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Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

REVIEW ARTICLE BIOSCIENCE RESEARCH, 202219(4):1976-1985. **OPEN ACCESS**

Bioactive compounds, Potential nutraceutical and Biopharmaceutical values of Jackfruit (*Artocarpus heterophyllus* Lam.): A Critical Review

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Artocarpus heterophyllus Lam. is an endemic plant that grows in subtropical and tropical regions of the world such as Western Ghats of India, Africa, Asia and South America regions. It is an evergreen fruit tree which is belonging to the Moraceae family, with the fruits being consumed in our daily diets. Being one of the well-known world's largest tree-borne fruit, the jackfruit has been confirmed to hold several health benefits and this species has been reported to have a wide variety of secondary metabolites such as phenolics, flavonoids, terpenoids, alkaloids, saponins, tannins, steroids and glycosides. Several parts of jackfruit tree including the leaves, stem bark and fruits have been used extensively in traditional folk medicine for the treatment of rheumatoid arthritis, anticancer, anti-inflammatory, anti-diabetic, antimicrobial, wound healing and anti-carcinogenic. The present review makes an attempt to highlight the nutraceutical and biopharmaceutical potential of this evergreen tree, with special emphasis on the phytochemical constituents in this plant species.

Keywords: ***Artocarpus heterophyllus,*** **secondary metabolites, phenolics, antidiabetic, biopharmaceutical**

INTRODUCTION

Artocarpus heterophyllus Lam., or commonly known as jackfruit is part of the Moraceae family and categorized as a non-seasonal fruit. Jackfruit is considered to be originated in the rainforest of India and Southeast Asia which is later spread to other countries such as Indonesia, Brazil, and Australia. Jackfruit known by various names, such as Nangka in Malaysia and Philippines (Debbarma et al. 2021), Mit in Vietnam and Khanun in Thailand. This fruit is considered as cheap and sustainable carbohydrate source since it is widely cultivated in Asia, Caribbean and Americas. In Malaysia itself, jackfruit cultivation covers almost 77% of the area involving five states, namely Johor, Pahang, Perak, Kedah and Terengganu (Zhang et al. 2021). The jackfruit is relatively large in size when compared to other fruits and has many fruits (syncarp) with green to yellow skin.

In India, jackfruit is known as the "poor food" which is available all seasons and contributes to the food supply of people and their livestock during short supplies of staple food and grains. From researchers' findings, it was found that jackfruit is a beneficial fruit due to bioactive constituents present. Seeds and aril which are usually considered as waste products from jackfruit are also found to be nutritious if eaten (Sreeletha et al. 2018). For instance, the vitamins that was found in jackfruit are retinol (A), thiamine (B1), riboflavin (B2) and ascorbic acid (C) while the minerals are potassium, phosphorus, calcium, and iron which corresponding in strengthening the immune system against diseases, in addition to maintaining healthy eyes and skin. Conventionally, some parts of the plant have been used in traditional medicine preparations in Southeast Asia to treat common diseases related to high blood pressure, diabetes, diarrhoea, inflammation, fever, liver cirrhosis, ulcers, wound, malaria and tapeworm infection (Ahasan et al. 2021; Palamthodi

et al. 2021). For example, the leaves are useful in skin diseases such as boils, wound and in the treatment of high fever. The ripe fruits are cooling, aphrodisiac, laxative and have been used in traditional folk medicine as a brain tonic, meanwhile the young fruits are pungent, astringent and useful in relieving flatulence (Mall, 2017).

Jackfruit morphology

Jackfruit tree is an evergreen tree with medium size up to 8-25 m height. The tree is easy to grow with the initial height can reach up to 1.5 m/year. When the tree was reached the maturity level, the growth become slow with the rate of 0.5 m/year. The tree is straight, has rough stem and brown-black skin colour with the tendency of producing milky latex (Sibi et al. 2021).

