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A review of ethnomedicinal uses, phytochemistry, nutritional values, and pharmacological activities of *Hylocereus polyrhizus*

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ABSTRACT

Hylocereus polyrhizus (Red dragon) fruit, a *Cactaceae* plant with traditional and medicinal uses, is found in America and South Asia. These fruits have diversified bioactive components, which make them both therapeutically and nutritionally important. This review focuses on the various aspects of this potential plant. This literature review looked at the nutritional information, botanical description, traditional medical use, nutritional values, medicinal uses, chemical compounds, and pharmacological activities of *H. polyrhizus.* To evaluate the required resources, Scopus, PubMed, Science Direct, Cochrane electronic databases, and Google Scholar search engines were searched (for example, *Hylocereus polyrhizus* OR dragon fruit, red pitaya OR pitaya, pharmacological AND phytochemical, nutritional AND ethnomedicinal). Prominent bioactive elements in this plant included phenolic compounds such as α-amyrin (15.87%) and β-amyrin (13.90%). *H. polyrhizus* also contains antioxidant, cardioprotective, anti-inflammatory, antifungal, antibacterial, hypolipidemic, antiviral, thrombolytic, antiplasmodial, anticancer, hepatoprotective, and antidiabetic activities. Because of its colouring pigments, carbohydrates, proteins, and fat substitution properties, the fruit is commonly used in culinary and grooming. An improved understanding of *H. polyrhizus*, according to this study, could pave the way for the discovery of new, beneficial chemicals with therapeutic potential.

Implication for health policy/practice/research/medical education:
This vital review on *Hylocereus polyrhizus* (Red dragon) fruit will provide a promising array for researchers to investigate the potential lead chemical compounds responsible for significant pharmacological activities at the molecular level and for pharmaceutical industries to build new therapeutics.

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Introduction

In many countries around the world, traditional medicines have been used for many years as herbal cures, dietary supplements, and other medicinal approaches (1). The use of traditional medicine has expanded in recent years, with people all across the nation relying on it for some of their primary therapy (2). According to the World Health Organization (WHO), approximately 88% of all countries are using traditional medicines in the form of herbal medicines, yoga, acupuncture, indigenous therapies, and other relevant traditional approaches (3). One of the most potent antidiabetic drugs, metformin, is linked to *Galega officinalis* (also known as goat's rue), a traditional medicine that essentially emerged in Europe (4). During the 1920s and 1930s, guanidine derivatives from *G. officinalis* were synthesized and used to mitigate diabetes (4).

Hylocereus polyrhizus (Red dragon) is a species of the Cactaceae family belonging to the genus *Hylocereus*. *H. polyrhizus* is distinguished by its red pulp compared to other *Hylocereus* species. Red pitaya is a common name,

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and further, it is known as a red dragon fruit in South Asia (5,6). It is widely cultivated in Malaysia, Thailand, Vietnam, Australia, Taiwan, and some other parts of the world. This fruit is survived in the dry tropical climate and can withstand temperature as high as 40 °C (7). It contains several secondary metabolites, including alkaloids, coumarins, flavonoids, phenols, and triterpenoids (8). Due to its betalains content, red dragon fruit has the potential to be used as a red pigment source. Betacyanin is a betalain pigment that produces purplish-red shades, whereas betaxanthin is a betalain pigment that may produce yellow-orange shades (9,10). One of the best uses for red pitaya is as a natural food colourant because of the presence of betacyanin pigments (11). The peels of this fruits are rich in vitamins, antioxidants, soluble and insoluble fibers, pectin, and betacyanin (12-14). Due to the presence of various phytochemicals, these fruits show different pharmacological activities (15).

Oxidative stress is defined by increased amounts of reactive oxygen species (ROS) and inadequate antioxidant mechanisms. Reactive stress may damage cells and cause tissue destruction (16). Extensive studies have been conducted on several antioxidants such as superoxide dismutase (SOD), epigallocatechin-3-O-gallate, catalase (CAT), lycopene, coenzyme Q10, ellagic acid, quercetin, indole-3-carbinol, genistein, vitamin E, and vitamin C for their potential in disease prevention and treatment (17). Studies have shown that polyphenol-rich extracts may be responsible for the antioxidant activity in red pitaya due to the presence of polyphenolic compounds (18,19). Cardiovascular illnesses are complex conditions caused by several factors (20,21). By reducing platelet aggregation or hyperactivation, the polyphenols in red pitaya provide anti-thrombotic and antiatherogenic actions (22,23). *H. polyrhizus* fruit exhibited superior antioxidant properties compared to other dragon fruits, for example, white meat dragon fruit (*Hylocereus undatus*) (24). *H. polyrhizus* fruit reduced plasma lipids and enhanced total and LDL (low-density lipoprotein) cholesterol, glucose levels, and serum antioxidant capacity in hyperlipidemic rats (25). Inflammation is a common reaction of an organism to mostly local tissue changes of many kinds. In general pathology, inflammation is a complicated pathological process that plays a key role in the development of diseases (26). *H. polyrhizus* includes metabolites that serve as precursors for the formation of betalains (betaxanthins and betaines), which are responsible for the plant anti-inflammatory properties (27). Betalain may suppress inflammatory genes such as TNF-alpha and IL-1 by blocking the transcription factor NF-κB in mouse models of endometriosis (22, 28). Betalanin in *H. polyrhizus* could slow down the progression of alcoholic liver disease (ALD) via modifying lipid metabolism and decreasing oxidative stress and inflammation via the betalanin pigment (29). Cancers are malignant neoplasms that result from the aberrant and uncontrolled division of cells, including both carcinoma and sarcoma. They penetrate and kill surrounding tissues (30). α-Amyrin (31) found in *H. polyrhizus* may be accountable for the cytotoxic effects on cancer cells. Anthocyanin and betacyanin pigments present in *H. polyrhizus* may alter the integrity of the mitochondrial inner membrane in K562 cells, leading to nuclear disintegration, cytochrome C leakage, and caspase activation, contributing to human chronic myeloid leukemia (32). The bioactive compounds in dragon fruit inhibit the growth and reproduction of human breast cancer MCF-7 cells and may disrupt the distribution of cell cycle phases (33).

Various research reviews have been undertaken on the dragon fruit, examining its phytochemicals, nutritional qualities, pharmacological activities, botanical features, and more (34-36). However, no detailed or succinct material was added about the red dragon or *H. polyrhizus*. Hence, our study covers several elements of red dragon fruit, such as phytochemical analysis, nutritional value, therapeutic uses, botanical characteristics, and laboratory-based experimental results. The research provides current information on red dragon fruit, focusing on its molecular-based mechanism of action against various ailments using a schematic diagram and a summary table. This review might improve our healthcare system by providing a detailed examination of its nutritional composition, potential health benefits, and any associated risks. Healthcare practitioners may use this information to advise patients on dietary choices, perhaps resulting in improved overall health outcomes. The findings in this review might open up further windows on research or clinical trials leading to the development of new medications or treatments using the health-promoting properties of red dragon fruit.

Methods

The results of the current review are based on a literature search on the phytochemistry, pharmacological properties, nutritional, traditional, and medicinal uses of *H. polyrhizus* (Red dragon) using information derived from several electronic databases and other additional sources. Electronic databases, including Google Scholar, Scopus, PubMed, Science Direct, and Cochrane were searched using suitable keywords such as *Hylocereus polyrhizus* OR red dragon fruit, red pitaya OR pitaya, pharmacological AND phytochemical, nutritional AND ethnomedicinal. All types of in vitro, in vivo, and clinical studies related to *Hylocereus polyrhizus* were considered for this review article.

Habitat

The dragon fruit is indigenous to tropical and subtropical forests in North, Central, and South America (37). Currently it is widely cultivated in tropical and subtropical regions worldwide, particularly in Asian countries like Malaysia, Vietnam, Thailand, the Philippines, and southern China (38).

Botanical description

The climbing cactus family Cactaceae includes the genus *Hylocereus*, which is the source of dragon fruit. Dragon fruit, particularly red-fleshed dragon fruit, may have grown due to the suitability of a tropical environment, rainfall demands, and soil types (37). In order to boost red-fleshed pitaya off-season yield, which is normally cultivated in Taiwan from May to December with a maximum output period from July to September, a night-breaking approach has been implemented (39). *H. polyrhizus* is a species of the genus *Hylocereus* with strong red and sweet flavored flesh and a climbing plant with aerial roots. These roots have a huge, scaly, glabrous berry, a peel with large scales, and a crimson pulp (40,41).

