Chinese Journal of Natural Medicines

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Citation: Xingchen Lu, Kejin Zhu, Yaping Huang, Ke Pan, Yucheng Zhao, Zhiqi Yin, Research progress on the main bioactive components and their corresponding biosynthetic enzymes in *Cyclocarya paliurus*, Chinese Journal of Natural Medicines, 2026, 24(2), 171−179. doi: 10.1016/S1875−5364(26)61088−6.

View online: https://doi.org/10.1016/S1875−5364(26)61088−6

Chinese Journal of Natural Medicines 24 (2026) 171-179

Contents lists available at ScienceDirect

Chinese Journal of Natural Medicines

journal homepage: www.cjnmcpu.com/

Review

Research progress on the main bioactive components and their corresponding biosynthetic enzymes in *Cyclocarya paliurus*

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ARTICLE INFO

Article history:
Received 1 February 2025
Revised 21 April 2025
Accepted 18 June 2025
Available online 20 February 2026

Keywords:
Cyclocarya paliurus
Triterpenoids
Flavonoids
Biosynthetic pathway

ABSTRACT

Cyclocarya paliurus (Batalin) Iljinsk., a medicinal and edible plant widely utilized in China, is a rich source of triterpenoids and flavonoids, which are recognized for their hypoglycemic, hypolipidemic, antioxidant, and antitumor properties. However, recent comprehensive summaries of its bioactive constituents and associated biosynthetic mechanisms remain limited. In this review, we systematically categorized the principal bioactive compounds isolated from *C. paliurus*, classifying triterpenoids into seven structural groups and flavonoids into four, based on their core skeletal frameworks. Notably, C-11 glycosylation was identified as a distinctive structural feature specific to *C. paliurus* triterpenoids. Furthermore, we summarized the key enzymes involved in the biosynthesis of these triterpenoids and flavonoids and, for the first time, proposed putative biosynthetic pathways by integrating current biochemical and genomic evidence. This review provides a comprehensive overview of the bioactive constituents and their associated biosynthetic enzymes in *C. paliurus*, offering valuable insights into the molecular basis of these natural products and establishing a foundation for future *in vitro* biosynthesis efforts.

1. Introduction

Cyclocarya paliurus (Batalin) Iljinsk., a member of the Juglans family, is the sole surviving species of the genus *Cyclocarya*. This plant, characterised by odd-pinnately compound leaves, is primarily distributed in southern and southeastern China [1]. Commonly known as the 'Money Tree' due to its coin-like fruits (Fig. 1A), the leaves of *C. paliurus* have been used for over a millennium to prepare nutraceutical tea (Fig. 1B) [2]. It is also referred to as the 'Sweet Tea Tree' because of the natural sweetness of its leaves, which have traditionally been valued for their anti-inflammatory, insecticidal, wind-dispelling and itch-relieving properties [3, 4]. Modern research demonstrated that *C. paliurus* leaves are rich in bioactive compounds, including flavonoids, triterpenoids, polysaccharides, and phenolic acids [5], offering health benefits, particularly for individuals with diabetes and hypertension [6-8].

Among the bioactive constituents, triterpenoids and flavonoids are considered the primary active ingredients [9]. The flavonoids in *C. paliurus* mainly occur as glycosides, exhibiting diverse sugar donors and glycosylation sites [10]. Notably, the triterpenoids in *C. paliurus* possess unique structural and pharmacological features compared to those in other triterpene-rich plants such as *Panax ginseng*, where triterpenes like ginsenoside Rg1 are predominantly glucose glycosides with a hydroxyl group at the C-6 position [11-14]. In contrast, *C. paliurus* triterpenoids feature distinctive sugar moieties—primarily quinovose (Qui) and arabinose (Arap/Araf)—along with a characteristic 3,4-*seco* structure, absence of propanaxatriol (PPT) skeletons, and hydroxyl groups at C-11 instead of C-12, resulting in unique glycosylation patterns (Fig. 1C) [15-17]. These structural distinctions suggest a novel biosynthetic mechanism for both triterpenoids and flavonoids in *C. paliurus*.

Despite extensive studies on the chemical composition, pharmacological properties, and biosynthetic processes of *C. paliurus* in recent years, a comprehensive review remains lacking. Herein, we aim to summarise the structures, biosynthetic pathways, and key genes associated with triterpenoids and flavonoids in *C. paliurus*, thereby enhancing understanding of these biosynthetic mechanisms and supporting the potential for *in vitro* biosynthesis of these compounds.

2. Bioactive components of *C. paliurus*

The bioactivities of *C. paliurus*, a traditional Chinese medicinal plant, have been extensively investigated. Numerous *in vivo* and *in vitro* studies have demonstrated that total triterpenoids, flavonoids, polysaccharides, and isolated compounds derived from *C. paliurus* exhibit significant pharmacological effects. The total triterpenoid fraction, termed *C. paliurus* triterpene (CPT), has been shown to attenuate kidney injury in diabetic rats by modulating the AMPK-mTOR-regulated autophagy pathway [18].

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https://doi.org/10.1016/S1875-5364(26)61088-6

