Ethnopharmacology, phytochemistry, and pharmacology of *Sterculia lychnophora* Hance (Pangdahai)

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**[ABSTRACT]** The matured, ripen, and dried seeds of *Scaphium affine* (Mast.) Pierre, known as Pangdahai (PDH) in Chinese and recorded as *Sterculia lychnophora* Hance (scientific synonym) in the 2015 edition of the Chinese Pharmacopeia, have been widely used in traditional Chinese medicine, Japanese folk medicine, Vietnamese traditional medicine, traditional Thai medicine and Indian traditional medicine. The decoctions of the seeds are used as a remedy for pharyngitis, laryngitis, constipation, cough, menorrhagia, and pain management. This review is aimed at fully collating and presenting a systematic and comprehensive overview of the ethnopharmacological uses of PDH, its phytochemical constituents, pharmacological activities, and toxicological profile. Additionally, this review aims to reveal the therapeutic potentials as well as the important scientific gaps in the research of this traditional medicine that need to be filled so as to provide a comprehensive data for its development, utilization and application. From our extensive review of literatures, the teas (water decoctions) of PDH, which largely contain very polar constituents like polysaccharides, are used in the treatment of constipation, pharyngitis, and pain traditionally and ethno-medicinally and their use have been justified by pharmacological studies carried out on the polysaccharides and aqueous extracts. Additionally, this review has revealed that the organic (ethanolic and methanolic) extracts of PDH possess diverse pharmacological (anti-inflammatory, anti-ulcer, anti-pyretic, anti-microbial, anti-obesity and analgesic) effects, yet have received little attention. Most studies on PDH have been focused on the polysaccharides (large molecular weight metabolites), resulting in a major scientific gap in our knowledge on PDH. Furthermore, this review has also shown that few studies have been done in the areas of quality control, pharmacokinetics, and toxicological studies of PDH.

**[KEY WORDS]** *Sterculia lychnophora* Hance; Pangdahai; Metabolites; Pharmacology

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**Introduction**

Pangdahai (PDH), the matured, ripened, and dried seeds of *Scaphium affine* (Mast.) Pierre (Malvaceae), is a traditional Chinese medicine (TCM), which has been used as both traditional medicine and health food in many Asian countries. In China, it is one of the herbs listed as both edible and medicinal resources (Medicine Food Homology) published by the Chinese Ministry of Health [1-4]. PDH is locally famous for its prevention and treatment of pharyngitis. The decoctions have also been traditionally used for the treatment of tussis, sore throat, toothache, constipation, laryngitis, cough, menorrhagia, and pain [5-7]. It has also been used in many Asian cuisines; especially its tea is drunk as a refreshing cooling drink. PDH soups are served as desserts in Laos, Vietnam, Cambodia, and Thailand [8-11]. Pharmacologically, both *in vitro* and *in vivo* studies have indicated that PDH exhibits a variety of pharmacological activities, including analgesic, anti-pyretic, anti-microbial, anti-hypertensive, anti-inflammatory, weight-losing, laxative, and calcium oxalate inhibition effects [1, 12-16]. Phytochemically, several bioactive compounds have been isolated from PDH, including polysaccharides, alkaloids, flavonoids, organic acids, and cerebrosides. The major constituents of
PDH are polysaccharides and lipids [1, 14, 17-18] which are the mostly studied constituents.

This review is aimed at fully collating and presenting a systematic and comprehensive overview of the ethnopharmacological uses of PDH, its phytochemical constituents, pharmacological activities, and toxicological profile. Also, emphasis is laid on revealing the scientific gaps and areas requiring more research, thus providing a reference for further research, utilization, and application of this TCM.

Methods for Literature Search

The literatures used for this review were obtained from accessible papers spanning from the middle 1990s to the end of 2017. The information was collected from papers retrieved from journals, books, dissertations, and online academic databases (CNKI, Web of science, SciFinder, PubMed, Science Direct, Springerlink, and Google Scholar). Information from non-scientific and commercial online sources was excluded. The keywords used for the search were Scaphium affine (Mast.) Pierre (Scientific name), Sterculia lychnophora Hance (Scientific synonym), Sterculiae Lychnophorae Semen (Pharmaceutical drug name), and Pangdahai (traditional/local name).

