A comprehensive review on bioactive compounds from *Lycium* seeds: extraction, characterization, bioactivities, and applications

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Abstract

Lycium, known for its medicinal, nutritional, and food applications, is widely utilized in various food, pharmaceutical, and health-related industries. However, *Lycium* seeds as a byproduct of *Lycium* processing are still not fully utilized, resulting in a waste of green resources. About 20-25% of *Lycium* seeds are wasted due to inefficient disposal practices. In this work, the bioactive compounds from *Lycium* seeds, including oils, phenolic compounds, polysaccharides, proteins, and other components, along with the methods used for their extraction are summarized. Differences in extraction techniques, yields, and bioactivities are analyzed to provide insights into optimizing these processes. The review also highlights the diverse bioactivities of *Lycium* seed extracts, such as anti-fatigue, neuroprotective, anti-diabetic, anti-aging, and anti-atherosclerotic effects, delving into their functional mechanisms. Furthermore, it explores the potential applications of *Lycium* seed-derived bioactive compounds in pharmaceuticals, functional foods, and animal husbandry, emphasizing their value in enhancing food processing practices. This comprehensive review aims to bridge the knowledge gap, offering theoretical support for the broader application of *Lycium* seeds in industries such as food, healthcare, and agriculture.

Introduction

Lycium, commonly known as 'goji', 'wolfberry', and 'gouqi', one of the traditional Chinese herbs, belongs to the Solanaceae family[1]. It is known for its unique nutritional profile, rich in polysaccharides, polyphenols, carotenoids, and other bioactive compounds. It has been demonstrated to have effects on aging, fatigue, diabetes, Alzheimer's disease, and immune system function[1–3]. Consequently, there has been a notable increase in interest in *Lycium*, with a particular focus on its health benefits. Traditionally, *Lycium* has been consumed in its fresh form, often soaked in water or used medicinally[1]. Nowadays, it is also utilized in various products, including juices, jams, bakery products, energy bars, and dietary supplements, catering to diverse health and nutritional needs[4,5]. Several species of *Lycium*, such as *Lycium barbarum* (*L. barbarum*), *Lycium ruthenicum* Murr. (*L. ruthenicum* Murr.), *Lycium dasystemum* (*L. dasystemum*), and *Lycium intricatum* Boiss. (*L. intricatum* Boiss.), are cultivated in various regions, including Central Asia, Southern Africa, and parts of the Americas and Australia[6]. At present, the global *Lycium* cultivation areas are estimated to be approximately 1.76×10^5 ha, and China is the world's largest producer of *Lycium*, with about 1.33×10^5 ha of planting areas. The production of fresh *Lycium* berries reached 1.4 million tons, with a processing conversion rate of 20%, yielding approximately 7,000 tons of *Lycium* seed waste.

Lycium seeds, which constitute 15%–20% of the total fresh fruit yield, are a significant byproduct of fruit processing[7–10]. However, the current utilization of *Lycium* seeds is limited. The annual production of *Lycium* seed oil in China is approximately 7 tons, with a sales volume of 3.85 tons. This highlights their significant untapped

potential, underscoring the importance of further research and development to fully explore their value. *Lycium* seeds contain a valuable source of carbohydrates (46.5%), oil (18%–22%), polyphenols (2%–6%), polysaccharides (7.78%), proteins (12%–15%), and minerals[8,9,11,12]. Despite their nutritional richness, the large number of seeds in the process of *Lycium* is a difficult problem for the food industry to solve. While there is basic public knowledge about the nutritional components of *Lycium*, due to the limited research focused on *Lycium* seeds, they are primarily used as animal feed, fertilizer, or discarded, leading to significant waste[13]. As a typical underutilized raw material, *Lycium* seeds have significant potential for further use. Therefore, this review summarizes and analyzes *Lycium* seeds from three aspects: bioactive compounds and extraction methods, bioactivity, and applications.

Existing literature has thoroughly explored the bioactive components, extraction methods, and molecular characteristics of *Lycium* seeds, which are rich in bioactive compounds such as oils, phenolic compounds, polysaccharides, and proteins. Studies have compared the effects of different varieties and extraction methods on yield and bioactivity. Additionally, this paper reviews the various bioactivities of *Lycium* seeds, including anti-fatigue, neuroprotective, anti-diabetic, anti-atherosclerotic, and anti-obesity effects, and provides an in-depth analysis of the mechanisms behind these functions. Furthermore, this work also examines the potential applications of *Lycium* seeds in pharmaceuticals, functional foods, and animal feed. This is with a view to promoting the efficient utilization of discarded by-products, contributing to sustainable development, and enhancing their industrial value in the fields of medicine, the food industry, and agriculture.

Nutrient compounds from *Lycium* seeds: extraction, composition, and characterization

Lycium seeds are a rich source of various nutrients. However, existing research has predominantly focused on *Lycium* seed oil. Optimizing extraction methods for *Lycium* seeds is crucial to maximizing yield and selectively extracting bioactive compounds. The selection of extraction methods can target specific nutrients, as shown in Tables 1−3.

Lycium seed oil

Lycium seed oil is highly valued as an edible oil due to its substantial content of unsaturated fatty acids (UFAs), including oleic acid, linoleic acid, and linolenic acid, as well as saturated fatty acids (SFAs), such as palmitic acid[13,14]. It also contains other beneficial compounds including tocopherols, phytosterols, and carotenoids[9,15].

The selection of an extraction method needs a balance between yield, product quality, process efficiency, cost, and environmental sustainability[16]. Several methods are available for extracting *Lycium* seed oil, as shown in Fig. 1, and the different operating conditions of each method affect the composition and yield of the *Lycium* seed oil. Pressing extraction is a conventional method that is characterized by its operational simplicity, safety, and environmentally benign nature. However, it is limited by relatively low extraction yields[13]. For commercial *Lycium* seed oil production using inedible oil, cold pressing is a commonly used method. Pressing extraction method yielded 10%−13% oil, while under hot pressing conditions,
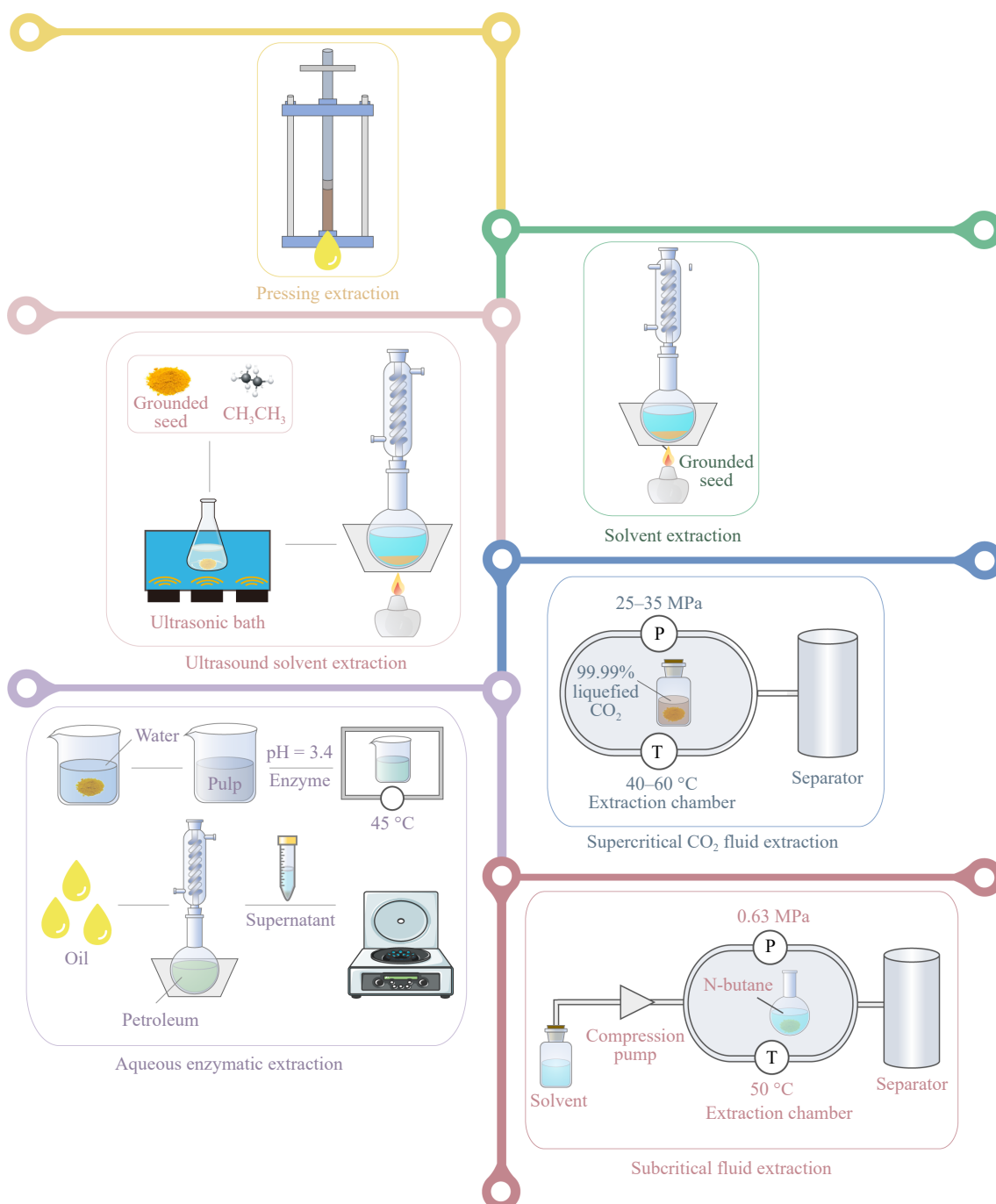

Fig. 1   Extraction method of *Lycium* seed oil.

the content of SFAs in *Lycium* seed oil was 5.2% higher than under cold pressing conditions[15]. However, the content of UFAs was 0.55% lower, likely due to the destruction of some unsaturated bonds by high temperatures[15]. Solvent extraction is widely used in industrial oil extraction, but it presents issues with organic solvent residues and pollution of the environment[13]. The yield of *Lycium* seed oil in this extraction method was 12%–20%[6,15,17]. Yield is also affected by the extraction solvent. The concentration of free fatty acids obtained from n-hexane extraction was approximately 4.28% higher than that from petroleum ether[18].

