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# Nuclear receptors and other molecular targets in type 2 diabetes mellitus

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| **ARTICLE INFO** | **ABSTRACT** |
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| | Diabetes is a group of metabolic disorders characterized by chronic hyperglycemia and glucose intolerance. Diabetes occurs because of defects in insulin secretion, insulin action, or both. Type 2 diabetes mellitus (T2DM), with a prevalence of more than 95%, is the most prevalent form of diabetes. Over the years, the effectiveness of the drugs used to treat diabetes has reduced. For this reason, targeting newer molecular targets might lead to the effectiveness of drugs. Over the years, there has been a great interest in targeting nuclear receptors for the treatment of T2DM. Some of these targets have been applied at the clinical level. However, other molecular targets belonging to G-coupled protein receptors, enzymes, and kinases have also been explored. Hence, in this review, we will discuss a few potential targets that have been applied clinically or could be the target for the treatment of T2DM. |

## INTRODUCTION

Nuclear receptors (NRs) have advanced remarkably in modern biomedical research and drug discovery (Mazaira *et al.*, 2018). Hollenberg *et al.* (1985) first discovered NRs as the receptors of the most familiar hormones, including 17β-estradiol, and corticosteroids/thyroid hormone (TH) (Holzer *et al.*, 2017). NRs play a significant role in physiological processes such as metabolism, osmoregulation, cell growth, immune response, enzymatic activities, development, and reproduction. The NRs superfamily comprises over 500 members and approximately 50 transcription factors (Alexander *et al.*, 2017; Burris *et al.*, 2013). NRs are an essential component of cellular physiology, which has attracted pharmaceutical interest. They serve as a target to treat diseases such as cancer, diabetes, inflammation, atherosclerosis,

and endocrine disorders (Alexander *et al.*, 2017; Burris *et al.*, 2013). For example, estrogen receptors (ERs) antagonists treat breast cancer. Also, peroxisome proliferator-proliferator receptors (PPARs) agonists treat type 2 diabetes mellitus (T2DM) and hyperlipidemia. Furthermore, the role of NRs in the circadian rhythm, cholesterol transport, and autoimmune disorders has taken utmost significance in treating infectious diseases (Khorasanizadeh and Rastinejad, 2016; Leopold Wager *et al.*, 2019).

NRs allow bone cells, such as osteoblasts, osteoclasts, and osteocytes, to sense their dynamic nature and respond to the development of bones and remodeling. Deficiency in specific NRs ligands can lead to bone loss; for example, estrogen loss in postmenopausal women can cause osteoporosis and increase the risk of bone fracture. On the other hand, glucocorticoids (GCs) could hamper one's health (Zuo and Wan, 2017). NRs classically act in three steps, i) repression, ii) derepression, and iii) transcriptional activation (Robinson-Rechavi *et al.*, 2003). The binding of NRs hormone to specific DNA sequences, termed hormone response elements (HRE), is responsible for the abovementioned functions (Escriva *et al.*, 2000). A significant objective of ongoing medication advancement programs has been to deliver ligands that display

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agonist or antagonist activity in the tissue in a receptor-particular way. The point is to lessen adverse reactions and, on account of certain malignant growths (Robinson-Rechavi *et al.*, 2003). NRs require multiple protein-protein interactions to regulate their target gene expression (Robinson-Rechavi *et al.*, 2003). Hence, the engagement with co-regulators offers functional flexibility to NRs (McKenna and O'Malley, 2002).

## NR CLASSIFICATION

NRs were grouped into three subfamilies based on their DNA-binding properties (Laudet *et al.*, 1992). Later, in 2004, it was divided into four subfamilies based on their DNA-binding properties and heterodimer priorities (Novac and Heinzel, 2004; Porter *et al.*, 2019). These are class I-steroid hormone receptors that primarily form ligand-induced homodimers. Receptors belonging to class I bind to DNA target sequences arranged in inverted repeats or palindromes. The second class (class II) is retinoid X receptors (RXRs) and thyroid receptors (TRs). The receptor belongs to class II heterodimerized and binds to symmetrical response elements. The third class (class III) is homodimerized and binds primarily to direct repeats. The fourth class (class IV) attaches to the core site of DNA as monomers (Novac and Heinzel, 2004; Porter *et al.*, 2019). In addition to this, based on the amino acid and dipeptide composition, NR classification has also been further designed into TH (TR, RAR, ROR), HNF4-like (HNF4, RXR, TLL, Coup, USP), Fushi tarazu-F1 like (SFI, FTF, FTZ-F1), and estrogen-like [ER, ERR, GC receptor (GR), mineralocorticoid receptor (MR), progesterone receptor (PR), androgen receptor (AR)] (Bhasin and Raghava, 2004). To date, the most acceptable one is the classification that classified NR into seven subfamilies. This classification numbered NR from zero to six based on the endogenous ligands that bind to specific receptors (Weikum *et al.*, 2018).

## OVERVIEW OF NR'S STRUCTURE

The general structure of NRs comprises five domains. These are the N-terminal domain (NTD), also known as the A/B domain, the DNA binding domain (DBD) or C domain, the hinge region (HRe) or D domain, the ligand-binding domain (LBD) or E domain, and the C-terminal domain (CTD) or F domain (Fig. 1) (Porter *et al.*, 2019). These domains play a vital role in receptor biology. NRs mass might vary but generally between 66 and 100 kDa (Weikum *et al.*, 2018). Unlike DBD, NTD is a highly variable region and least conserved in size and sequence. The NTD contains the activation function (AF) regions (Weikum *et al.*, 2018). These AF regions are responsible for transcriptional activation. AF is transcriptionally active and mediates ligand-independent activation function-1 (AF-1). AF-1 is the term used to distinguish them from the well-known AF-2 domain found at the C terminus of LBD. The AF-1 region can initiate transcription independent of LBD or synergize with the AF-2 (ligand-dependent) region to produce maximal receptor function (Onate *et al.*, 1998). AF-1 is a poorly structured activation domain that belongs to a broad category of intrinsically active compared to AF-2 (Almlöf *et al.*, 1998, 1997). The NTD region completely lacks conservation within the NRs subfamilies: PPARs (PPARα, PPARβ, PPARγ), ERs (ERα and ERβ) / ERRs (ERRα, ERRβ,
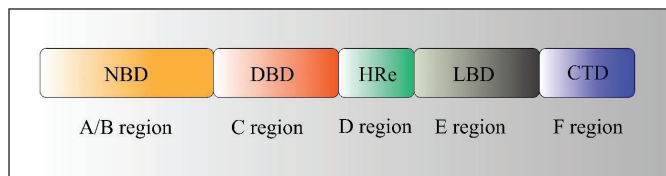


**Figure 1.** The general structure of NRs representing five domains.

and ERRγ) suggesting the functional roles of the NTD is highly receptor-specific (Gadaleta and Magnani, 2013).

DBD is adjacent to NTD and is the central, most highly conserved domain of NRs (Gadaleta and Magnani, 2013). DBD also has conserved zinc fingers that are accountable for binding to cognate HRE (Zhang *et al.*, 2004). Additionally, zinc fingers within the DBD are responsible for setting NRs apart from other DNA-binding proteins (Mangelsdorf *et al.*, 1995) and interacting with histone deacetylases 3 and 4 (Franco *et al.*, 2003). Zinc fingers contain a carboxy-terminal extension that provides DNA response elements and protein binding interfaces (Hart, 2002). Zinc finger motifs permit the specific recognition of short, imperfect inverted repeats of DNA (for steroid receptors) or direct repeats (for RXR-heterodimeric receptors) (Weatherman *et al.*, 1999). According to nuclear magnetic resonance and crystallographic research, four invariable cysteines in each zinc finger organize tetrahedrally on zinc ions. Both zinc finger modules fold together to produce a compact and interdependent structure. Zinc fingers contain the "P box" and "D box." These boxes are required to dimerize and discriminate core DNA recognition motifs. They are also responsible for direct interaction and binding specificity (Aranda and Pascual, 2001). The antiquated relationship between LBD and DBD has been demonstrated to be a profoundly influential association (Mangelsdorf *et al.*, 1995). DBD is required for gene activation, while other molecular regions in the carboxyl and amino terminus enhance its AF (Carson-Jurica *et al.*, 1990). DBD interacts with DNA sequences that are palindromic or direct repeats (six nucleotide segments in different configurations) or response elements (Fernandez, 2018).

