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Review

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Lycium L. flavonoids: extraction, purification, signal transduction pathways, and interactions with intestinal microbiota

Tian Lan[1,2,3,5], Kexin Zhou[1,5], Guozhen Duan[1,2], Yuxin Zhang[1], Yonggui Ma[4], Guanghui Fan[1,2] & Youchao Qi[1,2,3,4] ✉

Flavonoids are major bioactive constituents of *Lycium* L. with diverse pharmacological activities. This review summarizes recent advances in the extraction, characterization, and biological functions of *Lycium* flavonoids (LyFs). Evidence indicates that LyFs exert antioxidant, anti-inflammatory, and immunomodulatory effects via pathways such as NF-κB and Keap1–Nrf2/ARE. Notably, LyFs act as functional prebiotics by modulating gut microbiota and short-chain fatty acid production, supporting intestinal and metabolic health.

Wolfberry (*Lycium* L.), a perennial shrub belonging to the Solanaceae family, is widely recognized for its rich phytochemical composition and broad spectrum of biological activities. It has been consumed for centuries as both food and traditional medicine[1]. It is well-documented in classical material medica, such as the "Bencao Gangmu" (Compendium of Materia Medica), that wolfberry has been traditionally utilized for its multifaceted roles in supporting reproductive health, enhancing immune function, and promoting longevity[2]. Within the framework of traditional dietary culture, wolfberries have been extensively incorporated into a diverse array of culinary preparations, including soups, teas, porridges, and desserts, thereby reflecting their long-standing recognition as a medicinal food with mild nourishing properties. This historical usage underscores its integration into both therapeutic and dietary practices, highlighting its versatility and safety profile. In recent years, with the escalating global interest in natural health products and preventive medicine, wolfberry fruits and their bioactive extracts have been extensively developed into a wide spectrum of modern nutraceutical formulations. These include functional beverages, encapsulated supplements, powdered concentrates, and oral liquids, collectively forming a distinct and rapidly expanding segment of the functional food market[3]. To date, approximately 97 *Lycium* species have been identified worldwide, primarily distributed across Eurasia, North America, South America, and Southern Africa[4]. In China, seven species and three varieties are officially recognized, with major cultivation regions including Ningxia, Gansu, and Qinghai, featuring *Lycium barbarum* L. and *Lycium ruthenicum* Murr[5]. Phytochemical investigations have revealed that wolfberries contain a diverse array of bioactive compounds, including polysaccharides, flavonoids, alkaloids, terpenoids, amino acids, vitamins, carotenoids, and trace elements[6,7]. Among these constituents, polysaccharides have been extensively studied and are widely regarded as the primary bioactive components of wolfberry. However, previous studies have shown that flavonoids account for approximately 19.11% of wolfberry constituents, making them the most abundant active ingredient[8]. Anthocyanins (ANCs) are the signature secondary metabolites in *L. ruthenicum*.

Structurally, LyFs are characterized by a typical C6-C3-C6 backbone and occur predominantly as glycosylated derivatives[9]. These structural features underpin the diverse bioactivities of LyFs, including antioxidant and anti-inflammatory effects, which are mediated through the modulation of key signaling pathways such as NF-κB and Nrf2. Despite significant advancements in the field of wolfberry research, a comprehensive and systematic review addressing the multifaceted aspects of wolfberry polysaccharides remains conspicuously absent. Existing scholarly reviews have predominantly concentrated on isolated dimensions of this complex subject, with a predominant emphasis on either the extraction methodologies or the biological activities, while largely neglecting the intricate interconnections that span the entire research continuum. Specifically, prior reviews have largely overlooked the critical need for integrative analyses that holistically examine the progression from initial extraction and subsequent purification protocols to advanced structural characterization, elucidation of biological activities, exploration of mechanistic pathways, and investigation of interactions with the intestinal microbiota[3].

Consequently, a comprehensive and systematic synthesis of current knowledge on LyFs remains lacking. The isolation and characterization of

[1]College of Agriculture and Animal Husbandry, Qinghai University, Xining, China. [2]Academy of Agriculture and Forestry Sciences, Qinghai University, Xining, China. [3]College of Tibetan Medicine, Qinghai University, Xining, China. [4]Key Laboratory of Medicinal Animal and Plant Resources of Qinghai Tibetan Plateau, Qinghai Normal University, Xining, China. [5]These authors contributed equally: Tian Lan, Kexin Zhou. ✉e-mail: 2020990013@qhu.edu.cn

LyFs are inherently challenging due to their diverse glycosylation patterns and conjugated structures, which necessitate careful selection of extraction and purification strategies to preserve their structural integrity and biological activity. Variations in processing conditions not only influence extraction efficiency but also profoundly affect the chemical composition, structural features, and subsequent bioactivities of LyFs[10]. In this context, the present review provides a comprehensive overview of LyFs, with particular emphasis on the interconnections between extraction and purification strategies, structural characteristics, signaling pathway modulation, and interactions with the intestinal microbiota (Fig. 1). By synthesizing evidence across these interconnected domains, this review aims to clarify how processing-dependent structural variations translate into functional outcomes and systemic health effects. Bridging phytochemical, mechanistic, and gut–host interaction perspectives, this work establishes a coherent framework for understanding the structure-activity relationships of LyFs, informing their rational development and application in functional foods and health-related products.

Pretreatment and drying technology

The waxy epidermis of wolfberry fruits acts as an effective physical barrier to solvent penetration and moisture migration, thereby limiting extraction efficiency and necessitating appropriate pretreatment prior to drying and extraction. Common dewaxing strategies include chemical soaking (e.g., Na_2CO_3, Na_2SO_3, petroleum ether, and diethyl ether), ultrasonic treatment, and enzymatic hydrolysis. These approaches facilitate the removal of lipophilic surface components, enhance peel permeability, and improve mass transfer during subsequent processing steps[11,12]. Although different dewaxing agents may alter extraction kinetics, previous studies indicate that they exert no significant influence on the final flavonoid yield[13]. Moreover, moderately prolonged drying duration following pretreatment has been reported to increase total flavonoid content in wolfberries[14].

Fresh wolfberry fruits are characterized by high moisture content, a short harvest period, limited storage stability, and abundant sugars and mucilaginous substances[15,16], rendering them unsuitable for direct extraction. Drying is therefore indispensable for the preservation of wolfberry fruits and represents a critical processing step that directly influences the stability and retention of LyFs[17]. Available drying techniques range from traditional sun-drying and hot-air drying to advanced vacuum drying and freeze-drying methods[18]. Sun-drying is economically advantageous but time-consuming and highly susceptible to environmental variability, which may compromise the stability of bioactive compounds. Hot air drying offers operational simplicity and rapid moisture removal; however, inadequate temperature control or prolonged thermal exposure can lead to flavonoid degradation. By contrast, vacuum drying and freeze-drying generally provide superior preservation of thermosensitive compounds but are constrained by higher processing costs and limited industrial scalability[19]. However, under optimized and moderate temperature regimes, hot-air drying can inactivate endogenous degradative enzymes, shorten drying duration, and achieve relatively high flavonoid retention.

Empirical studies further underscore the importance of coordinated pretreatment and temperature control. Wang et al.[20] demonstrated that dewaxing pretreatment significantly shortened drying time, while staged variable-temperature regimes enhanced drying efficiency. Similarly, Luo et al.[17] reported that hot air drying of pretreated wolfberries resulted in the highest total flavonoid content, with ultrasonic treatment, osmotic dehydration, and hot water immersion facilitating flavonoid release. In contrast, Wu et al.[19] observed substantial flavonoid losses during post-dewaxing hot air drying at elevated temperatures (40 + 80 °C), highlighting the risks associated with excessive thermal exposure (≥80 °C). Collectively, the selection of an integrated pretreatment and drying strategy requires a careful balance among temperature control, processing duration, economic feasibility, and the preservation of LyFs bioactivity. Tables 1 and 2 summarize and compare the major drying approaches and their selection criteria.

Extraction and purification of LyFs

Efficient extraction and purification are prerequisite steps for the accurate characterization and functional evaluation of LyFs. Given their structural diversity, extensive glycosylation, and sensitivity to processing conditions, the selection of appropriate extraction and purification strategies plays a critical role in determining yield, structural integrity, and downstream bioactivity. This section summarizes commonly employed extraction techniques and purification approaches for LyFs, with particular emphasis on their principles, advantages, and limitations.

