



Nutritional and therapeutic potentials of rambutan fruit (*Nephelium lappaceum* L.) and the by-products: a review

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Abstract

The progressive development of functional foods and herbal medicine has enthused many researchers to explore novel plant sources. In this regard, the rambutan fruit (*Nephelium lappaceum* L.) appears to be a promising candidate primarily due to its nutritional and bioactive compositions. With that, this particular review presents a systematic depiction of chemical composition and bioactivities of the rambutan fruit peel, pulp, and seed. Numerous reports do not provide sufficient data pertaining to cultivar, stage of maturity or the environment of fruit, yet the summarized data suggest a myriad of therapeutic potentials derived from the rambutan fruit. In fact, the rambutan fruit has been proven to possess phytochemicals that demonstrate anticancer, anti-allergic, anti-obesity, antidiabetic, anti-HIV, antimicrobial, anti-dengue, anti-hypercholesterolemic, and antihyperglycemic effects in varied in-vitro and in-vivo models. Nonetheless, advance studies are indispensable to further highlight the therapeutic mechanisms involved. In addition, a phytochemical analysis would further establish the rambutan fruit as a sustainable candidate in developing functional foods and pharmaceuticals.

Keywords Rambutan · Therapeutic · Phytochemicals · Anticancer · Bioactivities

Introduction

Rambutan (*Nephelium lappaceum* L.) is a tropical fruit that derives from the family of Sapindaceae, which has approximately 1400–2000 species. The plant is a native to several tropical regions of the Southeast Asia, such as Malaysia and Indonesia, but its commercial cultivation has expanded to as far as Australia, India, Madagascar, Philippines, Singapore, South Africa, Syria, Thailand, Vietnam, and Congo [1, 2]. The rambutan tree is a medium-sized evergreen tree (12–20 m) with light to dark green compound leaves with 3–11 leaflets, in which each leaflet varies from 5 to 15 cm in length and 3–10 cm in breadth [2]. The fruit is an ovoid to ellipsoid-shaped berry, which color varies from pinkish to red, yellow to orange-yellow, bright red to maroon or yellowish-red. The fruit has a thin leathery skin that is approximately 2–4 mm thick, and it is covered by fleshy pliable spinterns of 0.5–2 cm length. Although the name

‘rambutan’ has been considered to be derived from a Malay-Indonesian word ‘rambut’ that infers ‘hair’, occasionally, it is also named as ‘hairy litchi’.

The flesh of the rambutan fruit (0.4–0.8 cm thick) is juicy, whitish, translucent, or pale pink with sweet or mild sour flavor. The seed that is covered by pulp is in ovoid or oblong shape with 2.5–3.4 × 1–1.5 cm dimension [3]. The rambutan fruit is non-climacteric and can be picked as it ripens. In the case of the red varieties, color development reflects the key criteria of harvesting maturity, while a minimum of 16% soluble solids can also indicate fruit maturity level. Furthermore, among the cultivars, soluble solids happen to vary widely at full maturity, ranging from 17 to 21% [4]. The fruit weighs 22.4–64.7 g based on cultivar and agronomic conditions [5–7]. The rambutan fruit is mostly consumed fresh and is favored for the bright color, the striking appearance, and its tangy flavor [8, 9].

The rambutan fruit can be processed to yield a variety of products, such as juice, marmalade, jam, and jellies [3]. Additionally, the rambutan fruit has been used to treat fever, dysentery, and diarrhea, as well as an astringent, stomachic, and anthelmintic. In Malaysia, the dried peel of rambutan fruit has been commonly applied in traditional medicine [3, 8]. A poultice of rambutan leaves is able to relieve headache,

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whereas the bark can be used as an astringent, and a decoction of the roots is typically consumed to relieve from fever [8, 10]. As such, this present review summarizes the detailed chemical composition, antioxidants, and bioactivities of the rambutan fruit flesh, peels, and seeds, in order to better comprehend its nutritional and therapeutic potentials.

Nutritional and antioxidant potentials of rambutan peels

Chemical composition of rambutan peels

Fruit peel has always been considered as waste while processing the fruit. As for the rambutan fruit, its peel contributes from 43.7 to 57.4 wt% of the total weight, depending on the aspects of cultivar and maturity [6, 7]. The proximate compositions of fresh and dehydrated peels have been determined by Fila et al. [11]. The dried peels presented three to fourfolds higher amount of protein and fat, in comparison to that of the fresh. This rise could be attributed to condensation by moisture loss. Similarly, thiamine, riboflavin, niacin, and ascorbic acid were found at varying concentrations. Nonetheless, lower amounts of vitamins were detected in the dried peel [12], which could be attributed to heat lability of vitamins when dried at 50 °C for 24 h. Table 1 presents the chemical composition of fresh fruit peel. Several anti-nutritional compounds have also been reported in the peel, for instance, saponins, alkaloids, tannins, phytates, and oxalates, with respective concentrations at 0.53, 2.17, 1.35, 0.17, and 0.12 g 100 g⁻¹. Nevertheless, the dried peel has higher concentration for each compound [11]. Alike citrus peel; rambutan peel also contains pectin in its cell wall structure. In fact, due to its gelling ability, pectin is used in spreads and confectionery. In fresh rambutan peel, 1.05–1.9 wt% pectin is present; but it is dark in color with low methoxy content

(11.0–11.7%). Additionally, pectin from the rambutan peel has lower solubility, when compared to that of pomelo [13, 14]. Unfortunately, limited information concerning cultivar and growth condition has made data comparison impossible.

Antioxidant potential of rambutan peels

Interestingly, the peel of some fruits has displayed higher bioactivity than the edible portion due to better antioxidants profile determined based on cultivar, maturity, extraction method, and pretreatment [15]. Phenolic acids and ellagitannins appear to be the primary antioxidants in rambutan peel [12, 16–19]. In fact, a variety of solvents, such as ethanol, chloroform, ethyl acetate, methanol, butanol, hexane, and water, have been reported for extraction of peel antioxidants [17, 20–23]. For example, ethanolic extract of rambutan recorded higher total phenolics at 762 mg GAE g⁻¹ (gallic acid equivalent), in comparison to a commercially available grape seed extract [8]. In another study, Muhtadi et al. [24] evaluated peel extracts using four solvents, in which ethyl acetate displayed the highest antioxidant activity. On top of that, when compared with vitamin E, lower IC₅₀ (a concentration that reduces the response to 50%) authenticated the greater bioactivity of rambutan peel. Besides, radial chromatography and vacuum liquid chromatography with nuclear magnetic resonance (¹³C-NMR and ¹H-NMR) analyses had confirmed the presence of ethyl gallate (Fig. 1).

