

Advances in Pharmacological Activities of Terpenoids

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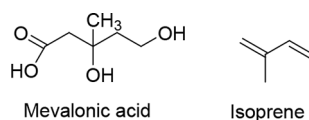
Abstract

Terpenoids, the most abundant compounds in natural products, are a set of important secondary metabolites in plants with diverse structures. Terpenoids play key roles in plant growth and development, response to the environment, and physiological processes. As raw materials, terpenoids were also widely used in pharmaceuticals, food, and cosmetics industries. Terpenoids possess antitumor, anti-inflammatory, antibacterial, antiviral, antimalarial effects, promote transdermal absorption, prevent and treat cardiovascular diseases, and have hypoglycemic activities. In addition, previous studies have also found that terpenoids have many potential applications, such as insect resistance, immunoregulation, antioxidation, antiaging, and neuroprotection. Terpenoids have a complex structure with diverse effects and different mechanisms of action. Activities and mechanisms of terpenoids were reviewed in this paper. The development and application prospect of terpenoid compounds were also prospected, which provides a useful reference for new drug discovery and drug design based on terpenoids.

Keywords

terpenoids, pharmacological activities, research progress

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Terpenoids constitute one of the largest and structurally diverse groups of naturally occurring compounds. Terpenoids are a class of natural products derived from mevalonic acid (MVA) which are composed of a plurality of isoprene (C5) structural units. Terpenoids are widely found in nature, with various structures and a wide variety. To date, more than 50 000 terpenoids have been found in nature,¹ and most of them are isolated from plants. Some terpenoids play an important role in plant growth and development, such as gibberellin, as plant hormones regulates plant development and carotenoids participates in photosynthesis; some terpenoids play a role in the interaction between plants and the environment, such as participating in plant defense systems in the form of phytoalexins and interspecies competition as interspecific sensing compounds.² Many volatile terpenoids such as menthol and perillyl alcohol are used as raw materials for spices, flavorings, and cosmetics.³ There are also some terpenoids with important economic value. They are used as pesticides, industrial raw materials, etc., such as pyrethrin and limonoids, which are often used as insecticides. Sesquiterpenes, farnesene and bisabolene, and

monoterpenes, pinene and limonene, are recognized as precursor compounds for fuels.⁴

In the 1960s, the biological activity of terpenoids began to be noticed by humans, but only limited to certain terpenoids. By the 1970s, the pace of research on the biological activity of terpenoids was gradually accelerated, and the first small peak appeared. The research on artemisinin against malaria was completed at this stage. It was not until the late 1990s that the study on terpenoids attracted attention again, and the research focused on the separation and purification of active components, chemical composition analysis, and chemical structure research. Since then, the biological activity of terpenoids has increased year by year.

In recent years, with the deepening of research on terpenoids (especially terpenoids in medicinal plants), it has been found that

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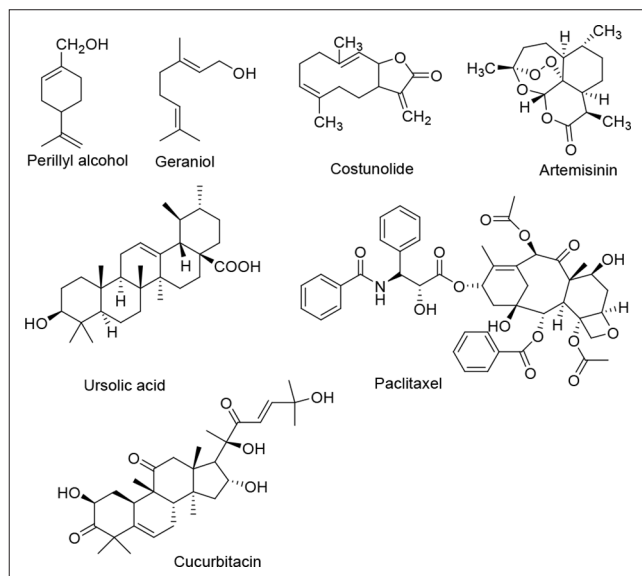


Figure 1. The structures of common terpenoids with antitumor activities.

such compounds play an increasingly prominent role in the field of medicine and have various biological activities such as antitumor, anti-inflammatory, antibacterial, antiviral, antimalarial, promoting the transdermal absorption, preventing and treating cardiovascular diseases, lowering blood sugar, and other effects. In addition, some terpenoids also have insecticidal, immunomodulatory, antioxidant, antiaging and neuroprotective effects; the terpenoids paclitaxel and artemisinin have been widely used in clinical practice. Therefore, the research on the biological activity of the terpenoids will contribute to the selection of drugs and the improvement of treatment methods and provide a theoretical basis for the development of new drugs, which are paid much attention by scholars.

Overview of Terpenoids

Terpenoids are a general term for a class of compounds consisting of several isoprene structural units. Based upon the number of isoprene units, these have mainly classified into

monoterpene (C₁₀), sesquiterpene (C₁₅), diterpene (C₂₀), triterpene (C₃₀), tetraterpene (C₄₀), and polyterpene (C > 40), etc. In addition to being in the form of terpene hydrocarbons, terpenoids are mostly present in the form of various oxygen-containing derivatives, including alcohols, aldehydes, carboxylic acids, ketones, esters, and glycosides. The synthetic pathways for terpenoids include the MVA pathway and the 1-deoxy-D-xylulose-5-phosphate (DXP) pathway. Isopentenyl diphosphate is the main metabolic intermediate for both ways. The MVA pathway exists in the cytoplasm and the secondary metabolites such as sesquiterpenes, sterols, and triterpenes are mainly synthesized through this way; the DXP pathway is mainly present in plastids, and monoterpenes, diterpenes, and tetraterpenes are synthesized by this way.⁵

Terpenoids are mostly present in the form of volatile oils in higher medicinal plants and mainly exists in the following medicinal plant groups: Compositae, Ranunculaceae, Araliaceae, Oleaceae, Magnoliaceae, Lauraceae, Aristolochiaceae, Rutaceae, Labiatae, Pinaceae, Umbelliferae, Celastraceae, Acanthaceae, Taxaceae, etc. Most of the terpenes with bioactivities have been isolated in medicinal plants. Monoterpenes and sesquiterpenes are mainly found in essential oils of the medicinal plant; larger molecular weight terpenes, such as triterpene, are mainly found in balsam and resin.