Ultrasound-assisted solvent extraction was demonstrated to improve the efficiency of solvent extraction, and the yield of specific varieties of *Lycium* seed oil can be increased by 15% using this method while retaining a higher content (90%) of UFAs[15]. Supercritical CO_2 fluid extraction and subcritical fluid extraction are novel extraction techniques with the advantages of non-toxicity, environmental friendliness, and high oil yield, whereas these two methods are limited in large-scale industrial production due to high investment cost[15,17]. Extraction of *Lycium* seed oil by supercritical CO_2 fluid extraction is used in the commercial production of high-grade edible oil. The yield of *Lycium* seed oil under supercritical CO_2 extraction was around 15%–19%, and the yield under subcritical fluid extraction was 21%[9,13,15,17,19]. Aqueous enzymatic extraction has the advantages of low energy consumption and less pollution, achieving high extraction efficiencies with 87.6%, however, this method has been found to result in the formation of formed emulsified oil[20]. The particular methodologies utilized by the researchers in the extraction of *Lycium* seed oil are delineated in Table 1.

It is crucial for maintaining the biological activity of the extract to select the appropriate extraction method. Compared to other extraction methods, supercritical CO_2 fluid extraction and subcritical fluid extraction are particularly effective in preserving antioxidant activity, as they operate under milder conditions that reduce the risk of oxidative degradation[9,13,15,17,19]. Under supercritical CO_2 fluid extraction conditions resulted in a peroxide value 50% lower than pressing extraction, indicating a reduced oxidative degradation under milder conditions[14]. Compared to supercritical CO_2 fluid extraction, subcritical fluid extraction operates at a lower pressure, thereby enhancing the retention of bioactive substances[17].

Lycium seed oil provides an abundance of UFAs as well as a small amount of SFAs. Table 2 provides a detailed comparison of the fatty acid profiles of *Lycium* seed oil. For instance, *L. barbarum* predominantly contains linoleic acid (65.18%–67.36%), oleic acid (15.64%–22.12%), palmitic acid (3.26%–7.12%), stearic acid (2.87%–4.89%), and *γ*-linolenic acid (1.16%–4.55%)[15,19]. *L. ruthenicum* Murr. and *L. dasystemum* exhibited similar profiles to *L. barbarum*, but *L. ruthenicum* Murr. provided the highest linoleic acid (70.19%–73.94%), 14.4% higher than *L. barbarum* and 16.4% higher than *L. dasystemum*, and *L. dasystemum* seed oil provided the least amount of stearic acid (1.1%–1.4%)[9,13–15,17,19]. *L. intricatum* Boiss. has a different profile, with lower concentrations of linoleic and oleic acids, but higher levels of palmitoleic acid (27.96%), erucic acid (13.62%), and myristic acid (5.3%)[6,9,13–15,17,19]. The variation in fatty acid composition of *Lycium* seed oil may play a significant role in its distinct bioactivities, including antioxidant, anti-inflammatory, and anticancer effects. Consequently, a detailed understanding of its fatty acid profile is essential for selecting the most suitable species for specific health benefits or industrial applications, such as in the healthcare and functional food sectors.

Table 1. Summary of extracted methods of *Lycium* seed oil.

Extraction method	Extraction conditions	Main composition of the oil	Yield (%)	Material	Ref.
Pressing extraction	Use a screw-press oil expeller to press seeds below 60 °C, then purifying through centrifugation at 4,000 rpm for 15 min.	C18:2, C18:1, C16, C18, C18:3	10.5–12.5	*L. barbarum*	[15]
	Use a centrifugal oil extractor to press the pretreated powder seeds for 2 h and then filtrating.	C18:2, C18:1, C16, C18	12.63	*L. ruthenicum* Murr.	[17]
	Use a screw-press oil expeller to press seeds at 150 °C, then purifying through centrifugation at 4,000 rpm for 15 min.	C18:2, C18:1, C16, C18:3, C18	11.0–13.0	*L. barbarum*	[15]
Solvent extraction	Extract with hexane for 30 min, then evaporating under vacuum at 45 °C.	C18:2, C18:1, C16, C18, C18:3	12.0–15.0	*L. barbarum*	[15]
	Extract with n-hexane using a Soxhlet extractor for 6 h, then evaporating under reduced pressure at 40 °C.	C18:2, C16:1, C22:1, C14, C18:1	20 ± 3	*L. intricatum* Boiss.	[6]
	Extract with n-hexane using a Soxhlet extractor at 40–60 °C for 4 h, then evaporating under vacuum at 70 °C.	C18:2, C18:1, C16, C18, C18:3	16.25	*L. ruthenicum* Murr.	[17]
Ultrasound-assisted extraction	Extract with hexane for 30 min in an ultrasonic bath with 750 W and 40 kHz and repeat twice, evaporating under vacuum at 70 °C.	C18:2, C18:1, C16, C18:3, C18	14.0–16.0	*L. barbarum*	[15]
Supercritical CO_2 fluid extraction	Extract with 99.99% CO_2 with a flow rate of 1 L/min at 35 MPa and 40 °C for 90 min.	C18:2, C18:1, C16, C18:3, C18	10.0–12.0	*L. barbarum*	[15]
	Extract with CO_2 with a flow rate of 30 g/min at 250 bar and 60 °C for 2 h, with the use of co-solvent 2% ethanol.	C18:2, C18:1, C18:3	17.0 ± 0.67 (without cosolvent), 15.2 ± 0.42 (with cosolvent)	*L. barbarum*	[13]
	Extract with CO_2 with a flow rate of 25 kg/h at 30 MPa and 45 °C for 60 min.	C18:2, C18:1, C16, C18, C20:6	19.28	*L. barbarum*	[19]
	Extract with CO_2 with at 35 MPa and 40 °C for 90 min.	C18:2, C18:1, C18:3, C16, C20	8.56	*L. ruthenicum* Murr.	[9]
	Extract with CO_2 with a flow rate of 80 L/h at 26 MPa and 55 °C for 60 min.	C18:2, C18:1, C16, C18	19.76	*L. ruthenicum* Murr.	[17]
Subcritical fluid extraction	Extract with n-butane in the form of subcritical fluid at 0.63 MPa at 50 °C for 48 min.	C18:2, C18:1, C16, C18, C18:3	21.20	*L. ruthenicum* Murr.	[17]
Aqueous enzymatic extraction	Enzymatic hydrolysis at pH 3.4 and 45 °C using Viscozyme L, centrifuge the obtained solution at 5,000 rpm for 30 min. Add petroleum ether to the supernatant to extract the oil, followed with rotary evaporation.	—	87.6	*L. barbarum*	[20]

Table 2. The relative content of fatty acids (FA) in *Lycium* seed oil under different extraction methods.

Material	Extraction method	C18:2 (%)	C18:1 (%)	C16 (%)	C18:3 (%)	C18 (%)	SFA (%)	UFA (%)	Ref.
L. barbarum	PE	65.8–65.95	20.11–20.42	6.28–6.63	2.61–2.90	3.36–3.7	9.65–10.15	89.85–90.35	[15]
	SE	65.24	19.76	7.03	2.75	3.99	11.08	88.92	
	USE	65.82	20.23	6.4	2.83	3.39	9.92	90.08	
	SCFE	60.32–67.36	15.64–22.12	3.26–7.68	1.16–4.55	2.87–4.89	8.15–13.61	84.21–91.85	[13,15,19,121]
L. ruthenicum Murr.	PE	73.53	18.81	3.89	0.75	1.10	—	> 92%	[17]
	SE	68.31–72.06	17.76–19.3	4.22–5.37	1.37–4.77	1.12–2.58	8.91	91.10	[17,85]
	SCFE	73.31–74.56	11.82–19.55	3.93–4.88	0.55–6.6	1.22–1.4	6.70	93.31	[9,17]
	SFE	73.36	18.7	4.09	0.92	1.17	5.26	92.98	[17]
L. dasystemnm	PE	63.05	21.13	1.49	2.82	3.5	> 9.52	> 86.19	[14]
	SCFE	67.19	18.17	6.24	0.83	3.12	> 5.56	> 87.00	
L. intricatum Boiss.	SE	49.47	2.99	0.63	—	—	5.93	94.04	[6]

FAs: fatty acids; SFA: saturated fatty acids; UFA: unsaturated fatty acids; PE: pressing extraction; SE: solvent extraction; USE: ultrasound-assisted solvent extraction; SCFE: supercritical CO_2 fluid extraction; SFE: supercritical fluid extraction.

Current extraction methods for *Lycium* seed oil are largely derived from techniques used for other seed oils, such as pumpkin seed oil and rapeseed oil, which employ similar extraction procedures[21,22]. The active components of *Lycium* seeds differ from those in other seeds, and the extraction method employed significantly influences the composition of the resulting extract. Additionally, variations in extraction conditions further impact the obtained components. These factors collectively contribute to the distinct differences in the extraction processes and outcomes of *Lycium* seed oil compared to oils derived from other seeds.