Taxonomy and Distribution

PDH is the matured, ripened and dried seeds of Scaphium affine (Mast.) Pierre [19] or Sterculia lychnophora Hance (Scientific Synonym) [5]. Sterculia lychnophora Hance Pierre is a flowering plant that belongs to the family Malvaceae and genus Sterculia. The genus Sterculia comprises of about 100–150 species. A total of 26 of these species are currently distributed in China, of which 14 are endemic and one introduced [20]. S. lychnophora is mainly distributed and produced in the tropical regions of Southeast Asia, such as Vietnam, Thailand, Cambodia, Laos, India, and Malaysia [1, 16, 21-22].

Pictures of the PDH seeds are shown in Fig. 1.

![Representative photographs of Pangdahai](image_url)

Fig. 1  Representative photographs of Pangdahai

Traditional Uses and Ethnopharmacology

The significance of Chinese medicine in the treatment of diseases and ailments cannot be underestimated. The long history of usage and efficacy of Chinese medicines have led to an increase in the level of confidence and acceptance by the public [23]. The medical application of PDH was first recorded in Ben Cao Gang Mu Shi Yi (Supplements to Compendium of Materia Medica), a famous monograph of Traditional Chinese Medicine written in 1765 by Xuemin Zhao in the Qing Dynasty [1]. PDH had been used to treat throat related diseases, especially pain and inflammation associated with tonsillitis and hoarseness of voice in Qing Dynasty (1644–1911). ‘Qing Yin Wan’ (Voice-clearing pill), a very famous prescription in that era contained PDH as one of its main ingredients [24].

According to TCM theory, PDH is sweet in flavor, cold in nature, and light in property and it is related to the lung and large intestine meridians. It has the action of clearing heat from the lungs, moistening the lung, disseminating/dispersing lung Qi, moistening the intestines, unblocking and relaxing the bowels, clearing away toxic substances, transforming phlegm, and stopping cough. Based on these actions, it is traditionally used in China for the treatment of pharyngitis (sore throat), constipation, non-productive cough (dry cough without sputum), and pain (headache and pain in the throat) [5].

PDH is often used alone or in combination with other herbs; the purpose of combination therapy is facilitating and enhancing their synergistic or additive effects as well as reducing or neutralizing their respective toxic effects [25]. For instance, the decoctions of PDH have been used alone to treat hoarseness of voice and in combination with honey to treat pharyngitis [26]. The tea of PDH has also been used as an oral antiseptic to relieve bad breath [27-28].

In a clinical investigation to study the effect of PDH tea in the treatment of acute tonsillitis, PDH tea prepared by soaking 4–8 pieces of PDH in adequate amount of boiling water for 30 min was drunk as ordinary tea every 4 h for 2–3 days. It was found that, out of 114 patients, 68 successfully recovered, 22 showed improved conditions (reduced symptoms but not full recovery) and 14 patients did not respond to treatment [1].

In a similar study, patients with chronic pharyngitis were randomly divided into two groups: test group (112 patients) and control group (70 patients). The test group was treated...
with PDH tea. The control group was treated with amoxicillin trihydrate. In the test group, 23 patients (20.50%) were healed, 78 patients (69.60%) had their conditions improved and 1 patient (9.80%) did not respond to treatment. In the control group, 8 patients (11.40%) were healed, 24 patients (34.30%) had their conditions improved and 38 patients (54.30%) did not respond to treatment. The study showed that PDH tea used for the treatment of chronic pharyngitis was significantly better than Amoxicillin trihydrate [29]. Similar clinical investigations have also confirmed the use of PDH in treating chronic pharyngitis and pharyngeal cough [26, 30].

PDH has been used in numerous Chinese prescriptions as either one of the main active ingredients or an adjunct in the treatment of several diseases. ‘Lun qin kou fu ye’ is a prescription that contains Pangdahai, Isatidis Radix (Isatis tinctoria L.), Gardeniae Fructus Praeparatus (Gardenia jasminoides J. Ellis) and Phellodendri Chinensis Cortex (Phellodendron chinense C. K. Schneid.) for the treatment of pharyngitis, chronic cough, and mouth ulcers [31-33].

PDH has also been used in combination with other heat-clearing and detoxifying herbal medicines like Gancao (root and rhizome of Glycyrrhiza uralensis), Chantui (slough of Cryptotympana postulata), Huangqi (root of Astragalus membranaceus), Dangshen (root of Codonopsis pilosula), and Maidong (root of Ophiopogon japonicus) to treat sore throat, hoarseness, and loss of voice. It has also been combined with Huangqi (root of Astragalus membranaceus), Yuxingcao (herb of Houttuynia cordata), and Lun (rhizome of Phragmites communis) to treat cough induced by lung heat, and Tianhuafen (root of Trichosanthes kirilowii), Maidong (root of Ophiopogon japonicus) and Pipaye (leaf of Eriobotrya japonica) to treat cough caused by lung dryness [1].

