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Chemical Constituents and Pharmacology of *Fomes fomentarius*: A Systematic Review

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Abstract: This paper mainly provides a systematic review of the chemical constituents and biological activities of *Fomes fomentarius*. As a widely distributed medicinal fungus, *F. fomentarius* has a long history of application in traditional medicine. Rich in chemical constituents, it contains over a hundred compounds such as steroids, triterpenes, and fatty acids. Pharmacological studies have demonstrated that this fungus exhibits multiple activities, including antitumor, immunomodulatory, antioxidant, antibacterial, anti-inflammatory and analgesic, antidiabetic, anti-hypoxic, and hepatoprotective effects. However, our current understanding of its action mechanisms and the synergistic effect among components remains limited. This review provides crucial references for further research and development of *F. fomentarius*.

Keywords: *Fomes fomentarius*; chemical constituents;pharmacological activities; *Pyropolyporus fomentarius.*

1. Introduction

Fomes fomentarius, which is known as "*Hua jun zhi*" in China, belongs to the genus Fomes of the family *Polyporaceae*. Its scientific name is *Fomes fomentarius* (Fr.) Kickx, and its synonym is

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Pyropolyporus fomentarius (L.ex Fr.) Teng [1-3]. The specific epithet "*fomentarius*" means "tinder-like" in Latin. Since its flesh is highly flammable when dried, it is also called "tinder fungus" and "fire starter fungus". The 2024 edition of the "*Catalogue of Chinese Biological Species*" records as many as 27,807 fungal species and infraspecific taxa [4]. Medicinal fungi, as a crucial part of natural medicine, play a key role in maintaining human health. As one of fungi medicine, *F. fomentarius* has a long history in the field of traditional Chinese medicine. Traditional medicine holds that *F. fomentarius* has the effects of promoting blood circulation to remove blood stasis and regulating qi to dissipate stagnation [2]. It has been commonly used in folk medicine to treat pediatric dyspepsia, esophageal cancer, gastric cancer, uterine cancer, and other diseases. In the 18th and 19th centuries, it was used as a hemostatic dressing and bandage [5]. In Japan, *F. fomentarius* is used to make a popular beverage, and people believe it has preventive effects against a variety of diseases [6]. In addition, it has also been applied in the treatment of gastrointestinal diseases, liver cirrhosis, oral ulcers, inflammations and various cancers [7-8].

With the gradual deepening of modern scientific research on natural products, fungi have become an important source of novel bioactive components due to their unique ecological adaptability and diverse metabolic pathways. *F. fomentarius* grows in specific forest ecosystems, and its chemical components may possess medicinal values and bioactive mechanisms that have not been fully explored. Current research has found that *F. fomentarius* has multiple activities such as anti-tumor, antioxidant and immunomodulatory effects. However, the material basis and mechanisms of these effects remain unclear and urgently need further in-depth exploration. Research on *F. fomentarius* not only helps to reveal its potential medicinal value and promote innovation in the medical field but may also provide new development ideas for the health product industry and other fields, thus having important research significance and broad application prospects. This paper reviews the chemical components and biological activities of *F. fomentarius*, aiming to promote its further research, development and utilization.

2. Search Strategy

In this paper, a comprehensive research and analysis of previously published literature was conducted to explore the phytochemical components and pharmacological activities of *F. fomentarius*. All the literature on *F. fomentarius* was collected by using databases such as Medline PubMed, Science Direct, Sci Finder, Baidu Scholar, Google Scholar and CNKI. Finally, 93 references were selected and used in this paper. The search keywords included: *Fomes fomentarius*, *Pyropolyporus fomentarius*, wood hoof fungus, patent reports, and uses of *F. fomentarius*. Some of the research materials for analysis were obtained by manually searching the articles in the reference lists of the included studies. The chemical structures were drawn with Chem Draw Professional 20.0 software.

3. Botany, Description, and Distribution

F. fomentarius is a wood-decaying fungus with a worldwide distribution. In China, it is mainly distributed in Shaanxi, Heilongjiang, Jilin, Inner Mongolia, Hebei, Shanxi, Henan, Gansu, Xinjiang, Sichuan, Guizhou, Yunnan, Guangxi and other regions. It parasitizes on broad-leaved trees such as birch and oak in low and middle mountainous areas. The basidiocarp is perennial, sessile, and woody. The pileus is hoof-shaped, with a surface color ranging from gray taupe to black, and it has a hard

and smooth crust. The context is light brown to brown. The tubes are the same color as the context and are arranged in layers. The pore surface is the same color as the tubes, the pores are regular, slightly round and of medium size. The hyphal system is trimitic; the generative hyphae have clamp connections; the skeletal hyphae and binding hyphae are thick-walled and light yellow. The basidiospores are cylindrical, transparent and smooth [9].

4. Chemical Constituents in *F. fomentarius*

F. fomentarius contains extremely rich chemical constituents. Up to now, numerous scholars from both home and abroad have isolated more than a hundred compounds. These compounds mainly consist of steroids, triterpenes, and fatty acid components. Besides, there are also some other types of components such as aldehydes, ketones, esters, etc. For detailed information, please refer to Table 1, Figure 1A-E.

Lu et al. demonstrated through chemical preliminary tests that in *F. fomentarius*, there are phenolic components, organic acids, polysaccharides and glycosides, lactones, coumarins and their glycosides, phytosterols, terpenoids, as well as anthraquinones and their glycosides [10]. Yin et al. measured that the polysaccharide content in the fruiting bodies of *F. fomentarius* was 1.7% and the amino acid content was 7.34% [11]. In terms of nutritional component analysis, Li analyzed the contents of main nutrients in the fruiting bodies of *F. fomentarius*. The results showed that the water content was 7.95%, the crude protein content was 2.56%, the crude fat content was 5.71%, and the ash content was 2.12%. The contents of 18 trace elements and 16 amino acids were measured by an automatic analyzer. In addition, a high-performance liquid chromatography method was established to determine that the ergosterol content in the fruiting bodies of *F. fomentarius* was 1.45 mg/g [12]. Aziz et al. determined 17 kinds of amino acids and their contents in *F. fomentarius* by post-column derivatization cation exchange chromatography [13]. Liu and Jia used the ethanol precipitation method to extract polysaccharides from the fermentation broth of *F. fomentarius*. The polysaccharides of *F. fomentarius* (PFF) were purified by ion exchange and gel chromatography, and the structure and composition of the polysaccharides were analyzed. The results showed that PFF contained only one type of polysaccharide. Thin-layer chromatography analysis indicated that PFF were polymerized from galactose. Infrared spectroscopy analysis of PFF revealed that the polysaccharide was pyranose, connected by α-glycosidic bonds and containing groups such as ester amines [14].

Table 1. The compound names in *F. fomentarius*

No	Name	Ref
Steroids		
1	*β*-Sitosterol	[12]
2	3*β*-Linoleyloxyergosta-7,22-diene	[15]
3	3*β*-linoleyloxyergosta-7-ene	[15]
4	3*β*-Linoleyloxyergosta-7,24(28)-diene	[15]
5	Ergosta-7,22-dien-3-one	[15]
6	Ergosta-7-en-3-one	[15]
7	5*α*,8*α*-Epidioxy-(22*E*,24*R*)-ergosta-6,22-dien-3*β*-ol	[16]
8	Ergosterol	[17]
9	Pyropolincisterol A	[18]
10	Pyropolincisterol B	[18]
11	3*β*,5*α*-Dihydroxy-6*β*-methoxyergosta-7,22-diene	[18]
12	(22*E*,24*R*)-3*β*,5*α*,9*α*-Trihydroxyergosta-7,22-dien-6-one	[18]
13	Volemolide	[18]
14	Salimyxin B	[18]
15	Ergosta-7,22-dien-3,6-dione	[19]
16	Ergosta-7,22-dien-3*β*-ol	[20]
17	(22*E*,24*R*)-3*β*,5*α*,6*β*,14*α*-Tetrahydroxyergosta-7,9(11),22-triene	[21]
18	(22*E*,24*R*)-3*β*,5*β*,6*α*,7*α*-Tetrahydroxy-8*α*,9*α*-dihydroergosta-14,22-diene	[21]
19	(22*E*,24*R*)-3*β*,5*α*-Dihydroxy-6*β* ethoxyergosta-7,22-diene	[21]
20	(22*E*,24*S*)-3*β*,25-Dihydroxy-15*α*-*O*-*β*-*D*-glucopyranosyl ergosta-7,22-dien-6-one	[21]
21	(22*E*,24*R*)-3*β*-Hydroxyergosta-7,22-diene,6-one	[21]
22	(22*E*,24*R*)-Ergosta-7,22-dien-3*β*,5*α*,6*β*-triol	[21]
23	(22*E*,24*R*)-Ergosta-7,22-dien-3*β*,5*α*,6*α*-triol	[21]
24	(22*E*,24*R*)-Ergosta-7,9(11),22-trien-3*β*,5*α*,6*β*-triol	[21]
25	(22*E*,24*R*)-Ergosta-7,22-dien-3*β*,5*α*,6*β*,9*α*-tetraol	[21]
26	3*β*-O-glucopyranosyl-5*α*,6*β*-dihydroxyergosta-7,22-diene	[21]
27	Ergosta-7,22-dien-3-palmitate	[22]
28	Ergosta-7,22-dien-3-one,dimethyl acetal	[22]
29	(22*E*,24*R*)-Ergosta-4,6,8(14),22-tetraen-3-one	[23]
30	Ergosta-22-en-3-one	[24]
Triterpenoids		
31	Acetyl oleanolic acid	[25]
32	3-Formyloxybetulin	[18]
33	3-Formyloxybetulinic acid	[18]
34	Betulin	[18]
35	28-Formyloxybetulin	[18]