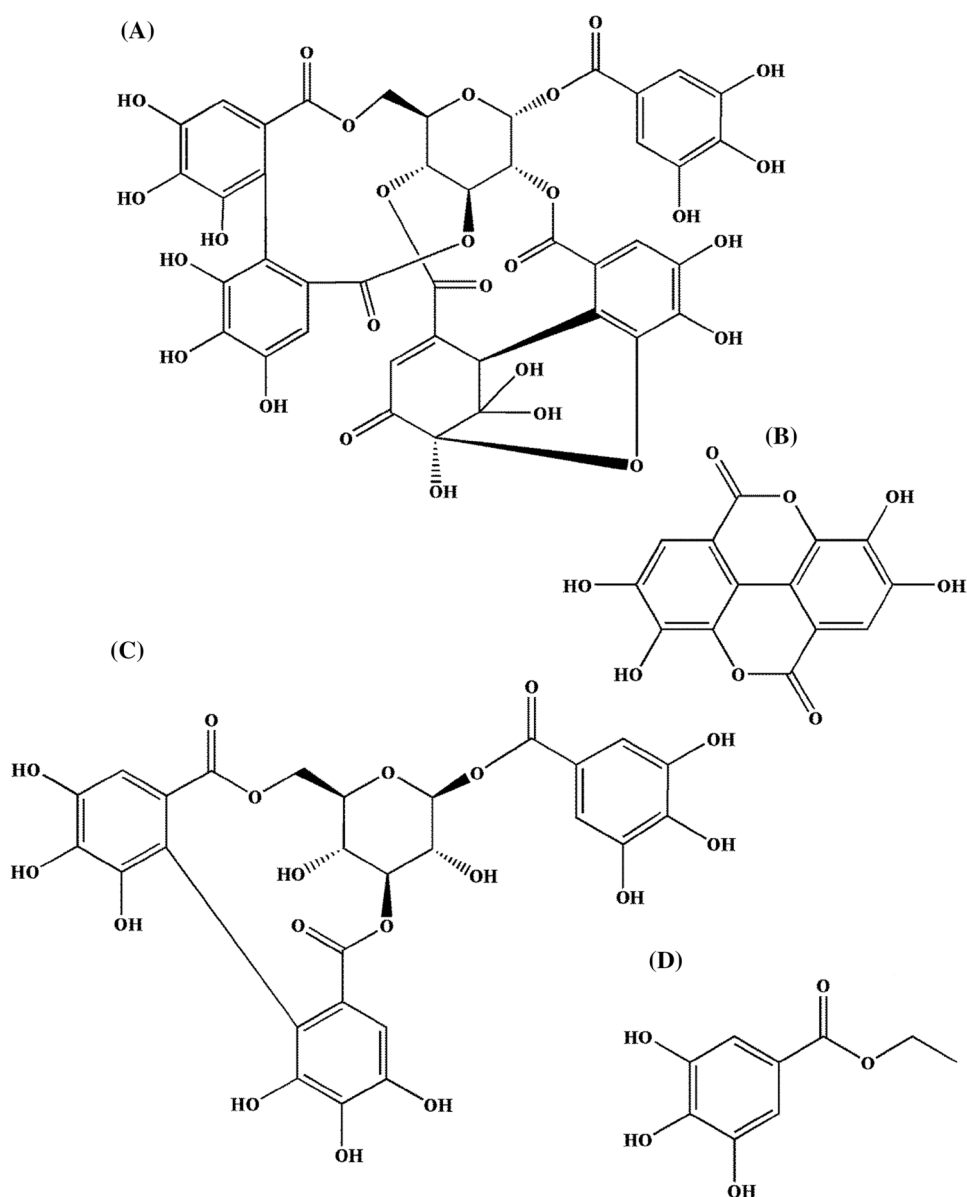
In a prior study, methanolic extract of peel showed better bioactivity when assessed with lipid peroxidation and diphenyl-1-picrylhydrazyl scavenging (DPPH) assays, whereby the researchers ascertained the presence of geraniin, coralligin, and ellagic acid as primary antioxidants found in the peel [12]. Nevertheless, Palanisamy et al. [17, 18] reported lower amount of the three antioxidants mentioned. The outcomes had been varied in both studies probably due to different cultivar and geological area of cultivation. Meanwhile, in another study, geraniin was purified from ethanolic extract of peel. As a result, elaeocarpusin and corilagin appeared to be the main impurities that portrayed structural and functional similarities with geraniin [25].

Fruit cultivar, maturity, and extraction methods have been proven to exert great influence upon the antioxidant activity of peel [12, 26]. Thitilertdech et al. [12] evaluated the phenolic compounds of ‘Rongrien’ and ‘Seechompoo’. The maximum total phenolics were recorded at the time of harvest. In addition, free radical scavenging activity of peel ethanolic extract was confirmed via DPPH assay [27]. The IC₅₀ was reported within the range of 1.4–4.7 µg mL⁻¹ through plant development [26]. Next, Gusman and Tsai [21] evaluated antioxidant potential of red and yellow rambutan cultivars via conventional (12 h) and ultrasonic (2 min) extraction methods. The ultrasonic extraction method enhanced the recovery process and displayed higher total phenolics with

Table 1 Rambutan fruit peel chemical composition

Ingredient	Amount	References
Moisture (g 100 g ⁻¹)	72.05	[15]
Lipids (g 100 g ⁻¹)	0.23	
Carbohydrates (g 100 g ⁻¹)	23.78	[12]
Protein (g 100 g ⁻¹)	2.04	
Fiber (g 100 g ⁻¹)	0.7	
Ash (g 100 g ⁻¹)	1.2	
Vitamins		
Carotene (µg 100 g ⁻¹)	10.60	
Thiamine (mg 100 g ⁻¹)	0.04	
Riboflavin (mg 100 g ⁻¹)	0.06	
Niacin (mg 100 g ⁻¹)	0.31	
Ascorbic acid (mg 100 g ⁻¹)	7.43	

Fig. 1 Structures of (A) geraniin, (B) ellagic acid, (C) corilagin and (D) ethyl gallate extracted from rambutan



better ferric-reducing ability (FRAP). Moreover, almost 20% upsurge in phenolics and 8% increment in FRAP had been observed with the ultrasonic extraction technique. Nonetheless, fruit blanching did not alter the activities of peel antioxidants [28].

Safety evaluation and bioactivities of rambutan peels

Safety evaluation of peels

Safety evaluation of any traditional herbal drug is essential to evaluate its toxicity effect upon model animals or cells. As such, numerous in-vivo and in-vitro studies have

validated the safety of rambutan peel [8, 23, 29, 30]. In a study, acute toxicity was estimated by feeding a single dose of peel ($1\text{--}5\text{ g kg}^{-1}\text{ BW}$) to male Wistar rats. The calculated LD_{50} (amount of active substance that kills half of the test sample) values had been higher than the studied range of dosage. Likewise, for trial of sub-chronic toxicity, an oral dose of $0.5\text{--}2\text{ g kg}^{-1}\text{ BW}$ was given for 30 days. Although no symptom of abnormality or mortality was observed for $1\text{ g kg}^{-1}\text{ BW}$ dose, 12.5% mortality rate had been recorded when $2\text{ g kg}^{-1}\text{ BW}$ dose was fed. Nevertheless, both studies reported a significant decrease in food consumption and bodyweight. Furthermore, in an acute toxicity study, serum triglycerides, alanine transferase, and aspartate aminotransferase remained unaltered. Conversely, serum triglycerides and blood-urea-nitrogen recorded a decrease in another

sub-chronic toxicity study, whereas alanine transferase and aspartate aminotransferase remained unaffected [29].

DPPH radical is a potential inducer of cell death through apoptosis. In a study, apoptotic death induced mouse fibroblasts (3T3) were cultured with the presence of aqueous and ethanolic extracts. The DPPH triggered cell death, but the mortality rate was reduced after addition of extract ($100 \mu\text{g mL}^{-1}$). Besides, no adverse effect was noted on the propagation of cells, thus signifying the non-toxic nature of both extracts [8]. Similarly, Okonogi et al. [23] determined the probable toxicity of methanolic extract against human peripheral blood mononuclear cells (PBMCs). The extract presented IC_{50} only at higher concentration ($> 100 \mu\text{g mL}^{-1}$). Similar cells were employed to assess potential toxicity for four various types of solvent extracts. The calculated IC_{50} and ED_{50} (effective doses with quantal effect in 50% population) for all extracts resulted in null to very mild toxicity. On the contrary, Chunglok et al. [30] reported a very weak cytotoxicity of rambutan pericarp against PBMCs when methanolic extract was used. Besides, the IC_{50} value exceeded $350 \mu\text{g mL}^{-1}$. Unfortunately, the scant number of reports with limited information concerning cultivar and standardized extracts has limited indefinite assurance on peel safety. As such, scientific mechanisms should be incorporated so as to gain thorough understanding pertaining to peel safety.

