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Review

Dioscin: A diverse acting natural compound with therapeutic potential in metabolic diseases, cancer, inflammation and infections

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ABSTRACT

Currently, the numbers of patients with cancer, fibrosis, diabetes, chronic kidney disease, stroke and osteoporosis are increasing fast and fast. It's critical necessary to discovery lead compounds for new drug development. Dioscin, one active compound in some medicinal plants, has anti-inflammation, immunoregulation, hypolipidemic, anti-viral, anti-fungal and anti-allergic effects. In recent years, dioscin has reached more and more attention with its potent effects to treat liver, kidney, brain, stomach and intestine damages, and metabolic diseases including diabetes, osteoporosis, obesity, hyperuricemia as well as its anti-cancer activities through adjusting multiple targets and multiple signals. Therefore, dioscin is a promising multi-target candidate to treat various diseases. This review paper summarized the progress on pharmacological activities and mechanisms of dioscin, which may provide useful data for development and exploration of this natural product in the further.

1. Introduction

In recent years, the numbers of patients with cancers, fibrosis, liver injury, cirrhosis, diabetes, chronic kidney disease, and osteoporosis are increasing (Table 1) [1]. Thus, development and exploration of new treatment modalities to reduce the burden and control the diseases are critical important.

Evidences have shown that drugs or functional products with single target have less treatment actions and more side effects when they are used to treat complex diseases involving multiple pathological changes [2,3]. In response to these challenges, there are growing interests to develop multi-target drugs or functional products. Traditional Chinese medicines (TCMs) have been used to treat various diseases in China for thousands of years [4,5]. In the past decades, the works of TCMs on multiple-target effects have significantly increased. Beyond that, TCMs process some positive features including diversity, broad continuity, relatively low cost, low side effects and high efficiency [6]. A large number of pharmacological researches on active natural products derived from TCMs have achieved tremendous progress in recent years (Fig. 1A). The works of artemisinin against malaria by *Youyou Tu* have won the "2015 Nobel Prize in Hysiology or Medicine". Therefore, it's feasible to discovery natural products from TCMs for development and exploration of innovative drugs.

Dioscin, a steroidal saponin, is an active ingredient in some TCMs including Liuwei Dihuang decoction and Di'ao Xinxue kang [7–10]. The data from "PubMed" and "CNKI" databases have indicated that the works on dioscin have markedly increased in recent years (Fig. 1B). As shown in Fig. 2, dioscin also is one active compound in *Dioscoreae* rhizoma (Shanyao in Chinese, one famous vegetable), and several *Dioscoreaceae* plants including *Dioscorea Zingiberensis* C.H. Wright and *Dioscorea nipponica* Makino [11,12]. The book of "Sheng Nong's Herbal Classic" has recorded that "*Dioscorea* is sweet to level the smell with the characteristics of reducing visceral injury and reinforcing insufficiency", which can also remove cold- and heat-evil, replenish Qi and promote muscle growth. In addition, *Dioscorea* can increase the sensitivity of hearing and vision, and extend life expectancy [13]. Pharmacological tests have shown that dioscin has anti-tumor, anti-inflammation, immuneregulation, hypolipidemic, anti-viral, anti-fungal and anti-allergic effects. Furthermore, some works in recent years have suggested that dioscin can protect liver, kidney, brain and gastrointestinal damages, and regulate the metabolic diseases including diabetes, osteoporosis, obesity and hyperuricemia through adjusting multiple targets and signals. Therefore, dioscin is a promising multi-target candidate to treat some diseases, suggesting that this natural product should have expansive application prospects.

Although these works have confirmed the pharmacological actions of dioscin, most of them focus on the effects in one disease or one mechanism. Therefore, we are trying to give a timely and comprehensive update on the pharmacological actions and targets of dioscin. References on this natural product have implemented by collecting

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Table 1
Deaths, YLDs, and DALYs attributable to various diseases (1990–2013).

Cause	Death rank	Deaths per 100,000	YLD rank	YLDs per 100,000	DALY rank	DALYs per 100,000
Cardiovascular diseases	1–1	231.3–241.4	11–9	211.2–295.6	3–1	4872.5–4601.7
Neoplasms	3–2	106.6–114.9	16–16	69.8–94.4	4–3	2873.4–2750.8
Chronic respiratory diseases	4–4	65.7–59.6	7–7	468.7–539.0	8–10	1900.0–1573.1
Diabetes, urogenital, blood, and endocrine diseases	8–5	29.6–41.2	5–4	714.7–915.0	12–8	1660.0–1976.6
Digestive diseases	11–13	19.8–16.3	14–14	128.2–118.0	18–17	747.4–521.4
Neurological disorders	13–9	19.2–27.6	6–5	700.3–828.5	15–13	1021.2–1173.0
Cirrhosis	14–12	15.8–17.0	21–21	7.9–7.6	19–18	511.5–514.4
Other non-communicable diseases	15–15	15.7–10.4	3–3	1535.0–1646.2	17–19	753.6–378.4
Mental and substance use disorders	19–19	3.5–3.9	1–1	2101.7–2258.4	7–5	2248.5–2417.0
Musculoskeletal disorders	21–20	1.2–1.6	2–2	1713.0–2040.9	11–7	1753.7–2085.7
Diarrhea, lower respiratory, and other common infectious diseases	2–3	148.4–66.3	10–11	268.8–200.0	1–2	10356.1–3487.2
Neonatal disorders	5–7	64.7–28.6	15–12	103.0–176.5	2–4	5684.9–2646.2
HIV/AIDS and tuberculosis	6–6	39.0–36.7	17–15	45.1–76.7	13–9	1612.8–1663.4
Neglected tropical diseases and malaria	10–14	20.6–13.9	8–10	390.9–280.5	9–12	1848.6–1265.6
Nutritional deficiencies	16–16	14.2–9.5	4–6	868.2–582.9	10–15	1777.7–1044.5
Other communicable, maternal, neonatal, and Nutritional diseases	17–17	10.1–5.7	18–18	61.0–49.8	5–6	2766.2–2385.9
Maternal disorders	18–18	7.1–4.1	19–19	21.4–18.7	20–20	428.3–251.6
Unintentional injuries	7–8	38.0–28.0	9–8	345.0–302.2	6–11	2510.7–1478.6
Transport injuries	9–10	21.7–20.7	12–13	180.3–142.3	14–14	1338.5–1101.5
Self-harm and interpersonal violence	12–11	19.8–17.4	20–20	19.4–14.7	16–16	971.2–789.6
Forces of nature, war, and legal intervention	20–21	1.99–0.70	13–17	151.5–54.9	21–21	257.1–85.3

YLDs = years living with disability. DALYs = disability-adjusted life-years.
Communicable and neonatal diseases (column 1–10), Non-communicable diseaes (column 11–17), Injuries (column 18–21).