Leaf

The jackfruit leaves are broad, elliptical, dark green and arranged alternately. The male head is usually sessile or on a container of short peduncles and is sometimes born on the main twig, while the female head is a long ovoid container.

Fruit

Jackfruit is a dicotyledonous compound fruit, which is found on the side branches and branches of the main tree. The fruit is cylindrical in shape between 22 to 90 centimetres long with a diameter of 13-50 centimetres. The weight of the fruit varies depending on the cultivation factor. Usually, sizes between 2 to 20 kilograms and some even reaching 50 kilograms have been recorded. Ripe jackfruit consists of 29% pulp, 12% seeds, and 54% rind.

Seed

Jackfruit seeds have a light brown colour, long shape with a size of 2-3 cm and a diameter between 1 to 1.5 cm. The seed is surrounded by flesh and white arils was covered surround the thin brown spermoderm, which cover the fleshy white cotyledons. The seeds rich in carbohydrates and proteins. Each jackfruit contains 100-500 seeds depending on the size (Swami & Kalse, 2019).

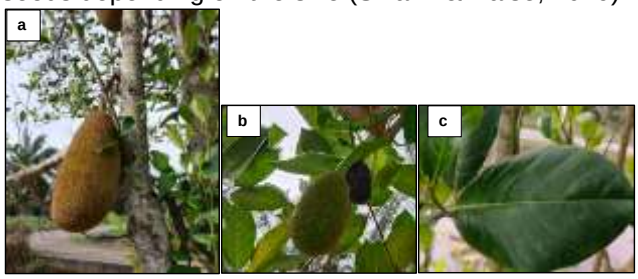


Figure 1: A jackfruit tree (a) Jackfruit tree with the fruit; (b) the flower buds of jackfruit; (c) the jackfruit leaves

Nutritional and health benefits of jackfruit

The phytonutrients content in either edible or inedible parts of *A. heterophyllus* plant plays a crucial role in human health. The high fibre content at 3.6g/100g helps in improving the digestion system and enhances the bowel movements (Ahasan et al. 2021). Examples of available sources are vitamins such as A, C, thiamine, riboflavin, niacin and minerals such as calcium, potassium, iron, sodium and zinc (Das & Saha, 2020). The mean proximate content (%) of raw *A. heterophyllus* seeds (without any treatment) was indicate; protein (15.88 ± 0.08), fibre (10.04 ± 0.09) ash (5.05 ± 0.07), moisture (29.25 ± 0.35), fat (10.26 ± 0.35) and carbohydrate (29.52 ± 0.4) (Ezim et al. 2020). According to a previous study conducted, the maximum sugar is 21%, carbohydrate is 31%, and protein is 2.3%) content in pieces of Valayan, Mondan, and Nettadivarika varieties, respectively (Sreeja et al. 2021). It is said that in *A. heterophyllus* seeds there is 31.1% protein, 66.2% carbohydrate and 1.3% crude lipid. The compound is very good for such health helps prevent constipation, a good source of protein with high solubility can help to prevent mental stress (Maurya, 2016). *A. heterophyllus* has a high fiber content of 3.6g/100g. Daily intake of *A. heterophyllus* can smooth out the digestive system through bowel movements and protect the large intestine by removing carcinogenic chemicals. Ripe *A. heterophyllus* is quickly damaged if not preserved in the right way. To avoid wastage, processing techniques such as drying, freezing, canning or by turning them into various products such as dehydrated raw *A. heterophyllus* slices, candy, jam and jelly can increase the shelf life of *A. heterophyllus* products. It also makes its availability out of season (Ranasinghe et al. 2019).