LBD, the third region of NRs, was discovered in 1995 and contained -300 amino acids (Bain *et al.*, 2007). This region shows diversity in sequence but exhibits certain similarities in its overall design. This region functions in a ligand-specific manner (Mahajan and Samuels, 2000). Generally, LBDs are 12α helices arranged in a three-layered antiparallel sandwich (van der Vaart and Schaaf, 2009). The "front" and "back" sheets are made up of helices that are parallel to one another. The middle sheet of helices runs across the two outer sheets and only takes up space in the domain's upper half. The lower section of the domain is relatively devoid of protein, which forms an internal cavity for small-molecule ligands in most NR LBDs (Franco *et al.*, 2003). This domain is required for efficient homo/heterodimerization and interaction with transcriptional co-factors and components of the general transcriptional machinery (Uppenberg *et al.*, 1998). In this region, mutational investigation of ERs led to the identification of activation function-2 (AF-2). AF-2 is a highly conserved subregion inside the LBD's distal carboxyl terminus and is required for transcriptional activation (AF-2) (Glass *et al.*, 1997). Many pharmaceutical companies are developing LBD ligands to

limit or modify hormone-dependent processes such as infertility, bone loss, tumor, and skin diseases (Egner, 2002).

HRe is also known as the DBD's C-terminal extension. This region has about 25 amino acids and has a low similarity and resemblance to other NRs (Pawlak *et al*., 2012; Tetel *et al*., 1997). It is flexible, least conserved, and vulnerable to protease cleavage. It connects or hinges between the DBD and LBD for proper DNA binding and dimerization (Haelens *et al*., 2007). HRe also plays a role in harboring nuclear localization signals and comprises residues that abolish NRs interaction with the NR compressor when the mutation occurs (Aranda and Pascual, 2001). Though this domain is regarded as a passive polypeptide linker in the initial stage, it is a hotspot for post-translational modifications that exert translocation, DNA binding, and transactivation (Weikum *et al*., 2018).

F domain or CTD is present at the C-terminus of ER alpha and beta but not in all the NRs. It is one of the least conserved regions and varies in size (19–80 residues) (Skafar and Zhao, 2008). Though varying in length, the F domain plays a common function by affecting the transcriptional activation, dimerization, interactions with other proteins, and stabilizing agonist or antagonist-bound conformations in the NRs LBD (Patel and Skafar, 2015). The LBD was the least conserved region among other domains. Alternative mRNA splicing has been reported to occur in this region, resulting in complete or partial loss of LBD. The formation of these splice variants further influences the canonical receptors by functioning as dominant-negative inhibitors (van der Vaart and Schaaf, 2009).

## NRS AS DRUG TARGETS

Drugs targeting NRs are explored as therapeutic targets and are among the most widely and commercially successful. Tamoxifen and raloxifene for ERs in breast cancer, thiazolidinediones for PPARs in type 2 diabetes, mifepristone for PRs in ovulation, and dexamethasone for GRs in inflammatory disorders are a few examples (Burris *et al*., 2013; Rastinejad *et al*., 2013). A few drugs targeting NRs are Cytosporone B, 6-mercaptopurine, Celastrol, and Amoitone B. These compounds have been reported to possess antitumor properties *in-vitro* and *in-vivo* (Zhang *et al*., 2018). In their study, Bertilsson *et al*. (1998) have shown that the search for other unknown/unexplored NR could be discovered using a few standard methods, viz., PCR or yeast two-hybrid interactions. Their findings demonstrated an hidden markov model (HMM) profile-based search strategy for identifying novel orphan NRs in expressed sequence tag databases. Using this technology, the authors discovered a previously unknown human NR called hPAR, which is effectively triggered by a group of pregnanes and a group of clinically used drugs known to stimulate the activation of human CYP3A enzymes selectively. As a result, it was concluded that hPAR would most likely intervene in a novel signal pathway important for CYP3A gene expression regulation, with possible implications for the therapeutic evaluation of drug reactions that are beneficial to humans (Bertilsson *et al.* 1998).

NRs play a significant role in the gut's intestinal functions like absorption of nutrients and transport, water secretion/absorption, and gut-to-liver communication and regulation of the gut microbiome (Ning *et al*., 2019). Recently, several members of NRs have been validated as a therapeutic target in patients with IBD regulating gut physiology that is ERβ, GR, FXR, PPARγ, PXR, RARα, vitamin D receptor (VDR), HNF4α, or NR2F6 (Klepsch *et al*., 2019). In line with this, a study on mice deficient in NR2f6 was reported to be highly susceptible to dextran sodium sulfate-induced colitis characterized by the increased loss of weight, colonic tissue destruction, and immune cell infiltration. Taken together, NR2f6 alters intestinal permeability and decreases Muc2 expression (Klepsch *et al*., 2018). Similarly, the deletion of VDR in mice exaggerates colitis and colon tumorigenesis (Takada and Makishima, 2016). Interestingly, scientists have extended the role of AR from prostate cancer to T2DM. It has been demonstrated that AR deficiency in males is associated with T2DM and vice versa in females. The activation of AR in males has shown a beneficial effect in preventing T2DM. This is corroborated by preventing visceral fat accumulation and promoting insulin sensitivity in adipose tissue, skeletal muscle, and liver, regulating energy homeostasis in the liver and improving β-cell functions (Navarro *et al*., 2015).

## DIABETES MELLITUS

According to WHO estimates from 2014, 422 million people worldwide have diabetes, with the majority living in low- and middle-income countries. According to WHO 2021, diabetes is accountable for 1.6 million mortality per year. Over the last 10 years, the number of incidents and the prevalence of diabetes has steadily increased. Type 1 diabetes mellitus (T1DM) affects 1.1 million children and adolescents aged 14–19 years, according to the International Diabetes Federation (IDF) report. Every year, over 4 million people die from chronic hyperglycemia. Additionally, it is expected that by 2025, India, China, and the United States will have the most significant percentage of diabetic patients (King *et al*., 1998). Diabetes is a group of metabolic diseases characterized by chronic hyperglycemia and glucose intolerance resulting from defects in insulin secretion, insulin action, or both (Kharroubi, 2015). Diabetes is a dangerous and potentially fatal disease marked by thirst, polyuria, blurred eyesight, and weight loss. The most severe clinical signs are ketoacidosis or a non-ketotic hyperosmolar condition, which can lead to dehydration and coma. Commonly, diabetes is categorized into T1DM, T2DM, gestational diabetes mellitus (GDM), prediabetes, and idiopathic diabetes. T1DM (due to autoimmune β-cell destruction, usually leading to total insulin deficiency) occurs at any age but most often happens in children and young adults. Family history plays a role, but only in about 10%–15% of people of this type (Gottlieb, 2004). T2DM is characterized by insulin resistance due to insulin secretory deficiency. GDM is diagnosed in the second or third trimester of pregnancy that is not overt diabetes before gestation. Prediabetes refers to blood glucose levels higher than usual but not yet high enough to be diagnosed as type 2 diabetes. In other words, prediabetes also refers to impaired fasting glucose, impaired glucose tolerance, or glycated hemoglobin (A1C) of 6.0%–6.4%. Although not everyone with prediabetes will develop type 2 diabetes, people are at a greater risk for developing diabetes and severe comorbidities (Gottlieb, 2004). Patients with idiopathic diabetes tend to have permanent insulinopenia and are also vulnerable to episodic ketoacidosis. A few cases with type 1 diabetes fall into this category (Zuo and Wan, 2017). Other types of diabetes, such as monogenic diabetes syndromes (like neonatal

diabetes and maturity-onset diabetes of the young), diseases of the exocrine pancreas (such as cystic fibrosis and pancreatitis, hemochromatosis), and drug-or chemical-induced diabetes (as with GCs, neuroleptics, HIV/AIDS treatment, or after organ transplantation) (Petersmann *et al.*, 2018).

Of all the different forms of diabetes, T2DM is globally burdened and rapidly increasing, affecting people of all ages (Al-Rifai *et al.*, 2019). It is reported that 90%–95% of patients suffer from T2DM (Galicia-Garcia *et al.*, 2020). T2DM prevalence in the adult population has nearly doubled in the last decade, from 4.7% in 1980 to 8.5% in 2014. The global burden of T2DM in adults aged 20–79 is expected to go up to 629 million in 2045 (Al-Rifai *et al.*, 2019). In the UK, the prevalence of T2DM was estimated at 4.5 million in 2016. According to audits, males are more likely to get T2DM than females, with men contributing to 56% of all adult diabetics. T2DM is linked with pancreatic, liver, and kidney cancer (Man Chu, 2018). According to the IDF, 415 million people worldwide have diabetes, with 91% suffering from T2DM. Those with diabetes have a greater cardiovascular disease (CVD) prevalence rate than adults without diabetes. T2DM can shorten life expectancy by up to 10 years. Other studies (Einarson *et al.*, 2018) found that, along with rising T2DM incidence, the associated risk of CVD due to T2DM increased from 5.4% in 1952–1974 to 8.7% between 1975 and 1998 in the Framingham Heart Study (Einarson *et al.*, 2018).