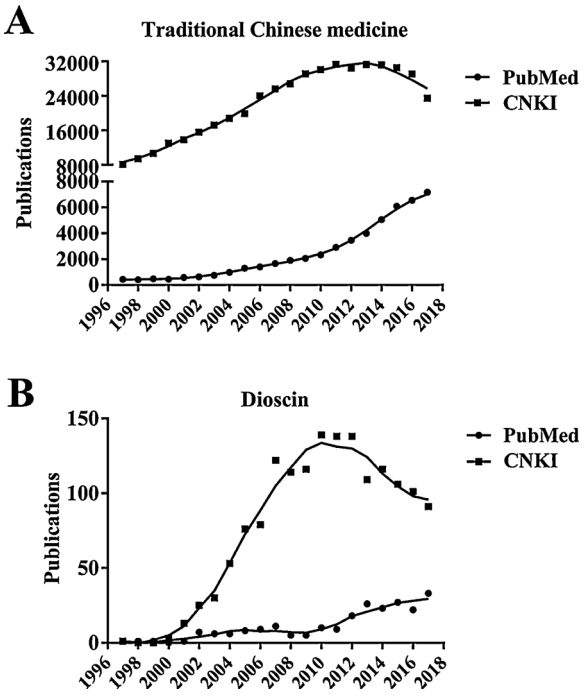

Fig. 1. The papers about (A) TCMs and (B) dioscin researches published in "PubMed" and "CNKI" databases from 1997 to 2017. The data from "PubMed" and "CNKI" databases have indicated that the works on traditional Chinese medicines (TCMs) and dioscin have achieved tremendous progress in recent years.

English literatures (PubMed, Elsevier ScienceDirect, Web of Science and Medline databases). The purpose of the review paper was to investigate and summarize the latest advances of pharmacological activities and functional mechanisms of dioscin, and then provide useful data for development and exploration of this natural product in the further.

2. Mechanisms and anti-tumor effects of dioscin

At present, cancer caused by a lot of factors is expected to exceed cardiovascular diseases to be the most important cause of mortality in next few years [14,15]. Although some chemical drugs are effective to treat cancer, a large number of serious side effects have found. Therefore, development of new candidates with high efficiency and low side effects is urgent.

2.1. Anti-breast cancer effect and mechanism of dioscin

Breast cancer is the most common cancer in worldwide with an estimated 1.7 million cases and 521,900 deaths in 2012. The survival rates of the breast cancer are currently estimated to be less than 5–10% for 10-year and 25% for 5-year [16]. In breast cancer, GATA-binding protein 3 (GATA3) has the ability to reverse epithelial mesenchymal transition in invasive breast cancer cells, which can result in inhibiting metastasis. Aumsuwan, P. et al., have found that dioscin can inhibit cellular invasion in human MDA-MB-231 breast cancer cells by up-regulating the expression of GATA3 [17]. In addition, microarray asays have shown that dioscin can up-regulate 36 genes and down-regulate 60 genes in MDA-MB-231 cells, as well as up-regulate 395 genes and down-regulate 406 genes in MCF-7 cells [18]. These data suggest the multiple networks and pathways associated with the anti-cancer effects of dioscin. After the appearance of apoptosis in breast cancer cells, apoptosis-inducing factor (AIF) translocates to the nucleus and participates in caspase-independent apoptotic events including chromatin condensation and large-scale DNA fragment. Dioscin can induce the death of MDA-MB-453, MDA-MB-231 and T47D cells via activating AIF-facilitating caspase-independent pathway and reducing the espression levels of anti-apoptotic related proteins [19]. In clinical, resistance to chemotherapeutic agents, especially to multi-drug resistance (MDR), is a major cause of treatment failure [20]. Importantly, regulating MDR1 level can up-regulate p-glycoprotein (p-gp) expression and suppress autophagy in cancer cells [21,22]. Dioscin can increase adriamycin (ADR) chemosen- sitivity by decreasing MDR1 levels, and improve the cytotoxicity of ADR through inducing autophagy [23].

2.2. Anti-gastric carcinoma effect and mechanism of dioscin

Owing to the high mortality and low survival rate, gastric cancer has become the second leading cause of cancer-related deaths [24]. Hu, M.M. et al., have investigated that dioscin processes potential actions against human gastric cancer through inducing cell apoptosis via activating the extrinsic and mitrochondrial pathways [25]. Loss of cell

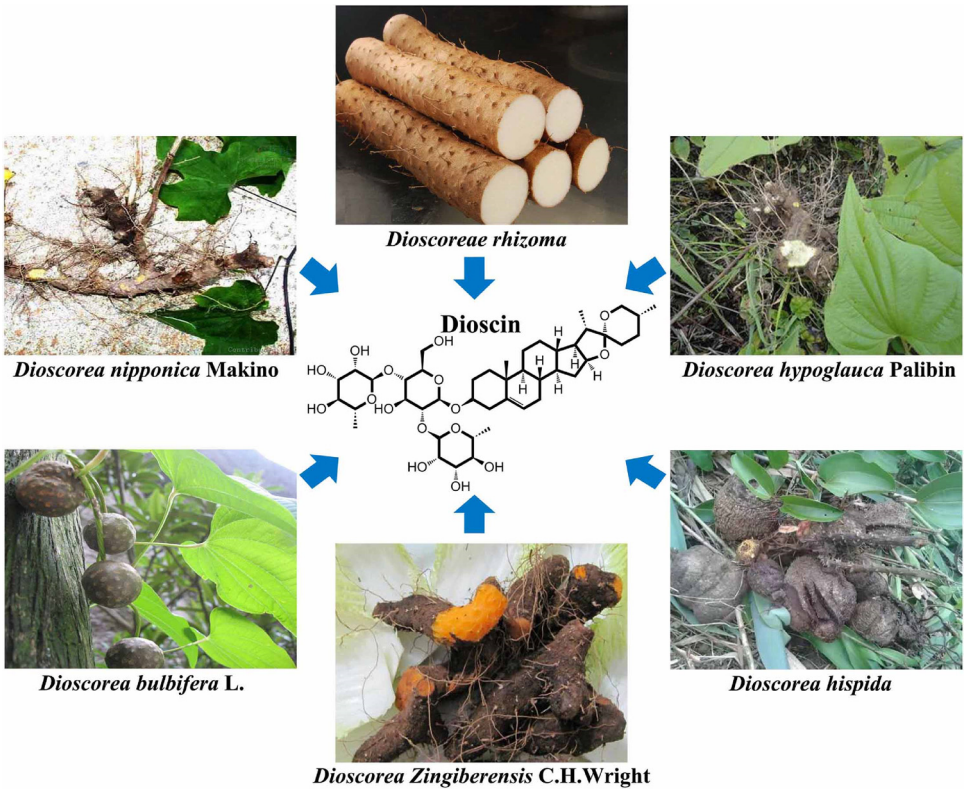

Fig. 2. Dioscin presents in several medicinal plants including *Dioscoreae* rhizoma, *Dioscorea nipponica* Makino, *Dioscorea hypoglauca* Palibin, *Dioscorea bulbifera* L, *Dioscorea Zingiberensis* C.H. Wright and *Dioscorea hispida*. The images of these medicinal plants are obtained from the internet.

cycle control can lead to the proliferation of uncontrolled cells for the development of cancer. Therefore, the selective cyclin dependent kinase (CDK) inhibitor is one potent agent to treat cancer [26]. Dioscin can induce G2/M phase arrest and apoptosis in SGC-7901 cells by inhibiting CDK-activating kinase activity [27]. Moreover, Zhao, X.W. et al., have found that dioscin shows cytotoxicity to human MGC-803 gastric cancer cells and significantly inhibits tumor growth of xenografts in nude mice via including DNA damage and cell cycle arrest [28]. In addition, isobaric tags for relative and absolute quantification (iTRAQ)-based proteomics approach has found 121 differentially expressed proteins associated with cell apoptosis, cycle and migration caused by dioscin. Recent studies have also indicated that long non-coding RNAs (lncRNAs) are involved in the development of cancer [29]. In the study of Ma, T. et al., high expression level of lncRNA HOTAIR has been found in gastric cancer tissue, which can be significantly down-regulated by dioscin [30].

