Drug repurposing for the treatment of Type 2 Diabetes and Gestational Diabetes Mellitus

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Abstract --Currently, repurposing an existing medicine for treatment of a different disease is a good and lucrative choice because of the long and time-consuming research and development process of new drugs and the high attrition rate. The utilization of low-risk chemicals, lower overall research costs, and shorter development timelines are all contributing to its growth and appeal. Ideal repurposed medication candidates have been found using a variety of date- and experimental-driven methodologies. However, there are a number of technological and legislative issues that must be addressed. Type 2 and gestational diabetes mellitus are both forms of diabetes mellitus, although gestational diabetes mellitus is a transitory condition that can lead to type 2 diabetes in the future. About 90% to 95% of diabetic people have type 2 diabetes, which is the most common form of the disease. Currently medications used for the treatment of these two diabetes is basically Metformin which often regarded as first line of treatment for Diabetes, but it is not affective too much and just control the condition. In order to identify a more effective therapy for Type 2 diabetes and gestational diabetes, we are going to use the Drug repurposing approach to look at novel pharmaceuticals and treatments and alternative combinations of current drugs. Medicine repurposing strategies and their usage in the search for a better drug or combination of drugs for the treatment of Type 2 Diabetes and Gestational Diabetes have been addressed in this review article.

Keywords

Cardiovascular, Drug Repurposing, Gestational Diabetes, Insulin, Metformin, Obesity, Type 2 Diabetes

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Introduction

Type 2 diabetes

Straight away, type 2 diabetes is one of the world's most pressing health-related issues. Almost all most of the developing nations face this health issue. Type 2 diabetes disease mostly causes vision defect, nephrosis and peripheral pathology, and is related to premature death. n sort one polygenic disease there's no production of internal secretion by the beta (ß) cells of the duct gland [**Laslett et al.,2012].** In sort two polygenic disease, that accounts for over eighty per cent of all cases of polygenic disease, internal secretion is made by the ß cells and is discharged into the blood, however it later fails to act properly at the sites of aldohexose uptake, that square measure muscle, liver and fatty tissue [**Mendis et al., 2015**].

The type two diabetes disease pathologic process primarily starts with the losing potency of exocrine gland ß cells to reply to chronic fuel surfeit that ends up in internal secretion resistance and fatness. This inability of the body to use internal secretion properly is delineate as 'insulin resistance,' and may lie undiscovered for years, generally even decades. internal secretion resistance is concerned within the aetiology of sort two polygenic disease, cardiovascular {disease} and arteria disease. it's additionally coupled with variety of different abnormalities. These embrace, disturbances in pressure level physiological state, hyperinsulinemia, central fatness, epithelial tissue operate, supermolecule metabolism and coagulation [**Pandey et al.,2015].**

Diabetes is also directly related to Obesity.Obestity has become a severe risk factor for various of the non-communicable disease particularly type 2 diabetes. As it is observed that most of the people suffering from type 2 diabetes are obese or overweight.

The term "diabesity" has been coined since obesity has been shown to play a significant influence in the development of diabetes. BMI is taken consideration in case of measuring the obesity, at present it is indicated that a person having BMI above 35 kg/m2 can have diabetes due to obesity [**Pandey et al.,2015].**

Gestational Diabetes Mellitus

GDM, or gestational diabetes mellitus, is one of the most frequent medical conditions that pregnant women face. During Pregnancy body faces insulin resistance and hyperinsulinemia which may lead to cause diabetes to some women. As soon as the first signs of pregnancy are seen, a woman is considered to have gestational diabetes mellitus (GDM). Several risk factors are connected with the development of GDM. Being overweight, having a family history of diabetes, polycystic ovarian syndrome (POS), and recurrent glucosuria are some of the most frequent risk factors. If you have a history of hypertension or have had several abortions throughout your pregnancy, you may be at risk for developing gestational diabetes. **[American Diabetes Association et al.,2018].**

GDM often arises before the end of the second trimester and subsides shortly after birth, however this is not always the case. This occurs because insulin output rises early in pregnancy but insulin sensitivity may stay stable, drop, or increase, and insulin sensitivity begins to decline in mid-pregnancy, reaching its worst by the third trimester. Pregnancy-related infertility (IR) often begins about the midpoint of the third trimester and continues into the fourth. This is the case with gestational diabetes mellitus (GDM). 21 Placental hormones and adipokines, as well as tumour gangrene factor (TNF)- α , human placental agent, and human placental internal secretion, are possible causes of IR in maternity. Aldohexose internal secretion equilibrium is disrupted during maternity because to a rise in steroids, progestin, and cortisone. 22 A woman's duct gland secretion increases during pregnancy to complete the peripheral IR **[Camelo Castillo et al.,2015]**. A woman develops GDM when her duct glands stop secreting enough internal secretion to keep up with the IR's metabolic demands. Aldohexose intolerance is exacerbated by factors such as increased maternal fat deposition, decreased activity, and increased calorie consumption **[Ehrlich SF et al.,2011].**

Pathophysiology of Type-2 Diabetes

Glucose uptake sites such as skeletal muscle, liver, adipose tissue, and heart are all affected by insulin resistance in Type 2 diabetes, which is distinct from Type 1 diabetes in that insulin is secreted into the circulation, but it is unable to function adequately at some of these sites **[Donnelley R et al.,1999**].

