A Narrative Review Unveiling Novel Molecular Targets in Advancing Antidiabetic Medications: An Emerging Perspective

BALAMURALI VENKATESAN[1], V NATARAJAN[2], A AKHILA KALYANI[3]

ABSTRACT

Diabetes Mellitus (DM) is a persistent metabolic disorder characterised by elevated glucose concentration in blood. Approximately, 422 million individuals globally suffer from diabetes, with the majority residing among middle-class and lower-class countries as per the reports of World Health Organisation (WHO) 2023. Strict blood sugar control in conjunction with high-dose insulin therapy might potentially prevent or delay the progression of microvascular issues, lower overall mortality, and lessen the chance of macrovascular problems. These conclusions were supported by the Diabetes Control and Complications Trial and the large longitudinal investigation known as the epidemiology of diabetes and its complications. Numerous drugs and receptors involved in glucose metabolism are currently being used to treat diabetes, including α-Glucosidase inhibitors, dopamine D-2 agonists, biguanides, glinides, amylin analogues, Peroxisome Proliferator-activated Receptors (PPARs), Glucagon-like Peptide-1 (GLP-1), and biguanides. Due to the associated side effects and the financial difficulties in obtaining traditional antidiabetic regimens, the current review has placed a higher priority on investigating novel molecular targets for the development of antidiabetic medications intended to manage the progression of the illness. This emphasises how important it is to find new molecular targets associated with the illness's onset instead of only treating its symptoms or outward signs.

INTRODUCTION

Diabetes Mellitus (DM) significantly increases morbidity and early mortality by affecting a person's quality of life and functional abilities. An estimated 1.5 million deaths each year are directly related to the condition [1,2]. However, the incidence and total diabetes cases have been steadily rising during the last few decades. A considerable proportion among the global population suffers from DM [3]. The International Diabetes Federation (IDF) reports that among Western IDF regions, the greatest incidence of diabetes (13%) was seen in people from North America and the Caribbean between 20 and 79 years of age. In South Asian nations, the greatest rates of diabetes prevalence are seen 22% in Mauritius, 10.7% in Sri Lanka, and 10.4% in India. DM affects over 425 million people globally, and because of poor diets and sedentary lives, it is expected that the number will rise to almost 629 million by 2045 [4,5].

The DM is notably associated with both major vascular issues like peripheral vascular disease, cerebrovascular disease, and ischaemic heart disease, as well as minor vascular problems, including nephropathy, retinopathy, and neuropathy. However, Type-2 Diabetes Mellitus (T2DM), a chronic metabolic condition with insufficient insulin secretion, resistance of body tissues to insulin, and a lack of effective compensatory mechanisms, is responsible for almost 90% of diabetes incidence [6]. It is characterised by a relative insulin shortage. Overnutrition can eventually lead to inflammation and stress on the β-cells, which can induce malfunction and additional stages of atrophy [7].

According to various studies, data from surveys indicates that the incidence of diabetes in adults will increase from 4% in 1995 to 6.4% by 2025 [6,7]. However, sulfonylureas, metformin, inhibitors of the Dipeptidyl Peptidase 4 (DPP-4) pathway, inhibitors of α-glucosidase, Thiazolidinedione (TZD), and short- and long-acting insulin are among the treatment methods available for the management of DM [8]. Due to their ineffectiveness and correlation with various adverse consequences, such as weight gain, hypoglycaemia, lactic acidosis, and gastric disorders, these therapeutic agents can only treat diabetes symptomatically. As a result, it is necessary to find targets or medications that are more effective than these in terms of safety and tolerability [9].

Recently, researchers have been focusing on discovering a new biological pathway in light of the disruption in endocrine homeostasis, which, if restored, may outperform current traditional treatments. But these drugs can't fully manage diabetes, therefore research is still being done to find a better cure [10,11]. There are some medications and receptors that are now being used to treat diabetes, including α-Glucosidase inhibitors, Peroxisome Proliferator-activated Receptors (PPARs), amylin analogues, Glucagon-like Peptide-1 (GLP-1), biguanides, glinides, gliptins, and dopamine D-2 agonists are among the substances that are involved in glucose metabolism. Given the increased incidence of diabetes over the past 20 years and the disease's irreversible nature, lifetime antidiabetic medication treatment is the standard of care [11,12].

Therefore, it has been anticipated that the evaluation would explore newly discovered molecular targets that potentially improve the development of drugs in the treatment of DM. By highlighting these novel molecular targets, this review emphasises the possible developments in antidiabetic drugs with improved effectiveness and novel methods of action as compared to existing therapies.

Diabetes Mellitus (DM)- An Overview

The inability of the body to use glucose is known as DM, a chronic, progressive metabolic condition. It could be brought on by a drop in the body's insulin release from pancreatic cells or a loss of insulin sensitivity. Blood glucose levels can stay in the 80-120 mg/dL range as insulin helps cells absorb glucose [12]. Hence, the deficiency of insulin leads to the body developing hyperglycaemia, marked by heightened blood glucose levels, which can result in a number of metabolic and potentially fatal conditions, such as neuropathy, cardiovascular, and nephropathic disorders. Nonetheless, given that 70% of Indians reside in rural regions

with inadequate access to healthcare, undeveloped healthcare systems is the main cause of the high incidence of diabetes [13]. Inadequate diabetes screening, a lack of preventive options, and a failure to follow diabetes care recommendations after diagnosis are all caused by these variables. Consequently, it has been demonstrated that increasing physical activity helps the body maintain glucose homeostasis and postpones the beginning of impaired glucose tolerance. Currently, there are three main forms of diabetes, which are explained below, based on insulin shortage and cell insensitivity to insulin [14,15].

Type 1 Diabetes Mellitus (T1DM)

Main characteristic of T1DM is the autoimmune-caused loss of pancreatic beta cells. As a result, beta cells are completely destroyed, which causes very little or no insulin to be produced. Although this form of diabetes affects individuals of all ages, children are more likely to have it than adults [16].