Pharmacological Activities of Terpenoids

Antitumor Activity

Tumors are the most serious diseases that threaten human health, and the incidence of cancer in China is increasing year by year. The research on new high-efficiency antitumor drugs is imminent. Terpenoids have attracted the interest of many medicinal chemists with their distinctive structural features and good antitumor activity and have the potential to be lead compounds to develop efficient and safe antitumor drugs. In the study of the antitumor effects of terpenoids (Figure 1), it was found that perillyl alcohol, geraniol, and paclitaxel are the terpenoids having antitumor activities (Table 1).

Perillyl alcohol is a monocyclic monoterpene mainly present in the essential oils of medicinal plants has attracted significant interest due to its potent antitumor activity. It has

Table 1. The Antitumor Activity of Terpenoids.

Classification	Compound	Function	Reference
Monoterpene	Perillyl alcohol	Broad-spectrum anticancer	6
	Geraniol	Antilung cancer, colon cancer, prostate cancer, pancreatic cancer, and liver cancer	7-13
Sesquiterpene	Costunolide	Antibladder cancer, ovarian cancer, leukemia cells, prostate cancer, nonsmall cell lung cancer, esophageal cancer	14-18
	Artemisinin and its derivatives	Antileukemia, melanoma, colon cancer, non-small cell lung cancer, lung cancer, prostate cancer, breast cancer, and ovarian cancer	19-22
Diterpene	Paclitaxel	Antiovarian and breast cancer	23,24
Triterpene	Ursolic acid	Antiliver cancer, breast cancer, osteosarcoma, prostate cancer, and cervical cancer	25-30
	Cucurbitacin	Antibladder cancer, liver cancer, pancreatic cancer, breast cancer, and leukemia	31

broad-spectrum, high efficiency, low-toxic antitumor properties. The growth of tumor cells was significantly inhibited after perillyl alcohol was added in the culture of tumor cells in many kinds of animals.⁶ And perillyl alcohol plays a preventive and therapeutic role in cancer. The results showed that the administration of perillyl alcohol at a dose of 1-2 g/kg in rats can significantly reduce the incidence and multiplicity of colonic invasive adenocarcinoma caused by the injection of carcinogen azomethane.⁶ Intraperitoneal injection of perillyl alcohol at a dose of 75 mg/kg 3 times per week significantly inhibited lung tumor formation caused by the simultaneous injection of the carcinogen 4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone.⁶ It was found that perillyl alcohol also exhibited high cytotoxic activity against OVCAR-8, HCT-116, and SF-295 human tumor cell lines, using the MTT assay. The cell growth inhibition percentage values were 90.92%-95.82%.³² Recent studies have revealed that the tumor growth inhibition rate of perillyl alcohol evaluated in mice was 35.3% and 45.4% at doses of 100 and 200 mg/kg/day, respectively. No toxicologically significant effect was found in liver and kidney parameters.³³ In *in vitro* anticancer studies, perillyl alcohol was found to exert cytotoxicity against HepG2 cell line with a half-maximal inhibitory concentration (IC_{50}) value of 409.2 $\mu\text{g/mL}$. However, this effect was not found to be selective.³⁴

Geraniol is widely found in essential oils of aromatic medicinal plants. Current experimental evidence indicates that geraniol has therapeutic or prophylactic effects on different types of cancer (eg, lung cancer,⁷ colon cancer,⁸ prostate cancer,⁹ pancreatic cancer,¹⁰ and liver cancer).¹¹ It has been demonstrated that geraniol can regulate a variety of signaling molecules and participate in a variety of life processes, such as cell cycle, cell proliferation, apoptosis, autophagy, and metabolism. It can be used as a multitarget drug for the treatment of cancer; the effect is significant and is not affected by adaptive resistance. For example, geraniol inhibits tumor cell growth by blocking the G1 phase of the Michigan Cancer Foundation (MCF)-7 breast cancer cell cycle. The levels of cyclin D1, cyclin-dependent kinase 4, cyclin E, and cyclin A were decreased in geraniol-treated MCF-7 cells, while the level of cyclin p27Kip1 was increased. At the same time, geraniol had no effect on the growth of MCF-10 normal breast epithelial cells, which demonstrated that its activity is tumor specific.¹² Kim et al¹³ found that in a structurally and functionally similar monoterpene, geraniol can effectively induce tumor cell apoptosis and autophagy. The expression level of HMG-CoA reductase is often upregulated in various human cancers. Studies have shown that geraniol inhibits the expression of the HMG-CoA reductase gene in most types of tumor cells, which may be the mechanism for the treatment of cancer by geraniol. Prostate cancer is a common cancer. Metastatic prostate cancer initially responds to androgen deprivation therapy, but eventually develops into castration-resistance prostate cancers, which is resistant to this treatment and obtained the ability to escape cell death in the absence of androgen. The study found that AKT can increase cell viability in prostate cancer cells in a

variety of ways, including mammalian target of rapamycin (mTOR) activation, to enhance cell resistance to death in androgen-deficient conditions. Other studies have found that 5' adenosine monophosphate-activated protein kinase (AMPK) can inhibit mTOR activity by phosphorylating TSC2 and/or Raptor to interfere with the AKT signaling pathway. Inhibition of AMPK can promote cell proliferation and promote the malignant behavior of cells. The results of the above studies indicate that the anticancer effect of AKT inhibition may be enhanced by AMPK activation. Geraniol can inhibit the AKT signaling pathway, activate the AMPK signaling pathway, inhibit the mTOR signaling pathway, and is more effective in the treatment of prostate cancer by the combination of inhibiting of AKT and activating the AMPK signaling pathway.

