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Review

Biological Functions and Synthesis of the Active Components in *Antrodia camphorata*

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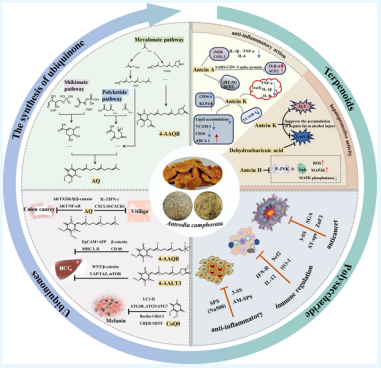
ABSTRACT: As a fungus endemic to Taiwan, *Antrodia camphorata* contains a variety of medicinally active substances, such as polysaccharides, triterpenoids, maleic acid and succinic acid derivatives, and ubiquinone derivatives. *A. camphorata* has attracted widespread attention due to its uniqueness, rarity, remarkable efficacy, and high economic value. In this work, we analyze the recent progress and future development of the artificial culture of mycelium of *A. camphorata*. This Review focuses on the types, properties, functions, and mechanisms of action of the characteristic active substances of *A. camphorata* and summarizes the methods of metabolic regulation and biosynthesis of the characteristic active substances. This Review provides valuable information for research on the metabolic regulation and efficacy analysis of the active substances and provides a theoretical basis for the in-depth development of the active ingredients in *A. camphorata*.



1. INTRODUCTION

Antrodia camphorata (*A. camphorata*), a wood-rot basidiomycete in the family Fomitopsidaceae, is a unique perennial mushroom endemic to Taiwan, China. It is also known as camphor, camphor mushroom, God mushroom, etc. It has been officially renamed *Taiwanofungus camphoratus* in Taiwan. The surface of its fruiting body is reddish brown, light brown, or orange yellow. The medicinal history of *A. camphorata* in Taiwan can be traced back 200−300 years ago, but it has only received public attention for 20 years. Wild *A. camphorata* grows very slowly in nature, and it generally takes 1−3 years before it can be picked. Owing to its uniqueness, rarity, significant physiological effects and high economic value, it has been widely considered and praised as the "Ruby of the forest" and "King of medicine".[1] Its wild fruiting body grows on the hollow and decaying inner wall of *Cinnamomum kanehirae*, a conservation tree species in Taiwan, or on the dark and moist surface of dead *Cinnamomum kanehirae*.[2] In addition, the extremely slow growth of wild-camphorated mushroom fruiting bodies makes it difficult to meet market demand, which far outstrips supply, leading to prices as high as $15,000 to $25,000 per kg.[3]

As a folk medicine in Taiwan, *A. camphorata* is often used to treat alcoholism and liver disease. Many cancer patients in Taiwan often use *A. camphorata* as an auxiliary therapeutic agent or nutritional agent in the process of cancer treatment.[4,5] *A. camphorata* contains dozens of active substances, such as polysaccharides, terpenoids, ubiquinone derivatives, succinic and maleic acid derivatives, and superoxide dismutase (Figure 1). These active substances have various physiological effects, such as treating skin itching, protecting the liver, antiviral, immune regulatory, antitumor, and anti-inflammatory effects, and treating hypertension.[6] Because of the extremely slow growth rate and strict host specificity of the fruiting body, mycelium, which has a short growth cycle and is easily cultivated, has received attention. At present, the mycelium of *A. camphorata* can be mainly obtained via two artificial culture methods: solid fermentation and liquid fermentation.[4,7] Solid fermentation can produce many bioactive metabolites via the use of different kinds of grains or agricultural byproducts as substrates, but fermentation usually takes several months. In addition, the solid fermentation of *A. camphorata* results in a low yield and is difficult to control, which makes it difficult to meet the needs of industrial production. In contrast, liquid fermentation can obtain mycelium in a much shorter time (1−2 weeks). It is also technically more suitable for large-scale industrial production than solid-state fermentation. This Review covers the research progress on the characteristic bioactive substances in *A. camphorata* to provide a reference for the efficient synthesis and wide application of characteristic bioactive substances.

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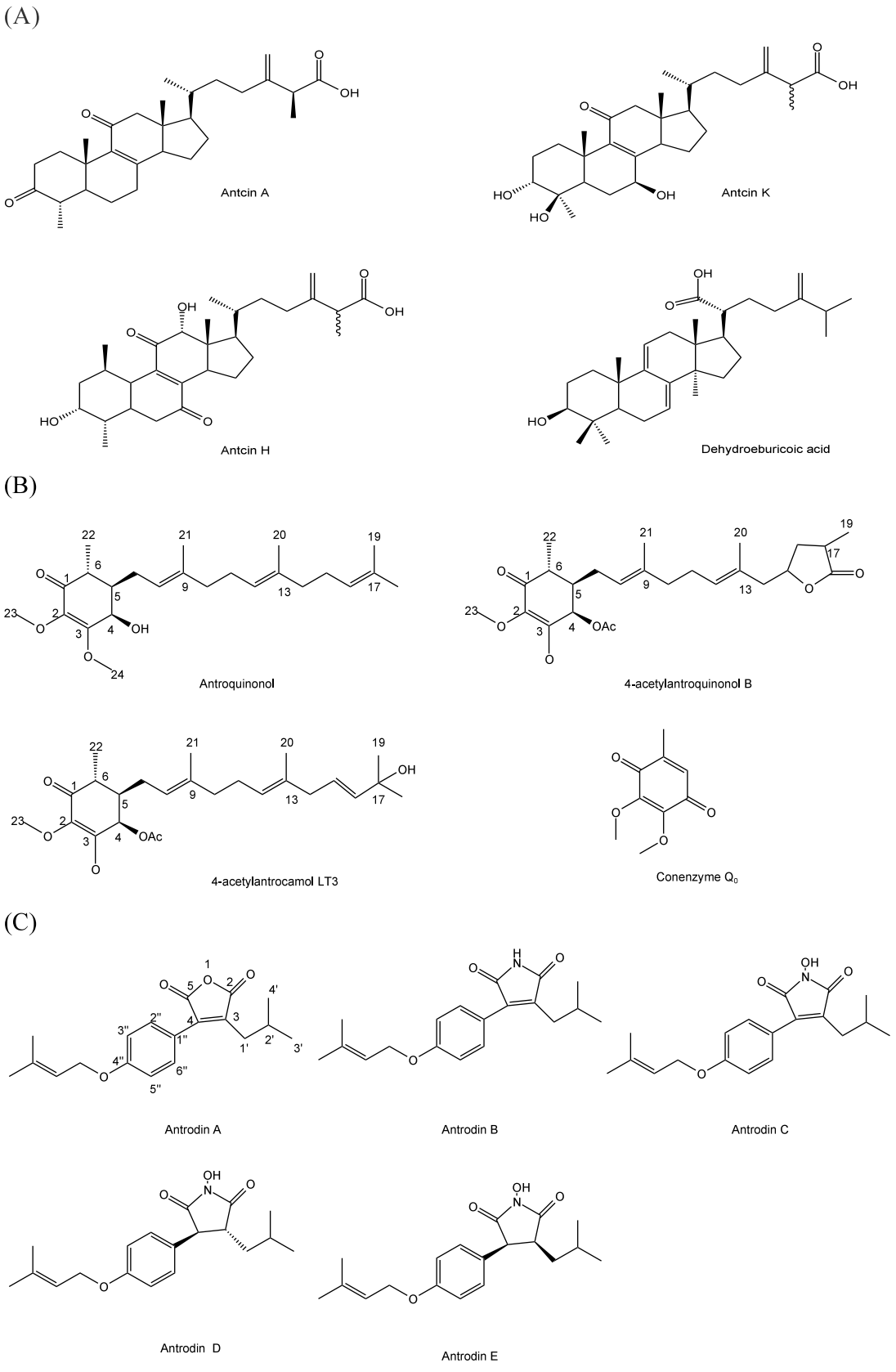

Figure 1. Structures of triterpenoid (A), ubiquinone derivatives (B), and maleic acid and succinic acid derivatives (C) in *A. camphorata*.

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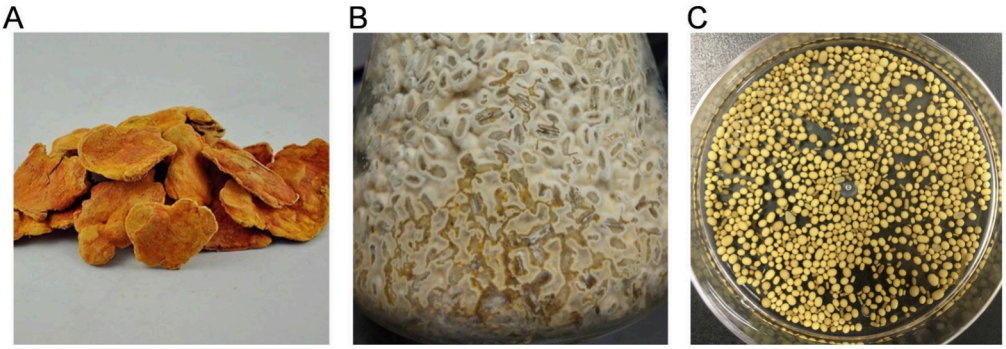

Figure 2. Artificial cultures of *A. camphorata* fruiting bodies (A) and mycelium (B and C).

2. METHODOLOGY

Data were obtained by searching various scientific online databases, including Google Scholar (https://scholar.google.com/), Baidu Scholar (https://xueshu.baidu.com/), ScienceDirect (https://www.sciencedirect.com/), Web of Science (https://www.webofscience.com/), PubMed (http://pubmed.cn/), Wiley (https://www.wiley.com/en-cn), Nature (https://www.nature.com/), SpringerLink (https://link.springer.com/), and ACS Publications (http://pubs.acs.org) using keywords such as *Antrodia camphorata*, artificial cultivation, active compounds, mechanism, biological functions, metabolic regulation, biosynthesis.

3. RESEARCH ON ARTIFICIAL CULTIVATION OF *A. CAMPHORATA*

The natural growth carrier of *A. camphorata* is an endemic tree species in Taiwan, and its number is rare. The fruiting body of wild *A. camphorata* grew very slowly. Therefore, the improvement and discovery of artificial cultivation technology of *A. camphorata* is a major key. Currently, artificial cultivation methods, such as liquid fermentation, solid fermentation, and basswood cultivation, are mostly used (Figure 2).

3.1. Basswood Cultivation. Basswood cultivation is to take a piece of basswood from a *Cinnamomum kanehirae* and make it grow in conditions similar to its natural state. This piece of basswood is used as the culture substrate of *A. camphorata*. At the same time, the basswood is inoculated with liquid bacteria by soaking or spraying, and then the basswood is placed in a suitable temperature and humidity environment for cultivation. At present, the fruiting body has been successfully developed and grown on different wood substrates, including two broad-leaved trees of *Cinnamomum kanehirae* (original host) and *Cinnamomum camphora*, as well as a coniferous tree of *Cunninghamia konishii Hayata*. Lin et al.[8] selected 13 representative fruiting body compounds of *A. camphorata* as index compounds. They analyzed the composition of fruiting body metabolites of *A. camphorata* on different culture ages and wood substrates. According to their results, the wood substrate is an important factor for metabolite production. When *A. camphorata* was planted in nonoriginal host wood, metabolites produced were different from those grown in original host wood. Lanosterane and ergosterane triterpenoids were found in the fruiting bodies of *Cinnamomum kanehirae* AC-9-9, but not found in *Camphor* AC-9-9-CC or KONISHII AC-9-9-CK. Although the active ingredients in the fruiting body cultured by this method are close to those in the wild fruiting body, the disadvantages of this method such as low yield, high cost, long cultivation time of 1−3 years, and difficulty in industrial production limit its large-scale application.

3.2. Solid Fermentation. The substrate used in solid state fermentation culture is mainly lignocellulosic waste from wheat and rice straw, bran, rice husk, forestry byproducts and corn cobs.[9] Compared with basswood culture, there were almost no typical triterpene compounds in the mycelium products of *A. camphorata* by solid fermentation, but some new active compounds could make up for the deficiency. In the solid-state fermentation system, the culture conditions of *A. camphorata* are more natural, which is conducive to the synthesis of active components. Previous studies have identified antrodins A, B, and C as the primary bioactive compounds produced during the solid-state fermentation of *A. camphorata*. Among these compounds, antrodin C exhibits the highest content.[10−12] Xia et al.[13] artificially optimized the cultivation conditions and investigated the effects of soybean meal concentration, initial moisture content, and inoculum size on antrodin C yield during solid fermentation using response surface methodology. The effects of different solid substrates and external nitrogen sources on its yield were mainly investigated. The experimental results showed that the optimal fermentation medium was 0.578 g of soybean meal, 0.05 g of Na_2HPO_4, 0.05 g of $MgSO_4$ (100 g of rice), initial moisture content of 51.83%, culture temperature of 22 days, culture temperature of 28 °C, and inoculum density of 35.54%. Under the optimized conditions, the yield of antrodin C was 6617.36 ± 92.71 mg/kg. Li et al.[14] studied a new strategy of *A. camphorata* cofermented with Chinese medicinal herb (AC-CF). It could enhance the antitumor effect of *A. camphorata* on human liver cancer HepG2 cells compared with the traditional cofermentation of two other extracts from fruiting bodies (AC-FB) or solid-state culture (AC-SS). The antitumor effect of *A. camphorata* could be enhanced by culturing it in a medium supplemented with a low percentage (3%, w/w) of licorice root powder. Liu et al.[15] studied the anti-inflammatory activity of *A. camphorata* mycelia obtained by solid culture and liquid fermentation in mouse microglia. The results indicate that the methanolic extract of *A. camphorata* solid culture had anti-inflammatory activity similar to that of the fruiting body in mouse experiments, but its anti-inflammatory activity on microglia was poor.