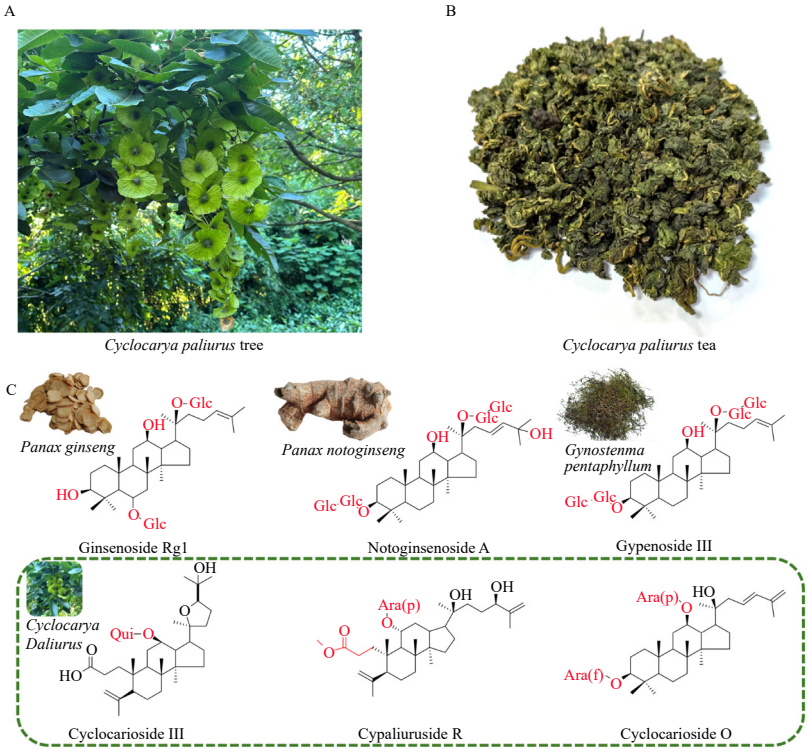


Fig. 1 Characteristics and triterpene structures of *Cyclocarya paliurus* and related plants. (A) *C. paliurus* tree. (B) *C. paliurus* tea. (C) Representative triterpene structures in other plants (*Panax ginseng*, *Panax notoginseng*, and *Gynostemma pentaphyllum*) and *C. paliurus*.

Additionally, CPT significantly reduces insulin resistance and hepatic steatosis in diabetic mice, indicating its potential for treating non-alcoholic fatty liver disease [19, 20]. *C. paliurus* flavonoid (CPF) plays a critical role in regulating the intestinal microbiome, particularly in high-fat diet-induced obese mouse models and those with circadian rhythm disruptions, helping to mitigate obesity-related metabolic disorders and positively influence host microbial composition [21, 22]. Moreover, CPF exhibits strong antioxidant and antibacterial activities [23]. Pharmacological studies have confirmed the bioactivity of dammarane-type triterpenoids from *C. paliurus*. For instance, cypaliuruside F (**68**) inhibits HepG2 cell proliferation by inducing apoptosis and cell cycle arrest [8]. Furthermore, cyclocariosides Z5–Z8 (**38**–**41**) are associated with hypoglycaemic effects [24], while cyclocariosides X, Y, Z2, and Z3 (**30**, **31**, **33**, **34**) demonstrate potent anti-inflammatory activity [25]. Among flavonoid compounds, afzelin (**168**) and kaempferol-3-*O*-*α*-L-(4''-*O*-acetyl)-rhamnoside (**171**) inhibit *α*-glucosidase, contributing further to the hypoglycaemic properties of *C. paliurus* [26]. Triterpenoids and flavonoids are the principal bioactive constituents responsible for the plant's blood sugar-lowering, lipid-lowering, anticancer, and antioxidant effects. This section summarises the classification and structural characteristics of these bioactive components in *C. paliurus*.

2.1. Triterpenes

The triterpenoids of *C. paliurus* can be classified based on ring structure into tetracyclic and pentacyclic types. Tetracyclic triterpenoids include dammarane-type and ocotillol-type compounds, whereas pentacyclic triterpenoids comprise oleanane-type and ursane-type structures. The first 3,4-*seco* dammarane-type triterpenoids isolated from *C. paliurus* were pterocaryoside A (**53**) and pterocaryoside B (**54**), identified in 1995 [27]. In the same year, two additional *seco*-dammarane triterpenoids, cyclocarioside II (**1**) and cyclocarioside III (**2**), were discovered [15]. Subsequent research has revealed a wide array of 3,4-*seco* tetracyclic triterpenoids, leading to their categorisation into A-ring *seco* and non-*seco* dammarane/ocotillol types. Nortriterpenoids such as cyclopalitin A (**85**) and cyclopalitin B (**86**) have also been identified from *C. paliurus* [28]. Notably, most tetracyclic triterpenoids from *C. paliurus* are glycosides, with aglycones being relatively rare (**55**–**61**, **85**, **86**, **115**) [29, 30]. This review provides a comprehensive summary of tetracyclic (**1**–**115**) and pentacyclic triterpenoid compounds (**116**–**163**) isolated from *C. paliurus*, with their names and structures detailed in Tables S1, S2 and Figs. 2, 3.

2.2. Flavonoids

The structural diversity of flavonoids in *C. paliurus* arises from a range of aglycones (sapogenins) and glycones (sugar chains). The flavonoids extracted from *C. paliurus* are predominantly flavonol glycosides, with kaempferol and quercetin as the main aglycones. Other flavonoid classes, including flavones, dihydroflavones, and isoflavones, also contribute to the glycoside profile of this plant. Sugar moieties typically include glucose, rhamnose, and glucuronic acid, with glycosylation occurring primarily at the 3-OH position [31-33]. Additional structural variation is introduced through functional groups such as methoxy (**205**), isoprenyl (**188**–**190**), and dioxolane (**172**), which can modify various positions within the flavonoid scaffold. This review summarises 55 flavonoid compounds (**164**–**219**) isolated from *C. paliurus*, with their names and structures detailed in Fig. 4 and Table S3.

3. Biosynthesis of triterpenoids and flavonoids in *C. paliurus*

3.1. General biosynthetic pathways of triterpenoids

Plants utilise two primary pathways for terpenoid biosynthesis: the mevalonate (MVA) pathway and the methylerythritol 4-phosphate/deoxyxylulose 5-phosphate (MEP/DOXP) pathway [34]. In *C. paliurus*, the MVA pathway, which operates in the cytoplasm and is primarily responsible for synthesising sesquiterpenes,

plant sterols, and triterpenes [35], dominates triterpenoid production.

