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Overview of Key Molecular and Pharmacological Targets for Diabetes and Associated Diseases

Seyed Hossein Shahcheraghi^{1,2}, Alaa A. A. Aljabali³, Mazhar S Al Zoubi⁴, Vijay Mishra⁵, Nitin B. Charbe⁶, Yusuf A Haggag⁷, Garima Shrivastava⁸, Abdulmajeed G Almutary⁹, Abdullah M Alnuqaydan⁹, Debmalya Barh¹⁰, Kamal Dua¹¹, Dinesh K Chellappan¹², Gaurav Gupta¹³, Marzieh Lotfi^{14,15}, Ángel Serrano-Aroca¹⁶, Bojlu Bahar¹⁷, Yogendra K Mishra¹⁸, Kazuo Takayama¹⁹, Pritam Kumar Panda²⁰ and Hamid A Bakshi²¹ and Murtaza M Tambuwala^{21*}

¹Infectious Diseases Research Center, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

²Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

³Department of Pharmaceutics & Pharmaceutical Technology, Yarmouk University, Irbid, Jordan

⁴Yarmouk University - Faculty of Medicine, Department of Basic Medical Sciences, Irbid, Jordan

⁵School of Pharmaceutical Sciences, Lovely Professional University, Phagwara 144411, Punjab, India

⁶Departamento de Química Orgánica, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Av. Libertador Bernardo O'Higgins, Santiago 340, Región Metropolitana, Chile

⁷Department of Pharmaceutical Technology, Faculty of Pharmacy, Tanta University, Tanta, Egypt

⁸Indian Institute of Technology, Delhi, India

⁹Department of Medical Biotechnology, College of Applied Medical Sciences, Qassim University, Saudi Arabia

¹⁰Centre for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied

¹¹Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, NSW 2007, Australia

¹²Department of Life Sciences, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia

¹³School of Pharmaceutical Sciences, Suresh Gyan Vihar University, Jaipur, India.

¹⁴Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

¹⁵Abortion Research Center, Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

¹⁶Biomaterials and Bioengineering Lab, Translational Research Centre San Alberto Magno, Catholic University of Valencia San Vicente Mártir, C/Guillem de Castro 94, 46001, Valencia, Spain.

¹⁷International Institute of Nutritional Sciences and Food Safety Studies, University of Central Lancashire, Preston, United Kingdom.

¹⁸University of Southern Denmark, Mads Clausen Institute, NanoSYD, Alsion 2, 6400 Sønderborg, Denmark.

¹⁹Center for IPS Cell Research and Application, Kyoto University, Kyoto, 606-8397, Japan.

²⁰Condensed Matter Theory Group, Materials Theory Division, Department of Physics and Astronomy, Uppsala University, Box 516, 75120, Uppsala, Sweden

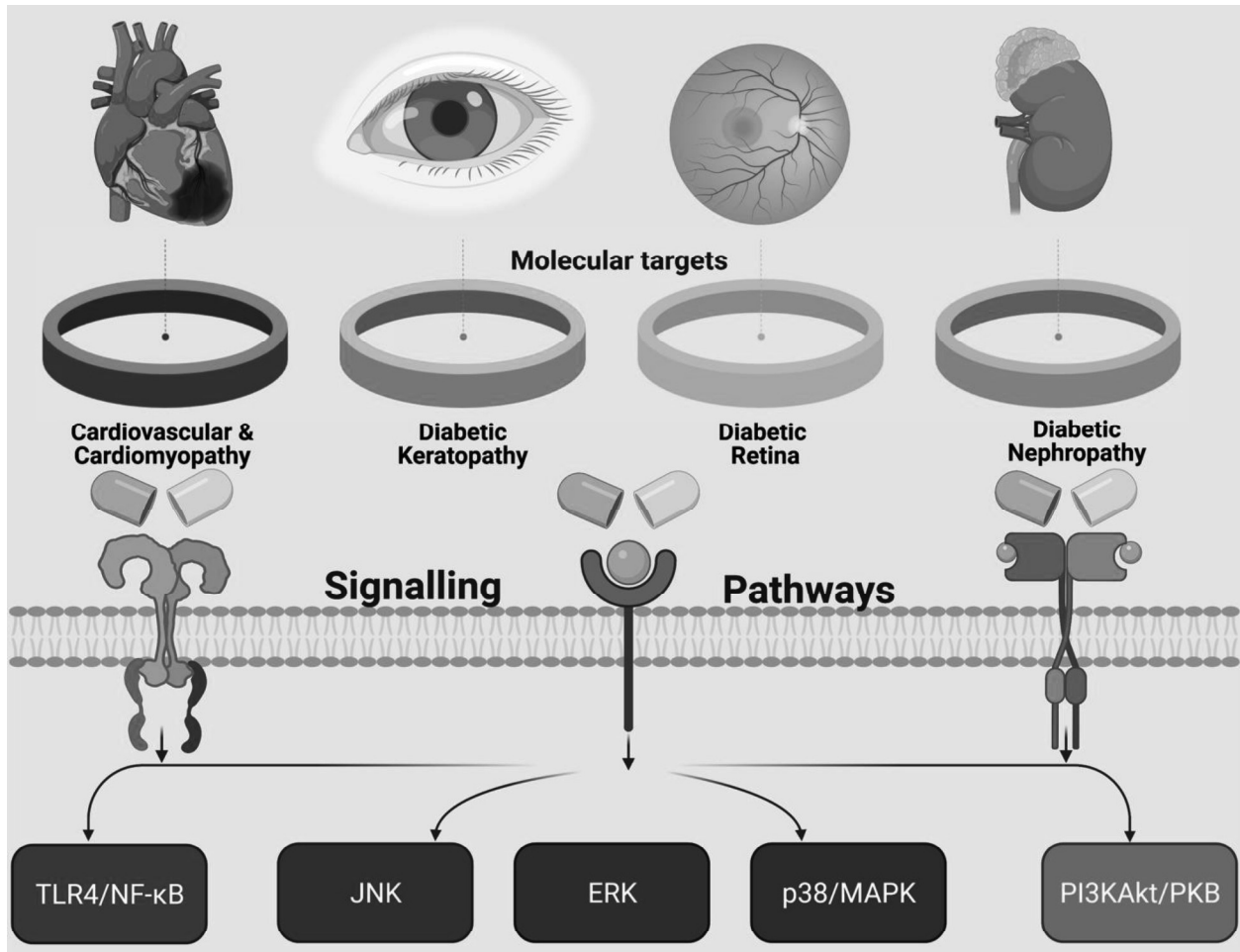
²¹School of Pharmacy & Pharmaceutical Sciences, Ulster University, Coleraine, County Londonderry, BT52 1SA, Northern Ireland, UK

* *Corresponding Authors:* Dr. Murtaza M Tambuwala & Marzieh Lotfi

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 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.

Keywords: Diabetes, Diabetic complications, Signaling pathways, Molecular pharmacology, Targets



Graphical Abstract

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% (Saeedi et al. , 2019). 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 (Bharadwaj et al. , 2017, Einarson et al. , 2018, Tsilidis et al. , 2015). 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 (Gregg et al. , 2014). 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 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 (Akbar et al. , 2017, Toma et al. , 2021). 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 (PPAR α) plays a key role in facilitating DCM-related molecular happenings. Pharmacological directing of PPAR α stimulation is one of the most effective methods for diabetic patients. Metformin and glucagon-like peptide-1 (GLP-1) agonists are PPAR α -associated medications that have confirmed their effectiveness and security in decreasing glucose and lipid in diabetic individuals throughout the clinical investigations (Wang et al. , 2021b). 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 (Yu et al. , 2021a).

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 (Liu et al. , 2017). In diabetic mice, cure with LXA4 factor has decreased expression markers related to inflammatory conditions such as IL-6 and IL-1 β , 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 (Brennan et al. , 2018).

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 (Chatham et al. , 2021, Chatham et al. , 2020, Marsh et al. , 2013, Slawson et al. , 2010).

2.4 Role of Reactive Oxygen Species (ROS) in development of diabetes

By way of oxidative stress is one of the main (and probable initial) helps to the growth and development of diabetic properties, plans to decrease the making Reactive oxygen species (ROS) high rates, or expand degradation, for example with anti-oxidant function, may be 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 (PKC β)) or augmenting the expression of cardio-defensive ways (e.g., Phosphoinositide 3-kinase (PI3K) (p110 α)) may characterize new approaches for the management of diabetic cardiomyopathy in treatment (Huynh et al. , 2014). 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 (Liu et al. , 2013).

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 (Chai et al. , 2021). 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 (Hou et al. , 2021).

