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•Review•

Promising natural lysine specific demethylase 1 inhibitors for cancer treatment: advances and outlooks

LI Zhong-Rui[1, 2], GU Meng-Zhen[2], XU Xiao[2], ZHANG Jing-Han[2], ZHANG Hai-Li[2], HAN Chao[2*]

[1] *Department of Medicinal Chemistry, School of Pharmacy, Nanjing Medical University, Nanjing 211166, China;*
[2] *State Key Laboratory of Natural Medicines, Jiangsu Key Laboratory of Bioactive Natural Product Research, School of Traditional Chinese Pharmacy, China Pharmaceutical University, Nanjing 210009, China*

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[ABSTRACT] Lysine specific demethylase 1 (LSD1), a transcriptional corepressor or coactivator that serves as a demethylase of histone 3 lysine 4 and 9, has become a potential therapeutic target for cancer therapy. LSD1 mediates many cellular signaling pathways and regulates cancer cell proliferation, invasion, migration, and differentiation. Recent research has focused on the exploration of its pharmacological inhibitors. Natural products are a major source of compounds with abundant scaffold diversity and structural complexity, which have made a major contribution to drug discovery, particularly anticancer agents. In this review, we briefly highlight recent advances in natural LSD1 inhibitors over the past decade. We present a comprehensive review on their discovery and identification process, natural plant sources, chemical structures, anticancer effects, and structure–activity relationships, and finally provide our perspective on the development of novel natural LSD1 inhibitors for cancer therapy.

[KEY WORDS] Histone lysine demethylase; LSD1 inhibitor; Natural product; Anticancer
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Introduction

In recent years, cancer has become the leading threat to human health worldwide, and patients with cancer tend to be younger than that in the past [1-3]. However, accessing safe and effective cancer medicines can be challenging [4]. Natural products have abundant scaffold diversity and structural complexity, which have played a crucial role in drug discovery, especially anticancer drugs [5]. Among the 1881 approved therapeutic agents from 1981 to 2019, approximately 50% were either derived from or are structurally similar to natural products [6]. Furthermore, more than 60% of the 247 approved anticancer drugs are nature-based agents. Indeed, some of the most effective anticancer drugs, including taxol, vinblastine, vincristine, camptothecin, colchicine, and harringtonine, were discovered in plants. Therefore, natural active ingredients are important sources of novel anticancer drugs.

Lysine specific demethylase 1 (LSD1, also known as KDM1A, BHC110, or AOF2), discovered in 2004, was the first reported functional protein that exhibited histone demethylase activity [7]. LSD1 is composed of 852 amino acids, which form the *N*-terminal Swi3p/Rsc8p/Moira (SWIRM) *α*-helical domain, the amine oxidase domain containing a noncovalent flavin adenine dinucleotide (FAD) and substrate binding site, and the TOWER domain [8, 9] (Fig. 1A). The TOWER domain contains a long helix-turn-helix structure that is associated with the RE1 silencing transcription factor corepressor (CoREST), which has an effect on its demethylase activity [10, 11]. LSD1 specifically removes mono- or dimethylated Lys4 of histone H3 (H3K4me1/2) or Lys9 of histone H3 (H3K9me1/2) [12, 13]. The catalytic demethylation activity of LSD1 is dependent on its cofactor FAD. The chemical reaction involves the first conversion of methylated lysine to an iminium cation, which is caused by the oxidized FAD extracting a hydride anion to form reduced $FADH_2$. Next, the iminium cation is hydrolyzed by molecular H_2O, which is then decomposed to formaldehyde and demethylated lysine. The reduced FAD generated in the first step is rapidly reoxidized by molecular O_2 to yield molecular H_2O_2 and ultimately regenerates oxidized FAD (Fig. 1B). LSD1 can also demethylate other nonhistone substrates such as the protein p53 [14], DNA methyltransferase 1 (DNMT1) [15], the transcription factor E2F1 [16], signal transducer and activator of transcription 3 (STAT3) [17], hypoxia-inducible factor HIF-

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[*Corresponding author] E-mail: hanchao@cpu.edu.cn
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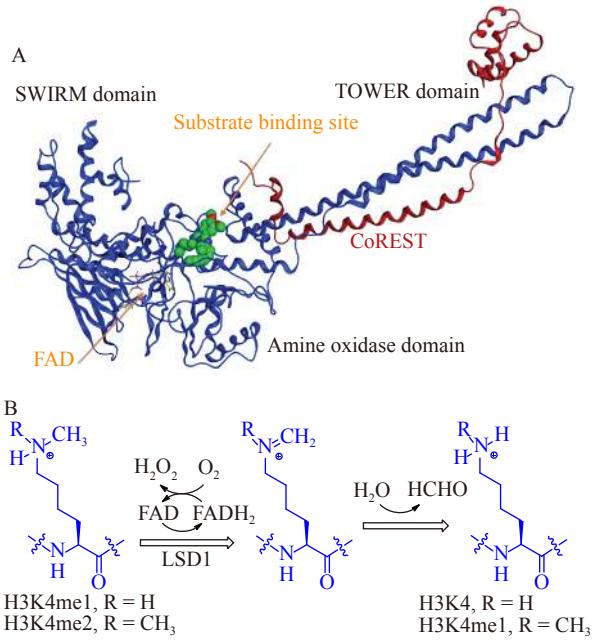


Fig. 1 (A) X-ray cocrystal structure of LSD1/CoREST complex (PDB: 2V1D). (B) Mechanism of the FAD-dependent histone demethylation mediated by LSD1

1α [18], and myosin phosphatase target subunit 1 (MYPT1) [19]. Furthermore, LSD1 has a similar amino acid sequence and protein structure as monoamine oxidases (MAO-A/B) [20] and histone lysine specific demethylase 2 (LSD2) [21]. Increasing evidence has indicated that LSD1 mediates crucial cellular signaling pathways (Fig. 2A) in numerous human diseases [22], such as angiocardiopathy, viral infections, stem cell differentiation, neurodegeneration, and particularly cancer [23]. LSD1 has been reported to be overexpressed in various cancers, such as breast cancer [24], acute myeloid leukemia [25], gastric cancer [26], prostate cancer [27], hepatocellular carcinoma [28], and esophageal cancer [29], making it a promising therapeutic target for the treatment of cancer.

Downregulating the expression of LSD1 using siRNAs or small molecules was shown to inhibit cancer cell proliferation, invasion, migration, and differentiation and improve prognosis in various cancer cells and animal models [30, 31]. These findings emphasize the significance of exploiting potent LSD1 inhibitors for cancer therapy. Since the discovery of LSD1 in 2004, there have been numerous studies on LSD1 inhibitors. Significant advances have been made toward the identification of both reversible and irreversible chemo-synthesized LSD1 inhibitors (Fig. 2B) [32-34]. To date, seven LSD1 inhibitors (tranylcypromine, ORY-1001, ORY-2001, GSK-2879552, INCB059872, CC-90011, and IMG-7289) [35] have been clinically assessed for cancer therapy, particularly for acute myeloid leukemia and small-cell lung cancer. However, only a few studies have focused on natural product-based LSD1 inhibitors [36]. Natural medicinal plants have been found to be rich sources of materials for developing new therapeutic agents. Therefore, it is both important and necessary to review the progress made in this promising field and outline the future prospects. This review presents a comprehensive summary of natural LSD1 inhibitors, including their discovery and identification process, natural plant sources, chemical structures, anticancer effects, and structure–activity relationships, which have been reported over the past decade. Natural inhibitors can be classified into nine categories based on their structural characteristics: flavonoids, alkaloids, terpenoids, phenanthraquinone, phenylpropanoids, polypeptides, stilbenes, diarylheptanoids, and others (Fig. 3). Finally, we summarize and discuss the characteristics and shortcomings of current research on natural LSD1 inhibitors. We also present future directions for the development of natural LSD1 inhibitors based on our research.

Natural LSD1 Inhibitors

Flavonoids

Flavonoids include a wide range of natural substances

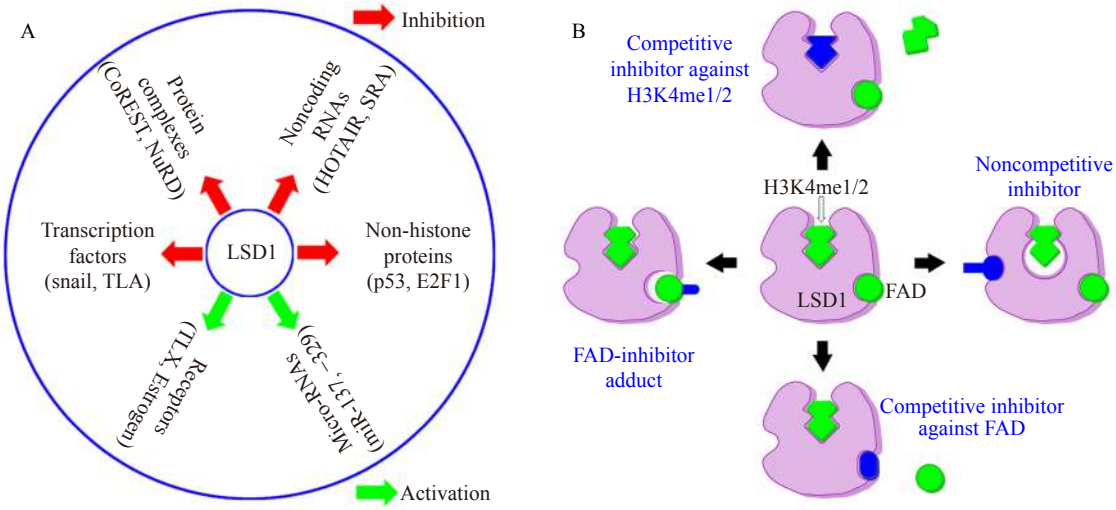


Fig. 2 (A) LSD1-mediated crucial cellular biological processes. (B) Mechanism of the competitive and noncompetitive inhibitors against LSD1