3.3. Liquid Fermentation. In contrast, the incubation time of liquid fermentation is 7−14 days, which is also technically more suitable for large-scale industrial production than solid fermentation. In this light, liquid fermentation seems to be a more promising method. However, liquid fermentation still faces several challenges, the first one is how to obtain sufficient amounts of stable active substances through liquid fermentation,

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Table 1. Liquid Fermentation of *A. camphorata*

Strain	Fermentation scale (L)	Metabolites	Production	Biomass (g/L)	Reference
BCRC35396	0.25			21.64	17
BCRC35396	0.25	EPS	0.15 g/L	8.87	18
BCRC35396	0.25	Lipase	6.17 U/L		19
BCRC35396	0.25	EPS	0.49 g/L	2.60	20
AC0623	700	Triterpenoids	63.0 mg/g		21
BCRC35396	0.25	EPS	1.36 g/L	8.70	22
BCRC35396	5000	EPS	1.2 g/L	27.10	23
		Triterpenoids	2.0 g/L		
ATCC200183	0.5	Triterpenoids	64.79 mg/L		24
CCRC35396	0.25	EPS	230.8 mg/g	21.96	25
		Triterpenoids	282.9 mg/L		
	0.5	Antrodin C	0.25 g/L	12.05	26
BCRC35716	5	4-acetylantroquinonol B	0.7 mg/g	6.0	27
	5	Antrodin C	1.55 g/L		28
	0.5	Antroquinonol	82.2 mg/L	8.5	29
ATCC200183	0.5	EPS	72.8 mg/g		30
		Antrodin A	1.4 mg/g		
BCRC35716	0.5	4-acetylantroquinonol B	27.8 mg/g	3.3	31
	0.25	EPS	1.03 g/L	10.58	32
BBZ-001	0.5	Antrodin C	605.1 mg/L		33
AY378094	0.25	Triterpenoid	532.3 mg/L		7
	0.5	Antrodin C	1615.7 mg/L	14.75	34

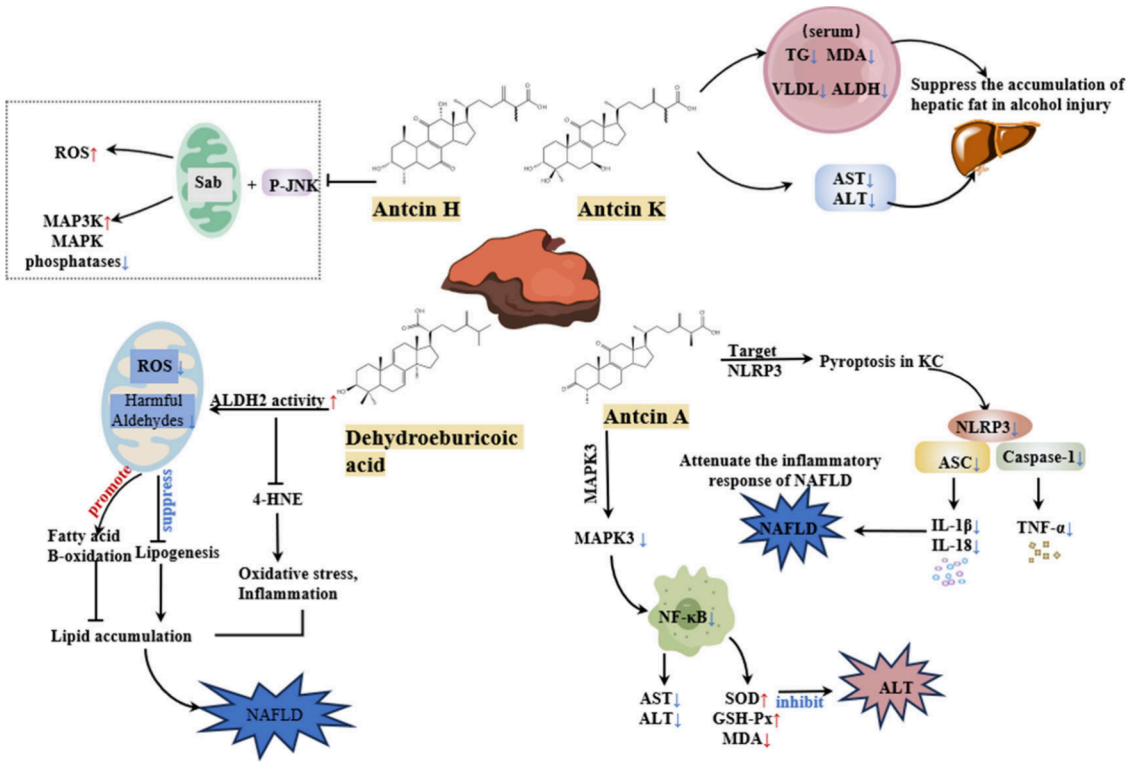

Figure 3. Mechanism of hepatoprotective activity of terpenoids in *A. camphorata*.

and another important issue is that the amount of bioactive compounds obtained from mycelial liquid fermentation is significantly less than that of wild substrates.[16] Therefore, it is essential to improve the yield of bioactive substances from liquid fermentation by optimizing the culture conditions and regulating the fungal metabolism. Since the submerged fermentation of *A. camphorata* has obvious advantages over the basswood cultivation method and solid-state fermentation, many experts and scholars have conducted in-depth studies in an attempt to increase the amount of its metabolites and mycelia. The purpose is to make liquid fermentation products more medicinal and competitive in the market. According to Table 1, the amount of mycelium and bioactive substances obtained from submerged fermentation using different strains differed greatly. It is indicated that the amount of metabolites was affected by factors such as strains, fermentation conditions, and so on.

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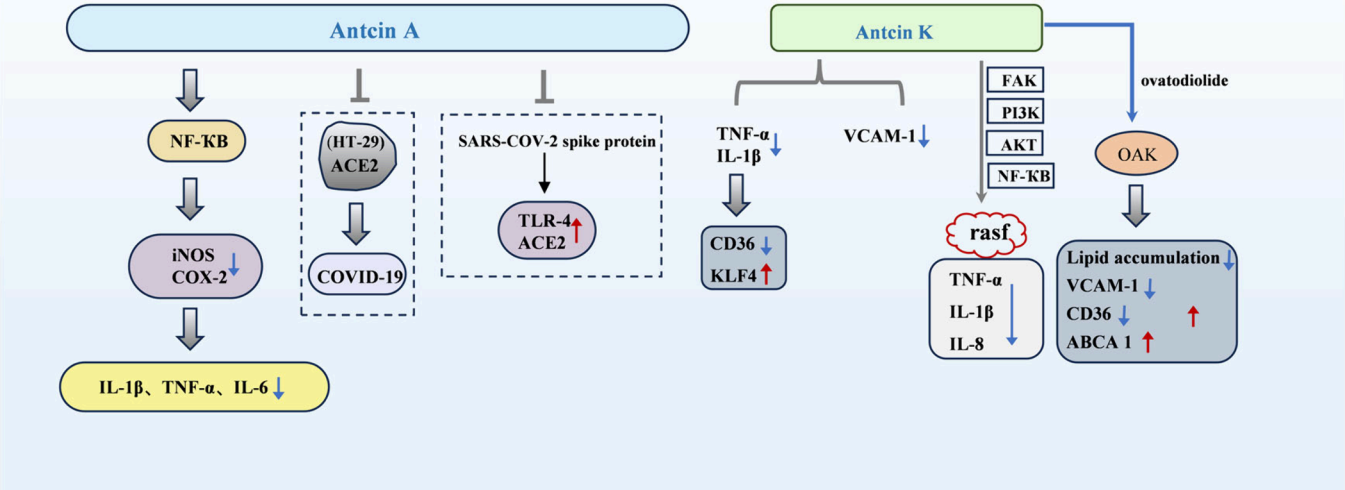

Figure 4. Mechanism of anti-inflammatory action of terpenoids in *A. camphorata*.

4. BIOACTIVE COMPONENTS OF *A. CAMPHORATA*

4.1. Terpenoids. Mushrooms are significant reservoirs of triterpenoids, with these compounds being identified in various species such as *A. camphorata*, *Ganoderma*, *Hericium erinaceus*, *bird's nest fungi*, and other related fungi. Experimental studies have demonstrated their broad-spectrum biological activities, which include notable antimicrobial, anti-inflammatory, neuroprotective, and antioxidant properties. These findings highlight their substantial pharmacological potential.[35−37] Terpenoids are the most diverse class of natural products in *A. camphorata*, which are composed of five carboisoprene units and have various effects such as anticancer, liver protection, anti-inflammatory, antidiabetes and neuroprotection.[38−40] *A. camphorata* contains triterpenes, diterpenes, sesquiterpenes, and other terpenoids. The high content of triterpenes is an important active ingredient in fruiting body, which is also the source of bitter taste. Based on the color appearance of the fruiting bodies of *A. camphorata*, they can be classified as red AC (RAC), yellow AC (YAC), and white AC (WAC). The total triterpene content of different phenotypes of *A. camphorata* varied significantly, with the highest content of RAC (116.4 mg/g), followed by YAC (63.9 mg/g), and the lowest content of WAC (51.3 mg/g).[41]

At present, most of the terpenoids were isolated from the fruiting body and mycelium, and a few were isolated from the culture medium. Chemical or enzymatic modifications can expand the structural diversity of terpenes and improve their physicochemical and pharmacological properties as drug candidates. For example, hydroxylation or glycosylation can improve the solubility, bioavailability and bioactivity of triterpenes.[42] Luo et al.[43] found for the first time that the methanol extract of *C. kanehirae* trunk (2 g/L) not only had a strong promotion effect on increasing triterpene production of *A. camphorata* (115.6 mg/L) but also significantly increased the types and abundance of many secondary metabolites in mycelium. Wang et al.,[44] in order to obtain a high yielding strain of triterpenes, used combined EMS and ARTP mutagenesis breeding and optimized the culture conditions. The optimal culture conditions for triterpene biosynthesis were 85 g/L glucose and 10 g/L yeast extract, pH 5.0, and 28 °C, and the triterpene yield was 255.5 mg/g, which was 47.9% higher than that before optimization. The contents of antcin A and antcamphin A were greatly increased, and the obtained triterpenes had significant protective effects against CCl_4-induced acute liver injury in mice. The therapeutic potential of triterpenes for a number of diseases is obvious. However, our understanding of the specific mechanisms of action and molecular targets of pure compounds is still limited, especially those that differ from those of currently known drugs. In addition, for complex terpene production, synthetic biology is a promising method, but biosynthesis studies are still at an early stage.[45] The fruiting body of *A. camphorata* contains a series of complex tetracyclic triterpenoids, including ergosteranes and lanosteranes, which have relatively similar structures except for differences in the number, position, or stereochemistry of hydroxyl groups. These triterpenoids are the main bioactive components with hepatoprotective, anti-inflammatory and antidiabetic activities.