Vitamin of B-complex, fiber and starch resistant that found in *A. heterophyllus* seeds have potential to reduce risk of heart disease, prevent constipation, control blood sugar and encourage weight loss (Roji et al. 2019). *A. heterophyllus* is also rich in potassium which can synchronize blood pressure, reducing the risk of heart attack or stroke (Parihar et al. 2021). *A. heterophyllus* has physicochemical such as amylose content, thermal properties, morphology, particle size, crystalline structure, pasting properties, swelling power, freeze-thaw stability, and gelation that potentially be used as an alternative starch in a wide range of food products (Wong et al. 2021). The increment in hydrophobicity exposure is due to the process of adsorption between oil and air in proteins. This will produce proteins with good solubility and provide high adsorption rates, emulsion stability and increased activity (Resendiz-Vazquez et al. 2019). Ahasan et al. in 2021 has reported that the jackfruits have been contributing to about 4% of human nutritional requirement due to the enrichment of nutrients in fruit.

Phytochemical compositions

According to previous qualitative analysis on the *A. heterophyllus* plant, many class of phenolic compounds, such as prenylated flavonoids, flavanones, flavones, xanthones, chalcones and alkaloids have been reported to

be present in the plant extracts (Liu et al.2020; Ye et al. 2019; Septama et al. 2018; Bhat et al. 2017 and Yuan et al. 2017). Tetracyclic triterpenoid compounds such as 9,19-cyclolanost-3-one-24,25-diol (24 *R*), 9,19-cyclolanost-3-one-24,25-diol (24 *S*), cycloartenone, and cycloartenol, were also previously reported from the ether extract of dried latex of this plant (Barik et al. 1994).

The chemical constituents in *A. heterophyllus* may also vary depending on the cultivation locations and plant variety. The fruit is rich in amino acid such as histidine, arginine, lysine, tryptophan, leucine, cysteine, free sugars (sucrose), fatty acids and ellagic acid (Swami & Kalse, 2019). The bark of the main stem contains the betulinic acid and two flavone pigments namely cycloheterophylline and heterophylol (Prakash et al. 2009; Chowdhury et al. 1997). Phytochemical screening on the leaves and stems of *A. heterophyllus* have shown the presence of sapogenins, cycloartenon, cycloartenol, β-sitosterol, and tannins which giving the estrogenic activity. Another two new prenylated chromones were also being isolated and characterized by other researchers, namely artoheterophines A and B, respectively together with another five known prenylated flavonoids and five known prenylated chromones. The five prenylated flavonoids are known as 2-(4-hydroxy- phenyl)-8-(3-methyl-but-2-enyl)-chroman-4-one, bracteflavone B, dinklagin C, 6-(3-methyl-(*E*)-1-butenyl) chrysin and 5,7,3′,5′-tetramethoxy-6-*C*-prenylflavone. Meanwhile, the prenylated chromones are cnidimol D, ficuformodiol B, harperamone, perforatin B and 5,7-dihydroxy-8-[(2*E*)-4-hydroxy-3-methylbut-2-enyl]-2-methyl-4H-1-benzopyran-4-one (Liu et al.2020).

Two novel flavanones namely 5-hydroxy-7,2′,4′,6′-tetramethoxyflavanone and 8-(γ,γ-dimethylallyl)5-hydroxy-7,2′,4′,6′-tetramethoxyflavanone together with the known cycloartenone, betulinic acid, β-sitosterol, tannins, lupeol and ursolic acid were also previously found in the roots of *A. heterophyllus* (Prakash et al. 2009; Barik et al. 1994; Chai-Ming & Chun-Nan, 1993). Yuan et al. in 2017 isolated four new flavonoids from the roots of *A. heterophyllus* namely artoheteroids A-D, together with six known ones such as artocarmin A, albanin A, euchrenone A, norartocarpanone, morin and steppogenine. Some of the isolated new compounds possessed the inhibitory effect against Cathepsin K (CatK) which is the promising therapeutic agent for osteoporosis. The major protein namely jacalin, which is a tetrameric two-chain fixture that combines with heavy chain of 133 amino acid residues was also found in the *A. heterophyllus* seeds (Ranasinghe et al. 2019). The jacalin is representing over 50% in seed and capable of binding to human IgA1 and T-Antigen (Phukan et al. 2018). However, the jacalin content is depends on the growth stage where the matured *A. heterophyllus* seed containing more protein constituents and vice versa (Dhierllate et al. 2020).

