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Review Article

Research advances in *Pimpinella thellungiana*: Nutrients, bioactive compounds, and functional properties benefitting livestock

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ABSTRACT

Growth retardation affects the health and production of livestock, while overexertion can cause sudden cardiac arrest. Both cases are considered to be metabolic disorders and are detrimental to livestock production. Effective measures for relieving or treating these disorders are scarce. However, *Pimpinella thellungiana* H. Wolff (*P. thellungiana*), a medicinal herb, has been reported to relieve growth retardation and overexertion in ethnopharmacological clinical trials. This paper summarizes and classifies a total of 106 bioactive compounds that were isolated and identified from *P. thellungiana*, including flavonoids, simple phenylpropanoids, coumarins, volatile compounds, and simple polyphenols, and discusses its pharmaceutical benefits, including its growth-promoting, antioxidant, anti-inflammatory, anti-atherosclerotic, and hepatoprotective properties. The nutrition, metabolism, biological activities, and pharmacological effects of the principal compounds of *P. thellungiana* in livestock are reviewed, as well as their potential molecular targets and metabolic signaling pathways in which these compounds are involved. However, the pharmacological and toxicological effects of some compounds have not been well documented, and further investigations of the bioactive compounds are needed. Such studies are crucial for the development of natural drugs or feed additives from *P. thellungiana* to alleviate growth retardation and mitigate injuries from overexertion in livestock.

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1. Introduction

With the increasing demand for high production in livestock, growth retardation and overexertion are occurring more frequently. Growth retardation is defined as delayed or arrested

growth during early life due to malnutrition or diseases (Kyle et al., 2015; Tang and Xiong, 2022). Overexertion is a sub-health state triggered by prolonged working hours and excessive work intensity, which leads to obstinate or persistent metabolic disorders in various organs, and is considered the primary cause of sudden cardiac arrest (Kyle et al., 2015). These two pathological conditions are characterized by metabolic disorders (Kobayashi et al., 2012; Rachakatla and Kalashikam, 2022), a weakened immune system (Ervasti et al., 2021), wasting, inflammation, oxidative stress, and gastrointestinal microbiota imbalance (Lee et al., 2021, 2022). Most stress-induced metabolic changes are short term and can be cured by reducing stress or by temporary pharmacological intervention, but metabolic abnormalities caused by growth retardation and overwork persist after the stress fades (Kyle et al., 2015; Tang and Xiong, 2022). With increasing concerns for growth retardation

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and overexertion, there is an urgent need to address these complex metabolic disorders, as effective intervention measures for these disorders are currently lacking.

Pimpinella thellungiana H. Wolff (*P. thellungiana*) belongs to the family Umbelliferae. The genus *Pimpinella* encompasses approximately 150 species that are distributed worldwide (Fernández Prieto et al., 2018). These plants have been used as medicines for more than 1700 years to treat gastrointestinal dysfunction, respiratory diseases and kidney ailments, as well as for deworming livestock (Fernández Prieto et al., 2018; Sun et al., 2019; Tepe and Tepe, 2015; Wu et al., 2023). In China, *P. thellungiana*, known as “Yang Hong Shan” and “Liu Yue Han”, is used for treating sexual dysfunction, and improving the cardiovascular system, lipid metabolism, immunity system, growth, and development. In addition, *P. thellungiana* can effectively alleviate growth retardation and injuries due to overexertion in livestock. In recent years, *P. thellungiana* has attracted increasing interest from researchers and pharmacologists. However, the bioactive ingredients, efficacy, and application of *P. thellungiana* in livestock have not been fully analyzed or widely reported (Hui et al., 2023).

Based on databases including Web of Science (1900 to July 2024), PubMed, Europe PMC, CNKI (1972 to July 2024), Ovid (1970 to July 2024), Agricola (from 1970 to July 2024), ProQuest (1946 to now), ScienceDirect, Springer Link, Worldlib, and Google Scholar, the keywords of “*Pimpinella*” and “*thellungiana*” were used to search the literature. After duplicates were removed, a total of 62 publications were accepted as appropriate. This paper reviews the botanical properties, medicinal values, progress in pharmacological research, key bioactive compounds and functions, and action mechanisms of *P. thellungiana*.

2. Botanical properties

P. thellungiana is widespread in Asia, predominantly in northern China, the Russian Far East, Mongolia, and Japan, and thrives at elevations ranging from 600 to 1700 m. It is a perennial herbaceous plant that grows to a height of 30 to 80 cm, and occurs commonly along rivers, on grassy slopes in forests, and among shrubs. This plant features a red-colored stem and oblong-ovate leaves with one pinnate and three to eight pairs of pinnae. The common name of *P. thellungiana* in Chinese, Yang Hong Shan, originated from the red color of its stem and the distinct pungent aroma resembling the smell of mutton when the root bark is torn (Hong, 2010). The umbels are 4 to 6 cm wide; the petals are white, ovate or obovate, with an incurved lobule at the apex; and the fruits are oblong-ovoid and measure approximately 3 mm × 2 mm (Fig. 1). The root or the whole plant of *P. thellungiana* is used as medicine.