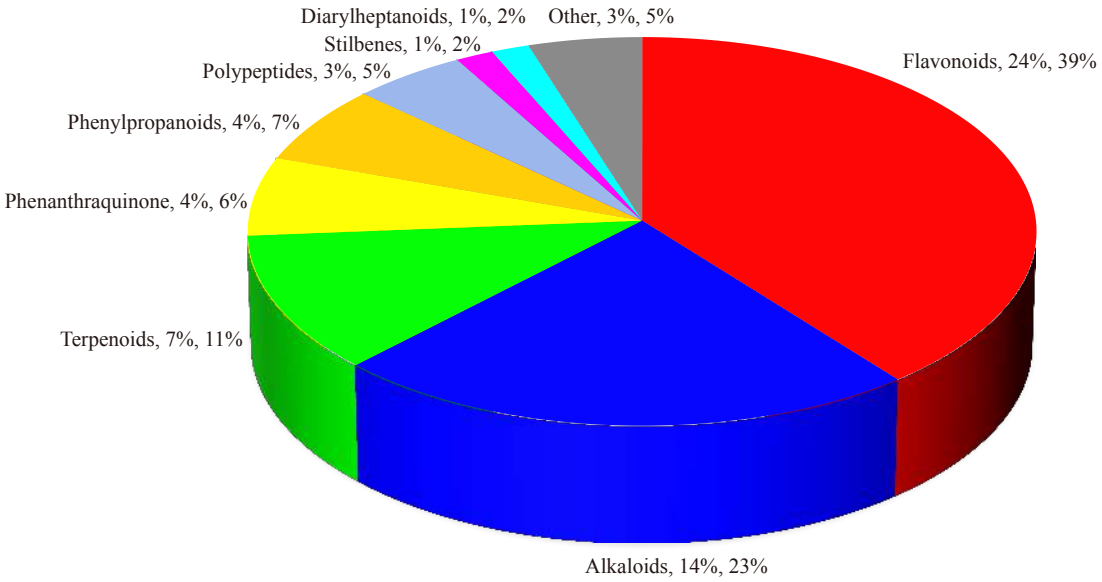


Fig. 3 All natural LSD1 inhibitors (n = 61)

that possess a 1,3-diphenylpropane or 1,2-diphenylpropane skeleton or more specifically have a C_6–C_3–C_6 carbon framework. They can be classified into various groups, such as flavones, flavonols, flavanones, flavanonols, isoflavones, xanthones, and flavanes [37-39]. Flavonoids exhibit many useful biological activities, such as anti-inflammatory, antioxidant, anticancer, antiallergic, anti-estrogenic, and antimicrobial effects as well as inhibition of angiogenesis [40, 41]. They show significant inhibitory activity against epigenetic targets such as LSD1. Thus far, approximately 24 natural flavonoid-based LSD1 inhibitors [42-47], including aglycone and glucoside, have been identified, and the IC_{50} values for the inhibitory activity of most inhibitors are less than 20 μmol·L^{-1} (Figs. 4 and 5, Table 1). Therefore, flavonoids contain a carbon skeleton that is promising for the development of LSD1 inhibitors.

To improve the efficiency of discovery from natural plants, our group was the first to establish bioactivity-guided countercurrent chromatography (CCC) [43]. Six flavonoid-based LSD1 inhibitors, including baicalin, wogonoside, baicalein, skullcapflavone II, wogonin, and oroxylin A, were identified from *Scutellaria baicalensis* Georgi using CCC. Zheng *et al*. [44] also showed that baicalin exhibited an LSD1 inhibitory effect in MGC-803 cells with an IC_{50} of 3.01 μmol·L^{-1}. In our study, wogonoside, similar to baicalin with a gluconic acid group at the 1-site, showed stronger LSD1 inhibitory activity than baicalin with an IC_{50} of 2.98 μmol·L^{-1}. Wogonoside increased the accumulation of H3K4me2 and the expression of CD86 in MDA-MB-231 cells, but it did not affect the expression of LSD1. Furthermore, LSD1 overexpression was shown to facilitate the migration and invasion of breast cancer cells [24, 48]. Wogonoside inhibited cell migration and invasion by inhibiting the expression of LSD1. Molecular docking (Fig. 6) showed that wogonoside docked well with the X-ray crystal structure of LSD1 (2V1D). The flavone carbon skeleton produces hydrophobic interactions with Ala814 and Pro626, and the oxygen atom (1-site), carbonyl group (4-site), and hydroxyl group (5-site) generate hydrogen bonds with Arg316, Thr624, Ser289, and Glu801. Additionally, the hydroxyls of the gluconic acid moiety produce hydrogen bonds with the residues Val811 and Ala809.

Differences in biological activity between the flavonoids aglycone and glycoside have been reported [49, 50]. To systematically study the structure–activity relationship, we selected 12 natural flavones, including four aglycones and their corresponding monoglycosides and diglucosides, to evaluate their LSD1 inhibitory activity [45] (Fig. 7). Regardless of whether the sugar moiety was located at the 7-site (hesperetin-7-*O*-glucoside and diosmetin-7-*O*-glucoside) or the 3-site (icariside II and isoquercitrin) of the flavone and whether the sugar group was rhamnose (icariside II) or glucose (isoquercitrin, hesperetin-7-*O*-glucoside and diosmetin-7-*O*-glucoside), all flavone monoglycosides exhibited stronger LSD1 inhibitory activity than their aglycones. In addition, the inhibitory activities of the flavone diglycosides were either stronger or weaker than those of their corresponding monoglycosides. Molecular docking was performed to demonstrate this phenomenon theoretically. The flavone skeleton moiety of monoglycoside exhibited π-π molecular stacking interactions with Trp751, whereas its sugar moiety formed hydrogen bonds with Val333 and Met332 (Fig. 8). Meanwhile, only the sugar moiety of the flavone diglycoside docked with LSD1, and the flavone aglycone docked with LSD1 lacking the interaction with the sugar moiety. We also found that diosmetin-7-*O*-glucoside (IC_{50} = 21.83 μmol·L^{-1}) showed weaker LSD1 inhibitory activity than hesperetin-7-*O*-glucoside (IC_{50} = 4.74 μmol·L^{-1}), although hesperetin-7-*O*-glucoside was the product of hydrogenation of diosmetin-7-*O*-glucoside on the carbon-carbon double bond (2-site and 3-site). Next, isoquercitrin exhibited the most potent LSD1 inhibitory activity