Previous communications on phytochemical content of *A. heterophyllus* have also reported the presence of phenolic acids such as tannic, ferulic, and gallic acid. During ripening process, the concentration of gallic acid was increased and resulted in decreasing of ferulic acid. Thus, the unique profile from phytochemical analysis of jackfruit is highly recommend because it has ability in promoting good health (Anaya-Esparza et al. 2018). Table 1 below summarizes some of chemical compounds present in this plant species.

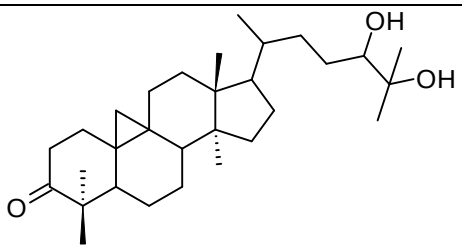
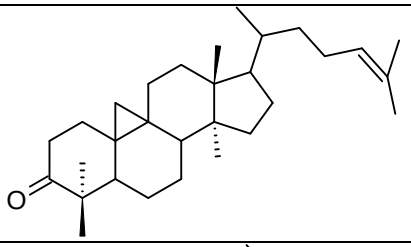
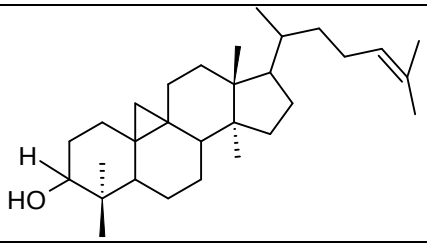
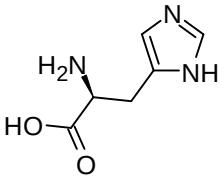
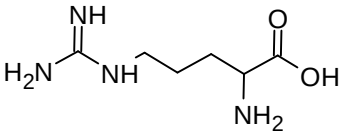
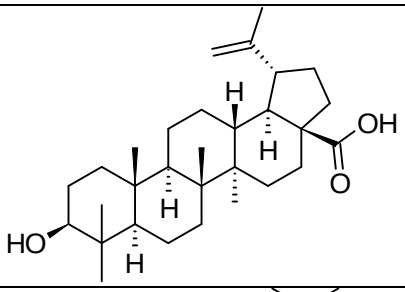
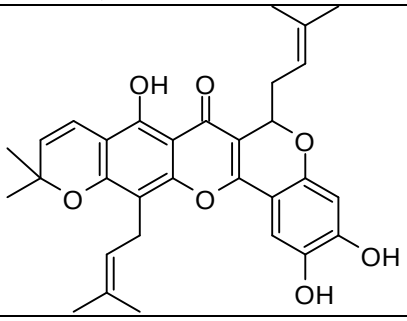
Pharmacological activities