Type 2 Diabetes Mellitus (T2DM)

Typically, T2DM has been distinguished as an imbalance between the synthesis of insulin and the response to it, resulting in impaired insulin function as well as β-cell malfunction [17]. Obesity and overweight contribute significantly to T2DM risk by raising the possibility of developing insulin resistance. This would therefore lead to a decrease in the absorption of glucose in tissues such as the heart or musculoskeletal system, and augmentation of production of glucose in tissues like liver. In order to confront such conditions, β-cells increase the release of insulin [18,19].

Gestational Diabetes

All diabetes that appears during pregnancy is called gestational diabetes. The exact cause of its onset is not yet fully understood. Furthermore, the excessive production of proinsulin is also a contributing factor to gestational diabetes, with some research suggesting that proinsulin might induce stress in beta cells [20]. There is conjecture that peripheral insulin sensitivity and β-cell activity may be impacted by increased levels of cortisol, progesterone, oestrogen, human placental lactogen, and prolactin [21,22].

Antidiabetic Medications

Precise management of blood sugar levels through rigorous glycaemic control and intensive insulin therapy has the capacity to prevent or delay the progression of microvascular complications, lower the risk of macrovascular issues, and decrease overall mortality. These findings were demonstrated in the Diabetes Control and Complications Trial, along with its extended observational study, the Epidemiology of Diabetes and its Complications [23]. T1DM is mostly managed with insulin treatment, which uses both long- and rapid-acting insulin analogues. When two to three months of lifestyle modification are not enough to establish glycaemic control or if the HbA1c climbs to 6.5%, pharmacological therapy for T2DM should be started [Table/Fig-1] [24,25]. Furthermore, [Table/Fig-2] details the mechanism and adverse effects of antidiabetic medications [26-34].

The main groups of oral antidiabetic drugs are: Sodium-Glucose Cotransporter Protein 2 (SGLT2) inhibitors, biguanides, inhibitors of DPP-4 pathway, sulfonylureas, meglitinide, α-glucosidase inhibitors and TZD. The need to combine two oral medications or initiate insulin therapy may arise when the HbA1c level reaches 7.5% despite using oral medications or if the initial HbA1c measurement was 9% or higher. Even though these drugs may be administered to any patient, regardless of body weight, some drugs, like liraglutide, may benefit obese individuals more than lean diabetics [35]. However, despite these challenges, [Table/Fig-3] outlines fewer novel antidiabetic medications that target molecular pathways [36-51].
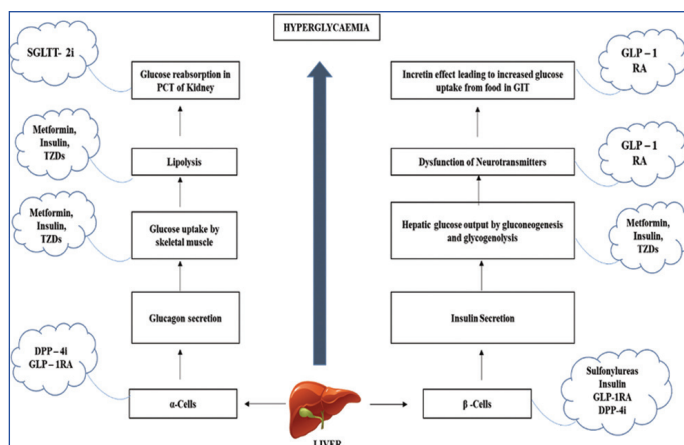
[Table/Fig-1]: Role of antidiabetic medications [24,25].

Class of antidi-abetic drugs	Antidiabetic drugs	Mechanism of action	Adverse reactions
DPP-4 inhibitor [26]	Linagliptin, Alogliptin, Sitagliptin, and Saxagliptin	Inhibit the degradation of incretins like Glucagon-Like Peptide-1 (GLP-1) and Glucose-dependent Insulinotropic Peptide (GIP)	Acute hepatitis, Upper Respiratory Tract Infections (URTI) and pancreatitis
Biguanide [27,28]	Metformin	Enhances insulin sensitivity and inhibits hepatic glucose production	Low folic acid and vitamin B12 levels leads to neuropathy and anaemia in the elderly and lactic acidosis
Insulin [29]	Humulin R, Novolin R, Lantus (Insulin Glargine), and Levemir	Increases the absorption of glucose in peripheral tissues and triggers the signaling pathways that regulate glucose downstream	Weight gain, hypoglycaemia, injection site response (lipohypertrophy and lipoatrophy) and insulin allergy
α- glucosidase inhibitors [30]	Acarbose and Miglitol	Delays the intake of glucose and reversibly inhibits α-glucosidase	Diarrhoea and disturbances of the stomach
GLP-1 receptor agonists [31,32]	Exenatide, Liraglutide, and Dulaglutide	Stimulates the GLP-1 receptor, secretes more insulin and less glucagon, promotes satiety, and postpones the emptying of the stomach	Risk of pancreatitis for cancer and cardiac incidence as well as intestinal effects
Thiazolidindiones (TZD) [33]	Pioglitazone and Rosiglitazone	They enhance adipogenesis via binding to PPAR-γ	Liver failure, heart problems, visual problems and increased weight
Sulphonylureas [34]	Glimepiride, Glipizide, and Glyburide	Promoting secretion of insulin	Hypoglycaemia Weight gain, risk for cardiac diseases, rashes, cholesteric jaundice photosensitivity, and damage in bone marrow

[Table/Fig-2]: Mechanism and adverse effects of antidiabetic medications [26-34].

