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Overview of key molecular and pharmacological targets for diabetes and associated diseases

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ABSTRACT

Diabetes epidemiological quantities are demonstrating one of the most important communities' health worries. The essential diabetic difficulties are including cardiomyopathy, nephropathy, inflammation, and retinopathy. Despite developments in glucose decreasing treatments and drugs, these diabetic complications are still ineffectively reversed or prohibited. Several signaling and molecular pathways are vital targets in the new therapies

Abbreviations: EC, Endothelial cell; AGE, Advanced Glycation End Products; ECD, Endothelial Cell Dysfunction; DCM, Diabetic cardiomyopathy; PPARα, Peroxisome proliferator-activated receptor α; GLP-1, Glucagon like peptide-1; YAP, Yes-associated protein; PRR, Pro renin receptor; Ad-PRR, Adenoviruses-carried-PRR-gene; LXA4, Lipoxin A4; O-GlcNAc, O-linked *N*-acetylglucosamine; ROS, Reactive oxygen species; PKCβ, Protein kinase C β; PKB or Akt, Protein kinase B; PI3K, Phosphoinositide 3-kinase; PKR, Protein kinase RNA; IRE1, Inositol-requiring enzyme-1; BMP9, Bone morphogenetic protein-9; HMGB1, High-mobility group box 1 protein; TLR4, Toll-like receptor 4; TGF-β, *Transforming growth factor beta*; VEGF, Vascular endothelial growth factor; MAPK, Mitogenactivated protein kinase; HIF-1, Hypoxia inducible factor-1; DR, Diabetic retinopathy; miRNAs, microRNAs; T2D, Type 2 diabetes; DN, Diabetic nephropathy; *NF*-κB, Nuclear factor-κB; GPR120, G protein-coupled receptor 120; GPER, G protein-coupled estrogen receptor; TNF-α, Tumor *necrosis factor- alpha*; Nrf-2, Nuclear factor erythroid 2-related factor 2; JNK, c-Jun amino terminal kinase; BHB, β-hydroxybutyrate; HSPs, Heat shock proteins; GSK-3β, Glycogen synthesis kinase-3β; mTOR, mammalian target of rapamycin; ICAM-1, Intercellular adhesion molecule 1.

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of diabetes. This review assesses the newest researches about the key molecules and signaling pathways as targets of molecular pharmacology in diabetes and diseases related to it for better treatment based on molecular sciences. The disease is not cured by current pharmacological strategies for type 2 diabetes. While several drug combinations are accessible that can efficiently modulate glycemia and mitigate long-term complications, these agents do not reverse pathogenesis, and in practice, they are not established to modify the patient's specific molecular profiling. Therapeutic companies have benefited from human genetics. Genome exploration, which is agnostic to the information that exists, has revealed tens of loci that impact glycemic modulation. The physiological report has begun to examine subtypes of diseases, illustrate heterogeneity and propose biochemical therapeutic pathways.

1. Introduction

Diabetes is a progressive chronic condition with a high and rapidly growing occurrence; by 2030, the worldwide prevalence of diabetes is estimated to exceed 10.2% [1]. The progressive diabetes characteristic will cause vascular problems, such as cardiovascular and kidney sicknesses, particularly nephropathy, cardiomyopathy, and other difficulties, including cancer, neurodegenerative problems, and retinopathy [2–4]. The reduced life quality of diabetic patients and the disease's social and economic impact highlight the necessity to identify the causative factors of diabetes, which will eventually lead to the development of novel diabetes therapies [5]. The signaling and molecular pathways are the vital targets in the new therapies of diabetes. This review investigates the newest research about the key molecules and signal pathways as molecular pharmacology targets in diabetes and its diseases.

2. Molecular targets in cardiovascular and cardiomyopathy complications

A growing number of people are affected by diabetes and its vascular complications. This now-epidemic disease includes defects in both small and large blood vessels, both of which begin with changes in endothelial cell (EC) activities. Diabetic patients' cardiovascular disorders are a leading cause of death and disability. The pathological rise in glucose and the presence of advanced glycation end products (AGE) connected to plasma proteins, including lipoproteins, cause EC dysfunction (ECD) in diabetes. AGE proteins bind to particular receptors on the EC lipid bilayer, causing signaling pathways to be activated, resulting in reduced nitric oxide biocompatibility, enhanced intracellular oxidative and inflammatory stress, and ultimately EC disruption and apoptosis. In vitro, anti-oxidant substances were found to be effective in alleviating ECD. Unfortunately, intracellular anti-oxidants declined to boost the oxidative status and HDL activity, affecting HDL's protective effect in EC.

2.1. PPAR-related pathways in diabetic cardiomyopathy pathogenesis

The use of the gene-editing technique [CRISPR/(d)-CAS9] in vivo to regulate gene expression related to intracellular anti-oxidant proteins, especially those linked to HDL, may be an interesting method to expand EC function in diabetes in the future [6,7]. Diabetic patients have a higher incidence of cardiomyopathy than non-diabetic patients. Many molecular proceedings help to the expansion of diabetic cardiomyopathy (DCM), which are involved in the changes in the cell metabolism (glucose, fatty acid, branched-chain amino acids, and ketone) and the defects of subcellular constituents in the human heart, including reduced signaling of insulin, improved inflammation, and oxidative stress. A key transcription factor as titled Peroxisome proliferator-activated receptor α (PPARα) plays a key role in facilitating DCM-related molecular happenings. Pharmacological directing of PPARα stimulation is one of the most effective methods for diabetic patients. Metformin and glucagon-like peptide-1 (GLP-1) agonists are PPARα-associated medications that have confirmed their effectiveness and security in decreasing glucose and lipid in diabetic individuals throughout the clinical investigations [8]. Yes-associated protein (YAP) and Pro renin receptor (PRR) are also main proteins in diabetes-related cardiovascular diseases. Nevertheless, it has been revealed that PRR–YAP pathway can stimulate pathological damages in DCM by starting redox. Animal studies are split into three sections to study the effects of the PRR facilitated YAP system on the pathogenesis of DCM, such as the effects of PRR increased expression, RNAi of PRR silencing, and YAP RNAi suppressing. Ad-PRR-shRNA, Recombinant-adenoviruses-carried-PRR-gene (Ad-PRR), and YAP-shRNA carried by lentivirus have been built the influence of PRR interceded YAP on the DCM pathogenesis have been assessed. The inhibitor of YAP - Verteporfin - has also been directed in fibroblasts related to the heart to discover the influence of PRR–YAP way on oxidative stress and heart fibrosis. Furthermore, PRR upregulation can aggravate oxidative stress as severe and fibrosis of myocardial in DCM condition, and these pathological variations can be improved by YAP inhibition. Thus, PRR–YAP key pathway has a key role in DCM pathogenesis [9].

2.2. Inflammatory mechanisms in diabetic complications

Since inflammatory mechanisms play a role in diabetic complications, such as atherosclerosis, resolving this chronic inflammation may be beneficial. For example, lipoxin A4 (LXA4) is an endogenous inflammation facilitator [10]. In diabetic mice, cure with LXA4 factor has decreased expression markers related to inflammatory conditions such as IL-6 and IL-1β, reducing aortic plaque expansion. Since the drug application was atheroprotective in diabetic mice with the proven disease, this offers pharmacological modulation of inflammation as an efficient treatment approach in diabetic cardiovascular events [11].

2.3. Protein O-GlcNAcylation in diabetic complications

The alteration of post-translational of threonine and serine residues of molecules by O-linked *N*-acetylglucosamine (O-GlcNAc) normalizes different cellular procedures for the cardiovascular organization. UDP-GlcNAc – a key goal of O-GlcNAc transferase- regulates the connection of O-GlcNAc to protein molecules. It catalyzes the elimination of O-GlcNAc from protein. UDP-GlcNAc is the final material of the biosynthesis process of hexosamine, which is controlled mainly via glucose-6-phosphate-Glutamine molecules: the enzyme of fructose-6-phosphate amidotransferase (GFAT). GFAT is the catalyzing enzyme of the creation of glucosamine-6-phosphate from glutamine and fructose-6- phosphate. Although O-GlcNAc is crucial for the cell's viability, continued improvements in O-GlcNAc rates have been concerned with the etiology of several chronic illnesses related to glucose poisonousness and diabetic problems in numerous organs specially the heart. Growing cardiac O-GlcNAc rates alone may be adequate to summarize the negative diabetic properties on the heart, according to a limited but rising number of studies; but a lessening of O-GlcNAc in the diabetes situation reduces these special effects, increases cardiac and vascular act. Therefore, directing O-GlcNAc rates as a therapeutic method for handling diabetic difficulties is possibly a fascinating subject [12–15].

2.4. Role of reactive oxygen species (ROS) in development of diabetes

Oxidative stress is one of the main (and probably initial) factor that helps to the growth and development of diabetes. Strategies to decrease the production of Reactive oxygen species (ROS), or increase its degradation, for example with anti-oxidant function, may be a defensive in contradiction of diabetes prompted cardiac defect. Particular inhibitors or gene-aimed treatment target at either reducing protein-related signaling complicated in hypertrophy (e.g., protein kinase C β (PKCβ)) or augmenting the expression of cardio-defensive ways (e.g., Phosphoinositide 3-kinase (PI3K) (p110α)) may characterize new approaches for the management of diabetic cardiomyopathy in treatment [16]. In ROS-mediated Endoplasmic reticulum (ER) stress-stimulated myocytes apoptotic futures in DCM, the triggering of protein kinase RNA (PKR)-similar ER kinase (PERK) signaling molecular pathways take the lead instead of inositol-requiring enzyme-1 (IRE1) or stimulating transcription factor-6 (ATF6) signaling [17].

3. Molecular improvement of wound healing and regulation of inflammatory responses in diabetes

BMP9 (bone morphogenetic protein-9) has been discovered to be a new accelerator in the healing of diabetic cutaneous wounds. Patients with diabetic foot have slightly lower circulating BMP9 levels, while there are no significant discrepancies in serum levels between unaffected patients and patients with diabetes without chronic wounds in either type 1 or type 2 diabetes. BMP9 enhances skin repair by directly stimulating dermal fibroblasts and keratinocytes via the Smad signaling pathway and cytoskeleton remodeling [18]. High-mobility group box 1 protein (HMGB1) is essential in diabetes and its complications as a damage-associated molecular template molecule. The findings show that diabetic keratopathy progresses in mice throughout their diabetes, with common symptoms such as weakened ocular surfaces and corneal nerves. The corneas in diabetes considerably raise expression levels of HMGB1 protein and its related receptors—the receptor for advanced glycation end materials and toll-like receptor 4 (TLR4). In brief, HMGB1 and its receptors are highly complicated in the expansion of keratopathy in diabetes. This shows that the inhibition of HMGB1 may apply as an approach to prompt corneal in diabetes and wound healing related to the nerve [19].

Molecular targets in diabetic complications have been shown in Fig. 1:

Hesperidin (hesperetin-7-rhamnoglucoside) is a vital plant flavonoid plentifully current in a diversity of citrus types such as *Citrus aurantium*. Studies have revealed hesperidin has many biological roles, such as anti-inflammatory, anti-diabetic, anti-ulcers, anti-oxidant, antifungal, anti-viral, hepatoprotective, anti-atherogenic, anti-hypertensive, and anti-cancer [20–22]. Treatment with hesperidin enhances wound healing in chronic diabetic foot ulcers by upregulating the expression of *Transforming growth factor-beta* (TGF-β), Small mothers against decapentaplegic (Smad-2/3), Vascular endothelial growth factor-c (VEGF-c), and Angiopoietin-1 (Ang-1)/Tie-2 mRNAs [23]. It has been confirmed that in the human umbilical vein endothelial cells (HUVECs), Cinnamaldehyde (CA) induces migration, proliferation, and tube creation. CA also stimulates the mitogen-activated protein kinase (MAPK) and PI3K pathways. Also, the secretion of VEGF from HUVECs is augmented

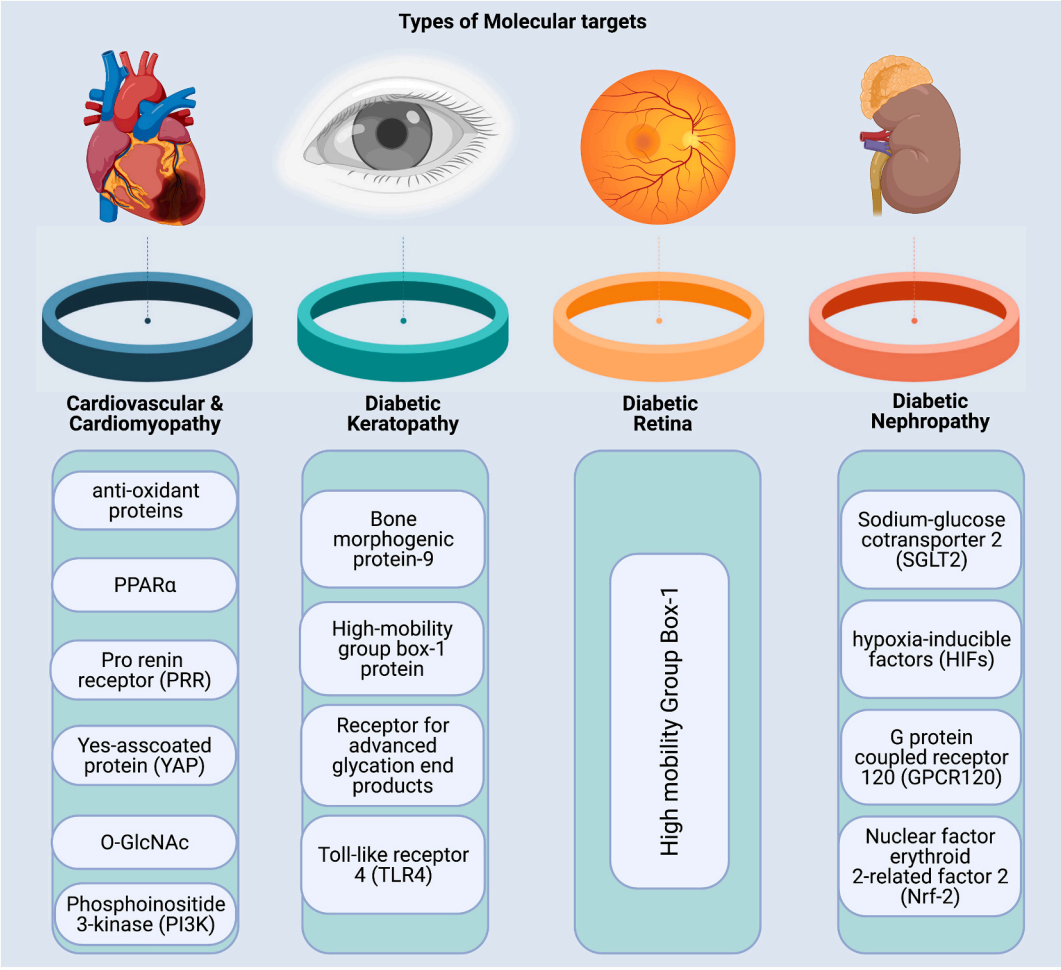

Fig. 1. Molecular targets in diabetic complications. Created with Biorender.com.