In Japanese and Vietnamese folk medicines, the use of S. lychnophora is similar to its usage in China. It is used for the treatment of hoarseness of voice, dry cough and dry throat due to heat in the lungs. It is also used to treat toothache and conjunctivitis (pink eyes) [35]. In Indian traditional medicine (Ayurveda and Siddha Medicine), S. lychnophora (locally known as Niranjan Phal or Umas mangu) is primarily used as a blood coagulant. It has been used for controlling excessive bleeding, heavy postmenopausal bleeding, and menorrhagia by traditional healers [6]. In Laos, decoctions of S. lychnophora are used for treating constipation [33], dysentry, and inflammatory related conditions [34]. In traditional Thai medicine, S. lychnophora, also known locally as Samrong, is used for the treatment of aphthous ulcer, sore throat, constipation, and cough. It has also been used to treat dehydration and obesity [8-9].

PDH is also used in many food recipes as health foods. For example, in Cambodia, Vietnam, and Thailand, the flesh obtained after removing the kernels from soaked seeds is served as a cooling drink after mixing it with granulated white sugar, ice, and soaked basil seeds. Malva puddings and malva cakes are also very famous [8, 9, 11]. ‘Pear dessert’ is also prepared from Asian pear (Ya li pear), Zhi mu (Anemarrhena Rhizome), and PDH with crystal rock sugar as sweetener. PDH tea (PDH and green tea) is listed among the top fifty Chinese dietary recipes compiled by the American Academy of Acupuncture and Oriental Medicine.

In the cosmetic industry, the extracts of PDH have been used as major component of cosmetic formulae used for the treatment of rough skin. The extracts have also been used to enhance the glossiness and growth of the hair [35].

Commercially, PDH is collected as a major non-timber forest product in Laos and Cambodia for export. Thus, PDH collection and marketing have become one of the most important economic activities in these countries [11, 36-37]. The tree is usually used for construction purposes (building, interior furniture, and boats) and as firewood [10]. The powdered PDH is also used as a component of poultry feed in China [38].

**Phytochemical Constituents**

From Traditional Chinese Medicine Records [39], PDH contains pentosan and viscous substances belonging to pectinic acids and are mainly composed of galacturonic acid, arabinose, and galactose acetic acid. The perisperm of the seeds contains volatile oil, tragacanth gum, and astringent substances. The kernel of the seeds contains fatty acids, spicy and bitter substances. The outer layer of seeds contains has sorin, and the peels contain 15.06% galactose and 24.7% pentose (mainly arabinose) [39]. Analysis of the chemical composition of PDH from Vietnam showed that PDH contained 12.36% crude proteins, 5.89% crude fats, 53.23% carbohydrates, and 29.45% reducing sugars [40]. Klinsukon et al. [41] have also reported that gums extracted from PDH are composed of 45.20% crude fiber, 38.30% carbohydrates, 4.90% protein, and 1.40% ash. Although numerous isolates have been characterized from other species of the Sterculia genus, very few have been identified from PDH. Among the few are alkaloids, flavonoids, organic acids and their derivatives, lipids, steroids, cerebrosides, and sugars. PDH owes its numerous pharmacological activities to these compounds. Even though PDH has compounds from different classes, the number of isolates from each class are very few.

**Saccharides**

Several types of sugars, ranging from mono, di, and poly saccharides, have been isolated from PDH. L-rhamnose, D-galactose, and sucrose are simple sugars from PDH [21-22, 42-44]. Four different types of polysaccharides have also been isolated. The polysaccharides are the major constituents of PDH and the most studied metabolites. Among the polysaccharides reported are water soluble, alkaline soluble and insoluble polysaccharides. It has been reported that these polysaccharides contain varying amounts of glucuronic acids and rhamnose units in their backbones with arabinose, galactose and xylose residues in their branched chains [21]. The water-soluble polysaccharides have been reported to be heterogeneous pectic polysaccharides with degree of esterification
value of 68\% \cite{21,43}. Other studies have also reported that gums extracted from PDH have similar carbohydrate composition as described above \cite{44}.

Alkaloids

Wang et al. \cite{22} have isolated two new quinolinone alkaloids: Sterculinine I (2-[(2-oxo-1, 2-dihydro-quinoline-4-carbonyl)-amino]-succinic acid 4-n-butyl ester) and Sterculinine II (2-[(2-oxo-1, 2-dihydro-quinoline-4-carbonyl)-amino]-succinic acid 4-methyl ester) from the ethyl acetate soluble fraction of PDH extracts.