Molecular targets in diabetic complications have been shown in Figure 1:

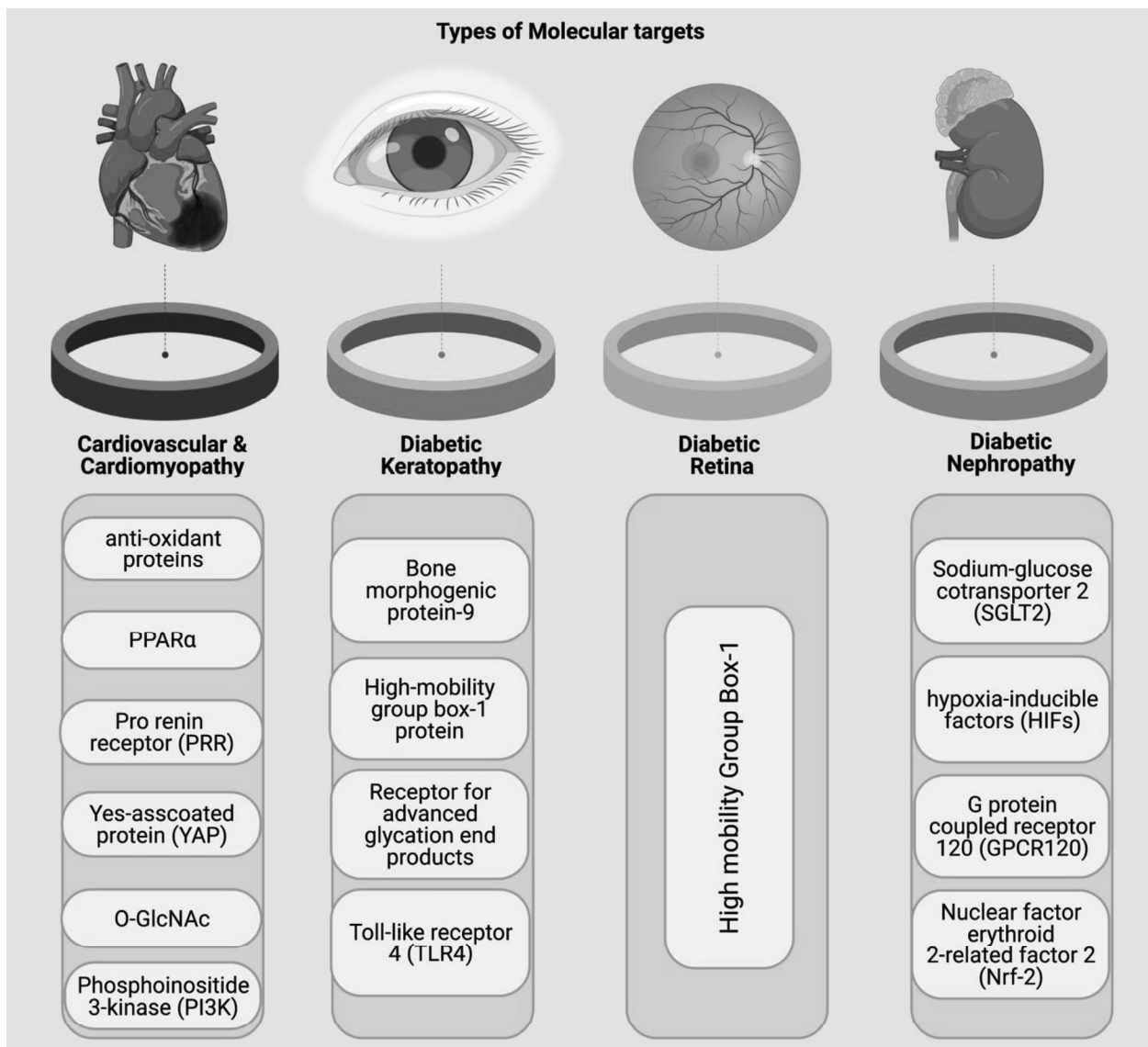


Figure 1: Molecular targets in diabetic complications. Created with Biorender.com

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, antiviral, hepatoprotective, anti-atherogenic, anti-hypertensive, and anti-cancer (Akiyama et al. , 2009, Haggag et al. , 2020b, Kandhare et al. , 2017). 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 (Li et al. , 2018b). 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 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 (Yuan et al. , 2018). 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 (Ye et al. , 2021). 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 (Abu El-Asrar et al. , 2015, Mohammad, 2014).

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 (Salvatore et al. , 2021).

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 (Zeng et al. , 2021). 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- κ B (NF- κ B) *in vivo*. Thus, Yishen capsule recovers DN by stimulating autophagy of podocytes by the SIRT1/ NF- κ B key pathway (Brosius et al. , 2010, Hu et al. , 2017, Liu et al. , 2021, Lu et al. , 2014, Su et al. , 2013).

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-2 α and HIF-1 α), 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-1 α while suppressing HIF-2 α . This alteration in the stability of HIF-1 α /HIF-2 α 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-1 α and activate HIF-2 α , 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 (Packer, 2021). 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- κ B p65, MAPK p38, IKK β 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 (Wei et al. , 2021).

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 Figure 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- κ B 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 (K Dua et al. , 2021). 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 (Sharma and Prossnitz, 2021). 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) (Sugama et al. , 2021).

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 (Chang et al. , 2021). Fucoidans - compound 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 (Mabate et al. , 2021, Xue et al. , 2019). The PI3K/PKB pathway, which controls insulin production, has been activated by Fucoidan (Gabbia et al. , 2017). 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 (Hu et al. , 2014, Sim et al. , 2019). Plant extract of *Hippophae rhamnoides* normalizes blood glucose via the PI3K/Akt pathway.

Furthermore, *Rosmarinus officinalis* extract inhibits NF- κ B 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 (Lee et al. , 2021). Liraglutide - human GLP-1 analog - reduces the IL-1 β , NF- κ B, and TNF- α expression in diabetic mice. According to the present findings, Liraglutide can meaningfully recover hepatic steatosis, mainly via decreasing the key inflammatory mediator's expression in the TNF- α pathway; therefore, it recovers non-alcoholic fatty liver problem in mice with diabetes (Luo et al. , 2019, Tong and D'Alessio, 2014). *Auricularia polytricha* (AP) and *Auricularia auricula* (AA) are prevalent eatable fungi. Their anti-diabetic roles may comprise the NF- κ B and related pathways (as NF- κ B actions at the crossroads of pathways number) (Xiang et al. , 2021).

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- α and IL-6 in these cells. Moreover, PMS pointedly inhibits high glucose-stimulated acts of NF- κ B/Akt signaling in HBZY-1 mentioned cells. Thus, PMS may be a potential agent with the cure DN's ability (Xiao et al. , 2021). The key factor of ketone bodies, β -hydroxybutyrate (BHB), has been newly considered a biologically potential molecule with many helpful characters, especially in diabetes (Newman and Verdin, 2017). 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 (Li et al. , 2021). 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- κ B function (Al Dubayee et al. , 2021, Ihling et al. , 1997, Wang and Bennett, 2012). 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 (Fryer et al. , 2002). 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 (Mackenzie and Elliott, 2014, Sun et al. , 2018). 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- κ B stimulation, TNF- α 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 (Mohanraj et al. , 2011).

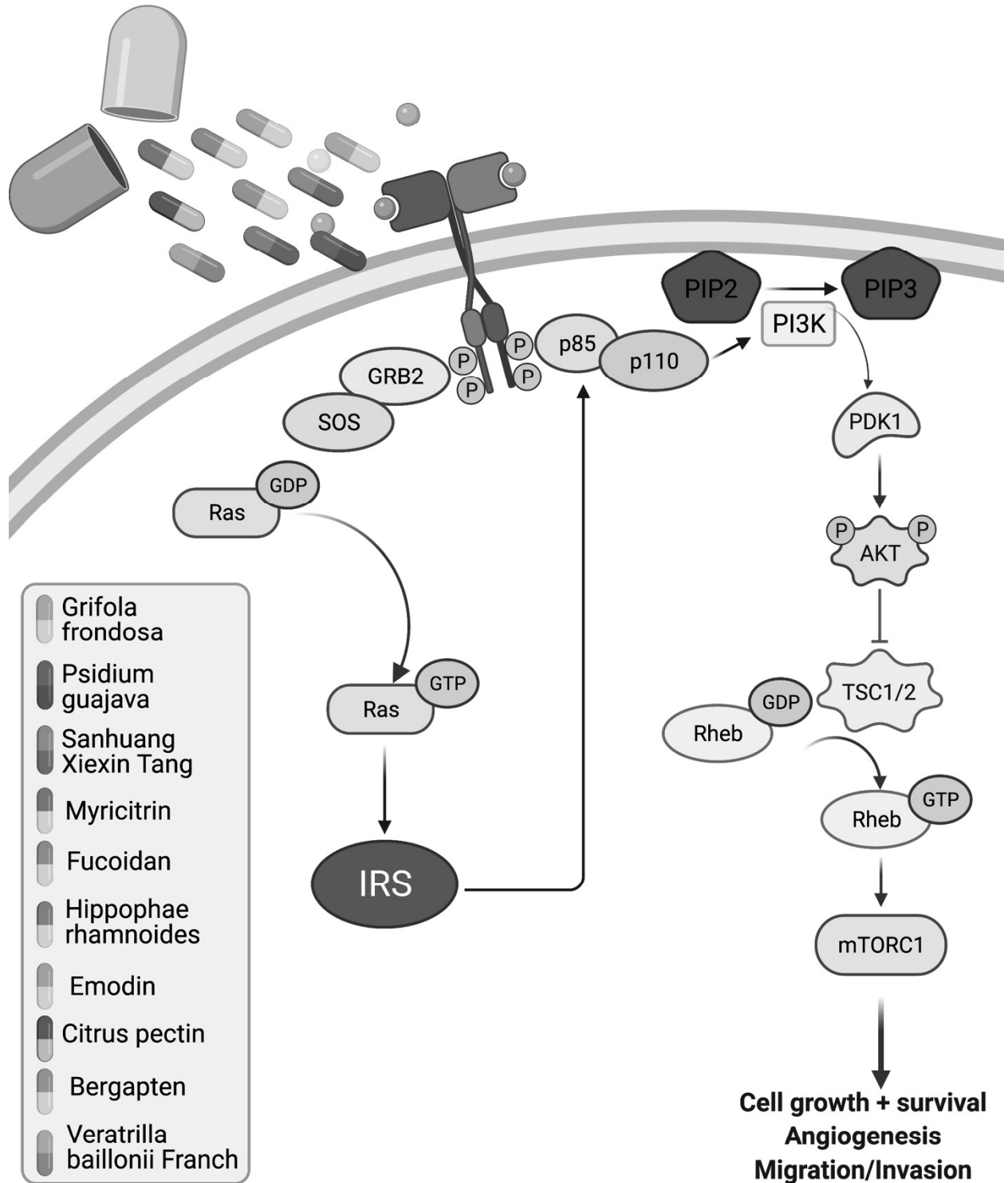


Figure 2: Anti-diabetic drugs affecting PI3K/Akt/PKB pathway. Created with Biorender.com

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 (Kang et al. , 2010). 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 (Fu et al. , 2010). 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 (Liu et al. , 2020).