4.1.1. Liver Protection. Triterpenoid extract from *A. camphorata* mycelium has been shown to be effective in preventing alcoholic liver injury (Figure 3). Liu et al.[46] found that it protects the body from liver injury caused by chronic alcohol intake by regulating lipid metabolism through mouse experiments, which may be related to mediating lipid metabolism related to PGC-1α and NF-κB signaling. Anctin K, antcin H, and antcin A are the major hepatoprotective compounds of *A. camphorata*. Anctin K is a promising candidate for liver injury due to its high natural abundance and good oral absorption.[47] Antcin K can correspondingly reduce the activities of AST and ALT, down-regulate the levels of TG, MDA, VLDL and ALDH in serum, and inhibit the accumulation of liver fat. It is an effective ingredient with liver protective activity against alcoholic liver disease.[48] Huo et al.[49] used APAP- and GalN/TNFα-induced acute liver injury models in mice to evaluate the protective effects of antcin H against pharmacological and immune-mediated hepatotoxicity. The results of the study showed for the first time that antcin H was effective against either APAP- or GalN/TNFα-mediated hepatotoxicity. Mechanistically, the hepatoprotective activity of antcin H was attributed to its ability to directly disrupt the interaction between JNK and mitochondria and prevent JNK-mediated mitochondrial dysfunction. Nonalcoholic fatty liver disease (NAFLD) is a common liver disease, but there are no specific drugs in clinical practice.[50] Antcin A can inhibit the pyroptosis of Kupffer cells by targeting NLRP3 inflammasome and reducing the inflammatory response of liver tissue in NAFLD, which is one of the mechanisms of antcin A to protect the liver.[51] In

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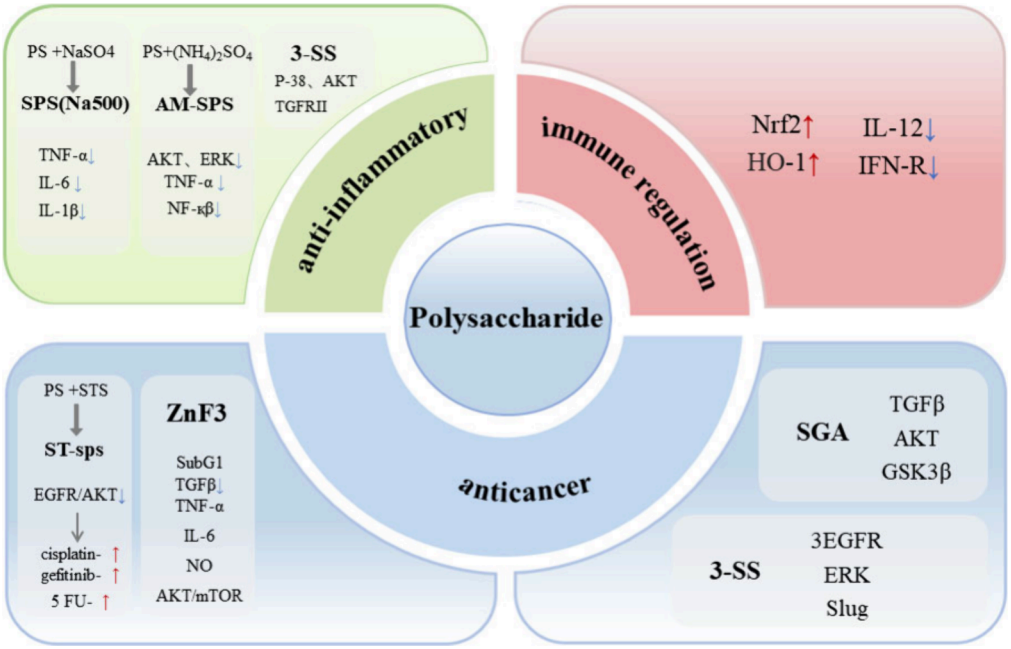

Figure 5. Mechanism of anti-inflammatory, anticancer and immune regulation activity of *A. camphorata* polysaccharide.

addition, Cao et al.[52] found that antcin A could play a protective role in liver through the MAPK3-NF-κB signaling pathway, thereby inhibiting acute liver injury (ALI) in mice through network pharmacological prediction combined with experiment. The mechanism is related to anti-inflammation, and MAPK3 is the main target of antcin A.

A. camphorata and its monomer dehydroeburicoic acid (DEA) can up-regulate the activity of ALDH2 in the liver of mice and accelerate the clearance of ROS and harmful aldehydes, thereby inhibiting NAFLD, reducing oxidative stress and inflammation, promoting fatty acid β oxidation, and inhibiting lipogenesis. Cao et al.[53] showed that DEA has anti-NAFLD efficacy mediated by ALDH2. *A. camphorata* and its monomer DEA can accelerate the clearance of ROS and harmful aldehydes by up-regulating ALDH2 activity in the mouse liver, thereby inhibiting NAFLD, reducing oxidative stress and inflammation, promoting fatty acid β-oxidation, and inhibiting lipogenesis.

4.1.2. Anti-inflammatory. Triterpenoids from *A. camphorata* subculture have been used to examine the anti-inflammatory effects in STZ-induced hyperglycemia mice, and triterpenoids with high anti-inflammatory properties have been used to observe their effects on wound healing in mice.[54] This study confirmed the promoting effect of triterpenes on wound recovery. The possible mechanism is that the extracted triterpenoids directly bind to GRE or indirectly bind to the M3 receptor to produce an anti-inflammatory response and induce wound healing. Antcin A inhibits the release of pro-inflammatory biomolecules by down-regulating the expression of iNOS and COX-2 via the NF-κB pathway, while decreasing the mRNA levels of IL-1β, TNF-α and IL-6[55] (Figure 4). Dakpa et al.[56] reported that antcin A can block ACE2 activity in HT-29 cells, suggesting that it may be a potential prophylactic agent for COVID-19. It was discovered that antcin A significantly reversed the alterations in metabolites mediated by the SARS-CoV-2 protein, such as methionine, phosphoenolpyruvate, Canadian purine, glutamine, ethanolamine, and phenylalanine.[56] Moreover, antcin A significantly inhibited the up-regulation of TLR-4 and ACE2 receptors mediated by the SARS-CoV-2 spike protein. These results suggest that SARS-CoV-2 spike protein alters metabolic pathways in macrophages that are unrelated to the signaling pathways associated with causing inflammation, which can be blocked by antcin A. Anctin A may be useful for the development of functional drugs and pharmacotherapy for viral infections associated with metabolomic abnormalities. Antcin K is a potential lipid-lowering agent and has anti-inflammatory effects. Antcin K has promising applications in the prevention and treatment of atherosclerosis. Lu et al.[57] used SVEC4-10 vascular endothelial cells and RAW264.7 macrophages as a cellular model to study high-fat injury induced by palmitoleic acid oil. The experiments demonstrated that antcin K possesses a favorable free radical scavenging capacity. Moreover, the treatment with antcin K significantly alleviated the high-fat injury of vascular endothelial cells and macrophages with high-fat injury and decreased the levels of inflammatory factors TNF-α and IL-1β. Additionally, antcin K significantly decreased the expression of vascular cell adhesion molecule 1 (VCAM-1) in vascular endothelial cells involved in monocyte migration and inflammation. Antcin K not only reduced the expression of the CD36 scavenger receptor but also increased the expression of Kruppel-like factor 4 (KLF4) transcription factor in macrophages. Rheumatoid arthritis (RA) is an autoimmune and chronic inflammatory disease. Achudhan et al.[58] first reported that antcin K inhibited the production of proinflammatory cytokines in rheumatoid synovial fibroblasts (Rasf), which is the main cause of rheumatoid arthritis (RA) disease. Among them, antcin K significantly inhibited the production of pro-inflammatory cytokines TNF-α, IL-1β, and IL-8 in Rasf through FAK, PI3K, AKT, and NF-kB signaling cascades. Antcin K also ameliorated cartilage degradation in collagen-induced arthritis (CIA) mice (Figure 4). This provides new ideas for the treatment of rheumatoid arthritis. It has been found that reduced levels of lipid deposition, down-regulated VCAM-1 and CD36 receptor expression, and up-regulated ABCA1 receptor expression in the arterial wall of apoe knockout mice fed a high-fat diet (HFD) treated with the supplement

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OAK (ovatodiolide and antcin K). This suggests that oral OAK supplementation treatment can alleviate HFD-induced cardiovascular dysfunction by reducing arterial lipid accumulation, oxidative stress and inflammation in cardiovascular tissues.[59]

4.1.3. Antidiabetic. Anctin K also plays a key role in the antidiabetic activity of *A. camphorata*. Kuang et al.[60] investigated the antidiabetic activity of *A. camphorata* and anctin K through network pharmacology and experiments on high-fat diet (HFD)-induced diabetic mice model. The results indicated that oral administration of *A. camphorata* and anctin K reduced blood glucose and lipid levels in HFD mice in a dose-dependent manner, potentially via the insulin resistance pathway. Additionally, anctin K regulated the expression of TNF-α, IL-6, and PPARγ. Sulfurenic acid (SA) has therapeutic effects on type 1 diabetes. The use of SA in STZ-induced diabetic mice revealed that SA compounds have hypoglycemic effects by increasing the islet size of Langerhans cells. SA treatment increased the expression level of phosphorylated AKT and activated AMPK and GLUT4 membranes, which increased glucose uptake in skeletal muscle. On the other hand, SA increased the hepatic expression level of p-Akt and p-FoxO1 but decreased the mRNA levels of PEPCK and G6 Pase, thus inhibiting hepatic glucose production. SA treatment increased the hepatic AMPK phosphorylation level, increased the PPARα expression level, decreased the lipid-derived FAS, and decreased the SREBP 2 mRNA level, which led to a decrease in blood TG and TC.[61]

4.2. Polysaccharide. Polysaccharide (PS) is a natural macromolecule with various biological activities in *A. camphorata*, which is extracted from the fruiting body, mycelium, and fermentation broth. Lipopolysaccharides (LPSs) from *A. camphorata* have excellent anti-inflammatory effects, and their detailed functional structures and bioactivities are completely different from those of bacterial LPSs. LPSs have been isolated from *A. camphorata*, which provide a new therapeutic target against *E. coli* infections.[62] PSs from *A. camphorata* mycelium effectively inhibited vascular endothelial growth factor (VEGF)-induced endothelial cell migration and reduced the expression of angiogenesis-related proteins, suggesting that PSs may be a potential molecule for medical supplementation.[63] Squalene can not only increase the triterpene content in *A. camphorata* and its anti-inflammatory activity but also enhance the production of polysaccharides with anticancer activity when used as a potential additive in the culture of *A. camphorate*[64,65] (Figure 5). Intervening in the metabolism of squalene as an anticancer dietary supplement could be a strategy for cancer therapy. PS was able to inhibit the LPS-induced activation of Kupffer cells, reduce inflammatory factor expression, increase SOD levels, and inhibit ROS expression. Yang et al.[66] found that PS could effectively ameliorate hepatic injury in mice, reduce ALT and AST levels, and inhibit the expression of inflammatory factors in the construction of a mouse model. PS inhibited inflammatory factor expression by activating Nrf2 signaling pathway inhibits ROS expression, which in turn regulates the ROS-induced TLR4-NF-κB signaling pathway and plays an important hepatoprotective role.

Sulfated polysaccharides (SPSs) make up a class of compounds containing a semiester sulfate group on the polysaccharide backbone. SPSs have been widely used in functional foods and pharmaceuticals because of their remarkable anti-inflammatory and anticancer properties. SPSs showed stronger inhibition of TNF-α and IL-6 release compared to that of unacidified PS. The sodium sulfate was able to increase the SPS sulfate content. Cheng et al.[67] used sodium sulfate for the enhanced culture of mycelia. SPSs have a stronger inhibitory effect than PS and show better inhibitory activity under the treatment of 5 mM. In addition, the degree of sulfation of PS may be related to its anti-inflammatory activity. Lu et al.[68] obtained SPS (Na500) by culturing *A. camphorata* with 500 mM sodium sulfate. Na500 presented a dose-dependent inhibition effect on TNF-α and IL-6 and significantly suppressed the secretion of IL-1β in LPS-induced macrophage inflammation. Moreover, Na500 F3, a galactose sulfate dextran with a molecular weight of 7.79 kDa, potently inhibited the secretion of TNF-α and TGF-β cytokines in LPS-induced macrophage inflammation.

It has also been shown that the culture of *A. camphorata* with sodium thiosulfate can improve the production of PS and SPSs in *A. camphorata*, further isolate ST-SPS. Lin et al.[69] first demonstrated that the characteristic changes in *A.camphorata* induced by sodium thiosulfate are related to the anticancer mechanism of ST-SPS. The specific anticancer mechanism is that sodium thiosulfate enhances the anticancer effect of ST-SPS in cancer cells by inhibiting EGFR/AKT signal transduction, and ST-SPS synergistically enhances the cytotoxic effects of cisplatin-, gefitinib-, and 5 FU-induced lung cancer H1975 cells and colon cancer CT26 cells. Ammonium sulfate is also an effective nutrient for the production of SPS. Lu et al.[70] studied the changes in the SPS of *A. camphorata* cultured in ammonium sulfate and evaluated its anti-inflammatory activity. They found that the content of SPS (361 kDa) increased by 26% when 1 mM ammonium sulfate was added. Furthermore, in the anti-inflammatory effect, 1 mM ammonium sulfate was used to cultivate *A. camphorata* polysaccharide sulfate (AM-SPS) by inhibiting AKT, and the ERK signaling pathway effectively inhibits the secretion of cytokines TNF-α. Meanwhile, restraining the NF-κB activation is the underlying cause of its anti-inflammatory effects. SPS has excellent anticancer activity. Lin et al.[71] identified a 7.9 kDa SPS, named ZnF3. They further found that ZnF3 not only directly inhibits cancer cells but also activates macrophage-mediated cytotoxicity against cancer cells. The mechanism of action is as follows: To suppress lung cancer cells by inducing the subG1 group and apoptosis, ZnF3 cut TGFβ beta receptor expression in lung cancer cells. Meanwhile, the activation of macrophages is accomplished by inducing the secretion of TNF-α and IL-6, the generation of NO, and phagocytosis. Moreover, the AKT/mTOR pathway is activated, and the polarization of M1-type macrophages is induced. The coculture of cancer cells with ZnF3 stimulates macrophages, which leads to the inhibition of lung cancer cells.