Antimicrobial and antiviral potentials

Since prehistoric times, herbs and extracts have been applied as natural antimicrobial agents. Mostly, the antimicrobial potential of rambutan peel has been determined by calculating the minimum inhibitory concentration (the lowest concentration of extract that prevents the visible growth of microbe after overnight incubation) and the minimum bactericidal concentration (the lowest concentration of extract for bacterial death). Besides, methanolic extract of peel was examined to test antibacterial and antifungal potencies. As a result, Gram positive bacteria (*Streptococcus mutans*, *Staphylococcus aureus*, and methicillin-resistant *Staphylococcus aureus*) displayed some sensitivity towards the extract, whereas Gram negative bacteria (*Escherichia coli*) and a fungus '*Candida albicans*' portrayed resistance [20]. Similarly, aqueous and hydroethanol extracts were tested on *Bacillus subtilis*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Candida albicans*. The aqueous extract showed good antimicrobial activity against *Staphylococcus aureus* with minimum inhibitory concentration of $250 \mu\text{g mL}^{-1}$, while $500 \mu\text{g mL}^{-1}$ for *Bacillus subtilis*. Nevertheless, *Candida albicans* and *Escherichia coli* remained insensitive [31]. Thitilertdech et al. [32] reported antimicrobial activity of aqueous, ether, and methanolic extracts on freeze dried peel of rambutan against bacteria. They discovered *Vibrio*

cholerae (Gram negative) was more sensitive for aqueous and methanolic extracts. Meanwhile, out of Gram-positive bacteria, *Staphylococcus epidermidis* appeared as the most sensitive for methanolic extract [32].

Numerous measurements have been put into practice so as to combat dengue virus—the cause of dengue fever. Dengue hemorrhagic fever and dengue shock syndrome are precarious types of fever due to multiple exposures to the closely related four serotypes. Ahmad et al. [33] described that the geraniin extract from rambutan peel is effective against the Asian strain of dengue virus type-2 (DENV-2). The findings of plaque reduction assay indicated that geraniin inhibited attachment of virus to the cells. Furthermore, the time-of-drug-addition assay showed that geraniin affected the early stages of virus replication by reacting with envelope protein (E-proteins). Moreover, the docking assay signified that geraniin interacted with viral proteins, prevented virus attachment, and disrupted infection process [33].

Anticancer and anti-allergic effects

The studies that have suggested the potential toxicity of peel extract against various animal and human cells [8, 30] have also examined the aspect of cytotoxicity upon cancerous cells. Viability of human mouth-epidermal carcinoma cells and colorectal adenocarcinoma cells (Caco-2) were tested in the presence of peel extract with butanol, ethyl acetate, hexane, and methanol [23, 27]. As a result, the calculated IC_{50} and ED_{50} of all the extracts suggested mild cytotoxicity for both types of cells [23]. Likewise, Chunglok et al. [30] revealed weak cytotoxicity for methanolic extract of rambutan pericarp against human mouth carcinoma cells (CLS-354). A dose-dependent reduction in viability was also observed via MTT assay. On the contrary, Ampasavate et al. [34] cultured four cancer cell lines (HL60, K562, Molt4, and U937) in peel ethanolic extract and discovered nil cytotoxicity [34]. Scant literature report on cultivar information and variation in assays that estimated anticancer activity disallows further comparison or definite conclusion for the exact extent of peel potential.

β -hexosaminidase is released when the body responds to allergens. Traditionally, herbal medicines have been employed to treat various types of allergic reactions. In a study, rambutan peel extracts were prepared by using water and aqueous ethanol to be tested as anti-allergic by inhibiting the release of β -hexosaminidase from basophilic leukemic cells (RBL-2H3 cells) [31]. At a given concentration ($100 \mu\text{g mL}^{-1}$), enhanced inhibition of β -hexosaminidase was displayed by ethanol (77.57%), and followed by hot water (65.71%). The reported study, however, is limited to release of β -hexosaminidase, in which histamine release should also be determined via inhibition mechanism.

Anti-obesity effect

Obesity appears to be a typical disorder that results from excessive accumulation of fat in adipose tissues due to hypertrophy and hyperplasia [35, 36]. The process of adipogenesis is supported by both insulin and insulin-like growth factors (Igf-1) [37, 38]. Insulin-like growth factor (Igf-1) has structural similarities to insulin. It has a vital role in growth during childhood that contributes to adipogenesis, apart from being part in various anabolic processes in adults. In addition, fatty acid synthase enzyme also equally contributes to adipogenesis. In an experiment regarding anti-obesity, the effect of rambutan peel was examined in *Rattus norvegicus* (brown rats). Doses of 15, 30, and 60 mg kg⁻¹ BW were fed at every second day up to 3 months. The bodyweight gain was reduced by 25 wt% at a dose of 30 mg kg⁻¹ BW although the feed consumption pattern was retained. However, both expressions of Igf-1 and Igf-1r had been affected, and consequently, a reduction in the size of adipocytes had been noted [39].

The best extract dose from a prior study (30 mg kg⁻¹ BW) was given to both normal and obese male Wistar rats, in which, interestingly, equal expressions of Igf-1 and Igf-1r in visceral fat tissues were observed. Thus, it was suggested that the reduced expressions of Igf-1 and Igf-1r inhibited extracellular signal-regulated kinases (1 and 2), and PPAR expression, which ultimately impeded adipogenesis [40]. In another experiment, similar animal model was fed with lower dose of rambutan peel extract. Again, bodyweight gain and Igf-1 expression were estimated. In fact, although lower dose turned to be more effective in lowering bodyweight gain, the least expression of Igf-1 was observed at higher dose. They suggested that the anti-obesity effect due to the extract did not adhere to Igf or tyrosine-kinase pathways [41]. Nonetheless, several chemical messengers, such as bone morphogenetic proteins, tumor growth, and necrosis factors, might have stimulated adipogenesis [42]. The peel extract dose was also found to be effective in lowering serum lipids, bodyweight gain, and visceral tissue protein (a carrier of fatty acids that aids in adipogenesis) in obese rats [43]. On the other hand, Lestari et al. (2014) carried out a study where rats with high caloric diet were treated with both peel extract and ellagic acid. The best dose of the peel (30 mg kg⁻¹ BW) and ellagic acid down-regulated the expressions of Igf-1 and Igf-1r in visceral fat tissues, thus resulting in the least bodyweight gain [44].

Fat deposition in adipocytes does not only alter lipid metabolism, but it also triggers the lipids to deposit in the liver, hence resulting in fatty liver [45]. The lipids in liver lead to the expression of peroxisome proliferator activating receptor (PPAR)—a transcription factor that controls insulin sensitivity, glucose regulation, and lipid metabolism in the liver, aside from generating excessive free radicals

in the body [46]. The production of free radicals further disrupts cellular activity due to oxidation of cell membrane lipids. Malondialdehyde (MDA) is an oxidation product of polyunsaturated fatty acids, and its accumulation has been considered as an indication of tissue damage. In an in-vivo study, rambutan peel extract was fed to male Wistar rats. A significant reduction in MDA was noted for doses 15 and 30 mg kg⁻¹ BW, but only slight down-regulation for PPAR γ [47]. This shows that rambutan peel can inhibit tissue damage by controlling the production of free radicals. Similarly, aqueous extract of peel resulted in down-regulating the expression of PPAR γ in obese rats [48]. Furthermore, reduction had been recorded for gain in BW, size of adipocytes, and triglycerides level. Additionally, fatty acid binding protein-4 (FABP-4) and messenger RNA (mRNA) for FABP-4 genes were down-regulated significantly ($p < 0.05$) [48]. Therefore, a suggested anti-obesity mechanism refers to inhibition of new fat cells formation.

Fatty acid synthase (FAS) refers to an enzyme with a complex multi-enzyme protein that regulates the synthesis of fatty acids, which appears to be a factor for obesity. Enzyme inhibition may also be a route to avoid adipogenesis. In a study, ethanolic extract of rambutan peel was fractionated by using water, petroleum ether, ethyl acetate, and butanol, which was then evaluated for anti-FAS activity in-vitro [49]. The IC₅₀ was observed within the range of 6.69 to 204.4 μ M, and flavonoid-like structures in the extract emerged as the highest anti-FAS activity. Nevertheless, the extracted oligoglycosides signified enhanced anti-FAS activity with increment noted for the acetyl groups in molecule. These olean-type triterpenes have been reckoned to inhibit pancreatic lipase activity [50, 51].

