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Anticancer mechanism of artonin E and related prenylated flavonoids from the medicinal plant *Artocarpus elasticus*

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Abstract. *Bailly C. 2021. Anticancer mechanism of artonin E and related prenylated flavonoids from the medicinal plant* Artocarpus elasticus*. Asian J Nat Prod Biochem 19: 44-56.* Plants of the *Artocarpus* genus are largely distributed throughout tropical Asia and Oceania. Species such as *A. altilis* (Parkinson) Fosberg and *A. heterophyllus* Lam. are popular trees known as breadfruit and jackfruit, respectively. They contain a large structural diversity of bioactive prenylated flavonoids. Here we have focused on the less known species *Artocarpus elasticus* Reinw. ex Blume which is well distributed in southeast Asia, and used in traditional medicine to treat dysentery, tuberculosis, and other diseases. Numerous prenylated flavonoids have been isolated from the leaves and bark of *A. elasticus*, such as artocarpesin, artocarpin, artelastin, and many others. They are endowed with antioxidant, anti-inflammatory, and anticancer properties. A focus is made of the subgroup of compounds designated artonins, with the derivative artonin E as a lead anticancer agent. Art-E has revealed marked anticancer effects *in vitro* and *in vivo*, after oral administration. The mechanism of action of Art-E is discussed, to highlight the structural and functional analogy between Art-E and the antitumor natural product morusin. Both compounds trigger TRAIL-mediated apoptosis of cancer cells. They can be considered further for the development of novel anticancer agents.

Keywords: *Artocarpus*, cancer therapeutics, natural products, phytotherapy, prenylated flavonoids

Abbreviations: iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species

INTRODUCTION

The genus *Artocarpus* refers to a large group of plants belonging to the Moraceae family (Zerega et al. 2010). The internet database www.theplantlist.org has recorded 68 taxonomically accepted species, while about 90 additional plant names are now in synonymy or have even been moved as synonyms to other genera. The name *Artocarpus* derives from the Greek *artos* for "bread" and *karpos* for "fruit". Some of the *Artocarpus* species are relatively well-known, such as *A. altilis* (Parkinson) Fosberg known as the breadfruit tree, and *A. heterophyllus* Lam. known as the jackfruit tree, which are two economically important *Artocarpus* species (Sikarwar et al. 2014; Mohammed Haleel et al. 2018; Sahu et al. 2019; Buddhisuharto et al. 2021). Their fruits are used for food production and several parts of these two trees including fruits, leaves, and barks have been used in traditional medicine in India and surrounding countries (Ranasinghe et al. 2019). Other *Artocarpus* species are used in traditional medicine, such as (i) decoctions prepared from the leaves of the tree *A. tonkinensis*, used in northern Vietnam to treat arthritis and backache (Adorisio et al. 2016), and (ii) extracts of *Artocarpus lacucha* (also known as Monkey jack) used in traditional Thai medicine as an anthelmintic agent (Aneklaphakij et al. 2020; Gupta et al. 2020), for examples. The ethnopharmacological use of *Artocarpus* species is widespread in subtropical and tropical regions of Asia where the trees are largely distributed. *Artocarpus* are believed to originate from the island of Borneo, from which species dispersed and diversified in several directions (Williams et al. 2017). *Artocarpus*-based remedies are used to treat multiple diseases and conditions, including malarial fever, diarrhea, diabetes, parasitic infections, and different inflammatory diseases (Jagtap and Bapat 2010).

These plants contain a large diversity of bioactive compounds, including many prenylated flavonoids and cyclized derivatives which have revealed interesting antimicrobial, anti-inflammatory and anticancer properties (Hakim et al. 2006; Hari et al. 2014). One particular species, *Artocarpus elasticus* Reinw. ex Blume (Figure 1) has shown marked anticancer effects against different cancer cell lines and tumor models, attributed to the presence of prenylated flavonoids isolated from the root bark or other parts of the tree. The lead compound is artonin E (Art-E), thoroughly investigated as an antitumor agent. Over the past ten years, the mechanism of action of Art-E has been delineated and the activated signaling pathways at the origin of antitumor activity have been defined. These studies gave us the impetus to analyze in deep the mode of action of Art-E and structurally related compounds. The present review will address successively the plant *A. elasticus* and plant extracts, the phytochemical compounds isolated from the plant, the specific flavonoid group known as artonins, and the molecular targets and pathways activated by Art-E, responsible for its pharmacological properties. The role of TRAIL in the mode of action of Art-E and related compounds is discussed, opening the door to the identification of novel anticancer molecules. The purpose of the study was to promote the knowledge of artonins and the use of artonin E as a lead anti-cancer compound.