Flavonoids

Only three flavonoids have been reported from PDH, i.e., kaempferol-3-O-β-D-glucoside, kaempferol-3-O-β-D-rutinoside, and isorhamnetin-3-O-β-D-rutinoside \cite{16,22}.

Cerebrosides

Cerebroside, a glycoside usually formed by sphingosine and saccharide, is an important component of animal muscle and nerve cell membranes. The sugar residue can be either glucose or galactose. The two major types are therefore called glucocerebrosides (glucosylceramides) and galactocerebrosides (galactosylceramides). Ga lactocerebrosides are typically found in neural tissue, while glucocerebrosides are found in other tissues. Two cerebrosides: soya- cerebroside I and 1-O-β-D-glucopyranosyl-(2S,3R,4E,8Z)-2-[(2-hydroxy-icosanoyl)amido]-4,8-octadecadiene-1,3-diol have been reported from PDH \cite{45}.

Organic acid and their derivatives

PDH contains both simple (short chain) and long chain organic acids. 2, 4-dihydroxybenzoic acid and succinic acid \cite{22,42} are examples of simple acids isolated from PDH. It is estimated that PDH contains about 5.5\% of fatty acids \cite{40}. GC-MS analysis of ethanolic extract of PDH has shown that PDH contains different types of fatty acids. The major saturated fatty acids include stearic and palmitic acids. The main unsaturated fatty acids include oleic and linoleic acids. Other fatty acids including palmitoleic, 10-nonadecenoic and 8-nonenenoic acids have also been detected in trace amounts \cite{42,46}.

Steroids

The two steroids reported from PDH are β-sitosterol and daucosterol \cite{22,55}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{chemical_structures.png}
\caption{Chemical structures of compounds 1–10 isolated/identified from Pangdahai}
\end{figure}
Fig. 3 Chemical structures of Compounds 11–20 isolated/identified from Pangdahai

Fig. 4 Chemical structures of compounds 21–45 isolated/identified from Pangdahai
Pharmacological Effects

PDH is used as a major component of many traditional formulations and has a wide range of ethnopharmacological applications. The fact that its metabolites exhibit potent bioactivities under laboratory conditions makes it a potential candidate for further research and development. In this section, a comprehensive summary of the biological and pharmacological activities of the metabolites discussed earlier and their possible mechanisms of action are provided. Specific areas that require further studies have also been highlighted.

Analgesic and anti-nociceptive effects

PDH is widely used to manage pain associated with too-"haches and sore throats in China, Thailand, and Vietnam [5, 8-9]. The analgesic effect is thought to be mediated both centrally and peripherally. The investigations carried out by Dhage et al. [13] and Surapanthanakorn [18] show that the ethanolic extracts of PDH (30–300 mg kg\(^{-1}\)) significantly inhibit acetic acid-induced writhing and increase the reaction time to thermal stimulus in tail immersion, hot plate, and tail flick tests. The extracts also inhibit paw licking in both neurogenic as well as inflammatory phases in formalin induced paw licking tests in mice. The observed effects are dose dependent and statistically significant. Surapanthanakorn [18] has further reported that the potency of the extracts at a dose of 200 mg kg\(^{-1}\) is comparable to acetyl-salicylic acid at same dose given orally. She has also reported that the analgesic effects of the extracts are inhibited by 2 mg kg\(^{-1}\) of naloxone administered intraperitoneally.

Anti-inflammatory effects

PDH is well noted for the treatment of pharyngitis since antiquity [5, 7-9]. The anti-inflammatory effect of PDH is believed to be due to inhibition of histamine, serotonin, bradykinin, and prostaglandins, which are key mediators of acute inflammation. Studies have shown that polysaccharides, the major constituents of PDH, significantly inhibit mice ear edema induced by dimethyl benzene and 2% croton oil. They have also shown significant inhibition of cotton pellet-induced granuloma tissues formation in rats [14, 43, 47]. Wu and co-researchers [43] have identified that oral administration of 50–200 mg kg\(^{-1}\) acidic water-soluble polysaccharides exhibits significant dose-dependent acute and chronic anti-inflammatory activities. They have also found the anti-inflammatory effects are comparable to acetyl-salicylic acid. Dhage et al. [13] and Surapanthanakorn [18] have also reported that intraperitoneal administration of 30–300 mg kg\(^{-1}\) ethanolic extracts of PDH results in significant dose-dependent inhibition of the carrageenan-induced rat paw edema. Surapanthanakorn [18] has further identified that the extracts significantly inhibit cotton pellet-induced granuloma formation in the rats.

