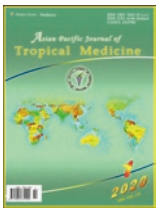

Review Article

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The phytochemical and pharmacological properties of artocarpin from *Artocarpus heterophyllus*

Nik Nurul Najihah Nik Mat Daud[1], Abdi Wira Septama[2✉], Nordin Simbak[1✉], Eldiza Puji Rahmi[3]

[1]*Faculty of Medicine, Universiti Sultan Zainal Abidin, Jalan Sultan Mahmud 20400, Kuala Terengganu, Terengganu, Malaysia*

[2]*Research Center for Chemistry, Indonesian Institute of Sciences, Kawasan PUSPIPTEK Serpong, Tangerang Selatan, Banten 15314, Indonesia*

[3]*Faculty of Medicine, UPN Veteran, Jl. Rs. Fatmawati, Pondok Labu, Jakarta Selatan, 12450, Indonesia*

ABSTRACT

Artocarpus heterophyllus Lam. (Moraceae) has been traditionally used in treating various diseases such as diabetes, diarrhea, malarial fever, inflammation, wound healing and other diseases. Since various bioactive compounds have been found in this plant, this review focuses on the phytochemical and pharmacological properties of a potent bioactive compound artocarpin. Despite its various functions, a mechanistic review on this compound has not been reviewed specifically. Here, pharmacological studies *in vitro* and *in vivo* on artocarpin are discussed thoroughly stressing on anticancer, antimicrobial, anti-tyrosinase, antioxidant and anti-inflammatory aspects of artocarpin. This review would be beneficial for future study to show the competency of natural products for their therapeutic characteristics.

KEYWORDS: *Artocarpus* sp.; Artocarpin; Flavonoid; Pharmacological; Phytochemical

1. Introduction

Natural product derived from plant plays an important role in drug discovery. It has gained an extensive attention for the treatment and managing human ailments such as inflammation, cancers and infectious diseases[1]. It has been reported that large numbers of population in the world particularly in developing countries are prone to rely entirely on herbal plants for medications[2]. In fact, many medicinal plants and their active compounds have been used in the prevention and curing of cancers[3]. Moreover, it is more fascinating that plants supply most of the active ingredients in producing anticancer drugs than using synthetic drugs in chemoprevention therapy[4].

Flavonoid has been used traditionally for a long time, becoming much more demanded throughout the days. Flavonoids belong to the largest secondary metabolites group in the plant kingdom. It is the major class of phytochemicals that is widely found in plants and is classified into 6 groups: flavonols, flavanone, flavolan, flavone, chalcone, and flavon-3-ol. The flavonoid compounds composed of diphenylpropane skeleton which has 2 benzene rings attached by 3 carbon chains and this molecular structure of flavonoid also referred to C6-C3-C6 carbon structure. These compounds composed of more than one of phenolic hydroxyl group and flavonoid consumption can give a favourable impact to health and its pharmacological properties.

Artocarpus is one of the plant genus species which has abundant isoprenylated flavonoids[5]. *Artocarpus (A.) heterophyllus* Lam. is one of the most important plants which has several primary metabolites including carbohydrate, protein, calcium, phosphorus, iron, vitamin A and thiamin[6]. Besides, this plant is also a source of volatile oil and several carotenoid compounds[7,8]. It is reported that *A. heterophyllus* contained various numbers of flavonoid compounds, such as artocarpanone, artocarpin, cycloartocarpin, cyanomaclurin[9]. Other prenylated flavonoids including cudraflavone C, 6-prenylapigenin, kuwanon C, norartocarpin, albanin A, cudraflavone B, and brosimone I, have been identified from the heartwood of *A. heterophyllus*[10]. Interestingly, among

✉To whom correspondence may be addressed. E-mail: abdiwiraseptama@gmail.com; nordinsimbak@unisza.edu.my

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these compounds, artocarpin is the major active compound in *A. heterophyllus*, particularly in the heartwoods[11].