2.3. Anti-liver cancer effect and mechanism of dioscin

Approximately 790,000 new cases and 818,000 deaths of liver cancer worldwide in 2013 have been reported [31]. Currently, the therapeutic methods including liver resection, palliative intra-arterial therapies and transplantation have been used. However, long-term prognosis of liver cancer remains poor because of chemotherapy -resistant and high tumor recurrence [32]. Dioscin can dose-dependently enhance caspase-3-dependent cell apoptosis in Huh7 cells [33]. The works of Zhang, G.X. et al., have also demonstrated that dioscin can inhibit the proliferation of hepatocellular carcinoma cells via inducing morphological changes and DNA damage in Bel-7402 cells [34]. Notably, dioscin can also suppress tumor growth via inducing apoptosis in nude mice bearing Bel-7402 cells. In addition, dioscin can effectively reverse multidrug resistance in HepG2/ADR cells via inhibiting the activity of MDR1 promoter and P-gp function [35].

2.4. Anti-acute myeloid leukemia effect and mechanism of dioscin

Acute myeloid leukemia is the most common form of adult leukemia, and little progression has been made on developing effective therapies. Mitogen-activated protein kinases (MAPKs) exert vital biological effects on apoptotic signals in myeloid leukemia [36]. In the study of Wang, Y. et al., dioscin can notably induce the apoptosis of myeloblast leukemia HL-60 cells through activating c-Jun N-terminal kinase (JNK) and p38 MAPK [37]. In addition, the action of dioscin on ADR-resistant erythroleukemic cells (K562/ADR) has been tested by Wang, L.J. et al., and dioscin can reverse ADR-induced MDR through reducing the mRNA and protein levels of MDR1 and NF-κB [38].

2.5. Anti-lung cancer effect and mechanism of dioscin

Lung cancer with high incidence, rapid progression and poor prognosis is the leading cause of cancer-related death. Wei, Y.L. et al., have proved that dioscin can significantly induce cell apoptosis on human A549, NCI-H446 and NCI-H460 lung cancer cells [39]. Furthermore, Hsieh, M. J. et al., have found that autophagy induced by disocin maybe one pathway for cell survival against apoptosis [40]. In addition, epithelial-to-mesenchymal transition (EMT) is a key cellular process during cancer development. Dioscin can suppress the migration and invasion of A549 lung cancer cells by inhibiting transforming growth factor-β1 (TGF-β1)-induced EMT [41]. Moreover, tyrosine kinase inhibitors (TKIs) exhibit good clinical benefits in the treatment of lung adenocarcinoma. The works of Wang, Y.C. et al., have indicated that dioscin can act as a dual inhibitor of MEK/ERK and PI3K/AKT signaling pathways to overcome TKIs resistance [42].

2.6. Anti-renal cancer effect and mechanism of dioscin

Total of 63,990 new cases and 14,400 deaths of renal cancer in 2017 have been found. TNF-related apoptosis inducing ligand (TRAIL) can

induce the apoptosis of tumor cells. The study of Kim, Y.S. et al., have found that dioscin can significantly enhance TRAIL-induced apoptosis [43]. Gap junction plays key roles in growth, differentiation and apoptosis on cancer cells. Zhang, G.Y. et al.,have indicated that dioscin can promote the function of gap junction in human renal carcinoma cell [44].

2.7. Anti-melanoma tumor effect and mechanism of dioscin

Melanoma has the features of high mortality, high invasion and high metastasis. Three major pigment enzymes including tyrosinase, tyrosinase-related protein (TRP)-1 and TRP-2 play important roles in melanoma tumor [45], and their activites can be regulated by microphthalmia-related transcription factor (MITF) [46]. Dioscin can inhibit α-melanocyte-stimulating hormone (α-MSH)-induced melanogenesis in B16 cells via decreasing the expression levels of tyrosinase, TRP-1, TRP-2 and MITF [47]. Connexin 43 (Cx43) is an important gap junction protein in tumor micro- environment (TME), and the works of Kou, et al., have found that dioscin can target Cx43 to activate macrophage sensitivity and inhibit tumor cell malignancy [48].

2.8. Anti-prostatic cancer effect and mechanism of diosicn

The patients with prostate cancer usually accept surgery or anti-androgen therapy at the early stage [49]. Prostate cancer stem cells (PCSCs) are the cell origin of prostatic cancer, which paly important roles in tumorigenesis. Our works have confirmed that dioscin has potent inhibitory activity on PC3 cell-derived mammos- pheres via activating estrogen receptor-β (ERβ) [50].

2.9. Other anti-cancer effects and mechanism of dioscin

Epithelial ovarian cancer is the leading cause of gynecologic cancer-associated deaths among women, and cell apoptosis is closely related to the occurrence, progress and metastasis of the cancer. Dioscin can dose- and time-dependently inhibit cell proliferation and induce cell apoptosis in human ovarian cancer SKOV3 cells [51]. ROS accumulation can cause cell apoptosis, mitochondrial damage, cytochrome C release and programmed cell death-5 (PDCD5) nuclear translation. Wang, Z.Y. et al., have found dioscin can induce ROS generation and apoptosis in human Kyse510 esophageal cancer cells through increasing oxidative stress via downregulating the espression levels of peroxiredoxin (PRDX)-1 and PRDX-6 [52]. Laryngeal cancer is the common malignant tumor of head and neck. In the works of Si, L.L. et al., dioscin causes cell apoptosis and DNA damage, up-regulates ROS level, induces S-phase arrest, and reduces invasion in human HEp-2 and TU212 laryngeal cancer cells [53]. The actions of dioscin on human cervical carcinoma HeLa and SiHa cells have been detected by Zhao, X.W. et al., and dioscin can cause cell apoptosis through regualting ROS-mediated DNA damage and mitochondrial signaling pathway [54]. Glioblastoma multiforme is a common malignant brain cancer, and dioscin exerts a promising inhibiting effect on glioblastoma cells via ehancing ROS accumulation, DNA damage and mitochondrial signals [55]. In addition, dioscin can markedly suppress tumor size and increase survival rate in glioma in vivo rat allograft model. Pancreatic cancer is one of the most lethal solid malignancies in the Western world. Recently, microRNA microarray analysis has been used to determine the underlying mechanisms of dioscin against pancreatic cancer, and total of 107 microRNAs with differential changes have been found to prove that dioscin exerts excellent activity against pancreatic cancer via miR-149-3 P/Akt1 signaling pathway [56]. In recent years, the incidents of bladder carcinoma in China have increased rapidly. Dioscin can induce demethylation of death-associated protein kinase-1 (DAPK-1) and ras-association domain family 1 isoform A (RASSF-1) to cause apoptosis on T24 cancer cells [57]. Song, X.L. et al., have checked the actions of dioscin on NOZ and SGC996 gallbladder cancer cells, and dioscin can significantly inhibit cell proliferation and migration [58]. Colorectal cancer is the second leading cause of cancer-related deaths in the USA. Li, S. et al., have found that dioscin can induce the apoptosis of colon cancer cells through adjusting the phosphorylation levels of JNK and p38-MAPK [59]. Osteosarcoma is one common primary bone tumor. Liu, W.H. et al., have adopted in vitro and in vivo models, and dioscin inhibits osteosarcoma stem- cell-like properties and tumor growth via repressing Akt/glycogen synthase kinase 3 (GSK3)/β-catenin pathway [60].