36	Betulinic acid 7′,8′-dihydroxycinnamate	[18]
37	Polyporenic acid	[18]
38	Dehydroeburiconic acid	[18]
39	(25*S*)-(+)-12*α*-Hydroxy-3*α*-methylcarboxyacetate-24-methyllanosta-8,24(31)-diene-26-oic acid	[18]
40	Igniaren D	[18]
41	Phellibarin A	[18]
42	Phellibarin B	[18]
43	Phellibarin C	[18]
44	Lup-20(29)-ene-3,28-diol,28-acetate	[22]
45	Lupeol	[24]
46	28-C-Methyl-lup-20(29)-en-3-ol	[24]
47	Betulinic acid	[24]
48	(17*R*,20*R*)-78,20,23,29-Tetrahydroxy-28-norlupane-3,16-dione	[24]
Aldehydes and Ketones		
49	4-(3,4-Dihydroxy-phenyl)-3-buten-2-one	[12]
50	Tetradecanal	[17]
51	(9*Z*)-9,17-Octadecadienal	[17]
52	2-Nonadecanone	[17]
53	Vanillin	[19]
54	2,4-Dihydroxy-3,5-dimethylacetophenone	[20]
55	4-(4-Hydroxyphenyl)-3*E*-buten-2-ketone	[20]
56	1,5-bis(3,4-Dihydroxy-phenyl)-1,4-pentadien-3-one	[20]
57	3,4-Dihydroxyacetophenone	[20]
58	4-Hydroxybenzaldehyde	[20]
59	4-Hydroxyacetophenone	[20]
60	3,4-Dihydroxybenzaldehyde	[20]
61	Nonanal	[26]
62	Octadecanal	[26]
63	Heptadecanal	[26]
Fatty Acids		
64	*α*-Linolenic acid	[12]
65	n-Hexadecanoi acid	[17]
66	9-Octadecenoic acid, (*E*)-	[17]
67	13-Octadecenoic acid, (*E*)-	[17]
68	9,10-Dihydroxyoctadec-12-enoic acid	[18]
69	Octadeca-9,12-dienoic acid	[18]
70	Octadecadienoic acid	[27]
71	Octadecanoic Acid	[22]
72	*β*-Hydroxyoctadecanoic Acid	[22]

73	9,10-Dihydroxyoctadecanoic Acid	[22]
Esters		
74	1,2-Benzenedicarboxylic acid, butyl 2-methylpropyl ester	[17]
75	Fomentarinin	[19]
76	Ethyl 2-Hydroxycerotate	[19]
77	Ethyl 3,4-Dihydroxybenzoate	[20]
78	Hexadecanoic acid ester	[27]
79	Octadecadienoic acid ester	[27]
80	Diethyl Phthalate	[26]
81	9(11)-Dehydro-ergoloyl benzoate	[26]
82	Triglyceride	[24]
83	Dimethyl phthalate	[24]
84	Tyrosol acetate	[24]
Phenyl Ethylene Glycols		
85	(1*R*)-(3-ethenylphenyl)-1,2-ethanediol	[28]
86	(1*R*)-(3-formylphenyl)-1,2-ethanediol	[28]
87	(1*R*)-(3-acetophenyl)-1,2-ethanediol	[28]
88	(3-ethylphenyl)-1,2-ethanediol	[28]
89	(4-acetophenyl)-1,2-ethanediol	[28]
Coumarins		
90	Daphnetin-8-methyl ether	[18]
91	7,8-Dimethoxycoumarin	[18]
92	5-Methoxy-8-hydroxycoumarin	[18]
93	Daphnetin	[22]
Others		
94	5,6-Dimethoxyphthalice	[29]
95	6-Carbomethoxyphthalide	[29]
96	α-phellandrene	[27]
97	i-phellandrene	[27]
98	Coenzyme Q9	[25]
99	Paulownin	[30]
100	5,6-Dimethoxybenzofuran-2-one	[18]
101	Fomentariol	[31]
102	Oxirane, heptadecyl-	[17]
103	(*Z*)-13-Docosen-1-ol	[17]
104	Syringic acid	[19]
105	Syringyl alcohol	[19]
106	Undecene	[27]
107	Ocymene	[27]
108	3,3-Dimethyl-8-hydroxy-3-octenyl cyclohexanol	[23]
109	5-Isobenzofurancarboxylic methyl ester	[24]

110	Cytosine	[24]
111	Uridine	[24]
112	8-Hydroxy-7-methoxy-isochromen-1-one	[24]
113	5-Hydroxymethyl-2-furancarboxaldehyde	[24]
114	Anhydrodehydrofomentariol	[32]
115	Dehydrofomentariol	[33]

5. Pharmacological Activities

Modern research has demonstrated that *F. fomentarius* exhibits multiple activities such as anti-tumor, immunomodulatory, antioxidant, antibacterial, anti-inflammatory and analgesic, and antidiabetic activities.

5.1 Antitumor Activity

The antitumor activity of *Fomes fomentarius* is primarily achieved through the induction of tumor cell apoptosis, inhibition of tumor cell proliferation, regulation of tumor-related proteins and gene expression, and enhancement of the body's immune function. Key cells involved include various tumor cell lines, such as melanoma cells, liver cancer cells (HepA, H22), esophageal cancer cells (Eca109), and others. Key factors include Ras protein, p53 protein, Bax and Bcl-2 gene products, as well as cytokines such as IL-2 and TNF-α.

Storsberg et al. found in their in vitro study that the alkaline aqueous extract (FFE) rich in polyphenols and β-glucan from the fruiting bodies of *F. fomentarius* exhibited specific cytotoxicity profiles against different cells. For L929 cells, there was a dose-dependent cytotoxicity, with a half-maximal inhibitory concentration of 0.44 mg/mL. Caco-2 cells, on the other hand, showed no response to FFE, indicating its safety for the intestinal epithelium. As for melanoma cells, they were affected by FFE in a dose-dependent manner even at low concentrations. Therefore, the topical application of FFE holds promise for the early prevention of melanoma [34]. Zhang investigated the apoptosis-inducing effect of the polysaccharide FFEP-1 from *F. fomentarius* and its derivative SFFEP-1 on Eca109 tumor cells. Using human esophageal cancer Eca109 cells as a model, as the concentration of the test substances increased, obvious cell apoptosis was observed. Different concentrations of FFEP-1 and its derivative could induce the generation of ROS inside the cells, regulate antioxidant enzymes, and inhibit the Nrf2-mediated antioxidant defense system. SFFEP-1 could cause Eca109 cells to arrest at the G2/M phase, while PFFEP-1 made the cells arrest at the S phase, thus prolonging the tumor cell cycle, inhibiting the DNA repair of damaged cells, and suppressing cell proliferation [35]. By using SDS-PAGE technique, Guo et al. investigated the influence of *F. fomentarius* polysaccharide on the serum protein components of HepA mice and separated and compared the serum protein components of each experimental group. The results demonstrated that under equal sample loading, the polysaccharide could lighten the specifically deeply stained component around 140 KD in molecular weight, which was closer to that of the normal group when compared with the tumor-bearing negative control group. It further implied that the polysaccharide could attenuate the deeply stained protein component at about 140 KD in the SDS-PAGE of HepA mouse serum [36].