SGA is a kind of sulfuric acid hydrochloride dextran from *A. camphorata*. SGA can inhibit tumor growth *in vitro* and *in vivo*.[72] TGFβ signaling and Slug overexpression are considered to be key factors in lung cancer malignancy. Lin et al.[73] demonstrated that the SGA target of the TGFβ/AKT/GSK3β axis plays a key role in enhancing Slug degradation and inhibiting lung cancer cells. SGA is a potential therapeutic agent for lung cancer. The extracellular polysaccharides (AEPS) of *A. camphorata* are classified as β-glucosides. Recently, a study was conducted to improve the production of AEPS by controlling the mycelial morphology using the microparticle-enhanced cultivation (MPEC) technique.[74] Moreover, AEPS cultivated with the addition of Al_2O_3 possesses a different structure and exhibits better antimicrobial properties. AEPS has a strong antidigestive ability. Lu et al.[75] found that AEPS could alleviate the adverse symptoms of diarrhea, inflammation, weight loss, and immune organ damage induced by lincomycin hydrochloride (LIH) in

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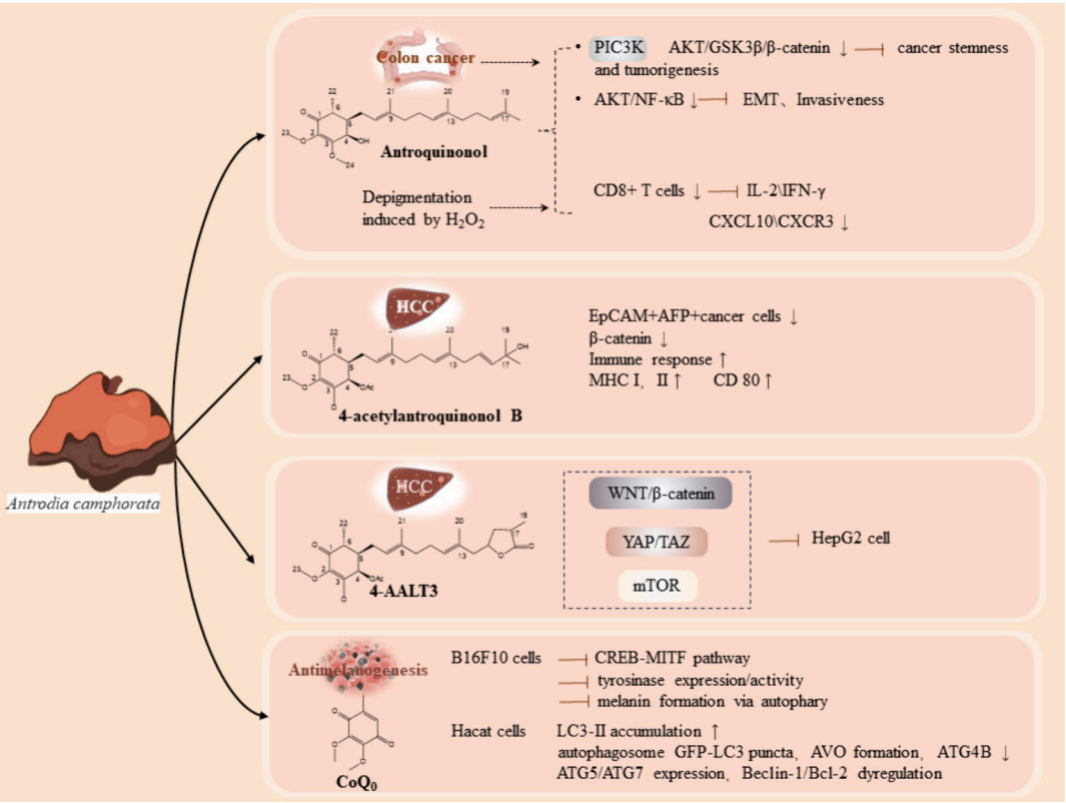

Figure 6. Bioactivity of ubiquinone derivatives in *A. camphorata*.

mice through *in vivo* experiments. The gavage of medium-dose AEPS (0.25 g/kg of bw) in mice could increase the relative abundance of some probiotics (*Lactobacillus*, *Roseburia*, *Ligilactobacillus*, *Lachnospiraceae*_NK4A136_group), reduce the relative abundance of some harmful microorganisms (Enterococcus, Shigella), and regulate the intestinal flora of mice. This is a fine example of the novel multifunctional carbohydrate probiotic. This adds new inspiration for the development of novel multifunctional carbohydrate prebiotics.

PS also has immunomodulatory effects (Figure 5). Liu et al.[76] experimentally found that PS had a protective effect against cyclophosphamide (CTX)-induced immunosuppression in BALB/c mice. It successfully improved the organ index of CTX-injected mice, enhanced the cytotoxicity function of T cells and NK cells, and regulated the levels of immunoglobulins and cytokines. This study demonstrated the relationship of PS to CTX-induced immunosuppression in BALB/c mice in relation to the Nrf2/HO-1 signaling pathway. PS is expected to be used as an effective anti-immunosuppressant. Lu et al.[77] identified a sulfated galactoglucan (3-SS) in *A. camphrata* with antiproliferative and anti-inflammatory activities, which is structurally characterized by a backbone containing 1,3/1,4-α/β-galactoglucan with 1,6-β-Glc branching and 2-O-sulfate substitutions. 3-SS has anti-inflammatory activity mediated through the p-38/AKT/TGFRII signaling pathway and also shows antilung cancer activity through the EGFR/ERK/slug signaling pathway.

Hypoglycemic activity is an important bioactivity of edible mushroom polysaccharides. The polysaccharides in *A. camphorata* are nondigestible dietary fibers, mainly composed of nonstarch polysaccharides such as β-glucans. They lower blood glucose by enhancing insulin secretion and sensitivity via pancreatic β-cell proliferation.[78] Additionally, *A. camphorata* polysaccharides may exert hypoglycemic effects through multiple mechanisms, including inhibition of gastrointestinal enzyme activity, enhancement of insulin sensitivity, improvement of pancreatic function, regulation of lipid metabolism, mitigation of oxidative stress and inflammatory responses, and modulation of gut microbiota composition.[79]

4.3. Ubiquinone and Its Derivatives. Ubiquinone, also known as coenzyme Q (CoQ), is a critical part of the electron transport pathway. Since it exists in almost every cell, it plays an important role in the human body and has therefore been widely studied. Ubiquinones are a group of lipid-soluble quinones, which are composed of two parts with different numbers of isoprene side chains and benzene. Among the different types of bioactive compounds in *A. camphorata*, the ubiquinone derivatives not only are specific in chemical structure but also are considered to be one of the most bioactive components. Until 2017, 12 new generic quinone derivatives have been isolated from *A. camphorata* identified including antroquinonol (AQ), antroquinonol B, antroquinonol C, antroquinonol D (AQD), antroquinonol L, antroquinonol M, antrocamol LT1, antrocamol LT2, antrocamol LT3, 4-acetyantroquinonol B (4-AAQB), 4-acetylantrocamol LT3, and antrocinnamon.[80] Among them, AQ is the first ubiquinone identified in the solid-state fermentation product of *A. camphorata*. AQ is also one of the characteristic metabolic components of the *A. camphorata* fruit body. The molecular formula of AQ is $C_{24}H_{38}O_4$, which is similar to the coenzyme Q_3 (CoQ_3) in structure. As one of the most important ubiquinone derivatives in *A. camphorata*, AQ has shown potent biological activity in the treatment of Alzheimer's disease and a variety of cancers, including liver cancer, leukemia, lung cancer, breast cancer, and pancreatic cancer. It can change the signal path or the activity of key proteins to inhibit proliferation or induce cell death. Ho et al.[81] elucidated the potential mechanism of anticancer activity of

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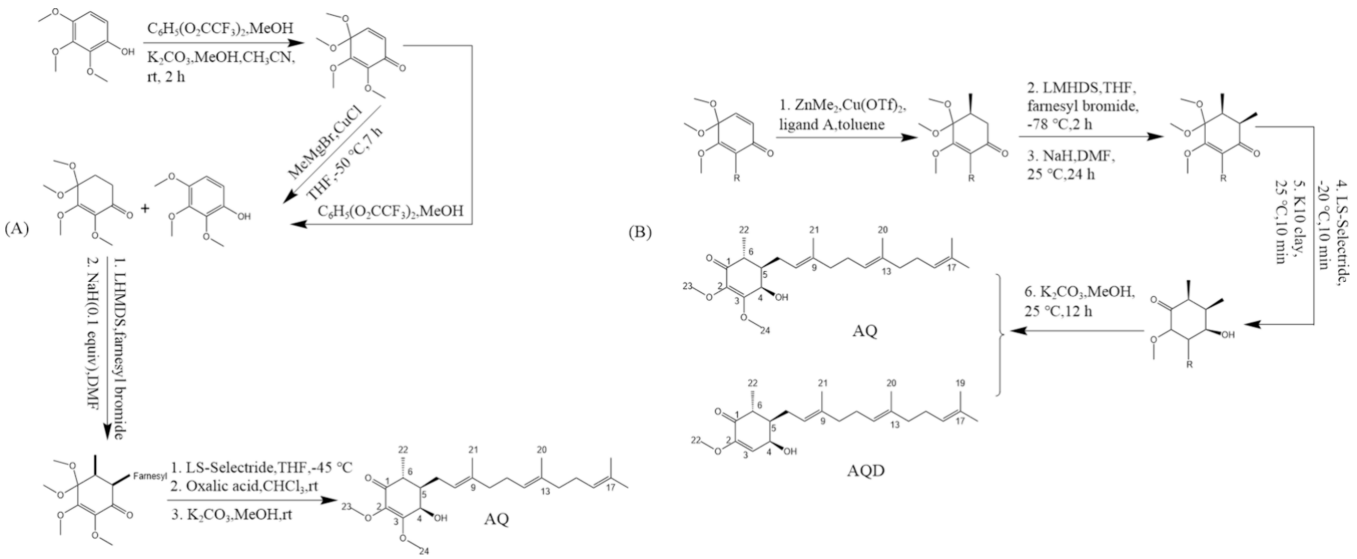

Figure 7. Chemical syntheses of AQ (A) and AQD (B).

AQ. It inhibits the activation of Ras and Ras-related GTP-binding proteins through inhibition of protein isopentenyl transferase activity, leading to activation of autophagy in cancer cells and the associated cell death pattern. AQ can also inhibit the growth of colon cancer cells and inhibit pluripotent stem cells and cancer stem cell-related genes. It down-regulates β-catenin/t-cell factor (TCF) signaling and inhibits stem cell-like properties by targeting the PI3K/AKT/β-catenin signaling pathway, suggesting that AQ may serve as a promising preventive agent for colon cancer.[82] AQ has potential therapeutic effects on depigmentation. Guan et al.[83] investigated the effects of AQ on an H_2O_2-induced vitiligo depigmentation model. It was found that AQ significantly attenuated histopathological changes in mouse skin, reduced $CD8^+$ T cell infiltration, and inhibited CXCL10 and CXCR3. In addition, AQ significantly reduced the production of cytokines IL-2 and IFN-γ and promoted the expression of tyrosinase (Figure 6). These results suggest that AQ may provide a therapeutic option to prevent pigment decolorization.

The ubiquinone derivative 4-AAQB possesses antitumorigenic ability to inhibit hepatocellular carcinoma stem cells and activate dendritic cells. Specifically, 4-AAQB can inhibit EpCAM, AFP and related pathways in HepG2 cells, significantly reduce the expression of β-catenin, inhibit tumorigenicity, and decrease the secretion of cytokines related to immune escape.[84] Additionally, 4-AAQB stimulates the proliferation of the immune cells. When immature dendritic cells were cocultured with EpCAM+ HepG2 cells, 4-AAQB enhanced the expression of MHC class I and class II on the surface of hepatocellular carcinoma stem cells and dendritic cells. It increased the expression of the dendritic cell costimulatory molecule CD80 and immune-activation-related cytokines. 4-AAQB has the potential for prevention and immunotherapy of liver cancer. The 4-acetylantrocamol LT3 (4-AALT3) is a novel ubiquinone compound with anticancer activity. The 4-AALT3 can inhibit liver cancer cell growth by targeting WNT/β-catenin, YAP/TAZ and mTOR signaling pathway, which is a kind of promising potential hepatocellular carcinoma treatment.[85] Coenzyme Q_0 (CoQ_0) is a novel ubiquinone derivative of *A. camphorata*, chemically known as 2,3-dimethoxy-5-methyl-1,4-benzoquinone. CoQ_0 has been shown to have a variety of effects such as stimulation of insulin production, antiangiogenesis, and antioxidant, as well as therapeutic and prophylactic effects on various cancers.[86] Recently, Hseu et al.[87] also reported that CoQ_0 has the ability to reduce skin pigmentation and its mechanism of action (Figure 6).