Together, the effects of dioscin against breast cancer, gastric carcinoma, acute myeloid leukemia, lung cancer, ovarian cancer, renal cancer, melanoma tumor, esophageal cancer, prostatic cancer, laryngeal cancer, cervical carcinoma, liver cancer, glioblastoma, pancreatic cancer, gallbladder cancer and bladder cancer have attracted more attentions, and these studies have described the mechanistic actions of dioscin on apoptosis, ROS generation, Ca^{2+} release, cell cycle and DNA damage.

3. Protective effects and mechanisms of dioscin against organ damages

3.1. Hepatoprotective effects of diosicn

Liver diseases are the major global public health problems in the world [61]. Among them, acute liver injury caused by adverse drug reactions accounts for more than 50% of the cases [62]. Moreover, liver can be damaged by many toxic chemicals including carbon tetrachloride (CCl_4), alpha-naphthylisothiocyanate (ANIT) and dimethylnitrosamine (DMN) [63]. In addition, chronic liver diseases induced by viral infection, alcohol abuse, and obesity can cause hepatic encephalopathy, fibrosis and liver cancer [64]. Therefore, it's urgent to explore and develop effective hepatopro- tective candidates. Many works have indicated that dioscin has potent hepatopro- tective effects through regulating multiple targets and biological processes (Fig. 3).

3.1.1. Protective effects and mechanism of dioscin against acute liver damage

Some chemicals and drugs including CCl_4, lipopolysaccharide (LPS), ANIT, DMN, acetaminophen (APAP) and ethanol have been widely used to establish experimental models for estimating the activities of medicines against acute liver injury. Extensive researches have proved that dioscin can reduce serum levels of alanine aminotran- sferase (ALT), aspartate transaminase (AST), and improve acute liver injury.

Cytochrome P450 2E1 (CYP2E1) can cause ROS production to induce hepatic oxidative stress, inflammation and apoptosis, and finally lead to cell necrosis and tissue damage. Lu, B.N. et al., have found that dioscin shows significant protective effect against CCl_4-induced acute liver damage in mice, and the proteins including heat shock protein 5 (HSPA5), annexin A6 (ANXA6), isovaleryl-CoA dehydrogenase (IVD), ribosomal protein S6 (RPS6), cytoglobin (Cygb), and nucleoside diphosphate kinase A (NDPK-A) may be the drug targets based on proteomics assay [65]. Lu B.N. et al., have further found that dioscin can inhibit inflammation, apoptosis, necrosis and lipid peroxidation [66]. In addition, Zhao, X.M. et al., have investigated the effect of dioscin against APAP-induced liver injury, and found that dioscin can improve AST release, mitochondrial dysfunction and apoptosis in mice. Some differentially expressed proteins including sulfite oxidase (Suox), cytoskeletal 18 (Krt18), regucalcin (Rgn), PRDX1, malate dehydrogenase (MDH) and purine nucleoside phosphorylase (PNP) may be the drug targets of the compound against APAP-induced liver injury, which should be considered as biomarkers for investigating acute liver injury [67].

LPS can induce serious sepsis, activate immunological system and macrophages. Yao, H. et al., have showed that dioscin has potent action against LPS-induced liver injury through inhibiting toll-like receptor 4 (TLR4) inflammatory signaling pathway [68]. In addition, Yao, H.

