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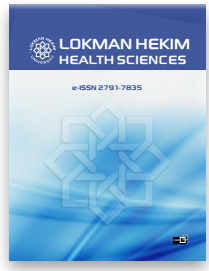

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REVIEW

Unlocking Oxyberberine Potential for Treating Human Diseases: Pharmacological Activity and Therapeutic Understanding

Oksiberberinin İnsan Hastalıklarının Tedavisindeki Potansiyelinin Ortaya Çıkarılması: Farmakolojik Aktivite ve Terapötik Anlayış

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Abstract

Oxyberberine is an important alkaloid class phytochemical found to be present in the Coptidis Rhizoma, *Thalictrum longistylum*, *Thalictrum lucidum*, *Thalictrum podocarpum* and *Phellodendron amurense*. Coptidis Rhizoma is a classical Chinese medicinal botanical drug for the treatment of gastrointestinal disorders. In order to give scientific information on the pharmacological activities and medicinal uses of oxyberberine, a large number of scientific databases were examined and scientific data about oxyberberine was gathered for this review article. Furthermore, the ultimate goal of this review is to provide scientific information on oxyberberine to facilitate its application in the treatment of human diseases. Here, keywords related to oxyberberine, Coptidis Rhizoma, herbal medicine and phytochemicals were searched in the scientific databases such as Science Direct, Google Scholar, and PubMed. The scientific data of this review demonstrate the biological potential of oxyberberine in medicine due to its therapeutic effectiveness on human diseases. Here we discussed the pharmacological activities of oxyberberine in colitis, lung injury, liver disease, intestinal mucositis, cardiotoxicity and lipoxygenase. The scientific evidence also described the therapeutic effects of oxyberberine in medicine due to its anti-cancer, anti-inflammatory, anti-bacterial, and hypoglycemic effects. However, its role in multidrug resistance and pharmacokinetic parameters was also discussed, which justifies conducting further preclinical research and clinical trials in the scientific field for future prospects of oxyberberine in the medicinal field.

Keywords: Antibacterial; Anticancer; Anti-inflammatory; Cardiotoxicity; Colitis; Herbal medicine; Hypoglycemic; Intestinal mucositis; Lipoxygenase; Liver disease; Lung injury; Oxyberberine; Phytochemical

Oxyberberine ($C_{20}H_{17}NO_5$) (Fig. 1) is one of the key phytochemicals of *Phellodendron Chinense* Cortex. Oxyberberine has a strong safety record and a variety of biological and pharmacological properties, such as anti-inflammatory, antioxidant, and anti-colitis effects. Additionally, oxyberberine decreased inflammation in lipopolysaccharide (LPS) induced acute lung damage. In comparison to the prodrug berberine, oxyberberine

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has a higher bioavailability in the colon and can be transformed by the gut microbiota.[1] Oxyberberine is the primary active component of Rhizoma Coptidis. Numerous biological actions, such as anti-inflammatory, anti-diabetic, antibacterial, anti-arrhythmic, anti-cancer, antioxidant, anti-hyperglycemic, antinociceptive and antigenic properties were reported in the scientific research work.[2–4] Oxyberberine inhibits the TLR4-MyD88-NF-κB signaling pathway, modifies the gut microbiota profile, and inhibits the inflammatory response in mice with experimental dextran sodium sulfate (DSS) colitis. Oxyberberine exhibits more favorable safety profile as compared to berberine (LD_{50} value of berberine; 713.57 mg/kg), with LD_{50} value above 5000 mg/kg in mice. Additionally, it was discovered that following oral berberine administration, a significant portion of protein-bound oxyberberine was observed in the hydrolyzed blood samples of rats.[5] Oxyberberine can be produced by metabolizing berberine, according to pharmacokinetic studies, and it binds to hemoglobin less strongly than berberine. Both ulcerative colitis and non-alcoholic fatty liver disease can benefit from oxyberberine.[6] Oxyberberine shielded β-cells from oxidative damage in diabetic (DM) rats.[7] *Phellodendron Chinense* Schneid and *Coptidis chinensis* Franch. contain trace amounts of oxyberberine, an oxidized protoberberine alkaloid.[8] The pharmacological effects of oxyberberine on colitis and its underlying processes were reviewed using a mouse colitis model generated by DSS.[9] By blocking the toll like receptor-4 (TLR4)-MyD88-NF-κB signaling pathway and NF-κB nuclear translocation p65 and subsequent signaling, oxyberberine significantly reduced DSS-induced colitis. Oxyberberine exhibits strong anticancer properties against human non-small cell lung cancer cells (NCI-H12997), human hepatoma cells (Hep-G2), and human hepatic adenocarcinoma cells (SK-Hep-1).[10] The entire plant of *Argemone mexicana* Linn has yielded four quaternary isoquinoline alkaloids, including oxyberberine.[11] Oxyberberine was isolated from *Thalictrum longistylum* DC., *Thalictrum lucidum* L., *Thalictrum podocarpum* Humb, and *Phellodendron amurense*.[12–16] The metabolic profiles of two varieties of *Polygonatum sibiricum*—the wide-type (Wtype) and the recently produced evergreen type (Gtype)—have been examined using an untargeted metabolomics technique based on ultra high-performance liquid chromatography (UHPLC)-Q-Orbitrap-MS. Oxyberberine content was substantially greater in Gtype samples than in Wtype samples.[17] Eleven active phytochemicals, including oxyberberine in Rhizoma Coptidis, were simultaneously quantified using a high-performance liquid chromatography technique combined with a photo array diode detector.[18]