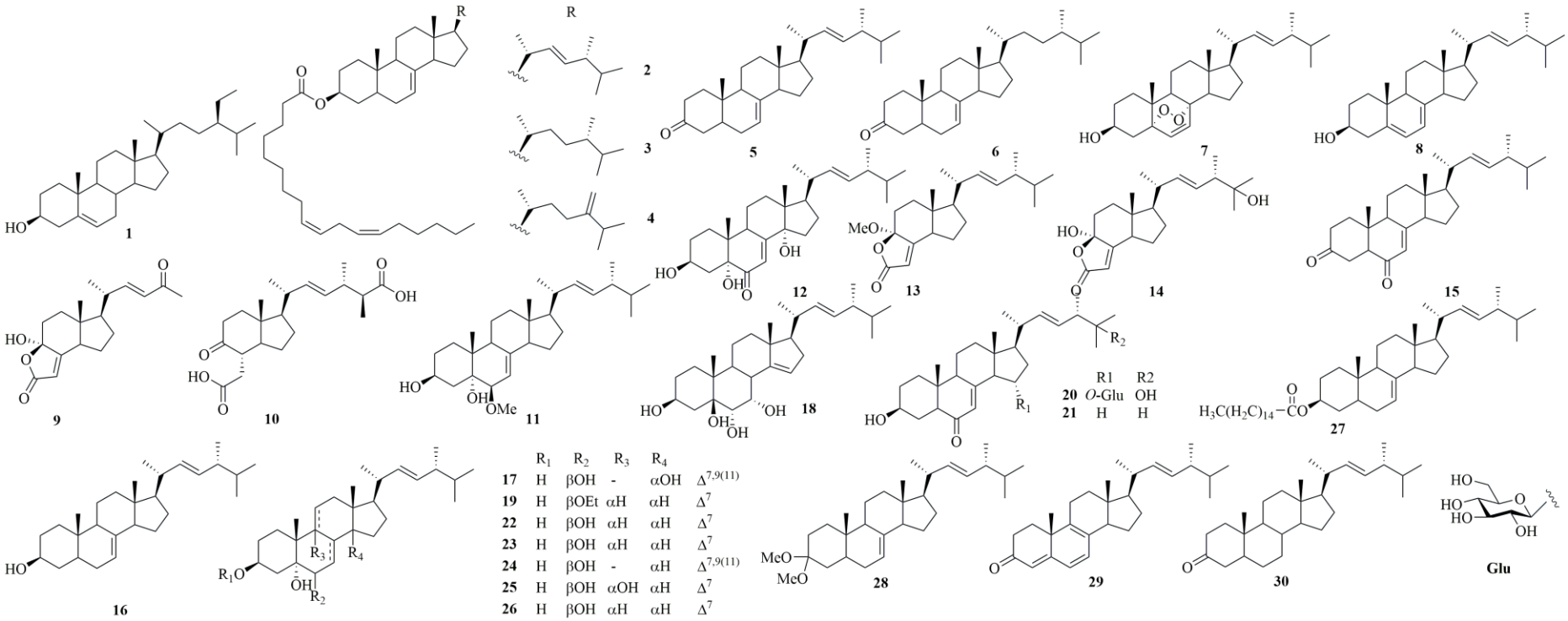
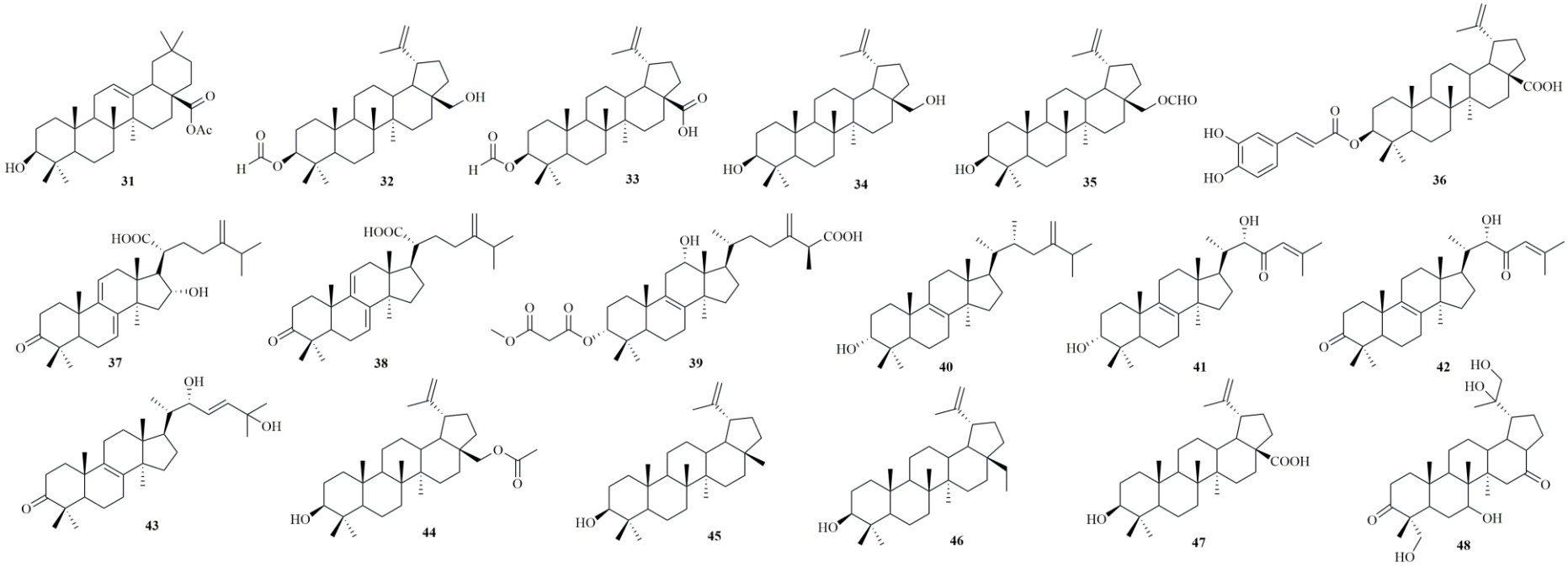
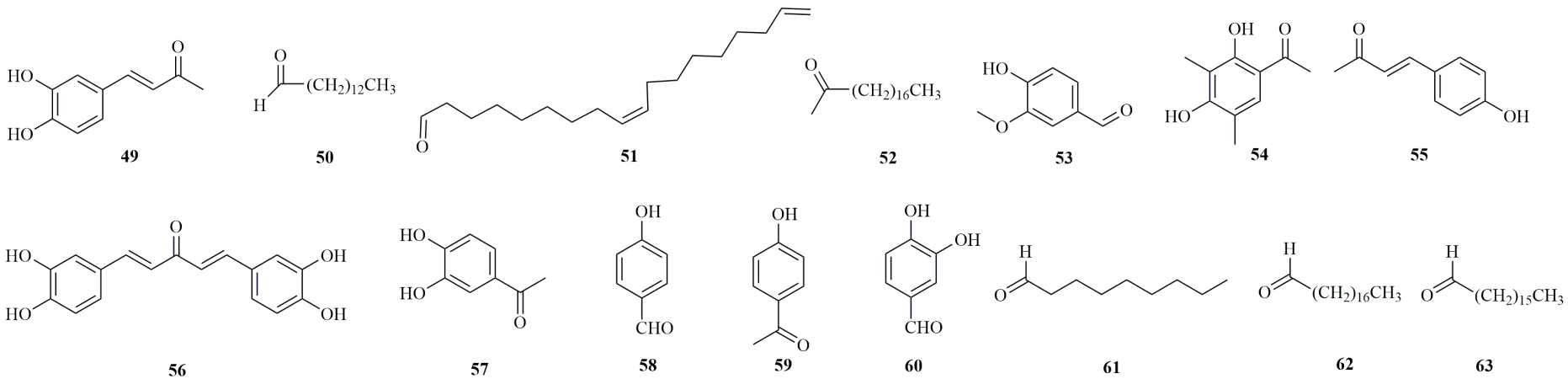


Figure 1A. The chemical structures of compounds reported in *F. fomentarius*



Triterpenoids (31-48)

Figure 1B. The chemical structures of compounds reported in *F. fomentarius*



Aldehydes and Keton (49~63)