The initial and rate-limiting step in terpenoid biosynthesis is the formation of the universal C5 building blocks isopentenyl diphosphate (IPP) and its isomer dimethylallyl diphosphate (DMAPP). Geranylgeranyl diphosphate synthase (GPS) catalyses the condensation of IPP and DMAPP to produce geranylgeranyl pyrophosphate (GGPP, C20), a precursor for diterpenoids. Farnesyl pyrophosphate synthase (FPS) then catalyses the condensation of IPP with geranyl pyrophosphate (GPP) to form farnesyl pyrophosphate (FPP, C15), a precursor for sesquiterpenoids. Squalene synthase (SQS) subsequently catalyses the head-to-head coupling of two form FPP molecules to generate squalene (C30), the central precursor for triterpenoid synthesis. Squalene is oxidised by squalene epoxidase (SQE), one of the key rate-limiting enzymes in triterpenoid biosynthesis, to yield 2,3-oxidosqualene [36,37].

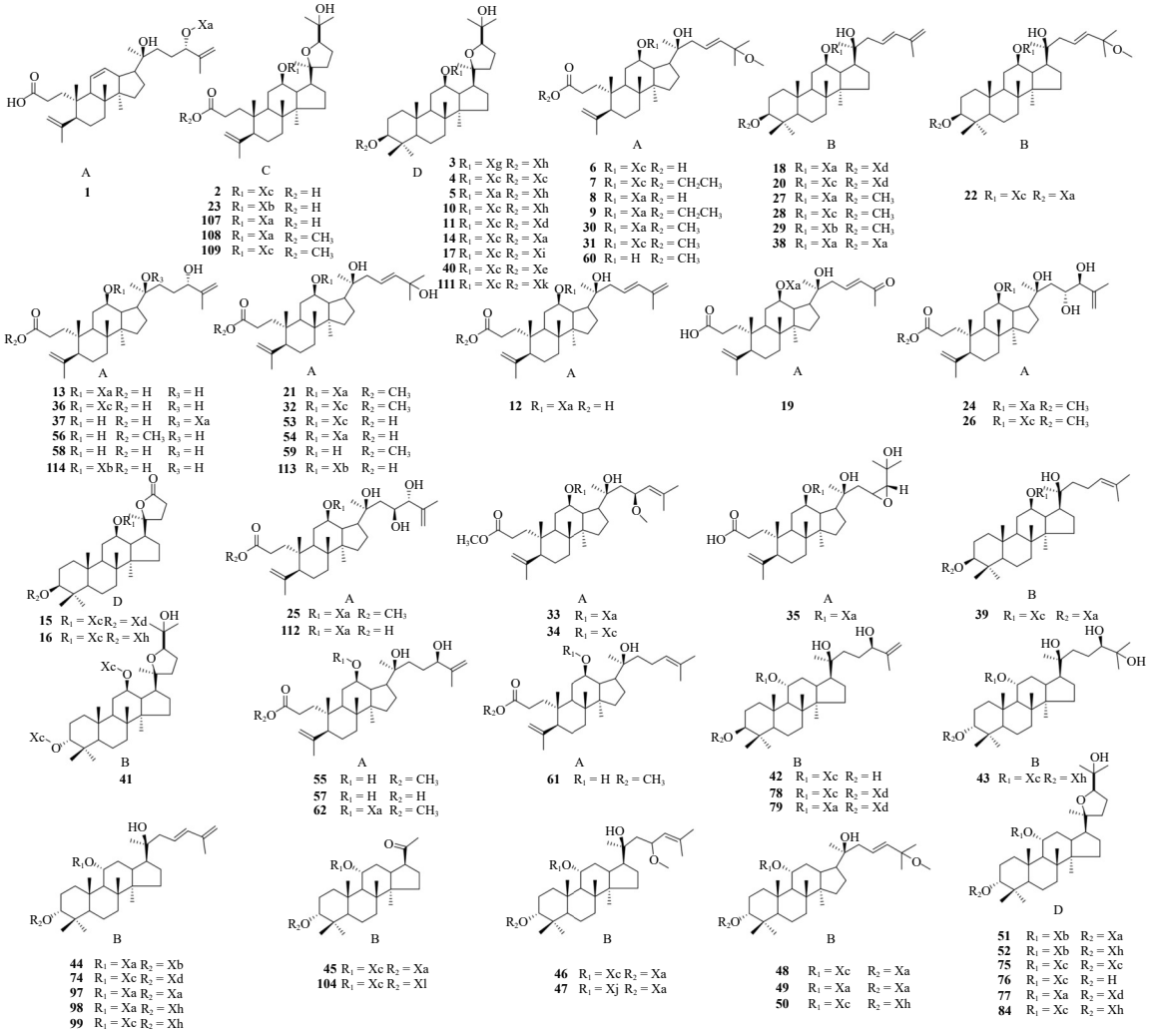
The cyclisation of 2,3-oxidosqualene proceeds *via* two distinct conformations: chair-boat-chair (CBC) and chair-chair-chair (CCC). The CBC conformation primarily leads to tetracyclic triterpenoids, whereas the CCC conformation predominantly yields pentacyclic triterpenoids [38]. Fig. 5 illustrates the general biosynthetic pathway for plant triterpenoids.

