



# Application of Amino Acids in the Structural Modification of Natural Products: A Review

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Natural products and their derivatives are important sources for drug discovery; however, they usually have poor solubility and low activity and require structural modification. Amino acids are highly soluble in water and have a wide range of activities. The introduction of amino acids into natural products is expected to improve the performance of these products and minimize their adverse effects. Therefore, this review summarizes the application of amino acids in the structural modification of natural products and provides a theoretical basis for the structural modification of natural products in the future. The articles were divided into six types based on the backbone structures of the natural products, and the related applications of amino acids in the structural modification of natural products were discussed in detail.

**Keywords:** derivatives, research progress, structure modification, natural products, amino acids

## INTRODUCTION

Amino acids are the basic units of proteins and the primary substance supporting biological life activities. They are closely related to the activities of a living body, playing very important roles. They are essential organic molecules in any organism. The amino acid chemical structure contains an amino group (-NH<sub>2</sub>), a carboxylic acid group (-COOH), and a unique side chain on the carbon that connects the amino group to the carboxyl group. Amino acids have many special physiological functions, playing roles in protein synthesis, metabolism, body development, osmotic pressure stability, and neurotransmission (Wu, 2009).

In addition to these functions, amino acids are also widely used in the food industry. For example, the main raw material of the sweetener aspartame is *L*-phenylalanine (Liu et al., 2019). Naturally occurring amino acids can be used to enhance the flavor of food and enhance nutrition (Ikeda, 2003). Additionally, amino acids are widely used in the medical and healthcare industries (Carubelli et al., 2015; Nitz et al., 2019). They also have a wide range of pharmacological activities, such as antitumor (Barnham et al., 1996), anti-HIV (Chen A. et al., 2006), and anti-fatigue (You et al., 2011) effects; in addition, they are used to cure chronic liver diseases (Kawaguchi et al., 2011).

The structures of amino acids are simple and diverse, and their pharmacological activities are extensive. These features are commonly employed in drug synthesis and structural modification. It has been reported that after a compound is combined with an amino acid, the pharmacological activity of the compound is enhanced (Ma et al., 2007; Zhang et al., 2008), water solubility is improved (Drag-Zalesinska et al., 2009; Kim et al., 2009), and cytotoxicity is reduced (Anbharasi et al., 2010).

Natural products and their molecular frameworks are valuable sources of medicinal chemistry and drug discovery (Lee, 2004). In the past decades, drugs that directly or indirectly replace derivatives and analogs of natural products have played important roles in the fight against diseases (Rodrigues et al., 2016). Although the biological activities of natural products are extensive, they are not strong and often have the disadvantages of low bioavailability and poor solubility (Shi et al., 2010). Therefore, to enhance their physchem properties and ADME, it is important to make necessary structural modifications to these products. Interestingly, amino acids can improve these shortcomings, and therefore, they have become the preferred natural product structural modifiers. Many natural products have shown improved biological activity and physicochemical properties following the introduction of amino acids (Ma et al., 2000; Brady et al., 2002), and successful modification results have been obtained. Glycolic acid (**1**) is the product of bile acid linked to glycine that shows anticancer activity by targeting the pump resistance-related and non-pump resistance-related pathways (Lo et al., 2008); it is currently undergoing Phase III clinical studies (Figure 1). Furthermore, HAO472 (**2**) is a TFA salt compound composed of oridonin and alanine that possesses potential activity to treat acute myelogenous leukemia and is presently undergoing a Phase I clinical trial in China conducted by Hengrui Medicine Co. Ltd. (Figure 1) (Sun et al., 2014). Additionally, valaciclovir hydrochloride (**3**), an adenine linked to valine via a glycol linker, is an antiviral drug that has been marketed for the treatment of herpes simplex, herpes zoster, and herpes B (Figure 1) (LaVail et al., 2003).

Natural products constitute a potential starting point for new drug design; thus, this review summarizes the structural modification of natural products by amino acid as has been reported between 2010 and 2020. Relevant articles were retrieved from various databases and analyzed. This review is expected to provide a theoretical basis for the structural modification of natural products in the future.

## APPLICATION OF AMINO ACIDS IN THE STRUCTURAL MODIFICATION OF NATURAL PRODUCTS

Numerous natural products exist; thus, to facilitate the classification and management of literature, this review classifies all relevant articles into six categories based on the lead framework, including phenylpropanoids, quinones, flavonoids, terpenes, alkaloids, and polyphenols.

### Phenylpropanoids Cinnamic Acid

Ferulic and isoferulic acids are cinnamic acid compounds containing phenolic hydroxyl groups and exert various biological effects. Gobec et al. (2018) discovered compound **4**, a tripeptide derivative of isoferulic acid, which is presently the most potent desmuramylpeptide NOD2 agonist, and the EC<sub>50</sub> value for NOD2 is 46 nM. Compound **4** can cooperate with lipopolysaccharide to increase the release of pro-inflammatory

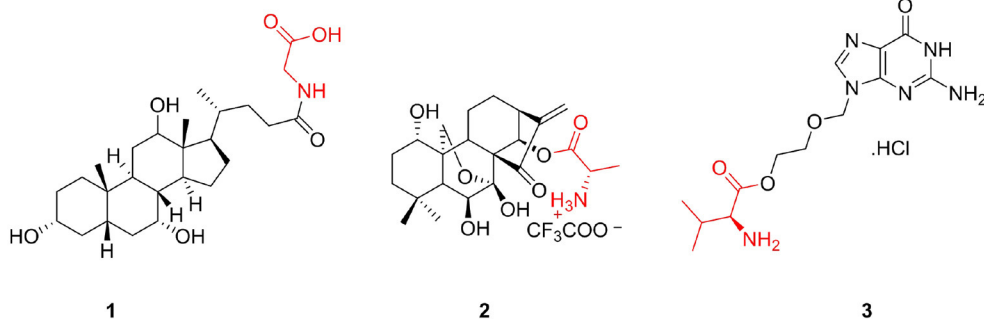
cytokines in human peripheral blood mononuclear cells, and it induces ovalbumin-specific IgG titers in a mouse model of adjuvant. Further, Hamed et al. (2020) synthesized a series of *N*-feruloyl dipeptides and conducted in-depth studies of these compounds as potential anticancer agents against 10 cancer cell lines from different tissue origins. Based on this, compound **5** showed the strongest cytotoxic activity for all cell lines with IC<sub>50</sub> values ranging from 2.1 to 7.9 μM, and its activity was stronger than that of ferulic acid (IC<sub>50</sub> > 30 μM) (Figure 2A).

### Coumarin

Coumarin compounds are an important class of natural heterocyclic compounds with antioxidant, antibacterial, anti-inflammatory, and anticancer properties. Since these compounds have a wide range of pharmacological activities and simple chemical structures, they are favored by many medicinal chemistry researchers. Ji et al. (2016) synthesized novel coumarin phosphoramidate derivatives and screened for chitin synthase inhibitory and antibacterial activities *in vitro*. It was found that most of these compounds have a good inhibitory effect on chitin synthase. Among them, compound **6**, with an IC<sub>50</sub> value of 0.08 mM, was shown to be the strongest chitin synthase inhibitor. Additionally, antifungal experiments have shown that these compounds have moderate or even excellent antibacterial activity against common clinical pathogens. Further, Patagar et al. (2019) designed and synthesized substituted coumarin-4-acetyl amino acids and determined their inhibitory activity against DHODH, a dual-target compound for malaria and cancer. The DHODH inhibitory activity of the newly synthesized compound was then determined. Compared with the standard product, compound **7** showed obviously the highest 70.6% inhibition of DHODH at 0.5 μM, and other compounds with terminal COOH showed moderate inhibition (Figure 2B).

Zhang et al. (2014) synthesized ethyl 6-fluorocoumarin-3-carboxy-*L*-theanine (**8**) and ethyl 6-nitrocoumarin-3-carboxy-*L*-theanine (**9**). These two compounds enhance the activities of the anticancer drugs cytarabine, vincristine, and methotrexate in inhibiting the growth of lung cancer cells and have no toxic effects on normal human embryonic lung fibroblasts and peripheral blood lymphocytes. TFC (IC<sub>50</sub> LLC = 0.125 mM and IC<sub>50</sub>A549 = 0.99 mM) and TNC (IC<sub>50</sub> LLC = 0.09 mM and IC<sub>50</sub>A549 = 0.064 mM) have shown strong inhibitory effects on the growth of highly metastatic LCC and A549 tumors in tumor-bearing mice and are non-toxic to mice. Additionally, Malysheva et al. (2014) obtained novel 4-arylcoumarin derivatives and found that water-soluble salts (**10**) show considerable cytotoxicity against the HaCaT cell line (IC<sub>50</sub> = 0.07 μM) (Figure 2B).

In addition to the amino acids in furanocoumarin, all synthetic compounds have been tested as EGFR and VEGFR-2 kinase inhibitors. The EGFR enzyme inhibition IC<sub>50</sub> values of all compounds range from 20.2 to 57.6 nM, while the EGFR-2 enzyme inhibition (IC<sub>50</sub>) ranges from 1.2 to 58.9 nM. In general, compound **16d** had the strongest inhibitory effect on the two targets. Francisco et al. (2012) synthesized two new tetracyclic benzofuranocoumarin (benzopsoralen) analogs (compounds **17** and **18**) and found that they significantly inhibited the proliferation of MDA MB 231, HeLa, and TCC-SUP



**FIGURE 1** | Successful cases of natural product modification with amino acids.

with  $GI_{50}$  of three tumor cell lines is between 0.043 and 0.205  $\mu\text{M}$ , which is thought to be mainly linked to the inhibition of CYP2A6 (Figure 2B).

### Lignans

Lignans are a kind of natural product formed by the oxidative polymerization of phenylpropanoids, containing two molecules of C6–C3 structure. Podophyllotoxin (PPT), a natural antimitotic product isolated from *Podophyllum peltatum* L. (Imbert, 1998), exhibits various interesting biological activities, such as antitumor and antiviral activities (Garcia and Azambuja, 2004). However, PPT displays many side effects, including damage to normal tissues, leading to the development of lower cytotoxicity and higher efficiency PPT derivatives.

Hu et al. (2011) synthesized a series of novel compounds at the C-4 of PPT and evaluated their cytotoxicity in the K562 cell line *in vitro*. Compound **19** exhibited better cytotoxicity ( $IC_{50} = 2.1 \mu\text{M}$ ) than those of PPT and etoposide, indicating that the antitumor effect might be because of the induction of apoptosis. Further, Wu et al. (2018) synthesized a series of PPT derivatives and tested their cytotoxicity in several cancer and L02 cell lines. Interestingly, some *N*-Boc amino acid target demonstrated high selectivity, especially compound **20**, which showed a high degree of selectivity for both cancer and normal cells. The  $IC_{50}$  values of compound **20** in A549, MCF-7, HepG2, and L02 cells were 9.5, 132.6, 96.4, and 160.2 nM, respectively, showing low cytotoxicity and high selectivity. Moreover, compound **20** induced apoptosis in A549 cells and prevented the transition of these cells from the S phase to the G2 phase; however, it had no significant effect on L02 cells. Han et al. (2016) screened an effective podophyllotoxin derivative, namely **21** ( $IC_{50}$  in MCF-7 cell line = 0.9  $\mu\text{M}$ ), with low cytotoxicity to non-cancer cells, including human embryonic kidney cells (293T) ( $IC_{50} = 54.4 \mu\text{M}$ ). Additionally, this derivative can cause a significant cell cycle arrest at the G2/M phase and induce MCF-7 cell apoptosis more than PPT. Moreover, the expression of cell cycle protein CDK1 was upregulated, while a protein required for mitotic initiation, Cyclin B1, was downregulated. This result showed that **21** was an effective tubulin polymerization inhibitor, and its effect is equivalent to that of positive control colchicine (Figure 3A).

Arctigenin (ARG) is a lignan-class compound isolated from *Arctium lappa* L. According to reports, it has a variety of biological activities, such as antitumor, anti-inflammatory, and antiviral activities. Although ARG has a variety of pharmacological activities *in vitro*, it is insoluble in the human body and thus cannot be absorbed, limiting its clinical application. Therefore, it is very important to use chemical or biological methods to modify ARG into derivatives with better solubility and higher bioavailability (Figure 3A).

