Review Article

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A review of the pharmacological activities and protective effects of *Inonotus obliquus* triterpenoids in kidney diseases

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Abstract: Kidney diseases are common health problems worldwide. Various etiologies ultimately lead to the development of chronic kidney disease and end-stage renal disease. Natural compounds from herbs or medicinal plants are widely used for therapy and prevention of various ailments, among which is *Inonotus obliquus*. *I. obliquus* is rich in triterpenoids and the main active ingredients include betulinic acid, trametenolic acid, inotodiol, and ergosterol. New evidence suggests that *I. obliquus* triterpenes may be an effective drug for the treatment and protection of various kidney diseases. The aim of this review is to highlight the pharmacological activities and potential role of *I. obliquus* triterpenes in the kidney disease treatment and protection.

Keywords: *Inonotus obliquus*, betulinic acid, trametenolic acid, inotodiol, kidney disease

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1 Introduction

In the past decade, kidney disease diagnosed with objective measures of kidney damage and function has been recognized as a major public health burden [1]. The prevalence rate of chronic kidney disease (CKD) in women is higher, but men are more likely to suffer kidney failure [2]. Hypertension and diabetes are the most common complications that eventually progress to CKD and end-stage renal disease (ESRD) [2]. According to statistics, about 850 million people worldwide suffer from some form of kidney disease [3]. Most of the diseases through renal replacement therapy for survival, high medical costs also produce an enormous obstacle for the treatment of kidney disease. Studies have shown that natural drugs can significantly improve the curative effect and reduce the incidence of adverse reactions [4]. *Inonotus obliquus*, commonly known as Chaga and birch antler, is a white-rot fungus with a high medicinal value called "Brown Ganoderma lucidum in birch." Zhang [5] believed that the *I. obliquus* can strengthen the body and dispel pathogenic factors to clear away heat and detoxify, invigorate the spleen and stomach, nourish liver and kidney, and nourish the mind.

Triterpenes constitute a large and important class of natural plant components with a variety of structures and functions. Their successes in traditional medicine usage have been attributed to a wide variety of chemical compositions of its members. The pharmacological activities of these triterpenoids have been associated with the important functional groups on the ring [6]. There are four main triterpenoids found in *I. obliquus*: betulinic acid (BA), trametenolic acid (TA), inotodiol, and

Table 1: Pharmacological profiles and their relevance to traditional uses

Compound	Uses in traditional medicine	Targets (*in vitro* and *in vivo*)	Related pharmacological studies	Section
Betulinic acid	Spleen oxidative damage	*In vivo* and *in vitro*: enhanced SOD, decreased MDA	Antioxidant	2.1.1
	Testicular injury	*In vivo*: decreased the protein expression of JAK2, STAT3, caspsae-3, and Bax in mice	Antioxidant	2.1.1
	Diabetic	*In vivo*: AMPK diminished blood glucose levels in alloxan-treated institute of cancer research (ICR) mice	Hypoglycemic properties	2.1.2
		In vivo: BA effectively ameliorates hyperglycemia through inhibition of hepatic gluconeogenesis via modulating the Ca2+-calmodulin dependent protein kinase–adenosine monophosphate activated protein kinase–cAMP response element-binding protein (CAMKK–AMPK–CREB) signaling pathway	Hypoglycemic properties	2.1.2
	Early atherosclerosis	*In vivo*: BA ameliorated the reduction of eNOS expression, inhibited ICAM-1 and ET-1 expression	Antidyslipidemic effects	2.1.3
	Obesity and nonalcoholic fatty liver disease	*In vitro*: BA inhibited the development of obesity	Antidyslipidemic effects	2.1.3
	Vascular inflammation	*In vitro*: inhibits ROS and nuclear factor (NF)-κB (NF-κB) in HUVEC	Anti-inflammatory activity	2.1.4
	Acute pancreatitis	*In vivo*: inhibiting pancreatic injury and inflammatory responses in mice	Anti-inflammatory activity	2.1.4
	Colorectal	*In vitro*: inhibit the metastasis of cancer cells	Anticancer	2.1.5
Inotodiol	Breast tumor	*In vivo*: downregulate β-catenin signaling can inhibit cancer cell activity in diabetic rats	Antitumor activity	2.2.1
	Diabetic	*In vivo*: reduce blood glucose in mice	Hypoglycemic properties	2.2.2
	Liver disease	*In vivo* and *in vitro*: regulating FXR/SHP/SREBP-1c pathway	Anti-nonalcoholic fatty liver disease (NAFLD) effects	2.2.5
Trametenolic acid	Lung cancer	*In vitro*: TA could reduce the cell viability of lung cancer cell lines	Antitumor activity	2.3.2
	Cerebral infarct	*In vivo*: inhibit cerebral infarct volume in rats with cerebral ischemia or reperfusion injury	Neuroprotective activities	2.3.3
	H1N1	*In vitro*: pandemic H1N1 strain A/Jena/8178/09	Antiviral	2.3.4
Ergosterol	Myocardial injury	*In vivo*: enhance Nrf2-mediated antioxidant activity by ISO in the rat model	Antioxidant	2.4.1
	Chronic obstructive pulmonary disease	*In vitro* and *in vivo*: the NF-κB/p65 pathway can inhibit the inflammation of COPD	Anti-inflammatory	2.4.2
	Gastrointestinal cancer	*In vitro* and *in vivo*: inhibits tumor cell migration *in vitro*, CT26 tumor growth *in vivo*	Anticancer activity	2.4.3
	Bladder cancer	*In vitro* and *in vivo*: a rat model of bladder cancer, inhibit bladder cancer by regulating the cell cycle, inflammatory signaling, and androgen signaling	Anticancer activity	2.4.3