Extraction of LyFs

A wide range of extraction techniques has been developed for LyFs, each characterized by distinct mechanisms, advantages, and limitations (Table 3). Commonly employed approaches include conventional organic solvent extraction, microwave-assisted extraction (MAE), ultrasonic-assisted extraction (UAE), enzymatic hydrolysis, high-pressure homogenization, and supercritical CO_2 extraction[21].

Organic solvent extraction. Conventional organic solvent extraction operates on the principle of polarity compatibility and typically employs solvents such as ethanol, methanol, acetone, or water under reflux or maceration conditions[22]. Owing to its simplicity and low equipment requirements, this method remains widely used. However, it is often associated with prolonged extraction times, relatively low efficiency, and co-extraction of impurities[23,24]. An et al.[25] reported an optimal extraction time of 2.47 h, yielding an average LyFs content of 14.57 mg/g. Extraction performance was strongly influenced by ethanol concentration and temperature, underscoring the need for methodological optimization to improve the efficiency of traditional solvent-based extraction.

MAE. MAE has attracted increasing attention due to its ability to rapidly heat both the solvent and plant matrix, thereby significantly reducing extraction time and enhancing flavonoid yield[26,27]. This technique is characterized by strong penetration capacity, reduced solvent consumption, and relatively favorable environmental performance[28]. Under optimized conditions, Chen et al.[29] reported a total flavonoid yield of 20.66 mg/g. Nevertheless, the effectiveness of MAE is highly dependent on precise control of processing parameters. Excessive microwave power or prolonged irradiation can induce rapid temperature increases, leading to glycosidic bond cleavage, oxidative degradation, or structural alteration of thermolabile flavonoids, ultimately compromising their stability and biological activity. Accordingly, careful regulation of temperature, microwave power, and extraction time is essential to preserve the structural integrity and bioactivity of LyFs during MAE.

UAE. UAE leverages ultrasonic vibrational and cavitation effects to disrupt cell walls, facilitating solvent penetration and accelerating the dissolution of target components, thereby improving extraction yield[30,31]. This technique is characterized by short processing time, high efficiency, and the preservation of antioxidant activity. Wang et al.[32] extracted the total flavonoids in 42 min with an extraction rate reaching 42.10 mg/g. However, scalability challenges exist for industrial applications, and high-intensity ultrasonic waves may adversely affect the structural integrity and bioactivity of LyFs, hindering large-scale production[24].

Biological enzymatic extraction. Enzymatic extraction employs specific enzymes to selectively degrade plant cell wall components and intercellular matrices, thereby facilitating the release and diffusion of intracellular flavonoids[33]. Commonly used enzymes include cellulase, pectinase, and various proteases. This approach offers high specificity and environmental compatibility but is associated with relatively high enzyme costs and stringent requirements for process control. Previous studies have shown that suboptimal conditions, such as excessive

Table 1 | Pretreatment and drying technologies of wolfberry

Drying technology	Pretreatment	Drying scheme	Conclusion	References
Natural drying	1:50(m/v): Na_2CO_3:Na_2SO_3	5.00 g of fresh fruits are soaked in the solution, quickly taken out, and placed in the sun. Samples are taken every 24 h.	1. The total flavonoid content increases with the extension of the sun-drying time. 2. The wax remover does not affect the changing trend of flavonoids during the sun-drying process, but it does affect the time to reach the maximum value.	14
Hot air drying	Soak in 2%, 4%, and 6% Na_2CO_3 for 1 min	The drying comparison was conducted respectively by two methods: constant temperature and humidity, 40 °C, 50 °C, 60 °C, and variable temperature.	1. The wolfberry dried by a heat pump at 50 °C with 2% Na_2CO_3 pretreatment had the highest flavonoid content. 2. The influence of LyFs content: heat pump drying > hot air drying, drying temperature > drying time.	91
Heat pump drying				
Natural drying	5% Na_2CO_3	At 20:00, put the wolfberries indoors. The next day at 8:00, dry the wolfberries indoors again and weigh them every 4 h.	1. Total flavonoid content: Solar drying > coal- drying > natural drying.	92
Coal drying		The humidity is 25%, the temperature is 70 °C, and the interval is 0.5 h. The amount of coal added is determined according to the strength of the coal fire.		
Solar drying		Drying is conducted by gradually increasing the temperature in sections.		
Stoving	1:50(m/v): Na_2CO_3:Na_2SO_3	Dry at 40 °C to reduce the moisture content to below 10%.	1. Total flavonoid accumulation: stoving > natural drying > freeze sublimation drying.	14
Natural drying		Dry at 40 °C to reduce the moisture content to below 10%.		
Freeze sublimation drying		Vacuum freeze-drying at 40 °C to reduce the moisture content to below 10%.		
Natural drying	3% Na_2CO_3, then ultrasound, 0.3 mg/g sucrose, pairwise combination.	—	1. Hot air is beneficial for the retention of LyFs. 2. Ultrasonic, sucrose, and hot blanching pretreatments have a promoting effect on the increase of LyFs content under hot air drying.	17
Hot air drying		Temperature: 50 °C, wind speed: 3 m/s.		
Far-infrared drying		Temperature: 50 °C.		
Far-infrared vacuum drying	Soak in 2% Na_2CO_3 for 3 min, then undergo ultrasonic.	Temperature: 70 °C, irradiation height: 210 mm, vacuum degree: −20 kPa; The ultrasonic frequency is 40 kHz, the ultrasonic power is 80 W, and the ultrasonic treatment time is 30 min.	1. The total flavonoid content increased by 28.69%.	93
Electrohydro-dynamic	Soak in 5% Na_2CO_3 for 10 min	At voltages of 0, 20, 24, 28, and 32 kV, multiple anti-plate electrodes are used for the AC electric field. Under the action of an alternating electric field, multiple electrodes targeting the plate were changed, and the voltage was 28 kV.	1. The drying speed of wolfberries has been increased, among which the influence of the electric field on the drying rate is the most significant.	94
Stoving	3% Na_2CO_3 and no dewaxing	Hot air drying at temperatures 40 °C, (40 + 60) °C, and (40 + 80) °C.	1. The LyFs content: after dewaxing, 40 °C hot air drying > 40 °C hot air drying > infrared drying > vacuum freeze-drying.	19
Infrared drying		Medium and short-wave infrared drying, with the temperature raised from 40 °C to 60 °C after the skin of the wolfberry shrinks.		
Microwave drying		Raise the temperature to 60 °C after the skin of the wolfberries shrinks at 40 °C.		
Vacuum freeze drying		Temperature −80 °C, vacuum degree −0.08 MPa.		

temperature, inappropriate pH, excessive enzyme dosage, prolonged reaction time, or high ethanol concentration, can markedly reduce extraction efficiency[34,35]. Consequently, achieving optimal enzyme activity and extraction performance requires precise regulation of temperature and pH.

Emerging and cooperative techniques. Emerging extraction technologies, including high-pressure homogenization, magnetic field-assisted extraction, deep eutectic solvents (DES), and supercritical CO_2 extraction, offer advantages such as improved efficiency, greener processing profiles, and enhanced preservation of bioactive compounds[36–38]. These methods show promise for large-scale industrial applications. In addition, cooperative extraction strategies-such as UAE or enzyme-MAE-integrate the strengths of individual techniques to achieve synergistic improvements in extraction performance[39,40]. For example, Ali et al.[41] reported that the combination of choline–ethylene glycol DES with UAE achieved an LyFs yield of 18.2 mg/g, representing a 26% increase over conventional ethanol extraction, with a flavonoid purity of 35.6%.

Purification of LyFs

Crude LyFs extracts obtained after extraction typically contain substantial amounts of co-extracted impurities, necessitating further separation and purification to obtain flavonoids of higher purity. Currently employed

Table 2 | Selection basis and application scope of LyFs pretreatment and drying

Application scenarios	Core requirements	Recommended technology portfolio	Selection criteria
Small-scale laboratory study	Preserve heat-sensitive LyFs	Ultrasonic pretreatment (without chemical reagents) + Freeze-drying	Freeze-drying minimizes thermal and oxidative stress, thereby favoring the preservation of native flavonoid structures.
Industrial-scale production (low cost)	balance yield and cost	2% Na_2CO_3 immersion (dewaxing) + hot air drying at 50 °C	Hot air drying is cost-effective; Na_2CO_3 pretreatment improves solvent penetration and process efficiency.
Production in high-humidity areas	Shorten drying time and reduce mold formation	Ultrasonic + Na_2CO_3 composite pretreatment + staged temperature drying	Composite pretreatment reduces drying time; staged temperature variation (40 → 60 °C) reduces thermal stress and improves drying uniformity.
Avoid chemical residues (organic products)	No chemical reagents involved	Pure ultrasonic pretreatment + solar drying (under suitable climatic conditions)	Solar drying is cost-effective; ultrasonic waves only physically disrupt the waxy layer without introducing chemical impurities.

