MALAYSIAN JOURNAL OF BIOCHEMISTRY & MOLECULAR BIOLOGY

The Official Publication of The Malaysian Society For Biochemistry & Molecular Biology (MSBMB)
http://mjbmb.org

Anacardium occidentale Linn. LEAVES AND ITS MEDICINAL PROPERTIES

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REVIEW ARTICLE

History
Received: 9 August 2021
Accepted: 29 November 2022

Keywords:

Anacardium occidentale; Cashew leaves; Antidiabetic; Medicinal properties

Abstract

Anacardium occidentale leaves, known as cashew leaves or Pucuk Gajus in Malay, is a member of the Anacardiaceae family that is widely grown in tropical countries such as Malaysia, India and Brazil. It had been traditionally used for treating many health problems as it contained many beneficial phytochemical compositions such as polyphenols, flavonoids, tannin, vitamin C and carotenoids. Its extract possesses antidiabetic activity, which prevents a sudden rise in postprandial blood glucose level by inhibiting α-amylase to slow down the breakdown of long-chain carbohydrates to glucose. It also controls the blood glucose level by inhibiting dipeptidyl peptidase IV (DPPIV), which prevents the rapid degradation of incretin and thus stimulates insulin secretion. Besides, it acts as an antioxidant agent to protect against lipid peroxidation and scavenge radicals. It showed antimicrobial properties by inhibiting the growth of pathogenic bacteria including Gram-positive *Staphylococcus aureus* and *Bacillus subtilis*, and Gram-negative *Escherichia coli* and *Klebsiella pneumonia*, and fungi which are *Aspergillus niger, Penicillium digitatum* and *Colletotrichum gloeosporiodes*. Furthermore, it exhibited antiulcerogenic effect by preventing gastric lesions and anti-inflammatory properties which interrupt the inflammation process by controlling cytokines secretion in macrophage lipopolysaccharide-stimulated cells. Therefore, *A. occidentale* may potentially be contributed to the treatment of various diseases, but continuous study is needed to determine further the bioactive compounds that are responsible for the mechanism of action.

INTRODUCTION

Anacardium occidentale (*A. occidentale*) leaves, commonly known as cashew leaves is one of those popular traditional vegetables in Malaysia. It is a member of the Anacardiaceae family that includes about 75 genera and 700 species [1]. The *A. occidentale* tree has 10 to 15 meter high and a short irregular-shaped trunk is widely grown in tropical countries such as Malaysia, India and Brazil [1, 2]. Its bark is brown and smooth to rough with longitudinal fissures, while the leaves are leathery and obovate with a rounded apex. When young, the leaves are pliable, lustrous and reddish (Figure 1), but they turn into dark green colour when mature with prominent yellow veins. Moreover, the *A. occidentale* flowers are whitish turning pinkish-red which occur as terminal panicles. There is the kidney-shaped nut that attached to the end of an enlarged pear-shaped receptacle called cashew fruit [3].

Cashew plant can be utilized for food and medicinal purposes. The cashew nut and fruit have many nutrients including fat, protein and carbohydrate and it can be consumed as fresh or processed food products. The real fruit

– cashew nuts can be eaten raw or roasted as snacks, or they can be processed into food byproducts [4–6]. The cashew nut is firstly processed by removing from the shell before it further been toasted and distributed around the world [7]. Moreover, the pseudo fruit or known as cashew apple is also processed into many products such as jams, juices, syrup and sweets. The juice is produced by pressing the cashew apple using an expeller press. Then, it is extracted and the dry pulp is separated from the juice. The juice is homogenized, thermally treated and bottled before it is commercialized as concentrated juice or ready to drink juice [7, 8]. Meanwhile, the young leaves or shoots are commonly consumed as a traditional vegetable or 'ulam' in Malaysia, either by blanched or freshly eaten with rice [3, 9].