3. Medicinal properties

The herb of *P. thellungiana* is harvested at two times of the year: most commonly during late spring and early summer for roots and/or shoots; and late autumn for roots, stems, leaves, flowers, and/or seeds (Yuan, 1979). This herb is either ground into powder and administered orally or distilled and extracted with water to form a 1:1 solution and is injected intramuscularly or intravenously (Yuan, 1979). Occasionally, it is prepared as a compound preparation, or the total flavonoids are extracted from the whole plant and injected intramuscularly or intravenously as a 3% flavonoid solution.

P. thellungiana has been used as a Chinese medicine for many decades, mainly for heart, kidney, lung, and spleen disorders (Liu et al., 2014). In animal husbandry, livestock wasting, growth retardation, and sexual dysfunction caused by malnutrition and overexertion are of high incidence. In Northern China, *P. thellungiana* is used commonly by farmers and veterinarians for fattening and treatment of growth retardation in cattle, sheep, and pigs (Yuan, 1979). Ten horses with weak spleen functions and diarrhea were cured with root powder of *P. thellungiana* at 0.75 g/kg BW (Yuan, 1979). In pigs (6–13 months old, 9.5–27.3 kg) suffering from prolonged growth retardation caused by malnutrition, a supplement of 30 to 50 g/d whole plant powder of *P. thellungiana* every two days for 10 days in two courses increased weight gain by up to 62% and weight-to-feed ratio by 40%, and, concomitantly, decreased white blood cell count and death rate (Animal Husbandry and Veterinary Science and Technology Cooperation Group in Shaanxi Weinan Area, 1976). *P. thellungiana* can alleviate injury due to overexertion and weight loss in livestock, and improve appetite and digestibility. For example, 34 of 35 pigs (97.1%) were cured of dyspepsia when treated daily with a *P. thellungiana* injection of 0.35 to 0.40 mL/kg body weight (BW) for 5 days (extracted and distilled with water to form a 1:1 injection liquid) (Yuan, 1979). In 41 sows with poor appetite after farrowing, 37 (90.2%) were cured or improved with the same dosage of *P. thellungiana* (Yuan, 1979). In 35 piglets with white dysentery symptoms caused by *Escherichia coli*, 33 (94.3%) were cured by an intramuscular injection of 3 to 5 mL solution (extracted from *P. thellungiana* and distilled with water to form a 1:1 injection liquid) twice daily for three days (Livestock Veterinary Work Station of Baishui County in Shaanxi Province, 1977). In addition, in a larger study of 642 piglets with white dysentery symptoms, 633 (98.5%) were cured with the above 1:1 liquid injection of *P. thellungiana* at 0.35 to 0.40 mL/kg BW (Yuan, 1979).

P. thellungiana also promotes gonadotropin secretion and improves reproductive performance in livestock. A dosage of 0.75 g/kg BW of *P. thellungiana* whole plant administered every two days for

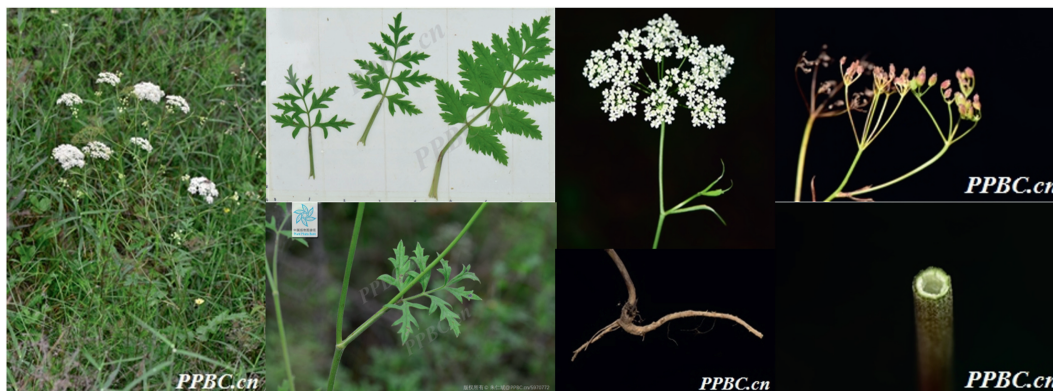


Fig. 1. Morphological characteristics of *P. thellungiana* (photo credit: Plant Photo Bank of China, <http://ppbc.iplant.cn/>).

10 days cured ovarian diseases in 146 mares and jennies (cure rate 87.0%), and the same dosage daily for 5 days induced reproductive behavior in 61 mares, jennies, and cows (cure rate 91.8%) (Yuan et al., 1979). A cure rate of 76.9% was reported in mares and jennies with ovarian diseases treated with 0.75 g/kg BW plant powder of *P. thellungiana* every other day for 10 days (Animal Husbandry and Veterinary Science and Technology Cooperation Group in Shaanxi Weinan Area, 1977). An intravenous injection of 0.35 to 0.40 mL/kg BW (extracted from *P. thellungiana* and distilled with water to form a 1:1 injection liquid) once daily for 5 days was effective in treating ovarian quiescence and atrophy in 15 cows (Yuan et al., 1981).

