

Antidiabetic and Antioxidant Activity of Jackfruit (*Artocarpus Heterophyllus*) Extract

Agung Biworo

Medical Pharmacology Department, School of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia.

Email: Agung_biworo@yahoo.com

Efrilia Tanjung¹, Iskandar², Khairina³, and Eko Suhartono⁴

¹Datuk Sanggul General Hospital Rantau, South Kalimantan, Indonesian.

²Research Unit Mutiara Bunda Mother and Child Hospital, Martapura, South Kalimantan, Indonesian.

³School of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia.

⁴Medical Chemistry and Biochemistry Department, School of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesian.

Email: {efriltanjung, iskandarthalib, ekoantioxidant}@gmail.com

Abstract—The *Artocarpus heterophyllus* (Jackfruit) is a species of tree of the mulberry family Moraceae. The plants of *Artocarpus* species have been used by traditional folk medicine in Indonesia. can be useful as anti-bacterial, anti-diabetic, anti-inflammatory, antioxidant and anti-helminthics. The present study was aimed to evaluate antidiabetic and antioxidant activity of aqueous extract of Jackfruit. The antidiabetic activity were determined by inhibition of haemoglobin glycation method. Phytochemical constituent like ascorbic acid, β -carotene and lycopene also determined. Antioxidant activity was measured by hydroxyl radical and hydrogen peroxide scavenging activity, and chellating effect of ferrous iron. From the result of this study we can see the increasing of haemoglobin glycation concentration is followed by the increasing of jackfruit extracts concentration. From this study also we found the IC 50 of jackfruit exctracts is 56,43 %. The result of this study also showed that the extract of jackfruit has a phytochemical constituent with ascorbic acid is the highest, and followed by β -carotene and lycopene. Jackfruit also has antioxidant activity. The highest antioxidant activity is scavenging hydroxyl radical activity and followed by scavenging hydrogen peroxide and chellating of ferrous iron. The result of this study suggest that the jackfruit extract potential as an diabetic agent.

Index Terms—antidiabetic, antiglycation, antioxidant activity, jackfruit

I. INTRODUCTION

The Diabetes Mellitus is being one of five leading causes of deaths and debilitating disease in the world. One hundred and fifty million people were suffering from diabetes wide reaching, which is almost five times more than the estimates one decade ago and it may double in the year 2030 [1]. With a population of 237.6 million people in 2010, Indonesia is the world's fourth most populated country. It also has the seventh largest number

of diabetic patients (7.6 million), despite relatively low prevalence (4.8% including both diabetes type 1 and 2 in individuals aged 20–79 years) in 2012 [2].

Diabetes mellitus or simply diabetes is a chronic metabolic disorder of carbohydrate, lipid and protein metabolism characterized by hyperglycemia, glycosurea, hyperlipidemia, negative nitrogen balance and sometimes ketonemia due to insufficient or complete cessation of insulin synthesis or secretion and/or peripheral resistance to insulin action [3]. The hallmark of diabetes mellitus is polyuria-excessive urine production, polydipsia-excessive thirst and polyphagia-excessive eating [4].

The development of diabetic complications is a major cause of morbidity and mortality and is an ever-increasing burden to healthcare authorities in both developed and developing nations. Epidemiological studies have confirmed that hyperglycemia is the most important factor in the onset and progress of diabetic complications [5].

There are several, well-researched theories of how chronic hyperglycemia can lead to micro or macrovascular disease in diabetes including the advanced glycation end product (AGE) theory [6]. AGE represent a heterogeneous class of compounds formed through non-enzymatic reaction between reducing sugars and proteins, known as glycation [7], [8].

In type-2 diabetic patients with coronary heart disease, elevated levels of AGEs and N- ϵ -carboxy-methyl-lysine (CML) have been reported [9]. AGEs have also been implicated in delayed wound healing associate with diabetes, presumably through vascular, neurological, or intermediary metabolic modifications [10]. CML can serve as a biomarker of oxidative stress resulting from sugar and lipid oxidation, and CML elevations are associated with diabetes and renal dysfunction. It follows from these observations that AGEs are formed in the context of hyperglycemia but that the relationship between blood glucose levels and CML levels is not a simple one [11].

