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A Retrospective Review of *Pereskia Bleo* (Kunth) DC on its Properties and Preclinical Insights for Future Drug Discovery Trends

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ABSTRACT

Pereskia bleo (Kunth) DC, a leafy cactus, is a therapeutic plant indigenous in subtropical along with tropical regions. It is traditionally used as concoction from brewed leaves or eaten raw 'ulam'. It is alleged to have anti-inflammatory, anticancer, antiulcer and antirheumatic properties and it is treated as alleviation for gastrointestinal pain, ulcers, headache, atopic dermatitis, haemorrhoids, and diabetes by locals. Numerous scientific studies have been done on characterizing the phytoconstituents and biological properties from plants belonging to the Cactaceae family, particularly *Pereskia bleo*. In this review the antimicrobial, antioxidant and antidiabetic findings and *in vitro* as well as *in vivo* pharmacological importance and traditional use of *P. bleo* has been covered that could be used in novel drug discovery.

Keywords
Leafy cactus;*Pereskia bleo*; phytoconstituents; pharmacological

Introduction

Natural products are compounds that derived from animals, plants, microorganisms, and insects. Natural products have been the premise of human ailments treatment and source of new drugs. Numerous effective medications in the market today were initially synthesized to mirror the molecular action of natural products(Shen, 2015). Secondary metabolites and their derivatives from plants are used for medicinal purposes. Metabolites could be served as competitive agents and agents of symbiosis, metal transporting agents, sexual hormones, and differentiation effectors(Demain & Fang, 2000; Shen, 2015).

In previous decades, natural products have been identified and validated as distinguished valuable remedial medications, for a wide variety of human, animal, and plant ailments. However, additional novel chemical structures are yet to be worked out that will be consolidated into future medicines. The secondary metabolites produced by plant and animals have brought about various applications such as fragrances, insecticides, or biomedical tools(Ignatet al.,2011).

Literature Review

Pereskia bleo (Kunth) DC

Pereskia bleo (Kunth) DC usually called 'Pohon Jejarum' or 'Jarum Tujuh Bilah' by Malay society followed by 'Cak Sing Cam' by Chinese society. While in English is known as wax rose, leaf cactus, and rose cactus. *P. bleo* has a few equivalent words, for instance, *Pereskia*

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cruenta,Pereskia corrugate, *Pereskia panamensis*, Pereskia rose desert flora, *Rhodocactus bleo*, and *Rhodocactus corrugate*(Yenet al., 2013).*P. bleo* has been used as herbal medicine. In Panama, local people utilize the entire plant to treat gastrointestinal issues(Gupta et al., 1996).In Malaysia, the locals use it to treat malignancy-related diseases, similar to uterine, breast carcinoma, and brain tumours. The grounded leaf paste is spread over to the cut or injury for pain alleviation(Yen et al., 2013).

This plant is unlike other cacti types, and it has thin stems and substantial leaves. *P.bleo* belongs to the cactus family that encompasses of non-succulent leaves. It can grow up to 8 meters high. The leaves are radiant green and broad and have long thorny stems. The young or immature branches are usually in red. It spines in fascicles of 5 to 6, however, premature shoots frequently bear 1 to 4. The spines exhibit from areoles. The flowers or blossoms either be seen singular otherwise in bunches. It commonly takes after as roses and reaches a diameter to 5cm. The shades of the flower rely on upon the type and shift from white, yellow to fuchsia or red(Zareisedehizadehet al., 2014).Fruits are commonly waxy round green and dark shading and change to yellow when ripe(Yen et al., 2013) as illustrated in **Figure 1**.

Figure 1.*Pereskia bleo* (Kunth) DC.(Cactaceae) Source: Jalan Semeling, Bedong, Kedah

Ecology and geographic distribution

P.bleo originates from Argentina, Korea, and Paraguay. Moreover, it has been propagated in Malaysia and used as customary pharmaceutical(Yen et al., 2013).

Biophysical limits

The vast majority of the Pereskia species are grown in tropical atmospheres with a dry season or dry forests aside from *P.bleo,* which is grown in highly precipitate forest(Edwards & Donoghue, 2006).

Phytoconstituents of *P. bleo*

There are a total of 20 reported constituents in leaves (**Figure 2a**) and 2 components from fruits (**Figure 2b**) as shown inTable 1(Abdul-Wahabet al., 2012; Doetschet al., 1980; Hassanbaglou et al., 2012; Maleket al.,2009; Murilloet al., 2010; K. S. Simet al., 2010).The reported constituents are carotenoid, sterol, terpenoid, lactones, fatty acid, glycosides, and alkaloids. However, the major constituent from *P. bleo* leaves is phytol(Hostettmannet al., 1995).

