Trop J Nat Prod Res, April 2024; 8(4):6751-6756 **ISSN 2616-0684 (Print)**
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Review Article

Oridonin: A Mini Review on the Anti-Cancer, Anti-Inflammatory, Cardioprotective, Hepatoprotective, Renoprotective and Lung Protective Properties

Eric W.C. Chan[1]*, H.T. Chan[2], S.K. Wong[3]

[1]*Faculty of Applied Sciences, UCSI University, 56000 Cheras, Kuala Lumpur, Malaysia.*
[2]*Secretariat of International Society for Mangrove Ecosystems (ISME), Faculty of Agriculture, University of the Ryukyus, Okinawa 903-0129, Japan.*
[3]*School of Foundation Studies, Xiamen University Malaysia, Bandar Sunsuria, 43900 Sepang, Selangor, Malaysia.*

ARTICLE INFO

Article history:
Received 21 March 2024
Revised 11 April 2024
Accepted 15 April 2024
Published online 01 May 2024

ABSTRACT

Oridonin (ORI), an *ent*-kaurane tetracyclic diterpenoid from *Isodon rubescens*, is renowned for its anti-cancer properties. Known as Donglingcao, *I. rubescens* is a traditional Chinese herbal medicine that is widely used to treat sore throat, inflammation and gastrointestinal disorders. This mini-review is focused on the pharmacological activities of ORI other than anti-cancer properties. They include cardioprotective, hepatoprotective, renoprotective and lung protective properties of ORI. The pharmacological properties of ORI have not been reviewed before. Information on the effects and mechanisms of ORI in each pharmacological activity are tabulated with some explanations of technical terms used. The anti-asthmatic, anti-inflammatory, neuroprotective, immuno-suppressive, osteoblast protective and analgesic properties of ORI deserve more in-depth investigation. References used in this review are derived from Google, Google Scholar, PubMed and JStage, with search words based on the title and keywords.

***Keywords*:** *Isodon rubescens*, *Rabdosia rubescens*, Donglingcao, diterpenoid, pharmacological properties

Introduction

The genus *Isodon* (Lamiaceae family) consists of more than 150 species of perennial herbs that are widely distributed in tropical Africa, tropical and subtropical Asia, including Australia and the Pacific Islands.[1] There are 90 species and 21 varieties in China, found mainly in the southwest provinces.

Isodon rubescens (Hemsl.) H. Hara (synonyms: *Plectranthus rubescens*, *Rabdosia rubescens*) is a perennial herb that grows up to a meter in height. Stem shoots are covered with dense tomentose. The leaf blade is ovate, thin, papery with acuminate apex and serrate margin (Figure 1). The flower is light purple with two lips. Stamens and the style are exserted. The fruit is a small brown nut.[2,3] The Chinese name of *I. rubescens* is Donglingcao. It is a traditional Chinese medicinal herb that has been widely used to treat sore throats, inflammation and gastrointestinal disorders.[4]

Oridonin (ORI) was first isolated by Fujita *et al*.[5] from the leaf of *Isodon japonicus*. The diterpenoid from *I. rubescens* is well-known for its anti-cancer properties. There are several reviews on ORI and its cancer therapy.[6-11] Some reviews have included information on its cytotoxicity[12] and the structure-activity relationship (SAR) against cancer cells.[6] Anti-tumor activities are well elaborated in reviews of the pharmacy of ORI.[13,14] ORI and its analogs have been shown to exhibit potent anti-cancer activities by promoting apoptosis, inducing cell cycle arrest, inhibiting angiogenesis and suppressing metastasis in a broad spectrum of cancer types.[15]

*Corresponding author. E mail: chanwc@ucsiuniversity.edu.my, erchan@yahoo.com
Tel: +603-9101 8880

Citation: Chan EWC, Chan HT, Wong SK. Oridonin: A Mini Review on the Anti-Cancer, Anti-Inflammatory, Cardioprotective, Hepatoprotective, Renoprotective and Lung Protective Properties. Trop J Nat Prod Res. 2024; 8(4):6751-6756. https://doi.org/10.26538/tjnpr/v8i4.1

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria

ORI is therefore a multi-functional anti-cancer compound that modulates a network of cancer related targets and signaling pathways. Other pharmacological properties of ORI and its derivatives are anti-inflammatory, anti-neuroinflammatory, anti-bacterial, cardioprotective, neuroprotective, hepatorenal protective, lung protective and osteoblast protective activities.[4,13,16,17]

Chemistry

ORI ($C_{20}H_{28}O_6$) (Figure 2) is a highly oxygenated 7,20-epoxy-*ent*-kaurane tetracyclic diterpenoid.[18] There is an exo-methylene cyclopentanone moiety at position 16 in the D ring and a 6-hydroxyl-7-hemiacetal group in the B ring. The former is the active site for the anti-cancer and anti-inflammatory properties.[6,19] The *α,β*-unsaturated ketone (enone) system at the D ring is a Michael receptor (demarcated in red) that is biologically active due to its electrophilic groups.[20] Compounds with Michael receptors possess bioactivities such as anti-inflammatory and anti-cancer activities.