T2DM is also called non–insulin-dependent diabetes/ type 2 diabetes/adult-onset diabetes. Patients suffering from this type are resistant to insulin, have relative (rather than absolute) insulin deficiency, and do not need insulin treatment to survive. There are probably several causes of this kind of diabetes (Galicia-Garcia *et al.*, 2020). Although the specific etiology of T2DM is unknown, most people suffering from T2DM are obese. These patients develop insulin resistance in the peripheral tissues, hyperglycemia, and ketoacidosis (rarely occurring). In addition to obesity, other risk factors are age, women having a history of GDM, and also in people with hypertension and dyslipidemia. Patients suffering from T2DM are also associated with cognition and moderate cognitive impairment. Altogether, T2DM impairs cerebral health, structural rigidity, and brain activity (Tiwari and Kumar, 2018). T2DM undergoes undiagnosed for several years because the hyperglycemia develops slowly and, at the initial stages, is often not severe enough for the patient to observe any of the symptoms of diabetes.

Nonetheless, patients are at higher risk of macrovascular and microvascular complications. Macrovascular complications include cerebrovascular diseases (heart attacks, stroke, insufficient blood flow to legs) and peripheral vascular and cardiovascular disease. Microvascular complications include retinopathies (blindness), nephropathy, neuropathy with the incidence of ulcers in the foot, Charcot joints, amputation, and autonomic and sexual dysfunction. Insulin levels in individuals with this type of diabetes may appear normal or increased. As a result, insulin secretion in these people is impaired and is inadequate to counteract insulin sensitivity (Tiwari and Kumar, 2018).

## Diabetes-related NRs

NRs are hormone-sensing transcription factors that convert changes in gene expression to nutritional or endocrine signals (Schupp and Lazar, 2010). Endogenous ligands for NRs include bile acids, phospholipids, steroid hormones, THs, retinoids, and vitamin D (Table 1) (Delerive *et al.*, 2000; Schupp and Lazar, 2010).

The endogenous ligands of ERs are: estrone (E1), estradiol (E2), and estriol (E3) and have also been shown to bind diverse compounds with varying activity (Nelson and Habibi, 2013). ERα and ERβ are the most widely studied ERs. These receptors play a significant role in reproduction. They are expressed in other species, such as zebrafish and sea bream (Bardet *et al.*, 2002). Both zebrafish (Menuet *et al.*, 2002) and sea bream (Muñoz-Cueto *et al.*, 1999) have receptors that are homologous to the human ERα (Green *et al.*, 1986). AR endogenous ligands include testosterone and the more active form, dihydrotestosterone. Reproductive, immunologic, cardiovascular, musculoskeletal, neurological, and hemopoietic systems rely on AR for their development and maintenance (Davey and Grossmann, 2016). PRs are of two types: PRA and PRB. Both these receptors are activated in response to hormonal stimuli such as progesterone (Banner *et al.*, 1992). Progesterone act on various tissues such as the uterus, mammary gland, brain, and bone and exerts diverse functions in these tissues (Graham and Clarke, 1997).

Bile acid is the endogenous ligand for FXR (Wang *et al.*, 1999). FXR regulates bile acid and glucose metabolism,

**Table 1.** Few examples of NRs and their endogenous ligands.

| Sl. No. | NR | Ligands |
|---|---|---|
| 1. | ER | Estrone, estradiol, estriol |
| 2. | AR | Testosterone, dihydrotestosterone |
| 3. | PR | Progesterone |
| 4. | Farnesoid X receptor or bile acid receptor | Bile acid, bile acid derivatives |
| 5. | VDR | 1,25-dihydroxy vitamin D3 |
| 6. | Thyroid hormone receptor (THR) | 3,5,3',5'-tetraiodo-l-thyronine, 3,5,3'-triiodo-l-thyronine |
| 7. | RXR | Retinol and retinol derivatives |
| 8. | Rev-Erb | Heme |
| 9. | PPAR | 15-Deoxy-$\Delta$-12,14-Prostaglandin J2, 9- and 13-Hydroxyoctadecadienoic acid, oleoylethanolamide (OEA) |
| 10. | Liver X receptor (LXR) | 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24(S)-25-epoxycholesterol |

inflammatory reactions, barrier function, bacterial translocation prevention in the digestive organs (Ding *et al.*, 2015), and cholesterol homeostasis (Wang *et al.*, 1999). FXR also prevents cardiovascular risk factors such as central obesity, glucose intolerance, high cholesterol, and hypertension (Lefebvre *et al.*, 2009). For VDRs, an endogenous ligand is 1,25-dihydroxy vitamin $D_3$ (1,25-$(OH)_2D_3$) (Teske *et al.*, 2016). The activation of VDR initiates the autocrine and endocrine processes that are involved in gene expression and calcium absorption regulation (Heaney, 2008), the normal functioning of bones (Tanaka and Deluca, 1974), and the immune system (Haug *et al.*, 1998).

THR's endogenous ligands include 3,5,3',5'-tetraiodol-thyronine (T4) and 3,5,3'-triiodo-l-thyronine (T3). These hormones are vital for mammals' average growth, development, and homeostasis. They also treat obesity, hyperlipidemia, depression, osteoporosis (Ye *et al.*, 2003), cardiac diseases, and cancer. They also improve cognitive function (Brent, 2012), regulate skeletal growth (Kim and Mohan, 2013), and maintain adult brain function (Schroeder and Privalsky, 2014). While any dysfunction in this receptor, such as mutations, leads to resistance to THs, which further causes thyroid cancer, pituitary tumor, dwarfism, and metabolic abnormality (Cheng *et al.*, 2010).

In mice, 9-cis-13,14-dihydroretinoic acid was reported to be the endogenous RXR ligand (Rühl *et al.*, 2018). All-trans retinoic acid is the principal endogenous ligand for RAR. It is formed by the enzymatic oxidation of dietary vitamin A (di Martino and Welch, 2019). It is beneficial in treating osteoporosis, autoimmune disorders, asthma, cancer, diabetes, and obesity (Solt *et al.*, 2010). From the experimental and clinical approach, it has been evidenced that vitamin A (retinol) and its active derivatives (i.e., the retinoids) exert various effects on vertebrate embryos. These effects include body shaping and organogenesis, tissue regeneration, cell growth, differentiation, apoptosis (Mark *et al.*, 2009), visual functions (Kam *et al.*, 2012), acute myeloid leukemia therapy (di Martino and Welch, 2019), and inflammation (Mihály *et al.*, 2013). For REV-ERB, the endogenous ligand is haem/ heme (Raghuram *et al.*, 2007). Heme comprises an iron atom and a heterocyclic tetrapyrrole ring structure known as porphyrin. Several heme-containing proteins, such as hemoglobin, use this as

a prosthetic group. Furthermore, the capacity of heme to organize an iron atom inside its structure and promote reduction-oxidation (redox) reactions is essential for the function of these proteins (Sawicki *et al.*, 2015).

15d-PGJ2 appears to be a promising PPARγ endogenous ligand. Two linoleate derivatives, 9- and 13-HODEare possible PPARγ ligands among the oxidized lipids. OEA is an endogenous ligand with a higher affinity for PPARα (Lathion *et al.*, 2006). Its primary role is discovered in many diseases such as adipogenesis and storage of fat and eventually obesity and associated metabolic diseases such as hypercholesterolemia, insulin sensitivity, T2DM; and cardiovascular disease including high blood pressure (Heikkinen *et al.*, 2007), inflammation (Zieleniak *et al.*, 2008), gastrointestinal cancer (Necela and Thompson, 2008), and suppress colon carcinogenesis (Thompson, 2007). LXR has two isoforms, LXRα and LXRβ. LXRα is predominantly found in the liver and gut, while LXRβ is found throughout the body. Endogenous ligands for LXR consist of cholesterol derivatives such as 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24(S)-25-epoxycholesterol. These ligands bind to both LXR isoforms and increase their transcriptional activity (Schulman, 2010). The involvement of NRs in diabetes has been studied since the discovery of PPAR agonists. Other NRs that act as potential targets for T2DM are discussed in Table 2.