Agonists for the serotonin 2C receptor (5-HT_{2C}R) 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-HT_{2C}Rs may increase glucose tolerance without weight changes and that this may demonstrate a new approach in the treatment of T2D (Zhou et al. , 2007). 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- κ B 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 (Lazaro et al. , 2015). 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-3 β (GSK-3 β) 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 (Joshi et al. , 2019, Li et al. , 2019).

Oridonin, a component obtained from *Rabdosia rubescens*, has several notable immunoregulatory, anti-inflammatory, and anti-tumor functions (Figure 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- κ B 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- κ B key pathways (Li et al. , 2018a, Mehta et al. , 2020, Rawat et al. , 2020, Tew et al. , 2020, Wang et al. , 2013, Zheng et al. , 2020).

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 (Fathalipour et al. , 2019). The diabetes-associated osteoporosis knowingly increases the triggering of the NF- κ B, 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- κ B, and JNK/MAPK pathways, thus defending trabecular construction and reducing bone tissue differentiation. This constituent can also decrease collagen's injury by its function (Li et al. , 2016).

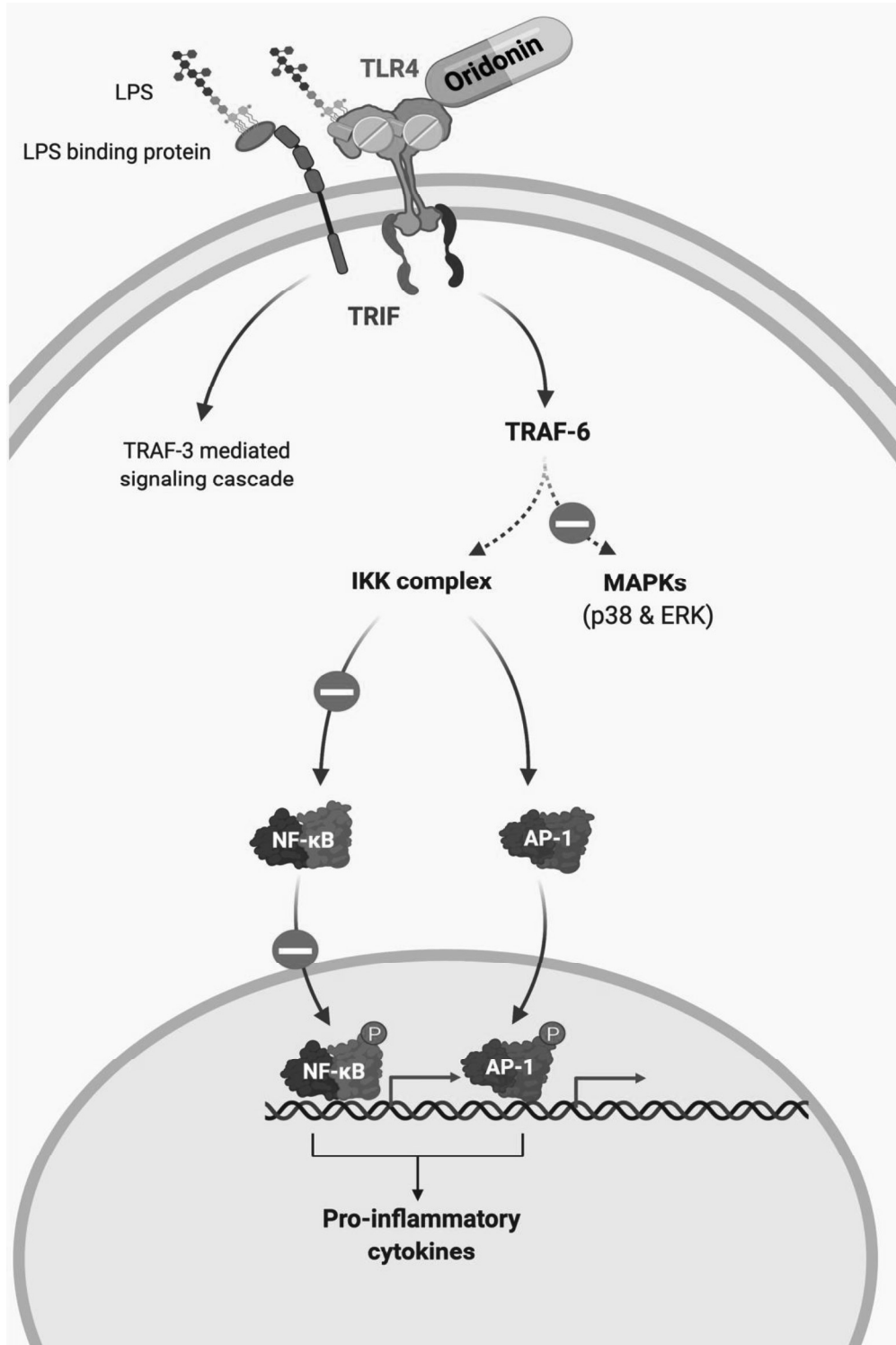


Figure 3: Anti-diabetic drugs affecting PI3K/Akt/PKB pathway. Created with Biorender.com

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 (Vinayagam et al. , 2018). 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- κ B-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 (Lu et al. , 2020).

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-3 β 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-3 β key pathway (Jing et al. , 2017). Isosteviol sodium prevents the cardiomyopathy-initiated promotion of both NF- κ B 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- κ B and ERK without altering AGEs or blood glucose (Tang et al. , 2018).

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 (Chen et al. , 2018, Wu et al. , 2020). 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-3K/Akt signaling of T2D is distinctly regulated via SXT application (Wei et al. , 2018).

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 (Xian et al. , 2018). 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 GSK3 β 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 (Liu et al. , 2016).

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 (He et al. , 2020). 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- κ B expression, and these impacts have a vital role in recovering DN (Yuan et al. , 2015).

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- κ B pathway (Feng and Qiu, 2018) (similar to Oleanolic acid (Li et al. , 2017b) 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 (Yang et al. , 2018). Figure 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 (Gao et al. , 2015). Ginsenoside Rg5 (Rg5) is a key monomer in the 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-1 β and IL-18 expression as inflammatory cytokines are repressed, and the NF- κ B expression and the p38 MAPK phosphorylation are decreased with Rg5 cure in DN mice (Zhu et al. , 2020). 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 (Liu et al. , 2019). Liuwei Dihaung decoction is a famous typical traditional Chinese medication. It can mediate insulin resistance by PI3K/Akt pathway regulation in T2D rats (Dai et al. , 2016).

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 (Huang et al. , 2013). 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 (Al-Rasheed et al. , 2016). 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- κ B pathway and caspase-3 in the rats with diabetes and therefore it may obtain clinical request to cure neuronal defects in the diabetes (Kuhad et al. , 2009). 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 (Zhang et al. , 2019).