The fruit of the plant has an oblong shape, a red covering, and a pulp that has a deep purple color (*H. costaricensis*). It may grow from the ground or scale trees via aerial roots and has a succulent stem (42). *H. polyrhizus* exhibits the smallest fruit size among all species of *Hylocereus*, with a maximum fruit weight of approximately 350 g. Seeds can be used for generative reproduction, but germination won't take place in the dark. The flesh possesses a pleasant texture and an ample quantity of delectable black seeds (41).

Hylocereus polyrhizus fruits are 14 cm long, 8 cm wide, and 500 g weight. Flowers need cross-pollination to produce fruit. Before morning, it is customary for huge flowers to attract a considerable number of bees, ranging from 10 to 20 each, due to their irresistible allure to these insects (43). The flowers have distinct borders and possess waxy white stems. The stigma lobes are quite short and have a yellowish coloration. Additionally, the outer perianth sediments are reddish in hue, particularly at the tips. The fruit is characterized by its oval shape, scales of different sizes, and reddish-purple flesh with numerous tiny black seeds. The fruit has a diameter ranging from 10 to 15 cm and weighs between 250 and 600 g (44).

Common/Vernacular name

Belle of the Night, Conderella plant, Nanettikafruit, Red-fleshed Dragon Fruit, Red-fleshed Pitahaya, Queen of the Night (45), Red pitaya (46), Dragon fruit in South Asia (English) (47), Buah Naga or Buag Naga or Buah mata naga (Indonesia/Malaysia) (48), Strawberry pear, Night blooming cereus (42), and prickly pear (49) are the popular names used in various countries.

Phytochemistry of *Hylocereus polyrhizus*

The phytochemical investigation of *H. polyrhizus* has yielded numerous bioactive constituents such as β-amyrin, α-amyrin, octacosane, octadecane, γ-sitosterol, octadecane, 1-tetracosanol, stigmast-4-en-3-one, and campesterol. In addition, there are other classes of phytochemicals including alkaloids, amino acids, phenolic compounds, phenolic acids, flavonoids, organic acids, lipids, lignans, coumarins, betacyanins/chromo alkaloids, and fatty acids. An overview of the phytochemical classes and their compound data has been represented in Table 1.

Ethnomedicinal uses of *Hylocereus polyrhizus*

Pitaya peels would be a potential alternative to artificial sunscreen agents due to the presence of naturally active constituents in the lucrative makeup business (53). The lipstick, derived from *H. polyrhizus* (54), contains betalain pigments that possess antioxidant and antibacterial properties.

In silico studies revealed a plausible link between the selected chemicals and their modes of action (55). In molecular docking research, 4-prenylresveratrol, vicenin, and luteolin successfully interacted with the target molecule, suggesting that *H. polyrhizus* contained anti-glycation and antioxidants and might have uses in the prevention and treatment of glycation linked to diabetes and aging problems (55). The ethnomedicinal background of this species revealed that it contained antioxidant, anticancer, antibacterial, hepatoprotective, antidiabetic, and wound-healing properties. Moreover, it has been used to treat cough, diabetes, asthma, hyperactivity, tuberculosis, mumps, bronchitis, and cervical lymph node TB in local medicines (56). Red dragon fruit increased the rate of milk fermentation, lactic acid concentration, total phenolic content, antioxidant activity, and organoleptic qualities of yoghurt (57). In addition to past uses of pitaya as a natural dye for food products (58), albedo sections of pitaya fruit were extracted to make a coloring powder as a natural food ingredient (59). The use of betalain, a secondary metabolite produced from L-tyrosine, as a natural food dye is well documented (60).

Nutritional values of *Hylocereus polyrhizus*

In order to yield dietary fiber with a high amount of soluble fiber, red pitaya pulp was dried at a low temperature, which showed its promise as a fat substitute in dieting as well as antioxidant properties (61). The fiber was added to strawberry ice cream, which eventually led to a product with a maximum acceptance rate and a 73.5% improvement in the overrun and rheological behavior of the sample's fat content (61). This suggests that the food sector has a choice in how to minimize fat while boosting the nutritional value of goods. When compared to Malaysian red pitaya, which was lyophilized, the crude fiber content of the syrup was around 3.8 times lower (62). In the study, the fiber and protein levels in Malaysian and Australian red pitaya juice were measured to be 1.45 g/100 g and 2.65 g/100 g, respectively. It was found that the protein level was higher than the fiber level (7).

Table 1. Classes and names of compounds from *Hylocereus polyrhizus*

Compound class	Compound name	Ref.
Alkaloids	N-benzylmethylene, dopamine hydrochloride, isomethylamine, choline, serotonin, spermine, trigonelline, 6-deoxyfagomine, choline, dopamine hydrochloride, amaranthine, N-cis-feruloyl tyramine, and gomphrenin I.	(46)
Amino acids and derivatives	L-valine, 2-aminoisobutyric acid, tryptophan, D-(-)-valine, L-tyramine, methionine sulfoxide, L-2-chlorophenylalanine, DL-norvaline, L-methionine, and pipecolic acid.	(46)
Lipids	γ-Linolenic acid, octadecadienoic acid, punicic acid, hexadecylsphingosine, 9S-hyroxy-10E, 9,10-EODE, 9-hydroxy-10, 13-hydroxy-9, 11-octadecadienoic acid, 12E-octadecadienoic acid, stearic acid, myristic acid, 12-octadecadienoic acid, and LysoPC (16:1).	(46)
Lignans and coumarins	esculin (6,7-dihydroxycoumarin-6-glucoside), pinoresinol, syringaresinol-aceGlu, 7-methoxycoumarin, pinoresinol-acetylglucose, syringaresinol-Hex, olivin diglucoside, (+)-medioresinol-aceGlu, pinoresinol diglucoside, and esculin hydrate.	(46)
Organic acids:	(Rs)-mevalonic acid, D-galacturonic acid (Gal A), 1-(+)-tartaric acid, methymalonic acid, 4-guanidinobutyric acid, sodium valproate, 6-aminocaproic acid, anchoic acid, aldehydo-D-galacturonate, and citraconic acid.	(46)
Nucleotides and derivatives:	5'-Deoxy-5'-(methylthio) adenosine, 2-deoxyryibose 5-phosphate, guanosine, cytidine, adenine, guanine, deoxyadenosine, 2-(Diethylaino) guanosine, adenosine 5'-monophosphate, and adenosine.	(46)
Phenolic acids	Chlorogenic acid, protocatechuic acid-4-glucoside, 1-0-[(E)-p-Cumaroyl)-B-D-glcopyranose, 2,5-dihydroxy benzonic acid O-hexside, coniferin, echinacoside, regaloside L, phthalic anhydride, 1-0-[(E)-Caffeoyl)-B-D-glucopyranose, and trihydroxycinnamoylquinic acid.	(46)
Flavonoids	Catechin (major flavonoids), calycosin, rutin, astragalin, quercetin, myricetin, kaempferol, tectorigenin, grosvenorine, typhaneoside, lonicerin, isoquercetin, nicotiflorin, isorhamnetin-3-O-neohesperidine, gentiopicrin, isorhamnetin, flavonol glycoside, and epicatechin.	(18,47)
Hydrocarbon (Alkanes)	Octacosane (12.2%) and octadecane (6.27%)	(31,50)
Steroids	γ-Sitosterol (9.35%), 1-tetracosanol (5.19%), stigmast-4-en-3-one (4.65%), and campesterol (4.16%).	(31,50)
Fatty acids	Stearic acid and oleic acid.	(50)
Phenolic compounds	Vanillin, esculetin, gallic acid, caffeic acid, syringic acid, ferulic acid, sinapic acid, cryptochlorogenic acid, p-hydroxycinnamic acid, chlorogenic acid, p-coumaric acid, isoferulic acid, vanillic acid, methyl 4-hydroxycinnamateb, and 7,8-dihydroxycoumarin.	(3,18,51)
Betacyanins/Chromo alkaloids	Cyclo-dopa 5-O-ß-glucoside, neobetanin, 17-decarboxybetanin, betalamic acid, isobetanidin 5-O-ß-glucoside(isobetanin), 17-decarboxyisobetanin, betanidin 5-O-(6'-O-3-hydroxybutyryl)- ß-glucoside, 15-decarboxybetanin, betanidin 5-O-(6'-O-3-hydroxy-3-methyl-glutaryl)-ß-glucoside (hylocerenin), betanidin 5-O-(6'-O-malonyl)-ß-glucoside (phyllocatin), isobetanidin 5-O-(6'-O-malonyl)-ß-glucoside (isophyllocactin), decarboxylated, neobetanidin 5-O-ß-glucoside (neobetanin), isobetanidin 5-O-(6'-O-3-hydroxy-3-methyl-glutaryl)- ß-glucoside(isohylocerenin), and betanidin 5-O-ß-glucoside(betanin).	(52)
Others	Ascorbic acid, abscisic acid, D-(+)-trehaloseanhydrous, galactinol, D-glucose, D-(+)-glucose, isomaltulose, D-(+)-sucrose, D-glucoronic acid, phenethylamine, N-hydroxy tryptamine, and D-pantothenic acid.	(18,46,47)