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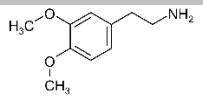
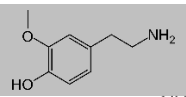
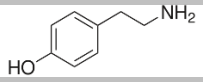
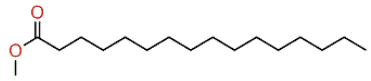
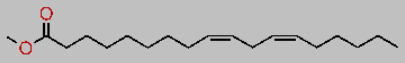
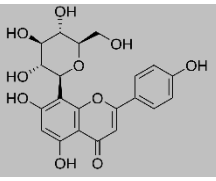
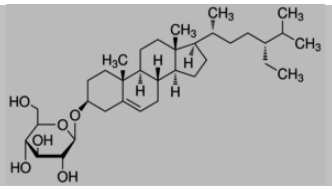
Figure 2a: *P.bleo* leaves and **Figure 2b**: *P.bleo* fruits

According to Loo et al., (2017), the cysteine-rich peptides of *P.bleo* has 36 amino acid residues, a 6-cysteine motif typical of the 6-cysteine-hevein-like peptide (6C-HLP) family, and a type I two-domain precursor comprising of the endoplasmic reticulum in addition to a domain by combining proteomic and transcriptomic methods(Loo et al., 2017). Followed by *in-silico* modeling, sequence and structural analysis showed a cation-polar-cation motif, which is a signature heparin-binding motif. NMR analysis also portrayed cystine-knot disulfide bond, 2-beta-sheet along with a 4-loop structural fold as shown in **Table 1.**

Table 1. Phytoconstituents present in the fruits and leaves of *P. bleo*

***P. bleo* leaves constituents**	
Alkaloids	
3,4-Dimethoxy-phenethylamine	
3-Methoxytyramine	
Tyramine	
Fatty acids	
Methyl palmitate	
Methyl linoleate	
Flavonoids	
Vitexin	
Phytosterol glycoside	
β-Sitosterol glucoside	
Lactone	

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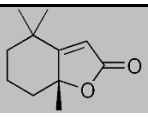
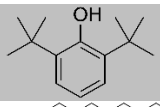
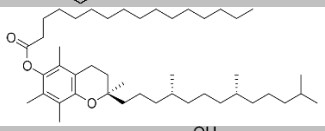
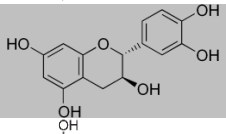
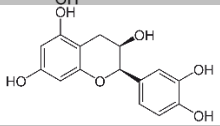
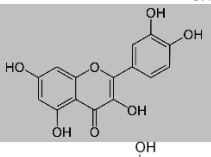
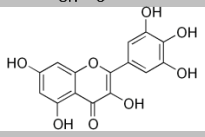
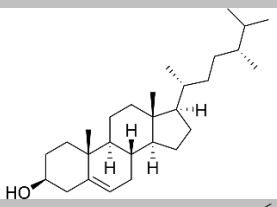
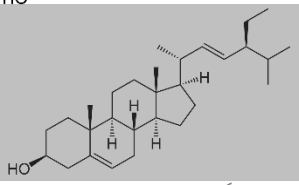
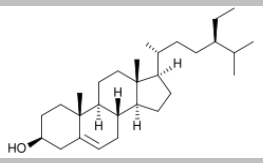
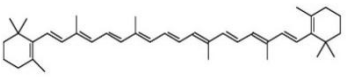
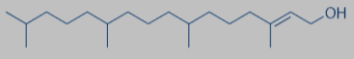
Dihydroactinidiolide	
Phenolic compounds	
2,4-Ditert-butylphenol	
α-Tocopherol	
Catechin	
Epicatechin	
Quercetin	
Myricetin	
Sterols	
Campesterol	
Stigmasterol	
β-Sitosterol	
Terpenoids	
β- Carotene	
Phytol	

***P.bleo* fruitsconstituents**

Carotenoids

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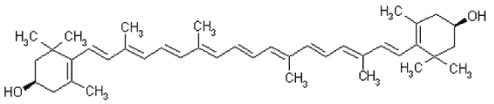
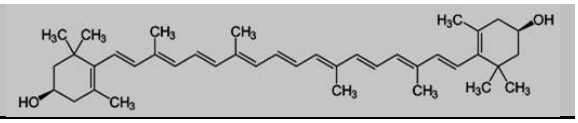
Lutein (β,é-carotene-3,3′-diol)	
Zeaxanthin (β, β-carotene-3,3′-diol)	

Antibacterial activity of *P. Bleo*

The increased event of multi-resistant pathogenic strains has constrained the impact of conventional antimicrobial treatment and has made a worldwide concern for new remedial agents(Larsenet al., 2005; Nigamet al., 2014).The following antibacterial findings on *P.bleo* are enlisted in **Table 2**.