Anti-pyretic effects

The work of Surapanthanakorn [18] shows that oral administration of 50–200 mg kg\(^{-1}\) ethanolic extracts of PDH significantly reduces the rectal temperature of rats following pyrexia induced by subcutaneous injection of 10 mL kg\(^{-1}\) of 20% W/V Brewer’s yeast suspension.

Anti-oxidant effects

In recent years, there has been an increasing interest in plant anti-oxidants because of their potential health-promoting properties. The anti-oxidant activity of PDH crude extracts is evaluated based on their ability to scavenge 2, 2-diphenyl-1-picrylhydrazyl (DPPH) radicals and reduce potassium ferrocyanide [K\(_2\)Fe (CN)\(_6\)]. Dhage and his team [13] have identified that 10–200 µg mL\(^{-1}\) ethanolic extracts of PDH are able to scavenge DPPH radicals in a concentration-dependent manner with an EC\(_{50}\) of 800 ppm. Similar studies conducted by Ogale et al. [12] and Lam et al. [48] have also shown that methanolic extracts of PDH show a high free radical scavenging activity with IC\(_{50}\) of 11.02 µmol L\(^{-1}\) and 98–200 µg mL\(^{-1}\), respectively. Dhage and his team [13] have also found that the extracts (80–400 µg mL\(^{-1}\)) exhibit a significant concentration-dependent reduction of potassium ferrocyanide, a result that is comparable to reducing power of Butylated hydroxytoluene (BHT), the reference anti-oxidant used in their study. They have also identified that the extracts show a significant dose-dependent increase in endogenous protective anti-oxidant enzymes superoxide dismutase (SOD) and catalase (CAT) and a reduction in glutathione (GSH) [13].

Anti-ulcer effects

The ethanolic extracts of PDH have also been reported to offer gastroprotective effects by inhibiting the mucosal lesions induced by both pyloric-ligation and ethanol. The studies by Dhage et al. [13] show that 100–500 mg kg\(^{-1}\) of ethanolic extracts of PDH exhibit a significant dose-dependent reduction in pyloric-ligation and ethanol-induced rise in volume of gastric acid secretion, total gastric acidity, pH of gastric content, and ulcer index. They have further proposed that the gastroprotective effect of the extract could be due to increase in the SOD, CAT and GSH levels, since reactive oxygen species are involved in the pathogenesis of pylorus ligation and ethanol induced gastric mucosal injury [13]. In a later study conducted by Ogale et al. and his team [12] to investigate the gastroprotective effects of PDH, they have confirmed the findings of Dhage et al [13].

Anti-hypertensive effect

The seed kernel of PDH has been reported to have hypotensive effects. Oral or intramuscular administration of 25% aqueous solution of the dried, defatted and powdered seed kernel of PDH shows a significant reduction in the systolic blood pressures of cats and dogs. The hypotensive effect was reported to have been sustained for 3–4 h in cats but only for 30 min in dogs. However, the exact mechanisms for the observed effect are not clear [17]. This is an area that requires extensive studies in order to provide scientific data to support its traditional use in managing hypertension.

Antimicrobial effects

The gram-positive Streptococcus mutans is an important...
cariogenic bacterium and the primary causative agent of dental caries \[49\]–[50]. \textit{S. mutans} metabolizes the carbohydrates contained in consumed foods and produce organic acids, which initiates the process of tooth decay and plaque formation. Yang \textit{et al.} \[53\] and Hwang \textit{et al.} \[52\] have investigated the effects of the ethanolic extracts of PDH on the cariogenic properties of \textit{Streptococcus mutans}. Their findings show that 0.01–0.04 mg·mL\(^{-1}\) PDH demonstrates a significant \((P < 0.05)\) concentration-dependent inhibition of the growth, acid production and biofilm formation of \textit{S. mutans}. Furthermore, a significant concentration-dependent bactericidal effect is observed at concentrations from 0.04 to 0.32 mg·mL\(^{-1}\) \[51–52\]. Other studies conducted to investigate the anti-bacterial effects of PDH have shown that 40–80 µg·mL\(^{-1}\) of methanol and water extracts of PDH have significant anti-bacterial activity against \textit{E. coli}, \textit{S. aureus}, \textit{S. typhi}, and \textit{B. dysenteriae} \[55–54\]. Palve \textit{et al.} \[53\] have further reported that the extracts have anti-fungal activity against \textit{C. albicans}. These antimicrobial activities of PDH support its traditional uses as an oral antiseptic and treatment of throat and gastro-intestinal infections \[27–28, 34\].