According to research, red pitaya pulp has 0.1% fat as opposed to 22.8% in the seeds (63). According to Ruzainah et al, it is also an excellent source of vitamin C (64), with 8-9 mg found in lyophilized red pitaya flesh and a varying quantity ranging from 63.71–132.95 mg found in the stems of red pitaya. Pitaya peel contains a wealth of nutrients, including pectin and dietary fiber, as well as functional phytonutrients like betacyanins. Studies have revealed that pitaya peels or their preparations may have therapeutic value and can be required to develop unique foods. Again, pitaya peels show promise for usage in food manufacturing, considering applications in food products, recovery of nutritive components (amylase, pectinase, pectin, and betacyanin), and packaged food as well as edible films (36). Pitaya possesses higher magnesium, potassium, phosphorus, salt, and potassium content than mangosteen, mango, and pineapple, as well as all other vitamin forms (65,66). The red surface of the fruit contains a high concentration of vitamins B1, B2, B3, C, and minerals (64); 50% of the necessary fatty acids (specifically linoleic and linolenic acids) are found in seeds (67). Compared to the flesh of the fruit, the immature stem of the dragon fruit has more ascorbic acid, which may also assist in the prevention of certain conditions such as anemia, fatigue, and scurvy (64). Nur Izalin et al proposed the use of dragon fruit peel pectin as a thickening agent in dietary items, such as low-viscosity foods and beverages (68).

As a low-calorie, cholesterol-free, and antioxidant-rich food, it helps to keep blood pressure stable and reduce the risk of cardiovascular disease (69). In pregnant women, it has enough iron to improve hemoglobin and erythrocyte levels (13). The powdered red dragon fruit peel can be added to meals as a supplement, which seems to claim to avoid hyperlipidemia risk and remain healthy (70).

Pharmacological activities of *Hylocereus polyrhizus*

Cardioprotective activity

Red pitaya has cardioprotective functions because of the presence of antioxidant and polyphenol elements. Polyphenols in red pitaya cause an anti-thrombotic effect by inhibiting numerous platelet-activation mechanisms, resulting in decreased platelet aggregation or hyperactivation (22,23). Polyphenols can contribute to inhibiting platelet degranulation (Figure 1). It can also downregulate thromboxane A2 receptors, inhibit collagen and adenosine diphosphate (ADP) receptors, and affect other platelet-activation pathways. As a result, it may operate as a replacement for presently employed anti-platelet medications by targeting new platelet activation pathways (23). In the 1st pathway, it has reduced the attachment of fibrinogen to (GPIIb-IIIa) receptors of platelets to inhibit further platelet recruitment (Figure 1). Finally, it inhibited the aggregation of platelets to show an antithrombotic effect. Besides this inhibition, it can also attenuate the other pathways of 2, 3, 5-mediated platelet activation (23). *H. polyrhizus* (RF) dragon fruits demonstrated better free radical-neutralizing qualities than white flesh (*Hylocereus undatus*) dragon fruits (24). It lowered plasma lipids while improving total and LDL cholesterol, glucose levels, and serum antioxidant capacity in hyperlipidemic rats (25). Consuming red pitaya juice for a duration of 8 weeks could enhance the diastolic stiffness of the heart in rats that were fed with maize starch (71).

Anti-diabetic activity

An experiment was conducted in insulin-resistant rats, and the results revealed that fresh pitaya dramatically reduced insulin resistance while also treating hyperinsulinemia, atherogenesis, and dyslipidemia. It increased serum insulin, insulin/glucose ratio, glucose, glucose intolerance, TC (total cholesterol), and TG (total triglycerides) levels, too. The inclusion of polyphenols, soluble dietary fiber, and antioxidant content contributed to its anti-insulin-resistant effect (72). Red dragon fruit extract (dosage 74.88 mg/200 g body weight) could demonstrate an impact against diabetes that was statistically equivalent to the standard diabetes treatment glibenclamide (sulfonylurea class medications) at a dose of 0.09 mg/200 g body weight. The fruit peel might exert its effect via reducing blood glucose levels in rats with diabetes (73). In another study, *H. polyrhizus* peel extract (150 mg/kg and 300 mg/kg) combined with glibenclamide reduced blood glucose levels in diabetic mice caused by alloxan (74).

Hypolipidemic activity

A dosage of 200 mg/kg BW (body weight) of red dragon fruit peel powder lowered total triglycerides, cholesterol, LDL-c, VLDL, body weight, Lee index, obesity, and total cholesterol ratio over HDL cholesterol. Furthermore, it could increase the quantity of blood serum HDL-c levels while also improving blood lipid levels. Experiments in male hyperlipidaemic Balb-C mice (Mus musculus) and obese female Wistar rats on a high-fat diet yielded these results. The red dragon fruit peel contains approximately 69.3% dietary fibre, which facilitates the production of fatty acid fermentation products. These products inhibit the synthesis of liver fatty acids and cholesterol and also decrease the release of triglycerol (70,75). In particular, soluble kinds can keep bile acids and cholesterol in check in the small intestine (70). Another in vivo investigation found that a methanol extract of red pitaya had a hypocholesterolemic impact on hypercholesterolemia-induced rats (76).

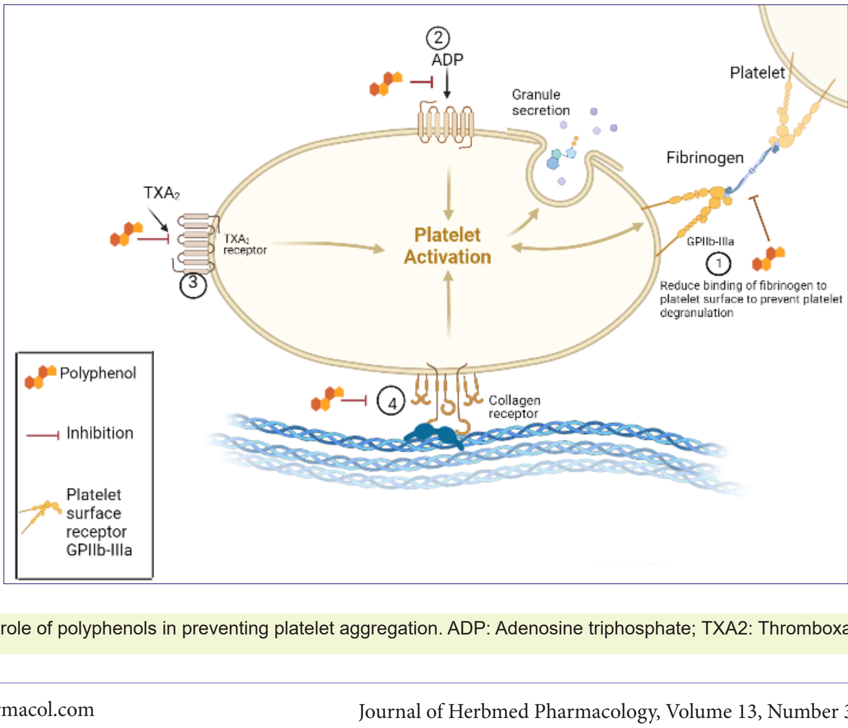

Figure 1. The schematic role of polyphenols in preventing platelet aggregation. ADP: Adenosine triphosphate; TXA2: Thromboxane A2; GP: Glycoprotein.

Anti-inflammatory activity

The ethanol extract of the fruit of *H. polyrhizus* can reduce hapten reagent 2, 4, 6-trinitrobenzene sulfonic acid-treated mice's colitis, production of pro-inflammatory cytokines, Ikb-alpha degradation, and nuclear NF-kb protein levels in the colon. As a result, this fruit may be useful as a treatment option for those suffering from inflammatory bowel disorders. Furthermore, the ethanolic extract of *H. polyrhizus* fruit contains luteolin and ellagic acid. Ellagic acid reduces NF-κB transcriptional activity, while luteolin suppresses both AP-1 and NF-κB. Luteolin specifically modulated the activity of Akt (protein kinase-B). Therefore, luteolin hindered the process of Akt phosphorylation and the translocation of c-Jun and p65 in LPS-activated RAW 264.7 cells, consequently decreasing the production of LPS-induced inflammatory transcriptional regulators and mediators (27,77) (Figure 2). *H. polyrhizus* ethanolic and methanolic extracts can both have anti-inflammatory properties. Its methanolic extract includes metabolites that can function as precursors for the production of betalains (betaxanthins and betaines), which are responsible for the anti-inflammatory activity (27). The ethanol extract of it, on the other hand, includes betalain and can inhibit inflammatory genes like TNF-alpha and IL-1 by inhibiting the transcription factor NF-kB in mouse models of endometriosis (22, 28).