P. thellungiana is used widely in China in the treatment of injuries due to overexertion, weight loss, and growth retardation in livestock, and it strengthens the spleen and stomach and improves appetite and digestion. These effects are closely related to the chemical composition, especially of flavonoids. The effective dosage administered ranges between 0.3 and 0.5 g/kg BW of air-dried whole plant of *P. thellungiana*.

4. Progress in pharmacological research

P. thellungiana is distributed widely in China and has been used extensively in clinical trials. According to pharmacological studies by the Shaanxi Academy of Traditional Chinese Medicine, the alcoholic extract of *P. thellungiana* dilates coronary arteries, lowers coronary resistance, and reduces myocardial oxygen consumption (Miao et al., 1982). This hypotensive effect was attributed to histamine release and vasodilatation, irrelevant to sympathetic ganglion, M-cholinergic system, adrenergic system, and intravascular receptors (Chen et al., 1982). The flavonoid glycosides isolated from *P. thellungiana* enhances the activities of succinic acid dehydrogenase in the myocardium and brain tissues, reduces myocardial oxygen consumption, and improves hypoxia tolerance (Xu et al., 1994). *P. thellungiana* also reduces the elevation of blood triglycerides and the incidence of liver steatosis (Shen et al., 1982).

P. thellungiana increases physical strength, hypoxia tolerance, and endurance during exercise in animals (Shen et al., 1982). Moreover, it alleviates dexamethasone-induced DNA synthesis inhibition in muscle tissue, and, therefore, promotes muscle protein renewal, growth and development (Wei et al., 1986). In addition, *P. thellungiana* protects against *p*-aminophenol-induced liver injury in mice (Wang and Wen, 2022), which is attributed to its potent antioxidant, anti-inflammatory, and hepatoprotective properties.

Studies have concluded that the whole plant of *P. thellungiana* lowers blood pressure and blood lipids, dilates coronary arteries, provides antioxidant protection, and improves immune function, which benefits mainly striated muscles (cardiac and skeletal muscles), liver, spleen, female reproductive organs, and blood vessels. No side effect has been detected with the administration of *P. thellungiana*, but future studies on long-term safety, residues, and toxicity risks are required.

5. Nutrients, bioactive compounds, and function

5.1. Nutritional composition

Nutrient contents of *P. thellungiana* and their effects on digestion and metabolism have not been reported. We measured that the whole plant of *P. thellungiana* contained 12.4% crude protein (CP), 65.0% neutral detergent fiber (NDF) and 42.1% acid detergent fiber (ADF) on a dry matter (DM) basis (Table 1). Therefore, it could be classified as roughage. In addition, the *in vivo* digestibility measured in donkeys using the nylon bag technique was 52.2% (unpublished data).

Table 1

Composition of the whole plant of *P. thellungiana* (DM basis).

Item	DM	CP	NDF	ADF	EE	CA
Content, %	90.7	12.4	65.0	42.1	3.49	14.6
SD	0.02	0.06	0.73	0.86	0.26	0.09

DM = dry matter; CP = crude protein; NDF = neutral detergent fiber; ADF = acid detergent fiber; EE = ether extract; CA = crude ash; SD = standard deviation.

5.2. Composition of bioactive compounds

Pimpinella plants contain mainly bioactive constituents of terpenoids, flavonoids, coumarins, sterols, and fatty acids. At present, 106 bioactive compounds have been identified in *P. thellungiana* (Table S1), including 20 volatile components (six sesquiterpenes and 14 low-molecular-weight volatile organic compounds [VOCs]), 34 simple phenylpropanoids (including 27 phenylpropanoic acids and their esters), 13 simple phenols and organic acids, 24 flavonoids, 10 coumarins, and five lipids and phytosterols. Among these, nine chemicals listed in Table 2 have been selected as the characteristic compounds of *P. thellungiana* (Cui et al., 2022).

The concentrations of major bioactive components in *P. thellungiana* are summarized in Table 3. Luteolin-7-O- β -D-glucuronide (L7GD), apigenin-7-O- β -D-glucuronide (A7GD) and chlorogenic acid (CGA) are most abundant in the whole plant, followed by isochlorogenic acid A, schaftoside, isochlorogenic acid C, quercetin-3-O- β -D-glucuronide (Q3GD) (Cui et al., 2020; Liu et al., 2017b, 2020d). The concentrations of these compounds vary greatly among plant parts. For example, the concentrations of L7GD, A7GD, and CGA were highest in the leaves, followed by the stems, and lowest in the roots (Cui et al., 2019). Generally, the concentrations of L7GD and A7GD range between 3.73 and 5.64 mg/g (air-dry basis) (Cui et al., 2019; Liu et al., 2017b, 2020d), but their concentrations also differ greatly among studies (Cui et al., 2020; Liu et al., 2020d). The different methods of measurements could explain, at least in part, these differences (such as, test wavelength 325 nm vs. 345 nm). Thus, a standard harvesting and analytical procedure is strongly recommended.