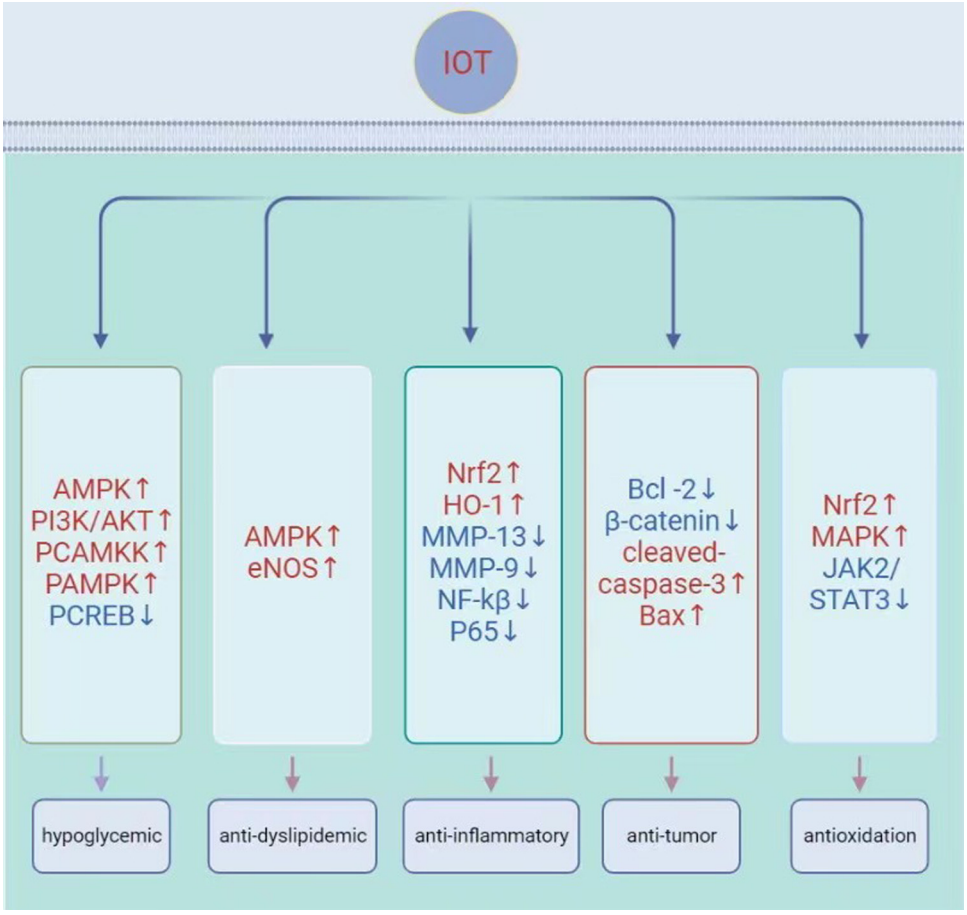


Figure 1: Molecular mechanisms for biological activities of triterpenoids from *Inonotus obliquus*. Hypoglycemic effects were induced by regulating PI3K/AKT and AMPK/ACC signaling pathways. The antidyslipidemic effects could be inhibited by IOT through increased AMPK/eNOS signaling pathway. ROS-mediated inflammation induced by stress/stimuli could be inhibited by IOT through inhibition of the NF-κB/p65 signaling pathway, particularly the phosphorylation-induced IκB degradation step which can prevent NF-κB from DNA binding. The antitumor effect is mainly to improve the apoptosis index. The ROS could be inhibited by IOT through inhibition of the JAK2/STAT3 signaling pathway and increased MAPK/Nrf2 signaling pathway. IOT, triterpenoids from Inonotus obliquus. ROS, reactive oxygen species. PI3K/Akt: PI3K, phosphatidylinositol-3-kinase; Akt, protein kinase B. AMPK/ACC: AMPK, adenosine monophosphate activated protein kinase; ACC, acetyl-CoA carboxylase. AMPK: adenosine monophosphate activated protein kinase. NF-κB: nuclear factor (NF)-κB.

ergosterol [7]. It has many pharmacological effects, such as anti-tumor, anti-allergy, anti-oxidation, anti-mutation, and anti-inflammatory activities, in addition to hypoglycemic properties (Table 1). These pharmacological effects are realized by various pathways (Figure 1). In the past few decades, a large number of related studies have been conducted on polysaccharides and polyphenols of *I. obliquus*. In nature, however, as one of the most important compounds of *I. obliquus*, few studies have been undertaken on triterpenoids. In recent years, literature increasingly has been published on triterpenoids. This review summarizes current knowledge on the beneficial effects of triterpenoids of *I. obliquus* in various kidney diseases (Figure 2).

2 *I. obliquus* triterpene components and pharmacological effects

2.1 Betulinic acid (BA)

BA, or 3β-hydroxy-lup-20(29)-en-28-oic acid (Figure 3) [8], is a pentacyclic triterpenoid with a lupine structure. It can be isolated from many plants, mainly *I. obliquus* in birch. BA has a wide range of pharmacological activities, including hypoglycemic, hypolipidemic, anti-inflammatory, antioxidant, and anticancer activities.