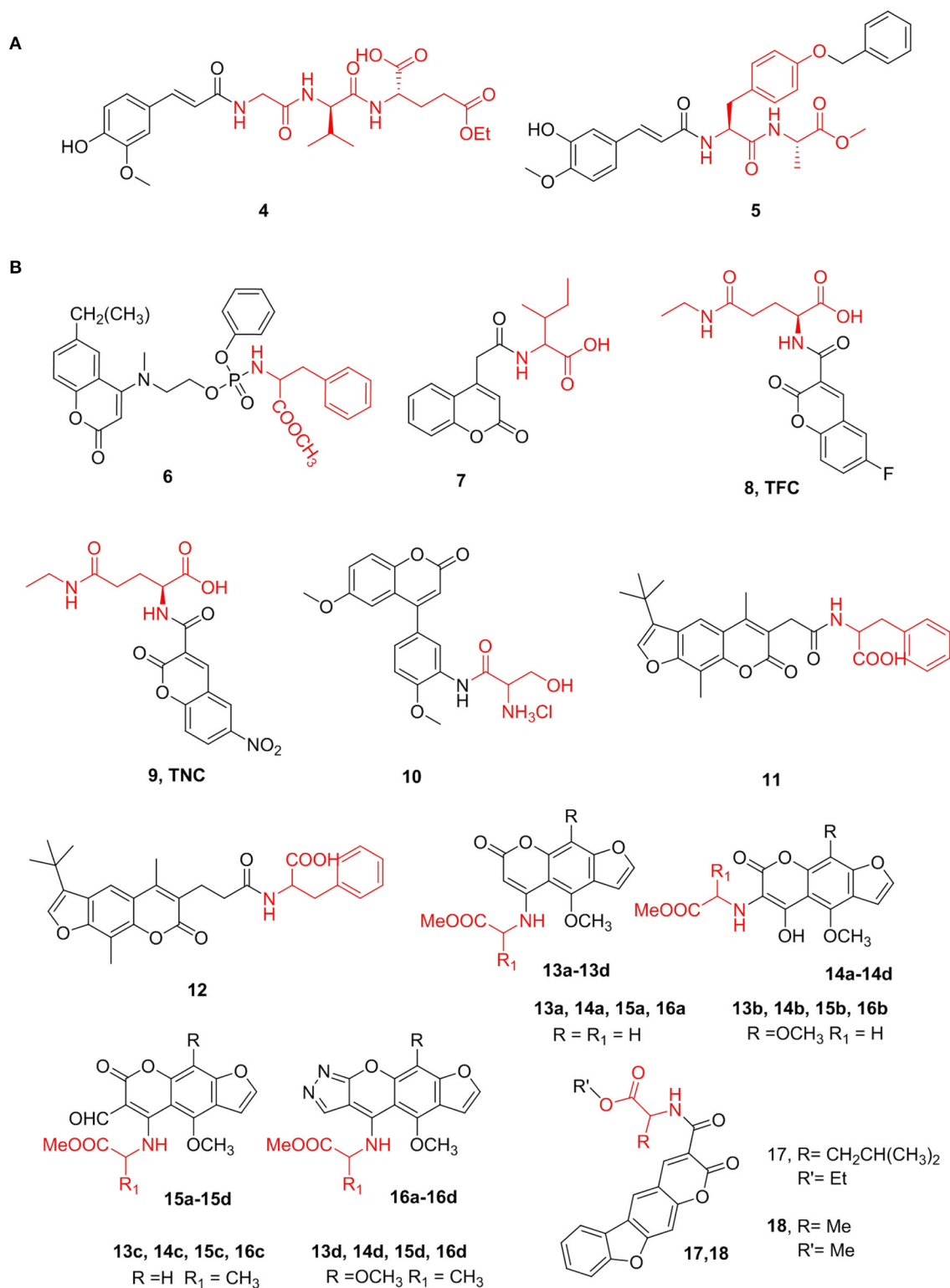
Cai et al. (2016) synthesized a series of ARG amino acid derivatives, all of which have better solubility and nitrite elimination ability than those of ARG. This compound and its two amino acid derivatives without a Boc protection group (**22**, **23**) were selected for *in vivo* antitumor activity evaluation. In H22 tumor-bearing mice, the tumor inhibition rates of compounds **22** and **23** were 69.3 and 43.6% at a dosage of 40 mg/kg, respectively, which was significantly higher than that of ARG. Besides, compared with the positive group, these compounds caused less damage to the liver, kidney, and immune organs of mice. Additionally, they synthesized five other amino acid derivatives (Cai et al., 2018) and measured the antitumor activity of these compounds. The inhibition rates of compounds **24** and **25** were 55.9 and 51.4% at a dosage of 40 mg/kg, respectively, which were twice than that of ARG. Moreover, the compounds were found to reduce damage to internal organs. Further, Zhang H. B. et al. (2018) prepared a series of ARG amino acid derivatives, measured their anti-*Toxoplasma gondii* activities *in vitro*, and calculated their selectivity indices. These derivatives showed greater selectivity indices than that of ARG and good anti-*Toxoplasma gondii* activities. The selectivity index of compound **26** was 3.2, which showed low toxicity to host cells and high anti-*Toxoplasma* activity (Figure 3A).

### Quinones

They are widely distributed in nature and are divided into four types: benzoquinone, naphthoquinone, phenanthrenequinone, and anthraquinone.

### Naphthoquinone

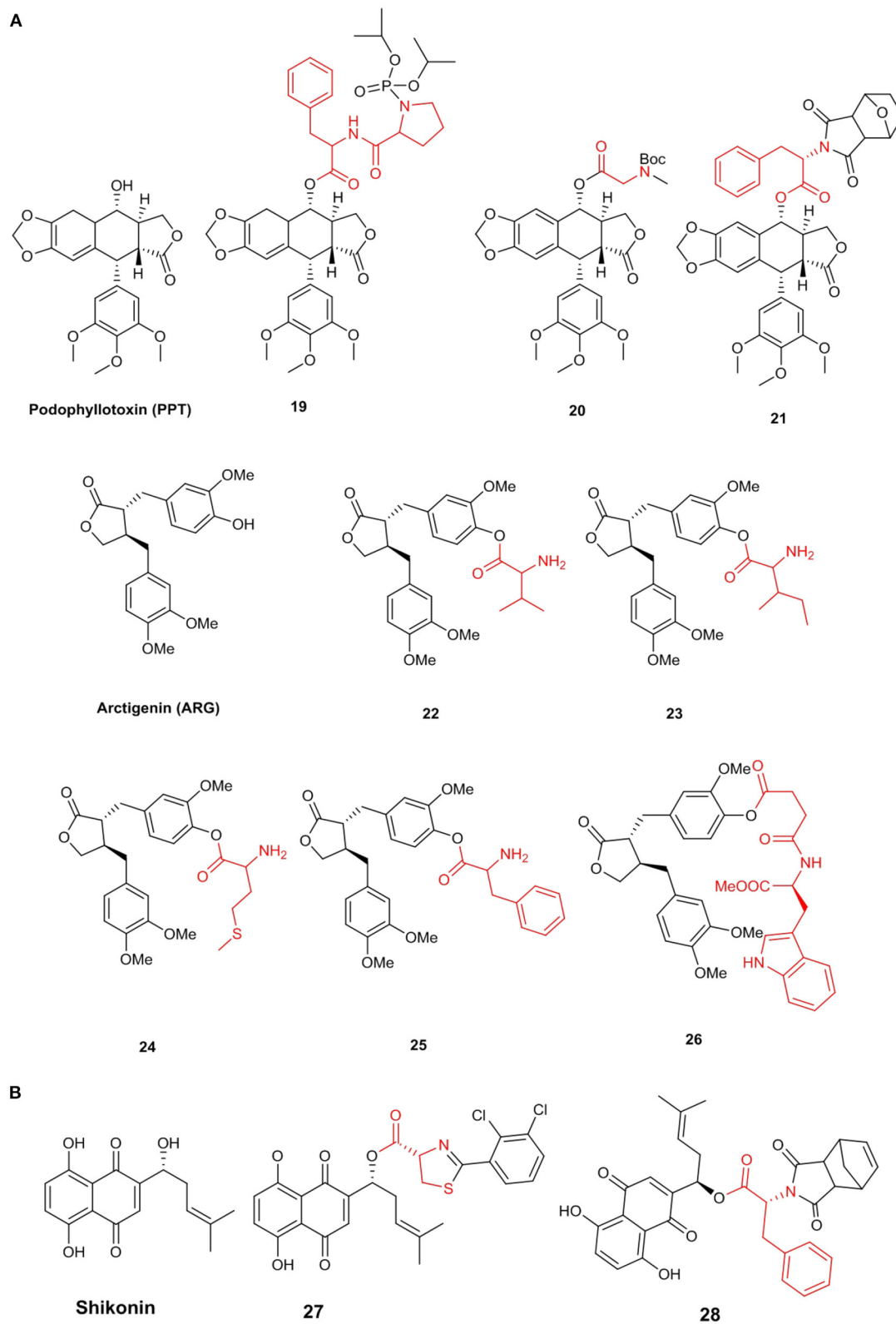
Shikonin is an active naphthoquinone compound isolated from the root of the traditional Chinese Medicine *Lithospermum*



**FIGURE 2 | (A)** Cinnamic acid derivatives. **(B)** Coumarins amino acid derivatives.

*erythrorhizon* Sieb. et Zucc. (Chen et al., 2002). Shikonin has received extensive attention from medicinal chemistry researchers due to its particularly good anticancer activity (Lin

et al., 2013). However, the side effects and cytotoxicity of shikonin limited its application as a new clinical anticancer drug (Cui et al., 2008). Lin et al. (2015) synthesized a series of shikonin



**FIGURE 3 | (A)** Lignans amino acid derivatives. **(B)** Shikonin amino acid derivatives.

derivatives containing a *L*-cysteine residue and determined their anticancer activities. Among them, compound **27** showed better antiproliferative activity with  $IC_{50} = 3.1 \mu M$  in HeLa cells than that of shikonin ( $IC_{50} = 5.8 \mu M$ ). In addition, this compound may cause cell cycle arrest in the G2/M phase, lead to apoptosis, reduce the adhesion ability of HeLa cells, and bind well to tubulin at the paclitaxel binding site, resulting in tubulin polymerization and destruction mitotic. Further, Baloch et al. (2015) synthesized a series of other shikonin derivatives and evaluated their antiproliferative activities against five cancer cell lines, including A549, HeLa, MCF-7, HepG2, and BGC, with  $IC_{50}$  values ranging from 1.3 to  $18.5 \mu M$ . Compared to shikonin itself and other compounds, compound **28** showed a better antiproliferative effect against all cancer cell lines and could induce apoptosis in a dose- and time-dependent manner, as well as arrest the cell cycle in the G2/M phase (**Figure 3B**).

### Anthraquinone

Anthraquinone is currently the most important quinone compound with various biological activities, such as purgative, antibacterial, and anticancer activities. Since anthraquinone compounds have a polyaromatic ring-condensed structure, their solubility is extremely poor ( $<0.1 \text{ g}/100 \text{ mL}$ ). Lee et al. (2012) synthesized a series of symmetrically dispersed 1,8-diamidoanthraquinones, evaluated their antiproliferative and telomerase inhibitory effects via a TRAP assay, and measured *hTERT* expression using SEAP. In particular, among all derivatives, compounds **29** and **30**, which are linked to valine and proline methyl esters, respectively, showed the most potent *hTERT* repressing activities, with  $IC_{50}$  both  $<10 \mu M$ . Aloe-emodin is a type of hydroxyanthraquinone found in aloe leaves (Pecere et al., 2000). Thimmegowda et al. (2015) focused on improving the water solubility of aloe-emodin and synthesized a series of amino acid derivatives, hoping to improve the efficacy of aloe-emodin. They found that the antitumor activity of derivative **31** against HepG2 ( $IC_{50} = 4.79 \mu M$ ) and NCI-H460 ( $IC_{50} = 19.0 \mu M$ ) tumor cell lines was better than that of aloe-emodin, which may be due to the increase in the number of hydroxyl groups and oxygen atoms of fatty acid esters. These groups and atoms increase solubility in water through hydrogen bonds and increase cell communication. Furthermore, Huang et al. (2017) synthesized the phospholipid amino acid alizarin and conducted an *in vitro* study on its inhibitory effect against tumor cell proliferation. All newly synthesized derivatives showed high cytotoxicity compared with alizarin and low cytotoxicity against the human normal liver HL-7702 cell line. Among them, compound **32** had the strongest killing effect on SK-OV-3 cells, with  $IC_{50} = 7.1 \mu M$ , slightly lower than that of doxorubicin. The anticancer activity of this compound depended on the apoptotic death of cancer cells by regulating members of the Bcl-2 family and arrest of the SK-OV-3 cell cycle in the G2 phase. Furthermore, Zhang T. J. et al. (2018) designed and synthesized a series of N-(9,10-anthraquinone-2-carbonyl) amino acid derivatives as novel xanthine oxidase inhibitors by mimicking the compound febuxostat. Among them, *L*-phenylalanine derivative **33** ( $IC_{50} = 3.0 \mu M$ ) and *D*-phenylalanine derivative **34** ( $IC_{50} = 2.9 \mu M$ ) demonstrated the

strongest effect, and both were better than allopurinol ( $IC_{50} = 8.1 \mu M$ ). Compared with the *L*-enantiomer, *D*-amino acid derivatives have the same or higher effect (**Figure 4**).

### Flavonoids

The basic nucleus of flavonoids is 2-phenylchromone. Flavonoids are widespread in nature and high in quantity in some plants and berries. They can be divided into flavones, isoflavones, chalcones, and other flavonoids according to their structure. These compounds, similar to the above-mentioned anthraquinones, have low solubility due to their long conjugated structures.

#### Flavones

Song X. et al. (2014) prepared a series of chrysin-like amino acid derivatives and measured their antiproliferative activities in gastric cancer MGC-803 cells. They found that compound **35** ( $IC_{50} = 3.8 \mu M$ ) had the strongest inhibitory effect on the growth of MGC-803 cells. This compound induced apoptosis of MGC-803 cells in a dose-dependent manner, increasing Bax and reducing Bcl-xl protein expressions. Baicalein, a natural flavonoid isolated from *Scutellaria baicalensis* Georgi (Lamiaceae), has been shown to have multiple biological activities. However, this flavonoid has poor solubility and low bioavailability, which limits its clinical application. Li et al. (2013) prepared baicalein amino acid derivatives and tested their *in vitro* cytotoxic activities. Compounds **36** ( $IC_{50} = 9.6 \mu M$ ) and **37** ( $IC_{50} = 13.5 \mu M$ ) showed significant increases in cytotoxicity compared with baicalein ( $IC_{50} = 40.2 \mu M$ ) in HepG2 cells (**Figure 5**).

Furthermore, Kim et al. (2014) prepared quercetin–amino acid derivatives and evaluated their MDR-modulatory effects. A quercetin–glutamic acid derivative **38**, with  $IC_{50}$  values of  $0.8\text{--}0.9 \mu M$ , was as effective as verapamil in reversing MDR and sensitizing MDR MES-SA/Dx5 cells to various anticancer drugs. The MDR reversal activity of this derivative is due to its hydrolyzable property. Additionally, there is evidence that the intact quercetin–glutamic acid derivative has stronger MDR-reversal activity than that of quercetin. Kim et al. (2017) synthesized quercetin derivatives with a glutamic acid attached at the 7-O position via a non-hydrolyzable linker. Derivative **39** showed significantly higher activities than those of quercetin. Compared with that of quercetin (1.9-folds), the structurally modified quercetin derivative (22.3-folds) with a non-cleavable linker showed significantly improved MDR-reversal activities. However, the quercetin derivatives were not as effective as verapamil in Pgp inhibition, thereby reversing MDR (**Figure 5**).