Molecular Targets

Traditionally, antidiabetic medications have targeted pancreatic β cells to boost insulin production. On the other hand, long-term use of these medications nearly always results in numerous side effects. So, scientists are searching for fresh methods to treat DM. Lately, there has been a goal among researchers to close the knowledge gap between studying signal transduction pathways primarily in diabetes, and the involvement of lipids [35,52]. It is necessary to look at the interactions between carbohydrates, kinases, and lipids under both regular and unusual conditions. These particular connections between lipids and proteins may be investigated on many levels: molecularly via the examination of potential structural interactions; biochemically through the

Antidiabetic drugs	Mechanism of action	Target
Staurosporine [36]	Activation of the canonical PI3K-AKT pathway for initiating exocytosis of storage vesicles in GLUT4	Glucose transporter protein type-4 (GLUT4)
AdipoRon [37-39]	Lowers adiponectin levels and reduces diabetes-induced oxidative stress and apoptosis which are linked to lipid accumulation and endothelial dysfunction	Adiponectin
Chenodiol and Ursodiol [40,41]	Boosts the uptake of long-chain and very Long-Chain Fatty Acids (LCFA) into the cells	Fatty acid transport protein-5
BDM44768, NTE-1, 6bK [42]	Thiol zinc-metalloendopeptidase splits small proteins with various sequences	Insulin degrading enzyme
Bromocriptine [43]	Enhances the absorption of glucose via the JAK2/STAT5 pathway	Prolactin receptor
Imatinib, Sunitinib, Dasatinib, Sorafenib, Erlotinib [44]	Reduces insulin resistance, extends the lifespan of β cells, reduces apoptosis of β cells and increases insulin production	Tyrosine Kinase
Piolitazone, aleglitazar, glitazones, GFT505 [45]	Weight gain, enhances insulin sensitivity, glucose homeostasis, serum lipid profile, and decreases inflammation	PPAR-γ
Dapagliflozin, canagliflozin, sergliflozin, remogliflozin, ipragliflozin, and empagliflozin, etc., [46]	Increases kidney-dependent glucose homeostasis	SGLT-2
SRT2104, resveratrol [47]	Enhances mitochondrial capacity, homeostasis of glucose, and insulin sensitivity	Sirtuin 1
INT-777 [48]	Accumulation of cAMP and improved GLP-1 production (intestine), as well as an anti-inflammatory impact (liver)	G-protein-coupled bile acid receptor 1
APD5979, MBX-2982 [49]	Increases cAMP signaling	G-protein-coupled receptor 119
INCB13739, MK-0916, and BI 135585 [50,51]	Blocking cortisol	11β-HSD1 (hydroxyl steroid dehydrogenase)

[Table/Fig-3]: Novel antidiabetic medications targeting molecular pathways [36-51].

examination of membrane microdomains under both normal and aberrant conditions; and genetically through the investigation of gene expression [53].

Dipeptidyl Peptidase-4 (DPP-4): DPP-4 has been linked to T2DM patients who have an incretin deficit. The incretin hormones like GLP-1 as well as Glucose-dependent Insulinotropic Polypeptide (GIP) were routinely generated in the digestive tract in reaction to meals, which mediated the glucose-dependent production of insulin. However, the reason behind their deactivation is DPP-4 [54]. Gliptins, a family of drugs known as DPP-4 inhibitors, can indirectly increase insulin production by reducing endogenous incretin breakdown. DPP-4 inhibitors work by blocking the enzyme, which raises the levels of these hormones. As a result, elevated insulin and reduced glucagon release lower blood glucose levels. Thus, it has been shown that molecular scaffolds, which function as DPP-4 inhibitors were found to be promising treatment for T2DM [55].

AMP-Activated Protein Kinase (AMPK): AMPK serves as the central controller of lipid and glucose metabolism and operates as an energy-sensing mechanism. However, it becomes triggered in response to elevated levels of AMP. Metformin, most commonly recommended first-line medication for diabetes, is known for its ability to increase the AMPK alpha-subunit's catalytic phosphorylation at Thr-172 in hepatocytes. This phenomenon induces muscle cells to absorb glucose and boosts fatty acid oxidation [56]. Increased AMP levels cause AMPK to be activated,

which in turn causes gluconeogenic enzymes to be downregulated and hepatic gluconeogenesis to be inhibited. A significant obstacle to "METC complex I/AMP/AMPK" axis is the need for millimolar doses of metformin to inhibit METC complex I. For most cell types, including enterocytes, millimolar concentrations of metformin are not expected to be reached with therapeutic dosages of the drug. Instead, millimolar concentrations are found after oral or intravenous administration of clinical doses of the drug. The precise molecular process is still unclear despite several studies and clinical applications [56,57].

Peroxisome Proliferator-Activated Receptor-γ (PPARγ): Nuclear receptors, specifically PPARs, exert influence over translation and transcription of multiple genes. PPARγ oversees lipid metabolism as well as maintaining glucose homeostasis. Numerous fatty acids have the ability to activate PPARs. Lipid-induced insulin resistance results from their suppression of hepatic gluconeogenesis and induction of glucose transporter (GLUT4) expression. Moreover, TZDs are PPARγ agonists that influence inflammatory and cardiovascular indicators in addition to bringing blood glucose levels back to normal [58].

ATP-sensitive K⁺ channel (K_{ATP}): Membrane electrical activity of β-cells is modulated by ATP-sensitive potassium (K_{ATP}) channels, which also control the inflow of K⁺. Elevated blood glucose concentrations promote glucose metabolism by shutting down K_{ATP} channels. Through the induction of K_{ATP} channel closure in the pancreatic β-cells, whole sulphonylurea medicines boost the generation of insulin. Consequently, the activation of voltage-dependent Ca^{2+} channels by Ca^{2+} inflow led to membrane depolarisation and the subsequent exocytosis of insulin granules. Meglitinides bind to the K_{ATP} channel similarly to sulphonylureas, however their affinity for binding is less. Unfortunately, a number of years of research have shown that these medications are not practical since they cause apoptosis of β-cells [59].

Challenges of Conventional Therapeutic Approach

The treatment of DM necessitates a multidisciplinary approach due to the complexity of the condition. For diabetic patients to maintain glycaemic control, medication adherence has shown to be a persistent difficulty. Research has indicated that there is especially low medication adherence to treatments that are seen as somewhat inconvenient, such as insulin therapy [60]. It is necessary to select the pharmaceutical treatments according to the patient's risk factors. Patients with congestive heart failure may be at risk for lactic acidosis and renal damage while taking insulin sensitisers like metformin. Metformin side effects including taste disturbance, dermatitis, and gastrointestinal issues have been reported in safety and effectiveness trials. In contrast, pioglitazone has exhibited an increased probability of bladder cancer development [61].