In addition, 28 compounds were isolated from volatile oil, accounting for 0.36% of the total root weight, and these compounds were dominated by 2,6-dimethyl-6-allylphenol (>37%) and 2-methyl butyric acid (>10%) (Wang et al., 1988). A unique group of compounds was identified in the volatile oil extracted from the roots of *P. thellungiana*, including the llungianin A to H (Li et al., 1998; Qiao et al., 1997, 1998a,b, 1999, 2000), 1-butyl-3,4,5-trihydroxy-cyclohexanol (Xue et al., 1998), and 3-methoxy-5-(1'-ethoxy-2'-hydroxypropyl)-phenic acid (Wang et al., 1983). These compounds have not been reported in other plant species. Thellungianin A, B, E, F, and G are derivatives of pseudo-isoegenol, which was identified exclusively in the *Pimpinella* genus (Reichling et al., 1995). These bioactive compounds may be responsible for the distinct effects of *P. thellungiana*.

Overall, *P. thellungiana* contains high levels of A7GD, L7GD, CGA and isochlorogenic acid A, followed by schaftoside, isochlorogenic acid C, and Q3GD, which are discussed below.

5.3. Functions of principle bioactive compounds

5.3.1. Apigenin and A7GD

The bioactive component A7GD, also known as scutellarin A or apigenin-7-glucuronide, is a natural derivative of apigenin (4',5,7-trihydroxyflavone) (Wang et al., 2019). In addition to A7GD, the apigenin glycosides identified in *P. thellungiana* include apigenin-7-O-glucoside, apigenin-7-O-glucuronide-6'-methyl ester, and

Table 2List of 9 main compounds in *P. thellungiana*.

No.	Common name	Chemical name	CAS no.	Formula
1	Protocatechuic acid	3,4-Dihydroxybenzoic acid	99-50-3	C ₇ H ₆ O ₄
2	Neochlorogenic acid	5-Caffeoylquinic acid	906-33-2	C ₁₆ H ₁₈ O ₉
3	Chlorogenic acid	3-Caffeoylquinic acid	327-97-9	C ₁₆ H ₁₈ O ₉
4	Cryptochlorogenic acid	4-O-Caffeoylquinic acid	905-99-7	C ₁₆ H ₁₈ O ₉
5	Luteoloside	Luteolin-7-O-glucoside	1268798	C ₂₁ H ₂₀ O ₁₁
6	3,5-Dicaffeoylquinic acid	3,5-O-Dicaffeoylquinic acid	89919-62-0	C ₂₅ H ₂₄ O ₁₂
7	Isochlorogenic acid C	4,5-Di-O-Caffeoylquinic acid	57378-72-0	C ₂₅ H ₂₄ O ₁₂
8	Cosmosiin	Apigenin-7-O-β-D-glucopyranoside, apigenin-7-O-β-D-glucoside, apigenin-7-O-glucoside	578-74-5	C ₂₁ H ₂₀ O ₁₀
9	Isochlorogenic acid A	3,5-Di-O-Caffeoylquinic acid	2450-53-5	C ₂₅ H ₂₄ O ₁₂

Table 3The concentrations of the main compounds in *P. thellungiana*.

Item	Concentration, mg/g (air-dry basis)						
Luteolin-7-O-β-D-glucuronide	3.73–4.69	3.88–4.62	0.13–0.78	3.80–4.82	0.04–0.13	0.23–1.79	
Apigenin-7-O-β-D-glucuronide	4.42–5.64	3.81–4.01	0.07–0.78	3.62–4.92	0.02–0.11	0.59–1.45	
Chlorogenic acid	3.28–6.02	–	0.06–0.40	2.14–2.78	0.42–0.72	0.75–1.22	
Isochlorogenic acid A	3.67–5.38	–	0.07–0.45	2.06–3.64	0.12–0.28	0.79–1.33	
Isochlorogenic acid C	1.35–1.72	–	0.04–0.19	1.58–2.25	0.10–0.20	0.13–0.67	
Quercetin-3-O-β-D-glucuronide	1.02–1.29	–	–	–	–	–	
Neochlorogenic acid	0.51–0.88	–	0.01–0.04	0.28–0.37	0.02–0.06	0.07–0.15	
Cryptochlorogenic acid	0.44–1.02	–	0.01–0.05	0.35–0.52	0.04–0.06	0.11–0.20	
Isochlorogenic acid B	0.21–0.37	–	0.05–0.14	–	–	–	
Schaftoside	–	–	0.19–0.85	–	–	–	
Protocatechuic acid	–	–	0.01–0.32	0.13–1.10	0.06–0.13	0.15–1.29	
Gallic acid	–	–	–	0.06–0.31	0.04–0.07	0.03–0.14	
Sample type	Whole plant	Whole plant	Whole plant	Leaf	Root	Stem	
Reference	Liu et al. (2020d)	Liu et al. (2017b)	Cui et al. (2020)	Cui et al. (2019)	Cui et al. (2019)	Cui et al. (2019)	

“–” indicates that it was measured.

apigenin-7-O-butylglucuronide. Their chemical structures are presented in Fig. 2.