Figure 1C. The chemical structures of compounds reported in *F. fomentarius*

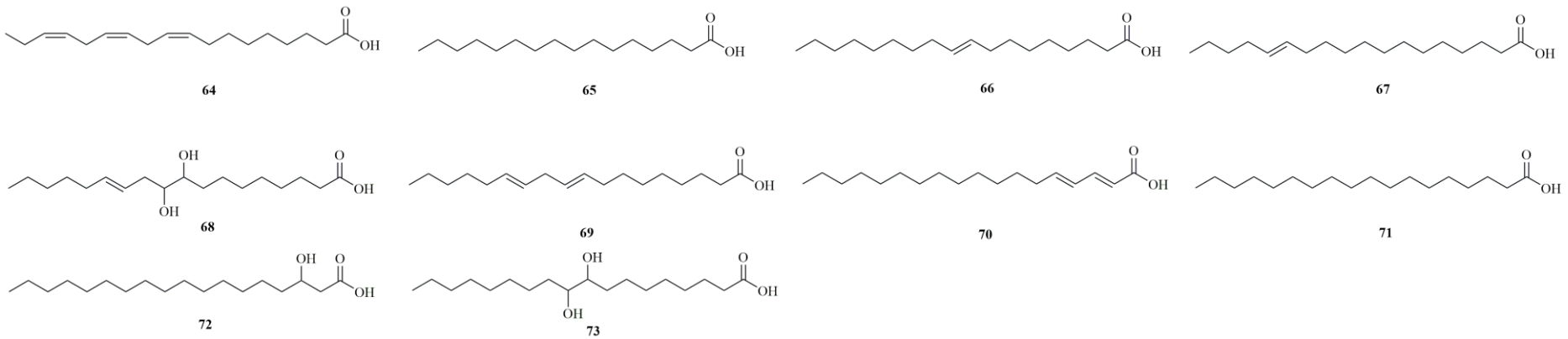
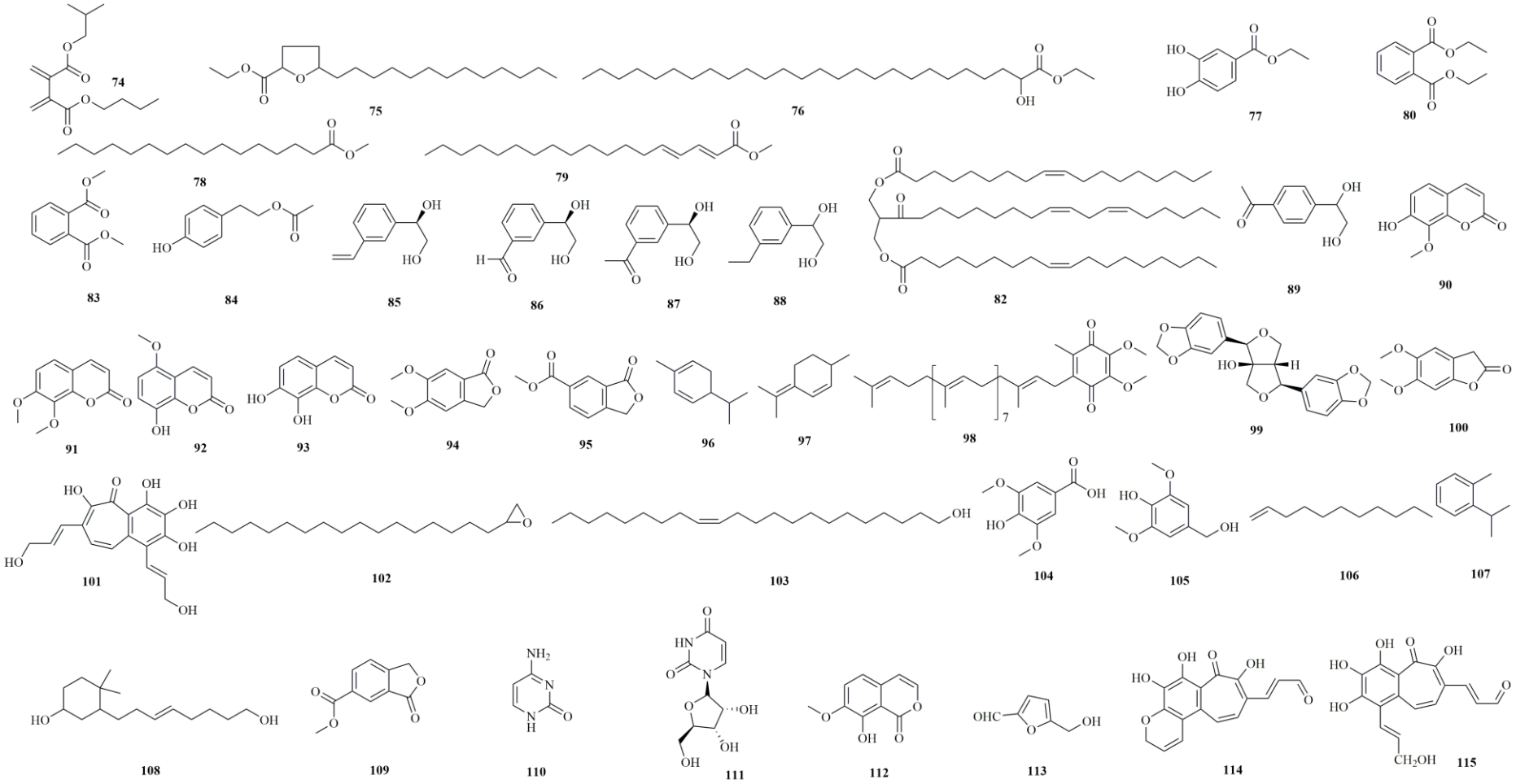


Figure 1D. The chemical structures of compounds reported in *F. fomentarius*



Others (74~115)

Figure 1E. The chemical structures of compounds reported in *F. fomentarius*

Guo et al. aimed to observe the effects of the polysaccharide from *F. fomentarius* on the tumor inhibition rate and serum NO content in HepA mice. The nitrate reductase method was employed to determine the NO content. The results indicated that the polysaccharide from *F. fomentarius* could achieve a tumor inhibition rate of 41.42% in HepA mice and increase the serum NO content ($P<0.05$). They concluded that the polysaccharide from *F. fomentarius* exhibited a potent inhibitory effect on ascitic metastatic cancer in HepA mice [37]

The research by Guo et al. showed that the polysaccharide from *F. fomentarius* had an obvious tumor-suppressive effect on HepA tumors in mice. It could reduce the expression of Ras protein, inhibit the proliferation of HepA tumor cells, and decrease the abnormal protein component (Mr 140,000) in the serum of HepA mice, making it tend to be normal [38]. Guo and colleagues' subsequent study provided crucial insights. They found that for medium and high-dose regimens of *F. fomentarius* polysaccharide, the expression of Ras gene in HepA tumor cells was markedly diminished. The disparity compared to the negative control group was statistically significant ($P<0.05$), which clearly indicated that the polysaccharide functions to impede tumor cell proliferation by curbing Ras gene expression [39]. In their research endeavor, Guo and her team further explored the role of *F. fomentarius* polysaccharide by focusing on its effect on the P21 protein expression in mouse S180 tumor cells. Intriguingly, they discovered that the polysaccharide led to a marked decline in the expression of Ras protein ($P<0.05$), providing initial evidence that it could potentially impede tumor cell proliferation via downregulating Ras protein expression. This finding adds a crucial piece to the puzzle of understanding the anti-tumor mechanisms of *F. fomentarius* polysaccharide [40]. Guo et al. aimed to explore the inhibitory effect of *F. fomentarius* polysaccharide on transplanted sarcoma S180 in mice and its impact on p53 protein expression in tumor tissues. They established an S180 mouse model. Then, they weighed the tumor tissues to calculate the tumor inhibition rate, measured the p53 protein content using the streptavidin-peroxidase immunohistochemical method, and analyzed the results with a multimedia image analysis system. It was found that the tumor inhibition rates of the high and medium-dose groups of *F. fomentarius* polysaccharide were 41.84% and 41.13% respectively, and the expression of mutant p53 protein was significantly reduced compared with the model group ($P<0.05$). It can be seen that the polysaccharide can inhibit S180 sarcoma and downregulate the expression of mutant p53 gene [41]. In a significant study, Qi and his team delved into the impact of the G-F group of *F. fomentarius* polysaccharide. Their findings were remarkable: the polysaccharide notably curbed HepA tumors in mice, achieving an impressive 40.60% tumor inhibition rate. Moreover, when compared to the negative control, the expression of Ras protein in the G-F group was substantially diminished ($P<0.05$). This not only established the potent anti - tumor activity of *F. fomentarius* polysaccharide but also unravelled its underlying mechanism: by downregulating Ras protein expression to impede the proliferation of HepA tumor cells. Such insights are invaluable for further research and potential clinical applications [42]. In a significant study, Qi and his associates found that the G-F fraction of *F. fomentarius* polysaccharide could prompt apoptosis in tumor cells of S180 tumor-bearing mice. Notably, this apoptotic induction was potentially linked to the diminished expression of mutant p53 protein within those tumor cells, shedding light on a possible mechanism underlying its anti-tumor activity [43-44].

