Acupuncture and Herbal Medicine

Poria cocos in traditional Chinese medicine: multifaceted insights

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Abstract

Poria cocos (Fu Ling), a traditional medicinal fungus with more than two millennia of documented use, occupies a central role in East Asian medical practice. This review systematically examines its historical development as recorded in classical materia medica, emphasizing the evolution of its medicinal sources and the specific fungal parts employed. The representative chemical constituents – namely triterpenoids and polysaccharides – are thoroughly summarized with regard to their structural types and distinguishing characteristics. Building on classical therapeutic indications such as promoting diuresis, strengthening the spleen, and calming the mind, recent research is reviewed to elucidate the expanded pharmacological profile of *P. cocos*. A particular focus is given to its antitumor effects, immunomodulatory activity, anti-obesity properties, mitigation of metabolic dysfunction-associated steatotic liver disease, and enhancement of intestinal barrier function. Current mainstream quality evaluation methodologies are outlined, followed by an in-depth discussion of the pharmacokinetics of its principal bioactive components, with special emphasis on the microbial fermentation of polysaccharides into short-chain fatty acids by the gut microbiota. The synergistic role of *P. cocos* in polyherbal formulations, exemplified by Sijunzi Decoction, is analyzed to highlight its compatibility-enhancing effects. Contemporary applications in modern pharmaceuticals and functional foods are also summarized. Finally, key challenges and prospective directions for future research and industrial development are addressed. This review aimed to provide a comprehensive reference for basic research, product innovation, and clinical utilization of *P. cocos*.

Keywords: *Poria cocos*, Triterpenoids, Polysaccharides, Pharmacological activity, Gut microbiota, Short-chain fatty acids, Pharmacokinetics

Graphical Abstract: https://links.lww.com/AHM/A199

Introduction

Poria cocos, the dried sclerotium of the fungus *Poria cocos* (family Polyporaceae, *P. cocos*), is one of the most important medicinal and edible homologous materials in traditional Chinese medicine (TCM)[1]. First documented as a "superior-grade" herb in the *Divine Farmer's Classic of Materia Medica*, it has been extensively referenced in classical materia medica texts across successive dynasties, underscoring its long-standing clinical significance. Characterized by a neutral property and a sweet, bland taste, *P. cocos* is believed to enter the heart, spleen, lung, and kidney meridians. Traditionally, it promotes diuresis and dampness elimination, strengthens the spleen, and calms the mind. Clinically, it is widely used to treat syndromes such as spleen deficiency with excessive dampness, restlessness of the spirit, edema, and dysuria. Often referred to as the "divine medicine for all seasons," *P. cocos* features prominently in numerous classical prescriptions, including Sijunzi decoction, Linggui Zhugan decoction, and Fuling Zexie decoction[2–3] In recent years, advances in modern pharmacology and phytochemistry have gradually elucidated the bioactive constituents, mechanisms of action, and extensive pharmacological activities of *P. cocos*. Notably, its potential has been highlighted in antitumor therapy, immune modulation, anti-obesity interventions, prevention and treatment of metabolic dysfunction-associated steatotic liver disease (MASLD), and enhancement of intestinal barrier function.

As a high-demand medicinal material, *P. cocos* has attracted increasing scholarly attention. Existing reviews have primarily focused on its chemical composition, pharmacological effects, and general applications[2,4–5].

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Building on a comprehensive analysis of both classical and modern materia medica literature from CNKI (China National Knowledge Infrastructure), PubMed, and SCI, to screen recent studies related to Poria cocos, this review aims to systematically summarize the historical evolution of its botanical origin and medicinal parts, characterize the structural types and representative monomers of its major chemical constituents – namely triterpenoids and polysaccharides – and explore its modern pharmacological developments grounded in traditional therapeutic functions. Furthermore, this review outlines current quality control methods and indicators, elucidates the pharmacokinetic (PK) characteristics of key bioactive components, and discusses their metabolic interactions with the gut microbiota. The synergistic and potentiating roles of *P. cocos* in classical polyherbal formulations, exemplified by Sijunzi Decoction, are also examined. Finally, this review provided an overview of its development and application in pharmaceuticals and functional foods, identifies current research hotspots and existing challenges, and proposes future directions for in-depth exploration. Overall, this work provided a systematic reference and theoretical basis for foundational research, clinical application, and industrial development of *P. cocos*.

Historical evolution of *P. cocos* in classical materia medica

Origins and historical perceptions of P. cocos

Since antiquity, *P. cocos* has been regarded as closely associated with pine trees, a view consistently documented in classical Chinese materia medica. In the *Divine Farmer's Classic of Materia Medica* from the Qin and Han dynasties, it was referred to as "Fu Tu," echoing the adage "Fu Ling below, Tu Si above" (ie, *P. cocos* below, *Cuscuta* above). In the records of the *Grand Historian* (Shiji), it was described as a product of "millennium-old pine roots," believed to bestow longevity when consumed.

In the Ming and Qing dynasties, authoritative pharmacopoeias, such as *Compendium of Materia Medica*, emphasized that *P. cocos* was a spiritual condensation of pine energy. Synthesizing these accounts, ancient sources generally posited that *P. cocos* formed through a convergence of pine resin, pine spirit, and pine roots.

Modern scientific research has established that *P. cocos* is a wood-decay fungus (eg, *Wolfiporia cocos*) whose mycelia parasitize decaying pinewood, degrading cellulose and hemicellulose to produce sclerotia – commercially referred to as "Song Fu Ling." Interestingly, when pine root segments are enclosed within the sclerotium during growth, the resulting product is called Poria cum Radix Pini (*Fu Shen*), which is considered pharmacologically distinct. Currently, *P. cocos* is predominantly cultivated: after the mycelium is cultured, it is inoculated into pinewood through artificial log cultivation or simulated wild-cultivation methods, yielding various commercial forms such as Fu Ling cubes, slices, rolls, and Fu Shen[6] (Figure 1).

Although ancient interpretations of the origin of *P. cocos* contain elements of mysticism, they are broadly consistent with the modern scientific understanding of its ecological niche and biological characteristics. However, discrepancies in its Latin nomenclature persist internationally. Standardizing its scientific name is therefore crucial for academic consistency and global coordination. In biological taxonomy, *Wolfiporia cocos* (Schwein.) Ryvarden & Gilb. is widely accepted, whereas in TCM and the pharmaceutical industry, *P. cocos* is commonly used as the official name.

Evolution of medicinal parts of P. cocos

Traditionally, based on morphological features and harvesting positions, *P. cocos* has been divided into four distinct medicinal parts arranged from the outer to the inner layer: Poriae Cutis (*Fu Ling Pi*), Rubra Poria (*Chi Fu Ling*), White Poria (*Bai Fu Ling*), and Poria cum Radix Pini (*Fu Shen*) (Figure 2). These subtypes differ in color, texture, and phytochemical composition, which contribute to their varying pharmacological effects and clinical applications.

Clinically, the different parts of *P. cocos* are utilized for their distinct therapeutic properties. Poriae Cutis is primarily used to promote urination and alleviate edema, whereas White Poria is widely used for its spleen-tonifying and tranquilizing effects. Rubra Poria is indicated for clearing damp-heat and tonifying the heart and lungs, and Poria cum Radix Pini (*Fu Shen*) is particularly effective in nourishing the heart and calming the mind. These differentiated applications reflect the diverse pharmacological functions attributed to each part of the *P. cocos* fungus in traditional clinical practice. Historical textual analysis indicates that prior to the Eastern Han dynasty, *P. cocos* was used as a unified medicinal entity. By the Eastern Han period, records of prescriptions containing Poriae Cutis emerged. During the Eastern Jin dynasty, a clear distinction between Poria (*Fu Ling*) and Poria cum Radix Pini (*Fu Shen*) began to appear. The Tang and Song dynasties further differentiated the medicinal effects of White Poria and Rubra Poria, and the Tang literature also referenced "*Fu Shen Mu,*" reflecting the evolving and increasingly refined understanding of the medicinal parts of *P. cocos*.

Modern pharmacological and phytochemical studies have validated many of these traditional distinctions, lending scientific support to their differentiated clinical use. Notably, the 2025 edition of the *Pharmacopoeia of the People's Republic of China* officially includes only White Poria and Poriae Cutis as standard medicinal materials. Rubra Poria and Poria cum Radix Pini are not formally listed, leaving their use largely empirical or confined to compound prescriptions. Further systematic research and standardization efforts are required to promote the rational and regulated utilization of these valuable medicinal resources.

Chemical constituents of *P. cocos*

Triterpenoids

With advances in analytical chemistry and natural product isolation techniques[7], increasing attention has been directed toward characterizing the chemical constituents of *P. cocos*[8]. Triterpenoids constitute one of the major

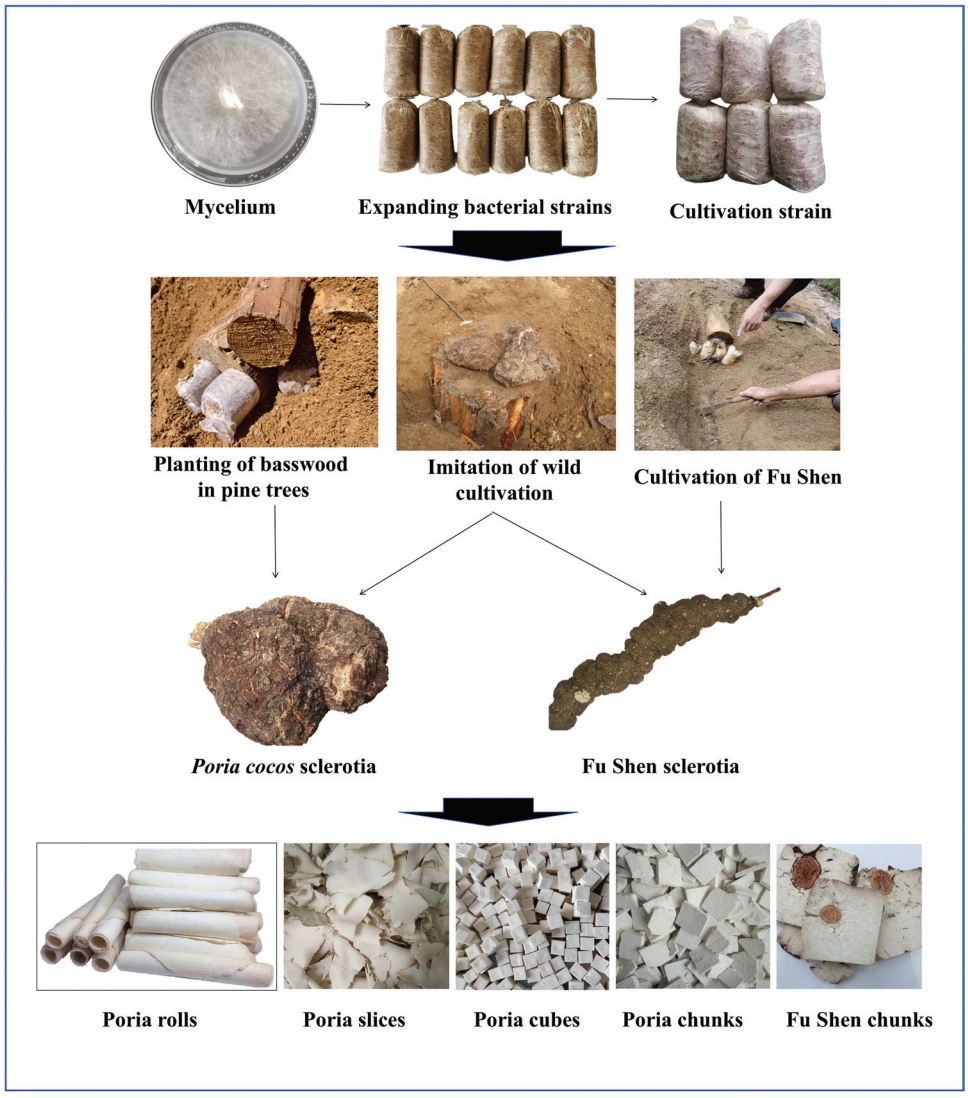


Figure 1. Formation and commercial specifications of *P. cocos*.

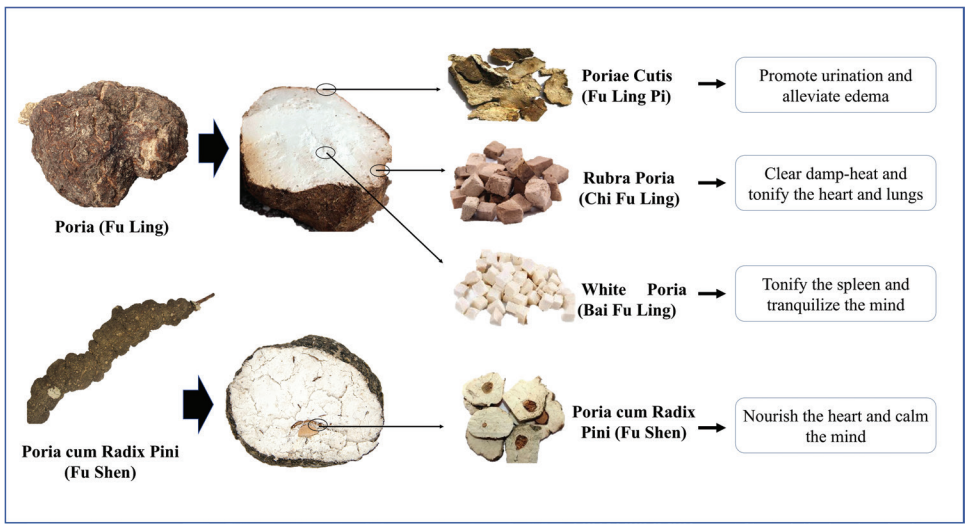


Figure 2. The efficacy and description of different medicinal parts of *P. cocos*.

classes of bioactive compounds in *P. cocos*. To date, more than 100 triterpenoids have been isolated, most of which possess tetracyclic lanostane-type skeletons. These tetracyclic triterpenes are structurally categorized into four main types, all derived from the parent lanostane skeleton: lanosta-8-ene, lanosta-7,9(11)-diene, 3,4-secolanosta-8-ene, and 3,4-secolanosa-7,9(11)-diene. This classification reflects variations in the degree of

unsaturation and cleavage within the lanostane core, thereby contributing to the structural diversity and potential bioactivity. Table 1 summarizes the representative core structures and typical compounds. Beyond these major categories, several structurally unique triterpenoids have also been identified in *P. cocos*, including daedaleanic acids D, E, and F, as well as 5α,8α-peroxydehydrotumulosic acid, among others[25–26,30].

