

# Research Progress on the Multi-target Pharmacological Effects of Isolinderalactone

Huizhen PEI, Jiaru YE, Shuang REN, Linbo JIA, Xichun HUANG, Chenghao JIN\*

College of Life Science and Biotechnology, Heilongjiang Bayi Agricultural University, Daqing 163319, China

**Abstract** By reviewing domestic and international literature, a systematic summary on the pharmacological effects and molecular mechanisms of isolinderalactone (Iso) was conducted. The results indicate that Iso mitigates A $\beta$ 42-induced neuronal damage by inhibiting the JNK signaling pathway, exerting an anti-Alzheimer's disease effect. Iso specifically inhibits *Helicobacter pylori*. By activating the LXR $\alpha$  pathway, Iso suppresses polarization of macrophage M1 and reduces production of inflammatory mediator, demonstrating anti-ulcerative colitis activity. By inducing ROS accumulation, regulating mitochondrial apoptosis pathways, and activating the MAPK pathway, Iso inhibits the cell proliferation of lung cancer, breast cancer, and colorectal cancer. Iso exhibits multi-target pharmacological activity and holds promise for applications in neurodegenerative diseases, infections, inflammation, and cancer prevention and treatment.

**Key words** Isolinderalactone, Anti Alzheimer's disease, Antibacterial, Anti-inflammatory, Anti-cancer, Molecular mechanism

## 1 Introduction

*Lindera aggregata* belongs to *Lindera* of Lauraceae, and is mainly produced in Zhejiang and Hunan province. Traditional Chinese medicine theory believes that it has the effects of promoting qi circulation, relieving pain, warming the kidneys, and dispersing cold<sup>[1]</sup>. Isolinderalactone (Iso) is a lipophilic sesquiterpene lactone natural compound extracted from dried root tubers of *L. aggregata*. Its molecular formula is C<sub>15</sub>H<sub>16</sub>O<sub>3</sub>, and it is a white needle shaped crystal that is soluble in organic solvents such as methanol, ethanol, and DMSO. Modern pharmacological research has found that Iso has various pharmacological effects such as anti (AD), antibacterial, anti-inflammatory, and anti-cancer effects, and has therefore received widespread attention from researchers at home and abroad. In this paper, the pharmacological effects and molecular mechanisms of Iso are reviewed, providing a theoretical basis for its in-depth research and development.

## 2 Pharmacological effects and molecular mechanisms

**2.1 Anti AD effect** Alzheimer's disease (AD) is a neurodegenerative disease with insidious onset and evolutionary development. The core pathological manifestation is abnormal deposition of  $\beta$ -amyloid protein in the brain, forming senile plaques, and excessive phosphorylation of microtubule associated protein tau protein, forming neurofibrillary tangles, which further leads to neuronal damage and brain tissue atrophy. Research has found that Iso has good anti AD effects.

Xiong Li<sup>[2]</sup> tested the effect of Iso treatment on  $\beta$ -amyloid 42 (A $\beta$ 42) induced pheochromocytoma 12 cells (PC12) in rat adre-

nal medulla and primary neuronal activity through cell viability assay. It was found that pretreatment with 10  $\mu$ M of Iso can restore the viability of PC12 cells from 50% to 80%, and the viability of primary neurons from about 38% to 65%, indicating that Iso can effectively improve the viability of PC12 cells and neurons. The effect of Iso on mitochondrial membrane potential induced by A $\beta$ 42 in PC12 cells and primary neurons was further investigated through mitochondrial membrane potential detection experiment (JC-1). The results showed that the JC-1 red-to-green fluorescence ratio in the Iso treatment group was significantly increased compared to the control group, indicating that Iso can improve mitochondrial disorder and reduce damage to PC12 cells and neurons. Further, the effect of Iso on the expression levels of neuronal apoptosis related proteins was detected by Western Blot (WB). The results showed that Iso can upregulate the expression level of anti-apoptotic protein B-cell lymphoma-2 (Bcl-2) and downregulate the expression level of pro-apoptotic protein Bcl-2 related X protein (Bax), indicating that Iso can exert an inhibitory effect on neuronal apoptosis by regulating the expression level of apoptosis related proteins. The molecular mechanism of Iso's anti AD effect was further investigated through WB experiments. The results showed that 10  $\mu$ M of Iso significantly reduced the expression levels of JNK phosphorylation in PC12 cells and in the hippocampus of double transgenic mice (APP/PS1), indicating that Iso mainly exerted its anti AD effect by inhibiting the JNK signaling pathway. In summary, Iso can alleviate A $\beta$ 42 induced damage to PC12 cells and neurons by inhibiting the expression levels of JNK phosphorylation, indicating that Iso has good anti AD activity and is expected to be developed as a novel drug for anti AD treatment.