Tyrosine-phosphorylation of insulin receptor substrate proteins is promoted by activating the insulin receptor itself, which results in the interaction of numerous scaffold proteins and the insulin receptor substrates (IRS).The IRS proteins most probably due to the action of multiple kinases it become phosphorylated on serine and threonine residues. There are also several others molecules that are involved in insulin signalling pathway like phosphatidylinositol 3kinase and m-TOR. These transmit the activation signal downstream and also offer upstream negative feedback signals.

Cytokines, peptide hormones, and the activation of intracellular stress response pathways are some of the mediators of interorgan communication.

Adipocytes produce adipokines, which play a key role in regulating insulin levels, and insulin resistance is related to this process. Due to the increased levels of adiponectin, NEFA, glycerol and several others proinflammatory cytokines insulin resistance is observed. Obese and Type 2 diabetes patients have been shown to have higher NEFA levels.

Pyruvate dehydrogenase and phosphofructokinase activity are inhibited sequentially when

NEFAs compete with glucose for substrate oxidation. There is a theory that the increased FFA consumption leads to an increase in acetyl-CoA levels in mitochondria, as well as a decrease in pyruvate dehydrogenase activity, which results in an increase in intracellular citrate concentration, which inhibits phosphofructokinase, resulting in a rise in glucose-6phosphate levels in the bloodstream, which is thought to be caused by the increased FFA oxidation rate. There is a decrease in glucose absorption due to elevated glucose-6-phosphate levels following hexokinase II inhibition.

beta-Cell Dysfunction(failure) in Type 2 diabetes

Since it results in decreased beta cell mass and worsening of key beta cell activities including glucose stimulated insulin production, b-cell failure is the most important factor influencing insulin resistance. Diabetes Type 2 is associated with an estimated 40% and 66% reduction in Beta cell mass, respectively, in lean and obese persons, as contrasted to nondiabetic individuals. When beta cells dysfunctions it leads to the secretion of proinsulin which is a specific markers along with amyloid fibrils by which we can observe the pathogenesis of their progressive destruction. Amyloid fibrils may be harmful to beta cells, resulting in their death, and amyloid cells may take their place in the pancreatic. Type 2 diabetes's beta cell degeneration is mostly controlled by this method.

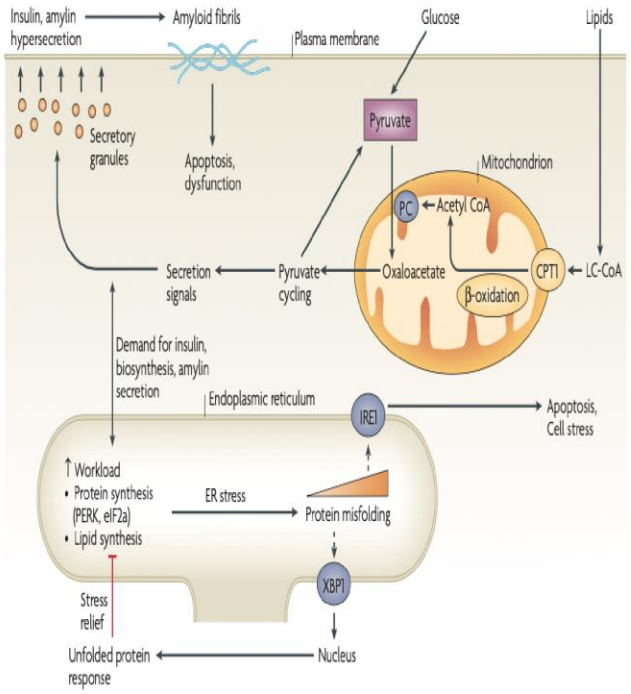

Figure 1 :Process of ß-cell failure in type 2 diabetes. The model includes metabolic overload (mitochondria). endoplasmic reticulum (ER) stress and deposition of harmful amyloid fibrils. Overnutrition and increased lipide provide induce enzymes of ß-oxidation, like carnitine palmitoyltransferase-1 (CPT1), leading to increased acyl group CoA levels, allosteric activation of pyruvate carboxylase (PC) and organic upregulation of pyruvate sport. This ends up in basal hypoglycaemic agent secernment and loss of the glucose-stimulated increment in pyruvate sport flux, thereby blunting aldohexose stirred up hypoglycemic agent secretion. The increased demand for hypoglycemic agent biogenesis will increase demand (workload) within the ER, step by step resulting in ER stress and increased supermolecule misfolding. ER stress is at the start mitigated by the unpleated supermolecule response (UPR), mediate by the transcription issue XBP1, however over time, the UPR becomes less effective and therefore the injurious effects of ER stress cause death, mediate by IRE1. Finally, hypoglycemic agent secernment is among amylin secretion, that in humans will kind amyloid fibrils that accumulate at the surface of B-cells to induce disfunction and apoptotic death. eIF2a, being translation initiation factor-2a; IRE1, inositol-requiring kinase-1; LC-CoA, long-chain radical CoA; PERK, supermolecule enzyme ribonucleic acid (PKR)-like ER-associated enzyme **[Muoio et al.,2011]**.