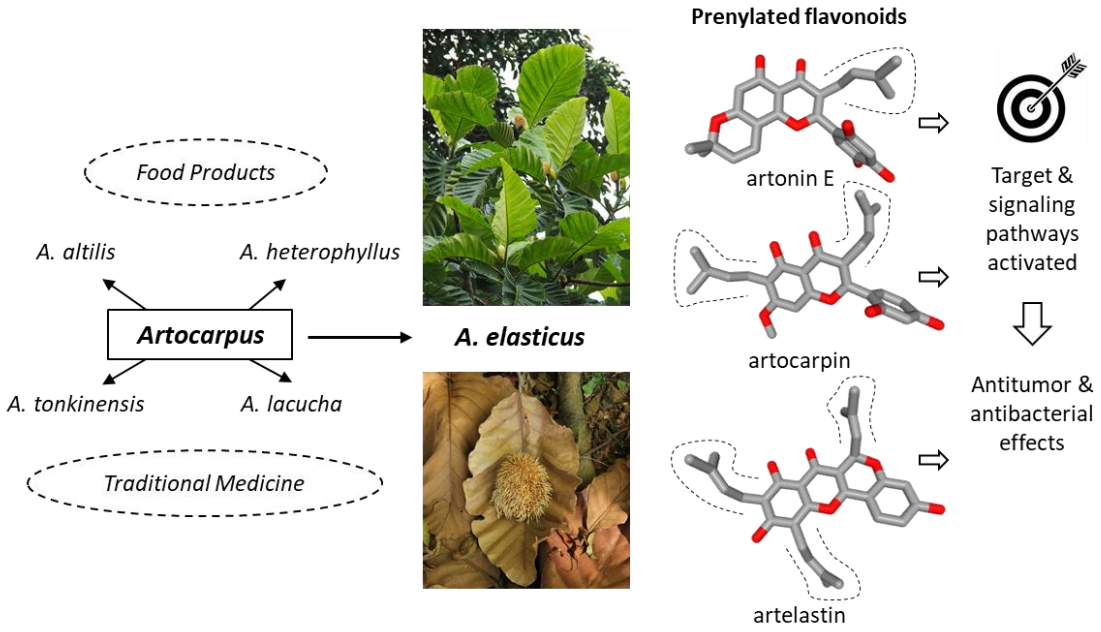

Figure 1. *Artocarpus elasticus* Reinw. ex Blume as a source of anticancer prenylated flavonoids. Different *Artocarpus* species are used in traditional medicine and as food products, such as *A. altilis* (Parkinson ex F.A.Zorn) Fosberg, *A. heterophylus* Lam., *A. tonkinensis* A.Chev. ex Gagnep. and *A. lacucha* Buch.-Ham. Similarly, *A. elasticus* is also a source of bioactive mono-, bis- and tris-prenylated flavonoids, endowed with anticancer properties. *A. blumei* Trécul and *A. kunstleri* King are synonyms for *A. elasticus* Reinw. ex Blume (http://www.theplantlist.org/)

ARTOCARPUS ELASTICUS AND ITS MEDICINAL USES

The plant *Artocarpus elasticus* Reinw. ex Blume is native to Southeast Asia and can easily be found in countries like Myanmar, Thailand, Malaysia, Indonesia and the Philippines. In some countries like Malaysia and Indonesia, *A. elasticus* is cultivated to maintain its sustainability (Susiarti et al. 2020). It is an evergreen, robust and tall tree (up to 45-65 m). Various vernacular names are used locally, such as Benda (Javanese Indonesia), Terap nasi (Peninsular Malaysia), and others (Teo and Nasution 2003)

The wood of *A. elasticus is sought* as a building material. Upon wounding, it exudes a white and thick latex which is elastic or flexible, hence the name *elasticus*. The sticky latex is used to catch birds but also to treat dysentery. Different parts of the tree are used in traditional medicines, the latex for dysentery, the bark for female contraception, and the young leaves mixed with rice to treat tuberculosis. The flesh of the fruits is eaten raw or cooked. The seeds are consumed fried or roasted (Susiarti et al. 2020).

The bark and the leaves of the plant are often used to identify new phytochemicals. In addition, an extract of the stem bark of *A. elasticus* has been used as a reducing and stabilizing agent for the synthesis of silver nanoparticles (Abdullah et al. 2015). The same type of antibacterial silver nanoparticles have been obtained with seed extract of *A. hirsutus* (Shobana et al. 2020).

PRENYL FLAVONOIDS FROM *ARTOCARPUS ELASTICUS*

Artocarpus elasticus is a rich reservoir of bioactive natural products, notably prenyl flavonoids particularly abundant in the bark of the tree and the roots. There is a large structural diversity of prenylated flavonoids isolated from *A. elasticus,* with compounds bearing one, two or three prenyl groups, with a classical flavonoid skeleton or a bulkier pentacyclic core (Nomura et al. 1998; Kijjoa et al. 1998; Cidade et al. 2001). The main isolated compounds are shown in Figure 2, with the exception of the artonins discussed below. Most of these compounds can be found in other *Artocarpus* species. Here, we will discuss only those found in *A. elasticus.*

The tetracyclic compound artelastin, with three prenyl side chains, has been isolated in 1996 from the wood of *A. elasticus together with* artelastochromene, artelasticin, and artocarpesin (Kijjoa et al. 1996). Artelastin has revealed marked cytotoxic properties against different cancer cell lines *in vitro*. It was found to disturb the microtubule network of MCF7 breast cancer cells and to interfere with the cell cycle progression. Artelastin caused an accumulation in S phase due to drug-induced delay in DNA replication (Pedro et al. 2005). It is a potent inhibitor of both T- and B lymphocyte mitogen-induced proliferation and an inhibitor of cytokines production, such as interferon-γ, interleukins IL-2, -4 and -10, in stimulated splenocytes (Cerqueira et al. 2003). Artelastin displays marked antioxidant properties, inhibiting the production of reactive oxygen species (ROS) and the expression of the inducible nitric oxide synthase (iNOS) in lipopolysaccharide-stimulated macrophages (Cerqueira et al. 2008).

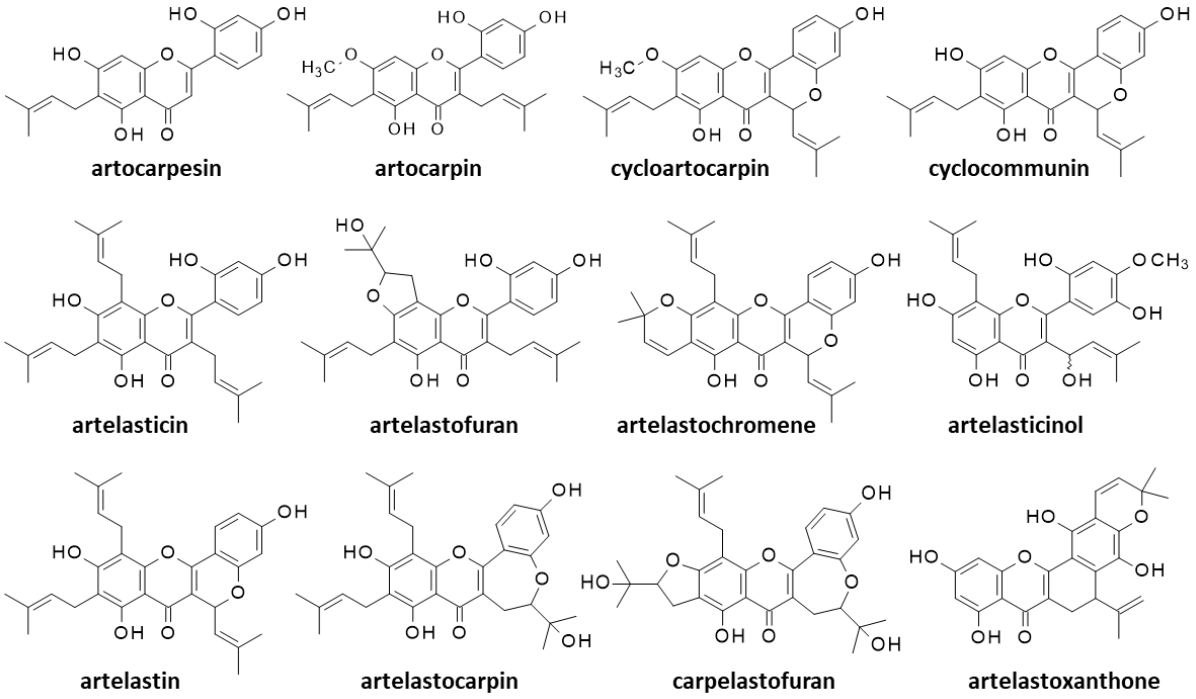

Figure 2. Chemical structures of prenylated flavonoids which have been isolated from *A. elasticus* Reinw. ex Blume