Table 3 | Selection basis and application scope of LyFs extraction

Methods	Scene	Yield	Selection criteria
Solvent extraction	Preliminary laboratory screening and low-cost small-batch preparation	10–14.57 mg/g	Simple to operate, but with low purity and limited yield
MAE	Large-scale rapid extraction and high yield; not suitable for heat-sensitive LyFs	18–20.66 mg/g	The yield is higher than that of the solvent method, with slightly higher purity, but high temperatures are prone to glycosidic bond cleavage.
UAE	Pilot test in the laboratory, high activity + medium yield	35–42.09 mg/g	Short extraction time, highest yield, uneven ultrasonic intensity
Biological enzymatic extraction	High-purity LFs, thermosensitive compounds	16–19 mg/g	Highest purity, moderate yield, requires temperature and pH control
Emerging combination technology (DES + UAE)	High environmental protection requirements, high purity + medium yield	18.2 mg/g	DES is free of volatile contaminants and achieves the highest purity, making it suitable for environmentally oriented production of high-purity raw materials.
Supercritical CO_2 extraction	High-end food/pharmaceutical raw materials, zero solvent residue	15–18 mg/g	High purity, with compound integrity reaching [value], moderate yield, and relatively high cost, only applicable to high-value-added applications requiring zero residue.

Table 4 | Selection basis and application scope of LyFs purification

Method	Scene	Purity	Yield	Selection criteria
Solvent extraction/ recrystallization	Preliminary purification, low-cost requirements	20%–30%	25%–28%	Simple operation, suitable for industrial pretreatment, but the purification efficiency is low
MAR	Industrial-scale purification, moderate purity requirements	40%–60%	32%–35%	High adsorption capacity (kg-scale raw materials), with a cost of only 1/10 that of chromatography
HPLC	Laboratory monomer separation and high-purity requirements	≥95%	10%–15%	Can isolate individual flavonoid monomers, but the preparation cost is high
Solvent flotation	High environmental requirements and medium purity demand	35%–45%	28%–32%	The amount of organic solvent used is only one-third of that in the extraction method, making it suitable for low-pollution processes.
Multi-stage cascade purification	Pharmaceutical-grade raw materials, ultra-high purity requirements	≥98%	8%–12%	The method of "solvent extraction-macroporous resin-silica gel chromatography" enables stepwise removal of impurities.

purification strategies include solvent extraction, recrystallization, chromatographic techniques, macroporous adsorption resin (MAR) methods, and solvent flotation (Table 4).

Solvent extraction & recrystallization. Solvent extraction and recrystallization are commonly employed as preliminary purification methods that rely on the differential solubility of flavonoids and co-extracted impurities. The approach is straightforward to implement and requires minimal specialized equipment. Zhang et al.[31] applied solvent extraction for the purification of LyFs and achieved a flavonoid purity of 24.39% with a yield of 27.28%. Although suitable for initial enrichment, the method is generally insufficient for the isolation of high-purity flavonoid fractions and is often used in combination with more selective techniques.

Chromatography. Chromatographic methods represent the most powerful tools for the separation, purification, and identification of individual LyFs. Commonly used chromatographic approaches include silica gel chromatography, polyamide chromatography, Sephadex LH-20 chromatography, and high-performance liquid chromatography (HPLC)[42,43]. Qi et al.[44] successfully isolated a novel flavonoid glucoside from *L. ruthenicum*. Despite their high separation efficiency, chromatographic methods are generally labor-intensive, solvent-consuming, and costly, which limits their applicability for large-scale industrial purification.

MAR. The adsorptive properties of MAR primarily rely on van der Waals forces and hydrogen bonding. By selecting an appropriate elution solvent based on the compound's adsorption affinity and molecular weight, this method achieves compound separation, purification, impurity removal,

Table 5 | LyFs extraction-purification technology combination recommendation scheme

Application target	Technology mix	Core advantage	Critical control parameter
Isolation and structural identification of laboratory monomers	Freeze-drying-Enzymatic extraction-HPLC	Purity ≥95%, with good compound integrity	Enzymatic hydrolysis temperature: 40 °C, HPLC mobile phase gradient elution
Industrial functional food ingredients	Hot air drying (50 °C)-Microwave extraction-Macroporous resin	yield ≥18 mg/g, low cost	Microwave power: 800 W; ethanol concentration of resin eluent: 70%
Environmentally friendly industrial production	Ultrasonic pretreatment-DES + UAE extraction-solvent flotation	Solvent residue <0.1%, yield 16 mg/g	DES system (choline-ethylene glycol), ultrasound power 150 W
Low-cost feed additive	Natural drying-solvent extraction-simple filtration	lowest cost, yield ≥10 mg/g	Ethanol concentration 60%, extraction temperature 60 °C

and concentration[45]. Liu et al.[46] demonstrated that MAR-based purification effectively enriched LyFs based on polarity and molecular size. Moreover, Zhang et al.[31] reported that, compared with conventional solvent extraction, MAR purification increased LyFs content by 19% and yield by 19.4%, highlighting its practical advantages for both laboratory and industrial applications.

Solvent flotation. Solvent flotation exploits differences in surface activity and hydrophobicity of compounds to achieve separation and enrichment, offering advantages such as high efficiency and low organic solvent consumption[47]. Gao et al.[48] and Chen[49] successfully applied solvent flotation for the purification of LyFs, demonstrating its potential for selective enrichment. Nevertheless, further optimization and scale-up studies are required to improve selectivity, process stability, and industrial feasibility.

Strategy selection summary

Overall, the development of LyFs extraction and purification technologies has gradually shifted from conventional solvent-based approaches toward integrated and environmentally friendly strategies. The selection of an optimal processing route depends on the intended application. For fundamental research and structural elucidation, high extraction yield and compound purity are of primary importance, whereas for industrial production, considerations such as process economy, scalability, operational simplicity, and environmental impact become increasingly critical. Increasing evidence suggests that the extraction, purification, structural characterization, and biological activity of LyFs are intrinsically interconnected rather than independent processes. Different extraction and purification strategies—including conventional solvent extraction, UAE, MAE, and enzymatic treatments—not only determine extraction efficiency but also profoundly influence the chemical composition, structural features, and bioactive profiles of LyFs.

For instance, conventional solvent extraction employing ethanol or methanol typically yields fractions enriched in flavonols such as quercetin, kaempferol, isorhamnetin, and their respective glycosides. In contrast, UAE and MAE demonstrate superior efficacy in generating aglycone-enriched fractions, with the latter additionally capable of producing anthocyanin-rich extracts from *L. ruthenicum*. Enzymatic treatments offer further refinement by modulating glycosylation patterns, thereby enabling selective enrichment of specific flavonoid glycosides, including rutin and hyperoside. Future investigations should prioritize the rational integration of complementary methodologies—such as combining UAE with deep eutectic solvents or coupling enzymatic pretreatment with assisted extraction techniques—to achieve synergistic enhancements in extraction efficiency while preserving the structural integrity and biological activity of LyFs. Table 5 systematically summarizes representative strategy selection options and their corresponding rationales across diverse application scenarios, providing a comprehensive framework for methodological optimization.

Physicochemical and structural features of LyFs

In wolfberry, a wide spectrum of LyFs has been characterized, including aglycones such as quercetin and kaempferol, their glycosylated derivatives (e.g., rutin and isoquercitrin), and ANCs in specific species such as *L. ruthenicum*[44,50]. The representative structures and reported bioactivities of major LyFs, including rutin, quercetin, hesperidin, and catechin, are summarized in Fig. 2 and Table 6. These structural variations directly determine physicochemical properties, including solubility, stability, and membrane permeability, and thereby influence biological activity.