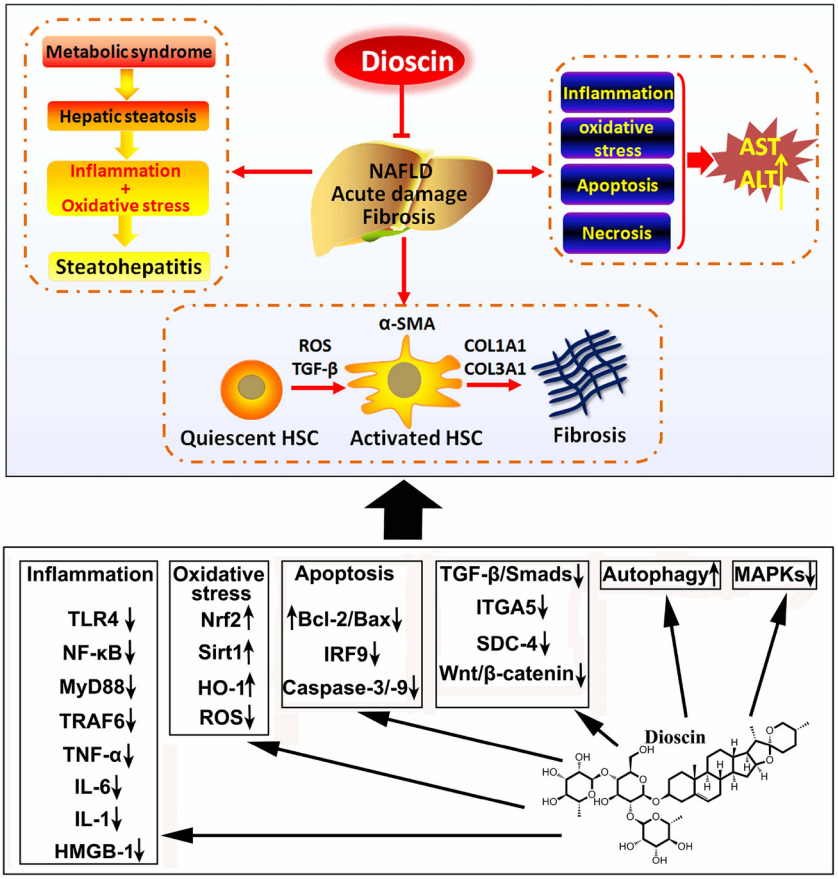

Fig. 3. Dioscin possesses hepatoprotective effects through regulating multiple targets and biological processes including steatosis, inflammatory response, oxidative stress, apoptosis, TGF-β/Smads, autophagy and MAPKs pathways. α-SMA, α-smooth muscle actin; ALT, alanine aminotransferase; AST, aspartate transaminase; Bax, Bcl2-associated X; Bcl-2, B-cell lymphoma-2; COL1 A1, collagen type I alpha 1; COL3A1, collagen, type III, alpha 1; HMGB-1, high mobility group box-1 protein; HO-1, heme oxygenase-1; IL, interleukin; IRF9, interferon regulatory factor 9; ITGA5, inhibiting integrin alpha-5; MAPKs, mitogen-activated protein kinases; MyD88, myeloid differentiation primary response 88; NAFLD, nonalcoholic fatty liver disease; Nrf2, nuclear factor (erythroid-derived 2)-like 2; ROS, reactive oxygen species; Sirt1, sirtuin 1; SDC-4, syndecan-4; TGF-β1, transforming growth factor-β; TLR4, toll-like receptor 4; TNF-α, tumor necrosis factor-α; TRAF6, TNF receptor associated factor 6.

et al., have also proved that dioscin has potent effects against ANIT-induced intrahepatic cholestasis through regulating apoptosis and ROS [69]. The study performed by Zhang, A.J. et al., have proved that dioscin can ameliorate cholestasis by restoring hepatic transporter expressions [70]. DMN is a potent hepatotoxin, mutagen and carcinogen, and thioacetamide (TAA) is another classic liver toxic chemical, which have been used to establish experimental models. The works of Zhang, W.X. et al., have indicated that dioscin exhibits protective effect against DMN-induced liver insult through inhibiting TLR4 inflammatory pathway and activating sirtuin 1 (Sirt1) antioxidant signaling pathway [71]. Zheng, L.L. et al., have investigated the protective effect of dioscin against TAA-induced acute liver injury, and dioscin can notably inhibit oxidative stress and inflammation in liver via adjusting farnesoid X receptor (FXR) signal pathway [72]. In addition, alcohol abuse can cause alcoholic liver diseases with the morphological features of steatosis, hepatitis, fibrosis and ultimately cirrhosis. In the paper of Xu, T.T. et al., the actions of dioscin against alcoholic liver disease have been investigated, and dioscin can notably improve liver steatosis, and decrease ALT and AST levels via ameliorating ethanol-induced oxidative stress, mitochondrial function, inflammatory cytokine production and apoptosis [73]. During I/R injury, activated Kupffer cells can produce massive ROS. Our study has also proved that the protective effects of dioscin against liver I/R injury may be through inhibiting inflammatory cytokines, oxidative stress, apoptosis and necrosis [74].

3.1.2. Protective effects and mechanism of dioscin against chronic liver damage

Overproduction of extracellular matrix (ECM) in liver can damage hepatic architecture and normal function, and finally cause fibrosis, cirrhosis and liver cancer. Molecular mechanistic researches have indicated that hepatic stellate cells (HSCs) activation is an important effector in the process of hepatic fibrosis [75]. Briefly, HSCs can be activated from quiescent cells to myofibroblast-like cells. Alcohol abuse, obesity, hepatitis, biliary disease, metabolic disorders, drug-induced chronic hepatic diseases, and continued exposure to chemicals or poisons can cause liver fibrosis [76,77].

Multiple studies have proved that dioscin can notably improve hepatic fibrosis, and inhibit cell viabilities of HSC-T6, LX-2 and primary rat HSCs. Dioscin can reduce HSCs activation and collagen accumulation based on the decreased levels of TGF-β1, α-SMA, collagen and vimentin. in vivo, the hepatic fibrosis models induced by CCl_4, alcoholic, TAA, bile duct ligation (BDL) and DMN have been used to test the actions of dioscin [78–82]. The results have confirmed that dioscin exerts anti-fibrotic activities with the improved body weights, serum AST, ALT and hydroxyproline levels via modulating multiple signaling pathways. TGF-β1 can phosphorylate downstream receptor-activated Smads signal [83]. Wnt/β-catenin pathway participates in HSCs activation [84]. Oxidative stress and inflammation also widely participate in HSCs activation and matrix degradation [85]. Among them, TLR4/MyD88 signaling exhibits potent action against inflammatory response by decreasing NF-κB, interleukin (IL)-1, IL-6 and tumor necrosis factor-α (TNF-α) levels [86]. Nrf2/Sirt1 signaling can reduce p38 MAPK phosphorylation, and decrease the levels of collagen type I alpha 1 (COL1 A1), collagen type III alpha 1 (COL3A1), α-SMA and fibronectin through inhibiting ROS production [87]. Our previous studies have proved that the effects of dioscin against hepatic fibrosis may be via inhibiting TGF-β1/Smads, Wnt/β-catenin and TLR4/MyD88 signal pathways and activating Nrf2/Sirt1 signal pathway [78–82].

As shown in Fig. 4A, two-dimensional differential in-gel electrophoresis technology (2D-DIGE) has been used to identify the differentially expressed proteins caused by dioscin in rats, and ten new biomarkers including protein disulfide isomerase A3 (PDIA3), selenium-binding protein 1 (SBP1), glutamine synthetase (GSS), senescence marker protein 30 (RGN), hemopexin, keratin 8, keratin 18, vimentin,