### Peroxisome proliferator-proliferator receptors

PPARs are the most widely studied NRs. PPAR subtypes, namely PPARα, γ, -β/δ, are members of the NR family that regulate glucose and lipid metabolism. PPARα agonist increases lipoprotein lipase activity and speeds up the process of β-oxidation (Wilding, 2012). Insulin sensitivity, blood pressure, and fatty acid (FA) uptake have all been demonstrated to improve when PPAR agonists are used (Ahmadian *et al.*, 2013). When used alone, rosiglitazone, pioglitazone, and troglitazone have been found to cause obesity, bone resorption, heart failure, and bladder cancer (Ma *et al.*, 2012). Troglitazone was also taken off the market due to its liver damage. However, using a dual PPAR agonist that activates PPARα and PPARγ has improved lipid profile and glycemic management. Remarkable, this dual activation displays

**Table 2.** NRs and potential ligands reported from preclinical studies for T2DM.

| Sl. No. | Target | Classification | Ligand | Classification |
|---------|--------|----------------|--------|----------------|
| 1. | PPAR | NR | Pioglitazone, rosiglitazone, LASSBio-1773 | Activator |
| 2. | LXR | NR | | Activator |
| 3. | ERβ | NR | DPN | Activator |
| 4. | AR | NR | Testosterone, dihydrotestosterone | Activator (in men) |
| 5. | VDR | NR | - | Activator |
| 6. | PR | NR | RU486 | Inhibitor |
| 18. | GR | NR | - | Inhibitor |
| 19. | THR | NR | - | - |
| 20. | REV-ERBα | NR | SR8278 | Inhibitor |
| 21. | MR | NR | - | Inhibitor |

PPARs: peroxisome proliferator-proliferator receptors; LXR: liver X receptor; ERβ: Estrogen receptor beta; AR: Androgen receptor; VDR: vitamin D receptor; PRs: Progesterone receptors; GR: Glucocorticoid receptor; THR: Thyroid hormone receptors; REV-ERBα: reverse erbα; MR: Mineralocorticoid receptor; DPN: Diarylpropionitrile.

fewer side effects. Such an approach has emerged as one of the most promising strategies for treating T2DM (Wei *et al.*, 2013). Another approach includes a combination of PPAR agonists and dipeptidyl peptidase 4 (DPP4) inhibitors. This strategy improved glycemia by increasing the expression of insulin receptor substrate (IRS)-2 and protecting pancreatic β-cells (Hirukawa *et al.*, 2015).

Growing evidence shows that PPARγ activation in adipocytes makes a significant contribution to its insulin-sensitizing effects by repressing the release of insulin-desensitizing factors like non-esterified fatty acids (NEFAs), tumor necrosis factor-α, leptin, interleukin-6, and resistin, and stimulating the release of insulin-sensitizing factors like adiponectin and visfatin (Kanatani *et al.*, 2007). Thiazolidinediones are progressively being demonstrated to reduce proteinuria and postpone the course of diabetic nephropathy, depending on or independent of glycemic management, in addition to their impact on insulin resistance and T2DM (Zheng and Guan, 2007). PPARγ has been linked to various renoprotective effects, including improved insulin resistance, reduced blood glucose, decreased rates of circulating NEFAs, and insulin-desensitizing cytokines, increased plasma adiponectin, lower blood pressure, and direct renal actions (Kollerits *et al.*, 2007). Recently, intraperitoneal administration of sulfonylhydrazone derivative, LASSBio-1773, showed hypoglycemic efficacy in a streptozocin-induced diabetic pain model, lowering heat hyperalgesia and mechanical allodynia and demonstrating potential new targets in T2DM (Zapata-Sudo *et al.*, 2016).

### Liver X receptors

The LXR is an NR that regulates triglycerides, fat metabolism, and inflammation. LXR also prevents the production of acellular capillaries caused by diabetes. Sirtuin-1 and LXR regulate retinal cholesterol metabolism and inflammation in diabetic retinas (Hammer *et al.*, 2017). The role of LXRs in diabetes has been correlated with the identification of their endogenous ligands, namely 22(R)-hydroxycholesterol, 24(S)-hydroxycholesterol, and 24(S),25-epoxycholesterol. The activation of LXRs increases the transcription of genes such as GLUT4 and insulin genes (Schulman, 2010) enhances glucose uptake and normalizes glycemia in mice with T2DM and insulin resistance (Baranowski, 2008). Interestingly, LXRβ is expressed in β-cells, and its ligands act as insulin sensitizers (Schulman, 2010). Additionally, LXR activation increased the transcription ABCA1 gene. ABCA1 participates in cholesterol efflux to acceptor proteins on pre β high-density lipoprotein (HDL), a process of reverse cholesterol transport. The loss of ABCA1 correlates with low HDL levels and increases the risk of T2DM (Fig. 2) (Haase *et al.*, 2015).

### Estrogen receptors

ERs consist of mainly three isoforms, ERα, ERβ, and GPER1. Among these, ERβ has a crucial role in diabetes prevention. ERβ is involved in adenosine triphosphate (ATP)-sensitive potassium ($K_{ATP}$) channel blockade. This effect occurs through the induction of 17β-estradiol (E2) in ERα-/- and ERβ-/- mice. Similarly, agonist activation of ERβ by diarylpropionitrile (DPN) lowered the activity of $K_{ATP}$ in a cGMP/PKG-dependent manner in β-cells of wild type (WT) but not in ERβ-/- mice.

Consequently, this leads to increased glucose-induced intracellular calcium $[Ca^{2+}]_I$ signals and induced insulin release (Soriano *et al.*, 2009). $K_{ATP}$ channels are complexes formed by the hetero-octameric and co-assembly of four Kir6.2 subunits called pore-forming subunits and four sulfonylurea receptor1 (SUR1) subunits called regulatory subunits. KCNJ11 and ABCC8 are the genes that code for both these two subunits. $K_{ATP}$ channels are crucial in physiological and pathophysiological states (Remedi and Nichols, 2016). $K_{ATP}$ converts metabolic status into electrical activity and processes as a metabolic sensor by sensing the metabolic changes in the pancreatic β-cells. This event occurs due to $K_{ATP}$ channel inhibition by ATP and activation by magnesium-ADP (Mg-ADP) (Szeto *et al.*, 2018). In diabetes mellitus, where normal glucose oxidation and a rise in [ATP]:[ADP] ratio fails to take place, inhibition or reduction of $K_{ATP}$ channels is necessary because this helps in membrane depolarization and is critical for voltage-dependent $Ca^{2+}$ channels opening. This further allows calcium entry into the cells and increases $[Ca^{2+}]$ concentration. Consequently, this is essential for insulin vesicles-plasma membrane fusion and subsequent insulin release (Remedi and Nichols, 2016). Hence, selective ERβ agonists could help increase insulin release (Fig. 3). In contrast, *in vivo* study of postmenopausal (performed
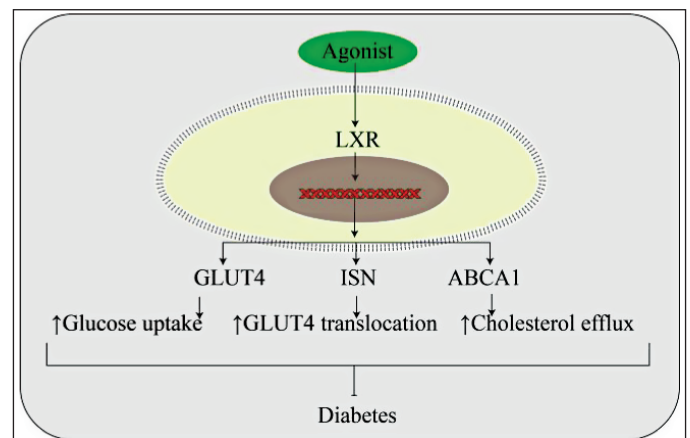


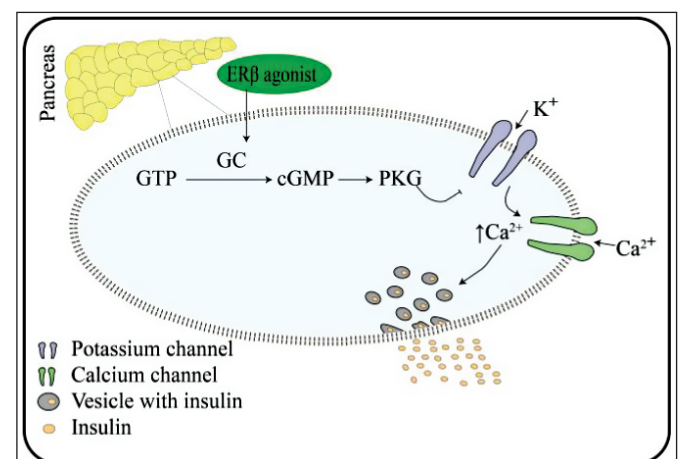**Figure 2.** Mechanism of action of LXRs in diabetes.