**Neuroprotective effects**

Neuroprotection is the mechanism and strategy used to protect against neuronal injury or degeneration in the central nervous system (CNS) following oxidative stress, inflammatory response and nervous system injury/trauma. PDH may owe its neuroprotection to its ability to prevent neuronal injury. The investigations of Wang and his colleagues \[45\] have identified that 1-\(O-\beta-D\)-glucopyranosyl-(2\(S\), 3\(R\), 4\(E\), 8\(Z\))-2-[2-hydroxyoctadecanoyl]amid]-4, 8-octadecadiene-1, 3-diol \(10\), a cerebroside, has a moderate protective effect against \textit{SH-SYSY} cell damage induced by hydrogen peroxide (\(\text{H}_2\text{O}_2\)) in a dose-dependent manner within the dose range of 0.025–2.5 µg·mL\(^{-1}\). However, they have found that the percentage of viable cells decreased (decrease in neuroprotective effect) as the dose was further increased above 2.5 µg·mL\(^{-1}\) \[49\]. Shetty and his team \[53\] have also shown through \textit{in silico} docking studies that compounds soya cerebroside \(1\) (9) and compound \textit{10} have very high affinity for amyloid precursor protein (APP). They have found that the APP-cerebrosides binding energies range from \(-239.3\) to \(-389\). They have further studied the protein-ligands interactions and predicted some possible binding sites \[53\].

**Skin depigmenting effects**

The methanolic extract of PDH has been shown to inhibit melanogenesis and has therefore been proposed to be safely used as a skin depigmenting agent. The proposed mechanism is thought to be due to inhibition of tyrosinase expression or enhancement of tyrosinase degradation and down-regulation of hyperpigmentation by anti-oxidants. The investigation of Lam \textit{et al.} \[48\] has indicated that 12.5–200 µg·mL\(^{-1}\) methanolic extracts of PDH show a significant concentration-dependent inhibition of melanin synthesis in \textit{B16F10} murine melanoma cells and \textit{C57BL/6} wild-type mice melan-a cells. They have also found that the extracts demonstrate significant inhibitory effects on mushroom tyrosinase and cellular tyrosinase activity. They have reported that 200 µg·mL\(^{-1}\) of the PDH extracts show 23.40% inhibition of mushroom tyrosinase activity. A similar concentration shows 48.65 and 88.56% inhibition of cellular tyrosinases extracted from \textit{B16F10} murine melanocytes and \textit{C57BL/6} wild-type mice melan-a cells, respectively. MTT assay has also indicated that, the extracts have no cytotoxic effect on the cells. Furthermore, Western blotting analysis has also revealed that, the extracts (200 µg·mL\(^{-1}\)) significantly reduce the expression of tyrosinase and tyrosinase related protein 1 (Tyrp1) \[48\].

**Anti-obesity effects**

Fatty acid synthetase (FAS) catalyzes the \textit{de novo} synthesis of fatty acids from acetyl-CoA and malonyl-CoA in the presence of Dihydronicotinamide-adenine dinucleotide phosphate (NADPH) \[56\] and the accumulation of these fatty acids eventually result in obesity. PDH has also been linked to type-2 diabetes and cancer \[57–61\]. Inhibition of FAS has been reported to be selectively cytotoxic to human cancer cells \[62\] and has also been suggested as a potential target in obesity therapy \[57\]. The work of Gao \textit{et al.} \[15\] and Zhao \textit{et al.} \[16\] have shown that the ethanolic extracts of PDH significantly inhibit FAS and consequently reduce hepatic lipogenesis. It also reduces appetite and adipose and promotes weight loss in rats. Zhao and his colleagues \[16\] have reported that the extracts exhibit both reversible and irreversible inhibition of FAS with an \textit{IC}_{50} \textit{of 3.5 µg·mL}^{-1} \textit{and an apparent inactivation rate constant, }k_{obs} \textit{of }2.2.3 \times 10^{23}/\text{min}. \text{They have also established that the extract inhibits acetyl-CoA uncompetitively but inhibits NADPH and malonyl-CoA both competitively and noncompetitively. They have further compared FAS inhibitory effects of the PDH extracts with known FAS inhibitors (2)-epigallocatechin gallate (EGCG) and (2)-epicatechin gallate (ECG): }\text{[63–65]} \text{and reported that the PDH extract is more potent than the gallated catechins. Additionally, they have isolated kaempferol-3-O-\beta-D-glucoside (3), kaempferol-3-O-\beta-D-rutinoside (4), and isorhamnetin-3-O-\beta-D-rutinoside (5) from the extract which could account for the observed effects }\text{[16].} \text{In another study conducted to determine the effect of PDH on weight loss, abdominal fat and serum leptin levels in obese women in Thailand, it has been found that the water extract of PDH (PDH gel) administered at a dose of 0.08% the body weight of obese women significantly reduces BMI, body weight, body fat, and serum leptin levels. It also has been found that PDH gel causes a significant decrease in hunger sensation but an increase in satiety behaviors in obese women }\text{[9].} \text{Furthermore, a recent study by Phlicharoenphon and his team }\text{[8] using an }\textit{ex vivo} \text{method involving mice inverted intestinal sac model has also demonstrated that water extract of PDH show a significant reduction in glucose uptake from its surrounding glucose containing medium }\text{[9]. These findings also support the use of pangdahai in controlling body fat and weight traditionally.}
Laxative effects