4.4. Other Bioactive Substances. The maleic acid and succinic acid derivatives in *A. camphorata* are a class of compounds with pharmacological effects, such as liver protection and anti-inflammation. Chien et al.[88] isolated and characterized three new succinic acid derivatives, three new maleic acid derivative, and one known compound from *A. camphorata* seed bodies. The anti-inflammatory activity of their methanolic extracts was also investigated. This is the first time that maleic and succinic acid derivatives were isolated from *A. camphorata* seed bodies in solid culture, and immunostimulant and anti-inflammatory effects were present for all of these compounds. Phuong et al.[89] examined the inhibitory activity of antrodin A-E as well as the *in vivo* metabolites of antrodin C and its analogues from *A. camphorata* against hepatitis C virus (HCV) protease. The results showed that most of the compounds exhibited strong inhibitory SOD that plays an important role in the prevention and treatment of a variety of diseases, such as cancer, diabetes, pulmonary hypertension, bronchopulmonary dysplasia, radiation-induced fibrosis and arthritis, etc.[90] SOD is able to effectively scavenge free radicals produced by biological organisms to achieve antioxidant and aging-delaying effect.[91] *A. camphorata* contains SOD, which can effectively remove free radicals and damage caused by reactive oxygen. Adenosine is also one of the main components of *A. camphorata*. It can inhibit platelet aggregation, prevent blood flow obstruction caused by thrombus, improve the circulatory system, and effectively prevent various cardiovascular disease.[92]

5. THE SYNTHESIS OF UBIQUINONE DERIVATIVES

The ubiquinone derivatives in *A. camphorata* have received increasing attention due to their remarkable active. However, the low content of these ubiquinone derivatives in *A. camphorata* is unable to meet the increasing research and market demand. Therefore, it is urgent to obtain these valuable compounds efficiently. Analyzing the synthetic pathways can help provide strategies to increase the yield in a targeted manner. There are

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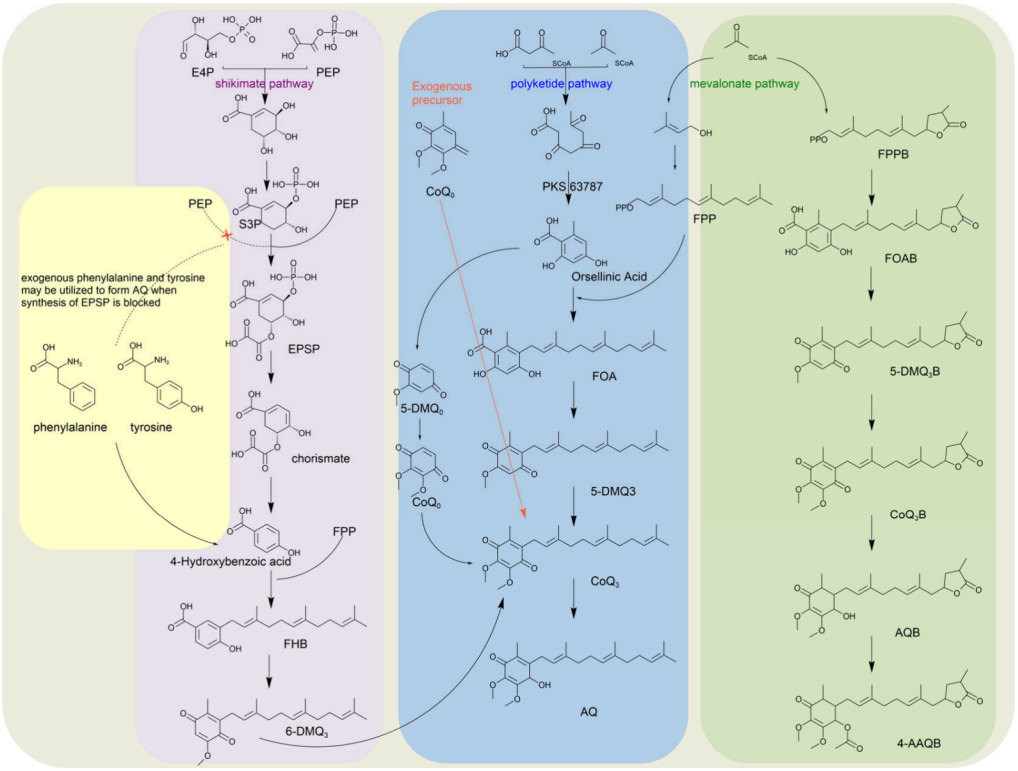

Figure 8. Biosynthesis of AQ and 4-AAQ.

two ways to synthesize these ubiquinone derivatives. One is chemical synthesis, and the second is biosynthesis.

5.1. Chemical Synthesis. Hsu et al.[93] proposed a simple method for the synthesis of AQ (Figure 7A). AQ has a unique core structure of 4-hydroxy-2,3-dimethoxycyclohexan-2-enone, which carries methyl, farnesyl, and hydroxyl substituents in 4,5-cis-5,6-trans configuration. The 2,3,4-trimethoxyphenol was used as the raw material and oxidatively converted to 2,3,4,4-tetramethoxycyclohexadienone as a highly electron-rich substrate in methanol. Dimethylcopper salt was used as the main raw material for Michael's reaction. Finally, a seven-step reaction of alkylation, reduction and differential isomerization was carried out to obtain (±) AQ. After that, AQ was synthesized from benzoquinone monoketones by an enantioselective Michael reaction followed by a sequence of alkylation, reduction, condensate hydrolysis, and conformational inversion.[94] In particular, the introduction of an electron-withdrawing chloro-substituted methoxyl substituent at the C-2 position facilitated the reaction. In the final step, after treatment with K_2CO_3 in MeOH, the chloro-substituted group was replaced by the methoxy group and the conformational inversion was carried out on C-6 to give AQ. Sulake et al.[95] accomplished the total synthesis of AQ and AQD for the first time. Based on iridium-catalyzed isomerization/Claisen rearrangement (ICR), lactonization, and Grubbs olefin complexation. The necessary α,β-unsaturation was then achieved by a selenation/oxidation scheme and elimination of β-methoxy, resulting in two products from a common intermediate. Sulake et al.[96] followed with a 16-step synthesis of AQ from readily available D-mannose in 5.9% overall yield (Figure 7B). The synthesis encompassed the 6-exo cyclization of the ring radical generated by Barton−McCombie deoxygenation to achieve the cis-geometry (C4-OH, C5-C7) and Suzuki−Miyaura coupling to synthesize sesquiterpene side chains.

Although good progress has been made in the chemical synthesis of ubiquinone derivatives, there are still some concerns about the efficacy of these synthetic compounds. These chemical methods also have some drawbacks, such as complex purification processes, the generation of byproducts, and the need for further modification of some substances to restore activity. In contrast, the production of these active compounds through biosynthetic methods is more natural and sustainable.

5.2. Biosynthesis. AQ is one of the most important biologically active compounds isolated from mycelia of *A. camphorata* in solid-state fermentation. While AQ can be easily synthesized in solid-state fermentation, it is not possible in submerged fermentation. Given the benefits of submerged over solid-state fermentation (fast growth rate, high yield, and low pollution), various attempts have been made to achieve and enhance AQ biosynthesis in submerged fermentation by currently regulating culture conditions.

The addition of CoQ_0 can up-regulate the expression of *S*-adenosylmethionine synthetase and provide methyl groups for the biosynthesis of AQ. Heat shock proteins and TCA cycle related proteins involved in the biosynthesis of AQ are regulated by CoQ_0.[97] The fermentation broth was supplemented with camphor wood extract, which, as a quinone nuclear donor, could provide the precursor of AQ.[98] Soybean oil can affect the composition of the mycelium cell membrane by significantly increasing the fatty acid content, especially oleic acid (C18:1) and linoleic acid (C18:2), and increase the permeability of *A. camphorata* mycelium cells, thus further promoting the effect of extracting intracellular hydrophobic AQ from mycelium.[98]

There are many different findings regarding the biosynthesis of AQ. It has been shown that AQ and 4-AAQB follow biosynthetic sequences similar to those of CoQ. AQ and 4-AAQB are synthesized from acetyl-CoA and malonyl-CoA via the polyketide pathway (polyketide pathway), and orsellinic

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ACS Omega 2025, 10, 15908−15922

acid is the precursor of AQ and 4-AAQB.[99] Subsequently, it was also shown experimentally that the benzoquinone ring of AQ can be derived via the mangiferic acid pathway, with 4-hydroxybenzoic acid (4-HBA) serving as the ring precursor of AQ.[100] The benzoquinone ring of 4-AAQB is synthesized via only the polyketide pathway. *A. camphorata* preferentially utilizes endogenous 4-HBA for AQ biosynthesis via the shikimate pathway (Figure 8). Yang et al.[101] proposed that the biosynthetic pathway of 4-AAQB is similar and closely related to that of CoQ. The benzoic acid segment and isoprenoid side chain of 4-AAQB are synthesized via the shikimate pathway and the mevalonate pathway, respectively. The 4-HBA is a precursor of 4-AAQB. It contributes to the formation of the benzoquinone ring of 4-AAQB. In addition, the addition of CoQ_0 to the fermentation broth was the most effective way to increase 4-AAQB production.

Liu et al.[102] employed the RNA-Seq transcriptomics approach to conduct in situ extractive fermentation on *A. camphorata* and investigated the differences in gene expression upon the addition of different extractants. It was discovered that when *n*-tetradecane was used as the extractant, the biosynthesis pathways of ubiquinone and other terpenoid quinones were significantly enriched, and the genes related to this pathway (*CoQ2*, *wrbA*, and *ARO8*) were also significantly up-regulated. During the in situ extractive fermentation process, the addition of oleic acid as an extractant could significantly up-regulate the genes (*IDI*, *E2.3.3.10*, *HMGCR*, *atoB*, and *CoQ2*) in the biosynthesis of the terpenoid backbone and the biosynthesis pathways of terpenoid quinones such as ubiquinone. Moreover, both of these pathways were significantly enriched. Wei et al.[103] found that the oxygen carrier *n*-hexadecane significantly increased the yields of 4-AAQB and AQ during submerged fermentation of *A. camphorata*. When 5% *n*-hexadecane was added to the medium, the yields of 4-AAQB and AQ were 15.8 and 61.6 times higher than those of the control group, respectively. This might be related to the accelerated farnesylation steps of upstream compounds $5\text{-}DMQ_0$ and CoQ_0 and the REDOX reactions of the benzoquinone ring of CoQ3B. These conversion steps might require additional oxygen, thus the increase in dissolved oxygen induced by the oxygen carrier contributes to the biosynthesis of 4-AAQB and AQ. In addition, the extraction of 4-AAQB, AQ, and their intermediates from the aqueous phase to the hydrophobic phase during fermentation may also alleviate the trans-inhibitory effect of the end-products, thus facilitating the biosynthetic process.

6. CONCLUSIONS AND FUTURE PERSPECTIVES

A. camphorata is a popular dietary supplement and a promising natural medicine. Over the past 30 years, hundreds of terpenoids, polysaccharides, ubiquinone derivatives, and other active substances have been identified from *A. camphorata*. These active ingredients have good biological functions, such as treating skin itching, protecting the liver, antiviral, immune regulatory, antitumor, and anti-inflammatory effects, and treating hypertension. Because of the influence of culture conditions and other environmental factors, there are large differences in the bioactive compounds found in the mycelium obtained from artificial cultures and in the substrates of wild *A. camphorata*. The types and contents of active substances in the fermentation products of *A. camphorata* can be significantly increased by metabolic modulation, precursor induction, and other techniques. However, the basic research and application of *A. camphorata* still have several important problems that need to be solved. *A. camphorata* and AQ have shown good safety in animal and human studies, but the toxicity of their main bioactive triterpenes needs to be continuously evaluated.[45] Currently, most solvents are used to extract polysaccharides and some small-molecule bioactive components from *A. camphorata*, but edible mushroom extraction residues still contain more functional components that have not yet been effectively developed, which results in a certain waste of resources. In some studies, alkaline extraction has been used to obtain dietary fiber, an important active ingredient in the residue of *A. camphorata*, and the extracted dietary fiber of *A. camphorata* residue, ACA-DK, has the structural characteristics of cellulose, high purity, and low molecular weight, which is highly important for the comprehensive utilization of *A. camphorata*.[104] The biochemical components of *A. camphorata* are complex and diverse, and more active substances may still be discovered and utilized. In addition, the training method, environmental conditions, and varieties of *A. camphorata* differ in terms of their influence on ingredients; thus, further research and analysis are needed. Although *A. camphorata* has been widely studied in the biomedical field and a variety of active ingredients in *A. camphorata* and their health benefits have been confirmed, the scientific basis for its pharmacological effects and its clinical application must be further elucidated. In this context, the rigorous application of scientific methodologies and the optimization of resource utilization efficiency are critical components for advancing research outcomes. Gökalp has demonstrated an innovative approach by integrating molecular docking and density functional theory (DFT) calculations to establish an efficient bioactive compound screening framework. This methodology maintains experimental rigor while significantly reducing research costs through the application of computational techniques. Such an integrated approach not only enhances the precision and efficiency of the screening process but also opens new avenues for cost-effective drug discovery and development.[105−110] In addition, the large-scale production and development of *A. camphorata* face many technical difficulties, such as the cultivation of good varieties, improvement of yield and quality control, etc. The innovation of artificial cultivation technology to increase the yield of *A. camphorata* seed bodies and active metabolites to reduce the cost of the development of the corresponding products is the key point of the current research. However, in general, with the deepening of research and increasing progress in science and technology, the value of *A. camphorata* will be better explored and utilized.