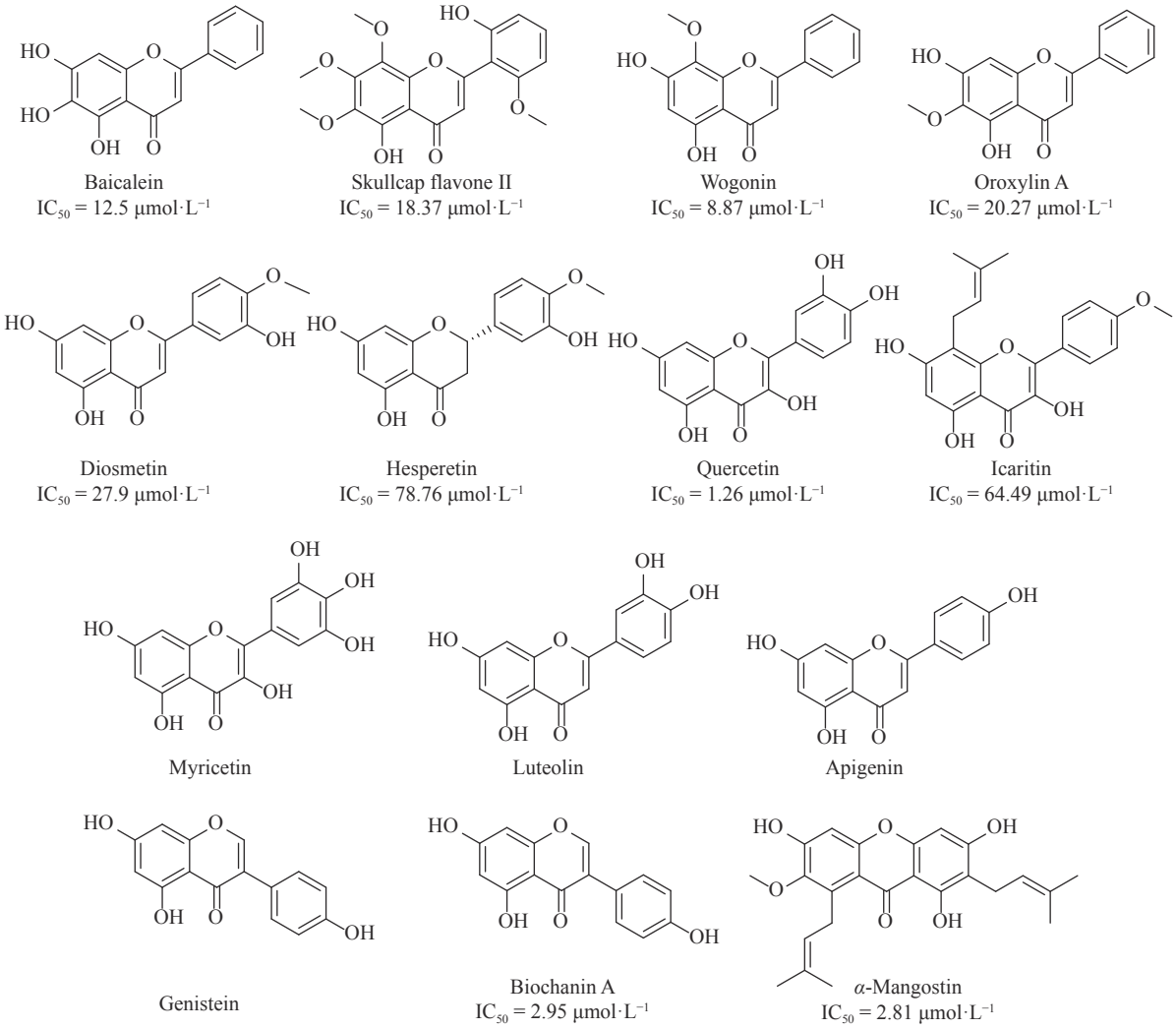


Fig. 4 Flavonoid aglycone-based LSD1 inhibitors

(IC_{50} = 0.95 μmol·L^{-1}). Using siRNA to knock down LSD1 expression, we found that isoquercitrin inhibited the LSD1-based proliferation of MDA-MB-231 cells. Moreover, isoquercitrin influenced the expression of key proteins in the mitochondrial-mediated apoptosis pathway and ultimately led to cellular apoptosis through the inhibition of LSD1.

Xanthones are a class of oxygenated heterocycles containing a dibenzo-*γ*-pirone scaffold; they are distributed in a variety of plants and exhibit different bioactivities depending on their chemical structure and substituents [51-53]. *α*-Mangostin is the most representative xanthone; it was first purified from the mangosteen fruit [54]. Its molecular skeleton and significant pharmacological properties make it a promising new drug candidate, especially as an antineoplastic agent [55, 56]. Our group [46] characterized *α*-mangostin as a xanthone-based LSD1 inhibitor with an IC_{50} value of 2.81 μmol·L^{-1}, which is seven times stronger than that of the control, tranylcypromine. *α*-Mangostin is a reversible inhibitor and exhibits cellular inhibitory activity against LSD1 by increasing the H3K4me2 accumulation and CD86 expression. Meanwhile, it inhibits breast carcinoma cell migration and invasion by increasing the expression of *E*-cadherin and decreasing the expression of *N*-cadherin. As the first xanthone-based LSD1 inhibitor, *α*-mangostin provided a unique flavonoid skeleton for LSD1 studies. Isoflavones are another class of flavonoids that have a 3-phenyl chromone structure and are found in leguminosae, iridaceae, and other natural plants [57, 58]. Biochanin A, a bioactive isoflavone isolated from *Trifolium pratense* L., has attracted attention because of its widespread pharmacological activities [59, 60]. Wang e*t al*. [47] identified biochanin A as an LSD1 inhibitor with an IC_{50} value of 2.95 μmol·L^{-1}. Biochanin A reversibly inhibits LSD1 activity and exhibits selective inhibition of LSD1 over MAO-A/B. At the cellular level, biochanin A increased the accumulation of H3K3 me1/2 in gastric MGC-803 cells. Additionally, it inhibited cell colony formation in a concentration-dependent manner, promoted cell apoptosis, and suppressed cell migration.

Alkaloids

Alkaloids are a group of important natural active com-

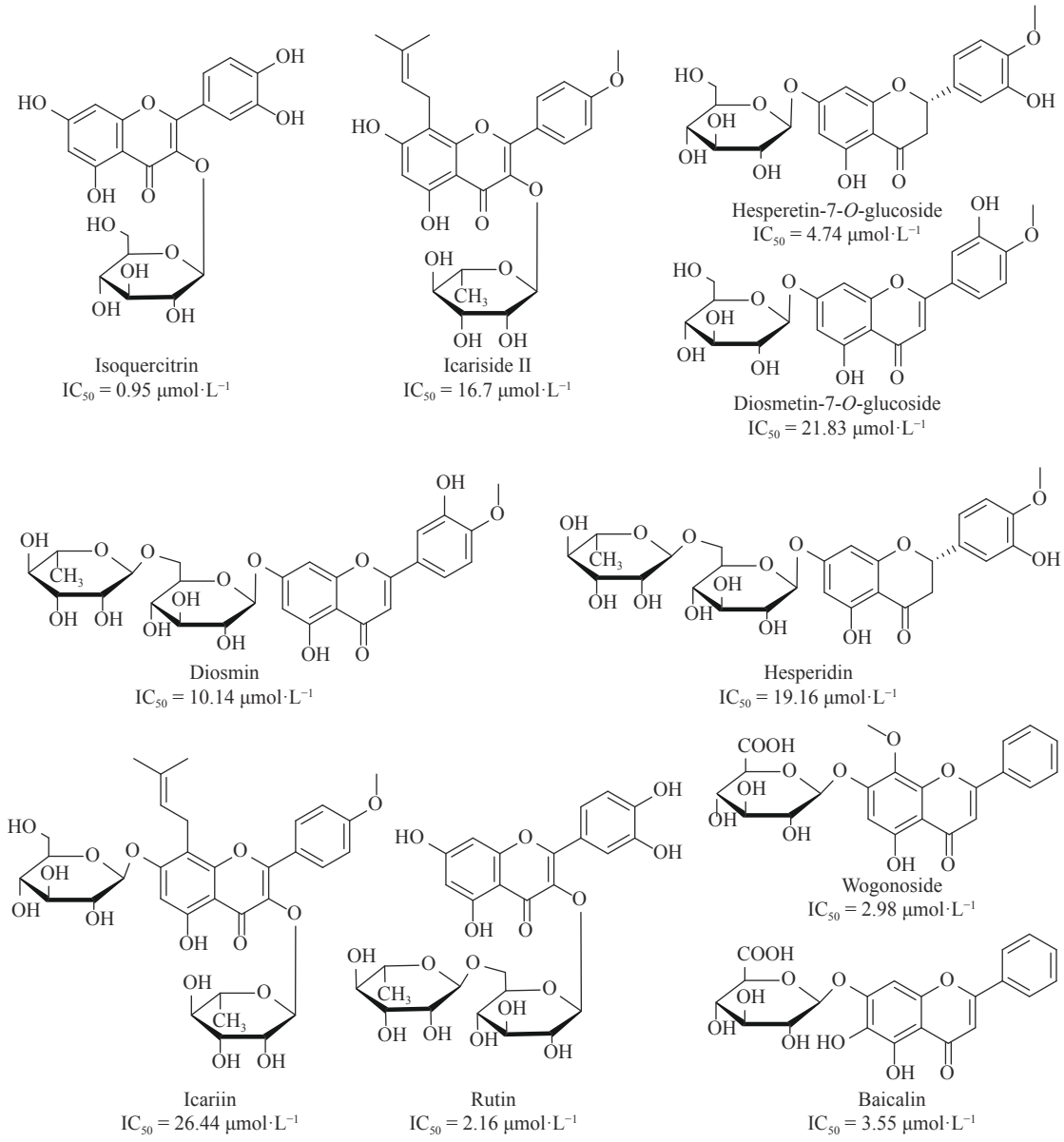


Fig. 5 Flavonoid glycoside-based LSD1 inhibitors

pounds containing basic nitrogen atoms, that are isolated from a large variety of plants, marine organisms, animals, bacteria, and fungi [61-63]. Three well-known anticancer drugs, namely, taxol, vincristine, and camptothecin, have been derived from plant alkaloids. Therefore, alkaloids are an important source of novel anticancer drugs. To data, fourteen natural alkaloids have been identified as LSD1 inhibitors, most of which are berberine- and protoberberine-type alkaloids [64-70] (Figs. 9 and 10, Table 2). Of these compounds, arborinine has shown the strongest activity against LSD1 (with a nanomolar IC_{50} value) [64].

