


## Review Article

# Targeting PINK1 Using Natural Products for the Treatment of Human Diseases

Yan-Qin Li <sup>1,2</sup>, Fan Zhang,<sup>1,2</sup> Li-Ping Yu <sup>1,2</sup>, Jian-Kang Mu <sup>1,2</sup>, Ya-Qin Yang <sup>1,2</sup>,  
Jie Yu <sup>1,2</sup> and Xing-Xin Yang <sup>1,2</sup>

<sup>1</sup>College of Pharmaceutical Science, Yunnan University of Chinese Medicine, 1076 Yuhua Road, Kunming 650500, China

<sup>2</sup>Yunnan Key Laboratory of Southern Medicine Utilization, 1076 Yuhua Road, Kunming 650500, China

Correspondence should be addressed to Jie Yu; [cz.yujie@gmail.com](mailto:cz.yujie@gmail.com) and Xing-Xin Yang; [yxx78945@163.com](mailto:yxx78945@163.com)

Yan-Qin Li and Fan Zhang contributed equally to this work.

Received 23 May 2021; Revised 20 August 2021; Accepted 25 August 2021; Published 30 October 2021

Academic Editor: Baojun Xu

Copyright © 2021 Yan-Qin Li et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

*PINK1*, also known as *PARK6*, is a *PTEN*-induced putative kinase 1 that is encoded by nuclear genes. *PINK1* is ubiquitously expressed and regulates mitochondrial function and mitophagy in a range of cell types. The dysregulation of *PINK1* is associated with the pathogenesis and development of mitochondrial-associated disorders. Many natural products could regulate *PINK1* to relieve *PINK1*-associated diseases. Here, we review the structure and function of *PINK1*, its relationship to human diseases, and the regulation of natural products to *PINK1*. We further highlight that the discovery of natural *PINK1* regulators represents an attractive strategy for the treatment of *PINK1*-related diseases, including liver and heart diseases, cancer, and Parkinson's disease. Moreover, investigating *PINK1* regulation of natural products can enhance the in-depth comprehension of the mechanism of action of natural products.

## 1. Introduction

*PINK1* (*PARK6*) is a *PTEN*-induced putative kinase 1 and one of the most abundant human protein kinases [1]. *PINK1* was first discovered nearly 20 years ago due its dysregulation in ovarian cancer and soon after was reported to be important in the development of Parkinson's disease [2]. To date, *PINK1* has been implicated in a range of pathologies including liver, heart, and skeletal muscle injury due to its role in mitochondrial quality control. More recent studies indicate that natural products can relieve human diseases through their ability to regulate *PINK1* activity.

This paper reviews the structure and function of *PINK1*, investigates the relationship between *PINK1* and human diseases, and highlights the regulatory effects of natural products on *PINK1*. We herein propose that the identification of *PINK1* regulators from natural products represents an attractive strategy for the treatment of *PINK1*-related dis-

eases. Furthermore, future in-depth and comprehensive analysis of the underlying mechanism(s) of action of natural products and the role of *PINK1* in these processes may further reveal its role during disease development.

## 2. PINK1 Structure

Human *PINK1* (hPINK) is located on 1p35-p36 of chromosome 1 and has 8 exons with a length of ~18 kB. hPINK1 is 581 amino acids in length and can be divided into several domains (Figure 1(a)). Its N-terminus possesses a mitochondrial targeting sequence (MTS), an outer membrane localization sequence (OMS), a transmembrane domain (TMD), and a nonconservative region. The middle region is composed of 367 amino acids that are highly homologous to serine/threonine kinases of the calmodulin family, forming a kinase domain (KD) with an N-lobe containing three insertions (Ins1, Ins2, and Ins3), a C-lobe containing a catalytic motif

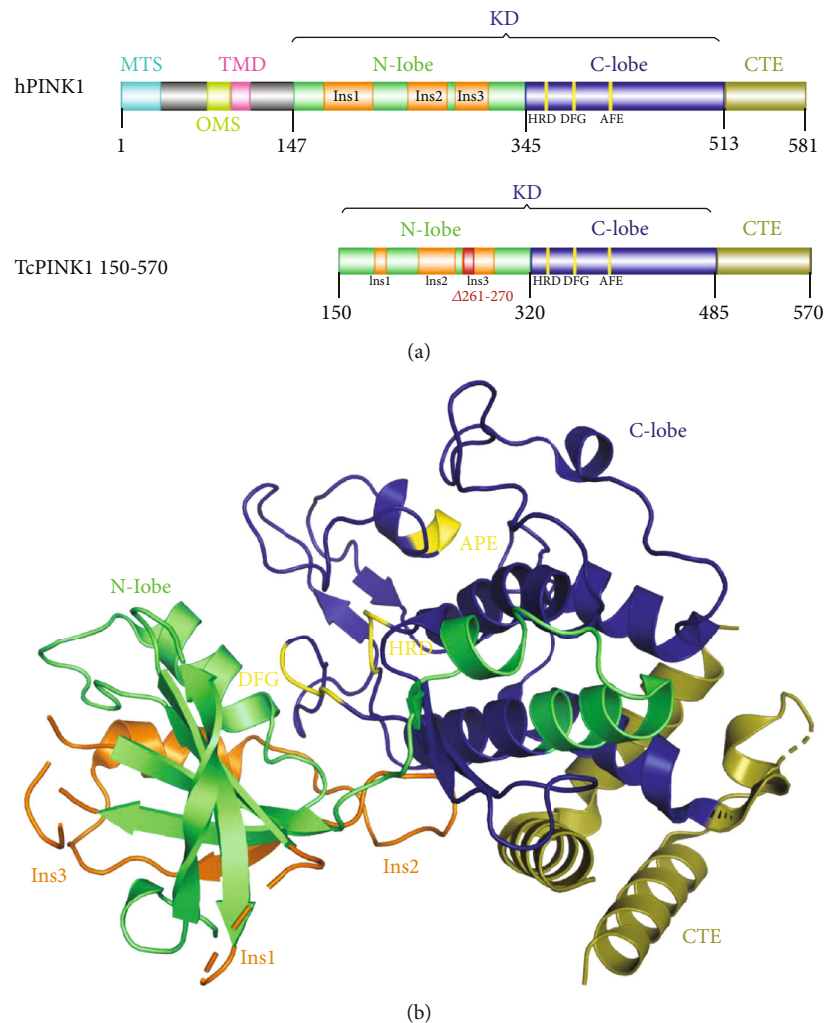


FIGURE 1: Structure of PINK1. (a) Domain architecture of human PINK1 (hPINK1) showing MTS (1-34), OMS (74-93), TMD (94-110), KD (147-513), and CTE (514-581) domains. Location of the N-lobe (147-345), C-lobe (346-513), three insertions: Ins1 (174-215); Ins2 (244-277); Ins3 (284-312), the catalytic motif HRD (360-362), and activation loop motifs: DFG (384-386) and APE (415-417). MTS: mitochondrial targeting sequence; OMS: outer membrane localization signal; TMD: transmembrane domain; KD: kinase domain; CTE: C-terminal extension; Ins: insertion. Created with IBS [60]. Domain architecture of the crystal structure of *Tribolium castaneum* PINK1 (TcPINK1, PDB ID: 5OAT) [3] is shown in the lower panel. KD (150-486), CTE (487-570), N-lobe (151-320), C-lobe (321-486), Ins1 (182-192), Ins2 (221-253), Ins3 (260-288), HRD (335-337) DFG (359-361), and APE (390-392).  $\Delta 261-270$  indicates deleted residues during the crystallization of TcPINK1. (b) Crystal structure of TcPINK1 (PDB ID: 5OAT) [3]. N-lobe, C-lobe, CTE, Ins1, Ins2, Ins3, HRD, DFG, and APE are colored as in (a); disordered regions are shown in dashed lines. Generated with PyMol [61].