The structure–activity relationships (SARs) among LyFs underscore the pivotal influence of substitution patterns on their biological and physicochemical properties. Quercetin, a prominent flavonoid, and its glycosides demonstrate exceptional antioxidant capabilities, primarily attributed to their efficient metal ion chelation and free-radical scavenging mechanisms[51]. These activities are critically dependent on the presence of specific hydroxyl groups, particularly the catechol moiety (3′,4′-dihydroxy) on the B ring, which facilitates electron delocalization and stabilization of radical intermediates. In contrast, kaempferol, lacking the 3′-hydroxyl group on the B ring, exhibits significantly diminished radical-scavenging activity, highlighting the structural determinants of redox efficiency. Similarly, isorhamnetin, a methylated derivative of quercetin, displays moderately attenuated antioxidant properties, suggesting that O-methylation may reduce redox potential by limiting hydrogen-donating capacity and altering steric accessibility to reactive oxygen species (ROS). Glycosylation, a common post-modification in flavonoid biosynthesis, profoundly influences the physicochemical behavior of these compounds. While glycosylated flavonoids such as rutin (quercetin-3-O-rutinoside) typically exhibit enhanced aqueous solubility and improved chemical stability due to the hydrophilic nature of sugar moieties, they often demonstrate reduced intestinal absorption efficiency compared to their aglycone counterparts. This phenomenon is primarily attributed to increased steric hindrance imposed by the glycosidic linkage, which impedes passive diffusion across lipid membranes, and lower membrane permeability resulting from augmented molecular polarity[52].

ANCs constitute a distinctive subclass of LyFs, characterized by their unique structural properties and bioactive potential. Among various botanical sources, *L. ruthenicum* has been identified as a particularly rich reservoir of these compounds, with delphinidin-3-O-glucoside and cyanidin-3-O-glucoside predominating its phytochemical profile. These ANCs are distinguished by the presence of multiple hydroxyl groups on their B-ring moieties, which confer exceptional radical-scavenging capabilities, thereby underscoring their significance as potent antioxidants. For example, petunidin-3-O-[rhamnopyranosyl-(trans-p-coumaroyl)]-5-O-[β-D-glucopyranoside], a specialized anthocyanin isolated from *L. ruthenicum*, has been demonstrated to exhibit pronounced antioxidant capacity, as evidenced by comprehensive in vitro and cellular assays[53]. The bioactivity and stability of ANCs are modulated by a spectrum of structural determinants, including the configuration of acyl groups, the nature of sugar substitutions, and the specific glycosylation patterns. Recent investigations have elucidated that trans acylation and increased glycosylation generally enhance both the stability and cellular antioxidant activity of these compounds, particularly in physiologically relevant cellular models[54].

Collectively, these structure-dependent physicochemical properties provide the molecular basis for the selective modulation of downstream signaling pathways by LyFs.

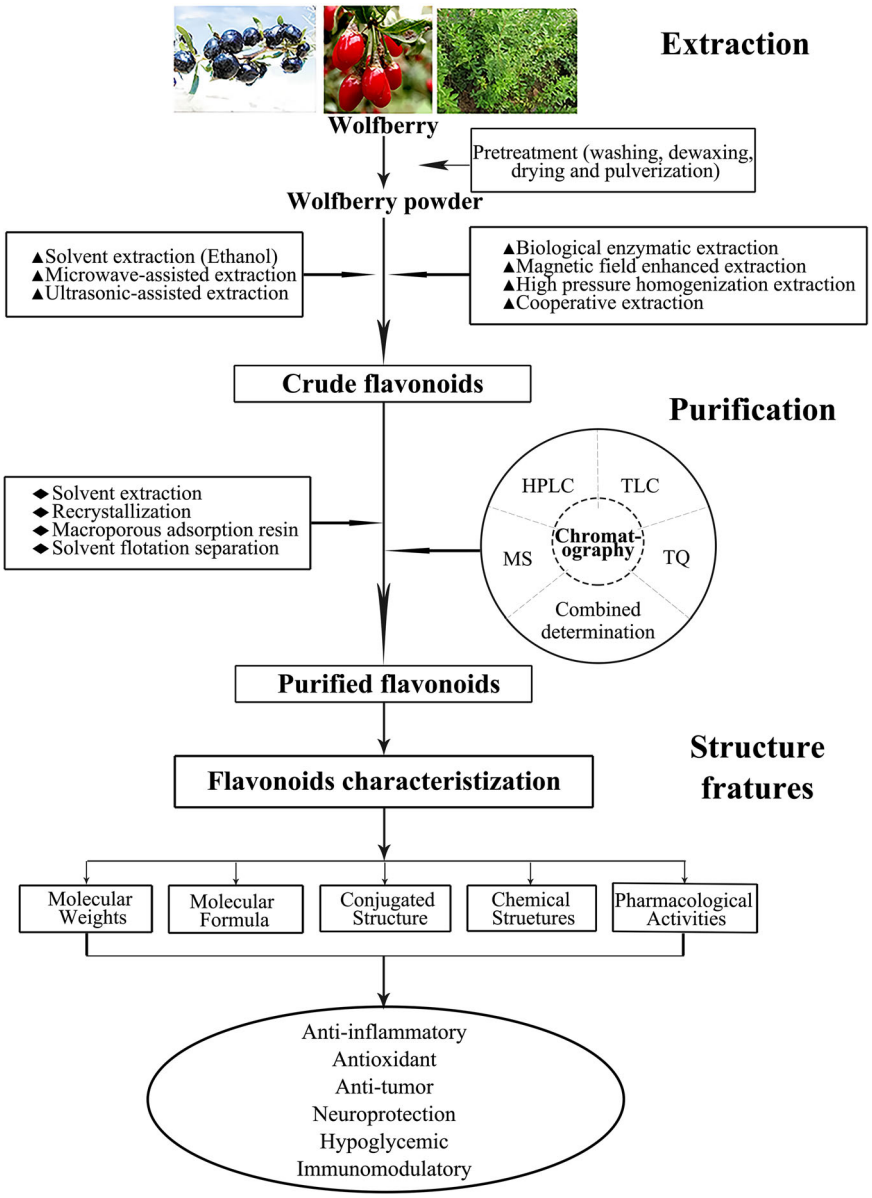

Fig. 1 | Schematic diagram of extraction, purification, structural features, and biological activities of LyFs. Created with Photoshop.

Signaling pathways associated with LyFs

Glycoside bond rupture under harsh extraction conditions, such as MAE, may lead to the degradation of flavonoid aglycones, thereby reducing their biological activity due to structural modification or oxidative degradation[55]. In biological systems, flavonoid aglycones generally exhibit higher bioactivity compared to their glycosylated counterparts, primarily owing to enhanced intestinal absorption and bioavailability. The diverse biological effects of LyFs are mediated through coordinated modulation of multiple cellular signaling pathways, enabling regulation of oxidative stress, inflammation, apoptosis, mitochondrial function, and metabolic homeostasis.

NF-κB signal transduction pathway

NF-κB is a central signaling pathway involved in the regulation of inflammation and oxidative stress[56]. Accumulating evidence suggests that LyFs may modulate NF-κB signaling, primarily by suppressing IκB phosphorylation and degradation, thereby inhibiting nuclear translocation of NF-κB subunits such as p65 and p50. Therefore, the expression of downstream pro-inflammatory mediators, including TNF-α, IL-6, IL-1β, COX-2, and adhesion molecules, is reduced. In addition, LyFs have been reported to indirectly influence NF-κB-related inflammatory responses through activation of short-chain fatty acid receptors (FFAR2, FFAR3, and GPR109A), highlighting a potential link between gut-derived metabolites and inflammatory signaling[57,58]. These mechanisms are summarized in Fig. 3. It should be noted that most mechanistic evidence is derived from in vitro studies, and further investigations are required to clarify the direct molecular targets of LyFs.

Keap1-Nrf2/ARE signal transduction pathway

The Keap1-Nrf2/ARE pathway represents a major cellular defense mechanism against oxidative stress. LyFs have been shown to modulate this pathway by interacting with Keap1, leading to stabilization and nuclear translocation of Nrf2. Activated Nrf2 subsequently binds to antioxidant response elements (AREs), inducing the transcription of cytoprotective genes such as NQO1, HO-1, GCLC, and GCLM[59,60]. Through activation of Nrf2 signaling, LyFs enhance cellular antioxidant capacity and reduce reactive oxygen species (ROS) accumulation. In addition, suppression of matrix metalloproteinase (MMP) expression has been reported, suggesting a protective role in maintaining skin barrier integrity[61]. These effects collectively support the involvement of LyFs in redox homeostasis (Fig. 4). Nevertheless, most available data originate from cellular models, and species-specific mechanisms in *Lycium* remain to be further validated.