Antidiabetic activity

Hyperglycemia is an attribute associated to diabetes, which mainly occurs due to defect in insulin production and its activity or both. Diabetes can be classified into two categories: first that depends on insulin or type-1 (IDDM), and second is non-insulin dependent or type-2 (NIDDM). Type-1 could be due to lack of partial or complete functionality of β -cells in pancreas, whereas in type-2, the development of lipid imbalance and impaired carbohydrates metabolism lead to enhanced postprandial blood glucose level [52, 53]. However, the elevated postprandial hyperglycemia can be addressed by preventing absorption of glucose by manipulating the functionality of several carbohydrate hydrolyzing enzymes, namely α -amylase and α -glucosidase [54–57]. Moreover, the formation of advanced glycation-end-products (glycated proteins or lipids) is also a contributing factor for diabetes. Some plant extracts have antidiabetic potential as the bioactive compounds possess the ability to rehabilitate

the activity of pancreatic β -cells (insulin producing cells), apart from inducing the antihyperglycemic effect.

The extract of rambutan peel has exhibited potential in managing type-1 and type-2 diabetes mellitus [17, 54–58]. For example, Suhendi and Muhtadi [58] induced type-1 diabetic conditions in male Wistar rats by injecting alloxan monohydrate. Alloxan refers to a glucose analog that destroys β -cells in pancreas, aside from generating type-1 diabetes that is also called alloxan diabetes. The effect of rambutan peel extract (ethanol:acetone) on blood glucose was successfully evaluated as maximum lowering was observed for the highest dose employed in the study. Similar results were retrieved when same doses of peel ethanolic extract were tested on alloxan-induced diabetic albino rats. As a result, the maximum reduction in glucose was 61.76% for the highest dose applied in the study [59].

In the attempt to cure type-2 diabetes mellitus, several studies have looked into controlling the activities of carbohydrate hydrolyzing enzymes. In a study, aqueous and ethanolic extracts from rambutan peel had been evaluated to regulate the responses of α -amylase and α -glucosidase. As for α -glucosidase, the ethanolic extract exhibited lower EC_{50} (a concentration that results in half-maximal response) than aqueous extract. Interestingly, both the extracts were more potent than the positive control acarbose. Nevertheless, the aqueous extract did not show any activity against α -amylase, but ethanolic extract proved potent enough. In addition, the ethanolic extract inhibited the activity of aldol reductase in polyol pathway, which prevented the formation of advanced glycation-end-products and it appeared to be far more effective than green tea [17]. Similarly, Thinkratok et al. [29] tested the hydroethanolic extract and purified tannins of the peel in the attempt to manipulate activities of α -amylase and α -glucosidase. At certain concentration of extract and tannins, the extract performed better inhibition towards α -amylase and α -glucosidase activities, when compared to purified tannins [29]. The better performance of crude extract can be attributed to the synergistic effect due to presence of other compounds with greater bioactivity. On the contrary, purified geraniin had been more potent in inhibiting the activities of α -amylase and α -glucosidase. While in the case of aldol reductase, the ethanolic extract exhibited greater reactivity. Such variation discovered in the inhibition activity of extracts could be due to the substrate-oriented reactivity of aldol reductase. On top of that, geraniin is superior to extract in inhibiting the formation of glycation end-products [17]. For instance, Widowati et al. [60] prepared peel ethanolic extract via maceration method and provided astonishing results. Interestingly, extract was revealed to perform better in inhibiting activities exerted by α - and α -glucosidases than did pure geraniin. The IC_{50} of geraniin in controlling α -glucosidase was almost threefold higher than that of the extract.

Anti-arthritic activities

Arthritis reflects inflammation, swelling, and stiffness of joints, tendons, muscles, and cartilages. In fact, it can be categorized into more than a hundred types based on symptoms. The anti-arthritic activity displayed by ethanolic extract of peel was tested on dark agouti rats. Type-2 collagen ($4 \text{ mg kg}^{-1} \text{ BW}$) was injected with complete Freund's adjuvant (immune booster) to induce arthritis. An oral dose of $100\text{--}200 \text{ mg kg}^{-1} \text{ BW}$ of the extract was administered to the animals. As a result, paw edema was significantly ($p < 0.05$) reduced by the extract dose. Similarly, a decrease was observed in C-reactive protein (plasma protein with enhanced level upon inflammation). A dose-dependent response was noted for matrix metalloprotease-13 and tissue inhibitors of metalloprotease-1 (enzymes responsible for collagen breakdown). The extract further suppressed histopathological, physiological, and biochemical alterations, and ultimately protected the tissues from any damage or inflammation in rats [61]. A summarized listing of the peel bioactivities is displayed in Table 2.

Improved cardiovascular response

Anesthetic is an important aspect of surgery that may result in unpredictable side effects at times. Srisawat et al. [63] determined the acute effect of rambutan peel extract on cardiovascular response in male rats. As such, pentobarbital-anesthetized rats were tested for heart rate, respiratory rate, and invasive arterial blood pressure for 2 h after a single dose of $1 \text{ g kg}^{-1} \text{ BW}$ was administered. Pentobarbital refers to a short-term anesthetic used in minor surgeries. As a result, the systolic pressure of rat heart exhibited a marked improvement with rambutan extract. Besides, the mean of arterial blood pressure, systolic and diastolic pressure, as well as heartbeat rate, were enhanced. However, the rate of respiration remained unchanged.

Nutritional and antioxidant potentials of rambutan pulp

Chemical composition of rambutan pulp

Fruit pulp makes up 38.5–46.7 wt% of the whole fruit based on cultivar and maturity [64, 65]. The flavor of the pulp is slightly sour to sweet, with 2.36% of acidity and pH values at 3.67 [62]. Wall [66] investigated six rambutan cultivars, namely, R9, Jitlee, R162, Rongrien, R134, and Silengkeng, to determine their macro- and micro-minerals. It has been claimed that the rambutan fruit can fulfill almost 20% of the daily recommended intake (DRI) for copper, while 8–10% for manganese. Similar to many other fruits, a fair amount of

Table 2 Rambutan peel safety and bioactivity in different in vitro and in vivo models

Study	Extract/compound	Extraction conditions	Model	Findings	References
Animal toxicity	Aqueous ethanol	Room temperature for 7 days	Male Wistar rats	Sub-chronic and acute toxicity studies with no symptoms of abnormality were observed	[31]
Cell toxicity	Ethanol	Room temperature for 24 h	Mouse normal fibroblasts (3T3)	No toxicity was observed	[8]
	Methanol	30 °C for 3 h	Human peripheral blood mononuclear cells (PBMCs)	No toxicity was observed	[32]
Anti-allergic activity	Ethanol	Room temperature for 3 days	PBMCs	A standard MTT assay was adopted. The extract exhibited very weak toxicity	[28]
	Butanol, ethyl acetate, hexane, methanol	Room temperature for 48 h	PBMCs	No toxicity was observed	[24]
	Hot water, ethanol	Hot water for 3 h Ethanol at room temperature for 3 h	Basophilic leukemic cells (RBL-2H3)	Ethanol presented the maximum release inhibition of β -hexosaminidase	[33]
Antimicrobial activity	Ethanol, hot water	Ethanol at room temperature for 3 h; Hot water for 3 h	<i>S. aureus</i> , <i>B. subtilis</i> , <i>P. aeruginosa</i>	The most potent were hot water extract	[33]
	Methanol	Room temperature	<i>S. aureus</i> , <i>S. mutans</i> , Methicillin-resistant <i>S. aureus</i> , <i>E. coli</i> , <i>C. albicans</i> (fungus)	Active against Gram-positive but inactive against Gram-negative and fungus	[22]
	Water, ether, methanol	–	Gram-negative: <i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. typhi</i> , <i>V. cholera</i> Gram-positive: <i>E. faecalis</i> , <i>S. epidermidis</i> , <i>S. aureus</i>	For all extracts, <i>V. cholerae</i> and <i>S. epidermidis</i> were the most sensitive	[34]
Anticancer activity	Methanol	30 °C for 3 h	Human mouth carcinoma cells (CLS-354)	A weaker cytotoxicity was observed	[32]
	Ethanol	Room temperature for 3 days	Human intestinal adenocarcinoma (Caco-2)	The extract exhibited a mild cytotoxic nature	[28]
Antidiabetic and anti-hypercholesterolemic activity	Butanol, ethyl acetate, hexane, methanol	Room temperature for 48 h	Human mouth epidermal carcinoma cells (KB), Caco-2	Hexane and ethyl acetate indicated mild toxicity for the cells	[24]
	Ethanol: acetone (4:1)	Room temperature for 3 days	Male Wistar mice	Reduced blood glucose and cholesterol levels were observed	[60]
	Ethanol	–	Alloxan induced diabetic male albino rats	Reduced blood glucose was observed	[61]