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The pathogenesis of diabetes mellitus and its complications is managed by insulin and oral administration of hypoglycemic drugs such as sulfonylureas and biguanides [12]. However, on chronic usage most of these agents produced several side effects, including hypoglycemic coma, insulin resistance, hypersensitivity, cholesterol jaundice, abdominal pain, anorexia and metallic taste [4].

For various reasons in recent years, the popularity of herbal medicines in diabetic control has increased. Natural plant drugs are frequently considered to be less toxic with lower side effects than synthetic ones [13]. In spite of presence of large number of medicines in the pharmaceutical market, remedies from medicinal plants are used with success to treat and this disease [14].

South Kalimantan Indonesia is a tropical country that has a variety of fruits that are consumed for food and health [15]. One of the interesting fruits is Jackfruit (*Artocarpus heterophyllus*). The *Artocarpus heterophyllus* (Jackfruit) is a species of tree of the mulberry family Moraceae. It is native to Western Ghats of India, Indonesia and also found in central and eastern Africa, south-eastern Asia, Florida, Brazil, Australia and many Pacific Islands [16].

The fruit has an average weight of 10 kg. The yellowish bulbs constituting the perianth portion of the fruit are fleshy, fibrous, and rich in sugars as well as carotenoids [17]. It is considered a rich source of carbohydrates, minerals, carboxylic acids, dietary fiber, and vitamins such as ascorbic acid and thiamine [18], [19]. Different classes of flavonoids are abundant in the jack fruit plant. In the market, a few jack fruit products, such as jack fruit with honey, canned jack fruit, and jack fruit flavors, are available. Jack fruit powders are used in instant soups, snacks, bakery products, beverages, dairy products, candy, ice cream, baby foods, pasta, etc [20].

The plants of *Artocarpus* species have been used by traditional folk medicine in Indonesia against inflammation, malarial fever, stomachache, ulcers, abscesses, dysentery, diarrhea, defective urinary secretion and skin disease [21]. *Nangka* (*Artocarpus heterophyllus*) can be useful as anti-bacterial, anti-diabetic, anti-inflammatory, antioxidant and anti-helminthics [15]. Several reports have cited the antidiabetic effects of jack fruit extracts, which could be attributed to its high proanthocyanidin and flavonoid contents, through inhibition of lipid peroxide formation, and via an α -amylase inhibitory effect, indicating that it could act as a starch blocker to decrease postprandial glucose level [20].

This study was undertaken to investigate the in vitro antidiabetic potentials of Jackfruit Extracts by studying their effects on inhibition of glycosylation of haemoglobin. Also, the study endeavored to investigate phytochemical constituent and antioxidant activity of jackfruit.

II. MATERIAL AND METHODS

A. Collection and Preparation of Fruit Extraxts

Fruit of *Artocarpus heterophyllus*, were obtained from Rantau, South Kalimantan, Indonesia. The fruit with seed were separated. Fruits were washed with distilled water. The collected fruits were cut into small pieces and blended by juicer.

B. Evaluation of Haemoglobin Glycation

Evaluation of haemoglobin glycation was estimated by the method of Adisa *et al* (2004) [22]. The blood was collected from a healthy human volunteer and transferred into a blood bottle containing an anticoagulant. Hemolysate was prepared based on the principle of hypotonic lysis. The red blood collected were washed thrice with 0.14 M NaCl solution and one volume of red blood cells suspension was lysed with two volumes of 0.01M phosphate buffer, pH 7.4 and 0.5 volume of CCl₄. The haemolysate was then freed from the debris by centrifugation at 2300 rpm for 15 min at room temperature. The haemoglobin rich fraction in the upper layer was separated and dispensed into sample bottle for storage and refrigerated until required for use.