3.2. Specific biosynthetic pathway of triterpenoids in *C. paliurus*

While the early stages of the triterpenoid biosynthesis pathway in *C. paliurus* are well characterised, downstream mechanisms remain less understood. Recent studies have identified seven oxidosqualene cyclases (OSCs) that play pivotal roles in forming various triterpenoid skeletons during the initial cyclisation steps [10]. In the downstream pathway, pentacyclic triterpenoids likely undergo C28 oxidation mediated by cytochrome P450 enzymes (CYPs), forming a carboxyl group. This is followed by post-modification reactions, including glycosylation by glycosyltransferases (GTs), methylation by methyltransferases (MTs), and other enzymatic modifications, generating diverse triterpenoid products. For tetracyclic triterpenoids, particularly the unique 3,4-*seco* tetracyclic triterpenoids in *C. paliurus*, the proposed biosynthetic pathway begins with oxidation of the 3-OH group to a ketone by short-chain dehydrogenases (SDRs). This is followed by a Baeyer–Villiger oxidation rearrangement catalysed by CYP enzymes, leading to a seven-membered lactone ring. Subsequent hydrolysis and dehydration yield the characteristic 3,4-*seco* triterpenoid structure. Further post-modifications involving GTs, MTs, and other enzymes complete the biosynthesis [10,29,30]. Notably, two enzymes in *Citrus sinensis*, CsSDR and CsCYP716AC1, catalyse the 3-position oxidation and ring expansion steps in melianol derivative biosynthesis—structurally analogous to *C. paliurus* tetracyclic triterpenoids—supporting the proposed pathway [39]. Fig. 6 illustrates this biosynthetic route.

3.3. The identified triterpene genes involved in *C. paliurus*

Recent advances in multi-omics analyses have significantly contributed to identifying genes associated with triterpene biosynthesis in *C. paliurus*. In 2023, the genomes of *C. paliurus* were successfully assembled, encompassing two diploid and one tetraploid accession [40], providing a valuable genomic resource for



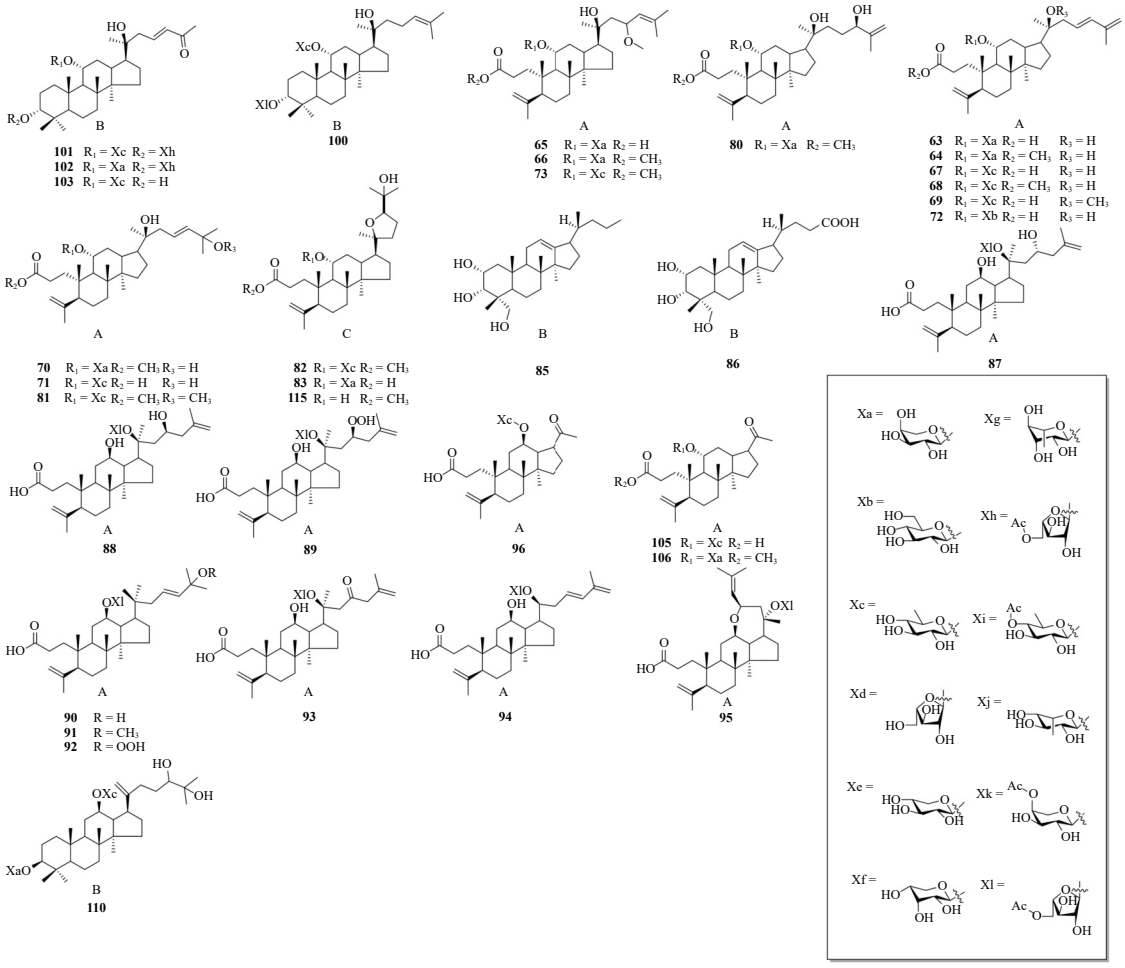


Fig. 2 Structure of tetracyclic triterpenoids in *C. paliurus*. Tetracyclic triterpene skeletons in plants can be divided into A-*seco* dammarane-type triterpenoids (A), non-A-*seco* dammarane-type triterpenoids (B), A-*seco* ocotillol-type triterpenoids (C), and non-A-*seco* ocotillol-type triterpenoids (D).