For medicinal purposes, the cashew leaves, flower and bark are commonly used as they generally contain many beneficial compounds such as phenolic compounds, tannin, vitamin C, carotenoids and organic acids [5]. These parts are widely employed in folk medicine for the treatment of inflammation, rheumatism, tumors, and infectious [3, 10]. The leaves are reported to have a number of pharmacological effects, which it is mainly been used traditionally as an antidiabetic remedy that reduces hyperglycemia [9, 11, 12]. Its extract can also exhibit potential antioxidant agents that modify the oxidation states of cells [10]. As mentioned in the previous studies, the cashew leaves extract has shown a higher antioxidant activity compared to coconut, sweet orange, lemon and papaya leaf extracts [5]. The *A. occidentale* leaves extract was found to possess antidiabetic, antibacterial, antiulcerogenic and anti-inflammatory properties, which making them as the major source for health problem treatment since ancient times [13, 14]. Therefore, this review will be discussed on the medicinal properties of *A. occidentale* leaves in order to determine the scientific gaps where the isolation and characterization of the bioactive compounds would be necessary to drive future research in the elucidation of their structures and mechanism of action [11, 15].

Figure 1. Leaves of *Anacardium occidentale*

PHYTOCHEMICAL CONSTITUENTS OF *A. occidentale* PLANT

The consumption of polyphenol-rich plant foods is commonly associated with a lower risk of severe health problems such as diabetes, cardiovascular disease and cancer [16, 17]. Polyphenols are a large phytochemicals group that contain phenol rings and they can be categorized into flavonoids, phenolic acids, stilbenes and lignans [18, 19]. Polyphenols may restrict the glucose release from the liver and promote the glucose absorption in peripheral tissues, via regulating the intracellular signalling. It also has the antioxidant properties and help to prevent the formation of advanced glycation endproducts (AGEs) [20]. Besides, each polyphenols compound can exhibit different effects either by synergistic, antagonistic or neutral [11]. As listed in Table 1 below, there are several studies had determined the chemical constituents in every physical part of the *A. occidentale* plant.

Table 1. The composition in every physical part of *A. occidentale* plant

Part of The Plant	Chemical Constituents	References
Leaves/Shoots	Kaempferol 3-O-glucoside Kaempferol 3-O-arabinofuranoside Quercetin 3-O-glucoside Quercetin 3-O-galactoside	[6]
	Quercetin Quercetin-3-O-rhamnoside Myricetin Myricetin-3-O-rhamnoside Amentoflavone	[21]
	Phenolic acid – gallic, cinnamic, p-coumaric, ferulic, protocatechuic and p-hydroxybenzoic Flavonoids – agathisflavone, quercetin 3-O-rutinoside and quercetin 3-O-rhamnoside	[22]
	Alkaloids Flavonoids Tannin Saponins	[23]
	Phenols Oxalate Quercetin-glycoside Phytate steroids Triterpenes Vitamins (A, B, B2, B3 and C) Minerals (Na, K, Ca, Mg, P, Fe, Cu and Se)	[24]
	Carotenoid	[25]
Stem Bark	Aromatic groups – phenols and flavonoids	[11]
	Tannins	[24, 26]
Apple/Fruits	Vitamin C	[10]
	Alkyl phenols – anacardic acids, cardanols and cardols	[6, 9]
	Quercetin Naringenin Phenolic acids (caffeic acid, p-coumaric acid, ferulic acid and gallic acid)	[27]
Seed/Nuts	Tannins Mono- and polyunsaturated fatty acids Proteins Sugars (+)-catechin (-)-epicatechin β-carotene Lutein α-tocopherol	[28]

MEDICINAL PROPERTIES OF *A. occidentale* LEAVES

ANTIDIABETIC

Diabetes mellitus (DM) is known as a disease associated with hyperglycemia, oxidative stress, polyurea, ketosis, nephropathy and cardiovascular disorders due to problems in insulin secretion, insulin action or both [11, 24]. In a normal condition, blood glucose levels in the body would be increased after a high carbohydrate meal intake. The increased in blood glucose levels would trigger and initiate the secretion of insulin from β-cells of pancreas. The β-cells that consist of many glucose transporters (GLUT 2), allow the influx of glucose hence it is important to recognize blood glucose levels and help in adjusting the insulin secretion. The insulin from β-cells is secreted into the blood, circulates in unbound form and reaches liver, muscle and kidney for maintaining the blood glucose levels. The increased in glucose absorption would lead to a rapid uptake of glucose by muscles and stored it into glycogen for future use, thus the blood glucose levels in the body are controlled [29]. However, in a diabetic condition, it causes a progressive β-cells dysfunction and loss of β-cells, which results to the unavailability or insufficient of insulin secretion from β-cells, therefore subsequently increased the blood glucose levels in the body, which called hyperglycemia. Prolong this condition will lead in long term of organ damages such as kidneys, liver, eyes, nerves, heart and blood vessels [23, 29].