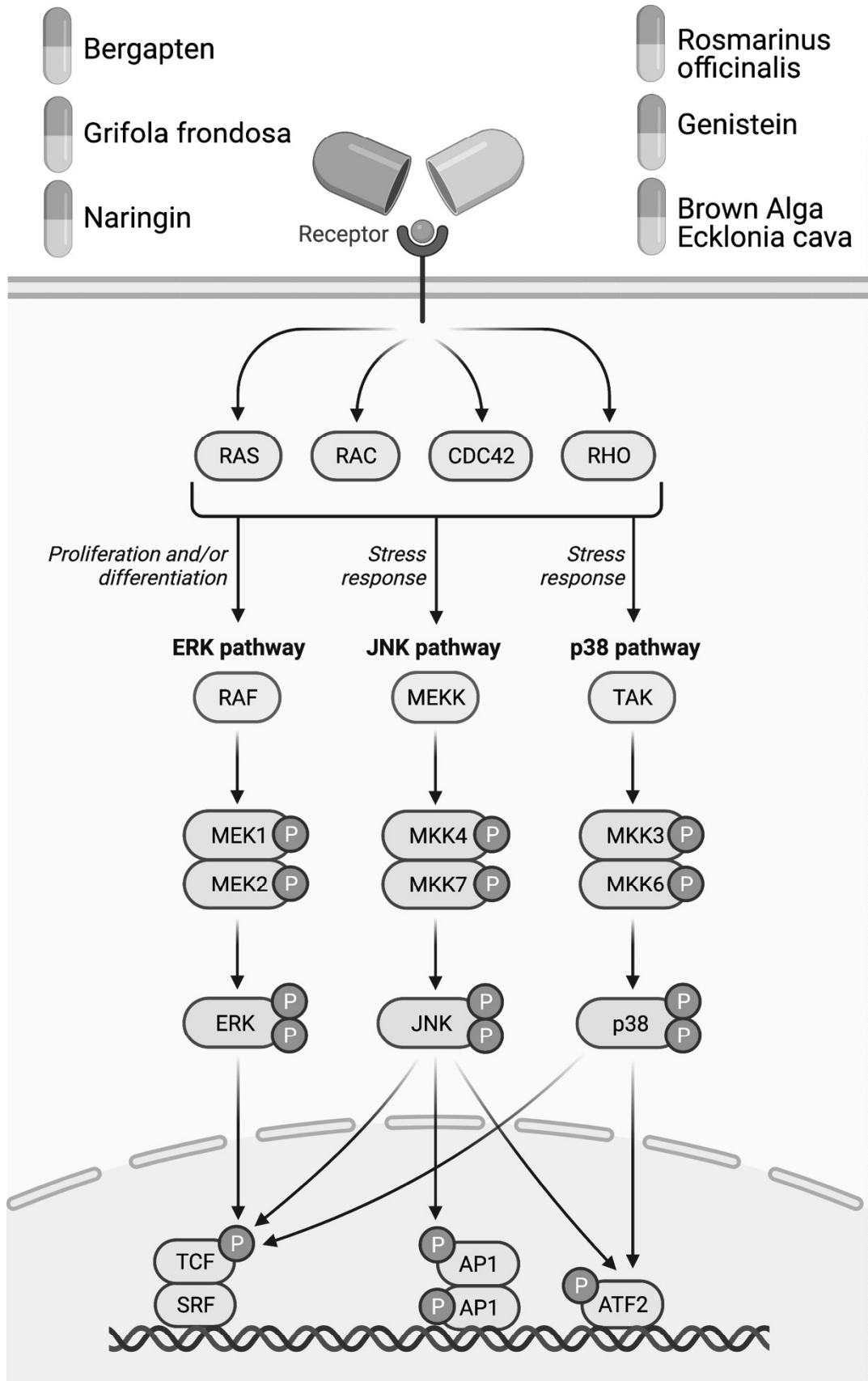


Figure 4: Anti-diabetic drugs and their target signaling pathways i.e., ERK, JNK and p38/MAPK pathways. Created with Biorender.com

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 (Schormann et al. , 2019). 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 (Cheng et al. , 2013, Yadav et al. , 2011)) and related to augmented PKM2 (Li et al. , 2020). This proposes that PKM2 may be the aim for DKD cure (Srivastava et al. , 2018). 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 (Lin et al. , 2021).

Furthermore, BI-2536 - an inhibitor of polo-like kinase 1 (PLK1) - reduces the Smad3 and NF- κ B signaling pathways in DKD. This proposes that the BI-2536 can be examined as a new treatment for DKD (Zhang et al. , 2021). 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- κ B and MAPK signaling factors. Therefore, RAP is anticipated to be planned as a leading composite for medications to treat renal fibrosis associated with DN (Zhang et al. , 2018).

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 (Behl et al. , 2021, Radhakrishnan and Kowluru, 2021, Yu et al. , 2011). 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 (Xie et al. , 2021).

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 (Yu et al. , 2021b). 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 (Zhou et al. , 2021). 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 (Wang et al. , 2021a). 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 (Wang et al. , 2021c). 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 Jagged1 and Notch1 in high glucose-cured cells, demonstrating a new and beneficial therapeutic aim for the diabetic nephropathy therapy (Liu et al. , 2015). 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 (Wu et al. , 2016).

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 (PPAR γ) molecular pathway (Kim et al. , 2013). Furthermore, studies have also revealed that fatty acids can be connected to stimulated PPAR α and prompt the FGF21 expression as the main task (Mai et al. , 2009). Because of the enhancing serum FGF21 rate in diabetic conditions, FGF21 can be a key predictor or good biomarker in diabetes (Guo et al. , 2021, Wente et al. , 2006).

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 (Alfaifi et al. , 2021). 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 (He et al. , 2021). 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- (Du et al. , 2021). Estrogen-related receptor α (ERR α) 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 (Aminizadeh et al. , 2021). ERR α triggers the PPAR α gene expression, which partially helps the process via which ERR α modulates metabolism (Huss et al. , 2007, Huss et al. , 2004).

The PPAR γ coactivator 1 (PGC-1) group of transcriptional coactivators stimulates biogenesis in mitochondria, oxidation of fatty acid, glucose absorption, and gluconeogenesis in different tissues (Finck and Kelly, 2006, Scarpulla, 2011). ERR α can modulate the expression of PGC-1 α in myocytes via transstimulation of PGC-1 α key gene (Arany et al. , 2007, Wang et al. , 2005). Therefore, the ERR α receptor and its co-regulator (PGC-1 α) are important molecular biomarkers in diabetes (Schreiber et al. , 2003, Shao et al. , 2010). 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

(Lee et al. , 2019). 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 (Lee et al., 2019) 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-GSK3 β -TGF β axis for fibrosis; 5) Rac1GTPase-MAPK-KLF5-CDK4/Cyclin D1 axis for proliferation and 6) Wnt/ β - catenin axis (Bose et al. , 2017, Chen et al. , 2021, Chen and Ma, 2017, Jin and Liu, Welters and Kulkarni, 2008) for both apoptosis and fibrosis mechanisms (Lee et al., 2019). 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 Ca²⁺ entrance and regulates the Ca²⁺ 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 (Vergès and Cariou, 2015). KCa3.1 blockade improved renal fibrosis in diabetes (Huang et al. , 2016). 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 (Li et al. , 2018c). *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 (Song et al. , 2018). 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 (Sun et al. , 2019). 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 β 2-adrenergic receptor (β 2AR) 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 β 2AR, brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB), and cAMP/protein kinase (PKA) key pathways (Gong et al. , 2020).

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 (Mohamed et al., 2020, El-Hakim et al. , 2021). 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 (Sacks et al. , 2018), 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 (Haggag et al. , 2016, Haggag et al. , 2018, Li et al. , 2017a). Nanoparticles of Polydatin-loaded chitosan are the potential good nano-carriers for the continued distribution of Polydatin (Mostafa et al. , 2021). 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- κ B and TNF α 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 (Al-Trad et al. , 2019, Aljabali et al. , 2018, Aljabali et al. , 2020, Alomari et al. , El-Hakim et al. , 2021, Haggag et al. , 2020a, Haggag et al. , 2020c, Mishra et al. , 2019, Mohamed et al. , 2020, Sharma et al. , 2020). AuNPs have shown to possess unique optical, chemical and biological properties such as anti-hyperglycemic, anti-inflammatory, anti-oxidative and antimicrobial activities (Barathmanikant et al. , 2010, Karthick et al. , 2014). ZnONPs have exhibited potent anti- hyperglycemic, anti- oxidative stress, and anti- inflammatory activities in a diabetic animal model (Jiang et al. , 2018, Nagajyothi et al. , 2015). 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 (Huang et al. , 2004). Therefore, BSA is biocompatibility, biodegradable, non-toxic, non-immunogenic, and thus can be use as efficient drug delivery system (Rodrigues et al. , 2013, Tambuwala et al. , 2019). 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 (Nanjwade et al. , 2009). Polymersomes are polymeric vesicles produced with amphiphilic block polymers of different molecular weights that are more stable in comparison with liposomes (Rideau et al. , 2018).

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- κ B, JNK/MAPK, PI3K/AKT/mTOR, GSK-3 β , FoxO3a. These novel findings will help improve the treatment and management of diabetes based on molecular and targeted therapy.

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Overview of Key Molecular and Pharmacological Targets for Diabetes and Associated Diseases

Seyed Hossein Shahcheraghi^{1,2}, Alaa A. A. Aljabali³, Mazhar S Al Zoubi⁴, Vijay Mishra⁵, Nitin B. Charbe⁶, Yusuf A Haggag⁷, Garima Shrivastava⁸, Abdulmajeed G Almutary⁹, Abdullah M Alnuqaydan⁹, Debmalya Barh¹⁰, Kamal Dua¹¹, Dinesh K Chellappan¹², Gaurav Gupta¹³, Marzieh Lotfi^{14,15}, Ángel Serrano-Aroca¹⁶, Bojlu Bahar¹⁷, Yogendra K Mishra¹⁸, Kazuo Takayama¹⁹, Pritam Kumar Panda²⁰ and Hamid A Bakshi²¹ and Murtaza M Tambuwala^{21*}

¹Infectious Diseases Research Center, Shahid Sadoughi Hospital, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

²Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

³Department of Pharmaceutics & Pharmaceutical Technology, Yarmouk University, Irbid, Jordan

⁴Yarmouk University - Faculty of Medicine, Department of Basic Medical Sciences, Irbid, Jordan

⁵School of Pharmaceutical Sciences, Lovely Professional University, Phagwara 144411, Punjab, India

⁶Departamento de Química Orgánica, Facultad de Química y de Farmacia, Pontificia Universidad Católica de Chile, Av. Libertador Bernardo O'Higgins, Santiago 340, Región Metropolitana, Chile

⁷Department of Pharmaceutical Technology, Faculty of Pharmacy, Tanta University, Tanta, Egypt

⁸Indian Institute of Technology, Delhi, India

⁹Department of Medical Biotechnology, College of Applied Medical Sciences, Qassim University, Saudi Arabia

¹⁰Centre for Genomics and Applied Gene Technology, Institute of Integrative Omics and Applied

¹¹Discipline of Pharmacy, Graduate School of Health, University of Technology Sydney, Ultimo, NSW 2007, Australia

¹²Department of Life Sciences, School of Pharmacy, International Medical University, Kuala Lumpur, Malaysia

¹³School of Pharmaceutical Sciences, Suresh Gyan Vihar University, Jaipur, India.