The teas and decoctions of PDH have been used to treat constipation [5, 46]. This laxative effect has been attributed to the ability of the extracts of PDH to increase and promote intestinal peristalsis [66] and also by increasing the bulk content of the gastro-intestinal tract. Wang [66] has reported that administration of PDH water infusion (p.o., IV, and IM) promoted intestinal peristalsis in dopey dogs. He also found that the water infusion of the kernel had the strongest effect. He has further identified that the water infusion of the kernel (1: 400 000) significantly promoted intestinal peristalsis in rabbits and the effect was antagonized by atropine [46]. The increase in the volume of gut content is also reported to be due to the presence of sterulin and bassorin which are present in high quantities in PDH.

Other effects

Studies conducted by Zhang et al. [67] have also suggested that water extracts of PDH inhibit calcium oxalate crystallization. The extract significantly reduces crystal growth index in an in vitro experiment, inhibits the growth and aggregation of calcium oxalate crystal in rat kidneys and also decreases the amount of calcium oxalate monohydrate crystal in the kidneys. Further studies by Wang et al. [66] have demonstrated that the water extract enhances the thermodynamic stability of calcium oxalate crystals in solution by inhibiting the conversion of calcium oxalate dihydrate to calcium oxalate monohydrate. Calcium oxalate monohydrate is more difficult to be removed by the kidneys since it is less water soluble than the dihydrate form. Further research into these findings is required to establish the metabolites that are responsible for the observed effects.

Quality Control and Evaluation Studies

Few studies on quality control and evaluation of PDH have been reported. Palve et al. [69] have reported an HPTLC fingerprint for preliminary qualitative analysis of PDH. Wang and his team have also established an HPLC fingerprint for the quality evaluation of PDH [70]. Also, GC-MS methods have been established for both qualitative and quantitative analysis of fatty acids from PDH [42, 46]. More importantly, Su et al. [71] have also established a simple and accurate HPLC-FLD method to analyze the content of aflatoxins in PDH.

Table 1 Summary of dose/concentration related pharmacological effects of Pangdahai

<table>
<thead>
<tr>
<th>Dose/Concentration</th>
<th>Pharmacological effect</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–300 mg kg⁻¹</td>
<td>Analgesic, Anti-inflammatory, Antipyretic effects</td>
<td>[13-14, 18, 43, 47]</td>
</tr>
<tr>
<td>10–400 µg mL⁻¹</td>
<td>Anti-oxidant effect</td>
<td>[12-13, 48]</td>
</tr>
<tr>
<td>100–300 mg kg⁻¹</td>
<td>Gastro-protective effect</td>
<td>[12-13]</td>
</tr>
<tr>
<td>10–320 µg mL⁻¹</td>
<td>Anti-microbial activity</td>
<td>[49-54]</td>
</tr>
<tr>
<td>0.25 g mL⁻¹</td>
<td>Anti-hypertensive effect</td>
<td>[17]</td>
</tr>
<tr>
<td>0.025–2.5 µg mL⁻¹</td>
<td>Neuroprotective effect</td>
<td>[45, 55]</td>
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<tr>
<td>12.5–200 µg mL⁻¹</td>
<td>Skin depigmenting effect</td>
<td>[48]</td>
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<tr>
<td>10–120 mg kg⁻¹</td>
<td>Anti-obesity effect</td>
<td>[15-16]</td>
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<tr>
<td>0.01 g mL⁻¹</td>
<td>Inhibition of calcium oxalate crystallization</td>
<td>[67-68]</td>
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<tr>
<td>0.65–2.60 g kg⁻¹</td>
<td>Laxative effect</td>
<td>[66]</td>
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Toxicological studies

The toxicological studies of PDH are very scanty. However, it is reported that not more than 3 seeds should be boiled per drink since overconsumption may result in white watery phlegm, nausea, cough, and swollen tongue [3]. It has also been reported that daily oral administration of 2–3 g kg⁻¹ for 10–15 days to dogs resulted in hypotenensive crisis and other adverse effects [17]. Additionally, PDH has been reported to cause dyspnoea, pulmonary congestion, pulmonary edema, and nerve suppression. It could also induce allergic reactions such as skin itching and body rash in susceptible individuals [17].