(HRD), and two activation loop motifs (DFG and APE). The C-terminal extension (CTE) forms a regulatory domain composed of 69 amino acids [2–6].

The 3D structure of hPINK1 has remained elusive due to its low levels of expression, susceptibility to degradation, and poor solubility. This restricts protein production and manipulation for structural studies by X-ray crystallography and nuclear magnetic resonance (NMR). However, the kinase domain of *Tribolium castaneum* PINK1 (TcPINK1) in the apo (PDB ID: 5OAT) [3] and ATP analogue AMP-PNP-bound forms (PDB ID: 5YJ9) [4], in addition to the kinase domain of *Pediculus humanus corporis* PINK1 (PhPINK1) in the Ub-bound form (PDB ID: 6EQI) [5], were successfully

crystallized using different strategies. These structures revealed that the PINK1 kinase domain adopts a well-known bilobal kinase fold, and the CTE forms a PINK1-specific extension (Figure 1(b)). The N-lobe of kinase domain contains a five-stranded antiparallel  $\beta$ -sheet, an  $\alpha$ -helix, and three predominantly disordered insertions that distinguish PINK1 from other kinase structures.

The Ins1 varies across species in terms of length and residue identity, whilst Ins3 and the C-distal region of Ins2 are highly conserved. Ins2 interacts with the C-lobe and CTE and may play a regulatory role during PINK1 activation. As the most conserved insertion, Ins3 is directly involved in substrate recognition and binding. The C-lobe of the

kinase domain possesses HRD, DFG, and APE motifs with highly conserved conformations and functions. The C-terminal extension is well conserved and regulates PINK1 activity through binding to the regulatory subunit, participating in the recruitment of PINK1-related substrates. PINK1 is not only restricted to the mitochondria, but is also expressed in the cytoplasm [7]. PINK1 participates in mitochondrial quality control, stress responses, and metabolic function.

Under normal physiological conditions, PINK1 is synthesized in the cytoplasm and is imported into the inner mitochondrial membrane, where it is subsequently degraded by proteolytic enzymes. When the membrane potential of the mitochondria dissipates due to mitochondrial damage, the transfer of PINK1 to the inner membrane is blocked, and PINK1 accumulates on the outer mitochondrial membrane. At the same time, Parkin is recruited from the cytoplasm by PINK1 and phosphorylated. Activated Parkin catalyzes the ubiquitination (UB) of mitochondrial proteins, enabling their recognition by connexin. UB proteins associate with yeast autophagy protein 8 family homologous proteins including microtubule-associated protein light chain 3 (LC3) and Golgi body-associated ATPase enhancer on phagocytic membranes to induce mitochondrial autophagy. Finally, the mitochondria-derived autophagosomes fuse with lysosomes to form mature mitochondrial autophagosomes, which subsequently imitate the degradation process.

### 3. PINK1 and Human Diseases

PINK1 is expressed in the brain, heart, liver, and skeletal muscle tissue. Its expression closely correlates with mitophagy regulation during human disease, highlighting its physiological significance.

**3.1. PINK1 and Parkinson's Disease (PD).** PD is a complex disorder caused by multiple genes and environmental factors [8]. The main pathological phenotypes of PD are due to the age-dependent loss of dopaminergic neurons in the substantia nigra [9]. PD leads to the loss of dopamine neurons by oxidative stress, mitochondrial dysfunction, inflammatory responses, apoptosis, and other pathological mechanisms. Genetic factors play a key role, with *PINK1* mutations leading to autosomal recessive PD. Mitochondrial dysfunction is implicated in sporadic and familial PD [10]. PINK1 maintains mitochondrial function and reduces mitochondrial oxidative stress. When PINK1 expression is suppressed, oxidative stress is impaired, resulting in decreased activity of mitochondrial complex I and excessive generation of oxygen free radicals, which are induced in PD [11]. In addition, PINK1 promotes the removal of  $\alpha$ -synuclein aggregates and protects neurons from  $\alpha$ -synuclein-mediated damage [12]. Overexpression of PINK1 also enhances the phosphorylation of Akt at Ser473, with activated Akt protecting SH-SY5Y neuronal cells from various cytotoxic substances including reactive oxygen species (ROS) [13]. PINK1 deficiency leads to the defective differentiation of neural stem cells into astrocytes, which induces neuronal death and/or the abnormal repair of damaged brain tissue, resulting in an

increased risk of PD [14]. Small interfering RNAs have also been shown to significantly inhibit the expression of *PINK1* in human dopaminergic cells such as SH-SY5Y, decreasing their viability [15]. Restoring the expression of PINK1 represents a promising strategy for future PD therapies.

**3.2. PINK1 and Cancer.** *PINK1* displays tumor suppressor activity [16]. PINK1 expression is not limited to the brain, but shows an ubiquitous distribution with a subcellular localization that is cell type dependent [17]. Early studies showed that PINK1 is highly expressed in breast, colorectal, and endometrial cancer tissues. In addition, the downregulation of PINK1 inhibits the proliferation, colony forming ability, and migration of cancer cells [16, 18] and increases the sensitivity of tumor cells to stressors [15, 19]. PINK1 promotes tumorigenesis by activating factor-1 receptor-photodynamic kinase 3/Akt signaling [13]. Through parallel high-throughput RNA interference screening, it was found that in the context of DNA mismatch repair defects in cancer, PINK1 silencing led to increased ROS production and subsequent oxidative DNA damage in the nucleus and mitochondria. In cancer patients with DNA mismatch repair defects, the development of drugs that trigger mitochondrial and nuclear oxidative DNA damage, therefore, represents a potential therapeutic approach [20]. The overexpression of PINK1 activates NF- $\kappa$ B signaling and promotes the development of non-small-cell lung cancer (NSCLC). The downregulation of PINK1 can enhance cisplatin- (CDDP-) induced apoptosis in NSCLC cells [18] and makes cervical cancer cells (including HeLa and BT474 cells) sensitive to paclitaxel, significantly increasing cell death [21]. It is however postulated that PINK1 possesses both pro- and anti-apoptotic activity that is dependent on the cell environment [16]. Mitophagy plays a dual role in hepatocellular carcinoma (HCC) development depending on the stage of tumorigenesis [22–24]. Therefore, PINK1 represents a potential target for anticancer therapeutics.