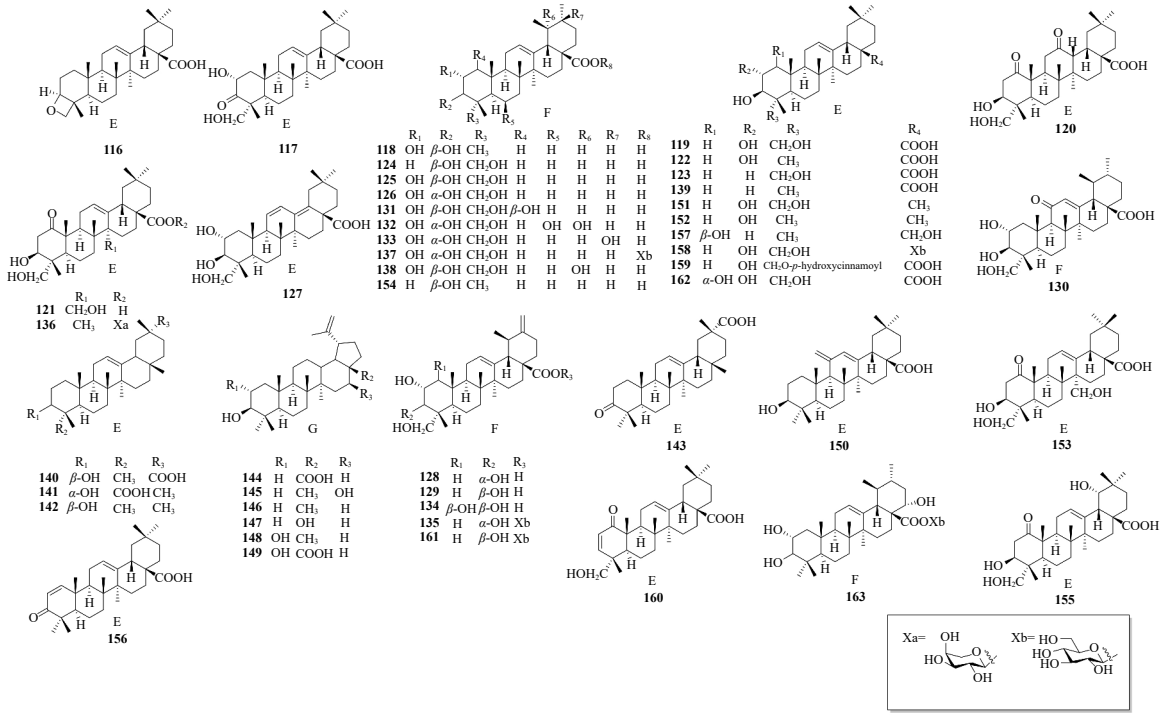


Fig. 3 Structures of pentacyclic triterpenoids in *C. paliurus*. Pentacyclic triterpene skeletons in plants can be divided into oleanane-type triterpenoids (E), ursane-type triterpenoids (F), and lupane-type triterpenoids (G).

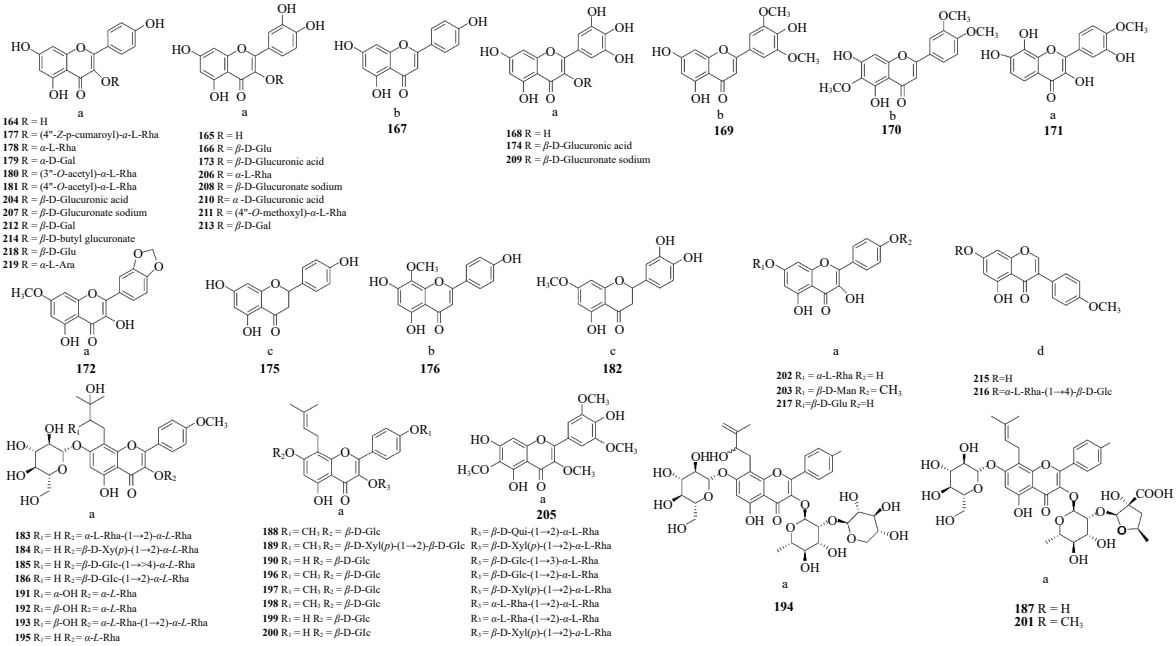


Fig. 4 Structures of flavonoids in *C. paliurus*. Flavonoid aglycones in plants can be divided into flavonol (a), flavone (b), dihydroxyflavone (c), and isoflavone (d).