through CA. CA also quickens wound healing in diabetes by prompting angiogenesis in the wound zone. This molecule may be used in clinical investigations for stimulating beneficial angiogenesis in long-lasting diabetic wounds [24]. The suppression of hypoxia-inducible factor-1 (HIF-1) stimulation by diabetes throughout pulmonary *Aspergillosis* disease is tenacious and helps to a severe inflammatory response with fatal significances. HIF-1 induction, both early and long-term, decreases inflammatory response and defends diabetic mice against pulmonary infection types, signifying an excellent therapeutic plan [25]. HMGB1 expression is upregulated in the membranes of epi-retinal and vitreous liquid from individuals with progressive diabetic retinopathy (DR) and in the diabetic retina, which activates inflammatory, apoptotic angiogenic signaling molecules as well as the break of the blood-retinal barrier in the retina. Hindering the HMGB1 release with continuous glycyrrhizin intake decreases diabetes-stimulated high expression of angiogenic and inflammatory signaling pathways. Thus, compounds hindering HMGB1 may be new helpful agents for diabetic retinopathy disease [26,27].

4. Molecular pharmacology in diabetes and related diseases

Endothelial function maintenance as a way of avoiding diabetic microangiopathies is a significant therapeutic problem for all health systems around the world. Many ways create endothelial dysfunctions (ED) in diabetic cases, often cross-talking each other: augmented ROS creation, mitochondrial defect, stimulation of polyol way, production of AGEs, triggering PKC, endothelial apoptosis, and microRNAs (miRNAs) dysregulation. Metformin is a game-changer in the treatment of type 2 diabetes (T2D). Among these patients, it is still the first-choice medication. Surprisingly, metformin has been found to have some extra-glycemic effects recently, with large preclinical and clinical findings supporting its efficiency against ED in T2D. AMP-activated protein kinase (AMPK) pharmacologic stimulation is a key factor, with metformin hindering inflammation and improving endothelial dysfunction [28].

Rhizoma coptidis (*R. coptidis*) is a vital herbal drug and has been broadly applied to cure diabetes for many years. It has been showing that *R. coptidis* is an antidiabetic agent chiefly via biological procedures and pathways, including steroid binding, hormone receptor action, etc. In vitro investigates have also presented that its extract hinders α-amylase and α -glucosidase and the production of AGEs; temporarily, the extract stimulates glucose absorption via adipocytes [29]. Diabetic nephropathy (DN) is a typical diabetic problem. In DN patients, the Yishen capsule, which is made up of Chinese herbs, helps the clinical outcome. Yishen capsule dismisses pathological alterations, declines urine protein, augmented the expression of LC3-II, SIRT1, and Beclin-1, and decreases acetylated Nuclear expression factor-κB (*NF*-κB) in vivo. Thus, Yishen capsule recovers DN by stimulating autophagy of podocytes by the SIRT1/*NF*-κB key pathway [30–34].

In the diabetic kidney, sodium/glucose cotransporter 2 (SGLT2) inhibitors have a significant renoprotective impact. These medications act on hypoxia-inducible factors (HIFs; especially, HIF-2α and HIF-1α), which may trigger their capability to decrease nephropathy development. Renal hypoxia, oxidative stress, and nutrient depletion signaling defects are all associated with type 2 diabetes, and they all can activate HIF-1α while suppressing HIF-2α. This alteration in the stability of HIF-1α/HIF-2α actions stimulates pro-fibrotic and pro-inflammatory pathways in glomerular cells. SGLT2 inhibitors reduce renal hypoxia and cellular stress while also improving nutrient deficiency signaling, which may clarify how they inhibit HIF-1α and activate HIF-2α, boosting erythropoiesis while reducing organellar defects, inflammation, and high fibrosis. Cobalt chloride, known as a hypoxia mimetic, has a molecular and cellular profile in the kidney close to SGLT2 blockers. As a result, many of SGLT2 inhibitors' renoprotective effects can be due to their ability to stimulate the signaling of oxygen deprivation in diabetic kidneys [35]. G protein-coupled receptor 120 (GPR120) agonist -TUG-891- in DN cases effectually regulates GPR120 high expression and decreases TAK1-binding protein expression along with the phosphorylation of NF-κB p65, MAPK p38, IKKβ in mice. Reduced expression of GPR120 in murine *podocyte* cells (MPC5) is also producing the conflicting properties of TUG-891. Consequently, triggering GPR120 in podocytes improves fibrosis and renal inflammation to defend against DN [36].

Myricitrin (Myr) - a glycosyloxyflavone related to *Myrica esculenta bark*- has shown an important hypoglycemic influence in great fat-fed and a particular little-dose streptozotocin-stimulated type 2 diabetic (T2D) rats. Myr has also been discovered to recover glucose absorption via the skeletal muscle and stimulating insulin receptor substrate-*1* (IRS-1)/Protein kinase B (*PKB* or Akt)/PI3K/Glucose transporter type 4 (GLUT4) signaling pathways in vivo and in vitro. The anti-diabetic drugs affecting the PI3K/AkT/PKB signaling pathways have been illustrated in Fig. 2. In the kidneys of T2D rats, Myr greatly decreases the toxicity caused by high glucose (HG). Myr has also been revealed to decrease diabetes-activated renal inflammation through inhibiting NF-κB stimulation. It hinders hyperglycemia-prompted fibrosis and apoptosis in renal cells, proven by the alterations in the fibrotic and apoptotic agents' expressions. Generally, Myr is a possible therapeutic agent for DN in future researches [37]. Several receptors facilitate estrogens' activities in the body, such as the conventional nuclear estrogen receptors (ER β and α) and the G protein-coupled estrogen receptor (GPER). Via its properties on metabolic organs, GPER controls fat spreading, body weight, homeostasis, and inflammation. In several murine models, GPER's agonist, G-1, can relieve indications of obesity and metabolic defect that leads to diabetes, reducing insulin resistance and inflammation, and refining in vivo glucose homeostasis. So, GPER characterizes a new therapeutic goal, with G-1 an initial-in-class beneficial agent in treatment, to cure diabetes [38]. In rats, SCO-792 raises fecal protein and enhances glycemic regulation as an enteropeptidase (a gut-decreased serine protease controlling protein digestion) blocker. It also reduces inflammation, fibrosis, and tubular damage indicators in the kidneys while normalizing the high glomerular filtration. Besides that, autophagy function in the glomerulus is increased in SCO-792-cured rats, which is decreased in diabetic kidney disease (DKD) [39].

Ginkgo biloba extract (GbE) - a plant drug- is utilized as a cure for DN. In DN mice, it enhances renal action via lowering glomerular hypertrophy and the kidney to body weight proportion. GbE also attenuates the augmentation of IL-6, tumor *necrosis factor-alpha* (TNF-α), and fibronectin in DN mice. In high glucose-induced podocytes, this medication inhibits the absorption of oxidized low-density lipoprotein and decreases ROS development. Nuclear factor erythroid 2-related factor 2 (Nrf-2) siRNA considerably decreases the beneficial properties of GbE by increased IL-6 and TNF-α expression rates. GbE defends podocyte cells from hyperglycemia and inhibits the onset of DN by activating Nrf-2. The results suggest that GbE may be used to gain further insight into its potential as a therapeutic agent in clinical DN [40]. Fucoidans - complex polysaccharides obtained from brown seaweeds - have many bioactive features. Among Fucoidan key activities, its anti-diabetic possessions have established the most research consideration in the past years [41,42]. The PI3K/PKB pathway, which controls insulin production, has been activated by Fucoidan [43]. Translocation of GLUT4 is also caused. In mice, some fucoidans decrease blood glucose and increase insulin sensitivity while lowering basal lipolysis in adipocytes, potentially lowering hyperglycemia through absorption of glucose [44,45]. Plant extract of *Hippophae rhamnoides* normalizes blood glucose via the PI3K/Akt pathway.

Furthermore, *Rosmarinus officinalis* extract inhibits NF-κB and c-Jun amino-terminal kinase (JNK) pathways, stimulating insulin resistance. Fatty acids oxidation and Lipogenesis, which are also related to the insulin resistance process, are planned by AMPK signaling pathway stimulation through *Helminthostachys zeylanica* extract [46]. Liraglutide - human GLP-1 analog - reduces the IL-1β, NF-κB, and TNF-α expression in diabetic mice. According to the present findings, Liraglutide can meaningfully recover hepatic steatosis, mainly via decreasing the key

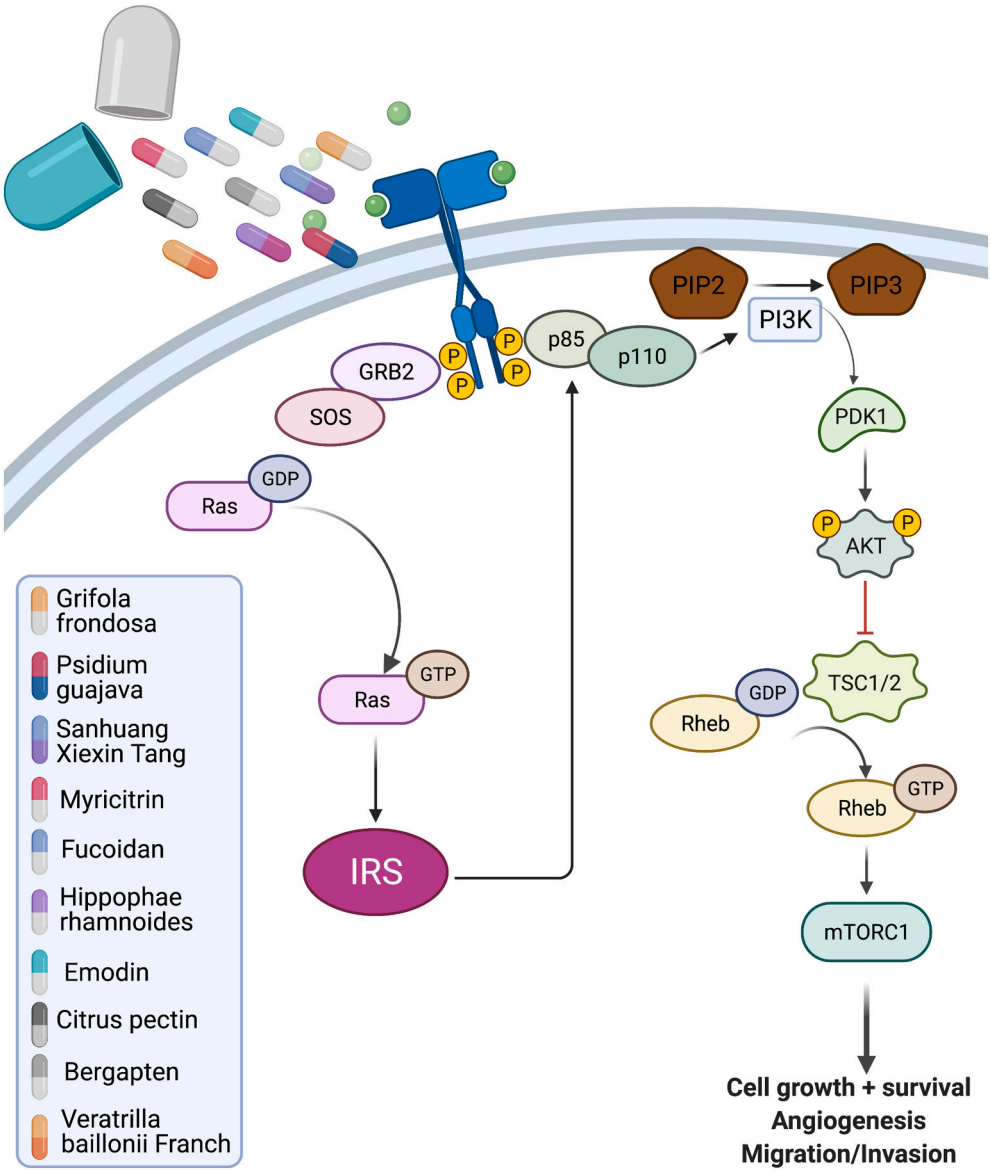

Fig. 2. Anti-diabetic drugs affecting PI3K/AkT/PKB pathway. Created with Biorender.com.

inflammatory mediator's expression in the TNF-α pathway; therefore, it recovers non-alcoholic fatty liver problem in mice with diabetes [47,48]. *Auricularia polytricha* (AP) and *Auricularia auricula* (AA) are prevalent eatable fungi. Their anti-diabetic roles may comprise the NF-κB and related pathways (as NF-κB actions at the crossroads of pathways number) [49].