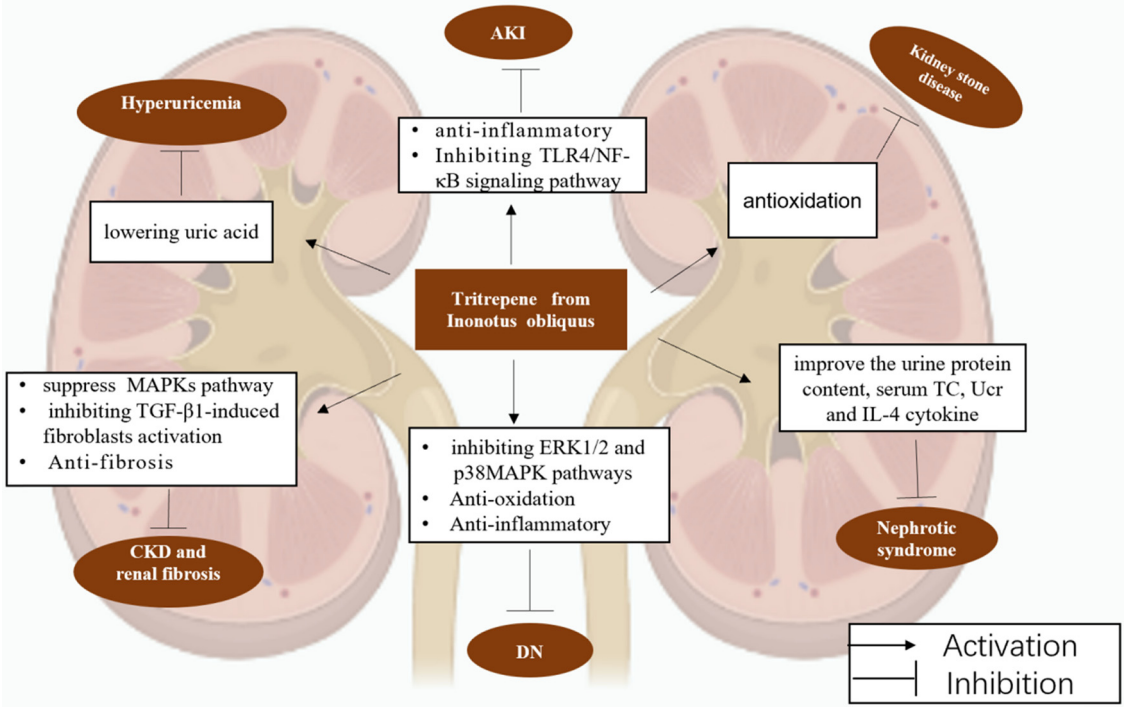


Figure 2: Renoprotective effects of triterpenes from *I. obliquus* against a broad spectrum of kidney diseases. Triterpene from *I. obliquus* could prevent kidney diseases by various mechanisms. AKI, acute kidney injury; CKD, chronic kidney disease; DN, diabetic nephropathy; NS, nephrotic syndrome; TC, total cholesterol; UCR, urine creatinine; IL-4, interleukin-4.

2.1.1 Antioxidant

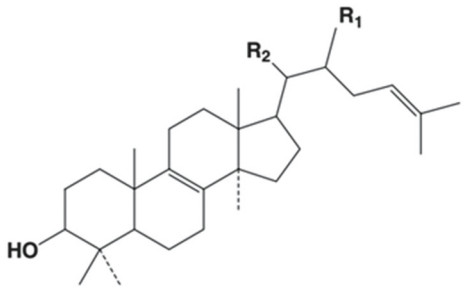
More and more researches have shown that BA has both direct and indirect antioxidation effects by promoting antioxidase activities, such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities, and decreasing the generation of malondialdehyde (MDA) and reactive oxygen species (ROS) *in vivo* and *in vitro* [9]. In another study, BA reduced the accumulation of ROS, enhanced the SOD activity, and decreased the MDA content, as well as increased the total antioxidant capacity in the spleen of T-2-toxin-exposed mice [10]. Wu et al. [11] reported that BA significantly decreased the protein expression of Janus kinase 2 (JAK2), signal transducers and activators of transcription 3 (STAT3), caspsae-3, and Bcl-2-associated X protein (Bax). BA also reduced the oxidative damage induced by T-2 toxin-induced testicular injury in mice, and that these protective effects may be partially mediated by the JAK2/STAT3 signaling pathway [11].

2.1.2 Hypoglycemic properties

BA diminished blood glucose levels in alloxan-treated ICR mice and untreated mice during the glucose tolerance test. These results indicate that BA can become a promising therapeutic agent for diabetes by activating AMPK (such as metformin) [12]. Oral administration of BA significantly reversed high-fructose diet-induced metabolic syndrome in rats. BA improves insulin sensitivity, elevated blood glucose, inflammation, dyslipidemia, and oxidative stress via PI3K/Akt pathways [13]. BA administration significantly decreased food and water intake, fasting blood glucose, weight loss, and polyuria in streptozotocin-diabetic rats [14]. In another study, similar preventive effects of BA on hepatic glucose production were examined in HepG2 cells and high fat diet-fed ICR mice. BA effectively ameliorates hyperglycemia through inhibition of hepatic gluconeogenesis via modulating the CAMKK–AMPK–CREB signaling pathway [15].