To 1 mL of haemoglobin solution, 5 μ L of gentamycin and 25 μ L of the plant extracts with different concentrations (0, 10, 20, 30%) were added. The reaction was started by the addition of 1 mL of 2% glucose in 0.01M phosphate buffer (pH 7.4) and incubated in the dark at room temperature. The concentrations of glycated haemoglobin at the incubation period of 24 hrs were estimated spectrophotometrically at 443nm.

C. Ascorbic Acid Content Assay

Ascorbic acid was determined according to the method of Klein and Perry (1982). The dried methanolic extract (100 mg) was extracted with 10 ml of 1% metaphosphoric acid for 45 minute at room temperature and filtered through Whatman No. 4 filter paper. The filtrate (1 ml) was mixed with 9 ml of 2,6-dichlorophenolindophenol and the absorbance was measured within 30 min at 515 nm against a blank. Content of ascorbic acid was calculated on the basis of the calibration curve of authentic L-ascorbic acid (0.020 – 0.12 mg/ml). The assays were carried out in triplicate; the results were mean values \pm standard deviations and expressed as mg of ascorbic acid/g of extract [23].

D. β -Carotene and Lycopene Content Assay

β -Carotene and lycopene were determined according to the method of Nagata and Yamashita (1992). The dried methanolic extract (100 mg) was vigorously shaken with 10 ml of acetone-hexane mixture (4:6) for 1 min and filtered through Whatman No. 4 filter paper. The absorbance of the filtrate was measured at 453, 505, 645 and 663 nm. Contents of β -carotene and lycopene were calculated according to the following equations: lycopene (mg/100 ml) = $-0.0458 A_{663} + 0.372 A_{505} - 0.0806 A_{453}$; β -carotene (mg/100 ml) = $0.216 A_{663} - 0.304 A_{505} + 0.452 A_{453}$. The assays were carried out in triplicate; the results were mean values \pm standard deviations and expressed as mg of carotenoid/g of extract [23].

E. Hydroxyl Radicals Scavenging Activity Assay

The scavenging activity for hydroxyl radicals was measured with Fenton reaction [24]. The absorbance of the mixture at 560nm was measured with a spectrophotometer. Hydroxyl radical scavenging activity was calculated using the equation: $(1 - \text{absorbance of sample} / \text{absorbance of control}) \times 100$. Each experiment was carried out in triplicate and results averaged expressed as mean \pm SD.

F. Chelating Effect of Ferrous Iron Assay

The chelating effect of ferrous ions was estimated by the method of Hung-Ju Chou *et al.* [24]. The absorbance of the mixture was measured at 562 nm. Chelating effect was calculated using the equation: $(1 - \text{absorbance of sample} / \text{absorbance of control}) \times 100$. Each experiment was carried out in triplicate and results averaged expressed as mean \pm SD.

G. Hydrogen Peroxide Scavenging Activity Assay

The hydrogen peroxide scavenging was determined according to the method of Ruch *et al.* [23]. The absorbance value of the reaction mixture was recorded at 230 nm. Hydrogen peroxide scavenging activity was calculated using the equation: $(1 - \text{absorbance of sample} / \text{absorbance of control}) \times 100$. Each experiment was carried out in triplicate and results averaged expressed as mean \pm SD.

III. RESULTS AND DISCUSSION

Diabetes mellitus is a persistent metabolic disorder characterized by abnormally elevated level of blood glucose because of deficiency in insulin secretion by the β cells of pancreas and/or resistance toward the action of antidiabetic hormone insulin associated with disturbances in the carbohydrates, lipids, and proteins metabolism which leads to macro and micro vascular dysfunction and long term health complications [25].

Increased concentration of glucose in the blood leads to its binding to hemoglobin which may result in the formation of the reactive oxygen species. This process is known as glycation [25]. In this present study, jackfruit extracts used as a compound to inhibit the haemoglobin glycation. Result of this study revealed the jackfruit extracts can inhibit the haemoglobin glycation. An increase of haemoglobin glycation concentration that can be inhibited by the extracts was observed with the increasing of jackfruit extracts concentration. From this study also we found the IC₅₀ of jackfruit extracts is 56.43 % (Fig. 1).