Polysaccharides

Based on their structural characteristics, *Poria cocos* polysaccharides can be classified into two main categories. The first is β-pachyman, which primarily consists of β-(1→3)-D-glucan with limited (1→6) and (1→2) branching and has a molecular weight of approximately 50 to 652 kDa. The second category comprises heteropolysaccharides composed mainly of glucose, and potentially including monosaccharides such as arabinose, fucose, xylose, mannose, and galactose, with molecular weights ranging from 9 to 243 kDa. Polysaccharides of *P. cocos* (PCP) are also divided into water-soluble (WPCP) and alkali-soluble (APCP) fractions based on solubility. WPCPs primarily include (1→6)-α-galactan and (1→3)-β-mannan-glucan structures, whereas APCPs are characterized by a (1→3)-β-D-glucan backbone[5,31]. Numerous polysaccharide fractions have been isolated from *P. cocos*, including PCP-1C, PCP-W1, PCM3, PC3, PC4, PCS3-II, ab-PCM3-II, ab-PCM4-I, ab-PCM4-II, PCS4-I, PCS4-II, PCSG, PPSW-1, PCM1, PCM2, PC1, PC2, PC2-A, ab-PCM0, ab-PCM1-I, ab-PCM2-I, ab-PCM2-II, ab-PCM3-I, PCS1, PCS2, PCS3-I, Pi-PCM0, Pi-PCM1, Pi-PCM2, PCP-I, PCP-II, PCWPS, and PCWPW (Table 2)[32–38,40–41]. Future research on WPCP should focus on elucidating their primary structural features, whereas studies on APCP should emphasize the structure–activity relationships. These efforts will help provide a scientific basis for the comprehensive development and utilization of this traditional medicinal fungus[31].

Sterols

Although sterols are present in *P. cocos* in relatively low amounts, they are of considerable pharmacological interest, particularly the ergosterol-type phytosterols. Identified sterols include a range of compounds such as ergosta-7,22-dien-3β-ol, cerevisterol, ergosta-7-en-3β-ol, pregn-7-ene-2β,3α,15α,20(S)-tetrol, ergosta-5,7,22-trien-3β-ol, 3β,5α-dihydroxyergosta-7,22-dien-6-one, stigmasterol, ergosta-4,22-dien-3-one, ergosta-5,6-epoxy-7,22-dien-3-ol, ergosta-4,6,8(14),22-tetraen-3-one, β-sitosterol, and β-daucosterol, among others (Table 3)[12,20–21,43]. Given that phytosterols are known for their anticancer and cardiovascular-protective effects, the sterol constituents of *P. cocos* warrant further pharmacological investigation.

Volatile components

Although volatile oils are present in *P. cocos* at low concentrations, they exhibit a considerable compositional diversity. Using organic solvent–water steam distillation, researchers have identified various volatile constituents, including aliphatic compounds, terpenes, and aromatic compounds. Reported volatiles include 1-octen-3-ol, trans-2-nonenal, terpinen-4-ol, n-heptanal, trans-2-octenal, benzaldehyde, camphor, borneol, neoisomenthol, nonylphenol, hexanal, nonanoic acid, 2-undecanone, T-muurolol, ylangene, α-cadinol, δ-cadinene, δ-longifolene, torreyol, nerolidol, α-calacorene, valencene, α-muurolene, (+)-aromadendrene, alloaromadendrene, among others[44–46]

Proteins and amino acids

As both a medicinal and edible fungus, *P. cocos* contains substantial levels of proteins and amino acids, which contribute to its nutritional value and potential functional activity. Hu et al.[47] isolated proteins from *P. cocos* fermentation broth and identified several enzymes such as catalase, mannitol dehydrogenase, protein kinase, amylase, and lysozyme *via* mass spectrometry. Multiple amino acids have also been identified, including aspartic acid, glutamic acid, serine, glycine, histidine, arginine, threonine, alanine, proline, tyrosine, valine, methionine, isoleucine, leucine, phenylalanine, and lysine[48].

Other compounds

In addition to the aforementioned constituents, Hu et al.[49] reported the isolation of several other compounds from *P. cocos*, including L-uridine, ethyl-β-D-pyranoglucoside, trimethyl citrate, and (R)-dimethyl malate. Other minor components include 7-oxo-15-hydroxydehydroabietic acid, hesperidin, protocatechuic acid, di-(2-ethylhexyl) phthalate, dibutyl phthalate, octadecanoic acid, octacosanoic acid, and pentacosanoic acid, along with trace elements – predominantly potassium[49–50].

Although numerous chemical constituents of *P. cocos* have been identified, their characterization largely relies on current analytical instrumentation technologies. With continuous advancements in detection methodologies, future research may uncover additional components. Nonetheless, whether these identified substances represent the true bioactive constituents of *P. cocos* remains uncertain and warrants further investigation through comprehensive, multidisciplinary approaches.

Pharmacological activities

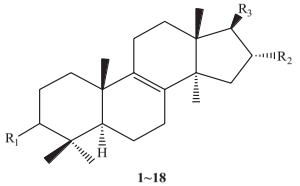
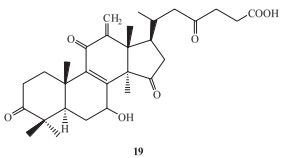
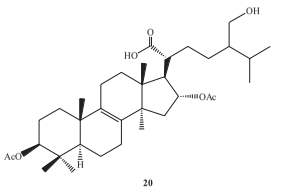
Pharmacological activities based on traditional functions

Diuretic and dampness-eliminating effects

P. cocos has long been used in TCM for its efficacy in promoting diuresis and resolving dampness, particularly in the treatment of dysuria and edema. Modern pharmacological investigations have revealed that its diuretic effects are primarily mediated through the modulation of aquaporins and renal ion transport mechanisms. For example, a water extract of Poriae Cutis was shown to downregulate both mRNA and protein expression of aquaporin-2 (AQP2), reduce urinary AQP2 excretion, and inhibit the expression of plasma arginine vasopressin and its receptor V2R, thereby alleviating urine retention and improving cardiac

Table 1

Classification of triterpenoids in P. cocos

Category	Number	Compound	structure	Reference
Lanosta-8-en	1	Pachymic acid	 1~18	R_1=OAc, R_2=OH, R_3=a	[9]
	2	Tumulosic acid		R_1=OH, R_2=OH, R_3=a	[9]
	3	25-Hydroxypachymic acid		R_1=OAc, R_2=OH, R_3=h	[9]
	4	Eburicoic acid		R_1=OH, R_2=H, R_3=a	[10]
	5	Pachymic acid methyl ester		R_1=OAc, R_2=OH, R_3=b	[10]
	6	25-Hydroxy-3-epitumulosic acid		R_1=α-OH, R_2=OH, R_3=c	[11]
	7	16α-Hydroxyeburicoic acid		R_1=O, R_2=OH, R_3=a	[11]
	8	16α,25-Dihydroxyeburicoic acid		R_1=O, R_2=OH, R_3=c	[11]
	9	Acetyleburicoic acid		R_1=OAc, R_2=H, R_3=a	[12]
	10	3-O-formyleburicoic acid		R_1=COOH, R_2=OH, R_3=a	[13]
	11	3-O-acetyl-16α-hydroxytrametenolic acid		R_1=OAc, R_2=OH, R_3=b	[13]
	12	O-acetylpachymic acid		R_1=OAc, R_2=OAc, R_3=a	[14]
	13	O-acetylpachymic acid methyl ester		R_1=OAc, R_2=OAc, R_3=b	[14]
	14	Pinicolic acid A		R_1=O, R_2=H, R_3=b	[15]
	15	3-Acetoxy-16α,26-dihydroxy-lanosta-8,24-dien-21-oic acid		R_1=OAc, R_2=OH, R_3=f	[15]
	16	3α,16α,26-Trihydroxylanosta-8,24-dien-21-oic acid		R_1=OH, R_2=OH, R_3=f	[16]
	17	16α-Hydroxytrametenolic acid		R_1=OH, R_2=OH, R_3=b	[17]
	18	Trametenolic acid		R_1=OH, R_2=H, R_3=b	[18]
	19	Ganoderic acid	 19		[14]
	20	O-acetylpachymic acid-25-ol	 20		[14]

(Continued)

Table 1

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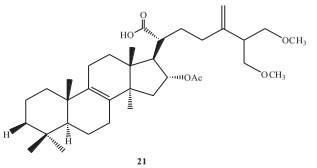
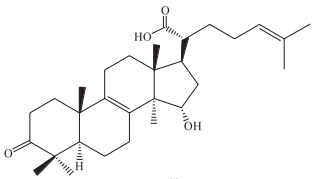
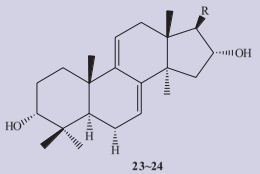
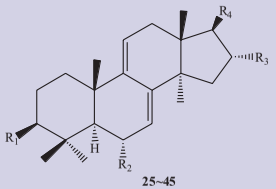
Category	Number	Compound	structure	Reference
	21	16α-Acetoxy-26,27-dimethoxyl-lanosta-8,24(31)-dien-21-oic acid		[15]
	22	15α-Hydroxy-3-oxolanosta-8,24-dien-21-oic acid		[16]
Lanosta-7,9(11) diene	23	3-Epi-dehydrotumulosic acid		R=a [9]
	24	25-Hydroxy-3-epi-dehydrotumulosic acid		R=c [11]
	25	Dehydropachymic acid		R_1=OAc, R_2=H, R_3=OH, R_4=a [9]
	26	Polyporenic acid C		R_1=O, R_2=H, R_3=OH, R_4=a [9]
	27	6α-Hydroxypolyporenic acid C		R_1=O, R_2=OH, R_3=OH, R_4=a [9]
	28	Dehydroeburicoic acid		R_1=OH, R_2=H, R_3=H, R_4=a [10]
	29	16α,27-Dihydroxydehydrotrametenoic acid		R_1=OH, R_2=H, R_3=OH, R_4=f [11]
	30	3-O-formyldehydrotrametenolic acid		R_1=COOH, R_2=H, R_3=H, R_4=b [13]
	31	Dehydrotrametenonic acid		R_1=O, R_2=H, R_3=H, R_4=b [13]
	32	Dehydrotrametenolic acid		R_1=OH, R_2=H, R_3=H, R_4=b [13]
	33	25-Hydroxypolyporenic acid C		R_1=O, R_2=H, R_3=OH, R_4=c [15]
	34	3β-Acetoxy-lanosta-7,9(11),24(31)-trien-21-oic acid		R_1=OAc, R_2=H, R_3=H, R_4=a [15]
	35	Lanosta-7,9(11),24(31)-trien-21-oic acid		R_1=H, R_2=H, R_3=H, R_4=a [15]
	36	3β,26-Dihydroxy-lanosta-7,9(11),24-trien-21-oic acid		R_1=OH, R_2=H, R_3=H, R_4=f [15]

(Continued)

Table1

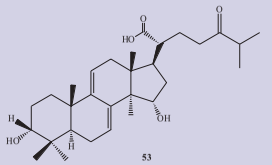
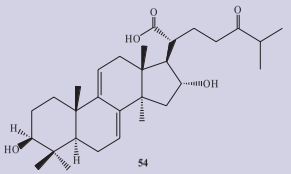
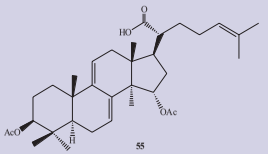
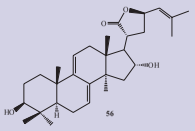
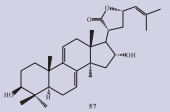
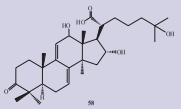
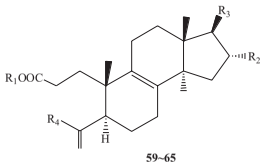
(Continued)

Category	Number	Compound	structure	Reference
	37	3-O-acetyl-16α-hydroxy-dehydrotrametenolic acid	R_1=OAc, R_2=H, R_3=OH, R_4=b	[16]
	38	3β-Hydroxy-16α-acetoxy-lanosta-7,9(11),24-trien-21-oic acid	R_1=OH, R_2=H, R_3=OAc, R_4=b	[16]
	39	16α-Hydroxydehydrotrametenolic acid	R_1=OH, R_2=H, R_3=OH, R_4=b	[16]
	40	Dehydrotumulosic acid	R_1=OH, R_2=H, R_3=OH, R_4=a	[16]
	41	16α-Acetyloxy-24-methylene-3-oxolanosta-7,9(11)-dien-21-oic acid	R_1=O, R_2=H, R_3=OAc, R_4=a	[16]
	42	Dehydroeburiconic acid	R_1=O, R_2=H, R_3=H, R_4=a	[19]
	43	3β-p-Hydroxybenzoyldehydrotumulosic acid	R_1=p-OHC$_6$H$_4$CO,R_2=H, R_3=OH, R_4=a	[20]
	44	6α-Hydroxydehydrotumulosic acid	R_1=OH, R_2=OH, R_3=OH, R_4=a	[21]
	45	6α-Hydroxydehydropachymic acid	R_1=OAc, R_2=OH, R_3=OH, R_4=a	[18]
	46	3-Epi-dehydropachymic acid	R_1=α-OAc, R_2=H, R_3=OH, R_4=a	[20]
	47	29α-Hydroxydehydropachymic acid	R=OH	[20]
	48	29-Hydroxypolyporenic acid C	R=O	[22]
	49	29α-Hydroxydehydrotumulosic acid	R=OAc	[16]
	50	Dehydroeburicoic acid methyl ester		[23]
	51	3β,15α-Dihydroxylanosta-7,9(11),24-trien-21-oic acid		[17]
	52	3α,16α-dihydroxy-24-oxo-lanosta-7,9(11)-dien-21-oic acid (Poriacosones A)		[22]

