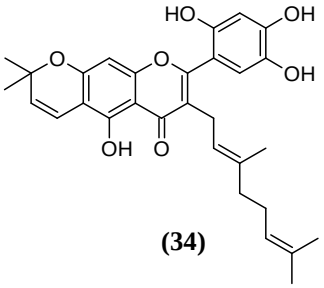
(31)



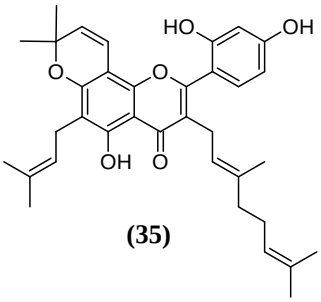
(32)



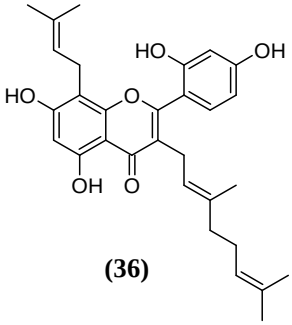
(33)



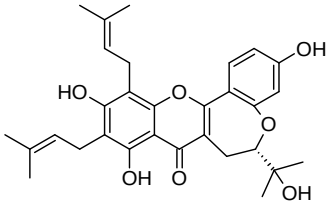
(34)



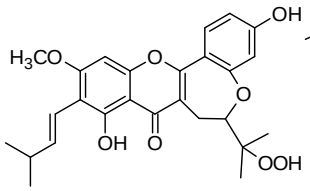
(35)



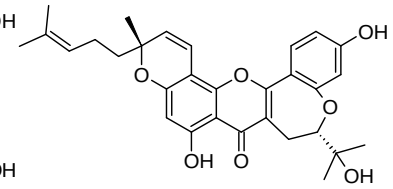
(36)



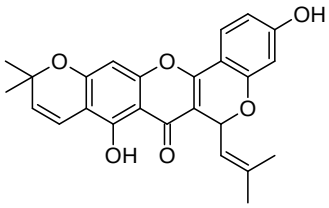
(37)



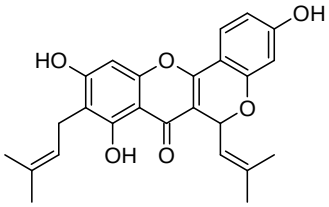
(38)



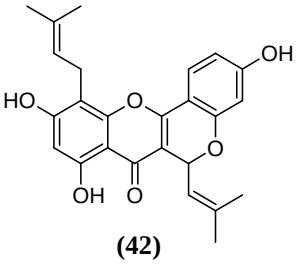
(39)



(40)



(41)



(42)

Prenyl flavon

Flavonoids are prenylated either by force or by geranyl isoprenoid which has been isolated from *Artocarpus* quite a lot. The prenylation is especially in ring A (C6 and C8) and C3 positions. Prenylated flavonoids are intermediate compounds for further biosynthesis. Prenyl flavone compounds are found in the bark or stem of both wood and root. Flavonoids compounds have been prenylated only at C6 or C8 that have been isolated, among others cycloartocarpin A (23) by Lin et al. (1995) from the root timber of *A. heterophyllus*. Kijjoa et al. (1996) isolate artocarpesin (24) of stem wood of *A. elasticus*. Wang et al. (2004) isolate artocamin C (25) from the root of *A. chama*, these compounds are reported to be active as anticancer. cycloaltilisin (26) that are isolated from the bud covers of *A. altilis* by Patil et al. (2002) is reported as an inhibitor of cathepsin.

Prenylated flavonoids on the C6 or C8 is found to have monooxygenation patterns at C4 'or dioxygenation at C3', C4 'or C2', C4 '. Cromen ring formation is a common matter in this class of compounds.

Another prenylflavon compound is class of 3-prenyl flavone. This prenylation process on C3 gives a lot of modifications to the structure of the flavonoids found in the genus of *Artocarpus*. The diversity of compound structure modification results also depends on the oxygenation pattern of ring B. Oxygenation pattern of flavonoids with 2', 4' and 5' produces more structural modifications. Compounds of 3-prenyl flavone with mono or dihydroxy in ring B which have been isolated, among others, are

cudraflavone C (27) which is isolated from *A. scortechinii* by Judge et al. (2002). Compound 27 had previously been isolated from *A. communis* by Han et al. (2006). Artocarpin (28) is isolated from the root timber of *A. heterophyllus* by Lin et al. (1995). Kijjoa et al. (1996) from the stem wood of *A. elasticus* managed to isolate artelastisin (29) and artelastofuran (30). Compound 30 is also been isolated from *A. scortechinii* by Hakim et al (2006).