2. Artocarpin

2.1. Phytochemical properties of artocarpin

Various bioactive compounds have been found in this plant and the most potent for anticancer properties is known as artocarpin: $C_{26}H_{28}O_6$ (Figure 1). Artocarpin compound derived from the family of flavonols which has 3-hydroxyflavone backbone. This 3D sugar structure is able to detect different types of sugar efficiently[12–17].

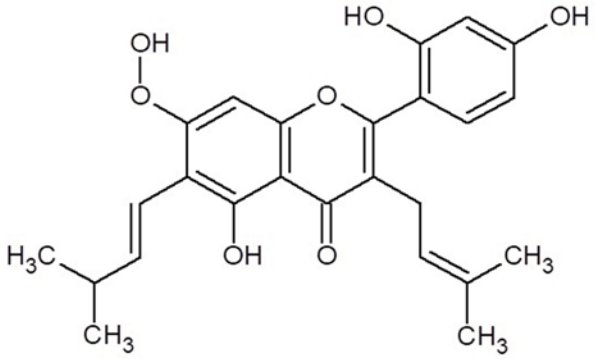

Figure 1. Chemical structure of artocarpin.

2.2. Biosynthesis of artocarpin

According to Das, the flavonoids are produced in plants during photosynthesis[18]. The aromatic amino acids will be synthesized into phenylalanine and tyrosine alongside acetate acid derivatives units[19]. The phenylalanine and tyrosine ammonia lyases convert the phenylalanine and tyrosine into cinamic acid and parahydroxycinnamic acid[20]. The acetate units condense with cinnamic acid to produce cinnamoyl structure of the flavonoids. The cinnamic acid derivatives composed of a diverse of phenolcarboxylic acids which are chlorogenic acid, ferulic acid, and caffeic acid. An ortho-hydroxyacetophenone catalyzed with a benzaldehyde derivative producing chalcones and flavonones[19]. The chalcones (precursors of flavonoids) synthesis through biotransformation process produces several compounds which were cytotoxic to several cancer cell lines[21]. About 110-121 mg of flavonoids is taken every day, which is suggested to be a healthy dosage required for an adult[22]. There are 9 and 12 schemes involved in total syntheses of artocarpin which have been achieved through a linear reaction sequence with the overall yields of 3.5% starting from 1,3,5-trimethoxybenzene[23]. The synthetic route is optimized by TMSI-quinoline as demethylation reagents. This synthetic route is a simple and empirical method for the production of flavonoids with two regioisomeric isoprenyl side chains (Figure 2)[23].

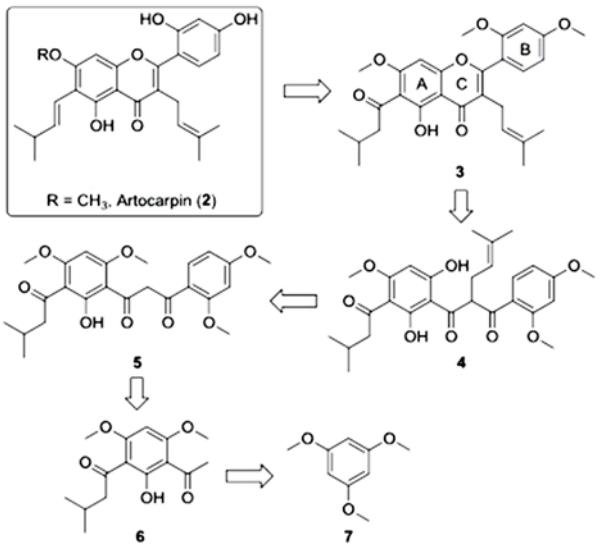

Figure 2. Retrosynthetic analysis of artocarpin[23].