Furthermore, the natural product simocyclinone D8 (SD8) inhibits DNA gyrase via a unique mechanism. Verghese et al. (2013) synthesized flavone-based analogs inspired by the complex compound SD8. However, these analogs do not act as catalytic inhibitors, as SD8 does. Analogs **40** ( $IC_{50} = 48.6 \mu M$ ) and **41** ( $IC_{50} = 84.7 \mu M$ ) were determined to be DNA intercalators and topoisomerase poisons.

Tricin has demonstrated diverse biological activities, including anti-inflammatory (Moscatelli et al., 2006) and anticancer (Jeong et al., 2007) activities. To improve its bioavailability and oral availability, Ninomiya and his team

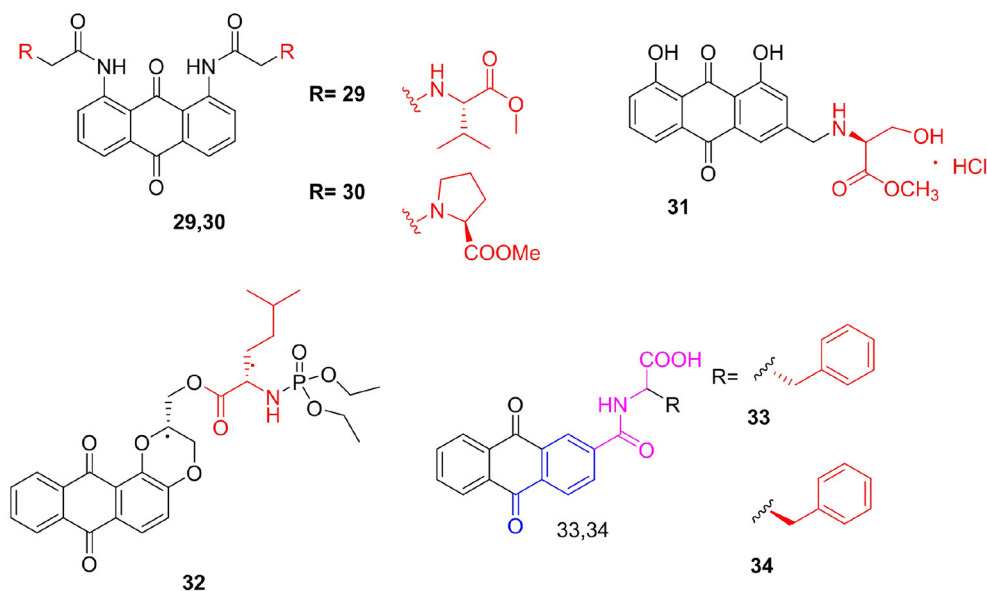


FIGURE 4 | Anthraquinones amino acid derivatives.

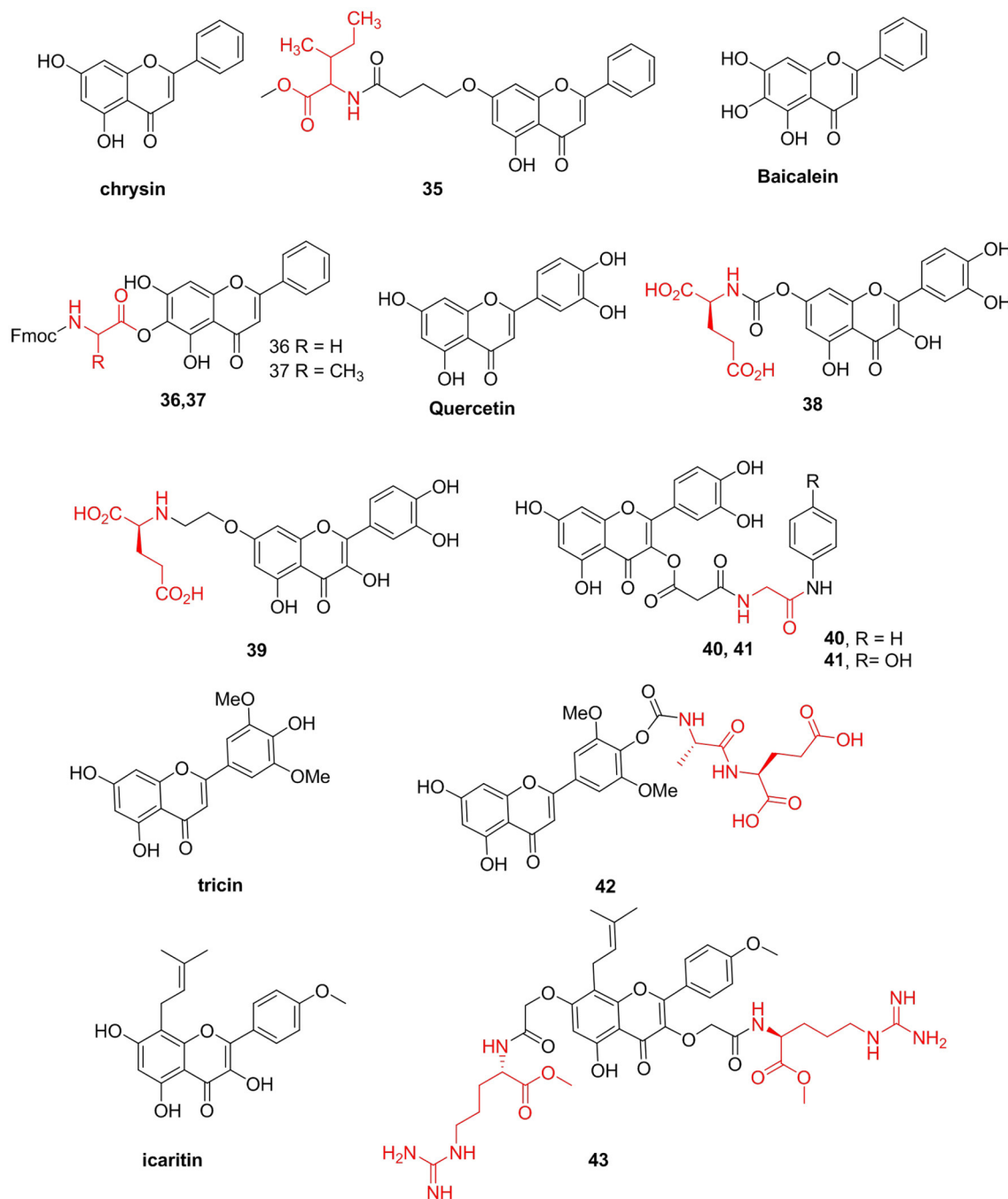
prepared triclin-amino acid derivatives as prodrugs and investigated their cell permeability, stability *in vitro*, and oral availability *in vivo*. Among the prodrugs, compound **42** exhibited enhanced permeability with an excellent relative permeation rate of 6.3, stability in MDCK cells ( $t_{1/2} = 165$  min), and increased bioavailability after oral administration with the maximum concentration of triclin being 2,497 ng/mL in the 100 mg/kg group. Additionally, icaritin exhibits various pharmacological activities, including anticancer and osteoporosis treatment (Chen et al., 2012; Zhao et al., 2015). Because this prenylflavone is very safe, it would be a good lead compound for further modification to obtain potent compounds with remarkably improved antimicrobial activities and low toxicity. Thus, Lin et al. (2017) designed a series of new hemiflavonoid-based small molecules that mimic antimicrobial peptides from icaritin to fight drug-resistant gram-positive bacterial infections. They found that compound **43** containing two arginine residues showed remarkable antibacterial activity (MICs = 1.56–3.13  $\mu\text{g/mL}$ ) against gram-positive bacteria MRSA. This compound has low cytotoxicity and selectivity  $>511$ , comparable to that of several antibiotics in clinical trials. Their data showed for the first time that icaritin derivatives effectively kill bacteria. Compound **43** showed rapid bactericidal activity by destroying bacterial membranes and circumventing the development of bacterial resistance (Figure 5).

Additionally, scutellarin is a flavonoid extracted from the Compositae plant *Erigeron breviscapus*. It is mainly used for the treatment of cardiovascular and cerebrovascular diseases (Lin et al., 2007). Results of recent pharmacodynamics and pharmacokinetic studies show that the actual form of absorption and pharmacodynamics of scutellarein in the body after oral administration is the compound itself. However, scutellarin aglycone still has defects such as low absolute bioavailability

(7% in rats) and difficulty in intestinal absorption (Chen X. et al., 2006). Thus, Fu et al. (2011) synthesized *L*-amino acid ester derivatives of scutellarin aglycone and found that the water solubility levels of derivatives **44** and **45** were 1,796 and 4,100  $\mu\text{g/mL}$ , respectively, which were much greater than that of scutellarin (14.4  $\mu\text{g/mL}$ ). Furthermore, Jiang et al. (2013) used scutellarin methyl ester and *L*-amino acid tert-butyl ester hydrochloride as raw materials to prepare a series of scutellarin methyl ester prodrugs and evaluated water solubility and the *in vitro* stability of the target compound. Their results indicated that compounds **46** (aqueous solubility = 123.1  $\mu\text{g/mL}$ ) and **47** (426.5  $\mu\text{g/mL}$ ) had better solubility and *in vitro* stability than those of scutellarin, respectively. Cha et al. (2014) also synthesized a series of 4'-*L*-amino acid derivatives of scutellarin methyl ester and reported that the designed target compounds had higher enzymatic and chemical stability and aqueous solubility. Among these compounds, compound **48** had the highest  $P_{\text{appAPtoBL}}$  value ( $1.9 \times 10^{-6}$  cm/s) and lowest ER ( $P_{\text{appBLtoAP}}/P_{\text{appAPtoBL}} = 0.56$ ) and protected PC12 cells from oxidative damage induced by  $\text{H}_2\text{O}_2$  by reducing the loss of MMP and reducing the generation of ROS induced by  $\text{H}_2\text{O}_2$  (Figure 6A).

### Isoflavones

Li et al. (2016) synthesized a series of isoflavone-7-phosphoramidate derivatives and determined their antiproliferative activity *in vitro* against the HepG2 cell line and L02 cell line. Compounds **49** ( $\text{IC}_{50} = 5.5$   $\mu\text{M}$ ) and **50** ( $\text{IC}_{50} = 6.6$   $\mu\text{M}$ ), which incorporated the methyl alanine, exhibited high inhibitory activities against the HepG2 cell line. Compound **49** can significantly induce G2/M arrest and lead to early apoptosis in HepG2 cells (Figure 6B).



**FIGURE 5** | Flavonoids amino acid derivatives.

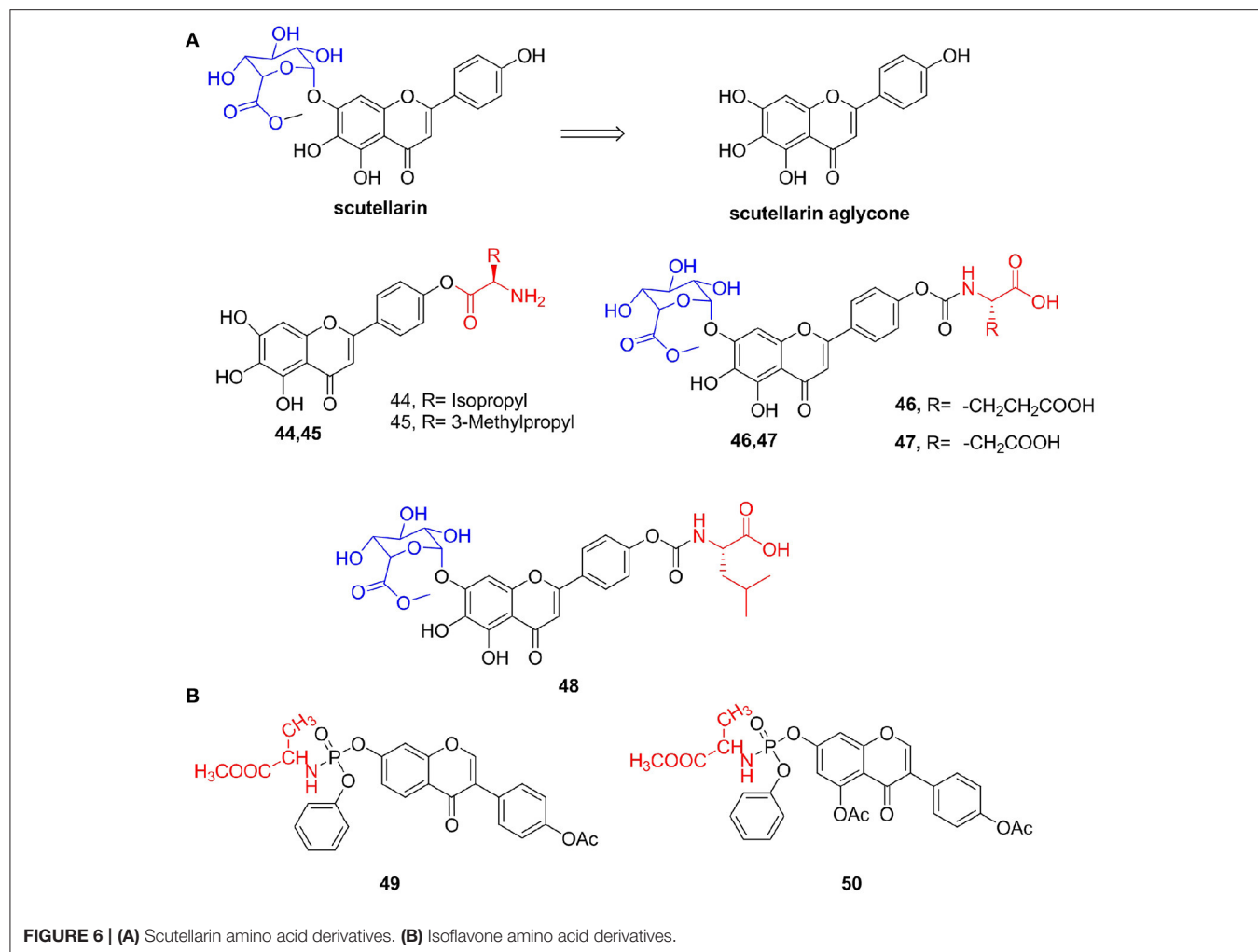
## Chalcones

Chalcones, with  $\alpha,\beta$ -unsaturated ketone structures, are derived from natural compounds and chemical synthesis, possessing a variety of biological properties (Zhuang et al., 2017). Jin et al. (2012) synthesized a chalcone derivative containing *L*-phenylalanine and evaluated its antibacterial activity. Among which compound **51** (MIC = 2 mg/mL) exhibited the best antimicrobial activity against *Staphylococcus aureus* RN4220.