Artelasticin can be found in *A. elasticus* (Kijjoa et al. 1996), in *A. lanceifolius* (Syah et al. 2001) *and other plants, such as the* Cameroon medicinal plant *Dorstenia psilurus*. It was found to activate AMPK (AMP-activated protein kinase) and stimulate glucose uptake in rat skeletal muscles. Its marked blood glucose-lowering effect can be useful for the treatment of type-2 diabetes (Choumessi et al. 2019). Artocarpesin was found to be moderately cytotoxic toward a panel of cancer cell lines (IC_{50} values in the 60-100 µM range) but its analog cycloartocarpesin is more potent (IC_{50} values in the 15-50 µM range) (Kuete et al. 2015). This compound can be found in many other plants. Like artelasticin, it presents marked anti-inflammatory and antioxidant properties (Fang et al. 2008). Its antioxidant activity contributes to the anti-browning effect observed with extracts of *A. heterophyllus* on fresh-cut apple slices. Remarkably, artocarpesin was found to exert a powerful inhibitory activity against mushroom tyrosinase (IC_{50} = 0.52 µM) whereas the related product artocarpin was totally inactive against the enzyme (Zheng et al. 2008, 2009). Artocarpesin, found in the twigs and woods of *A. heterophyllus*, *A. incisus,* and *A. elasticus*, has been considered for the design of skin whitening agents (Arung et al. 2008, 2011). Artocarpin has been reported in a dozen of *Artocarpus* species and displays antioxidant, anti-inflammatory and anti-parasitic properties, as well as skin-whitening activities (Chan et al. 2018a; Morrison et al. 2021).

The bis-prenyl flavonoid cyclocommunin is known for a long time for its potent capacity to inhibit platelet aggregation induced by collagen or arachidonic acid (Lin et al. 1993). It was first isolated from *A. communis*, hence its name cyclocommunin (Lin and Shieh, 1992), but it is also called isocyclomulberrin (Chen et al. 1993; Ma et al. 2010). Cyclocommunin is also an activator of protein kinase C (PKC) and a compound capable to elevate the level of intracellular calcium in rat neutrophils. As a result, cyclocommunin was found to stimulate respiratory burst in neutrophils (Wang et al. 1999), enhancing the production of superoxide anion, unlike artonin B which inhibited superoxide anion formation in these cells (Wei et al. 2005). Cyclocommunin displays modest anti-proliferative effects against hepatocellular carcinoma cells (IC_{50} = 14-33 µM depending on cell line) whereas Art-A and Art-B were inactive against these HCC cell lines (Ma et al. 2010). Recently, it was reported that cyclocommunin displays a significant antimycobacterial activity against *Mycobacterium tuberculosis* (laboratory strain H37Ra) with a minimum inhibitory concentration (MIC) of 12.3 µM (Boonyaketgoson et al. 2020).

Artelastocarpin and carpelastofuran were isolated from the wood of *A. elasticus*. They both revealed cytotoxic properties toward cancer cells, with an efficacy like that of artelastin, artelasticin, and artlastochromene (IC_{50} = 7-12 µM depending on cell lines) (Cidade et al. 2001). A series of compounds named artoindonesianins has been obtained from different *Artocarpus* species (Musthapa et al. 2010). Most of them have been isolated from species other than *A. elasticus*, such as the cytotoxic compounds artoindonesianins Z-4 and Z-5 found in the bark of *A. lanceifolius* (Musthapa et al. 2009a) and artoindonesianins A and B found in the roots of *A. champeden* (Hakim et al. 1999) and many other artoindonesianins, as indicated in Table 1.

Table 1. Artoindonesianin compounds isolated from *Artocarpus* species

Compound	*Artocarpus* species	References
Artoindonesianin A	*A. champeden*	Hakim et al. 1999
Artoindonesianin B	*A. champeden*	Hakim et al. 1999
Artoindonesianin C	*A. teysmanii*	Makmur et al. 2000
	A. rigidus	Namdaung et al. 2006 ;
	A. kemando	Ee et al. 2011
Artoindonesianin D	*A. maingayi*	Hakim et al. 2000
Artoindonesianin E	*A. champeden*	Hakim et al. 2001
Artoindonesianin F	*A. heterophyllus*	Rao et al. 2010
Artoindonesianin G	*A. lanceifolius*	Syah et al. 2001
Artoindonesianin H	*A. lanceifolius*	Syah et al. 2001
Artoindonesianin I	*A. lanceifolius*	Syah et al. 2001
Artoindonesianin J	*A. bracteata*	Ersam et al. 2002
Artoindonesianin K	*A. champeden*	Achmad et al. 2005
Artoindonesianin L	*A. rotunda*	Suhartati et al. 2001
Artoindonesianin M	*A. champeden*	Syah et al. 2002b
Artoindonesianin N	*A. gomezianus*	Hakim et al. 2002a
Artoindonesianin O	*A. gomezianus*	Hakim et al. 2002a
Artoindonesianin P	*A. lanceifolius*	Hakim et al. 2002b
	A. elasticus	Jenis et al. 2019
Artoindonesianin Q	*A. champeden*	Syah et al. 2002a
Artoindonesianin R	*A. champeden*	Syah et al. 2002a
Artoindonesianin S	*A. champeden*	Syah et al. 2002a
Artoindonesianin T	*A. champeden*	Syah et al. 2002a
Artoindonesianin U	*A. champeden*	Syah et al. 2004
Artoindonesianin V	*A.. champeden*	Syah et al. 2004
	A. altilis	Shamaun et al. 2010
Artoindonesianin W	*A. elasticus*	Jenis et al. 2019
Artoindonesianin X	*A. fretessi*	Soekamto et al. 2003
Artoindonesianin Y	*A. fretessi*	Soekamto et al. 2003
Artoindonesianin Z1	*A. lanceifolius*	Hakim et al. 2006
	A. anisophyllus	Noraini et al. 2013
Artoindonesianin Z2	*A. lanceifolius*	Hakim et al. 2006
Artoindonesianin Z3	*A. lanceifolius*	Hakim et al. 2006
Artoindonesianin Z4	*A. lanceifolius*	Musthapa et al. 2009b
Artoindonesianin Z5	*A. lanceifolius*	Musthapa et al. 2009b
Artoindonesianin Z4	*A. lanceifolius*	Musthapa et al. 2009b
Artoindonesianin Z5	*A. lanceifolius*	Musthapa et al. 2009b
Artoindonesianin A1	*A. champeden*	Syah et al. 2006b
Artoindonesianin A2	*A. champeden*	Syah et al. 2006a
Artoindonesianin A3	*A. champeden*	Syah et al. 2006a
Artoindonesianin B1	*A. altilis*	Syah et al. 2006b
	A. heterophyllus	Lang et al. 2016
Artoindonesianin E1	*A. elasticus*	Musthapa et al. 2009a