ORI has four hydroxy (OH) groups at positions 1, 6, 7 and 14, and two carbonyl groups at positions 15 and 16 of the D ring (Figure 2). The hydrogen bonding between the OH group at position 6 and the carbonyl group at position 15 has been shown to be critical for its anti-cancer activity.[5,6] The OH group at position 7 is also located very close to the active center and runs parallel with the OH group at position 14 position.[5] ORI is a molecule with a Michael receptor (demarcated in red) that had two carbonyl groups and an oxygen atom is biologically active due to its electrophilic groups.[20]

Pharmacological Activities

Selected pharmacological activities of ORI are listed in Table 1. The number of studies on cardioprotective, hepatoprotective, renoprotective and lung protective properties are seven, ten, six and ten, respectively.

The effects and mechanisms of the pharmacological activities of ORI in Table 1 are as follows:

Cardioprotective: ORI prolonged the survival of mice with cardiac allografts; inhibited NLR family pyrin domain containing protein 3 (NLRP3) inflammasomes; inhibited against myocardial fibrosis; preserved cardiac function; ameliorated cardiotoxicity in mice; and attenuated myocardial IR injury, oxidative injury, and cardiac

hypertrophy in mice. Mechanisms of ORI included attenuation of the nuclear factor kappa B (NF-κB) and NLRP3 pathways; suppression of apoptosis; regulation of autophagy activation; inhibition of gasdermin D (GSDMD)-induced pyroptosis; down-regulation of oxidative stress and the NLRP3 inflammasome pathway; promotion of p21-related autophagy; and modulation of the E2F transcription factor 1(E2F1)/sirtuin 6 (Sirt6)/peroxisome proliferator-activated receptor-γ coactivator 1α (PGC1α) pathway.

Hepatoprotective: ORI restored hepatic lipid homeostasis in mice; exerted potent anti-inflammatory effect in the liver of mice; protected against acute liver injury in mice; restored the hepatic urea cycle in mice; ameliorated liver fibrosis in mice; and exerted inductive effects on hepatic drug metabolizing enzymes, mRNA expression, and enzyme activity in humanized PXR mice. Amelioration of hepato-steatosis and lipo-toxicity *via* the liver X receptor α (LXRα)-(ATGL)/(EPT1) pathway; inhibition of the IκB kinase (IKK)/IκBα/NF-κB pathway in LX-2 cells; suppression of pro-apoptotic cytokine tumor necrosis factor-α (TNF-α) and c-Jun N-terminal kinases (JNK)-associated pro-apoptotic signaling; enrichment of the intestinal *Bacteroides vulgatus* microbiota; inhibition of liver inflammation, NLRP3 inflammasome, and xanthine oxidase activity; post-translational modifications of interleukin-1 receptor-associated kinase 4 (IRAK4) in the toll-like receptor 4 (TLR4) signaling pathway; and inhibition of the ATF4/PGC1α pathway and hepatic toxicity are the hepatoprotective mechanisms of ORI.

Renoprotective: ORI attenuated acute kidney injury (AKI) and renal fibrosis (RF) in mice; protected against inflammation of diabetic nephropathy in rats; and attenuated inflammation in human renal proximal tubular epithelial cells (HK-2 cells). Mechanisms of ORI included inhibition of oxidative stress, apoptosis and inflammation; reactive oxygen species (ROS) accumulation, JNK activation and NF-κB nuclear translocation; inhibition of the thioredoxin-interacting protein (TXNIP)/NLRP3 and NF-κB pathways; inhibition of the TLR4/p38- mitogen-activated protein kinase (MAPK) and TLR4/NF-κB signaling pathways; anti-inflammatory effect and inhibition of the activity of macrophage-inducible C-type lectin (Mincle), NF-κB and protein kinase B (Akt); and inhibition of inflammation in lipopolysaccharide (LPS)-induced bone marrow-derived (BMD) macrophages *via* suppression of the Akt-related pathways.