Antiviral activity

The red pitaya pulp contains betacyanins, which are red-violet pigments possessing antiviral properties. Betacyanin from red pitahaya, with an IC_{50} value of 125.8 μg/mL, proved efficacious against dengue virus type 2 (DENV-2) by attaching to viral particles and suppressing virus infection (78). The method by which betacyanins offer this function may include their attachment to a non-structural protein, namely the envelope (E) protein of DENV-2, which mediates initial engagement with target sites (79). Furthermore, the attachment of envelope protein to the targeted cell receptor may be an important sign of infectivity (80).

Antioxidant activity

Free phenolic constituents in the pulp of two pitaya species have excellent antioxidant activity (81). However, the antioxidant properties of pitaya peel-bound phenolics are unknown. The abundance of phenolic compounds is closely connected to the antioxidant properties of polyphenol-rich plant extracts (19). The base hydrolysis produced a considerable number of phenolic compounds after being extracted with 80% methanol. Nonetheless, the hydrolysis of acid and composite enzymes showed low effectiveness in liberating bound phenolics in WP (White pitaya) and RP (Red pitaya), which may contribute to limited antioxidant properties (18). In recent research, using the DPPH method, higher free radical-scavenging activity was shown by fruit peel pigment extract having IC_{50} of 159.6 μg/mL (82). Only the ethanol extract suppressed free radicals with significant antioxidant

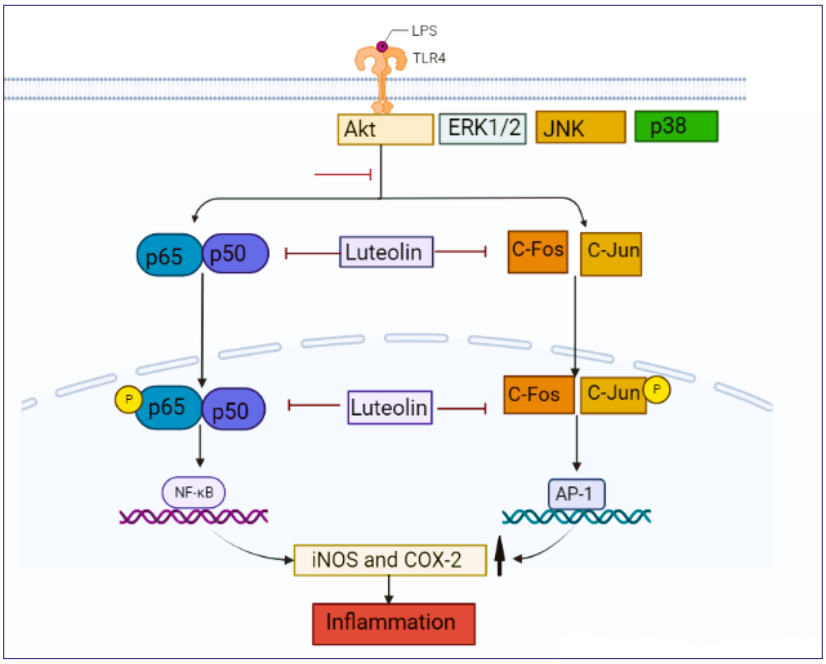

Figure 2. The role of luteolin in preventing lipopolysaccharides (LPS)-induced inflammation, depicted schematically. Luteolin inhibited LPS-induced inflammation signaling pathways in RAW 264.7 cells (a macrophage-like, Abelson leukemia virus-transformed cell line derived from BALB/c mice). MAPKs: Mitogen-activated protein kinases; Akt: a type of serine/threonine protein kinase, also called protein kinase B; JNK: Jun N-terminal kinase; ERK: extracellular signal-regulated kinase; TLR4: toll-like receptor 4; NF-κB: nuclear factor kappa B; p38: a mitogen-activated protein kinase; p65: transcription factor; p50: NF-κB1: an effector protein in the cytotoxic response to DNA methylation damage; C-Fos: cellular oncogene; C-Jun: Jun-Proto-Oncogene; AP-1: Activator protein 1; iNOS: inducible nitric oxide synthase; COX-2: cyclooxygenase 2.

activity in a dose-dependent mode, but the n-hexane and chloroform extracts showed very little effect. At 1000 µg/mL, the ethanolic extract scavenged 74.76% of DPPH free radicals, but the chloroformic and hexane extracts only scavenged 17.53% and 18.28%, respectively (47).

Antibacterial activity

Except for *Campylobacter jejuni*, the chloroform extract of this fruit inhibited practically all of the bacteria tested, including *Bacillus cereus, Staphylococcus aureus, Listeria monocytogenes, Escherichia coli, Enterococcus faecalis, Salmonella typhimurium, Klebsiella pneumoniae,* and *Yersinia enterocolitica*. At the same time, except for *S. aureus, B. cereus*, and *C. jejuni*, ethanol extract inhibited six of the bacteria tested, whereas hexane extract inhibited four: *E. coli*, *S. aureus, S. typhimurium,* and *K. pneumonia*. In this test, the disc diffusion assay at 0.2 mg/disc revealed that chloroform extract had the most antibacterial activity, followed by ethanol extract and then hexane extract (83). Freshly picked fruits had a higher antimicrobial response, with MIC values of 50 000 µg/mL against eight different bacterial species (84). It was more effective against gram-positive bacteria such as methicillin-resistant *S. aureus*, vancomycin-resistant, enterococci and *Bacillus*. Betacyanin is most probably the molecule accountable for the action, and it can easily pass through the cell wall of gram-positive bacteria, whereas tiny hydrophilic solutes may pass via porin channels on the outer membrane of gram-negative bacteria such as *E. coli* (84). At 20 µg/mL concentration, four distinct extracts of this fruit, including n-hexane, ethyl acetate, dichloromethane, and pigment, inhibited growth by 67%–94.9% against *S. aureus, E. coli, B. subtilis*, and *Vibrio alginolyticu* (85). *H. polyrhizus* peel extract concentrations of 100% inhibited *S. mutans* growth more successfully than 50% peel extract concentrations; fruit pulp extract concentrations of 100% also impeded *S. mutans* growth more successfully than 50% concentrations but less competently than the positive control group (chlorhexidine 0.2%) (86). Treating mice with different quantities of aqueous extract of the *H. polyrhizus* peel and chloramphenicol for 15 days had a substantial effect on the number of *Pseudomonas aeruginosa*, particularly in a group that represented 100 mg/mL of aqueous extract and chloramphenicol, and the number of bacteria was greatly decreased (87).

Antiplasmodial activity

The efficacy of the four extracts namely; pigment (betanin, a betacyanin), dichloromethane, ethyl acetate, and n-hexane) of the plant was examined. The extracts from betanin (a betacyanin) and ethyl acetate were not effective against the chloroquine-sensitive 3D7 and chloroquine-resistant W2 strains of *Plasmodium falciparum*. However, the extracts from dichloromethane and n-hexane showed a positive action. Dichloromethane had nearly three times the activity of n-hexane, with IC_{50} values of 2.13±0.42 and 6.51±0.49 g/mL, respectively (32). According to the WHO guidelines and fundamental prerequisites of antiparasitic pharmaceutical research, based on their IC_{50} values, extract activities were classified into four categories: high activity (IC_{50}≤ 5 µg/mL), promising activity (5 µg/mL <IC_{50} 15≤ g/mL), moderate activity (15 µg/ml< IC_{50} ≤50 µg/mL), and poor activity (IC_{50} >50 µg/mL) (33). As a result, n-hexane extracts and dichloromethane had strong and potential antiplasmodial effects (88).