¹⁴Department of Medical Genetics, School of Medicine, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

¹⁵Abortion Research Center, Reproductive Sciences Institute, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

¹⁶Biomaterials and Bioengineering Lab, Translational Research Centre San Alberto Magno, Catholic University of Valencia San Vicente Mártir, C/Guillem de Castro 94, 46001, Valencia, Spain.

¹⁷International Institute of Nutritional Sciences and Food Safety Studies, University of Central Lancashire, Preston, United Kingdom.

¹⁸University of Southern Denmark, Mads Clausen Institute, NanoSYD, Alsion 2, 6400 Sønderborg, Denmark.

¹⁹Center for IPS Cell Research and Application, Kyoto University, Kyoto, 606-8397, Japan.

²⁰Condensed Matter Theory Group, Materials Theory Division, Department of Physics and Astronomy, Uppsala University, Box 516, 75120, Uppsala, Sweden

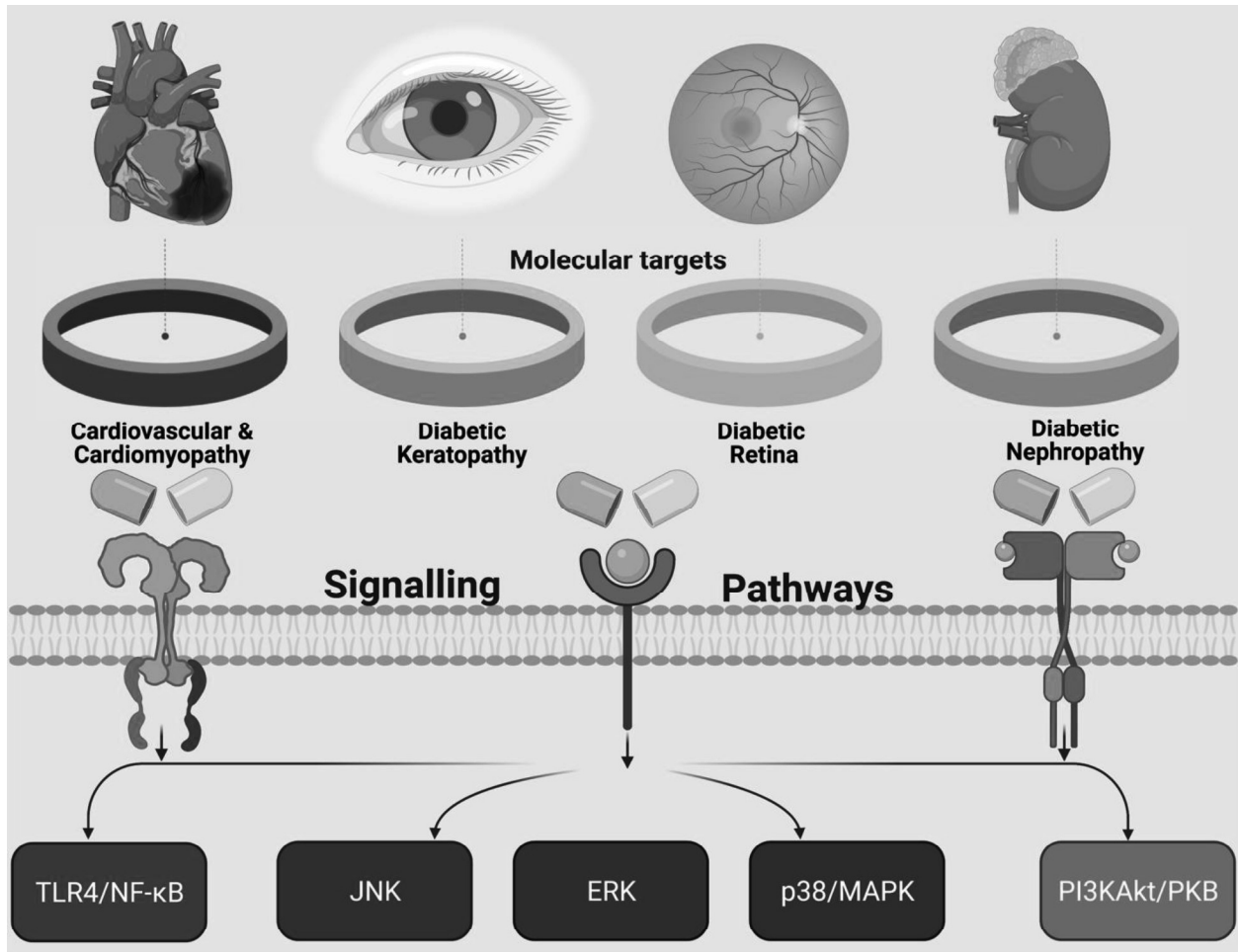
²¹School of Pharmacy & Pharmaceutical Sciences, Ulster University, Coleraine, County Londonderry, BT52 1SA, Northern Ireland, UK

* *Corresponding Authors:* Dr. Murtaza M Tambuwala & Marzieh Lotfi

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 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.

Keywords: Diabetes, Diabetic complications, Signaling pathways, Molecular pharmacology, Targets



Graphical Abstract

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% (Saeedi et al. , 2019). 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 (Bharadwaj et al. , 2017, Einarson et al. , 2018, Tsilidis et al. , 2015). 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 (Gregg et al. , 2014). 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 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 (Akbar et al. , 2017, Toma et al. , 2021). 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 (PPAR α) plays a key role in facilitating DCM-related molecular happenings. Pharmacological directing of PPAR α stimulation is one of the most effective methods for diabetic patients. Metformin and glucagon-like peptide-1 (GLP-1) agonists are PPAR α -associated medications that have confirmed their effectiveness and security in decreasing glucose and lipid in diabetic individuals throughout the clinical investigations (Wang et al. , 2021b). 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 (Yu et al. , 2021a).

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 (Liu et al. , 2017). In diabetic mice, cure with LXA4 factor has decreased expression markers related to inflammatory conditions such as IL-6 and IL-1 β , 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 (Brennan et al. , 2018).

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 (Chatham et al. , 2021, Chatham et al. , 2020, Marsh et al. , 2013, Slawson et al. , 2010).

2.4 Role of Reactive Oxygen Species (ROS) in development of diabetes

By way of oxidative stress is one of the main (and probable initial) helps to the growth and development of diabetic properties, plans to decrease the making Reactive oxygen species (ROS) high rates, or expand degradation, for example with anti-oxidant function, may be 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 (PKC β)) or augmenting the expression of cardio-defensive ways (e.g., Phosphoinositide 3-kinase (PI3K) (p110 α)) may characterize new approaches for the management of diabetic cardiomyopathy in treatment (Huynh et al. , 2014). 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 (Liu et al. , 2013).

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 (Chai et al. , 2021). 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 (Hou et al. , 2021).

Molecular targets in diabetic complications have been shown in Figure 1:

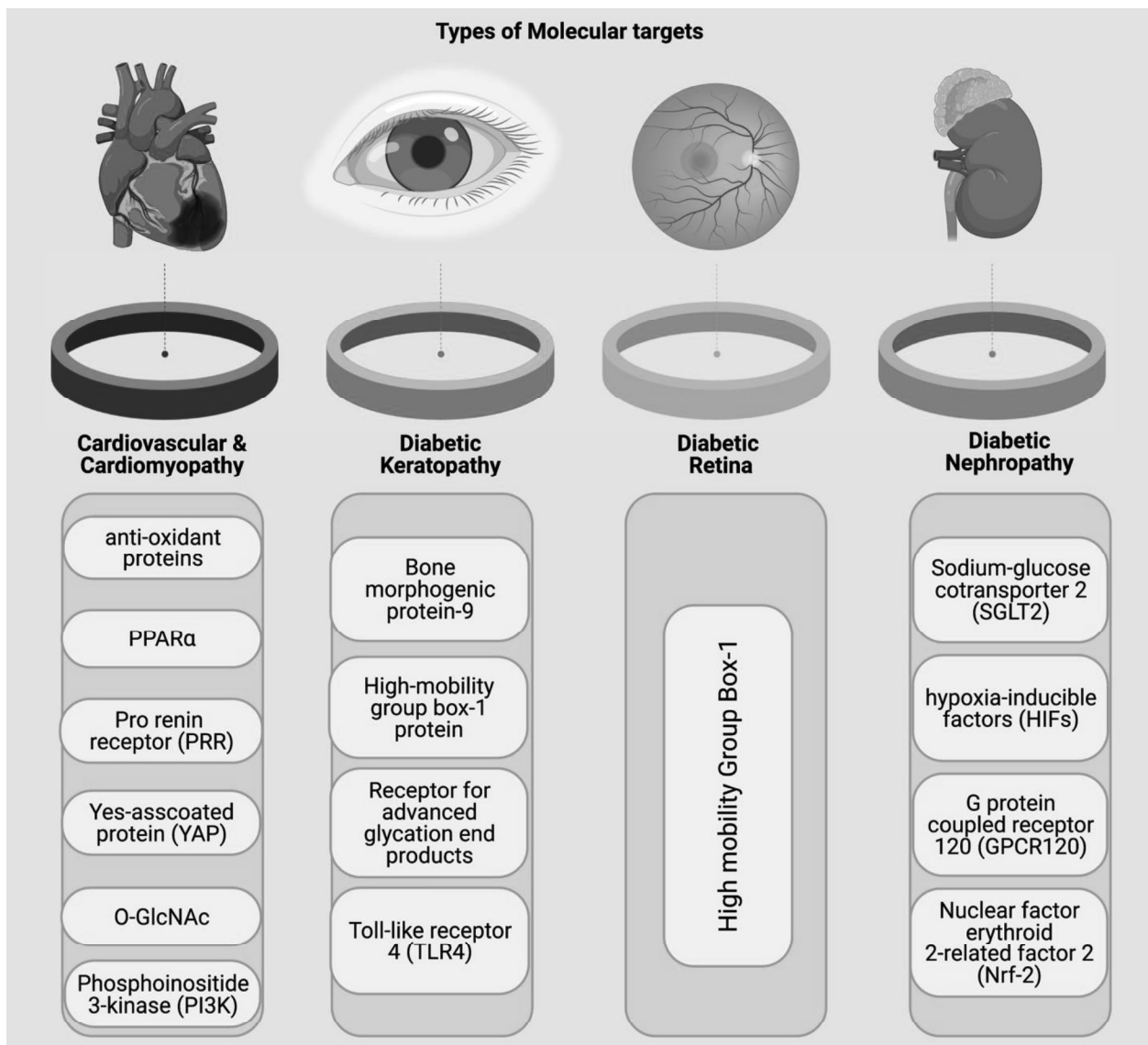


Figure 1: Molecular targets in diabetic complications. Created with Biorender.com

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, antiviral, hepatoprotective, anti-atherogenic, anti-hypertensive, and anti-cancer (Akiyama et al. , 2009, Haggag et al. , 2020b, Kandhare et al. , 2017). 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 (Li et al. , 2018b). 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 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 (Yuan et al. , 2018). 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 (Ye et al. , 2021). 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 (Abu El-Asrar et al. , 2015, Mohammad, 2014).

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 (Salvatore et al. , 2021).

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 (Zeng et al. , 2021). 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- κ B (NF- κ B) *in vivo*. Thus, Yishen capsule recovers DN by stimulating autophagy of podocytes by the SIRT1/ NF- κ B key pathway (Brosius et al. , 2010, Hu et al. , 2017, Liu et al. , 2021, Lu et al. , 2014, Su et al. , 2013).

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-2 α and HIF-1 α), 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-1 α while suppressing HIF-2 α . This alteration in the stability of HIF-1 α /HIF-2 α 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-1 α and activate HIF-2 α , 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 (Packer, 2021). 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- κ B p65, MAPK p38, IKK β 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 (Wei et al. , 2021).

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 Figure 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- κ B 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 (K Dua et al. , 2021). 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 (Sharma and Prossnitz, 2021). 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) (Sugama et al. , 2021).

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 (Chang et al. , 2021). Fucoidans - compound 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 (Mabate et al. , 2021, Xue et al. , 2019). The PI3K/PKB pathway, which controls insulin production, has been activated by Fucoidan (Gabbia et al. , 2017). 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 (Hu et al. , 2014, Sim et al. , 2019). Plant extract of *Hippophae rhamnoides* normalizes blood glucose via the PI3K/Akt pathway.

Furthermore, *Rosmarinus officinalis* extract inhibits NF- κ B 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 (Lee et al. , 2021). Liraglutide - human GLP-1 analog - reduces the IL-1 β , NF- κ B, and TNF- α expression in diabetic mice. According to the present findings, Liraglutide can meaningfully recover hepatic steatosis, mainly via decreasing the key inflammatory mediator's expression in the TNF- α pathway; therefore, it recovers non-alcoholic fatty liver problem in mice with diabetes (Luo et al. , 2019, Tong and D'Alessio, 2014). *Auricularia polytricha* (AP) and *Auricularia auricula* (AA) are prevalent eatable fungi. Their anti-diabetic roles may comprise the NF- κ B and related pathways (as NF- κ B actions at the crossroads of pathways number) (Xiang et al. , 2021).

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- α and IL-6 in these cells. Moreover, PMS pointedly inhibits high glucose-stimulated acts of NF- κ B/Akt signaling in HBZY-1 mentioned cells. Thus, PMS may be a potential agent with the cure DN's ability (Xiao et al. , 2021). The key factor of ketone bodies, β -hydroxybutyrate (BHB), has been newly considered a biologically potential molecule with many helpful characters, especially in diabetes (Newman and Verdin, 2017). 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 (Li et al. , 2021). 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- κ B function (Al Dubayee et al. , 2021, Ihling et al. , 1997, Wang and Bennett, 2012). 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 (Fryer et al. , 2002). 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 (Mackenzie and Elliott, 2014, Sun et al. , 2018). 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- κ B stimulation, TNF- α 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 (Mohanraj et al. , 2011).

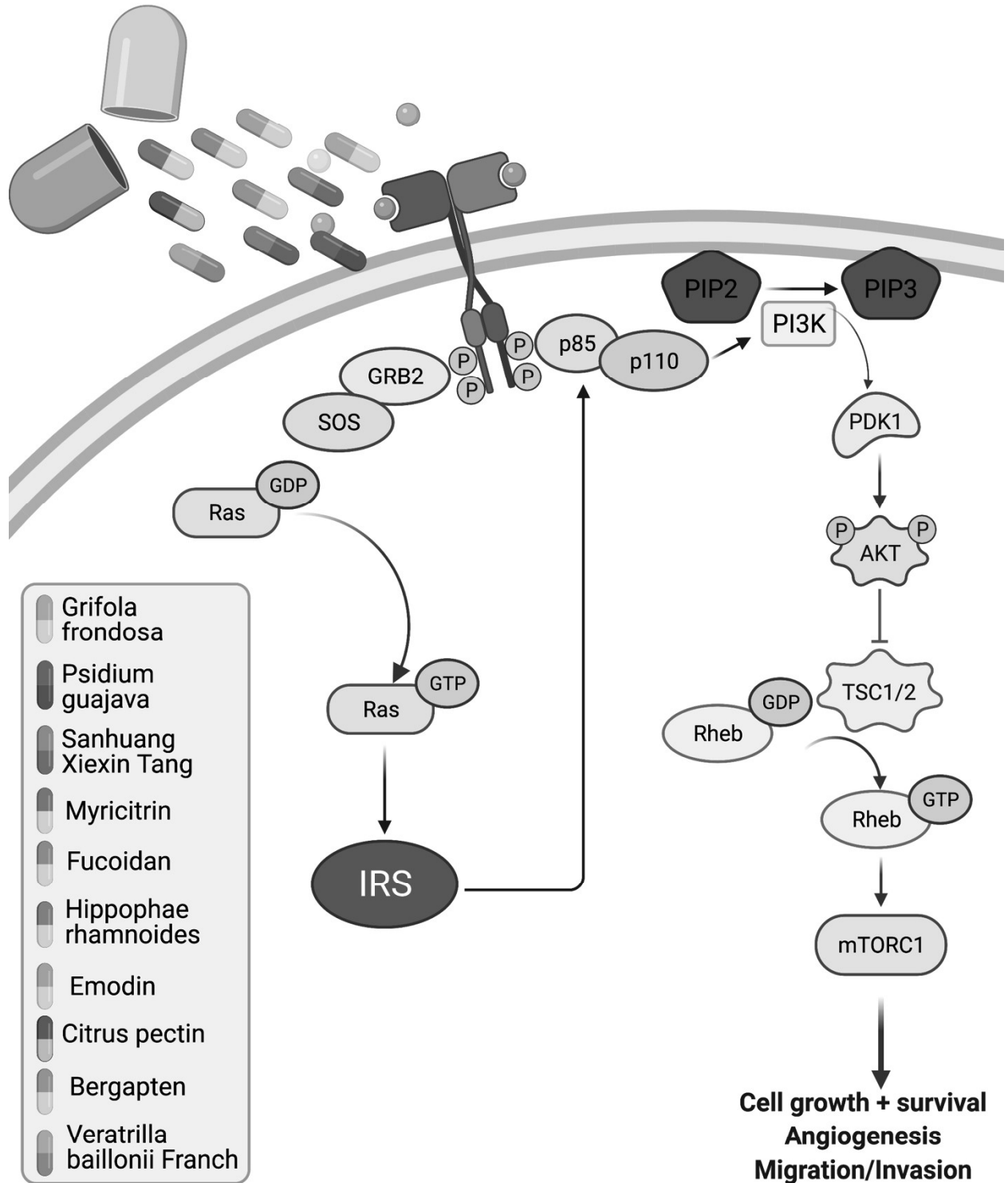


Figure 2: Anti-diabetic drugs affecting PI3K/Akt/PKB pathway. Created with Biorender.com

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 (Kang et al. , 2010). 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 (Fu et al. , 2010). 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 (Liu et al. , 2020).