Our group [65] established a new strategy for the precise isolation of LSD1 inhibitors from the rhizome of *Corydalis yanhusuo* using CCC guided by molecular docking and liquid chromatography-mass/mass spectrometry (LC-MS/MS) analysis. First, four representative berberine alkaloids and four representative protoberberine alkaloids were selected to dock with LSD1 for virtual screening. Berberine alkaloids and their derivatives are naturally occurring quaternary isoquinoline-based alkaloids [71, 72], whereas protoberberine alkaloids and their derivatives are based on a protoberberine moiety derived from 5,6-dihydrodibenzo[*a*,*g*]quinolizinium [73, 74]. The docking results revealed that the aromatic ring and isoquinoline skeleton were necessary for the inhibition of LSD1. Three high-purity target alkaloid-based LSD1 inhibitors, i.e., dehydrocorydaline, coptisine, and columbamine, were obtained using pH-zone refining CCC and LC-MS/MS analysis. The IC_{50} values of dehydrocorydaline, coptisine, and columbamine were 2.44, 5.22, and 7.06 μmol·L^{-1}, respectively, which were 7.7-, 3.6-, and 2.7-fold stronger than that of the control, tranylcypromine. Dehydrocorydaline also potentially inhibited the invasion and metastasis of human os-

Table 1 The compounds, type and *in vitro* LSD1-inhibitory activities of flavonoid-based agents

Compounds	Type	IC_{50} ($\mu mol \cdot L^{-1}$)	References
Baicalein	Flavone aglycone	12.5	[43]
Skullcap flavone II	Flavone aglycone	18.37	[43]
Wogonin	Flavone aglycone	8.87	[43]
Oroxylin A	Flavone aglycone	20.27	[43]
Diosmetin	Flavone aglycone	27.9	[45]
Hesperetin	Flavanone aglycone	78.76	[45]
Quercetin	Flavonol aglycone	1.26	[42, 45]
Icaritin	Flavonol aglycone	64.49	[45]
Biochanin A	Isoflavone aglycone	2.95	[47]
α-Mangostin	Xanthone aglycone	2.81	[46]
Baicalin	Flavone monoglycoside	3.55	[43, 44]
Wogonoside	Flavone monoglycoside	2.98	[43]
Diosmetin-7-*O*-glucoside	Flavone monoglycoside	21.83	[45]
Hesperetin-7-*O*-glucoside	Flavanone monoglycoside	4.74	[45]
Isoquercitrin	Flavonol monoglycoside	0.95	[45]
Icariside II	Flavonol monoglycoside	16.7	[45]
Diosmin	Flavone diglycoside	10.14	[45]
Hesperidin	Flavanone diglycoside	19.16	[45]
Rutin	Flavonol diglycoside	2.16	[45]
Icariin	Flavonol diglycoside	26.44	[45]

teosarcoma U2OS cells. The LSD1 inhibitory activity of berberine alkaloids was stronger than that of protoberberine alkaloids. Meanwhile, Li *et al*. [66] obtained similar results. The IC_{50} values of the five selected berberine alkaloids epiberberine, columbamine, jatrorrhizine, berberine, and palmatine were less than 13 $\mu mol \cdot L^{-1}$, whereas the IC_{50} values of the two selected protoberberine alkaloids canadine and tetrahydropalmatine were greater than 100 $\mu mol \cdot L^{-1}$. Epiberberine inhibited LSD1 with an IC_{50} value of 0.14 $\mu mol \cdot L^{-1}$ and was selective for LSD1 over MAO-A/B. Epiberberine also induced acute myeloid leukemia (AML) cell differentiation by increasing the abundance of H3K4me2, H3K9me2, CD86, CD14, and CD11b in monocyte leukemia THP-1 cells and human promyelocytic leukemia HL-60 cells. Furthermore, epiberberine could inhibit tumor growth in a xenograft model bearing THP-1 cells. High-dose, middle-dose, and low-dose epiberberine administration could significantly improve the median survival of mice (20, 23 and 25 days, respectively, versus 19 days for the control). Finally, epiberberine did not lead to evident loss in body weight during the treatment period and treatment cessation period, indicating the low toxicity of epiberberine during the treatment period.

Natural berberine alkaloids are characterized as potent LSD1 inhibitors for AML treatment. LSD1 is overexpressed in approximately 60% of AML cases [75], and suppressing LSD1 expression increased differentiation and apoptosis in mixed lineage leukemia (MLL)-rearranged AML models [76, 77]. Thus, Fang *et al*. [67] further explored the influence of LSD1 inhibitors on AML. They found that higenamine was a potent LSD1 inhibitor with a benzylisoquinoline-based alkaloid skeleton, which was selective toward LSD1 over MAO-A/B. Higenamine increased H3K4me1 and H3K4me2 levels and decreased the expression of HOXA9 and MEIS1 in MLL-rearranged leukemia MV4-11 and MOLM-13 cells. In addition, higenamine also increased the amount of CD11b, CD14, and CD86 to induce cell differentiation and increase the levels of p53 to promote cell apoptosis.

Abnormal LSD1 expression is closely related to the occurrence of gastric tumors [26]. Chu *et al*. [64] examined arborinine as an antiproliferative agent and demonstrated that it exhibited potent inhibition of gastric tumors. These tumor cells included gastric cancer cells (SGC-7901, MGC803, NCI-

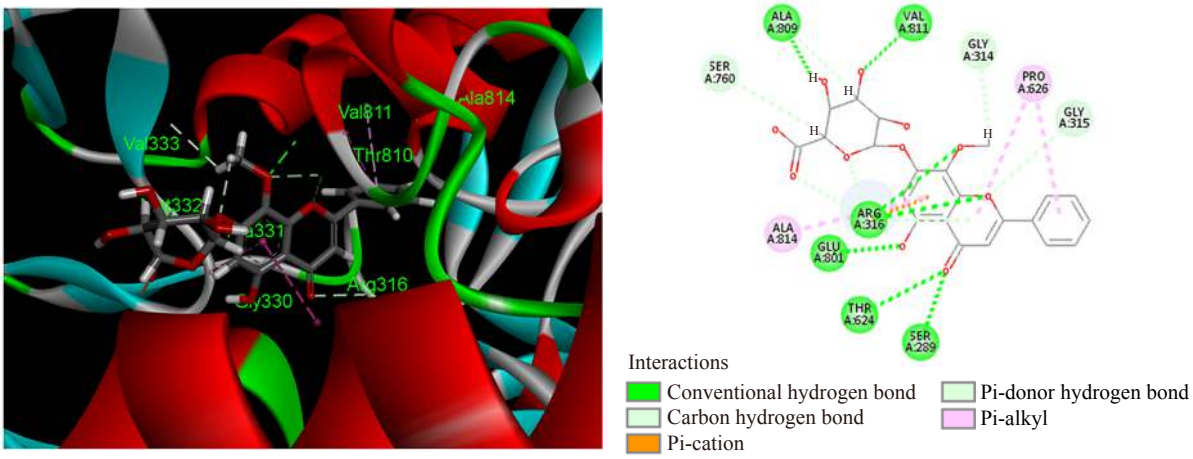


Fig. 6 Molecular docking of wogonoside binding in the active site of LSD1 (PDB code: 2V1D). Adapted from Ref. 43

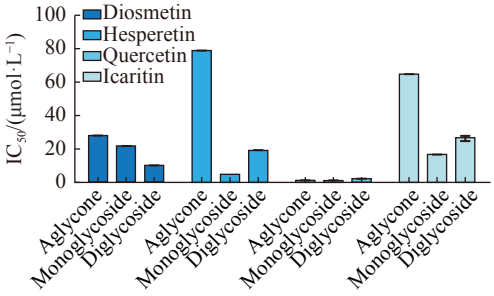


Fig. 7 *In vitro* LSD1-inhibitory activities of flavonoid-based agents

N87, HGC-27, and BGC-823) and drug-resistant gastric cancer cells (SGC-7901/ADR, MGC803/PTX, and SGC-7901/VCR). Furthermore, arborinine was first shown to be a selective and reversible LSD1 inhibitor with an acridone-type alkaloid skeleton. The IC_{50} value of arborinine was less than 100 nmol·L^{-1}, which had the strongest LSD1 inhibitory activity among all currently known natural inhibitors. Arborinine also inhibited epithelial-mesenchymal transition of SGC-7901 cells and SGC-7901/ADR cells *in vitro*. The *in vivo* antitumor effects of arborinine were also evaluated in the xenograft models bearing SGC-7901 or SGC-7901/ADR cells. Arborinine could remarkably reduce tumor growth and maintained the body weight, suggesting its antitumor efficacy without apparent toxicity. Overall, arborinine was demonstrated as an effective treatment for gastric cancer and adriamycin-resistant gastric cancer.

Capsaicin, isolated from the genus *Capsicum*, is a widely used food additive [78] that has anticancer and antarthritic effects as well as reduces or eliminates postoperative pain [79, 80]. Capsaicin was identified as a potent LSD1 inhibitor with an IC_{50} of 0.6 μmol·L^{-1}, and it induced the accumulation of H3K4me1/2 at the cellular level [68]. Capsaicin also inhibited the invasion and migration of gastric cancer BGC-823 cells by inhibiting LSD1.

Melatonin, a natural tryptamine indole-type alkaloid, is found in animals, microorganisms, and plants [81]. Melatonin has multiple physiological activities, such as antidepressant, analgesic, and anxiolytic activity [82] as well as anticancer effects [83]. In addition, melatonin promotes H3 acety lation [84, 85], the effect of which is the same as the inhibition of LSD1 activity [86]. Yang *et al*. [69] studied the LSD1-associated anticancer characteristics of melatonin. Using immunohistochemistry, they demonstrated that LSD1 was a therapeutic target and diagnostic marker in oral squamous cell carcinoma (OSCC) tissue. The oral cancer PDTX (patient-derived tumor xenograft) models were established and melatonin could significantly inhibit tumor growth in PDTX models compared with 5-fluorouracil as the positive control. No apparent toxicity in the mice was observed during the experimental period. On the other hand, the expressions of LSD1 and Ki-67 (a proliferation maker) in oral cancer-derived PDTXs were decreased after melatonin treatment in PDTX models compared with that in controls. Meanwhile, melatonin could also inhibit tumor growth in a xenograft model bearing SCC25 cells, and no weight loss in the mice was observed in the treatment group. Next, melatonin suppressed cell proliferation in a dose- and time-dependent manner at pharmacological concentrations in cell lines. It also induced G0/G1 arrest, decreased the expression of LSD1 and cyclin D1, increased p21 expression, and induced H3K4/H3K9 acetylation in OSCC, which further suppressed tumor growth in oral cancer cells. Therefore, the effects of melatonin in reducing OSCC proliferation were accompanied by reduced LSD1 expression in oral cancer PDTXs and oral cancer cell lines.