Hassan et al¹⁴ studied the health-promoting properties of *Thymus bovei* Benth. essential oil (TB-EO) for its possible use in clinical practice with regard to its cytotoxic, antiherpes simplex virus type 2 (HSV-2), and antihypertensive properties. TB-EO showed very weak cytotoxicity on the healthy human fetal lung fibroblast cells with an IC_{50} value of 118.34 $\mu\text{g/mL}$ compared with that of cisplatin ($IC_{50} = 10.08 \mu\text{g/mL}$). TB-EO and its main component geraniol have displayed anti-HSV-2 with the half-maximal effective concentration (EC_{50}) values of 2.13 and 1.92 $\mu\text{g/mL}$, respectively. TB-EO and geraniol at a concentration of 15 $\mu\text{g/mL}$ showed prominent inhibitory activities against angiotensin-converting enzyme with the percentage of inhibition 95.4% and 92.2%, respectively, compared with that of standard inhibitor captopril (99.8%; 15 $\mu\text{g/mL}$). The results may be a novel findings in the course of a search for new and active anticancer, anti-HSV-2, and antihypertensive agents.

Costunolide (CT) is a sesquiterpene lactone compound and is one of the main chemical constituents of the medicinal plant *Aucklandia lappa* Decne. Studies have shown that CT has effects of antibladder cancer,¹⁵ ovarian cancer,¹⁶ leukemia,¹⁷ and prostate cancer,^{18,19} mainly by inhibiting cancer cell proliferation, inducing apoptosis and differentiation of cancer cells, inhibiting metastasis and invasion of cancer cells, reversing multidrug resistance, and inhibiting angiogenesis.

Artemisinin and its derivatives, well-known as antimalarial drugs, in recent years have been reported to have specific inhibitory effects on tumors *in vitro* and *in vivo*, with small side effects, obvious effects, and low costs.^{20,21} For example, artesunate is a semisynthetic derivative of artemisinin that exhibits anticancer activity against various types of tumors, such as leukemia, melanoma, colon cancer, nonsmall cell lung cancer, lung cancer, prostate cancer, breast cancer, and ovarian cancer.²² The present studies have shown that semisynthetic artemisinin derivatives can exert anticancer effects by causing cell cycle G0/G1 arrest, inducing cell apoptosis, and participating in oxidative stress, which result in more efficient antitumor activity than monomeric compounds, but this mechanism of action has not been elucidated.²³

Paclitaxel is a kind of tetracyclic diterpenoid which is isolated from taxus plants and has a good therapeutic effect on cancers such as ovarian cancer and breast cancer.²⁴ Paclitaxel

was cytotoxic against SKOV3 cells in vitro with a viability rate of $38.2 \pm 1.3\%$ for $1 \mu\text{mol/L}$ of paclitaxel and the apoptotic rate of SKOV3 cells was 15.7 ± 1.7 for paclitaxel. Sun et al²⁵ found that paclitaxel can activate the toll-like receptor 4-nuclear factor-kappa B (NF- κ B) pathway and induce the expression of the *ABCB1* gene, which is of great significance for studying the drug resistance of paclitaxel in the treatment of ovarian cancer.

Ursolic acid can induce tumor cell apoptosis and has obvious antitumor effects, but its proapoptotic mechanism has not yet been elucidated. Recently, the mechanism of action of ursolic acid in the treatment of various types of tumors has been studied in depth.^{26–29} The current investigation demonstrated that ursolic acid could protect hepatoma cells and reduce HBx-mediated autophagy through modulation of Ras homolog gene family member A (RhoA).²⁶ In the present study, it was found that ursolic acid at the low micromolar range may promote its anticancer action by targeting glycolysis in phenotypically distinct breast cancer cells.²⁷ Ursolic acid can also inhibit proliferation and induce apoptosis of human osteosarcoma 143B cells by inactivating Wnt/ β -catenin signaling.²⁸ Research has shown that ursolic acid activates cell apoptosis in prostate cancer through rho-associated protein kinase/

phosphatase and tensin homolog-mediated mitochondrial translocation of cofilin-1.²⁹ In addition, ursolic acid is made into nanoparticles which can improve anticancer efficacy and bioavailability.^{30,31}

Cucurbitacin is a class of tetracyclic triterpenoids that also have antitumor activity.³⁵

Anti-Inflammatory Activity

Inflammation is a common and very important pathological process, often manifests as “red, swollen, hot, painful”. It is a defensive response of living tissue with a vascular system to various damage factors, and it is closely related to various diseases such as asthma, rhinitis, arthritis, and arteriosclerosis. If inflammation is allowed to develop and is not controlled, it can cause serious illness. The structures of terpenoids with anti-inflammatory activities were shown in Figure 2.