The other 3-prenyl flavonoids compounds is the pattern of oxygenation at C2 ', C4' and C5 '. This group of compounds has the highest level of oxidation. Many compounds have been reported to exist mainly in the subgenus *Artocarpus*. Some of them have been isolated, among others are artonin E (31) from the stem bark of *A. scortechinii* by Ferlinahayati (1999), artonin E (31) is also isolated from the root bark of *A. nobilis* (Jayasinghe et al. 2008), *A. lanceifolius* (Cao et al. 2003), *A. kemando* (Seo et al.), and *A. communis* (Aida et al. 1997). Artonin V (32) is isolated from the root bark of *A. altilis* by Hano et al. (1994). Ko (2008) isolates artelastoheterol (33) from the root bark of *A. elasticus*.

Geranyl group attached to C3 is also found in the flavonoids isolated from the *Artocarpus* genus. Like the other 3-prenyl flavonoids, the oxygenation pattern in ring B of these compounds is also dioxygenation or trioxygenation. Several compounds found, among others, is artoindonesianin L (34) of *A.rotunda* root bark (Suhartati et al. 2001). The compound is reported to have cytotoxic activity. Chan et al. (2003) from the root bark of *A. communis* isolates artocommunol CB (35) and artocommunol CD (36).

Oxepinoflavone

Compounds with oxepinoflavone framework are derived from 3-prenylflavone, where clusters of prenyl experiencing oxidative cyclization with hydroxy group at C2' form a heptagon ring. Compounds that have been found are not much. Oxepinoflavone compounds mostly have a pattern of 2', 4' dioxygenation on ring B. Compounds with oxepinoflavone structures among others are artelastinin (37) which is isolated from the stem wood of *A. elasticus* (Kijjoa et al. 1998), Artoindonesianin B (38) which is isolated from the root bark of *A. champeden* by Hakim et al. (1999) has cytotoxic properties. Chan et al. (2003) from the root bark of *A. communis* isolate artocommunol CC (39).

Pyranoflavone

The pyranoflavone framework differs from oxepinoflavone in terms of ring formed by cyclization prenyl group at C3 to hydroxyl at C2 '. Pyranoflavone forms a hexagon ring. Some piranoflavone compounds with dioxygenation in ring B which have been isolated by Chen et al. (1993) from the stem wood of *A. altilis*, among others are isocyclomorusin (40), isocyclomullberin (41), cyclomulberin (42).

Dihydrobenzoxanthone

In dihydrobenzoxanthone, C6' in ring B bound directly to the carbon from the group of prenyl hexagon forms a ring. It is quite interesting that dihydrobenzoxanthone is only formed from the flavone with ring B which is oxygenated with pattern of 2', 4' and 5'. This is because the two hydroxy groups at C2' and C5' activate C6' which is located at the ortho position of hydroxy group. Class of dihydroxanthone compounds which have been isolated are artobiloxanthone (43) which are isolated from the stem bark of *A. scortechinii* by Ferlinahayati (1999). Compound 43 is also isolated from *A. nobilis* (Sultanbawa et al. 1989, Jayasinghe et al. 2008). Syah et al. (2002) is succeeded in isolating artoindonesianin S (44) and artoindonesianin T (45) of stem wood of *A. champeden*.

Furanodihydrobenzoxanthone

Furanodihydrobenzoxanthone compounds are derived from dihydrobenzoxanthone experiencing further cyclization at the end of prenyl with hydroxy group at C5', then they form a furan ring. Several compounds are reported, namely artonin M (46) which is isolated from *A. rotunda* by Suhartati et al. (2001) and has cytotoxic characters. Cycloartobiloxanthone (47) is isolated from *A. scortechini* (Ferlinahayati 1999), *A. nobilis* (Jayasinghe et al. 2008), *A. heterophyllus* (Uno 1991). Hakim et al. (1999) isolate artoindonesianin A (48) from the root bark of *A. champeden*, these compounds have cytotoxic properties against P-388murine leukemia cells.

Pyranodihydrobenzoxanthone

Pyranodihydrobenzoxanthone is probably derived from dihydrobenzoxanthone experiencing cyclization to form Annex ring. Only one compound is that reportedly ever recovered from *A. lanceifolius* namely artoindonesianin Z-2 (49) by Hakim et al. (2006).

Quinonoxanthone

Quinonoxanthone is derived from dihydrobenzo-xanthone experiencing rearrangement on two hydroxy groups at C2' and C5' to form quinone ring. This class of compounds that is artomunoxantentrion (50) is isolated from the root bark of *A. communis* by Shieh and Lin (1992). Artonin O (51) from the root bark of *A. rotunda* which is isolated by Suhartati et al. (2001) are cytotoxic, these compounds are very interesting because they have experience of prenylation in ring B.