In carbohydrate metabolism, polyphenols play an important role to prevent a sudden rise in postprandial blood glucose level by retarding α-amylase and α-glucosidase enzymes activities in digestive tract to slow down the breakdown of long-chain carbohydrates to glucose [18, 30]. It not only prolongs the overall carbohydrate digestion time, but it is also causing a reduction in the rate of glucose absorption thus decreases the postprandial blood glucose level [31, 32]. Besides, dietary polyphenols were found to suppress sodium-dependent glucose transporter 1 (SGLT1)-activity for the glucose absorption in the gut, promote insulin secretion, and lower hepatic glucose production [20, 33]. There are several inhibitors of the enzymes that are in clinical use including acarbose, miglitol and voglibose [31, 34].

In vitro Studies

The *A. occidentale* plant had listed in the National Program of Medicinal Plants and Herbal Medicine of Brazil unique health system as it was reported to contain several total phenolic compounds such as flavonoids, anthocyanins and tannins that are recognized for the treatment of several conditions including diabetes and cardiovascular diseases [10]. The antidiabetic properties in the extract of *A. occidentale* had been determined by the phytochemical screening studies that the presence of bioactive compounds such as alkaloids, tannins, anthraquinones, flavonoids and terpenes in the extract may act as a competitive molecule that binds to the α-glucosidase enzyme for carbohydrate digestion, which it restricted the enzyme activity thus enhanced the blood glucose lowering effects [14, 29, 35].

In the study by Abdullah Thaidi et al. [36], it was reported a positive inhibition effect on dipeptidyl peptidase IV (DPPIV) by the *A. occidentale* leaves extract which the phenolic acid and flavonoids were presented. It would control the blood glucose level by preventing the rapid degradation of incretins such as glucagon-like peptide 1 (GLP-1) and gastric inhibitory peptide (GIP), which act to stimulate insulin secretion, lower glucagon concentration and slow gastric emptying [36]. In several studies, the use of *A. occidentale* was suggested as antidiabetic agent as it contained the bioactive compounds mainly polyphenols that may induce the initiation and secretion of insulin from β-cells and decrease the blood glucose levels [6, 11, 24, 29]. Besides, the presence of glycoside in the cashew extract that acts as a substrate for the digestive enzymes had changed the role of starch as a substrate, which it restricted the enzymes activities hence the breakdown of the starch to glucose in the body was delayed and the level of blood glucose can be controlled [37, 38]. This antidiabetic effect of the cashew leaves extract can be explained by two mechanisms which are the inhibition of sucrose degradation by intestinal α-glucosidase complex and the intestinal glucose release blockage via glucose transporter SGLT1 and GLUT2 [39].

In vivo Studies

It was reported that the *A. occidentale* leaves extract shown the antidiabetic properties which the blood glucose levels in normoglycemic and hyperglycemic rabbits had been controlled effectively [40]. Furthermore, the blood glucose level, total cholesterol, triglycerides, atherogenic index, urea, and creatinine in fructose-fed rats had been improved by introducing significantly a single daily dosage 200.0 mg/kg of *A. occidentale* methanol extract [3]. An increase in total plasma protein had been found in normal rats without altering their plasma levels of urea and creatinine. This result showed that cashew extract could not only improve the glycemic control and insulin secretion, but also enhance the protein synthesis rate [41]. Additionally, it was found that the methanol extract of *A. occidentale* controlled the blood glucose level in the streptozotocin-diabetic rats as the extract contained polyphenols mainly kaempferol, quercetol rhamnosides, and quercetin glycoside that acted as the α-glucosidase inhibitors, to control the glucose absorption in the stomach and the insulin resistance [2, 14, 33, 42]. By the presence of intramolecular nitrogen, polyphenol compound binds competitively to the carbohydrate binding site of the α-glucosidase enzyme, which interrupts the enzymatic reaction that ingested carbohydrate cannot be digested and glucose cannot be released for absorption [43]. These findings were consistent with the studies mentioned earlier

