Chemical constituents and biological activities of *Artocarpus heterophyllus* lam (Jackfruit): A review

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Abstract

*Artocarpus* (Moraceae) is a deciduous tree with appreciable importance as a source of edible fruit and is widely used in folk medicines. The extracts and metabolites of *Artocarpus heterophyllus* particularly those from leaves, bark, stem and fruit possess several useful bioactive compounds. This review intends to compile various studies on *A. heterophyllus* and critically evaluates its ethnomedical and ethnopharmacological properties. Several pharmacological studies from *A. heterophyllus* have conclusively established their mode of action in anti-inflammatory, antimicrobial, antioxidant and anticancer activities. Based on the available data, it is concluded that *Artocarpus* as a promising source of useful products and opens up new avenues for novel therapeutics.

Introduction

*Artocarpus heterophyllus* Lam (Jackfruit), belonging to the family Moraceae is distributed through tropics and subtropics. The tree has a straight rough stem and a green or black bark exuding milky latex. The leaves are broad, elliptic, dark green in colour and alternate. Jackfruit flesh and seeds contain more protein, calcium, iron, and Thiamine [1]. Jackfruit contains many classes of phytochemicals such as carotenoids, flavonoids, volatile acids sterols, and tannins, with varying concentrations. The exceptional medicinal value of *Artocarpus* has long been recognized.

Various parts of the tree such as seeds, leaves, latex, roots have been used as traditional medicines. Jackfruit is a rich source of phenolics and flavonoids having good antioxidant properties [2,3]. Jackfruit pulp is rich in carbohydrates, protein, amino acid, polyphenol, fatty acid, vitamin and minerals, which can be used as good sources for some important nutrients [4-7]. Jackfruit peel extract contains phenolics, flavonoids in which prenyllflavonoids, hydroxycinnamic acids and glycosides are the predominant bioactive compounds. Leaves are leaves are rich in phenolic acids, flavonoids, terpenoids, stilbenoids [8] and used for asthma, diarrhea, anemia and dermatitis treatment [9]. Wood and bark of this plant are rich sources of prenylated flavonoids, stilbenoids, triterpenoids, and steroids [10]. This review aimed to summarize the biological activities of bioactive compounds from various parts of *A. heterophyllus* reported in earlier studies.

Sources and methodology

The search was done in electronic databases of PubMed, Scopus, ScienceDirect, Web of Science and Google Scholar for studies using the key terms: *Artocarpus heterophyllus*, jackfruit, anticancer, antimicrobial, anti-inflammatory and bioactive compounds. The inclusion was based reported articles on biological activities of *A. heterophyllus* which are discussed in detail. All the data were extracted and explained in respective subheadings.

Phytochemicals

Tetracyclic triterpenoids, 9,19-cyclolanost-3-one-24,25-diol and 9,1-cyclolanost-3-one-24, 25diol along with cycloartenone and cycloartenol have been isolated by Barik, et al. [11]. Yuan, et al. [12] isolated flavonoids such as Artoheteroids A-D, morin, artocarmin A, albanin A, euchrenone A, norarthocarpanone and steppogenin from *A. heterophyllus*.

A new prenylated flavonoid, 3-prenyl luteolin (1) was isolated from *A. heterophyllus* wood extract [13]. In another study, an 2-arylenzofuran derivative, artocarstilbene B and
benzaldehyde derivative, \((E)-3,5\text{-dihydroxy-4-}\{3\text{-methylbut-1-}\text{enyl}\}\)benzaldehyde were obtained from the leaves of *A. heterophyllus* [14]. Liu et al. [15] isolated seven prenylated chromones and five prenylated flavonoids, including two new prenylated chromones, artoheterophelines A and B. Zheng et al. [16] isolated new phenolic compounds, artoheterophyllins E-J, 4-geranyl-2',3',4',5-tetrahydroxy-cis-stilbene, and 5-methylxomicran. Also 2 new natural compounds, 2,3-dihydro-5,7-dihydroxy-2-(2-hydroxy-4-methoxyphenyl)-4H-benzopyran-4-one and 6-\{(1S,2S)-1,2-dihydroxy-3-methylbutyl\}-2-(2,4-dihydroxyphenyl)-5-hydroxy-7-methoxy-3-(3-methyl-2-buten-1-yl)-4H-1-benzopyran-4-one were also isolated from the ethanol extract of *A. heterophyllus* wood. In the earlier studies, Zheng et al. [17] isolated furanoflavanone,7-(2,4-dihydroxyphenyl)-4-hydroxy-2-(2-hydroxypropen-2-yl)-2, 3-dihydrofuro\(\{(3, 2-g)\}\)chromen-5-one, together with 14 known compounds, dihydromorin, steppogenin, norartocarpin, artocarpapone, artocarpesin, artocarpin, cycloartocarpin, cycloartocarpesin, artocarpentin, brosimone I, cudraflavone B, carpachromene, isoartocarpesin, and cyanomadurin were isolated from the wood of *A. heterophyllus*.