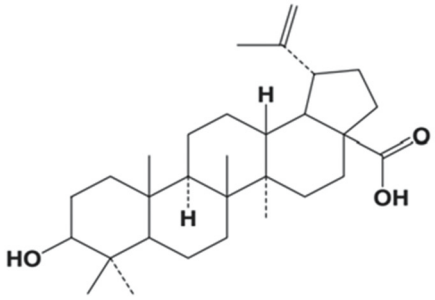
2.1.3 Antidyslipidemic effects

A study on the BA could prevent atherosclerosis in diabetic apolipoprotein-E gene knockout (ApoE KO) mice. The study showed that BA ameliorated the reduction of endothelial nitric oxide synthase (eNOS) expression, leading to the inhibition of intracellular adhesion molecule 1 (ICAM-1) and endothelin 1 (ET-1) expressions [16]. These results suggest that BA may be useful in the treatment and prevention of early atherosclerosis via the

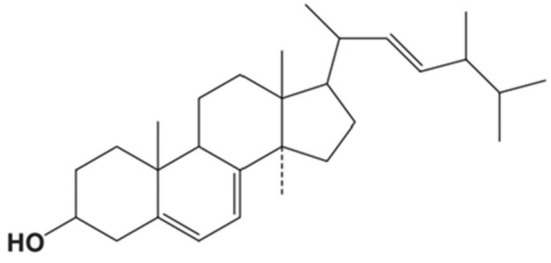


(1) inotodiol (R1 = OH, R2 = CH3)

(2) trametenolic acid (R1 = H, R2 = COOH)



(3) betulinic acid



(4) ergosterol

Figure 3: The structures of compounds 1–4.

attenuation of endothelial dysfunction in diabetic ApoE KO mice [16]. BA has shown the ability to reduce the abdominal fat accumulation, blood glucose, plasma triglycerides, and total cholesterol [17]. Mice fed a high-fat diet and treated with BA showed less weight gain and tissue adiposity [18]. In addition, BA markedly inhibited the development of obesity and nonalcoholic fatty liver disease (NAFLD) [18].

2.1.4 Anti-inflammatory activity

The selective TGR5 agonist BA ameliorated dextran sulfate sodium-induced colitis in mice via the glucagon-like peptide-2 (GLP-2) pathway, suggesting that other dipeptidyl peptidase enzymatic activities are involved in GLP-2 degradation [19]. BA can prevent vascular inflammation, potent inhibitory effect on vascular inflammation process by tumor necrosis factor-α (TNF-α) human umbilical vein endothelial cells (HUVEC). Therefore, BA inhibits ROS and NF-κB in HUVEC and has a significant protective effect on blood vessels [20]. Zhou et al. [21] reported that BA exerts a anti-inflammatory effect through the NF-κB pathway. The study demonstrated that BA attenuates the severity of acute pancreatitis, by inhibiting pancreatic injury and inflammatory responses. Huang et al. [22] reported that BA has a protective effect on cognitive impairment and oxidative stress caused by T-2 toxin in mice and BA inhibited mRNA expression of pro-inflammatory cytokines as well as enhanced mRNA expression of anti-inflammatory cytokine. Therefore, BA could improve the cognitive function, enhance the antioxidant capacity, and inhibit the secretion of proinflammatory cytokines in brain, thereby playing a preventive and protective role against brain damage caused by T-2 toxin.

2.1.5 Anticancer activities

Studies have shown that BA can promote the apoptosis of colorectal cancer cells and inhibit the metastasis of cancer cells, so BA may be a potential natural drug to inhibit the growth and metastasis of colorectal cancer [23]. Cell proliferation assessed by the MTT analysis indicates that BA has an antitumor activity [24].

2.2 Inotodiol

Inotodiol is a triterpenoid found only in Chaga mushroom. Inotodiol, a kind of lanostane triterpenoid isolated from *I. obliquus* (Figure 3), is a natural compound with many biological activities, including antitumor, antioxidant, anti-allergy, and hypoglycemic activity [25].

2.2.1 Antitumor activity

Zhao et al. [25] indicate that inotodiol isolated from *I. obliquus* inhibited the proliferation of HeLa cells and induced apoptosis *in vitro*. Nakata et al. [26] studied the inhibitory effect of inotodiol on mouse skin in carcinogenic tests and found that inotodiol showed a practical antitumor effect *in vivo* carcinogenic tests. Inotodiol can regulate blood glucose levels in diabetic rats and then control the proliferation of breast tumor progression by downregulating β-catenin signaling and inducing

apoptosis. It further suggests that inotodiol may inhibit cancer cell activity [27].

2.2.2 Hypoglycemic properties

Zhang et al. [28] established a model of C57BL/6 mice with type 2 diabetes induced by a high-fat diet plus low-dose streptozotocin and different doses of extracts were administered intragastrically every day. Hypoglycemic effects were induced by regulating PI3K/Akt and AMPK/ACC signaling pathways. Therefore, it was suggested that the extracts could alleviate blood glucose and insulin resistance in mice. Lu et al. [29] indicated that ethyl acetate fraction from *I. obliquus* could significantly reduce blood glucose in mice with alloxan-induced diabetes. In addition, it partially reduces serum total cholesterol level and increases GSH-Px activity.

2.2.3 Antioxidant effects

Inotodiol can protect cells from damage by inhibiting alanine aminotransferase, aspartate aminotransferase, and interleukin-6 (IL-6) expressions and protect mice from oxidative stress injury induced by CCl4 [30].

2.2.4 Anti-allergy activity

In a mouse model of food allergy-induced by chicken ovulating, evidence showed that the purified inotodiol had the activity of inhibiting the function of mast cells *in vivo*, so it was detected that inotodiol had a significant therapeutic effect on food allergy [31].

2.2.5 Anti-NAFLD effects

Peng et al. [32] demonstrated that the anti-NAFLD effects of inotodiol, a bioactive compound in *I. obliquus*, are through regulating FXR/SHP/SREBP-1c pathway. The results suggested that inotodiol may become promising drugs to treat NAFLD.

2.2.6 Anti-inflammatory activity

A study has shown that nitric oxide (NO), which is generated by inducible NO synthase (iNOS), is one of the inflammatory mediators. NO overexpressed by iNOS causes inflammation and damages cells by producing transcription factors, such as NF-κB and MAPK, and inflammatory mediators, such as COX-2 and PGE2. Hence, inhibition of NO production plays an important role in the treatment of inflammatory diseases [33]. Inotodiol without 7-carbonyl groups significantly inhibited lipopolysaccharide (LPS)-induced NO production. Inotodiol exerted potent inhibitory effect on NO production by Park et al. [34].