Lycium seed polyphenols

Polyphenols are a class of antioxidants that help protect lipids, proteins, enzymes, carbohydrates, and DNA in cells and tissues from oxidative damage[23]. The primary classes of polyphenols are flavonoids, lignans, stilbenes, and phenolic acids[24,25]. High-performance liquid chromatography (HPLC) analysis has identified several compounds in *Lycium* seeds, such as quercetin, kaempferol, and chlorogenic acid, which contribute significantly to the antioxidant activities of the extracts[26].

Ethanol is commonly used as an efficient solvent for extracting polyphenols from *Lycium* seeds. For instance, reflux extraction with 95% ethanol for 1.5 h, yielded 26.7 mg/g of polyphenols[26]. Another study reported that an initial extraction with 60% ethanol followed by ultrasonic treatment, yielded between 1.19 and 3.37 mg GAE/g of polyphenols, with *L. ruthenicum* Murr. seeds containing up to 2.63 times higher polyphenol content than *L. barbarum* seeds[27]. Additionally, geographical variations also have an impact, with polyphenol content varying from 2.23 mg GAE/g in Xinjiang Uyghur Autonomous Regione to 3.37 mg GAE/g in Qinghai Province for *L. ruthenicum* Murr. seeds[27].

Polyphenols in *Lycium* seeds are predominantly composed of flavonoids such as quercetin, kaempferol, and isorhamnetin, which are highly regarded for their strong free radical scavenging capabilities[26]. These flavonoid compounds play a critical role in mitigating oxidative stress-induced free radical damage, contributing significantly to the prevention of cardiovascular and degenerative diseases[28,29]. Additionally, *Lycium* seeds contain abundant phenolic acids, including chlorogenic acid and gallic acid, which are essential in antioxidative processes[26,30]. Current research on polyphenols in *Lycium* seeds primarily focuses on flavonoid compounds due to their significant health benefits and bioactivity. In Gao's study, ultrasonic extraction with 95% ethanol yielded approximately 5.8 mg/g flavonoids[26]. Another study reported yields of 0.62 and 2.37 mg CAE/g flavonoids, with the highest content observed in *L. ruthenicum* Murr. from Xinjiang Uyghur Autonomous Region.

This demonstrates that both the variety and geographical location can significantly influence flavonoid content[27]. The variability in polyphenol content observed between different regions and species can be attributed to factors such as soil composition, climate, and genetic differences, which affect the biosynthesis and accumulation of these compounds[31].

Lycium seed polysaccharides

Polysaccharides are a class of biomolecules composed of different monosaccharides linked by α or β glycosidic bonds and substituted by hydroxyl groups on hemiacetal groups[32]. The presence of hydroxyl groups in polysaccharides is responsible for their biological activities such as antitumor, antibacterial, antiviral, immunomodulatory, and antioxidant[32–34].

Typically, soaking in distilled water is used to extract polysaccharides from medicinal herbs[35]. After oil removal, water extraction at room temperature for 2 h yields 2.84% crude polysaccharides from *L. barbarum* seeds[26]. This method is simple and widely used, but it has relatively low extraction efficiency. The water decoction extraction method, involves three cycles of extraction, each lasting 40 min, with a material-to-liquid ratio of 1:40 (g/mL)[36], the average polysaccharide yield is 10.65% from *L. barbarum* seeds. This method effectively enhances extraction efficiency through multiple cycles, making it suitable for large-scale production, though it requires higher energy input. Both methods are effective for extracting integral polysaccharides but have limitations in separating and analyzing specific functional components.

In addition, a novel sequential extraction method has been developed, whereby the dregs undergo four stages of extraction with distinct solvents solution: hot buffer solution (HBSS), chelating agent solution (CHSS), dilute alkaline solution (DASS), and concentrated alkaline solution (CASS), as shown in Table 3[37]. This method yields polysaccharide fractions ranging from 2.79% to 5.60% from *L. barbarum* seeds[8]. Sequential extraction enables the separation of polysaccharides in various binding states, facilitating the analysis of different components. Although the yield is lower compared to water extraction methods, this approach is particularly suitable for in-depth studies of functional polysaccharides.

Extracted polysaccharides consist of rhamnose, xylose, arabinose, galactose, mannose, and glucose. These monosaccharides form complex structures through glycosidic bonds, with common linkages including β-(1→3), α-(1→4), and β-(1→6)[38]. Among the samples, HBSS has the highest rhamnose (15.34%) and xylose (64.63%) content. CHSS also has a high xylose content (70.00%) but lower rhamnose (12.59%). DASS has a considerable quantity of mannose (35.04%). CASS has the highest rhamnose content (17.23%) and also high xylose content (66.67%), but much lower

Table 3. Summary of the active compounds of *Lycium* seeds.

Compound	Method	Yield		Material	Ref.
Polyphenol	60% ethanol and Scientz-IID ultrasonic cell disrupter for 30 min, followed by centrifugation at 5,000 rpm for 10 min.	2.23 ± 0.93 to 3.37 ± 1.33 mg GAE/g 1.35 ± 0.29 mg GAE/g 1.19 ± 0.55 mg GAE/g		*L. ruthenicum* Murr. *L. barbarum* (big) *L. barbarum* (small)	[27]
	Extraction using a 500 mg Sepax Generik Diol column with methanol, hexane, ethyl acetate, and Folin-Ciocalteu reagent for 2 h.	HP: 113.87 ± 4.04 mg/kg SFE: 65.89 ± 1.39 mg/kg CP: 79.19 ± 2.93 mg/kg SE: 35.65 ± 0.42 mg/kg USE: 40.47 ± 1.95 mg/kg		*L. barbarum*	[15]
	Extract with 99.99% CO_2 with a flow rate of 1 L/min at 35 MPa and 40 ℃ for 90 min.	5.97 ± 0.10 to 10.21 ± 0.55 mg/100 g		*L. ruthenicum* Murr.	[9]
	Reflux extraction with 95% ethanol for 1.5 h.	~26.7 mg/g		*L. barbarum*	[26]
Total flavonoid	Ultrasonicated three times with 95% ethanol.	~5.8 mg/g		*L. barbarum*	[26]
	60% ethanol and Scientz-IID ultrasonic cell disrupter for 30 min, followed by centrifuge at 5,000 rpm for 10 min.	2.37 ± 0.91 to 1.79 ± 1.30 mg CAE/g 1.18 ± 0.07 mg CAE/g 0.62 ± 0.20 mg CAE/g		*L. ruthenicum* Murr. *L. barbarum* (big) *L. barbarum* (small)	[27]
Polysaccharide	Ether and 80% ethanol, by Soxhlet reflux method for 1 h	Seed: ~28.4 mg/g Seed dreg: ~13.2 mg/g		*L. barbarum*	[26] [26]
	HBSS extraction with 0.05 mol/L CH_3COONa at 70 ℃, pH 5.2, for 1 h.	~41.06 mg/g	Rha 15.34% Xly 64.63% Ara 4.48% Gal 9.35% Man 4.87% Glc 1.75%	*L. barbarum*	[8]
	CHSS extraction with 0.05 mol/L $(NH_4)_2C_2O_4$, CH_3COONa, and EDTA-2Na at 70 ℃, pH 5.2, for 1 h.	~23.04 mg/g	Rha 12.59% Xly 70.00% Ara 4.68% Gal 9.93% Man 1.49% Glc 1.31%		
	DASS extraction with 0.05 mol/L NaOH and 20 mmol/L $NaBH_4$ at 70 ℃ for 1 h.	~36.24 mg/g	Rha 9.39% Xly 44.71% Ara 2.84% Gal 6.27% Man 35.04% Glc 1.76%		
	CASS extraction with 5 mol/L NaOH and 20 mmol/L $NaBH_4$ at 4 ℃ for 2 h, then centrifuged at 7,155 rpm for 15 min.	~47.29 mg/g	Rha 17.23% Xly 66.67% Ara 4.55% Gal 9.75% Man 0.68% Glc 1.11%		
	—	46.50%		*L. barbarum*	[15]
Protein	Isolated protein extraction at 40 ℃, pH 9–9.5, for 2 h with a ratio of 1:12, followed by pH adjustment to 4.5 and centrifugation at 3,000 rpm for 10 min.	85.67%		*L. barbarum*	[11]
	Seed protein extraction at 40 ℃, pH 9–9.5, for 2 h with a ratio of 1:12, then pH adjustment to 4.5 for 10 min.	22.13%		*L. barbarum*	[11]
	Alkali extraction and acid deposition.	15%		—	[12]
α-tocopherol	Extract with n-butane in the form of subcritical fluid at 0.63 MPa at 50 ℃ for 48 min.	10.84 ± 0.42 to 21.35 ± 1.64 mg/100 g		*L. ruthenicum* Murr.	[17]
	HP with 150 ℃; Centrifugal condition: 4,000 rpm for 15 min.	36.18 ± 0.38 mg/kg		*L. barbarum*,	[15]
	CP with below 60 ℃; Centrifugal condition: 4,000 rpm for 15 min.	33.49 ± 0.75 mg/kg			
	SE: Extract with hexane for 30 min, then evaporating under vacuum at 45 ℃.	31.99 ± 1.27 mg/kg			
	USE: Extract with hexane for 30 min in an ultrasonic bath with 750 W and 40 kHz and repeat twice, evaporating under vacuum at 70 ℃.	32.88 ± 0.70 mg/kg			
	SCFE: Extract with 99.99% CO_2 with a flow rate of 1 L/min at 35 MPa and 40 ℃ for 90 min.	27.17 ± 1.02 mg/kg			
γ-tocopherol	Extract with n-butane in the form of subcritical fluid at 0.63 MPa at 50 ℃ for 48 min.	2.22 ± 0.11 to 9.22 ± 0.59 mg/100 g		*L. ruthenicum* Murr.	[17]
	HP with 150 ℃; Centrifugal condition: 4,000 rpm for 15 min.	452.31 ± 5.54 mg/kg		*L. barbarum*	[15]
	CP with below 60 ℃; Centrifugal condition: 4,000 rpm for 15 min.	380.80 ± 1.18 mg/kg			
	SE: Extract with hexane for 30 min, then evaporating under vacuum at 45 ℃.	384.19 ± 0.32 mg/kg			
	USE: Extract with hexane for 30 min in an ultrasonic bath with 750 W and 40 kHz and repeat twice, evaporating under vacuum at 70 ℃.	385.73 ± 0.59 mg/kg			
	SCFE: Extract with 99.99% CO_2 with a flow rate of 1 L/min at 35 MPa and 40 ℃ for 90 min.	265.48 ± 0.79 mg/kg			