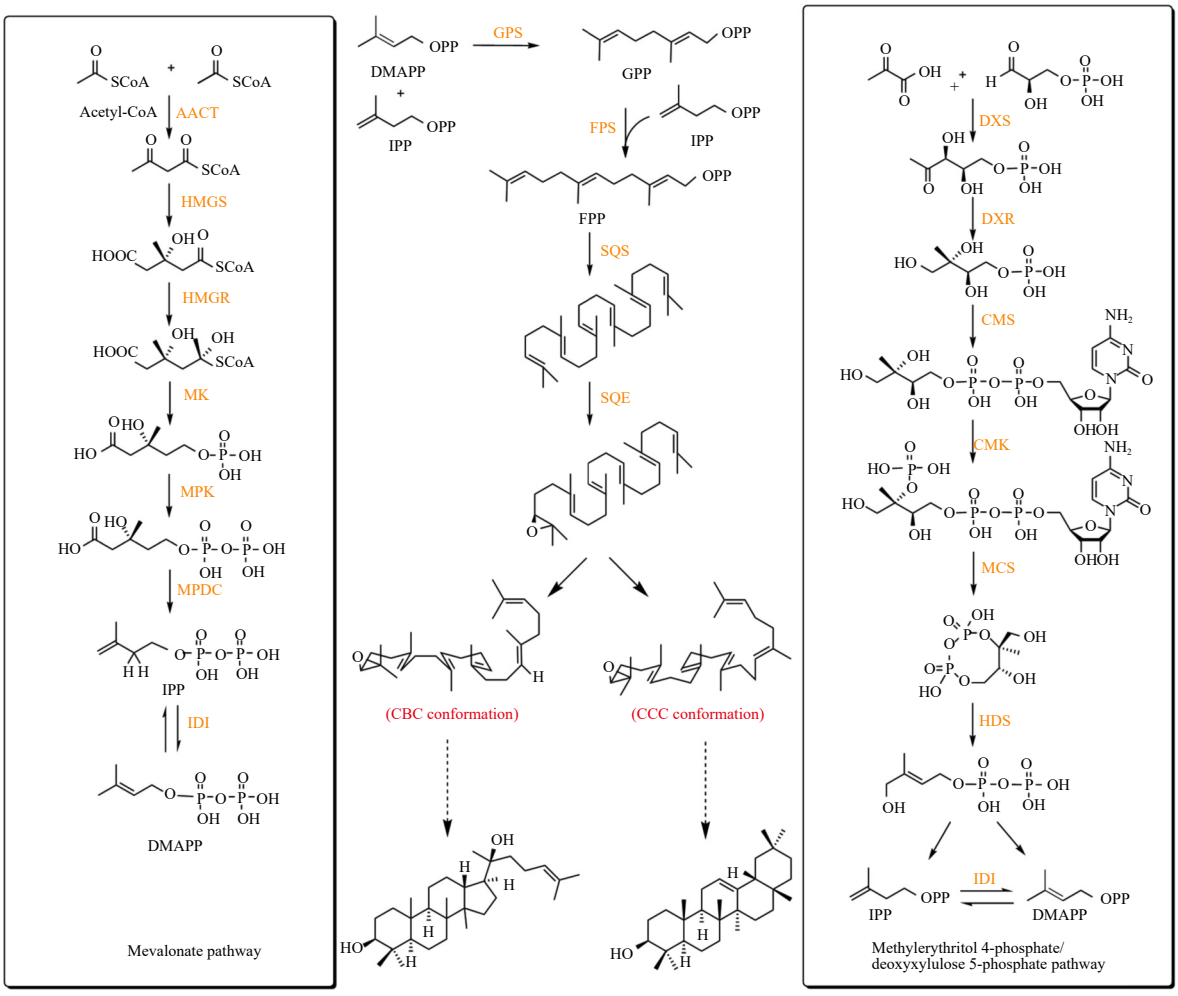


Fig. 5 The common biosynthetic pathway of triterpenoids. Enzymes catalyzing the different steps are highlighted in orange font. Enzyme abbreviations: AACT, acetoacetyl-CoA; HMGS, hydroxymethylglutaryl-CoA synthase; HMGR, hydroxy methylglutaryl CoA reductase; MK, mevalonate kinase; MPK, phosphomevalonate kinase; MPDC, mevalonate pyrophosphate decarboxylase; DXS, 1-deoxy-D-xylulose 5-phosphate synthase; DXR, 1-deoxy-D-xylulose 5-phosphate reductoisomerase; CMS, 4-diphospho-cytidyl-2C-methyl-D-erythritol-4-phosphate synthase; CMK, 4-diphosphocytidyl-2C-methyl-D-erythritol kinase; MCS, 2C-methyl-D-erythritol 2,4-diphosphate synthase; HDS, 1-hydroxy-2-methyl-2-butenyl-4-diphosphate synthase; IDI, isopentenyl diphosphate isomeras.