Anticancer activity

Concerning the chemical components of this species' peel, Lou et al detected one main phytosterol, α-amyrin (31), which could be responsible for the cytotoxicity against the cancer cell. It was also tested for cytotoxic action against the myoblasts (L-6) cells with an IC_{50} >90 µg/mL (89). According to Sreekanth et al (32), pitaya extract components (anthocyanin and betacyanin) and pigments function in K562 cells that cause human chronic myeloid leukemia by modifying the integrity of the mitochondrial inner membrane, resulting in cytochrome C leakage, nuclear disintegration, and caspase activation. These metabolic alterations are mirrored in the structural reforms seen in apoptotic cells (programmed cell death). The dragon fruit extract reduces the viability and multiplication of human breast adenocarcinoma MCF-7, and the bioactive chemicals in the dragon fruit have also been shown to interfere with the cell cycle distribution phases (33). Polymorphisms in the ER alpha-gene (ER-alpha) have been linked to prostate and breast cancer, osteoporosis, cardiovascular disease, and Alzheimer's disease (90). Pitaya's proliferative action appears to be based on lower ER alpha expression, which might directly activate processes of cell viability suppression or perhaps limit hormone affinity to the receptor and therefore impede cell growth (39).

Antifungal activity

According to one investigation, the extract with significant antimicrobial properties had high total phenolic and flavonoid contents, and there might be a link between phenolic and flavonoid chemicals with antifungal actions. The existence of flavonoid components in ethyl acetate extracts implies that they have antifungal properties. As a result, chromatography and spectroscopic methods are used to identify bioactive chemicals in extracts. All extracts had moderate to low antifungal activity, with ethyl acetate having the greatest activity, closely followed by the colored extract. However, these activities were lower than those of the positive control (91). For example, quercetin, and kaempferol exhibited antimicrobial activity against *Bacillus* spp (92). The antifungal activity of red dragon fruit against *Candida albicans* revealed a range of inhibition percentages at 500 ppm. The extracts with the greatest activity were ethyl acetate (74.27% inhibition) and pigment extracts (60.88%) (91).

Hepatoprotective activity

It has long been recognized that liver disorders are the most devastating illnesses induced by hazardous substances, whether by exposure or ingestion. For example, carbon tetrachloride (CCl_4) is a compound on a list of dangerous substances linked to significant liver injury (93). In comparison to the control group, administration of *H. polyrhizus* fruit extract at a dosage of 300 mg/kg considerably normalized the increased blood marker enzymes ALT, AST, ALP (alanine transaminase, aspartate transaminase, alkaline phosphatase, respectively), and bilirubin in the treatment group, showing that the extract reduced carbon tetrachloride-induced mortality (94). The red dragon fruit peel was also studied and discovered to have the capacity to lower triglyceride, total cholesterol, and LDL-C levels while increasing HDL-C levels (70). The extract's hepatoprotective properties were determined seven days after CCl_4 treatment by administering it to mouse models and analyzing their post-SGPT and SGOT levels. The results showed a positive response after seven days of treatment, showing that dragon fruit (*H. polyrhizus*) crude extract had a preventative effect on the liver from the ongoing effect of the induced carbon tetrachloride than the *H. polyrhizus* ethanolic extract, and the dosage used for the test compounds was 2500 mg/kg body weight (93). All the investigated findings in different pharmacological interventions have been compiled in a more specific way in Table 2.

Conclusion

Hylocereus polyrhizus, commonly referred to as red dragon, is a botanical specimen with a diverse range of bioactive compounds, which give rise to various therapeutic properties. This review article presented ethnobotanical descriptions and highlighted the various health benefits of red dragon fruit and its primary component through its antioxidant, anti-inflammatory, antibacterial, and anticancer properties, among others. Further investigation into the various components of the product is necessary to

Table 2. Summary of the pharmacological activities of different parts of *Hylocereus polyrhizus*

Activity	Parts used	Chemical responsible	Mechanism of action	References
Cardioprotective activity	Fruit pulp	Polyphenols and antioxidant	Red pitaya ↓ Inhibit several platelet-activation mechanisms ↓ Anti-thrombotic effect	(22, 23)
Anticancer activity	Peel	Phytosterol (α-amyrin)	Anthocyanin and betacyanin ↓ Effects in K562 cells modify the integrity of the mitochondrial inner membrane ↓ Leakage of cytochrome C nuclear disintegration, and caspase activation ↓ Apoptosis(programmed cells death)	(31, 33)
Antidiabetic activity	Whole fruit	Polyphenols, soluble dietary fiber, and antioxidant content	Red pitaya ↓ Decrease insulin resistance ↓ Increase serum insulin ↓ Antidiabetic effects	(72,73)
Anti-inflammatory activity	Flesh	Betalains (betaxanthins and betaines), luteolin and ellagic acid	Ellagic acid ↓ Inhibit the transcription factor NF-kB ↓ Inhibit inflammatory genes like TNF-alpha and IL-1 ↓ Anti-inflammatory activity	(22,27,28,77)
Antiviral activity	Pulp	Betacyanin	Betacyanin ↓ Attachment to a non-structural protein, namely the envelope (E) protein of DENV-2 ↓ Mediates initial engagement to target sites ↓ Proved efficacious against dengue virus type 2 (DENV-2)	(78, 79)

Table 2. Continued

Activity	Parts used	Chemical responsible	Mechanism of action	References
Antioxidant activity	Pulp	Phenolic compounds, betalains(betanidine 6-O-β-glucoside)	Phenolic compounds ↓ Inhibit the formation of free radicals ↓ Anti-oxidant activity	(19, 82)
Antibacterial activity	Peel, fruit	Betacyanin	Betacyanins ↓ Change the permeability of cellular membranes ↓ Lead to loss of cellular pH gradient ↓ Decrease ATP levels, and lose the proton motive force ↓ Cause cell death.	(84)
Antifungal activity	Peel	Quercetin, and kaempferol, phenolic and flavonoid compounds	Inhibit the cell growth of fungus ↓ Antifungal activity	(91)
Hypolipidemic activity	Fruit peel	Soluble fiber, unsaturated fatty acids, and minerals especially potassium, sodium, magnesium, phosphorus, and zinc	Dietary fiber ↓ Creation of fatty acid fermentation products ↓ Prevents the synthesis of liver fatty acids, cholesterol ↓ Reduces the release of triglycerol release	(75, 76, 95)
Antiplasmodial activity	Peel	β-Amyrin and β-sitosterol	β-sitosterol ↓ Inhibit SK-OV-3 cells ↓ Antiplasmodial activity	(88, 96)
Hepatoprotective activity	Whole fruits	Phenolic compounds and total tocopherol	Red pitaya ↓ Inhibit the synthesis of ALT, AST, ALP and Bilirubin ↓ Hepatoprotective activity	(94, 97)

ALT: Alanine transaminase; AST: Aspartate transferase; ALP: Alkaline phosphatase; K562: Myelogenous leukemia cell line; SK-OV-3 cells: Ovarian cancer cells; ATP: Adenosine triphosphate; DENV-2: Dengue virus 2; TNF-alpha: Tumor necrosis factor alpha; IL-1: Interleukin-1; ellagic: An acid; Caspase: a family of endoproteases; NF-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells.

ascertain the precise mechanism of action and the specific molecular processes involved in health management. This vital review provides a promising array for researchers to investigate the potential lead chemical compounds responsible for significant pharmacological activities at the molecular level and for pharmaceutical industries to build new therapeutics.

Authors' contribution

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Writing–review & editing: All authors.

Conflict of interests

The authors declare there are no conflicts of interest.

Ethical considerations

Authors have carefully counseled ethical issues. The study protocol was authorized in accordance with government directives under Pharm/P&D/CUDP-20, 2023:15 by the Department of Pharmacy, University of Chittagong, Chittagong, Bangladesh.