This compound showed the most potent activity against all the MDR clinical isolates tested. Based on compound **51**, Song M. X. et al. (2014) changed the types of amino acids and synthesized another series of derivatives and found that, among all, leucine (**52**, MIC = 1 mg/mL) was the most potent against two methicillin-resistant *S. aureus* (**Figure 7A**).

1,3-Diphenylpropanones is a positive allosteric modulator of  $\alpha 7$  nAChRs, which have good analgesic activity but poor

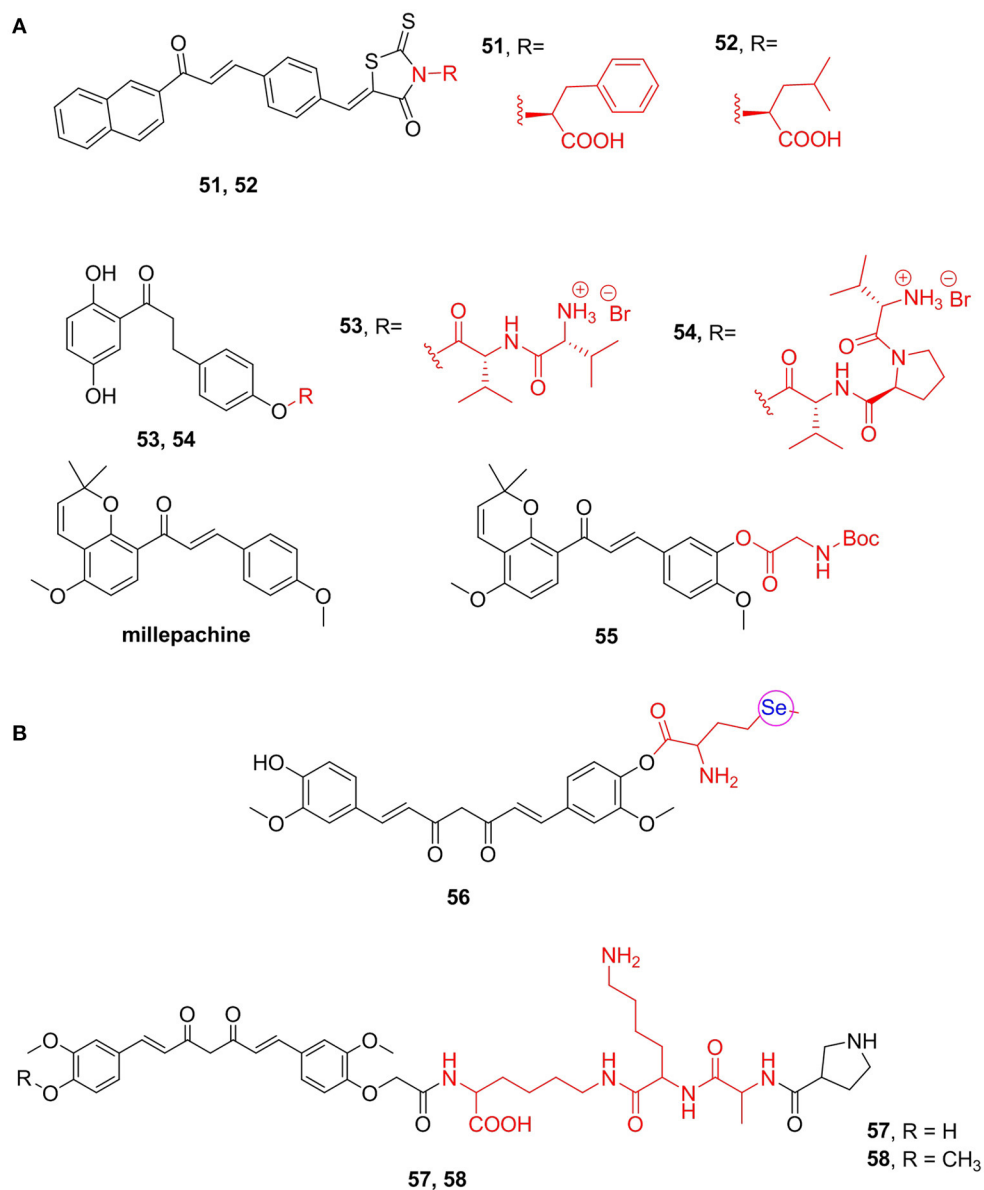




pharmacokinetics. To improve its biological activity *in vivo*, Criado et al. (2016) have prepared amino acid and peptide derivatives as prodrugs of these modulators. Compounds **53** (inhibition of  $\alpha 7$  nAChR currents = 14.7%) and **54** (inhibition of  $\alpha 7$  nAChR currents = 24.7), prodrugs of 1,3-diphenylpropanones, showed obviously antinociceptive activity *in vivo*. Compound **54** shows roughly the same analgesic effect as the parent compound but long-lasting effects (**Figure 7A**).

Furthermore, millepachine is a natural pyranochalcone isolated from *Millettia pachycarpa* (Zhou Z. Y. et al., 2019). This compound has a benzopyran structure, which has good cell membrane permeability (Nicolaou et al., 2000); however, its water solubility is not optimistic. Thus, Wu et al. (2015) prepared a series of amino acid derivatives of millepachine and tested their solubility and antitumor activity. They found that compound **55**, a glycine derivative, with an  $\text{IC}_{50}$  value for MDAMB-231 cells of  $0.13 \mu\text{M}$ , showed the best potency and long-term inhibition of cell viability and induced apoptosis. The solubility of compound **55** in human plasma is  $2.98 \text{ mg/mL}$ , which is significantly stronger than the lead compound millepachine ( $0.15 \text{ mg/mL}$ ) (**Figure 7A**).

Additionally, curcumin has been reported to have a variety of pharmacological activities, such as anticancer, antioxidant, and anti-inflammatory activities. However, low bioavailability, poor water solubility, and poor pharmacokinetics hinder the clinical application of curcumin (Kotha and Luthria, 2019). Thus, Cao et al. (2014) synthesized curcumin derivatives with enhanced bioactivity and reported that compounds containing one selenomethionine molecule (**56**) attached to the hydroxy group of curcuminoids showed high antimicrobial activity. Moreover, they exhibited strong DPPH scavenging ability, which was about 10 times stronger than that of curcumin and has good antiproliferative activity on a variety of cancer cells, with an  $\text{IC}_{50}$  value of  $<1 \mu\text{M}$ . Furthermore, Bi et al. (2016) got a new class of derivatives that can associate apoptosis induced by ischemia/reperfusion injury and reverse mitochondrial oxidative stress. The results suggest that selected curcumin polypeptide analogs **57** ( $\text{EC}_{50/\text{OH}} = 25.6 \mu\text{M}$ ) and **58** ( $\text{EC}_{50/\text{OH}} = 31.4 \mu\text{M}$ ) exhibited good hydroxyl radical scavenging activity and can facilitate the recovery of mitochondrial reticular networks and cell rescue (**Figure 7B**).



**FIGURE 7 | (A)** Chalcones amino acid derivatives. **(B)** Curcumin amino acid derivatives.

### Other Flavonoids

Gambogic acid (GA), the most important compound of *Garcinia*, has been reported to be a hopeful antitumor agent. Chemical modification of GA C-37 position by introducing hydrophilic amines can increase activity (Li et al., 2012). Notably, the antiproliferative activity of compound **59** was almost 2-fold more active than that of GA against HCT 116 cell lines with an IC<sub>50</sub> value of 1.35 μM (Figure 8A).

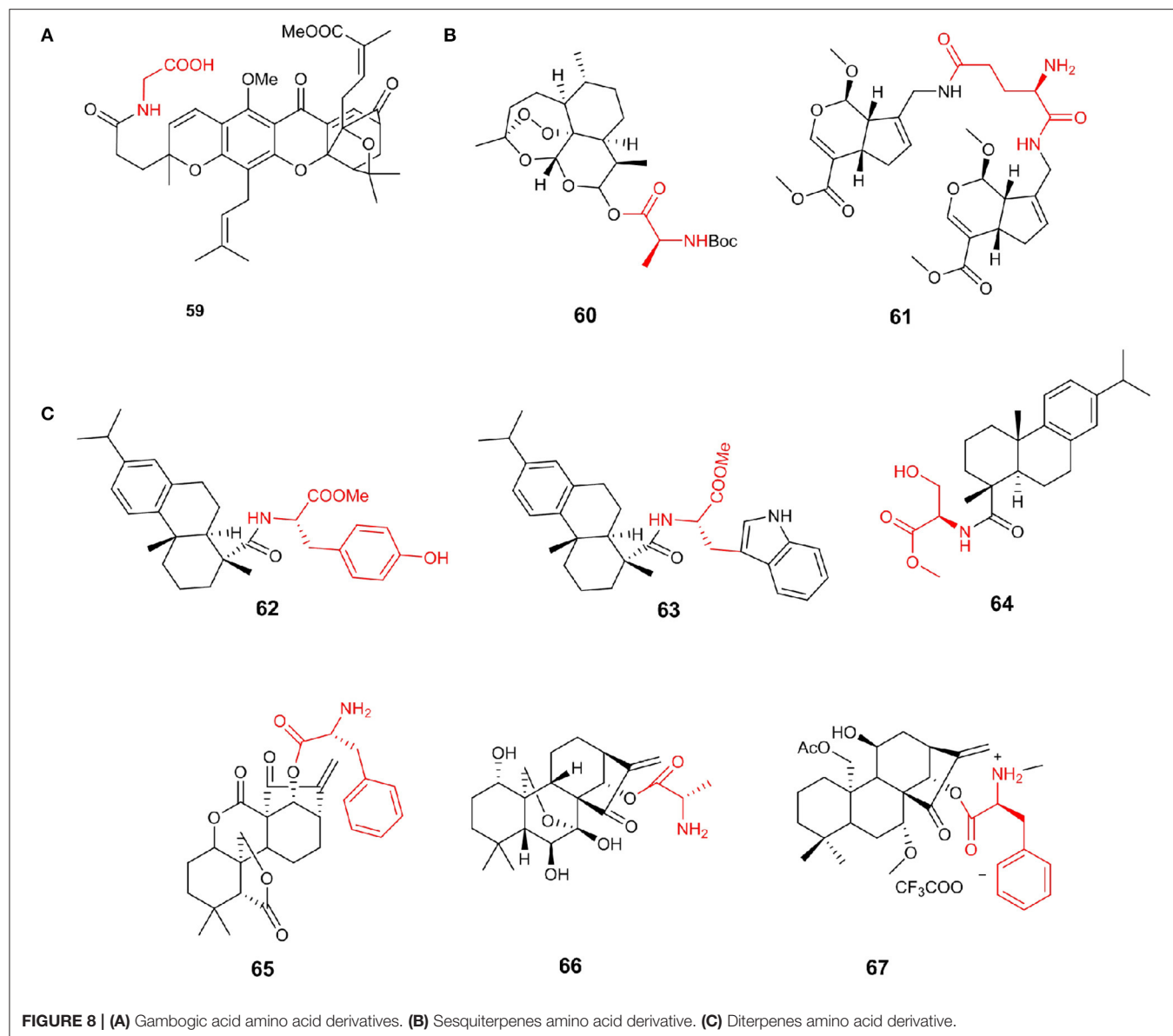
### Terpenoids

Terpenoids are the general term for polymers and their derivatives of isoprene or isopentane structural units, with general structural formula (C<sub>5</sub>H<sub>8</sub>)<sub>n</sub> and a very wide range of

biological activities. There are many natural products from terpenes used in clinical applications, such as the antimalarial drug artemisinin (Sowunmi et al., 2016), the antitumor drug paclitaxel (Shi et al., 2018), and the anti-infective drug andrographolide (Wen et al., 2015).

### Sesquiterpenes

It has been reported that artemisinin has anti-Toxoplasma activity; however, the activity is not strong (Sarciron et al., 2000). Deng et al. (2020) discovered that compound **60** (selectivity index = 6.44), showed the most effective anti-*T. gondii* activity and low cytotoxicity. Furthermore, compound **60** had better growth inhibitory activity on *T. gondii* than positive control



drug and remarkably reduced the number of tachyzoites *in vivo* ( $P < 0.01$ ). The mouse *Toxoplasma* infection model proved the effectiveness of compound **60** anti-*T. gondii* property *in vivo* and its role in the reduction of liver damage caused by *T. gondii*. Additionally, genipin is the product of geniposide hydrolysis by  $\beta$ -glucosidase and has anticancer activity. Fang et al. (2018) reported genipin analogs obtained by a biomimetic synthesis strategy and evaluated their cytotoxic activity. Compound **61** was reported to have a significantly stronger inhibitory effect on tumor cell proliferation than that of cisplatin, with  $IC_{50}$  values of 0.43–1.18  $\mu$ M (Figure 8B).

### Diterpenes

Abietic and dehydroabietic acids are a class of diterpenoids that show moderate cytotoxicity. Ukiya et al. (2013) prepared amino acid conjugated derivatives from these acids to evaluate

their cytotoxicities in a variety of cells. Among the derivatives, compound **62** showed potential cytotoxic activities against multiple cancer cell lines with  $IC_{50}$  values of 2.3–8.1  $\mu$ M, and the cytotoxic activity of leukemia cells has the highest selectivity. It is estimated that more than 65% of all bacterial infections resistant to chemotherapy are related to biofilms (Lebeaux et al., 2013). Dehydroabietic acid was reported to prevent the formation of *S. aureus* biofilms in the low micromolar range and only 2–4-fold higher concentrations to significantly reduce the viability and biomass of existing *S. aureus* biofilms (Fallarero et al., 2013). The combination of dehydroabietic acid scaffolds and different amino acids can simultaneously target planktonic bacteria and biofilm bacteria in *S. aureus* strains and has stronger anti-biofilm agents than conventional antibiotics (Manner et al., 2015). Compound **63** was the most potent abietane-type anti-biofilm agent and exhibits strong activity on pre-formed biofilms at a concentration

that is threefold higher than the concentration required to inhibit biofilm formation. Abietic acid and dehydroabietic acid, in a shortage of antibiotics and antimicrobial resistance problems looming against the growing respect, showing potential value. Helfenstein et al. (2017) discovered a dehydroabietic acid derivative **64** containing a serine side chain; its MIC<sub>90</sub> against *Staphylococcus aureus* ATCC 25923 was 60 µg/mL, and the IC<sub>50</sub> value on Balb/c 3T3L cells was 45 µg/mL (Figure 8C).