Glycation is a non-enzymatic reaction between free amino groups of proteins and reducing sugars. This reaction is known as Maillard reaction [26]. Glycation is closely associated with the pathogenesis of age- and diabetes-related complications like neuropathy, angiopathy and nephropathy [27]. This process represents a common posttranslational modification of proteins, which can impair their functions in living organisms. If the oxidative step is involved in glycation process, it is called as glycoxidation. Free radicals, products of the

autooxidation of the glycating sugar, and a heterogeneous group of substances called advanced glycation end products (AGEs) are formed in the course of glycoxidation [28], [29].

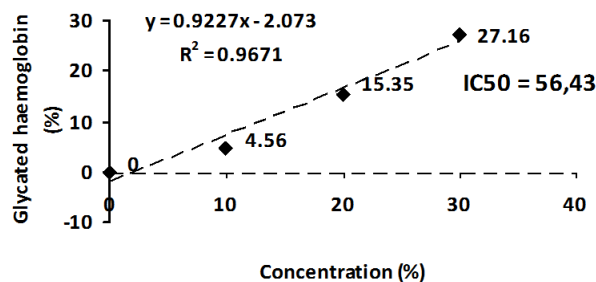


Figure 1. Effect of plant extract to haemoglobin glycation

The increasing concentration of glycated haemoglobin which can be inhibited by the jackfruit extracts might be caused by the presence of phytochemical constituent of jackfruit extracts. It is known reactive oxygen species (ROS) leads to many etiological and pathophysiological human diseases such as Diabetes. Oxygen free radicals i.e. ROS can initiate peroxidation of lipids, which in turn stimulates glycation of protein [26]. Glycation is a non-enzymatic reaction between free amino groups of proteins and reducing sugars [29]. This reaction initiates formation of reversible Schiff bases, which by intermolecular rearrangement are converted into stable, covalently-bonded Amadori products [30]. Over time, these products are transformed through glycoxidative process and further modifications, and result in the formation of advanced glycation end products (AGEs) [31].

It has been reported that antioxidants and radical scavengers inhibit these processes. In this regard, several natural extracts/compounds such as polyphenolic-rich extracts, curcumin, rutin and garcinol are known to possess antioxidative property and prevent AGE formation. In addition, recent studies have shown that compounds with combined antioxidant and antiglycation properties are more effective in treating diabetes mellitus [32].

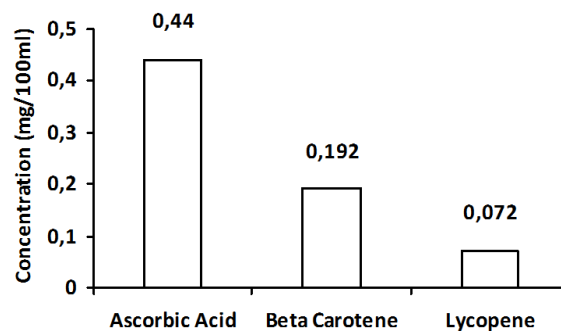


Figure 2. Phytochemical concentration in jack fruit

From Fig. 2 shows that the extracts of jackfruit contain phytochemical constituent. The highest phytochemical constituent in jackfruit extracts is ascorbic acid and followed by β -carotene and lycopene.

Ascorbic acid is known as vitamin C is a substance commonly found in fruits. Some studies suggest that the

consumption of fruits and vegetables are associated with reduced risks of diseases. [33], [34]. Ascorbic Acid is a water-soluble antioxidant. It was first isolated in 1928, by the Hungarian biochemist and Nobel Prize winner Szent-Gyorgyi. It is an unstable, easily oxidized acid and can be destroyed by oxygen, alkali and high temperature [34]. Ascorbic acid is an important antioxidant in human capable of scavenging oxygen-derived free radicals. Ascorbic acid is structurally similar to glucose and can replace it in many chemical reactions, and thus is effective in prevention of non-enzymatic glycosylation of proteins [35].

Several studies showed decreased basal vitamin C level in diabetic patients and also it is suggested that oxidative stress is increased in diabetes [35]. The consumption of foods high in ascorbic acid has been associated with lower risk of diabetes. Ascorbic acid status may influence glycemic control, protein glycation and the sorbitol pathway [36].