Zheng et al. [18] isolated phenolic compounds, including one isoprenylated 2-arylbenzofuran derivative, artoheterophyllin A, and three isoprenylated flavonoids, artoheterophyllin B, artoheterophyllin C, and artoheterophyllin D from the ethanol extract of the twigs of *A. heterophyllus*. Fu et al. [19] purified artocarheretones A-E from the ripe fruits of *A. heterophyllus*. In a study by Septama et al. [20], dihydromorin and norartocarpetin were isolated from *A. heterophyllus* heartwoods.

**Anti-inflammatory**

Extracts of jackfruit pulp showed anti-inflammatory activity by suppressing the lipopolysaccharide (LPS)-induced production of nitric oxide and prostaglandin E2 reactive oxygen species in RAW264.7 cells [21]. Similarly, prenylated chromones from *A. heterophyllus* exhibited significant inhibitory activities against nitric oxide production showing IC\(_{50}\) values in range of 0.48 to 19.87 \(\mu\)M [15]. Artoheterohoid displayed inhibitory effects against nitric oxide production with the IC\(_{50}\) values in the range of 0.72 to 5.93 \(\mu\)M [22]. Artocarpapone and artocarpin strongly inhibited myeloperoxidase activity of human phagocytes with an IC\(_{50}\) value of 23.3 \(\mu\)M and have potential to be developed into potent anti-inflammatory agents [23]. Meera et al. [24] studied the anti-inflammatory effect of ethanolic extracts of spine, skin and rind of jack fruit. The results revealed that skin extract exhibited maximum anti-inflammatory activity, rind had preferential inhibition on Cyclooxygenase-2 and spine and skin inhibited both Cyclooxygenase-1 and 2 in vitro.

Moracin significantly inhibited lipopolysaccharide-activated reactive oxygen species and nitric oxide release without marked cytotoxicity [25]. Furthermore, it effectively reduced LPS stimulated up-regulation of mRNA and protein expression of inducible nitric oxide synthase, cyclooxygenase-2 and serval pro-inflammatory cytokines, interleukin-6 and tumor necrosis factor \(\alpha\). The administration of jackfruit leaves extracts to streptozotocin-diabetic rats significantly reduced fasting blood glucose from 200 to 56 and 79 mg%, respectively; elevated insulin from 10.8 to 19.5 and 15.1 \(\mu\)U/ml, respectively; decreased lipid peroxides from 7.3 to 5.4 and 5.9 nmol/ml, respectively; decreased %glycosylated hemoglobin A1C (%HbA1C) from 6.8 to 4.5 and 5.0%, respectively; and increased total protein content from 2.5 to 6.3 and 5.7 mg%, respectively [26].

**Antioxidant activity**

Jackfruit contains many carotenoids including all-trans-\(\beta\)-carotene with an important antioxidant activity for human health [27,28]. Jackfruit exhibited not only free radical scavenging activities but also acted as a significant protective agent against H2O2 + UV and \(\gamma\)-irradiation induced DNA damage [29]. Zhu et al. [30] found polysaccharide from jackfruit pulp as a dietary source of antioxidant phytochemicals that survive the gastrointestinal digestion process. The authors also showed that jackfruit pulp exhibited strong DPPH and OH radical scavenging activities, with a relatively lower reducing power [31]. Similarly, ethyl acetate fraction of jackfruit showed radical scavenging activities between 80% - 94% inhibition due to the presence of phenolic compounds [32]. Another study revealed that protocatechuic acid and chlorogenic acid in rind and rachis extracts of jackfruit contribute to the antioxidant activity [33]. Whereas, Ko et al. [34] reported flavonoids from the leaf, root and bark methanol extracts of *A. heterophyllus* contributed significantly to the antioxidant activities.