Figure 1: Flowers (left) and leaf (right) of *Isodon rubescens*.[1]

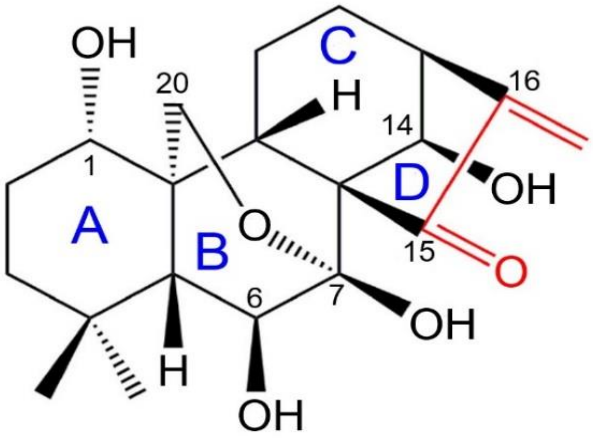

Figure 2: Chemical structure of oridonin.[15]

Table 1: Selected pharmacological activities of oridonin (ORI)

Activity	Effect and Mechanism	Reference
Cardioprotective		
	ORI, a natural IS agent, prolonged the survival of mice with cardiac allografts by attenuating the NF-kB and NLRP3 pathways.	21
	Exosomes from MSC treated with ORI alleviated myocardial IR injury in rats *via* suppressing apoptosis and regulating autophagy activation.	22
	ORI, a NLRP3 inflammasome inhibitor, inhibited MI-induced myocardial fibrosis and preserved cardiac function in mice.	23
	ORI protected myocardial IR injury in mice by inhibiting GSDMD-induced pyroptosis.	24
	ORI attenuated myocardial IR injury in mice *via* down-regulating oxidative stress and the NLRP3 inflammasome pathway.	25
	ORI promoted p21-related autophagy in mice and in cardiomyocytes by attenuating oxidative injury and cardiac hypertrophy.	26
	ORI ameliorated DOX-induced cardiotoxicity in mice by modulating the E2F1/Sirt6/PGC1α pathway.	27
Hepatoprotective		
	ORI restored hepatic lipid homeostasis in mice by ameliorating hepato-steatosis and lipo-toxicity *via* the LXRα-ATGL/EPT1 pathway.	28
	ORI strongly inhibited the IKK/IκBα/NF-κB pathway in LX-2 cells, HSC cell line, suggesting that it has a potent anti-inflammatory effect in the liver.	29
	ORI protected against LPS/D-gal-induced acute liver injury in mice *via* the suppression of pro-apoptotic cytokine TNF-α and JNK-associated pro-apoptotic signaling.	30

ORI restored the hepatic urea cycle by enriching the intestinal *Bacteroides vulgatus* microbiota and protected against APAP-induced liver injury in mice.	31
ORI ameliorated CCl_4-induced chronic liver injury and liver fibrosis in mice through the inhibition of liver inflammation and NLRP3 inflammasome.	32
ORI protected against acute liver injury in mice *via* post-translational modifications of IRAK4 in the TLR4 signaling pathway.	33
ORI protected against BPA-induced liver injury in rats *via* inhibition of xanthine oxidase activity.	34
ORI attenuated APAP-induced ALI in mice by inhibiting the ATF4/PGC1α pathway and hepatic toxicity.	35
ORI markedly exerted inductive effects on hepatic drug metabolizing enzymes mRNA expression and enzyme activity in humanized PXR mice.	36
ORI alleviated D-gal/LPS-induced acute liver injury in mice by inhibiting NLRP3 inflammasome.	37
Renoprotective	
ORI attenuated CP-induced AKI in mice *via* inhibition of oxidative stress, apoptosis and inflammation.	38
ORI attenuated LPS-induced inflammation in HK-2 cells *via* ROS accumulation, JNK activation and NF-*κ*B nuclear translocation.	39
ORI attenuated diabetes-induced RF in rats *via* inhibition of the TXNIP/NLRP3 and NF-*κ*B pathways.	40
ORI protected against inflammation of diabetic nephropathy in rats by inhibiting the TLR4/p38-MAPK and TLR4/NF-*κ*B signaling pathways.	41
ORI protected the rat kidney in AKI *via* significant anti-inflammatory effect and inhibition of the activity of Mincle, NF-*κ*B and Atk.	42
ORI alleviated IR-induced kidney injury in mice by inhibiting inflammation in LPS-induced BMD macrophages *via* Akt-related pathways.	43
Lung Protective	
ORI attenuated lung inflammation and fibrosis in mice with silicosis by suppressing iNOS.	44
ORI alleviated ARDS lung injury in mice by inhibiting the NF-*κ*B signaling pathway and suppression of inflammatory factors.	45
ORI protected the lung from hyperoxia-induced injury in mice by improving lung pathology, attenuated lung edema, reduced MDA and TNF-*α*, and increase GSH and IL-10 in the lung.	46
ORI alleviated LPS-induced acute lung injury in mice by inhibiting apoptosis, oxidative stress and inflammation by modulating VIP/cAMP/PKA/AQP signaling.	47
ORI exerted anti-asthmatic effect on OVA-induced asthmatic mice, by regulating the cytokine balance, inhibiting AHR, and reducing lung eosinophilia and mucus hypersecretion.	48
ORI attenuated apoptosis and NLRP3 inflammasome activation in IL-4-stimulated HBE cells, an *in vitro* pediatric asthma model.	49
ORI protected LPS-induced lung injury by modulating Nrf2-mediated oxidative stress and Nrf2-independent NLRP3 and NF-*κ*B pathways.	50
ORI protected mice from pulmonary fibrosis by inhibiting NLRP3-dependent inflammation, oxidative stress, impaired autophagy and EMT.	51
ORI attenuated acute lung injury in mice by inhibiting pro-inflammatory cytokines *via* the TLR4/MyD88/NF-*κ*B pathway.	52
ORI anti-CD31 nanoparticles was three times that of free ORI in suppressing IL-6 and TNF-*α* secretion, and ROS production, in an animal model of acute lung injury.	53