Table 2. Effects of P.bleo on various Antimicrobial studies

The model/strain used	Dose or frequency	Implications
Streptococcus pyogenes (ATCC 19615), *Staphylococcus aureus* (ATCC 29737), *Escherichia coli* (ATCC 10536), *Pseudomonas aeruginosa* (ATCC 9027)	14.07-1800 μg/mL of methanolic, chloroform and hexane leaves extract	Methanolic and chloroform extracts displayed strong antimicrobial activity except for hexane extract(Johari & Khong, 2019).
Staphylococcus aureus (MRSA), *Bacillus subtilis* B29, *Pseudomonas aeruginosa* 60690, *Salmonella choleraesuis*	100 mg/mL of hexane, dichloromethane, ethyl acetate, and methanol leaves extracts	Hexane extract showed high antibacterial activity against *P. aeruginosa* 60690 and *S. choleraesuis*. Dichloromethane showed high antibacterial activity against MRSA(Wahab et al., 2009).
Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus, Bacillus subtilis	50 and 500 mg/mL of methanolic, hexane, ethyl acetate and water leaves extracts	Neither of the extracts exhibited antimicrobial assay against S.aureus and E.coli. Hexane, ethyl acetate, and hexane exhibited antimicrobial activity against P. aeruginosa. However, hexane and ethyl acetate had antimicrobial activity again B. *subtilis*(Philip et al., 2009).
Candida albicans (ATCC 90028), *Candida parapsilosis* (ATCC 22019), *Issatchenkia orientalis* (ATCC 6258) and *Cryptococcus neoformans* (ATCC 90112), *Aspergillus brasiliensis* (ATCC 16404), *Trichophyton mentagrophytes* (ATCC 9533)	0.02 - 2.50 mg/mL of hexane, chloroform, ethyl acetate, ethanol, methanol, water leaves extracts	The most potent fungicidal activity (minimum fungicidal concentration=0.16 mg/mL) were exhibited by the hexane, chloroform, ethanol and methanol extracts(Chan et al., 2018).

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Antioxidant activity

Oxygen is an exceptionally reactive substance and known as free radicals(Birben et al.,2012; Floyd, 1981).Generally, free radicals are produced by radiation by ionization, random generation of free radicals, and the leakage of electron transport chain. Free oxygen radicals cause various diseases, including rheumatoid arthritis, senility, cataract, cancer, and cardiovascular disease(Phaniendraet al., 2015).The following antioxidant findings on *P.bleo* are enlisted in **Table 3.**

Table 3. Effects of P.bleo on various Antioxidant studies

The model used/Study design	Dose or frequency	Implications
Total phenolic content (TPC) - Folin-Ciocalteau's method Antioxidant activity - DPPH scavenging assay	15.62 -250 µg/mL of methanolic, chloroform and hexane leaves extract	The methanolic extract exhibited the most significant TPC content and antioxidant activity with the IC_{50} 33.83 µg/mL contrasted to the hexane and chloroform extracts(Johari & Khong, 2019).
TPC - Folin-Ciocalteau's method Antioxidant activity - DPPH scavenging assay	100-1000 µg/mL of methanolic, hexane, ethyl acetate and water leaves extract	The ethyl acetate extract exhibited the most significant phenolic content of 40.12 GAEs/g and had significant antioxidant activity. However, hexane extract showed a significantly highest scavenging assay with EC_{50}210 µg/mL and reducing power assay(Simet al.,2010).
Antioxidant activity - DPPH scavenging assay	500 µg/mL of hexane, dichloromethane, ethyl acetate, and methanol leaves extracts	Hexane extract had the most effective DPPH radical scavenger (37.55%). Ethyl acetate and dichloromethane extracts were less effective free radical scavenger (16.1%)(Wahab et al., 2009).
Antioxidant activity – ABTS scavenging assay	5-100 µg/mL of methanolic, ethyl acetate, aqueous, t-butanol stem extracts	The t-butanol extract had the highest antioxidant activity compared to other extracts(Honget al., 2009).
Antioxidant activity – DPPH scavenging assay fingerprinted by Infrared spectroscopy (IR) between 4000 to 400 cm−1 at a 2 cm−1 resolution	80%, 60%, 40%, 20%, absolute methanolic and water extracts	Significant correlation with R^2Y of 0.88 using IR for projected antioxidant assay of most extracts. The -CH, -OH, and -NH infrared were associated with biological activity, however -PO, -NO2, and -PH exhibited a negative correlation(Sharif et al., 2014).