Table 2 (continued)

Study	Extract/compound	Extraction conditions	Model	Findings	References
Anti-obesity study	Distilled water	Homogenization for 5 min	Male Wistar rats	Lower bodyweight gain, triglycerides, and smaller size adipocytes were observed	[42]
	Ethanol	–	Male rat	High-calorie diet was fed but a significant reduction in weight gain and triglycerides were noticed	[41]
	Ethanol	–	Normal, obese rats	In obese rats, reduced expression of insulin-like growth factor (Igf-1) and low weight gain were seen	[53]
	Ethanol: water; tannins	Room temperature for 7 days	α -Amylase, α -glucosidase	Above 90% inhibitions were seen for both enzymes	[62]
	Ethanol	Reflux conditions	Fatty acid synthase (FAS)	Better enzyme inhibition was found	[51]
Anti-hyperglycemic activity	Peel powder	–	<i>Rattus norvegicus</i>	Reduced size of adipocytes and inhibition in weight gain were observed	[46]
	Ethanol	–	Normal and obese Wistar rats	The expression of insulin-like growth factor and receptor (Igf-1 and Igf-1r) was similar to the normal group	[40]
	Ethanol	Room temperature for 4–5 days	Obese male Wistar rats	Less bodyweight-gain and lower igf-1 expression were observed	[49]
	Geraniin	Ethanol extraction at room temperature for 24 h	Aldol reductase, α -glucosidase, α -amylase	Stronger inhibition of all enzymes was seen	[21]
	Ethanol	–	α - and β -Glucosidases	A better inhibition of α -glucosidase was observed	[63]
Antiviral activity	Water, ethanol	Water at 40 °C for 24 h; ethanol at room temperature 24 h	$\alpha\alpha$ -Amylase, α -glucosidase, aldol reductase	The strongest inhibition of aldol reductase was seen for ethanolic extract	[21]
	Geraniin	–	Dengue virus type-2	Inhibition of viral attachment to cells and hindrance in its replication cycle were suggested	[35]

ascorbic acid is present ranging between 22.0 and 47.8 mg 100 g⁻¹ [66]. Nonetheless, Arenas et al. [67] reported higher (67.9 to 69.1 mg 100 g⁻¹) ascorbic acid contents in Mexican cultivars (RT-01, RT-02, RT-03, RT-04, and RT-05). The presence of other vitamins, such as thiamine, riboflavin, and niacin, was also recorded. Additionally, some anti-nutritional components, such as saponins (1.50 mg 100 g⁻¹), tannin (0.12 mg 100 g⁻¹), phytates (0.15 mg 100 g⁻¹), and oxalates (0.11 mg 100 g⁻¹), have also been observed [11]. Table 3 depicts the nutritional composition of the fruit pulp.

Antioxidant potential of rambutan pulp

Fresh fruit juices are appraised for abundant antioxidants, where flavonols, flavanones, carotenoids, and polyphenols are present in vast expanse. The total antioxidant capacity of rambutan fruit pulp was assessed by using ascorbic acid equivalent antioxidant capacity assay (AEAC) and resulted in 71.5 mg 100 g⁻¹ of pulp [69]. In addition, Supapvanich [68] reported the effect of salicylic acid and hot water pretreatment on antioxidants. Interestingly, enhanced antioxidant capacity and total phenolics had been noted, as secondary metabolites were triggered under stress. A plant pigment,

lycopene—a phytochemical—was present at a concentration of 148 µg 100 g⁻¹ of pulp [70]. Likewise, 181.3 mg 100 g⁻¹ of total anthocyanins are present [71]. Meanwhile, in another study, enzymatic extraction of anthocyanins had been performed by using cellulase. The highest anthocyanins were obtained at a solid to liquid ratio of 1:15, with pH ~ 5.2 and 55 °C [72].

Ellagic acid, corilagin, and geraniin (Fig. 1) are considered as the main contributors in fruit antioxidant activity. Ellagic acid is a secondary metabolite (phenolics) in plants that is often found in cell vacuoles. Furthermore, it is also well-known for possessing antioxidant, anti-atherogenic, antiproliferative, and chemopreventive properties [73]. Meanwhile, geraniin is a crystalline ellagitannin with slight astringency to human tongue and possesses the ability to bind proteins [74, 75]. In fact, several studies have proven that geraniin is a potential antioxidant, a nitrous oxide (NO) scavenger, and an anticancer agent [12, 76, 77]. For example, Thitilertdech and Rakariyatham [78] discovered increment in concentrations of ellagitannins and phenolics along with fruit development, hence contributing to radical scavenging activities. In addition, γ-aminobutyric acid (GABA) was noted in fresh ‘Rongrien’ cultivar at a fair amount (0.71 mg g⁻¹) [78]. In humans, the GABA enacts relaxation, diminishes anxiety, and regulates muscle tone [79, 80]. Apart from those, GABA has been revealed to lower blood pressure, improve long-term memory, function as diuretic, and counteract diabetes by enhancing secretion of insulin [81].

Table 3 Nutritional composition of rambutan fruit pulp

Component	Amount	References
Moisture (g 100 g ⁻¹)	78.5–84.7	[3, 15, 66]
Carbohydrates (g 100 g ⁻¹)	15.7–19.66	[3, 15, 66]
Protein (g 100 g ⁻¹)	0.46–1.05	[3, 15, 66]
Fiber (g 100 g ⁻¹)	0.3–2.8	[3, 15, 66]
Ash (g 100 g ⁻¹)	0.3–0.6	[15, 66]
Sugars (mg g ⁻¹)		[68]
Glucose	14.0	
Fructose	22.0	
Sucrose	23.0	
Minerals (g 100 g ⁻¹)		
Phosphorus	17.1	[69]
Potassium	229.0	
Calcium	8.7	
Magnesium	16.6	
Sodium	6.5	
Iron	0.53	
Manganese	0.19	
Zinc	0.21	
Copper	0.17	
Boron	0.14	
Vitamins (mg 100 g ⁻¹)		
Ascorbic acid	22.2–29.0	[66, 67]
Thiamine	0.02	[12]
Riboflavin	0.06	
Niacin	0.78	

Bioactivities of rambutan pulp

Anti-allergic activity

Allergy, which is a type of immune dysfunction, has emerged as a crucial health issue at the global scale. Allergens refer to substances that cause allergic reactions in cells. In response, histamine is released, along with β-hexosaminidase, from basophils. In a study, ethanolic and aqueous extracts of rambutan flesh were tested for allergic reaction in basophilic leukemic cells (RBL-2H3) by taking into account hexosaminidase release [82]. Inhibition of β-hexosaminidase by ethanolic and hot water extract had been 83.36 and 87.43%, respectively. Nonetheless, the IC₅₀ for hot water extract was higher (62.1 µg mL⁻¹) than that for ethanol (30.9 µg mL⁻¹).