Abbreviations: AHR = aryl hydrocarbon receptor, AKI = acute kidney injury, Akt = protein kinase B, ALI = acute liver injury, APAP = acetaminophen, AQP = aquaporin, ARDS = acute respiratory distress syndrome, ATF4 = activating transcription factor 4, ATGL = adipose triglyceride lipase, BMD = bone marrow-derived, BPA = bisphenol A, cAMP = cyclic adenosine monophosphate, CCl_4 = carbon tetrachloride, CP = cisplatin, D-gal = D-

galactosamine, DOX = doxorubicin, E2F1 = E2F transcription factor 1, EMT = epithelial mesenchymal transformation, EPT1 = ethanolamine phosphotransferase 1, GSDMD = gasdermin D, GSH = glutathione, HBE = human bronchial epithelial, HK-2 cells = human renal proximal tubular epithelial cells, HSC = hepatic stellate cells, IKK = IκB kinase, IL = interleukin, iNOS = inducible nitric oxide synthase, IR = ischemia/reperfusion, IRAK4 = interleukin-1 receptor-associated kinase 4, IS = immuno-suppressive, JNK = c-Jun N-terminal kinases, LPS = lipopolysaccharide, LXRα = liver X receptor α, MAPK = mitogen-activated protein kinase, MDA = malonaldehyde, MI = myocardial infarction, Mincle = macrophage-inducible C-type lectin, MSC = mesenchymal stem cells, NF-κB = nuclear factor kappa B, NLR = NOD-like receptor, NLRP3 = NLR family pyrin domain containing protein 3, Nrf2 = nuclear factor erythroid 2-related factor 2, OVA = ovalbumin, PGC1α = peroxisome proliferator-activated receptor-γ coactivator 1α, PKA = protein kinase A, PXR = pregnane X receptor, RF = renal fibrosis, ROS = reactive oxygen species, Sirt6 = sirtuin 6, TLR4 = toll-like receptor 4, TNF-α = tumor necrosis factor-α, TXNIP = thioredoxin-interacting protein and VIP = vasoactive intestinal peptide.

Lung protective: ORI attenuated lung inflammation and fibrosis in mice; attenuated apoptosis and NLRP3 inflammasome activation in human bronchial epithelial (HBE) cells; alleviated acute respiratory distress syndrome (ARDS) lung injury in mice; alleviated acute lung injury in mice; protected asthmatic mice; protected mice from pulmonary fibrosis; and protected the lung from hyperoxia-induced injury in mice. Suppression of inducible nitric oxide synthase (iNOS); inhibition of the NF-κB signaling pathway and suppression of inflammatory factors; inhibition of apoptosis, oxidative stress and inflammation; modulation of vasoactive intestinal peptide (VIP)/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA)/aquaporin (AQP) signaling; inhibition of aryl hydrocarbon receptor (AHR), and reducing lung eosinophilia and mucus hypersecretion; attenuated apoptosis and NLRP3 inflammasome activation; modulating Nrf2-mediated oxidative stress and Nrf2-independent NLRP3 and NF-κB pathways; inhibiting pro-inflammatory cytokines *via* the TLR4/MyD88/NF-κB pathway; and suppression of IL-6 and TNF-α secretion, and ROS production; inhibition of NLRP3-dependent inflammation, oxidative stress, impaired autophagy and epithelial mesenchymal transformation (EMT); attenuation of lung edema, reduced malonaldehyde (MDA) and TNF-α; and increased glutathione (GSH) and IL-10 in the lung are the mechanisms of ORI.