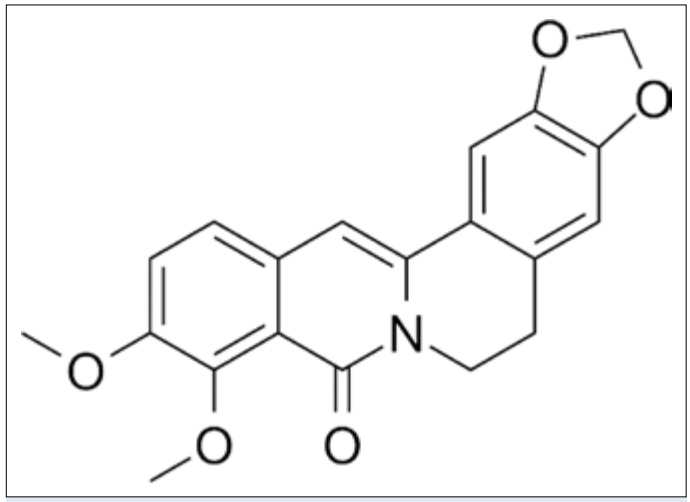

Figure 1. Chemical structure of oxyberberine.

Methods

This review objective is to collect scientific data on oxyberberinein so that its therapeutic potential, pharmacological activity, and medical significance can be examined. Using pertinent research articles from several scientific databases, including Science Direct, Google Scholar, and PubMed, the phrases herbal medicine, oxyberberine, and phytochemical are utilized in this review to characterize the biological potential of oxyberberine. Following the compilation of all oxyberberine-related scientific data, we go on to find pertinent oxyberberine literature regarding its pharmacological and biological potential. To comprehend the pharmacological action and molecular mechanism of oxyberberine, the authors also go over the full scientific research articles. Twenty-eight of the 120 scientific papers and review articles that were thoroughly examined were cited in this article. Thus, this article goal was to give readers a thorough understanding of oxyberberine pharmacological activity, molecular mechanisms, and medicinal significance.

Pharmacological Activity of Oxyberberine

Colitis

The biological potential of oxyberberine for anti-colitis activity and its potential mechanism of action were investigated in Balb/C mice with DSS-induced colitis. Oxyberberine significantly reduced DSS-induced clinical symptoms, colon shortening, and histological damage in colitis mice. Furthermore, oxyberberine significantly attenuated colonic inflammatory response and intestinal epithelial barrier dysfunction. Oxyberberine significantly inhibits the TLR4-MyD88-NF-κB signaling pathway by decreasing the expression of TLR4 and MyD88 proteins

and inhibiting IκBα phosphorylation and NF-κB p65 translocation from the cytoplasm to the nucleus. Moreover, oxyberberine significantly modulated the dysbiosis of the gut microbiota induced by DSS and restored the dysbiosis of the gut microbiota to normal levels. Oxyberberine effectively ameliorated experimental colitis caused by DSS by at least partially maintaining colonic integrity, inhibiting inflammatory responses, and modulating the gut microbiota profile.[8]