(to be continued)

Table 3. (continued)

Compound	Method	Yield	Material	Ref.
Carotenoid	Extract with n-butane in the form of subcritical fluid at 0.63 MPa at 50 °C for 48 min.	35.75 ± 3.66 to 49.61 ± 3.18 mg/100 g	*L. ruthenicum* Murr.	[17]
	HP with 150 °C; Centrifugal condition: 4,000 rpm for 15 min.	43.57 ± 0.20 mg/kg	*L. barbarum*	[15]
	CP with below 60 °C; Centrifugal condition: 4,000 rpm for 15 min.	33.71 ± 0.39 mg/kg		
	SE: Extract with hexane for 30 min, then evaporating under vacuum at 45 °C.	41.51 ± 0.10 mg/kg		
	USE: Extract with hexane for 30 min in an ultrasonic bath with 750 W and 40 kHz and repeat twice, evaporating under vacuum at 70 °C.	46.16 ± 0.15 mg/kg		
	SCFE: Extract with 99.99% CO_2 with a flow rate of 1 L/min at 35 MPa and 40 °C for 90 min.	4.17 ± 0.05 mg/kg		
Stigmasterol	HP with 150 °C; Centrifugal condition: 4,000 rpm for 15 min.	826.97 ± 55.53 mg/kg	*L. ruthenicum* Murr.	[15]
	CP with below 60 °C; Centrifugal condition: 4,000 rpm for 15 min.	778.40 ± 14.98 mg/kg		
	SE: Extract with hexane for 30 min, then evaporating under vacuum at 45 °C.	872.17 ± 53.48 mg/kg		
	USE: Extract with hexane for 30 min in an ultrasonic bath with 750 W and 40 kHz and repeat twice, evaporating under vacuum at 70 °C.	894.27 ± 50.52 mg/kg		
	SCFE: Extract with 99.99% CO_2 with a flow rate of 1 L/min at 35 MPa and 40 °C for 90 min.	671.15 ± 17.93 mg/kg		
	Solvent extraction with n-hexane, chloroform, and petroleum ether for 6 h at 40 °C.	~18.56 mg/100 g	*L. intricatum*	[6]
	Extract with CO_2 with at 35 MPa and 40 °C for 90 min.	3.34 ± 0.03 mg/100 g	*L. ruthenicum* Murr.	[9]
ß-Sitosterol	HP with 150 °C; Centrifugal condition: 4,000 rpm for 15 min.	1,901.48 ± 15.18 mg/kg	*L. ruthenicum* Murr.	[15]
	CP with below 60 °C; Centrifugal condition: 4,000 rpm for 15 min.	1,965.72 ± 45.97 mg/kg		
	SE: Extract with hexane for 30 min, then evaporating under vacuum at 45 °C.	1,940.95 ± 29.62 mg/kg		
	USE: Extract with hexane for 30 min in an ultrasonic bath with 750 W and 40 kHz and repeat twice, evaporating under vacuum at 70 °C.	2,062.34 ± 9.40 mg/kg		
	SCFE: Extract with 99.99% CO_2 with a flow rate of 1 L/min at 35 MPa and 40 °C for 90 min.	1,843.27 ± 39.05 mg/kg		
	Solvent extraction with n-hexane, chloroform, and petroleum ether for 6 h at 40 °C.	~13.04 mg/100 g	*L. intricatum*	[6]
	Extract with CO_2 with at 35 MPa and 40 °C for 90 min.	38.50 ± 0.09 mg/100 g	*L. ruthenicum* Murr.	[9]

HP, hot pressing extraction; CP, cold pressing extraction; SE, solvent extraction; USE, ultrasound-assisted solvent extraction; SCFE, supercritical CO_2 fluid extraction; Rha, rhamnose; Xly, xylose; Ara, arabinose; Gal, galactose; Man, mannose; Glc, glucose.

mannose (0.68%)[8]. These variations in monosaccharide composition highlight the structural differences in polysaccharide structures extracted by different methods, which may influence their biological activities.

Among the methods for selectively altering the structure and function of polysaccharides, chemical modification has proven to be the most effective[39]. Modifying *Lycium* seed residue polysaccharides through sulfation, phosphorylation, and carboxymethylation significantly enhances their functional properties[40]. After modification, the uronic acid content increased markedly, with sulfated polysaccharides showing an increase from 0.69% in natural polysaccharides to 7.03%. In terms of antioxidant activity, sulfated polysaccharides exhibited an improved 2,2'-azinobis(3-ethylbenzothiazoline 6-sulfonic acid) (ABTS$^{\cdot+}$) radical scavenging rate, rising from 20.17% to 37.22%, along with enhanced reducing power, reaching 0.13 mg/mg (VC equivalent). Phosphorylated polysaccharides showed the best Fe^{2+} chelating capacity, achieving 48.08%.

Lycium seed protein

Food protein and food-derived peptides have garnered attention as potential components in functional foods and natural health product formulations[41]. The proteins derived from *Lycium* seeds have been reported to possess antioxidant, anti-inflammatory, and antimicrobial activities[11]. Elucidating their structure-function relationships, including detailed analyses of their amino acid sequences and three-dimensional conformations, is essential for optimizing their application in diverse health-related fields[7,11,42].

Proteins from *Lycium* seeds are typically extracted using alkaline extraction (pH = 9–9.5) followed by acid precipitation (pH = 4.5). Protein isolate from *Lycium* seeds has been reported to contain 85.67% protein[11]. *Lycium* seed proteins are rich in essential amino acids, including leucine (3.88 mg/100 mg), which is crucial for muscle protein synthesis and repair, helping stimulate muscle growth and recovery. Phenylalanine (2.86 mg/100 mg) is vital for cognitive function and mood regulation, while valine (2.69 mg/100 mg) plays a role in energy metabolism[43,44]. Additionally, the protein extract contains non-essential amino acids, such as glutamic acid (9.38 mg/100 mg), which contribute to the overall nutritional value of the extract[43–45]. These amino acids contribute to a variety of physiological functions, making *Lycium* seed proteins a promising ingredient for enhancing immune function and alleviating conditions such as vascular diseases, diabetes, osteoporosis, and chronic inflammation.

Other compounds

In the extraction of *Lycium* seed oil, several bioactive compounds such as tocopherols, phytosterols, and carotenoids are also obtained.

Tocopherols, particularly *α*-tocopherol and *γ*-tocopherol, are prominent antioxidants in *Lycium* seed oil, playing a crucial role in preventing oxidative damage to cellular lipids and offering protective effects against cardiovascular and aging-related diseases[46,47]. The extraction yield of tocopherols varies depending on the method used. For instance, hot pressing yields the highest tocopherol content at 488.49 mg/kg due to the disruption of cell membranes, which facilitates the release into the oil phase, while subcritical fluid extraction results in lower yields at 29.26 mg/100 g[15,48]. Additionally, there is considerable variation in the tocopherol content of *L. ruthenicum* Murr. seeds, with values ranging from 31.35 mg/100 g to 14.84 mg/100 g depending on the geographical origin, with

α-tocopherol predominating form, representing approximately 70% of total tocopherols[17].

Phytosterols represent a distinctive category of structural lipids that enhance cell membrane stability and contribute to micro-fluidity, playing key roles in processes such as cell signaling and cellular sorting[49]. In *Lycium* seed oil, phytosterols, such as β-sitosterol (46%), Δ7-sitosterol (21%), campesterol (8%), and stigmasterol (5%), are known to reduce low-density lipoprotein cholesterol (LDL-C), thereby lowering the risk of cardiovascular diseases (CVDs)[3,50]. The extraction method significantly affects phytosterol yields. Ultrasound-assisted extraction yields the highest amount, at 16.68 mg/g, compared to 9.61 mg/g from subcritical fluid extraction[9]. Analysis of different *L. barbarum* seed oil (LBSO) revealed concentrations of campesterol at 22.50 mg/100 g, stigmasterol at 3.34 mg/100 g, and β-sitosterol at 38.50 mg/100 g. The sterol fraction extracted by organic solution was composed of stigmasterol (18.56 mg/100 g), β-sitosterol (13.04 mg/100 g), and ergosterol (8.12 mg/100 g). In comparison, total phytosterols were about 39.72 mg/100 g[6].