2.3 Trametenolic acid (TA)

TA is a lanostane-type triterpenoid isolated from the trametes lacinia (Figure 3) [35]. It has antitumor, anti-inflammatory activity, antiviral, and neuroprotective effects.

2.3.1 Anti-inflammatory activity

Park et al. [34] reported that the inhibitory activities of TA against LPS-induced NO production were evaluated in BV2 microglial cells; these results indicated that TA had anti-inflammatory effects on BV2 microglia.

2.3.2 Antitumor activity

Baek et al. [35] through induction of apoptosis accompanied by caspase-3 cleavage showed that TA could reduce the cell viability of all lung cancer cell lines, with IC50 values ranging from 75.1 to 227.4 μm. Another study demonstrated that TA had obviously cytotoxicity on human prostatic carcinoma cell PC3 and breast carcinoma MDA-MB-231 cell [36]. TA was identified as the primary constituent responsible for the cytotoxic effects of *I. obliquus* on breast cancer cells. Moreover, TA-enriched fractions both exhibited cytotoxic effects regardless of breast cancer cell subtypes and did not interfere with the cytotoxic effects of conventional drugs [37]. Kim et al. [38] demonstrated that TA in triterpenoid fractions from the inner and outer parts of *I. obliquus* was 94.5 ± 9.15 mg/g (db) and 106.3 ± 8.23 mg/g, respectively. Anti-proliferative activity of the triterpenoid fraction from the outer part against AGS, MCF-7, and PC3 was also significantly higher than that of the inner part.

2.3.3 Neuroprotective activities

TA can effectively improve the learning and memory ability of rats with cerebral ischemia injury. TA possessed neuroprotective property against ODG/R and I/R injury by suppressing miR-10a expression and activating PI3K/Akt/mTOR (mammalian target of rapamycin) signaling pathway, thereby reducing mitochondrial-mediated apoptosis [38]. TA may significantly improve neurological function deficit, cerebral edema, loss, and apoptosis of neuron cells and inhibit cerebral infarct volume in rats with cerebral ischemia or reperfusion injury [38].

2.3.4 Antiviral effects

TA against HK/68 and the 2009 pandemic H1N1 strain A/Jena/8178/09 with IC50 values of 14 and 11 μM. In a plaque reduction assay, this compound could bind to cell-free viruses and neutralize their infectivity [39].

2.4 Ergosterol

Ergosterol is widely distributed in medicinal fungi. It is a natural compound of the steroid family in fungi (Figure 3) with antioxidant, anti-inflammatory, and anticancer activities [40].

2.4.1 Antioxidant activity

Ergosterol significantly enhances Nrf2-mediated antioxidant activity and plays a protective role against myocardial apoptosis. Therefore, it is considered a potential therapeutic agent to prevent myocardial injury induced by isoproterenol (ISO) in a rat model [40]. Cui et al. [41] evaluated the solid antioxidant capacity of triterpenoids from *I. obliquus* by using human keratinocyte strain HaCaT.

2.4.2 Anti-inflammatory activity

Ergosterol inhibited the expression of MMP-9 and MMP-13 and increased the protein expression of Nrf2 and HO-1 in knee chondrocytes and articular cartilage [42]. Ergosterol was found to have cartilage protective effects by mediating the activation of the Nrf2-hemeo xygenase1 pathway and effectively alleviating the cartilage degeneration [42]. Sun et al. [43] established a model of chronic obstructive pulmonary disease (COPD) with cigarette spray extract. Ergosterol administration in 16HBE cells and BALB/C mice can inhibit the inflammation of COPD through the NF-κB/p65 pathway, which has excellent potential for the clinical treatment of COPD [43].

2.4.3 Anticancer activity

Ergosterol inhibits tumor cell migration *in vitro* and CT26 tumor growth *in vivo*, improves the survival rate of tumor mice, and is a potential drug for the treatment of gastrointestinal cancer [44]. Ikarashi et al. [45] established a rat model of bladder cancer induced by *N*-butyl-*N*-(4-hydroxy butyl nitrosamine). They showed that ergosterol could inhibit bladder cancer by regulating the cell cycle, inflammatory signaling, and androgen signaling. Therefore, the preventive effect of ergosterol on bladder cancer and its clinical application can be expected.

It is known that the chemical structure of both natural and synthetic molecules predetermines the biological activity, which makes it possible to analyze the structure–activity relationships [46]. *I. obliquus* triterpenoids have been reported to possess various pharmacological properties; the pharmacological activities of these triterpenoids have been associated with the important functional groups on the ring [46]. Indeed, the various pharmacological activities reported for some pentacyclic triterpenoids like anticancer have been attributed to the presence of the hydroxyl group. This was evident by racemosol, a polyhydroxy triterpenoid that showed significant anticancer activities against human cancer cells [47]. Glycemic control was considered an effective prevention and treatment for T2DM [48]. Management of high glucose can be achieved by inhibiting α-glucosidase and α-amylase [48]. It was found that most of the active triterpenes contained a hydroxy group in C-3. Hence, a hydroxy group substituted in C-3 may be a very important structural feature for the α-glucosidase inhibitory activity. Besides, for lanostane triterpenes, compounds with Δ8,9 double bond exhibited higher activities than that with Δ7,9(11) double bonds. The type of the side chain would affect the inhibitory activity. However, the increase in number of the hydroxy groups in the side chain could result in a decrease in activity [49].