Folate cofactors play an important role in normal physiological metabolism, are distributed between the cytosol and mitochondria, and transfer one-carbon units between human metabolic pathways [87]. Luka *et al*. [70] found that the nuclei of HeLa cells contained the LSD1-folate complex. The 6*R*, *S* form of pentaglutamate tetrahydrofolate exhibited the highest affinity to LSD1 with a K_d of 2.8 μmol·L^{-1}. Folate

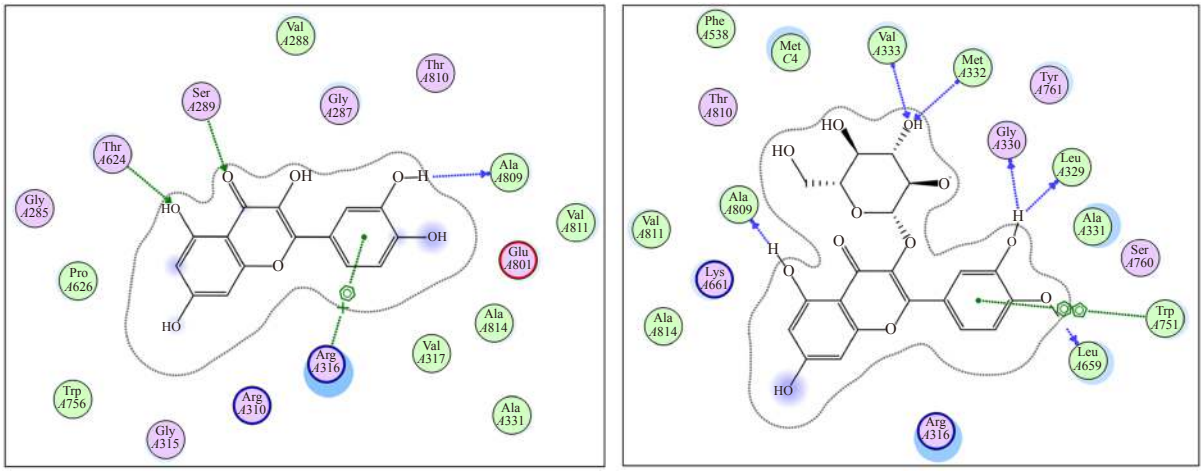


Fig. 8 Molecular docking of flavonoid aglycone and its monoglycoside (quercetin and isoquercitrin used as template) binding to LSD1 (PDB code: 2V1D). Adapted from Ref. 45

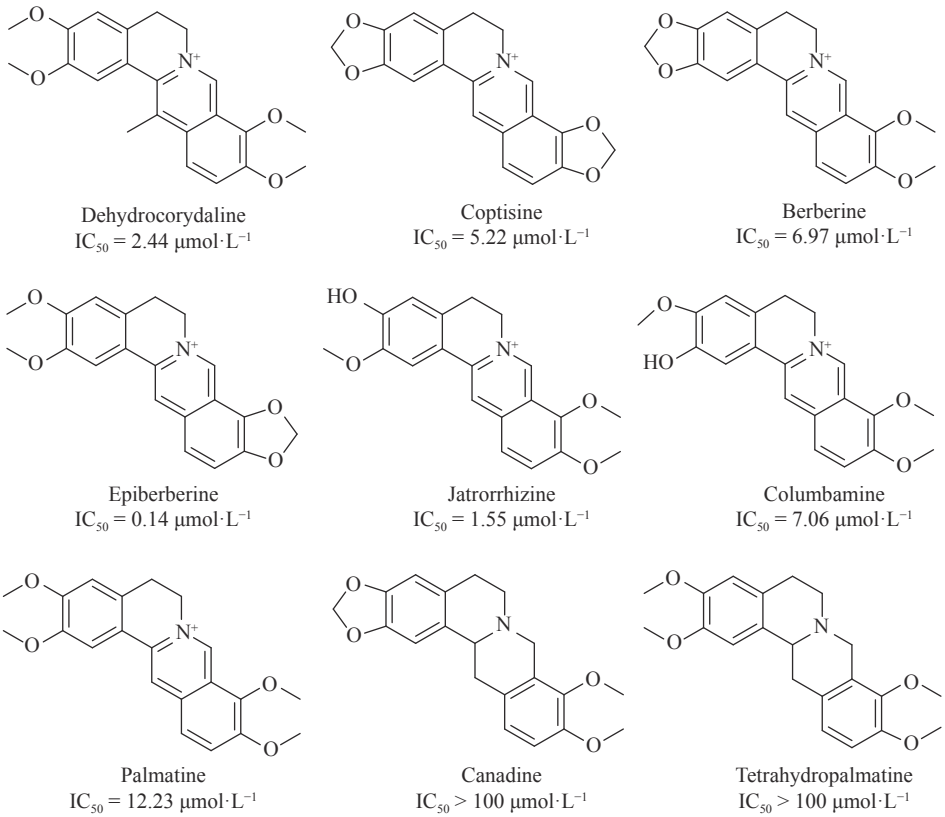


Fig. 9 Berberine and protoberberine alkaloids-based LSD1 inhibitors

Table 2 The compounds, type and *in vitro* LSD1-inhibitory activities of alkaloids-based agents

Compounds	Type	IC_{50} (μmol·L^{-1})	References
Dehydrocorydaline	Berberine-type alkaloid	2.44	[65]
Coptisine	Berberine-type alkaloid	5.22	[65]
Columbamine	Berberine-type alkaloid	7.06	[65,66]
Epiberberine	Berberine-type alkaloid	0.14	[66]
Jatrorrhizine	Berberine-type alkaloid	1.55	[66]
Berberine	Berberine-type alkaloid	6.97	[66]
Palmatine	Berberine-type alkaloid	12.23	[66]
Canadine	Protoberberine-type alkaloid	>100	[66]
Tetrahydropalmatine	Protoberberine-type alkaloid	>100	[66]
Higenamine	Benzylisoquinoline-type alkaloid	1.47	[67]
Capsaicin	Organic amine-type alkaloid	0.6	[68]
Arborinine	Acridone-type alkaloid	<0.1	[64]
Melatonin	Indole-type alkaloid	Untested	[69]

participates in the enzymatic demethylation of histones, which bind LSD1 to trap formaldehyde, as in the case of dimethylglycine dehydrogenase and sarcosine dehydrogenase. They further examined the crystal structure of the LSD1–CoREST–tetrahydrofolate complex to elucidate the demethylating reaction of folate [88]. Folate bound to the active center of LSD1, which is close to FAD. Further, the bound tetrahydrofolate received formaldehyde produced in the process of histone demethylation.

Terpenoids

Terpenoids are synthesized from isoprenoid structures with a $(C_5H_8)_n$ carbon skeleton [89, 90]. Based on the number of isoprenoid fragments, terpenoids are usually classified as monoterpenes (C_{10}), sesquiterpenes (C_{15}), diterpenes (C_{20}), sesterterpenes (C_{25}), and triterpenoids (C_{30}). Preclinical and clinical studies confirmed that plant terpenoids display a wide array of important pharmacological properties against malaria, cancer, inflammation, and infectious diseases [91, 92]. Terpenoids are mainly enriched in grains, green foods, and soybean plants and affect epigenetic modifications such as inhibiting histone deacetylase or increasing histone H3 acetylation levels to increase the expression of p21 and p27 [93, 94].

Rhizoma zedoariae is a well-known traditional Chinese medicine with its traditional efficacy of promoting blood circulation and removes blood stasis. It contains numerous terpenoid-based constituents and has exhibited strong anticancer activity in modern pharmacological studies [95, 96]. Therefore, we attempted to isolate LSD1 inhibitors from zedoary turmeric oil using a bioactivity-oriented CCC technique [97]. Four sesquiterpene-based inhibitors, including

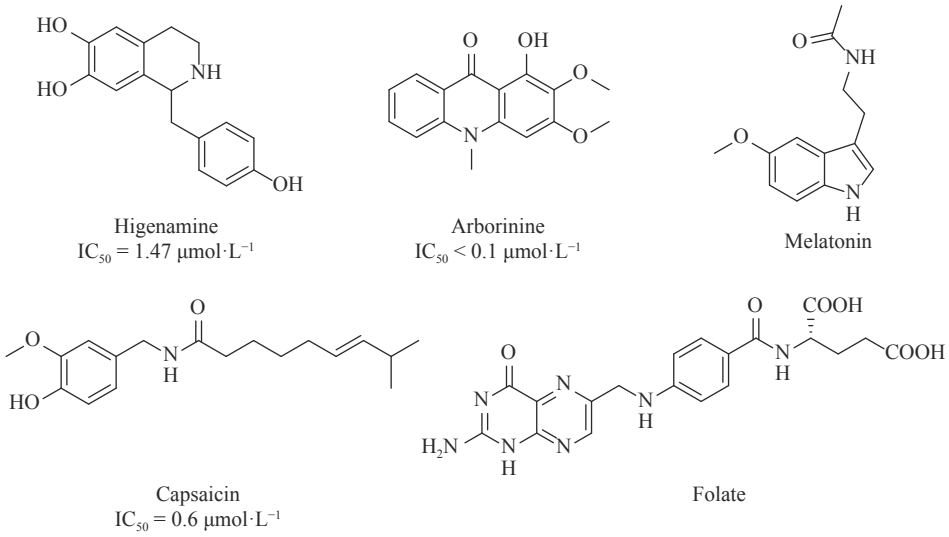


Fig. 10 Other alkaloids-based LSD1 inhibitors

curcumenone, isogermafurenolide, neocurdione, and curcumol, were isolated (Fig. 11). Their IC_{50} values were 6.61, 3.97, 9.81 and 21.22 μmol·L^{-1}, respectively, with inhibition ratios stronger than or equal to that of the positive control, tranylcypromine. Furthermore, isogermafurenolide is a reversible noncompetitive inhibitor of LSD1 that dose-dependently promotes H3K4me2 accumulation and increases CD86 expression in MDA-MB-231 cells. Isogermafurenolide also inhibited MDA-MB-231 cell migration in a dose-dependent manner by increasing the expression of E-cadherin and decreasing the expression of N-cadherin, and it showed nearly no toxicity to normal human mammary MCF-10A cells at 100 μmol·L^{-1}.