#### 3.3. PINK1 and Liver Disease

**3.3.1. PINK1 and Metabolic-Associated Fatty Liver Disease (MAFLD).** MAFLD is the most common chronic liver disorder worldwide. MAFLD encompasses a broad spectrum of hepatic disorders [25] that may advance to hepatitis, liver cirrhosis, and liver cancer [26, 27]. The removal of damaged mitochondria through mitophagy is widely regarded as a protective mechanism during long-term MAFLD development. In mouse models induced by a high-fat diet, mitophagy defects are related to a series of phenotypes related to MAFLD [28–30]. The PINK1-Parkin pathway is a major regulator of hepatocyte mitophagy and is key to the cyanidin-3-O-glucoside-mediated alleviation of MAFLD [31]. In mouse models of MAFLD, hepatic ALCAT1 (an acyl-CoA-dependent lysocardiolipin acyltransferase) is significantly overexpressed, whilst its deficiency increases the expression of PINK1 and prevents the onset of MAFLD [28]. Hepatic inflammation can be regulated by autophagy, which limits ROS production and the release of DAMPs (damage-associated molecular patterns) [32]. Inflammation is an important

TABLE 1: Neuroprotection by natural products through PINK1 regulation.

Type	Natural products	Disease	Experimental models
Mixture	Da-Bu-Yin-Wan and Qian-Zheng-San [62]	Parkinson's disease	PINK1 knockdown and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induction in SH-SY5Y cells
	<i>Eucommia ulmoides</i> Oliver leaf extracts [63]	Parkinson's disease	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced zebrafish model
	Grape skin extracts [64]	Parkinson's disease	<i>Drosophila melanogaster</i> model of Parkinson's disease combined with <i>PINK1</i> loss-of-function mutations
	<i>Panax notoginseng</i> saponins [65]	Cerebral ischemia reperfusion injury	Cerebral ischemia and reperfusion rat model
	<i>Acanthopanax senticosus</i> extracts [66]	Parkinson's disease	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced mouse model
	Tenuifolin [67]	Alzheimer's disease	A $\beta$ -induced apoptosis in SH-SYHY cells
Monomer	Schisandrin A [68]	Parkinson's disease	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced male C57BL/6 model
	Celastrol [69]	Parkinson's disease	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced SH-SY5Y cells and mouse model
	Salidroside [70]	Parkinson's disease	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced model in male C57BL/6 mice and MN9D cells
	Carnosic acid [71]	Parkinson's disease	6-hydroxydopamine-induced SH-SY5Y cells

cause of hepatitis [33]. In mouse models of hepatitis, the expression of PINK1 and Parkin are suppressed, leading to impaired mitophagy and increased activation of the NLRP3 inflammasome [33]. Mitophagy inhibition with 3-methyladenine/PINK1-directed siRNA weakens the liraglutide-mediated suppression of inflammatory injury [34]. As such, therapeutic efforts to increase PINK1-mediated mitophagy may not only reverse the hepatic manifestations of MAFLD such as hepatocellular steatosis and injury, but suppress metabolic abnormalities associated with disease progression.

**3.3.2. PINK1 and Liver Ischemia/Reperfusion (IR) Injury.** I/R injury occurs when cellular damage in an organ is initiated during hypoxia or anoxia and becomes exacerbated upon the restoration of oxygen and tissue pH [35]. The liver is the second largest organ in the body. As inferred from its unique dual blood supply, it is vulnerable to ischemic attack due to its highly aerobic nature [36]. There is evidence that mitophagy functions preserve hepatic function and cell survival post-I/R [37, 38]. In mouse liver IR injury models, mitochondrial biogenesis and PINK1-Parkin-mediated mitophagy are attenuated, whilst pharmacological stimulation that increases the expression of PINK1-Parkin enhances mitophagy and improves the outcome of IR, supporting their protective role in IR-induced liver injury [39, 40]. In addition, when AMPK $\alpha$  is activated, PINK1-dependent mitophagy is upregulated, which plays a protective role in I/R injury and liver protection [41]. Future studies are required to advance our understanding of the relationship between mitophagy dysfunction and hepatic I/R injury.

**3.4. PINK1 and Heart Disease.** Heart disease is a public health concern and a primary cause of mortality worldwide. The heart has the highest mitochondrial content of all tissues, in which changes in mitochondrial homeostasis severely impact its function [42]. Mitochondrial function

and quality control are essential for myocardial contraction [43]. PINK1 can prevent abnormal ROS production and can prevent cardiomyocyte apoptosis. PINK1 knockout mice show spontaneous age-dependent cardiac hypertrophy. PINK1 deficiency alters the mitochondria transmembrane potential ( $\Delta\psi$  m) in cardiomyocytes, and the expression of PINK1 in the left ventricle of patients with end-stage heart failure is significantly reduced [42]. PINK1 deficiency disrupts mitophagy mediated by PINK1, leading to the inactivation of mitophagy, a loss of myocardial tissue movement, and the development of cardiac hypertrophy [44]. Recent studies reveal new protective pathways of myocardial I/R injury. PINK1 overexpression alleviates hypoxia-reoxygenation-induced cell damage in H9c2 cells through the phosphorylation of TNF receptor-associated protein 1 (TRAP-1) [45]. E2F1 is essential for heart function and affects the metabolism of cardiomyocytes. The E2F1/miR-421/PINK1 axis regulates mitochondrial fracture and cardiomyocyte apoptosis. E2F1 knockout reduces miR-421 levels and promotes PINK1 expression to inhibit mitochondrial damage, apoptosis, and myocardial infarction [46]. AMPK $\alpha$ 2 in cardiomyocytes phosphorylates PINK1 at ser495 and activates PINK1-Parkin-mediated mitophagy to prevent heart failure [47–49]. It is also reported that specific signaling molecules protect the heart from I/R injury by enhancing PINK1-dependent mitophagy. These signaling molecules include thyroid hormone post-conditioning (THPostC), tumor susceptibility gene 101 (TSG101), phosphatase and tensin homolog (PTEN), and apurinic/aprimidinic endonuclease 1 (APE1) [50–53]. The regulation of PINK1 expression and enhanced PINK1-dependent mitophagy should form the focus of future treatment strategies for heart disease.

**3.5. PINK1 and Skeletal Muscle Injury.** Skeletal muscle is the most abundant tissue in the human body, accounting for 40% of the total body weight. Due to the role of skeletal muscle in



TABLE 2: Liver protection of natural products through the regulation of PINK1.

Type	Natural products	Disease	Experimental models
Mixture	Zhiganfang [72]	Nonalcoholic steatohepatitis	High-fat diet-induced SD rats
Monomer	Cyanidin-3-O-glucoside [31]	Nonalcoholic fatty liver disease	High-fat diet-induced mice, palmitic acid-induced AML-12 cells and HepG2 human hepatocarcinoma cells
	Genipin [73]	Hepatic ischemia and reperfusion injury	Ischemia and reperfusion-induced hepatic injury in C57BL/6 mice
	Quercetin [74]	Non-alcoholic fatty liver disease	High-fat diet-induced C57BL/6 model and andoleate/palmitate-induced HepG2 cells
	Matrine [75]	Liver cancer	HepG2 and Huh7 cell lines
	Ginsenoside Rg1 [76]	Nonalcoholic fatty liver disease	Oleic acid-induced HL-7702 cells

TABLE 3: Anticancer activity of natural products through regulation of PINK1.