Paeniflorin is a monoterpene glycoside compound isolated from the root of *Paeonia lactiflora* Pall. Bi et al³⁶ studied the anti-inflammatory activity and the mechanism of action of paeniflorin, paeniflorin derivatives, 4-*O*-methyl paeniflorin, 4-*O*-methylbenzoyl paeniflorin, and other monoterpenoids in peony. The results showed that most of the monoterpenes

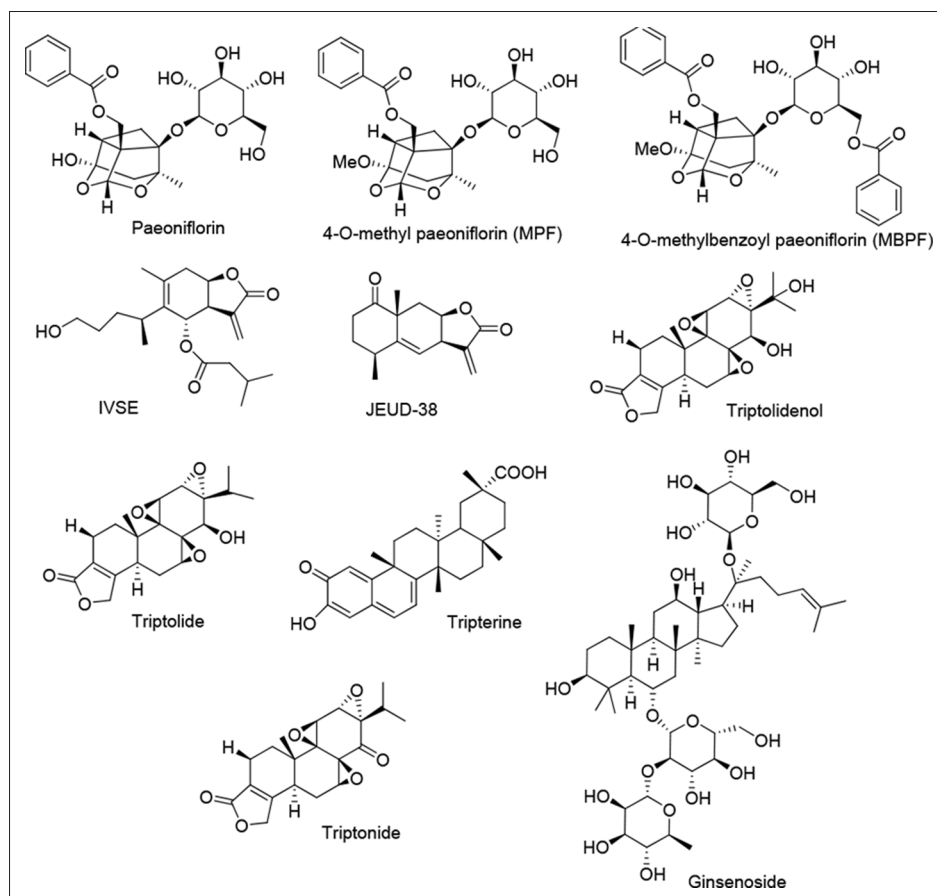


Figure 2. The structures of common terpenoids with anti-inflammatory activities.

could inhibit the production of inflammatory factor nitric oxide (NO), interleukin-6 (IL-6) and tumor necrosis factor- α (TNF- α) induced by lipopolysaccharides (LPS). And it has a significant correlation with the dose.

Inula flower (*Inula japonica* Thunb.) is a traditional Chinese herbal medicine of the genus Asteraceae. Chen et al³⁷ found that the sesquiterpene lactone compound IVSE in the inula flower can inhibit the production of NO induced by LPS, thereby exhibiting the anti-inflammatory activity. Wang et al³⁸ isolated a novel sesquiterpene lactone compound JEUD-38 in the Inula flower; this compound significantly attenuated LPS-induced NO production and had the effect of preventing and treating inflammatory diseases. In this research, the results showed that under the stimulation of LPS, the amount of NO increased by about 11 times compared with the blank group. After the addition of JEUD-38 (the cells were treated with different concentrations of JEUD-38), the production of NO was significantly inhibited, and the inhibitory effect was significantly correlated with the dose.

The Chinese traditional medicine *Tripterygium wilfordii* Hook. f. has been used to treat immune system diseases and inflammatory diseases for hundreds of years. Triptolidenol is the main bioactive component of *Tripterygium wilfordii*. It is also one of the most effective natural products of inflammation and immune regulation that has been found to treat various autoimmune and inflammation-related disorders.³⁹ Its main mechanism is to inhibit the production of inflammatory cytokines.⁴⁰ Researches also have shown that triptolide, tripterine, and triptonide all have obvious anti-inflammatory effects.⁴¹⁻⁴³ In one study, it was found that both triptolide and triptonide significantly relieved the symptoms of acute lung injury (ALI) in mice. Triptolide can improve the pathological state of lung tissue in ALI mice. Triptonide can significantly reduce the expression of chemokines MIP-1 α , MIP-1 β , RANTES, MCP-1, and IP-10 induced by LPS.

Ginseng is a traditional Chinese medicine; its main component is ginsenoside. With the deepening of research, it has been found that ginsenoside-Rb1 (G-Rb1) is a potential anti-inflammatory agent. G-Rb1 can significantly inhibit the activation of NF- κ B (NF- κ B is a key factor in inflammation, and is also a regulatory factor of the production of TNF- α). In addition, it was found that ginsenoside-Rb2 (G-Rb2) and ginsenoside-Rd (G-Rd) exhibited neuroprotective effects.⁴⁴

Antibacterial Activity

Terpenoids (Figure 3) also have strong antibacterial effects⁴⁵⁻⁴⁹ (Table 2). The monoterpenoids in terpenoids are mainly found in the genus *Mentha*, and previous studies have found that most of the compounds extracted from plants of the genus *mentha* have strong antimicrobial activity.⁵⁰ Menthol is a cyclic monoterpene which has been shown to have antibacterial activity.⁵¹⁻⁵⁴ Raut et al⁵⁵ found that menthol showed significant inhibitory activity of biofilm when studying the effects of plant-derived terpenoids on *Candida albicans*.

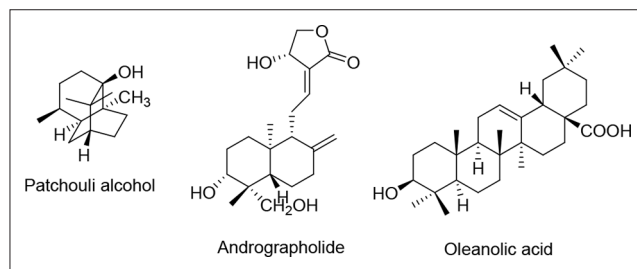


Figure 3. The structures of common terpenoids with antibacterial activities.