3 Current knowledge on *I. obliquus* triterpenoids in kidney diseases

3.1 Diabetic nephropathy (DN)

DN is a significant cause of diabetic morbidity and mortality and is the most common cause of proteinuric and non-proteinuric forms of ESRD [50]. The proliferation of mesangial cells and the accumulation of extracellular matrix are considered to be the main pathogenic events in the progression of DN. Early diagnosis and standardized treatment are essential for DN, which can reduce or delay the progression of DN [50]. Therapeutic strategies usually include blood pressure control by regulation of the renin–angiotensin system and monitoring of sugar and lipid profiles [51]. So far, DN is not effectively treated. For this reason, it is necessary to develop more effective medicines to prevent or delay DN progression. Results from a recent phase IIb clinical trial reported that bardoxolone methyl was associated with improvement in the estimated glomerular filtration rate in patients with advanced chronic kidney disease (CKD) and Type 2 diabetes. However, increases in albuminuria, serum transaminase, and frequency of adverse events were noted in Zucker diabetic fatty rats with overt Type 2 diabetes [52].

The potentiality of plant-derived triterpenoids as novel renal protectants has been confirmed in various animal models. BA, a natural triterpenoid, has been shown to have hypoglycemic properties. Several molecular signaling studies have shown that BA inhibited the HG-induced cell proliferation and fibronectin expression in mice mesangial cells via inhibiting ERK1/2 and p38MAPK pathways and also reversed the HG-inhibited expression of p21Waf1/Cip1and p27Kip1 [53]. Therefore, it may be a potential drug for the treatment of DN [53]. Another study in diabetic inbred C57BL/6 male mice showed consistent findings demonstrating that BA had renoprotective effects against DN [54]. BA could increase insulin and C-peptide and decrease fasting blood sugar, kidney lesions, TNF-α, IFN-γ, and IL-1 in the treated groups [54].

In addition, BA decreased the levels of serum insulin, IL-6, IL-1β, TNF-α, and blood glucose. In addition, BA increased the activities of SOD and CAT and reduced the contents of MDA, IL-6, IL-1β, and TNF-α in kidney tissues. BA can also protect STZ-induced DN rats through the attenuation of AMPK/NF-κB/Nrf2 pathway [55].

In a C57BL/6 diabetic mouse model induced by STZ, ergosterols were found to reduce mesangial cell proliferation and the subsequent extracellular matrix deposition by regulating the transforming growth factor-β1 (TGF-β1/decapentaplegic 2; Smad2) signaling pathway, suggesting that ergosterols have therapeutic effects on DN [56]. Liu et al. [57] established a mouse model of DN by intraperitoneal injection of 30 mg/kg streptozotocin. They found that ergosterol significantly reduced fasting glucose levels, inflammatory cytokine levels and kidney damage, as well as increased insulin levels. Mechanically, the NF-κB signaling pathway was involved in improving ERG-mediated DN [57]. Therefore, ergosterol might be a potential drug for clinical the DN treatment.

3.2 Kidney disease caused by hyperuricemia

Hyperuricemia is a metabolic disease caused by purine metabolism disorder, and the blood urate saturation value is more than 6 mg/dL [58]. Elevated uric acid levels are associated with abnormal nucleic acid metabolism in the body and reduced renal excretion [59]. Studies have shown that increased serum urate concentration can lead to renal diseases like glomerulosclerosis, renal interstitial fibrosis, and renal inflammation caused by hyperuricemia [59]. It will gradually worsen with the deterioration of renal function. Studies have shown a direct causal relationship between serum uric acid level and the development of renal disease [60]. Due to the potential nephrotoxicity and contraindications of other common comorbidities, there are few long-term safe and effective drugs available at present, so it is urgent to develop new natural drugs.

In recent years, Yong et al. [61] studied the use of BA to treat hyperuricemia. Among the alcohol extracts of BA, the ion strength index of BA was 121.10 ± 4.57, which was closest to the ion strength index of allopurinol (148.10 ± 5.27). Therefore, BA is one of the bioactive substances against hyperuricemia. Serum uric acid (SUA) is the primary marker in the study of hyperuricemia. In hyperuricemia mice, different doses of extracts can significantly reduce SUA, indicating that BA has the effect of lowering uric acid [61]. In addition, BA showed similar efficacy against allopurinol and benzbromarone, demonstrating the potential value of BA in treating hyperuricemia [61].

3.3 Kidney stone disease

Kidney stones are minerals in the renal tubules and pelvis free from or attached to the renal papilla. Among all types

of kidney stones, calcium oxalate (CaOx) stones are the most common. Stone formation is prevalent, with the incidence of up to 14.8%, and presents a gradually increasing trend, recurrence rate as high as 50%. Obesity, diabetes, hypertension, and metabolic syndrome are considered risk factors for stone formation, leading to CKD and ESRD [62]. The mechanism of kidney stone formation is still not clear, and there is no effective strategy to prevent the occurrence and recurrence of the disease. Therefore, it is urgent to better understand the pathogenesis of the disease and find effective strategies to prevent the formation of kidney stones [63]. Antiurolithiatic herbal drugs have been more promising as they are cost-effective with fewer or no side effects.

Nirala et al. [64] demonstrated the affinity of betulin and L-ascorbate with the antioxidant enzyme and matrix metalloproteinase (MMP-2 and -9) that act as biomarkers of kidney fibrosis or stone. BA has a significant scavenging activity against 1,1-diphenyl-2-picrylhydrazyl, NO, and superoxide radicals. BA also has the capacity to inhibit the crystallization, nucleation, and aggregation in comparison to cyston. It has been also observed that BA inhibited the crystallization of CaOX in urine; at higher concentration of betulin, there were increased numbers of smaller CaOx particles [64]. The standard therapy that prevents and treats urinary stones has pronounced side effects. BA, as a natural compound, can treat kidney stones caused by CaOx [65]. BA could alter proteins on apical membranes of renal tubular epithelial cells that have an affinity to CaOx crystals and lower crystal deposition [65].