**Figure 3.** Mechanism of action of ERs in diabetes.

via bilateral ovariectomy) diabetes-induced vascular dysfunction (VD) in rats, selective ERβ agonists, and DPN did not show any improvement in impaired glycemia, VD, oxidative stress (OS), or inflammation (Bansal and Chopra, 2014).

### Androgen receptor

ARs have been found in different tissues and are involved in both central and peripheral physiology and insulin action (Diamanti-Kandarakis *et al.*, 2019). Androgens have a bidirectional effect on glucose homeostasis in males and females (Navarro *et al.*, 2015). Excess androgen in women, as observed in polycystic ovarian syndrome, can impair insulin levels and lead to excess body weight, adiposity dysfunction, and metabolic syndrome (Diamanti-Kandarakis *et al.*, 2019). The link between testosterone and diabetes, on the other contrary, has emerged as a significant risk factor for T2DM in the male population. In contrast to women, multiple studies in the last decade have found that androgen depletion in men is associated with an increased prevalence of T2DM (Yao *et al.*, 2018). Several reports have shown that testosterone therapy improved visceral obesity, insulin resistance, glycemic control, and lipid profile in hypogonadism males with T2DM (Li *et al.*, 2020). Also, testosterone administration has been shown to protect β-cell from apoptosis and stress-induced accelerated senescence. These effects of testosterone have been linked with the activation of the AR/PI3K/AKT pathway (Divakar *et al.*, 2017; Dong *et al.*, 2020). The activation of AR/PI3K/AKT could be the reason for the anti-inflammatory effect of testosterone in hypogonadism men with T2DM (Fig. 4) (Navarro *et al.*, 2016; Yamaguchi *et al.*, 2019). Altogether, the activation of AR in the male sex contributes to reversed impaired glucose tolerance in the skeletal muscle and decreased cholesterol in obese men (Pal *et al.*, 2019). Since testosterone can improve the β-cell function of the pancreas, improve insulin resistance, and reduce inflammatory milieu, targeting the androgen pathway could be a novel therapeutic option for developing anti-diabetic drugs.

### Vitamin D receptor

VDR is a nonsteroidal NR. VDR heterodimerized with retinoid X receptor to transcribe genes (Lei *et al.*, 2020). Apart from immune cells, VDR is also found in the liver, muscle fibers, adipocytes, and islets of the pancreas and may improve insulin sensitivity upon activation. In both T1DM and T2DM models, it has been found that VDR expression is decreased, suggesting that a decrease in VDR expression is a potential risk for diabetes development (Morró *et al.*, 2020). Recently, the potential role of VDR agonists and the bromodomain-containing protein 9 (BDCP9) inhibitor (iBDCP9) in partially restoring β-cell function and ameliorating hyperglycemia has been reported. The activation of VDR prevents the activities of inflammatory genes, while the use of iBDCP9 prolongs the activation and enhances the activity of VDR. In physiological condition and at the chromatin level, BDCP9 bind with acetylated lysine 91 residue of VDR and inhibit its activity (Wei *et al.*, 2018). Further, mechanistic insight into the anti-inflammatory activity of VDR activation has been linked with the inhibition of inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) alpha (IκBα) kinase (IκK), a key signaling component of NF-κB. Consequently, this improves insulin sensitivity (Dong *et al.*, 2020) and could be one of the mechanisms for preserving
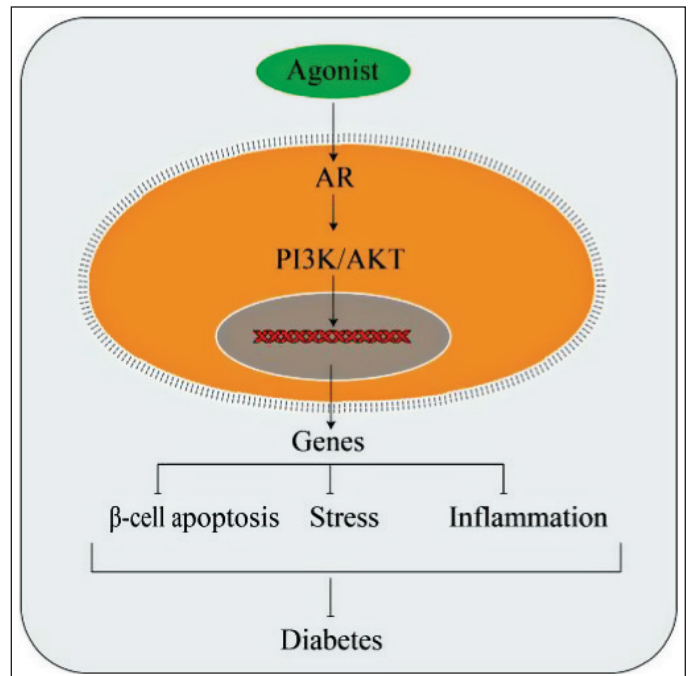


**Figure 4.** Mechanism of action of AR activation in diabetes.

β-cells, reducing inflammation, and preventing Streptozotocin (STZ)-induced diabetes (Morró *et al.*, 2020).

### Progesterone receptors

PR is a steroidal receptor of two isoforms, PRA and PRB (Gao and Nawaz, 2002). Using an animal model, progesterone and PRs have been linked with the pathogenesis of gestational diabetes (Picard *et al.*, 2002). When compared to the vehicle-treated group, female db/db mice treated with progesterone exhibited a significant rise in glucose levels (320 *vs*. 215 mg/dl, $p < 0.002$) after 9 weeks of treatment (Picard *et al.*, 2002). The increase in glucose levels is correlated with the decreased GLUT4 protein when rats are treated with progesterone (Campbell and Febbraio, 2002). While treatment with progesterone antagonist RU486 (30 mg/kg) for 2 weeks significantly reduces glucose levels. Further, using PR-knockout (PR−/−) female mice, the study reported that this group improved in glucose tolerance, secreted more insulin, and showed increased β-cell numbers when compared to the WT. In a similar study, female PR−/− mice improved β-cell functions such as insulin production and lower blood glucose levels (De Sa *et al.*, 2021).

### GC receptor

GCs are stress hormones that are produced by the adrenal cortex. Besides stress-related processes, GCs are also involved in glucose homeostasis, adipocyte formation, and inflammation regulation. Clinically, GCs such as dexamethasone, betamethasone, and hydrocortisone are employed to manage acute and chronic inflammatory diseases (Li and Cummins, 2022). However, an excess of GCs is linked to the development of hyperglycemia, insulin resistance, and abdominal obesity (Bauerle and Harris, 2016; Li and Cummins, 2022). Furthermore, these conditions were associated with risk factors such as hypertension,

obesity, coronary heart disease, single nucleotide polymorphisms, impaired renal functions, cytomegalovirus infection, smoking, race and ethnicity, concomitant immunosuppressive, and hyperlipidemia (Li and Cummins, 2022). The pathophysiology behind the involvement of GCs in diabetes includes multi-organs crosstalk. These organs are the brain, skeletal muscle, liver, adipose tissue, pancreas, and bone.

In the brain, particularly in the arcuate nucleus of the hypothalamus, GCs increase the transcription and functional activities of neuropeptide Y-agouti-related peptide neurons leading to increased appetite and leptin resistance (Li and Cummins, 2022). GCs cause muscle atrophy in skeletal muscle by decreasing glucose uptake and protein synthesis and increasing protein degradation. In the liver, GCs cause liver steatosis and hepatic insulin resistance. Liver steatosis is caused by the synergetic effects of GCs and insulin that stimulate the uptake of NEFAs by hepatocytes and triglyceride synthesis in the liver. Insulin resistance causes GCs-mediated increased enzyme expression and activity that participates in gluconeogenesis. In adipose tissue, GCs decrease glucose but increase lipid uptake and storage (Li and Cummins, 2022). GCs also increase adipogenesis, de novo lipogenesis, and triglyceride synthesis. In the pancreas, long-term exposure to GCs interferes with insulin synthesis and secretion and causes β-cell apoptosis. In bone, GCs inhibit the expression of osteocalcin, a protein secretes by osteoblast cells and promotes the activity of β-cell in secreting insulin. Hence, the inhibition of osteocalcin is indirectly linked to inhibiting insulin secretion (Li and Cummins, 2022). From a perspective, inhibition of GR could be beneficial in managing and treating diabetes.