In order to attain glycaemic control, injectables may be a preferable option for many patients due to diabetes's progressive nature, however lifestyle modifications and oral hypoglycaemic medications are still the initial methods of management. Regretfully, most patients associate starting an injectable treatment with bad feelings that stem from behavioural, psychological, and practical concerns. Consequently, in order to overcome patients' anxiety of injectable medicines and lessen psychological stress, it is crucial to provide proper information and contact with patients [60]. As of now, there is no known cure for diabetes; the only available treatment is management. The next generation of medicines may be greatly aided by basic mechanistic research to better understand the intricate biology behind the benefits and drawbacks of treating diabetes [62].

Emerging Molecular Targets of Antidiabetic Medication

Protein Tyrosine Phosphatase 1B (PTP1B): Protein Tyrosine Phosphatases (PTPs) are involved in various cellular functions,

encompassing immune response, cell growth, differentiation, as well as mitochondrial processes [63]. PTP1B is one of PTPs that can negatively alter the insulin and leptin signal pathway, rendering it a crucial therapeutic target for the obesity and T1DM management [64,65]. Tyrosine phosphorylation is a crucial stage in the transmission of the insulin signal within the loop that activates insulin receptors. Insulin signalling has been negatively regulated when the phosphor-tyrosine residues in the insulin receptor kinase activation areas are dephosphorylated by PTP1B [66]. Considerable diversity in the actions of PTP1B inhibitors led to the identification of several synthetic compounds suitable for further development as medicines. Additionally, PTP1B contributes to the growth of β-cells in the pancreas. For example, according to Fernandez-Ruiz R et al., PTP1B knockout mice exhibit elevated β-cell proliferation and increased insulin production regarding glucose stimulation. These results offer strong evidence for PTP1B's involvement in diabetes, which has sparked interest in PTP1B inhibitors and led to the discovery and synthesis of many PTP1B inhibitors [67].

Free Fatty Acids (FFA): These have the capacity to function as signaling molecules. Based on the length of their chain, FFAs are commonly classified into three subcategories: Short-Chain Fatty Acids (SCFAs), Medium-Chain Fatty Acids (MCFAs), and Long-Chain Fatty Acids (LCFAs), characterised by differing chain lengths. It is known that FFAs with these different chain lengths stimulate FFA1, FFA2, and FFA3 transmembrane receptors. An increase in insulin production that is triggered by glucose is also significantly influenced by the activation of these receptors. Therefore, a number of FFA1 ligands have been found and investigated because to its evident function in glucose-stimulated insulin production [40]. Although FFA2 and FFA3 have a complicated involvement in insulin, they function similarly to FFA1 receptors and are activated by SCFAs neutrophils in particular have high expression levels of FFA2 receptors in their immune cells. It is known that intestinal bacteria in the body digest food fibres to form ligands for FFA2 [41]. However, Tang C et al., demonstrated the FFA2 and FFA3 expression on β cells of human pancreas. By attaching to Gi-type G-proteins, these receptors have been demonstrated to suppress insulin release. Moreover, insulin production was increased in pancreatic β cells when FFA2 and FFA3 receptors were removed. These results showed that FFA2/FFA3 antagonists could be helpful for those with T2DM [68].

11β-Hydroxysteroid Dehydrogenase: The transformation of cortisone from its inactive to its active state is catalysed by the enzyme 11β-Hydroxysteroid dehydrogenase (11β-HSD). A number of illnesses, including obesity, diabetes, high blood pressure, and dyslipidaemia, are influenced by elevated levels of active glucocorticoids, such as cortisol. Also, transgenic mice lacking 11β-HSD exhibited improved sensitivity to insulin as well as demonstrated that increased fat content produces a stronger defence against obesity. However, there is also evidence linking overexpression of 11β-HSD in mice to an increased risk of metabolic syndrome. For this reason, 11β-HSD is regarded as a crucial therapeutic target for T2DM [69].

FoxO1: One important target for T2DM is the fork head transcription factor of the class O 1 (FoxO1), which is also known as mediating factor of insulin signalling in β cells. It has been shown that insulin and glucose tolerance were improved by dominant negative FoxO1 adipocytes. Furthermore, FoxO1 in the pancreas causes stress and apoptosis, which leads to β-cell malfunction. Phosphorylation and acetylation represent the two most prevalent post-translational modifications of FoxO1, which alter the activity of many genes [70]. One major way that FoxO1 exits the nucleus and gets broken down by ubiquitination is through phosphorylation. Under circumstances akin to oxidative stress in diabetic livers, O-GlcNAcylation even activates FoxO1, and this, in turn, leads to the enhanced activation of numerous genes involved in gluconeogenesis and the detoxification of Reactive Oxygen Species (ROS). However, the gluconeogenesis gene series is activated during fasting by PGC1-α activation, which then binds directly to FoxO1, leading to its phosphorylation and subsequent translocation out of the nucleus, effectively rendering it inactive [71].

Nuclear Factor (Erythroid-derived 2)-Like 2 (NRF2): In several illnesses, one essential molecular node that offers cytoprotection is NRF2. It is anticipated that it would be a key target in drug discovery because of its diverse involvement in a range of disorders. Four NFE2L2 gene Single Nucleotide Polymorphisms (SNPs) were found to have a significant variance in their genotypic and allelic frequencies, which is concerning for T2DM patients. Furthermore, a study used NRF2 induction to induce hyperglycaemia in diabetic animals and found that there was a reduction of hepatic glucose 6 phosphatase via cAMPCREB signalling by reducing levels of blood glucose. This implies that NRF2 is involved in adipogenesis and a number of metabolic diseases. Acute glucose administration has been suggested to raise NRF2 levels, however, chronic glucose circumstances are thought to be ineffective in doing so [72,73].

Peroxisome Proliferator-activated Receptor Gamma Co-activator Alpha (PGC-1α): Among humans, the PPAR Gamma Coactivator 1-Alpha (PPARGC1A) gene encodes the protein PGC-1α. PGC-1α averts mitochondrial failure and metabolic illnesses linked to adipocyte malfunction by maintaining energy balance and regulating insulin signalling expression, uncoupling proteins, as well as mitochondrial biogenesis, dynamics, and antioxidant genes [74]. When PGC-1α is dysregulated, cells lose their inflammatory response and homeostasis gets worse, which typically results in metabolic issues [75]. Low levels of PGC-1α promote atomic factor κ-B activation, induce inflammation and oxidative pressure, and downregulate mitochondrial quality articulation during adipocyte failure. Treatment for PGC-1α quality was found to enhance fat tissue function and have a favourable impact on distant organs such as the liver. This suggests that targeting PGC-1α quality is a tempting corrective approach to enhance metabolism, insulin affectability, vascular capacity, and insulin processing in metabolic diseases [76].