Cyclopentenoxanthone

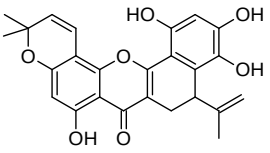
Compounds with a cyclopentenoxanthone framework is derived from xanthone experiencing rearrangement so that the ring B turned into a pentagon. The reported compounds are artoindonesianin C (52) which is isolated from the stem bark of *A. scortechinii* (Armin 1999) and root bark of *A. teysmanii* (Makmur 2000). This compound has been reported to have activities as anti-mycobacterial.

Xanthonolide

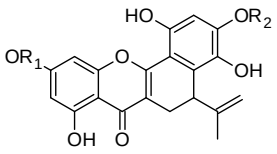
The isolated xanthonolide compounds namely artonol B (53) is derived from the stem bark of *A. scortechinii* (Armin 1999) and from the root bark of *A. rigidus* (Namdaung et al. 2006). The compound is reported to have cytotoxic properties.

Dihydroxanthone

Dihydroxanthone is derived from xanthonolide experiencing bond disconnection as to form compounds with a more stable structure. So far only one compound had been reported namely artonol A. (54) which were isolated from the stem bark of *A. scortechinii* by Armin (1999).

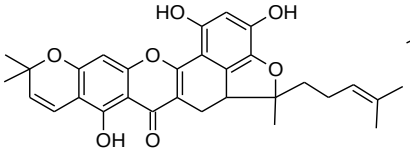


(43)

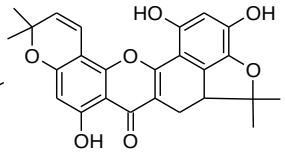


(**44**) $R_1=R_2=CH_3$

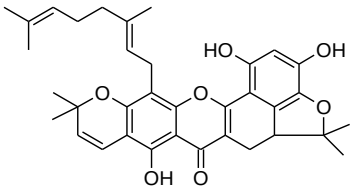
(**45**)$R_1=H$, $R_2=CH_3$



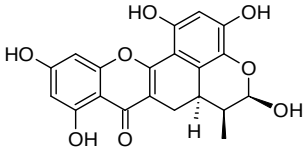
(46)



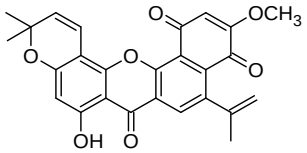
(47)



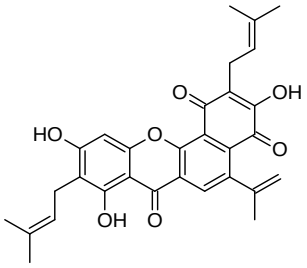
(48)



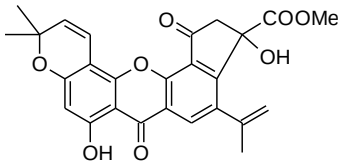
(49)



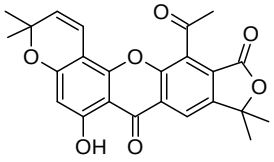
(50)



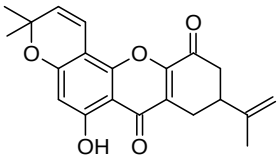
(51)



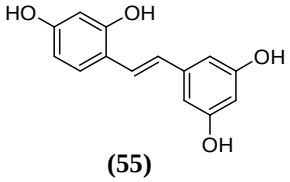
(52)



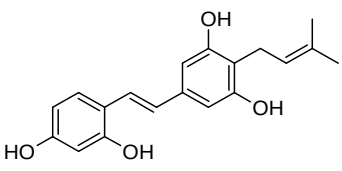
(53)



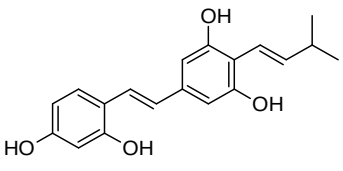
(54)



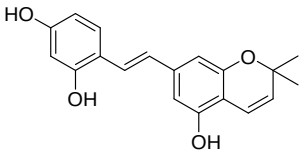
(55)



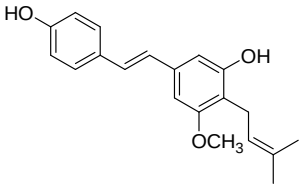
(56)



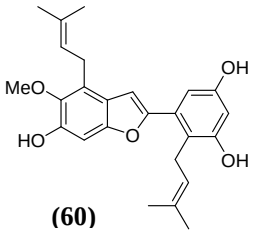
(57)



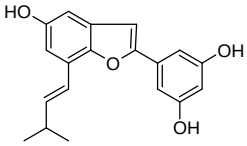
(58)



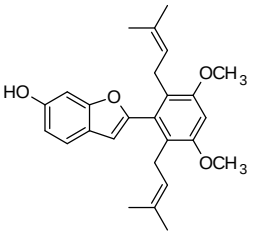
(59)