Natural products	Disease	Experimental models
Alantolactone [77]	Liver cancer	HepG2 cells
Tanshinone I [77]	Liver cancer	HepG2 cells
Polyphyllin I [78]	Breast cancer	Human breast cancer cells (MDA-MB-231 and MCF-7) and human mammary stromal cells (Hs-578Bst)
Ginsenoside Rh2 [79]	Breast cancer	Human breast epithelial cell line MCF-10A and breast cancer cell line MCF-7-GFP stable cells
Ursolic and Oleanolic Acids [80]	Lung cancer	A549 human lung cancer cells
Chalcomoracin [81]	Breast cancer	Human breast cell MDA-MB-231 and female nonthymic nude mice
Chalcomoracin [81]	Prostate cancer	Prostate cancer cells PC-3 and LnCAP

TABLE 4: Protection of myocardial injury by natural products through PINK1 regulation.

Type	Natural products	Disease	Experimental models
Mixture	Yimai Granule [82]	Hyperlipidemia combined with myocardial ischemia-reperfusion injury	High-fat diet combined with myocardial ischemia-reperfusion injury in SD rats
	Tongxinluo [83]	Myocardial ischemia-reperfusion injury	Left anterior descending coronary artery ligation performed for 50 min and reperfusion for 4 h for animal models of myocardial ischemia -reperfusion injury
Mixture	Shenmai Injection [84]	Myocardial ischemia and reperfusion injury	H9c2 cardiomyocytes subjected to 12 h hypoxia followed by 2 h of reoxygenation to induce cell injury
	Tongxinluo capsule [85]	Myocardial ischemia and reperfusion injury	Left anterior descending artery ligation and surgery, with 50 min ischemia followed by 4 h reperfusion in SD rats.
	Gualou Xiebai Banxia decoction [86]	Myocardial ischemia reperfusion injury	Reversible ligation of the left anterior descending coronary artery for 30 min and reperfusion for 2 h to prepare animal models of myocardial ischemia-reperfusion injury
Monomer	Gerontoxanthone I [87]	Myocardial ischemia and reperfusion injury	H9c2 cells incubated in a hypoxic chamber with ischemia-mimetic solution, then transferred into a normoxic incubator with fresh DMEM to establish the model
	Macluraxanthone [87]	Myocardial ischemia and reperfusion injury	H9c2 cells incubated in a hypoxic incubator with ischemia-mimetic solution, then transferred into a normoxic incubator with fresh DMEM to establish the model

exercise, respiration, and energy metabolism, its dysfunction or degradation seriously impacts human health. Mitophagy maintains the homeostasis of skeletal muscle cells [54], but excessive mitophagy can damage skeletal muscle mitochondria [55]. The PINK1-Parkin axis is related to exercise-induced mitochon-

drial degeneration [56], and in patients with sporadic amyotrophic lateral sclerosis (ALS), the expression of PINK1 is significantly reduced [57]. Traumatic freezing injury leads to mitochondrial dysfunction in skeletal muscle. During this condition, PINK1 expression doubles and mitophagy enhances the

TABLE 5: Other diseases alleviated by natural products through PINK1 regulation.

Type	Natural products	Disease	Experimental models
Mixture	<i>Pueraria lobata</i> extracts [88]	Diabetic nephropathy	Cadmium combined with high-fat and high-sugar feed in mice
	<i>Astragalus mongholicus</i> Bunge and <i>Panax notoginseng</i> (Burkill) F.H. Chen [89]	Diabetic nephropathy	<i>In vivo</i> autophagy deficiency model established in C57BL/6 mice by streptozocin combined with a high-fat and high-sugar diet. <i>In vitro</i> autophagy deficiency model induced by high glucose in renal mesangial cells.
	Huangqi-Danshen decoction [90]	Diabetic nephropathy	Male diabetic <i>db/db</i> mice and nondiabetic littermate <i>db/m</i> mice
Monomer	Astragaloside IV [91]	Diabetic nephropathy	Male diabetic <i>db/db</i> mice and nondiabetic littermate control <i>db/m</i> mice
	Mangiferin [92]	Obesity	C3H10T1/2 mesenchymal stem cells and human adipose-derived MSCs
	Curcumin [93]	Acute kidney injury	Cisplatin-induced injury model in rats
	Palmitate [94]	Ulcerative colitis	Dextran sodium sulfate-induced ulcerative colitis in mice. NLRP3 inflammasome activation in THP-1 cells

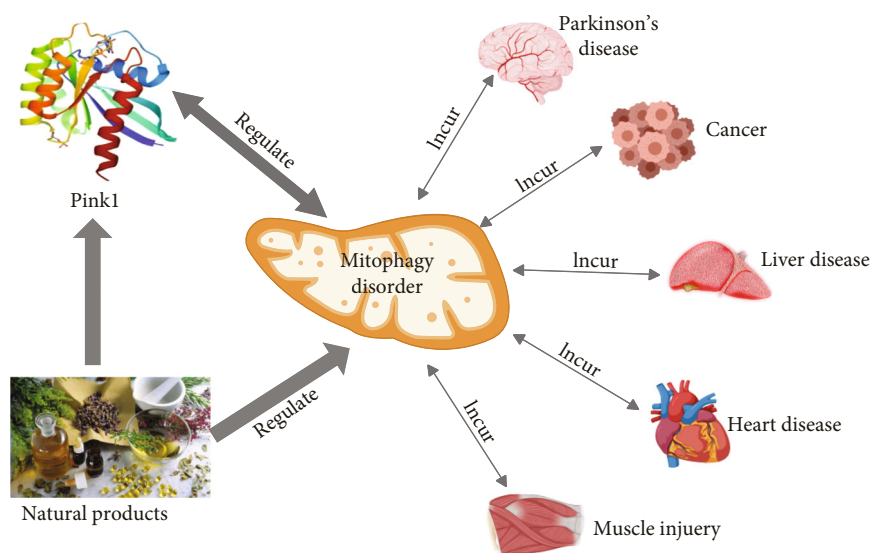


FIGURE 2: Regulation of PINK1 by natural products for the treatment of human disease.

clearance of inactivated mitochondria posttrauma [58]. Taken together, the expression of PINK1 can activate mitophagy to clear damaged mitochondria and protect skeletal muscle cells. However, during heavy load exercise, the structure and quantity of skeletal muscle mitochondria are damaged, and a large number of autophagosomes form. During this time, PINK1 and Parkin levels in the mitochondria are significantly elevated which excessively activates mitophagy, leading to mitochondrial damage in skeletal muscle. In models of exhaustive exercise-induced fatigue in mice, *Rhodiola crenulata* oral liquid (RCOL) reduced the expression of PINK1 and Parkin, highlighting that its antifatigue effects are mediated through the inhibition of mitophagy [59]. These results indicate that moderate exercise training can increase PINK1 expression and activate autophagy, which is conducive to maintaining skeletal muscle homeostasis. When the body is exposed to adverse stress, abnormal increases in PINK1 lead to excessive

autophagy, abnormal mitochondrial function, and decreased cell viability.

#### 4. Regulation of PINK1 by Natural Products

Natural products remain a highly significant source for drug/nutrients development, because of the novel structures, therapeutic abilities, and certain unique pharmacological effects of the chemical substances in natural products. Natural products are widely used to prevent, treat, and diagnose diseases and perform rehabilitation and healthcare. They mainly originate from natural plants, animals, minerals, and their processed products. Both of the monomers and mixtures can be used for the treatment of diseases. With the societal development, the need for disease prevention, medical treatment, rehabilitation, and health maintenance

is increasing. Thus, the application of natural products has received unprecedented attention.