3.4 CKD and renal fibrosis

CKD is still a public health problem with severe complications and increased mortality worldwide [66]. Regardless of the initial degree of renal injury, CKD will progress to an ESRD characterized by fibrosis and irreversible function. Renal fibrosis is a pathological feature found in CKD and the pathogenesis of renal fibrosis involves extracellular matrix components and many renal and infiltrating cell types [67]. The treatment of renal tubule interstitial fibrosis has been considered potential in the treatment of CKD. Still, there is no specific and effective treatment for renal fibrosis and CKD. Renin–angiotensin system inhibitors have always been the primary treatment for CKD, but the benefits of renin–angiotensin system inhibitors for patients with advanced CKD are controversial [68]. Although many attempts have been made to identify the primary molecule causing renal fibrogenesis. Currently, there is no specific treatment for renal fibrosis and CKD. Thus, there is a need for new therapeutic targets and drugs to recover renal fibrosis and CKD.

Evaluation of beneficial effects of BA in DN was initially made in adenine-induced CKD rats [69]. The results showed that rats developed CKD as reflected by kidney function and injury markers. Furthermore, the fibrosis marker proteins were also elevated in the kidney pointing the set-up of fibrotic condition [69]. Interestingly, in adenine-induced chronic renal disease rats, BA administration has been shown to improve renal biochemical and histological features and reduce creatinine and neutrophil gelatinase-associated lipocalin (NGAL) levels in renal injury mice. The results showed that BA might be mediated by the inhibition of pro-fibrotic protein production, thereby hindering the kidney tissue damage along with improvement in kidney function [69]. Thus, there is a possibility of using BA as therapeutic agent to treat CKD and renal fibrosis [69]. A study found that ergosterol peroxides inhibited the TGF-β1-induced normal rat kidney fibroblast cell line (NRK-49F) fibroblast activation with reduced proliferation, reduced cytoskeletal protein expression, and inhibition of extracellular matrix accumulation [70]. Ergosterol peroxide directly suppresses TGF-β1-induced MAPKs pathway activation. It has been shown that ergosterol peroxide has therapeutic potential to prevent renal fibrosis and ergosterol peroxide kidney disease in intervention application prospect is infinite [70].

3.5 Acute kidney injury (AKI)

AKI is characterized by a rapid increase in serum creatinine and a decrease in urine production. The leading causes of AKI include sepsis, renal ischemia–reperfusion, exposure to nephrotoxins. Sepsis accounts for nearly half of all cases of AKI [71]. Sepsis is a systemic inflammatory response caused by microbial infection, which significantly increases the mortality of AKI. At the same time, it is one of the significant causes of death in intensive care units [72]. The incidence of acute renal injury in intensive care exceeds 50% [73]. Despite all the advances made in medicine over the past few decades, sepsis-associated AKI mortality remains unacceptable [74]. The U.S. FDA Adverse Event Reporting System (FAERS) reported 101 cases of AKI in canagliflozin and dapagliflozin-treated T2DM patients. The data raised the possibility that the use of SGLT2 inhibitors in T2DM patients may lead to AKI. The

severity of which may vary depending on a patient's medical history and/or on concomitant use of other treatments. The role of NF-κB in septic pathophysiology and the signal transduction pathways leading to NF-κB activation during sepsis have been an area of intensive investigation [75,76].

Lingaraju et al. [77] evaluated the role of BA in acute sepsis kidney injury by a mouse model of cecal ligation and puncture (CLP). They found that BA can prevent CLP-induced AKI by restoring the imbalance of these inflammatory mediators, oxidants, and antioxidants. This evidence suggests that BA is a potential therapeutic agent for sepsis-induced AKI.

3.6 Nephrotic syndrome (NS)

NS is a hallmark of glomerular disease, and the clinical criteria for diagnosis are high albuminuria (>3.5 g/24 h), low albuminemia (<30 g), edema, and hyperlipidemia. Jobst-Schwan et al. [78] reported that NS is the second most frequent cause of CKD in the first 3 decades of life, requiring dialysis or transplantation for survival. Also, corticosteroid treatment exacerbates NS in a zebrafish model of magi2a knockout. The incidence of idiopathic NS ranges from 1.15 to 16.9 cases per 100,000 children, and its pathogenesis is related to immune dysregulation, systemic circulatory factors, or genetic structural abnormalities of podocytes [79]. The primary treatment is prednisone, and the disease may frequently recrudesce, requiring an alternative immunosuppressant. However, long-term use will cause irreversible damage to the body, so it is necessary to develop new drugs to replace traditional medicines [79]. A study focused on the effects of TA on the treatment of NS rat showed that TA can improve the urine protein content, total cholesterol, urine creatinine, and IL-4 and has a significant effect on inhibiting NS, which provides a scientific basis for the treatment of kidney disease with TA, and also pave the way for the treatment of NS with traditional Chinese medicine (TCM). It will be an effective drug for the clinical treatment of NS [80].

4 Results

In recent years, the research on the mechanism of triterpenoid monomer compounds in *I. obliquus* is insufficient, especially TA and inotodiol. The research on the mechanism of triterpenoid monomer compounds in animals and cells on nephropathy is limited. In addition, the structural diversity exhibited by some rare compounds requires further studies about their potential bioactivities and their chemotaxonomic roles. At present, the research on the dosage, dosage form, administration route, pharmacodynamics, toxic, and side effects of phytoconstituents is not comprehensive. Some phytoconstituents show worrying toxicity when used exceeding a particular dose. Therefore, it is necessary to control the doses of phytoconstituents administered during treatment and further study their pharmacology and toxicology. There are no unified diagnosis and treatment standards, most research in this field is still in the experimental animal stage, and few phytoconstituents have entered clinical trials.