Carotenoids are essential for all photosynthetic organisms due to their significant photoprotective and antioxidant properties, with compounds such as β-carotene being effectively dissolved and extracted using various techniques[51]. Ultrasound-assisted extraction was demonstrated to be particularly efficient, achieving the highest carotenoid concentration at 4.62 mg/100 g, whereas supercritical fluid extraction offered the lowest at 0.417 mg/100 g[15]. The disruptive effect of ultrasound on cell structures significantly enhanced carotenoid extraction[52]. The β-carotene content of *L. ruthenicum* Murr. seeds exhibited a modest degree of variation between different origins. The highest concentration, 49.61 mg/100 g, was observed in Nuomuhong Qinghai Province, while the lowest, 35.75 mg/100 g, was identified in Cele Xinjiang Uyghur Autonomous Region[17].

Lycium seeds also contain many additional components[15]. These include crude fiber (7.78 g/100 g), calcium (112.5 mg/100 g), iron (8.42 mg/100 g), nucleic acid (4.32 mg/100 g), and riboflavin (1.27 mg/100 g), which are present in higher quantities compared to fresh and freeze-dried fruits. Furthermore, *Lycium* seeds are also rich in potassium (1.132%), phosphorus (0.178%), sodium (0.1498%), zinc (0.0021%), and other nutrients or components. These minerals have been demonstrated to have anti-aging and metabolic benefits, which contribute to the overall health-promoting properties of *Lycium* seeds[15].

Bioactivities of *Lycium* seeds

Lycium seeds contain a diverse range of bioactive compounds such as fatty acids, polysaccharides, polyphenols, and others. These compounds have gained considerable attention due to their potential health benefits, such as antioxidant, anti-aging, anti-inflammatory, antibacterial, antihypertensive, hypolipidemic, and cardiovascular protective properties[9,15,53]. Consequently, a comprehensive investigation of these functions and mechanisms is imperative to fully comprehend the potential benefits of *Lycium* seeds. The studies related to these benefits are summarized in Table 4 and Fig. 2.

Anti-fatigue

Fatigue is a significant factor affecting physical performance[54]. Persistent fatigue has been demonstrated to reduce exercise ability and an increased risk of both physical and mental ill-health[55]. Chronic fatigue is associated with a higher likelihood of developing autoimmune diseases, depression, and cancers[56,57]. Jiang et al. demonstrated that various doses of LBSO significantly extended the swimming time of the experimental mice and their survival time under hypoxia, with higher doses yielding more positive results[58]. Similarly, Zheng administered LBSO *via* oral gavage at low (0.025 mL/10 g), medium (0.05 mL/10 g), and high (0.1 mL/10 g) doses to mice, followed by 28 d of chronic unpredictable stress (CUS)[59]. The results demonstrated that LBSO improved open-field test scores and alleviated depression-like behaviors in the mice, with the most notable improvements observed in the high-dose group.

The mechanism of action of *Lycium* seed involves multiple bioactive compounds and signaling pathways that contribute to its significant health benefits. UFAs in *Lycium* seed oil, such as linoleic acid and oleic acid, enhance the body's antioxidant capacity by increasing the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px)[58,60]. Additionally, *Lycium* seed polysaccharides regulate the brain-derived neurotrophic factor (BDNF)/tyrosine receptor kinase B/xtracellular signal-regulated kinase pathway, which is critical for neuroprotection and neurogenesis[61,62]. Furthermore, studies indicate that LBSO significantly reduces serum corticosterone levels by modulating the cyclic adenosine monophosphate (cAMP)/cAMP response element binding protein (CREB)/BDNF signaling pathway in the central nervous system, which supports stress resistance, fatigue recovery, and cognitive function[59,63]. Its antioxidant components, including tocopherols and β-sitosterol, further promote neuroprotection by alleviating oxidative stress-induced inflammation[64,65].

Anti-diabetes

Diabetes is a chronic metabolic disease characterized by high blood glucose levels[66]. Type 2 diabetes (T2D) is the most prevalent form of the disease, characterized by insulin resistance and β-cell dysfunction, which are closely related to poor diet and obesity[67,68]. The study by Zhu et al. indicated that a high-dose group (0.1 mL/10 g) of LBSO showed a 34% reduction in blood glucose levels after a five-week treatment period[69]. The medium-dose group (0.05 mL/10 g) exhibited the most remarkable improvement compared to the diabetic model group, with a 36% increase in SOD activity, a 61% reduction in malondialdehyde (MDA) content, and a 26% elevation in glutathione content[69]. These findings indicate that LBSO improves antioxidant capacity and reduces blood glucose levels in mice with T2D induced by a high-fat diet. In severe cases, diabetes can lead to diabetic nephropathy, a microvascular complication that reduces the quality of life[70]. Yang et al. found that in the high-dose group (0.1 mL/10 g), LBSO reduced blood glucose (35%), urine glucose (91%), urine volume (62%), urine protein (51%), renal mass index (23%), glomerular area (22%), and renal tissue interleukin-8 (IL-8) (59%) in diabetic mice[71]. These results suggest that the anti-diabetic effects of LBSO may be attributed to its ability to enhance antioxidant defenses, lower blood glucose levels, and reduce urine protein levels.

The anti-diabetic effects of *Lycium* seeds are mediated through two main mechanisms. First, supercritical CO_2 fluid extracts enhance glucose uptake by activating the AMP-activated protein kinase (AMPK) pathway, which increases the translocation of glucose transporter type 4 (GLUT4) to the cell membrane, thereby improving insulin sensitivity and reducing blood glucose levels[34,72]. The second mechanism involves flavonoids that inhibit digestive enzymes such as α-glucosidase and α-amylase, which slows carbohydrate digestion and absorption, thus reducing postprandial blood glucose increase[24,73]. In conclusion, *Lycium* seeds have the potential to be an effective dietary supplement for managing diabetes by improving antioxidant capacity, enhancing insulin sensitivity, and lowering blood glucose levels.

Table 4. Summary of *Lycium* seed bioactivity.

Bioactivity	Method	Result	Mechanism	Ref.
Anti-fatigue	Low dose (10 mg/kg body weight (BW)), Medium dose (20 mg/kg BW), High dose (40 mg/kg BW) for 3 weeks.	Significantly extended swimming time and survival time under hypoxia.	Enhance blood oxygen capacity and antioxidant ability	[58]
Anti-fatigue	LBSO (2.5, 5.0, 10.0 mg/kg BW) and fluoxetine (20 mg/kg BW) were administered daily. CUS modeling for 28 d.	LBSO improved behavior in CUS mice, increasing horizontal crossing and decreasing immobility in tail suspension and forced swimming tests.	Reduce serum corticosterone levels and promote hippocampal CREB-BDNF pathway	[59]
Anti-diabetes	Low dose (2.5 mg/kg BW), medium dose (5 mg/kg BW), high dose (10 mg/kg BW) after a high-fat diet for 4 weeks.	Improved antioxidant capacity and reduced blood glucose levels in T2D mice.	Antioxidant capacity	[69]
Anti-diabetes	C57BL/6J mice diabetes induced by streptozotocin injection (70 mg/kg BW). LBSO (5, 10 mg/kg BW) and metformin (300 mg/kg BW) groups were administered daily for 5 weeks.	Reduced blood glucose, urine glucose, and renal tissue IL-8 in diabetic mice.	Decreased blood glucose and urine protein quantity	[71]
Neuroprotection	SD rats underwent common carotid artery ligation surgery. Five groups: sham-operated, model, and three LBSO dose groups (80, 40, 20 mg/kg BW).	LBSO increased T-AOC activity and decreased MDA levels. Cognitive function improved significantly in rats, as shown by Morris water maze tests.	Inhibition of acetylcholinesterase activity and antioxidants	[77]
Neuroprotection	LBSO was administered at low, medium, and high doses (2.5, 5.0, 10.0 mg/kg BW) by gavage for 35 d.	LBSO significantly improved cognitive function in CUS mice, reducing escape latency and increasing platform crossings in memory tests.	Inhibition of acetylcholinesterase activity and antioxidants	[59]
Anti-aging	The LBSO group received an additional daily dose of 1,000 mg/kg BW for 4 weeks.	LBSO treatment increased INHB and testosterone levels. In vitro, LBSO upregulated SIRT3, HO-1, and SOD expression, enhancing cell proliferation. SIRT3 overexpression also increased AMPK and PGC-1α levels.	Protective effects against oxidative damage and improved reproductive hormone levels	[90]
Anti-aging	LBSO was administered in low (1,000 mg/kg BW), medium (1,750 mg/kg BW), and high (2,500 mg/kg BW) doses along with D-gal (125 mg/kg BW) for 8 weeks to establish a subacute aging model in rats.	LBSO significantly increased the expression of Nrf2 pathway proteins and its downstream targets (GCLC, SOD2, NQO1) in the testes of subacute aging rats.	Protective effects against oxidative damage and improved reproductive hormone levels	[92]
Anti-atherosclerosis	Low dose group (LLSO, gavage with 1 mg/kg BW) and the high dose group (HLSO, gavage with 2 mg/kg BW) for 56 d.	Decreased LDL-C, TC, and TG in serum, increased HDL-C in plasma.	Blood lipid reduction	[95]
Lipid Metabolism	Five groups (normal diet, high-fat diet, 10% insoluble dietary fiber, 10% low carboxylation degree of substitution (DS), 10% high carboxylation DS) for 8 weeks.	Insoluble dietary fiber inhibited weight gain and reduced lipid levels in hyperlipidemic mice. It also improved liver function, reduced inflammation, and increased short-chain fatty acid (SCFA) levels, promoting cholesterol reduction through gut microbiota changes.	IDF can improve gut function in hyperlipidemic mice by increasing SCFAs synthesis, thereby controlling lipid metabolism and preventing lipid accumulation in the body.	[97]
Photoprotection	HaCaT cells were treated with different concentrations of LBSO (75, 150, 300, 600 mg/kg BW) and exposed to UVB (40 mJ/cm²). Cells were incubated for 24 h post-irradiation.	LBSO increased the survival rate of UVB-damaged cells, promoted Bcl-2 expression, inhibited ROS generation, reduced apoptosis, and lowered levels of pro-apoptotic factors and inflammatory markers (TNF-α, IL1β, IL-6).	LBSO alleviated UVB-induced photodamage by regulating apoptosis and reducing inflammation through increased Bcl-2 and decreased Bax, Caspase-3, and inflammatory markers.	[98]