(Continued)

Table1

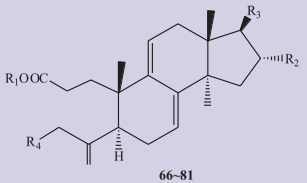
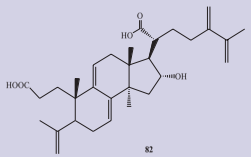
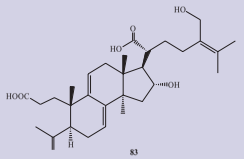
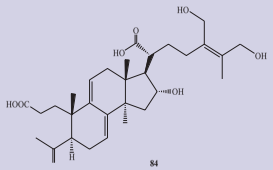
(Continued)

Category	Number	Compound	structure	Reference
	53	3α,16α-dihydroxy-24-oxo-lanosta-7,9(11)-dien-21-oic acid (Poriacosones B)		[22]
	54	3,15-Diacetyl-dehydrotrametenolic acid		[24]
	55	15α-Hydroxydehydrotumulosic acid		[16]
	56	Porilactone A		[24]
	57	Porilactone B		[24]
	58	Pinicolic acid F		[24]
3,4-secolanosta-8-ene	59	Poricoic acid G		R_1=H, R_2=OH, R_3=b, R_4=H	[11]
	60	Poricoic acid GM		R_1=CH_3, R_2=OH, R_3=b, R_4=H	[11]
	61	Poricoic acid H		R_1=H, R_2=OH, R_3=a, R_4=H	[11]
	62	Poricoic acid HM		R_1=CH_3, R_2=OH, R_3=a, R_4=H	[11]
	63	26-Hydroxyporicoic acid G		R_1=H, R_2=OH, R_3=f, R_4=H	[15]
	64	25-Hydroxyporicoic acid H		R_1=H, R_2=OH, R_3=c, R_4=H	[25]
	65	Poricoic acid GE		R_1=C_2H_5, R_2=OH, R_3=b, R_4=H	[17]

(Continued)

Table1

(Continued)

Category	Number	Compound	structure	Reference
3,4-secolanosta-7,9(11)-diene	66	Poricoic acid A	 66~81	R_1=H, R_2=OH, R_3=a, R_4=H	[11]
	67	Poricoic acid AM		R_1=Me, R_2=OH, R_3=a, R_4=H	[11]
	68	25-Methoxyporicoic acid A		R_1=H, R_2=OH, R_3=d, R_4=H	[11]
	69	Poricoic acid B		R_1=H, R_2=OH, R_3=b, R_4=H	[11]
	70	25-Hydroxyporicoic acid C		R_1=H, R_2=H, R_3=c, R_4=H	[11]
	71	Poricoic acid DM		R_1=Me, R_2=OH, R_3=c, R_4=H	[11]
	72	26-Hydroxyporicoic acid DM		R_1=Me, R_2=OH, R_3=e, R_4=H	[11]
	73	Poricoic acid C		R_1=H, R_2=H, R_3=a, R_4=H	[16]
	74	16-Deoxyporicoic acid B		R_1=H, R_2=H, R_3=b, R_4=H	[25]
	75	Poricoic acid CM		R_1=Me, R_2=H, R_3=a, R_4=H	[25]
	76	Poricoic acid D		R_1=H, R_2=OH, R_3=c, R_4=H	[25]
	77	Poricoic acid AE		R_1=C_2H_5, R_2=OH, R_3=a, R_4=H	[17]
	78	Poricoic acid L		R_1=H, R_2=OH, R_3=e, R_4=H	[26]
	79	Poricoic acid BM		R_1=Me, R_2=OH, R_3=b, R_4=H	[17]
	80	Poricoic acid E		R_1=H, R_2=OH, R_3=f, R_4=H	[17]
	81	Poricoic acid F		R_1=H, R_2=OH, R_3=a, R_4=OH	[17]
	82	16α-Hydroxy-3,4-secolanosta-4(28),7,11(9),24(31),25(27)-pentaene-3,21-dioic acid	 82		[17]
	83	Poricoic acid I	 83		[24]
	84	Poricoic acid J	 84		[24]

(Continued)

Table1

(Continued)

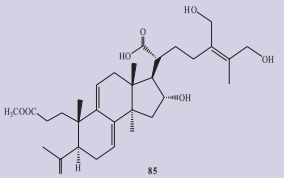
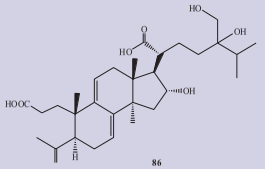
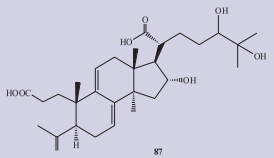
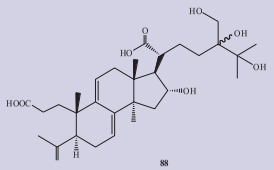
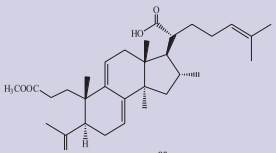
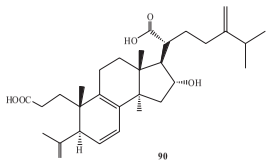
Category	Number	Compound	structure	Reference
	85	Poricoic acid JM		[24]
	86	Poricoic acid K		[24]
	87	Poricoic acid M		[24]
	88	Poricoic acid N		[24]
	89	16-Deoxyporicoic acid BM		[24]
other triterpenoid	90	6,7-Dehydroporicoic acid H		[11]

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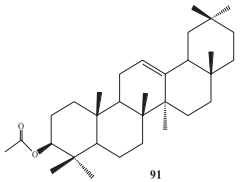
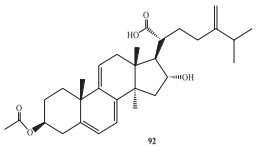
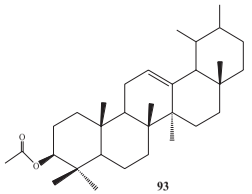
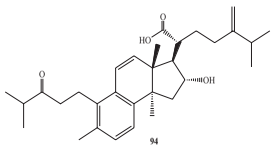
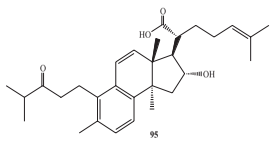
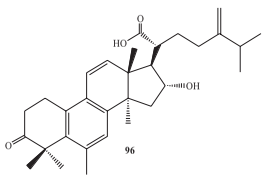
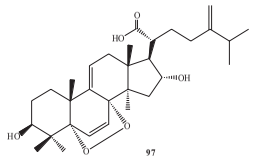
Table1

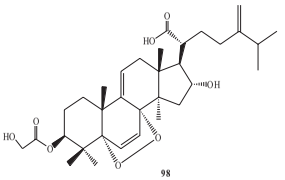
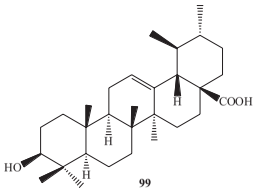
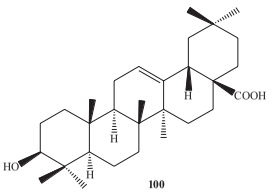
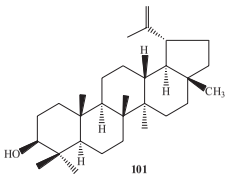
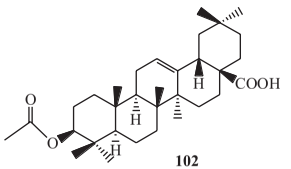
(Continued)

Category	Number	Compound	structure	Reference
	91	β-Amyrin acetate		[14]
	92	(3β,16α)-3-Acetyloxy-16-hydroxy-24-methylenelanosta-5,7(9),11-tetraene-21-oic acid		[17]
	93	α-Amyrin acetate		[21]
	94	Daedaleanic acid D		[24]
	95	Daedaleanic acid E		[24]
	96	Daedaleanic acid F		[24]
	97	5α,8α-Peroxydehydrotumulosic acid		[25]

(Continued)

Table1

(Continued)

Category	Number	Compound	structure	Reference
	98	3-(2-hydroxyacetoxy)-5α,8α-peroxydehydrotumulosic acid		[27]
	99	Ursolic acid		[28]
	100	Oleanolic acid		[28]
	101	Lupeol		[28]
	102	Oleanolic acid 3-O-acetate		[29]

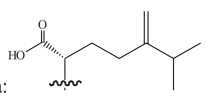
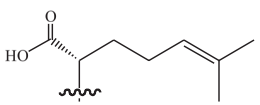
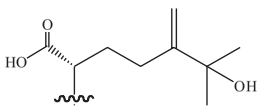
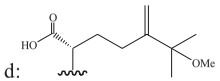
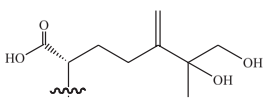
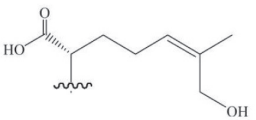
Note：Side chain a:  b:  c:  d:  e:  f: 

Table 2.

Structural characters of polysaccharides isolated from *P. cocos*

Compound name	Molecular weight (kDa)	Monosaccharide composition	Main chain	Reference
PCP-W1	18.38	Gal:Glc:Fuc:Man = 35.87: 28.56: 21.77: 13.64	t-Fucp, 1,3-Fucp, t-Glcp, t-Manp, 1,3Glcp, 1,4-Glcp, 1,6-Glcp, 1,6-Galp, and 1,2,6-Galp	[32]
PCP-1C	17	Gal: Glc: Man: Guc = 43.5: 24.4: 17.4: 14.6	1,6-α-D-Galp	[33]
PCS1	11.6	Fuc:Man:Glc:Gal = 9.2: 25.7: 17.1: 47.9	(1→3)-D-glucan with (1→6)-linked branches; (1,6)-D-Gal,(1-4,6)-D-Gal, (1-2,6)-D-Man, (1-3,6)-D-Man	[34]
PCS3-II	12.3	Glc	Linear β-(1→3)-D-glucan	
PCS4-I	9.1	Fuc: Man: Glc = 1.2: 2.9: 93.1	β-(1→3)-D-glucan with β-(1→6) branches	
PCS4-II	21.2	Glc	β-(1→3)-D-glucan with β-(1→2) and β-(1→6) branches	
PCSG	–	–	β-(1→3)-D-glucan	[35]
PPSW-1	30.6	–	α-(1→3)-linked D-Gal with side chains of α-(1→6)-linked D-Gal	[36]
PCP-I	30	Fuc: Man: Glc: Gal = 1.00:1.81:0.27:7.27	Containing both α- and β-pyranose units, with a main chain composed of 1→6 glycosidic linkages and side chains formed by 1→4 glycosidic linkages	[37]
PCP-II	9	Fuc: Man: Glc: Gal = 1.00:1.63:0.16:6.29	–	
PCWPW	37	Fuc: Man: Glc: Gal = 15.33: 36.90: 7.30: 40.48	–	[38]
PCWPS	18	Fuc: Man: Glc: Gal = 10.10: 30.07: 16.60: 41.47	–	
PCP2	2.35	Glc:Gal:Man:Fuc = 42.0: 35.0: 13.9: 9.1	1,3-β-D-Glc and 1,6-β-D-Glc as the backbone glucans and 1,6-α-D-Gal as the backbone heterogalactan	[39]
Pi-PCM0	64.6	Xyl: Man: Glc: Gal: Ara = 1.5: 70.6: 7.0: 18.5: 2.5	–	[40]
Pi-PCM1	304	Fuc: Xyl: Man: Glc: Gal: Ara = 10.9: 2.8: 23.6: 25.2: 36.5: 1.0	–	
Pi-PCM2	1 030	Fuc: Man: Glc: Gal = 1.9: 29.6: 29.7: 38.9	β-D-galactofuranan, (1→3)-α-D-glucan, and mannana	
Pi-PCM3-1	149	Glc	(1→3)-α-D-glucan	
Pi-PCM3-2	452	Man: Glc: Gal = 10.9: 68.1: 21.0	(1→3)-α-D-glucan with a small amount of β-D-galactose	
Pi-PCM4-1	2 010	Glc	(1→3)-α-D-glucan	
Pi-PCM4-2	4 360	Glc: Gal = 54.5: 45.6	(1→3)-β-D-glucan with a small amount of β-D-galactofuranoside	
wb-PCM0	14.4	Xyl: Man: Glc: Gal: Ara = 3.9: 11.4: 71.1: 5.9: 71.7	(1,3)-α-D-glucan, β-D-mannose, β-D-galactose	[41]
wb-PCM3-I	–	Xyl: Man: Glc:=1.0: 2.2: 95.6	α-(1→3)-D-glucan	
wb-PCM3-II	–	Xyl: Man: Glc: Gal: Ara = 2.0: 1.2: 91.4: 2.0: 2.6	β-(1→3)-D-glucan	
wb-PCM4-I	–	Man: Glc = 5.8: 94.1	β-(1→3)-D-glucan	
wb-PCM4-II	–	Glc: Gal = 76.1:23.9	β-(1→3)-D-glucan	
wc-PCM3-I	–	Xyl: Man: Glc = 6.4: 16.7: 76.9	Protein-bound α-(1→3)-D-glucan	
wc-PCM3-II	8.9	Glc	Protein-bound α-(1→3)-D-glucan	
Suc40 F1	616.23	Gal:Glc:Man = 0.2:10:1	–	[42]
Suc40 F2	82.57	Gal:Glc:Man = 1.5:3:1	–	
Suc40 F3	6.21	Gal:Glc:Man = 0.5:10:1	–	

"–" indicates that this item was not detected. Ara: Arabinose; Fuc: Fucose; Gal: Galactose; Glc: Glucose; Man: Mannose; Xyl: Xylose.