Song et al. found that *F. fomentarius* polysaccharide could evidently suppress H22 hepatocarcinoma tumors in mice, achieving a tumor inhibition rate of 39.39%. Moreover, it was capable of increasing the weights of immune organs in tumor-bearing mice, enhancing the activity of serum IL-2, and strengthening the function of mononuclear phagocytes. It was suggested that the

obvious anti-tumor effect of *F. fomentarius* polysaccharide might be realized through improving the body's immune function [45]. In a significant study, Wang focused on the role of *F. fomentarius* polysaccharide in relation to the Bax and Bcl-2 genes in H22 liver cancer mouse tumor tissues. The research revealed that the polysaccharide possessed a notable anti-tumor capacity, attaining a tumor inhibition rate of 41.49%. It was further demonstrated that it augmented Bax expression and curtailed Bcl-2 expression in the tumor tissues. Notably, the reduction in the Bcl-2/Bax ratio by the polysaccharide in these tissues hinted at a potential link to apoptotic pathways, shedding light on its possible mechanism of action [46]. In a significant research effort, Zhang et al. explored the anti-tumor activities of diverse extracts of *F. fomentarius*. Their findings were illuminating. The ethanol extract was shown to impede the proliferation of K562 cells, with the underlying mechanism tied to DNA damage and, notably, without hepatic toxicity. The ethyl acetate fraction emerged as a potent inhibitor of K562 cell growth, operating via cell cycle arrest and apoptosis induction. It triggered apoptotic events while sparing normal cells from growth inhibition, with dibutyl phthalate as its principal constituent. The chloroform fraction also curtailed K562 cell proliferation, achieving this through membrane damage, modulation of Ca^{2+} levels, ROS generation, and mitochondrial membrane potential decline to prompt apoptosis. The petroleum ether fraction demonstrated concentration- and time-dependent cytotoxicity against S180 cells in vitro, inducing apoptosis through mitochondria-dependent and reactive oxygen species-mediated pathways. Remarkably, in vivo it curbed the growth of S180 sarcoma in tumor-bearing mice with minimal impact on immune organs [47-48]. As reported by Li et al., their research unveiled the potential anti-tumor and immunomodulatory traits of the ethanol extract of *F. fomentarius*. The results manifested that the extract of *F. fomentarius* inhibited the viability of murine leukemia L1210 cells in a dose-dependent manner, with an IC_{50} value of 69.35 mg/ml. Flow cytometry analysis divulged that the extract could prompt apoptosis in L1210 cells. Additionally, a decline in mitochondrial membrane potential was detected, along with alterations in caspase-3, caspase-9, Bcl-2, and Bax proteins, intimating that the pro-apoptotic effect of the extract was implicated in the mitochondria-related pathway. Concurrently, the *F. fomentarius* extract remarkably enhanced the proliferation and activation of splenic lymphocytes in a dose-dependent manner. Evidently, this *F. fomentarius* extract harbors potential applications as a natural anti-tumor agent endowed with immunomodulatory activity [49]. Xie et al. investigated the volatile components of *F. fomentarius*. Through experiments, they found that these components exhibited a relatively high inhibitory effect on the tumor cell line A549, with an IC_{50} value of 268.675 mg/L [26]. Kim et al. isolated a polysaccharide MFKF-AP1β from the fruiting bodies of *F. fomentarius* and explored its anti-tumor effect on human lung cancer A549 cells. The results indicated that MFKF-AP1β exerted a potent anti-tumor effect by inducing cell apoptosis [50]. Utilizing an H22 tumor-bearing mouse model, Li and Bao focused on exploring how the petroleum ether, chloroform, and methanol extracts from the fruiting bodies of *F. fomentarius* influenced tumor suppression and immune function in vivo. They gauged the efficacy of these extracts via parameters like tumor inhibition rate, immune organ indices, and survival time. Their findings were remarkable: all extracts manifested antitumor activities, but the precipitate of the petroleum ether extract stood out, achieving a tumor inhibition rate of 56.29% at 100 mg/kg, nearing that of the positive drug. It also augmented the body mass, spleen, and thymus indices of mice, extended survival, and within an appropriate dose range, curbed tumor growth and bolstered immune function [51]. He and colleagues conducted in vitro anti-tumor tests on the compound extract of *F. fomentarius*. The results showed that the water extract of the compound extract of *F. fomentarius* (WECF) had IC_{50} values of 0.29,

0.45, 0.32, 0.32, 0.83, and 0.23 g/L against six cell lines, namely A549, HeLa, QGY, DU145, MDA-MB-435S, and SGC-7901, respectively. After being treated with 1 g/L of WECF for 24 h, the apoptosis rate of A549 cells was 22.0%. It was concluded that WECF had a strong in vitro anti-tumor effect, significantly inhibited the growth of multiple tumor cells, and could induce apoptosis in A549 cells [52]. He and his team further investigated the in vivo anti-tumor activity of the compound of *F. fomentarius.* They constructed S180 and Lewis lung cancer mouse models, grouped the mice, and administered drugs continuously. The effects of the compound extract (ECF) on tumor mass, immune organ indices, and the levels of serum tumor necrosis factor-*α* (TNF-*α*) and macrophage colony-stimulating factor (M-CSF) of tumor-bearing mice were observed. The results indicated that ECF exhibited inhibitory effects on tumors in both types of tumor-bearing mice. Some dose groups could suppress tumor growth, improve immune indices, and regulate the levels of related factors. This demonstrated that ECF had a significant inhibitory effect on the tumor growth of the two types of tumor-bearing mice, with strong anti-tumor activity. Its mechanism of action might be related to increasing immune organ indices and regulating the expression of TNF-*α* and M-CSF in serum [53]. Chen et al. found in a significant study that the EEM and IPS from *F. fomentarius* mycelium exhibited a direct inhibitory effect on the proliferation of human gastric cancer cell lines SGC-7901 and MKN-45 in a dose-dependent fashion. Significantly, compared with the cancerous cells, the human normal gastric cell line GES-1 was much less responsive to the EEM and IPS stimuli [54]. Chen found that the polysaccharide extracted from *F. fomentarius* had the ability to boost the humoral, cellular, and non-specific immunity in S180 tumor-bearing mice. Additionally, it promoted the secretion of TNF-*α* and IFN-*γ* by the immune cells of the tumor-bearing mice. Evidently, the anti-tumor efficacy of this polysaccharide was potentially tied to its capacity to fortify the immune system [55]. Du et al. conducted research on the petroleum ether fraction of *F. fomentarius*. It was found that the main components were ergosta-3-one-7,22-diene and ergosta-3-ol-5,24(28)-diene, and the compound with the highest anti-tumor activity was ergosta-3-one-7,22-diene [56]. Chen et al. found in an important study that the extracellular polysaccharide derived from *F. fomentarius* possessed a direct anti-proliferative capacity against human gastric cancer cell SGC - 7901 in vitro, with the effect being dose- and time- dependent. Remarkably, following 24-hour treatment, the extracellular polysaccharide at a non-cytotoxic concentration of 0.25 mg/mL was able to amplify the growth inhibition of doxorubicin (Dox)-induced SGC-7901 cells by nearly three times [57]. Liu et al.'s research focused on the ethanol extract of *F. fomentarius* (EEF). They used the ICR mouse S180 sarcoma model. After intragastric administration of multiple doses of EEF, they found that each dose group exhibited a certain tumor - inhibiting effect. Moreover, positive performances were observed in immune function-related indexes such as spleen index, lymphocyte transformation, antibody production of splenocytes, and NK cell activity, indicating *in vivo* anti-tumor activity [58]. Liu et al.'s research revealed that the ethanol extract of *F. fomentarius* (EEF) exerted a significant inhibitory effect on HeLa cells growing in vitro, remarkably enhanced the apoptosis rate of S180 cells and the survival days of tumor-bearing mice, and markedly decreased the MDA content in the liver and kidneys of normal mice [59]. Further investigations demonstrated that EEF also possessed a strong anti-tumor activity against S180 sarcoma, could comprehensively improve the immune function of tumor-bearing mice, enhance the antioxidant capacity of normal mice. Its possible anti-tumor mechanisms included strong direct killing of tumor cells, promotion of tumor cell apoptosis, cell cycle arrest, and inhibition of cell division and proliferation [60]. Lee et al. found through research

that the ethanol extract of *F. fomentarius* exerted effects of inhibiting cell growth, suppressing cell motility and inducing cell apoptosis by targeting AKT in human breast cancer MDA-MB-231 cells [61]. Huang et al. discovered through the AlamarBlue assay that among the monomeric compounds isolated from the fruiting bodies of *F. fomentarius*, compound (ergosta-3-one-7,22-diene) exhibited the highest inhibitory activity against human lung cancer cell line NCI-H460, while compound (betulinol) showed the highest inhibitory activity against human gastric cancer cell line SGC-7901. This provides a potential foundation of active compounds and research directions for the subsequent development of related anticancer drugs [22]. Dogan et al. prepared aqueous, methanol, and ethanol extracts of *F. fomentarius* to combat cancer multi-drug resistance. XTT assays showed their cytotoxicity against paclitaxel- and vincristine-resistant, P-glycoprotein-overexpressing MCF-7 cells. The IC_{50} values were 1.08-1.80 mg/mL for MCF-7/Vinc and 1.11-2.83 mg/mL for MCF-7/Pac. Notably, the methanol extract has potential as an MDR-reversing agent for drug-resistant breast cancer cells [62].