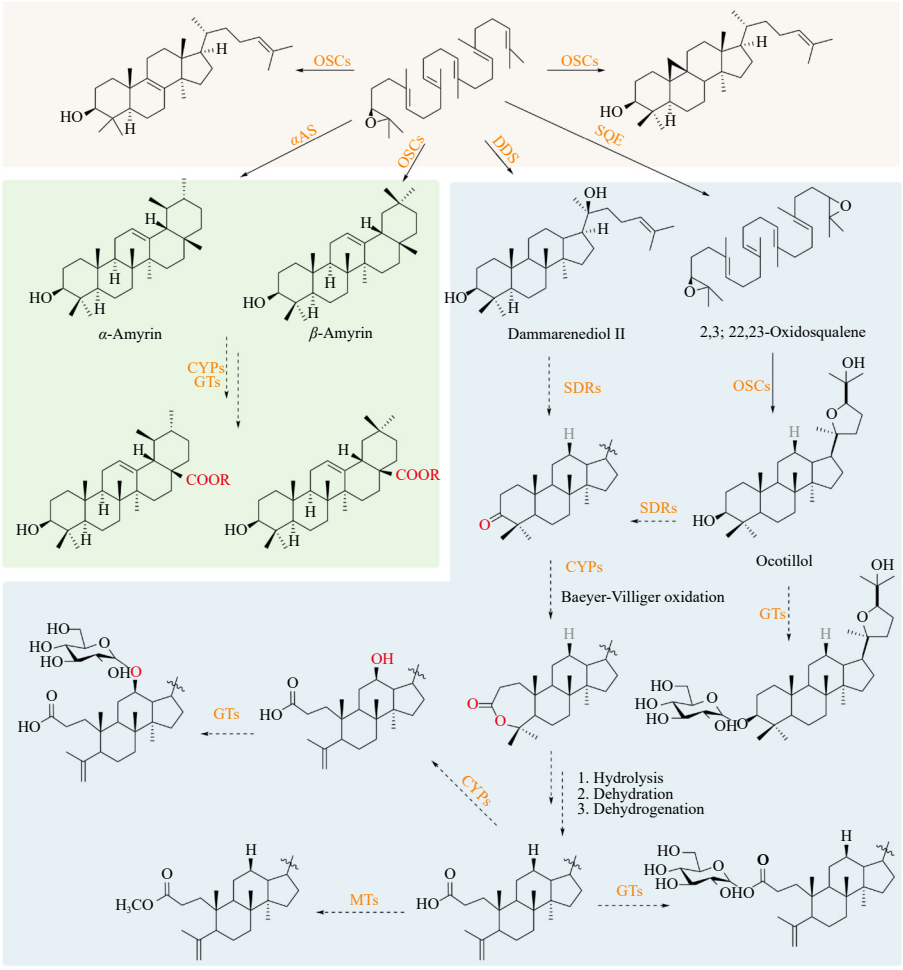


Fig. 6 The biosynthetic pathway of triterpenoids in *C. paliurus*. Solid lines represent steps that have been verified, while dashed lines indicate steps that have not yet been confirmed. Enzymes catalyzing the various steps are highlighted in orange font.

studying its biosynthetic pathways. Metabolomic analysis revealed that tetraploid *C. paliurus* exhibits enhanced triterpenoid metabolism, suggesting it as an ideal model for biosynthesis studies. Research on the triterpenoid pathway in *C. paliurus* has focused on key enzymes such as HMGS, HMSR, FPS, OSC, and UGT [41]. However, functional characterisation of these enzymes remains limited. In the MVA pathway, essential structural genes including *HMGS*, *HMSR*, *MPDC*, and *FPS* contribute to triterpenoid accumulation. Comparative metabolomic and transcriptomic analyses across different growth stages revealed that triterpenoids predominantly accumulate during leaf greening, coinciding with upregulation of MVA pathway genes in seedling and new leaf stages [42, 43]. Water stress enhances terpenoid accumulation, prompting gene expression studies under varying conditions, which identified 11 differentially expressed genes linked to terpenoid biosynthesis, primarily within the MVA pathway [44]. Key genes *SQS* and *SQE* play crucial roles in forming the triterpenoid precursor skeleton. Studies examining triterpenoid content and gene expression following treatment with *Aspergillus niger* elicitor (ANE) and across growth stages found a strong positive correlation between *SQS* and *SQE* expression and total triterpenoid levels [45, 46]. Downstream GTs such as UGT73C, UGT85A, and UGT85K have been identified in *C. paliurus* [42]. Using desorption electrospray ionisation (DESI)-MSI combined with non-targeted metabolomics, researchers inferred that upstream triterpenoid biosynthetic enzymes are localised in leaf veins, whereas post-modifying enzymes are primarily located in the leaf mesophyll [47]. Finally, Weighted Gene Correlation Network Analysis identified several transcription factors, including MYB and WRKY family members, that are highly positively correlated with triterpenoid production, suggesting their involvement in regulating triterpenoid and phenolic acid biosynthesis [41, 48, 49].

Recent studies have also partially elucidated the specific functions of certain *OSC* genes. To overcome challenges in validating gene functions *in vitro*, chassis fungus have been employed, enabling successful characterisation of *CpalOSC2* to *CpalOSC8*, which exhibit distinct epoxy SQS activities [10].

3.4. Biosynthetic pathway of flavonoids in *C. paliurus*

C. paliurus is rich in flavonoids, including flavonols, isoflavones, and dihydroflavones. The highly conserved and well-characterised flavonoid biosynthetic pathway offers valuable insights into flavonoid skeleton synthesis in this plant [50]. Biosynthesis begins with the conversion of phenylalanine to *trans*-cinnamic acid, catalysed by phenylalanine ammonia-lyase (PAL). *Trans*-cinnamic acid is then hydroxylated to 4-coumaric acid by cinnamate-4-hydroxylase (C4H), followed by activation to *p*-coumaroyl-CoA *via* 4-coumarate: CoA ligase (4CL). As a key precursor, *p*-coumaroyl-CoA undergoes multiple enzymatic transformations to yield dihydroflavonoids, isoflavones, flavonols and flavones. These conversions are mediated by chalcone synthase (CHS), chalcone isomerase (CHI), isoflavone synthase (IFS), flavonoid synthase (FNS), and various flavonoid hydroxylases. Finally, flavonoid compounds are modified through glycosylation and methylation, catalysed by GTs and MTs, respectively [51-53]. The flavonoid biosynthetic pathway in *C. paliurus* is depicted in Fig. 7.