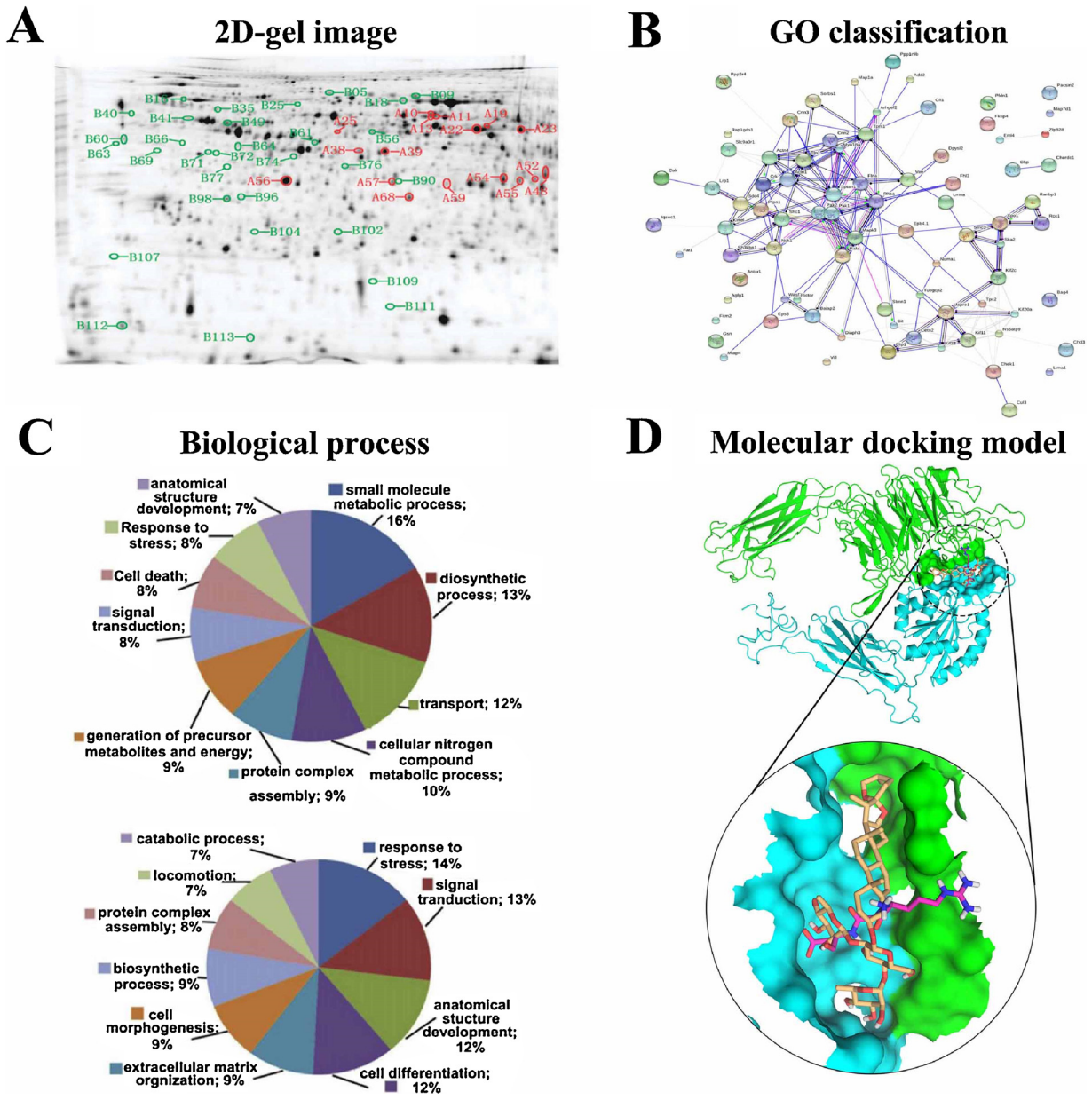

Fig. 4. Dioscin exerts anti-liver fibrosis effects via affecting mutiple signaling pathways and biological processes. (A) Representative 2D-gel image marked with a total of 48 differentially expressed protein spots with red color for indicating the up-regulation of protein expressions and green color for showing the down-regulation of protein expressions. (B) The network of the differentially expressed proteins found by the iTRAQ method in HSC-T6 cells treated by dioscin. (C) Classification of the differentially expressed proteins found by SILAC proteomics in LX-2 cells treated by dioscin according to biological process. (D) The binding mode of dioscin and ITGA5 protein. These images are obtained from our previous results published in the References [81,87,88].(For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

annexin A5 (ANXA5) and dermatopontin (DPT) have been found [81]. Syndecan-4 (SDC-4) plays a crucial role in effects of dioscin on HSC-T6 cell adhesion and migration [87], and the network of the differentially expressed proteins analyzed by the String 9.1 software is shown in Fig. 4B. In addition, as shown in Fig. 4C, Xu L.N. et al., have adopted the method of stable isotope labeling with amino acids in cell culture (SILAC) and found that dioscin can alleviate hepatic fibrosis via affecting multi-biological processes [88]. Moreover, dioscin can reduce collagen synthesis in LX-2 cells, and integrin alpha-5 (ITGA5) is a potent drug-target of dioscin based on molecular docking test (Fig. 4D).

3.1.3. Dioscin promotes liver regeneration

Currently, liver regeneration is a critical process after partial hepatectomy [89]. Many studies have suggested that Notch1 and Jagged1 are critical players in liver proliferation [90]. Jagged1 can activate Notch1 signal pathway, and cause the release of Notch1 intracellular domain (NICD1). Then, NICD1 translocates into nucleus and results in the transcription of proliferation-related genes. Dioscin can activate Notch1 /Jagged1 pathway to promote liver proliferation [91].

3.2. Protective effects and mechanism of dioscin on cardiovascular and cerebral vessels

Although arterial bypass and other surgical operations have been widely applied, myocardial I/R injury has become a primary factor in the treatment of coronary heart disease [92]. In the study of Qin, J. *et al.,* the apoptosis of H9c2 cells induced by myocardial I/R can be prevented by dioscin via adjusting apoptotic pathway [93]. Doxorubicin is

an efficient chemotherapeutic drug which has been widely used in clinical treatment. However, the acute and chronic cardiotoxicities including arrhythmia, tachycardia, hypotension and refractory late-onset cardiomyopathy limit its clinical application. Zhao, L.S. et al., have found that dioscin can alleviate doxorubicin-induced cardiotoxicity via inhibiting oxidative stress through modulating miR-140-5p signaling pathway [94]. Cerebral I/R injury is one challenging clinical problem in the treatment of acute ischemic stroke. Some pathological mechanisms associated with cerebral I/R injury including oxidative stress, inflammation, and apoptosis have been implicated [95]. Dioscin shows protective effect against cerebral I/R injury *in virto* and in vivo [96,97] via inhibiting the expression level and nuclear translocation of high mobility group box-1 protein (HMGB-1). Moreover, dioscin can decrease transcriptional activities of NF-κB to suppress inflammatory response via inhibiting TLR4 signal. Also, small interfering RNA (siRNA) and over-expression experiments have confirmed that diosicn processes neuroprotective effect via regulating HMGB-1/TLR4 signal pathway. Atherosclerosis, a chronic disease with the accumulation of lipids and fibrous elements in large arteries, is the main cause of coronary artery disease. Monocyte-endothelial adhesion is an early step in the process of atherosclerosis. Dioscin can decrease monocyte adhesion via down-regulating the expression levels of vascular cell adhesion molecule-1 (VCAM-1) and intercellular adhesion molecule 1 (ICAM-1), and inhibit endothelial lipase (EL) expression and NF-κB signal pathway [98].

3.3. Nephroprotective effects and mechanism of dioscin

Acute kidney injury associated with high morbidity and mortality is one common disease in clinical. Hyperuricemia, kidney transplantation and renal surgery-induced renal I/R injury, endotoxic (LPS) shock and chemotherapy are the common causes of kidney injury [99]. Renal I/R injury can cause the clinical syndrome of delayed graft function after transplantation. Dioscin exerts protective effects against renal I/R injury through inhibiting inflammatory response via down-regulating HSP70/TLR4 signaling pathway [100]. Dioscin can also decrease BUN and Cr levels, and ameliorate oxidative stress in vivo and in vitro models of LPS-induced inflammatory kidney injury via increasing miRNA let-7i level and thereby decreasing TLR4 inflammatory pathway [101]. Cisplatin, an inorganic platinum compound with broad-spectrum activities against tumours, can cause serious nephrotoxicities, which limit its clinical applications. The works of Zhang, Y.M, et al., have found that dioscin can attenuate cisplatin-induced renal injury in rats and mice via down- regulating miR-34a level, and then activacting Sirt1 signaling pathway [102]. Furthermore, Zhang, Y.M. et al., have also investigated the action of dioscin against doxorubicin-induced nephrotoxicity, and found that dioscin can markedly attenuate cell injury and nephrotoxicity in rats through inhibiting ROS level [103] via activating FXR siganling pathway. In addition, some food additives can also cause renal injury, and recent studies have shown excessive consumption of fructose can promote acute and chronic kidney injury. The works of Qiao, Y.J. et al., have indicated that dioscin can significantly reduce fructose-induced renal injury through decreasing the levels of Cr, BUN, and rehabilitating histopathological changes [104] via adjusting sirtuin 3 (Sirt3)-mediated signaling pathway.