Cholesterol-mediating effect

Cholesterol is a sterol and a type of lipid that supports vast functions in the human body. Cholesterol can be classified as good or bad cholesterol. Bad cholesterol is the cause of many cardiovascular ailments in humans. In a study, the rambutan fruit was evaluated to determine

cholesterol-regulating activity in humans [83]. As such, the rambutan fruit (400–500 g) was included in the diet of an equal number of both genders for 30 days. Serum cholesterol and high-density lipoproteins (HDL-cholesterol) were identified prior to supplementation, as well as at second and fourth week. Interestingly, by supplementation, only the female subjects displayed significant reduction in cholesterol level. Nevertheless, this lowering effect was recorded for only 3 weeks until termination of the rambutan dose in diet. However, the cholesterol-lowering effect appeared to be the most prominent in the group with high basal cholesterol in their diets. With that, the exact mechanism to lower cholesterol demands further investigation.

Nutritional and antioxidant potentials of rambutan seeds

Chemical composition of rambutan seeds

Similar to peel, the rambutan seed is also typically considered as a waste by-product in the fruit processing industry. Nevertheless, roasted seeds are edible and consumed in some Asian countries [2, 6]. In a rambutan fruit, the flattened oblong seed adds 4.0–9.5 wt% in the total weight based on cultivar and maturity [6, 7, 84]. The chemical composition of the fresh rambutan seed is shown in Table 4. Dried seed displayed higher values for protein, fat, and carbohydrates when compared to fresh seed [64]. The profile of amino acid suggests that the seed has good quality protein due to the presence of most essential and non-essential amino acids [7].

Table 5 presents the detailed listing of amino acids, along with their relative amounts, found in the rambutan seed. A greater variation in seed lipids is observed in literature based

Table 4 Chemical composition of rambutan raw seed

Component	Amount	References
Moisture (g 100 g ⁻¹)	34.28–34.6	[7, 15]
Lipids (g 100 g ⁻¹)	18.19–38.9	
Carbohydrates (g 100 g ⁻¹)	33.65–61.6	[7, 15, 85]
Protein (g 100 g ⁻¹)	11.06–14.1	
Fiber (g 100 g ⁻¹)	0.62–6.6	
Ash (g 100 g ⁻¹)	2.20–2.9	
Minerals (mg 100 g ⁻¹)		[85]
Calcium	30.4	
Iron	2.80	
Vitamins		[12]
Carotene (µg 100 g ⁻¹)	3.42	
Thiamine (mg 100 g ⁻¹)	0.02	
Riboflavin (mg 100 g ⁻¹)	0.09	
Niacin (mg 100 g ⁻¹)	0.08	

Table 5 Amino acid (AA) profile for rambutan seeds

Essential AA	Amount (g 100 g ⁻¹ protein)	Non-essential AA	Amount (g 100 g ⁻¹ protein)
Isoleucine	3.29–3.34	Alanine	4.65–4.83
Leucine	5.48–5.78	Arginine	4.63–5.75
Lysine	5.07–7.13	Aspartic acid	7.24–9.80
Methionine	1.35–1.63	Cysteine	1.45–1.82
Phenylalanine	2.49–3.32	Glutamic acid	10.85–14.95
Valine	4.21–5.11	Glycine	8.51–9.92
Histidine	1.29–1.68	Proline	1.96–2.93
–	–	Serine	4.44–5.56
–	–	Threonine	3.59–5.41
–	–	Tyrosine	2.58–3.29

From: [7]

on cultivar, extraction conditions, and agronomic area of cultivation. The presence of substantial lipids amount (18–39%) suggests a novel source. The main fatty acids in seed lipids are arachidic acid, oleic acid, stearic acid, and palmitic acid [6, 84, 86]. Table 6 enlists the complete profile of saturated and unsaturated fatty acids of the rambutan seed.

Recently, the idea of partially replacing cocoa butter with rambutan seed fat in chocolate has been made viable. Table 7

Table 6 Fatty acid composition of rambutan seed lipids

Fatty acids	Composition (%)			
	[87] ^a	[88] ^b	[6] ^c	[89] ^d
Saturated				
Myristic acid (C _{14:0})	0.02	0.01	–	0.13
Palmitic acid (C _{16:0})	4.69	7.39	6.1	4.60
Stearic acid (C _{18:0})	7.03	16.58	7.1	7.88
Arachidic acid (C _{20:0})	34.32	12.34	34.5	31.53
Heneicosanoic acid (C _{21:0})	0.05	–	–	–
Behenic acid (C _{22:0})	3.10	8.91	2.9	2.10
Tricosanoic acid (C _{23:0})	0.03	–	–	–
Lignoceric acid (C _{24:0})	0.33	–	–	–
Mono-unsaturated				
Palmitoleic acid (C _{16:1})	0.49	0.49	1.5	0.72
Elaidic acid (C _{18:1})	0.03	0.02	–	–
Oleic acid (C _{18:1})	36.79	52.18	40.3	43.09
Gadoleic acid (C _{20:1})	–	–	–	5.89
Erucic acid (C _{22:1})	0.66	–	–	0.10
Poly-unsaturated				
Linolenic acid (C _{18:3})	6.48	2.02	–	0.74
Linoleic acid (C _{18:2})	1.37	–	–	3.22
Eicosadienoic acid (C _{20:2})	0.04	–	–	–

Solvents used in extraction of lipids in different studies: ^ahexane [87]; ^bsupercritical-CO₂ [88]; ^chexane [6]; ^dpetroleum ether [89]

Table 7 Main triglycerides of rambutan seed lipids

Triglycerides (%)	[90] ^a	[89] ^b
AAA	1.40	–
OOO	1.426	0.91
ALnO	3.035	–
ALO	0.976	–
ALP	6.327	–
ALnS	1.486	–
AOO	49.840	–
AOP	12.822	–
ASO	15.058	–
ASP	9.030	–
LLL	–	2.18
PLP	–	0.64
POL + SLL	–	0.39
POO	–	1.40
PPO	–	0.90
SOO	–	3.0
POS	–	1.63
PPS	–	0.26
Unknown	–	87.29

Palmitic acid (P), stearic acid (s), oleic acid (o), linolenic acid (ln), linoleic acid (l), arachidic acid (a)

AAA triarachidin, OOO triolein, ALnO 1-arachidyl-2-linolenyl-oleoyl-glycerol, ALO 1-arachidyl-2-linoleoyl-3-oleoyl-glycerol, ALP 1-arachidyl-2-linoleoyl-3-palmitoyl-glycerol, ALnS 1-arachidyl-2-linolenyl-3-stearoyl-glycerol, AOO 1-arachidyl-2,3-dioleoyl-rac-glycerol, AOP 1-arachidyl-2-oleoyl-3-palmitoyl-glycerol, ASO 1-arachidyl-2-stearoyl-3-oleoyl-glycerol, ASP 1-arachidyl-2-stearoyl-3-palmitoyl-glycerol, LLL trilinolein, PLP 1,3-di palmitoyl-2-linoleoyl-glycerol, POL 1-palmitoyl-2-oleoyl-3-linoleoyl-rac-glycerol; SLL 1,2-dilinoleoyl-3-stearoyl-glycerol, POO 1,2-dioleoyl-3-palmitoyl-rac-glycerol, PPO 1,2-dipalmitoyl-3-oleoyl-glycerol, SOO 1,2-dioleoyl-3-stearoyl-glycerol, POS 1-palmitoyl-2-oleoyl-3-stearoyl-glycerol, PPS 1,2-dipalmitoyl-3-stearoyl-glycerol

^a‘Anak sekolah’ seed fat (extracted by hexane)

^bClone R199 seed (extracted by petroleum ether)

shows the triglycerides and their respective proportions found in seed fat. In 100 g of fresh seeds, anti-nutritional, such as saponins (0.98 mg), alkaloids (0.82 mg), tannins (0.15 mg), phytates (0.40 mg), and oxalates (0.26 mg) had been observed [11]. Nevertheless, approximately 50–60% of reduction was noted in seed tannins and saponins after 10 days of fermentation [87]. In fact, Fang and Ng [85] reported trypsin inhibitor in fresh seed [85].