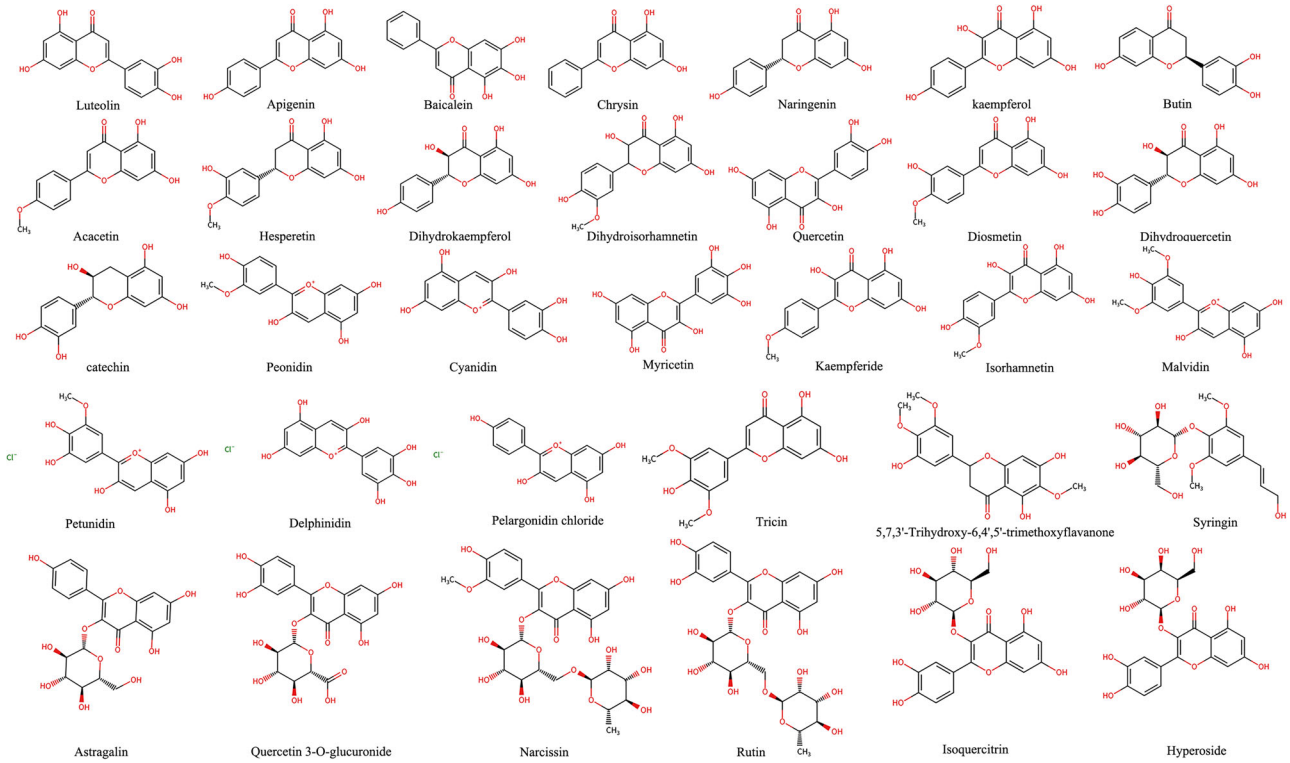

Fig. 2 | Structural characteristic map of LyFs. Created with Integle.

p38-MAPK signal transduction pathway

The p38-MAPK pathway is a key mediator of cellular responses to stress and inflammatory stimuli. LyFs have been reported to regulate p38-MAPK phosphorylation and activity, thereby influencing downstream processes related to inflammation, apoptosis, and stress resistance (Fig. 5). Representative flavonoids structurally identical to those identified in *Lycium* species, such as rutin and epigallocatechin-3-gallate, have demonstrated anti-inflammatory and antioxidant effects through modulation of MAPK signaling in cellular and model organism studies[51,62]. In addition, LyFs have been shown to upregulate stress-resistance genes (e.g., sod-2, gcs-1) and extend lifespan via MAPK-related pathways[63]. Furthermore, LyFs have been implicated in the alleviation of anxiety-like behaviors and protection against photoaging, effects that appear to be at least partly mediated by MAPK signaling[64]. However, direct molecular interactions between LyFs and MAPK components require further investigation.

PINK1/Parkin signal transduction pathway

The PINK1/Parkin pathway plays a critical role in mitochondrial quality control through regulation of mitophagy[65]. Emerging evidence indicates that LyFs, particularly ACNs can modulate this pathway by influencing PINK1 and Parkin expression levels. This regulation promotes the clearance of dysfunctional mitochondria and reduces excessive ROS generation[66]. By enhancing mitochondrial homeostasis, LyFs may contribute to neuroprotective effects and exhibit therapeutic potential against mitochondrial dysfunction-related disorders (Fig. 6). Nevertheless, current evidence is limited, and additional mechanistic studies are necessary to establish causality and specificity.

PI3K-Akt signal transduction pathway

The PI3K-Akt pathway is a major regulator of cell survival, proliferation, and metabolism[67]. LyFs have been reported to modulate this pathway by affecting the phosphorylation status of PI3K and Akt, thereby influencing downstream targets involved in apoptosis and oxidative stress responses. Notably, ACNs have been shown to inhibit PI3K/Akt signaling in cancer cell models, leading to cell cycle arrest and ROS-dependent apoptosis[68,69]. These findings suggest that LyFs may exert antitumor effects through targeted modulation of the PI3K-Akt axis (Fig. 7). However, most studies remain at the cellular level, and further investigations are required to evaluate in vivo relevance and translational potential.

Crosstalk among signaling pathways

Increasing evidence indicates that the biological effects of LyFs arise from coordinated regulation of multiple signaling pathways rather than isolated pathway modulation. Reciprocal interactions between the Nrf2 and NF-κB pathways have been widely reported in the context of oxidative stress and inflammation. Representative flavonoids identified in *Lycium* species, such as kaempferol, have been shown to activate Nrf2 signaling (e.g., upregulation of HO-1) while concomitantly suppressing NF-κB activation (e.g., downregulation of COX-2), thereby exerting synergistic antioxidant and anti-inflammatory effects[51,70]. In addition, crosstalk between the PI3K-Akt and p38-MAPK pathways has been implicated in the regulation of apoptosis and stress responses, suggesting that LyFs may influence cell fate decisions through coordinated pathway modulation[71]. Collectively, these observations support the concept that the multifaceted bioactivities of LyFs are mediated through their capacity to simultaneously target interconnected signaling networks. However, most current evidence is derived from reductionist models, and future studies integrating systems biology, network pharmacology, and multi-omics approaches will be essential to delineate pathway crosstalk and to better understand the holistic and multi-targeted nature of LyFs.

Interaction between LyFs and the intestinal ecosystem

The intestinal tract, particularly the gut microbiota and the intestinal epithelial barrier, represents a primary interface for interaction and biotransformation of dietary flavonoids. LyFs engage in a complex bidirectional interplay with this ecosystem, which is increasingly recognized as a critical determinant of their systemic health-promoting effects. Conceptually, this interaction follows a sequential cascade: LyFs are first metabolized by the gut microbiota, inducing microbial remodeling and the generation of key metabolites such as short-chain fatty acids (SCFAs); these metabolites