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Notes

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■ REFERENCES

(1) Li, H. X.; Wang, J. J.; Lu, C. L.; Gao, Y. J.; Gao, L.; Yang, Z. Q. Review of bioactivity, isolation, and identification of active compounds from *Antrodia cinnamomea*. *Bioengineering.* **2022**, *9* (10), 494.

(2) Chang, T.T.; Chou, W.N. *Antrodia cinnamomea* sp. nov. on *Cinnamomum kanehirai* in Taiwan. *Mycol. Res.* **1995**, *99*, 756−758.

(3) Lu, M. C.; El Shazly, M.; Wu, T. Y.; Du, Y. C.; Chang, T. T.; Chen, C. F.; Hsu, Y. M.; Lai, K. H.; Chiu, C. P.; Chang, F. R. Recent research and development of *Antrodia cinnamomea*. *Pharmacol. Ther.* **2013**, *139* (2), 124−156.

(4) Ao, Z. H.; Xu, Z. H.; Lu, Z. M.; Xu, H. Y.; Zhang, X. M.; Dou, W. F. Niuchangchih (*Antrodia camphorata*) and its potential in treating liver diseases. *J. Ethnopharmacol.* **2009**, *121* (2), 194−212.

(5) Qiao, X.; Wang, Q.; Ji, S.; Huang, Y.; Liu, K.; Zhang, Z.; Bo, T.; Tzeng, Y.; Guo, D.; Ye, M. Metabolites identification and multi-component pharmacokinetics of ergostane and lanostane triterpenoids in the anticancer mushroom *Antrodia cinnamomea*. *J. Pharm. Biomed. Anal.* **2015**, *111*, 266−276.

(6) Zhang, Y.; Lv, P.; Ma, J.; Chen, N.; Guo, H.; Chen, Y.; Gan, X.; Wang, R.; Liu, X.; Fan, S. *Antrodia cinnamomea* exerts an anti-hepatoma effect by targeting PI3K/AKT-mediated cell cycle progression in vitro and in vivo. *Acta Pharm. Sin. B* **2022**, *12* (2), 890−906.

(7) Meng, L.; Luo, B.; Yang, Y.; Faruque, M. O.; Zhang, J.; Li, X.; Hu, X. Addition of vegetable oil to improve triterpenoids production in liquid fermentation of medicinal fungus *Antrodia cinnamomea*. *J. Fungi.* **2021**, *7* (11), 926.

(8) Lin, T. Y.; Chen, C. Y.; Chien, S. C.; Hsiao, W. W.; Chu, F. H.; Li, W. H.; Lin, C. C.; Shaw, J. F.; Wang, S. Y. Metabolite profiles for *Antrodia cinnamomea* fruiting bodies harvested at different culture ages and from different wood substrates. *J. Agric. Food Chem.* **2011**, *59* (14), 7626−7635.

(9) Lu, H.; Lou, H.; Hu, J.; Liu, Z.; Chen, Q. Macrofungi, A review of cultivation strategies, bioactivity, and application of mushrooms. *Compr. Rev. Food Sci. Food Saf.* **2020**, *19* (5), 2333−2356.

(10) Hsieh, Y. Y.; Lee, K. C.; Cheng, K. C.; Lee, K. F.; Yang, Y. L.; Chu, H. T.; Lin, T. W.; Chen, C. C.; Hsieh, M. C.; Huang, C. Y.; Kuo, H. C.; Teng, C. C. Antrodin C isolated from *Antrodia cinnamomea* induced apoptosis through ROS/AKT/ERK/P38 signaling pathway and epigenetic histone acetylation of TNFα in colorectal cancer cells. *Antioxidants.* **2023**, *12* (3), 764.

(11) Tsay, H. J.; Liu, H. K.; Kuo, Y. H.; Chiu, C. S.; Liang, C. C.; Chung, C. W.; Chen, C. C.; Chen, Y. P.; Shiao, Y. J. EK100 and antrodin C improve brain amyloid pathology in APP/PS1 transgenic mice by promoting microglial and perivascular clearance pathways. *Int. J. Mol. Sci.* **2021**, *22* (19), 10413.

(12) Yang, H.; Bai, X.; Zhang, H.; Zhang, J.; Wu, Y.; Tang, C.; Liu, Y.; Yang, Y.; Liu, Z.; Jia, W.; Wang, W. Antrodin C, an NADPH dependent metabolism, encourages crosstalk between autophagy and apoptosis in lung carcinoma cells by use of an AMPK inhibition-independent blockade of the Akt/mTOR pathway. *Molecules.* **2019**, *24* (5), 993.

(13) Xia, Y.; Wang, Y.; Zhang, B.; Xu, G.; Ai, L. Effect of cultural conditions on antrodin C production by basidiomycete *Antrodia camphorata* in solid-state fermentation Biotechnol. *Appl. Biochem.* **2014**, *61* (6), 724−732.

(14) Li, S. L.; Huang, Z. N.; Hsieh, H. H.; Yu, W. C.; Tzeng, W. Y.; Lee, G. Y.; Chen, Y. P.; Chang, C. Y.; Chuu, J. J. The augmented anti-tumor effects of *Antrodia camphorata* co-fermented with Chinese medicinal herb in human hepatoma cells. *Am. J. Chin. Med.* **2009**, *37* (4), 771−783.

(15) Liu, D. Z.; Liang, H. J.; Chen, C. H.; Su, C. H.; Lee, T. H.; Huang, C. T.; Hou, W. C.; Lin, S. Y.; Zhong, W. B.; Lin, P. J.; Hung, L. F.; Liang, Y. C. Comparative anti-inflammatory characterization of wild fruiting body, liquid state fermentation, and solid state culture of *Taiwanofungus camphoratus* in microglia and the mechanism of its action. *J. Ethnopharmacol.* **2007**, *113* (1), 45−53.

(16) Zhang, B. B.; Guan, Y. Y.; Hu, P. F.; Chen, L.; Xu, G. R.; Liu, L.; Cheung, P. C. K. Production of bioactive metabolites by submerged fermentation of the medicinal mushroom *Antrodia cinnamomea*, recent advances and future development. *Crit. Rev. Biotechnol.* **2019**, *39* (4), 541−554.

(17) Yang, F. C.; Huang, H. C.; Yang, M. J. The influence of environmental conditions on the mycelial growth of *Antrodia cinnamomea* in submerged cultures. *Enzyme Microb. Technol.* **2003**, *33* (4), 395−402.

(18) Shu, C. H.; Lung, M. Y. Effect of pH on the production and molecular weight distribution of exopolysaccharide by *Antrodia camphorata* in batch cultures. *Process Biochem.* **2004**, *39* (8), 931−937.

(19) Lin, E. S.; Ko, H. C. Glucose stimulates production of the alkaline-thermostable lipase of the edible Basidiomycete *Antrodia cinnamomea*. *Enzyme and Microb. Technol.* **2005**, *37* (2), 261−265.

(20) Lin, E. S.; Sung, S. C. Cultivating conditions influence exopolysaccharide production by the edible Basidiomycete *Antrodia cinnamomea* in submerged culture. *Int. J. Food Microbiol.* **2006**, *108* (2), 182−187.

(21) Chang, C. Y.; Lee, C. L.; Pan, T. M. Statistical optimization of medium components for the production of *Antrodia cinnamomea* AC0623 in submerged cultures. *Appl. Microbiol. Biotechnol.* **2006**, *72* (4), 654−661.

(22) Lin, E. S.; Chen, Y. H. Factors affecting mycelial biomass and exopolysaccharide production in submerged cultivation of *Antrodia cinnamomea* using complex media. *Bioresour. Technol.* **2007**, *98* (13), 2511−2517.

(23) Ho, Y. C.; Lin, M. T.; Duan, K. J.; Chen, Y. S. The hepatoprotective activity against ethanol induced cytotoxicity by aqueous extract of *Antrodia cinnamomea*. *J. Chin. Inst. Chem. Eng.* **2008**, *39* (5), 441−447.

(24) Lu, Z. M.; Lei, J. Y.; Xu, H. Y.; Shi, J. S.; Xu, Z. H. Optimization of fermentation medium for triterpenoid production from *Antrodia camphorata* ATCC 200183 using artificial intelligence-based techniques. *Appl. Microbiol. Biotechnol.* **2011**, *92* (2), 371−379.

(25) He, Y. C.; He, K. Z.; Pu, Q.; Li, J.; Zhao, Z. J. Optimization of cultivating conditions for triterpenoids production from *Antrodia cinnmomea*. *Indian J. Microbiol.* **2012**, *52* (4), 648−653.

(26) Zhang, H.; Xia, Y.; Wang, Y. L.; Zhang, B. B.; Xu, G. R. Coupling use of surfactant and in situ extractant for enhanced production of antrodin C by submerged fermentation of *Antrodia camphorata*. *Biochem. Eng. J.* **2013**, *79*, 194−199.