Oridonin was isolated from isodon with a special structural scaffold and has excellent bioactivity, including anticancer activity (Wang L. et al., 2012). However, poor solubility and moderate bioavailability of oridonin hindered its clinical research on cancer treatment. Many researchers have modified the structure of oridonin, hoping to obtain good anticancer drugs, including the candidate drug HAO472, which is undergoing phase I clinical trials. Hu et al. (2019) designed and synthesized a series of enmein-type diterpenoid amino acid ester derivatives according to HAO472 and tested their antiproliferative activity on various cancer cell lines and L-02 normal hepatocytes. The results show that compound **65** (IC<sub>50/Bel-7402</sub> = 0.07 µM) has the strongest cytotoxicity against human liver cancer Bel-7402 and chronic myeloid leukemia K562 cells at the submicromolar level more potent than *L*-alanine-(14-oridonin) ester **66** (IC<sub>50/Bel-7402</sub> = 9.56 µM). Simultaneously, it shows low cytotoxicity (IC<sub>50</sub> for L02 cells > 50 µM) to normal cells and high selectivity. At the same time, Ke et al. synthesized a series of Flexicaulin A amino acid derivatives and evaluated their antiproliferative activity against four kinds of cancer cells. Compared with Flexicaulin A, the anticancer activity and solubility of most derivatives were remarkably improved. Compound **67** showed the most excellent activity, and its IC<sub>50</sub> value for TE-1 cells was 0.75 µM. It could inhibit the proliferation of cancer cells and the formation of cell colonies and increase the level of ROS in TE1 cells (Figure 8C).

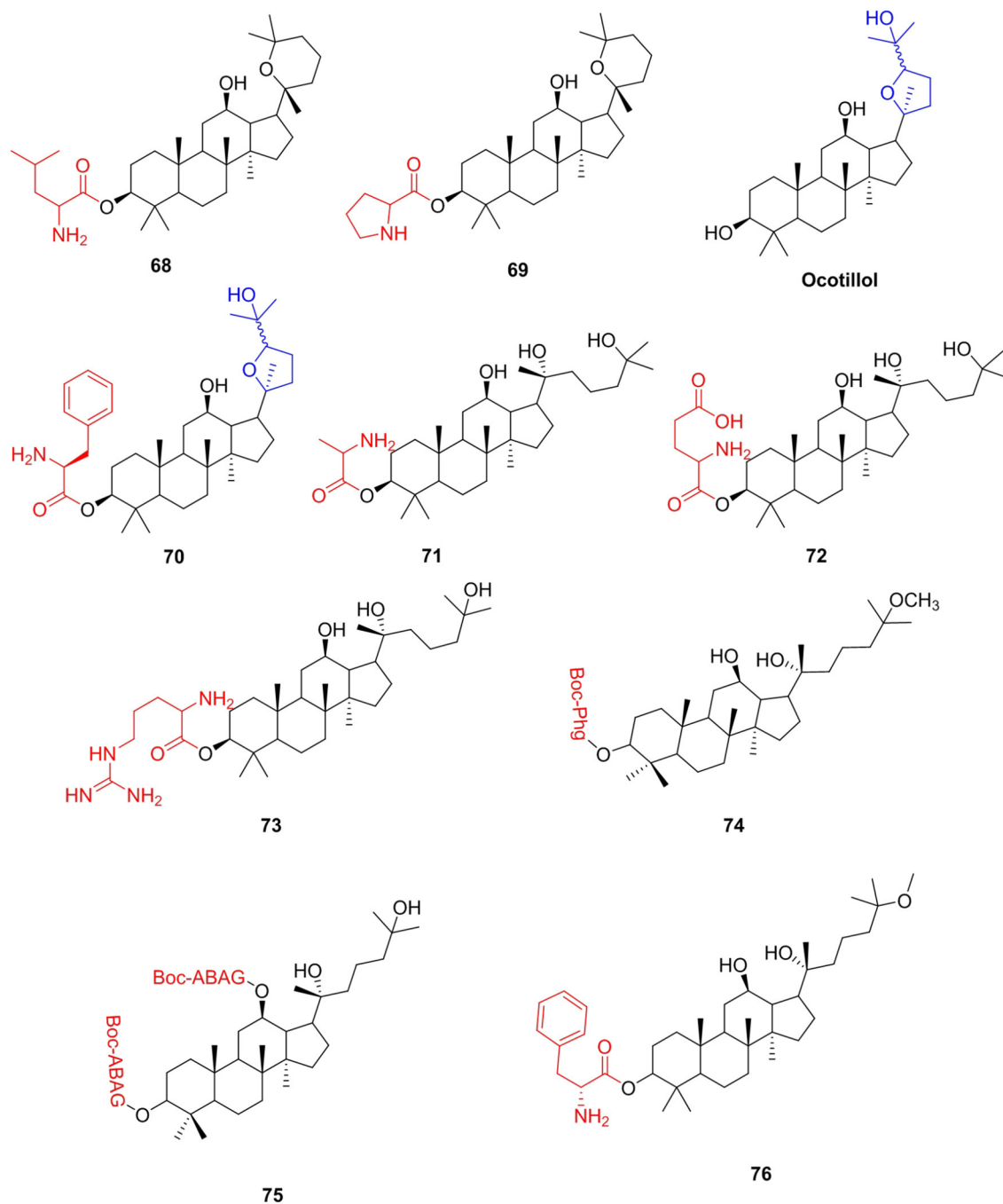
### Triterpenoids

*Panax ginseng* is widely used as a healthy functional food due to its obvious health benefits. Ginsenosides are the main bioactive constituents of *Panax ginseng*. Panaxadiol (PD), protopanaxadiol (PPD), 25-methoxyprotopanaxadiol (AD1), and 25-hydroxyprotopanaxadiol (AD2) are obtained by hydrolysis of ginsenosides and have a variety of biological activities, including anticancer (Zhang et al., 2007; Salvador et al., 2017), antiliver fibrosis (Han et al., 2018), and antibacterial (Amoussa et al., 2016) activities. Many researchers have introduced amino acids into ginsenosides and obtained ginsenoside amino acid derivatives with enhanced activity. Liu et al. (2011) synthesized a series of PD amino acid derivatives by modifying the 3-hydroxyl group of panaxadiol and evaluated their activities against a panel of human tumor cell lines. All amino acid derivatives showed stronger antiproliferative activities than PD on the growth of different cancer cells *in vitro*. From the results of the antitumor tests in HepG2, compound **68** (IC<sub>50</sub>, 5.03 µM) exhibited 7.5 times the strongest activities than that of PD (IC<sub>50</sub>, 37.91 µM). For the A549 cell line, compound **69** (IC<sub>50</sub>, 7.63 µM) showed the strongest activity, which was 5.6 times stronger than PD (43.13 µM). Ocotillol enantiopure

and its derivatives showed good antibacterial activity anti-gram-positive bacteria (Bi et al., 2015; Ren et al., 2019), and they can be obtained by the oxidation of PPD with *m*-CPBA. Wang et al. (2018) introduced free amino groups at the C-3 position to confirm whether the group can enhance the antibacterial activity. The results showed that compound **70** showed excellent antibacterial activity with MIC of 2 µg/mL against MRSA USA300 and 4 µg/mL against *B. subtilis*. Derivatives of AD2 were measured on six distinct human tumor cell lines (Wang et al., 2013). Compound **71** exhibited the best antitumor activity with IC<sub>50</sub> values ranging from 2.77 to 6.83 µM for six cell lines compared to the parent AD2. Qu et al. (2015) continued to synthesize AD-2 amino acid derivatives and evaluated the *in vitro* antitumor activities of five human tumor cell lines. Compounds **72** (IC<sub>50</sub> = 4.2–9.9 µM) and **73** (IC<sub>50</sub> = 4.2–7.1 µM) displayed the most potent anticancer activities. The two derivatives could remarkably induce the apoptosis of human prostatic carcinoma DU145 cells and have low toxicity in IOSE144 cells and HOSEpC cells. Yuan et al. (2018) modified AD1 and AD2 with non-protein amino acids and obtained two series of derivatives of AD1 and AD2. Compounds **74** and **75** exhibited strong biological activity against HCT-116 and BGC-823 cell lines, with IC<sub>50</sub> values in the range of 4.76–9.03 µM, and exhibited higher cytotoxic activity than AD-2 and AD-1. The relative plasma stability of esters is closely related to the hydrolytic enzymes in plasma. It is reported that the increase in steric hindrance near the hydrolyzable group will reduce the affinity between the compound and the hydrolase, thereby improving the plasma stability of the compound (Borthwick et al., 2003; Carroux et al., 2013). Therefore, among these ginsenoside compounds, the plasma stability of compound **70** should be the strongest.

Research has demonstrated that AD-1 could regulate c-FLIP pathway-mediated activation of NF-κB, thereby showing liver protection and reversal of activated HSC (Wu et al., 2011). At the same time, AD-1 improved hepatic injury, fibrosis, and inflammation induced by thioacetamide in C57BL/6 mice (Han et al., 2018). The present study aimed to introduce amino acids to AD-1 and obtained safer, more effective, and developable derivatives, which could be used to prevent or improve liver fibrosis, and simultaneously provide amino acid dietary supplements. Conjugate **76** has a significant inhibitory effect on cell proliferation in activated t-HSC/Cl-6 cells (IC<sub>50</sub> = 3.8 µM) and appeared to be non-toxic to L02 cells (Figure 9).

23-Hydroxybetulinic acid existed in the root of *Pulsatilla chinensis*, which has anti-HIV and antitumor activities similar to betulinic acid and botulin (Bi et al., 2007; Zhu et al., 2009). Unfortunately, both betulinic acid and botulin are very poorly soluble in aqueous buffers; thus, their bioavailability and biodistribution are inadequate in terms of medical applications (Drag-Zalesinska et al., 2009). Suitable modification at the right positions of natural products may yield analogs with significantly improved potency. A set of 17-carboxylic acid-modified 23-hydroxybetulinic acid derivatives that displayed slightly improved antiproliferative potencies were reported previously (Bi et al., 2007). To increase the anticancer activity and structural diversity of 23-hydroxybetulinic acid, Lan et al. (2011) prepared a series of new compounds and screened these



**FIGURE 9** | Ginsenosides amino acid derivatives.

compounds for *in vitro* antiproliferative activity against various cancer cell lines. The amino acid derivatives **77** and **78** with  $IC_{50} < 10 \mu M$  in all tested cell lines were considered to be the most hopeful compounds.

Betulinic acid exhibits anticancer and anti-HIV biological activities, and its derivative Bevirimat (**79**) is undergoing phase II clinical trials against HIV (Smith et al., 2007). Bevirimat exhibited

promising pharmacokinetic profiles in clinical trials, but its effectuality was compromised by the high baseline resistance of HIV-1 variants with polymorphism. A series of betulinic acid (BA) derivatives were measured for their inhibition of the chymotrypsin-like activity of the 20S proteasome (Qian et al., 2011). Compounds **80** and **81**, comprising leucine, illustrated the best proteasome inhibition activity with  $IC_{50}$  values of

1.56 and 1.80  $\mu\text{M}$ , respectively, which are 3–4-fold more potent than the proteasome inhibition controls LLM-F and lactacystin. To determine whether the viruses with bevirimat-resistant polymorphism also altered their sensitivity to betulinic acid derivatives that inhibit HIV-1 entry, a series of new betulinic acid inhibitors were tested for their activities against HIV-1 NL4-3 and NL4-3 variants resistant to bevirimat (Dang et al., 2012). The results show that the bevirimat-resistant viruses were ~5–10-fold more sensitive to three new glycine ester derivatives **82**, **83**, and **84**, and showed potent anti-HIV activity with  $\text{EC}_{50}$  ranging from 0.04 to 0.12  $\mu\text{M}$ . In contrast, wild-type NL4-3 and bevirimat-resistant variants were equally sensitive to the HIV-1 RT inhibitor AZT. Compound A43D exhibited the most potent anti-HIV-1 entry activity (Huang et al., 2006). Compared with A43D ( $\text{CL}_{\text{int}} = 0.37$  ml/min/mg), these three new compounds **82** ( $\text{CL}_{\text{int}} = 0.23$  ml/min/mg), **83** ( $\text{CL}_{\text{int}} = 0.17$  ml/min/mg), and **84** ( $\text{CL}_{\text{int}} = 0.22$  ml/min/mg) showed significantly improved microsomal stability (Figure 10).

The new amino acid derivatives of betulinic acid and betulin were synthesized, and their anticancer activity was evaluated (Drag-Zalesinska et al., 2015). In particular, compounds containing a lysine side chain (**85**,  $\text{IC}_{50} = 7$   $\mu\text{M}$ ) and ornithine (**86**,  $\text{IC}_{50} = 10$   $\mu\text{M}$ ) are stronger than the parent compounds, and the biggest advantage was that new compounds are safe for normal human keratinocytes. In addition, the literature reports that the introduction of amino acids into triterpenes could enhance selective cytotoxicity and water solubility (Schwarz et al., 2014). Based on the above, researchers attempted the synthesis of several ligustrazine-betulinic acid (TBA) amino acid derivatives BAX by introducing several amino acids to the C3 of TBA to enhance its antitumor activities and tumor targeting. These compounds were screened for selective cytotoxic activity against five cancer cell lines and the non-malignant MDCK cell line. Most of the tested TBA-amino acid derivatives showed better antiproliferative activity against all tumor cell lines than TBA. Among them, compound **87** showed the best cytotoxic activity on tumor cell lines ( $\text{IC}_{50} = 2.31$   $\mu\text{M}$ ), which was 2-fold higher than that of the positive drug cisplatin (DDP), while it showed lower cytotoxicity in MDCK cells than DDP cells (Figure 10).