Flavonoid aglycones such as apigenin, luteolin, are typically insoluble or poorly soluble in water, but their water solubility increases upon glycosylation. Flavonoid glycosides undergo hydrolysis by brush border hydrolases in the small intestine (e.g., epithelial β-glucosidase) or by ruminal and colonic microorganisms in livestock (Hostetler et al., 2017). Alternatively, they can be transported into enterocytes via sodium-dependent glucose transporters, where the glycosyl moiety is hydrolyzed by β-glucosidase. Following the cleavage of the glycosyl moiety, flavonoid aglycones undergo various coupling reactions, such as glucuronidation, sulfonation, or methylation, in intestinal cells and the liver. As a result, most flavonoids in plasma and urine exist in conjugated forms rather than as aglycones (Hostetler et al., 2017).

Apigenin and its glycosides possess antioxidant (Kashyap et al., 2022), anti-inflammatory (Ha et al., 2022), anti-apoptotic, and anti-autophagy effects (Liu et al., 2020b). Apigenin-7-O-β-D-glucuronide exhibits anti-tumor, blood pressure-lowering, and matrix metalloproteinase-inhibiting activities (Liu et al., 2020b), and was reported to inhibit the uptake of oxidized low-density lipoprotein by macrophages and the intracellular accumulation of triglycerides (Ma et al., 2017). Of note, in skeletal muscle cells, apigenin promotes glucose uptake and protein synthesis through the mechanistic target of rapamycin (mTOR) complex 1 pathway (Xu et al., 2022), and stimulates skeletal muscle hypertrophy and myogenic differentiation via the protein arginine methyltransferase 7 (Prmt7)/peroxisome proliferator-activated receptor-gamma coactivator -1 alpha (PGC-1α)/G-protein-coupled receptor 56 (GPR56) and Prmt7/p38 mitogen-activated protein kinases (p38)/myogenic differentiation 1 (MyoD) pathways (Jang et al., 2017). Additionally, it mitigates age-related skeletal muscle atrophy by reducing oxidative stress and inhibiting hyperactive autophagy and apoptosis (Wang et al., 2020).

Among bioactive compounds of *P. thellungiana*, the concentrations of apigenin glycosides are relatively high, especially of A7GD which ranges between 3.62 and 5.6 mg/g. This serves as the biochemical basis of *P. thellungiana* in alleviating atherosclerosis and promoting muscle growth in individuals with growth restriction. However, reports on the effects of apigenin or its glycosides on nutrient digestion, production, or quality of animal products in pigs, cattle and/or equine are lacking.

5.3.2. Luteolin and L7GD

Luteolin and its glycosides identified in *P. thellungiana* include luteolin, luteolin-7-O-glucoside, L7GD, L7GD-6''-methyl ester, and luteolin-7-O-rutinoside (Fig. 2). The digestion, metabolism and absorption of luteolin glycosides are similar to those of apigenin glycosides. Luteolin and its glycosides exhibit mainly antioxidant, anti-inflammatory, antitussive and expectorant properties, and protect from acute liver injury (Muruganathan et al., 2022), and reduce hypertension (Gao et al., 2023). The mechanisms of luteolin are related closely to proto-oncogene C-Src (Src)/nuclear factor-κB (NF-κB) pathway, mitogen-activated protein kinase (MAPK)/activator protein-1 (AP-1) pathway, suppressor of cytokine signaling 3 (SOCS3)/ signal transducer and transcription activator (STAT) 3 pathway (Aziz et al., 2018), and the signaling pathways mediated by Janus kinase (JAK)/STAT, Notch, mTOR, and tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) (Farooqi et al., 2020). In livestock, luteolin inhibits replication of the African swine fever virus by regulating the NF-κB/STAT3/activating transcription factor 6 (ATF6) (Chen et al., 2022b). Few reports on the effects of luteolin and its glycosides on nutrient digestion and performance in livestock have been published. Recently, it was reported that luteolin displays inhibitory and bactericidal activities against multidrug-resistant *Staphylococcus aureus* isolated from dairy goats (Liu et al., 2023).