To some extent, other nutrients also affect insulin production in healthy pancreatic islets, but glucose is by far

the most significant. glucose metabolism results in a rise in the ATP:ADP ratio and the closing of K+ channels, which in turn activates voltage-gated ca2+ channels, which in turn stimulates granule exocytosis from beta cells via ca2+-mediated stimulation. K+ channels are another name for the signal that initiates insulin release within the first 10 minutes of glucose stimulation.

Beta cells' vulnerability to decompensation and development of type 2 polygenic illness can be determined in part by genetic studies. Many types of maturity-onset polygenic disorder of the young (MODY) are mono-genetic diseases that result from mutations in vital Beta cell transcription factors or metabolic regulators, such as hepatocyte nuclear factor-4α (HnF4α; leading to MoDY1), glucokinase (resulting in MoDY2), and exocrine gland and small intestine PDX1 mutations. These disorders are characterized by an impaired GSIS and a premature onset of polygenic condition.

If Beta cell failure happens as a result of metabolic excess and aerophilic stress, as well as increased cell death, then certain genetic changes that favour those events may be present in non-MODY patients. Type 2 diabetes is still an enigma.

Pathophysiology of Gestational diabetes(GDM)

GDM is mostly caused by a malfunctioning beta cell owing to pre-existing chronic insulin resistance. Excessive insulin production as a consequence of prolonged fuel excess causes beta cell malfunction. Pro-insulin production and post-translational changes, as well as detecting blood glucose levels, granule storage, and the intricate machinery that governs exocytosis, may all be affected.

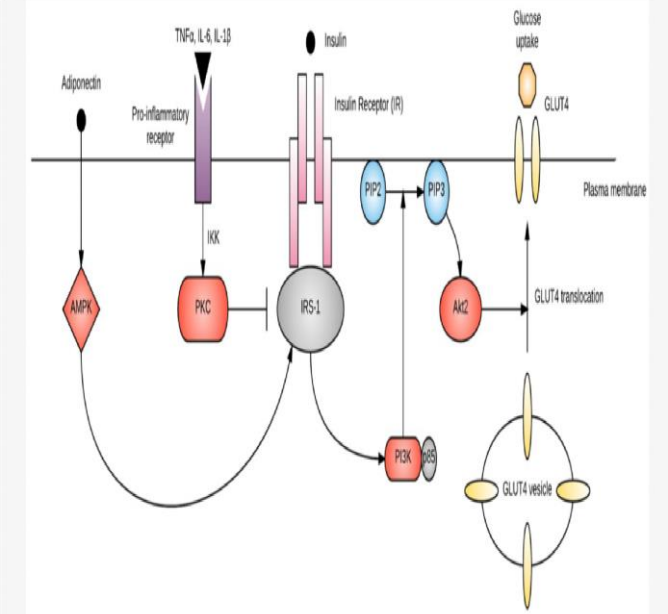

Figure:2 Above picture represents a diagram of Insulin signalling. It shows that when insulin is binded to insulin receptor(IR) then IR-1 is activated. As shown in the figure Adiponectin promotes IRS-1 activation through AMP-activated protein kinase (AMPK), whereas pro-inflammatory cytokines activate protein kinase C (PKC) via IKB kinase (IKK), that inhibits IRS-1. IRS-1 activates phosphatidylinositol-3-kinase (PI3K), that phosphorylates phosphatidylinositol-4, 5-bisphosphate (PIP2) to phosphatidylinositol-3, 4, 5-phosphate (PIP3). PIP3 activates Akt2, that promotes GLUT4 translocation and aldohexose uptake into the cell **[Plows et al.,2018].**

Hormone resistance exacerbates β-cell dysfunction. Symptoms are worsened by a decrease in insulin-stimulated glucose absorption, which overloads the -cells and causes them to produce additional hormones in response. Aldohexose's direct role in β-cell failure has been defined as glucotoxicity. As a result, a vicious cycle of symptoms, resistance to hormones, and greater dysfunction ensues when the -cell dysfunction starts.

Insulin resistance occurs when cells are unable to respond to hormones properly. GLUT4 is the major transporter responsible for delivering aldohexose into cells for utilization as energy, and a lack of hormone signalling may result in insufficient cell wall translocation of GLUT4. A fifty-four percent decrease in aldohexose absorption is seen in GDM as compared to normal gestation. Reduced aminoalkanoic acid or increased serine/threonine phosphorylation of the hormone receptor dampens

hormone signalling, which is occasionally unaffected. As a result, GDM has been shown to have changed expression and/or phosphorylation of downstream regulators of the hormone sign, such as hormone receptor substrate IRS-1 (IRS1), PI3K (PI3K), and GLUT4. Pregnancy does not eliminate all of these alterations in molecular structure.

There are various other factors which influences GDM like:

Leptin

In the case of enough fuel reserves, the endocrine hormone Leptin is released by adipocytes. For the most part, it works by increasing energy expenditure and decreasing appetite in cells around the curving nucleus of the brain's structure.