that the *A. occidentale* leaves extract possessed the antidiabetic effect as it contained polyphenols that could slow down the carbohydrate digestion and reduce the glucose absorption rate resulting decrease in the postprandial blood glucose [37].

ANTIOXIDANT

Free radicals can be produced by autoxidation reaction, including the oxidation of sugars and sugar adducts to protein, and the oxidation of unsaturated lipids in plasma and membrane proteins, hence it contributed to the possible sources of oxidative stress, lipid peroxidation and cell damages that developed in health complications such as diabetes, cancer, Alzheimer and Parkinson [29, 44, 45]. The amount of tissue damage in human body can also cause by the imbalance of the generated free radicals and the antioxidant defense system. Besides, reactive oxygen species (ROS) is involved in activation and progression of inflammatory pathways and can induce the oxidative damages to all biomolecules including lipids, carbohydrates, proteins, enzymes, DNA and RNA thus it results in developing many health complications [29, 46–48]. Antioxidants can be defined as bioactive compounds that inhibit or delay the oxidation of molecules caused by ROS [49, 50]. Fruits and vegetables are generally described to contain flavonoid and phenolic compounds which act as antioxidant agent that delays the oxidation reaction by inhibiting the initiation or propagation of free radicals in oxidizing chain reactions therefore, it can reduce the oxidative damage in the body and be the protective factors against cancer and heart diseases [9, 26, 27, 51].

In vitro Studies

It was reported in several studies that the consumption of *A. occidentale* leaves as ‘ulam' particularly could offer some dietary benefits as it able to act as an antioxidant agent to protect against lipid peroxidation and to scavenge free radicals’ activities [6, 23, 24]. These were caused by the high number of phenolic compounds in the extract of cashew leaves positively contributed to the antioxidant activity [27]. As compared to other species of ‘ulam’ leaves, *A. occidentale* leaves was found to contain highest concentration of the total phenolic content (3890 mg GAE/100 g) and free radical scavenging ability (6620 mg AA/100 g), which was one to three times higher than *Persicaria hydropiper* and, 16-30 times higher than *Centella asiatica* [52, 53]. Moreover, it was reported that the total phenolic content and antioxidant activities of *A. occidentale* leaves were significantly revealed the strongest antioxidant activities amongst herbs and vegetables such as rosemary, thyme and marjoram [52, 54, 55]. These comparatively high total phenolic content described that polyphenol compounds are abundant in *A. occidentale* leaves [56].

Besides, the hypoglycemic and antioxidant effects of cashew leaves methanol extract are mainly due to the synergistic effects of its constituents including flavonoids, phenolics and the antioxidants (vitamins A and C) [57]. The highest total antioxidant activities in *A. occidentale* due to the presence of these phenolic compounds, predominantly flavonol glycosides with levels ranged from 6.4-12.4 ± 0.3 mg/g fresh weight (fw) [6, 9]. The presence of anacardic acids, myricetin and quercetin glycosides were also found in *A. occidentale* and they have exhibited a very high antioxidant activity [9, 10]. In the study conducted by Souza et al. [47] found that *A. occidentale* leaves extract exhibited the antioxidant effect by reducing the oxidative damage in macrophage cells after treated with 0.5-5.0 µg/mL of the extract. It was suggested that the antioxidant agent, polyphenols can minimize the oxidative damage either directly *via* interacting with free radicals or indirectly by suppressing the activity of free radical generating enzymes and enhancing the activity of intracellular antioxidant enzymes to properly detoxify ROS [58, 59].