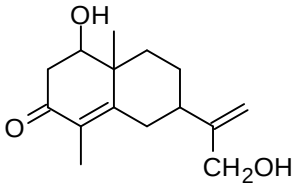
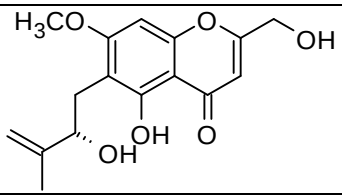
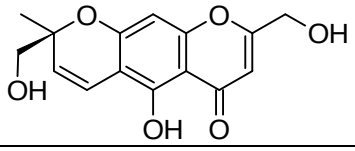
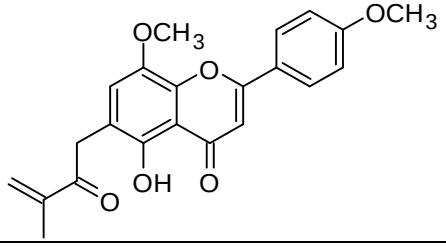
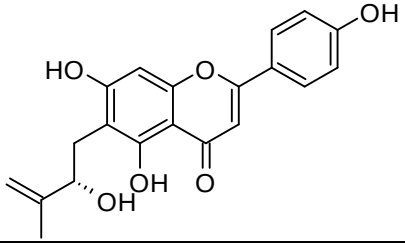
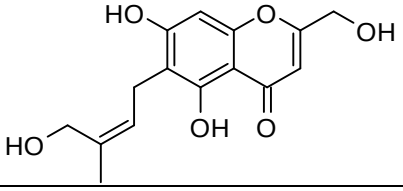
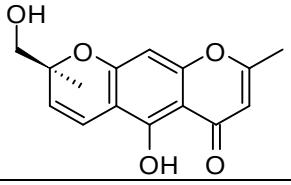
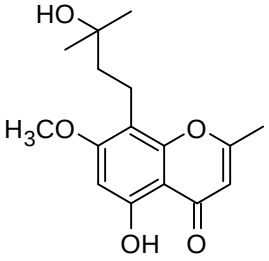
A. heterophyllus preparations have also been cited in scientific literature as having a wide range of pharmacological properties due to the presence of phytonutrients such as proteins, vitamins, carbohydrates, minerals, organic acids, fatty acids, carotenoids, flavonoids, lectins, volatiles, and tannins. Each of these phytonutrients has their respective functions in lowering the blood pressure and healing stomach ulcers. Other phytonutrients in *A. heterophyllus* such as saponins, isoflavones, and lignans have been reported to possess anticancer, antiulcer, and anti-aging properties. Other bioactive constituents that commonly found in*A. heterophyllus* are alkaloids, flavonoids, carbohydrates, proteins and triterpenoids (Srivastava and Singh, 2020). Aluminum chloride is a commonly used method to screen the flavonoid content in the plant extract. In *A. heterophyllus* seed, the flavonoid content was found to be is higher in germination seed compared to non-germination seed (Sivaranjini & Abarajitha, 2020).

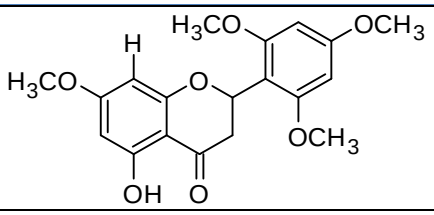
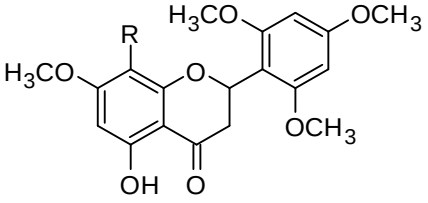
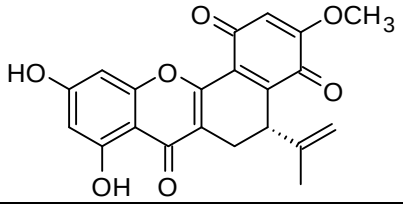
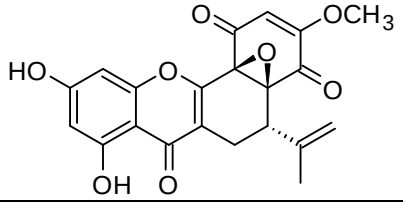
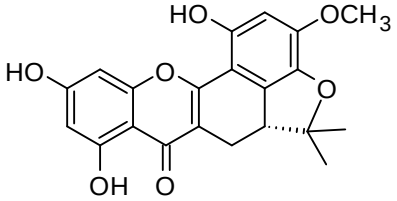
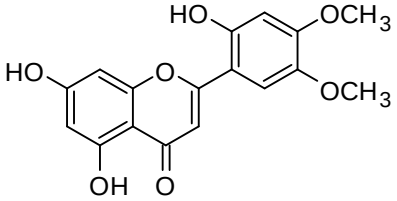
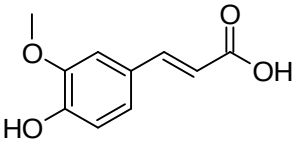
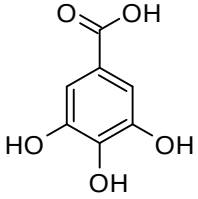
The other pharmacological activities are antibacterial, anti-inflammatory, anti-diabetic, antioxidant and antipyretic. *A. heterophyllus* can boost immunity and acts as a remedy for snake bites. Meanwhile, *A. heterophyllus* seeds have diuretic and laxative effects (Arora and Parle, 2016). Pharmacological research on *A. heterophyllus* seeds has been done, therefore this plant seed extract should be supported by safety tests. These safety tests are intended as quality control by determining the potential toxicity of the compounds produced by conducted acute, sub-acute toxicity tests and teratogenic test to determine the toxic effects (Dwitiyanti et al.2019).