Glycyrrhetic acid (GA) is the main component of licorice root (Baltina, 2003; Schwarz and Csuk, 2010); its antitumor activity is low compared with other members of the triterpenoid family (Tatsuzaki et al., 2007). GA is easily inexpensive and shows apoptotic effects on tumor cells. These facts make GA and its derivatives the focus of our scientific interest. In addition, GA demonstrated only poor selectivity (Schwarz et al., 2010). Here, we tried to enhance the poor cytotoxicity of GA via simple derivatization. Csuk et al. (2011a) make use of various glutamyl and aspartyl substituents for the synthesis of C esters of GA methyl ester. Compound **88** ( $\text{IC}_{50} = 1.27$ – $2.33$   $\mu\text{M}$ ) demonstrated 67-fold higher cytotoxicity and an up to 140-fold better selectivity toward tumor cells than that of GA. To improve the cytotoxicity of GA, Csuk et al. (2011b) synthesized new derivatives of GA, differing in structure and lipophilicity. The most active compound **89**, a benzyl glycyrrhizinate with an extra 3-N-(3-aminopropyl)glycyl substituent, showed an  $\text{IC}_{50}$  between 1.96 and 5.14  $\mu\text{M}$  for five human cancer cell lines

and triggers apoptosis in 80% of the cells. Use various amino acids, including methionine (**90**), threonine (**91**), valine (**92**), and phenylalanine (**93**), to modify glycyrrhetic acid to obtain more effective derivatives (Wang J. et al., 2012). These compounds could protect the growth of *E. coli*, *Bacillus subtilis*, and yeast against high concentrations of DMF. To improve the cytotoxicity of GA and explore the effect of the bonding mode on antitumor activity, Zhou F. et al. (2019) synthesized a series of amino acid derivatives and evaluated their antitumor activity. All the deprotected (without Boc group) derivatives displayed much stronger cytotoxic activity than GA, and surprisingly enough, all the GA-NH<sub>2</sub> series of the compounds were more effective than GA-OH series against different tumor cells. Among them, compound **94** showed better antitumor activity against A549 ( $\text{IC}_{50} = 2$   $\mu\text{M}$ ) than cisplatin ( $\text{IC}_{50} = 9$   $\mu\text{M}$ ). Further studies indicated that compound **94** could induce A549 apoptosis by nuclei fragmentation and prevented the transition from S to G<sub>2</sub> phase (Figure 11).

In addition to those listed above, other pentacyclic triterpene compounds often react with amino acids to improve their unfavorable properties. Ursolic acid is abundant in the plant kingdom. Ursolic acid and its derivatives have been reported to have interesting bioactivities (Choi et al., 2000; Chattopadhyay et al., 2002). Shao et al. (2011) synthesized some ursolic acid derivatives and determined their cytotoxic activity on various cancer cells. Among them, the derivative **95** introduced into serine showed greater anti-A549 cell activity than ursolic acid, with an  $\text{IC}_{50}$  of 35.3  $\mu\text{M}$ . Fu H. J. et al. (2014) prepared a series of new ursolic acid derivatives under the guidance of virtual screening and used RBL2H3 cells and ovariectomized (OVX) rats for biological evaluation. Compound **96**, which contains a glycine structure, showed potent inhibitory activity on serotonin biosynthesis, which inhibited the protein and mRNA expression of Tph-1 and lowered serotonin contents in the serum and gut without influencing brain serotonin. Due to their strong hemolytic activity, the clinical development of Pulsatilla saponins A (PSA) and D (PSD) is limited ( $\text{HD}_{50} = 10$   $\mu\text{M}$ ) (Wang and Fang, 2009). To solve the problem, Chen et al. (2015) prepared C-28 position derivatives of PSA/PSD and evaluated the hemolytic activity and cytotoxicity of these compounds. Compared with PSA, the acute toxicity of compound **97** to mice is greatly reduced. At the same time, compound **97** ( $\text{HD}_{50} > 500$   $\mu\text{M}$ ) is a potential antitumor agent, thereby preventing hemolysis (Figure 12).

Asiatic acid, an active pentacyclic triterpenoid found in *Centella asiatica*, can be easily prepared by the hydrolysis of asiaticoside. Asiatic acid also has many biological effects (Mook-Jung et al., 1999; Park et al., 2005), but the efficacy of the original asiatic acid is relatively poor. Jing et al. (2015) synthesized the derivatives of Asiatic acid and evaluated their biological activities. The derivative **98**, containing the proline structure, had markedly better antitumor activity ( $\text{IC}_{50} < 10$   $\mu\text{M}$ ) than both Asiatic acid and other derivatives, with stability similar to that of its parent compound Asiatic acid. Celastrol has many important pharmacological activities, including anticancer (Zheng et al., 2014), anti-inflammatory (Jia et al., 2015), and resistance to neurodegenerative disease activity (Paris et al.,

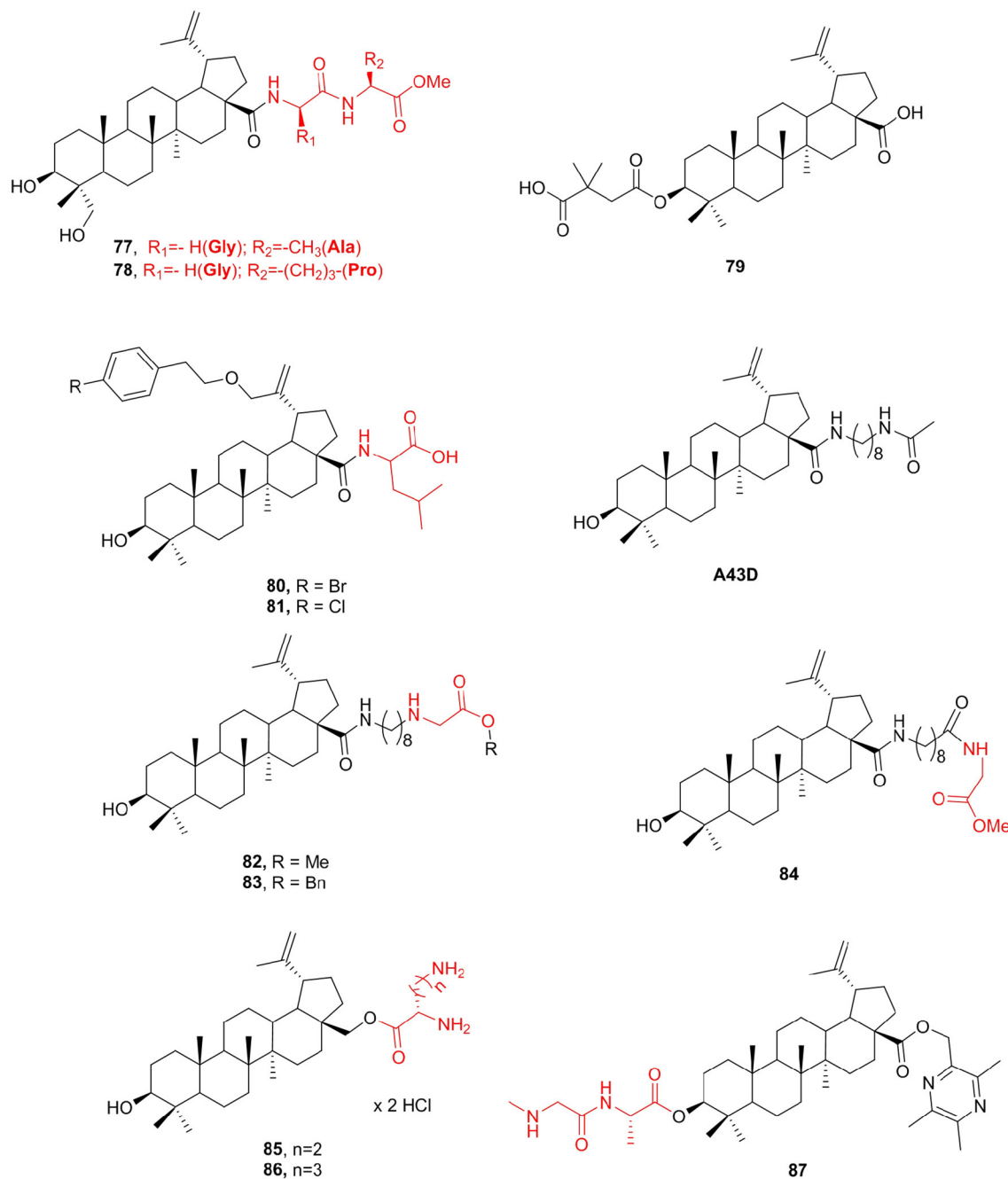
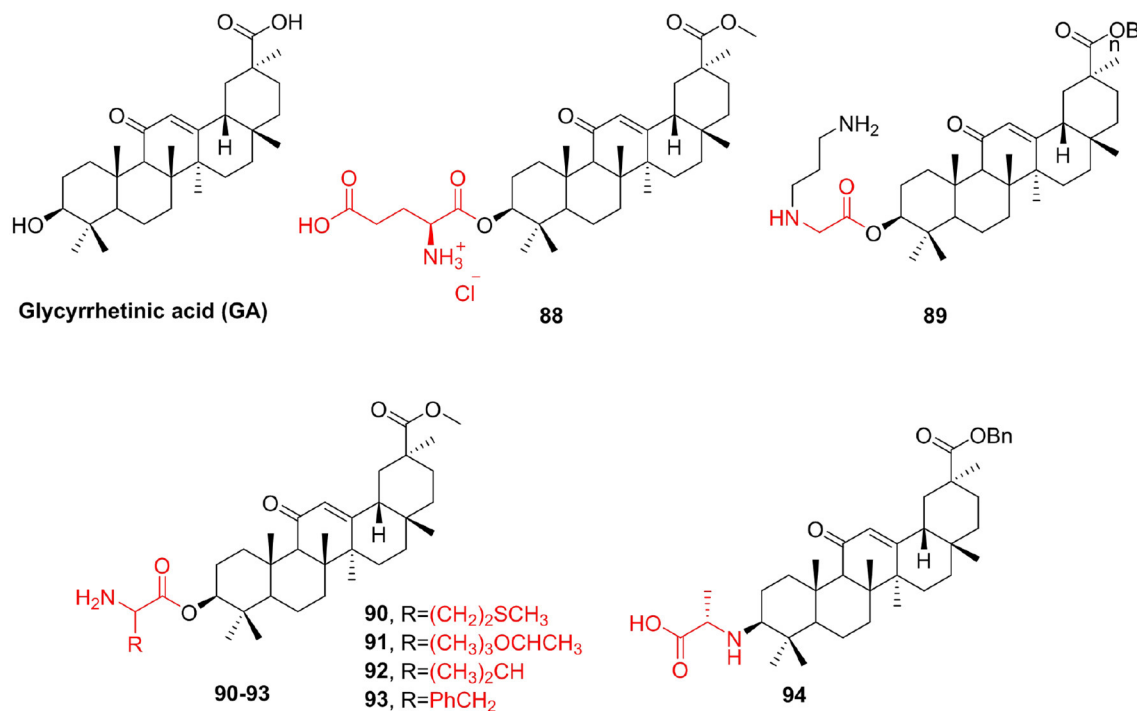


FIGURE 10 | Betulinic acid derivatives.

2010), but it has several drawbacks such as poor water solubility, high toxicity, and poor stability, which restrict its clinical application. Zhang et al. (2017) designed and synthesized new celastrol derivatives and evaluated their anticancer activities. In the series of amino acid derivatives, compound **99** showed the highest anticancer activity against AGS cell lines ( $\text{IC}_{50} = 0.44 \mu\text{M}$ ) and showed better anticancer activity against HCT-116, BEL-7402, and HepG-2 cell lines than the other compounds.

Eight novel celastrol amino acid derivatives were synthesized, which displayed strong cytotoxic activities against A549, HeLa, and HepG-2 cell lines (Pang et al., 2018). In particular, the cytotoxicities of **100** and **101** against HeLa and A549 cells with  $\text{IC}_{50}$  values ranging from 0.109 to 0.371  $\mu\text{M}$ , the effect of cytotoxic activity was remarkably stronger than that of celastrol and cisplatin. The most potent compound **101** showed 10- and 55-fold better antiproliferative activity of anti-A549 cell than



**FIGURE 11** | Glycyrrhetic acid derivatives.

celastrol and cisplatin, respectively. Compounds 100 and 101 can induce apoptosis in A549 cells at the concentration of 0.2  $\mu\text{M}$  (Figure 12).

## Alkaloids

Alkaloids are a class of nitrogen-containing natural compounds with physiological effects. Most of them have complex nitrogen heterocyclic structures, and a few are non-nitrogen heterocyclic organic amines. Alkaloids are widely distributed in nature, especially in the plant kingdom, but also in the animal kingdom, such as bufotenine from toads (Kostakis and Byard, 2009) and hypoxanthine from earthworms (Huang et al., 2016). Camptothecin (CPT) is a plant anticancer drug extracted from *Camptotheca acuminata* (Pu et al., 2020), which plays an important role in clinical cancer treatment, and its derivatives are a favorite of pharmaceutical chemists. CPT mainly forms a ternary complex by interacting with DNA and topoisomerase I, blocking DNA replication, leading to cell death, and thus showing significant antitumor activity (Fan et al., 1998; Cincinelli et al., 2013). The shortcomings of CPT, such as poor solubility and large side effects, have seriously affected its clinical application (Ye et al., 2012). Many researchers have synthesized a large number of CPT derivatives, hoping to find targets with fewer side effects. 10-Hydroxycamptothecin (HCPT) is a natural CPT derivative that was approved for marketing in 1988 (Guerrant et al., 2013). Meng et al. (2014) synthesized a series of amino acid derivatives to improve the antitumor activity and reduce the side effects of irinotecan. Among them, the derivative **102** ( $\text{IC}_{50}$  for KB cell line = 1.39 nM,  $\text{LogP}$

= 0.74) of valine and HCPT not only maintained the tumor proliferation inhibitory activity equivalent to HCPT ( $\text{IC}_{50}$  for KB cell line = 1.48 nM), but also its water solubility was significantly improved compared with  $\text{LogP}$  of HCPT of 1.53 (Figure 13).