MicroRNA: Non-coding Ribonucleic Acids (RNAs) called microRNAs (miRNAs) take part in a variety of biological and molecular processes to carry out epigenetic regulation. miRNAs can modify a few basic processes associated with T2DM pathogenesis, including insulin production and insulin granule exocytosis. [Table/Fig-4] shows the pancreatic β-cell regulations mediated by miRNA actions [77]. The pathophysiology of diabetes may be impacted by the dysregulation of several miRNAs, including those that target the pancreatic β-cells, including miR-15, miR-21, miR-144, miR-150, miR-375, miR-503, miR-510, miR-214, and miR-191. Ying C et al., have reported that resistin is upregulated when miR-492 is downregulated, which causes insulin intolerance. As a result, microRNAs may provide fresh approaches to controlling diabetes-related processes [78].

SLC16A11: The Slim Initiative in Genomic Medicine for the Americas (SIGMA) conducted genome-based research that revealed a genetic region that is highly connected to T2DM. These haplotypes linked to diabetes decreased the expression of SLC16A11 in the liver and interfered with its interaction with basigin, resulting in a reduction in SLC16A11's cell surface localisation. Fatty acid and lipid metabolism are modulated in primary human hepatocytes upon SLC16A11 knockdown [79]. Because insulin resistance is associated with higher triglyceride levels, SLC16A11 polymorphisms may raise the risk of diabetes via controlling how fat is metabolised. The gene SLC16A11 is the eleventh member among a group of 14 potent SLC16 genes responsible for encoding

[Table/Fig-4]: Function of miRNA in pancreatic β-cells [77].
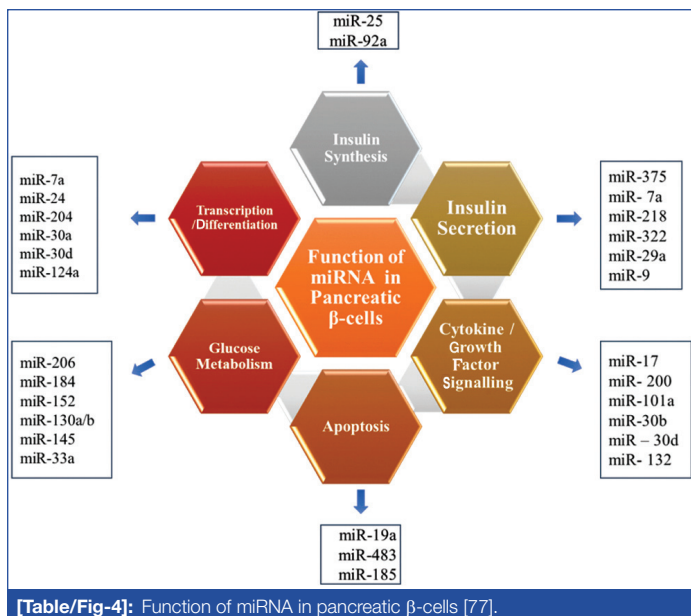
Monocarboxylate Transporters (MCTs). For primary human hepatocytes with decreased MCT11 activity, siRNA-mediated suppression of the SLC16A11 gene led to enhanced cellular fatty acid and lipid metabolism. Numerous concerns, such as what the special substrates are linked to the transit of mediators aimed at the physiological and biochemical pathways influencing T2DM, are still unsolved [80].

Cholesteryl Ester Transfer Protein (CETP) Gene: CETP is a glycoprotein released by the liver that aids in the transfer of cholesteryl esters from High-Density Lipoprotein (HDL) to Very-Low-Density Lipoprotein (VLDL) and Low-Density Lipoprotein (LDL). Thus, when CETP is inhibited, blood levels of LDL-C and HDL-C rises, respectively. According to reports, CETP inhibition is regarded as a desirable antiatherogenic target that reduces the chance of developing coronary heart disease [81,82]. A meta-analysis was conducted to assess the influence of CETP inhibitors on glucose regulation, with the hypothesis that HDL Cholesterol (HDL-C) might have potential antidiabetic properties [81]. The analysis unveiled a 12% decrease in the occurrence of diabetes. It's important to note that T2DM is a well-established contributing risk factor for the development of cardiovascular atherosclerosis. However, the study conducted by Barter et al., showed that the concurrent administration of a statin and a CETP inhibitor lowers the occurrence of diabetes in individuals with cardiovascular disease. Hence, further research is required to obtain a comprehensive understanding of how CETP inhibitors impact glycaemic control and mitigate the risk of diabetes onset [82].

Future Perspective

Globally, the prevalence of diabetes has suddenly increased in recent decades, with T2DM accounting for the majority of cases. More effective treatments are needed in light of the concerning rise in diabetes cases. Long-term macrovascular and microvascular-related problems, such as heart problems, Alzheimer's disease, kidney, eye, and foot damage, among other conditions can arise from inadequate control and treatment. The biggest challenges in DM include a lack of therapeutic agents and restricted treatment options, despite several attempts to manage this metabolic illness. The solution to this therapeutic conundrum lies in the discovery of new therapeutic targets and medications. The majority of medicines on the market today work by inhibiting specific enzymes that reduce the symptoms of an illness, but more recently, drug candidates have been developed that work by blocking the development of the disease using peptides or nucleotides. This highlights the necessity of discovering novel molecular targets associated with the onset of illness instead of addressing its manifestations.

CONCLUSION(S)

In developing new drugs to treat diabetes, attention should be paid to shared molecular targets such as Toll-like receptors (TLR), GLP-1, PPAR-γ, Transient Receptor Potential (TRP) channels, and targets related to inflammation that originate from adipose tissue. A comprehensive analysis of the potential molecular targets in relation to their therapeutic rationale made it abundantly evident that several established molecular targets remain unutilised in large-scale antidiabetic drug screens. As of now, assay development has been most frequently focused on SGLT2 inhibitors, DPP-4, and agonists for GLP-1 receptors of every known diabetes molecular target. Hence, these should be investigated in the future in order to develop novel bioassays and, eventually, potent diabetic multi-targeting treatments.