Given its roles in multiple tissue types, PINK1 has emerged as a key drug target, with natural products that regulate its expression holding promise for therapeutic interventions. Some natural products (including mixtures and monomers) that regulate PINK1 effectively alleviate its associated diseases (Tables 1–5), including but not limited to liver disease, cancer, and myocardial injury. More in-depth assessments of the constituents of natural products that regulate PINK1 function may further reveal their underlying utility for PINK1-associated disease.

## 5. Conclusions

PINK1 participates in mitochondrial quality control, stress responses, and metabolic signaling. It is also a key regulator of mitophagy. PINK1 dysfunction leads to mitochondrial dysfunction and subsequent disease development, including PD, cancer, liver disease, heart disease, and skeletal muscle injury. It has been reported that some natural products display their therapeutic effects through PINK1 regulation (Figure 2). However, only a few have become clinical drugs for treating patients. It is necessary to explore the regulatory effects of natural products on the expression/activity of PINK1 and its related mechanisms to identify novel compounds that can restore PINK1 function in disease states. In addition, the monomers that regulate PINK1 in many natural extracts remain undefined, and further studies are warranted to assess their utility for the treatment of human disease. With the deepening of research, it is believed that more natural products that can regulate PINK1 may be used to treat diseases, which is of utmost importance.

## Abbreviations

hPINK:	Human PINK1
MTS:	Mitochondrial targeting sequence
OMS:	Outer membrane localization sequence
TMD:	Transmembrane domain
KD:	Kinase domain
CTE:	C-terminal extension
NMR:	Nuclear magnetic resonance
TcPINK1:	Tribolium castaneum PINK1
PhPINK1:	Pediculus humanus corporis PINK1
UB:	Ubiquitination
LC3:	Light chain 3
PD:	Parkinson's disease
ROS:	Reactive oxygen species
NSCLC:	Non-small-cell lung cancer
CDDP:	Cisplatin
HCC:	Hepatocellular carcinoma
MAFLD:	Metabolic-associated fatty liver disease
DAMPs:	Damage-associated molecular patterns
IR:	Ischemia/reperfusion
AMPK:	AMP-activated protein kinase
$\Delta\Psi_m$ :	Mitochondria transmembrane potential
TRAP-1:	TNF receptor-associated protein 1
THPostC:	Thyroid hormone postconditioning

TSG101:	Tumor susceptibility gene 101
PTEN:	Phosphatase and tensin homolog
APE1:	Apurinic/aprimidinic endonuclease 1
RCOL:	<i>Rhodiola crenulata</i> oral liquid.

## Conflicts of Interest

The authors declare that they have no competing interests.

## Authors' Contributions

YQL organized the outline and wrote the manuscript. FZ participated in research design. LPY, JKM, and YQY analyzed the literature. JY and XXY contributed to the final version of the manuscript. All authors read and approved the final manuscript. Yan-Qin Li and Fan Zhang contributed equally to this work. Publication of this manuscript has been approved by all co-authors.

## Acknowledgments

This study was supported by grants from the National Natural Science Foundation of China (Grants 82104381, 82060707, 81660596, and 81460623), the Application and Basis Research Project of Yunnan China (Grants 2019FF002-061 and 2017FF117-013), and the Young and Middle-Aged Academic and Technological Leader of Yunnan (Grant 202005AC160059).

## References

- [1] G. Manning, D. B. Whyte, R. Martinez, T. Hunter, and S. Sudarsanam, "The protein kinase complement of the human genome," *Science*, vol. 298, no. 5600, pp. 1912–1934, 2002.
- [2] S. Rasool and J. F. Trempe, "New insights into the structure of PINK1 and the mechanism of ubiquitin phosphorylation," *Critical Reviews in Biochemistry and Molecular Biology*, vol. 53, no. 5, pp. 515–534, 2018.
- [3] A. Kumar, J. Tamjar, A. D. Waddell et al., "Structure of PINK1 and mechanisms of Parkinson's disease-associated mutations," *eLife*, vol. 6, 2017.
- [4] K. Okatsu, Y. Sato, K. Yamano et al., "Structural insights into ubiquitin phosphorylation by PINK1," *Scientific reports*, vol. 8, no. 1, p. 10382, 2018.
- [5] A. F. Schubert, C. Gladkova, E. Pardon et al., "Structure of PINK1 in complex with its substrate ubiquitin," *Nature*, vol. 552, no. 7683, pp. 51–56, 2017.
- [6] N. Wang, P. Zhu, R. Huang et al., "PINK1: the guard of mitochondria," *Life Sciences*, vol. 259, p. 118247, 2020.
- [7] D. N. Hauser, A. Mamais, M. M. Conti et al., "Hexokinases link DJ-1 to the PINK1/parkin pathway," *Molecular neurodegeneration*, vol. 12, no. 1, p. 70, 2017.
- [8] L. Krohn, F. P. Grenn, M. B. Makarios, J. J. Kim, and C. Blauwendraat, "Comprehensive assessment of \_PINK1\_ variants in Parkinson's disease," *Neurobiology of Aging*, vol. 91, pp. 168.e1–168.e5, 2020.
- [9] N. Matsuda and K. Yamano, "Two sides of a coin: physiological significance and molecular mechanisms for damage-induced mitochondrial localization of PINK1 and Parkin," *Neuroscience Research*, vol. 159, pp. 16–24, 2020.