Irinotecan (**103**) is a water-soluble prodrug of the CPT derivative SN-38. However, high individual variation in efficacy, toxicity, and side effects of irinotecan preclude its clinical use (Dodds and Rivory, 1999). Novel derivatives of SN-38 were synthesized by conjugating amino acids to the 10-hydroxyl group via a carbamate linkage (Zhou et al., 2014). All prodrug compounds showed much greater *in vitro* antitumor activities against SGC-7901 cells and HeLa cells than irinotecan. The most active compounds **104–107** exhibited  $\text{IC}_{50}$  values that were 1,000 times lower against HeLa cells and 30 times lower against SGC-7901 cells than that of irinotecan, and the inhibitory activities of these prodrugs against AchE were remarkably reduced, with  $\text{IC}_{50}$  values more than 6.8 times better than that of irinotecan. In addition, compound **108** showed the same level of tumor growth inhibitory activity (Inhibitory Rate = 51%) as irinotecan (Inhibitory Rate = 51%) *in vivo*. In an attempt to improve the antitumor activity of camptothecins (CPTs), novel 10-fluoro-CPT derivatives were designed, synthesized, and evaluated for cytotoxicity against various human cancer cell lines (Yang et al., 2017). Remarkably, compound **109** ( $\text{IC}_{50}$  = 99.2 nM) displayed the strongest cytotoxicity against the MDR KB-VIN cell line. Yu et al. (2012) prepared a series of CPT prodrugs that exhibit histone deacetylase (HDAC) inhibition activity based on the synergistic effect between camptothecin derivatives and HDAC



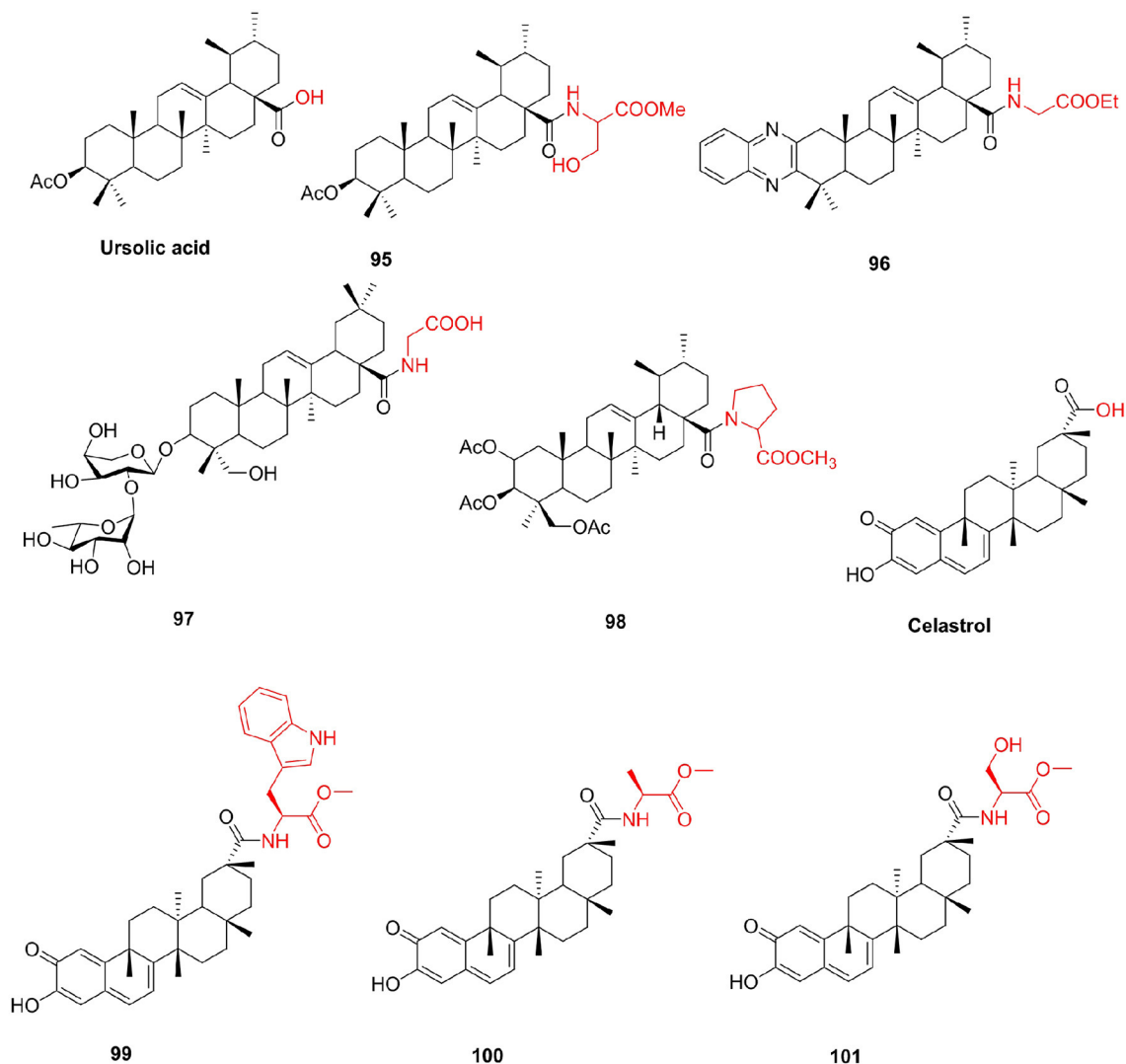


FIGURE 12 | Other triterpenoids derivatives.

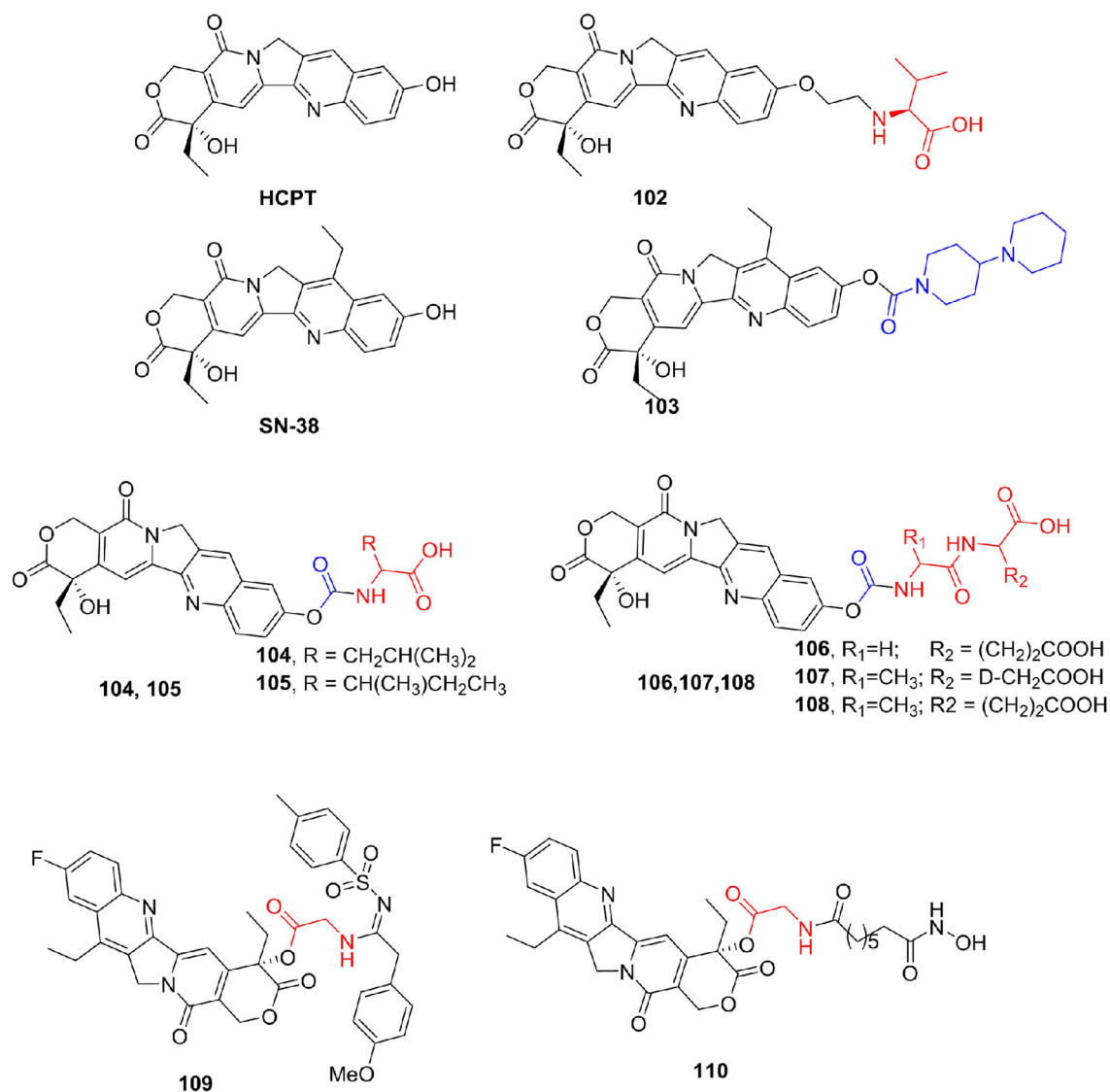
inhibitors. Compound **110** exhibited strong antiproliferative activity in A549 ( $IC_{50} = 137.7$  nM) and HCT-116 ( $IC_{50} = 30.5$  nM) cell lines (Figure 13).

Based on the reported anti-Leishmanial activity of the natural alkaloid piperine (Kapil, 1993), the combination of piperine is synthesized by hydrolyzing piperine to piperonic acid and then reacting with amino acid methyl ester (Singh et al., 2010). All the compounds showed better activity than piperine. Piperoyl-valine methyl ester (**111**) was the strongest active compound with an  $IC_{50}$  of 0.075 mM against the amastigotes.

Liguzinediol (Ligu) is a para-xylene derivative of ligustrazine, an alkaloid compound, which is a potential treatment for heart failure, but its safety is low (Liu et al., 2009). To determine whether Ligu metabolites have positive inotropic effects, Zhu et al. (2018) synthesized two amino acid-linked metabolite derivatives (**112**, **113**). Through pharmacological evaluation, Ligu's positive inotropic activity is mainly since the parent drug

and its metabolites have no adverse reactions such as arrhythmia. Through pharmacokinetics, it was found that Ligu is eliminated faster *in vivo* and has a shorter half-life. After studying the structure–activity relationship between Ligu metabolites *in vivo*, Li et al. (2017) synthesized Ligu valine ester (**114**) prodrugs and determined the solubility of the compound (224 mg/mL) and the ester–water partition coefficient ( $-0.47$ ). The experimental results show that the amino acid ester prodrug retains the solubility characteristics of the original drug, and the *in vivo* and *in vitro* experiments have obtained good experimental results, which significantly prolong the *in vivo* action time of Ligu; but the fat solubility of the compound was not improved (Figure 14).

Evodiamine is an indole alkaloid that exists in the fruits of the traditional Chinese herb *Evodiae fructus*, which is widely used to treat a variety of human diseases (Yu et al., 2013). Although evodiamine showed good antitumor activity, the development of evodiamine for clinical cancer treatment was



**FIGURE 13** | Camptothecin derivatives.

stunted by its relatively moderate potency. Hu et al. (2017) reported a series of novel evodiamine with antiproliferative properties. All derivatives showed antiproliferative activities against tested human tumor cell to some extent and almost non-toxic ( $>200\ \mu\text{M}$ ) to human normal PBMCs. Compound **115** showed the strongest cytotoxicity against two tumor cell lines (THP-1 and HL-60) with IC<sub>50</sub> values of 4.05 and 0.50  $\mu\text{M}$ , respectively, and selected for further mechanism study in HL-60 cells, and compound **115** could induce HL-60 cell apoptosis and arrest at the G<sub>2</sub> phase at low concentrations. ( $\pm$ )-Vasicinone was isolated from the seeds of *P. harmala*. Filali et al. (2019) reported the synthesis of a new series of  $\alpha$ -amino acid ester derivatives of ( $\pm$ )-vasicinone and tested for their *in vitro* AChE, anti-5-LOX, and cytotoxic activities (MCF-7, OVCAR-3, and HCT-116 cell lines). Most of the derivatives showed cytotoxic activity against

the three cell lines used. Only two diastereoisomers, **116** and **117**, exhibited activity against the 5- LOX enzyme with IC<sub>50</sub> values of 63 and 79  $\mu\text{M}$ , respectively (Figure 14).