Either a deficiency in barrier leptin transport or living thing processes similar to hypoglycaemic agent resistance will lead to leptin resistance. To supplement fat reserves beyond what would be required in a non-pregnant condition, much as with hypoglycemic agent resistance, a degree of leptin resistance occurs in a conventional physiological state as well. Hyperleptinemia is a result of increased leptin resistance in patients with GDM. Pre-pregnancy BMI, on the other hand, may be a better indicator of present leptin levels than GDM.

Throughout a person's life, the placenta also secretes leptin. For the most part, the placenta is responsible for producing most of the body's plasma leptin. Hyperleptinemia is exacerbated in women with gestational diabetes mellitus as a consequence of increased synthesis of leptin in the placenta. Foetal macrosomia is hypothesized to be caused in part by an increase in the ease with which organic compounds may cross the placenta.

During human gestation leptin is secreted by placenta. Majority of plasma leptin is secreted by placenta.

In GDM, placental leptin production is likely to be elevated as a consequence of placental resistance to hypoglycaemic agents, which adds to hyperleptinemia. The placenta's ability to transfer aminoalkanoic acid across the membranes may also be responsible for the development of craniate macrosomia.

Liver

Unregulated glucose synthesis in the gastrointestinal tract is also linked to GDM

(gluconeogenesis). Fasting increases gluconeogenesis, which is thus not sufficiently reduced in the fed state. Because the bulk of aldohexose absorption by the liver (around 70%) is not hypoglycaemic agent dependent, this is typically not thought to be wholly the consequence of erroneous aldohexose sensing due to hypoglycaemic drug resistance. PI3K, which is involved in gluconeogenesis and the hypoglycaemic agent signalling pathway, may have a role in these effects. Gluconeogenesis may also be sped up by increased supermolecule consumption and muscle breakdown. The liver does not seem to be the major cause of T2DM or GDM, despite this.

Placental Transport

The placenta's hormone and cytokine production contributes to internal secretion resistance throughout the physiological state. Additionally, the placenta is vulnerable to hyperglycaemia because it serves as a barrier between the maternal and vertebrate habitats. aldohexose, amino acids, and lipid transport via the placenta might be affected by this:

Glucose—Glucose is the foetus and placenta's principal energy source, hence it must always be readily available. Because of this, the placental transfer of aldohexose does not need internal secretion. Instead, aldohexose transport is carried out by GLUT1 via sodium independent diffusion, rather than by GLUT1 and GLUT2. internal signaling will continue to regulate placental aldohexose metabolism despite a decrease in aldohexose production in the placenta. Since aldohexose absorption in the placenta is susceptible to maternal hyperglycaemia, the placenta is more likely to accumulate growth in vertebrates, leading to macrosomia and fetal stunted growth

Vertebrate growth is also heavily influenced by the placental transfer of proteins and amino acids. GDM is linked to cumulative activity in the A and L systems. Pro-inflammatory cytokines, such as IL-6, may influence these processes. The altered transport of aminoalkanoic acids may also play a role in the development of GDM.

The growth in obesity-related GDM has shifted attention away from the disease's original definition as a hyperglycemic disorder. Aldohexose pathways account for just 9 percent of placental organic phenomenon modifications in GDM, while supermolecule routes account for 67 percent of these changes. Those findings are in line with those found in the HAPO Study, which examined the effects of aldohexose and maternal blubber on excessive growth in vertebrates. Since GDM is likely to affect aldohexose, amino acids, and fatty acid transport in the

placenta, all three should be considered when examining the effect of GDM on placental function and vertebrate growth **[Plows JF et al.,2018].**

Treatment of Type 2 Diabetes

At present time actually there is no cure for diabetes, but we can control and treat it. We can delay the onset of diabetes-related health problems by using pharmaceutical treatment and insulin to keep blood glucose levels as close to normal as feasible.

When treating Type 2 Diabetes, Metformin is one of the most often prescribed medications. Insulin-stimulating effects on tissues including the liver, striated muscle, epithelium and animal tissue have been shown to have a wide range of effects. Additional medication is often suggested if the HbA1c level is greater than 7.0 percent after three months **[McGovern et al.,2018].**

Aldohexose-lowering effects of metformin are primarily achieved by suppressing gluconeogenesis and increasing insulin suppression of endogenous glucose production, as well as by reducing aldohexose absorption from the internal organs and possibly increasing aldohexose uptake and utilization by peripheral tissues, such as muscle and fat **[Natali et al.,2006]**. A done through various between increased muscle hypoglycemic drug sensitivity and using more potent anti-diabetic doses is also conceivable GLP-1 (glucagon-like amide one) may also have a role in improving aldohexose balance by interacting with the incretin axis **[Maida et al.,2011]**.