Glossary of Terms

Some technical terms used in Table 1 may require explanations for clarification. The following are the terms:

a. Pyroptosis: This is an inflammatory form of programmed cell death that forms part of the immune response. It is caused by gasdermin D, an inflammasome protein that forms pores in the membrane, and this releases intracellular pathogens and pro-inflammatory mediators.[54] Pyroptosis has been viewed as a new paradigm of cell death to combat against cancer.[55]

b. GSDMD: Gasdermin D is an important factor leading to pyroptotic cell death caused by caspase-1 (canonical inflammasome) and caspase-11 (non-canonical inflammasome) that may be implicated in ischemia reperfusion (IR) injury.[56]

c. NLRP3: The NOD-like receptor protein 3 is a protein inflammasome that regulates immune responses by activating caspase-1 and the inflammatory cytokines interleukin (IL)-1β and IL-18.[28] Many studies have shown the importance of the NLRP3 inflammasome in the development of immune and inflammation-related diseases, such as arthritis, Alzheimer's disease and inflammatory bowel disease.

d. SIRT 6: Mammalian sirtuin 6 is a protein deacylase that regulates metabolism and chromatin homeostasis.[57] Activation protects against metabolic and aging-related diseases while inhibition is considered a therapy for cancer.

e. Silicosis: A fibrotic lung disease caused by inhalation of free crystalline silicon dioxide (SiO_2) or silica.[58]

f. ARDS: Acute respiratory distress syndrome is an important cause of acute respiratory disorder that is often associated with multiple organ failure.[59] Causes include pneumonia, sepsis, aspiration of gastric contents and major trauma.

g. Pediatric asthma: Childhood asthma is characterized by recurrent wheezing, breathlessness, chest tightness, and coughing. Causes include inflammation of the airways and clinical treatment may be necessary to reduce chronic inflammation.[60]

h. Diabetic nephropathy: A kidney disease caused by diabetes, is the most devastating complication in patients with diabetes. The key characteristic of diabetic nephropathy is glomerulosclerosis that resides in renal glomeruli.[61]

i. PXR-humanized mice: They are mice with knock-out rodent pregnane X receptor (PXR) gene that is replaced with the human PXR to establish a 'humanized' mouse model.[62] Such a mouse model proved to be useful in predicting and avoiding drug–drug interactions.

Conclusion

The pharmacological activities of ORI from other *Isodon* species such as *I. japonica* and *I. serra*, and of other diterpenoids such as ponicidin and lasiodonin from *I. rubescens* are worthy of further research. The anti-asthmatic activity of ORI especially that of pediatric asthma and other pharmacological activities such as anti-inflammatory, neuroprotective, immuno-suppressive, osteoblast protective and analgesic properties deserve more in-depth investigation. Finally, the synthesis of ORI derivatives with enhanced bioactive efficacy including anti-cancer properties and their SAR present an exciting field of research.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

References

1. Chen X, He X. *Isodon rubescens* (Hemls.) Hara.: A comprehensive review on traditional uses, phytochemistry, and pharmacological activities. Front Pharmacol. 2022; 13:766581.
2. Li XW, Hedge IC. *Isodon*. Flora of China. 1994;17:269-291.
3. Wiarts C. *Isodon rubescens* (Hemsl.) H. Hara. In: Lead Compounds from Medicinal Plants for the Treatment of Cancer. Academic Press & Elsevier, 2013.
4. Ye S, Sun S, Cai J, Jiang J. Research progress and future development potential of oridonin in pharmacological activities. Curr Mol Pharmacol. 2023;16(7):691-706.
5. Fujita E, Fujita T, Katayama H, Shibuya M. Oridonin, a new diterpenoid from *Isodon* species. Chem Commun. 1967; 6:252-254.
6. Zhang W, Huang Q, Hua ZC. Oridonin: A promising anticancer drug from China. Front Biol. 2010;5:540-545.
7. Zhang YH, Wu YL, Tashiro SI, Onodera S, Ikejima T. Reactive oxygen species contribute to oridonin-induced apoptosis and autophagy in human cervical carcinoma HeLa cells. Acta Pharmacol Sin. 2011;32(10):1266-1275.
8. Tian W, Chen SY. Recent advances in the molecular basis of anti-neoplastic mechanisms of oridonin. Chin J Integr Med. 2013;19(4):315-320.
9. Liu X, Xu J, Zhou J, Shen Q. Oridonin and its derivatives for cancer treatment and overcoming therapeutic resistance. Genes Dis. 2021;8(4):448-462.
10. Ali MA, Khan N, Ali A, Akram H, Zafar N, Imran K, Khan T, Khan K, Armaghan M, Palma-Morales M, Rodríguez-Pérez C. Oridonin from *Rabdosia rubescens*: An emerging