(27) Chiang, C. C.; Huang, T. N.; Lin, Y. W.; Chen, K. H.; Chiang, B. H. Enhancement of 4-acetylantroquinonol B production by supplementation of its precursor during submerged fermentation of *Antrodia cinnamomea*. *J. Agric. Food Chem.* **2013**, *61* (38), 9160−9165.
(28) Zhang, H.; Hu, Y. D.; Lu, R. Q.; Xia, Y. J.; Zhang, B. B.; Xu, G. R. Integrated strategy of pH-shift and glucose feeding for enhanced production of bioactive Antrodin C in submerged fermentation of *Antrodia camphorata*. *J. Ind. Microbiol. Biotechnol.* **2014**, *41* (8), 1305−1310.
(29) Hu, Y. D.; Zhang, H.; Lu, R. Q.; Liao, X. R.; Zhang, B. B.; Xu, G. R. Enabling the biosynthesis of antroquinonol in submerged fermentation of *Antrodia camphorata*. *Biochem. Eng. J.* **2014**, *91*, 157−162.
(30) Li, H. X.; Lu, Z. M.; Geng, Y.; Gong, J. S.; Zhang, X. J.; Shi, J. S.; Xu, Z. H.; Ma, Y. H. Efficient production of bioactive metabolites from *Antrodia camphorata* ATCC 200183 by asexual reproduction-based repeated batch fermentation. *Bioresour. Technol.* **2015**, *194*, 334−343.
(31) Yang, S. H.; Lin, Y. W.; Chiang, B. H. Biosynthesis of 4-acetylantroquinonol B in *Antrodia cinnamomea* via a pathway related to coenzyme Q synthesis. *Biochem. Eng. J.* **2017**, *117*, 23−29.
(32) Chen, L.; Wang, Z.; Zhang, B.; Ge, M.; Ng, H.; Niu, Y.; Liu, L. Production, structure and morphology of exopolysaccharides yielded by submerged fermentation of *Antrodia cinnamomea*. *Carbohydr. Polym.* **2019**, *205*, 271−278.
(33) Hu, P. F.; Huang, J.; Chen, L.; Ding, Z.; Liu, L.; Molnár, I.; Zhang, B. B. Oxidative stress induction is a rational strategy to enhance the productivity of *Antrodia cinnamomea* fermentations for the antioxidant secondary metabolite antrodin C. *J. Agric. Food Chem.* **2020**, *68* (13), 3995−4004.
(34) Fan, J. H.; Lai, K. S.; Huang, Y. Y.; Chen, H. Y.; Xiong, L. Q.; Guo, H. K.; Yang, Q. Q.; Zhang, B. B. Efficient production of antrodin C by microparticle-enhanced cultivation of medicinal mushroom *Antrodia cinnamomea*. *J. Biosci. Bioeng.* **2023**, *135*, 232−237.
(35) Qi, J. Z.; Gao, Y. Q.; Kang, S. J.; Liu, C. W.; Gao, J. M. Secondary metabolites of bird's nest fungi: chemical structures and biological activities. *J. Agric. Food Chem.* **2023**, *71* (17), 6513−6524.
(36) Qi, J. Z.; Wu, J.; Kang, S. J.; Gao, J. M.; Hirokazu, K.; Liu, H. W.; Liu, C. W. The Chemical Structures, Biosynthesis, and Biological Activities of Secondary Metabolites from the Culinary-Medicinal Mushrooms of the Genus Hericium: A Review. *Chin. J. Nat. Med.* **2024**, *22* (8), 676−698.
(37) Ahmad, M. F.; Ahmad, F. A.; Hasan, N.; Alsayegh, A. A.; Hakami, O.; Bantun, F.; Tasneem, S.; Alamier, W. M.; Babalghith, A. O.; Aldairi, A. F.; Kambal, N.; Elbendary, E. Y. Ganoderma Lucidum: Multifaceted Mechanisms to Combat Diabetes through Polysaccharides and Triterpenoids: A Comprehensive Review. *Int. J. Biol. Macromol.* **2024**, *268*, 131644.
(38) El Baba, C.; Baassiri, A.; Kiriako, G.; Dia, B.; Fadlallah, S.; Moodad, S.; Darwiche, N. Terpenoids' anti-cancer effects, Focus on autophagy. *Apoptosis.* **2021**, *26* (9), 491−511.
(39) Wang, Q.; Zhao, X.; Jiang, Y.; Jin, B.; Wang, L. Functions of representative terpenoids and their biosynthesis mechanisms in medicinal plants. *Biomolecules.* **2023**, *13* (12), 1725.
(40) Zhao, P.; Guan, M.; Tang, W.; Walayat, N.; Ding, Y.; Liu, J. Structural diversity, fermentation production, bioactivities and applications of triterpenoids from several common medicinal fungi: Recent advances and future perspectives. *Fitoterapia.* **2023**, *166*, 105470.
(41) Su, C. H.; Hsieh, Y. C.; Chng, J. Y.; Lai, M. N.; Ng, L. T. Metabolomic profiling of different *Antrodia cinnamomea* phenotypes. *J. Fungi.* **2023**, *9* (1), 97.
(42) Li, K.; Feng, J.; Kuang, Y.; Song, W.; Zhang, M.; Ji, S.; Qiao, X.; Ye, M. Enzymatic synthesis of bufadienolide O-glycosides as potent antitumor agents using a microbial glycosyltransferase. *Adv. Synth. Catal.* **2017**, *359* (21), 3765−3772.
(43) Luo, Z. S.; Lu, Z. M.; Hu, M. M.; Li, X. Y.; Xu, G. Q.; Gong, J. S.; Shi, J. S.; Xu, Z. H. Characterization of *Cinnamomum kanehirae* extract-stimulated triterpenoids synthesis in submerged fermentation of *Antrodia camphorata* via untargeted metabolomics. *J. Agric. Food Chem.* **2023**, *71*, 9175−9186.
(44) Wang, H. J.; Cui, C.; Gong, X. M.; Wang, S.; Li, C. X.; Guo, H.; Wang, Y. L.; Huang, Y. D.; Jiang, J. L.; Luo, X. M.; Miao, J. H.; Liu, T. Q.; Zhao, S.; Feng, J. X. Improvement of triterpenoid production in mycelia of *Antrodia camphorata* through mutagenesis breeding and amelioration of CCl_4-induced liver injury in mice. *Heliyon.* **2023**, *9* (9), e19621.
(45) Kuang, Y.; Li, B.; Wang, Z.; Qiao, X.; Ye, M. Terpenoids from the medicinal mushroom *Antrodia camphorata*: Chemistry and medicinal potential. *Nat. Prod. Rep.* **2021**, *38* (1), 83−102.
(46) Liu, Y.; Chen, R.; Li, L.; Dong, R.; Yin, H.; Wang, Y.; Yang, A.; Wang, J.; Li, C.; Wang, D. The triterpenoids-enriched extracts from *Antrodia cinnamomea* mycelia attenuate alcohol-induced chronic liver injury via suppression lipid accumulation in C57BL/6 mice. *Food Sci. Hum. Wellness.* **2021**, *10* (4), 497−507.
(47) Li, Z.; Kuang, Y.; Tang, S.; Li, K.; Huang, Y.; Qiao, X.; Yu, S.; Tzeng, Y.; Lo, J. Y.; Ye, M. Hepatoprotective activities of *Antrodia camphorata* and its triterpenoid compounds against CCl_4-induced liver injury in mice. *J. Ethnopharmacol.* **2017**, *206*, 31−39.
(48) Wu, Y.; Tian, W. J.; Gao, S.; Liao, Z. J.; Wang, G. H.; Lo, J. M.; Lin, P. H.; Zeng, D. Q.; Qiu, D. R.; Liu, X. Z.; Zhou, M.; Lin, T.; Chen, H. F. Secondary metabolites of petri-dish cultured *Antrodia camphorata* and their hepatoprotective activities against alcohol-induced liver injury in mice. *Chin. J. Nat. Med.* **2019**, *17* (1), 33−42.
(49) Huo, Y.; Win, S.; Than, T. A.; Yin, S.; Ye, M.; Hu, H.; Kaplowitz, N. Antcin H protects against acute liver injury through disruption of the interaction of C-Jun-N-terminal kinase with mitochondria. *Antioxid. Redox Signaling.* **2017**, *26* (5), 207−220.
(50) Powell, E. E.; Wong, V. W. S.; Rinella, M. Non-alcoholic fatty liver disease. *Lancet.* **2021**, *397* (10290), 2212−2224.
(51) Ruan, S.; Han, C.; Sheng, Y.; Wang, J.; Zhou, X.; Guan, Q.; Li, W.; Zhang, C.; Yang, Y. Antcin A alleviates pyroptosis and inflammatory response in Kupffercells of non-alcoholic fatty liver disease by targeting NLRP3. *Int. Immunopharmacol.* **2021**, *100*, 108126.
(52) Cao, C.; Zhong, H.; Chen, Z.; Song, Z.; Hu, B.; Wang, X. Triterpene acid from *Antrodia camphorata* alleviates inflammation in acute liver injury. *Aging.* **2023**, *15* (10), 4524−4532.
(53) Cao, Y.; Yue, S.; Wang, A.; Xu, L.; Hu, Y.; Qiao, X.; Wu, T. Y.; Ye, M.; Wu, Y. C.; Qi, R. *Antrodia cinnamomea* and its compound dehydroeburicoic acid attenuate nonalcoholic fatty liver disease by upregulating ALDH2 activity. *J. Ethnopharmacol.* **2022**, *292*, 115146.
(54) Wu, Y. S.; Chen, S. N. Extracted triterpenes from *Antrodia cinnamomea* reduce the inflammation to promote the wound healing via the STZ inducing hyperglycemia-diabetes mice model. *Front Pharmacol.* **2016**, *7*, 154.
(55) Senthil Kumar, K. J.; Gokila Vani, M.; Hsieh, H. W.; Lin, C. C.; Wang, S. Y. Antcins from *Antrodia cinnamomea* and *Antrodia salmonea* inhibit angiotensin-converting enzyme 2 (ACE2) in epithelial cells, can be potential candidates for the development of SARS-CoV-2 prophylactic agents. *Plants.* **2021**, *10*, 1736.
(56) Dakpa, G.; Senthil Kumar, K. J.; Tsao, N. W.; Wang, S. Y. Antcin A, a phytosterol regulates SARS-CoV-2 spike protein-mediated metabolic alteration in THP-1 cells explored by the 1H-NMR-based metabolomics approach. *Phytother. Res.* **2023**, *37* (3), 885−902.
(57) Lu, C. W.; Nguyen, N. T. K.; Shen, S. C.; Wu, Y. B.; Liang, H. J.; Wu, C. H. Botanical antcin K alleviates high fat damage in palm acid oil-treated vascular endothelial cells and macrophages. *Plants.* **2022**, *11* (21), 2812.
(58) Achudhan, D.; Liu, S. C.; Lin, Y. Y.; Huang, C. C.; Tsai, C. H.; Ko, C. Y.; Chiang, I. P.; Kuo, Y. H.; Tang, C. H. Antcin K inhibits TNF-α, IL-1β and IL-8 expression in synovial fibroblasts and ameliorates cartilage degradation, implications for the treatment of rheumatoid arthritis. *Front. Immunol.* **2021**, *12*, 790925.
(59) Lu, C. W.; Wu, W. J.; Nguyen, T. K. N.; Shen, S. C.; Wu, Y. B.; Liang, H. J.; Wu, C. H. Alleviating effects of ovatodiolide and antcin K supplements on high-fat diet-induced cardiovascular dysfunction in apoE-knockout mice by attenuating oxidative stress. *Nutrients.* **2023**, *15* (18), 4074.