Lung Injury

To assess the possible involvement of mitophagy *in vitro* using adenocarcinomic human alveolar basal epithelial cells A549, the biological effects of oxyberberine on its inhibitory ability against LPS-induced acute lung injury (ALI) has been investigated. Oxyberberine significantly inhibited LPS-induced pathological lung injury and pulmonary edema, as shown by changes in the wet-to-dry ratio of mouse lungs and total protein levels in bronchoalveolar lavage fluid (BALF). Moreover, oxyberberine inhibited inflammation in both the lung and BALFin ALI mice. Oxyberberine alleviated LPS-induced inflammation in ALI via inhibition of Parkin-mediated mitophagy.[19] The biological potential of oxyberberine in acute inflammation in mice and A549 cells by using LPS has been investigated in order to investigate the influence and underlying mechanisms of oxyberberine on ALI. Oxyberberine reduced lung injury, pulmonary edema, and inflammatory responses in BALF and lung tissue. Oxyberberine, in combination with its downstream factors, significantly decreased RhoA expression. Oxyberberine had RhoA/ROCK inhibitor-like effects on moderate disruption and permeability of the alveolar epithelial barrier, ultimately preventing progression of ALI.[6]

Liver Disease

The biological potential of oxyberberine and berberine against nonalcoholic fatty liver disease (NAFLD) was comparatively studied in obese and high-fat diet-induced rats. Oxyberberine significantly reduced the clinical symptoms of NAFLD in a dose-dependent manner, achieving the same therapeutic effect as metformin (300 mg/kg), and at the same dose was superior to BBR. Oxyberberine significantly inhibited aberrant IRS-1 phosphorylation and enhanced the expression and phosphorylation of downstream proteins (PI3K, p-Akt/Akt, and p-GSK-3β/GSK-3β), thereby Improved insulin signaling in the liver. Oxyberberine can better maintain lipid homeostasis between the liver and WAT by reducing hepatic insulin pathway and adipocyte inflammation, which is associated with its properties as a good AMPK activator.[4] The biological potential of oxyberberine, a major intestinal metabolite of *Phellodendron Chinense* Cortex, for its hepatoprotective role via HO-1 signaling pathway in lipopolysaccharide/D-galactosamine (LPS/D-GalN)-induced ALI was studied. Oxyberberine obviously improved histopathological deteriorations and liver function. In addition, Oxyberberine has greatly improved oxidative stress and liver inflammation. In addition, Oxyberberine showed HO-1 great agonist activity. Moreover, oxyberberine modulates inflammation and oxidative stress parameters through the HO-1-dependent pathway. Oxyberberine exerted hepatoprotective effects by inducing HO-1 through co-activation of erythrocyte metabolism and the Nrf2/HO-1 pathway.[1]

Hypoglycemic Effect

The antidiabetic effect and the potential mechanism of oxyberberine in streptozotocin (STZ)-induced diabetic rats have been investigated. Oxyberberine existed mainly as protein-bound form in blood, while protein-bound oxyberberine was significantly depleted in antibiotic-induced pseudo germ-free rats. Treatment with oxyberberine effectively decreased clinical symptoms of diabetic rats, reduced blood glucose level, ameliorated the pancreatic damage, and mitigated oxidative stress and inflammatory markers. In addition, oxyberberine had an excellent antidiabetic effect, significantly increased the mRNA expression of Nrf2 signaling pathway, and significantly increased the levels of PI3K/Akt signaling pathway in the pancreas. Oxyberberine had beneficial hypoglycemic and protective effects on pancreatic β-cells.[5] The relationship between the antidiabetic effects of oxyberberine and its potential to induce heme oxygenase-1 (HO-1) expression was studied using a rat model of type 2 diabetes. Administration of oxyberberine significantly reduced fasting blood glucose, blood fat, and inflammatory cytokines, while increasing the antioxidant capacity of the pancreas. On the other hand, oxyberberine treatment significantly stimulated hepatic gluconeogenesis and inhibited hepatic gluconeogenesis. Moreover, oxyberberine improved glucose utilization in muscle. In particular, oxyberberine inhibited islet cell apoptosis and improved pancreatic function. Furthermore, oxyberberine effectively improved glucose consumption in insulin-resistant HepG2 cells. Additionally, in silico modeling revealed that oxyberberine exhibits excellent affinity for HO-1. Oxyberberine effectively ameliorated

hyperglycemia, dyslipidemia, and insulin resistance, improved oral glucose tolerance, and maintained glucose metabolism homeostasis.[7] The biological potential and underlying mechanism of action of Huanglian-Renshen-Decoction (HRD) on hepatic glucose production (HGP), a classical traditional Chinese herb medicine has been investigated using *in vivo* experiments, network pharmacology, molecular docking, transcriptomics and molecular biology. HRD can reduce weight gain and blood glucose and increase fasting insulin, glucose clearance, and insulin sensitivity in T2DM mice. The abnormal lipid profile was also corrected by HRD administration. Additionally, the study was further supported by molecular docking and *in vitro* experiments, in which identified HRD compound, oxyberberine, was proven to have an obvious effect on Akt.[20]