## Polyphenols

Danshensu is one of the main water-soluble active ingredients of *Salvia miltiorrhiza* Bunge (Danshen), which has been applied in clinical practice for centuries in Asia (Zhang et al., 2010). After the hydroxyl group of Danshensu is esterified or etherified, Danshensu is not easily oxidized, fat solubility is improved, and toxicity is reduced. Jia et al. (2012) designed and synthesized a series of novel amide and thioester conjugates between Danshensu and cysteine derivatives under the guidance of “medicinal chemical hybridization” (MCH). The amide conjugates **118–120** displayed widely protective effects against

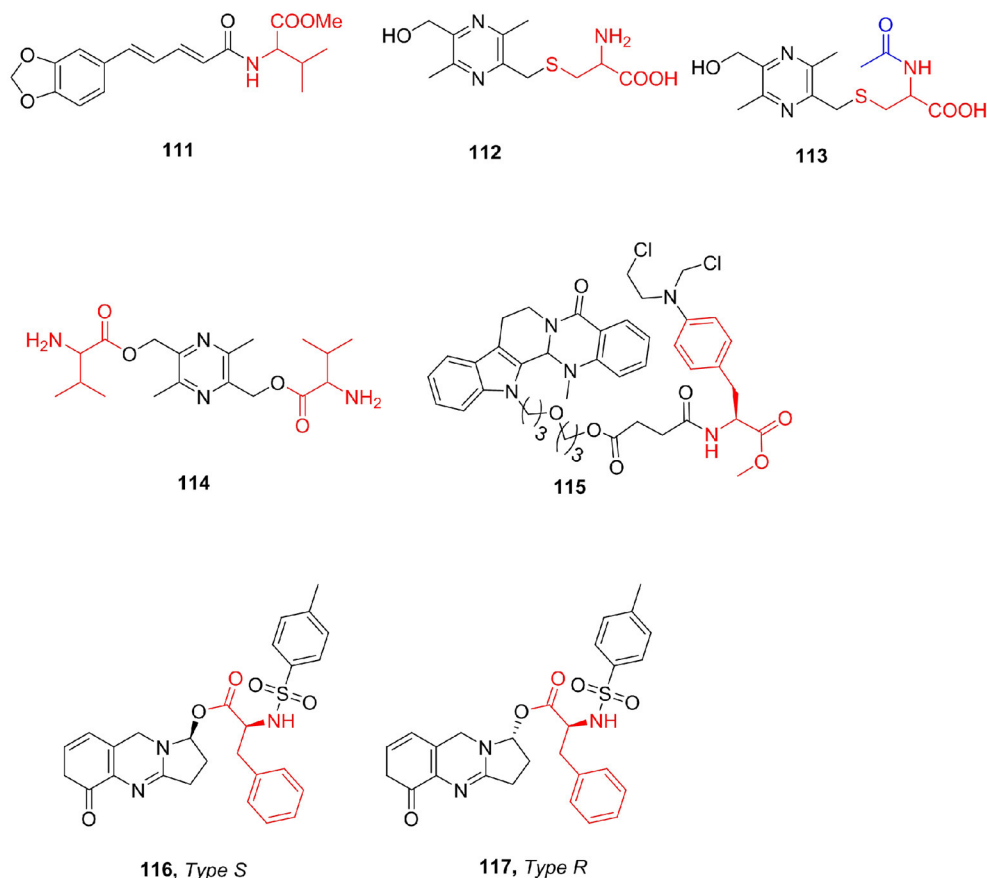


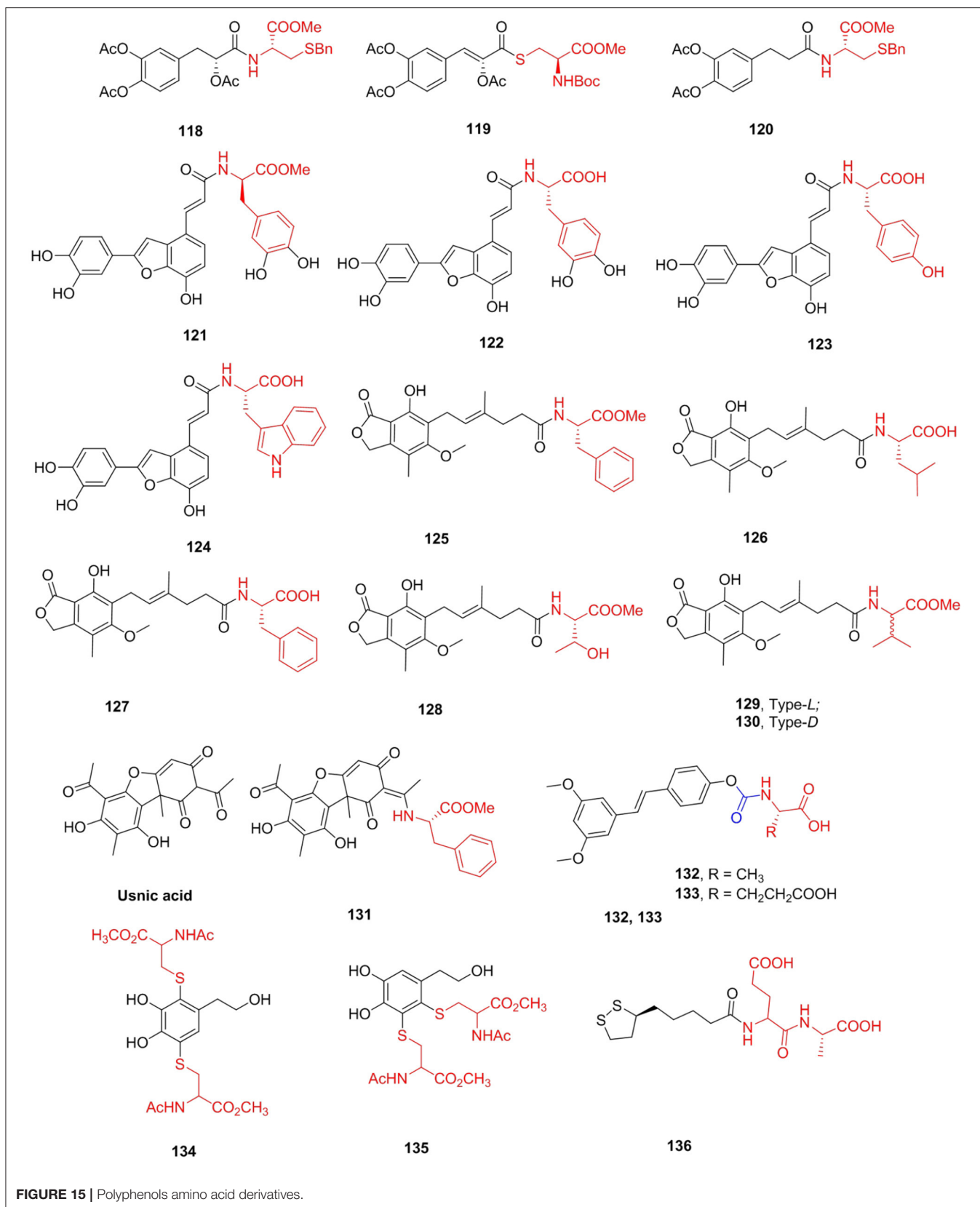
FIGURE 14 | Alkaloids amino acid derivatives.

H<sub>2</sub>O<sub>2</sub>-HUVECs. Pretreatment with these derivatives could increase GSH levels and decrease MDA levels. Salvianolic acid C, a polyphenolic benzofuran derivative that exists in Danshen, is reported to have a potent XO inhibitory activity (Fu Y. et al., 2014). Nevertheless, few have attempted to study salvianolic acid C except for the total synthesis and pharmacokinetic study of rat plasma (Shen et al., 2012). A series of 2-arylbenzo[b]furan derivatives were prepared based on salvianolic acid C and tested for XO inhibitory and antioxidant activities (Tang et al., 2016). Compounds **121–124** showed effective XO inhibitory activities with IC<sub>50</sub> values ranging from 4.0 to 6.4 mM, which were comparable with that of allopurinol. The representative derivative **123** could bind to either XO or the xanthine oxidase–xanthine complex, showing a mixed-type competitive mechanism (Figure 15).

Mycophenolic acid (MPA), first isolated in 1896 by Gosio from *Penicillium stoloniferum* and was probably the first antibiotic (Bentley, 2000), is one of the most effective inhibitors of hIMPDPH (human IMPDPH; K<sub>i</sub> = 7 nM) (Hedstrom, 2009). MPA reduces the availability of guanine nucleotides, especially GTP. Mycophenolate mofetil (MMF, CellCept) and mycophenolate sodium (MPS, Myfortic) are used clinically as immunosuppressants. Many structural modifications were made to MPA, but only a few showed similar or better immunosuppressive activity. Iwaszkiewicz-Grzes et al. (2013)

synthesized 11 amino acid derivatives of MPA and evaluated new analogs as growth inhibitors of Jurkat cells and hPBMCs cells from healthy donors. The cytotoxicity depends on the substituent and configuration of the chiral center in the amino acid unit. Compounds **125** (SI = 2871.4), **126** (SI = 33,787.9), and **127** (SI = 7166.7) exhibited higher potency than MPA *in vitro*. In addition, Siebert et al. (2018) obtained novel amino acid MPA derivatives as potential antibacterial agents. Peptide derivatives proved to be the most versatile, and their strains were relative to most MIC values lower than MPA. Among them, the MIC value of compound **128** against *S. aureus* MSSA ATCC 25923 was 8 μg/mL, which was almost equivalent to kanamycin (MIC = 7.8 μg/mL) and significantly stronger than that of MPA (MIC > 178 μg/mL). As can be seen, the activity of amino acid derivatives depends on the configuration at the chiral center in the amino acid unit, and methyl esters revealed better antimicrobial activity than derivatives with free carboxylic groups. Felczak et al. (2014) prepared mycophenolic adenine dinucleotide analogs linked by amino acids. Mycophenolic-(L)- and (D)-valine adenine diamide derivatives **129** (K<sub>i</sub> = 9 nM) and **130** (K<sub>i</sub> = 3 nM) were found to be very potent enzymatically but did not inhibit the proliferation of cancer cells (Figure 15).

Usnic acid (UA), isolated from lichen, has a variety of biological activities (Galanty et al., 2017), including antiparasitic activity. However, the toxicity of usnic acid, especially liver failure



(Piska et al., 2018) and cultured mouse hepatocyte necrosis (Foti et al., 2008), has also been reported. Nevertheless, poor solubility in water (Erba et al., 1998) limits the application of usnic acid to some extent. Guo et al. (2019) synthesized some (+)-usnic acid derivatives containing amino acids and evaluated their anti-*Toxoplasma* activity. Compared with positive control drugs sulfadiazine (selectivity 1.15), pyrimethamine (selectivity index = 0.89), spiramycin (selectivity index = 0.72), and the lead compound (+)-usnic acid (selectivity index = 0.96), compound **131** showed the most effective anti-*T. gondii* activity (selectivity index > 2.77). Furthermore, compound **131** had better inhibitory effects on *T. gondii* (inhibition rates 76.0%) *in vivo* than spiramycin (inhibition rate 55.2%). The number of tachyzoites was significantly reduced ( $p < 0.001$ ) and reduced hepatotoxicity and significantly increased antioxidative effects in comparison to the normal group (Figure 15).

The peroxisome proliferator-activated receptor subtype  $\alpha$  (PPAR $\alpha$ ) has been established as a target in drug discovery studies of new lipid-lowering drugs. Pterostilbene is a naturally occurring PPAR $\alpha$  agonist that has been shown to decrease plasma lipid concentrations through activation of PPAR $\alpha$  (Kim and Chong, 2013). Of the conjugates investigated, 4-OMe-pterostilbene had a lower activating effect than pterostilbene, but the pterostilbenes with either amino acids **132** (FI = 18.4) and **133** (FI = 18.9) demonstrated a small but remarkable increase in PPAR $\alpha$  activity compared with pterostilbene (FI = 17.1) (Figure 15).

Polyphenols are one of the biologically active substances in many plant-derived foods. They have effective reducing properties, which can inhibit the oxidative deterioration of food. Previous attempts have been made to use this polyphenol to avoid oxidative browning of MbO<sub>2</sub>. However, the effective antioxidant polyphenols accelerated the oxidation of MbO<sub>2</sub> to MetMb (Masuda et al., 2013). Honda et al. (2016) synthesized some polyphenols linked to amino acid compounds. Dihydroxytyrosol substituted with dicysteine **134** and **135** showed the most effective reduction effect on MetMb and no oxidation effect on MbO<sub>2</sub> (Figure 15).

Lipoic acid (LA) is a pharmacophore with unique antioxidant (Whiteman et al., 1996) and cytoprotective properties (Pugazhenthii et al., 2007). Based on its chemical and biological properties, LA is an attractive candidate for modification. Kates et al. (2014) prepared and screened a selection of LA analogs for cytoprotective activity. Compound **136** was selected based on these attributes as well as a favorable ADMET and receptor screen profile for further preclinical and clinical investigation, which showed statistically remarkable protection against myocardial damage associated with percutaneous coronary intervention (Figure 15).

## CONCLUSION

Natural products have long been considered an important source of effective therapeutic drugs. About 60% of the world's population relies on herbal medicines and natural medicines to treat diseases. With natural products as lead compounds, the relationship between structure and biological activity and

metabolic research can be further carried out for structural modification and analog synthesis, which can improve drug efficacy and reduce toxicity. Amino acids are an important class of bioorganic molecules. They have the characteristics of structural diversity, ease of availability, and easy connection with other amino acids and biologically active molecules. They can effectively change the low solubility and biological activity of natural products. The introduction of amino acids into natural compounds can often improve the solubility and increase the pharmacological activities of natural products, and a few amino acids are used to increase the selectivity of these products. Certain compounds, such as anthraquinones and flavonoids, are difficult to dissolve in water. The introduction of amino acids into their structures and the preparation of amino acid hydrochlorides can greatly improve their solubility. Some compounds have strong activity. For example, PPT lacks favorable selectivity to normal cells, which leads to its increased toxicity and side effects. After the introduction of amino acids, its selectivity increases and cytotoxicity to normal cells decreases. Regarding the amino acid-protecting group, *N*-Boc, there is no clear conclusion about whether it needs to be deprotected at the end when the structure is modified.

According to previous studies, natural products have diverse structure types and pharmacological activities. For compounds with weak biological activity and low water solubility, we can first consider amino acids. For compounds with strong activity and high toxicity, we can consider adding amino acids to prepared prodrugs to reduce toxicity. When we modify the structure of a natural compound, we should first fully understand the various properties of the natural product, such as solubility, reported pharmacological activity, and structural modification. Combined with computer-simulated drug design and rapid determination of activity, researchers can quickly and efficiently modify the directional structure of natural compounds. In the structural modification of natural products, the application of amino acids can improve many properties. Therefore, amino acids have great application prospects in the structural modification of natural products.

## AUTHOR CONTRIBUTIONS

QX and HD conceptualized the project. QX, HD, and XL contributed to the development and writing of the manuscript. XL and Z-SQ contributed in validating, reviewing, and supervising the project. All authors contributed to the article and approved the submitted version.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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