Table 3.

Steroidal Components of *P. cocos*

Number	Compound name	Molecular Formula	Reference
1	Ergosta-7,22-dien-3β-ol	$C_{28}H_{46}O$	[12]
2	Cerevisterol	$C_{28}H_{46}O_3$	[12]
3	Ergosta-7-en-3β-ol	$C_{28}H_{48}O$	[12]
4	Pregn-7-ene-2β,3α,15α,20(S)-tetrol	$C_{21}H_{34}O_4$	[20]
5	Ergosta-6,22-dien-5α,8α-epidioxy-3-ol	$C_{28}H_{44}O_3$	[21]
6	Ergosta-5,7,22-trien-3β-ol	$C_{28}H_{44}O$	[21]
7	3β,5α-Dihydroxyergosta-7,22-dien-6-one	$C_{28}H_{44}O_3$	[21]
8	3β,5α,9α-Trihydroxyergosta-7,22-dien-6-one	$C_{28}H_{44}O_4$	[21]
9	Ergosta-7,22-dien-3-one	$C_{28}H_{44}O$	[21]
10	6,9-Epoxy-ergosta-7,22-dien-3β-ol	$C_{28}H_{44}O_2$	[21]
11	Ergosta-4,22-dien-3-one	$C_{28}H_{44}O$	[21]
12	Ergosta-5,6-epoxy-7,22-dien-3-ol	$C_{28}H_{44}O_2$	[21]
13	Ergosta-4,6,8(14),22-tetraen-3-one	$C_{28}H_{40}O$	[21]
14	β-Sitosterol	$C_{29}H_{50}O$	[21]
15	β-Daucosterol	$C_{35}H_{60}O_6$	[21]
16	Stigmasterol	$C_{29}H_{48}O$	[27]
17	9,11-Dehydroergosta peroxide	$C_{28}H_{42}O_3$	[21]

function in a chronic heart failure rat model[51]. Similarly, *P. cocos* water extract suppressed AQP2 expression, serum- and glucocorticoid-induced kinase 1 phosphorylation, and cAMP/PKA pathway activation under hyperosmotic stress, while attenuating Bax/caspase-3-mediated apoptosis in renal collecting duct cells, indicating a protective effect on tubular epithelial integrity[52].

Triterpenoids are considered the major bioactive constituents responsible for the diuretic activity of *P. cocos*. Niet al[53]. identified methyl dehydroabietate as a potential active compound with strong binding affinities to aquaporin-1 (AQP1), aquaporin-4 (AQP4), and aquaporin-5 (AQP5), suggesting it may serve as a material basis for the traditional concept of "invigorating the spleen and promoting diuresis." Ethanol extracts of Poriae Cutis enriched in medium-polarity triterpenes (eg, lanostane-type tetracyclic triterpenoids) promoted sodium and chloride excretion without affecting potassium levels, demonstrating a "potassium-sparing natriuretic" effect[54], consistent with findings by Hu et al.[55] and Zhao et al.[56]. Additional studies have associated specific triterpenoids – such as 16α-hydroxydehydrotumulosic acid, present in Poriae Cutis and Poria cum Radix Pini (*Fu Shen*) – with the observed diuretic effects[57]. *In vivo*, *P. cocos* administration significantly reduced the pulmonary permeability index, lung wet-to-dry ratio, and serum creatine kinase levels, while increasing serum albumin concentrations, indicating its potential to mitigate pulmonary fluid retention in rat models of upper-jiao water-dampness accumulation[58].

In summary, *P. cocos* promotes water excretion while preserving yin by regulating the expression of AQP1/2/4/5 and enhancing renal Na^+/Cl^- elimination. Triterpenoids constitute its key active components. However, current mechanistic studies remain limited, particularly regarding the pharmacological differences among distinct medicinal parts (eg, Poriae Cutis, *Fu Shen*). Future research integrating metabolomics and molecular imaging is warranted to further elucidate its role within the broader water metabolism regulatory network and to establish a comprehensive pharmacodynamic evaluation framework.

Spleen-fortifying and stomach-regulating effects

In TCM, the sweet and neutral properties of *P. cocos* are believed to strengthen the spleen and harmonize the stomach. Modern pharmacological studies support these actions, particularly highlighting the role of WPCPs in restoring gastrointestinal function. In spleen-deficiency-induced diarrhea models, aqueous extracts of *P. cocos* have been shown to inhibit intestinal motility[59].

The gut microbiota plays a critical role in the TCM concept that "the spleen governs transformation and transportation." Aqueous extracts from different parts of *P. cocos* appear to act through distinct mechanisms to ameliorate spleen deficiency. White *P. cocos* enhances immune responses by increasing secretory immunoglobulin A (IgA) and interleukin-2 (IL-2) levels, whereas Rubra Poria improves digestive absorption (evidenced by reduced fecal water content and increased D-xylose) and restores intestinal barrier integrity through upregulation of Claudin and Occludin[60]. This discrepancy may be attributed to the compositional differences between white *P. cocos* and Rubra Poria. White *P. cocos* contains higher levels of pachyman, whereas Rubra Poria is richer in pachymic acid. However, the exact causal relationships remain unclear[61]. Our studies demonstrate that WPCPs from white *P. cocos* modulate gut microbiota composition and function, thereby enhancing

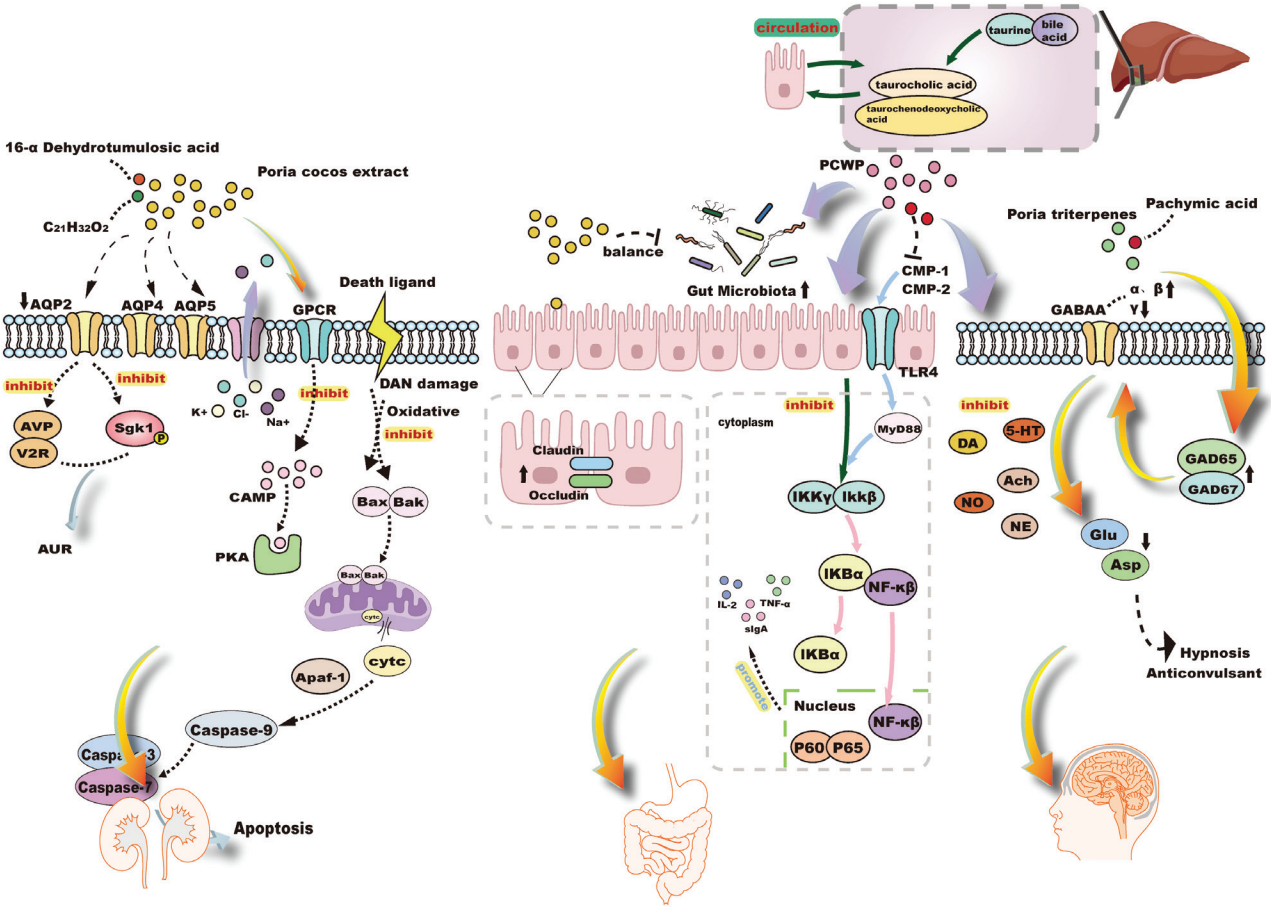


Figure 3. Pharmacological activities based on traditional functions of *P. cocos*. AChE: Acetylcholinesterase; AQP2: Aquaporins 2; AUR: Aurora kinase; AVP: Arginine vasopressin; cAMP: Cyclic adenosine monophosphate; CMP-1: Recombinant Human Cytidine Monophosphate Kinase 1; IKB: Inhibitor of kappa B; OX1R/OX2R: Orexin receptors 1/2; PCWP: A water-soluble polysaccharide; PKA: Protein kinase A; Sgk1: Serum-and glucocorticoid-induced kinase 1; TLR4: Toll-like receptor 4.

intestinal barrier integrity[62]. Further research showed that these polysaccharides improve immune function in spleen-deficient rats by modulating the gut microbiota (increasing the *Bacteroidetes/Firmicutes* ratio and *Prevotella* while reducing *Enterococcus*) and stimulating immune responses[63]. Additionally, aqueous extracts have been shown to normalize microbial imbalances, including those involving unidentified *Clostridiales* and *Dubosiella*, contributing to the restoration of intestinal homeostasis[64]. Nevertheless, differences in polysaccharide content and their regulatory effects on gut microbiota between white *P. cocos* and Rubra Poria have yet to be systematically investigated.

Modified APCPs also exhibit spleen-tonifying effects. Liu et al.[65] found that carboxymethylated *P. cocos* polysaccharides (CMP-1 and CMP-2) enhanced spleen immune activity by regulating the TLR4-MyD88-NF-κB pathway. This immunomodulatory effect was accompanied by increased tumor necrosis factor-alpha (TNF-α) and IL-2 expression, as well as beneficial alterations in gut microbiota composition, particularly an increase in *Bacteroidetes* and reduction in *Erysipelatoclostridium*. Similarly, triterpenoids exhibit promising digestive-enhancing properties. Zhang et al.[66] demonstrated that total triterpenoids alleviated high-fat diet–induced spleen deficiency, and Min et al.[67] further showed that triterpenoid-rich extracts regulated gastrointestinal hormones (gastrin and motilin), improved renal AQP2 expression related to water metabolism, enhanced digestive function, and increased serum IL-2 levels.

Future research should explore potential synergistic effects between *Poria cocos* polysaccharides and triterpenoids. Polysaccharides may confer therapeutic benefits primarily through modulation of gut microbiota and their metabolites, whereas triterpenoids may act through direct target interactions, with the two components potentially working in concert to produce enhanced efficacy. However, the underlying synergistic mechanisms among active constituents and the specific regulatory networks involved in spleen-stomach functions require further elucidation through multi-omics approaches and gut–spleen axis-based research frameworks.

Tranquilizing and sedative effects

P. cocos has long been used in traditional medicine for its tranquilizing ("calming the spirit") properties[68]. Recent pharmacological investigations indicate that its bioactive constituents exert multi-target regulatory effects on the central nervous system (CNS), demonstrating therapeutic potential for insomnia and anxiety. Experimental studies have confirmed that the significant sedative and hypnotic effects of the aqueous extract of *P. cocos* are primarily attributable to specific triterpene acids, including polyporenic acid C, poricoic acid A, and dehydropachymic acid[69]. Furthermore, an

integrated analysis combining 16S rDNA sequencing, metabolomics, and the TNF-α/NF-κB signaling pathway systematically elucidated that the aqueous extract of *P. cocos* alleviates anxiety-like behavior induced by chronic sleep deprivation by modulating gut microbiota composition, ameliorating metabolic disorders, and suppressing neuroinflammation[70]. Using computational drug screening approaches, Ranteh et al.[71]. found that several *P. cocos* compounds exhibited stronger affinity to orexin receptors OX1R/OX2R than commercial drugs, including the potent nortriterpenoid 7-(2-hydroxypropan-2-yl)-1,4a-dimethyl-9-oxo-3,4,10,10a-tetrahydro-2H-phenanthrene-1-carboxylic acid. With favorable drug-likeness, PK profiles, and low predicted toxicity, these compounds represent promising low-risk anti-insomnia candidates.