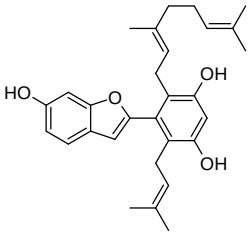
(60)



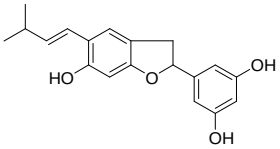
(61)



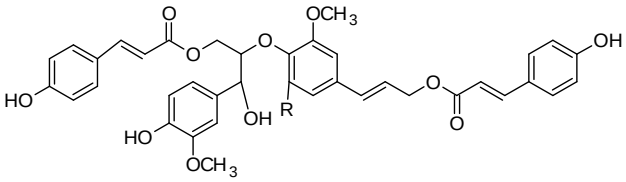
(62)



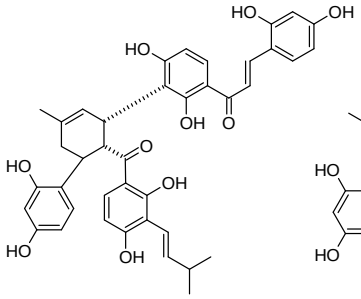
(63)



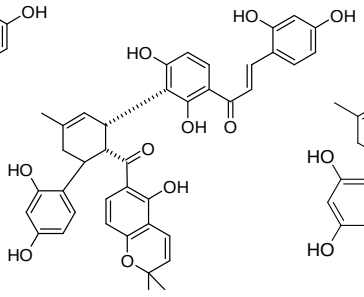
(64)



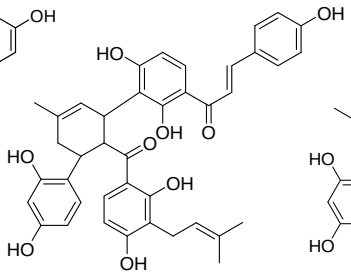
(65) R=OMe
(66) R=H



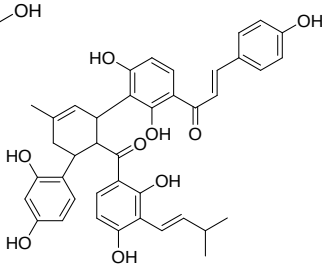
(67)



(68)



(69)



(70)

STILBENE

As in flavonoids, prenylated stilbene is also found. The prenylations are found on the two rings like the pattern on chalcon. Some stilbene compounds which have been isolated, among others, oxyresveratrol (55) from the stem bark of *A. nitida* (Yuliani 1997) and from the bark of *A. reticulatus* (Murniana 1995). Boonlaksiri et al. (2000) isolate stilbene compounds which are anti-malarial from aerial parts of *A. integer* which is 3,4-trans-4-isopentenyl-3, 5.2 ', 4'-tetrahydroxy stilbene (56), 3,5-trans-4-(3-methyl-E-but-1-enil)-3,5,2 ', 4'-tetrahydroxystilbene (57) and 4-methoxy-2 ,2-dimethyl-6-(2 (2,4-dihydroxy) phenyl-trans-etenil) cromen or also known as artocarben (58) (Boonlaksiri 2000) which also have been isolated from *A. incisus* (Shimizu et al. 1997). Artoindonesianin N (59), the first derivative stilben reported containing methoxy group, were isolated from the bark of *A. gomezianus* (Judge et al. 2002).

ARYLBENZOFURAN

As with stilben, the arylbenzofuran compounds found are also prenylated in both rings. These compounds include artohetetophyllin A (60) which were isolated from