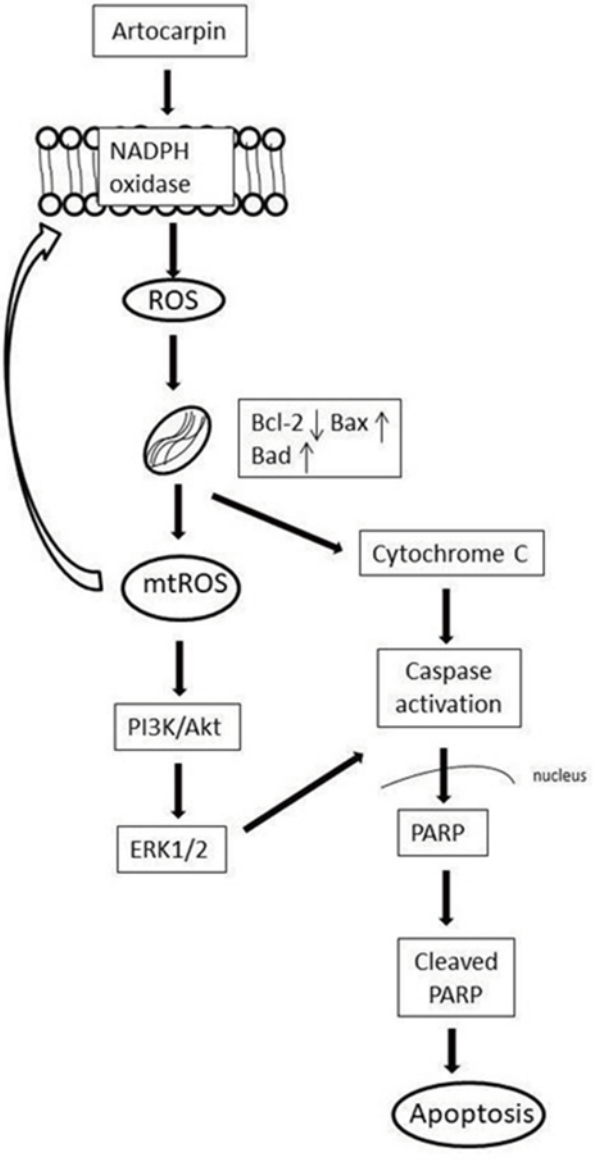

Figure 3. Anticancer activity of artocarpin[37].

2.3. Extraction and isolation of artocarpin

The use of bioactive compounds in different commercial sectors indicates the need of the most proper standard method of extraction. Thoo had listed several factors responsible to investigate the efficiency of extraction which are extraction method, extraction time, temperature, and concentration of solvent[24]. Among conventional methods used, reflux condition is the best method to keep the active ingredient intact. For instance, the high quality content of the sample was obtained using reflux condition before starting the HPLC analysis process[25].

Soxhlation is a continuous and discrete extraction method. The system of soxhlet will run in a continuous mode and will be recirculated through solid sample[26]. In this case, the longer extraction time with soxhlet extraction will degrade the components in it. Microwave assisted extraction, solid-phase micro extraction, accelerated solvent extraction, and supercritical fluid extraction are among the conventional extraction methods that required a greater expenses support while the use of water in a sample can cause a blockage and destroy the extraction process[27-29].

3. Pharmacological properties

Artocarpin is known as a flavonoid compound which is found in *Artocarpus* spp. This compound possesses several pharmacological properties and its biological activities are explained below.

3.1. Anticancer activity

It has been reported that methanolic extracts of *A. heterophyllus* showed cytotoxic effect on MCF-7 and MDA-MB-231 with IC_{50} of 119 μg/mL[30]. Matsuo and the group ensured the cytotoxicity of the extract because of the presence of phenolic groups in flavonoids[31]. The seeds extract of *A. heterophyllus* showed significant of cytotoxicity against the A549 cell line with IC_{50} value of 35.26 μg/mL[32].