Agonists for the serotonin 2C receptor (5-HT_{2C}R) 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-HT_{2C}Rs may increase glucose tolerance without weight changes and that this may demonstrate a new approach in the treatment of T2D (Zhou et al. , 2007). 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- κ B 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 (Lazaro et al. , 2015). 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-3 β (GSK-3 β) 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 (Joshi et al. , 2019, Li et al. , 2019).

Oridonin, a component obtained from *Rabdosia rubescens*, has several notable immunoregulatory, anti-inflammatory, and anti-tumor functions (Figure 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- κ B 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- κ B key pathways (Li et al. , 2018a, Mehta et al. , 2020, Rawat et al. , 2020, Tew et al. , 2020, Wang et al. , 2013, Zheng et al. , 2020).

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 (Fathalipour et al. , 2019). The diabetes-associated osteoporosis knowingly increases the triggering of the NF- κ B, 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- κ B, and JNK/MAPK pathways, thus defending trabecular construction and reducing bone tissue differentiation. This constituent can also decrease collagen's injury by its function (Li et al. , 2016).

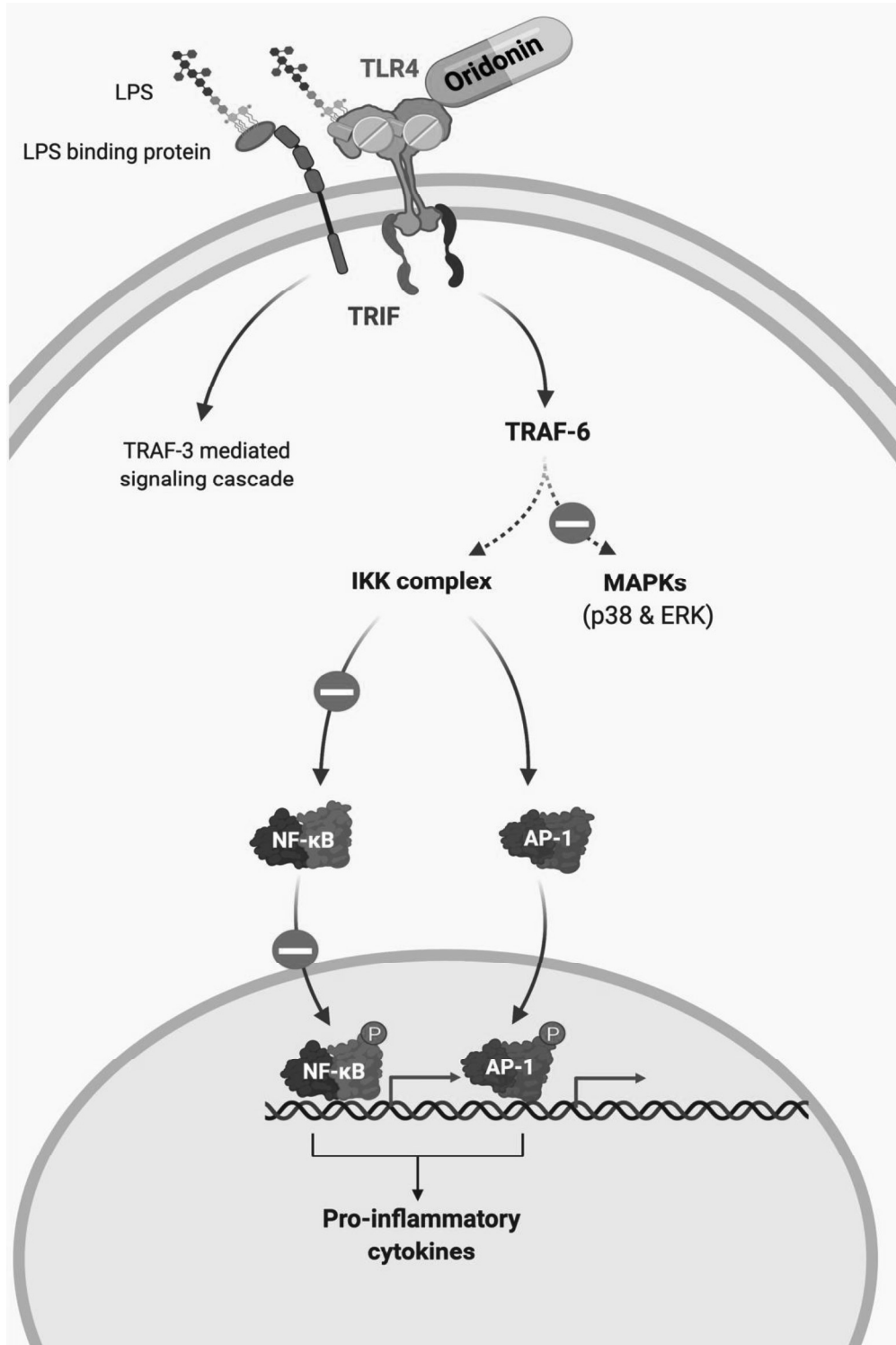


Figure 3: Anti-diabetic drugs affecting PI3K/Akt/PKB pathway. Created with Biorender.com

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 (Vinayagam et al. , 2018). 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- κ B-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 (Lu et al. , 2020).

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-3 β 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-3 β key pathway (Jing et al. , 2017). Isosteviol sodium prevents the cardiomyopathy-initiated promotion of both NF- κ B 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- κ B and ERK without altering AGEs or blood glucose (Tang et al. , 2018).

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 (Chen et al. , 2018, Wu et al. , 2020). 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-3K/Akt signaling of T2D is distinctly regulated via SXT application (Wei et al. , 2018).

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 (Xian et al. , 2018). 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 GSK3 β 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 (Liu et al. , 2016).

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 (He et al. , 2020). 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- κ B expression, and these impacts have a vital role in recovering DN (Yuan et al. , 2015).

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- κ B pathway (Feng and Qiu, 2018) (similar to Oleanolic acid (Li et al. , 2017b) 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 (Yang et al. , 2018). Figure 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 (Gao et al. , 2015). Ginsenoside Rg5 (Rg5) is a key monomer in the 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-1 β and IL-18 expression as inflammatory cytokines are repressed, and the NF- κ B expression and the p38 MAPK phosphorylation are decreased with Rg5 cure in DN mice (Zhu et al. , 2020). 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 (Liu et al. , 2019). Liuwei Dihaung decoction is a famous typical traditional Chinese medication. It can mediate insulin resistance by PI3K/Akt pathway regulation in T2D rats (Dai et al. , 2016).

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 (Huang et al. , 2013). 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 (Al-Rasheed et al. , 2016). 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- $\kappa\beta$ pathway and caspase-3 in the rats with diabetes and therefore it may obtain clinical request to cure neuronal defects in the diabetes (Kuhad et al. , 2009). 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 (Zhang et al. , 2019).