Patchouli alcohol (PA) is a tricyclic sesquiterpenoid compound found in *Pogostemon cablin* (Blanco) Benth. Xu et al⁵⁸ found that it had anti-*Helicobacter pylori* activity in vitro and in vivo. The experimental data show that the bactericidal effect of PA is dependent on time and dose under different pH conditions, and the minimal bactericidal concentrations (MBCs) of PA were 25-75 μ g/mL. In addition, PA has a significant inhibitory effect on the movement of *H. pylori* and the formation of flagella.

Studies have found that artemisinin drugs have different antibacterial activities against anaerobic bacteria, facultative anaerobic bacteria, microaerophilic bacteria, and aerobic bacteria. This antibacterial activity has specificity and concentration dependence, which is reflected in different bacteria with different antibacterial activities.⁵⁹⁻⁶¹

Pseudomonas aeruginosa is a clinically important conditional pathogen with strong pathogenicity and high mortality. Due to the widespread use of antibiotics, its sensitivity to most antibiotics is reduced. It is a common pathogen. Andrographolide is a diterpene lactone compound in the Chinese medicine *Andrographis paniculata* Nees. Cheng et al⁶² found that andrographolide had a significant inhibitory effect on the biofilm of *P. aeruginosa* and synergistic antibacterial effect with azithromycin. Banerjee et al⁶³ found that andrographolide exhibited potential antibacterial activity against most of the tested Gram-positive bacteria, among which it was most sensitive to *Staphylococcus aureus* with a minimal inhibitory concentration (MIC) value of 100 μ g/mL and was found to have an inhibitory effect on the formation of the biofilm of *S. aureus*.

Oleanolic acid is a pentacyclic triterpene compound isolated from plants. The results of one study showed oleanolic acid has a certain inhibitory effect on *S. aureus*, methicillin-resistant *S. aureus*, and *Streptococcus mutans*.⁶⁴ Kim also found^{65,66} that oleanolic acid can kill *Listeria monocytogenes*, *Enterococcus faecium*, and *Enterococcus faecalis* by destroying cell membranes of the bacteria, and the MICs were 16-32 μ g/mL for *L. monocytogenes* and 32-64 μ g/mL for *E. faecium* and *E. faecalis*, and bacterial cell viability decreased after exposure to 2 \times MIC of oleanolic acid.

Table 2. The Antibacterial Activity of Terpenoids.

Classification	Compound	Antibacterial range	Reference
Monoterpene	1,8- eucalyptus	<i>Staphylococcus aureus</i> , <i>Bacillus subtilis</i> , <i>Escherichia coli</i> , and <i>Streptococcus</i> , <i>Listeria</i> , <i>Bacillus cereus</i>	45,46
	Limonene,	<i>B. subtilis</i> , <i>S. aureus</i> , <i>Streptococcus mutans</i> , <i>E. coli</i> , <i>Candida albicans</i> , methicillin-resistant <i>S.</i>	56
	Geranialdehyde	<i>aureus</i> and <i>Saccharomyces cerevisiae</i>	
	Sabinene	<i>S. aureus</i> (Gram-positive) and <i>E. coli</i> (Gram-negative)	57
	Menthol	<i>S. aureus</i> , <i>Streptococcus pneumoniae</i> , <i>Streptococcus pyogenes</i> , <i>Haemophilus influenzae</i>	50–55
	Sabinol	Oral bacteria	47
Sesquiterpene	Carvone	<i>S. aureus</i> , <i>E. coli</i> , <i>B. subtilis</i> , <i>Salmonella typhimurium</i> , <i>Listeria</i>	48,49
	Patchouli Alcohol	<i>Helicobacter pylori</i>	58
Diterpene	Artemisinin	Various pathogens such as <i>B. subtilis</i> , <i>E. coli</i> , <i>Pseudomonas aeruginosa</i> , <i>S. cerevisiae</i> , <i>S. aureus</i> , <i>Mycobacterium tuberculosis</i>	59-61
	Andrographolide	<i>P. aeruginosa</i>	62,63
Triterpene	Oleanolic acid	<i>S. aureus</i> , methicillin-resistant <i>S. aureus</i> , <i>S. mutans</i> and <i>Listeria monocytogenes</i> , <i>Enterococcus faecium</i> , <i>Enterococcus faecalis</i>	64-66

Antiviral Effect

Terpenes are among the very promising source of new antimicrobials agents that have shown to have activity against viruses, bacteria, fungi, and protozoa.⁶⁷ The structures of terpenoids with antiviral effects are shown in Figure 4. Monoterpenoids, isborneol and borneol, have strong activities against herpes simplex virus-1 (HSV-1). Isborneol is a monoterpene found in a wide range of plant essential oils. This compound showed total inhibition of HSV-1 replication at a concentration of 0.06%.⁶⁸ Other monoterpene compounds such as thymol, α -terpinene, γ -terpinene, 1,8-cineole, α -terpineol, and citral isolated from tea tree, thyme, and eucalyptus demonstrated in vitro antiviral activity against HSV-1 by inhibition of virus greater than 80%.⁶⁹

Hassan et al⁷⁰ isolated 12 pure compounds from the leaves and twigs of *Eucalyptus globulus* and all of them were tested for antitherpetic activity against the replication of antigen types HSV-1 and HSV-2. The results demonstrated that the compound tereticornate A (IC₅₀: 0.96 μ g/mL; selectivity index CC₅₀/IC₅₀: 218.8) showed the strongest activity in the anti-HSV-1 assay, even greater than acyclovir (IC₅₀: 1.92 μ g /mL; selectivity index CC₅₀/IC₅₀: 109.4), a standard antiviral drug. And the compound also displayed moderate antibacterial effects and anti-inflammatory activity.