The data is partially in accordance with the findings of Vinson and Howard. They quantitated amadori product by thiobarbituric acid colorimetry in normal subjects after ascorbic acid supplementation. Serum protein glycation was decreased at an average of 46.8% ($p < 0.01$). Contrary to these observations, Shoff et al. examined the relationship between glycosylated hemoglobin and intake of vitamins E, C and β -carotene in a population-based sample of middle-aged and older adults participating in the Beaver Dam Eye Study. In people without diabetes, energy-adjusted vitamin C intake was negatively associated with glycosylated hemoglobin [36].

The second phytochemical constituent that found in jackfruit extracts is β -carotene. β -Carotene is commonly known as a radical scavenger and a physical scavenger of singlet oxygen and is believed to play an important role in the inhibition of initial stages of lipid peroxidation. The antioxidant properties of β -Carotene have been suggested as being the main mechanism by which they afford their beneficial effects [37].

In recent years the antioxidant properties of carotenoids has been the major focus of research. More than 600 carotenoids have so far been identified in nature. However, only about 40 are present in a typical human diet. Of these 40 about 20 carotenoids have been identified in human blood and tissues. Close to 90% of the carotenoids in the diet and human body is represented by β -carotene, α -carotene, lycopene, lutein and cryptoxanthin [38], [39].

β -Carotene is commonly known as a radical scavenger and a physical scavenger of singlet oxygen and is believed to play an important role in the inhibition of initial stages of lipid peroxidation [40]. Several studies reported the beneficial effect of β -carotene intake in decreasing oxidative stress in diabetes [41]. Previous study also reported a significant correlation between plasma β -carotene levels and HbA1c and fructosamine in both diabetics and non-diabetics [42].

The third phytochemical constituent is lycopene. Lycopene is present in many fruits and vegetables, with tomatoes and processed tomato products being among the

richest sources. Several recent studies suggest that dietary lycopene is able to reduce the risk of chronic diseases such as cancer and cardiovascular diseases. Although several mechanisms have been implicated in health-beneficial effects of lycopene, such as modulation of intercellular gap junction communication, hormones, immune system and metabolic pathways, the antioxidant properties of lycopene are thought to be primarily involved in its preventive effects in chronic diseases. Because of its high number of conjugated dienes, lycopene is one of the most potent antioxidants, with a singlet-oxygen-quenching ability twice as high as that of β -carotene and 10 times higher than that of α -tocopherol [38].

Previous studies showed Lycopene, ascorbic acid and α -tocopherol can decrease of glycated LDL. Other studies suggest that lycopene play an important role in the prevention of glycation. The mechanism by which these nutrients suppress glycation is still unknown. Generation inhibition and/or scavenging of free radicals resulted from glycation process and subsequent inhibition of protein modification is one of the probable mechanisms of anti-glycation effect of these nutrients. Kiho et al. also showed, lycopene with its unique structure (11 conjugated double bonds and no cyclic groups) can quench singlet oxygen and subsequently inhibit the formation of AGEs. Thus, we could suggest that antiglycation activity of lycopene possibly correlate with their radicals scavenging [28].

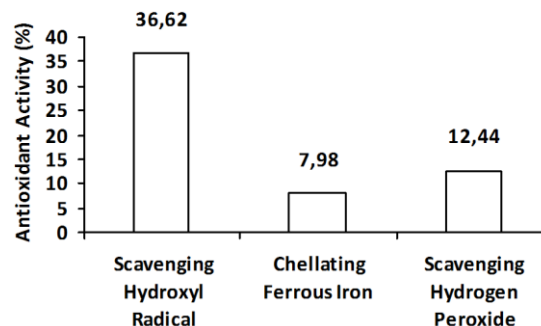


Figure 3. Antioxidant Activity of Jackfruit

From Fig. 3 we can also see that jackfruit extracts has antioxidant activity. The highest antioxidant activity is scavenging hydroxyl radical activity and followed by scavenging hydrogen peroxide and chellating of ferrous iron.