In a study conducted by Rajesh et al. [60], the antioxidant effect of *A. occidentale* leaves extract was determined using DPPH radical scavenging method, which it showed better antioxidant activity than *Terminalia catappa* leaves extract with a percentage inhibition of 94.4% and 91.98% respectively. It might be correlated to higher concentration of polyphenols in the cashew leaves extract which have scavenge the DPPH free radicals better by their hydrogen donating ability [61–64]. Polyphenols, mainly flavonoids were reported to be the most effective antioxidant because it can easily scavenger superoxide anions by transferring electrons to protect against free radical-induced damages [2, 65, 66]. It can also control the significant decrease in the enzymatic defence mechanism, super oxide dismutase (SOD) and catalase (CAT) that caused by the high amount of ROS [40, 67].

ANTIMICROBIAL

The use of *A. occidentale* plant as the antimicrobial agent has been widely introduced in years. There are three major influences of the antimicrobial agent on the destroyed cell microbial, which the antimicrobial agent can delay the replication of genetic information, and then transfer the degradation genetic to stop the protein synthesis. Next, it can change the function and cell wall structure of those pathogenic bacteria and fungi [5].

In vitro Studies

In several studies, the *A. occidentale* leaves extract exhibited an antimicrobial effect by inhibiting the growth of pathogenic bacteria and fungi which was due to the presence of polyphenol compounds known as anacardic [5, 28, 68, 69]. Both Gram-positive and Gram-negative which are

Staphylococcus aureus and, *Escherichia coli* and *Klebsiella pneumonia* respectively were found to be sensitive towards the cashew leaves extract [68, 70, 71]. The antimicrobial effect of *A. occidentale* leaves extract against *E. coli* had indicated the traditional use in the treatment of diarrhea, dysentery, pile, toothache, sore gums and oral thrush in ancient times [72, 73]. Besides, the leaves extract of *A. occidentale* was reported to restrict the growth of fungi which are *Aspergillus niger*, *Penicillium digitatum* and *Colletotrichum gloeosporiodes* that the result showed *A. niger* was more sensitive to cashew leaves extract compared to *P. digitatum* and *C. gloeosporiodes* [5]. In the study by Varghese et al. [73], it was found that the presence of high concentration of tannins in the cashew leaves extract demonstrated high antimicrobial activities which it can bind and precipitate proteins, thus the positive inhibition of the growth of pathogenic bacteria and fungi.

In addition, the antimicrobial activity of cashew leaves extract using aqueous, acetone and ethanol solvents showed a different outcome after it had been tested against two Gram-positive human pathogenic bacteria like *Micrococcus luteus* and *S. aureus*, and four Gram-negative human pathogenic bacteria including *Salmonella typhi, K. pneumonia, E. coli* and *Pseudomonas aeruginosa*, respectively. It was reported that the acetone extract of the cashew leaves was the most potentially active against all the test organisms with a zone of inhibition ranging from 12.0 - 28.0 mm [72]. It might be due to the solvent used for the extraction of medicinal plants that depends on the nature of the bioactive compounds, which lead to the presence of tannins in *A. occidentale* leaves [72, 73, 75].

ANTIULCEROGENIC

Gastric ulcer is generally known as a gastrointestinal system disease located in the stomach as a sore or wound, which occurred by the factors that act against the system, and a damaged gastric barrier [69]. It may cause by stress, food or intake of drugs such as non-steroidal anti-inflammatory drugs (NSAIDs). The drugs that are commonly used for the treatment of gastric ulcer are H2 – inhibitors; cimetidine, ranitidine and omeprazole; the proton pump inhibitor [76, 77]. In South America, the cashew leaves in the form of tea have been widely utilized as folk medicine for the treatment of various diseases including ulcers [21]. The use of cashew leaves remedies to treat the gastric ulcer was introduced as it had high potency compared to the use of Orthodox drugs [69].