Putranjivain A, a diterpene isolated from *Euphorbia jolkini*, demonstrated antiviral effect against HSV-2 in Vero cells with an IC₅₀ value of 6.3 μ M.⁷¹ The two triterpenes compounds, moronic acid and betulonic acid, extracted from the plant *Rhus javanica* showed in vitro potent inhibitory effect on HSV-1 with EC₅₀ values of 3.9 and 2.6 μ g/mL, respectively.⁷² Notoginsenoside ST-4i, isolated from the Chinese herb *Panax notoginseng*, demonstrated in vitro remarkable inhibitory activities against HSV-1 and HSV-2 with EC₅₀ values of 16.4 and 19.44 μ M, respectively.⁷³ The results of inhibitory activity against HSV-1 of glycyrrhizin (GR) indicated that GR eliminated the increased susceptibility of thermally injured mice to

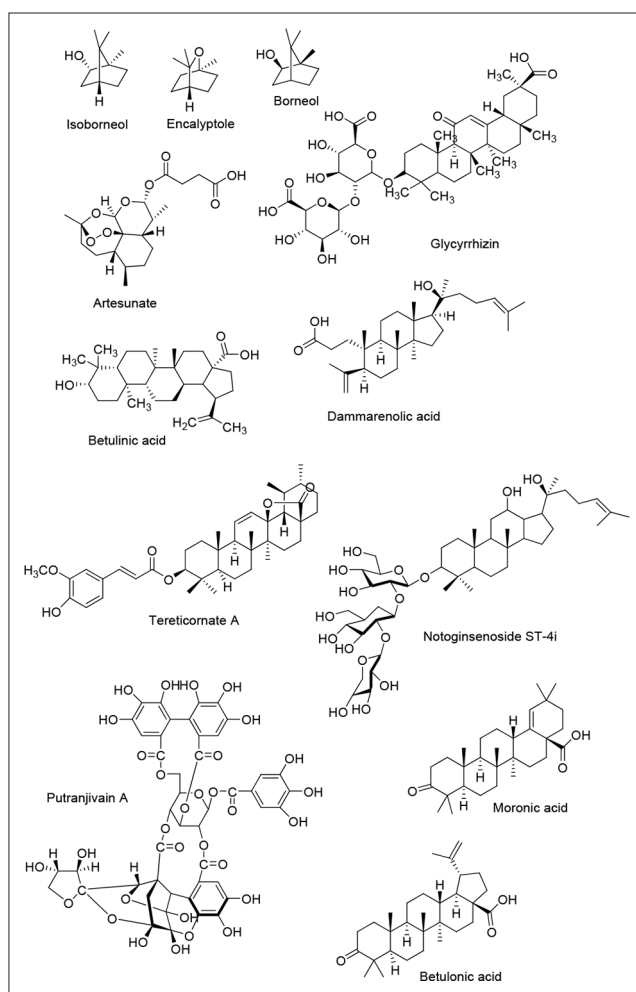


Figure 4. The structures of common terpenoids with antiviral effects.

HSV infectivity during the induction of CD4⁺ contrasuppressor T cells.⁷⁴

Artemisinin and its derivatives showed significant inhibitory activity on the hepatitis B virus (HBV) and hepatitis C virus (HCV).⁷⁵ Artesunate is the semisynthetic derivative of artemisinin, which has a more pronounced inhibitory effect on hepatitis B surface antigen (HBsAg). A synergistic effect was observed by combining artesunate with lamivudine (a drug for treating HBV).

Recent studies have found that andrographolide has a significant inhibitory effect on the replication process of the chikungunya virus (CHIKV) (a mosquito-borne alphavirus).⁷⁶ Andrographolide showed good inhibition of CHIKV infection and reduced virus production by approximately $3\log_{10}$ with a 50% EC₅₀ of 77 μM without cytotoxicity. Time-of-addition and RNA transfection studies showed that andrographolide affected CHIKV replication and the activity of andrographolide was shown to be cell type independent. Dengue fever is the most common viral disease transmitted by arthropods in humans, but there are currently no drugs against the dengue virus (DENV). Panraksa showed that andrographolide exhibited significant anti-DENV activity in both cell lines (HepG2 and HeLa), significantly reducing both the levels of cellular infection and virus output, with 50% EC₅₀ for DENV of 21.304 μM and 22.739 μM for HepG2 and HeLa, respectively.⁷⁷

Harada et al.⁷⁸ found that GR (a triterpenoid saponin) can inhibit the replication of severe acute respiratory syndrome-associated virus and regulate the mobility of the envelope of the human immunodeficiency virus (HIV).

Betulinic acid is a pentacyclic triterpenoid compound isolated from *Syzygium claviflorum*. Betulinic acid and its derivatives have anti-HIV activity, and it is considered to be the earliest discovered pentacyclic triterpenoid compound with anti-HIV activity, which can affect the fusion between virus and cells, and also inhibit the activity of the reverse transcriptase and assembly of the virus.^{79,80} Oleanolic acid, dammarenolic acid, and ursolic acid also have anti-HIV activity.⁸¹⁻⁸³

Antimalarial Effect

Artemisinin is a sesquiterpene lactone compound isolated from *Artemisia annua* Linn in the 1970s. It is the most effective antimalarial drug after pyrimethamine, chloroquine, and primaquine and has the characteristics of low toxicity and high efficiency. Later, antimalarial drugs such as artesunate, arteether,

and artemether have been synthesized by modifying the chemical structure of artemisinin (Figure 5). These drugs have small adverse reactions and can effectively kill the plasmodium in the red blood cell phase. Current research shows that when red blood cells are phagocytosed by plasmodium, heme molecules in high concentrations are released. Artemisinin is activated by heme in the place where the plasmodium metabolized vigorously and binds to the parasite proteins in the plasmodium body to make the proteins inactivated, achieving the purpose of killing plasmodium.⁸⁴ In addition, sarcoplasmic endoplasmic reticulum calcium ATPase (PfATP6),⁸⁵ translational controlled tumor protein,⁸⁶ and glutathione S transferase⁸⁷ have also been identified as nonheme protein substances that interact with artemisinin in the plasmodium. The antimalarial mechanism of artemisinin still needs further study.