Anticancer

The cytotoxicity of *Berberis lycium* root bark extract against cancer cell lines was investigated in HepG2 cells, and the most cytotoxic chemical components of the extract were isolated. Oxyberberine contained in the chloroform of *Berberis lycium* inhibited SK-Hep-1 cell proliferation under a dose-dependent manner with an IC_{50} value of 34.26 ± 3.34 µM while HepG2 cells showed 50% inhibition at 62.96 ± 4.12 µM. The cytotoxic potential of extracts and compounds isolated from *Berberis lycium* Royle suggests that it is a promising candidate for anticancer drug discovery.[21] Potential cytotoxic effects of alkaloids isolated from aerial part of *Argemone mexicana* Linn. has been investigated on SW480 human colon cancer cell line. 8-Oxyberberine was mildly cytotoxic at 24 h but was more potent at 48 h and indicates that some alkaloids of *Argemone mexicana* strongly inhibit the cell proliferation in human colon cancer cells, and it might be a basis for future development of a potent chemotherapeutic drug.[22] Cytotoxicity of oxyberberine isolated from the bark of *Phellodendron amurense* against five human tumor cell lines has been investigated *in vitro* using the SRB method. Oxyberberine showed significant cytotoxicity against the five tumor cell lines with ED_{50} values ranging from 0.30 to 3.0 microg/mL.[13]

Anti-inflammatory

Biological potential of oxyberberine for their anti-inflammatory activity has been investigated in order to know the possible underlying mechanism by LPS-induced RAW264.7 macrophages cells, and three typical *in vivo* acute inflammation murine models. The *in vitro* assay indicated that oxyberberine pretreatment significantly decreased the levels of pro-inflammatory cytokines tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), prostaglandin E2 (PGE2) and nitric oxide (NO), and inhibited the mRNA expressions of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in a dose-dependent manner. Oxyberberine (5, 10, and 20 mg/kg) pretreatment significantly ameliorated the xylene-induced ear edema, carrageenan-stimulated paw edema, and acetic acid-elicited vascular permeability in mice in a dose-dependent manner.[3]

Cardiotoxicity

The biological function of cardiomyocytes (CMs) in the treatment of nine alkaloids in Rhizoma Coptis has been investigated through the real-time cellular analysis cardio system and the high-content analysis. Luciferase-coupled adenosine triphosphate (ATP) assay was used to detect cell viability and oxyberberine was found to be cardiotoxic, which resulted in arrhythmia and cardiac arrest on CMs in a time and dose-dependent manner. Meanwhile, oxyberberine caused shrinkage and detachment on CMs at 10 µM.[23]

Antibacterial Activity

The biological potential of *Berberis lyceum* and *Fagonia cretica* were tested *in vitro* against *Brucella Melitensis* via a well diffusion method in order to know their antibacterial activity. Further, previously identified phytochemicals were also docked with a homology model of the cytotoxic factor malate synthase G (MSG) highly conserved among Brucella spp., in Molecular Operating Environment (MOE) to predict a potential drug against *Brucella melitensis*. Additionally, a molecular dynamic simulation was also performed to predict the stability of MSG through MOE". *In silico* screening predicted phytic acid as the most potent inhibitor followed by oxyberberine.[24]

Lipoxygenase

The biological potential of four protoberberine alkaloids, including oxyberberine isolated from *Mahonia aquifolium*, was tested for their lipoxygenase inhibitory potential. Oxyberberine was found to be the most potent lipoxygenase inhibitors. Further, a strong linear correlation between lipoxygenase inhibition and lipid antioxidant properties of oxyberberine was also found which signified that the mechanism of lipoxygenase inhibition may be linked to the inhibition of lipid hydroperoxide substrate accumulation.[25]

Intestinal Mucositis

Protective effects of oxyberberine on intestinal mucositis (IM) induced by 5-fluorouracil (5-FU) has been investigated with its potential underlying molecular mechanism using IM mice model. Oxyberberine (12.5, 25, and 50 mg/kg) ameliorated body weight loss, anorexia, diarrhea, and histopathological damage in 5-FU-induced IM mice. The amounts of MDA, SOD, and GSH altered by IM were remarkably restored after oxyberberine administration. Oxyberberine was also decreases the levels of TNF-α, IL-8, IL-6, COX-2, and iNOS and promoted the release of IL-10. Oxyberberine displayed a superior therapeutic effect in alleviating 5-FU-induced IM mice which signified its biological potential against IM.[26]