5.2 Immunomodulatory Activity

The immunomodulatory activity of *F. fomentarius is* mainly achieved by enhancing the metabolic activity of immune cells, promoting the secretion of cytokines, and regulating the functions of immune cells. The key cells involved include splenic lymphocytes, macrophages, monocytes, etc.; the key cytokines include TNF-α, IFN-γ, IL-2, etc. These cells and cytokines interact with each other to jointly regulate the immune function of the body and maintain immune balance.

Zhao et al. studied the impact of *F. fomentarius* ethanol extract on mouse liver and immune cells. Mice received low, medium, high doses (100, 250, 500 mg/kg) orally for 14 days. The results showed no ALT, AST activity differences compared with the control ($P>0.05$); all doses boosted splenic lymphocyte proliferation, the high dose enhanced macrophage phagocytosis, and there was no effect on NK cell killing. Conclusively, it's non-toxic to the liver, harmless to the immune system and promotes lymphocyte growth [63]. In a significant study by Gao, it was demonstrated that *F. fomentarius* polysaccharide (FFP) played an immunostimulatory role in normal mice. It remarkably augmented the metabolic vigor of immune cells, drove the production of cytokines like TNF-*α*, IFN-*γ*, and IL-2, and bolstered humoral immunity. Potentially, the enhancement of humoral immune function was linked to the facilitation of IL-2 and IFN-*γ* secretion. Notably, in mice suffering from immunosuppression due to cyclophosphamide, FFP could markedly enhance their non-specific and specific immune responses [64]. Gao et al. explored the immunomodulatory effect of *F. fomentarius* polysaccharide (FFP). Using multiple methods, they found FFP (at certain concentrations/doses) promoted splenocyte & peritoneal exudate cell metabolic activities, cytokine secretion, specific antibody generation, and macrophage phagocytic function in mice, indicating its immunomodulatory role [65]. Zhou et al. explored the impacts of *F. fomentarius* polysaccharides (FFP) on monocytes/macrophages' phagocytic function, humoral immune function and T lymphocytes' secretion of IL-2 and IFN-*γ* in immunosuppressed mice. They established models by injecting cyclophosphamide (15 mg/kg) subcutaneously for 7 d. Then, via carbon clearance, rabbit red blood cell immunization, microscopic counting, Con A stimulation and ELISA methods, relevant functions and cytokine contents were detected. Results showed FFP (200, 100 mg/kg) significantly enhanced phagocytic function, promoted antibody production, increased peripheral white blood cell count and strengthened cytokine production ability of splenocytes in immunosuppressed mice. Thus, FFP can improve nonspecific and humoral immunity and enhance T lymphocyte's cytokine production in

these mice [66].

5.3 Antioxidant Activity

The antioxidant activity of *F. fomentarius* mainly originates from components such as polysaccharides and polyphenols contained in it. These components can scavenge various free radicals, such as DPPH free radicals, ABTS free radicals, superoxide anion radicals, and hydroxyl radicals, etc., thus exerting an antioxidant effect. Its antioxidant capacity is related to the concentration of the components, and there are differences in the antioxidant activities of different extracts and monomeric compounds.

Nowacka et al. measured the scavenging effect of *F. fomentarius* on DPPH• free radicals, and the IC_{50} was 1.39±0.02 mg/mL [67]. Xu et al. discovered that *F. fomentarius* polysaccharide exhibited scavenging effects on both DPPH free radicals and ABTS free radicals, and its scavenging capacity was significantly and positively correlated with the polysaccharide concentration, indicating that polysaccharide was the main antioxidant active component of *F. fomentarius* [68]. Zhang et al. extracted extracellular polysaccharides from the culture of *F. fomentarius* and studied the scavenging ability of these extracellular polysaccharides against DPPH radicals and that of derivative polysaccharides against superoxide anion radicals and hydroxyl radicals. The results showed that the extracellular polysaccharides and derivative polysaccharides of *F. fomentarius* possess certain antioxidant activities [69]. Bojin used different solvents to extract *F. fomentarius* and evaluated its free radical scavenging ability by the DPPH (2,2-diphenyl-1-picrylhydrazyl-hydrate) method. The methanol and ethanol extracts showed the highest antioxidant activities, and this was independent of the concentration of the DPPH ethanol solution used. However, the water extracts and petroleum ether extract only exhibited higher antioxidant activities when the concentration of the DPPH ethanol solution was decreased [70]. Li isolated 11 monomeric compounds from *F. fomentarius*. These compounds all exhibited certain activities in scavenging DPPH free radicals. Notably, compound 7 (3,4-dihydroxyacetophenone) showed a relatively high scavenging rate of 71.99% [20]. In the study by Brovko et al., they employed ethanol for sub- and supercritical fluid extraction of *F. fomentarius* fruiting bodies. Notably, the resulting extracts possessed remarkable antiradical activity, reaching up to 350 μmol Troloxeq/g. Moreover, a significant relationship was identified between the antiradical potency of the extracts and the phenolic compound levels within them [71]. Peng et al. investigated the antioxidant capacity of *F. fomentarius* extracellular polysaccharides. They used the in vitro DPPH assay to measure the scavenging capabilities against free radicals, superoxide radicals and hydroxyl radicals and found that these extracellular polysaccharides had definite in vitro antioxidant activities, highlighting their potential in antioxidation [72]. Glumac et al. investigated the antiradical activities of the hydrodistilled extracts of *F. fomentarius*. The preliminary screening covered multiple free radical species. In particular, relevant assays showed that the extract exhibited good anti-DPPH radical activity under in vitro conditions [73].

5.4 Antibacterial Activity

The antibacterial activity of *F. fomentarius* is mainly achieved through the inhibition of bacterial growth and the disruption of bacterial cell membranes by its extracts or the compounds contained therein. It has a certain inhibitory effect on both Gram-positive bacteria and Gram-negative bacteria. The antibacterial effects and mechanisms of action of different extracts and compounds vary. Some

extracts can also be used to synthesize antibacterial active nanoparticles.

Pavić et al. utilized the methanolic extract of *F. fomentarius* as a reducing agent to synthesize silver nanoparticles (AgNPs), which exhibited significant antibacterial activity, especially against Staphylococcus aureus and showed higher efficacy against Gram-positive bacteria [74]. Xie et al. investigated the antibacterial activity of the volatile components of *F. fomentarius*. The results indicated that the volatile components had a relatively strong effect on Staphylococcus aureus, while having a weaker effect on Escherichia coli, Pseudomonas aeruginosa and Bacillus subtilis [26]. Nowacka et al. investigated the antibacterial effects of the ethanol extract of *F. fomentarius* against Gram-positive (S. epidermidis, S. aureus, B. subtilis, M. luteus) and Gram-negative (E. coli, K. pneumoniae, P. aeruginosa, P. mirabilis) microbial strains. The minimum inhibitory concentration (MIC) for Gram-positive bacteria was 1.25 mg/ml, and the minimum bactericidal concentration (MBC) ranged from 2.5 to 5 mg/ml. For Gram-negative bacteria, the MIC was 1.25 to 2.5 mg/ml, and the MBC was 1.25 to 2.5 mg/ml, indicating its certain antibacterial potential [67]. Kolundžić et al. conducted antibacterial activity tests using cyclohexane, dichloromethane, methanol and aqueous extracts of *F. fomentarius* against 9 common bacterial strains and related strains of Helicobacter pylori (10 clinical isolates and 1 reference strain). They discovered that the minimum inhibitory concentrations (MICs) of all extracts against the 9 common bacterial strains fell within the range of 125-250 μg/ml, and the methanol and aqueous extracts demonstrated significant antibacterial activity against Helicobacter pylori, with MIC values between 4-32 μg/ml [75]. Yuan et al. adopted the Oxford cup method to test the antibacterial activity of the ethanol extract of *F. fomentarius* against Ralstonia solanacearum, Xanthomonas oryzae pv. oryzae, Pectobacterium carotovorum subsp. carotovorum and Xanthomonas axonopodis pv. citri. Moreover, they employed the growth rate method to evaluate its antifungal activity against Sclerotinia sclerotiorum, Fusarium graminearum, Valsa mali, Elsinoë ampelina, Alternaria mali, Fusarium oxysporum f. sp. vasinfectum and Pythium aphanidermatum. The results demonstrated that the extract exhibited favorable activity against plant pathogens. This could be further utilized in the isolation of antibacterial active ingredients and the development of biopesticides [76]. Li isolated the compound 1,5-2(3,4-dihydroxyphenyl)-1,4-pentadien-3-one from the fruiting bodies of *F. fomentarius*. Through experiments, it was determined that this compound could inhibit Staphylococcus aureus and Bacillus subtilis, with the minimum inhibitory concentrations being 64 mg/L and 128 mg/L respectively [20]. Xu et al. extracted polysaccharides from *F. fomentarius* by water extraction and ethanol precipitation. Using the filter paper method, they measured the antibacterial activities and MICs of these polysaccharides against four bacteria (E. coli, S. aureus, B. subtilis, M. tetragenus). The results showed significant inhibitory effects, with the strongest on E. coli, and the MICs were 1.25, 1.25, 2.50, 5.00 mg/mL respectively [68]. Li explored the antibacterial activity of the methanol extract from the fruiting bodies of *F. fomentarius*. Through stability experiments on heat and medium pH, it was proved that the antibacterial effect of the extract remained unaffected under appropriate conditions and was not damaged during soap making. Antibacterial tests on the prepared antibacterial soap verified its effect. Moreover, an optimal addition amount of the extract (1.25% of the soap base) was determined, under which the antibacterial soap showed remarkable antibacterial effect, comfortable use, and good sensory properties [12].