3.4. Pulmonary protective effects and mechanism of dioscin

Airway mucus plays important roles against noxious chemicals, invading pathogenic microorganisms and particles. Abnormality in mucins always can cause severe pulmonary diseases. Lee, H.J. et al., have investigated the effect of dioscin on airway epithelial NCI-H292 cells, and found that dioscin can inhibit the gene expression and production of MUC5AC mucin induced by epidermal growth factor (EGF) or phorbol 12-myristate 13-acetate (PMA) [105]. Silicosis is caused by the inhalation of respirable crystalline silica dust, which can result in pulmonary fibrosis and even respiratory failure [106]. Li, C. et al., have found that dioscin can postpone crystalline silica-induced pulmonary fibrosis and exert protective actions in mice via inhibiting the secretion of pro-inflammation and pro-fibrotic cytokine [107]. In addition, dioscin can also inhibit signal-regulating kinase 1 (ASK-1)-p38/JNK pathway and Smad3 phosphorylation in fibroblast. Furthermore, Zeng, H.Q. et al., have investigated the protective effect and underlying mechanism of dioscin against acute lung injury induced by LPS, and found that dioscin can significantly decrease total number of alveolar macrophages and water content of lung in LPS-treated mice through HSP70/TLR4 inflammatory signaling pathway [108].

3.5. Protective effects and mechanism of dioscin against gastric I/R injury

Many clinical conditions including ischemia gastrointestinal disease, vascular rupture or surgery and hemorrhagic shock can cause gastric I/R injury. Dioscin can attenuate H/R insult in GES-1 cells and gastric I/R injury in rats through inhibiting NF-κB and AP-1 transcriptional activities, and pro-inflammatory cytokine responses via inhibiting PKC/ERK1/2 signal pathway [109].

4. Anti-metabolic diseases effects and mechanism of dioscin

Metabolic diseases are caused by a group of risk factors including osteoporosis, diabetes, obesity and insulin resistance [110,111]. Non-alcoholic fatty liver disease (NAFLD) is a clinicopathologic spectrum of liver pathologies with excessive accumulation of fat in liver [112]. The activity of dioscin against NAFLD has been investigated by Xu, L.N. et al., and dioscin exerts obvious protective effects against NAFLD through affecting multiple drug targets and signal pathways [113]. Using iTRAQ labeling coupled with nano-LC-TOFMS/MS analysis, 22 proteins including enoyl-CoA delta isomerase 1 (Eci1), acyl-CoA dehydrogenase short chain (ACADS), acyl-CoA synthetases long-chain 5 (ACLS5), aldehyde dehydrogenase 7 family member A1 (ALDH7A1), aldehyde dehydrogenase 2 (ALDH2) and cytochrome P450 4 A2 (CYP4 A2) maybe the drug tragets of dioscin against NAFLD. Furthermore, obesity is featured by an excessive storage of body fat associated with a great number of metabolic complications. Liu, M. et al., have proved that dioscin can alleviate liver lipid accumulation symptoms, increase oxygen consumption and energy expenditure in high-fat diet-induced C57BL/6 J mice and ob/ob mice via inhibiting oxidative damage, inflammation and MAPK phosphorylation levels [114]. Poudel, B. et al., have also showed that dioscin can inhibit adipocyte differentiation in 3T3-L1 cells and decrease weight gain in mice against high-fat diet-induced obesity [115].

Osteoporosis can be caused by excessive bone resorption, and correcting the imbalance between bone resorption and formation is effective method for treating osteoporosis [116]. Dioscin can inhibit the receptor activator of NF-κB ligand (RANKL) -mediated osteoclast differentiation and bone resorption in vitro. Furthermore, in vivo study has verified the protective activity of dioscin in LPS-induced osteolytic mice modle by inhibiting NF-κB signaling pathway and nuclear factor of activated T-cells 1 (NFATc1) transcriptional activity [117]. Our previous paper has also found that dioscin can notably improve the biochemical indexes and microarchitecture in ovariectomy (OVX)-induced animal models through promoting osteoblastogenesis and inhibiting osteoclastogenesis [118]. Osteoblasts are also regulated by hormonal and local factors including Wnt/Lrp5/β-catenin and estrogen receptor (ER) signaling pathways. Zhang, C.F. et al., have found that dioscin can increase the proliferation and differentiation of osteoblasts by up-regulating ER and Wnt/Lrp5/ β-catenin signaling pathways [119]. In addition, Zhun, C. et al., have identified that dioscin can promote MC3T3-E1 cell proliferation and differentiation by regulating autophagy [120]. Dioscin maybe a novel and potent candidate for the treatment of osteoporosis.

Hyperuricemia with high level of blood uric acid has been recognized as a risk factor of hypertension, gout, cardiovascular disease,