Multidrug Resistance

Biological potential of isolated compounds from rhizome of *Coptis japonica* Makino were tested for their cytotoxicity against five tumor cell lines *in vitro* by SRB method, and also for its multidrug resistance (MDR) reversal activities. 8-oxocoptisine but not the oxyberberine was found to have significant P-gp MDR inhibition activity in MES-SA/DX5 cell and 0 in HCT15 cell.[27]

Pharmacokinetics

A simultaneous quantitative method of ten alkaloids, including oxyberberine in rat plasma has been investigated. Furthermore, the pharmacokinetics of those alkaloids after administration of crude and wine-processed Rhizoma Coptidis aqueous extracts was compared using an ultra high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (UHPLC-ESI-MS/MS). Chromatographic separation was achieved on a C18 column using gradient elution with the mobile phase consisting of acetonitrile and water (containing 0.2% formic acid) at a flow rate of 0.2 ml/min. The validated method showed good linearity over a wide concentration range (r>0.99), and lower limits of quantification less than 5.46 ng/ml for each analyte. The validated method has been successfully applied to pharmacokinetic comparison after administration of crude and wine-processed Rhizoma Coptidis aqueous extracts.[2] An ultra-high performance liquid chromatography method coupled with Orbitrap mass spectrometry (UHPLC-Orbitrap-MS) technology was applied to detect and identify prototype components and metabolites in rat intestinal contents and serum samples after oral administration of a *Berberis kansuensis* extract. A total of 16 prototype components and 40 metabolites were identified. By comparing the differences of metabolites between diabetic and pseudo-germ-free diabetic rats, we found that the metabolic transformation of some chemical components in *Berberis kansuensis* extract, including 8-oxyberberine was affected by the gut microbiota.[28]

Table 1. Biological source of oxyberberine

S. No	Biological source	Reference
1.	*Argemone mexicana*	[11, 22]
2.	*Berberis kansuensis*	[28]
3.	*Berberis lycium*	[21]
4.	*Coptidis chinensis*	[8]
5.	*Coptis japonica*	[27]
6.	*Mahonia aquifolium*	[25]
7.	*Phellodendron amurense*	[13]
8.	*Phellodendron chinense*	[1, 8]

Conclusion

This review objective is to gather and examine all of the scientific information on oxyberberine that is currently accessible from a range of scientific sources in order to assess their potential health benefits. This review gathers scientific data regarding the pharmacological activity and therapeutic uses of oxyberberine. Furthermore, the ultimate objective of this review is to provide scientific proof of oxyberberine in order to stimulate further research into its potential for therapeutic usage in medicine to cure human illnesses. Coptidis Rhizoma is a traditional Chinese medicinal herb that is used to treat digestive disorders contains oxyberberine. Coptidis Rhizoma, *Thalictrum longistylum*, *Thalictrum lucidum*, *Thalictrum podocarpum*, *Phellodendron amurense*, and other therapeutic plants listed in Table 1 contain significant amount of oxyberberine. Here, oxyberberine pharmacological action in relation to its efficacy in intestinal mucositis, colitis, lung damage, liver disease, cardiotoxicity, and lipoxygenase were outlined. Due to its antibacterial, anti-inflammatory, anticancer, and hypoglycemic properties, oxyberberine was also described for their therapeutic efficacy which was presented in Figure 2. However, the current review also looked at and assessed how it affects multidrug resistance and pharmacokinetic characteristics. By providing scientific information about oxyberberine from numerous scientific literature studies, this article also addresses its bioanalytical aspects. The scientific data on oxyberberine presented in this review article suggested several molecular mechanisms that are primarily responsible for