For the record, the structure of artoindonesianin C, first isolated from *A. teysmanii* (Makmur et al. 2000), has been printed on a post stamp on the occasion of the international year of chemistry 2011 (Figure 3). The oxepinoflavone derivative artoindonesianin E1 was isolated from the bark of *A. elasticus*, together with the related compounds artocarpin, cycloartocarpin, and cudraflavones A and C (Figure 2). The derivative artoindonesianin A-3 was initially isolated from *A. champeden* (Syah et al. 2006a) and latter re-discovered from the bark of *A. elasticus* tree collected from Alor Island in Indonesia (Kuran and Ersam 2017). Other artoindonesianins have been found in *A. elasticus*, such as artoindonesianin P which was found to inhibit the enzyme α-glucosidase (IC_{50} = 25.4 μM) but with a reduced efficacy compared to Art-E and artobiloxanthone (IC_{50} = 16.2 and 8.6 μM, respectively) (Jenis et al. 2019). Recently, artoindonesianins P and W were isolated from *A. elasticus* and found to inhibit human neutrophil elastase (IC_{50} = 28.7 and 11.2 μM, respectively) whereas artobiloxanthone was slightly more active (IC_{50} = 9.8 μM) (Ban et al. 2020).

Other prenylated flavonoids have been identified, such as artelastoheterol, artelasticinol, artelastoxanthone, artobiloxanthone, cycloartelastoxanthone, cycloartobiloxanthone, cycloartelastoxanthendiol, elastixanthone, and artonol A, all isolated from the root bark of *A. elasticus* (Figure 2). Artelastoxanthone has revealed modest antiproliferative activities against different cancer cell lines *in vitro* (Ko et al. 2005). Cycloartelastoxanthone and cycloartobiloxanthone and artobiloxanthone have shown protective effects on DNA damage caused by superoxide anion radicals $O_2^{\bullet-}$ (Lin et al. 2009). Elastixanthone and cycloartobiloxanthone have shown antimicrobial activities (Ramli et al. 2016). Artobiloxanthone and cycloartobiloxanthone have been found in many *Artocarpus* species, not limited to *A. elasticus*. The latter compound is interesting because it was found to potently inhibit migration and invasion of H460 lung cancer cells, via inhibition of the phosphorylation of focal adhesion kinase (FAK) and the expression of cell division cycle 42 (CDC42) (Tungsukruthai et al. 2017). Cycloartobiloxanthone dose-dependently reduces proliferation of other lung cancer cell lines (H23, H292 and A549) and triggers caspase-dependent apoptosis with an efficacy comparable to that of the standard DNA-damaging anticancer drugs cisplatin and etoposide, at least *in vitro* (Losuwannarak et al. 2018). But the ROS scavenging activity of cycloartobiloxanthone is much weaker than that of artobiloxanthone and Art-E (Sritularak et al. 2010). A recent molecular docking analysis has predicted that artobiloxanthone can bind to the active site of the enzyme transglutaminase 2 (TG2), possibly inhibiting this enzyme considered as an anticancer target (Parvatikar and Madagi 2021).

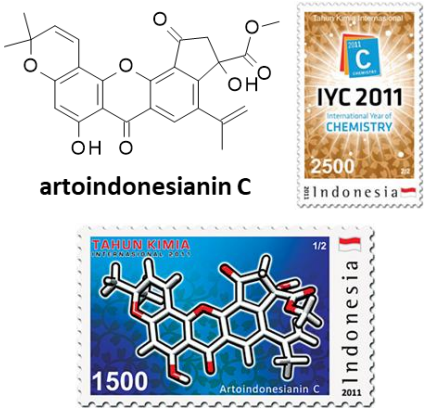

Figure 3. The structure of artoindonesianin C, isolated from *A. teysmanii*. A post stamp with the structure of the compound was emitted to celebrate the international year of chemistry 2011 in Indonesia

Here we focused mostly on prenylated flavonoids isolated from *A. elasticus* but the whole *Artocarpus* genus the structural diversity is huge, as previously reported in specific review articles on *Artocarpus* species (Achmad et al. 2005; Hakim et al. 2006; Hakim 2010; Veitch and Grayer 2008). A recent analysis of a root extract of *A. heterophyllus* led to the identification of 47 prenylated flavonoids (Ye et al. 2019). There must be that many in the related species *A. elasticus*. An important group of prenylated flavonoids commonly found in *Artocarpus* species is called artonin, with the lead compound Art-E. Given the importance of the lead, this family is presented hereafter.