Antioxidant activities of non-extractable polyphenols from jackfruit pulp were tested by ABTS+, oxygen radical scavenging activity and peroxy radical scavenging ability assays [35]. The results indicated that polyphenols recovered from alkaline hydrolysis showed the most scavenging abilities. Biworo et al. [36] reported that jackfruit extract exhibited antioxidant activities by decreasing the formation of reactive oxygen species. Leaf extracts of *A. heterophyllus* showed significant antioxidant activity tested in DPPH, ABTS, FRAP and Fe\(^{2+}\) chelating activity assays [37]. In DPPH assay, *A. heterophyllus* total extract exhibited a strong antiradical activity with an IC\(_{50}\) value of 73.5 \(\mu\)g/ml while aqueous fraction exerted the highest activity in FRAP assay (IC\(_{50}\) value of 72 \(\mu\)g/ml). Jagtap et al. [2] showed jackfruit pulp extract has higher ability to reduce DPPH, Fe\(^{2+}\) to Fe\(^{2+}\) and N,N-dimethyl-p-phenylenediamine in vitro.

**Antimicrobial activity**

Jackfruit leaves exhibited antifungal activity against *Colletotrichum gloeosporioides* and *Penicillium italicum* due to the presence of quinic acid, catechin and chlorogenic acid [9].
In another study, butanol fractions of the root bark and fruits exhibited a broad spectrum of antibacterial activity [38]. Antimicrobial activity of protease from jackfruit latex was evaluated by Siritapetawee, et al. [39] and the results revealed that it could inhibit the growths of Pseudomonas aeruginosa ATCC 27853 and Candida albicans at minimum inhibitory concentration of 2.2 mg/ml and minimum microbicidal concentration of 8.8 mg/ml. Similarly, antifungal activity of A. heterophyllus latex against post-harvest fungal pathogens was reported by Sibi, et al. [40]. Dihydromorin had a strong effect against Streptococcus pyogenes with MIC and MBC values of 15.62 and 31.25 μg/ml, respectively [20].

In a study by Septama and Panichayupakaranant [41], antibacterial compounds such as cycloartocarpin, artocarpin, artocarpanone and cyanomaclurin were isolated from heartwood of A. heterophyllus. The compounds exhibited the strongest antibacterial activity Streptococcus mutans, S. pyogenes, Bacillus subtilis, Staphylococcus aureus and S. epidermidis with MICs of 4.4, 4.4, 17.8, 8.9 and 8.9 μM, respectively and MBCs of 8.9, 8.9, 17.8, 8.9 and 8.9 μM, respectively. The authors also reported that artocarpin showed antibacterial activity against methicillin-resistant Staphylococcus aureus with MIC and MBC value of 62.5 μg/ml, and against P. aeruginosa with an MIC value of 250 μg/ml. The authors also also investigated the activity of artocarpanone against diarrheal pathogenic bacteria including Escherichia coli, Vibrio cholera, Shigella sonnei, Salmonella typhimurium, and S. typhi. Artocarpanone displayed strong antibacterial activity against E. coli with MIC and MBC value of 3.9 and 7.8 μg/mL, respectively by altering membrane cell [42].

A. heterophyllus leaves extracts exhibited minimum inhibitory concentration in the range of 221.9-488.1 μg/ml against E. coli, Listeria monocytogenes, Salmonella typhimurium, Salmonella enterica, Bacillus cereus, Enterococcus faecalis and Staphylococcus aureus [37]. Chromones from A. heterophyllus fruits showed remarkable anti-HIV-1 effects with EC50 values ranging from 0.09 to 9.72 μM [19].

**Anticancer activity**

Swami, et al. [7] reported about the dietary supplementation with jackfruit pulp may help to prevent and control the development of certain cancers. Organic extracts obtained from jackfruit pulp reduced the number of revertants caused by aflatoxin B1 (AFB1) and proliferation of cells M12. C3.F6 [43]. Bioactive compounds from A. heterophyllus leaves showed inhibitory activity against the proliferation of the PC-3, NCI-H460, and/or A549 cancer cell lines [14]. Anticancer effects of the isolated phenolic compounds were examined in MCF-7, H460, and SMMC-7721 human cancer cell lines by Zheng, et al. [16]. The compounds exhibited IC50 Values of 15.85 and 12.06 μM in MMC-7721 cell line and IC50 value of 5.19 μM in NCI-H460 cell line.