There are other therapies like Incretin Based Therapies:
As indicated in Figure 4, incretin-based medicines utilize the effects of the GIP and GLP-1 **[Irwin et al.,2015]**, which are represented in the figure. Intraluminal carbohydrates trigger the release of these incretin hormones from the stomach, which are critical regulators of postprandial glycemic control. Numerous beneficial effects may be linked to these glands, including stimulating hormone production and hormone organic phenomenon, increasing aldohexose sensitivity in cells and lowering internal secretion. The extra-pancreatic activities of incretin hormones, in addition to targeting duct gland isle cells, also slow down the elimination of internal organs, as well as reduce food intake and aid in weight loss **[Drucker et al.,2015].**

We can also target other systems like:

SGLT-1/SGLT-2 Inhibitors

Sodium-glucose co-transporter-2 is responsible for 80–90% of nephritic proximal tubule aldohexose organic reactions (SGLT-2). As a result of its suppression, the treatment of T2DM could benefit from its administration.. GLP-1R agonists are used in conjunction with SGLT-2 inhibitors to provide a manageable treatment plan. Because they decrease the nephritic aldohexose organic process and increase urine aldohexose excretion, these combination inhibitors enhance glycaemia control with a decreased risk of hypoglycaemia **[Inzucchi, et al., 2015].**

Twin SGLT-1/SGLT-2 inhibitors have emerged as an innovative approach to combating obesity. Aldohexose absorption in the stomach is facilitated by SGLT-1, which is also found in the nephrotic proximal tubule. To reduce aldohexose absorption in the digestive tube, these medications use an inhibitor of SGLT-1 and an inhibitor of both transporters to reduce nephritic aldohexose organic process. Sotaglifozin (LX4211) suppresses both SGLT-1 and 2mediated glucagon-like amide-1 and peptide YY production, which is important in the treatment of hypoglycaemia as well as weight gain, according to eye-catching literature data shown in Figure 9. For the treatment of type 1 and type 2 diabetes, Lexicon is actively developing sotagliflozin [**Zambrowicz et al., 2012].**

PPARs-Based Therapies

PPARs are divided into three categories, each with a specific tissue distribution: PPAR-α, PPAR-δ (sometimes known as PPAR-β), and PPAR-γ. Plasma HDL-Cholesterol rises as a result of increased lipoid metabolism (HDL-C). Lipoid metabolism in organs like the liver, renal tubular epithelium, and heart muscle is promoted by PPAR-α activation. PPAR-α has been shown in several studies to have anti-inflammatory and anti-atherogenic properties, which may be due to a reduction in a variety of inflammatory mediators and adhesion molecules. Reduced lipotoxicity and inflammation in semipermanent PPAR- α agonist therapy improves the vascular functioning of diabetic patients and reduces diabetes-related risk factors.

With a wide expression pattern, PPAR-δ regulates cell proliferation and differentiation in many distinct cell types, including fat cells. According to research on PPAR-δ, the phagocyte is involved in the inflammatory process, which

implies that blocking this process might reduce inflammation and halt the course of disease **[Dent et al.,1997]**. PPAR-γ is primarily found in adipose tissue, intestinal cells, and mononucleate leukocytes when it comes to adipocyte proliferation and differentiation. PPAR-γ ligands have been shown in several studies to have pleiotropic effects on fluid overload.

PPARs, when activated by matter and heterodimerized with the 9-cis retinoic acid receptor, control sequence transcription by binding to particular polymer response components (RXR). Many commercial drugs, such as thiazolidinediones and fibrates, which are hypolipidemic and work via the PPPAR- subtypes, have been shown to activate these subtypes, as have endogenous ligands including free fatty acids, eicosanoid molecules, and vitamin B3. An effort is now underway to produce PPARs agonists that may deliver synergistic anti-diabetic and cardioprotective benefits that are more cost-effective than therapy with PPARs selective agonists **[Pourcet et al.,2006].**

There is also other natural techniques like Herbal Medicines.

Herbal Plants in treatment of Type 2 Diabetes: Various plant extracts are being used to treat diabetic people. Garlic (Allium sativum), ivy gourd (Coccinia indica), psyllium (Plantago ovatum), cinnamon (Cinnamomum cassia), and gurmar (Gymnema sylvestre) have all been shown to be effective in the treatment of type 2 diabetes. **[Ota et al.,2017]**. Some plants' mechanisms of action in Type 2 Diabetes are very well.:

Momordica Charantia

This tropical and climatic zone plant, Momordica Charantia or Bitter Melon (BM), is native to South America, Asia and the Asian nation/geographic area. To treat Type 2 Diabetes Mellitus, it has been utilised in Asian phytotherapy (T2DM) **[Ahmed et al.,2004]**.A number of studies were conducted to investigate the many medical specialty mechanisms of action. These include increased expression of PPAR- γ in white fat tissues, as well as a reduction in leptin expression in white fat tissues, and the enhancement of glucose uptake by skeletal muscles in rats given high fructose. Internal secretion sensitivity and tolerance, aldohexose intolerance and the internal secretion signal pathway in rats given a high-fat diet were all enhanced by its extracts [Sridhar et al.,2008]. The alpha-glucosidase protein activity was decreased while the postprandial symptom was suppressed by cucurbitane-type triterpene glycosides and seed trehalose **[Artasensi A et al.,2020].**

There are several others herbal plants such as *Panax Ginseng, Trigonella Foenum Graecum, Scutellariae Radix , Coptidis Rhizoma .*

Coptidis Rhizoma

Coptis chinensis, a species of Coptis, is the source of CR. Berberine, coptisine, and palmatine are the primary alkaloids responsible for its pharmacological properties. The antibacterial and anti-cancer properties of metal have recently been discovered by scientists. As a result, berberine may reduce glucose and promote the release of a hypoglycemic agent.