Artocarpin exhibited high significant toxic effect against T47D breast cancer cells. This compound promoted an activation of two apical caspases in which both caspase 8 and 10 were engaged in extrinsic death receptor pathway. Activation of caspase 8 was implied by sturdy signal intensity of cleaved-caspase 8 and feeble signal intensity of caspase 10 markers spotted after treatment with artocarpin[33]. In molecular level, artocarpin exhibited extensive biological properties. Hu and his team reported that artocarpin introduced cell death in cancer cells *via* inflection of Akt/mTOR and MAPK route. The binding of artocarpin to FBS proteins can prevent cell consumption and reduce the toxic effect of artocarpin on cancer cells[34].

Furthermore, a study performed by Sun and his colleagues about chemo-preventive activity of artocarpin towards colorectal cancer showed that artocarpin directly attached to Akt 1/2 kinase *via in vitro, ex vivo* binding assay as well as Akt downstream cellular signal transduction. Principally, oral induction of artocarpin has weakened the colorectal colitis in mice. Through the studies on artocarpin, it has been proposed that artocarpin extracts possess the latent qualities to be emerged as therapeutic promoter to impede the tumors growth and cancers[35].

Artocarpin has also been identified as an attributor for tumor inducer p53 through reactive oxygen species (ROS)-mediated MAPKs and activation in non-small cell lung cancer cells[36]. The proposed figure apoptosis pathway induction of artocarpin on U87 cells was showed in a figure *via* caspase activation of caspase and cleavage of Poly (ADP-ribose) polymerase (PARP) (Figure 3). Mitochondrial depolarization causes cytochrome c to be released and antiapoptotic Bcl-2 protein to decrease. The oxidative stress upon artocarpin treatment triggers the production of ROS and cell death induction *via* PI3K/Akt/ERK1/2, which suggested that artocarpin had a high potential as a chemotherapeutic agent to prevent cancer[37]. Recently, reported by Lee and his team, artocarpin enabled to induce apoptosis in osteosarcoma cell in which this activity is associated with increased reactive oxygen species production[38].

3.2. Antibacterial activity

Antibacterial resistance is still a major public health problem in the world. The resistance occurred when there is a change in a bacterium that affects the efficacy of designed drugs[39]. WHO has listed most dangerous antibiotic-resistant bacteria in early 2017 (Table 1)[40]. Therefore, alternative source of antibacterial is needed to explore. It has been reported that artocarpin exhibited strong antibacterial activity against several pathogenic bacteria including *Escherichia coli* and *Pseudomonas aueruginosa* with MIC values in the range of 2-125 μg/mL[9]. Study by Sato *et al*, showed that artocarpin has a potent antibacterial activity against cariogenic bacteria with MIC value of 3.13-12.5 μg/mL. This compound at MIC enabled to inhibit the growth of cariogenic bacteria[41]. Recently, in our previous study on the antibacterial activity of artocarpin against *Streptococcus mutans*, it found that this flavonoid compound demonstrated antibacterial activity with MIC of 1.95 μg/mL. Artocarpin at 2 MIC killed the tested bacteria by altering membrane cells permeability and led to release protein intracellular[42].

In order to overcome resistance problem, an alternative approach that may be applied is the use of drug combination to produce synergistic effect. The synergistic study of artocarpin in

Table 1. List of most dangerous antibiotic resistant bacteria[40].

Critical	High	Medium
Acinetobacter baumannii carbapenem-resistant	*Enterococcus faecium* vancomycin-resistant	*Streptococcus pneumoniae* penicillin-non-susceptible
Pseudomonas aeruginosa carbapenem-resistant	*Staphylococcus aureus* methicillin-resistant, vancomycin-intermediate and resistant	*Haemophilus influenzae* ampicillin-resistant
Enterobacteriaceae, carbapenem-resistant, ESBL-producing	*Helicobacter pylori* clarithromycin-resistant	*Shigella* spp., fluoroquinolone-resistant
	Campylobacter spp., fluoroquinolone-resistant	
	Salmonellae, fluoroquinolone-resistant	
	Neisseria gonorrhoeae cephalosporin-resistant, fluoroquinolone-resistant	