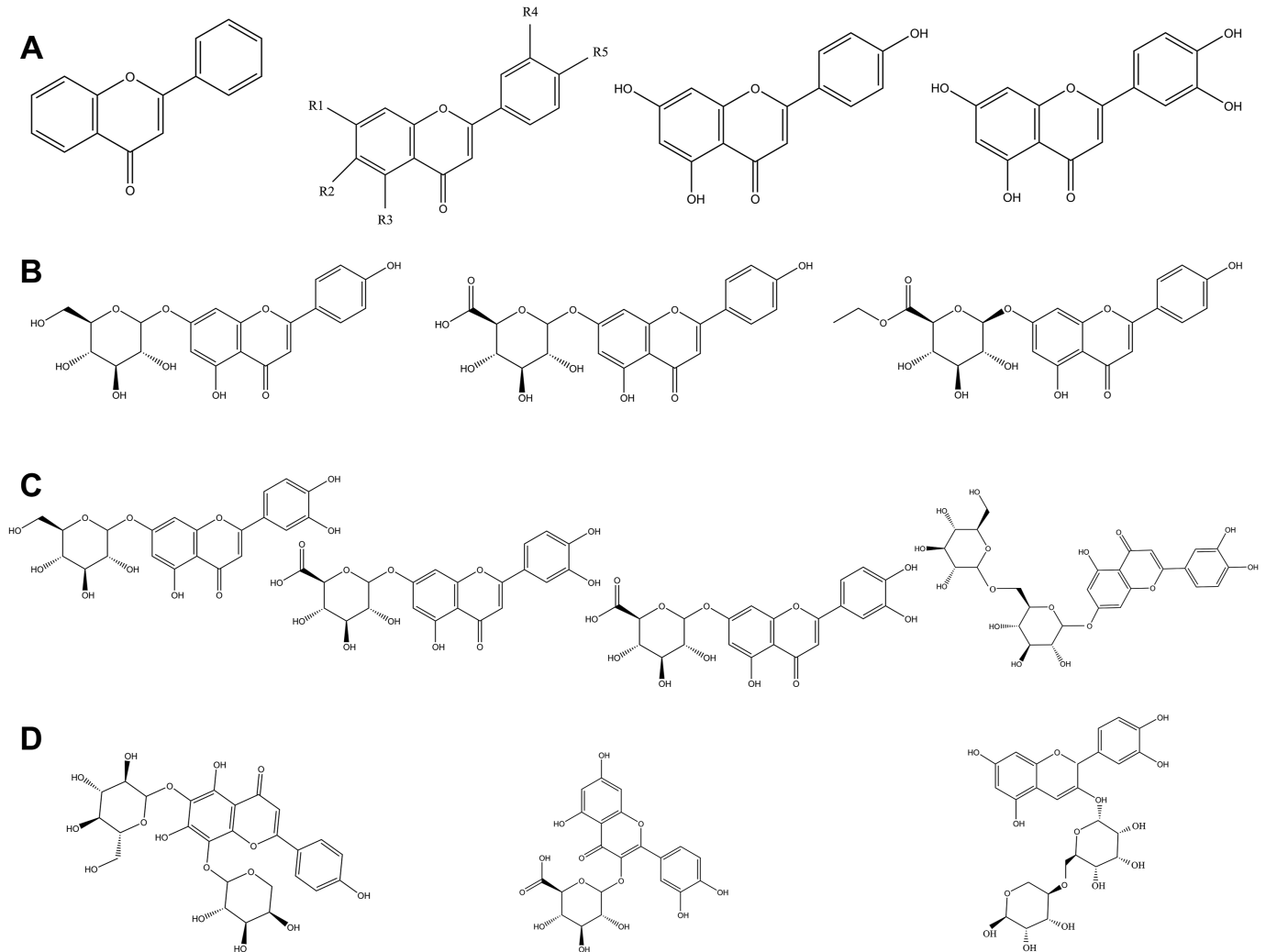


Fig. 2. Chemical structures of flavonoids and their glycosides in *P. thellungiana*. (A) From left to right: flavonoid, flavone, apigenin, and luteolin. (B) From left to right: apigenin-7-O-glucoside, apigenin-7-O-glucuronide, and apigenin-7-O-glucuronide-6''-methyl ester. (C) From left to right: luteolin-7-O-glucoside, luteolin-7-O-glucuronide, luteolin-7-O-glucuronide-6''-methyl ester, and luteolin-7-O-rutinoside. (D) From left to right: quercetin 3-O-glucuronide, and quercetin 3-O-rutinoside.

L7GD, known as luteolin-7-O-glucuronide or luteolin 7-O- β -D-glucosiduronic acid, is the most abundant luteolin glycoside in *P. thellungiana*, with concentrations ranging from 3.7 to 4.8 mg/g (Table 3). Its antioxidative activity is greater than that of luteolin (Min et al., 2006). Its antioxidant and anti-inflammatory activities are exerted by inhibiting the production of NO and pro-inflammatory cytokines (Ma et al., 2018), while its role in inhibiting matrix metalloproteinase activity (Ende and Gebhardt, 2004) is associated with the O atom at position 4 of the carbonyl group in the luteolin molecule (Zhang et al., 2012). Furthermore, L7GD displays therapeutic potential for alleviating stress due to sleep deprivation by activating the brain derived neurotrophic factor (BDNF) signaling pathway (Ryu et al., 2022). The high concentrations of luteolin and its glycosides in *P. thellungiana* are suggested to be the main reason for the beneficial properties of *P. thellungiana*.

5.3.3. Schaftoside

Schaftoside, known as apigenin-6-glucoside-8-arabinoside, is a trihydroxyflavone derived from apigenin (Fig. 2). It exhibits anti-nematodal, antioxidant, and anti-inflammatory activities (Yi et al., 2022), and enhances autophagy, and reduces apoptosis and inflammation. In addition, Schaftoside mitigates cerebral

ischemia–reperfusion injury through the AMP-activated protein kinase/mTOR signaling pathway (Zhang et al., 2022), and acetaminophen-induced hepatotoxicity by activating farnesol X receptors (Liu et al., 2020a). Schaftoside also prevents cholesterol gallstone formation, at least in mice, by activating ileal liver X receptor α and hepatic farnesoid X receptor (Liu et al., 2017a), and treats calcium oxalate stones in kidneys (Liu et al., 2020c). However, the effects of schaftoside on nutrient digestion, performance, and product quality of livestock are unknown.