https://doi.org/10.1021/acsomega.5c01669
ACS Omega 2025, 10, 15908−15922

(60) Kuang, Y.; Chai, Y.; Su, H.; Lo, J. Y.; Qiao, X.; Ye, M. A network pharmacology based strategy to explore the pharmacological mechanisms of *Antrodia camphorata* and antcin K for treating type II diabetes mellitus. *Phytomedicine.* **2022**, *96*, 153851.
(61) Lin, C. H.; Hsiao, L. W.; Kuo, Y. H.; Shih, C. C. Antidiabetic and antihyperlipidemic effects of sulphurenic acid, a triterpenoid compound from *Antrodia camphorata*, in streptozotocin-induced diabetic mice. *Int. J. Mol. Sci.* **2019**, *20* (19), 4897.
(62) Cheng, J. J.; Yang, C. J.; Cheng, C. H.; Wang, Y. T.; Huang, N. K.; Lu, M. K. Characterization and functional study of *Antrodia camphorata* lipopolysaccharide. *J. Agric. Food Chem.* **2005**, *53* (2), 469−474.
(63) Cheng, J. J.; Lu, M. K.; Lin, C. Y.; Chang, C. C. Characterization and functional elucidation of a fucosylated 1, 6-α-D-mannogalactan polysaccharide from *Antrodia cinnamomea*. *Carbohydr. Polym.* **2011**, *83* (2), 545−553.
(64) Chen, Y. T.; Shen, Y. C.; Chang, M. C.; Lu, M. K. Precursor feeding strategy on the triterpenoid production and anti-inflammatory activity of *Antrodia cinnamomea*. *Process Biochem.* **2016**, *51* (8), 941−949.
(65) Lin, T. Y.; Lu, M. K.; Tseng, A. J.; Chao, C. H. Effects of sterol type elicitors on biochemical characterization of polysaccharides from *Antrodia cinnamomea*. *Int. J. Biol. Macromol.* **2020**, *162*, 1476−1483.
(66) Yang, Y.; Han, C.; Sheng, Y.; Wang, J.; Li, W.; Zhou, X.; Ruan, S. *Antrodia camphorata* polysaccharide improves inflammatory response in liver injury via the ROS/TLR4/NF-κB signal. *J. Cell. Mol. Med.* **2022**, *26* (9), 2706−2716.
(67) Cheng, J. J.; Chao, C. H.; Chang, P. C.; Lu, M. K. Studies on anti-inflammatory activity of sulfated polysaccharides from cultivated fungi *Antrodia cinnamomea*. *Food Hydrocolloids.* **2016**, *53*, 37−45.
(68) Lu, M. K.; Lee, M. H.; Chao, C. H.; Hsu, Y. C. Sodium sulfate addition increases the bioresource of biologically active sulfated polysaccharides from *Antrodia cinnamomea*. *Int. J. Biol. Macromol.* **2024**, *257*, 128699.
(69) Lin, T. Y.; Chang, C. C.; Tseng, A. J.; Chao, C. H.; Lu, M. K. Sodium thiosulfate enhances production of polysaccharides and anticancer activities of sulfated polysaccharides in *Antrodia cinnamomea*. *Carbohydr. Polym.* **2019**, *216*, 204−212.
(70) Lu, M. K.; Lee, M. H.; Chao, C. H.; Hsu, Y. C. Physiochemical changes and mechanisms of anti-inflammation effect of sulfated polysaccharides from ammonium sulfate feeding of *Antrodia cinnamomea*. *Int. J. Biol. Macromol.* **2020**, *148*, 715−721.
(71) Lin, Z. H.; Lu, M. K.; Lo, H. C.; Chang, C. C.; Tseng, A. J.; Chao, C. H.; Lin, T. Y. ZnF3, a sulfated polysaccharide from *Antrodia cinnamomea*, inhibits lung cancer cells via induction of apoptosis and activation of M1-like macrophage-induced cell death. *Int. J. Biol. Macromol.* **2023**, *238*, 124144.
(72) Lu, M. K.; Lin, T. Y.; Chang, C. C. Chemical identification of a sulfated glucan from *Antrodia cinnamomea* and its anti-cancer functions via inhibition of EGFR and mTOR activity. *Carbohydr. Polym.* **2018**, *202*, 536−544.
(73) Lin, T. Y.; Tseng, A. J.; Qiu, W. L.; Chao, C. H.; Lu, M. K. A sulfated glucan from *Antrodia cinnamomea* reduces Slug expression through regulation of TGFβ/AKT/GSK3β axis in lung cancer. *Carbohydr. Polym.* **2019**, *210*, 175−184.
(74) Fan, J. H.; Xiong, L. Q.; Huang, W.; Hong, J. Q.; Guo, H. K.; Wong, K. H.; Cheung, P. C. K.; Yang, Q. Q.; Zhang, B. B. Exopolysaccharides produced by *Antrodia cinnamomea* using micro-particle-enhanced cultivation, optimization, primary structure and antibacterial property. *Int. J. Biol. Macromol.* **2024**, *259*, 128872.
(75) Lu, C.; Lee, B. H.; Ren, Y.; Ji, D.; Rao, S.; Li, H.; Yang, Z. Effects of exopolysaccharides from *Antrodia cinnamomea* on inflammation and intestinal microbiota disturbance induced by antibiotics in mice. *Food Biosci.* **2022**, *50*, 102116.
(76) Liu, Y.; Yang, A.; Qu, Y.; Wang, Z.; Zhang, Y.; Liu, Y.; Wang, N.; Teng, L.; Wang, D. Ameliorative effects of *Antrodia cinnamomea* polysaccharides against cyclophosphamide-induced immunosuppression related to Nrf2/HO-1 signaling in BALB/c mice. *Int. J. Biol. Macromol.* **2018**, *116*, 8−15.
(77) Lu, M. K.; Chao, C. H.; Chang, T. Y.; Cheng, M. C.; Hsu, Y. C.; Chang, C. C. A branched 2-O sulfated 1, 3-/1, 4-galactoglucan from *Antrodia cinnamomea* exhibits moderate antiproliferative and anti-inflammatory activities. *Int. J. Biol. Macromol.* **2023**, *241*, 124559.
(78) Cui, Y. L.; Li, B. Hypoglycemic effects of edible fungus polysaccharides: A mini review. *Food Med. Homol.* **2025**, *2*, 9420046.
(79) Arunachalam, K.; Sreeja, P. S.; Yang, X. The antioxidant properties of mushroom polysaccharides can potentially mitigate oxidative stress, beta-cell dysfunction and insulin resistance. *Front. Pharmacol.* **2022**, *13*, 874474.
(80) Zhang, B. B.; Hu, P. F.; Huang, J.; Hu, Y. D.; Chen, L.; Xu, G. R. Current advances on the structure, bioactivity, synthesis, and metabolic regulation of novel ubiquinone derivatives in the edible and medicinal mushroom *Antrodia cinnamomea*. *J. Agric. Food Chem.* **2017**, *65* (48), 10395−10405.
(81) Ho, C. L.; Wang, J. L.; Lee, C. C.; Cheng, H. Y.; Wen, W. C.; Cheng, H. H. Y.; Chen, M. C. M. Antroquinonol blocks Ras and Rho signaling via the inhibition of protein isoprenyltransferase activity in cancer cells. *Biomed. Pharmacother.* **2014**, *68* (8), 1007−1014.
(82) Lin, H. C.; Lin, M. H.; Liao, J. H.; Wu, T. H.; Lee, T. H.; Mi, F. L.; Wu, C. H.; Chen, K. C.; Cheng, C. H.; Lin, C. W. Antroquinonol, a ubiquinone derivative from the mushroom *Antrodia camphorata*, inhibits colon cancer stem cell-like properties, insights into the molecular mechanism and inhibitory targets. *J. Agric. Food Chem.* **2017**, *65* (1), 51−59.
(83) Guan, C.; Li, Q.; Song, X.; Xu, W.; Li, L.; Xu, A. Antroquinonol exerts immunosuppressive effect on $CD8^+$ T cell proliferation and activation to resist depigmentation induced by H_2O_2. *Oxid. Med. Cell. Longevity.* **2017**, *2017* (1), 9303054.
(84) Li, T.-Y.; Chiang, B.-H. 4-Acetylantroquinonol B from *Antrodia cinnamomea* enhances immune function of dendritic cells against liver cancer stem cells. *Biomed. Pharmacother.* **2019**, *109*, 2262−2269.
(85) Chen, Y. L.; Yen, I. C.; Lin, K. T.; Lai, F. Y.; Lee, S. Y. 4-Acetylantrocamol LT3, a new ubiquinone from *Antrodia cinnamomea*, inhibits hepatocellular carcinoma HepG2 cell growth by targeting YAP/TAZ, mTOR, and WNT/β-catenin signaling. *Am. J. Chin. Med.* **2020**, *48* (05), 1243−1261.
(86) Yang, H. L.; Huang, S. T.; Lyu, Z. H.; Bhat, A. A.; Vadivalagan, C.; Yeh, Y. L.; Hseu, Y. C. The anti-tumor activities of coenzyme Q_0 through ROS-mediated autophagic cell death in human triple-negative breast cells. *J. Funct. Foods.* **2023**, *102*, 105454.
(87) Hseu, Y. C.; Yeh, J. T.; Vadivalagan, C.; Chen, S. J.; Gowrisankar, Y. V.; Pandey, S.; Hsu, Y. T.; Yen, H. R.; Huang, H. C.; Hseu, J. H.; Yang, H. L. The in vitro and in vivo depigmentation activity of coenzyme Q_0, a major quinone derivative from *Antrodia camphorata*, through autophagy induction in human melanocytes and keratinocytes. *Cell Commun. Signaling.* **2024**, *22* (1), 151.
(88) Chien, S. C.; Chen, M. L.; Kuo, H. T.; Tsai, Y. C.; Lin, B. F.; Kuo, Y. H. Anti-inflammatory activities of new succinic and maleic derivatives from the fruiting body of *Antrodia camphorat*. *J. Agric. Food Chem.* **2008**, *56* (16), 7017−7022.
(89) Phuong, D. T.; Ma, C. M.; Hattori, M.; Jin, J. S. Inhibitory effects of antrodins A-E from *Antrodia cinnamomea* and their metabolites on hepatitis C virus protease. *Phytother. Res.* **2009**, *23* (4), 582−584.
(90) Borgstahl, G. E. O.; Oberley Deegan, R. E. Superoxide dismutases (SODs) and SOD mimetics. *Antioxidants.* **2018**, *7* (11), 156.
(91) Dong, L.; Chen, Y.; Gu, L.; Gan, M.; Carrier, A.; Oakes, K.; Zhang, X.; Dong, Z. Oral delivery of a highly stable superoxide dismutase as a skin aging inhibitor. *Biomed. Pharmacother.* **2023**, *164*, 114878.
(92) Lu, M. K.; Cheng, J. J.; Lai, W. L.; Lin, Y. R.; Huang, N. K. Adenosine as an active component of *Antrodia cinnamomea* that prevents rat PC12 cells from serum deprivation-induced apoptosis through the activation of adenosine A2A receptors. *Life Sci.* **2006**, *79* (3), 252−258.
(93) Hsu, C. S.; Chou, H. H.; Fang, J. M. A short synthesis of (±) antroquinonol in an unusual scaffold of 4-hydroxy-2-cyclohexenone. *Org. Biomol. Chem.* **2015**, *13* (19), 5510−5519.

https://doi.org/10.1021/acsomega.5c01669
ACS Omega 2025, 10, 15908−15922

(94) Hsu, C. S.; Fang, J. M. Synthesis of (+) antroquinonol and analogues by using enantioselective michael reactions of benzoquinone monoketals. *Eur. J. Org. Chem.* **2016**, *2016* (22), 3809−3816.
(95) Sulake, R. S.; Chen, C. Total synthesis of (+) antroquinonol and (+) antroquinonol D. *Org. Lett.* **2015**, *17* (5), 1138−1141.
(96) Sulake, R. S.; Lin, H. H.; Hsu, C. Y.; Weng, C. F.; Chen, C. synthesis of (+) antroquinonol, an antihyperglycemic agent. *J. Org. Chem.* **2015**, *80* (12), 6044−6051.
(97) He, Y. C.; He, K. Z.; Pu, Q.; Li, J.; Zhao, Z. J. Optimization of cultivating conditions for triterpenoids production from *Antrodia cinnmomea*. *Indian J. Microbiol.* **2012**, *52* (4), 648−653.
(98) Hu, Y. D.; Zhang, B. B.; Xu, G. R.; Liao, X. R.; Cheung, P. C. K. A mechanistic study on the biosynthetic regulation of bioactive metabolite antroquinonol from edible and medicinal mushroom *Antrodia camphorata*. *J. Funct. Foods.* **2016**, *25*, 70−79.
(99) Chou, K. C. C.; Yang, S. H.; Wu, H. L.; Lin, P. Y.; Chang, T. L.; Sheu, F.; Chen, K. H.; Chiang, B. H. Biosynthesis of antroquinonol and 4-acetylantroquinonol B via a polyketide pathway using orsellinic acid as a ring precursor in *Antrodia cinnamomea*. *J. Agric. Food Chem.* **2017**, *65* (1), 74−86.
(100) Chou, K. C. C.; Wu, H. L.; Lin, P. Y.; Yang, S. H.; Chang, T. L.; Sheu, F.; Chen, K. H.; Chiang, B. H. 4-Hydroxybenzoic acid serves as an endogenous ring precursor for antroquinonol biosynthesis in *Antrodia cinnamomea*. *Phytochemistry.* **2019**, *161*, 97−106.
(101) Yang, S. H.; Lin, Y. W.; Chiang, B. H. Biosynthesis of 4-acetylantroquinonol B in *Antrodia cinnamomea* via a pathway related to coenzyme Q synthesis. *Biochem. Eng. J.* **2017**, *117*, 23−29.
(102) Liu, X.; Xia, Y.; Zhang, Y.; Sang, K.; Xiong, Z.; Wang, G.; Liu, X.; Ai, L. RNA-Seq transcriptomic analyses of *Antrodia camphorata* to determine antroquinonol and antrodin C biosynthetic mechanisms in the in situ extractive fermentation. *J. Sci. Food Agric.* **2020**, *100* (11), 4252−4262.
(103) Wei, Y. Y.; Chou, K. C. C.; Yang, S. H.; Chiang, B. H. Oxygen vector accelerates farnesylation and redox reaction to promote the biosynthesis of 4-acetylantroquinonol B and antroquinonol during submerged fermentation of *Antrodia cinnamomea*. *Food Bioprod. Process.* **2020**, *120*, 80−90.
(104) Xia, Y.; Meng, P.; Liu, S.; Tan, Z.; Yang, X.; Liang, L.; Xie, F.; Zhang, H.; Wang, G.; Xiong, Z. Structural and potential functional properties of alkali-extracted dietary fiber from *Antrodia camphorata*. *Front Microbiol.* **2022**, *13*, 921164.
(105) Temel, Y.; Koçyigit, U. M.; Taysı, M. Ş.; Gökalp, F.; Gürdere, M. B.; Budak, Y.; Ceylan, M.; Gülçin, İ.; Çiftci, M. Purification of Glutathione S-transferase Enzyme from Quail Liver Tissue and Inhibition Effects of (3a R,4 S,7 R,7a S)-2-(4-((E)-3-(Aryl)Acryloyl)-Phenyl)-3a,4,7,7a-tetrahydro-1 H −4,7-methanoisoindole-1,3(2 H)-dione Derivatives on the Enzyme Activity. *J. Biochem. Mol. Toxicol.* **2018**, *32* (3), No. e22034.
(106) Gökalp, F. The Inhibition Effect of Garlic-derived Compounds on Human Immunodeficiency Virus Type 1 and Saquinavir. *J. Biochem. Mol. Toxicol.* **2018**, *32* (11), No. e22215.
(107) Gökalp, F. The Investigation of the Healing Effect of Active Ingredients in Traditional Medicinal Plants on Lung Cancer. *Med. Oncol.* **2020**, *37* (11), 102.
(108) Gökalp, F. The Inhibition Effect of Natural Food Supplement Active Ingredients on TP63 Carcinoma Cell. *Med. Oncol.* **2020**, *37* (12), 120.
(109) Gökalp, F. Therapeutic Effect of Some Natural Active Compounds for Breast Cancer. *Med. Oncol.* **2022**, *39* (8), 115.
(110) Gökalp, F. An Investigation into the Usage of Black Cumin Derivatives against Cancer and COVID-19 as the Nature Medicine. *J. Biomol. Struct. Dyn.* **2024**, 1−8.

https://doi.org/10.1021/acsomega.5c01669
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