That's why SR and metal may be able to reduce inflammation, hypoglycemic agent resistance, hyperglycemia, and hyperlipidemia, which are the primary contributors to illness and disease. T2DM may be effectively treated using a 1:1 mixture of SR and metal extracts, as used in traditional Chinese medicine. Despite this, metabolomics and MAPK/PI3K/Akt signalling pathways were able to determine their compatibility mechanism, which is still known.[**Angelica et al.,2020].**

Treatment of Gestational Diabetes Mellitus(GDM)

There are different approaches that we can take during treatment of GDM. Like we can have nutritional therapy, (2) physical activity (in few cases) (3) maintaining weight gain within the proper recommendation and (4) pharmacological therapy**[Yaktine et al.,2009].**

Nutritional Techniques

Nutritional intervention for girls with GDM has been found to be one of the most beneficial and effective medical aid, and it's suggested for all girls to boost glycemic control and to produce adequate nutrients. For rotund girls, modest calorie restriction of one,600–1,800 kcal/day or up to a thirty third reduction in intake looks to be safe and more practical for limiting physiological state weight gain and getting adequate glycemic management.

regarding carbohydrates, in 2013, the Endocrine Society steered that girls with GDM limit their supermolecule intake to 35–45% of the overall calorie intake[**Blumer et al.,2013].**

Most organic process interventions have targeted on the categories and quantity of

Carbohydrates and therefore the glycemic indexes of specific food things, however there are but ten such studies in total. concerning the glycemic index, a scientific review from 2010**[Louis et al.,2010].** It showed that coffee glycemic index diet shouldn't replace the present recommend-disfunction physiological condition diets, because it has no consistent helpful impact on glycemic values. Recent trials shows that using a low content carbohydrate diet did not

reduce the insulin requirement rather than it shows positive impact on maternal weight gains[**Laitinen K et al.,2009].**

Physical Activity (Exercise)

It has been determined that exercise plays a big role in maintaining GDM i.e. by up the glycemic management. differing kinds of physical activity is accomplished throughout physiological condition, like resistance and endurance activities, with the advantage that some is applied up to delivery. Daily traditional exercise of half-hour or a lot of is ample. There are 5 interventions which incorporates differing kinds of physical activity, like arm ergometry, stationary sport, walking and resistance coaching. Their durations varied from twenty to forty five minutes, and their frequencies ranged from three to four times per week**[Metzger et al.,2007].**

Pharmacological Techniques We apply pharmacological therapy to the women who have not achieved their glycemic target with nutritional or physical activities. We then use insulin for this purpose. Insulin should be administered in accordance with the patient's blood glucose levels. Basal insulin, long-acting insulin analogue, or neutral protamine Hagedorn should be prescribed if the fasting glucose is more than 90-95 mg/dl (whole blood capillary) (NPH). When treating GDM in the past, normal insulin and NPH were the most prevalent options. The current preference in pregnancy is for rapid-acting insulin analogues over conventional insulin, owing to their lower risk of hypoglycemia and the possibility that they enhance PP blood glucose management. **[Pettitt et al., 2003].**

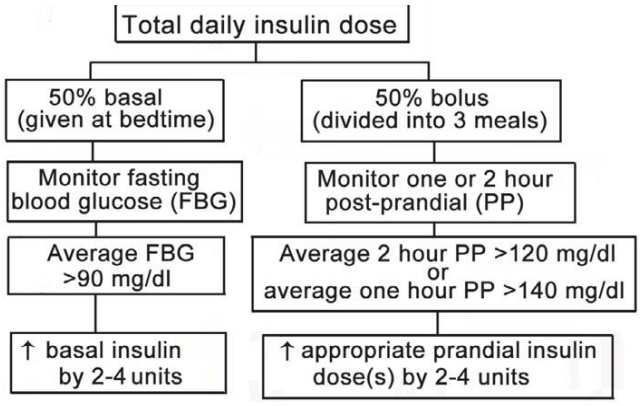

Figure3: Insulin therapy in hyperglycaemia during pregnancy.[Pic: Eman et al.,2015]

Drug Repurposing

An licensed or experimental pharmaceutical that has been given a new use outside of its original medical indication may be repurposed. This process is known as "drug repurposing." These advantages outweigh the disadvantages of generating an entirely new medicine for a specific indication**[Ashburn et al.,2004]**. It offers several advantages over developing new medications, one of the most important of which is that the chance of failure is very low since it has previously been tested and proved to be safe in preclinical studies. As a result, pharmaceuticals can be produced much more quickly because the preclinical research, safety requirements and in some cases formulation development have already been completed. Furthermore, repurposing an existing drug requires less capital than creating a program from scratch, albeit this varies depending on the stage of development we are repurposing from. In addition to these benefits, it has the potential to become less hazardous and more profitable as the failure cost decreases**[Breckenridge et al.,2018]**.