THE ARTONIN GROUP OF PRENYL FLAVONOIDS

There are 24 compounds named artonins A to Y (Table 2). The first two compounds, Art-A and -B, were isolated in 1989 for the root bark of *A. heterophylus* (Hano et al. 1989) followed by Art-C and -D one year later from the same plant (Hano et al. 1990a). They can be found in a few other *Artocarpus* species and display antioxidant properties (Ko et al. 2005). Art-B is an interesting compound, much more potent than Art-A at inhibiting the proliferation of nasopharyngeal cancer KB cells and the growth of the parasite *Trypanosoma brucei brucei*, *in vitro* (Bourjot et al. 2010). Art-B can reduce proliferation of different types of cancer cells, such as human CCRF-CEM leukemia cells, via the induction of mitochondria-dependent apoptosis (Lee et al. 2006). Art-A is less cytotoxic than Art-B, nevertheless, it is a more potent inhibitor of the papain-like cysteine protease cathepsin K (IC_{50} = 1.9 and 9.0 μM, for Art-A and Art-B respectively) largely implicated in bone resorption (Zhai et al. 2017). Art-A also displays antimalarial activity, at least *in vitro* (Widyawaruyanti et al. 2007).

Table 2. Artonin compounds isolated from *Artocarpus* species

Compound	CID[a]	Formula (g/mol)[b]	*Artocarpus* species	References
Artonin A	14557102	$C_{30}H_{30}O_7$ (502.6)	*A. heterophylus*	Hano et al. 1989
			A. styracifolius	Bourjot et al. 2010
			A. hypargyreus	Qiao et al. 2011
			A. xanthocarpus	Jin et al. 2015
			A. champeden	Widyawaruyanti et al. 2007
Artonin B	11964501	$C_{30}H_{30}O_7$ (502.6)	*A. heterophylus*	Hano et al. 1989
			A. champeden	Hakim et al. 1999s
			A. styracifolius	Bourjot et al. 2010
Artonin C	14681571	$C_{40}H_{38}O_{10}$ (678.7)	*A. heterophylus*	Hano et al. 1990a
Artonin D	14681573	$C_{40}H_{36}O_{10}$ (676.7)	*A. heterophylus*	Hano et al. 1990a
Artonin E	5481962	$C_{25}H_{24}O_7$ (436.5)	*A. communis*	Hano et al. 1990b
			A. kemando	Seo et al. 2003
			A. lanceifolius	Cao et al. 2003
			A. chama	Wang et al. 2004
			A. nobilis	Jayasinghe et al. 2008
			A. lanceifolius	Musthapa et al. 2009
			A. gomezianus	Plaibua et al. 2013
			A. rotunda	Suhartati et al. 2001
			A. rigida	Suhartati et al. 2018
Artonin F	14680593	$C_{30}H_{30}O_7$ (502.6)	*A. rigidus*	Namdaung et al. 2006
			A. styracifolius	Bourjot et al. 2010
			A. integer var. silvestris Corner	Shaha et al. 2016
Artonin G	46887714	$C_{30}H_{30}O_7$ (502.6)	*A. rigida*	Hano et al. 1990
Artonin H	21595104	$C_{30}H_{34}O_7$ (506.6)	*A. rigida*	Hano et al. 1990
Artonin I	57335177	$C_{40}H_{36}O_{11}$ (692.7)	*A. heterophyllus*	Hano et al. 1992
Artonin J	44258663	$C_{25}H_{24}O_7$ (436.5)	*A. heterophyllus*	Aida et al. 1993
Artonin K	15340661	$C_{21}H_{18}O_7$ (382.4)	*A. heterophyllus*	Aida et al. 1993
Artonin L	44258662	$C_{22}H_{20}O_7$ (396.4)	*A. heterophyllus*	Aida et al. 1993
Artonin M	44258661	$C_{30}H_{30}O_7$ (502.6)	*A. altilis*	Hano et al. 1993
			A. rotunda	Suhartati et al. 2001
Artonin N	44258669	$C_{30}H_{30}O_7$ (502.6)	*A. rigida*	Hano et al. 1993
Artonin O	46887814	$C_{30}H_{30}O_7$ (502.6)	*A. rigida*	Hano et al. 1993
			A. rotunda	Suhartati et al. 2001
Artonin P	44258658	$C_{25}H_{20}O_8$ (448.4)	*A. rigida*	Hano et al. 1993
			A. communis	Chan et al. 2018b
Artonin Q	131753034	$C_{31}H_{30}O_8$ (530.6)	*A. heterophyllus*	Aida et al. 1994
Artonin R	131753035	$C_{31}H_{30}O_{10}$ (562.6)	*A. heterophyllus*	Aida et al. 1994
Artonin S	44258666	$C_{26}H_{28}O_7$ (452.5)	*A. heterophyllus*	Aida et al. 1994
Artonin T	44258664	$C_{26}H_{26}O_7$ (450.5)	*A. heterophyllus*	Aida et al. 1994
Artonin U	44258358	$C_{21}H_{20}O_5$ (352.4)	*A. heterophyllus*	Aida et al. 1994
Artonin V	129687399	$C_{25}H_{26}O_7$ (438.5)	*A. altilis*	Hano et al. 1994
Artonin X	(FDB021143)	$C_{40}H_{38}O_9$ (662.7)	*A. heterophyllus*	Shinomiya et al. 1995
Artonin Y	15541482	$C_{20}H_{18}O_6$ (354.4)	*A. heterophyllus*	Shinomiya et al. 2000

Note: [a]Compound Identity number (PubChem CID). [b]Formula and molecular weight.

The most important compound in the series is arguably Art-E (also known as 5'-hydroxymorusin), initially isolated from the stem bark of *A. communis* Forst., together with Art-F (Hano et al. 1990b). It was later found in several other *Artocarpus* species, including *A. elasticus* (Ramli et al. 2016). The compound, bearing an isoprenoid group at position *C-3*, was initially characterized as a potent and selective inhibitor of arachidonate 5-lipoxygenase (IC_{50} = 0.36 μM) expressed on cells involved in regulation of immune responses (Reddy et al. 1991). Art-E has revealed a very modest capacity to inhibit ADP-induced platelet aggregation *in vitro*, with an IC_{50} of 192 μM (Jantan et al. 2010). Later, Art-E was found to exert potent antiproliferative activities against different cancer cell lines, notably against breast adenocarcinoma MCF-7 and MDA-MB-231 cells (ED_{50} = 2.2 and 3.0 μg/ml, respectively) (Wang et al. 2004). It is slightly less active against another type of cancer cells derived from solid tumors, but also exerts a potent cytotoxic action against P-388 leukemia cells (Musthapa et al. 2009b). Art-E is the lead product in the series, with interesting anticancer and antimicrobial properties (see below). The anticancer effects have been characterized using different experimental models *in vitro* and *in vivo*. In particular, the compound has revealed a robust dose-dependent effect in a 4T1 breast carcinoma xenograft model. The oral administration of Art-E at 25, 50 and 100 mg/kg reduced drastically the growth of tumor in mice and reduced the appearance of metastasis, without any apparent toxicity (Etti et al. 2017a). The compound is well tolerated; it can be administered orally for up to consecutive 10 days at 30 mg/kg, without any significant effect on cholesterol, creatinine and blood urea nitrogen levels (Fukai et al. 2003).