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References

1. Sendker J, Sheridan H. History and current status of herbal medicines. In: Pelkonen O, Duez P, Vuorela PM, Vuorela H, eds. Toxicology of Herbal Products. Cham: Springer International Publishing; 2017. p. 11-27. doi: 10.1007/978-3-319-43806-1_2.
2. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177. doi: 10.3389/fphar.2013.00177.
3. World Health Organization (WHO). Global Centre for Traditional Medicine. Available from: https://www.who.int/initiatives/who-global-centre-for-traditional-medicine. Accessed April 22, 2023.
4. Bailey CJ. Metformin: historical overview. Diabetologia. 2017;60(9):1566-76. doi: 10.1007/s00125-017-4318-z.
5. Mercado-Silva EM. Pitaya—*Hylocereus undatus* (Haw). In: Rodrigues S, de Oliveira Silva E, de Brito ES, eds. Exotic Fruits. Academic Press; 2018. p. 339-49. doi: 10.1016/b978-0-12-803138-4.00045-9.
6. Choo WS, Yong WK. Antioxidant properties of two species of *Hylocereus fruits*. Adv Appl Sci Res. 2011;2(3):418-25.
7. Nurul SR, Asmah R. Variability in nutritional composition and phytochemical properties of red pitaya (*Hylocereus polyrhizus*) from Malaysia and Australia. Int Food Res J. 2014;21(4):1689-97.
8. Le NL. Functional compounds in dragon fruit peels and their potential health benefits: a review. Int J Food Sci Technol. 2022;57(5):2571-80. doi: 10.1111/ijfs.15111.
9. Panjaitan RG, Amelia S. Antihypercholesterolemic power of red dragon fruit (*Hylocereus polyrhizus*) peel extract. Pharmacogn J. 2022;14(3):518-23. doi: 10.5530/pj.2022.14.65.
10. Yeh WJ, Tsai CC, Ko J, Yang HY. *Hylocereus polyrhizus* peel extract retards alcoholic liver disease progression by modulating oxidative stress and inflammatory responses in C57BL/6 mice. Nutrients. 2020;12(12):3884. doi: 10.3390/nu12123884.
11. Gengatharan A, Dykes G, Choo WS. Betacyanins from *Hylocereus polyrhizus*: pectinase-assisted extraction and application as a natural food colourant in ice cream. J Food Sci Technol. 2021;58(4):1401-10. doi: 10.1007/s13197-020-04651-8.
12. Liaotrakoon W, De Clercq N, Van Hoed V, Dewettinck K. Dragon fruit (*Hylocereus* spp.) seed oils: their characterization and stability under storage conditions. J Am Oil Chem Soc. 2013;90(2):207-15. doi: 10.1007/s11746-012-2151-6.
13. Nurliyana R, Syed Zahir I, Mustapha Suleiman K, Aisyah MR, Kamarul Rahim K. Antioxidant study of pulps and peels of dragon fruits: a comparative study. Int Food Res J. 2010;17(2):367-75.
14. Paśko P, Galanty A, Zagrodzki P, Luksirikul P, Barasch D, Nemirovski A, et al. Dragon fruits as a reservoir of natural polyphenolics with chemopreventive properties. Molecules. 2021;26(8):2158. doi: 10.3390/molecules26082158.
15. Marques CG, da Silva BB, Lira SM, Dionísio AP, van Tilburg MF, Guedes MI, et al. Red pitaya (*Hylocereus polyrhizus*) as a functional food nutritional value, phytochemical content and health-promoting effects. In: Bioprospection of Co-products and Agro-industrial Wastes. CRC Press; 2023. p. 232-52.
16. Preiser JC. Oxidative stress. JPEN J Parenter Enteral Nutr. 2012;36(2):147-54. doi: 10.1177/0148607111434963.
17. Ratnam DV, Ankola DD, Bhardwaj V, Sahana DK, Kumar MN. Role of antioxidants in prophylaxis and therapy: a pharmaceutical perspective. J Control Release. 2006;113(3):189-207. doi: 10.1016/j.jconrel.2006.04.015.
18. Tang W, Li W, Yang Y, Lin X, Wang L, Li C, et al. Phenolic compounds profile and antioxidant capacity of pitahaya fruit peel from two red-skinned species (*Hylocereus polyrhizus* and *Hylocereus undatus*). Foods. 2021;10(6):1183. doi: 10.3390/foods10061183.
19. Wang L, Bei Q, Wu Y, Liao W, Wu Z. Characterization of soluble and insoluble-bound polyphenols from *Psidium guajava* L. leaves co-fermented with *Monascus anka* and *Bacillus* sp. and their bio-activities. J Funct Foods. 2017;32:149-59. doi: 10.1016/j.jff.2017.02.029.
20. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017;135(10):e146-603. doi: 10.1161/cir.0000000000000485.
21. Dubois-Deruy E, Peugnet V, Turkieh A, Pinet F. Oxidative stress in cardiovascular diseases. Antioxidants (Basel). 2020;9(9):864. doi: 10.3390/antiox9090864.
22. Safira A, Savitri SL, Putri AR, Hamonangan JM, Safinda B, Solikhah TI, et al. Review on the pharmacological and health aspects of *Hylocereus* or pitaya: an update. J Drug Deliv Ther. 2021;11(6):297-303. doi: 10.22270/jddt.v11i6.5181.
23. Santhakumar AB, Bulmer AC, Singh I. A review of the mechanisms and effectiveness of dietary polyphenols in reducing oxidative stress and thrombotic risk. J Hum Nutr Diet. 2014;27(1):1-21. doi: 10.1111/jhn.12177.
24. Liaotrakoon W, De Clercq N, Van Hoed V, Van de Walle D, Lewille B, Dewettinck K. Impact of thermal treatment on physicochemical, antioxidative and rheological properties of white-flesh and red-flesh dragon fruit (*Hylocereus* spp.) purees. Food Bioproc Tech. 2013;6(2):416-30. doi: 10.1007/s11947-011-0722-4.
25. Omidizadeh A, Mohd Yusof R, Ismail A, Roohinejad S, Nateghi L, Zuki M, et al. Cardioprotective compounds of red pitaya (*Hylocereus polyrhizus*) fruit. J Food Agric Environ. 2011;9(3-4):152-6. doi: 10.1234/4.2011.2242.
26. Gusev E, Zhuravleva Y. Inflammation: a new look at an old problem. Int J Mol Sci. 2022;23(9):4596. doi: 10.3390/ijms23094596.
27. Macias-Ceja DC, Cosín-Roger J, Ortiz-Masiá D, Salvador P, Hernández C, Calatayud S, et al. The flesh ethanolic extract of *Hylocereus polyrhizus* exerts anti-inflammatory effects and prevents murine colitis. Clin Nutr. 2016;35(6):1333-9. doi: 10.1016/j.clnu.2016.02.013.
28. Hapsari A, Pujiastutik YE. The potential effect of red dragon fruit (*Hylocereus polyrhizus*) peel ethanol extract on endometriosis progressivity in endometriosis mice. J Kedokt Hewan. 2018;12(2):53-6. doi: 10.21157/ j.ked.hewan.v12i2.10497.
29. Wahdaningsih S, Wahyuono S, Riyanto S, Murwanti

R. Terpenoid-lupeol of red dragon fruit (*Hylocereus polyrhizus*) and its immunomodulatory activity. Pak J Pharm Sci. 2020;33(2):505-10.