- [10] M. Verma, J. Zhu, K. Z. Q. Wang, and C. T. Chu, "Chronic treatment with the complex I inhibitor MPP<sup>+</sup> depletes endogenous PTEN-induced kinase 1 (PINK1) via up-regulation of Bcl-2-associated athanogene 6 (BAG6)," *The Journal of Biological Chemistry*, vol. 295, no. 23, pp. 7865–7876, 2020.
- [11] V. A. Morais, D. Haddad, K. Craessaerts et al., "PINK1 loss-of-function mutations affect mitochondrial complex I activity via NdufA10 ubiquinone uncoupling," *Science (New York, N.Y.)*, vol. 344, no. 6180, pp. 203–207, 2014.
- [12] R. B. Creed and M. S. Goldberg, "Enhanced susceptibility of PINK1 knockout rats to  $\alpha$ -synuclein fibrils," *Neuroscience*, vol. 437, pp. 64–75, 2020.
- [13] H. Murata, M. Sakaguchi, Y. Jin et al., "A New Cytosolic Pathway from a Parkinson Disease-associated Kinase, BRPK/PINK1," *The Journal of Biological Chemistry*, vol. 286, no. 9, pp. 7182–7189, 2011.
- [14] I. Choi, D. J. Choi, H. Yang et al., "PINK1 expression increases during brain development and stem cell differentiation, and affects the development of GFAP-positive astrocytes," *Molecular Brain*, vol. 9, no. 1, 2016.
- [15] H. Deng, J. Jankovic, Y. Guo, W. Xie, and W. Le, "Small interfering RNA targeting the PINK1 induces apoptosis in dopaminergic cells SH-SY5Y," *Biochemical and Biophysical Research Communications*, vol. 337, no. 4, pp. 1133–1138, 2005.
- [16] C. H. O'Flanagan, V. A. Morais, W. Wurst, B. De Strooper, and C. O'Neill, "The Parkinson's gene PINK1 regulates cell cycle progression and promotes cancer-associated phenotypes," *Oncogene*, vol. 34, no. 11, pp. 1363–1374, 2015.
- [17] A. Berthier, S. Navarro, J. Jiménez-Sáinz et al., "PINK1 displays tissue-specific subcellular location and regulates apoptosis and cell growth in breast cancer cells," *Human Pathology*, vol. 42, no. 1, pp. 75–87, 2011.
- [18] R. Zhang, J. Gu, J. Chen et al., "High expression of PINK1 promotes proliferation and chemoresistance of NSCLC," *Oncology Reports*, vol. 37, no. 4, pp. 2137–2146, 2017.
- [19] T. Cui, C. Fan, L. Gu et al., "Silencing of PINK1 induces mitophagy via mitochondrial permeability transition in dopaminergic MN9D cells," *Brain Research*, vol. 1394, pp. 1–13, 2011.
- [20] S. A. Martin, M. Hewish, D. Sims, C. J. Lord, and A. Ashworth, "Parallel high-throughput RNA interference screens identify PINK1 as a potential therapeutic target for the treatment of DNA mismatch repair-deficient cancers," *Cancer Research*, vol. 71, no. 5, pp. 1836–1848, 2011.
- [21] J. P. MacKeigan, L. O. Murphy, and J. Blenis, "Sensitized RNAi screen of human kinases and phosphatases identifies new regulators of apoptosis and chemoresistance," *Nature Cell Biology*, vol. 7, no. 6, pp. 591–600, 2005.
- [22] X. Ma, T. McKeen, J. Zhang, and W. X. Ding, "Role and mechanisms of mitophagy in liver diseases," *Cells*, vol. 9, no. 4, p. 837, 2020.
- [23] K. Liu, J. Lee, J. Y. Kim et al., "Mitophagy controls the activities of tumor suppressor p53 to regulate hepatic cancer stem cells," *Molecular cell*, vol. 68, no. 2, pp. 281–292.e5, 2017.
- [24] H. Qian, X. Chao, and W. X. Ding, "A PINK1-mediated mitophagy pathway decides the fate of tumors—to be benign or malignant?," *Autophagy*, vol. 14, no. 4, pp. 563–566, 2018.
- [25] M. Meroni, M. Longo, A. L. Fracanzani, and P. Dongiovanni, "MBOAT7 down-regulation by genetic and environmental factors predisposes to MAFLD," *eBioMedicine*, vol. 57, p. 102866, 2020.
- [26] S. L. Friedman, B. A. Neuschwander-Tetri, M. Rinella, and A. J. Sanyal, "Mechanisms of NAFLD development and therapeutic strategies," *Nature Medicine*, vol. 24, no. 7, pp. 908–922, 2018.
- [27] M. Rinella, "Nonalcoholic fatty liver disease: a systematic review," *Jama the Journal of the American Medical Association*, vol. 313, no. 22, pp. 2263–2273, 2015.
- [28] L. Wang, X. Liu, J. Nie et al., "ALCAT1 controls mitochondrial etiology of fatty liver diseases, linking defective mitophagy to steatosis," *Hepatology (Baltimore, Md.)*, vol. 61, no. 2, pp. 486–496, 2015.
- [29] T. Zhou, L. Chang, Y. Luo, Y. Zhou, and J. Zhang, "Mst1 inhibition attenuates non-alcoholic fatty liver disease via reversing Parkin-related mitophagy," *Redox Biology*, vol. 21, p. 101120, 2019.
- [30] D. H. Lee, Y. Y. Jung, M. H. Park et al., "Peroxiredoxin 6 confers protection against nonalcoholic fatty liver disease through maintaining mitochondrial function," *Antioxidants & Redox Signaling*, vol. 31, no. 5, pp. 387–402, 2019.
- [31] X. Li, Z. Shi, Y. Zhu et al., "Cyanidin-3-O-glucoside improves non-alcoholic fatty liver disease by promoting PINK1-mediated mitophagy in mice," *British Journal of Pharmacology*, vol. 177, no. 15, pp. 3591–3607, 2020.
- [32] C. Brenner, L. Galluzzi, O. Kepp, and G. Kroemer, "Decoding cell death signals in liver inflammation," *Journal of Hepatology*, vol. 59, no. 3, pp. 583–594, 2013.
- [33] N. P. Zhang, X. J. Liu, L. Xie, X. Z. Shen, and J. Wu, "Impaired mitophagy triggers NLRP3 inflammasome activation during the progression from nonalcoholic fatty liver to nonalcoholic steatohepatitis," *Laboratory investigation; a journal of technical methods and pathology*, vol. 99, no. 6, pp. 749–763, 2019.
- [34] X. Yu, M. Hao, Y. Liu et al., "Liraglutide ameliorates non-alcoholic steatohepatitis by inhibiting NLRP3 inflammasome and pyroptosis activation via mitophagy," *European Journal of Pharmacology*, vol. 864, p. 172715, 2019.
- [35] M. Mendes-Braz, M. Elias-Miró, M. B. Jiménez-Castro, A. Casillas-Ramírez, F. S. Ramalho, and C. Peralta, "The current state of knowledge of hepatic ischemia-reperfusion injury based on its study in experimental models," *Journal of Biomedicine & Biotechnology*, vol. 2012, Article ID 298657, 20 pages, 2012.
- [36] K. L. Go, S. Lee, I. Zendejas, K. E. Behrns, and J. S. Kim, "Mitochondrial dysfunction and autophagy in hepatic ischemia/reperfusion injury," *BioMed Research International*, vol. 2015, Article ID 183469, 14 pages, 2015.
- [37] J. C. Goldstein, N. J. Waterhouse, P. Juin, G. I. Evan, and D. R. Green, "The coordinate release of cytochrome c during apoptosis is rapid, complete and kinetically invariant," *Nature Cell Biology*, vol. 2, no. 3, pp. 156–162, 2000.
- [38] P. Pacher, "Propagation of the apoptotic signal by mitochondrial waves," *EMBO JOURNAL*, vol. 20, no. 15, pp. 4107–4121, 2001.
- [39] J. M. Hong and S. M. Lee, "Heme oxygenase-1 protects liver against ischemia/reperfusion injury via phosphoglycerate mutase family member 5-mediated mitochondrial quality control," *Life Sciences*, vol. 200, pp. 94–104, 2018.
- [40] J. W. Kang, H. S. Choi, and S. M. Lee, "Resolvin D1 attenuates liver ischaemia/reperfusion injury through modulating thioredoxin 2-mediated mitochondrial quality control," *British*