Sakane *et al*. [98] first studied the LSD1 inhibition of the acyclic sesquiterpene farnesol and the diterpenoid geranylgeranoic acid (GGA). GGA is a naturally all-*trans* linear terpenoid derived from medicinal plants [99]. GGA and farnesol dose-dependently inhibited LSD1 activity, with IC_{50} values of 47 and 120 μmol·L^{-1}, respectively. GGA induced neurotrophin receptor kinase-2 (*NTRK2*) gene expression along with up-regulation of H3K4me2 on the regulatory regions of *NTRK2* in human neuroblastoma SH-SY5Y cells. Schulte *et al*. [100] discovered that LSD1 inhibition resulted in the accumulation of H3K4me2 in SH-SY5Y cells and SH-SY5Y cell-loaded xenograft mice. GGA also inhibited the proliferation and neuronal phenotype of SH-SY5Y cells through upregulation of *NTRK2* or tropomyosin-related kinase receptor B gene expression [101]. Yabuta *et al*. [102] further found that GGA induced the dissociation of LSD1 from chromatin and its relocation to the cytoplasmic space in human hepatoma-derived huH-7 cells. Therefore, GGA was shown to be a promising cancer-preventive epigenetic therapeutic agent.

Phenol secoiridoids, a special type of terpenoids, are naturally present in extra virgin olive oil and have anticancer properties [103]. Oleacein is a biophenol secoiridoid that suppresses the demethylase activity of LSD1 in a dose-dependent manner, with a mean IC_{50} of 2.5 μmol·L^{-1} [104]. *In silico* docking and molecular dynamic simulation approaches showed that oleacein produced hydrogen bonds with M332, K661, and A331 as well as hydrophobic interactions with

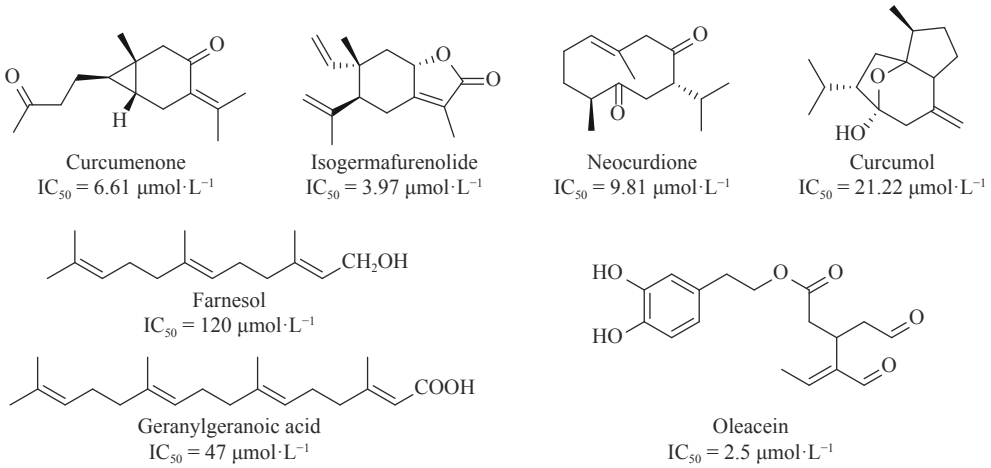


Fig. 11 Terpenoids-based LSD1 inhibitors

V811, F538, R316, and V333. Oleacein was also predicted to generate π-cation interactions with W751 and alter the binding of LSD1 to chromatin. Moreover, oleacein completely inhibited stemness-related SOX2 protein expression in cancer stem cells and induced pluripotent stem cells, which specifically occurs via an LSD1-targeted distal enhancer. Nest, Javier' group [105] utilized three-dimensional (3D) quantitative structure–activity relationship-based virtual profiling with phenotypic analysis to predict that oleacein could reduce the proportion of aldehyde dehydrogenase-positive cancer stem cell-like proliferating cells. Overall, oleacein as a secoiridoid-based LSD1 inhibitor suppressed the functional traits of cancer stem cells.

Phenanthraquinone and phenylpropanoids

Our group [106] used bioactivity-guided CCC to isolate natural LSD1 inhibitors from *Salvia miltiorrhiza* (Danshen), a famous traditional Chinese medicine used for its traditional effects of activating blood circulation to remove blood stasis, and modern pharmacological studies have shown that it possesses antitumor activity [107, 108]. Because *S. miltiorrhiza* contains hydrosoluble and liposoluble compounds, we performed an integrative CCC separation. Hydrosoluble and liposoluble fractions from *S. miltiorrhiza* were first separated, and then the two fractions were further separated using a solvent system: *n*-butanol : acetic acid : water (4 : 1 : 5, *V*/*V*) and petroleum ether : ethyl acetate : methanol : water (5 : 5 : 4 : 6, *V*/*V*), respectively. Ultimately, two hydrosoluble compounds (salvianolic acid B and rosmarinic acid) and four liposoluble compounds (dihydrotanshinone I, cryptotanshinone, tanshinone I, and tanshinone IIA) were obtained (Fig. 12). The LSD1 IC_{50} values of salvianolic acid B and rosmarinic acid were 0.11 and 20.93 μmol·L^{-1}, respectively. Salvianolic acid B, a phenylpropanoid tetramer, is used to prevent cancer, treat cardiocerebral vascular diseases, promote stem cell proliferation and differentiation, and antagonize hepatic/renal fibrosis [109, 110]. Salvianolic acid B was shown to dose-dependently increase H3K4me2 accumulation and CD86 expression in MDA-MB-231 cells and served as a reversible inhibitor. Molecular docking analysis showed that phenol hydroxyls and carboxyls of salvianolic acid B form hydrogen bonds with Glu801, Glu308, and Ser289, and the benzene ring of salvianolic acid forms hydrophobic or π–π stacking interactions. Furthermore, salvianolic acid B dose-dependently reduced MDA-MB-231 cell viability and inhibited cell migration.

The other four phenanthraquinones (dihydrotanshinone I, cryptotanshinone, tanshinone I, and tanshinone IIA) had LSD1 IC_{50} values of 15.85, 9.02, 16.45, and 1.20 μmol·L^{-1}, respectively. Cryptotanshinone, a widely studied active ingredient, has diverse pharmacological properties, including anticancer, anti-inflammatory, and antifibrotic effects, as well as protecting against metabolic, cardiovascular, and neural disorders [111, 112]. Wu *et al*. [113] found that cryptotanshinone increased the expression of H3K9me1 and H3K9me2 in human prostate cancer LNCaP cells. Additionally, it altered the interaction between LSD1 and the androgen receptor and

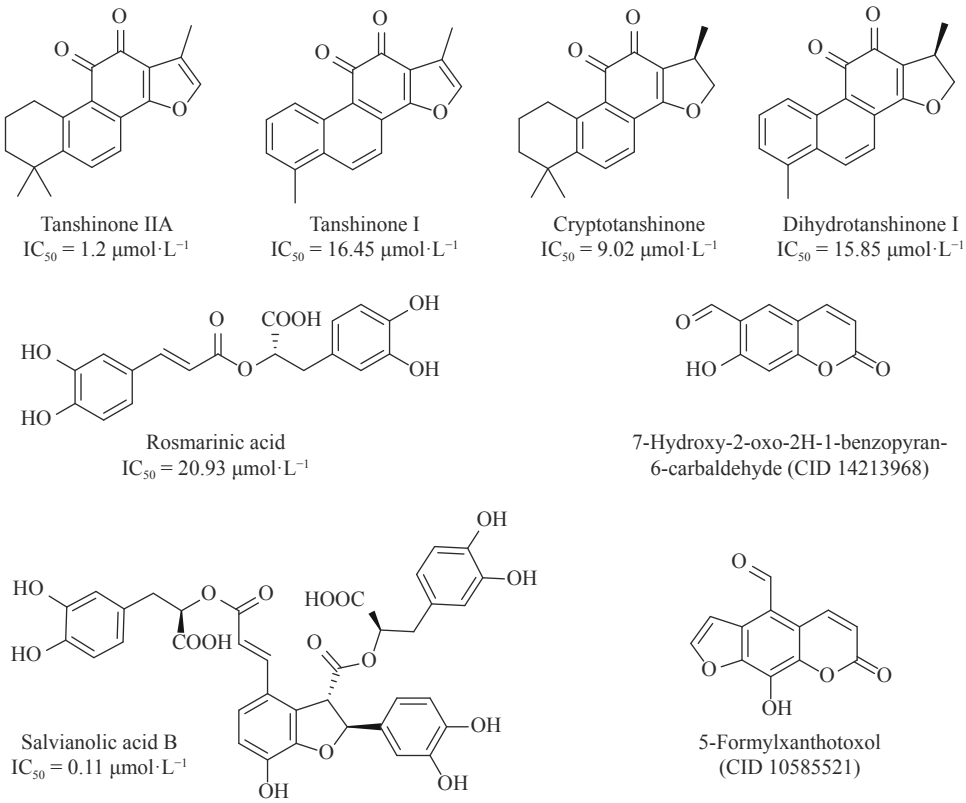


Fig. 12 Phenanthraquinone and phenylpropanoids-based LSD1 inhibitors

repressed the promoter of androgen receptor target genes without influencing the translocation or degradation of the androgen receptor. Therefore, cryptotanshinone downregulated androgen receptor signaling through the inhibition of LSD1 and the transcriptional activity of the androgen receptor to inhibit the growth of androgen receptor-positive prostate cancer cells. This could serve as the basis for the development of cryptotanshinone as a potential therapeutic agent for androgen receptor-positive prostate cancer.