Triterpenoid acids are widely considered the principal active constituents responsible for the sedative and hypnotic effects of *P. cocos*. Gao et al.[72] demonstrated that these compounds upregulate the α- and β-subunits while downregulating the γ-subunit of $GABA_A$ receptors, concurrently reducing. They also reduce the levels of excitatory neurotransmitters, including glutamate and aspartate, thus thereby producing anti-convulsant and hypnotic effects – findings consistent with those reported by Shah et al.[73]. In clinical settings, poricoic acids have been shown to improve sleep architecture in patients with insomnia, with effects including prolonged total sleep duration and fewer nocturnal awakenings[74]. Xu et al.[75] further found that various *P. cocos* extracts – including aqueous decoctions, ethyl acetate and petroleum ether fractions, and both crude and purified polysaccharides – significantly inhibited acetylcholinesterase (AChE) activity in mouse brain tissue, suggesting a synergistic, multicomponent mechanism underlying its sedative-hypnotic effects.

Polysaccharides also contribute substantially to the neuroactive properties of *P. cocos*. Pachyman, a β-glucan polysaccharide, also potentiated the CNS depressant effect of pentobarbital[76]. Furthermore, Zhang et al.[77] reported that a WPCP ameliorated anxiety-like behavior in rats subjected to chronic sleep deprivation by regulating hypothalamic neurotransmitter levels, suppressing TNF-α/NF-κB-mediated inflammation, improving gut dysbiosis (eg, increasing *Rikenellaceae_RC9_gut_group*), and modulating sphingolipid and taurine metabolism.

In summary, triterpenoid acids and PCP exert sedative-hypnotic effects primarily through modulation of the GABAergic system (including alterations in $GABA_A$ receptor subunit composition and GABA biosynthesis) and orexin receptors (OX1R/OX2R) (Figure 3). However, the interplay among these bioactive components and their interaction with other neurotransmitter systems remain insufficiently understood. Future studies integrating multi-omics with neural circuit mapping are needed to clarify the integrative mechanisms underlying the tranquilizing efficacy of *P. cocos*.

Extended pharmacological activities

Antitumor effects

Both PCP and triterpenoids exhibit broad-spectrum antitumor activity[78–79]. Both WPCPs and APCPs have shown promising efficacy in models of colorectal and lung cancer. Chen et al.[80] reported that PCP improved colorectal cancer outcomes in mice by reshaping the gut microbiota (eg, reducing *Helicobacter* and increasing *Limosilactobacillus*), enhancing intestinal barrier integrity (*via* upregulation of E-cadherin, zonula occludens-1, Claudin-3, and mucin 2), and modulating inflammatory responses (eg, decreasing TNF-α, IL-6, and IL-1β, while increasing IL-10). Polysaccharide fractions with high sulfate content also induce apoptosis in lung cancer cells through activation of the PARP/CHOP pathway[81]. Additionally, a fucosylated mannoglucan derived from *P. cocos* mycelia suppressed the migration of highly metastatic lung cancer cells by inhibiting the TGFβRI/FAK/AKT signaling cascade and downregulating Slug expression[82].

Triterpenoids – including poricoic acids and dehydrotumulosic acid – also exhibit potent antitumor effects across various solid tumor models. Xie et al.[83] found that an ethanol extract of *P. cocos* inhibited gastric cancer cell proliferation *via* regulation of the MAPK and PI3K-Akt signaling pathways. Wang et al.[84] further demonstrated that *P. cocos* triterpenoids suppressed gastric cancer cell migration and invasion by upregulating E-cadherin, downregulating N-cadherin and Vimentin, and inhibiting MMP-2/9 activity. Multiple studies have confirmed that poricoic acids exert antitumor effects against gastric[85–87], renal[88], and breast cancers[89] through modulation of PI3K/Akt and NF-κB signaling pathways[90].

Other triterpenoid compounds, such as poricoic acid A and B, have been shown to activate reactive oxygen species (ROS)-p53 signaling and inhibit the expression of matrix metalloproteinases and vascular cell adhesion molecule-1, thereby inducing apoptosis and inhibiting metastasis in hepatocellular carcinoma *via* crosstalk between PI3K/Akt and MAPK pathways[91]. Poricoic acid A also inhibits ovarian cancer cell viability in a dose-dependent manner and induces autophagy and apoptosis by suppressing the mTOR/p70S6K axis[92]. In pancreatic cancer models, triterpenoids such as dehydropachymic acid and polyporenic acid C downregulate CDC20 expression, thereby inhibiting PANC-1 cell migration[93]. In addition, the triterpenoid component tumulosic acid, within multi-herb formulations, induces apoptosis in ovarian cancer cells *via* the BCL2L1 and PI3K/Akt pathways[94], whereas Compound *P. cocos* Granules have been shown to regulate cyclin-dependent kinase 2, mucin 1, and DICER1 expression to inhibit proliferation and promote apoptosis[95]. In leukemia models, pachymic acid A induces autophagic cell death and triggers ferroptosis through activation of the AMPK/mTOR pathway[96].

In summary, PCP and triterpenoids exhibit broad-spectrum antitumor effects by modulating gut microbiota, strengthening intestinal barrier function, and regulating apoptosis, autophagy, and ferroptosis. These effects are mediated largely through key signaling pathways such as PI3K/Akt, MAPK, NF-κB, and mTOR, highlighting their potential as multi-target antitumor agents.

Immunomodulatory activity

Polysaccharides are recognized as the principal immunoactive components of *P. cocos* and have been

extensively validated to activate immune cells, modulate cytokine profiles, and restore micro-ecological homeostasis *via* multiple signaling pathways[5]. Zhang et al.[97] reported that two water-soluble polysaccharide fractions, PCWPW and PCWPS, bind to mannose receptors on macrophages and activate the NF-κB/MAPK signaling pathway to promote TNF-*α* secretion. The presence of a 1,3-β-D-glucan backbone was identified as a key structural motif closely associated with their immunomodulatory efficacy. In a subsequent study, Liu et al.[65] demonstrated that carboxymethylated derivatives (CMP-1 and CMP-2) activate the TLR4/MyD88/NF-κB axis to stimulate TNF-*α* and IL-2 production and modulate gut microbiota composition (eg, increased *Bacteroidetes*, decreased *Erysipelatoclostridium*), thereby enhancing humoral immunity and repairing splenic injury.

Our group recently showed that a homogeneous polysaccharide, PCP-1C, activates the Notch1/Jagged1/Hes1 signaling pathway, promoting M1 polarization of macrophages as evidenced by increased TNF-*α* and IL-6 and decreased IL-10 levels. PCP-1C also exhibits a characteristic "scale-like" surface morphology, which may be associated with its immunological activity[98]. We further isolated a neutral polysaccharide, PCP-W1, with demonstrable immunomodulatory activity. PCP-W1 induces M1-type macrophage polarization *via* the TLR4/MD2/NF-κB pathway, and molecular docking and dynamics simulations revealed that its galactose chain stably binds to the TLR4/MD2 complex, thereby exerting immunoregulatory effects[32].

Xie et al.[99] found that a compound polysaccharide derived from Astragalus and *P. cocos* enhances serum IgA/IgG levels and pro-inflammatory cytokines (IL-6 and TNF-*α*), while restoring microbial balance by increasing the abundance of *Butyricicoccaceae* and *Parabacteroides* and reducing *Anaerotruncus*. PCP also activates macrophages *via* the TLR4/TRAF6/NF-κB axis to promote the secretion of NO and Th1/Th17 cytokines (eg, IL-2, IL-6, IL-17A, TNF-*α*, and IFN-γ), thereby inhibiting tumor growth in Lewis lung carcinoma models[100]. Chang et al.[101] isolated an immunoprotein PCP, which exerted macrophage-stimulating effects similar to those of polysaccharides by activating the TLR4/MyD88 signaling cascade and inducing TNF-*α* and IL-1β release. Additionally, PCP activated RAW264.7 macrophages *via* the Ca^{2+}/PKC/p38/NF-κB signaling pathway to stimulate the production of diverse cytokines[102].

The immunological activity of PCP is significantly influenced by processing methods. Steam-explosion pretreatment has been shown to reduce molecular weight and induce a 1,3-β-D-glucopyranosyl backbone-based porous honeycomb structure, thereby markedly enhancing immunostimulatory activity[103]. Fungal immunomodulatory proteins derived from *P. cocos* also significantly upregulate TNF-*α* and IL-1β expression in RAW264.7 cells[104]. Pachymaran was reported to ameliorate cyclosporine A-induced immunosuppressive lung injury by regulating the gut-lung microbiota metabolic axis[105]. Li et al.[106] isolated four distinct polysaccharide fractions from *P. cocos*, all of which showed significant immunomodulatory effects closely associated with NF-κB pathway activation.

In summary, PCP – particularly those with 1,3-β-D-glucan structures – exert potent immunomodulatory effects by activating macrophages, modulating cytokine secretion, restoring gut microbiota balance, and enhancing humoral and cellular immunity. These effects are primarily mediated through pathways such as TLR4/NF-κB, MAPK, and Notch, and can be further influenced by structural features and processing methods, underscoring their potential as natural immunotherapeutic agents.

Anti-inflammatory effects

Both polysaccharides and triterpenoids derived from *P. cocos* exhibit significant anti-inflammatory activities, primarily through suppression of inflammatory signaling pathways, modulation of the gut microbiota, and regulation of immune responses[6]. The *P. cocos* polysaccharide PDB10 has been shown to significantly inhibit lipopolysaccharide (LPS)-induced release of pro-inflammatory cytokines in macrophages by downregulating the ERK/AKT/p38/TGFβRII signaling cascade[107]. The anti-inflammatory and immunomodulatory activities of carboxymethylated polysaccharides (CMPs) are influenced by their molecular weight and degree of substitution. Notably, medium-molecular-weight CMPs display the strongest immunoregulatory activity, whereas high-molecular-weight CMPs exert superior anti-inflammatory effects, with Dectin-1 identified as a critical receptor[108]. Sulfated polysaccharide Suc40 suppresses IL-6 and TNF-*α* production *via* inhibition of the p38/JNK and AKT pathways and also demonstrates anti-proliferative effects against lung cancer cells[42,81]. PCP further demonstrated therapeutic efficacy in dextran sulfate sodium (DSS)-induced ulcerative colitis (UC) by enhancing the expression of tight junction proteins, thereby restoring intestinal barrier integrity. PCP also attenuated inflammatory responses *via* inhibition of the NF-κB pathway and promoted the growth of beneficial gut microbiota (eg, *Akkermansiaceae*) while reducing the abundance of pathogenic taxa (eg, *Erysipelotrichaceae*)[109], consistent with the findings of Song et al.[110]. PCP has also demonstrated synergistic effects in sepsis treatment through its anti-inflammatory, anti-oxidant, and immunomodulatory activities, significantly reducing cytokine levels and cellular apoptosis[111].

Triterpenoids from *P. cocos* consistently exert anti-inflammatory effects across various disease models. Ethanolic extracts of *P. cocos* inhibit IκB degradation and NF-κB p65 nuclear translocation, thereby downregulating iNOS, COX-2, and downstream inflammatory mediators[112]. In a model of glandular cystitis, pachymic acid demonstrated therapeutic potential by regulating the TNF-*α*/TP53 signaling axis and targeting key inflammatory proteins such as COX-2 and EGFR[113]. Pachymic acid also alleviates chondrocyte inflammatory injury in osteoarthritis by upregulating SIRT6 and inhibiting the NF-κB pathway[114]. Other triterpenoids, such as poricoic acid A and poricoic acid GM, likewise exhibit potent anti-inflammatory properties. Lee et al.[115] reported that poricoic acid A and related triterpenoids significantly