5.5 Anti-inflammatory and Analgesic Effects

The anti-inflammatory and analgesic effects of *F. fomentarius* are mainly achieved through mechanisms such as inhibiting the secretion of inflammatory factors, regulating intracellular

signaling pathways, and reducing the production of inflammatory mediators. The key inflammatory factors involved include IL-8, IL-1*β*, IL-6, TNF-*α*, etc., and the related signaling pathways include the extracellular signal-regulated kinase (ERK) pathway, the STAT3 pathway, and the nuclear factor-κB pathway, etc.

Cai et al. selected *F. fomentarius* to prepare the fermented liquid of edible and medicinal fungi with pearl powder, used lipopolysaccharide (LPS)-induced immortalized human epidermal cells (HaCaT) as the research model to explore its potential anti-inflammatory ability. The results showed that the fermented liquid of *F. fomentarius* and its pearl fermented liquid at lower concentrations had cell proliferation effects. Compared with the model group, these fermented liquids could significantly reduce the contents of some inflammatory factors to a certain extent, and the addition of pearl powder was more effective in reducing the secretion of inflammatory indicators, showing anti-inflammatory effects. Among them, the FF-pearl fermented liquid had better performance in reducing the contents of IL-8, IL-1*β* and KLK7 [77]. Seo et al. isolated fomentariol from *F. fomentarius* and explored its anti-inflammatory effect on murine macrophages (RAW264.7 cells) stimulated by lipopolysaccharides (LPS). Fomentariol inhibited the production of nitric oxide and intracellular reactive oxygen species induced by LPS and differentially regulated cytokine production. It suppressed IL-1*β* and IL-6 but not tumor necrosis factor-*α*. The inhibitory effects were likely mediated by downregulating the extracellular signal-regulated kinase signaling pathway. Their results suggested that fomentariol differentially modulated inflammatory responses triggered by LPS in macrophages and was one of the bioactive compounds mediating the physiological effects of *F. fomentarius* [78]. Choe et al. investigated the anti-inflammatory activity of methyl 9-oxo-(10*E*,12*E*)-octadecadienoate (FF-8) purified from *F. fomentarius*. The results showed that FF-8 suppressed nitric oxide, prostaglandin E2 secretion and reduced levels of inflammatory cytokines such as TNF-*α* and IL-6 in lipopolysaccharide (LPS)-stimulated murine macrophages by interfering with STAT3 phosphorylation rather than affecting other common pathways. It demonstrated FF-8's anti-inflammatory effect in vitro, though further in vivo studies are needed [79]. Park et al. discovered that when the methanol extract of *F. fomentarius* (MEFF) was orally administered at doses of 50 and 100 mg/kg/day, it could alleviate carrageenan-induced acute paw swelling in rats. They confirmed that MEFF had an analgesic effect through the acetic acid writhing test and hot plate test in mice. The mechanism was most likely achieved by down-regulating the binding activity of nuclear factor-κB and subsequently inhibiting the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2(COX-2) [80]. Wang et al. utilized the roots of Berberis amurensis and the fruiting bodies of *F. fomentarius* as raw materials. Based on the compatibility theory of traditional Chinese medicine and by employing pharmaceutical preparation methods, they developed the Berberis-Fomes oral ulcer film. This film exhibited remarkable curative effects on oral ulcers in rats, with a high healing rate. It possessed antibacterial, anti-inflammatory, and wound-healing-promoting functions [81].

5.6 Antidiabetic Activity

The antidiabetic activity of *F. fomentarius* is mainly achieved by inhibiting key enzymes such as α-glucosidase and DPP-4, regulating blood glucose metabolism, improving insulin secretion and insulin resistance, and thus reducing blood glucose levels. Some of the compounds and polysaccharides contained in it play an important role in antidiabetic effects. Some studies also

involve the improvement of diabetes-related complications.

Ravnikar et al. isolated fomentariol from the ethanol extract of *F. fomentarius*. Their experiments demonstrated that fomentariol is an effective inhibitor of *α*-glucosidase and DPP-4 (a cell-surface serine protease). Moreover, its activity against *α*-glucosidase is higher than that of acarbose. Fomentariol offers a new approach for diabetes treatment as it can simultaneously inhibit key enzymes in glucose metabolism. However, comprehensive clinical studies are required to assess its safety and efficacy in humans [82]. Keshavarz-Rezaei et al. first prepared extracellular polysaccharide PS of *F. fomentarius*, then added Na_2SeO_3 to obtain PS-Se. They synthesized SLN-PS and SLN-PS-Se via microemulsion method. After 28 days oral administration to STZ-induced diabetic rats, PS, PS-Se, SLN-PS and SLN-PS-Se reduced blood glucose by 48.24%, 49.96%, 55.50% and 60.47% respectively, improving insulin secretion, body weight, HbA1c, lipid profiles, liver enzymes and serum proteins. Analyses of liver antioxidants and histopathology of liver, pancreas and kidney verified their antidiabetic effects. Selenium enhanced PS's anti-hyperglycemic effect, and SLN-PS and SLN-PS-Se were more effective than free PS and PS-Se [83]. Lee examined the effects of WEFF on hepatic antioxidant enzymes, blood glucose, and lipid levels in STZ-induced diabetic male Sprague-Dawley rats. Rats were grouped as non-diabetic, diabetic, and diabetic with WEFF supplementation. WEFF (100 mg/kg BW) was orally administered daily for 2 weeks. WEFF decreased serum glucose by suppressing insulin elevation, mitigated the increase of total cholesterol and triglycerides in serum and liver, enhanced high-density lipoprotein cholesterol and glutathione peroxidase activity, and reduced superoxide dismutase and catalase activities. Thus, WEFF might be beneficial for managing hyperglycemia and preventing diabetic complications [84]. Li separated 1,5-bis(3,4-dihydroxyphenyl)-1,4-pentadien-3-one, 3,4-dihydroxyacetophenone, and 3,4-dihydroxybenzaldehyde from *F. fomentarius* and tested their *α*-glucosidase inhibitory activities via the PNPG method. These compounds demonstrated inhibitory effects, with inhibition rates of 84.63%, 75.68%, and 62.57% and IC_{50} values of 137.69, 550.86, and 274.53 μM. In contrast, the positive drug acarbose had an inhibition rate of 39.14%. These findings contribute to the understanding of potential anti-diabetic agents from *F. fomentarius* [20].

5.7 Anti-hypoxia Activity

Zhang obtained the extracellular polysaccharide of *F. fomentarius* (FFEP) through large-scale deep culture and purified a heteropolysaccharide named FFEP-1. The results of the hypoxia tolerance activity test showed that FFEP-1 at different concentrations (≥50 mg/kg) could significantly prolong the survival time of mice under different hypoxic conditions. Moreover, the number of red blood cells and the concentration of hemoglobin in the treatment group increased significantly, approaching those of the positive drug-administered group [35]. Zhang et al. purified a novel water-soluble polysaccharide, FFEP-1, from *F. fomentarius* and investigated its anti-hypoxia effect through experiments. The results showed that FFEP-1 had a similar anti-hypoxia effect to propranolol hydrochloride, and its anti-hypoxia mechanism might be achieved by increasing the number of red blood cells and hemoglobin content [85]. Research by Li et al. indicated that *F. fomentarius* could significantly enhance the endurance of mice under hypobaric hypoxia, prolong the survival time of animals, possessed anti-fatigue and anti-high-temperature effects, and affect the flow velocity and pattern of the mesenteric microcirculation in hypoxic organisms, thus improving microcirculation [86].