**2.2 Antibacterial effect** *Helicobacter pylori* is a gram negative bacterium that can colonize in the gastric mucosa for a long time<sup>[3]</sup>. Long-term infection can lead to gastric mucosal atrophy and intestinal metaplasia, induce peptic ulcers, and promote the occurrence of precancerous lesions such as dysplasia and even gastric cancer. Research has found that Iso has a good anti *H. pylori* effect.

Received: March 15, 2026 Accepted: May 5, 2026

Supported by Central Government Funds for Local University Reform and Development (Talent Cultivation Program) (2020GSP16); the College Students Innovation and Entrepreneurship Training Program Project in Heilongjiang Province (202510223075).

\* Corresponding author. Chenghao JIN, professor, doctoral supervisor.

Qin Chun *et al.*<sup>[4]</sup> detected the minimum inhibitory concentration (MIC) of Iso against *H. pylori* and non *H. pylori* using microdilution method. The results showed that the MIC of Iso against both sensitive and resistant *H. pylori* was between 8 – 16  $\mu\text{M}$ , indicating that Iso has a good inhibitory effect on *H. pylori*. Further research on non *H. pylori* revealed that their MIC was all  $>128$   $\mu\text{M}$ , indicating that Iso does not have a significant inhibitory effect on non *H. pylori* and can specifically target *H. pylori*. In summary, Iso has a good inhibitory effect on both sensitive and drug-resistant *H. pylori*, and it can specifically act on *H. pylori*, indicating that Iso has good anti *H. pylori* activity and is expected to be developed as a novel drug against *H. pylori*.

**2.3 Anti-inflammatory effect** Ulcerative colitis (UC) is a chronic non-specific inflammatory disease of colitis, with lesions mainly concentrated in the mucosa and submucosa of the rectum and colon, showing continuous and diffuse distribution. The core pathological manifestations are abdominal pain, diarrhea, and mucous purulent bloody stools<sup>[5]</sup>. Research has found that Iso has a good anti UC effect.

Huang M *et al.*<sup>[6]</sup> detected the effect of Iso on the anti-inflammatory activity of macrophages through macrophage polarization and inflammation medium detection experiments. The results showed that 3  $\mu\text{M}$  of Iso significantly inhibited macrophage M1 polarization and the production of inflammatory mediators such as nitric oxide (NO) and interleukin-6 (IL-6), indicating that Iso has significant anti-inflammatory activity. The effect of Iso on phagocytic function of macrophage was further investigated through flow cytometry experiments. The results showed that 1.5 – 3.0  $\mu\text{M}$  of Iso can promote macrophage phagocytosis of apoptotic intestinal epithelial cells, and the phagocytic index increased to 20% – 25%, indicating that Iso can alleviate intestinal damage by enhancing macrophage phagocytic function. The effect of Iso on the expression level of liver X receptor  $\alpha$  (LXR $\alpha$ ) target genes was further investigated through WB experiments. The results showed that Iso can significantly upregulate the expression level of LXR $\alpha$  target genes, indicating that Iso can exert anti UC effects by regulating the expression of LXR $\alpha$  and its target genes. Small interfering RNA (siRNA) technology was further used to silence LXR $\alpha$  and detect its role in Iso's anti UC disease. It was found that when LXR $\alpha$  was silenced or inhibited, the anti-inflammatory effect of Iso completely disappeared, indicating that Iso can exert its anti UC effect by activating the LXR $\alpha$  signaling pathway. In summary, Iso can activate the LXR $\alpha$  pathway, inhibit macrophage M1 polarization, reduce the production of inflammatory mediators, enhance macrophage phagocytic ability, and thus exerting significant anti UC effects. It indicates that Iso has good anti UC activity and is expected to be developed as a novel drug for anti UC.

**2.4 Anti-cancer effect** Cancer cells are highly invasive and prone to developing resistance to drugs such as cisplatin and 5-fluorouracil, making current clinical treatment extremely difficult. Chinese herbal medicine has shown unique advantages in cancer treatment due to its low drug resistance. Studies have shown that

Iso has a good inhibitory effect on lung cancer, breast cancer and colorectal cancer.

**2.4.1 Anti lung cancer effect.** The core pathological manifestation of lung cancer is abnormal proliferation and differentiation disorders of bronchial mucosa or alveolar epithelial cells, forming invasive malignant tumor tissue, which invades surrounding normal lung tissue, and causes distant metastasis. Research has found that Iso has good anti lung cancer effects.