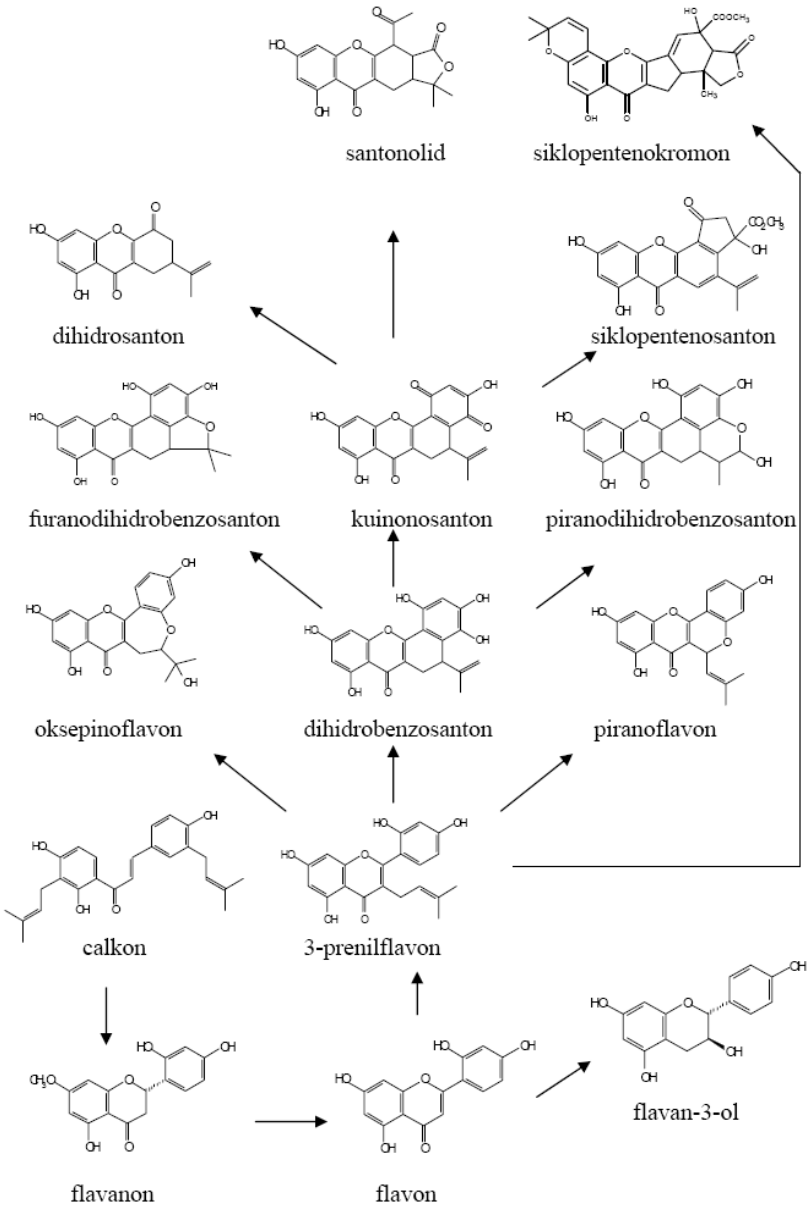
A.heterophyllus by Zong et al. (2009), 3-(γ, γ-dimethylpropenil) morasin M (61) of bark and twigs of *A. dadah* (Su et al. 2002). Puntumchai et al. (2004) successfully isolate two anti-microbacterial compounds from root of *A. lakoocha* named lakoochin A (62) lakoochin B (63). From the bark of *A. tonkinensis*, it is found artotonkin (64) (Lien et al. 1998)

NEOLIGNAN

Neolignan derivative compounds were also reported by Su et al. (2002) namely dadahol A (65) and dadahol B (66) which were isolated from the twigs of *A. medicine*. This group of compound has never been reported to be isolated from other species of *Artocarpus*. The discovery of neolignan compounds which is a combination of the two compounds of arylpropanoid is very interesting.

DIELS-ALDER ADDUCTS COMPOUNDS

From the root bark of *A. heterophyllus*, Hano et al. (1990) isolate the two compounds of Diels-Alder adducts namely artonin C (67) and D (68). Artonin X (69) and kuwanon R (70) are isolated from the bark of *A. heterophyllus* by Kazuki et al. (1995). Of the framework, it can be seen that this compound comes from two chalcone which experienced a reaction of Diels-Alder adducts. It is interesting that the two units of chalcon making up two compounds are derived from the same compound.



Gambar 1. Biogenesis of several progeny compound of flavonoid from *Artocarpus*

FLAVONOIDS BIOGENESIS AND ITS PROGENY IN *ARTOCARPUS*

Flavonoid compounds have been isolated from the *Artocarpus* genus comprise chalcone, flavanones, flavan-3-ol and flavone. The flavone compounds are especially the prenylated one. Prenylated flavone with oxygenation pattern of ring B on C2', C4' and C5' can produce a more complex flavone derivatives especially xanthone compounds. Experimental information about the biosynthesis of these compounds from xanthone group of *Artocarpus* does not exist, but its presence in the secondary metabolites of flavone derivatives are found together in the *Artocarpus* genus. This reinforces allegations regarding biogenesis path, which usually begins from the 3-prenylflavon and produce dihydrobenzoxanthone as an intermediates precursor.