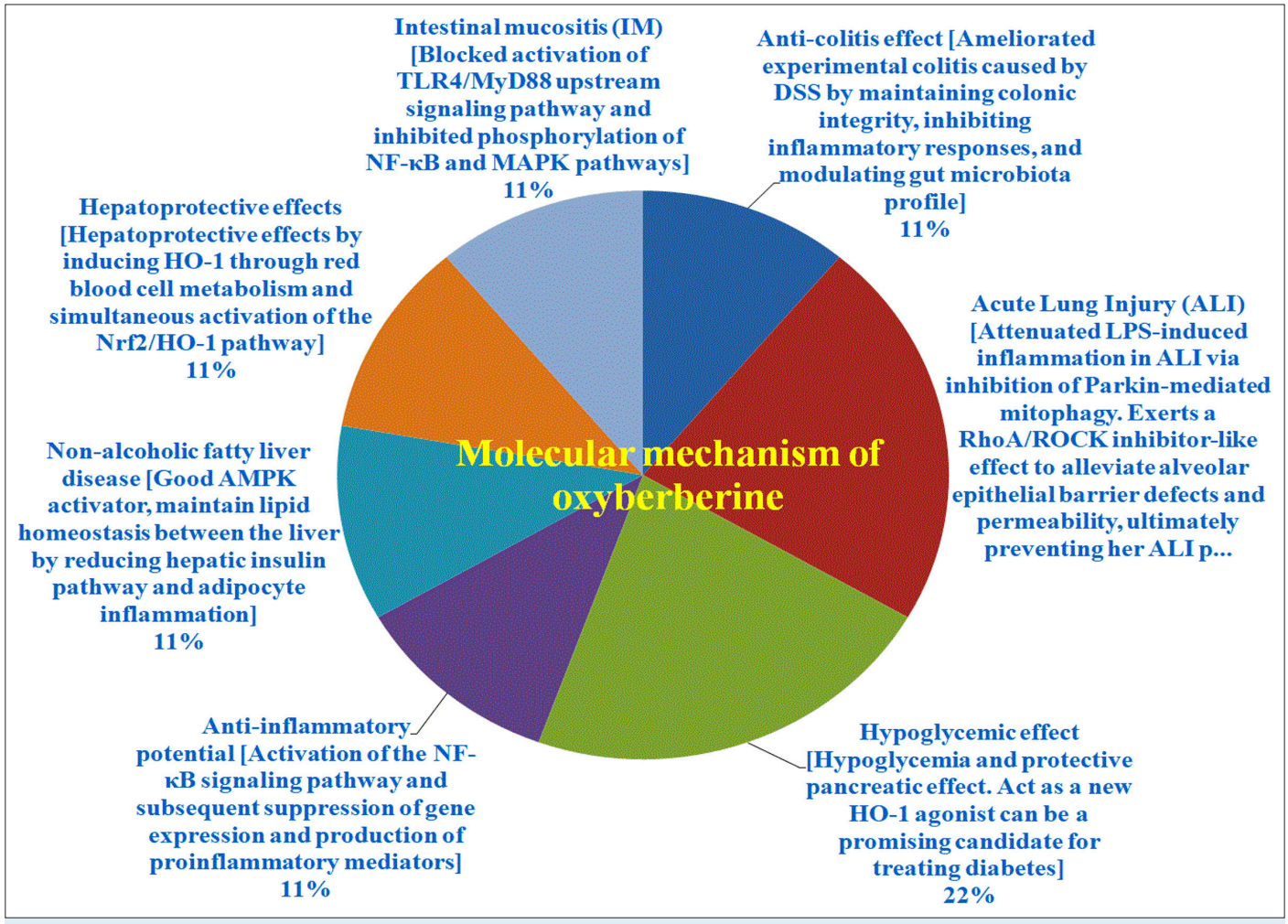

Figure 2. Molecular mechanism of oxyberberine.

its pharmacological activity in medicine. However, the scientific community requires thorough preclinical and clinical proof before claiming oxyberberine therapeutic efficacy in human illnesses. Further, rational pre-clinical research and clinical trials in the scientific field should be done to investigate the possible medical applications of oxyberberine. Analysis of scientific data showed that oxyberberine was present in many plant materials, including *Argemone Mexicana*, *Berberis kansuensis*, *Berberis lyceum*, *Coptidis Chinensis*, *Coptis japonica*, *Mahonia aquifolium*, *Phellodendron amurense* and *Phellodendron chinense*, however, additional research should be done to find out if oxyberberine is found in other plant materials as well. The impacts of oxyberberine on relevant secondary human complication should also be investigated in scientific domains to ascertain its therapeutic efficacy in modern medical science. Furthermore, oxyberberine biological relevance as a food additive should also be investigated in scientific fields due to its numerous health beneficial effects and natural occurrence. To determine the safety parameter of oxyberberine in clinical medicine, we should also determine its plasma profile through a variety of clinical investigations. Based on its claimed pharmacological activities, oxyberberine has to be studied in order to develop better molecules from the perspective of human health.

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Conflict of Interest: None declared.

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