- Journal of Pharmacology*, vol. 175, no. 12, pp. 2441–2453, 2018.
- [41] J. Zheng, L. Chen, T. Lu et al., “MSCs ameliorate hepatocellular apoptosis mediated by PINK1-dependent mitophagy in liver ischemia/reperfusion injury through AMPK $\alpha$  activation,” *Cell death & disease*, vol. 11, no. 4, p. 256, 2020.
- [42] F. Billia, L. Hauck, F. Konecny, V. Rao, J. Shen, and T. W. Mak, “PTEN-inducible kinase 1 (PINK1)/Park6 is indispensable for normal heart function,” *Proceedings of the National Academy of Sciences of the United States of America*, vol. 108, no. 23, pp. 9572–9577, 2011.
- [43] J. Piquereau, F. Caffen, M. Novotova et al., “Mitochondrial dynamics in the adult cardiomyocytes: which roles for a highly specialized cell?,” *Frontiers in Physiology*, vol. 4, 2013.
- [44] A. Moyzis and Å. Gustafsson, “Multiple recycling routes: canonical vs. non-canonical mitophagy in the heart,” *Biochimica et biophysica acta. Molecular basis of disease*, vol. 1865, no. 4, pp. 797–809, 2019.
- [45] Y. Li, L. Qiu, X. Liu, Z. Hou, and B. Yu, “PINK1 alleviates myocardial hypoxia-reoxygenation injury by ameliorating mitochondrial dysfunction,” *Biochemical and Biophysical Research Communications*, vol. 484, no. 1, pp. 118–124, 2017.
- [46] K. Wang, L. Y. Zhou, J. X. Wang et al., “E2F1-dependent miR-421 regulates mitochondrial fragmentation and myocardial infarction by targeting Pink1,” *Nature Communications*, vol. 6, no. 1, p. 7619, 2015.
- [47] Y. H. Jiang, H. L. Wang, J. Peng et al., “Multinucleated polyploid cardiomyocytes undergo an enhanced adaptability to hypoxia via mitophagy,” *Journal of Molecular and Cellular Cardiology*, vol. 138, pp. 115–135, 2020.
- [48] S. E. Shires and Å. Gustafsson, “Regulating renewable energy: connecting AMPK $\alpha$ 2 to PINK1/Parkin-mediated mitophagy in the heart,” *Circulation Research*, vol. 122, no. 5, pp. 649–651, 2018.
- [49] B. Wang, J. Nie, L. Wu et al., “AMPK $\alpha$ 2 protects against the development of heart failure by enhancing mitophagy via PINK1 phosphorylation,” *Circulation Research*, vol. 122, no. 5, pp. 712–729, 2018.
- [50] W. Tang, D. Lin, M. Chen et al., “PTEN-mediated mitophagy and APE1 overexpression protects against cardiac hypoxia/reoxygenation injury,” *In Vitro Cellular & Developmental Biology. Animal*, vol. 55, no. 9, pp. 741–748, 2019.
- [51] W. Bi, J. Jia, R. Pang et al., “Thyroid hormone postconditioning protects hearts from ischemia/reperfusion through reinforcing mitophagy,” *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, vol. 118, p. 109220, 2019.
- [52] K. Essandoh, X. Wang, W. Huang et al., “TSG101 regulates Parkin-mediated mitophagy,” *The Journal of Biological Chemistry*, vol. 294, no. 48, pp. 18057–18068, 2019.
- [53] C. Kang, M. A. Badr, V. Kyrchenko, E. L. Eskelinen, and N. Shirokova, “Deficit in PINK1/PARKIN-mediated mitochondrial autophagy at late stages of dystrophic cardiomyopathy,” *Cardiovascular Research*, vol. 114, no. 1, pp. 90–102, 2018.
- [54] H. Shang, Z. Xia, S. Bai, H. E. Zhang, B. Gu, and R. Wang, “Downhill running acutely elicits mitophagy in rat soleus muscle,” *Medicine and Science in Sports and Exercise*, vol. 51, no. 7, pp. 1396–1403, 2019.
- [55] D. Yeo, C. Kang, M. C. Gomez-Cabrera, J. Vina, and L. L. Ji, “Intensified mitophagy in skeletal muscle with aging is down-regulated by PGC-1 $\alpha$  overexpression in vivo,” *Free Radical Biology & Medicine*, vol. 130, pp. 361–368, 2019.
- [56] C. C. W. Chen, A. T. Erlich, and D. A. Hood, “Role of Parkin and endurance training on mitochondrial turnover in skeletal muscle,” *Skeletal muscle*, vol. 8, no. 1, p. 10, 2018.
- [57] S. Knippenberg, J. Sipos, N. Thau-Habermann et al., “Altered expression of DJ-1 and PINK1 in sporadic ALS and in the SOD1(G93A) ALS mouse model,” *Journal of Neuropathology and Experimental Neurology*, vol. 72, no. 11, pp. 1052–1061, 2013.
- [58] A. S. Nichenko, W. M. Southern, K. F. Tehrani et al., “Mitochondrial-specific autophagy linked to mitochondrial dysfunction following traumatic freeze injury in mice,” *American Journal of Physiology. Cell Physiology*, vol. 318, no. 2, pp. C242–C252, 2020.
- [59] Y. Hou, Y. Tang, X. Wang, X. Ai, and J. Zhang, “Rhodiola crenulata ameliorates exhaustive exercise induced fatigue in mice by suppressing mitophagy in skeletal muscle,” *Experimental and therapeutic medicine*, vol. 20, no. 4, 2020.
- [60] W. Liu, Y. Xie, J. Ma et al., “IBS: an illustrator for the presentation and visualization of biological sequences,” *Bioinformatics (Oxford, England)*, vol. 31, no. 20, pp. 3359–3361, 2015.
- [61] L. L. C. Schrodinger, *The PyMOL Molecular Graphics System*, Version 1.8, 2015.
- [62] H. J. Ma, *Investigating the Protective Mechanism of Da-Bu-Yin-Wan and Qian-Zheng-San on Mitochondria of Parkinson's Cell Model Based on PINK1 Gene*, Beijing University of Chinese medicine, 2018.
- [63] S. Zhang, Z. Yu, J. Xia et al., “Anti-Parkinson's disease activity of phenolic acids from *Eucommia ulmoides* Oliver leaf extracts and their autophagy activation mechanism,” *Food & Function*, vol. 11, no. 2, pp. 1425–1440, 2020.
- [64] Z. Wu, A. Wu, J. Dong, A. Siggers, and B. Lu, “Grape skin extract improves muscle function and extends lifespan of a *Drosophila* model of Parkinson's disease through activation of mitophagy,” *Experimental Gerontology*, vol. 113, pp. 10–17, 2018.
- [65] B. Tang, *The Role of Autophagy-NLRP3 Inflammatory Mitochondrial Body Pathway in Cerebral Ischemia-Reperfusion Injury and the Intervention of Panax Notoginseng Saponins and Astragaloside IV*, Hunan University of Chinese Medicine, 2019.
- [66] S. M. Liu, L. I. Xu-Zhao, S. N. Zhang et al., “*Acanthopanax senticosus* protects structure and function of mesencephalic mitochondria in a mouse model of Parkinson's disease,” *Chinese Journal of Integrative Medicine*, vol. 24, no. 11, pp. 835–843, 2018.
- [67] F. L. You, *Tenuifolin Protects Against A $\beta$  Induced Apoptosis of Cells through Regulating Mitophagy*, Guangdong Pharmaceutical University, 2017.
- [68] Y. Zhi, Y. Jin, L. Pan, A. Zhang, and F. Liu, “Schisandrin A ameliorates MPTP-induced Parkinson's disease in a mouse model via regulation of brain autophagy,” *Archives of Pharmacological Research*, vol. 42, no. 11, pp. 1012–1020, 2019.
- [69] M. W. Lin, C. C. Lin, Y. H. Chen, H. B. Yang, and S. Y. Hung, “Celastrol inhibits dopaminergic neuronal death of Parkinson's disease through activating mitophagy,” *Antioxidants (Basel, Switzerland)*, vol. 9, no. 1, 2020.
- [70] R. Li and J. Chen, “Salidroside protects dopaminergic neurons by enhancing PINK1/Parkin-mediated mitophagy,” *Oxidative*