Table 6 | Structural characteristics and reported bioactivities of LyFs

Chemical name	Molecular formula	Molecular weight	IUPAC	Bioactivity
Luteolin	$C_{12}H_{10}O_6$	286.240	2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one	Anti-inflammatory, anti-tumor, antioxidant
Apigenin	$C_{12}H_{10}O_5$	270.240	5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one	Anti-inflammatory, antioxidant, anti-tumor
Hesperetin	$C_{16}H_{14}O_6$	302.280	(2S)-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-2,3-dihydrochromen-4-one	Antioxidant, anti-inflammatory, neuroprotection
Narcissin	$C_{28}H_{32}O_{16}$	624.500	5,7-dihydroxy-2-(4-hydroxy-3-methoxyphenyl)-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one	Anti-inflammatory, antioxidant, hypolipidemic
Baicalein	$C_{15}H_{10}O_5$	270.240	5,6,7-trihydroxy-2-phenylchromen-4-one	Anti-tumor, anti-inflammatory, anti-infection
Chrysin	$C_{15}H_{10}O_4$	254.240	5,7-dihydroxy-2-phenylchromen-4-one	Anti-tumor, neuroprotection, anti-inflammatory
Acacetin	$C_{16}H_{12}O_5$	284.260	5,7-dihydroxy-2-(4-methoxyphenyl)chromen-4-one	Anti-inflammatory, antioxidant, anti-tumor
Naringenin	$C_{15}H_{12}O_5$	272.250	(2S)-5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one	Anti-inflammatory, antioxidant, anti-tumor
Diosmetin	$C_{16}H_{12}O_6$	300.260	5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)chromen-4-one	Anti-tumor, anti-inflammatory, antioxidant
Rutin	$C_{27}H_{30}O_{16}$	610.500	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-[[(2R,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxymethyl]oxan-2-yl]oxychromen-4-one	Antioxidant, anti-inflammatory, anti-tumor
Quercetin	$C_{15}H_{10}O_7$	302.23	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	Antioxidant, antiobesity, antiviral
Hyperoside	$C_{21}H_{20}O_{12}$	464.400	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5R,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	Anti-inflammatory, analgesia, antiallergic
kaempferol	$C_{15}H_{10}O_6$	286.240	3,5,7-trihydroxy-2-(4-hydroxyphenyl)chromen-4-one	Antioxidant, anti-inflammatory, neuroprotection
Kaempferide	$C_{16}H_{12}O_6$	300.260	3,5,7-trihydroxy-2-(4-methoxyphenyl)chromen-4-one	Anti-inflammatory, anti-tumor, antioxidant
Isorhamnetin	$C_{16}H_{12}O_7$	316.260	3,5,7-trihydroxy-2-(4-hydroxy-3-methoxyphenyl)chromen-4-one	Cardiovascular and cerebrovascular protection, anti-tumor
Myricetin	$C_{15}H_{10}O_8$	318.230	3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one	Anti-inflammatory, analgesia, antioxidant
Tricin	$C_{17}H_{14}O_7$	330.290	5,7-dihydroxy-2-(4-hydroxy-3,5-dimethoxyphenyl)chromen-4-one	Antioxidant, anti-inflammatory, anti-tumor
Isoquercitrin	$C_{21}H_{20}O_{12}$	464.400	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	Anti-inflammatory, antioxidant, hypoglycemic
Astragalin	$C_{21}H_{20}O_{11}$	448.400	5,7-dihydroxy-2-(4-hydroxyphenyl)-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	Antioxidant, anti-inflammatory, neuroprotection
Cyanidin	$C_{15}H_{11}O_6^+$	287.240	2-(3,4-dihydroxyphenyl)chromenylium-3,5,7-triol	Antioxidant, anti-inflammatory, neuroprotection
Malvidin	$C_{17}H_{15}O_7^+$	331.300	2-(4-hydroxy-3,5-dimethoxyphenyl)chromenylium-3,5,7-triol	Anti-inflammatory, antioxidant
Peonidin	$C_{16}H_{13}O_6^+$	301.270	2-(4-hydroxy-3-methoxyphenyl)chromenylium-3,5,7-triol	Antioxidant, anti-inflammatory, neuroprotection
Petunidin	$C_{16}H_{13}ClO_7$	352.720	2-(3,4-dihydroxy-5-methoxyphenyl)chromenylium-3,5,7-triol	Anti-inflammatory, antioxidant
Delphinidin	$C_{15}H_{11}ClO_7$	338.690	2-(3,4,5-trihydroxyphenyl)chromenylium-3,5,7-triol	Anti-tumor, antioxidant, anti-inflammatory
Syringin	$C_{17}H_{24}O_9$	372.400	(2R,3S,4S,5R,6S)-2-(hydroxymethyl)-6-[4-[(E)-3-hydroxyprop-1-enyl]-2,6-dimethoxyphenoxy]oxane-3,4,5-triol	Anti-inflammatory, anti-tumor, brain-protective
Butin	$C_{15}H_{12}O_5$	272.250	(2S)-2-(3,4-dihydroxyphenyl)-7-hydroxy-2,3-dihydrochromen-4-one	Anti-inflammatory, antioxidant
Catechin	$C_{15}H_{14}O_6$	290.270	(2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol	Anti-tumor, antioxidant, anti-inflammatory

subsequently function as signaling mediators that reinforce intestinal barrier integrity and contribute to host immune-metabolic homeostasis.

Biotransformation by gut microbiota and microbial remodeling

Disruptions in the gut microbiota have been increasingly recognized as a critical factor in the pathogenesis and progression of numerous diseases, including but not limited to asthma, diabetes, non-alcoholic fatty liver disease, colitis, cancer, and Alzheimer's disease[72]. The intricate interplay between gut microbial homeostasis and host physiology underscores the potential of targeting this axis for therapeutic interventions. Among the various dietary components that influence gut microbial ecology, flavonoids —particularly the glycosylated forms of LyFs—have garnered significant attention due to their stability and bioactivity within the gastrointestinal tract. Following oral administration, LyFs, especially their glycosylated derivatives, exhibit remarkable stability in the upper gastrointestinal tract, a phenomenon attributed to the protective effects of the food matrix and plant cell wall components. This stability ensures that a substantial proportion of LyFs reaches the colon in either intact or partially transformed forms, where they serve as substrates for microbial metabolism. Specific bacterial taxa, such as *Bacteroides*, *Bifidobacterium*, and *Lactobacillus*, possess enzymatic machinery capable of hydrolyzing flavonoid glycosides, thereby releasing the aglycone moieties for further biotransformation. This process, termed gut microbiota–mediated flavonoid metabolism, culminates in the generation of a diverse array of low-molecular-weight phenolic metabolites, including but not limited to gallic acid, caffeic acid, and other phenolic acids[73,74]. These metabolites may also create a luminal environment that favors the proliferation of beneficial microbial populations.

In parallel, LyFs exert pronounced prebiotic-like effects, reshaping the microbial community structure. Dietary LyFs have been shown to selectively enrich beneficial genera, including Bifidobacterium, Lactobacillus, and the mucin-degrading genus Akkermansia[75,76]. A notable outcome of this remodeling is the attenuation of diet-induced dysbiosis, often reflected by a

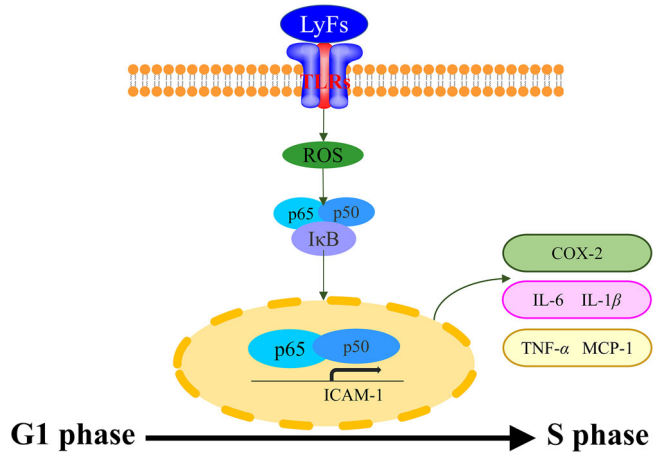

Fig. 3 | NF-κB signal transduction pathway. Created with Integle.

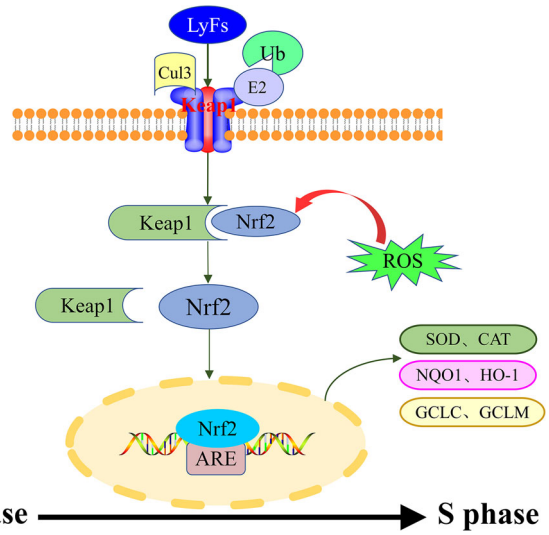

Fig. 4 | Keap1-Nrf2/ARE signal transduction pathway. Created with PowerPoint.

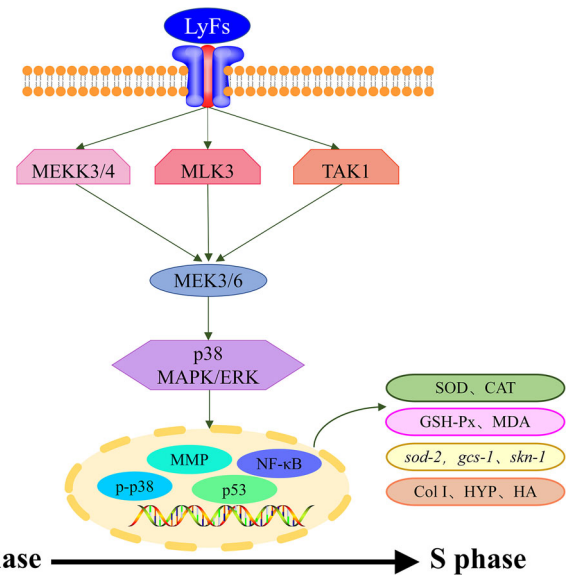

Fig. 5 | p38-MAPK signal transduction pathway. Created with PowerPoint.