Plantamajoside (PMS) is a phenylpropanoid glycoside that has an anti-diabetic effect. The results have shown that PMS improves the cell damage prompted by high glucose in HBZY-1 cells as titled rat glomerular mesangial cells. The evaluations have verified an anti-inflammatory action of PMS, as showed by diminished levels of TNF-a and IL-6 in these cells. Moreover, PMS pointedly inhibits high glucose-stimulated acts of NF-κB/Akt signaling in HBZY-1 mentioned cells. Thus, PMS may be a potential agent with the cure DN's ability [50]. The key factor of ketone bodies, β-hydroxybutyrate (BHB), has been newly considered a biologically potential molecule with many helpful characters, especially in diabetes [51]. BHB cure suppresses histone deacetylase-3, resulting in a rise in acetylated H3K14 rates in the Claudin-5 promoter, which helps to 'turn on' claudin-5 development and reduces diabetic heart microvascular problems. These findings can offer valuable proof for BHB's cardiovascular-protective properties, making its clinical use easier [52]. Expression of senescence proteins including p16INK4a, p53 and p21Cip1/WAF are repressed meaningfully in T2D by metformin.

Metformin prevents Senescence-associated secretory phenotype (SASP) by suppressing IKK/NF-κB function [53–55]. AMPK is triggered within the cell in response to many stresses that raise the intracellular AMP/ATP proportion. An amount of the useful impacts of the thiazolidinediones can be facilitated via stimulation of AMPK. Metformin stimulates AMPK in the nonappearance of any growth in the AMP/ATP proportion. Therefore, anti-diabetic drugs of rosiglitazone and metformin act via prompting AMPK [56]. Zn deficiency is linked to the development of several chronic diseases, including diabetes. Zn has insulin-similar possessions and triggers the insulin-related signaling by the Akt/PKB pathway, which finally leads to improved cellular glucose absorption. Zn has also been shown to influence epigenetic control and autophagy, proposing a novel mechanism for Zn's advantageous effects on DN. Nevertheless, the therapeutic efficiency of Zn on inhibition and curing diabetic problems remains to be recognized, which licenses next clinical studies [57,58]. Cure with cannabidiol is capable to reduce the nitrative-oxidative stress (lessening the cardiac ROS production) and changes of the pro-survival related to Akt and stress-related pathways

molecules (JNK and p38) in the diabetic heart. It also reduces the NF-κB stimulation, TNF-a and ICAM-1 expression, death of cells, fibrosis in cardiac diabetes, and recovers the related typical practical changes. Therefore, this drug may have tremendous beneficial probable effect in diabetic cardiovascular treatment [59].

The anti-diabetic therapeutic impact of *Ecklonia cava*, a brown alga, in type 1 diabetes is made by stimulating both PI3K/Akt and AMPK signaling key factors [60]. Genistein, a flavonoid found in legumes and several herbal medicines, can act as a natural anti-diabetic by activating the cAMP/PKA-related extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway, which regulates pancreatic beta cell activity [61]. Results show that Dendrobium officinale polysaccharide (DOP) can knowingly hinder the glucagon-facilitated cAMP-PKA pathway. This polysaccharide also promotes hepatic glycogen synthesis by increasing the expression of glycogen synthase and decreasing the expression of glycogen phosphorylase, as well as inhibiting hepatic glycogen destruction in diabetic mice. For the meantime, DOP can reduce the expressions of phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, which will hinder cellular gluconeogenesis by the glucagon-facilitated Akt/FoxO1 signaling in diabetic mice. As a result, DOP will enhance hepatic glucose metabolism by increasing hepatic glucose consumption and decreasing hepatic glucose intake, ultimately helping to relieve hyperglycemia in T2D mice [62].

Agonists for the serotonin 2C receptor (5-HT2CR) increase glucose tolerance and decrease blood insulin levels in T2D mice. These impacts on glucose homeostasis need melanocortin-4 receptors (MC4Rs) downstream stimulation, but not MC3Rs. These findings propose that aiming 5-HT2CRs may increase glucose tolerance without weight changes and

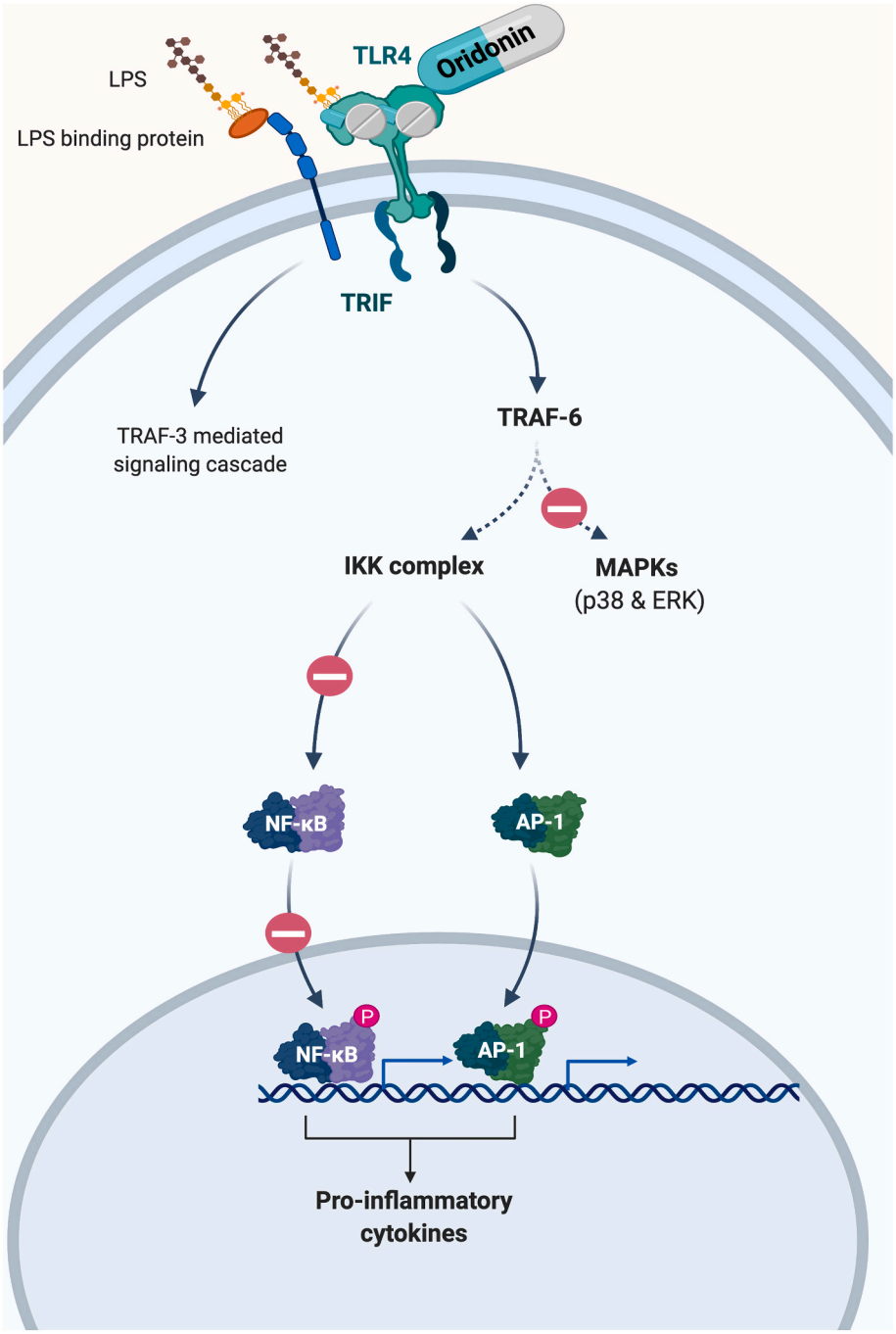

Fig. 3. Anti-diabetic drugs affecting PI3K/AkT/PKB pathway. Created with Biorender.com.

that this may demonstrate a new approach in the treatment of T2D [63]. Heat shock proteins (HSPs) are molecular chaperones that regulate protein folding and are caused by cellular stress. Many HSPs, including HSP70 and HSP90, which are the main controllers of pathological mechanisms complicated in diabetes problems, are affected by diabetes. Cure of diabetic mice with 17-dimethylaminoethylamino-17-demethoxygeldanamycin (DMAG) recovers renal action. Besides, DMAG considerably decreases atherosclerotic injuries. The anti-atherosclerotic and renoprotective impacts of DMAG are facilitated by the stimulation of defensive HSP70 accompanied by NF-kB inactivation and signal transducers and activators of transcription (STAT) and aim genes expression, both in diabetic mice and in many cells under hyperglycemic situations. In experimental diabetes, HSP90 repression by DMAG slows renal and vascular damage progression, which could have implications for diabetes problem prevention [64]. Gymnemic acid obtained from *Gymnema sylvestre* has been shown to have an anti-hyperglycemic function; nevertheless, it increases the PI3K expression and glycogen production and stimulates the Akt phosphorylation while decreases the glycogen synthesis kinase-3β (GSK-3β) expression in T2D rats. Furthermore, in Gymnemic acid-cured T2D rats, key proteins complicated in AMPK-facilitated gluconeogenesis are expressed lowly. Briefly, the hypoglycemic effects of Gymnemic acid may be associated with stimulating signal transduction of insulin and stimulating AMPK- and PI3K/Akt-mediated pathways in T2D rats [65,66].

Oridonin, a component obtained from *Rabdosia rubescens*, has several notable immunoregulatory, anti-inflammatory, and anti-tumor functions (Fig. 3). It pointedly recovers inflammatory cell infiltration, especially in the kidney, and decreases cytokine levels such as TNF-α and IL-6, both in vivo and in vitro. TLR4 is a major facilitator of innate immune and responses related to the inflammation expansion in DN. Oridonin administration substantially reduces TLR4 expression in DN, according to molecular studies. The results also have exhibited that Oridonin suppresses the phosphorylation of p65 and p38 and NF-κB DNA-connecting action. Indeed, these results may be ascribed to Oridonin and other components such as Wogonin and Urtica dentata anti-inflammatory and regulatory properties on the TLR4/p38-MAPK and TLR4/NF-κB key pathways [67–72].

In diabetic rats, administration of caffeic acid hexyl (CAF6) and dodecyl (CAF12) amide compounds raises retinal superoxide dismutase action. CAF6 and CAF12 have also been shown to have neuroprotective properties in the DR animal models. These mechanisms appear to be mediated by (a) increased anti-oxidant function in diabetic retinal tissue through the anti-oxidant enzyme superoxide dismutase, (b) avoiding ERK high stimulation in retinal tissue, and (c) activation of AKT signaling pathways to promote retinal neuron survival and development. As a result, these compounds' neurotrophic properties may hold great promise to produce new therapeutics for DR and other diabetic abnormalities [73]. The diabetes-associated osteoporosis knowingly increases the triggering of the NF-κB, JNK/MAPK, and PI3K/AKT pathways and enhances the expression of related factors. Bergapten has been demonstrated to repress the stimulation of the PI3K/AKT/mammalian target of rapamycin (mTOR), NF-κB, and JNK/MAPK pathways, thus defending trabecular construction and reducing bone tissue differentiation. This constituent can also decrease collagen's injury by its function [74].

Psidium guajava is a small plant or tree cultured in hot and subtropical areas everywhere the world. *Psidium guajava* reduces the total cholesterol, free fatty acid, phospholipids, and LDL and enhances HDL. It noticeably stimulates Akt, PI3K, p-Akt, GLUT2 – *Psidium guajava* enhances the GLUT-2 translocation from cytoplasm to the cell membrane. Here, AMPK and p-AMPK, as the PI3K/Akt pathway key effector agents in streptozotocin injected diabetic rats, have the main role; finally, hepatic gluconeogenesis will be inhibited [75]. Deep seawater (DSW) has beneficial properties on cardiac apoptosis and hypertrophy prompted by hypercholesterolemia. The phosphorylation rates of the TNF-α-regulated downstream factors and P38 MAPKs are particularly increased in diabetic heart tissues. These greater phosphorylation rates consequently increase NF-κB-regulated inflammatory agents. Treatment with DSW and MgSO4, the key mineral in DSW, has been shown to reduce myocardial hypertrophy. DSW may have therapeutic potential in the prevention of diabetes-related cardiovascular diseases, according to available results [76].

Emodin is the active ingredient in rhubarb, a Chinese drug with a wide range of pharmacological effects and a high therapeutic value. Treatment with this component pointedly inhibits inflammation-associated proteins and oxidative stress process, represses the B-cell lymphoma 2-associated X protein (Bax) and intercellular adhesion molecule 1 (ICAM-1) expression, enhances p-GSK-3β and p-Akt expression, and suppresses caspase-3 action in diabetic rats. Thus, it is obvious that emodin defends against DN and that the fundamental process may include the repression of inflammation, Bax and ICAM-1, and stimulation of the PI3K/Akt/GSK-3β key pathway [77]. Isosteviol sodium prevents the cardiomyopathy-initiated promotion of both NF-κB and ERK pathways in diabetic patients. These results show that Isosteviol sodium may be advanced into a potential treatment for diabetic cardiomyopathy that its process includes the repression of inflammation and oxidative stress by hindering NF-κB and ERK without altering AGEs or blood glucose [78].

Grifola frondosa, a beneficial medicinal mushroom variant, is commonly eaten as traditional drugs and health nourishments in Japan and China. It is one of the herbal medicines conventionally utilized for curing inflammation, diabetes and cancer. Its bioactive composite has anti-diabetic properties via the repression of ROS creation, high expression of glucose uptake, and regulation of MAPKs, PI3K/Akt, and GLUT-4 signaling pathways. Therefore, *G. frondosa* can apply as a prospective candidate for clinical application in refining T2D [79,80]. Sanhuang Xiexin Tang (SXT), a typical medicament, has been clinically utilized to treat diabetes for many years. The expression of Akt, PI3K, GLUT4 mRNA, and their protein complicated in the PI-3 K/Akt signaling of T2D is distinctly regulated via SXT application [81].