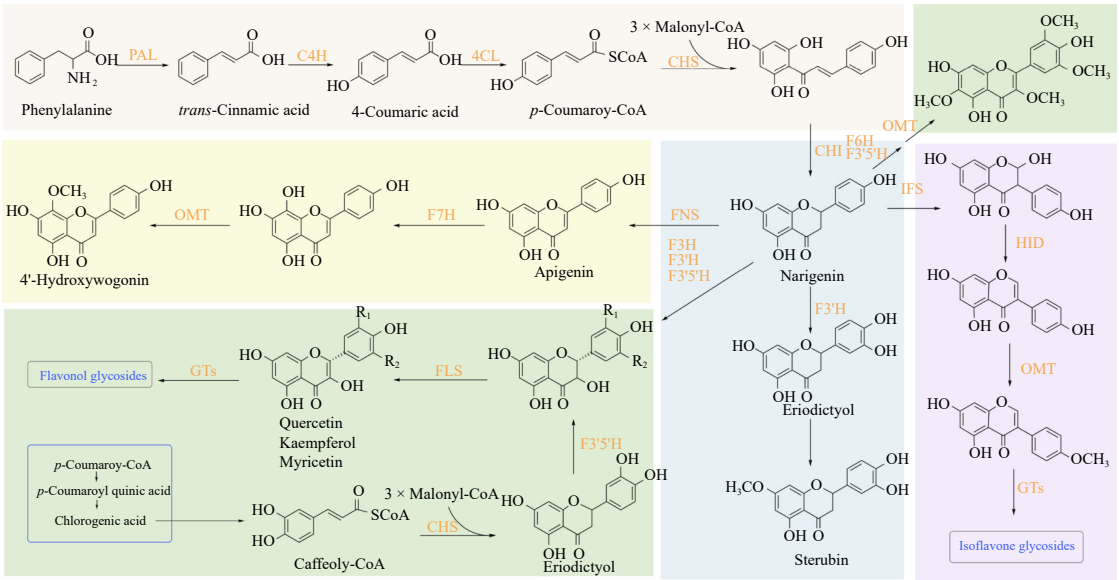


Fig. 7 The biosynthetic pathway of flavonoids in *C. paliurus*. Enzymes catalyzing the various steps are highlighted in yellow font. Enzyme abbreviations: HID, 2-hydroxyisoflavanone dehydratase; F3H, flavanone 3-hydroxylase; F3'H, flavanone 3'-hydroxylase; F5'H, flavanone 5'-hydroxylase; F3'5'H, flavanone 3',5'-hydroxylase; FLS, flavonol synthase; F7H, flavanone 7-hydroxylase.

3.5. The identified flavonoid genes involved in C. paliurus

Recent research has revealed a strong correlation between gene expression and flavonoid metabolic levels in *C. paliurus*. Enzymes such as PAL, C4H, and 4CL, responsible for producing *p*-coumaroyl-CoA, a key precursor in flavonoid biosynthesis, have been identified. Notably, PAL, associated with flavonoid accumulation, is upregulated under salt stress [54, 55]. Transcriptomic and metabolomic analyses have identified C4H and 4CL as key enzymes in flavonoid biosynthesis across developmental stages [56]. Interestingly, CHS, typically the first committed enzyme in the flavonoid pathway, has not been identified as a pivotal gene in *C. paliurus*, as CHS activity does not correlate positively with flavonoid accumulation under different nitrogen treatments [57]. However, analysis of transcriptome and metabolome data from four leaf developmental stages has identified CHI [58]. Genes involved in synthesising various flavonoid skeletons—including *FNS*, *IFS*, flavonoid 3'5'-hydroxylase (*F3'5'H*), flavonoid 3'-hydroxylase (*F3'H*), and *CYP*—have been validated by correlating gene expression with compound accumulation under hormonal stimuli [59].

Considerable research has also focused on downstream GTs in *C. paliurus*. In particular, three UGTs from the CpUGT71 family have been highly correlated with the accumulation of flavonoid glucuronides in tetraploid *C. paliurus* [60]. Specific GT functions have been characterised: CpGT1 exhibits high activity toward flavones and flavonols but reduced activity toward isoflavones, flavanones, or triterpenoids. Mutations such as A43F, V84P, and M201Y significantly alter regioselectivity and enzymatic activity. The W283M mutation and deletion of the V309–D320 region enhance activity and disaccharide formation, providing key insights into the molecular mechanism of CpGT1 [9]. Recombinant CpalUGT100 facilitates glycosylation at the C-3 position using UDP-glucose as the sugar donor and genistein as the acceptor. Meanwhile, recombinant CpalUGT015 catalyses C-5 and C-6 glycosylation of genistein and apigenin, yielding genistin and apigetrin [10].

4. Conclusion and perspective

C. paliurus is a valuable source of bioactive compounds, with triterpenoids and flavonoids recognised as the primary active constituents. These compounds display considerable structural diversity: triterpenoids are mainly categorised into pentacyclic and tetracyclic forms, while flavonoids are classified into flavonols, flavones, isoflavones, and dihydroflavonoids based on their aglycone structures.

Despite significant progress in identifying bioactive molecules in *C. paliurus*, the biosynthetic mechanisms governing their production remain largely unresolved. Current research has primarily focused on correlating the expression levels of enzyme-coding genes under various growth conditions with corresponding triterpenoid and flavonoid levels. Key genes in triterpenoid biosynthesis, including *HMGS*, *HMSR*, *FPS*, *OSCs*, and *GTs*, have been identified. For flavonoid biosynthesis, genes such as *PAL*, *C4H*, *4CL*, *FLS*, *CHS*, *F3'H*, *F3'5'H*, *DFR*, and *GTs* have been characterised. These findings have advanced the understanding of the biosynthetic pathways in *C. paliurus*. However, several critical issues remain. First, many genes encoding biosynthetic enzymes are insufficiently characterised, particularly those involved in the cleavage of 3,4-*seco* tetracyclic triterpenoids and downstream post-modification enzymes, which require functional validation. Second, although several transcription factors related to triterpenoid and flavonoid biosynthesis have been identified, further investigation into their regulatory mechanisms is needed to understand their roles in secondary metabolite accumulation. Third, there is a notable gap in research on the spatial and temporal distribution of biosynthetic genes within the plant; exploring this could greatly enhance understanding of metabolic compartmentalisation. Finally, determining the structures of specialised enzymes responsible for unique reactions is essential for elucidating the underlying molecular mechanisms.

Overall, while substantial advancements have been made in understanding the biosynthetic pathways of *C. paliurus*, challenges persist in confirming enzyme functions, analysing regulatory networks, deciphering metabolic distributions, and elucidating molecular mechanisms. With ongoing technological advancements and interdisciplinary collaborations [61-63], these challenges are expected to be addressed, paving the way for developing bioactive compound-enriched varieties and enabling *de novo* biosynthesis of these compounds *in vitro*.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82574280), the Natural Science Foundation of Jiangsu Province of China (No. BK20252070), and the TCM Science and Technology Development Plan of Jiangsu Province (No. ZD202418).

Availability of supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

These authors have no conflict of interest to declare.

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