In vitro Studies

As reported in the phytochemical tests, the *A. occidentale* leaves extract contains various flavonoids, mainly quercetin glycoside which it protects the gastric mucosa by the presence of glycoprotein thus preventing the gastric ulcer [69]. Quercetin plays an important role in ulcerative and erosive lesion of the gastrointestinal tract. It has been shown to enhance the amount of neutral glycoproteins, the most essential proteins in the gastric mucosa, which may contribute in the defence against aggressive action [21]. It had been supported by the studies that found the phenolic compounds in the cashew leaves possessed antiulcer and anti-dysentery properties [26]. In addition, it was found that the *A. occidentale* leaves extract reduced the gastric lesion by 88.20% which glycosylated quercetin, amentoflavone derivate and a tetramer of proanthocyanidin were the compounds that responsible for the active principle of the antiulcerogenic effect [21].

In vivo Studies

As reported in the study by Chan et al. [3], the *A. occidentale* leaves extract showed the anti-ulcerogenic effect in rats which the extract doses (100 mg/kg) were more effective than one of Orthodox drugs, lansoprazole (30 mg/kg) in preventing the gastric lesions. It was also observed in the other studies that high dose of the cashew leaves extract could decrease the ulcer count and gastric secretion in rats as compared to that with the Orthodox drug, omeprazole [69]. These findings were consistent with the studies mentioned earlier that the *A. occidentale* leaves extract exhibited the antiulcerogenic effect as it contained flavonoids – quercetin glycosides hence could control the gastric lesions in rats [21, 76].

ANTI-INFLAMMATORY

Inflammation is known as a protective reaction of the body cells or tissues towards irritation, infections or injury which resulted to pain, heat, redness and swelling. It causes the dilation of the blood vessels and increased intercellular spaces which lead to the loss of function, hence results in the movement of leukocytes, proteins and fluids into the inflamed regions [77]. Histamine known as neurotransmitter for brain, spinal cord and uterus, is involved in the inflammatory response and acts as a mediator of itching [78, 79]. It is also a potent vasodilator which dilates the blood vessels to allow blood flows more easily and increases vascular permeability. By introducing histamine to rat paw, the stimulation of histaminic receptor caused the vasodilation which led to the exudation of fluid from the venular end of vessels, thus resulted in edema and extravasation of cells [78, 80].

In vitro Studies

In the studies by Awakan et al. and Souza et al. [47, 78], it was reported that *A. occidentale* leaves extract showed the anti-inflammatory effect which preventing the secretion of cytokines in the macrophage lipopolysaccharide-stimulated cells. Cytokines are the proteins mediator that important for immune system, which it can be developed by lymphocytes

(lymphokines), or monocytes (monokines) with anti-inflammatory effects [80]. The anti-inflammatory properties of the *A. occidentale* plant extract was found to be due to phytochemical compositions, mainly polyphenols compounds including quercetin, anthocyanins and tannins that are able to inhibit the expression of various cytokines and chemokines [47, 81, 82].

In vivo Studies

The anti-inflammatory properties of *A. occidentale* leaves extract has been analyzed on histamine-induced paw edema in rats by measuring the percent edema inhibition. It was found that the *A. occidentale* leaves extract contained oleamide as the most abundant bioactive compound, caused a significantly increased of anti-inflammatory activities on paw edema rats by 98.41% edema inhibition by interrupting the inflammation process which involved the formation of inflammatory mediators cycle [78, 83]. Besides, it was reported that the ethanolic extract of *A. occidentale* leaves was more effectively active in reducing the edema of carrageenan-induced rat paw as compared to that with aqueous extract [83]. It might be due to the ability of the active ingredients presented in *A. occidentale* leaves to dissolve more in ethanol rather than water, and can be used for treating inflammation [75, 84].

CONCLUSION

In a conclusion, *A. occidentale* leaves have possessed many medicinal properties including antidiabetic, antioxidant, antimicrobial, antiulcerogenic and anti-inflammatory properties that are beneficial for human health in treating the chronic diseases. As Malaysia is rich in *A. occidentale* plants, it is advantageous to investigate further and formulate plant-based medicines using cashew leaves which are biodegradable, inexpensive and safe with fewer side effects. It can be used as an alternative to conventional drugs and further enhance the growth of the pharmaceutical industry in natural products in Malaysia.

ACKNOWLEDGEMENTS

This work is part of a research project, FRGS/1/2019/STG04/UIAM/02/04, supported by the Ministry of Higher Education, Malaysia, and the International Islamic University Malaysia.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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