The anti-insulin resistance and anti-diabetic impacts of *Coriolus versicolor* extract in myoblast cells (L6 cells) and muscle of T2D rat display enhancement of insulin resistance translocation and GLUT4 protein expression in skeletal muscle, in which both p38 MAPK and PI3K/Akt pathways are complicated. Consequently, this extract may be used as a promising drug for curing T2D when involved in infectious diseases or cancer [82]. Citrus pectin increases hepatic glycogen production, glucose tolerance, and blood lipid levels in T2D rats used as an anti-diabetic drug. It also decreases high insulin resistance. Furthermore, after the pectin cure, Akt protein expression is increased, and expression of GSK3β is decreased, representing that the probable anti-diabetic process of pectin may happen via regulation of the PI3K/Akt. Overall, the results suggest that this citrus can improve T2D and possibly be utilized as an adjuvant cure [83].

Veratrilla baillonii Franch (VBF) is broadly consumed as tea or drug for preventing and treating many complaints in the minority zones of Southwest China. VBF decreases the injuries of kidneys and liver in diabetic mice. The results show that IRS1/PI3K/AKT pathway is complicated in the anti-diabetic action of VBF. This proves that *V. baillonii* can be a beneficial candidate for increasing research about its novel anti-diabetic impacts [84]. Timosaponin B-II (TB-II), a significant steroidal saponin component, has many anti-inflammatory and hypoglycemic properties. TB-II reduces the blood glucose rates and improves renal damage in an alloxan-stimulated diabetic animal model. Also, TB-II hinders the mTOR, thioredoxin-cooperating protein, and NF-κB expression, and these impacts have a vital role in recovering DN [85].

Tanshinone IIA (TSN IIA) is one of the most bioactive constituents of traditional Chinese herbal medicine, and it is widely used in China to treat cerebrovascular and cardiovascular diseases. It has been confirmed that TSN IIA improves neuropathic ache by triggering the Nrf2/anti-oxidant response elements (ARE) pathway and preventing the NF-kB pathway [86] similar to Oleanolic acid [87] in diabetic rats. Naringin

is a flavanone glycoside present in a wide variety of fruits, including grapes and citrus. According to pharmacokinetics studies conducted on rats, this glycoside and its metabolites, which are extremely lipophilic, are rapidly distributed to body organs such as the stomach, kidney, and liver after oral administration. Hindering the JNK/MAPK and ERK1/2 pathways is a new potential mechanism by which Naringin improves renal fibrosis in vitro in diabetes [88]. Fig. 4 illustrates the anti-diabetic drugs affecting JNK, ERK and p38/MAPK signaling pathways.

D-pinitol -a composite obtained from *leguminosae* and *pinaceae* herbal drugs- has a positive character in the regulation of insulin facilitated glucose absorption in the liver via PI3K/Akt pathway activation in rats with T2D [89]. Ginsenoside Rg5 (Rg5) is a key monomer in the

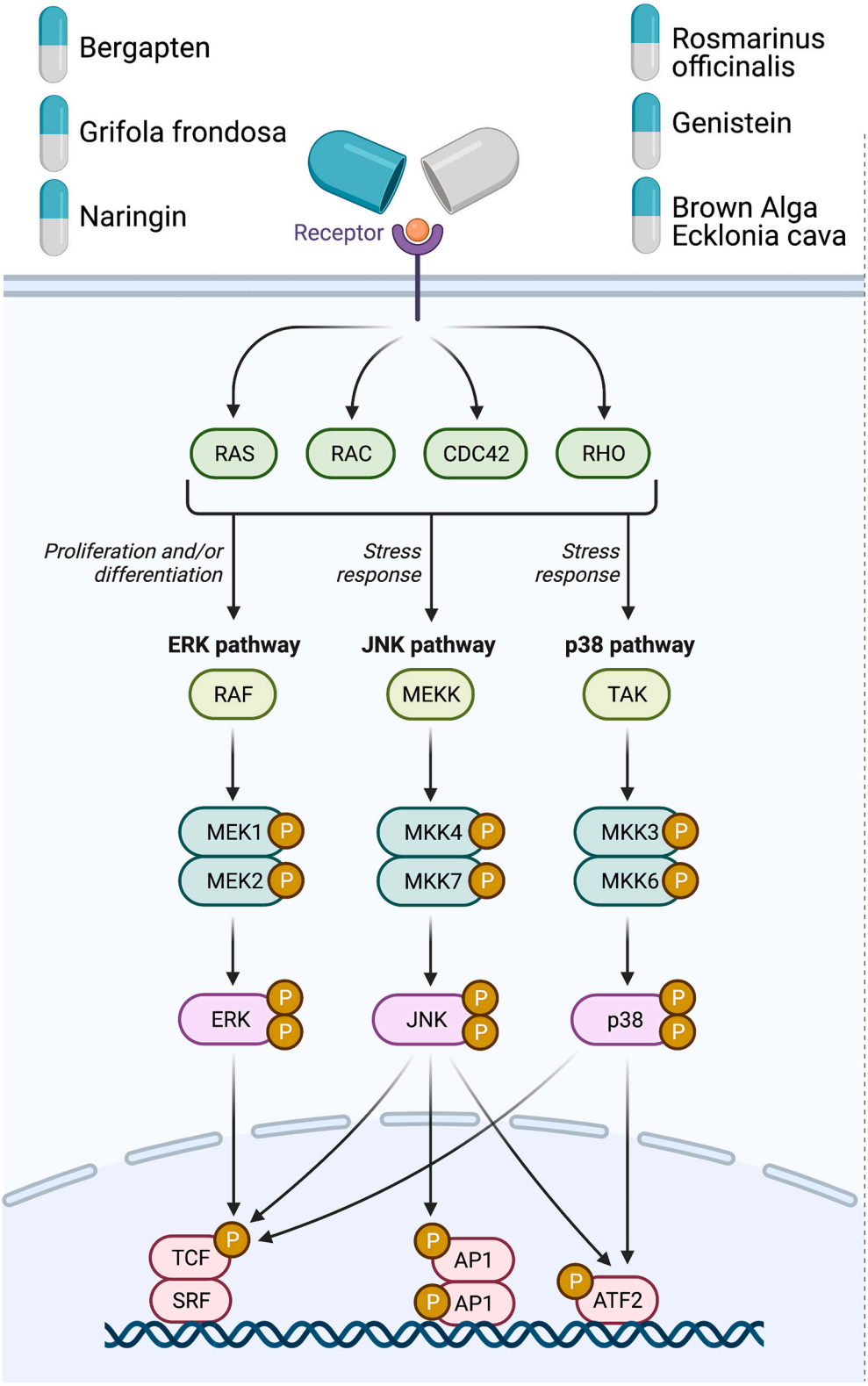

Fig. 4. Anti-diabetic drugs and their target signaling pathways i.e., ERK, JNK and p38/MAPK pathways. Created with Biorender.com.

important protopanaxadiol constituent of black ginseng. The development of ROS and the expression of oxidative stress indicators in DN mice's kidneys decreases after curing with Rg5. Moreover, the IL-1β and IL-18 expression as inflammatory cytokines are repressed, and the NF-kB expression and the p38 MAPK phosphorylation are decreased with Rg5 cure in DN mice [90]. Rk3 (G-Rk3), another Ginsenoside, is one of the most active ingredients in ginsenosides. It improves T2D mice by mediating hepatic gluconeogenesis by stimulating the AMPK/Akt pathway [91]. Liuwei Dihaung decoction is a famous typical traditional Chinese medication. It can mediate insulin resistance by PI3K/Akt pathway regulation in T2D rats [92].

Curcumin, the main polyphenol from the *Curcuma longa* frequently recognized as turmeric, has been investigated to have renoprotective impacts on DN. It has been confirmed that the sphingosine kinase 1-sphingosine 1-phosphate (SphK1-S1P) pathway plays a way with a key role in the DN. Moreover, curcumin suppresses the DNA-connecting action of activator protein 1 (AP-1). Furthermore, low expression of the SphK1-S1P is a new process by which curcumin recovers DN's development. Curcumin's therapeutic targets for modulating the SphK1-S1P signaling pathway include inhibiting AP-1 stimulation and preventing renal fibrosis in diabetes [93]. Sitagliptin as an inhibitor of dipeptidyl peptidase-4 has been described to stimulate cardiosafety in diabetic patient's heart by decreasing hyperlipidemia and hyperglycemia. Its function is via decreasing expression of the Janus kinase (JAK)/STAT pathway factors [94]. Tocochromanols are a class of compounds that have vitamin E activity and are necessary for human nutrition. These composites, particularly tocotrienol, not only decrease the diabetic situation but also converse cognitive defects via regulation of TNF-α-prompted NF-κβ pathway and caspase-3 in the rats with diabetes and therefore it may obtain clinical request to cure neuronal defects in the diabetes [95]. Punicalagin, which is mainly in the peel of the pomegranate, is the key pomegranate polyphenols constituent. Punicalagin has been revealed in previous studies to have anti-tumor, anti-oxidant, anti-inflammatory, and other biological properties. Punicalagin defends versus liver damage prompted by T2D via reinstating autophagy via the Akt/FoxO3a pathway [96].

5. Diabetic kidney disease and molecular therapy

Pyruvate kinase catalyzes phosphoenolpyruvate (PEP) conversion to pyruvate, the final and physiologically unavoidable stage in glycolysis. PKM2 is an enzyme isoform found mainly in cancerous cells, embryonic tissue, and several normal adult tissues [97]. The DKD mice have upper rates of the PKM2dimeric type in comparison with the non-diabetic animal. Oppositely, repression of Sirtuin 3 (SIRT3) factor is related to DKD fibrosis through stimulation of TGF-β/Smad pathways (This signaling pathway is also essential in other studies on diabetes [98,99]) and related to augmented PKM2 [100]. This proposes that PKM2 may be the aim for DKD cure [101]. Disulfide-bond A oxidoreductase-like protein (DsbA-L) is a crucial factor in adiponectin interrelating protein with very high adipose expression. The axis of adipo-renal includes signaling factors that are employed to regulate the human kidney act. The high expression of DsbA-L in the mice adipocytes can defend against renal damage in diabetes by anti-inflammatory factors and may be arbitrated by the adipo-renal fundamental axis [102].

Furthermore, BI-2536 - an inhibitor of polo-like kinase 1 (PLK1) - reduces the Smad3 and NF-κB signaling pathways in DKD. This proposes that the BI-2536 can be examined as a new treatment for DKD [103]. Studies have shown that the YWDHNNPQIR peptide (titled RAP), a peptide obtained from a protein as titled rapeseed, has an anti-oxidative impact that is a critical process in DN. RAP concurrently decreases extracellular matrix gathering in mice of DN. Additionally, RAP decreases high glucose-stimulated cell growth. RAP can reduce DN fibrosis in vitro and in vivo by antagonizing the NF-κB and MAPK signaling factors. Therefore, RAP is anticipated to be planned as a leading composite for medications to treat renal fibrosis associated with DN [104].

6. The molecular investigations in diabetic retinopathy

In diabetes, the retina is exposed to more oxidative stress, and the transcriptional activity of Nrf2, which is essential for regulating many anti-oxidant genes, is reduced. The intracellular inhibitor Keap1 mediates the nuclear movement transcriptional function of Nrf2, which is a crucial biomarker, and retinal Keap1 levels are elevated in diabetes. A long non-coding RNA (LncRNA) as titled LncRNA *MALAT1* modulates anti-oxidant protection in diabetic retinopathy via Nrf2- Keap1 factors. Prohibition of LncRNA *MALAT1* has a possible role in defending the retina from oxidative injury and inhibits diabetic retinopathy development [105–107]. Moreover, in diabetic retinopathy, erythropoietin defends the inner blood-retinal barrier via hindering microglia phagocytosis rate by Src/Akt/cofilin key pathway in vitro examination. This emphasizes erythropoietin's therapeutic properties for curing retinopathy in diabetes [108].

7. miRNA studies in diabetes

The vital roles of prostaglandin E receptor 3 (PTGER3) low expressions and MMP-2 high expressions in the kidney tissue from DN patients have been verified. They are controlled by lncRNAs (such as LINC00960 and RP11-363E7.4) and miRNAs (including hsa-miR-1237-3p and hsa-miR-106b-5p) that have been infrequently described in DN. These regulatory disorders may be the defense process in contradiction of renal damage following diabetes [109]. In the rat model of diabetic retinopathy, miR-199a-3p suppresses retinal pericytes and endothelial cell migration, proliferation, and invasion by directing fibroblast growth factor 7 (FGF7), suppressing the stimulation of the PI3K/AKT/Epidermal Growth Factor Receptor (EGFR) signaling pathway [110]. LncRNA XIST eases the invasion, proliferation, and migration and represses the apoptosis process through SMAD2/miR-34a axis in diabetic cataract problem; therefore, XIST knockdown represses cell proliferation and growth and also induces apoptosis in cataract via the SMAD2 central axis [111]. Occlusion is a primary aim of miR-132, modulating cell mobility and viability under high glucose situation via the JAK/STAT3 pathway.

Researchers have discovered that great glucose-cured human ARPE-19 cells related to retinal epithelium display miR-132 enhanced expression, reduced expression of the tight-junction factors such as E-cadherin Occludin, and augmented cell permeability and mobility. Therefore, aiming to impact miR-132 on Occludin and the JAK/STAT3 signaling pathway can characterize a new actual diabetic retinopathy-therapy approach [112]. miR-34c has been observed to prohibit fibrosis and the transition of mesenchymal-epithelial of kidney cells.

Moreover, miR-34c high expression enhances the anti-apoptotic Bcl-2 gene expression, reduces the pro-apoptotic Bax protein expression, and cuts Caspase-3. Taken together miR-34c high expression suppresses the Notch pathway through directing Jaggged1 and Notch1 in high glucose-cured cells, demonstrating a new and beneficial therapeutic aim for the diabetic nephropathy therapy [113]. miR-18b is acting as a negative modulator by aiming insulin growth factor-1 (IGF-1), a key agent for VEGF creation and proliferation in the retinal endothelial cells. miR-18b employs its action on VEGF production and proliferation via repressing the IGF-1 receptor pathway, subsequently prohibiting the phosphorylation downstream (MAPK/ERK *kinase*) MEK, Akt, and ERK. It will offer a novel vision into understanding the process of retinopathy in diabetes and an attractive therapeutic aim for diabetic proliferative retinopathy [114].