5.8 Others

Chen et al. discovered that the aqueous extract of *F. fomentarius* compound (AEFFC) has a significant protective effect on CCl_4-induced chemical hepatocyte injury. The proposed mechanism is related to scavenging oxygen free radicals, inhibiting lipid peroxidation, protecting the integrity of liver cell membranes and mitochondrial membranes, anti-apoptotic, and reducing the release of the inflammatory cytokine TNF-α [87]. Chen et al. further investigated the effects of the aqueous extract of *F. fomentarius* compound on acute liver injury in mice induced by CCl_4. Their findings showed that this extract significantly reduced the elevated ALT levels in mouse serum, enhanced the SOD activity in liver tissue, and inhibited the increase of MDA levels in liver tissue. Pathological microscopy revealed significant hepatoprotective effects. The mechanism may be related to its antioxidant capacity to scavenge free radicals and inhibiting lipid peroxidation damage [88]. Zhang purified a heteropolysaccharide, FFEP-1, from the extracellular polysaccharide of *F. fomentarius* (FFEP). Further research showed that FFEP-1 at different doses (≥100 mg/kg) had varying degrees of lipid-lowering and liver-protecting effects on model mice. It could reduce multiple serum and liver indexes, increase antioxidant indexes, decrease the levels of anti-inflammatory-related factors, and promote liver tissue remodeling. Additionally, an ointment with 5% FFEP-1 could promote scab formation and wound healing of burn wounds, shorten the repair time, accelerate the metabolism of wound cells by regulating the secretion of related factors, and facilitate the late-stage repair and regeneration of wounds [35]. Lee and Hyun et al. conducted a study where muscle loss was induced by dexametasone, and the effectiveness of the extract was explored in a muscle-loss animal model. The experimental animals were grouped into five sets. The weight changes of the animals were monitored for 5 weeks. Post-sacrifice, muscle mass was measured, and animal behavior was evaluated via the grip strength test and pole test. Muscle samples were used to measure the expression level of MAFbx protein. The results indicated that oral administration of *F. fomentarius* extract could effectively inhibit muscle atrophy and increase muscle mass, as verified by animal behavior assessment and muscle-related protein expression analysis. This research provides valuable insights into potential treatments for muscle-loss conditions [89]. Hale et al. discovered that adding sodium selenite to the exopolysaccharides of *F. fomentarius* significantly enhanced the antibacterial activity against Staphylococcus aureus and the antioxidant activity of the exopolysaccharides. The cytotoxicity of these exopolysaccharides against 5637, A549, and KYSE30 cancer cells was also remarkably increased. The viability of 5637 cells treated with selenium-containing exopolysaccharides (EPS-Se) dropped to less than 10% after 72 hours [90]. Park et al. obtained *F. fomentarius* L. (FFL) extracts with different ethanol concentrations. In the assessment of antioxidant activity, only the hot water extract had weaker antioxidant activity compared to other ethanol extracts. Moreover, all extracts showed significant antimutagenic effects only in the presence of a metabolically active enzyme system (S9 mix), among which the 70% ethanol extract exhibited the most potent antimutagenic activity [91]. Qi et al. studied the effects of *F. fomentarius* polysaccharide on the micronucleus rate and chromosomal aberration rate changes in mice induced by cyclophosphamide (CP) to explore its antagonistic effect on mutation. Compared with the positive control group, the micronucleus formation and chromosomal aberration rates in high, medium, and low-dose groups showed significant differences (P<0.05), indicating that *F. fomentarius* polysaccharide has antimutagenic effects [92]. Ahad et al. aimed to evaluate the in vivo anticoccidial

effects of the aqueous extract of *F. fomentarius* compared with the reference drug amprolium in broilers suffering from coccidiosis, based on oocysts per gram of faeces, weight gain, and feed conversion ratio. Their study showed that treating with *F. fomentarius* led to a significant reduction in the number of coccidian oocysts in faeces, improved weight gain, and a better feed conversion ratio, demonstrating the effectiveness of *F. fomentarius* extract against coccidian oocysts [93].

6. Discussion and Prospects

Significant progress has been made in the research of *F. fomentarius*, yet there are still several aspects that require further attention and exploration. In terms of chemical composition, more than a hundred compounds have been isolated, providing a rich resource for potential drug research and development. The proportion of each component is shown in Figure 2. From a pharmacological perspective, it possesses multiple activities, including anti-tumor, immunomodulatory, antioxidant, antibacterial, etc. (Figure 3), highlighting its enormous potential in the development of new drugs and functional foods. However, some challenges and limitations have become increasingly evident.

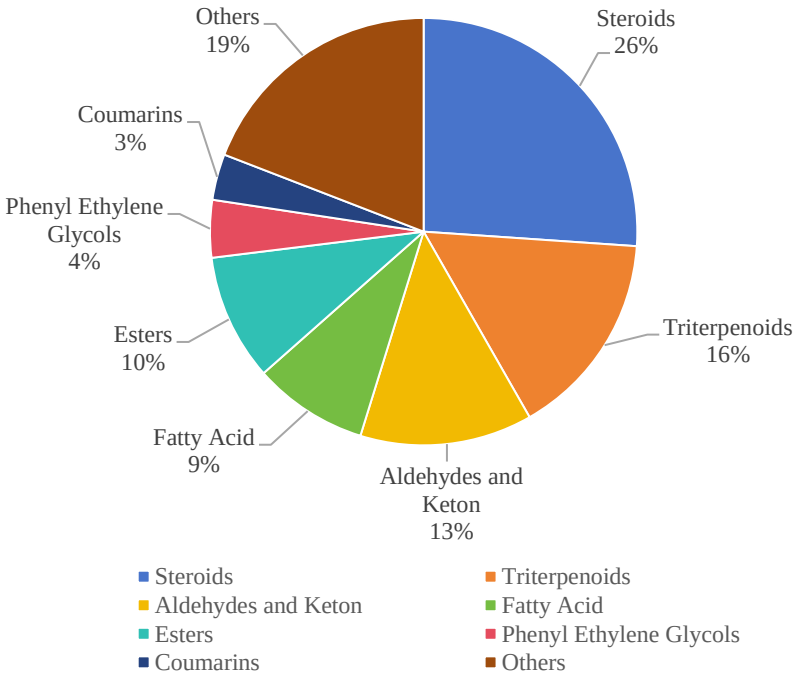


Figure 2. Proportion of various compounds in *F. fomentarius*

Currently, the understanding of the underlying mechanisms of these pharmacological activities remains superficial. Although some studies have demonstrated the effects of certain extracts or compounds on specific cellular processes, the detailed molecular pathways and interactions remain unclear. For example, although the polysaccharides of *F. fomentarius* have exhibited anti-tumor effects, the exact molecular mechanisms by which they regulate tumor cell proliferation, apoptosis, and metastasis are still not well-defined. This lack of in-depth understanding restricts the development of more effective and targeted therapeutic strategies. Another crucial issue is the limited exploration of the synergistic effects among various chemical components. Given the complexity of its chemical composition, it is highly likely that these components work in concert to exert their biological functions. However, current research has not systematically investigated these synergistic

relationships. Without understanding the interactions between different components, it is difficult to optimize the formulation and fully exploit the therapeutic potential of *F. fomentarius*. In addition, the lack of standardized methods for the extraction and isolation of chemical components further exacerbates the difficulty of comparing the results of different studies, hindering the research progress in this field. Looking ahead, future research should focus on several key directions. Advanced technologies such as genomics, proteomics, and metabolomics should be employed to elucidate its detailed mechanisms of action. These technologies can help identify the key targets and signaling pathways involved in its pharmacological activities, thus providing a more comprehensive understanding of how *F. fomentarius* exerts its effects. For instance, by using gene

Figure 3. A brief summary of the pharmacological effects of *F. fomentarius*

knockout or overexpression models,we can precisely determine the roles played by individual genes and proteins in mediating the responses to the extracts or compounds of *F. fomentarius*. Systematic studies on the synergistic effects among chemical components are of vital importance. High-throughput screening and combinatorial chemistry approaches can be utilized to identify combinations of components that exhibit enhanced biological activities. Understanding these synergistic effects will contribute to the formulation of more effective and efficient drug regimens. For example, the combination of different active compounds may have a more significant impact on tumor cell growth inhibition or immunomodulation than individual components used alone. Biotechnological approaches hold great promise in improving the yield and quality of *F. fomentarius* and its active components. Fermentation technology can be optimized to increase the production of active compounds. Genetic engineering techniques can also be applied to modify this fungus to produce higher levels of specific components or to introduce new beneficial traits. Moreover, synthetic biology approaches may enable the production of active components through artificial biosynthetic pathways, offering a more efficient and sustainable way to obtain these valuable

substances. In addition to the medical field, *F. fomentarius* also has potential applications in other fields such as the food and cosmetics industries. Its antioxidant and antibacterial properties make it a promising ingredient for the development of functional foods and natural preservatives. In the cosmetics industry, its anti-inflammatory and skin-protective effects can be utilized to develop skincare products. Exploring these applications in multiple fields can further expand the utilization scope of *F. fomentarius* and bring more benefits to human health and daily life.

In conclusion, although significant progress has been made in the research of *F. fomentarius*, there is still much work to be done. By addressing the existing challenges and focusing on these future research directions, we can fully unlock the potential of this extraordinary fungus and make contributions to the development of new therapies and products that are beneficial to human health.

Author contributions

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Competing Interests

The authors declare that there is no conflict of interest.

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