30. Nurmik M, Ullmann P, Rodriguez F, Haan S, Letellier E. In search of definitions: cancer-associated fibroblasts and their markers. Int J Cancer. 2020;146(4):895-905. doi: 10.1002/ijc.32193.
31. Luo H, Cai Y, Peng Z, Liu T, Yang S. Chemical composition and in vitro evaluation of the cytotoxic and antioxidant activities of supercritical carbon dioxide extracts of pitaya (dragon fruit) peel. Chem Cent J. 2014;8(1):1. doi: 10.1186/1752-153x-8-1.
32. Sreekanth D, Arunasree MK, Roy KR, Chandramohan Reddy T, Reddy GV, Reddanna P. Betanin a betacyanin pigment purified from fruits of *Opuntia ficus-indica* induces apoptosis in human chronic myeloid leukemia cell line-K562. Phytomedicine. 2007;14(11):739-46. doi: 10.1016/j.phymed.2007.03.017.
33. de Almeida Bauer Guimarães D, Dos Santos Bonfim De Castro D, de Oliveira FL, Nogueira EM, da Silva MAM, Teodoro AJ. Pitaya extracts induce growth inhibition and proapoptotic effects on human cell lines of breast cancer via downregulation of estrogen receptor gene expression. Oxid Med Cell Longev. 2017;2017:7865073. doi: 10.1155/2017/7865073.
34. Singh S, Kumar S. A review on nutritional, medicinal and bio-active compound of dragon fruit *Hylocereus polyrhizus* (FAC Weber) Britton & Rose. Int J Biochem Res Rev. 2023;32(5):57-67.
35. Safira A, Savitri SL, Putri AR, Hamonangan JM, Safinda B, Solikhah TI, et al. Review on the pharmacological and health aspects of *Hylocereus* or pitaya: an update. J Drug Deliv Ther. 2021;11(6):297-303. doi: 10.22270/jddt.v11i6.5181.
36. Jiang H, Zhang W, Li X, Shu C, Jiang W, Cao J. Nutrition, phytochemical profile, bioactivities and applications in food industry of pitaya (*Hylocereus* spp.) peels: a comprehensive review. Trends Food Sci Technol. 2021;116:199-217. doi: 10.1016/j.tifs.2021.06.040.
37. Dy KS, Wonglom P, Pornsuriya C, Sunpapao A. Morphological, Molecular identification and pathogenicity of *Neoscytalidium dimidiatum* causing stem canker of *Hylocereus polyrhizus* in southern Thailand. Plants (Basel). 2022;11(4):504. doi: 10.3390/plants11040504.
38. Long H, Chen Y, Pei Y, Li H, Sun Y, Feng T. Occurrence and identification of root-knot nematodes on red dragon fruit (*Hylocereus polyrhizus*) in Hainan, China. Agronomy. 2022;12(5):1064. doi: 10.3390/agronomy12051064.
39. Chu YC, Chang JC. High temperature suppresses fruit/seed set and weight, and cladode regreening in red-fleshed 'Da Hong' pitaya (*Hylocereus polyrhizus*) under controlled conditions. HortScience. 2020;55(8):1259-64. doi: 10.21273/hortsci15018-20.
40. Then KH, Faiz OM, Norshafiqah K. The flowering pattern and fruit production of red pitaya (*Hylocereus polyrhizus*) under Malaysian growing condition. Int J Agric Innov Res. 2020;8(4):311-7.
41. Jaya IK. Morphology and physiology of pitaya and it future prospects in Indonesia. CROP AGRO Sci J Agron. 2018;3(1):44-50.
42. Jamaludin NA, Ding P, Hamid AA. Physico-chemical and structural changes of red-fleshed dragon fruit (*Hylocereus polyrhizus*) during fruit development. J Sci Food Agric. 2011;91(2):278-85. doi: 10.1002/jsfa.4182.
43. Hart G. From prickly pear to dragon fruit. Cact Succ J. 2005;77(6):293-9. doi: 10.2985/0007-9367(2005)77[293:fpptdf]2.0.co;2.
44. Le Bellec F, Vaillant F. Pitahaya (pitaya) (*Hylocereus* spp.). In: Yahia EM, ed. Postharvest Biology and Technology of Tropical and Subtropical Fruits. Woodhead Publishing; 2011. p. 247-271, 272e-273e. doi: 10.1533/9780857092618.247.
45. Lim TK. *Hylocereus polyrhizus*. In: Edible Medicinal and Non-Medicinal Plants: Volume 1, Fruits. Dordrecht: Springer; 2012. p. 643-9. doi: 10.1007/978-90-481-8661-7_91.
46. Lin X, Gao H, Ding Z, Zhan R, Zhou Z, Ming J. Comparative metabolic profiling in pulp and peel of green and red pitayas (*Hylocereus polyrhizus* and *Hylocereus undatus*) reveals potential valorization in the pharmaceutical and food industries. Biomed Res Int. 2021;2021:6546170. doi: 10.1155/2021/6546170.
47. Adnan L, Osman A, Abdul Hamid A. Antioxidant activity of different extracts of red pitaya (*Hylocereus polyrhizus*) seed. Int J Food Prop. 2011;14(6):1171-81. doi: 10.1080/10942911003592787.
48. Saediman H, Mboe IS, Budiyanto B, Sarinah S, Hidrawati H. Smallholder adoption of horticultural crops: the case of dragon fruit in Southeast Sulawesi. IOP Conf Ser Earth Environ Sci. 2021;819(1):012043. doi: 10.1088/1755-1315/819/1/012043.
49. Gonzaga NR, Gonzaga AB Jr, Taylaran RD, Pajinag RT, Quirino RA. Productivity and fruit quality of red-fleshed dragon. J Multidiscip Stud. 2017;6(2):27-46. doi: 10.7828/jmds.v6i2.1043.
50. Foong JH, Hon WM, Ho CW. Bioactive compounds determination in fermented liquid dragon fruit (*Hylocereus polyrhizus*). Borneo Sci. 2012;31:37-56.
51. Zitha EZ, Magalhães DS, do Lago RC, Carvalho EE, Pasqual M, de Barros Vilas Boas EV. Changes in the bioactive compounds and antioxidant activity in red-fleshed dragon fruit during its development. Sci Hortic. 2022;291:110611. doi: 10.1016/j.scienta.2021.110611.
52. Kunnika S, Pranee A. Influence of enzyme treatment on bioactive compounds and colour stability of betacyanin in flesh and peel of red dragon fruit *Hylocereus polyrhizus* (Weber) Britton and Rose. Int Food Res J. 2011;18(4):1437-48.
53. Vijayakumar R, Abd Gani SS, Zaidan UH, Halmi MIE, Karunakaran T, Hamdan MR. Exploring the potential use of *Hylocereus polyrhizus* peels as a source of cosmeceutical sunscreen agent for its antioxidant and photoprotective properties. Evid Based Complement Alternat Med. 2020;2020:7520736. doi: 10.1155/2020/7520736.
54. Azwanida NN, Normasarah N, Afandi A. Utilization and evaluation of betalain pigment from red dragon fruit (*Hylocereus polyrhizus*) as a natural colorant for lipstick. J Teknol. 2014;69(6):139-42. doi: 10.11113/jt.v69.3326.
55. Ravichandran G, Lakshmanan DK, Murugesan S, Elangovan A, Rajasekaran NS, Thilagar S. Attenuation of protein glycation by functional polyphenolics of dragon fruit (*Hylocereus polyrhizus*); an in vitro and in silico evaluation. Food Res Int. 2021;140:110081. doi: 10.1016/j.