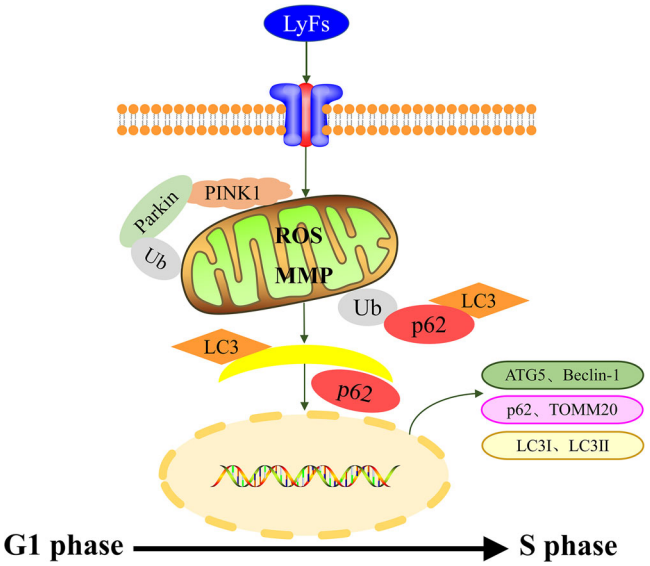

Fig. 6 | PINK1/Parkin signal transduction pathway. Created with PowerPoint.

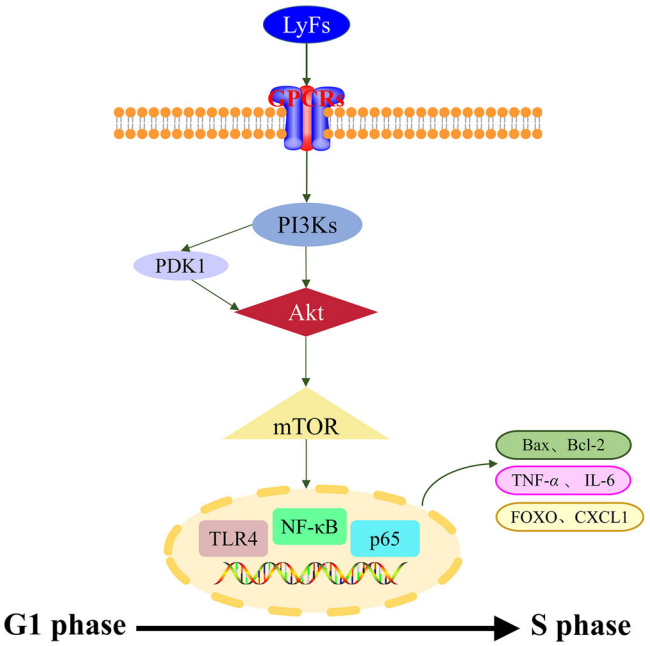

Fig. 7 | PI3K-Akt signal transduction pathway. Created with PowerPoint.

reduction in the Firmicutes/Bacteroidetes ratio, a microbial signature frequently associated with metabolic disorders[77–80].

Furthermore, LyFs exhibit a protective capacity against drug-induced dysbiosis[81]. Unlike conventional chemotherapeutic agents, which can damage gut microbiota, flavonoid compounds can counteract these shifts. They have been shown to reverse the proliferation of potentially harmful taxa (such as Ruminococcaceae and Desulfovibrionaceae) induced by cyclophosphamide and enhance the abundance of beneficial genera like *Faecalibaculum* and *Lactobacillus*[82]. Moreover, the abundance of these beneficial microbes has been positively correlated with immune parameters, including cytokines (IL-2 and IL-6) and immunoglobulins (IgA, IgG, SIgA), suggesting a functional link between LyFs-modulated microbiota and host immune regulation[83].

Collectively, shifts in dominant microbial phyla, particularly Bacteroidetes, Firmicutes, and Proteobacteria, serve as indicators of microbial ecological balance and are intricately linked to host metabolic and immune

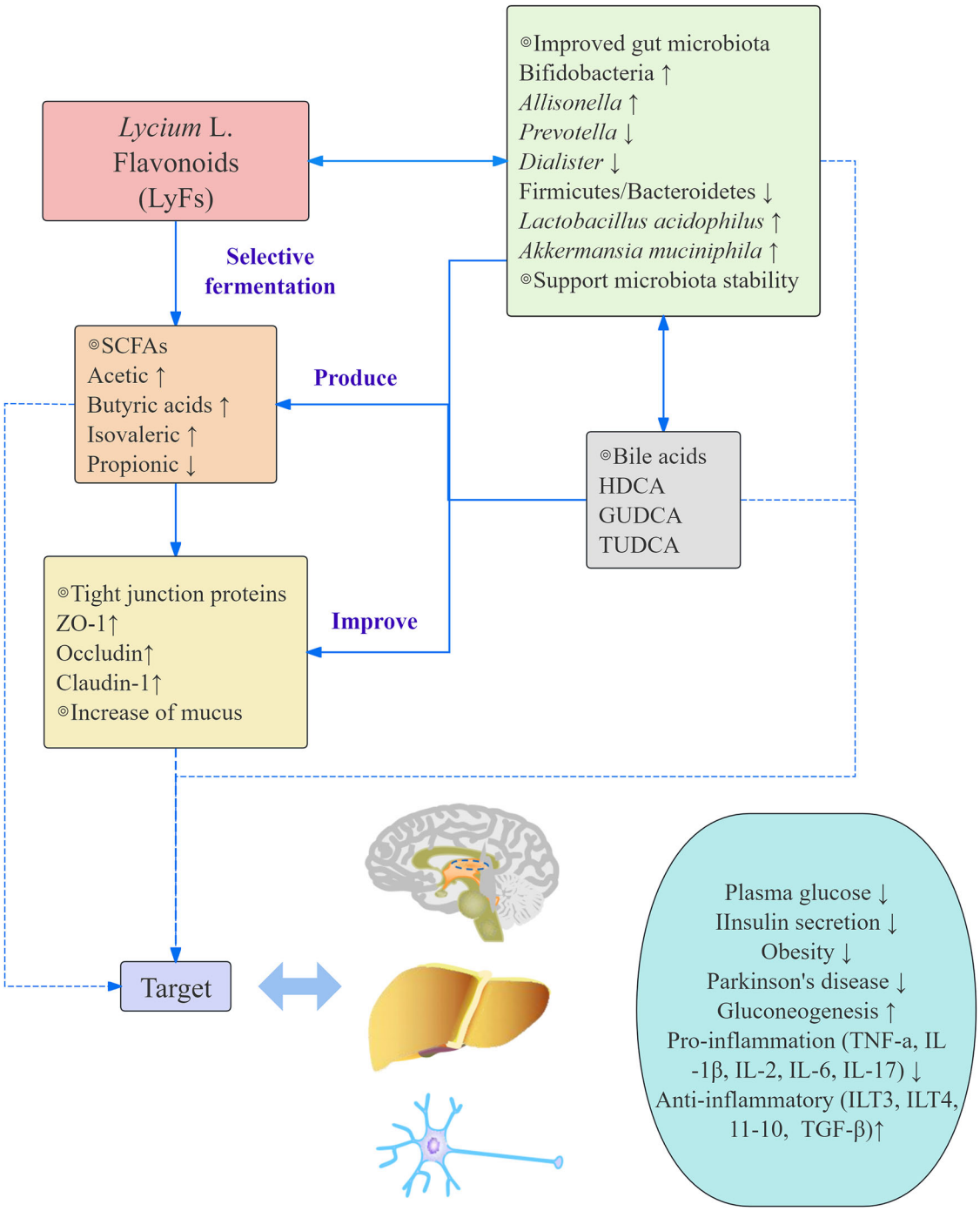

Fig. 8 | The interaction between LyFs and gut microbiota. Created with Photoshop.

status[84]. The dynamic interplay between LyFs and the gut microbiota is summarized in Fig. 8.

SCFAs-mediated reinforcement of the intestinal barrier

Microbial remodeling induced by LyFs culminates in a functional hallmark: enhanced production of SCFAs, primarily acetate, propionate, and butyrate. These metabolites are not merely microbial by-products but function as critical signaling molecules that mediate many of the local and systemic benefits attributed to LyFs[85].