Based on studies that have been conducted, *A. heterophyllus* is known to have many medicinal properties. Isolation of phenolic compounds from *A. heterophyllus* have shown anti-inflammatory effects while prenylflavonoids have exhibit strong antioxidant properties. In Ayurveda, the treatment for hyperglycaemia and diabetes is by extracting the flavonoid content through leaves placed in hot water. While extracts from *A. heterophyllus* seeds and roots produce lectins and crude methanolic. Lectin showed antifungal properties, while crude methanolic extract showed broad -spectrum antibacterial activity. The remarkable antioxidant activity by showing a decrease in hyperglycaemia and hyperlipidaemia was obtained through leaves extract (Swami &Kalse,2019).

Table 1: Chemical compounds of *Artocarpus heterophyllus* Lam.

Compounds	Chemical formula	Chemical structure
9,19-cyclolanost-3-one-24,25-diol (24 *S*)	$C_{21}H_{30}O_2$	
Cycloartenone	$C_{30}H_{48}O$	
Cycloartenol	$C_{30}H_{50}O$	
Histidine	$C_6H_9N_3O_2$	
Arginine	$C_6H_{14}N_4O_2$	
Betulinic acid	$C_{30}H_{48}O_3$	
Cycloheterophylline	$C_{31}H_{32}O_7$	

Heterophyllol	$C_{15}H_{22}O_3$	
Artoheterophines A	$C_{16}H_{18}O_6$	
Artoheterophines B	$C_{15}H_{14}O_6$	
Bracteflavone B	$C_{22}H_{20}O_6$	
Dinklagin C	$C_{20}H_{18}O_6$	
Cnidimol D	$C_{15}H_{16}O_6$	
Ficuformodiol B	$C_{15}H_{14}O_5$	
Harperamone	$C_{16}H_{20}O_5$	

5-hydroxy-7,2′,4′,6′ -tetramethoxyflavanone	$C_{19}H_{20}O_7$	
8-(γ,γ-dimethylallyl)5-hydroxy-7 ,2′,4′,6′-tetramethoxyflavanone	$C_{19}H_{19}O_7$	 where R= $CH_2CH=C(CH_3)_2$
Artoheteroids A	$C_{21}H_{16}O_7$	
Artoheteroids B	$C_{21}H_{16}O_8$	
Artoheteroids C	$C_{21}H_{18}O_7$	
Artoheteroids D	$C_{17}H_{14}O_7$	
Ferulic acid	$C_{10}H_{10}O_4$	
Gallic acid	$C_7H_6O_5$	