### *TH receptors*

THs regulate body temperature, appetite, and sympathetic activity. THs also regulate metabolic rate through its metabolite (Teixeira *et al.*, 2020). The work which pioneered a link between hyperthyroidism and diabetes worsening was carried out by Coller and Huggins (1927). However, such a study conflicts with other studies. Recent studies have shown that insulin resistance occurs in a hypothyroidism state due decrease in GLUT2 gene expression and activity and missense variation in TH (Thr92Ala) (Mohammed Hussein and AbdElmageed, 2021). Results from these conflicting studies suggest a bidirectional role of thyroids in diabetes (Teixeira *et al.*, 2020). In that, both decreased (hyperthyroidism) and decreased (hypothyroidism) thyroid levels cause insulin resistance, impaired glucose tolerance (Wang, 2013), and high blood pressure (influencing adiposity). These bidirectional effects could result from genomic and non-genomic action of THs on the vasculature and in the hearts (Teixeira *et al.*, 2020). Hence, from these studies, the role of THR in diabetes is inconclusive.

### *Reverse erb A (REV-ERB A)*

The clock gene REV-ERB is an element of the biological clock's molecular machinery and has multiple metabolic activities in several organs, including the endocrine pancreas (Vieira *et al.*, 2012). REV-ERB is a transcription factor that controls lipids and glucose homeostasis, metabolism, adipocyte, and muscle development, and mitochondrial activity. In the endocrine pancreas, REV-ERB regulates glucose, insulin release, and pancreatic cell proliferation (Vieira *et al.*, 2012). REV-ERB is also implicated

in inhibiting inflammation by preventing the phosphorylation of IκK and nuclear translocation of the NF-κB subunit, p65. Consequently, this leads to the suppression of expression and secretion of pro-inflammatory markers (Guo *et al.*, 2019) that act as vital pro-diabetogenic stressors of T2DM (Brown *et al.*, 2022). In contrast to the REV-ERB activation, other studies (Brown *et al.*, 2022) demonstrated that REV-ERB inhibition in β-cell provides partial protection from inflammation and glucotoxicity-induced β-cell failure (Brown *et al.*, 2022). Hence, from these studies, the role of REV-ERB in diabetes is inconclusive.

### *Mineralocorticoid receptor*

Enhanced renin-angiotensin-aldosterone system activation has been associated with diabetes. Evidence suggests that aldosterone-binding MR may have a role in obesity and diabetes-related VD (Bender *et al.*, 2013; Schäfer *et al.*, 2013). In addition, regardless of race, blood pressure, or body weight, mineralocorticoid activity is associated with glucose intolerance. Increasing MR activity may indicate the typical relationship between obesity, high blood pressure, hyperlipidemia, and insulin resistance. The contribution of MR to the pathogenesis of diabetes involves a decreased transcription of the IR gene and increased degradation of IRS. MR also influences adipocyte production and increases OS and inflammation (Garg and Adler, 2012).

## OTHER THERAPEUTIC TARGETS IN T2DM

Current T2DM treatments aim to increase pancreatic β-cell production and decrease insulin resistance. Other treatment includes lifestyle counseling, oral anti-hyperglycemic medications, and/or insulin secretion (Esther Chan *et al.*, 2012). Currently approved therapies for T2DM are metformin, sulfonylureas, meglitinides, alpha-glucosidase inhibitors, thiazolidinediones, glucagon-like peptide1 (GLP-1) receptor agonists, DPP4 inhibitors, and sodium-glucose co-transporter-2 inhibitors. These therapies, in some cases, are ineffective in maintaining long-term glycemic control and display severe side effects. Problems related to sulfonylureas and meglitinides include loss of effectiveness, hypoglycemia, and weight gain. Also, metformin, alpha-glycosidase inhibitors, and GLP-1 receptor agonists have gastrointestinal side effects. At the same time, weight gain and heart failure are possible side effects of thiazolidinediones (Marín-Peñalver *et al.*, 2016). A few examples of the targets for T2DM are discussed in Table 3.

## G Protein-coupled receptors (GPCRs)

GPCRs are the most diverse and widely studied transmembrane receptors. These cell surface receptors are targeted for a wide range of diseases. In diabetes, these receptors may be divided into two main groups. One group increases insulin secretion and maintains β-cell mass; the other acts on adipose tissue and skeletal muscle. The second group contributes to glycogen storage and inhibiting glycogenolysis and gluconeogenesis in the liver. Other GPCRs are present in gastrointestinal enteroendocrine cells (GECs), the hypothalamus, and the gastrointestinal tract (GIT). These GPCRs are targeted to induce incretin secretion, decrease appetite, and reduce glucose after food intake (Atanes and Persaud, 2019). Of these, GPCRs that are targeting on induce incretin secretion have gained attention in recent times. A few examples

**Table 3.** Other molecular targets and potential ligands reported from preclinical studies for T2DM.

| Sl. No. | Target | Classification | Ligand | Classification |
|---|---|---|---|---|
| 1. | Gpr119 | GPCR | PSN632408 | Activator |
| 2. | Ffar1/gpr40 | GPCR | TAK-875, AMG-837 | Activator |
| 3. | Tgr5 | GPCR | SB-756050 | Activator |
| 4. | Glucokinase (GK) | Hexokinase | Piragliatin | Activator |
| 5. | FGF | Tyrosine-protein kinase | Fgf21, LY2405319, Fgf1, | Activator |
| 6. | Glycogen synthase kinase 3 (GSK-3) | Serine/Threonine protein kinase | CT118637, CT98014 | Inhibitor |
| 7. | Protein tyrosine phosphatase 1B (PTP1B) | PTP | Thiazolidinedione derivative, JTT-551, CCF06240 | Inhibitor |
| 8. | AMPK | Serine/Threonine protein kinase | Resveratrol, berberine | Activator |
| 9. | 11β-HSD1 | Oxidoreductase enzyme | Adamantyl triazoles, aryl sulfonamidothiazoles, anilinothiazolones, BVT.2733, INCB-13739, MK-0916, and MK-0736 | Inhibitor |
| 10. | Nox | Membrane-bound enzyme | GKT137831, apomycin, HET0016, apocynin, 4-(-2-aminoethyl)-benzenesulphonyl fluoride (AEBSF), and diphenylene iodonium (DPI), VAS3947 | Inhibitor |
| 11. | Aldose Reductase (ALR) | Aldo-keto reductase | ARI-809, sorbinil, ranirestat, M79175, kinostat, epalrestat, fidarestat, ginsenoside 20(s)-Rh2, 3'-o-(-3-chloropiraloyl)quercetin, pyrido(2,3-6) pyrazin-3 (4H), esculetin, kinostat | Inhibitor |

GPCRs: G-protein-coupled receptors; GPR40/FFAR1: G protein-coupled receptor 40/Free FA receptor 1; TGR5: (also known as G protein-coupled bile acid receptor 1 and membrane-type bile acid receptor); FGF: Fibroblast growth factor; AMP: Activated protein kinase (AMPK); 11β-HSD1: 11β- Hydroxysteroid dehydrogenase 1; Nox3: NADPH oxidase 3.

of GPCRs targeting in diabetes are GLP1R, GIPR, GPR119, free FA receptor 1 (FFAR1) (GPR40), FFAR4 (GPR120), and the bile acid receptor GPBAR1 (TGR5). GLP1 analogs such as exenatide, lixisenatide, and liraglutide target GLP1 receptors, bromocriptine target dopamine D2 receptors, and pramlintide target calcitonin/RAMP receptors are at the forefront GPCRs that have been approved for the treatment of diabetes (Atanes and Persaud, 2019).