Several biochemical mechanism how the antioxidant activity of jackfruit extracts involved in anti-glycation reactions have been proposed. During the early stage of glycation, Schiff bases are prone to oxidation, generating free radicals, reactive carbonyl groups and the formed AGEs. Scavenging hydroxyl radicals and hydrogen peroxide can alleviate oxidative stress and reduce the generation of reactive carbonyl compounds. In addition, transition metal also catalyzes auto-oxidation of glucose and further generates reactive carbonyl compounds to form AGEs. Thus, metal chelators may retard the process of AGEs by preventing further oxidation of Amadori products and metal-catalyzed glucose oxidation. It has

been reported that many antioxidant-containing foods can scavenge free-radicals generated during the glycation process as well as prevent reducing sugars and Amadori products from self-oxidation, leading to the inhibition of AGEs formation [43].

From the results obtained in the present study, jackfruit extracts showed potent antioxidant properties. According to the abovementioned antiglycation mechanisms, RGSE may inhibit AGEs formation by decreasing the ROS formation or by scavenging the ROS formed *in vitro* by auto-oxidation of sugars and/or oxidative degradation of Amadori products. However, the antioxidant activity of jackfruit extracts might not be the only reason for explanation of the mechanism of antiglycation. Other mechanisms of antiglycation have been proposed, such as breaking the cross-linking structures in the formed AGEs and inhibiting the formation of late-stage Amadori products. Further comprehensive studies of jackfruit extracts are required to evaluate the antiglycation mechanisms described above [43].

Our study revealed that jackfruit extracts can inhibit the haemoglobin glycation. Glycated haemoglobin (HbA1c) is produced by the non-enzymatic glycation of haemoglobin. The degree of glycation reflects the mean plasma glucose over the life of the red blood cell (approximately three months). Testing HbA1c is attractive as it measures chronic glycaemia rather than instantaneous blood glucose. It has been used as an objective marker of average glycaemic control for many years and has an accepted place in the monitoring of patients with diabetes [44]. This result suggest the jackfruit extracts has potential antidiabetic activity by decreased the levels of HbA1c.

IV. CONCLUSION

The results of this study concluded that jackfruit extract can inhibit the glycation of haemoglobin. The inhibition might be caused by the presence of phytochemical constituent in jackfruit extract such as ascorbic acid, β -carotene and lycopene. Furthermore, the jackfruit extract has antioxidant activity, so the extract can inhibit the haemoglobin glycation. The result of this study suggest that the jackfruit extract potential as an diabetic agent because the extracts can lower the glycated hemoglobin levels (HbA1c).

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Agung Biworo was born in Sleman, Indonesia, in Agustus 1966. He received his general dokter and public health master from Gadjah Mada University, Yogyakarta, Indonesia. He is currently a lecturer in Medical Pharmacology Department, School of Medicine Lambung Mangkurat University, Banjarmasin, Indonesia.



Efrilia Tanjung was born in Rantau, Indonesia, in April 1987. She received his medical doctor in 2012 from Lambung Mangkurat University, Banjarbaru, Indonesia. He is currently a general physician in Datuk Sanggul General Hospital, Rantau, Indonesia.



Iskandar was born in Jakarta, Indonesia, in April 1987. He received his medical doctor in 2011 from Lambung Mangkurat University, Banjarbaru, Indonesia. He is currently a general physician in Mutiara Bunda Mother and Child Hospital, Martapura, Indonesia.



Khairina was born in Banjarmasin, South Kalimantan, Indonesia, in Mei 1994. He currently study medical doctor in School of Medicine, Lambung Mangkurat University, Banjarmasin, Indonesia.



Eko Suhartono was born in Surabaya, Indonesia, in September 1968. He received his Drs. and M.Sc degree in 1991 and 1998 from Surabaya Technic Institute, Surabaya, East Java and Gadjah Mada University, Yogyakarta, Indonesia. He currently study environmental science and technology graduate program in Brawijaya University, Malang, Indonesia. His research is mainly focused on free radical and natural product antioxidant, ecotoxicology.