Butyrate serves as a major energy source for colonocytes and plays a central role in maintaining epithelial integrity by promoting mucus secretion and strengthening tight junction architecture. These effects are mediated, at least in part, through activation of AMP-activated protein kinase (AMPK) signaling via FFAR3 engagement on intestinal epithelial cells. Acetate and propionate readily enter the portal circulation and influence host glucose metabolism, lipid homeostasis, and immune regulation[85].

Consistent with these mechanisms, ANCs have been reported to significantly elevate intestinal SCFA concentrations in high-fat-diet-fed mice, concomitantly alleviating insulin resistance and colonic inflammation[66,78]. Through SCFA signaling, LyFs-associated microbial remodeling has been mechanistically linked to reduced systemic inflammation, improved metabolic flexibility, and neuroprotective effects along the gut–brain axis[58,86]. Nevertheless, most current evidence remains correlative, and causal relationships require validation using germ-free or gnotobiotic animal models.

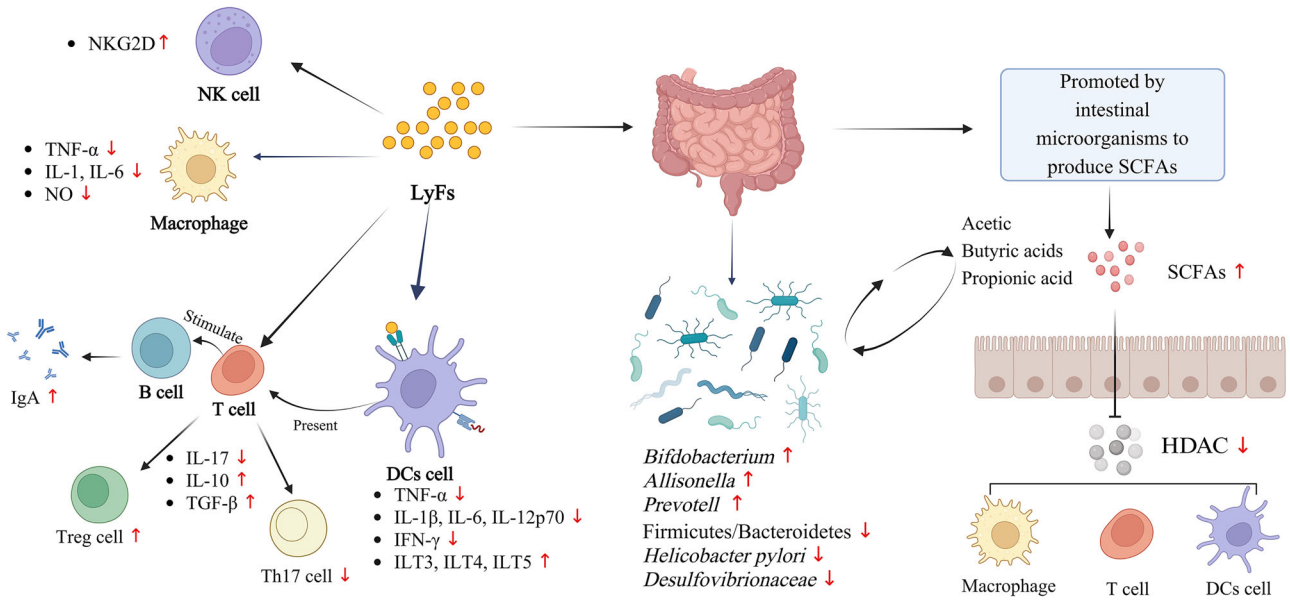

Fig. 9 | LyFs and SCFAs-mediated immune regulation and effects on intestinal microbes. Created with BioRender.com.

Reinforcement of the intestinal barrier

The ultimate functional consequence of LyFs-induced microbial remodeling and SCFA production is the reinforcement of the intestinal epithelial barrier, achieved through both direct and microbiota-dependent mechanisms.

Direct effects: LyFs have been shown to directly enhance barrier integrity by upregulating tight junction proteins, including zonula occludens-1 (ZO-1), occludin, and claudin-1, partially via activation of the PPAR-γ signaling pathway[87]. Strengthening of the tight junction complex reduces intestinal permeability and limits translocation of pro-inflammatory microbial components such as lipopolysaccharides into systemic circulation, thereby mitigating "leaky gut"–associated inflammation[88].

Microbiota-dependent effects: In parallel, LyFs indirectly support barrier function by fostering SCFA-producing microbial communities. SCFAs —particularly butyrate—have been well documented to enhance mucus secretion and reinforce tight junction protein expression, providing an additional layer of epithelial protection[89,90]. Together, these complementary mechanisms underscore the role of LyFs in maintaining intestinal homeostasis, which forms a critical foundation for systemic immune balance and inflammatory control (Fig. 9).

Conclusions and future perspective

This review systematically synthesizes current knowledge on *L.* flavonoids, spanning extraction strategies, structural characteristics, biological activities, and underlying molecular mechanisms. Despite substantial progress, several critical challenges remain. Notably, the identification of monomer-specific molecular targets is still incomplete, and the influence of processing and extraction methods on structure–activity relationships remain insufficiently characterized.

Current evidence on LyFs is largely derived from in vitro experiments and animal models, while human clinical data remains limited, typically involving small cohorts and short intervention periods. Consequently, the clinical relevance of many reported bioactivities has yet to be firmly established. In addition, insufficient understanding of synergistic or antagonistic interactions among minor flavonoid components and other bioactive constituents of wolfberry constrain a holistic evaluation of its health benefits. Variability in cultivation conditions, extraction procedures, and lack of standardized quality control further compromise comparability, reproducibility, and translational potential.

Future research should prioritize several interconnected directions to systematically advance the scientific understanding and practical application of LyFs:

(1) "Standardization and quality control": The establishment of validated, reproducible protocols for extraction, purification, and quantitative analysis is imperative to ensure batch-to-batch consistency and reliability. This includes the development of reference standards, harmonization of analytical methodologies (e.g., HPLC, LC-MS, and NMR), and implementation of Good Manufacturing Practices (GMP) to meet regulatory requirements.

(2) "Mechanistic and structure–activity relationship (SAR) studies": A paradigm shift from crude extracts to well-defined flavonoid monomers is necessary to elucidate the precise molecular mechanisms underlying their bioactivities. This should be complemented by integrative approaches, including multi-omics (genomics, transcriptomics, proteomics, metabolomics), artificial intelligence (AI)-driven predictive modeling, and advanced molecular biology techniques (e.g., CRISPR-Cas9 and gene editing) to uncover SARs and identify key structural determinants of efficacy.

(3) "Clinical translation and safety evaluation": Rigorously designed, large-scale human trials are essential to bridge the gap between preclinical findings and clinical applications. These studies should focus on determining optimal dosages, establishing safety margins, assessing long-term toxicity, and evaluating potential drug–nutrient interactions. Additionally, pharmacokinetic and pharmacodynamic profiling will be critical to ensure therapeutic efficacy and minimize adverse effects.

(4) "Application-oriented technological innovation": The development of advanced delivery systems (e.g., nanoparticles, liposomes and micelles) and formulation strategies (e.g., encapsulation and co-crystallization) is paramount to overcome the inherent limitations of flavonoids, such as poor bioavailability, low solubility, and instability. Innovations in food and pharmaceutical engineering will also facilitate the integration of LyFs into functional foods, nutraceuticals, and therapeutic agents with enhanced stability and bioavailability.

In summary, although LyFs possess a solid scientific foundation supporting their health-promoting potential, their successful translation from basic research to evidence-based applications requires coordinated, interdisciplinary advances across chemistry, biology, clinical medicine, and food and pharmaceutical engineering. Addressing these multifaceted challenges will be essential to fully unlock the therapeutic and commercial value of LyFs and to support the development of safe, effective, and sustainable natural health products. This integrated approach will not only advance the field of flavonoid research but also contribute to the broader goal of harnessing natural compounds for precision nutrition and preventive healthcare.

Data Availability

No datasets were generated or analysed during the current study.

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Author contributions

Tian Lan: Formal analysis, Investigation, Writing—original draft, Writing—review and editing. Kexin Zhou: Investigation, Writing—original draft. Guozhen Duan: Visualization, Writing—review and editing. Yuxin Zhang: Writing—original draft. Yonggui Ma: Writing—review and editing. Guanghui Fan: Writing—review and editing. Youchao Qi: Conceptualization, Supervision, Writing—review & editing.

Competing interests

The authors declare no competing interests.

Additional information

Correspondence and requests for materials should be addressed to Youchao Qi.