potential in cancer therapy – A comprehensive review. Food Sci Nutr. 2024; http://doi.org/10.1002/fsn3.3986
11. Hu X, Huang S, Ye S, Jiang J. The natural product oridonin as an anticancer agent: current achievements and problems. Curr Pharm Biotechnol. 2024;25(6):655-664.
12. Chen J, Wang S, Chen D, Chang G, Xin Q, Yuan S, Shen Z. The inhibitory effect of oridonin on the growth of fifteen human cancer cell lines. Chin J Clin Oncol. 2007;4:16-20.
13. Cheng W, Huang C, Ma W, Tian X, Zhang X. Recent development of oridonin derivatives with diverse pharmacological activities. Mini Rev Med Chem. 2019; 19(2):114-124.
14. Li J, Wu Y, Wang D, Zou L, Fu C, Zhang J, Leung GP. Oridonin synergistically enhances the anti-tumor efficacy of doxorubicin against aggressive breast cancer *via* pro-apoptotic and anti-angiogenic effects. Pharmacol Res. 2019;146:104313.
15. Yao J, Liu L, Sun Q, Shen X. Direct cellular targets and anticancer mechanisms of the natural product oridonin. MedComm–Futur Med. 2023;2(1):e35.
16. Xu J, Wold EA, Ding Y, Shen Q, Zhou J. Therapeutic potential of oridonin and its analogs: from anticancer and anti-inflammation to neuroprotection. Molecules. 2018; 23(2):474.
17. Li X, Zhang CT, Ma W, Xie X, Huang Q. Oridonin: A review of its pharmacology, pharmacokinetics and toxicity. Front Pharmacol. 2021;12:645824.
18. Ding C, Zhang Y, Chen H, Yang Z, Wild C, Ye N, Ester CD, Xiong A, White MA, Shen Q, Zhou J. Oridonin ring A-based diverse constructions of enone functionality: Identification of novel dienone analogues effective for highly aggressive breast cancer by inducing apoptosis. J Med Chem. 2013; 56(21):8814-8825.
19. Li J, Zhang D, Wu X. Synthesis and biological evaluation of novel exo-methylene cyclopentanone tetracyclic diterpenoids as antitumor agents. Bioorg Med Chem Lett. 2011;21(1):130-132.
20. Liang ST, Chen C, Jiang GH. Michael acceptor molecules in natural products and their mechanism of action. Front Pharmacol. 2022;13:1033003.
21. Du X, Que W, Hu X, Yu X, Guo WZ, Li XK. Oridonin prolongs the survival of mouse cardiac allografts by attenuating the NF-κB/NLRP3 pathway. Front Immunol. 2021; 12:719574.
22. Fu M, Xie D, Sun Y, Pan Y, Zhang Y, Chen X, Shi Y, Deng S, Cheng B. Exosomes derived from MSC pre-treated with oridonin alleviates myocardial IR injury by suppressing apoptosis *via* regulating autophagy activation. J Cell Mol Med. 2021;25(12):5486-5496.
23. Gao RF, Li X, Xiang HY, Yang H, Lv CY, Sun XL, Chen HZ, Gao Y, Yang JS, Luo W, Yang YQ, Tang YH. The covalent NLRP3-inflammasome inhibitor Oridonin relieves myocardial infarction induced myocardial fibrosis and cardiac remodeling in mice. Int Immunopharmacol. 2021; 90:107133.
24. Lin J, Lai X, Fan X, Ye B, Zhong L, Zhang Y, Shao R, Shi S, Huang W, Su L, Ying M. Oridonin protects against myocardial ischemia–reperfusion injury by inhibiting GSDMD-mediated pyroptosis. Genes. 2022;13(11):2133.
25. Lu C, Chen C, Chen A, Wu Y, Wen J, Huang F, Zeng Z. Oridonin attenuates myocardial ischemia/reperfusion injury *via* down-regulating oxidative stress and NLRP3 inflammasome pathway in mice. Evid-Based Complement Altern Med. 2020; Article ID 7395187: 9 pp.
26. Xu M, Wan CX, Huang SH, Wang HB, Fan D, Wu HM, Wu Q, Ma Z, Deng W, Tang QZ. Oridonin protects against cardiac hypertrophy by promoting P21-related autophagy. Cell Death Dis. 2019;10(6):403.
27. Yu D, Li J, Wang Y, Guo D, Zhu C, Sun B, Zhou Z. Oridonin ameliorates doxorubicin induced-cardiotoxicity *via* the E2F1/Sirt6/PGC1α pathway in mice. Food Chem Toxicol. 2023;181:114050.