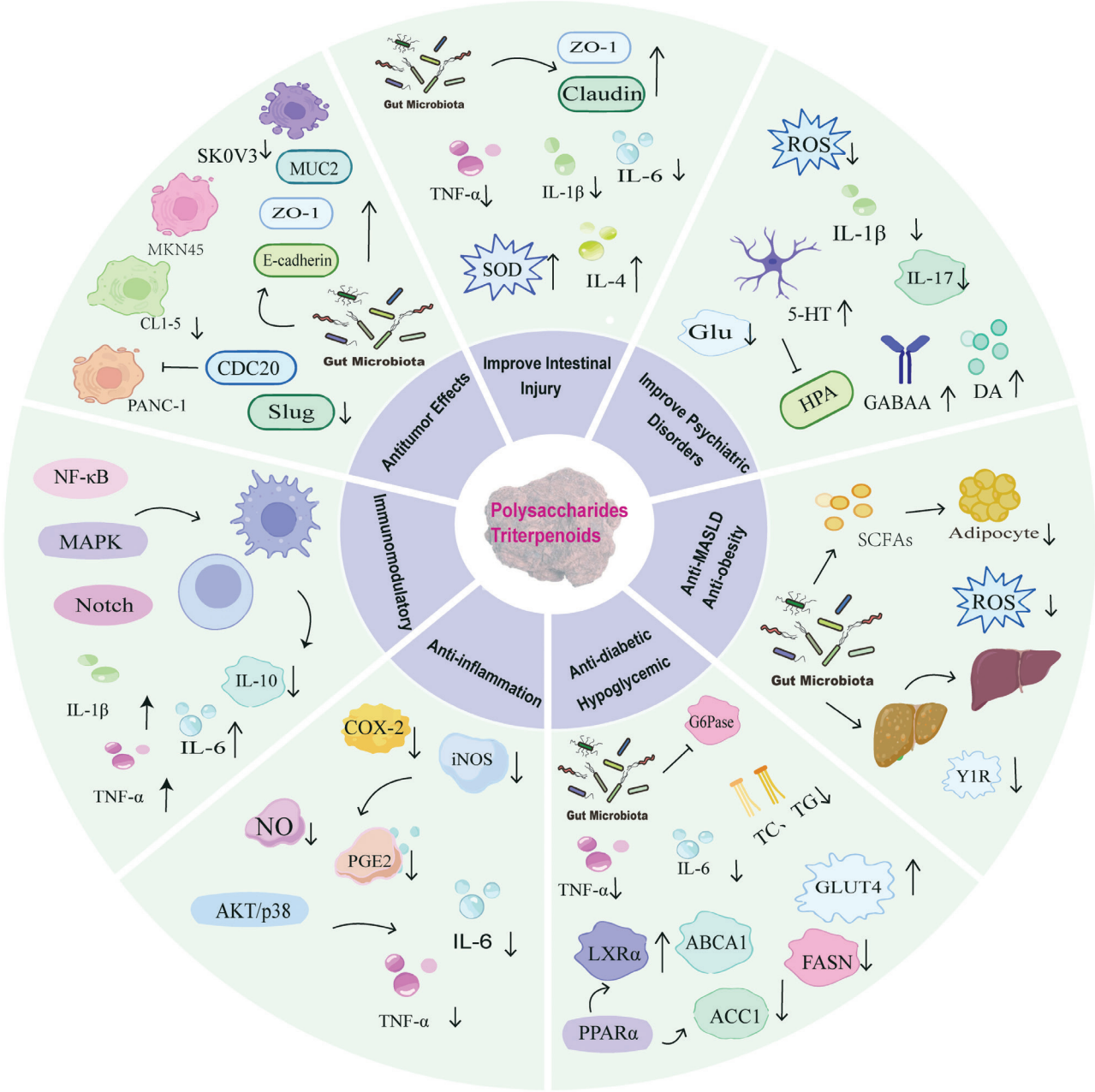


Figure 4. Extended pharmacological activities of *P. cocos*. ABCA1: ATP-binding cassette transporter A1; ACC1: Acetyl-CoA carboxylase 1; FASN: Fatty acid synthase; GABAA: Gamma-aminobutyric acid type A receptor; Glu: Glutamate; GLUT4: Glucose transporter type 4; HPA: Hypothalamic-pituitary-adrenal axis; LXRa: Liver X receptor alpha; MAPK: Mitogen-activated protein kinase; MKN45: Human gastric carcinoma cell line; MUC2: Mucin 2; PANC-1: Human pancreatic carcinoma cell line; PPARa: Peroxisome proliferator-activated receptor alpha; SCFAs: Short-chain fatty acids; SKOV3: Human ovarian adenocarcinoma cell line; Slug: Snail family zinc finger protein 2; ZO-1: Zonula occludens-1; Y1R: Neuropeptide Y receptor type 1.

inhibited LPS-induced NO and iNOS expression in RAW264.7 cells, while downregulating COX-2 and reducing PGE2 levels. Bao et al.[116] identified 17 novel triterpenoids from *P. cocos*, with poricoic acid GM showing the strongest anti-inflammatory activity by blocking NF-κB and activating Nrf2 signaling, confirming triterpenoids as major anti-inflammatory constituents.

Collectively, *P. cocos* polysaccharides and triterpenoids exert anti-inflammatory effects through modulation of NF-κB, MAPK, and gut microbiota. However, current studies often lack integrative mechanistic insight. Future research should adopt multi-omics and evidence-based approaches to support clinical translation.

Hypoglycemic and lipid-lowering effects

P. cocos and its bioactive constituents exert significant regulatory effects on glucose and lipid metabolism. PCP alleviates dyslipidemia and vascular inflammation in atherosclerotic mice by suppressing the TLR4/NF-κB signaling pathway, lowering serum TNF-α, IL-6, low-density lipoprotein cholesterol, triglycerides, and total cholesterol levels, enhancing superoxide dismutase (SOD) activity, and reducing oxidative stress, thereby improving aortic pathology[117]. Similarly, *P. cocos* oligosaccharides (PCO) improve glycemic control in high-fat diet-fed mice by modulating the gut microbiota (eg, increasing *Lactobacillus* and *Clostridium*), inhibiting

lipogenesis (*via* regulation of G6Pase and TNF-*α*), and altering bile acid and short-chain fatty acids (SCFAs) metabolism[118].

Alcoholic extracts of *P. cocos* activate the PPAR*α* pathway and upregulate LXR*α*, ABCA1, CYP7A1, and LDLR expression while suppressing SREBP-1, ACC1, and FASN, thereby improving hepatic cholesterol homeostasis and lipid clearance[119]. Triterpenoids, such as poricoic acid, enhance GLUT4 expression and membrane translocation, promote phosphorylation of IRS-1, Akt, and AMPK, and facilitate glucose uptake, while also modulating triglyceride metabolism[120]. Compounds such as dehydrotumulosic acid, dehydropachymic acid, acetyl eburicoic acid, pachymic acid D, and poricoic acid C have demonstrated insulin-sensitizing and glucose-lowering effects[26,121]. In metabolic disease models, *P. cocos* exhibits multi-target therapeutic potential. Tumulosic acid alleviates hyperuricemia by suppressing TNF-*α* and IL-6[122], while poricoic acid A activates the AMPK*α*/FUNDC1 axis, promoting autophagy and reducing apoptosis and oxidative stress in podocytes under hyperglycemic conditions – suggesting therapeutic potential in diabetic nephropathy[123]. Additionally, *P. cocos* components inhibit xanthine oxidase activity, regulate fatty acid synthase expression, and modulate purine, fatty acid, and bile acid metabolism, ultimately lowering serum uric acid and creatinine levels[124]. Meta-analysis findings further indicate that *P. cocos*-containing formulations outperform conventional treatments in diabetic nephropathy, significantly improving renal function and glycemic parameters[125].

Collectively, *P. cocos* polysaccharides and triterpenoids exert hypoglycemic and lipid-lowering effects primarily through modulation of TLR4/NF-κB, PPAR*α*, and AMPK signaling pathways, with promising applications in managing hyperglycemia, dyslipidemia, and related metabolic complications.

Anti-obesity and MASLD-modulating effects

In recent years, obesity and MASLD have emerged as major global health challenges, highlighting the urgent need for effective and safe interventions. As a traditional medicinal fungus, *P. cocos* and its active constituents – particularly polysaccharides and triterpenoids – have shown promising potential for regulating metabolic disorders and maintaining gut microbiota homeostasis, offering novel insights into the prevention and treatment of obesity and MASLD.

PCP have been shown to ameliorate high-fat diet-induced metabolic disorders by regulating gene networks involved in lipid metabolism, insulin signaling, and inflammation. PCP also reshape gut microbial composition, notably influencing genera such as *Eisenbergiella* and *Dorea*, thereby contributing to restored energy homeostasis[126]. Our research group further demonstrated that WPCPs enhance the abundance of SCFA-producing bacteria (eg, *Lactobacillus*), thereby increasing acetate, propionate, and butyrate production. These SCFAs activate the FGF21/PI3K-AKT/GLUT4 axis, improving insulin sensitivity in adipose tissue – a regulatory mechanism dependent on the microbiota–SCFAs axis[127]. In MASLD models, PCP upregulates beneficial microbes such as *Faecalibaculum*, reduces endotoxin burden, and suppresses the NF-κB/CCL3/CCR1 axis, alleviating methionine- and choline-deficient diet-induced hepatic injury[128].

In addition, molecular docking and PK screening have identified compounds such as β-amyrin acetate, 3-epi-dehydrotumulosic acid, and ergosterol as high-affinity antagonists of the neuropeptide Y1 receptor (Y1R), exhibiting favorable drug-likeness and low predicted toxicity. These compounds interact with key Y1R residues and stabilize extracellular loop conformations, potentially blocking neuropeptide Y-mediated feeding pathways and offering new leads for anti-obesity drug development[129]. Ethanol-extracted *P. cocos* triterpenoids have also been shown to improve hepatic lipid homeostasis and bile acid metabolism by regulating FXR/PPAR*α*-SREBPs signaling[130]. Moreover, these triterpenoids and their metabolites promote mitochondrial fatty acid β-oxidation and redox balance, suggesting a regulatory role in mitochondrial homeostasis during MASLD progression[131].

In summary, active components of *P. cocos* exert anti-obesity and MASLD-mitigating effects through multiple mechanisms, including modulation of the gut microbiota–SCFAs axis, suppression of inflammatory pathways (eg, NF-κB/CCL3/CCR1), regulation of lipid metabolism (eg, FXR/PPAR*α*/SREBPs), and attenuation of central appetite signaling *via* Y1R.

Protective effects on intestinal injury

Intestinal inflammatory disorders and chemotherapy-induced enteropathy remain major therapeutic challenges. *P. cocos* and its bioactive components exhibit notable advantages in maintaining intestinal barrier integrity and regulating gut microbiota. Tan et al.[132] reported that carboxymethylated *P. cocos* polysaccharides CMP I and CMP II alleviated DSS-induced UC by suppressing pro-inflammatory cytokines (IL-1β, IL-6, TNF-*α*), enhancing IL-4 secretion and SOD activity, and modulating gut microbial composition. Notably, CMP I exhibited superior effects in improving mucosal barrier function. Similarly, Zou et al.[133] demonstrated that WCPCs mitigated cisplatin-induced intestinal injury by reducing pathogenic *Proteobacteria*, restoring key metabolites such as hypoxanthine and linoleic acid, and lowering inflammatory markers (eg, IL-2, IL-6). In DSS-induced colitis models, PCP also enhanced tight junction protein expression, suppressed NF-κB activation, and remodeled the microbiota (eg, increasing *Akkermansiaceae* and decreasing *Erysipelotrichaceae*), leading to notable anti-inflammatory and barrier-protective effects[109–110].

Jiang et al.[109] further demonstrated that ethanol extracts of *P. cocos* activated the p38 MAPK/ERK signaling pathway, upregulated intestinal barrier-related proteins, and improved gut integrity in breast cancer-bearing mice by promoting beneficial microbial populations – highlighting a strong association between microbial composition and barrier function. In addition, 16*α*-hydroxytrametenolic acid, a triterpenoid isolated from *P. cocos*, functions as a novel glucocorticoid receptor (GR) agonist. By activating GR, HTA suppresses the

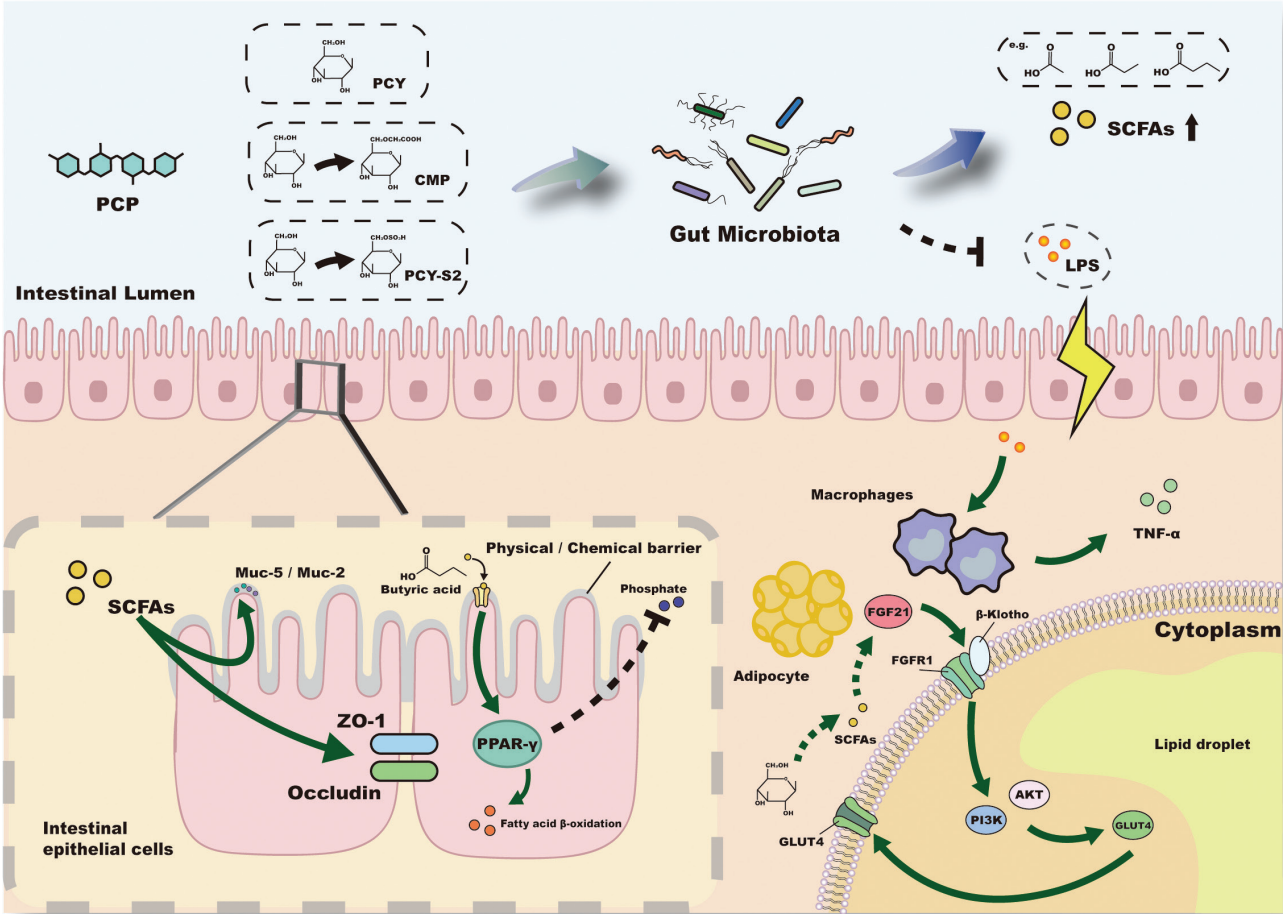


Figure 5. The metabolic process of PCP in the gut. FGFR1: Fibroblast growth factor receptor 1; FGF21: Fibroblast growth factor 21; GLUT4: Glucose transporter type 4; Muc-2: Mucin 2; PPARr: Peroxisome proliferator-activated receptor gamma; SCFAs: Short-chain fatty acids; ZO-1: Zonula occludens-1.