This drug repurposing process has been mostly accidental and coincidental; once an effect or a newly found on-target effect was revealed in a treatment, commercialization began straight away. Repurposing of Viagra for impotence was based on retrospective clinical information, but repurposing of thalidomide for erythema leprosum (ENL) and multiple myeloma was backed by serendipity. Indeed, the most dependable cases of pharmacological repurposing to date haven't employed a scientific process. 1 As a result of Pfizer's repurposing and promotion of Viagra as an antierectile dysfunction treatment, Pfizer has a 47% share of the erectile dysfunction drug market.. **[Phillips et al.,2013].**

Techniques and approaches for Drug Repurposing

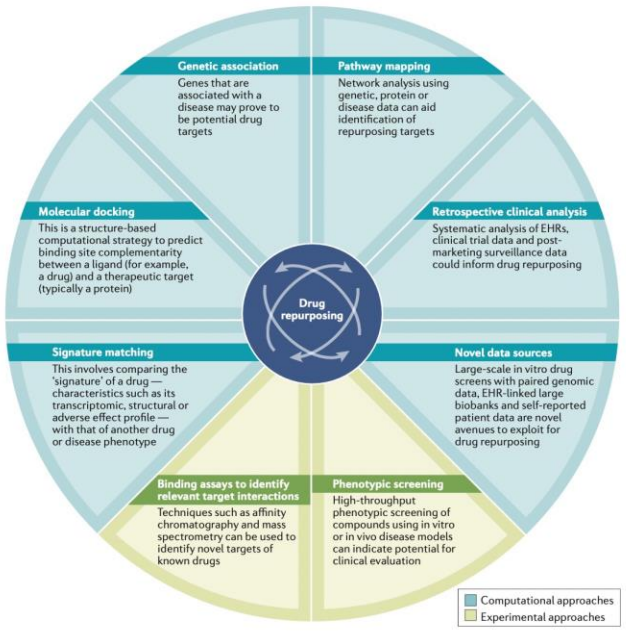

Figure: Above picture shows about different process involved in Drug repurposing **[Pushpakom et al.,2019].**

Computational approaches

Computing approaches are based on systematic examination of any type of information, and this study could lead to the formulation of creative hypotheses, such as organic phenomena, chemical structure, or genetic or proteomic knowledge [**Hurle et al.,2013].**Few of the common computational approaches used in drug repurposing are mentioned below.

Pathway or network mapping.

Approaches that use pathways or networks to identify possible repurposing targets are common **[Smith et al., 2012]**. This does not mean, however, that all of the genes discovered by GWAS or other approaches are necessarily good candidates for medication development, as previously noted. If a pathway-based method can offer information on genes upstream or downstream of the GWASassociated target, repurposing options may arise **[Greene et al.,2016]**. Network analysis develops drug or disease networks based on organic phenomenon patterns, disease pathology, supermolecule interactions, or GWAS knowledge to help in the repurposing of therapeutic candidates.The network analysis method has been used in many of the signature matching studies already mentioned **[Iorio et al.,2013].**

Signature matching. To do signature matching, researchers compare a medicine's distinctive properties, or "signature," to those of a different drug, illness, or clinical phenotype **[Keiser et al.,2009]**. It is possible to extract the signature of a medicine from one or more forms of data: transcriptomics (RNA), proteomics (proteins), or metabolomics (metabolites).

Matching transcriptomic signatures is accustomed create drug–disease comparisons (estimating drug– illness similarity)**[Dudley et al.,2011]** and drug– drug comparisons (drug– drug similarity)**[Iorio et al.,2013].** Before and after treatment, organic phenomenon profiles of biological material such as cells or tissues are compared to a disease-associated expression profile that has been similarly obtained by using differential expression analysis of disease and important factor in the success. The resultant differential organic phenomenon signature (the molecular signature of the drug) is then compared to that of the disease-associated profile.

Computational molecular docking.

An approach to anticipate the compatibility of the matter (for example, a drug) and the target (for example, a receptor) may be possible by using molecular tying. There are various drugs that can be tested against a specific receptor target if there is prior information of that target's role in an illness (conventional docking: one target and multiple ligands). It is also possible to do reverse docking (target-ligand pairing) in which a drug library is used to target several receptors concurrently (inverse docking).

The Experimental approaches:

Binding assays to spot target interactions.

More and more medications are being found by affinity activity association degreed mass spectroscopy, which is a proteomic method **[Brehmer et al.,2005]**. Drug repurposing and off-target research were natural bedfellows for target validation during the associate degree time in chemical biology. Cellular Thermostability Assay (CETSA) uses thermodynamic principles to predict the thermal stability of target proteins by drug-like ligands with the right cell affinity, and this technology has been used to map target engagement in cells **[Martinez et al.,2013].**

Drug Repurposing in Type 2 diabetes and Gestational Diabetes

Treatment for Type 2 diabetes is now feasible using a wide range of previously used medications. Antiparasitic drugs such as Niclosamide ethanolamine (NEN) enable parasitic worms uncouple their mitochondria **[Tao et al.,2014]**. In a research, it was shown that NEN might be utilized to treat and control Type 2 diabetes. NEN, when taken orally in mice, improves energy distribution and the metabolism of biomolecules. You can better control your blood sugar levels because of the HFD, which increases visceral steatosis and makes you resistant to hypoglycemic agents in the first place. Hypoglycaemic agent resistance and type 2 diabetes have a same pathogenic process, inflammation, which is a connection between avoirdupois and hypoglycaemic agent resistance. Hypoglycaemic drug sensitivity and glycemic

control may be restored by reducing inflammation **[Marin et al.,2016]**.