8. Biomarkers

Examining the pharmacological process of biomolecules as biomarkers insight of pathogenesis is a tangible way to investigate novel drugs. Fibroblast growth factor 21 (FGF21) is an important cytokine, chiefly expressed in liver, muscle tissue, and fat answering to exercise

and nourishment, and has a key role in enhancing lipid and glucose metabolism. Research displays that fatty acids can induce the FGF21 expression via triggering the peroxisome proliferator-activated receptor-gamma (PPARγ) molecular pathway [115]. Furthermore, studies have also revealed that fatty acids can be connected to stimulated PPARα and prompt the FGF21 expression as the main task [116]. Because of the enhancing serum FGF21 rate in diabetic conditions, FGF21 can be a key predictor or good biomarker in diabetes [117,118].

Four lncRNAs may impress the harshness of disease among T2D patients. They include metastasis-associated lung adenocarcinoma transcript (MALAT), myocardial infarction-associated transcript (MIAT), NF-kappaB interacting lncRNA (NKILA), and nuclear enriched abundant transcript 1 (NEAT1). These lncRNAs as circulating factors can help us identify the diabetes pathophysiology and its associated problems and thus apply these as biomarkers to adapt cure approaches and improve and increase new therapeutic methods [119]. In the field of T2D, sphingosine 1 phosphate (S1P), an endogenous lipid material in the human body, has gotten much publicity. S1P is a crucial factor in the anti-apoptotic impact of adiponectin on β cells of the pancreas. The results have exhibited that adiponectin key factor requests to be dependent on to S1P factor to perform its tasks. In cellular experiments, adiponectin has inhibited ceramide gathering and decreased ceramide-stimulated apoptosis.

The impacts of S1P as a key biomarker on T2D can be shortened as follows: (1) S1P can antagonize β cell apoptosis and induce its proliferation; (2) S1P antagonizes resistance of insulin in human muscle tissues; (3) S1P increases the Akt pathway and induces absorption of hepatic glucose, so decreasing blood glucose [120]. Silent information regulator 1 (Sirt1) - a deacetylase - is a vital biomarker in renal tubular transition of mesenchymal–epithelial related to diabetic nephropathy by arbitrating deacetylation of Yin yang 1- a extensively expressed zinc finger RNA/DNA -connecting key transcription factor- [121]. Estrogen-related receptor α (ERRα) is a key aim for detecting new therapies for diabetes, especially on the gene and protein expression of factors involved in lipids metabolism in the diabetic rat model [122]. ERRα triggers the PPARα gene expression, which partially helps the process via which ERRα modulates metabolism [123,124].

The PPARγ coactivator 1 (PGC-1) group of transcriptional coactivators stimulates biogenesis in mitochondria, oxidation of fatty acid, glucose absorption, and gluconeogenesis in different tissues [125,126]. ERRα can modulate the expression of PGC-1α in myocytes via transstimulation of PGC-1α key gene [127,128]. Therefore, the ERRα receptor and its co-regulator (PGC-1α) are important molecular biomarkers in diabetes [129,130]. Most tissues and bodily fluids contain lysophosphatidic acid (LPA), a bioactive phospholipid. LPA works by combining G protein with unique LPA receptors (LPAR1 to LPAR6). LPA, as a biomarker, causes cell damage through several interconnected pathways, including the production of ROS and inflammatory cytokines [131]. Several studies have shown that the LPA–LPAR axis is implicated in several diseases, including diabetic nephropathy.

LPA signaling can modulate proliferation, fibrosis, and the main inflammatory responses or stimulate the apoptotic process [131] via several signaling pathways, including 1) PI3K-AKT axis for apoptosis; 2) LPA-RAGE axis for glomerular injury; 3) TLR4-NADPH oxidase-ROS–NF-KB/MAPK or TLR4-NF-KB/MAPK axis for inflammatory response; 4) PI3K-AKT-GSK3β-TGFβ axis for fibrosis; 5) Rac1GTPase-MAPK-KLF5-CDK4/Cyclin D1 axis for proliferation and 6) Wnt/β- catenin axis [132–136] for both apoptosis and fibrosis mechanisms [131]. It has been well recognized that KCa3.1 is extensively expressed all over the body, especially in platelets, erythrocytes, B and T cells, monocytes, epithelia, microglia, vascular endothelial cells, vascular smooth muscle cells, and fibroblasts. KCa3.1 modulates Ca^{2+} entrance and regulates the Ca^{2+} signaling pathway in the mentioned cells. It has been revealed that KCa3.1 is a possible molecular target and key biomarker for pharmacological effects in restenosis of vascular and diabetic nephropathy. Autophagy is developing as a vital pathway in several diseases such as diabetic nephropathy. It is recognized that oxidative stress is a critical process in autophagy defect and diabetic nephropathy. KCa3.1 stimulation helps to defective tubular autophagy in diabetic nephropathy via PI3K/Akt/mTOR key pathway [137]. KCa3.1 blockade improved renal fibrosis in diabetes [138]. Diabetic macular edema is the main agent of vision damage related to diabetic retinopathy. Failure of the blood-retinal barrier, especially the inner part, is an early happening in the pathogenesis of diabetic retinopathy. Apelin, an endogenous ligand, facilitates angiogenesis and is complicated in the expansion of diabetic retinopathy.

Apelin-13 enhances the biological action of endothelial cells of the human retinal and expression of both tight junction and cytoskeleton in macular edema by MAPK/ERK and PI3K/Akt signaling pathways. Apelin-13 as an initial promoter of vascular permeability may suggest a new plan and apply as a beneficial biomarker in the early treatment of diabetic retinopathy [139]. *AQR* is also a new T2D related gene and biomarker that modulates vital signaling pathways for glucose metabolism. The repression of *AQR* hinders the mTOR and its pathway and the ubiquitination procedure of protein [140]. C-X-C chemokine ligand 6 (CXCL6) - a key inflammatory cytokine that recalls inflammatory cells to the inflammation place via connecting to the CXCR1, 2 receptors - in diabetic nephropathy condition can induce fibrosis-associated agents to precipitate the expansion of nephropathy interstitial-renal fibrosis by inducing JAK/STAT3 pathway. Therefore, CXCL6 can be a potential new therapeutic aim and applicant biomarker for JAK/STAT3 signaling to cure diabetic nephropathy [141]. Diabetes may enhance the occurrence and mortality related to cardiac disappointment after severe myocardial infarction in patients. Caveolin-3 - a biomarker protein recognized to keep in contradiction of myocardial damage that modulates cardiomyocyte β2-adrenergic receptor (β2AR) placement on the cell membrane and is a mediator cyclic adenosine monophosphate (cAMP) downstream pathway and in myocytes from usual hearts. The regulation by Caveolin-3 is restricted to T-tubules - employs a protective impact on diabetic hearts in contradiction of reperfusion-ischemia injury via the β2AR, brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB), and cAMP/protein kinase (PKA) key pathways [142].

9. Nano studies

Livers from a great fat diet/Streptozotocin (STZ)-cured rats have displayed several circulatories, cytotoxic and inflammatory changes. Combined therapy with metformin and chitosan stabilized nanoparticles (CTS-Se-NPs) leads to a better notable anti-diabetic impact that has been confirmed by a considerable reduction in fasting blood glucose and insulin rates, and also a high expression of anti-apoptotic genes and low expression of apoptotic genes [143,144]. Furthermore, it improves the heart and hepatic tissue injury, decreases lipid gathering and pro-inflammatory cytokines rates, and reinstates the anti-oxidant ability. The nanoparticles used were composed of selenium (Se), which is an important micronutrient used to treat and prevent diseases [145], and chitosan, a natural biocompatible, non-immunogenic, biodegradable, and non-toxic cationic polysaccharide that is very promising for insulin delivery besides polymeric nanoparticles for effective insulin delivery [146–148]. Nanoparticles of Polydatin-loaded chitosan are the potential nano-carriers for the continued distribution of Polydatin [166]. These nanoparticles are also more active than metformin and polydatin in improving diabetic cardiomyopathy via anti-inflammatory and anti-oxidant effects. Their properties are applied more in protecting the heart through decreased heart rates of NF-κβ and TNFα and activation of Nrf2 pathway. The use of other types of nanoparticles made of gold (AuNPs), zinc oxide (ZnONPs), biodegradable polymers, bovine serum albumin (BSA), dendrimers and polymersomes have been proposed as nanosized carriers for the efficient delivery of antidiabetic drugs to treat diabetes, cancer and other diseases [143,144,149–156]. AuNPs have shown to possess unique optical, chemical and biological properties such as anti-hyperglycemic, anti-inflammatory, anti-oxidative and

antimicrobial activities [157,158]. ZnONPs have exhibited potent anti-hyperglycemic, anti-oxidative stress, and anti-inflammatory activities in a diabetic animal model [159,160]. BSA is a 3D nanostructure that can bind with drugs in a non-covalent manner and presents a homologous composition to the human serum albumin [161]. Therefore, BSA is biocompatibility, biodegradable, non-toxic, non-immunogenic, and thus can be use as efficient drug delivery system [162,163]. Dendrimers are 3D homogenous nanosized polymeric structures consisting tree-like branches that have gained much attention in the field of drug delivery and personalized medicine [164]. Polymersomes are polymeric vesicles produced with amphiphilic block polymers of different molecular weights that are more stable in comparison with liposomes [165].

10. Conclusions

This review has documented about types of complications in patients with diabetes. The most important complications in diabetes include cardiomyopathy, nephropathy, inflammation, retinopathy. Also, this review has brought the main and new drugs and molecular targets. Finally, according to this review's findings, the most important signaling pathways and factors related to diabetes and its complications are *NF-κB*, JNK/MAPK, PI3K/AKT/mTOR, GSK-3β, FoxO3a. These novel findings will help improve the treatment and management of diabetes based on molecular and targeted therapy.

References

[1] P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, et al., Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, Diabetes Res. Clin. Pract. 107843 (2019) 157.

[2] P. Bharadwaj, N. Wijesekara, M. Liyanapathirana, P. Newsholme, L. Ittner, P. Fraser, et al., The link between type 2 diabetes and neurodegeneration: roles for amyloid-β, amylin, and tau proteins, J. Alzheimers Dis. 59 (2017) 421–432.

[3] T.R. Einarson, A. Acs, C. Ludwig, U.H. Panton, Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017, Cardiovasc. Diabetol. 17 (2018) 1–19.

[4] K.K. Tsilidis, J.C. Kasimis, D.S. Lopez, E.E. Ntzani, J.P. Ioannidis, Type 2 diabetes and cancer: umbrella review of meta-analyses of observational studies, Bmj 350 (2015).

[5] E.W. Gregg, D.E. Williams, L. Geiss, Changes in diabetes-related complications in the United States, N. Engl. J. Med. 371 (2014) 286–287.

[6] N. Akbar, J.E. Digby, T.J. Cahill, A.N. Tavare, A.L. Corbin, S. Saluja, et al., Endothelium-derived Extracellular Vesicles Promote Splenic Monocyte Mobilization in Myocardial Infarction 2, 2017.

[7] L. Toma, C.S. Stancu, A.V. Sima, Endothelial dysfunction in diabetes is aggravated by glycated lipoproteins; novel molecular therapies, Biomedicines 9 (2021) 18.

[8] S.-S. Wang, X. Liao, F. Liu, Q. Zhang, J.-J. Qiu, S.-H. Fu, miR-132 mediates cell permeability and migration by targeting occludin in high-glucose-induced ARPE-19 cells, Endocr. J. (2021) EJ20–0277.

[9] S. Yu, X. Dong, M. Yang, Q. Yu, J. Xiong, J. Chen, et al., (Pro) renin receptor involves in myocardial fibrosis and oxidative stress in diabetic cardiomyopathy via the PRR–YAP pathway, Sci. Rep. 11 (2021) 1–12.

[10] X. Liu, X. Wang, X. Duan, D. Poorun, J. Xu, S. Zhang, et al., Lipoxin A4 and its analog suppress inflammation by modulating HMGB1 translocation and expression in psoriasis, Sci. Rep. 7 (2017) 1–11.

[11] E.P. Brennan, M. Mohan, A. McClelland, M. De Gaetano, C. Tikellis, M. Marai, et al., Lipoxins protect against inflammation in diabetes-associated atherosclerosis, Diabetes 67 (2018) 2657–2667.

[12] J.C. Chatham, M.E. Young, J. Zhang, Role of O-linked N-acetylglucosamine (O-GlcNAc) modification of proteins in diabetic cardiovascular complications, Curr. Opin. Pharmacol. 57 (2021) 1–12.

[13] J.C. Chatham, J. Zhang, A.R. Wende, Role of O-linked N-acetylglucosamine (O-GlcNAc) protein modification in cellular (patho) physiology, Physiol. Rev. 101 (2) (2021) 427–493, https://doi.org/10.1152/physrev.00043.2019.

[14] S.A. Marsh, P.C. Powell, L.J. Dell'Italia, J.C. Chatham, Cardiac O-GlcNAcylation blunts autophagic signaling in the diabetic heart, Life Sci. 92 (2013) 648–656.

[15] C. Slawson, R. Copeland, G.W. Hart, O-GlcNAc signaling: a metabolic link between diabetes and cancer? Trends Biochem. Sci. 35 (2010) 547–555.

[16] K. Huynh, B.C. Bernardo, J.R. McMullen, R.H. Ritchie, Diabetic cardiomyopathy: mechanisms and new treatment strategies targeting antioxidant signaling pathways, Pharmacol. Ther. 142 (2014) 375–415.

[17] Z.-W. Liu, H.-T. Zhu, K.-L. Chen, X. Dong, J. Wei, C. Qiu, et al., Protein kinase RNA-like endoplasmic reticulum kinase (PERK) signaling pathway plays a major role in reactive oxygen species (ROS)-mediated endoplasmic reticulum stress-induced apoptosis in diabetic cardiomyopathy, Cardiovasc. Diabetol. 12 (2013) 1–16.

[18] P. Chai, J. Yu, X. Wang, S. Ge, R. Jia, BMP9 promotes cutaneous wound healing by activating Smad1/5 signaling pathways and cytoskeleton remodeling, Clin. Transl. Med. 11 (2021).