Prevention and Treatment of Cardiovascular Diseases

In recent years, the incidence of cardiovascular diseases in humans has increased year by year. Finding effective drugs for treating cardiovascular diseases is an urgent task for researchers. Tanshinone IIA (TS) (Figure 6) is an active ingredient isolated from the rhizome of Chinese herbal medicine *Salvia miltiorrhiza* Bunge. The latest findings suggest that TS can prevent the formation of atherosclerosis and the damage and hypertrophy of the heart. In atherosclerosis, TS can inhibit the oxidation of low-density lipoprotein and the expression of proinflammatory factors, and TS also has certain activity and potential to stabilize atherosclerotic plaque.⁸⁸ In addition, TS has significant therapeutic effects on a variety of cardiovascular diseases, such as antismyocardial infarction, dilation of blood vessels, improvement of microcirculation, antiangina, etc.⁸⁹⁻⁹¹

Ginsenosides (Figure 6), in addition to its anti-inflammatory effects, also have significant therapeutic effects on various cardiovascular diseases, such as regulating vascular function, inhibiting cardiomyocyte hypertrophy, and inhibiting thrombosis.⁹²

Hypoglycemic Effect

Diabetes is a metabolic disease characterized by high blood sugar. The long-standing high blood sugar in diabetics can cause chronic damage and dysfunction in various tissues. Diterpenoid stevioside (SVS) (Figure 7) is an active ingredient isolated from plant stevia (*Stevia rebaudiana* (Bertoni) Hemsl.). In the study by Jeppesen et al.,⁹³ it was found that SVS can significantly improve the hyperglycemia of rats. Its antihyperglycemic effect may be related to the expression of glycolytic-related genes, phosphorylation of liver mitochondrial ATP, and inhibition of nicotinamide adenine dinucleotide-oxidase activity, thereby achieving the effect of lowering blood sugar.

In recent years, artemisinin has been found to be a potential drug to improve type 1 diabetes. Ginsenosides have also made great progress in the research of the prevention of diabetes and hypoglycemic activity.

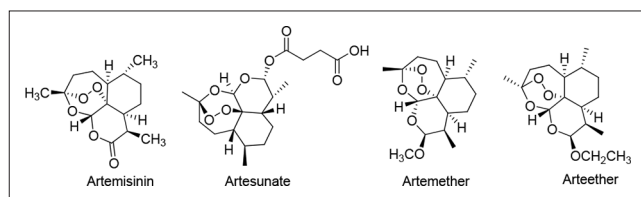


Figure 5. The structures of common terpenoids with antimalarial effects.

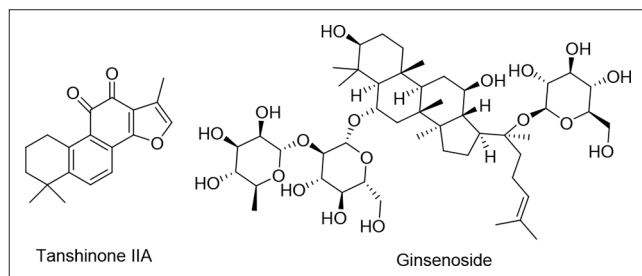


Figure 6. The structures of terpenoids with prevention and treatment of cardiovascular diseases.

Promote Transdermal Absorption

The presence of the stratum corneum of the skin is a major obstacle in the percutaneous administration process.⁹⁴ In order to enhance the permeability of drugs through the skin, researchers have done a lot of research. The most popular method currently is the application of penetration enhancers, including natural terpenes; the most commonly used terpenes being menthol, menthone, 1,8-cineole, cinene, and nerolidol (Figure 8).⁹⁵ Natural terpene has high activity, little skin irritation, and low toxicity and can safely and effectively promote transdermal absorption of drugs. In addition, several terpenes (such as 1,8-cineole, menthol, and menthone) have been included in the list of “Generally Recognized As Safe” issued by the US Food and Drug Administration. Hydrocarbon terpenes, such as D-cinene, have been approved as steroid activity enhancers.⁹⁶ Another study reported that α -terpineol is used as a transdermal enhancer for zidovudine and buspirone hydrochloride,^{97,98} and limonene has the effect of enhancing the skin penetration of ketoprofen and aceclofenac.^{99,100}

Terpenes interfere with the lipid arrangement in the intercellular regions of the stratum corneum (SC),¹⁰¹ which leads to increased permeability of the skin and thus aids in drug absorption.

The molecular mechanism studies suggested that monocyclic monoterpenes, such as menthol and menthone, enhanced the skin permeability by disordering the ordered organization of SC lipids and extracted part of SC lipids.¹⁰² Recently, Wang et al¹⁰³ studied the mechanism of transdermal absorption of menthol and menthone on ligustrazine hydrochloride (LH). The results suggest that the mechanism of action may involve hydrogen

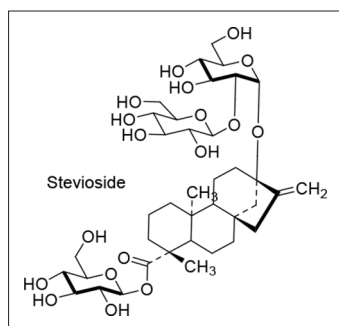


Figure 7. The structure of terpenoids with hypoglycemic effect.