Modest antibacterial effects have been reported with Art-E against *Escherichia coli* and *Bacillus subtilis* (Suhartati et al. 2008), and with Art-O against *B. subtilis* (Suhartati et al. 2016). Mild antibacterial effects have been noted with Art-E against *Pseudomonas aeruginosa* strain PA01 (MIC = of 32 μg/ml) whereas the compound was essentially inactive against the microorganisms *Providencia stuartii*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Salmonella typhi* and *Escherichia coli* (Kuete et al. 2011). Art-E showed little activity against *S. aureus* strain ATCC25922 (MIC = 256 μg/ml) (Kuete et al. 2011) whereas a significant antibacterial effect has been reported with the strain ATCC 25923 (MIC = 3.9 μg/ml) and the methicillin-resistant strain ATCC BAA-1720 (MIC = 13.3 μg/ml) (Zajmi et al. 2015). A structural analysis using transmission electron microscopy revealed that Art-E disrupted the architecture of the bacterial cell, so as to facilitate the penetration of antibiotics (Zajmi et al. 2015). A similar type of effect on the bacterial cell wall has been reported with Art-I, despite it is structurally distinct from Art-E. Importantly, the membrane destabilizing effects of Art-E are reminiscent of those reported with morusin, which is able to disrupt the cell membrane architecture and inhibiting the phosphatidic acid biosynthesis pathway of *S. aureus* (Pang et al. 2019). In many ways, morusin and Art-E behave similarly.

The flavonoid Art-F displays little cytotoxic effects against cancer cells but has shown antimycobacterial activity against *Mycobacterium tuberculosis* (MIC = 6.25 μg/ml) (Namdaung et al. 2006). It has also revealed significant anti-plasmodial activity against the chloroquine-resistant strain FcB1, being only slightly less active than Art-B and more active than Art-A (IC_{50} = 4.9, 1.56, 2.20 μM for Art-A, B and F, respectively) (Bourjot et al. 2010). Art-F, isolated from *A. integer* var. silvestris Corner, has revealed a weak capacity to inhibit 15-lipoxygenase (Shaha et al. 2016). Art-F can be found in different *Artocarpus* species, including a hybrid between *A. heterophyllus* (jackfruit) and *A. integer* (champedak) which has been specifically developed in Thailand to produce tastier and larger fruits, and for disease resistance (Panthong et al. 2013).

The isolation and structural characterization of several artonins have been reported but no specific effect has been pointed out, such as with Art-G and -H (Hano et al. 1990b), Art-J, -K and -L (Aida et al. 1993), and Art-M, -N, O, -P (Hano et al. 1993). Art-O, found in *A. rigida*, has shown a modest anti-proliferative action against HT-29 human colon cancer cell (ED_{50} = 3.2 μM) (Ren et al. 2010).

Art-I is much more interesting because the compound has revealed activities against multidrug-resistant (MDR) *Staphylococcus aureus* strains. It is a complex molecule (Figure 4) initially isolated from *A. heterophyllus* (Hano et al. 1992) but also from the leaves of *Morus mesozygia* (Fozing et al. 2012). Art-I has been found to inhibit the enzyme phosphodiesterase I *in vitro* (IC_{50} = 15.4 μM) (Fozing et al. 2012) and to function as an efflux pump inhibitor and a generator of ROS in *S. aureus*. Interestingly, the compound revealed an unanticipated capacity to promote considerably the activity of antibiotics (reducing the MIC 500- to-1000 fold), via Art-I-induced cell membrane damages (Farooq et al. 2014). It could be a useful natural product to treat multi-drug resistant *Staphylococcus* infections. The total synthesis of these complex molecules has been reported recently, opening the door to the design of simpler, more active analogs (Liu et al. 2020).

Art-V has been first isolated from *A. altilis* (Hano et al. 1994). This plant, known as paparahua tree, is largely used as a traditional medicine in Amazonian Ecuador and other countries in Oceania and South America. Many flavones and terpenoids have been isolated from this plant (Luzuriaga-Quichimbo et al. 2019). Art-X is a rare compound, isolated from *A. heterophyllus*, analogous to the diarylheptanoid kuwanon R which has been characterized as an inhibitor of protein tyrosine phosphatase 1B (PTP1B) (Shinomiya et al. 1995; Hoang et al. 2009).