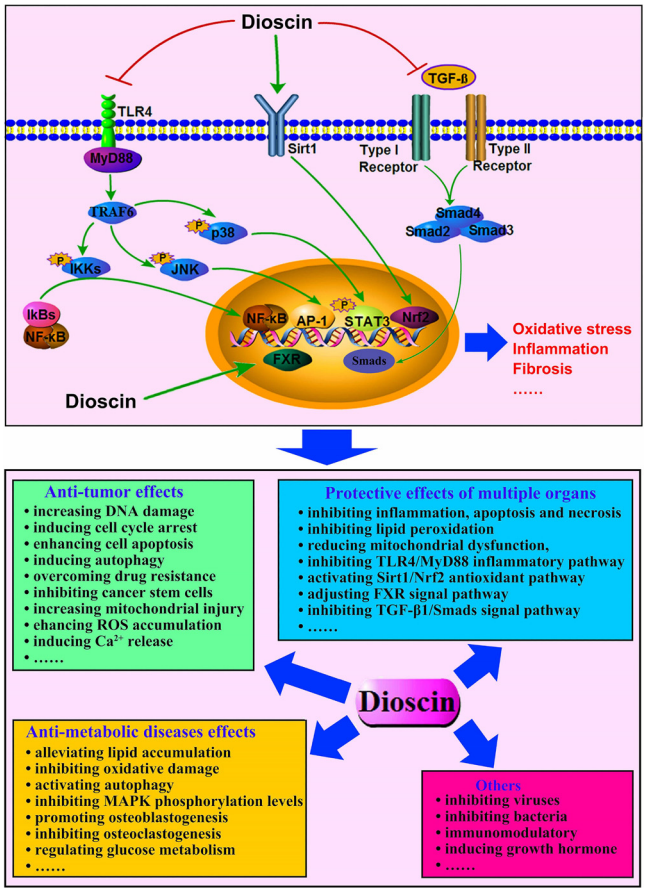

Fig. 5. Pharmacological activities of dioscin reported in recent years. In recent years, dioscin has reached more and more attention with its potent effects to treat multiple organ injuries and metabolic diseases as well as its anti-cancer activities through adjusting multiple targets and multiple signals. TLR4, toll-like receptor 4; MyD88, myeloid differentiation primary response 88; TRAF6, TNF receptor associated factor 6; IKKs, IkB kinases; JNK, c-Jun N-terminal kinase; AP-1, activating protein-1; NF-κB, nuclear factor κB; STAT3, signal transducer and activator of transcription 3; FXR, farnesoid X receptor; Nrf2, nuclear factor (erythroid-derived 2)-like 2; Sirt1, sirtuin 1; TGF-β, transforming growth factor-β.

diabetes and chronic kidney disease [121,122]. Dioscin can significantly decrease serum uric acid and Cr levels, and reduce renal pathological lesions caused by hyperuricemia in mice [123]. Urate transporter 1 (URAT1) has been identified to be involved in renal transportion of uric acid. Moreover, ATP-binding cassette subfamily G member 2 (ABCG2) is an efficient urate exporter to mediate renal and intestinal urate excretion, and controls serum uric acid levels. Dioscin can decrease serum level of uric acid through inhibiting URAT1 and promoting ABCG2.

Furthermore, type 2 diabetes is one common metabolic disorder. However, current therapies have some undesirable side effects including weight gain, dropsy, drug resistance and high rates of econdary failure [124]. Hence, it is necessary to disover more effective anti-diabetic drugs with less side effects. Yu, H. et al., have evaluated the efficacy of the total saponins from *Dioscorea nipponica* Makino (TSDN) against T2DM [125]. The results showed that TSDN can significantly decrease the fasting blood glucose, ameliorate the levels of oral glucose and insulin tolerance test, and markedly increase body weight and serum insulin. Via adjusting MAPKs, NF-κB, peroxisome proliferatoractivated receptor γ (PPARγ) and glycogen synthase kinase-3beta (GSK-3β) pathways.

5. Other pharmacological activities of dioscin

Adenovirus, a common cause of diarrhea, accounts for about 10% of acute respiratory infections in young children [126]. Vesicular stomatitis virus (VSV), a member of *Rhabdoviridae* family, can lead to oral diseases including mucosal vesicles and ulcers in mouth [127]. Hepatitis B virus (HBV) belongs to *Hepadnaviridae* family, and HBV infection can cause liver disease and hepatocellular carcinoma [128]. Up to now, there have no efficient antiviral drugs to treat adenoviral infections, VSV and HBV. According to the research of Liu, C.H. et al., antiviral effects of dioscin have been tested and dioscin can block the initial stage of adenovirus infection in 293 cells and affect the host cell's response for viral infection [129]. Moreover, dioscin exerts anti- VSV infection action prior to infection. In addition, dioscin has potent inhibitory effect on the secretion of Hepatitis B e-antigen (HBeAg) and Hepatitis B surface antigen (HBsAg) in HepG2 2.2.15 cells. Candida albicans can lead to candidiasis, which is the primary cause of notable morbidity and mortality in immunocom- promised patients [130]. In the study of Cho, J.Y. *et al,* dioscin exerts the effect of membrane disruption via inducing morphological change and rhodamine leakage of the giant unilamellar vesicles (GUVs) [131]. Rheumatoid arthritis is a chronic autoimmune disease associated with serious cardiovascular complications. Guo, Y.C. et al., have detected the therapeutic effect of dioscin on collagen-induced arthritis (CIA), and found that dioscin can regulate the proportion of Th1/Th2 cells [132]. In addition, dioscin can also balance the Th17 and Treg cell specific transcription factor retinoic acid receptor-related orphan receptor gamma (RORγ) and forkhead box P3 (Foxp3), and inhibit inflammatory reaction in CIA [133–135]. Growth hormone is a peptide hormone consisting 191 amino acids, which has been used to treat dwarfism and some diseases including obesity, osteoporosis and aging; and Lee, H.Y. et al., have also found that dioscin can induce the release of growth hormone in rats [136].

6. Clinical application

Currently, there have no clinical studies about dioscin because it is only one lead compound not a drug that can not be used on humans. However, some traditional Chinese medicines (TCMs) containing dioscin as the major active compound have been widely used in clinical. Liuwei Dihuang decoction (LW) is one of the most famous TCM formulae, which has been used to treat some kinds of diseases including cancer, neurosis, neurasthenia, dementia, Parkinson's disease, osteoporosis, diabetics, hypertension, nephritis, and thrombocytopenic purpura with the characteristic features of kidney Yin deficiency since Song Dynasty probably 900 years ago [137,138]. In addition, another popular formula-Di'ao Xinxue kang (Di'ao XXK) prepared from *Dioscorea nipponica* Makino has anti-coronary disease, anti- angina pectoris, and anti-myocardial ischemia effects [139], which has been used for many years in China to treat coronary heart disease [140]. Furthermore, *Dioscornin* Tablet contains some kinds of saponins that are extracted from *Dioscorea nipponica*, which has been used to treat Ca^{2+} overload in cardiomyocytes of coronary heart disease in clinical [141]. Therefore, dioscin maybe a potential drug candidate for the further clinical trials.

7. Conclusions

In conclusion, dioscin has attracted a great attention worldwide, and hundreds of papers have been reported to describe the pharmacological activities and mechanisms of this natural product (Fig. 5). Most of these researchers have described the mechanistic effects of dioscin on oxidative stress, inflammation, apoptosis, autophagy, lipid-lowering and immunization on multiple body systems. This review paper addressed the effects of dioscin on multiple targets and signal pathways in a variety of diseases. Dioscin exerts the potent anti-cancer activities through regulating DNA damage, cell cycle arrest, apoptosis, autophagy, ROS level and Ca^{2+} release, and protects multiple organs

injuries via the inhibiton of inflammation, apoptosis, necrosis, lipid peroxidation and mitochondrial dysfunction. Moreover, dioscin has the abilities against metabolic diseases through affecting lipid accumulation, oxidative damage, autophagy and glucose metabolism. Meanwhile, dioscin can also inhibit viruses and bacteria, regulate immunization and induce growth hormone. These years, we have done many works on dioscin, and found that these diverse therapeutic actions may involve in the TLR4/MyD88, Sirt1/Nrf2, FXR and TGF-β/Smads signal pathways. However, the currently available pharmacodynamic and mechanistic data are derived from in vitro cell experiments and in vivo rodent models, which require additional translator work before the human-specific clinical conclusions to be drawn.

Competing financial interests

The authors declare no competing financial interests.

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