Neuroprotection

Neurodegenerative diseases are movement disorders characterized by the progressive loss of neurons and neuronal apoptosis, leading to cognitive disorders and memory impairment. These conditions result in a decline in motor functions and cognitive abilities over time, profoundly impacting the quality of life of patients[74,75]. Wu et al. demonstrated that LBSO increased total antioxidant capacity (T-AOC) in brain tissue and significantly reduced MDA levels. Additionally, in the Morris water maze test, LBSO-treated rats showed significant improvements in cognitive performance, indicating that LBSO can effectively alleviate cognitive impairment induced by chronic cerebral ischemia[77]. Zheng further showed that LBSO improved open-field test campaign scoring, shortened the immobility time in both the tail suspension and forced swimming tests, and decreased the escape latency and the traveled distance in the Morris water maze test learning process[59]. Furthermore, corticosterone levels in the serum were significantly reduced when induced by CUS, and the impairments in the hypothalamic-pituitary-adrenal axis feedback regulation caused by CUS were reversed[59,78].

The neuroprotective effects of *Lycium* seeds are attributed to its bioactive compounds, which modulate key pathways involved in oxidative stress, neuroinflammation, neurotransmission, and neurogenesis. Antioxidants such as tocopherols and carotenoids activate the nuclear factor erythroid 2–related factor 2 (Nrf2)/heme oxygenase 1 (HO-1) pathway, reducing reactive oxygen species (ROS) and lipid peroxidation, thereby protecting neuronal integrity[79]. Additionally, polysaccharides enhance the activity of SOD and GSH-Px, mitigating oxidative damage, while suppressing the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling pathway to decrease pro-inflammatory cytokines like IL-1β, interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α), thereby reducing neuroinflammation[80,81].β-sitosterol, another active compound, inhibits microglial activation, further enhancing anti-inflammatory responses[82]. UFAs, such as linoleic and oleic acids, inhibit acetylcholinesterase to maintain acetylcholine levels and support cognitive functions like learning and memory[59]. Furthermore, polysaccharides activate the cAMP/CREB/BDNF pathway, promoting neurogenesis and synaptic plasticity, essential for repairing neuronal damage caused by aging or oxidative stress[79]. These mechanisms
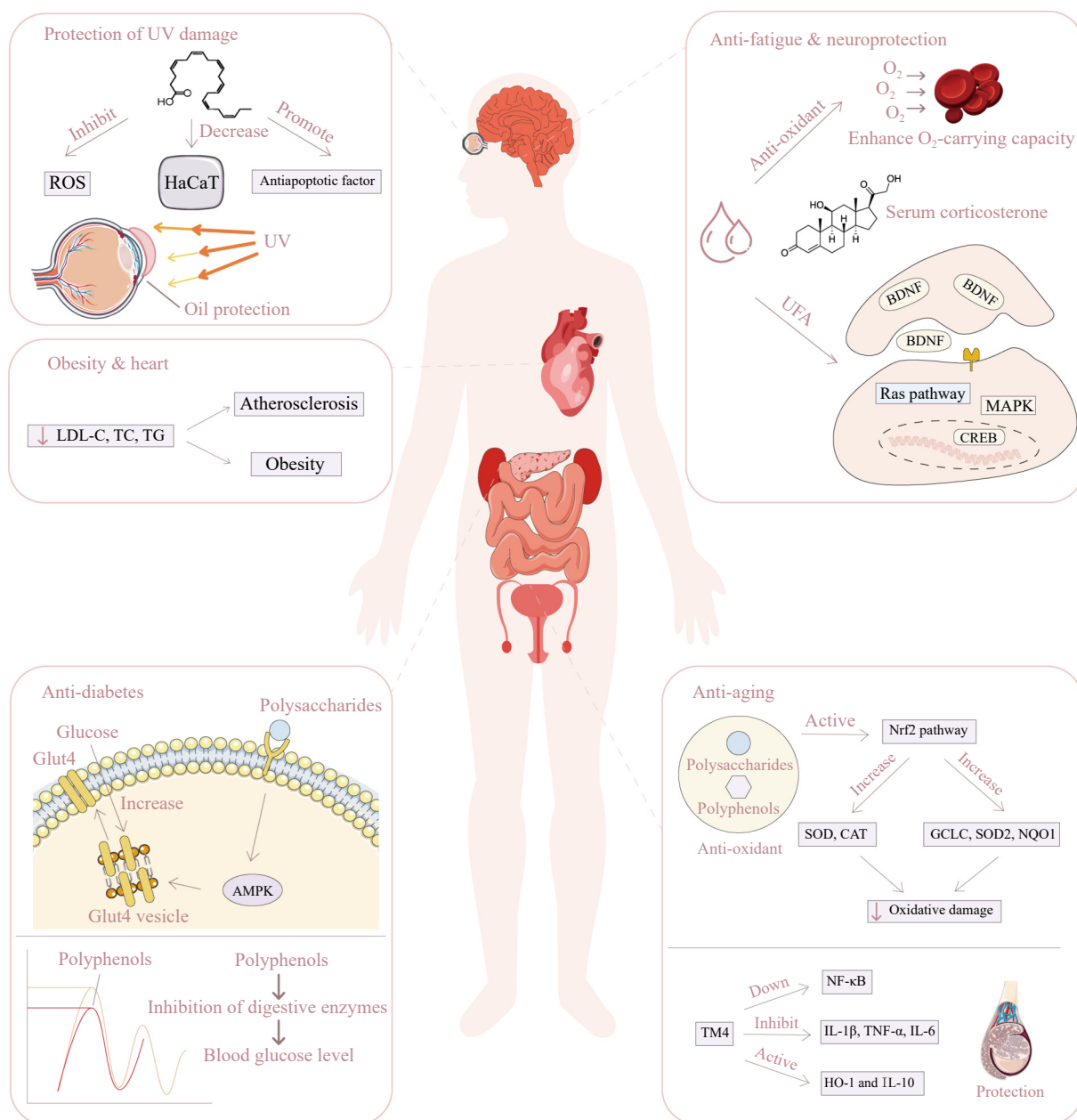
Fig. 2 Biological activities of *Lycium* seed extracts and potential mechanisms. ROS: Reactive Oxygen Species; HaCaT: Human Keratinocyte; UFA: Unsaturated Fatty Acids; LDL-C: Low-Density Lipoprotein Cholesterol; TC: Total Cholesterol; TG: Triglycerides; Glut4: Glucose Transporter Type 4; AMPK: AMP-activated Protein Kinase; Nrf2: Nuclear Factor Erythroid 2–Related Factor 2; SOD: Superoxide Dismutase; CAT: Catalase; GCLC: Glutamate-Cysteine Ligase Catalytic Subunit; SOD2: Superoxide Dismutase 2; NQO1: NAD(P)H Quinone Dehydrogenase 1; NF-κB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; IL-1β: Interleukin 1 beta; TNF-α: Tumor Necrosis Factor alpha; IL-6: Interleukin 6; HO-1: Heme Oxygenase 1; IL-10: Interleukin 10; CREB: cAMP Response Element-Binding Protein; BDNF: Brain-Derived Neurotrophic Factor; MAPK: Mitogen-Activated Protein Kinase.

collectively suggest that LBSO has significant potential as a neuroprotective agent for managing neurodegenerative diseases such as Alzheimer's and Parkinson's disease[83].

Anti-aging

The antioxidant activity of *Lycium* is attributed to its high content of UFAs and minor components such as tocopherols and phytosterols, which help neutralize free radicals and reduce oxidative stress. These components contribute to the oil's anti-aging attributes[1,13,84]. Seeds from *L. ruthenicum* Murr. and *L. barbarum* exhibited significant 2,2-diphenyl-1-picrylhydrazyl and ABTS radical scavenging capacities, indicating its potential as a dietary antioxidant[9,85]. Since oxidative stress is a significant contributing factor to

aging and age-related diseases, the antioxidants in *Lycium* seed oil activate the Nrf2 pathway, which increases the expression of antioxidant enzymes, such as SOD and catalase[86]. This activation helps mitigate oxidative damage in cells and tissues, thereby slowing the aging process.

Particularly, as a traditional Chinese medicine, *Lycium* has the function of maintaining male fertility by alleviating testicular aging[87,88]. Treatment with LBSO in TM4 cells inhibited cell proliferation by 14.89% ± 0.89% through the downregulation of NF-κB and the suppression of inflammatory cytokines IL-1β, TNF-α, and IL-6[89]. Additionally, LBSO activated HO-1 and *IL-10*, contributing to its anti-inflammatory effects. Also, LBSO (1,000 mg/kg/d) alleviated oxidative stress in the testes of aging subjects induced by D-galactose

both *in vivo* and *in vitro* using Sertoli cells (TM4)[90]. *In vitro*, half maximal effective concentration of LBSO was determined to be 86.72 ± 1.49. Intervention with LBSO (100 μg/mL) in TM4 cells resulted in an 87.82% increase in cell number, accompanied by upregulation of silent information regulator of transcription 3 (SIRT3), HO-1, and SOD.