PI3K/Akt/NF-κB signaling pathway, reduces IκB phosphorylation and NF-κB nuclear translocation, and consequently alleviates TNF-α-induced intestinal epithelial barrier dysfunction[134].

In summary, *P. cocos* polysaccharides and triterpenoids exert protective effects against UC and chemotherapy-associated intestinal injury by modulating the gut microbiota, enhancing epithelial barrier function, and suppressing key inflammatory pathways such as PI3K/Akt/NF-κB. These findings provide a molecular basis for developing therapeutic strategies targeting intestinal barrier dysfunction.

Neuropsychological benefits

In recent years, increasing attention has been paid to the multi-target and multi-pathway regulatory effects of *P. cocos* and its bioactive components in neuropsychiatric disorders such as depression, Alzheimer disease (AD), and sleep disturbances. Accumulating evidence highlights its promising therapeutic potential.

Water extracts of *P. cocos* have been shown to exert anti-depressant-like effects by downregulating the p38/NF-κB/TNF-α inflammatory signaling pathway in the prefrontal cortex and modulating dopamine and 5-hydroxytryptamine (5-HT) metabolism. This combined anti-inflammatory and neurotransmitter-regulatory action significantly improved sucrose preference and behavioral despair in chronic stress models[135]. In AD research, bioaffinity ultrafiltration and molecular docking studies identified several triterpenes from *P. cocos* – including pachymic acid, dehydropachymic acid, poricoic acid C, tumulosic acid, and 3-epidehydrotumulosic acid – as AChE inhibitors with high binding affinities and potential multisite inhibitory effects, offering promising candidates for anti-AD drug development[136]. In the context of sleep regulation, ethanol extracts of *P. cocos* have been reported to enhance sleep quality through activation of γ-aminobutyric acid A ($GABA_A$) receptors[137]. A recent meta-analysis further supports its potential as an adjuvant therapy for epilepsy, expanding its role in neurological modulation[138].

Pachymic acid also exhibits neuroprotective properties by regulating genes within the NF-κB and IL-17 pathways (eg, IL1B, CXCL8), reducing Fe^{2+}-induced ROS, and stabilizing mitochondrial membrane potential, thereby preventing neuronal apoptosis – suggesting therapeutic relevance for neurodegenerative conditions associated with iron dysregulation[139]. Moreover, total triterpenes from *P. cocos* exert anti-depressant effects *via* multiple mechanisms, including upregulation of hippocampal 5-HT, reduction of glutamate levels, inhibition of hypothalamic-pituitary-adrenal axis hyperactivation, and suppression of NLRP3 inflammasome activation (NLRP3/ASC/caspase-1) in the prefrontal cortex, which lowers

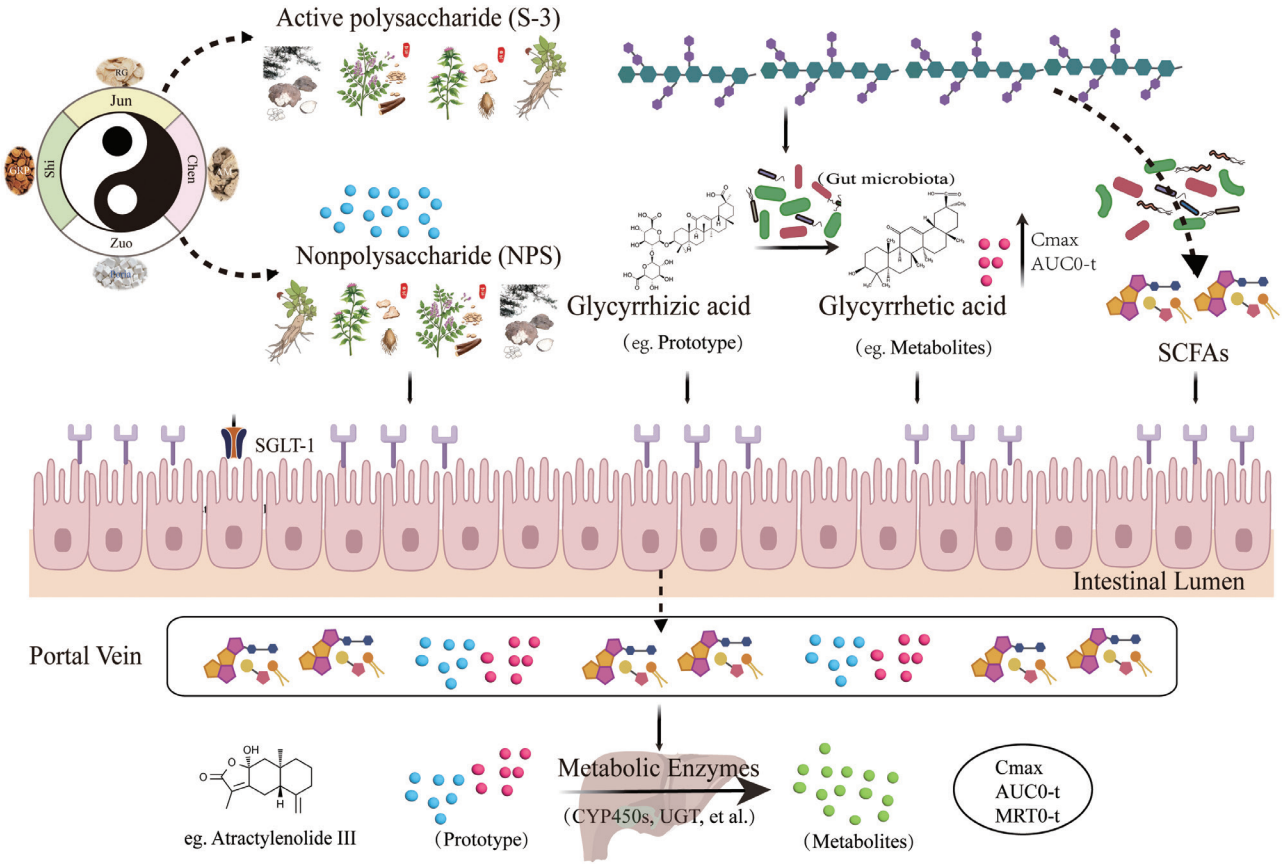


Figure 6. Mechanisms of herbal compatibility in compound formulations of *P. cocos*. AUC: Area under the curve; CYP450: Cytochrome P450; MRT: Mean residence time; SCFAs: Short-chain fatty acids; UGT: Uridine diphosphate glucuronosyltransferase.

pro-inflammatory cytokine release (eg, IL-1β)[140]. These effects are attributed to the presence of 69 lanostane-type triterpenoids. Additionally, 62 triterpenoid compounds identified in *P. cocos* water extracts were found to alleviate anxiety-like behaviors induced by sleep deprivation, potentially by modulating neurotransmitters, suppressing TNF-α/NF-κB signaling, and restoring gut microbiota balance and associated metabolic pathways[70].

In summary, the active constituents of *P. cocos*, particularly triterpenes and polysaccharides, exert therapeutic effects on neuropsychiatric disorders through diverse mechanisms, including neurotransmitter regulation (5-HT, dopamine, GABA), inhibition of neuroinflammation (eg, NF-κB/NLRP3), and mitochondrial protection (Figure 4). These findings not only enrich the pharmacological profile of *P. cocos* but also provide theoretical support and novel molecular targets for its clinical application in mental and neurological disorders.

Other pharmacological effects

In addition to the pharmacological effects described above, *P. cocos* exhibits a broad spectrum of biological activities, including antimicrobial, hepatoprotective, renoprotective, pulmonary-protective, and cardioprotective effects.

A carboxymethylated derivative of *P. cocos* water-insoluble β-D-glucan (PCSG) shows potent antibacterial activity against *Pseudomonas aeruginosa*[141]. PCP alleviates acetaminophen-induced liver injury through activation of the P38 MAPK pathway and enhancement of CYP3A4-mediated detoxification[142–143]. PCP also mitigates alcohol-induced hepatic dysfunction by suppressing NF-κβ-dependent inflammation[144]. Emerging evidence highlights the nephroprotective effects of pachymic acid A and triterpenoid acid ZA, which ameliorate chronic kidney disease through multiple mechanisms, including modulation of gut microbiota composition, regulation of microbial metabolites, and inhibition of TGF-β/Smad signaling pathway[145–146]. Pachymic acid also reduces bleomycin-induced pulmonary fibrosis by targeting fibrotic, inflammatory, and oxidative pathways[147], while PCO alleviates acute lung injury by modulating histidine/fatty acid metabolism and upregulating AQP5/ENaC-α[148]. In cardiac protection, pachymic acid pretreatment attenuates hemorrhagic shock-induced cardiac injury by blocking NF-κB p65 activation, reducing IL-1β/IL-6/TNF-α, and regulating macrophage polarization.

Quality evaluation system

A robust quality evaluation system is essential for ensuring the clinical efficacy and safety of TCMs. For *P. cocos*, its pharmacological activity primarily depends on the content and synergistic effects of polysaccharides (eg, β-(1→3)-glucans) and triterpenoids (eg, pachymic acid). However, current market practices often rely on superficial physical characteristics rather than quantitative analysis of bioactive components, leading to

Figure 7. Applications of *P. cocos* in medicine, food, nutrition, and daily chemical products.

significant quality inconsistencies. Although the "*Chinese Pharmacopoeia*" (Chinese Pharmacopoeia Commission, 2025) has established a mandatory standard for β-(1→3)-glucan content (≥50.0%) and ISO 9319:2024 (TCM *P. cocos* sclerotium) recommends triterpenoid quantification (eg, pachymic acid), existing standards remain fragmented and fail to comprehensively assess *P. cocos* quality. Therefore, establishing a multidimensional quality evaluation system that integrates chemical profiling with bioactivity assessment is critical for ensuring the rational utilization and industrial advancement of *P. cocos* resources.

Recent advances in analytical technology have significantly enhanced the precision of *P. cocos* quality assessment. For triterpenoid analysis, high-performance liquid chromatography (HPLC) with wavelength switching (210/241 nm) enables the simultaneous quantification of five triterpenoids, including pachymic acid and dehydrotumulosic acid[149]. The quantitative analysis of multi-components with a single marker (QAMS) method improved efficiency by quantifying six triterpenoids using a single standard. Combined with principal component analysis and hierarchical cluster analysis, it enabled the construction of a multidimensional quality evaluation model[150]. Our research group successfully applied this approach to quantify four key triterpenoids (eg, pachymic acid and dehydropachymic acid)[151], providing a reliable method for standardized quality control. Additionally, UHPLC-QTOF-MS/MS combined with orthogonal partial least squares-discriminant analysis (OPLS-DA) has differentiated *P. cocos* samples from four major producing regions and identified 10 region-specific triterpenoids (eg, dehydrotumulosic acid)[152], offering novel chemical markers for authenticity and geographical traceability. In polysaccharide analysis, the integration of high-performance gel filtration chromatography-evaporative light scattering detection (HPGFC-ELSD) and hydrophilic interaction liquid chromatography (HILIC-HPLC-ELSD), supported by chemometrics, has revealed correlations between molecular weight distribution and geographical origin, while identifying specific monosaccharide compositions as potential quality markers[153].

Emerging rapid detection technologies have facilitated industrial-scale quality control. Near-infrared spectroscopy combined with chemometrics has established predictive models for non-destructive quantification of polysaccharides and total triterpenoids[154], significantly improving evaluation efficiency. Thin-layer chromatography-spray ionization mass spectrometry (TLC-SI-MS) further overcomes the limitations of traditional methods by enabling *in situ* separation and identification of triterpenoids in different medicinal parts[155], supporting refined quality control. Moreover, DNA barcoding based on ITS sequences ensures accurate species authentication[156], prevents market adulteration with substitutes.

Although significant progress has been made, several critical challenges continue to impede further development. A persistent issue is the lack of standardized fragmentation methods, where notable discrepancies exist between pharmacopeial and ISO standards, compounded by incomplete coverage of bioactive components. Current research also faces technical limitations stemming from insufficient integration of chemical, spectroscopic, and molecular biological approaches. Most notably, over 90% of studies focus on component quantification without linking chemical profiles to pharmacological activity or clinical efficacy. To overcome these limitations, the development of a comprehensive and intelligent evaluation system that effectively links chemical composition, biological activity, and clinical outcomes should be prioritized in future studies.

Pharmacokinetic

P. cocos triterpenoids

The triterpenoids (eg, pachymic acid, tumulosic acid, and dehydrotumulosic acid) represent the primary bioactive constituents of *P. cocos*, and their PK profiles have been preliminarily elucidated using modern analytical techniques. Animal studies reveal that orally administered triterpenoids predominantly accumulate in intestinal and hepatic tissues, with metabolites detected in liver mitochondria in MASLD models[131]. Highly sensitive analytical methods (eg, LC-QQQ-MS/MS[157] and UPLC-Q-TOF/MS[158]) have enabled quantification of these prototypical compounds in plasma. Although largely resistant to gut microbial transformation, triterpenoids undergo extensive hepatic metabolism, as evidenced by the concurrent detection of parent molecules and metabolites in serum[159]. These findings underscore the liver as the principal site of biotransformation.