[19] Y. Hou, J. Lan, F. Zhang, X. Wu, Expression profiles and potential corneal epithelial wound healing regulation targets of high-mobility group box 1 in diabetic mice, Exp. Eye Res. 202 (2021), 108364.

[20] S. Akiyama, S.-I. Katsumata, K. Suzuki, Y. Ishimi, J. Wu, M. Uehara, Dietary hesperidin exerts hypoglycemic and hypolipidemic effects in streptozotocin-induced marginal type 1 diabetic rats, J. Clin. Biochem. Nutr. 46 (2009) 87–92.

[21] Y.A. Haggag, N.E. El-Ashmawy, K.M. Okasha, Is hesperidin essential for prophylaxis and treatment of COVID-19 infection? Med. Hypotheses 144 (2020), 109957.

[22] A. Kandhare, A. Mukherjee, Bodhankar S. effect of hesperidin in bleomycin-induced pulmonary fibrosis in rats: critical role of Nrf-2, TNF-A, and IL-1B, Value Health 20 (2017) A887–A888.

[23] Y. Li, Y.-J. Bai, Y.-R. Jiang, W.-Z. Yu, X. Shi, L. Chen, et al., Apelin-13 is an early promoter of cytoskeleton and tight junction in diabetic macular edema via PI-3K/Akt and MAPK/Erk signaling pathways, Biomed. Res. Int. 2018 (2018).

[24] X. Yuan, L. Han, P. Fu, H. Zeng, C. Lv, W. Chang, et al., Cinnamaldehyde accelerates wound healing by promoting angiogenesis via up-regulation of PI3K and MAPK signaling pathways, Lab. Investig. 98 (2018) 783–798.

[25] Y. Ye, Y. Chen, J. Sun, H. Zhang, W. Li, W. Wang, et al., Repressed hypoxia inducible factor-1 in diabetes aggravates pulmonary aspergillus fumigatus infection through modulation of inflammatory responses, Clin. Transl. Med. 11 (2021).

[26] A.M. Abu El-Asrar, G. Mohammad, M.I. Nawaz, M.M. Siddiquei, High-mobility group box-1 modulates the expression of inflammatory and angiogenic signaling pathways in diabetic retina, Curr. Eye Res. 40 (2015) 1141–1152.

[27] G. Mohammad, High-mobility group box-1 modulates the expression of inflammatory and angiogenic signaling pathways in diabetic retina, Invest. Ophthalmol. Vis. Sci. 55 (2014) 1036.

[28] T. Salvatore, P.C. Pafundi, R. Galiero, L. Rinaldi, A. Caturano, E. Vetrano, et al., Can metformin exert as an active drug on endothelial dysfunction in diabetic subjects? Biomedicines 9 (2021) 3.

[29] Q.-Q. Zeng, J.-W. Cai, Y. Xu, L. Li, Q. Chen, R.-S. Yue, Network pharmacology-based analysis of effective components and mechanism of Rhizoma coptidis in treating diabetes, Asian Pac. J. Trop. Biomed. 11 (2021) 29.

[30] F.C. Brosius, C.C. Khoury, C.L. Buller, S. Chen, Abnormalities in signaling pathways in diabetic nephropathy, Expert. Rev. Endocrinol. Metab. 5 (2010) 51–64.

[31] X. Hu, X. Zhang, G. Jin, Z. Shi, W. Sun, F. Chen, Geniposide reduces development of streptozotocin-induced diabetic nephropathy via regulating nuclear factor-kappa B signaling pathways, Fundam. Clin. Pharmacol. 31 (2017) 54–63.

[32] Y. Liu, W. Liu, Z. Zhang, Y. Hu, X. Zhang, Y. Sun, et al., Yishen capsule promotes podocyte autophagy through regulating SIRT1/NF-κB signaling pathway to improve diabetic nephropathy, Ren. Fail. 43 (2021) 128–140.

[33] H.-J. Lu, T.-F. Tzeng, S.-S. Liou, S. Da Lin, M.-C. Wu, I.-M. Liu, Polysaccharides from Liriopes Radix ameliorate streptozotocin-induced type I diabetic nephropathy via regulating NF-κB and p38 MAPK signaling pathways, BMC Complement. Altern. Med. 14 (2014) 1–12.

[34] J. Su, L. Zhou, X. Kong, X. Yang, X. Xiang, Y. Zhang, et al., Endoplasmic reticulum is at the crossroads of autophagy, inflammation, and apoptosis signaling pathways and participates in the pathogenesis of diabetes mellitus, J. Diabetes Res. 2013 (2013).

[35] M. Packer, Mechanisms leading to differential hypoxia-inducible factor signaling in the diabetic kidney: modulation by SGLT2 inhibitors and hypoxia mimetics, Am. J. Kidney Dis. 77 (2021) 280–286.

[36] T.-t. Wei, L.-t. Yang, F. Guo, S.-B. Tao, L. Cheng, R.-s. Huang, et al., Activation of GPR120 in podocytes ameliorates kidney fibrosis and inflammation in diabetic nephropathy, Acta Pharmacol. Sin. 42 (2021) 252–263.

[37] T. K Dua, S. Joardar, P. Chakraborty, S. Bhowmick, A. Saha, V. De Feo, et al., Myricitrin, a glycosyloxyflavone in Myrica esculenta bark ameliorates diabetic nephropathy via improving glycemic status, reducing oxidative stress, and suppressing inflammation, Molecules 26 (2021) 258.

[38] G. Sharma, E.R. Prossnitz, Targeting the G protein-coupled estrogen receptor (GPER) in obesity and diabetes, Endocr. Metab. Sci. 2 (2021), 100080, https://doi.org/10.1016/j.endmts.2021.100080.

[39] J. Sugama, Y. Katayama, Y. Moritoh, M. Watanabe, Enteropeptidase inhibition improves kidney function in a rat model of diabetic kidney disease, Diabetes Obes. Metab. 23 (2021) 86–96.

[40] T.-T. Chang, Y.-A. Chen, S.-Y. Li, J.-W. Chen, Nrf-2 mediated heme oxygenase-1 activation contributes to the anti-inflammatory and renal protective effects of Ginkgo biloba extract in diabetic nephropathy, J. Ethnopharmacol. 266 (2021), 113474.

[41] B. Mabate, C.D. Daub, S. Malgas, A.L. Edkins, B.I. Pletschke, Fucoidan structure and its impact on glucose metabolism: implications for diabetes and cancer therapy, Mar. Drugs 19 (2021) 30.

[42] M. Xue, H. Liang, X. Ji, Y. Liu, Y. Ge, L. Hou, et al., Fucoidan prevent murine autoimmune diabetes via suppression TLR4-signaling pathways, regulation DC/Treg induced immune tolerance and improving gut microecology, Nutr. Metab. 16 (2019) 1–15.

[43] D. Gabbia, S. Dall'Acqua, I.M. Di Gangi, S. Bogialli, V. Caputi, L. Albertoni, et al., The phytocomplex from Fucus vesiculosus and Ascophyllum nodosum controls postprandial plasma glucose levels: an in vitro and in vivo study in a mouse model of NASH, Mar. Drugs 15 (2017) 41.