28. Chen Y, Jiang H, Zhan Z, Lu J, Gu T, Yu P, Liang W, Zhang X, Zhong X, Tang L. Oridonin restores hepatic lipid homeostasis in an LXR*α*-ATGL/EPT1 axis-dependent manner. J Pharm Anal. 2023;13(11):1281-1295.
29. Cummins CB, Wang X, Sommerhalder C, Bohanon FJ, Nunez Lopez O, Tie HY, Rontoyanni VG, Zhou J, Radhakrishnan RS. Natural compound oridonin inhibits endotoxin-induced inflammatory response of activated hepatic stellate cells. BioMed Res Int. 2018; Article ID 6137420, 10 pp.
30. Deng Y, Chen C, Yu H, Diao H, Shi C, Wang Y, Li G, Shi M. Oridonin ameliorates lipopolysaccharide/D-galactosamine-induced acute liver injury in mice *via* inhibition of apoptosis. Am J Translat Res. 2017;9(9):4271-4279.
31. Hong MK, Liu HH, Chen GH, Zhu JQ, Zheng SY, Zhao D, Diao J, Jia H, Zhang DD, Chen SX, Gao L, Li J. Oridonin alters hepatic urea cycle *via* gut microbiota and protects against acetaminophen-induced liver injury. Oxid Med Cell Longev. 2021; Article ID 3259238, 15 pp.
32. Liu D, Qin H, Yang B, Du B, Yun X. Oridonin ameliorates carbon tetrachloride-induced liver fibrosis in mice through inhibition of the NLRP3 inflammasome. Drug Devel Res. 2020;81(4):526-533.
33. Shi M, Deng Y, Yu H, Xu L, Shi C, Chen J, Li G, Du Y, Wang Y. Protective effects of oridonin on acute liver injury via impeding post-translational modifications of interleukin-1 receptor-associated kinase 4 (IRAK4) in the toll-like receptor 4 (TLR4) signaling pathway. Mediators Inflamm. 2019; Article ID 7634761: 11 pp.
34. Wang X, Gao M, Wang Z, Cui W, Zhang J, Zhang W, Xia Y, Wei B, Tang Y, Xu X. Hepatoprotective effects of oridonin against bisphenol A induced liver injury in rats *via* inhibiting the activity of xanthine oxidase. Sci Total Environ. 2021;770:145301.
35. Yu D, Li J, Wang Y, Guo D, Zhang X, Chen M, Zhou Z. Oridonin ameliorates acetaminophen-induced acute liver injury through ATF4/PGC-1*α* pathway. Drug Devel Res. 2023;84(2):211-225.
36. Zhang YW, Bao MH, Lou XY, Cheng Y, Yu J, Zhou HH. Effects of oridonin on hepatic cytochrome P450 expression and activities in PXR-humanized mice. Biol Pharm Bull. 2018;41(5):707-712.
37. Zhang T, Chen Y, Zhan Z, Mao Z, Wen Y, Liu S, Tang L. Oridonin alleviates d-GalN/LPS-induced acute liver injury by inhibiting NLRP3 inflammasome. Drug Devel Res. 2021; 82(4):575-580.
38. Gu H, Gwon MG, Kim JH, Leem J, Lee SJ. Oridonin attenuates cisplatin-induced acute kidney injury *via* inhibiting oxidative stress, apoptosis, and inflammation in mice. BioMed Res Int. 2022; Article ID 3002962, 10 pp.
39. Huang JH, Lan CC, Hsu YT, Tsai CL, Tzeng IS, Wang P, Kuo CY, Hsieh PC. Oridonin attenuates lipopolysaccharide-induced ROS accumulation and inflammation in HK-2 cells. Evid-based Complement Altern Med. 2020; Article ID 9724520, 8 pp.
40. Huang G, Zhang Y, Zhang Y, Zhou X, Xu Y, Wei H, Ma Y. Oridonin attenuates diabetes-induced renal fibrosis *via* inhibition of the TXNIP/NLRP3 and NF-*κ*B pathway in rats. Research Square. 2021; https://doi.org/10.21203/rs.3.rs-1144780/v1
41. Li J, Bao L, Zha D, Zhang L, Gao P, Zhang J, Wu X. Oridonin protects against the inflammatory response in diabetic nephropathy by inhibiting the TLR4/p38-MAPK and TLR4/NF-*κ*B signaling pathways. Int Immuno-pharmacol. 2018;55:9-19.
42. Tan RZ, Yan Y, Yu Y, Diao H, Zhong X, Lin X, Liao Y, Wang L. Renoprotective effect of oridonin in a mouse model of acute kidney injury *via* suppression of macrophage