Authors contribution: All authors hold significant and sincere participation in the present research work and have accepted it for publishing.

REFERENCES

[1] Khan MAB, Hashim MJ, King JK, Govender RD, Mustafa H, Al Kaabi J. Epidemiology of Type 2 Diabetes - global burden of disease and forecasted trends. J Epidemiol Glob Health. 2020;10(1):107-11.

[2] Diabetes. World Health Organization [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/diabetes [Last Accessed November 3, 2023].

[3] Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021;69(11):2932-38.

[4] Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183;109119.

[5] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843.

[6] Goedecke JH, Mendham AE. Pathophysiology of type 2 diabetes in sub-Saharan Africans. Diabetologia. 2022;65(12):1967-80.

[7] Bellou V, Belbasis L, Tzoulaki I, Evangelou E. Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. PLoS One. 2018;13(3):e0194127.

[8] Barnett AH. Complementing insulin therapy to achieve glycemic control. Adv Ther. 2013;30(6):557-76.

[9] Khursheed R, Singh SK, Wadhwa S, Kapoor B, Gulati M, Kumar R, et al. Treatment strategies against diabetes: Success so far and challenges ahead. Eur J Pharmacol. 2019;862:172625.

[10] Röder PV, Wu B, Liu Y, Han W. Pancreatic regulation of glucose homeostasis. Exp Mol Med. 2016;48(3):e219.

[11] Dhankhar S, Chauhan S, Mehta DK, Nitika, Saini K, Saini M, et al. Novel targets for potential therapeutic use in diabetes mellitus. Diabetol Metab Syndr. 2023;15(17):01-18.

[12] Guo H, Wu H, Li Z. The pathogenesis of diabetes. Int J Mol Sci. 2023;24(8):6978.

[13] Dilworth L, Facey A, Omoruyi F. Diabetes mellitus and its metabolic complications: The role of adipose tissues. Int J Mol Sci. 2021;22(14):7644.

[14] Adhikari M, Devkota HR, Cesuroglu T. Barriers to and facilitators of diabetes self-management practices in Rupandehi, Nepal- multiple stakeholders' perspective. BMC Public Health. 2021;21(1):1269.

[15] Janssen JAMJL. Hyperinsulinemia and its pivotal role in aging, obesity, type 2 diabetes, cardiovascular disease and cancer. Int J Mol Sci. 2021;22(15):7797.

[16] Quattrin T, Mastrandrea LD, Walker LSK. Type 1 diabetes. Lancet. 2023;401(10394):2149-62.

[17] Chatterjee S, Khunti K, Davies MJ. Type 2 diabetes. Lancet. 2017;389(10085):2239-51.

[18] Wondmkun YT. Obesity, insulin resistance, and type 2 diabetes: Associations and therapeutic implications. Diabetes Metab Syndr Obes. 2020;13:3611-16.

[19] Reed J, Bain S, Kanamarlapudi V. A review of current trends with type 2 diabetes epidemiology, aetiology, pathogenesis, treatments and future perspectives. Diabetes Metab Syndr Obes. 2021;14:3567-602.

[20] Gestational Diabetes. Mother To Baby | Fact Sheets [Internet]. Brentwood (TN): Organization of Teratology Information Specialists (OTIS). Available from: https://www.ncbi.nlm.nih.gov/books/NBK582729/ [Last Accessed November 3, 2023].

[21] Khant Aung Z, Kokay IC, Grattan DR, Ladyman SR. Prolactin-induced adaptation in glucose homeostasis in mouse pregnancy is mediated by the pancreas and not in the forebrain. Front Endocrinol (Lausanne). 2021;12:765976.

[22] Zheng J, Wang H, Ren M. Influence of exercise intervention on gestational diabetes mellitus: A systematic review and meta-analysis. J Endocrinol Invest. 2017;40(10):1027-33.

[23] Almigbal TH, Alzarah SA, Aljanoubi FA, Alhafez NA, Aldawsari MR, Alghadeer ZY, et al. Clinical inertia in the management of type 2 diabetes mellitus: A systematic review. Medicina (Kaunas). 2023;59(1):182.

[24] Davies MJ, Aroda VR, Collins BS, Gabby RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65(12):1925-66.

[25] Padhi S, Nayak AK, Behera A. Type II diabetes mellitus: A review on recent drug based therapeutics. Biomed Pharmacother. 2020:131:110708. PMID:32927252.

[26] Godinho R, Mega C, Teixeira-de-Lemos E, Carvalho E, Teixeira F, Fernandas R, et al. The place of dipeptidyl peptidase-4 inhibitors in type 2 diabetes therapeutics: A "me too" or "the special one" antidiabetic class? J Diabetes Res. 2015;2015:806979.

[27] Miller RA, Chu Q, Xie J, Foretz M, Viollet B, Birnbaum MJ. Biguanides suppress hepatic glucagon signalling by decreasing production of cyclic AMP. Nature. 2013;494(7436):256-60.

[28] Di Magno L, Di Pastena F, Bordone R, Coni S, Canettieri G. The mechanism of action of biguanides: New answers to a complex question. Cancers (Basel). 2022;14(13):3220. Published 2022 Jun 30.

[29] Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018;98(4):2133-23.

[30] van de Laar FA. Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes. Vasc Health Risk Manag. 2008;4(6):1189-95.

[31] Müller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72-130. PMID: 31767182

[32] Meloni AR, DeYoung MB, Lowe C, Parkes DG. GLP-1 receptor activated insulin secretion from pancreatic β-cells: Mechanism and glucose dependence. Diabetes Obes Metab. 2013;15(1):15-27.

[33] Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM, Kliewer SA. An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor gamma (PPAR gamma). J Biol Chem. 1995;270(22):12953-56.

[34] Proks P, Reimann F, Green N, Gribble F, Ashcroft F. Sulfonylurea stimulation of insulin secretion. Diabetes. 2002;51(Suppl 3):S368-S376.

[35] Majety P, Lozada Orquera FA, Edem D, Hamdy O. Pharmacological approaches to the prevention of type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2023;14:1118848.