Diabetes mellitus

Diabetes mellitus (DM) is a generally known metabolic disease described by an elevated level of blood glucose or hyperglycemia. The insufficiency of insulin release commonly brings it about, insulin function otherwise both. The clinical indications of DM are exhibited as polyuria, bodyweight reduction, obscuring of vision, thirst, neuropathy, renal failure, and foot ulcers. In the

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long term, it will prompt to macrovascular and microvascular diseases(Alberti & Zimmet, 1998; Verhulstet al., 2019).

According to Rani et al., (2019), 500 mg/kg BW, 250 mg/kg BW and 125 mg/kg BW of aqueous fraction, aqueous, methanol, chloroform, and petroleum ether leave extracts did not portray the hypoglycaemic effect in streptozotocin (50 mg/kg BW)-induced Sprague Dawley rats. However, aqueous, petroleum ether, and chloroform extracts showed significant ($P<0.05$) reduction in blood glucose levels in the intraperitoneal (IP) glucose tolerance test. Both aqueous fraction and extract significantly ($P<0.05$) reduced the blood glucose level and restored the serum insulin of diabetic rats. Thus, *P.bleo* has the potential to act as a natural anti-diabetic agent or other diabetic-related treatments(Rani et al., 2019).

In vitro and *in vivo* preclinical findings

In toxicity findings, the acute oral administration at the highest dose (2500 mg/kg BW) of methanolic crude leaves extracts does not have adverse effects or mortalities in ICR mice(Sim et al., 2010).Likewise studied done in ICR mice, ethanolic crude extract (50, 125, and 1000 mg/kg BW) showed significant inhibition in plasma testosterone level, lumen diameter in the seminiferous tubules and diameter of the seminiferous tubules contrasted with the control group(Boohet al., 2015).Guilhon et al., (2015) did a study that showed that butanol crude leaves extract (100 mg/kg) showed significantly superior to the morphine-treated group. L-Nitro-arginine methyl ester (L-NAME) portrayed the effect against ethanol, butanol, and ethyl acetate extracts. Also, Glutamate-induced licking response was blocked by hexane, ethyl acetate, butanol crude leaves extracts(Guilhonet al., 2015).

According to Matsuse et al., (1998), whole *P.bleo* water extract does not portray positive anti-HIV results in HIV-1 induced cytopathic effect on MT-4 cells(Matsuse et al., 1998).Methanolic leaves extract tested for cytotoxicity activity against T-47D cells showed an EC50 value of 2.0 µg/mL. The mRNA expression levels of caspase 3 and c-myc were high in the treated cells. Although, p53 expression was moderately increased as compared to c-myc and caspase 3 levels. The ultrastructural study also showed apoptotic features (the presence of apoptotic bodies and chromatin margination) within the treated cells(Tanet al., 2005).Aqueous and methanol extracts (6.25 - 300 g/mL) tested had an insignificant antiproliferative effect and apoptosis level against both NIH/3T3 and 4T1 cell lines. Though, growing apoptosis within the cells given with increasing concentrations of the aqueous extract was shown. Correspondingly formed mutagenic substance subsequent the metabolization by liver enzymes(Er, Cheng, & Radhakrishnan, 2007).Recent studies conducted by Hong et al., (2009) display that 400 µg/mL of methanolic, ethyl acetate, aqueous, t-butanol stem extracts did not show significant antiproliferative activity in 4T1 and NIH/3T3 cell lines(Hong et al., 2009). similarly to Er et al., (2007) findings(Er et al., 2007).According to Malek et al., (2009), 2,4-di-tertbutyl-phenol showed potent cytotoxic activity against Human nasopharyngeal epidermoid carcinoma (KB) cells, with an IC50 value of 0.81 µg/mL(Malek et al., 2009).

Conclusionand Future Studies

Numerous medicinal plants, particularly *Pereskia bleo* (Kunth) DC have multifaceted of chemical compounds or phytocompounds, which display different biological and

pharmacological activities. They have been used as traditional medicines. According to the long-established hypothesis, plant-derived phytocompounds could retain the fundamental mechanism and vitality in the human body that permits them to be utilized as a part of our well-being. This review uncovers the compelling use of P.bleo in various biological activities. Thus, its phytoconstituents that be able to be used in novel drug discovery.

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Conflict Of Interest

The authors declare no conflict of interest.

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None

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