Apigenin C-glycoside identified as 2"-O-β-D-xylosylvitexin showed good antiproliferative activities against HepG2 and MCF-7 cells in the range of 0–400 μM. The IC50 values were 38.5 and 29.6 μM to HepG2 and MCF-7 cells, respectively [44]. Arung, et al. [45] reported that artocarpin caused a reduction of cell viability in a concentration-dependent manner and an alteration of cell and nuclear morphology on human T47D breast cancer cells. Moreover, the percentage of the sub-G1 phase formation was elevated dose-dependently. Artocarpin induced activation of caspase 8 and 10 as indicated by stronger signal intensity of cleaved-caspase 8 and weaker signal intensity of caspase 10 markers detected after artocarpin treatment. Jackfruit seeds extract was effective in cancer cell lines like T47D, TH29 and B16F10 [46]. IC50 obtained from extracts was 46.67 μg/ml of chloroform extract in T47D cells, 23.42 μg/ml of Ethanolic extract in HT29 cells, and 74.31 μg/ml of ethyl acetic extract in B16F10 cells.

In a study by Sun, et al. [47], artocarpin impaired the anchorage-independent growth capability, suppressed colon cancer cell growth, and induced a G1 phase cell cycle arrest which was followed by apoptotic as well as autophagic cell death. Mechanistic studies revealed that artocarpin directly targeted Akt 1 and 2 kinase activity evidenced by in vitro kinase assay, ex vivo binding assay as well as Akt downstream cellular signal transduction. Recently, A. heterophyllus exhibited significant biological activity towards many types of both normal and cancerous cells [48]. In melanin formation inhibition on B16 melanoma cells, 3-prenyl luteolin exhibited IC50 of 56.7 μM with less cytotoxicity [45] thus making it a promising compound that could be useful for treating hyperpigmentation, as a skin-whitening agent. Heterophyllene C from this tree exhibited cytotoxicity against the MCF-7 cell line with an IC50 value of 12.56 μM [49]. Additionally, norartocarpin and artocarpin showed cytotoxic activity against MCF-7 and KB cell lines with IC50 values of 10.04 and 13.57 μM, respectively.

**Anti-osteoporotic activity**

Cathepsin-K (Cat-K) is known to play a pivotal role in osteoclast-mediated bone resorption and is evidenced as an important target for the treatment of osteoporosis. Flavonoids from A. heterophyllus found to have suppression capabilities against Cat-K with IC50 values ranging from 1.4 to 93.9 μM [12].

**Other Pharmacological activities**

Tyrosinase inhibitory activity of morachalcone A from wood of A. heterophyllus was determined by Nguyen, et al. [50]. Similarly, bioactive compounds from A. heterophyllus wood showed strong mushroom tyrosinase inhibitory activity with IC50 values lower than 50 μM, more potent than kojic acid, a well-known tyrosinase inhibitor [17]. It was also found that norartocarpetin and artocarpesin in the twigs and woods of A. heterophyllus, contributed to the tyrosinase inhibitory activity [18].

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α-glucosidase inhibitors are suppressor of postprandial hyperglycaemia in diabetic mellitus patients by inhibiting the activity of α-glucosidase in the intestine, this reduces glucose absorption by delaying carbohydrate digestion and increases digestion time [51]. In another study, extracts of jackfruit peel, pulp, fruit flake and seeds were capable of inhibiting the α-glucosidase activity which was correlated with total phenolic content [4]. α-amylase inhibitors contain substances that prevent dietary starch from being absorbed into the body system, which may be useful in the management of diabetes [52]. Ethanolic extract of A. heterophyllus stem bark was observed to show inhibitory activities on α-amylase and α-glucosidase with IC$_{50}$ of 4.18 and 3.53 mg/ml, respectively [53].

**Conclusion**

There are many studies that have focused on biological activities of *A. heterophyllus* and the results devoted for discovering possible bioactive compounds with potential lead compounds. Active compounds from parts of *A. heterophyllus* could be considered as potential drugs for the further development novel drugs. The evidence presented in this review suggests the potential of *Artocarpus* as source of useful products and opens up new avenues for novel therapeutics.

**References**