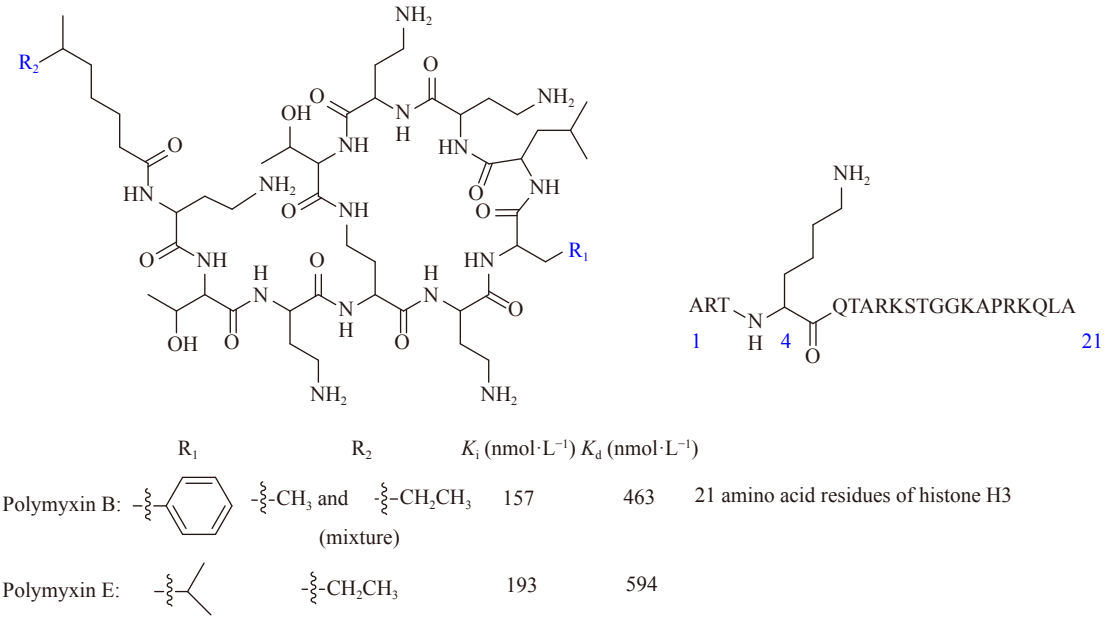
7-Hydroxy-2-oxo-2H-1-benzopyran-6-carbaldehyde and 5-formylxanthotoxol are coumarin-based compounds. They were selected from the traditional Chinese medicine database and are expected to be good candidates for inhibiting LSD1 activity using Lipinski's rule and steered molecular dynamics simulation [114]. However, *in vitro* and *in vivo* experiments should be performed to verify their LSD1 inhibitory activity.

Polypeptides

Polymyxins (also known as colistin) are natural cyclic peptides that act as antibiotics and are used against multidrug-resistant bacteria [115-117]. The chemical structure of polymyxins B and E are similar except for the side chains in the R_1 and R_2 groups (Fig. 13). Polymyxins B and E were shown to increase the melting temperature of the LSD1-CoREST complex by 6°C and competitively inhibit LSD1 against H3K4, with K_i values of 157−193 nmol·L^{-1}, respectively [118]. However, polymyxin E did not affect cell proliferation or the accumulation of H3K4me1/H3K9me2 in cultured leukemia MV4-11 cells. In the co-crystallization of LSD1-CoREST and polymyxins, electron density maps showed large circular peaks. The macrocyclic region of polymyxin B/E could be modeled in these maps, whereas the linear aliphatic chain was assigned zero occupancy. Next, polymyxins exhibited high-affinity binding with the negatively charged residues of LSD1 because the affinity for inhibitors is 10-fold decreased (K_d = 4.7 mmol·L^{-1}) in a mutated LSD1 with a Glu379 substitution. Overall, the positive charges of polymyxins with a circular crown are critical for the interaction with the negatively charged residues of LSD1.

LSD1 can catalyze the oxidative demethylation of mono- and dimethylated H3K4, thus H3K4me1/2 were LSD1 substrates. In the 3D structure of LSD1-CoREST bound to a 21 N-terminal amino acid of histone H3 peptide, the core of the peptide structure formed intramolecular H-bonds with Arg2, Gln5, and Ser10, and charged side chains on the surface reduced electrostatic interactions with the peptide [119, 120]. Methylated Lys4 interacted with a solvent inaccessible position in front of FAD. Therefore, H3K4me1/2 residues (21 N-terminal amino acids of histone H3) were a stronger inhibitor, with a K_m value of 3.4 μmol·L^{-1} and a K_i value of 0.098 μmol·L^{-1} [121]. Meng *et al*. [122] designed an LSD1 peptide inhibitor on the strength of its substrate H3 peptide. Gold nanorods were used to deliver the native peptide into human mesenchymal stem cells. This stable H3 peptide inhibited the activation of LSD1 and further induced the differentiation of human mesenchymal stem cells.

Suzuki' group [123-126] synthesized many LSD1 inactivators based on the H3 peptide. Phenylcyclopropylamine (PCPA) was coupled to a lysine carrier moiety at the nitrogen atom of Lys-4 of a 21-amino-acid LSD1 substrate peptide to yield PCPA-Lys-4 H3-21 [123]. PCPA-Lys-4 H3-21 strongly inhibited LSD1 activity with an IC_{50} of 0.16 μmol·L^{-1} in a time- and concentration-dependent manner. They also replaced the PCPA moiety of PCPA-Lys-4 H3-21 with 2,5-dihydro-1H-pyrrole (DHP) to obtain DHP-Lys-4 H3-21, which inhibited LSD1 activity with an IC_{50} of 0.223 μmol·L^{-1} [124]. Next, 11 *N*-terminal amino acids of histone H3



	R_1	R_2	K_i (nmol·L^{-1})	K_d (nmol·L^{-1})	
Polymyxin B:		(mixture)	157	463	21 amino acid residues of histone H3
Polymyxin E:			193	594	

Fig. 13 Polypeptides-based LSD1 inhibitors

based LSD1 inactivators were also designed and synthesized [125]. H3-21 of PCPA-Lys-4 H3-21 were replaced with a histone H3-11 peptide to obtain PCPA-Lys-4 H3-11, which inhibited LSD1 activity with an IC_{50} of 0.154 μmol·L^{-1}. The side-chain length of Lys-4 of PCPA-Lys-4 H3-11 was shortened to acquire PCPA-Orn-4 H3-11, which also inhibited LSD1 activity with an IC_{50} of 0.180 μmol·L^{-1}. Furthermore, they designed and synthesized new peptide-based LSD1 inactivators by incorporating *α*,*α*-disubstituted amino acids into PCPA-Lys-4 H3-21 [126]. These compounds were the most potent and selective LSD1 inactivators with a smaller IC_{50} values of 0.0891, 0.0548, and 0.0724 μmol·L^{-1}, respectively. Culhane *et al*. [127] further replaced the substituent groups of PCPA-Lys-4 H3-21, including hlorovinyl, *endo*-cyclopropylamine, and hydrazine, to synthesize a series of LSD1 inhibitors. Propargyl-Lys-4 H3-21, *N*-methylpropargyl-Lys-4 H3-21, *cis*-3-chloroallyl-Lys-4 H3-21, *trans*-3-chloroallyl-Lys-4 H3-21, and hydrazino-Lys-4 H3-21 were obtained, of which the K_i values were 0.775, 0.107, 0.955, 0.763, and 0.00435 μmol·L^{-1}, respectively. Therefore, histone H3 peptide-based LSD1 inactivators have broad prospects.