- Medicine and Cellular Longevity*, vol. 2019, Article ID 9341018, 11 pages, 2019.
- [71] C. Y. Lin and C. W. Tsai, "PINK1/parkin-mediated mitophagy pathway is related to neuroprotection by carnosis acid in SH-SY5Y cells," *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association*, vol. 125, pp. 430–437, 2019.
- [72] C. F. Qin, *Correlation between PINK1 and Parkin, P62 and LC3 in Mitochondria Selective Autophagy on NASH Hepatocytes and the Intervention Effect of Zhiganfang*, Guangxi University of Chinese Medicine, 2019.
- [73] J. K. Shin and S. M. Lee, "Genipin protects the liver from ischemia/reperfusion injury by modulating mitochondrial quality control," *Toxicology and Applied Pharmacology*, vol. 328, pp. 25–33, 2017.
- [74] P. Liu, H. Lin, Y. Xu et al., "Frataxin-mediated PINK1-Parkin-dependent mitophagy in hepatic steatosis: the protective effects of quercetin," *Molecular nutrition & food research*, vol. 62, no. 16, 2018.
- [75] R. Wei, J. Cao, and S. Yao, "Matrine promotes liver cancer cell apoptosis by inhibiting mitophagy and PINK1/Parkin pathways," *Cell Stress & Chaperones*, vol. 23, no. 6, pp. 1295–1309, 2018.
- [76] W. Y. Hu, M. Li, and H. B. Liu, "Ginsenoside Rg1 protects HL-7702 cells against oleic acid-induced injury via aldolase/AMPK/PINK1 signalling," *Chinese Journal of Clinical Pharmacology and Therapeutics*, vol. 25, no. 6, pp. 633–639, 2020.
- [77] Kang, *Study of the Effect and Molecular Mechanism about Alantolactone and Tashinone I on Apoptosis in Hepatoma HepG2 Cell Line*, Northwest University, 2019.
- [78] G. B. Li, R. Q. Fu, H. M. Shen et al., "Polyphyllin I induces mitophagic and apoptotic cell death in human breast cancer cells by increasing mitochondrial PINK1 levels," *Oncotarget*, vol. 8, no. 6, pp. 10359–10374, 2017.
- [79] J. Hou, Y. Yun, J. Xue, B. Jeon, and S. Kim, "Doxorubicin-induced normal breast epithelial cellular aging and its related breast cancer growth through mitochondrial autophagy and oxidative stress mitigated by ginsenoside Rh2," *Phytotherapy research: PTR*, vol. 34, no. 7, pp. 1659–1669, 2020.
- [80] N. S. Castrejón-Jiménez, K. Leyva-Paredes, S. L. Baltierra-Uribe et al., "Ursolic and oleanolic acids induce mitophagy in A549 human lung cancer cells," *Molecules (Basel, Switzerland)*, vol. 24, no. 19, p. 3444, 2019.
- [81] R. Y. Li, *Anti-Tumor Mechanisms of Four Monomer Compounds on Prostate and Breast Cancer Cell Lines*, Zhejiang University, 2016.
- [82] D. W. Zhang, *Effects of Yimai Granule Regulating Mitochondrial Autophagy on Myocardial Injury in Rats with High Fat Complicated and Myocardial Ischemia-Reperfusion Injury*, Liaoning University Of Traditional Chinese Medicine, 2019.
- [83] H. X. Yang, *The Autophagy Mechanism and Related Micro-RNA Pathways of Tongxinluo Intervention on Myocardial Ischemia-Reperfusion Injury in Rats*, Beijing University of Chinese Medicine, 2019.
- [84] J. Yu, Y. Li, X. Liu et al., "Mitochondrial dynamics modulation as a critical contribution for Shenmai injection in attenuating hypoxia/reoxygenation injury," *Journal of Ethnopharmacology*, vol. 237, pp. 9–19, 2019.
- [85] H. X. Yang, P. Wang, N. N. Wang, S. D. Li, and M. H. Yang, *Tongxinluo Ameliorates Myocardial Ischemia-Reperfusion Injury Mainly via Activating Parkin-Mediated Mitophagy and Downregulating Ubiquitin-Proteasome System*, Chinese journal of integrative medicine, 2019.
- [86] X. Li, *Study on Mechanism of Gualou Xiebai Banxia Decoction on the Mitophagy and PINK1/Parkin Pathway in Rats with Myocardial Ischemia Reperfusion Injury*, Yunnan University of Chinese Medicine, 2020.
- [87] Q. Xiang, M. Wu, L. Zhang et al., "Gerontoxanthone I and macluraxanthone induce mitophagy and attenuate ischemia/reperfusion injury," *Frontiers in Pharmacology*, vol. 11, p. 452, 2020.
- [88] D. Tian, *Study on the Protective Effect of Pueraria lobata Extract on Cadmium-Induced Diabetic Nephropathy in Mice*, Shaanxi University of Science & Technology, 2019.
- [89] D. Wen, R. Z. Tan, C. Y. Zhao et al., "Astragalus mongholicus Bunge and Panax notoginseng (Burkill) F.H. Chen Formula for renal injury in diabetic Nephropathy—In Vivo and In Vitro evidence for autophagy regulation," *Frontiers in Pharmacology*, vol. 11, 2020.
- [90] X. Liu, J. Lu, S. Liu et al., "Huangqi-Danshen decoction alleviates diabetic nephropathy in mice by inhibiting PINK1/Parkin-mediated mitophagy," *American Journal of Translational Research*, vol. 12, no. 3, pp. 989–998, 2020.
- [91] X. Liu, W. Wang, G. Song et al., "Astragaloside IV ameliorates diabetic nephropathy by modulating the mitochondrial quality control network," *PloS one*, vol. 12, no. 8, 2017.
- [92] M. S. Rahman and Y. S. Kim, "PINK1-PRKN mitophagy suppression by mangiferin promotes a brown-fat-phenotype via PKA-p38 MAPK signalling in murine C3H10T1/2 mesenchymal stem cells," *Metabolism: clinical and experimental*, vol. 107, p. 154228, 2020.
- [93] B. Ortega-Domínguez, O. E. Aparicio-Trejo, F. E. García-Arroyo et al., "Curcumin prevents cisplatin-induced renal alterations in mitochondrial bioenergetics and dynamic," *Food and Chemical Toxicology: An International Journal Published for the British Industrial Biological Research Association*, vol. 107, no. Part A, pp. 373–385, 2017.
- [94] C. T. Mai, *The Effect and Mechanism of Palmatine on DSS-Induced Ulcerative Colitis*, Guangzhou University of Chinese Medicine, 2019.