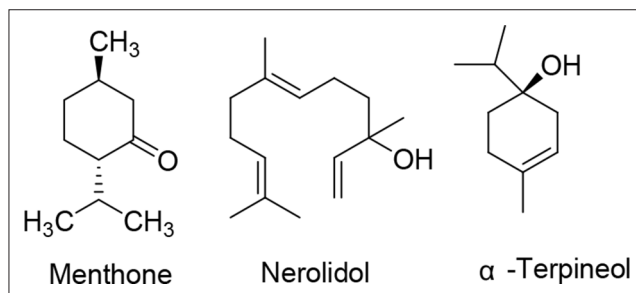


Figure 8. The structures of terpenoids with transdermal absorption.

bonding and interference with the SC lipid arrangement. In addition, the polarity of terpenes is a key factor affecting drug absorption. Terpenes, such as limonene, have a strong promoting effect on the penetration of lipophilic drug molecules,¹⁰⁴ while terpenes with polar groups, such as menthol, have a better penetration enhancing effect on hydrophilic drug molecules.¹⁰⁵

Other Biological Activity

In addition to the above-mentioned antitumor activity, anti-inflammatory activity, antibacterial activity, antiviral activity, anti-malarial activity, prevention and treatment of cardiovascular diseases, hypoglycemic activity, terpenoids also have other biological and pharmacological activities, such as insect resistance, immunoregulation, antioxidation, antiaging, and neuroprotection.

The results showed that the monoterpene thymol (Figure 9) and its derivatives, menthol derivatives, have certain insecticidal activity.^{106,107} Through a series of screening and determination, it was found that 3,7-dimethyl-1-octanol (dihydrocitronellol) is the most effective terpene with antischistosomal activity (IC_{50} values of 13–52 μ M)¹⁰⁸; confocal laser scanning microscopy revealed that the compound induced severe tegumental damage in adult schistosomes and a correlation between viability and tegumental changes was observed.

Oleanolic acid, ursolic acid, triterpene acids of loquat (TAL) have good immunomodulatory effects.^{109,110} They are potent immunomodulators of macrophages infected with virulent *Mycobacterium tuberculosis* and their immunomodulatory activity induced through activation of macrophages.

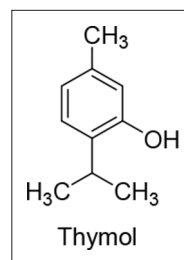


Figure 9. The structure of thymol.

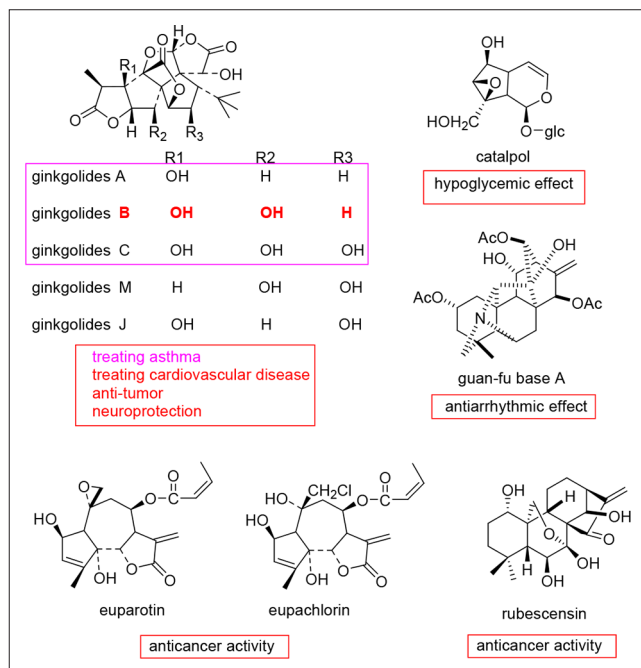


Figure 10. Structures of the most promising terpenoids.

The ginsenoside Re isolated from American ginseng has an antioxidation effect and can protect cardiomyocytes from oxidative damage of internal and external oxidants.¹¹¹ Ginsenoside Rg1 regulates the expression of regulatory factors in the cell cycle and then exerts its antiaging effects. Currently, ginsenoside Rd is widely used for neuroprotection. In addition, Wan et al¹¹² found that ginsenoside Rd can alleviate cognitive dysfunction.

Conclusions and Outlooks

The structures of the most promising terpenoids that could be used as templates for further investigations were listed in Figure 10. The current research results show that various terpenoids have been shown to have significant disease prevention and treatment effects, and have antitumor, anti-inflammatory, antibacterial, antiviral, antimalarial effects and also show potential functions in immune regulation, neuroprotection, anti-allergy. The activity exhibited by terpenoids has a considerable role in the development of new drugs and improvements in existing treatment options. At the same time, the biological activities of many terpenoids still require in-depth and meticulous research.

The terpenoids are abundant in medicinal plants, and terpenoids are widely used, have enormous application potential, and broad development prospects. Terpenoids not only can be extracted and isolated from plants but also can be obtained based on metabolic engineering, synthetic biology, and biotransformation which are new sources of the synthesis of terpenoid and also solve the shortage of terpenoids. Structurally optimized terpenoids can be prepared in large quantities by synthetic biology to meet the needs of drug research and development.

At present, the mechanism of action of many terpenoids has not yet been elucidated. The combination of “omics” technology and molecular network pharmacology can be used to further study the mechanism and structure–activity relationship of terpenoids. Screening the activity of terpenoids is still a key step in the development of new drugs, the compounds with higher activity can be directly developed into new drugs, or structurally modified as lead compounds, and then screening new compounds with significant activity. It is an important means for the research and development of the drug, and it is also a hot spot in the field of natural product research. The new dosage form of terpenoids can be developed in combination with the new progress of pharmaceuticals to maximize its pharmacological activity. Or terpenoids can be added as additives to health care products and cosmetics, which has broad market prospects and economic benefits.

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Declaration of Conflicting Interests

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