5 Discussion

TCMs has been used effectively in China for centuries to treat and delay progression of kidney diseases. The pharmacological activities of *I. obliquus* triterpenoid compounds have been verified by researchers around the world. Moreover, a number of studies have shown the beneficial protective effects of triterpene active ingredients from *I. obliquus*, such as BA, ergosterol, TA, and inotodiol, on a variety of renal diseases. Most of the studies in the treatment of nephropathy are related to BA, followed by ergosterol, TA, and inotodiol. But the drug targets are not clear. Whether TA and inotodiol are involved in the treatment of kidney disease, there is a lack of relevant studies. The therapeutic value of TCMs and their isolated compounds in the treatment of kidney disease has been demonstrated by a large number of animal and cell experiments based on the modern pharmacologic research. *I. obliquus* triterpenoids are used traditionally to treat a variety of kidney diseases, including DN, kidney disease caused by hyperuricemia, kidney stone disease, CKD, renal fibrosis, AKI, and NS (Table 2). Most of its main mechanism mediated by intervention in some pathways, such as inhibiting ERK1/2 and p38MAPK, attenuating AMPK/NF-κB/Nrf2, and suppressing TGF-β1-induced MAPKs pathways to treat renal disease.

The drug dose should be selected according to the disease type, disease progression, age, and gender to ensure the effective concentration of the drug and to prevent side effects caused by excessive concentrations. Studies have shown that high-dose and long-term caffeine and baicalin intake can cause changes in induced kidney injury and fibrosis [81,82]. Long-term treatment with ferulic acid often aggravates the condition of CKD [83]. Liu et al. [84] confirmed that resveratrol lost its antifibrotic effect or aggravated kidney disease at high doses

Table 2: Renoprotective effects of triterpenes from *I. obliquus*

Disease	Phytochemical	Effective concentration/dose	Study model	Tested living system/organ/cell	Result	Reference
[a]DN	BA	20, 40 μm	Mice mesangial cells diabetic	Mesangial cells	Decreased the levels of ERK1/2 and p38MAPK	[53]
		20.00 mg kg^{-1}	Inbred C57BL/6 male mice	Mice	Increase insulin, C-peptide, fasting blood sugar, kidney lesions and TNF-α, IFN-γ, IL-1	[54]
		20 mg/kg, 40 mg/kg	Streptozotocin (STZ) induced diabetic rats	Rats	Decreased serum insulin, IL-6, IL-1β, TNF-α and blood glucose. increased SOD, CAT and reduced MDA, IL-6, IL-1β, and TNF-α	[55]
	Ergosterol	10, 20, 40 mg/kg/day	Streptozotocin (STZ)-inducedC57BL/6 diabetic mice	Mice	Quenching the mesangial cell proliferation and ECM deposition	[56]
		10 or 20 Mm	Rat mesangial cells	Mesangial cells	Decreased fasting blood glucose levels, inflammatory cytokine levels, and renal injury, enhanced the insulin level	[57]
		50 mg/kg	Diabetic nephropathy mice	Mice		
[a]Hyperuricemia	BA	30, 60, 120 mg/kg	SPF mice	Mice	Suppressed xanthine oxidase	[61]
[a]CKD and renal fibrosis	BA	30 mg/kg	Adenine-induced CKD rats	Rats	Decreased BUN, creatinine and uric acid, cystatin C NGAL, connective tissue growth factor (CTGF), fibronectin, collagen type I and hydroxyproline	[69]
	Ergosterol	0, 6.25, 12.5, or 25 μm	Normal rat kidney fibroblast cell line	Cell line	Attenuated TGF-1-induced renal fibroblast proliferation, expression of cytoskeleton protein and CTGF, blocked TGF-1-stimulated phosphorylation of ERK1/2, p38 and JNK pathway	[70]
[a]AKI	BA	4 mg/kg (Betulin L) or 8 mg/kg (Betulin H)	Cecal ligation puncture (CLP) mouse	Mouse	Decreased creatinine and BUN (72.91 ± 21.84 μmol/L, 32.88 ± 6.99 mg/dL, respectively, $P < 0.01$ vs CLP group)	[77]
		2 μg/mL, 4 μg/mL, or 8 μg	LPS-induced rat HBZY1 cell	HBZY1 cell	Decreased TNF-α, IL-1β and IL-6	[76]
		10 and 30 mg/kg	Cecal ligation and puncture (CLP) induced septic rat	Rat	Balanced the inflammatory cytokine response, MMP-9 mediated kidney damage and down-regulated the expression of iNOS and NF-kB in kidney tissues	[77]
[a]NS	TA	24 g/(kg day)	Male Wistar rats	Rat	The urine protein content, serum TC, Ucr and IL-4 cytokine were improved	[80]

AKI, acute kidney injury; CKD, chronic kidney disease; DN, diabetic nephropathy; NS, nephrotic syndrome; BA, betulinic acid; TA, trametenolic acid.
[a] Used by traditional medicines practitioners without clinical studies.

(50 mg/kg). Although the efficacy of phytoconstituents in the treatment of kidney disease has been widely recognized, they are still in their infancy. Because the mechanism of action of some natural components, such as TA and inotodiol, is inconclusive.

6 Conclusion

Future researches should combine biological and clinical studies to explore the material basis of triterpenoids of *I. obliquus* in the treatment of nephropathy. We also hope that this review will stimulate further research on triterpenoids and their analogs and that this most valuable compound will be used in human trials for the treatment of kidney disease.

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