Stilbenes and diarylheptanoids

Stilbenes are an important active ingredient in natural substances. Stilbene-based compounds have wide biological activities [128, 129]. Resveratrol (Fig. 14) is a well-known natural stilbene that has promising effects against cardiovascular disease, inflammation, Alzheimer's disease, and cancer [130-132]. Duan *et al*. [133] found that resveratrol showed inhibitory activity against LSD1 with an IC_{50} value of 10.20 μmol·L^{-1}. They then designed and synthesized a sequence of resveratrol-based inhibitors. Compounds 4e and 4m (Fig. 14), with hydroxyl, bromine, and amidoxime substituents on the two phenyl rings, displayed more potent LSD1 inhibition than resveratrol, with IC_{50} values of 121.23 and 123.86 nmol·L^{-1}, respectively. Compounds 4e and 4m dose-dependently increased the H3K4me2 abundance and the mRNA level of CD86 in MGC-803 cells. Next, they further designed and synthesized stilbene-based LSD1 inhibitors [134]. The pyridine ring was replaced with a benzene ring of stilbene to obtain compound 8c with a fluorophenol and amidoxime substituent. Compound 8c showed active LSD1 inhibition (IC_{50} = 283 nmol·L^{-1}), and it up-regulated the expression of H3K4me2 and CD86 in human leukemia THP-1 cells. Furthermore, compound 8c inhibited the proliferation of THP-1 and MOLM-13 cells.

Curcumin is a natural diarylheptanoid (Fig. 14) found in the rhizome of *Curcuma longa* (turmeric) and in other *Curcuma* spp. [135]. It has been shown to be beneficial against metabolic syndrome, inflammatory conditions, and pain and has diverse anti-inflammatory and anticancer properties [136, 137]. Wang *et al*. [138] found that curcumin has an inhibitory effect on LSD1 with an IC_{50} value of 9.6 μmol·L^{-1}. Based on a structure-based drug design strategy, they synthesized a series of curcumin analogs that were identified as novel LSD1 inhibitors. The compounds WA20 and WB07 (Fig. 14) showed potent LSD1 inhibitory activity, with IC_{50} values of 2.8 and 0.8 μmol·L^{-1}, respectively, which were both stronger than that of curcumin. Molecular docking analysis indicated that WA20 and WB07 bound to the active site of

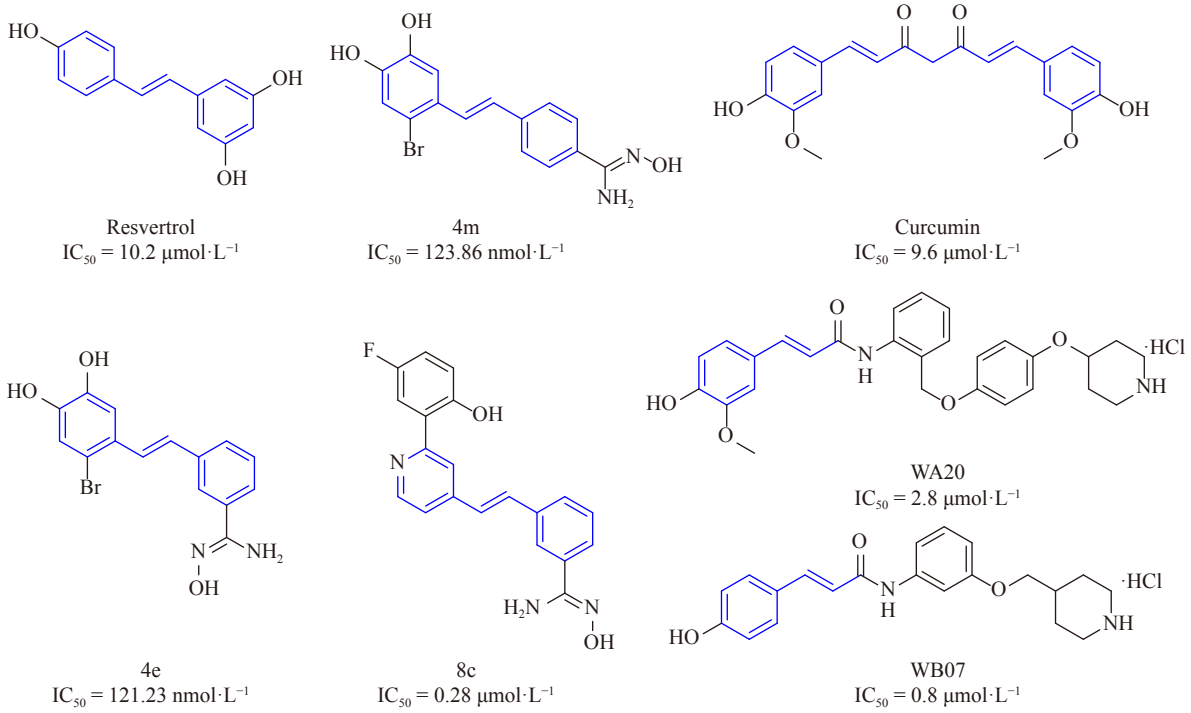


Fig. 14 Stilbenes and diarylheptanoids-based LSD1 inhibitors

LSD1 with the key residues of Asp555 and Asp556. Moreover, WA20 showed an antiproliferative effect on A549 cells.

Others

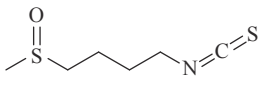
Sulforaphane (Fig. 15) is an isothiocyanate that is present in cruciferous vegetables and is a promising compound for cancer treatment [139, 140]. Sulforaphane, a histone deacetylase 5 (HDAC5) inhibitor, inhibits HDAC5 transcription by blocking upstream transcription factor 1 activity. Additionally, it facilitates the ubiquitination and degradation of LSD1 [141]. Therefore, sulforaphane blocks breast cancer growth *via* the HDAC5–LSD1 axis. In addition, combination treatment with sulforaphane and HCI-2509 (a highly potent, specific LSD1 inhibitor) led to synergistic tumor growth inhibition in MDA-MB-231 cells and in athymic nude mice bearing MDA-MB-231 xenografts. The reduced level of full-length PARP-1 in xenograft tumors proved that the combination therapy promoted tumor cell apoptosis. Meanwhile, the expressions of HDAC5 and LSD1 in xenograft tumors were attenuated following treatment with sulforaphane alone or in combination with HCI-2509. During the *in vivo* experiment, drug toxicity was acceptable, as verified by a modest weight loss in mice treated with the combination treatment. Therefore, sulforaphane effectively inhibited the growth of MDA-MB-231 xenografts and showed significant growth inhibition when treated in combination with HCI-2509 *in vivo*. Thai *et al*. [114] screened natural LSD1 inhibitors from a traditional Chinese medicine database using docking and molecular dynamic simulations. Using a multi-step screening approach involving Lipinski's rule, docking, and steered molecular dynamics simulations, two candidates, i.e., *cis*-1,2,5,6 tetrahydrophthalic anhydride (CID 6810) and chelidonic acid (CID 4678324) (Figs. 15), were identified as having inhibitory LSD1 activity better than that of the conference compound. Their IC_{50} values were predicted to be in the nanomolar range, and these compounds are non-toxic with LD_{50} values larger than 1000 $mg \cdot kg^{-1}$ for both mouse and rat models. These compounds were found to be more selective toward LSD1 than MAO-A/B.

Discussion and Outlooks

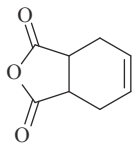
LSD1 was the first enzyme reported to exhibit histone demethylase activity in 2004. The biological functions of LSD1 have since been shown to play various roles in mammalian biology. LSD1 mediates multiple biological processes and is related to the initiation and development of cancer. Inactivation of LSD1 has been shown to inhibit cancer cell proliferation, invasion, and migration. Therefore, LSD1 has been considered a potential therapeutic target for cancer.

In view of its enzyme activity and overexpression in numerous human malignancies, many studies have focused on the development of its pharmacologic inhibitors. Natural products offer unique features compared with general synthetic agents, including abundant scaffold diversity and structural complexity. These features confer advantages for novel drug research and development. At present, many anticancer drugs are derived from natural active ingredients. To data, dozens of natural product-based LSD1 inhibitors have been discovered. These natural products include flavonoids, alkaloids, terpenoids, phenanthraquinone, phenylpropanoids, polypeptides, stilbenes, and diarylheptanoids and serve as potential LSD1 inhibiting agents for the treatment of cancer.

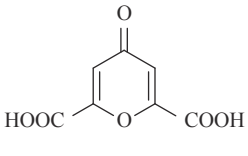
Accumulating evidence from current studies indicates that flavonoids and alkaloids show stronger LSD1 inhibitory activity than other compounds. The carbon skeleton of flavonoids can dock well with the active site of LSD1, and the different substitutions and substituent sites of the skeleton affect its inhibition ratio. Research has shown that flavonoid monoglycosides exhibit stronger inhibitory activity against LSD1 than that of their aglycones, and the sugar moiety may play a role in this inhibition. As for alkaloids, quaternary berberine alkaloids have been shown to exhibit stronger inhibitory activity than that of tertiary protoberberine alkaloids. Therefore, the positive charge of berberine alkaloids is a crucial factor for benzyl isoquinoline alkaloids. In general, research on exploring natural product-based LSD1 inhibitors lags behind that of numerous synthetic inhibitors. Natural active molecules should be used as templates for structural modification to obtain better LSD1 inhibitors with stronger suppressing activity and fewer side effects, and the LSD1-based anticancer pharmacological effects of natural inhibitors should also be further explored. Moreover, some significant natural active ingredients including coumarin [142], lignans [143], triterpenoids [144], natural steroids [145], marine natural products [146], and fungal metabolites [147] could be sources of novel natural LSD1 inhibitors.



Sulforaphane



Cis-1, 2, 5, 6-tetrahydrophthalic anhydride (CID 6810)



Chelidonic acid (CID 4678324)

Fig. 15 Other natural LSD1 inhibitors

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