Several hypotheses about the biogenesis of this *Artocarpus* flavonoids have been reported in the literature, ranging from flavanones derivatives such as artocarpanon that have a pattern of 2', 4'-dioxygenation in ring B followed by a series of related framework establishment of flavone derivatives such as norartocarpetin, followed by prenylation and hydroxylation reactions. 3-prenylflavon compound is the primary precursor for all types of flavonoid derivatives in *Artocarpus*. Through isoprenoid cyclization on the C3 with oxygen at C2', the pyranoflavone or oxepynoflavone is formed. Isoprenyl group at C-3 of compounds with 2', 4', 5' trioxygenation can bind to the C6' to form dihydrobenzoxanthone, subsequent cyclization of isopropyl with oxygen at C-5' forms the furanodihydrobenzoxanthone or pyranodihydrobenzoxanthone framework. Xanthone compounds as flavone derivatives resulting from several stages of degradation reaction or rearrangement of B ring framework of the original flavone, such as found out in dihydroxanthone, xanthonolide and cyclopentenoxanthone. The original path of cyclopentenocromene framework is still indefinable because it has not been found between the corresponding compounds. General description of flavonoid compounds biogenesis and their derivatives, which are found in the genus of *Artocarpus* are shown in Figure 1.

CONCLUSION

Secondary metabolites have been isolated from *Artocarpus* comprises of terpenoid, flavonoids, stilbenoid, arylbenzofuran, neolignan, and Diels-Alder adducts compounds. Flavonoid compounds are most abundant class of compounds from *Artocarpus*. Flavonoids which are successfully isolated from *Artocarpus* consists of a variety of frameworks such as derivatives of chalcone, flavanones, flavan-3-ol, simple flavone, prenylflavone, oxepinoflavone, pyranoflavone, dihydrobenzoxanthone, furanodihydro-benzoxanthone, pyranodihydrobenzoxanthone, quinonoxanthone, cyclopentenoxanthone, xanthonolide, and dihydroxanthone. Terpenoid compounds isolated from *Artocarpus* have cycloartan framework. The simplest stilbene compounds of the *Artocarpus* genus are the resveratrol compound isolated from *A. caplasha*.

REFERENCES

Achmad SA, Hakim EH, Juliawaty LD, Makmur L, Suyatno, Aimi N, Ghisalberti EL. 1996. A new prenylated flavone from *Artocarpus champeden*. J Nat Prod 59: 878-879.

Aida M, Yamaguchi N, Hano Y, Nomura T. 1997. Constituents of the Moraceae plants. 30. Artonols A, B, C, D, and E, five new isoprenylated phenols from the bark of *Artocarpus communis* forst. Heterocycles 45(1): 163-175.

Altman LJ, Zito SW. 1976. Sterols and triterpenes from the fruit of *Artocarpus altilis*. Phytochemistry 15: 829–830.

Armin AN. 1999. 5'Hidroksikudraflavon dan beberapa senyawa turunan santon dari tumbuhan *Artocarpus scortechinii* King. [Thesis]. Institut Teknologi Bandung, Bandung. [Indonesian]

Barik BR, Bhaumik T, Kundu AK, Kundu AB. 1997. Triterpenoids of *Artocarpus heterophyllus*. J Indian Chem Soc 74: 163-164.

Boonlaksiri C, Oonanant W, Kongsaeree P, Kittakoop P, Tanticharoen M, Thebtaranonth Y. 2000. An antimalarial stilbene from *Artocarpus integer*. Phytochem 54 415-417.

Cao S, Butler MS, Buss AD. 2003. Flavonoids from *Artocarpus lanceifolius*. Nat Prod Res 17(2): 79-81.

Chan SC, Ko HH, Lin CN. 2003. New prenylflavonoids from *Artocarpus communis*. J Nat Prod 66: 427-430.

Chen CC, Huang YL, Ou JC, Lin CF, Pan TM. 1993. Three new prenylflavones from *Artocarpus altilis*. J Nat Prod 56: 1594-1597.

Dave KG, Telang SA, Venkataraman K. 1962. Flavonoid pigments of the heartwood of *Artocarpus integrifolia*. Tetrahedron Lett 9-14.

Dayal R, Seshadri TR. 1976. Colourless compounds of the roots of *Artocarpus heterophyllus*. Isolation of new compound artoflavone. Indian J Chem 12: 895-898.

Djakaria YK. 1999. Artocarpanone, A flavanone derivative from root trunk of *Artocarpus champeden* Spreng. [Dissertation]. Bandung Institute of Technology, Bandung. [Indonesian]

Ersam T. 2001. Senyawa kimia mikromolekul beberapa tumbuhan *Artocarpus* hutan tropika Sumatera Barat [Dissertation]. Bandung Institute of Technology, Bandung. [Indonesian]

Ferlinahayati. 1999. Norartokarpetin dan flavonoid terisoprenilasi dari kulit batang *Artocarpus scortechinii* King. [Thesis]. Bandung Institute of Technology, Bandung. [Indonesian]

Hakim EH, Aripin A, Fahriyati A, Kau MS, Achmad SA, Makmur L, Ghisalberti EL, Nomura T. 1999. Artoindonesianins A and B, two new prenylated flavones from the root of *Artocarpus champeden*. J Nat Prod 62: 613-615.