Antioxidant potential of rambutan seeds

Solvents of different polarity have been applied in extracting seed bioactives. In fact, the literature depicts that water, butanol, hexane, ethanol, ether, ethyl acetate, and methanol have been used to determine seed antioxidants

[30, 32, 88, 89]. As such, Maisuthisakul et al. [91] discovered a substantial amount of flavonoids (13.3 mg g⁻¹ RE) in ethanolic extract of seed. A greater variation in total phenolics for seed (3.05–124.14 mg GAE g⁻¹) is reported in literature when extracted with varied solvents [30, 88, 91]. Next, Thitilertdecha et al. [32] looked into antioxidant potentials of seed extracts via reduction in power, free radical scavenging, linoleic peroxidation, and β -carotene bleaching assays. Likewise, Soeng et al. [89] adopted the superoxide-dismutase (SOD) assay to determine the antioxidant properties of ethanolic extract. The ethanolic extract was fractionated into water, butanol, ethyl acetate, and hexane. Nevertheless, the most active fraction was ethyl acetate, and followed by water. Meanwhile, Fidrianny et al. [88] employed ABTS and DPPH assays to identify antioxidant activities of seeds from Lebak bulus, Rajah, Rapihah, and Binjai varieties. Ethanolic and ethyl acetate solvent extracts of all the four types exhibited very strong antioxidant potential.

Safety evaluation and bioactivities of rambutan seed

Seed safety evaluation

In a cytotoxicity study, dried seed powder was extracted by using 70% ethanol, and it was further partitioned into varied fractions. Mouse adipocytes were incubated with the extract fractions at concentrations of 10, 20, and 100 μ g mL⁻¹. As a result, a decrease in concentration-dependent was noted for cells viability. Next, ethanolic and hexane extracts exhibited the least cytotoxicity with maximum viability of adipocytes [89]. As the seed possesses adequate lipids amount, examination of seed safety is required. Thus, in the attempt to evaluate acute toxicity, Wistar rats were given seed lipids at a single dose of 5 g kg⁻¹ BW. No lethality or mortality was recorded until 2 weeks of post-treatment. The Wistar rats of both sexes with dorsal fur clipped off had been applied with 2 g of seed lipids and assessed for dermal toxicity. Nevertheless, the treated animals did not display any change in bodyweight. As for dermal irritation studies, 0.5 g of seed lipids had been applied on the back skin of white albino rabbits. The skin was shaved off to examine edema, but no symptom was noted after 72 h of application [92]. Next, Eiamwat et al. [90] investigated acute toxicity of defatted seed flour among male and female Wistar rats by administering 2 and 15 g kg⁻¹ BW. The treated animals displayed insignificant weight loss, although no abnormality or mortality was noted for the studied range of dosage [90].

Anti-allergic effect

The release of β -hexosaminidase from white blood cells has been reckoned as a reaction against allergens. Therefore, the anti-allergic efficiency of rambutan seed extract had been examined by weighing in inhibition of β -hexosaminidase release from basophilic leukemic cells (RBL-2H3 cells). As such, four solvents; ambient-temperature water, hot water, hydroethanol (50% ethanol), and ethanol (95%), were used to prepare the extract. At $100 \mu\text{g mL}^{-1}$ concentration, β -hexosaminidase inhibition had been recorded at 67.40, 66.97, 61.79, and 33.71% for ambient-temperature water, hot water, hydroethanol, and ethanol, respectively. Table 8 presents a summary of studies that looked into seed safety and bioactivity [31].

Anticancer activity

Proteases are essential due to their vital role in signal transduction pathways, in regulating cell division, and in responding to inflammatory responses in apoptosis [93, 95]. Moreover, inhibitors of proteases have projected promising therapeutic potentials in ameliorating various bodily issues [94, 96]. A trypsin inhibitor (22.5 kDa) was extracted from the seed of red-skin rambutan and tested for anticancer potential against human nasopharynx cancer cells (CNE-2), malignant hepatoma cells (HepG2), as well as breast cancer cells (MCF-7) [85]. The respective IC_{50} values for CNE-2, HepG2, and MCF-7 were 215.6 μM , 337.7 μM , and 266.2 μM . As nitric oxide (NO) has been considered as an anti-tumor agent [96], a dose-dependent induction of NO was noted in mouse peritoneal macrophages (BALB/c), hence ascertaining the antitumorigenic activity of trypsin inhibitor. The trypsin-inhibitor was recorded to be stable at high temperature (70 °C) and a wide range of pH (2–10). In another study, the methanolic extract of seed fat (0–400 $\mu\text{g mL}^{-1}$) was examined against human mouth-carcinoma cells (CLS-354). The viability of the cell was determined via MTT reduction assay. The high IC_{50} (305 $\mu\text{g mL}^{-1}$) observed among the cells signified very weak anticancer activity by the seed fat [30].

Anti-HIV potential

Trypsin- and chymotrypsin-inhibitors from varying legume plants have been proven to possess manifolds medicinal functionalities [94, 96, 97]. Reverse transcription is a significant step in producing multiple copies of genetic material in HIV. Reverse transcriptase-inhibitors have been designed, which reflect analogs of nucleotides and nucleosides, in order to combat the rigorous HIV expansion. Accordingly, Fang and Ng [85] extracted a trypsin inhibitor (22.5 kDa) from red-skin rambutan seed and evaluated the

HIV-1-reverse transcriptase inhibition activity. As a result, successful inhibition of reverse transcriptase had been recorded at IC_{50} of 0.73 μM [85].

Anti-adipogenic and antidiabetic activity

Several bioactive compounds, such as phenols, alkaloids, terpenoids, and triterpenoids, have been proven to possess antihyperglycemic and antidiabetic activities [98, 99]. One antihyperglycemic mechanism is to manipulate the activity of carbohydrates and lipid hydrolyzing enzymes. The α -glucosidase refers to an enzyme that hydrolyzes oligosaccharides and disaccharides to monosaccharides [100–102]. In addition, glucose-6-phosphate dehydrogenase (G6PD) is vital for pentose-phosphate pathway so as to reduce energy generated to cells. Thus, it has been suggested that decreasing glucose in serum is an efficient therapeutic tactic to combat type-2 diabetes mellitus [100]. Aside from that, controlling plasma triglycerides also can aid in obesity control [103]. In a study, hexane extract of seed was assessed to identify probable inhibition of α -glucosidase, G6PD, and triglycerides in mouse adipocytes (3T3-L1). In the differentiated 3T3-L1 cells, at extract concentration of $10 \mu\text{g mL}^{-1}$, maximum inhibition of α -glucosidase and the lowest triglycerides had been recorded. Nonetheless, inhibition of G6PD was only noted at higher extract concentration (50 $\mu\text{g mL}^{-1}$) [89].

Similarly, seed infusion was prepared by steeping the seed powder in hot water. Alloxan-induced diabetic ddY mice (*Mus musculus*) were treated with seed infusion for 2 weeks. Next, glibenclamide (an antidiabetic drug of class sulfonylureas) was applied as positive control. Pancreas histology studies confirmed that the extract responded similar to glibenclamide, the discovery of β -cells alike for both. Moreover, a comparable decrease in blood glucose and bodyweight were observed at the studied dose [104].