### *G Protein-coupled receptor 119 (GPR119)*

GPR119 is a Gs-coupled receptor expressed in GECs, GIT, and pancreatic β-cells. It plays a crucial role in regulating energy balance and body weight. GPR119 coupled to Gs in response to lipid metabolites such as lysophosphatidylethanolamine, palmitoylethanolamide, oleoylethylamide, and OEA. Upon activation, GPR119 transduced the signal by increasing cGMP levels and cAMP response element-binding protein (CREB) activation leading to glucose-stimulated insulin secretion (GSIS) from β-cells (Atanes and Persaud, 2019; Oliveira de Souza *et al.*, 2021). GPR119 regulates glucose uptake in two ways: directly at the β-cell level and indirectly by releasing incretin hormones. Unfortunately, GPR119 activation has a negative impact on the heart and liver (Ritter *et al.*, 2016). Additionally, GPR119 knockout mice in β-cells failed to show glucose tolerance, and insulin secretory responsiveness remains unaffected (Atanes and Persaud, 2019). Perhaps these could be the additional reasons for the failure of GPR119 agonists in clinical trials apart from the lack of efficacy and pharmacodynamic and pharmacokinetic limitations. Hence, a better promising approach, such as a combination therapy of GPR119 agonist and DPP-4 inhibitor or other standard regiments,

could prove the beneficial effect of GPR119 agonists in T2DM patients (Ansarullah *et al.*, 2013).

### *Free FA receptor 1*

FFAR1/GPR40isa new therapeutic target for T2DM that regulates insulin secretion. It is also present in pancreatic β-cells, and its regulation occurs by activating medium and long-chain FAs (Itoh *et al.*, 2003). As a receptor for medium and long-chain free FAs, FFAR1 plays a vital function in insulin release in the presence of rising glucose levels. As a result, using particular agonists to target FFAR1 is a viable strategy to improve insulin secretion in T2DM patients. Selective agonists of FFAR1 increase cytosolic calcium, activate protein kinase C isoforms and enhance insulin signaling (Bailey, 2012). Many FFAR1 agonists, such as TAK-875 and AMG-837, have been pulled off the market due to their hepatotoxicity. Compound 11K (GPCR40/FFAR1 agonist containing 3,5-dimethylisoxazole) possessed a promising target. Also, novel agents such as yhhu4488, structurally different from other GPCR40 agonists, lowered serum glucose levels and improved β-cell function in T2DM (Guo *et al.*, 2015).

### *Takeda G protein-coupled receptor 5 (TGR5)*

TGR5 activation in GECs enhances GLP-1 release and maintains blood glucose homeostasis by enhancing GSIS. TGR5 activation also suppresses glucagon release, delaying gastric emptying time, inducing satiety, and improving glucose disposal in the peripheral tissues (Donnelly, 2012). During energy expenditure, TGR5 also engages in brown fat and skeletal muscle metabolism (Watanabe *et al.*, 2006). TGR5 agonists, for instance: SB-756050, have shown promise as a T2DM treatment

(Duan *et al.*, 2015) but have a negative role on the heart and gall bladder (Duan *et al.*, 2012).

**Glucokinase**

GK is an isoenzyme that is involved in glucose metabolism to glucose-6-phosphate. GK does so by phosphorylating glucose in β-cells, causing insulin release. GK activators act by attaching to the allosteric site of the GK enzyme. Piragliatin, for example, has been shown to have an immediate glucose-reducing impact in T2DM patients with no significant adverse effects. It has also been used to treat obesity-related issues. The only drawbacks of GK activators are the increased hepatic glycogen storage deposition of lipids in the liver and muscles. However, because combination therapy is already widely practiced, GK activators' combined pancreatic and hepatic effects may be more successful than currently available oral anti-diabetic drugs (Chu *et al.*, 2020).

**Fibroblast growth factors (FGFs)**

FGFs are a group of growth factors that are involved in the repair and regeneration of tissues. Originally, FGF was identified as a protein responsible for promoting fibroblast proliferation. In humans, a total of 22 FGFs have been identified (FGF1-14 and FGF16-23), out of which 18 are FGF receptor (FGFR) ligands, and 4 (FGF11, FGF12, FGF13, and FGF14) do not bind to FGFR as FGF homologous factors (Yun *et al.*, 2010). Based on sequence homology and phylogeny, these 22 FGFs are further grouped into 6 subfamilies: i) FGF1 and FGF2; ii) FGF3, FGF7, FGF10, FGF22; iii) FGF4, FGF5, and FGF6; iv) FGF8, FGF17, and FGF18; v) FGF9, FGF16, and FGF20; and vi) FGF19, FGF21, and FGF23. Classically, FGFs are considered paracrine factors, while recently, FGF19 and FGF21-22 actin an endocrine manner. These three FGFs (FGF19, FGF21-22) regulate cholesterol, bile acid, vitamin D, glucose, and phosphate homeostasis (Beenken and Mohammadi, 2009). Certain FGFs influence metabolism, energy homeostasis, and adipogenesis making them promising therapeutic targets for obesity and obesity-related cardiometabolic illness.

***Fibroblast growth factor 21***

FGF21 increases glucose uptake, which lowers lipid content in skeletal muscle (Mashili *et al.*, 2011). In addition, it stimulates FA metabolism, reduces triglyceride levels, and prevents growth hormone (GH) signaling in the liver (Camporez *et al.*, 2013), decreased lipolysis, improved glucose uptake, and adiponectin release in white adipose tissue (Lee *et al.*, 2014). FGF21 also stimulates glucose uptake in brown adipose tissue (Hondares *et al.*, 2011), enhancing peripheral insulin sensitivity. FGF21 also aids in the maintenance of insulin secretion and cell growth of pancreatic islets, and it primarily enhances β-cell survival and GSIS and inhibits GH signaling (Wente *et al.*, 2006). According to clinical studies, LY2405319 improves lipid profiles by reducing harmful cholesterol levels, low-density lipoprotein (LDL), and triglycerides while increasing good cholesterol levels, HDL (Gaich *et al.*, 2013). More research into novel FGF21 analogs and their side effects is needed, as this could be a chance to provide a favorable impact in the treatment of T2DM.

***Fibroblast growth factor 1***

FGF1 is a prototype of the FGF protein family with autocrine/paracrine signaling function upon binding to heparan sulfate proteoglycans. FGF1 is the standard FGFR ligand. It can connect and trigger the other splice variants of four tyrosine kinase FGF receptors (FGFRs 1–4). Studies have shown that the FGF1 knockout mouse exhibited glucose intolerance, representing a new target in T2DM. The mechanism improves skeletal muscle insulin-dependent glucose absorption while suppressing hepatic glucose synthesis, improving glycemic control (Suh *et al.*, 2014). Recent studies show that FGF1 administration to db/db mice significantly reduced blood glucose levels and strengthened autophagy dysfunction and diabetes-induced liver steatosis, fibrosis, and apoptosis. Mechanistically, FGF1 exhibits these effects by inhibiting OS and endoplasmic reticulum stress (Xu *et al.*, 2020). Additionally, FGF1 has been shown to prevent lipolysis and hepatic glucose production by activating FGFR1/PED4D leading to the inhibition of the cAMP-PKA pathway (Sancar *et al.*, 2022).

**GS kinase-3**

GSK-3 is a widely expressed serine/threonine-protein kinase that is considered to be cytosolic in origin. However, it was also reported in mitochondria, nuclei, and other subcellular compartments. It is the principal GS regulator and plays a significant role in its regulation. Mammal GSK-3 exists as two isoforms, GSK-3α and GSK-3β, which are 51 and 46 kDa, respectively. Their functional domain is 98% identical in sequencing, but their N- and C-terminal sections differ. Despite significant similarities, GSK-3α knock-out animals show lower weight gain and improved glucose and insulin sensitivity. For this reason, GSK-3α has been associated with the development of T2DM when compared to GSK-3β (MacAulay and Woodgett, 2008). Other studies revealed that GSK-3β's role in the development of T2DM was associated with the induction of inflammation through the activation of signal transducer and activator of transcription 3 (STAT3). This activation of STAT3 occurs through its phosphorylation at tyrosine 705. To further confirm the role of GSK-3β/STAT3-mediated inflammation, lithium was used to inhibit GSK-3β. The use of lithium abolished the inflammatory markers by phosphorylation of GSK-3β at serine 9 (inactive GSK-3β). The inhibition of GSK-3β also correlates with improved glucose-induced insulin secretion, decreased hyperglycemia, and increased pancreatic insulin content (Pitasi *et al.*, 2020). Other GSK-3 inhibitors, such as CT118637 and CT98014 have also enhanced insulin signaling (MacAulay and Woodgett, 2008). Although GSK-3 represents a potential target in TD2M, developing an inhibitor(s) specific to GSK-3 isoforms poses a challenging step (Gupte *et al.*, 2022).