Hakim EH, Achmad SA, Juliawaty LD, Makmur L, Syah YM, Aimi N, Kitajima M, Takayama H, Ghisalberti EL. 2006. Prenylated flavonoids and related compounds of the Indonesian *Artocarpus* (Moraceae). J NatMed 60: 161-184.

Han AR, Kang YJ, Windono T, Lee SK, Seo EK. 2006. Prenylated Flavonoids from the Heartwood of *Artocarpus communis* with Inhibitory Activity on Lipopolysaccharide-Induced Nitric Oxide Production. J Nat Prod 69 (4): 719-721.

Hano Y, Aida M, Nomura T. 1990. Two new natural diels-alder type adducts from the root bark of *Artocarpus heterophyllus*. J Nat Prod 53: 391-395.

Hano Y, Inami R, Nomura T. 1994. Constituents of Moraceae plants. 20. a novel flavone, artonin V, from the root bark of *Artocarpus altilis*. J Chem Res Syn 9: 348-349.

Heyne K. 1987. Useful Plants of Indonesia II. Penerbit Badan Litbang Kehutanan, Jakarta. [Indonesian]

Khan MR, Omoloso AD, Kihara M. 2003. Antibacterial activity of *Artocarpus heterophyllus*. Fitoterapia 74: 501-505.

Ko HH, Lu YH, Yang SZ, Won SJ, Lin CN. 2005. Cytotoxic prenylflavonoids from *Artocarpus elasticus*. J Nat Prod 68: 1692-1695.

Kochummen KM. 1987. Moracea in tree flora of Malaya. Vol. 2. Forest Research Institute, Kepong, Malaysia.

Jayasinghe L, Balasooriya BAIS, Padmini WC Hara N, Fujimoto Y. 2004. Geranyl chalcone derivatives with antifungal and radical scavenging. Phytochem 65: 1287-1290.

Jayasinghe L, Rupasinghe GK, Hara N, Fujimoto Y. 2006. Geranylated phenolic constituents from the fruits of *Artocarpus nobilis*. Phytochem 67: 1353-1358.

Jayasinghe ULB, Samarakoon TB, Kumarihamy BMM, Hara N, Fujimoto Y. 2008. Four new prenylated flavonoids and xanthones from the root bark of *Artocarpus nobilis*. Fitoterapia 79: 37-41.

Judge AD, Zhang X, Fujii H, Surh CD, Sprent J. 2002. Interleukin 15 controls both proliferation and survival of a subset of memory-phenotype CD8+ T cells. J Exp Med 196: 935–946.

Kazuki S, Aida M, Hano Y, Nomura T. 1995. A diels-alder-type adduct from *Artocarpus heterophyllus*. Phytochemistry 40: 754-756

Kijjoa A, Cidade HM, Pinto MMM, Gonzalez MJTG, Anantachoke C, Gedris TE, Herz W. 1996. Prenylflavonoids from *Artocarpus elasticus*. Phytochem 43: 691-694.

Kijjoa A, Cidade HM, Gonzalez MJTG, Afonso CM, Silva AMS, Herzt W. 1998. Further prenylflavonoids from *Artocarpus elasticus*. Phytochem 47: 875-878.

Lien TP, Ripperger H, Porzel A, Sung TV, Adam G. 1998. Constituents of *Artocarpus tonkinensis*. Pharmazie 53 : 353-355.

Lin CN, Lu CM, Huang PL. 1995. Flavonoids from *Artocarpus heterophyllus*. Phytochem 39: 1447-1451.

Makmur L, Syamsurizal, Tukiran Achmad SA, Aimi N, Hakim EH, Kitajima M, Takayama H. 2000. Artoindonesianin C, a new xanthone derivative from *Artocarpus teysmanii*. J Nat Prod 63: 243-244.

Murniana. 1995. Several compounds of secondary metabolites from bark of *Artocarpus reticulatus* [Thesis]. Bandung Institute of Technology. Bandung. [Indonesian]

Nomura T, Hano Y, Aida M. 1998. Isoprenoid substitued flavanoids from *Artocarpus* plants (Moraceae). Heterocycles. 47: 1179-1205.

Patil AD, Freyer AJ, Killmer L, Offen P, Taylor PB, Votta BJ, Johnson RK. 2002. A new dimeric dihydrochalcone and a new prenylated flavone from the bud covers of *Artocarpus altilis*: potent inhibitors of cathepsin K. J Nat Prod 65: 624-627.

Puntumchai A, Kittakoop P, Rajviroongit S, Vimuttipong S, Likhitwitayawuid K, Thebtaranonth Y. 2004. Lakoochins A and B, new antimycobacterial stilbene derivatives from *Artocarpus lakoocha*. J Nat Prod 67: 485-486.