[44] S. Hu, G. Xia, J. Wang, Y. Wang, Z. Li, C. Xue, Fucoidan from sea cucumber protects against high-fat high-sucrose diet-induced hyperglycaemia and insulin resistance in mice, J. Funct. Foods 10 (2014) 128–138.
[45] S.-Y. Sim, Y.-E. Shin, H.-K. Kim, Fucoidan from Undaria pinnatifida has anti-diabetic effects by stimulation of glucose uptake and reduction of basal lipolysis in 3T3-L1 adipocytes, Nutr. Res. 65 (2019) 54–62.
[46] J. Lee, S. Noh, S. Lim, B. Kim, Plant extracts for type 2 diabetes: from traditional medicine to modern drug discovery, Antioxidants 10 (2021) 81.
[47] Y. Luo, P. Yang, Z. Li, Y. Luo, J. Shen, R. Li, et al., Liraglutide improves non-alcoholic fatty liver disease in diabetic mice by modulating inflammatory signaling pathways, Drug Des. Dev. Ther. 13 (2019) 4065.
[48] J. Tong, D. D'Alessio, Give the receptor a brake: slowing gastric emptying by GLP-1, Diabetes 63 (2014) 407–409.
[49] H. Xiang, D. Sun-Waterhouse, C. Cui, Hypoglycemic polysaccharides from Auricularia auricula and Auricularia polytricha inhibit oxidative stress, NF-κB signaling and proinflammatory cytokine production in streptozotocin-induced diabetic mice, Food Sci. Human Wellness 10 (2021) 87–93.
[50] D. Xiao, R. Yang, L. Gong, Y. Zhang, Y. Xie, S. Ni, Plantamajoside inhibits high glucose-induced oxidative stress, inflammation, and extracellular matrix accumulation in rat glomerular mesangial cells through the inactivation of Akt/NF-κB pathway, J. Recept. Signal Transduct. 41 (2021) 45–52.
[51] J.C. Newman, E. Verdin, β-Hydroxybutyrate: a signaling metabolite, Annu. Rev. Nutr. 37 (2017) 51–76.
[52] B. Li, Y. Yu, K. Liu, Y. Zhang, Q. Geng, F. Zhang, et al., β-Hydroxybutyrate inhibits histone deacetylase 3 to promote claudin-5 generation and attenuate cardiac microvascular hyperpermeability in diabetes, Diabetologia 64 (2021) 226–239.
[53] M. Al Dubayee, A. Alshahrani, M. Almalk, A. Hakami, B. Homoud, N. Alzneidi, et al., Metformin alters peripheral blood mononuclear cells (PBMC) senescence biomarkers gene expression in type 2 diabetic patients, J. Diabetes Complicat. 35 (2021), 107758.
[54] C. Ihling, G. Menzel, E. Wellens, JrS Mönting, H.E. Schaefer, A.M. Zeiher, Topographical association between the cyclin-dependent kinases inhibitor P21, p53 accumulation, and cellular proliferation in human atherosclerotic tissue, Arterioscler. Thromb. Vasc. Biol. 17 (1997) 2218–2224.
[55] J.C. Wang, M. Bennett, Aging and atherosclerosis: mechanisms, functional consequences, and potential therapeutics for cellular senescence, Circ. Res. 111 (2012) 245–259.
[56] L.G. Fryer, A. Parbu-Patel, D. Carling, The anti-diabetic drugs rosiglitazone and metformin stimulate AMP-activated protein kinase through distinct signaling pathways, J. Biol. Chem. 277 (2002) 25226–25232.
[57] R.W. Mackenzie, B.T. Elliott, Akt/PKB activation and insulin signaling: a novel insulin signaling pathway in the treatment of type 2 diabetes, Diabetes Metab. Syndr. Obes. Targets Ther. 7 (2014) 55.
[58] W. Sun, J. Yang, W. Wang, J. Hou, Y. Cheng, Y. Fu, et al., The beneficial effects of Zn on Akt-mediated insulin and cell survival signaling pathways in diabetes, J. Trace Elem. Med. Biol. 46 (2018) 117–127.
[59] R. Mohanraj, P. Mukhopadhyay, S. Bátkai, V. Patel, B. Horváth, D.A. Wink, et al., Cannabidiol Attenuates Cardiac Dysfunction, Oxidative Stress, Fibrosis, Inflammatory and Cell Death Signaling Pathways in Diabetic Cardiomyopathy, Wiley Online Library, 2011.
[60] C. Kang, Y.B. Jin, H. Lee, M. Cha, E.-T. Sohn, J. Moon, et al., Brown alga Ecklonia cava attenuates type 1 diabetes by activating AMPK and Akt signaling pathways, Food Chem. Toxicol. 48 (2010) 509–516.
[61] Z. Fu, W. Zhang, W. Zhen, H. Lum, J. Nadler, J. Bassaganya-Riera, et al., Genistein induces pancreatic β-cell proliferation through activation of multiple signaling pathways and prevents insulin-deficient diabetes in mice, Endocrinology 151 (2010) 3026–3037.
[62] Y. Liu, L. Yang, Y. Zhang, X. Liu, Z. Wu, R.G. Gilbert, et al., Dendrobium officinale polysaccharide ameliorates diabetic hepatic glucose metabolism via glucagon-mediated signaling pathways and modifying liver-glycogen structure, J. Ethnopharmacol. 248 (2020), 112308.
[63] L. Zhou, G.M. Sutton, J.J. Rochford, R.K. Semple, D.D. Lam, L.J. Oksanen, et al., Serotonin 2C receptor agonists improve type 2 diabetes via melanocortin-4 receptor signaling pathways, Cell Metab. 6 (2007) 398–405.
[64] I. Lazaro, A. Oguiza, C. Recio, B. Mallavia, J. Madrigal-Matute, J. Blanco, et al., Targeting HSP90 ameliorates nephropathy and atherosclerosis through suppression of NF-κB and STAT signaling pathways in diabetic mice, Diabetes 64 (2015) 3600–3613.
[65] T. Joshi, A.K. Singh, P. Haratipour, A.N. Sah, A.K. Pandey, R. Naseri, et al., Targeting AMPK signaling pathway by natural products for treatment of diabetes mellitus and its complications, J. Cell. Physiol. 234 (2019) 17212–17231.
[66] Y. Li, Y. Liu, J. Liang, T. Wang, M. Sun, Z. Zhang, Gymnemic acid ameliorates hyperglycemia through PI3K/AKT-and AMPK-mediated signaling pathways in type 2 diabetes mellitus rats, J. Agric. Food Chem. 67 (2019) 13051–13060.
[67] W. Li, A.D. Kandhare, A.A. Mukherjee, S.L. Bodhankar, Hesperidin, a plant flavonoid accelerated the cutaneous wound healing in streptozotocin-induced diabetic rats: role of TGF-ß/Smads and Ang-1/Tie-2 signaling pathways, EXCLI J. 17 (2018) 399.
[68] M. Mehta, D.S. Dhanjal, K.R. Paudel, B. Singh, G. Gupta, S. Rajeshkumar, et al., Cellular Signalling Pathways Mediating the Pathogenesis of Chronic Inflammatory Respiratory Diseases: An Update, 2020, pp. 1–23.
[69] S. Rawat, G. Gupta, S. Pathak, S.K. Singh, H. Singh, A. Mishra, et al., Current Biological and Pharmacological Updates on Wogonin 19, 2020, pp. 635–640.
[70] X.N. Tew, Lau NJX, D.K. Chellappan, T. Madheswaran, F. Zeeshan, M. M. Tambuwala, et al., Immunological Axis of Berberine in Managing Inflammation Underlying Chronic Respiratory Inflammatory Diseases 317, 2020, p. 108947.
[71] J. Wang, J. Lu, Y. Lan, H. Zhou, W. Li, M. Xiang, Total coumarins from Urtica dentata hand prevent murine autoimmune diabetes via suppression of the TLR4-signaling pathways, J. Ethnopharmacol. 146 (2013) 379–392.
[72] Z.-c. Zheng, W. Zhu, L. Lei, Liu X-q, Wu Y-g, Wogonin ameliorates renal inflammation and fibrosis by inhibiting NF-κB and TGF-β1/Smad3 signaling pathways in diabetic nephropathy, Drug Des. Dev. Ther. 14 (2020) 4135.
[73] M. Fathalipour, M. Eghtedari, F. Borges, T. Silva, F. Moosavi, O. Firuzi, et al., Caffeic acid alkyl amide derivatives ameliorate oxidative stress and modulate ERK1/2 and AKT signaling pathways in a rat model of diabetic retinopathy, Chem. Biodivers. 16 (2019), e1900405.
[74] X.-J. Li, Z. Zhu, S.-L. Han, Z.-L. Zhang, Bergapten exerts inhibitory effects on diabetes-related osteoporosis via the regulation of the PI3K/AKT, JNK/MAPK and NF-κB signaling pathways in osteoprotegerin knockout mice, Int. J. Mol. Med. 38 (2016) 1661–1672.
[75] R. Vinayagam, M. Jayachandran, S.S.M. Chung, B. Xu, Guava leaf inhibits hepatic gluconeogenesis and increases glycogen synthesis via AMPK/ACC signaling pathways in streptozotocin-induced diabetic rats, Biomed. Pharmacother. 103 (2018) 1012–1017.
[76] C.H. Lu, H.C. Ou, C.H. Day, H.I. Chen, P.Y. Pai, C.Y. Lee, et al., Deep sea minerals ameliorate diabetic-induced inflammation via inhibition of TNFα signaling pathways, Environ. Toxicol. 35 (2020) 468–477.
[77] D. Jing, H. Bai, S. Yin, Renoprotective effects of emodin against diabetic nephropathy in rat models are mediated via PI3K/Akt/GSK-3β and Bax/caspase-3 signaling pathways, Exp. Ther. Med. 14 (2017) 5163–5169.
[78] S.-G. Tang, X.-Y. Liu, J.-M. Ye, T.-T. Hu, Y.-Y. Yang, T. Han, et al., Isosteviol ameliorates diabetic cardiomyopathy in rats by inhibiting ERK and NF-κB signaling pathways, J. Endocrinol. 238 (2018) 47–60.
[79] Y. Chen, Y. Liu, M.M.R. Sarker, X. Yan, C. Yang, L. Zhao, et al., Structural characterization and antidiabetic potential of a novel heteropolysaccharide from Grifola frondosa via IRS1/PI3K-JNK signaling pathways, Carbohydr. Polym. 198 (2018) 452–461.
[80] S.-J. Wu, Y.-J. Tung, L.-T. Ng, Anti-diabetic effects of Grifola frondosa bioactive compound and its related molecular signaling pathways in palmitate-induced C2C12 cells, J. Ethnopharmacol. 260 (2020), 112962.
[81] X. Wei, J. Tao, Y. Shen, S. Xiao, S. Jiang, E. Shang, et al., Sanhuang Xiexin Tang ameliorates type 2 diabetic rats via modulation of the metabolic profiles and NF-κB/PI-3K/Akt signaling pathways, Front. Pharmacol. 9 (2018) 955.
[82] H.M. Xian, H. Che, Y. Qin, F. Yang, Meng Sy, Xg Li, et al., Coriolus versicolor aqueous extract ameliorates insulin resistance with PI3K/Akt and p38 MAPK signaling pathways involved in diabetic skeletal muscle, Phytother. Res. 32 (2018) 551–560.
[83] Y. Liu, M. Dong, Z. Yang, S. Pan, Anti-diabetic effect of citrus pectin in diabetic rats and potential mechanism via PI3K/Akt signaling pathway, Int. J. Biol. Macromol. 89 (2016) 484–488.
[84] C.-J. He, L.-Q. Ma, M.S. Iqbal, X.-J. Huang, J. Li, G.-Z. Yang, et al., Veratrilla baillonii Franch exerts anti-diabetic activity and improves liver injury through IRS/PI3K/AKT signaling pathways in type 2 diabetic db/db mice, J. Funct. Foods 75 (2020), 104204.
[85] Y.-L. Yuan, C.-R. Guo, L.-L. Cui, S.-X. Ruan, C.-F. Zhang, D. Ji, et al., Timosaponin B-II ameliorates diabetic nephropathy via TXNIP, mTOR, and NF-κB signaling pathways in alloxan-induced mice, Drug Des. Dev. Ther. 9 (2015) 6247.
[86] F.-B. Feng, H.-Y. Qiu, Neuroprotective effect of tanshinone IIA against neuropathic pain in diabetic rats through the Nrf2/ARE and NF-κB signaling pathways, Kaohsiung J. Med. Sci. 34 (2018) 428–437.
[87] W.F. Li, P. Wang, H. Li, T.Y. Li, M. Feng, S.F. Chen, Oleanolic acid protects against diabetic cardiomyopathy via modulation of the nuclear factor erythroid 2 and insulin signaling pathways, Exp. Ther. Med. 14 (2017) 848–854.
[88] Y. Yang, W. Gong, C. Jin, Z. Chen, L. Zhang, Y. Zou, et al., Naringin ameliorates experimental diabetic renal fibrosis by inhibiting the ERK1/2 and JNK MAPK signaling pathways, J. Funct. Foods 50 (2018) 53–62.
[89] Y. Gao, M. Zhang, T. Wu, M. Xu, H. Cai, Z. Zhang, Effects of D-pinitol on insulin resistance through the PI3K/Akt signaling pathway in type 2 diabetes mellitus rats, J. Agric. Food Chem. 63 (2015) 6019–6026.
[90] Y. Zhu, C. Zhu, H. Yang, J. Deng, D. Fan, Protective effect of ginsenoside Rg5 against kidney injury via inhibition of NLRP3 inflammasome activation and the MAPK signaling pathway in high-fat diet/streptozotocin-induced diabetic mice, Pharmacol. Res. 155 (2020), 104746.
[91] Y. Liu, J. Deng, D. Fan, Ginsenoside Rk3 ameliorates high-fat-diet/streptozocin induced type 2 diabetes mellitus in mice via the AMPK/Akt signaling pathway, Food Funct. 10 (2019) 2538–2551.
[92] B. Dai, Q. Wu, C. Zeng, J. Zhang, L. Cao, Z. Xiao, et al., The effect of Liuwei Dihuang decoction on PI3K/Akt signaling pathway in liver of type 2 diabetes mellitus (T2DM) rats with insulin resistance, J. Ethnopharmacol. 192 (2016) 382–389.
[93] J. Huang, K. Huang, T. Lan, X. Xie, X. Shen, P. Liu, et al., Curcumin ameliorates diabetic nephropathy by inhibiting the activation of the SphK1-S1P signaling pathway, Mol. Cell. Endocrinol. 365 (2013) 231–240.
[94] N.M. Al-Rasheed, N.M. Al-Rasheed, I.H. Hasan, M.A. Al-Amin, H.N. Al-Ajmi, A. M. Mahmoud, Sitagliptin attenuates cardiomyopathy by modulating the JAK/STAT signaling pathway in experimental diabetic rats, Drug Des. Dev. Ther. 10 (2016) 2095.
[95] A. Kuhad, M. Bishnoi, V. Tiwari, K. Chopra, Suppression of NF-κβ signaling pathway by tocotrienol can prevent diabetes associated cognitive deficits, Pharmacol. Biochem. Behav. 92 (2009) 251–259.

[96] Y. Zhang, Y. Cao, J. Chen, H. Qin, L. Yang, A new possible mechanism by which punicalagin protects against liver injury induced by type 2 diabetes mellitus: upregulation of autophagy via the Akt/FoxO3a signaling pathway, J. Agric. Food Chem. 67 (2019) 13948–13959.

[97] N. Schormann, K.L. Hayden, P. Lee, S. Banerjee, D. Chattopadhyay, An overview of structure, function, and regulation of pyruvate kinases, Protein Sci. 28 (2019) 1771–1784.

[98] X. Cheng, W. Gao, Y. Dang, X. Liu, Y. Li, X. Peng, et al., Both ERK/MAPK and TGF-Beta/Smad signaling pathways play a role in the kidney fibrosis of diabetic mice accelerated by blood glucose fluctuation, J. Diabetes Res. 2013 (2013).

[99] H. Yadav, C. Quijano, A.K. Kamaraju, O. Gavrilova, R. Malek, W. Chen, et al., Protection from obesity and diabetes by blockade of TGF-β/Smad3 signaling, Cell Metab. 14 (2011) 67–79.

[100] J. Li, Y.B.Y. Sun, W. Chen, J. Fan, S. Li, X. Qu, et al., Smad4 promotes diabetic nephropathy by modulating glycolysis and OXPHOS, EMBO Rep. 21 (2020), e48781.

[101] S.P. Srivastava, J. Li, M. Kitada, H. Fujita, Y. Yamada, J.E. Goodwin, et al., SIRT3 deficiency leads to induction of abnormal glycolysis in diabetic kidney with fibrosis, Cell Death Dis. 9 (2018) 1–14.

[102] P.H. Lin, F.L. Zeng, M. Yang, C. Hu, L. Zhao, H.X. Chen, et al., DsbA-L protects against diabetic renal injury through the adipo-renal axis, bioRxiv (2021).

[103] L. Zhang, Z. Wang, R. Liu, Z. Li, J. Lin, M.L. Wojciechowicz, et al., Connectivity mapping identifies BI-2536 as a potential drug to treat diabetic kidney disease, Diabetes 70 (2021) 589–602.

[104] M. Zhang, Z. Yan, L. Bu, C. An, D. Wang, X. Liu, et al., Rapeseed protein-derived antioxidant peptide RAP alleviates renal fibrosis through MAPK/NF-κB signaling pathways in diabetic nephropathy, Drug Des. Dev. Ther. 12 (2018) 1255.

[105] T. Behl, I. Kaur, A. Sehgal, E. Sharma, A. Kumar, M. Grover, et al., Unfolding Nrf2 in diabetes mellitus, Mol. Biol. Rep. (2021) 1–13.

[106] R. Radhakrishnan, R.A. Kowluru, Long noncoding RNA MALAT1 and regulation of the antioxidant defense system in diabetic retinopathy, Diabetes 70 (2021) 227–239.

[107] Z. Yu, W. Shao, Y. Chiang, W. Foltz, Z. Zhang, W. Ling, et al., Oltipraz upregulates the nuclear respiratory factor 2 alpha subunit (NRF2) antioxidant system and prevents insulin resistance and obesity induced by a high-fat diet in C57BL/6J mice, Diabetologia 54 (2011) 922–934.

[108] H. Xie, C. Zhang, D. Liu, Q. Yang, L. Tang, T. Wang, et al., Erythropoietin protects the inner blood–retinal barrier by inhibiting microglia phagocytosis via Src/Akt/cofilin signalling in experimental diabetic retinopathy, Diabetologia 64 (2021) 211–225.

[109] Y. Yu, Y.-Y. Jia, M. Wang, L. Mu, H.-J. Li, PTGER3 and MMP-2 play potential roles in diabetic nephropathy via competing endogenous RNA mechanisms, BMC Nephrol. 22 (2021) 1–11.

[110] L. Zhou, S. Zhang, L. Zhang, F. Li, H. Sun, J. Feng, MiR-199a-3p inhibits the proliferation, migration, and invasion of endothelial cells and retinal pericytes of diabetic retinopathy rats through regulating FGF7 via EGFR/PI3K/AKT pathway, J. Recept. Signal Transduct. 41 (2021) 19–31.

[111] C. Wang, R. Zhao, S. Zhang, LncRNA XIST knockdown suppresses cell proliferation and promotes apoptosis in diabetic cataract via miR-34a/SMAD2 axis, bioRxiv (2021).

[112] L. Wang, Y. Cai, L. Jian, C.W. Cheung, L. Zhang, Z. Xia, Impact of peroxisome proliferator-activated receptor-α on diabetic cardiomyopathy, Cardiovasc. Diabetol. 20 (2021) 1–15.

[113] X.-D. Liu, L.-Y. Zhang, T.-C. Zhu, R.-F. Zhang, S.-L. Wang, Y. Bao, Overexpression of miR-34c inhibits high glucose-induced apoptosis in podocytes by targeting Notch signaling pathways, Int. J. Clin. Exp. Pathol. 8 (2015) 4525.

[114] J.-h. Wu, Y.-h. Wang, W. Wang, W. Shen, Y.-z. Sang, L. Liu, et al., MiR-18b suppresses high-glucose-induced proliferation in HRECs by targeting IGF-1/IGF1R signaling pathways, Int. J. Biochem. Cell Biol. 73 (2016) 41–52.

[115] K.H. Kim, S.H. Kim, Y.-K. Min, H.-M. Yang, J.-B. Lee, M.-S. Lee, Acute exercise induces FGF21 expression in mice and in healthy humans, PLoS One 8 (2013), e63517.

[116] K. Mai, J. Andres, K. Biedasek, J. Weicht, T. Bobbert, M. Sabath, et al., Free fatty acids link metabolism and regulation of the insulin-sensitizing fibroblast growth factor-21, Diabetes 58 (2009) 1532–1538.