foodres.2020.110081.
56. Ibrahim SR, Mohamed GA, Khedr AI, Zayed MF, El-Kholy AA. Genus *Hylocereus*: beneficial phytochemicals, nutritional importance, and biological relevance—a review. J Food Biochem. 2018;42(2):e12491. doi: 10.1111/jfbc.12491.
57. Zainoldin KH, Baba AS. The effect of *Hylocereus polyrhizus* and *Hylocereus undatus* on physicochemical, proteolysis, and antioxidant activity in yogurt. World Acad Sci Eng Technol. 2009;60(3):361-6. doi: 10.5281/zenodo.1078639.
58. Esquivel P, Araya Quesada Y. Pitahaya (*Hylocereus* sp.): fruit characteristics and its potential use in the food industry. Revista Venezolana de Ciencia y Tecnología de Alimentos. 2012;3(1):113-29.
59. Moshfeghi N, Mahdavi O, Shahhosseini F, Malekifar S, Taghizadeh SK. Introducing a new natural product from dragon fruit into the market. Int J Recent Res Appl Stud. 2013;15(2):269-72.
60. Fadzliana NA, Rogayah S, Shaharuddin NA, Janna OA. Addition of L-tyrosine to improve betalain production in red pitaya callus. Pertanika J Trop Agric Sci. 2017;40(4):521-32.
61. Utpott M, Ramos de Araujo R, Galarza Vargas C, Nunes Paiva AR, Tischer B, de Oliveira Rios A, et al. Characterization and application of red pitaya (*Hylocereus polyrhizus*) peel powder as a fat replacer in ice cream. J Food Process Preserv. 2020;44(5):e14420. doi: 10.1111/jfpp.14420.
62. Mohd Adzim Khalili R, Norhayati AH, Rokiah MY, Asmah R, Mohd Nasir MT, Siti Muskinah M. Proximate composition and selected mineral determination in organically grown red pitaya (*Hylocereus* sp.). J Trop Agric Food Sci. 2006;34(2):269-75.
63. Tamby Chik C, Bachok S, Baba N, Abdullah A, Abdullah N. Quality characteristics and acceptability of three types of pitaya fruits in a consumer acceptance test. J Tour Hosp Culin Arts. 2011;3(1):89-98.
64. Ruzainah AJ, Ahmad R, Nor Z, Vasudevan R. Proximate analysis of dragon fruit (*Hylecereus polyhizus*). Am J Appl Sci. 2009;6(7):1341-6. doi: 10.3844/ajassp.2009.1341.1346.
65. Stintzing FC, Schieber A, Carle R. Evaluation of colour properties and chemical quality parameters of cactus juices. Eur Food Res Technol. 2003;216(4):303-11. doi: 10.1007/s00217-002-0657-0.
66. To LV, Ngu N, Duc ND, Trinh DT, Thanh NC, Mien DV, et al. Quality assurance system for dragon fruit. ACIAR Proc. 1999;100:101–114.
67. Sonawane MS. Nutritive and medicinal value of dragon fruit. Asian J Hort. 2017;12(2):267-71. doi: 10.15740/has/tajh/12.2/267-271.
68. Nur Izalin MZ, Kharidah M, Jamilah B, Noranizan MA. Functional properties of pectin from dragon fruit (*Hylocereus polyrhizus*) peel and its sensory attributes. J Trop Agric Food Sci. 2016;44(1):95-101.
69. Hossain FM, Numan SM, Akhtar S. Cultivation, nutritional value, and health benefits of dragon fruit (*Hylocereus* spp.): a review. Int J Hort Sci Technol. 2021;8(3):259-69. doi: 10.22059/ijhst.2021.311550.400.
70. Hernawati, Setiawan NA, Shintawati R, Priyandoko D. The role of red dragon fruit peel (*Hylocereus polyrhizus*) to improvement blood lipid levels of hyperlipidaemia male mice. J Phys Conf Ser. 2018;1013(1):012167. doi: 10.1088/1742-6596/1013/1/012167.
71. Ramli NS, Brown L, Ismail P, Rahmat A. Effects of red pitaya juice supplementation on cardiovascular and hepatic changes in high-carbohydrate, high-fat diet-induced metabolic syndrome rats. BMC Complement Altern Med. 2014;14:189. doi: 10.1186/1472-6882-14-189.
72. Omidizadeh A, Mohd Yusof R, Roohinejad S, Ismail A, Abu Bakar MZ, El-Din A. Bekhit A. Anti-diabetic activity of red pitaya (*Hylocereus polyrhizus*) fruit. RSC Adv. 2014;4(108):62978-86. doi: 10.1039/c4ra10789f.
73. Panjaitan RG. Anti-diabetic activity of the red dragon fruit peel (*Hylocereus polyrhizus*) in ethanol extract against diabetic rats. Pharmacogn J. 2021;13(5):1079-85. doi: 10.5530/pj.2021.13.140.
74. Solikhah T, Rani CA, Septiani M, Putra YA, Rachmah Q, Solikhah GP, et al. Antidiabetic of *Hylocereus polyrhizus* peel ethanolic extract on alloxan induced diabetic mice. Iraqi J Vet Sci. 2022;36(3):797-802. doi: 10.33899/ijvs.2022.132178.2061.
75. Adhi NG, Suastuti NW, Putra AA. Activity of *Hylocereus costaricensis* extract as antiobesity and hypolipidemic of obese Rats. Int J Pharm Res Allied Sci. 2018;7(1):201-8.
76. Rohin MA, Ali AM, Mat Hasan SA. Hypocholesterolemic effect of red pitaya (*Hylocereus* sp.) on hypercholesterolemia induced rats. Int Food Res J. 2009;16(3):431-40.
77. Park CM, Song YS. Luteolin and luteolin-7-O-glucoside inhibit lipopolysaccharide-induced inflammatory responses through modulation of NF-κB/AP-1/PI3K-Akt signaling cascades in RAW 264.7 cells. Nutr Res Pract. 2013;7(6):423-9. doi: 10.4162/nrp.2013.7.6.423.
78. Chang YJ, Pong LY, Hassan SS, Choo WS. Antiviral activity of betacyanins from red pitahaya (*Hylocereus polyrhizus*) and red spinach (*Amaranthus dubius*) against dengue virus type 2 (GenBank accession no. MH488959). Access Microbiol. 2020;2(1):acmi000073. doi: 10.1099/acmi.0.000073.
79. Chen Y, Maguire T, Marks RM. Demonstration of binding of dengue virus envelope protein to target cells. J Virol. 1996;70(12):8765-72. doi: 10.1128/jvi.70.12.8765-8772.1996.
80. Chen Y, Maguire T, Hileman RE, Fromm JR, Esko JD, Linhardt RJ, et al. Dengue virus infectivity depends on envelope protein binding to target cell heparan sulfate. Nat Med. 1997;3(8):866-71. doi: 10.1038/nm0897-866.
81. García-Cruz L, Dueñas M, Santos-Buelgas C, Valle-Guadarrama S, Salinas-Moreno Y. Betalains and phenolic compounds profiling and antioxidant capacity of pitaya (*Stenocereus* spp.) fruit from two species (*S. pruinosus* and *S. stellatus*). Food Chem. 2017;234:111-8. doi: 10.1016/j.foodchem.2017.04.174.
82. Hendra R, Masdeatresa L, Abdulah R, Haryani Y. Red dragon peel (*Hylocereus polyrhizus*) as antioxidant source. AIP Conf Proc. 2020;2243(1):030007. doi: 10.1063/5.0001391.
83. Nurmahani MM, Osman A, Hamid AA, Ghazali FM, Dek MS. Antibacterial property of *Hylocereus polyrhizus* and *Hylocereus undatus* peel extracts. Int Food Res J. 2012;19(1):77-84.
84. Yong YY, Dykes G, Lee SM, Choo WS. Effect of refrigerated storage on betacyanin composition, antibacterial activity of red pitahaya (*Hylocereus polyrhizus*) and cytotoxicity

evaluation of betacyanin rich extract on normal human cell lines. LWT. 2018;91:491-7. doi: 10.1016/j.lwt.2018.01.078.
85. Hendra R, Masdeatresa L, Abdulah R, Haryani Y. Antibacterial activity of red dragon peel (*Hylocereus polyrhizus*) pigment. J Phys Conf Ser. 2019;1351(1):012042. doi: 10.1088/1742-6596/1351/1/012042.
86. Rahayu YC, Sabir AR, Setyorini DY. Antibacterial activity of red dragon fruit extract (*Hylocereus polyrhizus*) on *Streptococcus mutans*. Int J Appl Pharm. 2019;11(4):60-3. doi: 10.22159/ijap.2019.v11s4.35293.
87. Temak Y, Cholke P, Mule A, Shingade A, Narote S, Kagde A, et al. In vivo and in-vitro evaluation of antimicrobial activity of peel extracts of red dragon fruit (*Hylocereus polyrhizus*). Res J Pharmacogn Phytochem. 2019;11(1):23-6. doi: 10.5958/0975-4385.2019.00005.0.
88. Hendra R, Khodijah R, Putri R, Amalia R, Haryani Y, Teruna HY, et al. Cytotoxicity and antiplasmodial properties of different *Hylocereus polyrhizus* peel extracts. Med Sci Monit Basic Res. 2021;27:e931118.
89. Mwangi ES, Keriko JM, Machocho AK, Wanyonyi AW, Malebo HM, Chhabra SC, et al. Antiprotozoal activity and cytotoxicity of metabolites from leaves of *Teclea trichocarpa*. J Med Plants Res. 2010;4(9):726-31. doi: 10.5897/jmpr09.188.
90. Jakimiuk A, Nowicka M, Bogusiewicz M, Adamiak A, Skorupski P, Miotla P, et al. Prevalence of estrogen receptor alpha PvuII and XbaI polymorphism in population of Polish postmenopausal women. Folia Histochem Cytobiol. 2007;45(4):331-8.
91. Hendra R, Masdeatresa L, Almurdani M, Abdulah R, Haryani Y. Antifungal activity of red dragon peel (*Hylocereus polyrhizus*). IOP Conf Ser Mater Sci Eng. 2020;833(1):012014. doi: 10.1088/1757-899x/833/1/012014.
92. Cushnie TP, Lamb AJ. Antimicrobial activity of flavonoids. Int J Antimicrob Agents. 2005;26(5):343-56. doi: 10.1016/j.ijantimicag.2005.09.002.
93. Cauilan PL. Hepatoprotective potential of *Hylocereus polyrhizus* (dragon fruit) on carbon tetrachloride induced hepatic damages in albino Wistar rats. Int J Sci Basic Appl Res. 2019;46(2):49-61.
94. Islam AM, Chowdhury MA, Uddin ME, Rahman MM, Habib MR, Uddin MG, et al. Protective effect of methanolic extract of *Hylocereus polyrhizus* fruits on carbon tetra chloride-induced hepatotoxicity in rat. Eur J Med Plants. 2013;3(4):500-7. doi: 10.9734/ejmp/2013/5090.
95. Mohd Adzim Khalili R, Norhayati AH, Rokiah MY, Asmah R, Mohd Nasir MT, Siti Muskinah M. Proximate composition and selected mineral determination in organically grown red pitaya (*Hylocereus* sp.). J Trop Agric Food Sci. 2006;34(2):269-75.
96. Luo H, Cai Y, Peng Z, Liu T, Yang S. Chemical composition and in vitro evaluation of the cytotoxic and antioxidant activities of supercritical carbon dioxide extracts of pitaya (dragon fruit) peel. Chem Cent J. 2014;8(1):1. doi: 10.1186/1752-153x-8-1.
97. Lim HK, Tan CP, Karim R, Ariffin AA, Bakar J. Chemical composition and DSC thermal properties of two species of *Hylocereus cacti* seed oil: *Hylocereus undatus* and *Hylocereus polyrhizus*. Food Chem. 2010;119(4):1326-31. doi: 10.1016/j.foodchem.2009.09.002.