Zheng Qian *et al.*<sup>[7]</sup> detected the inhibitory effect of Iso on the growth of lung cancer A549 cells through CCK-8 experiment. The results showed that Iso inhibited the growth of A549 cells in a concentration (5, 10, 15, 20  $\mu\text{M}$ ) and time (24, 48, 72 h) dependent manner. Moreover, the inhibitory effect was most significant after 48 h of treatment, and the half inhibitory concentration ( $IC_{50}$ ) was 15  $\mu\text{M}$ , indicating that Iso has a good inhibitory effect on A549 cells. The effect of Iso on apoptosis of A549 cells was further investigated using flow cytometry and Annexin V-FITC/PI fluorescence double staining assay. It was found that after 48 h of treatment with Iso, A549 cells showed significant apoptosis compared to the control group, and the apoptosis rate was significantly increased, indicating that Iso has a promoting effect on apoptosis of A549 cells. The effect of Iso on ROS levels in A549 cells was further investigated through flow cytometry experiments. The results showed that treatment with 15  $\mu\text{M}$  of Iso alone for 48 h could increase the level of ROS in A549 cells, indicating that Iso can induce a large accumulation of ROS in A549 cells and trigger intracellular oxidative stress response. The effect of Iso on the expression levels of apoptosis related proteins was further investigated through WB experiments. The results showed that Iso could upregulate the expression level of pro apoptotic protein Bax and downregulate the expression level of anti apoptotic protein Bcl-2 in A549 cells, and the Bax/Bcl-2 ratio was significantly increased. In summary, Iso can induce a large accumulation of ROS in A549 cells, regulate the expression of apoptosis related proteins, ultimately induce cell apoptosis, and inhibit A549 cell growth. It indicates that Iso has good anti lung cancer activity, and is expected to be developed as a novel drug for the treatment of lung cancer.

**2.4.2 Anti breast cancer effect.** Breast cancer is a malignant tumor originating from breast duct epithelium. According to statistics, one in seven women is affected<sup>[8]</sup>. The core pathological manifestation is abnormal proliferation of mammary ductal epithelial cells, forming invasive malignant tumor tissue, invading surrounding normal mammary tissue, and causing distant metastasis. Studies have found that Iso has a good anti breast cancer effect.

Liu Ziyao *et al.*<sup>[9]</sup> tested the inhibitory effect of Iso on the proliferation of breast cancer MCF-7 cells through MTT test. The results showed that Iso inhibited the proliferation of MCF-7 cells in a concentration (3.125, 6.250, 12.500, 25.000  $\mu\text{M}$ ) and time (24, 48, 72 h) dependent manner. The  $IC_{50}$  values for 24, 48, and 72 h were 31.08, 25.61, and 17.86  $\mu\text{M}$ , respectively, indicating that Iso has a significant inhibitory effect on the proliferation of MCF-7 cells. The effect of Iso on the cell cycle of MCF-7

cells was further investigated using flow cytometry. The results showed that after 48 h of treatment with different concentrations (10, 20, and 40  $\mu\text{M}$ ) of Iso, the number of cells in G2/M phase increased by 5.39%, 19.22%, and 19.97%, respectively, indicating that a certain concentration of Iso can inhibit cell proliferation by blocking MCF-7 cells in the G2/M phase. The effect of Iso on mitochondrial membrane potential in MCF-7 cells was further investigated through JC-1 experiments. The results showed that after 48 h of treatment with different concentrations of Iso (10, 20, 40  $\mu\text{M}$ ), the mitochondrial membrane potential significantly decreased, indicating that Iso can induce apoptosis in MCF-7 cells by regulating the mitochondrial membrane potential. The expression levels of apoptosis related proteins were further detected through WB experiments. The results showed that Iso could upregulate the expression level of cleaved caspase-3, which promotes the activation of apoptotic proteins, and downregulate the expression level of anti apoptotic protein Bcl-2. In conclusion, Iso inhibits the proliferation of MCF-7 cells in a concentration and time dependent manner. Its mechanism is to regulate the expression of apoptosis related proteins and induce apoptosis of MCF-7 cells by regulating mitochondrial membrane potential. It indicates that Iso has good anti breast cancer activity, and is expected to be developed as a new drug against breast cancer.

**2.4.3 Anti colorectal cancer effect.** The core pathological manifestation of colorectal cancer (CRC) is abnormal proliferation of colorectal mucosal epithelial cells, forming invasive malignant tumor tissue, invading surrounding normal colorectal tissue, and causing distant metastasis. Research has found that Iso has good anti colorectal cancer effects.