PK properties vary significantly between triterpenoids derived from different anatomical sources (eg, sclerotium *vs*. mycelium)[160], suggesting that material origin influences systemic exposure. In multi-compound formulations (eg, Yinling Qushi granule), 11 triterpenoids exhibit favorable PK profiles, implying enhanced absorption through synergistic interactions[161]. Mechanistic studies further show that specific triterpenoids (eg, pachymic acids A/B and polyporenic acid C) modulate bile acid metabolism *via* competitive inhibition of NTCP/ASBT transporters[162], whereas 7,9-(11)-dehydropachymic acid demonstrates the dual advantages of potent tyrosinase inhibition and excellent ADME properties (oral bioavailability > 70%)[163]. However, several components (eg, pachymic acid) still present challenges, including poor oral bioavailability and the need for complex solubilization techniques for intravenous delivery[164]. Advances in high-resolution mass spectrometry have substantially improved the elucidation of triterpenoid metabolic pathways. For instance, a study using UPLC-MS/MS combined with UNIFI software systematically identified 62 parent triterpenoids and 59 metabolites in *P. cocos* by simulating intestinal flora– and liver microsome–mediated metabolism *in vitro*. This analysis clarified the relationships between parent structures and downstream metabolites. Notably, oxygenated metabolites (eg, M + O, M + O_2) were shown to interact with key AD-related targets (such as CYP17A1 and VDR), offering mechanistic insights into potential neuroprotective effects through pathways involving neuroinflammation and amyloid-β deposition[159].Consistent with these findings, LC-ESI-MS(n) detected seven urinary triterpenoid metabolites and one plasma-derived metabolite in rats, further confirming the *in vivo* metabolic transformation of triterpenoids[165].

Despite these advances, current research on *P. cocos* triterpenoids still faces several critical challenges. Major gaps persist in pharmacodynamic evaluations of both prototype compounds and their metabolites. Moreover, conventional drug-delivery systems remain insufficient for improving the bioavailability of poorly soluble constituents. Most notably, most existing studies remain confined to component identification and preliminary activity screening, failing to establish systematic PK -pharmacodynamic (PD) correlation models. Future studies should prioritize novel delivery platforms and prodrug strategies, and incorporate multi-omics with physiologically based PK modeling to establish comprehensive exposure-response relationships[164–166].

P. cocos polysaccharides

As a key bioactive component, the PK profile of PCP is closely associated with gut microbiota metabolism. Although direct PK data remain scarce, current evidence indicates that PCP is primarily degraded by gut microbiota into oligosaccharides or monosaccharides, which are further metabolized into SCFAs (eg, acetate, butyrate, and propionate) to exert pharmacological effects[167]. PCP with diverse physicochemical properties – including WPCPs, APCPs, and structurally modified polysaccharides – demonstrate significant regulatory effects on gut microbiota composition and SCFA production (Figure 5).

Our group revealed that WPCPs enhance the intestinal mucosal barrier function by modulating microbial composition and increasing SCFA generation[62]. Further studies showed that WPCP ameliorates obesity-induced adipose tissue insulin resistance by enriching Lactobacillus and SCFA-producing bacteria, boosting SCFAs levels, and activating the FGF21/PI3K-AKT/GLUT4 pathway[127]. APCPs selectively elevate butyrate-producing bacteria (eg, *Lachnospiraceae* and *Clostridium*), augment intestinal butyrate levels, and activate the gut PPAR-γ pathway, thereby improving glucose/lipid metabolism and hepatic steatosis in ob/ob mice[168]. Additional studies have confirmed that APCP restores gut barrier integrity *via* microbial restructuring and enhanced SCFA production[169–170]. Notably, a β-1, 3-glucan from APCP exhibits anti-depressant effects by modulating gut microbiota (eg, altering *Romboutsia* and *Ruminococcus* abundance), increasing SCFA levels, and downregulating indoleamine-2,3-dioxygenase/kynurenine-3-monooxygenase enzyme expression[171].

Carboxymethylated PCPs (CMPs) alleviate 5-FU-induced intestinal mucositis in colorectal cancer mice by enriching SCFA-producing taxa (eg, *Bacteroidetes* and *Lactobacillus*), restoring SCFA levels, and coordinately regulating NF-κB/Nrf2-ARE/MAPK pathways[172]. Ma et al.[173] further demonstrated that

sulfated APCP dually modulates gut ecology by promoting probiotics (eg, *Bifidobacterium*/*Streptococcus*) and SCFA-producing *Muribaculaceae*, while simultaneously suppressing pro-inflammatory cytokines (IL-6/TNF-α).

Although polysaccharide degradation by carbohydrate-active enzymes is well documented[174–175], the specific metabolic fate and effector mechanisms of PCP require further exploration. Future studies employing fluorescent labeling or isotopic tracing could directly track PCP *in vivo* to advance PK understanding.

Mechanisms of herbal compatibility in compound formulations

P. cocos has traditionally been described as "found in nine out of ten prescriptions" due to its extensive clinical applications, and modern research has elucidated its compatibility mechanisms from multiple pharmacological perspectives. In Sijunzi decoction, the bioactive polysaccharide fraction (S-3) of *P. cocos* enhances intestinal immune function through dual mechanisms involving direct repair of the intestinal barrier and indirect modulation of the gut microbiota, characterized by increased abundance of *Butyricimonas* and *Collinsella* and enhanced production of SCFAs[176]. Simultaneously, the non-polysaccharide fraction acts independently of microbiota regulation to improve gastrointestinal hormone secretion, establishing a complementary therapeutic paradigm that constitutes the core material basis for treating spleen-deficiency syndrome[176]. Further PK investigations revealed that *P. cocos* critically influences the absorption, distribution, and excretion of co-administered compounds, with its removal from Sijunzi decoction accelerating the clearance of active components, such as ginsenosides and atractylenolides[177–178]. Mechanistically, *P. cocos* modulates the enterohepatic metabolic system to enhance targeted tissue accumulation and delay excretion of these compounds, thereby optimizing their spatiotemporal PK profiles[177]. As a minister herb, *P. cocos* also demonstrates synergistic potential with courier herbs, such as *Glycyrrhiza uralensis,* by facilitating the intestinal biotransformation of glycosides into more pharmacologically active aglycones, while its polysaccharide components prolong the systemic exposure of non-polysaccharide compounds[178].

Research on Dingzhi pill using Caco-2 cell models revealed that *P. cocos* triterpenes and ginsenosides achieve high apparent permeability coefficients through formulation synergy, with *Polygala tenuifolia* enhancing ginsenoside absorption and *Acorus tatarinowii* promoting *P. cocos* triterpene uptake[63]. Advanced analytical approaches, such as UPLC-ESI-QTOF-MS combined with multivariate statistics, have further identified characteristic differential components in Zhenwu decoction resulting from herbal compatibility, with *P. cocos* particularly influencing the dissolution profiles of gingerol-like compounds[141].

Contemporary research highlights how herbal compatibility achieves enhanced efficacy through coordinated modulation of gut microbiota and microbial metabolites, where *P. cocos*-containing herb pairs specifically reshape microbial community structure and regulate SCFAs production[179]. Modern research strategies, such as the Compound Component Molecular Framework approach, are bridging traditional knowledge with contemporary science by utilizing three-dimensional cell cultures and organoid models to decode compatibility principles[180]. These innovative methodologies maintain the multicomponent therapeutic advantages of traditional formulations, while ensuring compositional clarity and quality control, thereby establishing a rigorous framework for scientifically validating TCM compatibility theories. Together, accumulating evidence positions *P. cocos* as a pharmacologically versatile herb whose compatibility mechanisms operate through interconnected PK, microbial metabolic, and multi-target regulatory pathways (Figure 6).

Applications of *P. cocos*

P. cocos, one of the earliest medicinal materials formally recognized in China as both food and medicine, has a long history of use in both traditional medicine and dietary practices. Known as a "superior-grade immortal herb" in ancient texts, it was historically included in the saying "nine out of ten prescriptions contain *P. cocos*." Today, a comprehensive application system has been established around *P. cocos*, encompassing traditional Chinese decoction pieces, patent medicines, general foods, functional foods, cosmetics, and veterinary pharmaceuticals (Figure 7).

Medicinal value

P. cocos is a widely used traditional Chinese medicinal herb, historically referred to as "the divine medicine of all seasons." *P. cocos* is an essential component in numerous classical formulas, such as Wuling San and Sijunzi decoction. According to statistics, over 700 of the 4,052 patent medicines recorded in the Chinese Materia Medica Preparations contain *P. cocos*. The "*Chinese Pharmacopoeia*" (Chinese Pharmacopoeia Commission, 2025) lists over 200 *P. cocos*-containing patent drugs, covering a wide range of dosage forms. In 2015, the "Polysaccharidum of *P. cocos* Oral Solution" was approved by the Chinese Food and Drug Administration for the treatment of various cancers and hepatitis, both as a monotherapy and as an adjuvant to chemotherapy or radiotherapy. To date, it remains the only approved antitumor auxiliary drug formulated primarily from *P. cocos* polysaccharides[79].

Nutritional and edible value

P. cocos has long been recognized as a dual-purpose substance used in both food and medicine. In 2014, it was officially listed in the Catalogue of Substances Traditionally Used as Both Food and Chinese Medicine issued by the National Health Commission of China. Its use as a medicinal food dates back to *Divine Farmer's Classic of Materia Medica*, where it was classified as a top-grade herb suitable for long-term consumption. Historical records indicate that prominent

figures such as Su Shi used it in tonics like "*P. cocos* with sesame and honey" to treat illness, and Empress Dowager Cixi frequently included it in restorative prescriptions, highlighting its health-promoting and anti-aging properties.

In traditional Chinese culinary culture, *P. cocos* has been consumed in various forms. Classic examples include *P. cocos* cakes (fuling bing), *P. cocos* pastries, herbal teas (eg, fuling-coix tea, traditional dampness-clearing teas), herbal extracts such as Sijunzi Decoction paste, and innovative products such as *P. cocos*-fortified yogurt. Recent data show that over 830 functional food products containing *P. cocos* as a key ingredient have been registered in China, aimed at enhancing immunity, improving sleep, and aiding digestion. These products come in diverse dosage forms, such as capsules, oral liquids, and tablets, meeting the diverse health needs of modern consumers.

Other applications

Beyond medicinal and edible uses, *P. cocos* also demonstrates considerable application potential in cosmetics and veterinary medicine. According to the ancient text *Zheng Lei Ben Cao*, wine-infused *P. cocos* was believed to nourish the skin, prolong life, and maintain a youthful appearance. Modern studies have confirmed that *P. cocos* polysaccharides exhibit beneficial cosmetic properties, including whitening, moisturizing, and humectant activities, and are widely used in facial masks, cleansers, creams, and serums[181].

In recent years, various *P. cocos*-derived veterinary products, such as pachymaran powder, have been developed and commercialized. Additionally, studies have explored the potential of *P. cocos* in cryopreservation techniques, iron supplement development, aquaculture, and food preservation[182–186].

Conclusion and perspective

P. cocos, a long-established TCM with both medicinal and dietary value, has demonstrated broad pharmacological activities and significant application potential across diverse research domains, including pharmacology, immunology, metabolism, and oncology. In recent years, advances in extraction and purification technologies, multi-omics platforms, and animal models have facilitated deeper insights into the structure–function relationships of its bioactive components, particularly polysaccharides. These studies have progressively clarified the mechanisms through which *P. cocos* exerts anti-inflammatory, anti-oxidant, immunoregulatory, antitumor, and gut microbiota-modulating effects.

Despite these advances, several challenges persist. First, the structural complexity of PCP hinders the establishment of standardized quality control systems. Second, most pharmacological evidence is derived from *in vitro* and animal models, and robust clinical validation is still lacking. Third, the mechanisms underlying the synergistic and potentiating effects of *P. cocos*-containing herbal formulas remain insufficiently elucidated. Fourth, the translational pathway from basic research to product development lacks efficient and systematic integration.

Future research on *P. cocos* should focus on the structural characterization and standardization of its active constituents, along with the development of comprehensive quality assessment and traceability frameworks. Integrative multi-omics approaches are needed to elucidate pharmacodynamic mechanisms and therapeutic target networks. Notably, *P. cocos* is so widely used in TCM formulations that it has earned the epithet "found in nine out of ten prescriptions." This prevalence underscores the critical need to delineate its specific roles and mechanisms of action within polyherbal combinations. Future research should systematically elucidate the mechanisms by which *P. cocos* contributes to polyherbal formulations, specifically its roles in enhancing therapeutic efficacy, reducing toxicity, and modulating the body's internal environment. Emerging technologies such as artificial intelligence and big data analytics hold promise for constructing intelligent compatibility models to deepen mechanistic understanding of polyherbal formulations. Such progress will be critical for elucidating the scientific basis of herbal compatibility and advancing the modernization of TCM. Additionally, clinical translation should be strengthened to bridge the gap between experimental findings and clinical application. Moreover, in light of growing interest in nutrition and health-related industries, the development of *P. cocos*–based functional foods and wellness products warrants active exploration.

Through coordinated progress in fundamental research, clinical validation, theoretical innovation, and industrial transformation, *P. cocos* – as a representative model of TCM – holds strong potential for modernization and global integration.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Yue Zhang, Nianjun Yu, and Daiyin Peng conceived and designed this original draft. Gaoxiong Rao, Xian Zhang, Jie Yu, and Jian Liu filtered the articles and performed the figures. Yanyan Wang, Lei Wang, and Weidong Chen participated in writing, editing, and funding acquisition.

Huiping Zhouparticipated in editing. All of the authors have read and approved the published version of the manuscript.

Ethical approval of studies and informed consent

The work presented is based on a systematic analysis, synthesis, and evaluation of previously published scientific literature and does not involve any new human subject studies, animal experiments, or the collection of original clinical data.

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Data availability

All relevant data are within the manuscript.

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