combination with commercial antibiotic has previously been studied. Checkerboard method was used to evaluate the interaction between artocarpin and antibiotic. The result showed that artocarpin increased the antibacterial activity of several antibiotics such as tetracycline, ampicillin, and norfloxacin against MRSA with FIC index in the range of 0.15-0.37. The time-killed assay also confirmed the synergistic effect of these combinations. However, the combination of artocarpin only produced synergistic effect against *Pseudomonas aeruginosa* when combined with norfloxacin[43]. Recently, we also performed the synergistic study of artocarpin in combination with another natural compound. It showed that combination of artocarpin with lawsone methyl ether produced a synergistic effect against MRSA with FIC index of 0.31. The interaction of these compounds in combination enhanced antibacterial effect of each compound by inhibiting the bacterial growth compared to single compound[44].

Whenever the pathogenic bacteria start to induce infections, it overcomes through antibiotics. However, antibiotics can either prevent the bacteria from growth or kill the bacteria. Bacteriostatic antibiotics tend to slow the growth of bacteria by impeding with the differentiation of bacteria including DNA replication, metabolism, and protein production; meanwhile bactericidal antibiotics tend to get rid of bacteria by inhibiting the bacteria from forming a cell wall[45]. Besides, antibiotics can either be broad or narrow spectrum, triggering numerous bacteria in our body. Morphologically, most bacteria have a cell membrane and a cell wall. Gram negative bacteria have a thin coat of peptidoglycan with outer layer of cell membrane while gram positive bacteria have a thick coat of peptidoglycan without cell membrane[46]. The bacterial cell walls have sturdy structures that provide a defensive outer layer around the bacterial cell. When the antibiotics present, the peptidoglycan cannot be cross-linked properly, so the cell wall will rupture. By interrupting the plasma membrane, it causes fast depolarization and membrane damage resulting in protein reduction, synthesis in DNA and RNA which literally caused bacterial cell death[47].

3.3. Tyrosinase inhibitor

Artocarpin is regarded as one of the tyrosinase inhibitors. Tyrosinase is an enzyme involved in melanin biosynthesis and its inhibitors used as hypopigmenting agents[48]. Melanogenesis is the formation process of dark pigment where this dark pigment prevents enough good sunlight from stimulating vitamin D production. As a result, there are some mutations that produce less melanin. Similar to melanogenesis, oxidative polymerization also leads to the browning phenomenon in fruit and fungi. The oxidative polymerization is the loading method in polycondensation[49]. Melanin has a role to play in preserving the skin from UV rays and any harmful effects. The browning occurrences in fruit and fungi are unenviable[50]. Usually, the commercial value of the products will be decreased after browning phenomenon occurs. The phenomenon of hyperpigmentation has triggered researchers to search for tyrosinase inhibitors. Since artocarpin is a flavonoid and tyrosinase inhibitor and it is one of the mechanisms found in flavonoid, artocarpin seems to have a high potential value in anti-tyrosinase inhibition[51].

According to Dej-adisai[52], 3 pure substances including artocarpin, cudraflavone C and artocarpanone were successfully separated and tested for its antityrosinase activity. Artocarpanone tends to exhibit effect of anti-tyrosinase meanwhile artocarpin and cudraflavone C exhibited latent qualities of antibacterial activity on *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Propionibacterium acne* with MIC at 2, 4 and 2 μg/mL, respectively and MBC at 32 μg/mL. In other studies, the antioxidant activity of flavonoid including artocarpin was evaluated using DPPH, ABTS and FRAP assays while the tyrosinase inhibitory activity of all compounds was tested against mushroom tyrosinase. This study revealed that flavonoids isolated from *A. lowii* might be beneficial in the development of antioxidant and anti-tyrosinase agents[53].

3.4. Antioxidant activity

Antioxidants are molecules that help to detain, avert or abolish oxidative stress by unsteady molecules that can cause distress to cellular structures. Rakesh and his team[54], has reported that the artocarpin was commonly used in treating chronic conditions. Since herbal plant consists a wide variety of organic compounds that have synergistic effect, the suppression of new vasa vasorum through multi-step process which can affect all mode of action and the interaction of cancer cells with the immune system[55].