Chen JS *et al.*<sup>[10]</sup> detected the inhibitory effect of Iso on the proliferation of CRC cells through MTT assay. The results showed that Iso inhibited proliferation of CRC cells in a dose-dependent manner (10, 15, 20, 25, 30  $\mu\text{M}$ ). At 24 h, the  $IC_{50}$  values of HCT15 and HCT116 CRC cells were (22.1  $\pm$  0.3) and (22.4  $\pm$  0.1)  $\mu\text{M}$ , respectively, indicating that Iso has significant inhibitory activity on proliferation of CRC cells. The effect of Iso on apoptosis of CRC cells was further investigated using flow cytometry. It was found that treatment of CRC cells with 40  $\mu\text{M}$  of Iso for 24 h resulted in a maximum increase of 15.9% in apoptosis rate, indicating that Iso can significantly induce apoptosis in CRC cells. The effects of Iso on the expression levels of CRC cell cycle related proteins and the molecular mechanism of Iso induced apoptosis in CRC cells were further detected through WB experiments. The results showed that treatment with 40  $\mu\text{M}$  of Iso for 24 h significantly upregulated the expression level of cyclin dependent kinase inhibitor 1A protein (p21) and downregulated the expression level of cyclin B and other related proteins. Moreover, Iso treatment could sustainably upregulate the expression level of MAPK related protein extracellular signal regulated kinase (ERK), temporarily upregulate the expression levels of mitogen activated protein kinase (P38) and JNK without significant changes in total

protein. In addition, ERK inhibitors can partially rescue Iso induced cell apoptosis. In summary, Iso induces apoptosis in CRC cells by activating the MAPK pathway, and its dose-dependent inhibition of CRC cell proliferation indicates that Iso has good anti CRC activity, and is expected to be developed as a novel drug for the treatment of CRC.

### 3 Conclusions and prospects

Iso has various pharmacological effects such as anti AD, antibacterial, anti-inflammatory, and anticancer. As a key sesquiterpene lactone compound in *L. aggregata*, its chemical separation, purification, and pharmacological activity research have achieved phased results. However, the research and clinical application of its drug functional mechanism are still in the early stages. In the future, it is necessary to continuously combine relevant molecular biology, cell biology, laboratory animal science, pharmacology, basic medicine and other knowledge theories and experimental techniques to conduct more comprehensive and deeper research on Iso at the cellular, molecular and animal levels, providing theoretical basis and data support for further drug development of Iso.

### References

- [1] YAN LL, WANG JF, LI QY, *et al.* Study on chemical constituents of *Lindera aggregata* (Sims) Kosterm. [J]. China Pharmaceuticals, 2013, 22(2): 16–17. (in Chinese).
- [2] XIONG L. Effect and mechanism of isolinderalactone against Alzheimer's disease[D]. Hangzhou: Zhejiang Academy of Medical Sciences, 2024. (in Chinese).
- [3] YU JY. Correlation between *Helicobacter pylori* and gastroesophageal reflux disease[J]. Journal of Ezhou University, 2025, 32(4): 110–112. (in Chinese).
- [4] QIN C, XU JY, WANG X, *et al.* Screening of the anti-*H. pylori* and its antibacterial spectrum of isolinderalactone[J]. Journal of Youjiang Medical University for Nationalities, 2022, 44(2): 155–157. (in Chinese).
- [5] VOELKER R. What is ulcerative colitis[J]. JAMA, 2024, 331(8): 716.
- [6] HUANG MC, LAN MY, LIU X, *et al.* Isolinderalactone regulates macrophage polarization and efferocytosis by activating the LXR $\alpha$  pathway against ulcerative colitis[J]. Chinese Medicine, 2025, 20: 152.
- [7] ZHENG Q, WANG XS, LIN MT, *et al.* Isolinderalactone induced A549 cells apoptosis via ROS-mediated mitochondrial apoptotic pathway[J]. Journal of Huizhou University, 2023, 43(3): 35–39. (in Chinese)
- [8] GADALETA E, THORN GJ, ROSS-ADAMS H, *et al.* Field cancerization in breast cancer[J]. The Journal of Pathology, 2022, 257(4): 561–574.
- [9] LIU ZY, YANG F, ZHAO CY, *et al.* Inhibitory effect of isolinderalactone on growth of human breast cancer MCF-7 cells and its mechanism [J]. Chinese Traditional and Herbal Drugs, 2019, 50(12): 2922–2927. (in Chinese)
- [10] CHEN JS, CHIU SC, HUANG SY, *et al.* Isolinderalactone induces apoptosis, autophagy, cell cycle arrest and MAPK activation through ROS-mediated signaling in colorectal cancer cell lines[J]. International Journal of Molecular Sciences, 2023, 24(18): 14246.