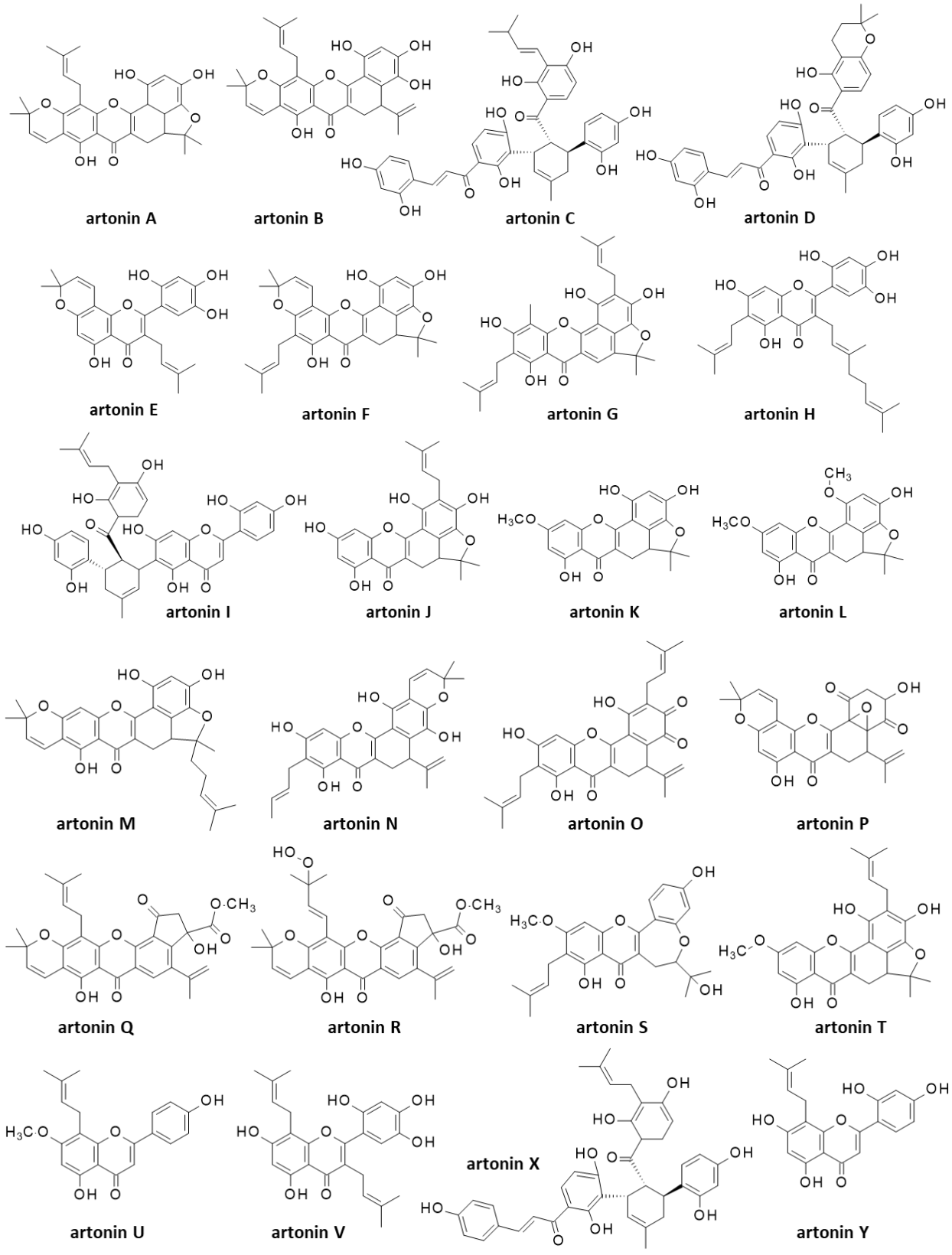

Figure 4. Chemical structures of artonins

ANTICANCER MECHANISM AND MOLECULAR TARGETS OF ARTONIN-E

The mechanism of action of Art-E has been thoroughly investigated, at least at the cellular level. The compound triggers a down-regulation of the anti-apoptotic protein MCL1 (myeloid leukemia cell sequence-1) in human A549 and H292 non-small cell lung cancer cells and sensitizes them to anoikis (detachment-induced apoptosis) (Wongpankam et al. 2012). In these NSCLC cells, Art-E down-regulates several proteins involved in cell migration and invasion, such as FAK (focal adhesion kinase) and CDC42 (Cell division cycle-42). At non-cytotoxic low concentrations (0.05-05 µg/ml), the compound markedly reduced the migration of H460 NSCLC cells *in vitro* (Plaibua et al. 2013). But the main characteristic of Art-E is certainly its capacity to overcome resistance of cancer cells induced by the ligand TRAIL (tumor necrosis factor-related apoptosis-inducing ligand). In gastric cancer cells, the effect is coupled with an Art-E-induced up-regulation of the death receptor 5 (DR5) and tumor suppressor p53 (Toume et al. 2015). A similar enhancement of TRAIL-induced apoptosis by Art-E has been reported recently with LoVo colorectal cancer cells. The compound down-regulated DR5 while it up-regulated the other major regulator of TRAIL-induced apoptosis called cFLIP (cellular FADD-like-IL-1beta-converting enzyme-inhibitory protein) on LoVo cells (Sophonnithiprasert et al. 2019). Remarkably, Art-E can trigger cell cycle arrest (S phase) and a massive mitochondria-dependent apoptosis in SKOV-3 ovarian cancer cells (Rahman et al. 2016) and in HCT116 colon cancer cells, Art-E induced apoptosis through upregulation of p-ERK1/2 (Nimnuan-ngam et al. 2020).

The capacity of Art-E to overcome TRAIL-resistance in cancer cells echoes the effects reported many years ago with Art-B and three other prenylated flavonoids isolated from *A. champeden*. Art-B and the structural analog heterophyllin were found to potently overcome TRAIL resistance in human gastric adenocarcinoma cells and to enhance the expression of DR5 (Minakawa et al. 2014). Many other bioactive natural products have been found to suppress TRAIL resistance, or to enhance TRAIL-induced apoptosis via the death receptor pathway (Dai et al 2015; Ahmed and Ishibashi 2016; Shahwar et al. 2019) but the potency of Art-E and Art-B is noticeably high. A similar capacity to induce TRAIL sensitization by regulating DR5 has been observed with morusin in glioblastoma cells (Park et al. 2016), suggesting thus a class effect. TRAIL emerges as a master element of the antitumor action of Art-E and its analogs (Figure 5).