5.3.4. Quercetin glycosides

Two quercetin glycosides have been identified in *P. thellungiana*: Q3GD and quercetin 3-O-rutinoside (also called rutin or vitamin P). The digestion and absorption of Q3GD are similar to apigenin or luteolin glycosides, and it is eventually excreted in urine (Li et al., 2016). Quercetin-3-O- β -D-glucuronide is more readily absorbed than rutin (Li et al., 2016). The bioactivities of quercetin have been reviewed comprehensively (Li et al., 2016; Yang et al., 2020). Quercetin-3-O- β -D-glucuronide is the main active form in plasma and tissues following the oral administration of quercetin (Yang et al., 2016), while rutin is derived from quercetin through the replacement of the hydroxyl group at the C-3 position with glucose

and rhamnose. Thus, their bioactive functions are similar to that of quercetin, which are exerted mainly through the Wnt– β -catenin pathway, the tumor suppressor p53 (p53)-independent pathway, and the phosphoinositide 3-kinase (PI3K)/Akt, JAK/STAT, MAPK, p53, and NF- κ B signaling pathways (Imani et al., 2021).

Quercetin or rutin was studied extensively in livestock, and approved as a safe and natural antioxidant in feed (Yang et al., 2020). In ruminants, quercetin is degraded rapidly into 3,4-dihydroxyphenylacetic acid and 4-methylcatechol in the rumen (Berger et al., 2015; Guo et al., 2021), but the absolute bioavailabilities of quercetin aglycone and rutin after intraruminal or oral application were only 0.1% and 0.5%, respectively (Berger et al., 2012; Wein et al., 2018). Supplementation with quercetin or rutin does not affect the ruminal microbes or fermentation (Berger et al., 2015). In cattle and goats, quercetin alleviates oxidative stress and inflammation of rumen epithelial cells induced by lipopolysaccharide or high-grain feed (Jiang et al., 2023; Zhan et al., 2024). Quercetin treats bacterial bovine mastitis (Disbanchong et al., 2021), prevents bovine viral diarrhea (Chen et al., 2022a), reduces liver damage in periparturient dairy cows (Stoldt et al., 2015), and exhibits anti-apoptotic effects in sheep (Ding et al., 2022).

Rutin regulates energy metabolism (Stoldt et al., 2016), increases milk yield, and enhances rumen fermentation and nitrogen metabolism in dairy cows (Cui et al., 2015), and improves meat quality in sheep (Zhan et al., 2023). In addition, rutin and isoquercetin from mulberry leaves improve growth performance, inhibit fat synthesis, and improve fatty acid distribution and nutritional quality in finishing pigs (Liu et al., 2024). Quercetin improves reproduction by enhancing the quality of bovine oocytes (Davoodian et al., 2022), alleviates H₂O₂-induced impairment in goat luteinized granulosa cells (Li et al., 2020) and promotes maturation of goat oocytes in vitro (Silva et al., 2018). It also protects goat sperm and pre-implanted embryos from Cd²⁺-induced oxidative stress (Bhardwaj and Panchal, 2021; Mao et al., 2018), and maintains the integrity of frozen goat semen (Borges et al., 2020). Generally, supplementation with quercetin or rutin improves production performance of livestock and relieves oxidative stress and inflammatory responses in the rumen, mammary glands, and reproductive organs.

5.3.5. Chlorogenic acid

A total of 34 simple phenylpropanoids have been identified in *P. thellungiana*, with caffeoylquinic acid and isochlorogenic acid A the most abundant. Chlorogenic acid (CGA) improves antioxidant capacity, growth performance, muscle protein biosynthesis, meat quality traits, reproductive performance, intestinal health, and disease resistance in pigs through the mTOR/ribosomal protein S6 kinase 1 (S6K1)/eukaryotic initiation factor 4E - binding protein 1 (4EBP1), toll like receptor 4 (TLR4)/NF- κ B, and nuclear factor erythroid 2-related factor 2 (NRF2)/heme oxygenase-1 (HO-1) (Dai et al., 2023). It is being considered as a replacement for antibiotics in feed for pigs. In ruminants, CGA could potentially replace antibiotics for the treatment of mastitis in dairy cows through the NF- κ B signaling pathway and by directly targeting bacterial cell walls and membranes (Feng et al., 2023; Xu et al., 2023). Chlorogenic acid alleviates *S. aureus*-induced milk protein synthesis inhibition in bovine mammary epithelial cells (Ji et al., 2022), and inflammation induced by *E. coli* in sheep by inhibiting the TLR4/NF- κ B signaling pathway of endometrial epithelium cells (Hu et al., 2020).

Isochlorogenic acid A (3,5-di-O-caffeoylquinic acid) exhibits fungistatic effects against *Alternaria alternata* (Harrison et al., 2008; Kodoma et al., 1998) and specifically inhibits the proliferation of

respiratory syncytial viruses (Li et al., 2005). In addition to the antioxidant and metabolism-regulating activities, CGA and its derivatives possess potent anti-bacterial, anti-fungal, and anti-viral activities, which contribute to the treatment of pathogenic diarrhea.