[36] Li Y, Zheng L, Wang D, Zhang X, Li J, Ali S, et al. Staurosporine as an agonist for induction of GLUT4 translocation, identified by a pH-sensitive fluorescent IRAP-mOrange2 probe. Biochem Biophys Res Commun. 2016;480(4):534-38.

[37] Okada-Iwabu M, Yamauchi T, Iwabu M, Honma T, Hamagami K, Matsuda K, et al. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. Nature. 2013;503(7477):493-99.

[38] Achari AE, Jain SK. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int J Mol Sci. 2017;18(6):1321. Published 2017 Jun 21.

[39] Kim Y, Park CW. Mechanisms of adiponectin action: Implication of adiponectin receptor agonism in diabetic kidney disease. Int J Mol Sci. 2019;20(7):1782.

[40] Priyadarshini M, Wicksteed B, Schiltz GE, Gilchrist A, Layden BT. SCFA receptors in pancreatic β cells: Novel diabetes targets?. Trends Endocrinol Metab. 2016;27(9):653-64.

[41] Ulven T. Short-chain free fatty acid receptors FFA2/GPR43 and FFA3/GPR41 as new potential therapeutic targets. Front Endocrinol (Lausanne). 2012;3:111.

[42] Leissring MA, González-Casimiro CM, Merino B, Suire CN, Perdomo G. Targeting insulin-degrading enzyme in insulin clearance. Int J Mol Sci. 2021;22(5):2235.

[43] Cincotta AH. Brain dopamine-clock interactions regulate cardiometabolic physiology: Mechanisms of the observed cardioprotective effects of circadian-timed bromocriptine-qr therapy in type 2 diabetes subjects. Int J Mol Sci. 2023;24(17):13255.

[44] Althubiti M. Tyrosine kinase targeting: A potential therapeutic strategy for diabetes. Saudi J Med Med Sci. 2022;10(3):183-91.

[45] Frkic RL, Richter K, Bruning JB. The therapeutic potential of inhibiting PPARγ phosphorylation to treat type 2 diabetes. J Biol Chem. 2021;297(3):101030.

[46] Vivian EM. Sodium-glucose co-transporter 2 (SGLT2) inhibitors: A growing class of antidiabetic agents. Drugs Context. 2014;3:212264.

[47] Zhang HH, Ma XJ, Wu LN, Zhao YY, Zhang PY, Zhang YH, et al. SIRT1 attenuates high glucose-induced insulin resistance via reducing mitochondrial dysfunction in skeletal muscle cells. Exp Biol Med (Maywood). 2015;240(5):557-65.

[48] Wang XX, Edelstein MH, Gafter U, Qiu L, Luo Y, Dobrinskikh E, et al. G Protein-coupled bile acid receptor TGR5 activation inhibits kidney disease in obesity and diabetes. J Am Soc Nephrol. 2016;27(5):1362-78.

[49] Ritter K, Buning C, Halland N, Pöverlein C, Schwink L. G protein-coupled receptor 119 (GPR119) agonists for the treatment of diabetes: Recent progress and prevailing challenges. J Med Chem. 2016;59(8):3579-92.

[50] Martocchia A, Stefanelli M, Falaschi GM, Toussan L, Ferri C, Falaschi P. Recent advances in the role of cortisol and metabolic syndrome in age-related degenerative diseases. Aging Clin Exp Res. 2016;28(1):17-23.

[51] Hamilton BS, Himmelsbach F, Nar H, Schuler-Metz A, Krosky P, Guo J, et al. Pharmacological characterization of the selective 11β-hydroxysteroid dehydrogenase 1 inhibitor, BI 135585, a clinical candidate for the treatment of type 2 diabetes. Eur J Pharmacol. 2015;746:50-55.

[52] Davies MJ, Aroda VR, Collins BS, Gabby RA, Green J, Maruthur NM, et al. Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2022;65(12):1925-66.

[53] Glycaemic Targets: Standards of Medical Care in Diabetes-2022. American Diabetes Association Professional Practice Committee [Internet]. Available from: https://diabetesjournals.org/care/article/45/Supplement_1/S83/138927/6-Glycaemic-Targets-Standards-of-Medical-Care-in [Last Accessed November3, 2023].

[54] Saini K, Sharma S, Khan Y. DPP-4 inhibitors for treating T2DM-hype or hope? an analysis based on the current literature. Front Mol Biosci. 2023;10:1130625.

[55] Berger JP, Sinha Roy R, Pocai A, Kelly TM, Scapin G, Gao YD, et al. A comparative study of the binding properties, dipeptidyl peptidase-4 (DPP-4) inhibitory activity and glucose-lowering efficacy of the DPP-4 inhibitors alogliptin, linagliptin, saxagliptin, sitagliptin and vildagliptin in mice. Endocrinol Diabetes Metab. 2017;1(1):e00002.

[56] Kim J, Yang G, Kim Y, Kim J, Ha J. AMPK activators: Mechanisms of action and physiological activities. Exp Mol Med. 2016;48(4):e224.

[57] Salt IP, Johnson G, Ashcroft SJ, Hardie DG. AMP-activated protein kinase is activated by low glucose in cell lines derived from pancreatic beta cells, and may regulate insulin release. Biochem J. 1998;335(Pt 3):533-39.

[58] Dixon ED, Nardo AD, Claudel T, Trauner M. The role of lipid sensing nuclear receptors (PPARs and LXR) and metabolic lipases in obesity, diabetes and NAFLD. Genes (Basel). 2021;12(5):645.

[59] Ashcroft FM, Rorsman P. K(ATP) channels and islet hormone secretion: New insights and controversies. Nat Rev Endocrinol. 2013;9(11):660-69.

[60] Demoz GT, Berha AB, Alebachew Woldu M, Yifter H, Shibeshi W, Engidawork E. Drug therapy problems, medication adherence and treatment satisfaction among diabetic patients on follow-up care at Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia. PLoS One. 2019;14(10):e0222985.

[61] Rajasurya V, Anjum H, Surani S. Metformin use and metformin-associated lactic acidosis in intensive care unit patients with diabetes. Cureus. 2019;11(5):e4739.