**Protein tyrosine phosphatase 1B**

PTP1B is an enzyme that is negatively participating in the insulin cascade. PTP1B interrupts insulin signaling by dephosphorylation of IR and IRS (Rocha *et al.*, 2021). This is further demonstrated by PTP1B-KO mice that resist high-fat diet-induced obesity and enhanced insulin sensitivity (Klaman *et al.*, 2000). A strong relationship between insulin sensitivity and PTP1Bat the clinical level has been demonstrated (Cheung *et al.*, 1999). Other than insulin signaling disruption, PTP1B is a negative leptin signaling regulator. Leptin is a hormone mainly expressed in adipose tissue-leptin functions by increasing tolerance to dietary fats and thereby maintaining FA homeostasis. When leptin signaling is disrupted, lipid content is increased in tissues such

as the liver and muscle, leading to prolonged lipid accumulation in these tissues and favoring lipotoxicity. Mechanistically, leptin binds to the obesity receptor and causes Janus kinase 2 (JAK2) phosphorylation. Further, this leads to the activation of downstream intracellular signaling crucial for FA homeostasis. PTP1B disrupts leptin signaling by inhibiting JAK2 phosphorylation and causing leptin resistance (Rocha *et al.*, 2021). Hence, PTP1B inhibitors such as compound 3e (thiazolidinedione derivative), JTT-551, and CCF06240 have been employed to manage and treat diabetes. These inhibitors improve insulin sensitivity, improve glucose tolerance and suppress weight gain (Fukuda *et al.*, 2010).

### Activated protein kinase (AMPK)

AMPK enhances glucose transport, FA metabolism, GLUT4 translocation, and mitochondrial biogenesis in skeletal muscle and liver. AMPK promotes lipolysis in adipose tissue by phosphorylating AMPK downstream targets (acetyl-CoA carboxylase). AMPK inhibits FA production and lipolysis (Steinberg and Kemp, 2009). Hence, AMPK activation is a prospective T2DM target. Natural substances such as resveratrol and berberine activate AMPK, but they are not safe for the elderly due to protein synthesis inhibition (Drummond *et al.*, 2009). In light of these findings, more research into innovative AMPK activation techniques for treating T2DM is needed.

### 11β- Hydroxysteroid dehydrogenase 1·(11β-HSD1)

11βHSD1, a GC generating enzyme in the liver and adipocytes, facilitates the intra-cellular regeneration of activated GCs (cortisol, corticosterone) from inert 11-keto forms (Cooper and Stewart, 2009). Overexpression of GCs inhibits glucose uptake in peripheral tissue by blocking GLUT4 translocation, resulting in insulin resistance via reducing pancreatic β-cell insulin production. Upregulation of 11β -HSD1 in adipocytes and excess GCs have been linked to T2DM (Wamil and Seckl, 2007). Insulin sensitivity in skeletal muscle has been reported to be improved by 11β-HSD1 blockers (Morgan *et al.*, 2009). Many new 11-HSD1 inhibitors have been identified, including adamantly-triazoles, aryl sulfonamidothiazoles, anilinothiazolones, BVT.2733, INCB-13739, MK-0916, and MK-0736. This help reduce body weight without producing hypoglycemia and improve cardiovascular disease (Hughes *et al.*, 2008), and total cholesterol, LDL, and triglyceride reductions in hyperlipidemia patients (Rosenstock *et al.*, 2010). According to numerous studies, 11β-HSD1 inhibitors are efficacious and potential targets for T2DM, and their possible mechanism should be identified in other tissues and considered for further clinical evaluation.

### Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox)

The critical enzyme (Nox) produces reactive oxygen species (ROS) and causes OS. This is often associated with T2DM and its major cardiovascular complications (Asmat *et al.*, 2016; Brown *et al.*, 2021). In humans, four isoforms of NoXs have been identified; these are NoX1, NoX2, NoX4, and NoX5. Out of these, NoX1, NoX2, and NoX5 overexpression play a significant role in the pathogenesis of T2DM by the generation of $O_2^-$. At the same time, NoX4 overexpression is considered to play a more physiological role by increased $H_2O_2$ production rather than a pathological role (Brown *et al.*, 2021). In pancreatic β-cells, the overexpression of these NoX isoforms has a negative regulator on insulin secretory responses. This effect occurs due to ROS generation and adenylate cyclase/cAMP/PKA signaling inhibition (Li *et al.*, 2012). Additionally, gene polymorphism (C242T) in p22phox, an essential subunit of NoXs, has been shown to correlate positively with endothelial dysfunction in T2DM (Osmenda *et al.*, 2021). In line with these findings, inhibitors of NoXs have a positive effect on diabetes-related cardiovascular disorders. GKT137831, apomycin, HET0016, apocynin, AEBSF, and DPI, VAS3947 are specific Nox inhibitors that prevent OS (Gray *et al.*, 2013). Hence, further studies should focus on discovering novel NADPH oxidase inhibitors and also clarify their exact mechanism of action by *in-vivo* studies for T2DM.

### Aldose reductase

ALR is an NADPH-dependent enzyme that catalyzes the transfer of D-glucose to D-sorbitol utilizing reductant (NADPH) in the polyol pathway (Brownlee, 2001). ALR converts glucose to sorbitol (a generally non-metabolizable sugar) in patients with hyperglycemia via the active polyol pathway. When intracellular D-sorbitol concentrations rise, NADPH is consumed at greater levels, resulting in an osmotic pressure imbalance that produces peripheral neuropathy, cataract, nephropathy, and angiopathy problems (Hotta *et al.*, 2001). Increased sorbitol via the polyol cascade causes myo-inositol depletion and decreased Na/K$^+$ ATPase activity, resulting in loss of nerve function and vascular disease. ARI-809, sorbinil, ranirestat, M79175, kinostat, epalrestat, and fidarestat are ALR inhibitors that have been reported and tested (Kador *et al.*, 2016; Zhu, 2013). Many more compounds as ALR inhibitors have recently been identified, including pyrido(2,3-6), pyrazin-3 (4H), compound 9c, and compound 1a, as well as flavonoids, phenols, terpenes, and alkaloids (Han *et al.*, 2016; Saito *et al.*, 2016) ginsenoside 20(s)-Rh2, 3'-o-(-3-chloropiraloyl) quercetin, esculetin, and kinostat. All of these compounds showed positive effects. *In-vivo*, kinostat and M79175 showed favorable outcomes. However, due to its unacceptable toxicity in clinical trials, it has not been employed in diabetic retinopathy to delay the formation of sugar cataracts in diabetic patients (Fatmawati *et al.*, 2014; Kim *et al.*, 2016).

### CONCLUSION

T2DM is the most common type of diabetes, causing a global burden. Recently, it has been demonstrated that NRs deficiency, namely AR (in males), ERβ, LXR, VDR, REV-ERB A, PPAR, and NRs overexpression, PR, GR, and MR are associated with T2DM. Therefore, the activation of AR (in males), ERβ, and LXR and the inactivation of PR, GR, and MR could be a potential strategy for managing and treating T2DM. Several recent studies have shown great interest in AR activation for T2DM. These studies, however, focus on the uses of AR's endogenous ligands, such as testosterone and Dihydrotestosterone (DHT). Particularly in men, the use of these agents is controversial because they are androgenic and could potentially promote prostate cancer development. Since AR activation is required in men with T2DM, the search for modulators that are cell-specific, non-steroidal, and non-androgenic is the need of the hour. For this reason, we are currently working on identifying selective AR modulators

(SARMs) that are cell-specific. Importantly, we focus on plant-derived compounds because they offer fewer side effects. These compounds are currently under development for pancreatic β-cell regeneration since β-cell apoptosis has been reported in most cases of T2DM. Further, we are working on targeting pancreatic β-cell of the male population since clinical data on T2DM shows a positive correlation with androgen deficiency. The successful development of SARMs could revolutionize the harmful impact of T2DM on males.

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## AUTHOR CONTRIBUTION

Deepa initiated the conception, design, and data collection. Deepa also wrote and prepared the entire manuscript. Emdormi contributed to data collection, diagrammatic illustration, and manuscript preparation. Soumya contributed to data collection. Divakar contributed to manuscript suggestions and corrections. Divakar also contributed to proofreading the whole manuscript. All the authors approved the final manuscript for submission and publication.

## CONFLICT OF INTEREST

The authors declared no conflicts of interest.

## ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

## DATA AVAILABILITY

All data generated and analyzed are included in this research article.

## PUBLISHER'S NOTE

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