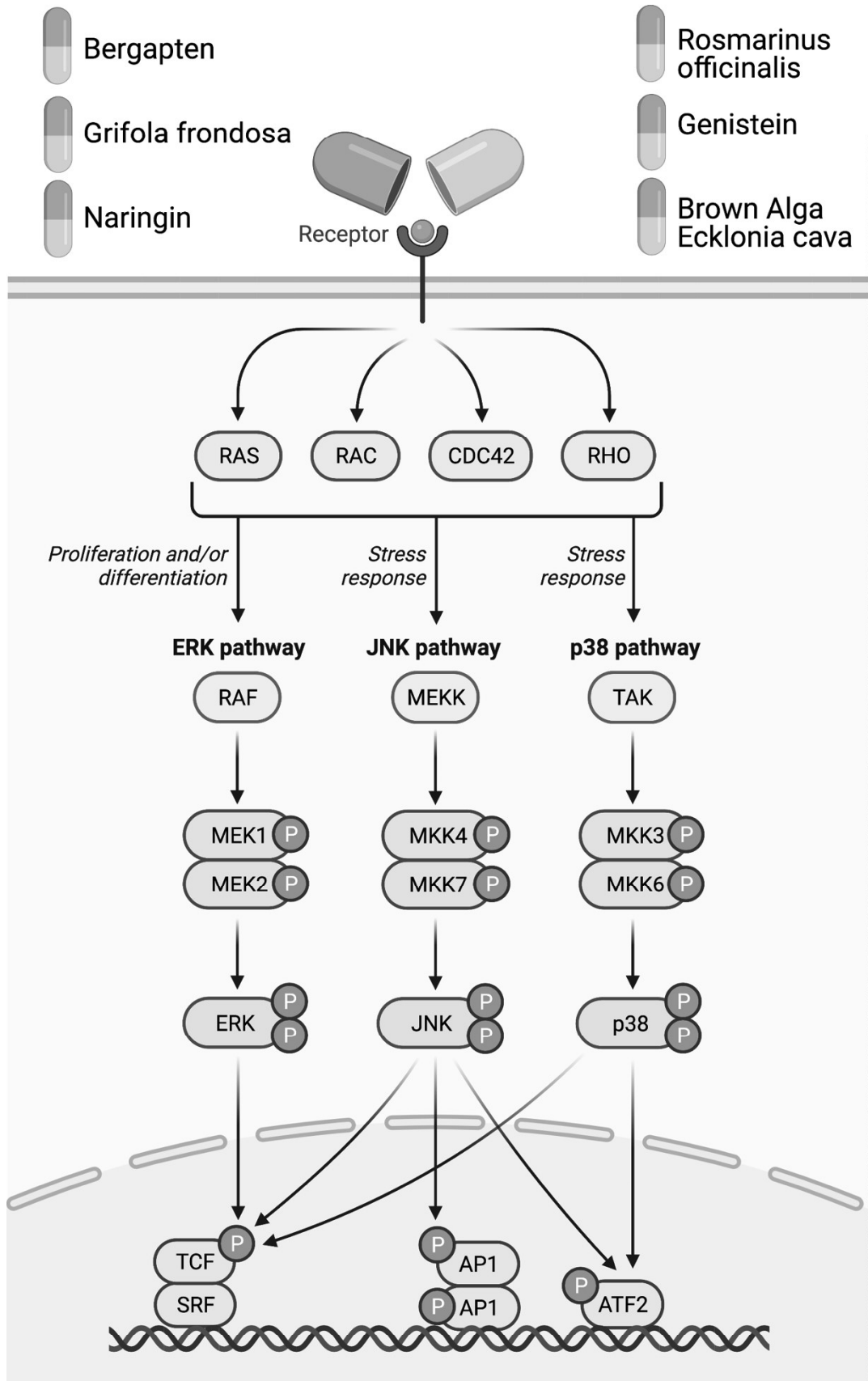


Figure 4: Anti-diabetic drugs and their target signaling pathways i.e., ERK, JNK and p38/MAPK pathways. Created with Biorender.com

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 (Schormann et al. , 2019). 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 (Cheng et al. , 2013, Yadav et al. , 2011)) and related to augmented PKM2 (Li et al. , 2020). This proposes that PKM2 may be the aim for DKD cure (Srivastava et al. , 2018). 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 (Lin et al. , 2021).

Furthermore, BI-2536 - an inhibitor of polo-like kinase 1 (PLK1) - reduces the Smad3 and NF- κ B signaling pathways in DKD. This proposes that the BI-2536 can be examined as a new treatment for DKD (Zhang et al. , 2021). 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- κ B and MAPK signaling factors. Therefore, RAP is anticipated to be planned as a leading composite for medications to treat renal fibrosis associated with DN (Zhang et al. , 2018).

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 (Behl et al. , 2021, Radhakrishnan and Kowluru, 2021, Yu et al. , 2011). 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 (Xie et al. , 2021).

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 (Yu et al. , 2021b). 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 (Zhou et al. , 2021). 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 (Wang et al. , 2021a). 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 (Wang et al. , 2021c). 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 Jagged1 and Notch1 in high glucose-cured cells, demonstrating a new and beneficial therapeutic aim for the diabetic nephropathy therapy (Liu et al. , 2015). 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 (Wu et al. , 2016).

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 (PPAR γ) molecular pathway (Kim et al. , 2013). Furthermore, studies have also revealed that fatty acids can be connected to stimulated PPAR α and prompt the FGF21 expression as the main task (Mai et al. , 2009). Because of the enhancing serum FGF21 rate in diabetic conditions, FGF21 can be a key predictor or good biomarker in diabetes (Guo et al. , 2021, Wente et al. , 2006).

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 (Alfaifi et al. , 2021). 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 (He et al. , 2021). 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- (Du et al. , 2021). Estrogen-related receptor α (ERR α) 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 (Aminizadeh et al. , 2021). ERR α triggers the PPAR α gene expression, which partially helps the process via which ERR α modulates metabolism (Huss et al. , 2007, Huss et al. , 2004).

The PPAR γ coactivator 1 (PGC-1) group of transcriptional coactivators stimulates biogenesis in mitochondria, oxidation of fatty acid, glucose absorption, and gluconeogenesis in different tissues (Finck and Kelly, 2006, Scarpulla, 2011). ERR α can modulate the expression of PGC-1 α in myocytes via transstimulation of PGC-1 α key gene (Arany et al. , 2007, Wang et al. , 2005). Therefore, the ERR α receptor and its co-regulator (PGC-1 α) are important molecular biomarkers in diabetes (Schreiber et al. , 2003, Shao et al. , 2010). 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

(Lee et al. , 2019). 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 (Lee et al., 2019) 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-GSK3 β -TGF β axis for fibrosis; 5) Rac1GTPase-MAPK-KLF5-CDK4/Cyclin D1 axis for proliferation and 6) Wnt/ β - catenin axis (Bose et al. , 2017, Chen et al. , 2021, Chen and Ma, 2017, Jin and Liu, Welters and Kulkarni, 2008) for both apoptosis and fibrosis mechanisms (Lee et al., 2019). 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 Ca²⁺ entrance and regulates the Ca²⁺ 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 (Vergès and Cariou, 2015). KCa3.1 blockade improved renal fibrosis in diabetes (Huang et al. , 2016). 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 (Li et al. , 2018c). *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 (Song et al. , 2018). 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 (Sun et al. , 2019). 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 β 2-adrenergic receptor (β 2AR) 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 β 2AR, brain-derived neurotrophic factor (BDNF)/tropomyosin receptor kinase B (TrkB), and cAMP/protein kinase (PKA) key pathways (Gong et al. , 2020).

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 (Mohamed et al., 2020, El-Hakim et al. , 2021). 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 (Sacks et al. , 2018), 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 (Haggag et al. , 2016, Haggag et al. , 2018, Li et al. , 2017a). Nanoparticles of Polydatin-loaded chitosan are the potential good nano-carriers for the continued distribution of Polydatin (Mostafa et al. , 2021). 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- κ B and TNF α 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 (Al-Trad et al. , 2019, Aljabali et al. , 2018, Aljabali et al. , 2020, Alomari et al. , El-Hakim et al. , 2021, Haggag et al. , 2020a, Haggag et al. , 2020c, Mishra et al. , 2019, Mohamed et al. , 2020, Sharma et al. , 2020). AuNPs have shown to possess unique optical, chemical and biological properties such as anti-hyperglycemic, anti-inflammatory, anti-oxidative and antimicrobial activities (Barathmanikant et al. , 2010, Karthick et al. , 2014). ZnONPs have exhibited potent anti- hyperglycemic, anti- oxidative stress, and anti- inflammatory activities in a diabetic animal model (Jiang et al. , 2018, Nagajyothi et al. , 2015). 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 (Huang et al. , 2004). Therefore, BSA is biocompatibility, biodegradable, non-toxic, non-immunogenic, and thus can be use as efficient drug delivery system (Rodrigues et al. , 2013, Tambuwala et al. , 2019). 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 (Nanjwade et al. , 2009). Polymersomes are polymeric vesicles produced with amphiphilic block polymers of different molecular weights that are more stable in comparison with liposomes (Rideau et al. , 2018).

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- κ B, JNK/MAPK, PI3K/AKT/mTOR, GSK-3 β , FoxO3a. These novel findings will help improve the treatment and management of diabetes based on molecular and targeted therapy.

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Endothelial cell (EC)

Advanced Glycation Products (AGE)

Endothelial Cell Dysfunction (ECD)

Diabetic cardiomyopathy (DCM)

Peroxisome proliferator-activated receptor α (PPAR α)

Glucagon like peptide-1 (GLP-1)

Yes-associated protein (YAP)

Pro renin receptor (PRR)

Adenoviruses-carried-PRR-gene (Ad-PRR)

Lipoxin A4 (LXA4)

O-linked N-acetylglucosamine (O-GlcNAc)

Reactive oxygen species (ROS)

Protein kinase C β (PKC β)

Protein kinase B (PKB or Akt)

Phosphoinositide 3-kinase (PI3K)

Protein kinase RNA (PKR)

Inositol-requiring enzyme-1 (IRE1)

Bone morphogenetic protein-9 (BMP9)

High-mobility group box 1 protein (HMGB1)

Toll-like receptor 4 (TLR4)

Transforming growth factor beta (TGF- β)

Vascular endothelial growth factor (VEGF)

Mitogenactivated protein kinase (MAPK)

Hypoxia inducible factor-1(HIF-1)

Diabetic retinopathy (DR)

microRNAs (miRNAs)

Type 2 diabetes (T2D)

Diabetic nephropathy (DN)

Nuclear factor- κ B (NF- κ B)

G protein-coupled receptor 120 (GPR120)

G protein-coupled estrogen receptor (GPER)

Tumor necrosis factor- α (TNF- α)

Nuclear factor erythroid 2-related factor 2 (Nrf-2)

c-Jun amino terminal kinase (JNK)

β -hydroxybutyrate (BHB)

Heat shock proteins (HSPs)

Glycogen synthesis kinase-3 β (GSK-3 β)

mammalian target of rapamycin (mTOR)

Intercellular adhesion molecule 1 (ICAM-1)