Namdaung U, Aroonrerk N, Suksamrarn S, Danwisetkanjana K, Saenboonrueng J, Arjchomphu W, Suksamrarn A. 2006. Bioactive constituents of the root bark of *Artocarpus rigidus* subsp. *rigidus*. Chem Pharm Bull 54: 1433-1436.

Seo EK, Lee D, Shin YG, Chai HB, Navarro HA, Kardono LBS, Rahman I, Cordell GA, Farnsworth NR, Pezzuto JM, Kinghorn AD, Wani MC, Wall ME. 2003. Bioactive prenylated flavonoids from the stem bark of *Artocarpus kemando*. Arch Pharm Res 26 (2): 124-127.

Shieh WL, Lin CN. 1992. A quinonoid pyranobenzoxanthone and pyranodihydrobenzoxanthone from *Artocarpus communis*. Phytochem 31 364-367.

Shimizu K, Kondo R, Sakai K. 1997. A stilbene derivative from *Artocarpus incisus*. Phytochem 45: 1297-1298

Su BN, Cuendet M, Hawthorne ME, Kardono LBS, Riswan S, Fong HHS, Mehta RG, Pezzuto JM, Kinghorn AD. 2002. Constituents of the bark and twigs of *Artocarpus dadah* with cyclooxygenase inhibitory activity. J Nat Prod 65: 163-169.

Suhartati T, Achmad SA, Aimi N, Hakim EH, Kitajima M, Takayama H, Takeya K. 2001. Artoindonesianin L, a new prenylated flavone with cytotoxic activity from *Artocarpus rotunda*. Fitoterapia 72 912-918.

Sultanbawa MUS, Surendrakumar, Sivagnanasundram. 1989. Two pyranodihydrobenzoxanthones from *Artocarpus nobilis*. Phytochem 28(2): 599-605.

Syah YM, Achmad SA, Ghisalberti EL, Hakim EH, Makmur L, Mujahidin D. 2002. Artoindonesianins Q–T, four isoprenylated flavones from *Artocarpus champeden* Spreng. (Moraceae). Phytochem 61 949-953.

Syah YM, Juliawaty LD, Achmad SA, Hakim EH, Ghisalberti EL. 2006 Cytotoxic prenylated flavones from *Artocarpus champeden*, Journal Natural Medicine 60: 308-312.

Udjiana SS. 1997. Several compounds of flavan and stilbene derivatives from root bark of *Artocarpus reticulatus* [Thesis]. Bandung Institute of Technology. Bandung. [Indonesian]

Uno Y, Aida Y, Shiina M, Nomura T, Kagei K. 1991. Isolation of flavone derivatives from *Artocarpus heterophylla*. Jpn. Kokai Tokkyo Koho 8: 197-200.

Venkataraman K. 1972. Wood phenolics in the chemotoxonomy of the Moraceae. Phytochem 11: 1571-1586

Verheij EWM, Coronel RE (eds). Plant Resources of South Asia No. 2 Edible Fruits and Nuts. Prosea Foundation. Bogor.

Wang Y, Xu K, Lin L, Pan Y, Zheng X. 2007. Geranyl flavonoids from the leaves of *Artocarpus altilis*. Phytochem 68: 1300-1306.

Wang YH, Hou AJ, Chen L, Chen DF, Sun HD, Zhao QS, Bastow KF, Nakanishi Y, Wang XH, Lee KH. 2004. New isoprenylated flavones, artochamins A-E and cytotoxic principles from *Artocarpus chama*. J Nat Prod 67: 757-761.

Weng JR, Chan SC, Lu YH, Lin HC, Ko HH, Lin CN. 2006. Antiplatelet prenylflavonoids from *Artocarpus communis*. Phytochem 67: 824-829.

Widyawaruyanti A, Subehan, Kalauni SK, Awale S, Nindatu M, Zaini NC, Syafruddin D, Asih PBS, Tezuka Y, Kadota S. 2007. New prenylated flavones from *Artocarpus champeden*, and their antimalarial activity in vitro. J Nat Med 61: 410-413.

Yamazaki M, Okuyama E, Matsudo T, Takamaru T, Kaneko T. 1987. Principles of Indonesian herbal drugs having an antiulcerogenic activity. I. Isolation and identification of (+/-)-catechin from *Artocarpus* integra merr. Yakugaku Zasshi 107(11) : 914-916

Yuliani E. 1997. Stilbene derivatives compound from wood of *Artocarpus nitida* Trec [Thesis]. Bandung Institute of Technology. Bandung. [Indonesian]

Zong P, Zheng, Sibao C, Shiyun W, Xia CW, KaWC, Jia JW, Dajiang Y, Mingfu W. 2009. Chemical Components and Tyrosinase Inhibitors from the Twigs of *Artocarpus heterophyllus*. J Agric Food Chem 57: 6649-6655.