[62] Whittemore R, Vilar-Compte M, De La Cerda S, Marron D, Conover R, Delvy R, et al. Challenges to diabetes self-management for adults with type 2 diabetes in low-resource settings in Mexico City: A qualitative descriptive study. Int J Equity Health. 2019;18(1):133.

[63] DeMarsilis A, Reddy N, Boutari C, Filippaios A, Sternthal E, Katsiki N, et al. Pharmacotherapy of type 2 diabetes: An update and future directions. Metabolism. 2022;137:155332.

[64] Akash MSH, Rehman K, Liaqat A. Tumor necrosis factor-alpha: Role in development of insulin resistance and pathogenesis of type 2 diabetes mellitus. J Cell Biochem. 2018;119(1):105-10.

[65] He RJ, Yu ZH, Zhang RY, Zhang ZY. Protein tyrosine phosphatases as potential therapeutic targets. Acta Pharmacol Sin. 2014;35(10):1227-46.

[66] Bakke J, Haj FG. Protein-tyrosine phosphatase 1B substrates and metabolic regulation. Semin Cell Dev Biol. 2015;37:58-65.

[67] Fernandez-Ruiz R, Vieira E, Garcia-Roves PM, Gomis R. Protein tyrosine phosphatase-1B modulates pancreatic β-cell mass. PLoS One. 2014;9(2):e90344.

[68] Tang C, Ahmed K, Gille A, Lu S, Gröne HJ, Tunaru S, et al. Loss of FFA2 and FFA3 increases insulin secretion and improves glucose tolerance in type 2 diabetes. Nat Med. 2015;21(2):173-77.

[69] Watterson KR, Hudson BD, Ulven T, Milligan G. Treatment of type 2 diabetes by free fatty acid receptor agonists. Front Endocrinol (Lausanne). 2014;5:137.

[70] Li X, Wan T, Li Y. Role of FoxO1 in regulating autophagy in type 2 diabetes mellitus (Review). Exp Ther Med. 2021;22(1):707.

[71] Wu Y, Pan Q, Yan H, Zhang K, Guo X, Xu Z, et al. Novel mechanism of foxo1 phosphorylation in glucagon signaling in control of glucose homeostasis. Diabetes. 2018;67(11):2167-82.

[72] Campbell WB, Fleming I. Epoxyeicosatrienoic acids and endothelium-dependent responses. Pflugers Arch. 2010;459(6):881-95.

[73] Tan Y, Ichikawa T, Li J, Si Q, Yang H, Chen X, et al. Diabetic downregulation of Nrf2 activity via ERK contributes to oxidative stress-induced insulin resistance in cardiac cells in vitro and in vivo. Diabetes. 2011;60(2):625-33.

[74] Waldman M, Bellner L, Vanella L, Schragenheim J, Sodhi K, Singh SP, et al. Epoxyeicosatrienoic acids regulate adipocyte differentiation of mouse 3T3 cells, via PGC-1α activation, which is required for HO-1 expression and increased mitochondrial function. Stem Cells Dev. 2016;25(14):1084-94.

[75] Pagel-Langenickel I, Bao J, Joseph JJ, Schwartz DR, Mantell BS, Xu X, et al. PGC-1α integrates insulin signaling, mitochondrial regulation, and bioenergetic function in skeletal muscle. J Biol Chem. 2008;283(33):22464-72.

[76] Oropeza D, Jouvet N, Bouyakdan K, Perron G, Ringuette LJ, Philipson LH, et al. PGC-1 coactivators in β-cells regulate lipid metabolism and are essential for insulin secretion coupled to fatty acids. Mol Metab. 2015;4(11):811-22.

[77] Almasi F, Mohammadipanah F. Prominent and emerging anti-diabetic molecular targets. J Drug Target. 2021;29(5):491-506.

[78] Ying C, Sui-Xin L, Kang-Ling X, Wen-Liang Z, Lei D, Yuan L, et al. MicroRNA-492 reverses high glucose-induced insulin resistance in HUVEC cells through targeting resistin. Mol Cell Biochem. 2014;391(1-2):117-25.

[79] Mardones L, Petermann-Rocha F, Martinez-Sanguinetti MA, Leiva AM, Troncoso-Pantoja C, Martorell M, et al. Genetic variants in the SLC16A11 gene are associated with increased BMI and insulin levels in nondiabetic Chilean population. Arch Endocrinol Metab. 2021;65(3):305-14.

[80] Schumann T, König J, von Loeffelholz C, Vatner DF, Zhang D, Perry RJ, et al. Deletion of the diabetes candidate gene Slc16a13 in mice attenuates diet-induced ectopic lipid accumulation and insulin resistance. Commun Biol. 2021;4(1):890.

[81] Masson W, Lobo M, Siniawski D, Huerín M, Molinero G, Valéro R, et al. Therapy with cholesteryl ester transfer protein (CETP) inhibitors and diabetes risk. Diabetes Metab. 2018;44(6):508-13.

[82] Barter PJ, Cochran BJ, Rye KA. CETP inhibition, statins and diabetes. Atherosclerosis. 2018;278:143-46.

PARTICULARS OF CONTRIBUTORS:
1. Tutor, Department of Microbiology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr. MGR Educational and Research Institute, Service Road, Maduravoyal, Adayalampattu, Chennai, Tamil Nadu, India.
2. Professor and Head, Department of Microbiology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr. MGR Educational and Research Institute, Service Road, Maduravoyal, Adayalampattu, Chennai, Tamil Nadu, India.
3. Assistant Professor, Department of Microbiology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr. MGR Educational and Research Institute, Service Road, Maduravoyal, Adayalampattu, Chennai, Tamil Nadu, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Balamurali Venkatesan,
Tutor, Department of Microbiology, Sri Lalithambigai Medical College and Hospital, Faculty of Medicine, Dr. MGR Educational and Research Institute, Service Road, Maduravoyal, Adayalampattu, Chennai-600095, Tamil Nadu, India.
E-mail: balajai96@gmail.com

AUTHOR DECLARATION:
• Financial or Other Competing Interests: None
• Was informed consent obtained from the subjects involved in the study?   No
• For any images presented appropriate consent has been obtained from the subjects.   No