involved inflammation. Biol Pharm Bull. 2021;44(5):714-723.
43. Yan Y, Tan RZ, Liu P, Li JC, Zhong X, Liao Y, Lin X, Wei C, Wang L. Oridonin alleviates IRI-induced kidney injury by inhibiting inflammatory response of macrophages *via* Akt-related pathways. Int Med J Exper Clin Res. 2020; 26:e921114-1.
44. Gao J, Li C, Wang X, Sun X, Zhang R, Yu M, Liu Y, Zhu Y, Chen J. Oridonin attenuates lung inflammation and fibrosis in silicosis *via* covalent targeting iNOS. Biomed Pharmacother. 2022;153:113532.
45. Jiang J, Shan X, Zhu L. Effects and mechanisms of oridonin in the treatment of acute respiratory distress syndrome mice. Int J Clin Exp Med. 2017;10:6191-6197.
46. Liu Y, Zhang PX, Han CH, Wei D, Qiao T, Peng B, Liu K, Zheng J, Liu W. Oridonin protects the lung against hyperoxia-induced injury in a mouse model. Undersea Hyperb Med. 2017;44(1):33.
47. Liu Q, Shang W, Zhang J, Chen R, Wei L, Wang H, Zhang M, Yue M. Oridonin alleviates lipopolysaccharide-induced acute lung injury in mice through inhibiting apoptosis, oxidative stress, and inflammation by modulating VIP/cAMP/PKA/AQPs signaling pathway. Research Square. 2023; https://doi.org/10.21203/rs.3.rs-3022672/v1
48. Wang J, Li F, Ding J, Tian G, Jiang M, Gao Z, Tuyghun E. Investigation of the anti-asthmatic activity of oridonin on a mouse model of asthma. Mol Med Rep. 2016; 14(3):2000-6.
49. Wang W, Ming D. Oridonin attenuates apoptosis and NLRP3 inflammasome activation in IL-4-stimulated human bronchial epithelial cells in an *in vitro* pediatric asthma model. Adv Clin Exper Med. 2024;33(2):163-170.
50. Yang H, Lv H, Li H, Ci X, Peng L. Oridonin protects LPS-induced acute lung injury by modulating Nrf2-mediated oxidative stress and Nrf2-independent NLRP3 and NF-κB pathways. Cell Commun Signal. 2019;17:1-5.
51. Yang H, Wang L, Yang M, Hu J, Zhang E, Peng L. Oridonin attenuates LPS-induced early pulmonary fibrosis by regulating impaired autophagy, oxidative stress, inflammation and EMT. Eur J Pharmacol. 2022;923:174931.
52. Zhao G, Zhang T, Ma X, Jiang K, Wu H, Qiu C, Guo M, Deng G. Oridonin attenuates the release of pro-inflammatory cytokines in lipopolysaccharide-induced RAW264.7 cells and acute lung injury. Oncotarget. 2017;8(40):68153.
53. Zhao Y, Jin H, Bai LP, Pan H, Wang C, Tang Y, Guo Z, Cai J, Li T. Oridonin inhibits inflammation of epithelial cells *via* dual-targeting of CD31 Keap1 to ameliorate acute lung injury. Front Immunol. 2023;14:1163397.
54. Liu X, Zhang Z, Ruan J, Pan Y, Magupalli VG, Wu H, Lieberman J. Inflammasome-activated gasdermin D causes pyroptosis by forming membrane pores. Nature. 2016; 535 (7610):153-158.
55. Tan Y, Chen Q, Li X, Zeng Z, Xiong W, Li G, Li X, Yang J, Xiang B, Yi M. Pyroptosis: A new paradigm of cell death for fighting against cancer. J Exper Clin Cancer Res. 2021; 40(1):153.
56. Zhang D, Qian J, Zhang P, Li H, Shen H, Li X, Chen G. Gasdermin D serves as a key executioner of pyroptosis in experimental cerebral ischemia and reperfusion model both *in vivo* and *in vitro*. J Neurosci Res. 2019;97(6):645-660.
57. You W, Zheng W, Weiss S, Chua KF, Steegborn C. Structural basis for the activation and inhibition of Sirtuin 6 by quercetin and its derivatives. Sci Rep. 2019;9(1):19176.
58. Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012; 379(9830):2008-2018.
59. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. J Clin Investig. 2012;122(8): 2731-2740.
60. Clark NM, Brown RW, Parker E, Robins TG, Remick Jr DG, Philbert MA, Keeler GJ, Israel BA. Childhood asthma. Environ Health Perspect. 1999;107(suppl 3):421-429.
61. Kikkawa R, Koya D, Haneda M. Progression of diabetic nephropathy. Am J Kidney Dis. 2003;41(3):19-21.
62. Xie W, Barwick JL, Downes M, Blumberg B, Simon CM, Nelson MC, Neuschwander-Tetri BA, Brunt EM, Guzelian PS, Evans RM. Humanized xenobiotic response in mice expressing nuclear receptor SXR. Nature. 2000; 406 (6794):435-439.