The anti-aging effects of *Lycium* seeds are mediated by its ability to regulate key pathways involved in oxidative stress, mitochondrial function, and reproductive health. Research indicates that silencing of SIRT3 led to dysregulation of HO-1 and SOD, while lentiviral over-expression of SIRT3 upregulated AMPK and peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1α) expression[90]. Furthermore, *Lycium* seed oil has been shown to modulate reproductive hormone levels by increasing serum testosterone and follicle-stimulating hormone levels, while decreasing luteinizing hormone levels. This modulation likely occurs through *Lycium* seed oil regulatory effects on testicular reproductive function via the hypothalamic-pituitary-gonadal axis[91,92]. Additionally, in subacute aging rats, *Lycium* seed oil significantly enhanced the expression levels of Nrf2 and its downstream targets, including glutamate-cysteine ligase catalytic subunit (GCLC), SOD2, and nicotinamide adenine dinucleotide (phosphate) (NAD(P)H) quinone dehydrogenase 1 (NQO1), providing protective effects against oxidative damage and further protecting testicular tissue from aging induced by oxidative stress[92].

Other functions

In addition to the functions mentioned above, *Lycium* seeds have shown remarkable health benefits, especially in managing blood lipids, reducing inflammation, and protecting against ultraviolet (UV) damage. It is important to explore how these benefits work and what potential applications they might have.

Atherosclerosis is a chronic low-inflammatory disease and is considered an underlying cause of CVDs[93]. It is characterized by high-density lipoprotein cholesterol (HDL-C), LDL-C, and triglyceride (TG), which are major contributing factors[94]. Consequently, reducing these risk factors can help alleviate atherosclerosis. *Lycium* seed oil has demonstrated significant anti-atherosclerotic properties by targeting lipid metabolism and inflammation-related pathways. Jiang et al. showed that high-dose LBSO (2 mL/kg) reduced LDL-C (30.73%), total cholesteryl (TC) (58.52%), and TG (68.01%) levels in serum, while simultaneously increasing HDL-C (377.42%) in plasma[95]. These effects are primarily mediated through *Lycium* seed oil modulation of lipid profiles, potentially by regulating the protein kinase C pathway, which contributes to reduced proliferation of smooth muscle cells and collagen secretion by inhibiting matrix metalloproteinases[96].

Beyond its anti-atherosclerotic effects, *Lycium* seeds also contribute to managing obesity-related health issues. Carboxymethylated *L. barbarum* seed dreg insoluble dietary fiber (LBSDIDF) effectively mitigates hyperlipidemia induced by a high-fat diet in mice. In the high-dose LBSDIDF group, substantial reductions were observed in TC (39.66%), TG (52.86%), and LDL-C (56.98%), compared to the high-fat (HF) group, indicating a significant improvement in lipid profiles[97]. However, HDL-C levels decreased by 33.56% in the high-dose LBSDIDF group compared to the HF group. This suggests that while the intervention was successful in lowering harmful cholesterol levels, it also led to a reduction in beneficial HDL-C, which may require further investigation or additional dietary adjustments to optimize overall health benefits[97].

Furthermore, *Lycium* seed oil has shown protective effects against UV-induced photodamage in immortalized human keratinocytes[98]. Studies have shown that *Lycium* seed oil significantly increases the survival rate of UV-damaged human keratinocyte cells, promotes the expression of anti-apoptotic factors such as Bcl-2, inhibits intracellular ROS production, and reduces apoptosis rates[99]. Additionally, *Lycium* seed oil suppresses the expression of pro-inflammatory cytokines, such as *IL-6* and *TNF-α*, through regulation of the NF-κB signaling pathway, which is essential for reducing UV-induced inflammation and photodamage[98].

Applications

Lycium seeds, rich in bioactive compounds, contribute antioxidant, anti-inflammatory, antibacterial, and antihypertensive effects. These properties make *Lycium* seeds highly valuable across various sectors, with applications in pharmaceuticals, functional food, and animal husbandry[69,89,92]. This section will examine the practical uses of *Lycium* seeds, highlighting their potential as a valuable resource in different industries.

Daily diet

Lycium seeds are typically consumed as the fruit, either fresh or dried. The fruit has a slightly sweet flavor, and its seeds are small and soft, making them easy to chew together with the whole fruit[88]. Including *Lycium* in daily meals can significantly boost the nutritional value of dishes, and regular consumption may help strengthen the body and enhance disease resistance[15,73]. With their flavor and small size, *Lycium* seeds are easily incorporated into a variety of foods, such as porridge, soups, baked goods, and beverages, meeting the modern demand for health benefits. Their unique taste complements a wide range of ingredients, making them a practical and popular nutritional additive that provides natural support for health enhancement.

Pharmaceuticals

Since oil extraction is the most common and convenient method for processing *Lycium* seeds, research has primarily focused on oil-based applications. The bioactive compounds extracted from *Lycium* seeds have demonstrated significant therapeutic potential in various pharmaceutical formulations. *Lycium* seeds indicate considerable promise in encapsulation and microencapsulation technologies, which enhance the stability and efficacy of bioactive compounds[13,100]. For example, microencapsulation of *Lycium* seed oil using octenyl succinic anhydride-starch, gum Arabic, and maltodextrin at a stabilizer concentration of 0.3% (w/v) through spray drying has effectively prevented lipid degradation, achieving high encapsulation efficiency and superior oxidative stability[100]. Compared to unencapsulated LBSO, the inhibitory concentrations (IC50) value for -OH radicals scavenging was reduced by approximately 88%, approaching the antioxidant potential of vitamin C. Similarly, the IC50 value for ABTS radical scavenging was reduced by around 82%. This improvement suggests that the LBSO Pickering emulsion has markedly enhanced radical scavenging capacity, exhibiting superior antioxidant efficacy compared to LBSO alone. This enhancement is likely due to the increased dispersibility of LBSO, which facilitates interactions with radicals. Additionally, the emulsification and encapsulation of the UFAs in LBSO with gelatin and bacterial cellulose nanofiber helped reduce oxidation, thus preserving the nutritional components of LBSO[101].

Furthermore, gel formulations containing 2% *Lycium* seed oil microemulsions with Tween-80, have enhanced drug retention, bioavailability, hydrophilicity, and phase transition temperature, facilitating more efficacious drug delivery[102]. The addition of Tween-80 enhances the hydrophilic properties of the *Lycium* seed oil microemulsion, with increased polyoxyethylene content elevating the cloud point and, consequently, the phase transition temperature. These advances underscore the medicinal value of *Lycium* seed extracts in enhancing drug delivery and stability.

Beyond pharmaceutical oil-based formulations, *Lycium* seed extracts have shown hypotensive effects and potential benefits for erectile function, emphasizing their broad pharmacological potential[103]. These findings underscore the medicinal value of *Lycium* seed-derived products, particularly in enhancing drug stability and providing diverse therapeutic benefits. Nevertheless, ensuring safety remains critical for the commercial production of these products. The safety of *Lycium* seed oil is primarily influenced by potential contamination, oxidative degradation during storage, and variability caused by different processing methods[104]. Improper handling of raw materials during production may result in microbial or other contaminants, compromising product safety. To mitigate these risks, raw materials must adhere to stringent sensory and technical standards, such as being free from mold and off-odors[105]. During storage, the high content of UFAs in *Lycium* seed oil makes it oxidation, leading to increased acid and peroxide values, which can negatively affect its quality and safety[106]. Consequently, storage conditions must be carefully controlled through measures. Furthermore, processing methods significantly affect the concentration of bioactive compounds. For example, compared to solvent methods, supercritical CO_2 extraction is more effective at retaining active components while avoiding residual organic solvents, thereby improving product safety[15,17]. To overcome these challenges, it is essential to implement rigorous quality control measures and standardization protocols to ensure the safety, consistency, and efficacy of *Lycium* seed-derived products, thereby supporting their expanded use in pharmaceutical industries[107].

Functional food

With their rich antioxidant, anti-inflammatory, and metabolic regulation properties, *Lycium* seeds, and their derivatives hold significant potential for application in functional foods. *Lycium* seeds can enhance the nutritional value and flavor of a wide variety of food products. For example, when the concentration of *Lycium* seed juice is 30%, with 5% β-cyclodextrin added, the resulting noodles display an appealing dark red color. Under these optimal conditions, the noodles achieved the highest sensory evaluation score, with a maximum water absorption rate of 216.13%, indicating significant improvements in texture and sensory properties[108]. The incorporation of *Lycium* seeds into flour, noodles, and other food items not only enhances taste but also offers potential health benefits.

Further enhancement of nutritional profiles and sensory characteristics was achieved by optimizing enzymatic hydrolysis processes and Maillard peptide salt formulations. *Lycium* seed oil, rich in UFAs and polysaccharides, significantly improved the antioxidant capacity and sensory quality of these products. The formulated salt scored 95.75 in sensory evaluation, with an antioxidant capacity of 91.72% and superior thermal stability. It also contained 264.78 g/kg sodium and 139.79 g/kg potassium, with an electronic tongue salinity response 1.71% higher than refined salt. Additionally, the Maillard peptide salt contained higher levels of umami nucleotides compared to refined salt, enhancing saltiness while allowing for reduced salt content[109].