[117] C. Guo, L. Zhao, Y. Li, X. Deng, G. Yuan, Relationship between FGF21 and drug or nondrug therapy of type 2 diabetes mellitus, J. Cell. Physiol. 236 (2021) 55–67.

[118] W. Wente, A.M. Efanov, M. Brenner, A. Kharitonenkov, A. Köster, G.E. Sandusky, et al., Fibroblast growth factor-21 improves pancreatic β-cell function and survival by activation of extracellular signal–regulated kinase 1/2 and Akt signaling pathways, Diabetes 55 (2006) 2470–2478.

[119] M. Alfaifi, Beg MMA, M.Y. Alshahrani, I. Ahmad, A.G. Alkhathami, P.C. Joshi, et al., Circulating long non-coding RNAs NKILA, NEAT1, MALAT1, and MIAT expression and their association in type 2 diabetes mellitus, BMJ Open Diabetes Res. Care 9 (2021), e001821.

[120] Q. He, J. Bo, R. Shen, Y. Li, Y. Zhang, J. Zhang, et al., S1P signaling pathways in pathogenesis of type 2 diabetes, J. Diabetes Res. 2021 (2021).

[121] L. Du, X. Qian, Y. Li, X.-z. Li, L.-l. He, L. Xu, et al., Sirt1 inhibits renal tubular cell epithelial–mesenchymal transition through YY1 deacetylation in diabetic nephropathy, Acta Pharmacol. Sin. 42 (2021) 242–251.

[122] S. Aminizadeh, A. Habibi, Y. Masoumi-Ardakani, B. Shahouzehi, H. Marefati, S. Shakerian, The role of estrogen-related receptor α (ERRα) in metabolic adaptations by endurance training in skeletal muscle of streptozotocin-induced diabetic rats, Sport Sci. Health (2021) 1–12.

[123] J.M. Huss, K.-I. Imahashi, C.R. Dufour, C.J. Weinheimer, M. Courtois, A. Kovacs, et al., The nuclear receptor ERRα is required for the bioenergetic and functional adaptation to cardiac pressure overload, Cell Metab. 6 (2007) 25–37.

[124] J.M. Huss, I.P. Torra, B. Staels, V. Giguere, D.P. Kelly, Estrogen-related receptor α directs peroxisome proliferator-activated receptor α signaling in the transcriptional control of energy metabolism in cardiac and skeletal muscle, Mol. Cell. Biol. 24 (2004) 9079–9091.

[125] B.N. Finck, D.P. Kelly, PGC-1 coactivators: inducible regulators of energy metabolism in health and disease, J. Clin. Invest. 116 (2006) 615–622.

[126] R.C. Scarpulla, Metabolic control of mitochondrial biogenesis through the PGC-1 family regulatory network, Biochim. Biophys. Acta Mol. Cell Res. 1813 (2011) 1269–1278.

[127] Z. Arany, N. Lebrasseur, C. Morris, E. Smith, W. Yang, Y. Ma, et al., The transcriptional coactivator PGC-1β drives the formation of oxidative type IIX fibers in skeletal muscle, Cell Metab. 5 (2007) 35–46.

[128] L. Wang, J. Liu, P. Saha, J. Huang, L. Chan, B. Spiegelman, et al., The orphan nuclear receptor SHP regulates PGC-1α expression and energy production in brown adipocytes, Cell Metab. 2 (2005) 227–238.

[129] S.N. Schreiber, D. Knutti, K. Brogli, T. Uhlmann, A. Kralli, The transcriptional coactivator PGC-1 regulates the expression and activity of the orphan nuclear receptor estrogen-related receptor α (ERRα), J. Biol. Chem. 278 (2003) 9013–9018.

[130] D. Shao, Y. Liu, X. Liu, L. Zhu, Y. Cui, A. Cui, et al., PGC-1β-regulated mitochondrial biogenesis and function in myotubes is mediated by NRF-1 and ERRα, Mitochondrion 10 (2010) 516–527.

[131] J.H. Lee, D. Kim, Y.S. Oh, H.-S. Jun, Lysophosphatidic acid signaling in diabetic nephropathy, Int. J. Mol. Sci. 20 (2019) 2850.

[132] M. Bose, S. Almas, S. Prabhakar, Wnt signaling and podocyte dysfunction in diabetic nephropathy, J. Investig. Med. 65 (2017) 1093–1101.

[133] J. Chen, C. Ning, J. Mu, D. Li, Y. Ma, X. Meng, Role of Wnt signaling pathways in type 2 diabetes mellitus, Mol. Cell. Biochem. (2021) 1–14.

[134] Q. Chen, J.-x. Ma, Canonical Wnt signaling in diabetic retinopathy, Vis. Res. 139 (2017) 47–58.

[135] T. Jin, L. Liu, The wntsignalig pathway effector TCF7L2 and type 2 diabetes mellitus, MolEndocrinol 22 (11) (2008) 2383–2392.

[136] H.J. Welters, R.N. Kulkarni, Wnt signaling: relevance to β-cell biology and diabetes, Trends Endocrinol. Metab. 19 (2008) 349–355.

[137] B. Vergès, B. Cariou, mTOR inhibitors and diabetes, Diabetes Res. Clin. Pract. 110 (2015) 101–108.

[138] C. Huang, M.Z. Lin, D. Cheng, F. Braet, C.A. Pollock, X.-M. Chen, KCa3. 1 mediates dysfunction of tubular autophagy in diabetic kidneys via PI3k/Akt/mTOR signaling pathways, Sci. Rep. 6 (2016) 1–12.

[139] J. Li, L. Bao, D. Zha, L. Zhang, P. Gao, J. Zhang, et al., Oridonin protects against the inflammatory response in diabetic nephropathy by inhibiting the TLR4/p38-MAPK and TLR4/NF-κB signaling pathways, Int. Immunopharmacol. 55 (2018) 9–19.

[140] C. Song, H. Yan, H. Wang, Y. Zhang, H. Cao, Y. Wan, et al., AQR is a novel type 2 diabetes-associated gene that regulates signaling pathways critical for glucose metabolism, J. Genet. Genomics 45 (2018) 111–120.

[141] M.-Y. Sun, S.-J. Wang, X.-Q. Li, Y.-L. Shen, J.-R. Lu, X.-H. Tian, et al., CXCL6 promotes renal interstitial fibrosis in diabetic nephropathy by activating JAK/STAT3 signaling pathway, Front. Pharmacol. 10 (2019) 224.

[142] J. Gong, F. Zhou, S. Xie, X. Wang, J. Xu, F. Xiao, Caveolin-3 protects diabetic hearts from acute myocardial infarction/reperfusion injury through β2AR, cAMP/PKA, and BDNF/TrkB signaling pathways, Aging (Albany NY) 12 (2020), 14300.

[143] A. El-Hakim, M. Yasmina, A. Abdel-Rahman Mohamed, S.I. Khater, A. Hamed Arisha, M.M. Metwally, et al., Chitosan-stabilized selenium nanoparticles and metformin synergistically rescue testicular oxidative damage and steroidogenesis-related genes dysregulation in high-fat diet/Streptozotocin-induced diabetic rats, Antioxidants 10 (2021) 17.

[144] A.A.-R. Mohamed, S.I. Khater, A.H. Arisha, M.M. Metwally, G. Mostafa-Hedeab, E.S. El-Shetry, Chitosan-stabilized selenium nanoparticles alleviate cardio-hepatic damage in type 2 diabetes mellitus model via regulation of caspase, Bax/Bcl-2, and Fas/FasL-pathway, Gene 768 (2020), 145288, https://doi.org/10.1016/j.gene.2020.145288.

[145] D. Sacks, B. Baxter, Campbell BCV, J.S. Carpenter, C. Cognard, D. Dippel, et al., Multisociety consensus quality improvement revised consensus statement for endovascular therapy of acute ischemic stroke, Int. J. Stroke 13 (2018) 612–632.

[146] Y. Haggag, Y. Abdel-Wahab, O. Ojo, M. Osman, S. El-Gizawy, M. El-Tanani, et al., Preparation and in vivo evaluation of insulin-loaded biodegradable nanoparticles prepared from diblock copolymers of PLGA and PEG, Int. J. Pharm. 499 (2016) 236–246.

[147] Y.A. Haggag, A.M. Faheem, M.M. Tambuwala, M.A. Osman, S.A. El-Gizawy, B. O'Hagan, et al., Effect of poly(ethylene glycol) content and formulation parameters on particulate properties and intraperitoneal delivery of insulin from PLGA nanoparticles prepared using the double-emulsion evaporation procedure, Pharm. Dev. Technol. 23 (2018) 370–381.

[148] L. Li, L. Yang, M. Li, L. Zhang, A cell-penetrating peptide mediated chitosan nanocarriers for improving intestinal insulin delivery, Carbohydr. Polym. 174 (2017) 182–189.

[149] B. Al-Trad, A. Aljabali, M. Al Zoubi, M. Shehab, SjIjon Omari, Effect of Gold Nanoparticles Treatment on the Testosterone-Induced Benign Prostatic Hyperplasia in Rats 14, 2019, p. 3145.

[150] A.A. Aljabali, Y. Akkam, M.S. Al Zoubi, K.M. Al-Batayneh, B. Al-Trad, O. Abo Alrob, et al., Synthesis of Gold Nanoparticles Using Leaf Extract of *Ziziphus zizyphus* and their Antimicrobial Activity 8, 2018, p. 174.

[151] A.A. Aljabali, H.A. Bakshi, F.L. Hakkim, Y.A. Haggag, K.M. Al-Batanyeh, M.S. A. Zoubi, et al., Correction: Aljabali, AAA; et al. albumin Nano-encapsulation of piceatannol enhances its anticancer potential in colon cancer via down regulation of nuclear p65 and HIF-1α, Cancers 12 (113) (2020) 3587, 2020;12.
[152] Alomari G, Al-Trad B, Hamdan S, Aljabali AA, Al Zoubi MS, Al-Batanyeh K, et al. Alleviation of diabetic nephropathy by zinc oxide nanoparticles in streptozotocin-induced type 1 diabetes in rats.
[153] Y. Haggag, M. Elshikh, M. El-Tanani, I.M. Bannat, P. McCarron, M.M. Tambuwala, Nanoencapsulation of sophorolipids in PEGylated poly(lactide-co-glycolide) as a novel approach to target colon carcinoma in the murine model, Drug Deliv. Transl. Res. 10 (2020) 1353–1366.
[154] Y.A. Haggag, R.R. Ibrahim, A.A. Hafiz, Design, formulation and in vivo evaluation of novel Honokiol-loaded PEGylated PLGA nanocapsules for treatment of breast cancer, Int. J. Nanomedicine 15 (2020) 1625–1642.
[155] V. Mishra, N. Yadav, G.K. Saraogi, M.M. Tambuwala, NjCpd Giri, Dendrimer Based Nanoarchitectures in Diabetes Management: An Overview 25, 2019, pp. 2569–2583.
[156] A.K. Sharma, P. Prasher, A.A. Aljabali, V. Mishra, H. Gandhi, S. Kumar, et al., Emerging Era of "Somes": Polymersomes as Versatile Drug Delivery Carrier for Cancer Diagnostics and Therapy 10, 2020, pp. 1171–1190.
[157] S. Barathmanikanth, K. Kalishwaralal, M. Sriram, S.R. Pandian, H.S. Youn, S. Eom, et al., Anti-oxidant effect of gold nanoparticles restrains hyperglycemic conditions in diabetic mice, J. Nanobiotechnol. 8 (2010) 16.
[158] V. Karthick, V.G. Kumar, T.S. Dhas, G. Singaravelu, A.M. Sadiq, K. Govindaraju, Effect of biologically synthesized gold nanoparticles on alloxan-induced diabetic rats-an in vivo approach, Colloids Surf. B: Biointerfaces 122 (2014) 505–511.
[159] J. Jiang, J. Pi, J. Cai, The advancing of zinc oxide nanoparticles for biomedical applications, Bioinorg. Chem. Appl. 2018 (2018), 1062562.
[160] P.C. Nagajyothi, S.J. Cha, I.J. Yang, T.V. Sreekanth, K.J. Kim, H.M. Shin, Antioxidant and anti-inflammatory activities of zinc oxide nanoparticles synthesized using Polygala tenuifolia root extract, J. Photochem. Photobiol. B 146 (2015) 10–17.
[161] B.X. Huang, H.Y. Kim, C. Dass, Probing three-dimensional structure of bovine serum albumin by chemical cross-linking and mass spectrometry, J. Am. Soc. Mass Spectrom. 15 (2004) 1237–1247.
[162] N.F. Rodrigues, E. van Tilburg Bernardes, R.P. Rocha, L.C. da Costa, A. C. Coutinho, M. dos Santos Muniz, et al., Bovine serum albumin nanoparticle vaccine reduces lung pathology induced by live Pseudomonas aeruginosa infection in mice, Vaccine 31 (2013) 5062–5066.
[163] M.M. Tambuwala, M.N. Khan, P. Thompson, P.A. McCarron, Albumin nano-encapsulation of caffeic acid phenethyl ester and piceatannol potentiated its ability to modulate HIF and NF-kB pathways and improves therapeutic outcome in experimental colitis, Drug Deliv. Transl. Res. 9 (2019) 14–24.
[164] B.K. Nanjwade, H.M. Bechra, G.K. Derkar, F.V. Manvi, V.K. Nanjwade, Dendrimers: emerging polymers for drug-delivery systems, Eur. J. Pharm. Sci. 38 (2009) 185–196.
[165] E. Rideau, R. Dimova, P. Schwille, F.R. Wurm, K. Landfester, Liposomes and polymersomes: a comparative review towards cell mimicking, Chem. Soc. Rev. 47 (2018) 8572–8610.
[166] F. Mostafa, A. Abdel-Moneim, M. Abdul-Hamid, S.R. Galaly, H.M. Mohamed, Polydatin and polydatin-loaded chitosan nanoparticles attenuate diabetic cardiomyopathy in rats, J Mol Histol. 52 (2) (2021) 135–152, https://doi.org/10.1007/s10735-020-09930-4.