Antioxidant properties

Vitamin C cannot be produced naturally in the human body. Therefore, humans need to consume from sources rich in vitamin C to get health benefits. vitamin C is rich in high antioxidant content and is able to protect the body from free radicals, strengthen the immune system, and maintain healthy gums. *A. heterophyllus* is also one of the fruits that is rich in Vitamin C (Swami et al.2012). A study was conducted to trace the content of antioxidants and hypoglycaemic in the jackfruit skin, pulp and seeds. The extracted results were analysed through HPLC and obtained phenolic compounds and the highest amounts of flavonoids are from pulp and seeds. Prenylflavonoids, acids, hydroxycinnamic and glycosides which are the main bioactive are found in the skin extract and this in turn implies the *A. heterophyllus* peel as a source of natural antioxidants and new hypoglycaemic agents (Akter & Haque, 2019). The presence of free radicals should be prevented, and the step is through the intake of substances that have antioxidant content. Free radicals can contribute to bad health condition such as cancer, high blood pressure, diabetes mellitus and neurodegenerative diseases (Ojwanget al. 2018).

Maintaining blood sugar level

Diabetes mellitus is one of the most common chronic diseases of the 21st century. A report from the WHO stated that diabetes mellitus is in seventh place for the number of deaths due to non-communicable diseases. A typical symptom of people with diabetes mellitus is excessive urine production of polyuria, polydipsia-excessive thirst, and polyphagia-excessive eating (Biworo et al. 2015). The process of transporting glucose into cells is carried out by the activity of insulin which is a hormone produced by the pancreas (Koh Maarof, 2020). The oral antidiabetic drug currently used is sulfonylurea. Sulfonylurea medications are medications given to patients with new adult diabetes and have never had a previous ketoacidosis disorder such as gestational diabetes mellitus. The mechanism of this drug is to increase insulin secretion in the pancreas and is effective in diabetics who's pancreatic β cells are still functioning properly.

The continual use of sulfonylurea able contributing an adverse effect such as cardiovascular disease and disorders of the gastrointestinal tract. Furthermore, the side effects that also identified are vertigo which caused by interruption in central nervous system. An alternative to reducing blood glucose levels in the body is to use *A. heterophyllus* herbal remedies. The compound found in *A. heterophyllus* seeds namely β -carotene -epoxide5,6α can interact with sulfonylurea receptor 1 (SUR1) well compared to glibenclamide with the lowest Gibbs free energy value of -161,381 kcal/mol while glibenclamide -97, 5607 kcal/mol (Dwitiyantiet al. 2019).

The high content of proanthocyanidins and flavonoids obtained through *A. heterophyllus* extract is able to form lipid peroxides, and through amylase inhibitory effect, suggests that it can act as a starch blocker to lower glucose levels. (Omar et al.2011) Studies related to ethanol extract of *A. heterophyllus* seed powder as antidiabetic potential have also been conducted with control blood glucose levels and its effectiveness on various biochemical parameters such as total cholesterol, triglycerides (TGL), high density lipoprotein, (HDL), high density lipoprotein low, (LDL), low -density lipoprotein, (VLDL).

Anticancer properties

Dietary supplementation with *A. heterophyllus* pulp can help prevent and control the development of certain cancers. The researchers found that organic extracts from *A. heterophyllus* pulp can reduce the number of revertants caused by aϭlatoxin B1 (AFB1) and cell proliferation. Bioactive compounds from *A. heterophyllus* leaves show inhibitory activity against the proliferation of cancer cell lines. The anticancer effects of isolated phenolic compounds were examined in the human cancer cell lines MCF-7, H460, and SMMC-7721 and the compounds showed IC_{50} values in the MMC-7721 cell lines and IC_{50} values in the NCI-H460 cell lines (Sibi et al. 2021).

Rheumatoid arthritis treatment

Previous study has reported the *A. heterophyllus* leaves extract with methanol have shown analgesic and immunomodulatory effects. The inhibitory effect of three phenolic compounds is characterized as artocarpesin, norartocarpetin, and oxyresveratrolagainst the production of pro inflammatory mediators on murine macrophage cells has beenevaluated. The study began with an acute anti-inflammatory test followed by anti-rheumatoid arthritis in a rat model. Rheumatoid arthritis is an autoimmune disease characterized by inflammation, involvement of the humoral and cellular immune systems and synovial hyperplasia that can lead to joint destruction. The disease involves an inflammatory response and immune system suppression (Asmaliani & Iwo, 2016).