The mode of action of artocarpin includes direct inhibiting of ROS[56] and obstruction of oxidases generating superoxide anion[57,58], followed by stimulation of enzymes[59–61], chelating trace metals[62] and reduction of oxidative stress[63]. In the study of pre-analysis of latent characteristics of *A. heterophyllus* shell powder, phenolic and flavonoid compounds showed the highest percentage amount present in plant with (0.21±0.012) mg GAE/g (pulp), 27.7 mg GAE/g (seed) and (10.5±0.21)/mg 100 mg (pulp), 1.20 mg of RE/g (seed), respectively. These results showed that the shell of *A. heterophyllus* plant also displayed a highly significant of antioxidant and scavenging activity[64].

Selection of extraction method plays an important part in extracting antioxidant compound[65–67]. In another study of different extraction methods on *A. heterophyllus* fruit performed by Daud[68], it is interesting to note different extraction methods produced yield in different amounts of antioxidant. Despite the conventional method of soxhlet and percolation, maceration seems to exhibit the highest antioxidant activities compared to the other two extraction methods.

3.5. Anti-inflammatory activity

Artocarpin from *A. communis* has a potential in anti-inflammation activity. Previously, Lee and his team assessed the photoprotective properties of artocarpin using hairless mice on UVB-induced skin damage. Here, artocarpin showed a photoprotective effect by decreasing histopathological changes at topical dose of 0.05% and 0.1%. Artocarpin also exhibited the decrease in the level of TNF-α and IL-β for reducing the response of a stimulus from the inflammation protein. The result showed that no skin damage occurs upon artocarpin treatment due to its antioxidant anti-inflammation properties[69]. In our previous study, it has been shown the potency of flavonoid compounds including artocarpin to modulate activity of human phagocyte cells. Artocarpin exhibited anti-inflammatory activity by inhibiting ROS production and chemotaxis of phagocyte cells. Interestingly, this compound also showed strong inhibiting myeloperoxidase activity with IC_{50} which was higher than indomethacin as positive control[11].

Artocarpin with 90% w/w content in extract has been assessed for its antioxidant properties and fibroblasts with UV A-irradiation, its capability in restoring type Ⅰ collagen, and inhibition of elevation of the metalloproteinase-1 matrix. Previously, the extract with 45% w/w artocarpin exhibited the antioxidant activity, antimelanogenesis and restoration of fibroblasts of the wrinkled skin[70,71]. The result showed that extract containing 90.6%±5.1% w/w artocarpin had a free radical scavenger activity with EC_{50} of (116.0±5.1) μg/mL at 0.625-50 μg/mL. This is a total lack of toxicity towards fibroblast of human skin. Furthermore, the extract suppressed the UVA-induced metalloproteinase-1 matrix expression and promoted the synthesis of type Ⅰ procollagen. The extract facilitated epidermal thickening followed by increased type Ⅰ procollagen synthesis and deposition in the dermis in aged skin from donor with a history of solar exposure. These mechanisms were close to those of all-trans retinoic acid which suggested that the extract could be used to recover aging skin[72].

4. Conclusions

In this mini review, the pharmacological properties of artocarpin have been briefly explained. This review was made based on current available data and from the data obtained, we consider that artocarpin has a lot of things to be offered and mechanism underlies on its anticancer, antibacterial, antioxidant, and anti-inflammatory properties need to be further explored. Even though lots of studies have been done on artocarpin, more clinical studies need to be done in the future to investigate in more details on its toxicity study.

Conflicts of interest statement

The authors declare that there are no conflicts of interest.

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Authors' contributions

NNN conducted the research and drafted the manuscript. AWS is the leader who is editing the manuscript. NS contributed the idea and reviewed the manuscript. EPR is a member who contributed in the design.

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