Aflatoxins (B1, B2, G1 and G2) have also been detected and quantified from this drug due to fungal contamination resulting from inappropriate and poor storage conditions [71-72]. The climatic conditions of the production areas of PDH (tropical regions of South-East Asia) make this drug susceptible to fungal contamination and consequently mycotoxic production [73-75]. It is therefore recommended that the amount of these aflatoxins should be checked prior to use. Consequently, it is specified that, 1000 g of PDH should not contain more than 5 µg of aflatoxin B1 and not more than 10 µg of total aflatoxins (B1, B2, G1 and G2 combined) [3]. However, a maximum limit of 2 µg kg⁻¹ for aflatoxin B1 and 4 µg kg⁻¹ for total aflatoxins in herbal drugs have been set by the European Pharmacopoeia [76]. This is also another area that requires more research, especially toxicity studies on the liver and kidney due to the extensive use of PDH both as food and medicine.

Conclusions

In this review, the traditional and ethnomedical uses, major metabolites, pharmacological, quality control, and toxicological studies of the extracts and isolates from the matured, ripened and dried seeds of Scaphium affine (Mast.) Pierre (PDH) are summarized. The main traditional and
ethno-medicinal uses of PDH are for the treatment of constipation, pharyngitis, and pain. The tea (water decoction) of PDH, which are mainly used would largely contain very polar constituents like polysaccharides. The pharmacological studies carried on the polysaccharides and aqueous extracts of PDH reviewed in this review [8-9, 14, 17, 21, 43, 47, 53-54, 66] have justified the traditional and ethno-medicinal uses of PDH tea. Different types of compounds, including alkaloids, saccharides, flavonoids, organic acids, cerebrosides, and steroids, have been isolated from PDH. The crude extracts and isolates from PDH have exhibited numerous pharmacological activities such as antipyretic, anti-inflammatory, antihypertensive, antibacterial, anti-obesity, laxative, anti-ulcer, antioxidant, and neuroprotective effects.

Although PDH tea is used traditionally, this review has revealed that the ethanolic and methanolic extracts of PDH [12-13, 15-16, 18, 48, 51-52] possess diverse pharmacological (anti-inflammatory, anti-ulcer, anti-pyretic, anti-microbial, anti-obesity and analgesic) effects, but little attention has been given to them, and that majority of the reported studies have focused on the polysaccharides (large molecular weight metabolites). Furthermore, preliminary TLC and HPTLC screening has shown strong presence of alkaloids, phenolic compounds and organic acids [69] in these extracts. The little attention paid to the organic extracts (methanol and ethanol) has created a major scientific knowledge gap which requires more research especially in the areas of isolation and characterization, pharmacological studies of isolates, among others. This could result in the discovery of the specific metabolites responsible for the diverse pharmacologic effects and new bioactive compounds as well.

Furthermore, pharmacokinetic and metabolomics studies on the bioactive compounds isolated from PDH should be conducted to provide detailed understanding of their mechanisms of action and their therapeutic effects. Additionally, more research on the quality control and evaluation, and toxicological profile (liver and kidney) of this TCM should be done to ensure its efficacy and safety in clinical use.

It is evident from this review that scientific knowledge available on PDH is not comprehensive. In order to obtain a comprehensive data on this species, future research should prioritize the phytochemical investigations of the organic extracts of PDH so as to fully compile its secondary metabolites. Also, bioactivity studies on these metabolites should be conducted in order to establish the specific metabolites responsible for the various effects of PDH. Lastly, due to the extensive use of PDH both as medicine and health food, extensive and vigorous quality control studies as well as toxicological studies, especially liver and kidney toxicities, must be carried out to ensure the safety and efficacy of PDH.

<table>
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<th>Abbreviation</th>
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<tr>
<td>APP</td>
<td>Amyloid precursor protein</td>
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<td>BHT</td>
<td>Butylated hydroxytoluene</td>
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