The optimal enzymatic hydrolysis conditions for preparing angiotensin-converting enzyme (ACE) inhibitory peptides from *Lycium* seed meal were determined as follows: alkaline protease activity of 1.42×10^4 U, ultrasonic power of 122 W, hydrolysis time of 36.5 min, and hydrolysis temperature of 50 °C. Under these conditions, the ACE inhibition rate of the *Lycium* seed's ACE inhibitory peptides reached a maximum of 71.28% ± 0.86%[110]. Using LBSO as a base, three oleogels—beeswax oil, rice bran wax oil (GRO), and lac wax oil—were prepared and tested as partial cocoa butter substitutes in chocolate. GRO demonstrated the highest hardness (1457 g)

and oil binding capacity (99.82%), along with superior gel properties. GRO-based oleogel chocolate displayed the most stable rheological properties, best mouthfeel, and highest overall acceptability[111,112].

Animal husbandry

Currently, the primary market application of *Lycium* seeds is in animal feed production, where research indicates that *Lycium* seed bio-feed exhibits antimicrobial properties, inhibiting the growth of pathogenic bacteria in livestock[113]. Supplementation with *Lycium* seeds has been associated with improved fermentation quality of silage, enhanced performance, and health indicators in ruminants[114,115]. The beneficial effects of *Lycium* seeds in animal husbandry can be attributed to their high content of bioactive compounds, including antioxidants, polysaccharides, and unsaturated fatty acids. These compounds help reduce oxidative stress and inflammation in livestock, leading to improved immune responses and resistance to infections. Additionally, *Lycium* seeds promote beneficial microbial growth in the gut, which enhances nutrient absorption and feed efficiency[112]. By improving animal health and productivity, the use of *Lycium* seeds in livestock feed contributes to more sustainable and efficient agricultural practices. The utilization of *Lycium* seeds in animal husbandry underscores their potential to enhance animal health and productivity, thereby contributing to the sustainability of agricultural practices.

Discussion

Lycium seeds, a by-product of *Lycium* fruit processing, are rich in bioactive compounds and hold significant health potential. This review summarizes and analyzes existing research, finding substantial progress in understanding the extraction of nutritional components, health benefits, and applications, as shown in Fig. 3. However, several challenges and opportunities remain to be explored.

Extraction methods have been the subject of considerable research, as different methods can be selected to specifically maximize the extraction of various nutrients. This review explores the differences among *Lycium* seed varieties and examines how optimizing extraction methods can affect both yield and bioactivity. Despite the progress made in current extraction technologies, several issues still require further investigation. Firstly, extraction methods vary in efficiency when isolating bioactive compounds, leading to the loss of key bioactive compounds and reduced bioavailability[116]. Secondly, the complex composition of *Lycium* seeds and the difficulty in controlling extraction parameters pose challenges to achieving large-scale industrial production, both technically and financially[117]. The inconsistency in extraction outcomes affects not only the yield but also the effectiveness of bioactive compound extraction, creating a significant barrier to industrial applications[35].

Existing research on the functions of *Lycium* seeds has primarily focused on animals, demonstrating its health benefits. However, further rigorous clinical trials are necessary to confirm the efficacy of *Lycium* seed extracts in humans. While several clinical studies have established the health benefits of *Lycium* fruits, such as improved energy levels, sleep quality, and mental focus through *Lycium* juice, clinical studies on *Lycium* seeds specifically are lacking[118]. For instance, formulations containing *Lycium* fruit have shown potential for liver health improvement in heavy drinkers and skin hydration and wrinkle reduction in eye serums[119,120]. Nevertheless, similar studies on *Lycium* seeds are essential, as are studies validating their safety and efficacy in clinical applications. Additionally, the molecular mechanisms underlying these health benefits require further
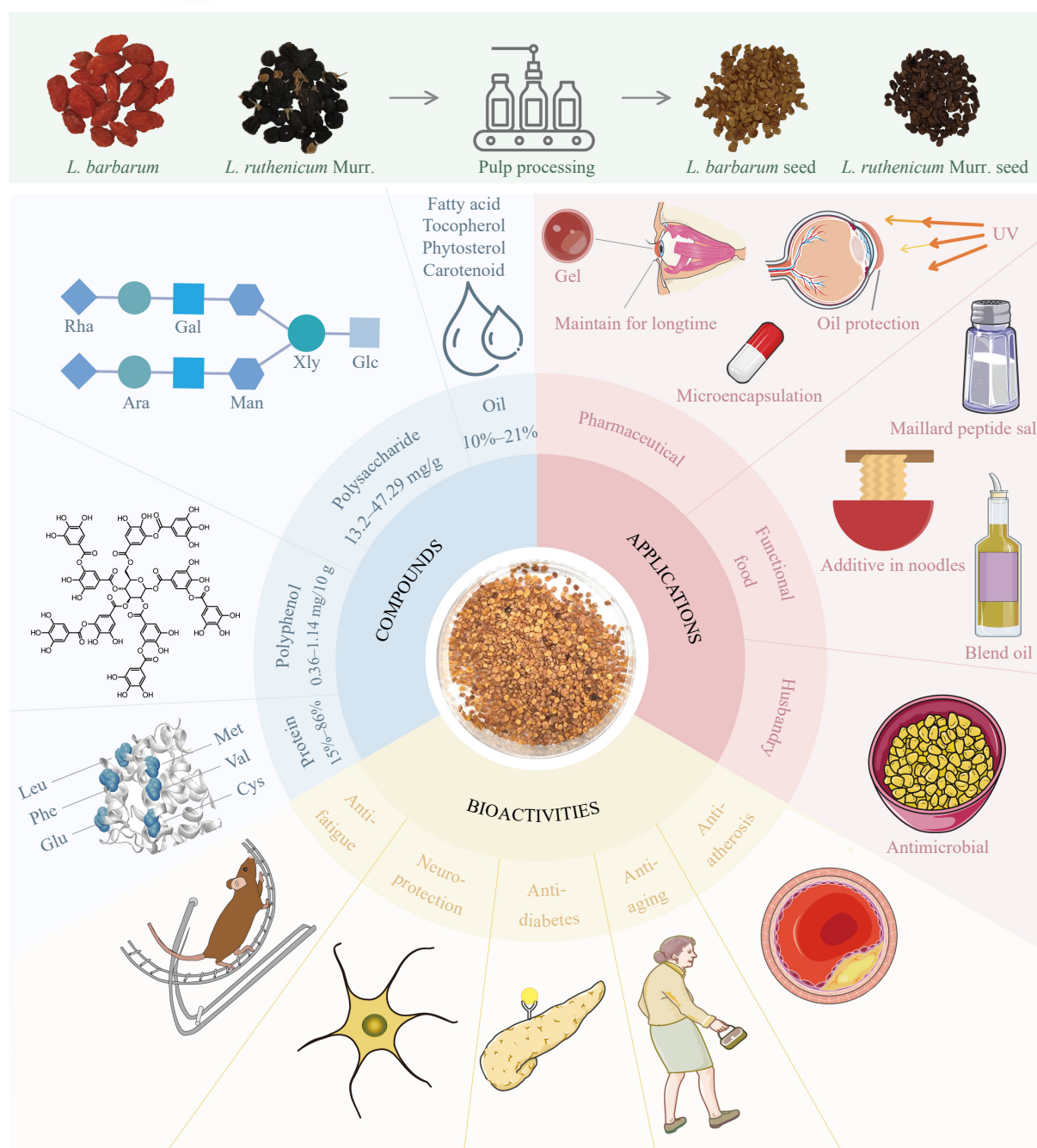
Fig. 3   The summary of composition, biological activity, and application of *Lycium* seeds. Rha – Rhamnose; Gal – Galactose; Xyl – Xylose; Glc – Glucose; Ara – Arabinose; Man – Mannose; Leu – Leucine; Phe – Phenylalanine; Glu - Glutamic acid; Met – Methionine; Val – Valine; Cys – Cysteine; UV - Ultraviolet.

investigation, particularly for bioactive components such as proteins and polyphenols. Their specific molecular mechanisms and effects still need to be explored using advanced technologies such as metabolomics[35].

Future research should prioritize efficient and eco-friendly extraction technologies to enhance yield and bioactivity while minimizing environmental impact. Establishing standardized industrial processes is crucial to ensure consistent product quality, safety, and efficacy. Lastly, evaluating the environmental and economic impacts of *Lycium* seed production and utilization will be vital to optimizing agricultural and industrial practices, reducing resource waste, and fostering sustainable development.

Conclusions

This review shows that *Lycium* seeds are a rich source of bioactive compounds with several potential health benefits. Research progress has been made in understanding the nutritional components, extraction methods, and potential health applications of *Lycium* seeds. However, key challenges such as inconsistent extraction outcomes, limited human studies, and the need for industrial optimization must be addressed. The integration of innovative extraction methods, rigorous clinical validation, and sustainable industrial practices will be pivotal for fully realizing the value of *Lycium* seeds in food, pharmaceutical, and husbandry industries.

Author contributions

The authors confirm contribution to the paper as follows: Li Y: wrote the main manuscript text and prepared Figs 1 & 2, the graphical abstract, and Tables 3 & 4; Shen R: wrote the main manuscript text prepared Fig. 1, Tables 1 & 2; Wang S: participated in literature analysis and contributed to the main manuscript text; Zhang J: contributed to the manuscript text and assisted with revisions; Deng J: performed the final review and editing of the manuscript; Liu Y: provided critical revisions to the structure and content of the manuscript and conducted proofreading; Sun Q: performed the final review and editing of the manuscript; Yang H: supervised and guided the entire writing process, provided academic support, and performed the final review and editing of the manuscript. All authors reviewed the results and approved the final version of the manuscript.

Data availability

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Conflict of interest

The authors declare that they have no conflict of interest.

Dates

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