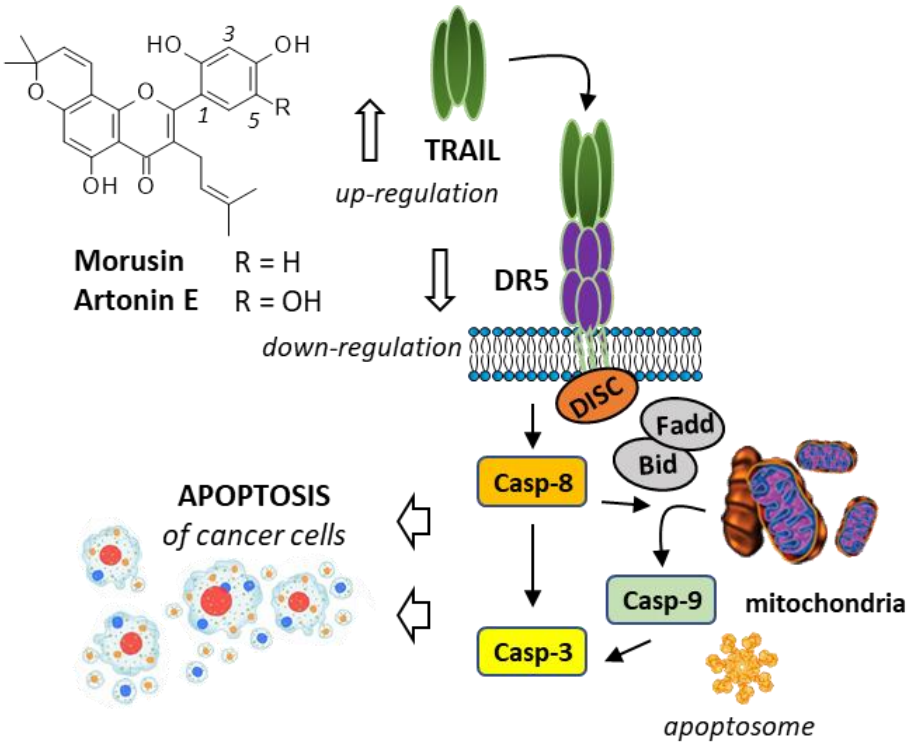

Figure 5. A schematic illustration of the anticancer mechanism of action common to morusine and artonin E (5-hydroxy-morusin). Both compounds trigger an up-regulation of the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and a down-regulation of the death receptor 5 (DR5). Upon trimerization of TRAIL and binding to DR5, the complex promotes the sequential recruitment of Fadd (Fas-associated protein with death domain) and caspase-8 (Casp-8) to form the death-inducing signaling complex (DISC). Processing of Bid (a BH3 domain-containing proapoptotic Bcl2 protein family member) by Casp-8 mediates mitochondrial damages. Activation of Casp-8 also directly induced Casp-3 activation, which concurs to the amplification of apoptosis.

Art-E has revealed marked activities against breast cancer cell lines. The compound inhibited the growth of estrogen receptor (ER) positive breast cancer cells MCF7 with an efficacy superior to that of the reference estrogen receptor modulator tamoxifen, at least *in vitro* (IC_{50} = 3.8 and 18.9 μM for Art-E and tamoxifen, at 72 hours, respectively). Molecular modeling predicted that Art-E can interact directly with the ligand-binding domain of hERα. The docking analysis indicated that Art-E can form more stable complexes with hERα compared to its analogs Art-U, -L, -S, and -T, and artoelastin (Etti et al. 2016). The analog isocyclomorusin is predicted to exhibit an even better binding capacity to hERα than Art-E (Fitriah et al. 2018). Art-E induces caspase-dependent apoptosis of MCF7 cells, associated with elevated production of ROS and an up-regulation of the cyclin-dependent protein kinase inhibitor p21 (Etti et al. 2017b). Similar results have been reported using MDA-MB 231 triple-negative breast cancer cells: up-regulation of p21, G2/M cell cycle arrest, and caspase-dependent apoptosis (Etti et al. 2017c). Binding of Art-E to hERα is entirely plausible but this computational hypothesis has not been validated experimentally. Other targets have been proposed for Art-E, based on *in silico* modeling, such as the inflammatory cytokine-induced ubiquitin-like modifier FAT10 which is known to target hundreds of proteins for degradation by the 26S proteasome. A molecular modeling analysis has predicted that Art-E could bind and inhibit FAT10 implicated in hepatic carcinoma, but here again, there is no experimental validation of this hypothesis (Chaturvedi 2015). In brief, from a mechanistic point of view, Art-E can be considered as a TRAIL regulator in cancer cells, but more work in needed to better evidence the upstream molecular targets. Proteins such as hERα and FAT10 may provide a receptor for the compound but more works are needed to validate these molecular modeling proposals.

DISCUSSION

Artocarpus species have been largely investigated to characterize their pharmacological properties, in line with the traditional medicinal uses of these plants. Thus far, most phytochemical studies have been centered around *A. altilis* and *A. heterophyllus* (Nomura et al. 1998; Sikarwar et al. 2014; Mohammed Haleel et al. 2018; Mainasara and Abu Bakar 2019; Buddhisuharto et al. 2021). The species *A. elasticus* has been less investigated, although this bark-fiber producing plant is used traditionally to treat inflammatory conditions, but also to design crafts, clothes, ropes, and building materials (Veriyan et al. 2019). The phytochemical analysis indicates that like its congeners, *A. elasticus* is rich in prenylated flavones, in particular compounds with a C-3 prenyl side chain, sometimes cyclized into a 5 or 6 membered ring, and occasionally with an additional prenyl chain on ring A or B. These types of C-prenylated flavonoids are frequent in *Artocarpus* species (Šmejkal et al. 2014; Molčanová et al. 2019).

The present analysis sheds light on the artonin group of prenylated compounds and points out the prenylflavone Art-E as an interesting anticancer natural product. Art-E displays a range of pharmacological activities, chiefly antioxidant and anti-inflammatory effects, similar to those reported with the analogous isoprene flavonoid morusin (Choi et al. 2020). It is a potent anticancer agent, inspiring for the design and development of novel anticancer agents. The structural analogy between morusin and Art-E deserves further attention. Morusin has been much more studied than Art-E as an anticancer agent but also for its antiviral and antidiabetic effects (Choi et al. 2020; Kim et al. 2021). The *in vitro* and *in vivo* anticancer effects of morusin have been extensively characterized and the compound appeared promising against cancer stem cells (Zoofishan et al. 2018). We have a lot to learn from morusin to better understand the mode of action of Art-E.

Art-E and related prenylated flavonoids represent interesting anticancer agents, potentially useful to design novel bioactive compounds. Promising data have been reported with morusin-loaded nanoparticles for the treatment of glioblastoma (Agarwal et al. 2019; Zheng et al. 2021) and with artocarpin (Tzeng et al. 2016). A similar potency could be anticipated with Art-E using nanoparticle delivery systems. This compound deserves further attention.

CONCLUDING REMARK

In conclusion, this review exposes the potential health benefit of *Artocarpus elasticus* Reinw. ex Blume used as a traditional medicine in Asia and presents for the first time the complete series of artonin bioactive natural products. An extensive analysis of the scientific information led us to underline the value of the lead compound artonin E for the design of novel anticancer agents. The anticancer properties of Art-E have been well-established, demonstrating its capacity to trigger apoptosis of different types of cancer cells, but additional research efforts are required to better characterize its molecular targets. Another takeaway message is that Art-E can be considered as a morusin derivative, endowed with similar, if not superior, anticancer properties. This isoprene flavonoid warrants further studies.

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