Antimicrobial properties

Terpenoids are byproducts produced during the process of *A. heterophyllus* seed fermentation solution and it found the antifungal properties. The mechanism carried out by terpenoids is to disrupt the fungal cell wall and cause loss of membrane integrity. The incidental discovery of antifungal agents showed the potential for food borne pathogens preservation which caused to large number of diseases with significant impact on human health. Flavonoids are aromatic compounds that also obtained from *A. heterophyllus* seed fermentation solution. An identified of sulphur content in *A. heterophyllus* seed give the responsible for antimicrobial action in which inhibits food borne pathogens (Kusuma et al. 2020).

Different skin, fiber and core extracts of *A.*

heterophyllus was carried in two different solvents extraction of acetone and ethyl acetate. The highest antibacterial activity found in *A. heterophyllus* skin and the lowest was in the core. This is because the peel forms the outer protective layer of the fruit and is more susceptible to microbial pathogens compared to the inside of the fruit and therefore antimicrobial compounds are more likely to be present on the peel. The unused portion of *A. heterophyllus* (skin and core) is a good source of phenolics, flavonoids and tannins that have microbial properties (Adan et al. 2020).

Anti-inflammatory properties

Previous study has also isolated phenolic compounds from *A. heterophyllus* via ethyl acetate extract. Three phenolic compounds obtained are artocarpesin, norartocarpetin and oxyresveratrol (Prakash et al. 2009). These phenolic compounds are examined of their inhibitory effects on the production of proinflammatory mediators in lipopolysaccharide-activated (LPS) RAW 264.7 macrophage cells. The results showed that artocarpesin suppresses the production of nitric oxide (NO) and prostaglandin E_2 (PGE_2) induced by LPS through downregulation of nitric oxide synthase (iNOS) and protein cyclooxygenase2 (COX-2) expression. Thus, artocarpesin could provide a potential therapeutic approach for inflammation-related disorders.

Antivirus properties

Several study related lectins from *A. heterophyllus* extract was conducted in vitro to find an inhibitory activity towards virus type HSV-2, Varicella zoster virus (VZS) and Cytomegalovirus (CMV). For example, *A. heterophyllus* lectin has been found to inhibit in vitro infection of HIV-1 without preventing the virus from binding to the host cell. The antiviral activity of *A. heterophyllus* lectin in response to HSV-2 and CMV, either before or after viral infection of cell monolayers, was observed at different doses (Moke et al. 2017). Studies on metabolites derived from *A. heterophyllus* leaf ethanol extract has found to possess anti-herpes viral properties Herpes viruses are a family of common viruses that can invite disease on a wide variety of hosts (Dhierllate et al.2020).

CONCLUSION

A comprehensive updated information was revealed through this review paper regarding the benefit of *A. heterophyllus* in both medicinal and nutrition health value. Various type of biochemical constituent consists in different part of *A. heterophyllus* and they are promising as new natural resources. For instance, it is known that *A. heterophyllus* also rich with vitamins A and C (antioxidants) which can help to strength the body's resistance to attacks from disease, besides maintain eye health and skin. For nutrition and health benefit, the content of protein and β-carotene in *A. heterophyllus* can provide information to society in general about food diversification alternatives and to add economic value.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

ACKNOWLEDGEMENT

Authors would like also to thank Institute of Bioproduct Development (IBD) and Research Management Center at UTM, Malaysia, for partial support through grant No. R.J130000.7609.4C359 and R.J130000.7609.4C336.

AUTHOR CONTRIBUTIONS

SM, MY, ZI, NI, DS involved in data collection, SM, MY, DJD, NIA, LHH, HEE writing the manuscript and work design. MY, DJD, DS, HEE reviewed the manuscript. All authors read and approved the final version.

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