5.3.6. Other compounds

Ten coumarin compounds have been identified in *P. thellungiana*, including scopoletin, scoparone, esculin, marmesin, bergapten, and isofraxidin (Table S1). Coumarin and its derivatives have anti-cancer (Al-Warhi et al., 2020), antioxidant, anti-bacterial, anti-inflammatory, anti-coagulant, neuroprotective, anti-diabetic, and anti-convulsant properties (Hassanein et al., 2020), but they also inhibit appetite (Ahmed et al., 2023) and the synthesis of vitamin K, and exert hepatotoxic effects (Pitaro et al., 2022). No report on the effect of coumarins in *P. thellungiana* on digestion, metabolism, or utilization of nutrients in livestock is available. Although the concentrations of coumarins in *P. thellungiana* are relatively low, they should be tested as a risk factor for their use as a feed additive or medicine.

The VOCs identified in the volatile oil of *P. thellungiana* can be classified into low-molecular-weight compounds and terpenes. Fifteen low-molecular-weight VOCs in *P. thellungiana* roots include alkanes, acids, aldehydes, esters, and ketones (C₅–C₁₁), while 19 terpenes in the whole plant and roots belong to the sesquiterpenes, with β -bisabolene (17.3% to 19.4%), caryophyllene oxide (12.9% to 15.7%) and β -pinene (5.31% to 6.62%) the main ingredients (Cheng et al., 2024). Terpenes differ in composition among *Pimpinella* species and possess anti-tumor, anti-inflammatory, antioxidant, anti-bacterial, and insecticidal properties (Wu et al., 2023). The VOCs profile in animal products is considered a chemical fingerprint that characterizes the food source and in livestock diets affects the flavor of milk and meat (Basdagianni et al., 2019; Borge et al., 2016; O'Callaghan et al., 2017). Few reports on the VOCs in *P. thellungiana* are available, and the concentrations of VOCs have not been determined. Although low in content, VOCs can be used to distinguish the origin of *P. thellungiana*.

Twelve simple phenols were identified in *P. thellungiana*, including gentianic, salicylic, shikimic, and gallic acids. Simple phenols are known for their anti-bacterial, anti-cancer, anti-inflammatory, and antimutagenic properties (Kumar and Goel, 2019). Dietary supplementation with phenol extract did not affect the fatty acid composition of muscles in pigs, but reduced the thiobarbituric acid reactive substance (TBARS) values in pork chops (González and Tejada, 2007). Supplementary gallic acid decreased the incidence of diarrhea and maintained intestinal integrity in weaning piglets (Cai et al., 2022). Gallic acid is also inhibited the proliferation and adipogenesis of bovine subcutaneous adipocytes in vitro (Jin et al., 2022).

P. thellungiana contains fatty acids (mainly oleic acid and palmitic acid) and phytosterols (β -sitosterol and γ -sitosterol). β -sitosterol has antioxidant, anti-cancer, anti-diabetic, anti-bacterial, and immunomodulatory activities (Babu and Jayaraman, 2020), and γ -sitosterol shows potential as a hypolipidemic agent (Balamurugan et al., 2015). Furthermore, pseudo-iso Eugenol compounds identified in *P. thellungiana* (thellungianin A, B, E, F, and G) belong to eugenol and isoeugenol, which have antioxidant, anti-bacterial, anesthetic, anti-inflammatory, analgesic, neuroprotective, anti-diabetic, and anti-cancer properties (Taleuzzaman et al., 2021). However, high concentrations of isoeugenol can have carcinogenic effects on the liver and cause damage to the stomach, nose, and kidneys (National Toxicology Program, 2010). The

concentration and safety of pseudo-isoeugenol compounds in *P. thellungiana* have not been established and warrant further investigation.

6. Conclusions

P. thellungiana is a medicinal herb that has been used as an ethnobotanical feed additive for decades to treat growth retardation, overexertion, reproductive disorders and diarrhea in livestock in northeastern Asia. It also reduces blood pressure and liver tissue damage, enhances immunity, and possesses anti-hyperlipidemic, antioxidant, and antibacterial properties. These properties are attributed mainly to the bioactive compounds of L7GD, A7GD, CGA, isochlorogenic acid A, schaftoside, and Q3GD. However, the optimum dosages and methods of delivery of *P. thellungiana* still need to be established. In addition, identification of all bioactive substances in *P. thellungiana*, their pharmacological effects and their risk factors require further research.

CRedit authorship contribution statement

Shuxian Zhang: Writing – original draft. **Minglu Yang:** Writing – review & editing, Visualization. **Tao Xu:** Formal analysis, Data curation. **Qiongxin Yan:** Writing – review & editing. **Allan Degen:** Writing – review & editing, Data curation. **Xiaoling Zhou:** Funding acquisition, Conceptualization.

Declaration of competing interest

We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work, and there is no professional or other personal interest of any nature or kind in any product, service and/or company that could be construed as influencing the content of this paper.

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Appendix. Supplementary data

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