Antimicrobial activity

In a study, air-dried seeds of commercial rambutan fruit had been extracted by using dichloromethane. Two monoterpene lactones were purified by employing high-performance size exclusion chromatography (HPLC), while characterization was performed via nuclear magnetic resonance ($^1\text{H-NMR}$). The monoterpene lactones, namely lappaceolide-A and -B (colorless needle-like crystals), were examined for antibacterial and antifungal properties, following the agar-well method. The highest activity index (0.4) of lactones was noted against fungus *Trichophyton mentagrophytes*, but an index less or equivalent to 0.3 for Gram positive and Gram negative. However, the extracted lactones displayed relatively weaker activity against the tested microbes, in

Table 8 Rambutan seed safety and bioactivity studies in various models

Study	Extract/compound	Extraction condition	Model	Method/findings	References
Cells toxicity	Ethanol, hexane, ethyl acetate, butanol, water	Room temperature for 3–5 days	3T3-L1 murine adipocytes	MTS cell proliferation assay was used; ethanolic extract and hexane fraction presented mild cytotoxicity	[93]
Oral and dermal toxicity	Methanol	30 °C for 3 h	Human peripheral blood mononuclear cells (PBMCs)	MTT reduction assay was used and no toxicity was observed	[32]
	Lipids	Supercritical CO ₂ , 45 °C and 35 MPa	Male/female Wistar rats	In case of acute oral toxicity, no lethality observed	[88]
	Lipids	Supercritical CO ₂ , 45 °C, and 35 MPa	Albino rabbits	No abnormal symptoms appeared in acute dermal toxicity, and no dermal irritation was observed	[88]
	Defatted seed flour	Supercritical CO ₂ , 45 °C at 350 bar	Wistar rats	In acute oral toxicity study, no abnormality was noticed	[94]
Anti-cancer activity	Methanol	30 °C for 3 h	Human mouth carcinoma (CLS-354)	A very weak cytotoxicity was observed through MTT reduction assay	[32]
Anti-adipogenesis activity	Trypsin inhibitor	0.02 M ammonium bicarbonate buffer (pH 9.4), 4 °C for 40 min	Tumor cells: MCF-7, Hep-G2, CNE-2	Good anti-tumorigenic activity was observed	[92]
	Hexane	Room temperature for 3–5 days	α -glucosidase, glucose-6-phosphate- dehydrogenase (G6PD) in 3T3-L1	Maximum inhibition concentration was 10 $\mu\text{g mL}^{-1}$ for α -glucosidase and for G6PD it was 50 $\mu\text{g mL}^{-1}$	[93]
	Water	Steeping at 100 °C for 10 min	Alloxan induced diabetic rats (<i>Mus mus-culus</i>)	A significant reduction in glucose production. The live pancreatic β -cells were comparable to the positive control	[58]
Anti-HIV activity	Trypsin inhibitor	0.02 M ammonium bicarbonate buffer (pH 9.4), 4 °C for 40 min	HIV-1	Inhibition of reverse transcriptase activity in virus was observed	[92]

comparison to chloramphenicol and canesten that served as model antibiotics [10] (Fig. 2).

Rambutan fruit volatiles

Fruit flavor refers to a product of a complex mixture of various volatiles present in the structural tissues. Albeit rambutan is less aromatic than lychee, its fresh pulp contains almost 48 volatile compounds with some others yet to be detected. Amongst the main aromatics, aliphatic alcohols constitute 49%, sesquiterpenoids 20.5%, and carbonyl compounds contribute to 19.5%. Additionally, amongst the 16 aliphatic alcohols (49%), the following four major compounds; (i) 2-methylbut-3-en-2-ol, (ii) hexan-1-ol, (iii) 3-methylbutan-1-ol, and (iv) pentan-1-ol, contribute to 21.9%, 6.5%, 5.7%, and 5.2%, respectively. Nonetheless, α - and β -caryophyllene, as well as α -humulene, appear to be the only three sesquiterpenoids for the total 20.5%. Similarly, 15 compounds shared the total carbonyl compounds (19.5%) with 3-hydroxybutan-2-one, hexanal, and (*E*, *Z*)-deca-2,4-dienal as the primary ones. Others include three aromatics (2.6%), four esters (1.4%), five aliphatic acids (1.4%), a monoterpene hydrocarbon (0.4%), and a lactone (0.3%) [105]. Meanwhile, in another study, the red-skin cultivar 'Jitlee' had been reported to possess over 100 volatiles, and at least 60 with odorous activity. The 20 most active odorous volatile compounds were: β -damascenone, cinnamic acid, δ -decalactone, (*E*)-4,5-epoxy-(*E*)-2-decenal, ethyl-2-methylbutyrate, maltol, m-cresol, 2,6-nonadienal, nonanal, (*E*)-2-nonenal, furaneol, guaiacol, heptanoic acid, phenylacetic acid, 2-phenylethanol, 3-phenylpropionic acid, γ -nonalactone, vanillin, and (*Z*)-2-nonenal. Hence, the exotic aroma of rambutan fruit reflects a blend of fruity sweet, fatty-green, sweet, woody, and spicy tinge, thus contributing to the complexity of rambutan flavor [106].

Future research

Rambutan, being a rich source of phenolics and ellagitannins, has been explored for both nutritional and therapeutic potentials. Nevertheless, with exception of several reports, most studies have failed in providing complete information regarding cultivar, maturity, agronomic practices, and geological area of cultivation. Such scant information disables further comparison or assessment of phytochemicals efficacy. In addition, apart from the abundant health-promoting effects of rambutan bioactives summed in this current review, elaboration on the systematic mechanisms of action seeks further exploration. The aspects of bioactivity and safety data for most of the extracted compounds are lacking, hence resulting in underestimation or overestimation of the real potential projected by a particular phytochemical. Additionally, data reported for bioavailability and safety of rambutan are inconsistent as no standard extraction or analyses protocols are present, thus making comparisons intricate. Therefore, pharmacokinetic evaluations are required to highlight the bioavailability of a particular compound to design herbal medicine. Besides, most of the in-vitro studies dismissed the stability of the extracted phytochemical and the conditions to maintain cell culture prior to experiment, which may imitate the actual results. Furthermore, it is suggested that the compound of interest should be tested at a wider range of doses and models to extrapolate its applicability. At the same line, more studies are sought to elaborate the single or the combined effect of various bioactive compounds in ameliorating a particular physiological condition. On top of that, the in-vivo and in-vitro model studies should be expanded to real time human trials, but only after assessing the safety of a particular extract or compound of interest. Finally, so as to shed the waste burden from the environment, rambutan peels and seeds should be employed as cheaper alternatives to produce multifunctional prebiotics and drugs with least to null side effects.

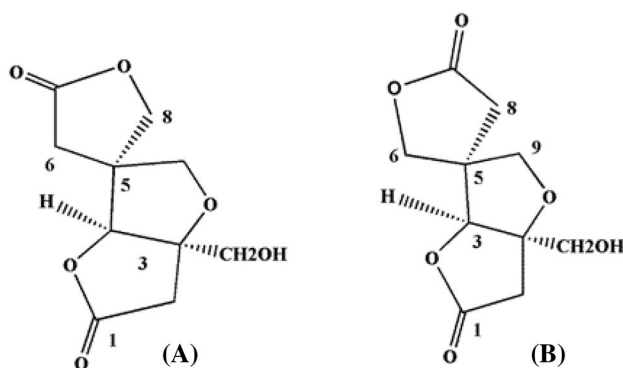


Fig. 2 Seed monoterpene lactones: lappaceolide A (left); lappaceolide B (right)

Conclusion

Rambutan, due to significant bioactives, has been applied in traditional medicine to treat fever, diarrhea, dysentery, giardiasis, stomachache, and skin diseases. Recent scientific studies have further confirmed the presence of various bioactive compounds in rambutan. In fact, higher concentrations of phenolics and ellagitannins, such as geraniin, ellagic acid, corilagin, elaeocarpusin, and ethyl-gallate, have been observed in both peels and seeds than in fruit pulp. Peels and seeds of the rambutan fruit have been

studied for safety and bioactivities in various in-vitro, in-vivo, and human clinical trials. Furthermore, a number of studies have instigated the significance of rambutan in mediating major ailments, including cancer, HIV, dengue, obesity, diabetes, allergy, cardiovascular risks, and microbial infections. Besides, the seeds appear to have good amount of fats, including oleic, linoleic, and arachidic acids. In fact, the presence of most of the essential amino acids makes the seed flour a good source of protein. Despite of the numerous scientific reports, many bioactive compounds are in need to be isolated and purified from peels and seeds. Moreover, their mechanisms of action and biosafety evaluations should be performed in human-based clinical trials so as to valorize waste into its best potential.

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Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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