Another drug. One of the most popular and widely prescribed medications in history was an analgesic derived from salicylate, a pre-existing medicine used to treat pain and inflammation. Patients with Type 2 diabetes who take salicylate see improvements in their blood sugar levels, as well as a decrease in inflammatory mediators **[Gentilella et al.,2019]**. Fat-induced deficiencies in hypoglycaemic agent communication activity are inhibited by greater doses of nonsteroidal anti-inflammatory drugs and IKK-b inactivation, suggesting a new class of therapeutic drugs for Type 2 diabetes **[Pereira et al.,2013].**

Some of the Drug Repurposed for Type 2 Diabetes are:

Name of Drugs	Original indications	Mode of Action	Status of Drug repurposed	References
Niclosamide ethanolamine	Anthelmintic drug	Mitochondrial uncoupler	N/A	[Tao et al.,2014]
Clobetasol	Inflammation and itching	Phospholipase A2	Approved	[Jones et al.,2004]
Phenoxybenzamine	Hypertension	Alpha-2A adrenergic receptor	Approved	[Zhang et al.,2015]
Carprofen	Pain	Prostaglandin G/H synthase 2	Approved	[Wang et al.,2020]
Buspirone[	Anxiety disorder	Serotonin-1A	Approved	[Paulmann et al.,2009]
Matrine	Hepatitis B	HSP90 /HSP72	N/A	[Zeng et al.,2015]
Hydrocortisone	Inflammatory diseases	Nitric oxide synthase	Approved	[Aggarwal et al.,2020]

Repurposing nonsteroidal anti-inflammatory drugs(NSAIDS) for Diabetes

DPP-4 inhibitors and antagonists have been found to be effective in managing glucose metabolism in diabetes mellitus, and this has been proven in clinical studies in addition to varied treatments such as insulin and sulfonylurea, biguanides, meglitinides, thiazolidinediones and alpha-glucose inhibitor **[Marn-Pealver et al]**.

When used in conjunction with incretin hormones like GLP-1 and GIP, the primary mechanism of DPP-4 inhibitor therapy is to prevent the DPP-4 catalyst from degrading these hormones, resulting in improved glucose homeostasis **[Zhong et al.,2013]** show that DPP-4 inhibitors have a role in dominant inflammatory disorders by degrading chemokines and growth factors simultaneously. Hypoglycaemic agent (Insulin) secretion and glucagon release are stimulated, and beta cell death is reduced, by incretin hormones **[Drucker et al.,2006]** Diabetic patients may benefit from Piroxicam, an NSAID.

Using molecular docking simulations and Activity Atlas mode, the researchers discovered that piroxicam inhibits the human DPP-4 protein in the study. The Activity Atlas model showed that both positive and negative electrostatic and hydrophobic inhibition in murine models were similar. In terms of form, Piroxicam and an authorized DPP-4 inhibitor are very comparable Piroxicam binds to the DPP-4 druggable area, as shown by docking simulations using FlexX molecules and 3D-RISM calculations.

In order to demonstrate Piroxicam's repurposing as a DPP-4 inhibitor, the medicine was evaluated at doses of 135 µM, 27.2 µM, 4 µM, and 1.8 µM. DPP-4 activity was increased decreased by piroxicam (74.5 percent, 65.5 percent, 36.5 percent, and 29.6 percent, respectively) ($p<0.05$). Sitagliptin (a diabetic medicine) reduced DPP-4 activity by 51% at a concentration of 0.018µ M, whereas piroxicam had an IC50 value of 9.9 µM **[Veera et al.,2019].**

In spite of that, the biological half time of piroxicam was about 45h **[Dhake et al.,1990]** ,whereas it was about 8-14h for sitagliptin. So, if we consider this then it correlates us with the number of dosages,**[Smith et al.,2018]** piroxicam alone or one of its derivatives can be considered as a probable anti diabetes drug in future.

Repurposing Calcium Channel blockers for Potential drug for GD and T2D

Type 2 diabetes and hypertension have been shown to be connected. Diabetes develops as a consequence of hypertension-induced decreased glucose tolerance and insulin resistance **[Gress et al.,2000].** New cases of diabetes mellitus have been linked to certain antihypertensive medication types, according to a recent research **[Elliot et al.,2007]**. The CCB-based medication Azelnidipine helps hypertensive people lower their blood pressure without raising their heart rate. Azelnidipine inhibits tumor mortification and has a wide range of unique fundamental and clinical effects (TNF) -a inhibited the synthesis of nicotinamide, a precursor to lymphokine (IL)-8, in human umbilical vein epithelial tissue cells. Dinucleotide phosphate oxidase mediates reactive chemical element species to reduce urinary macromolecule secretion, urinary 8-hydroxydeoxyguanine trigonometric function, and liver-type carboxylic acid binding macromolecule (L-FABP) levels [10], as well as current levels of advanced glycation end-product (AGE) and soluble AGE **[Yamagisgi et al.,2004]**.

As a result of current experimental research, Azelnidipine lowered the risk of hyperglycaemia-induced metabolic complications in diabetic mice **[Iwai et al., 2006]**. The study by Kain et al. Mice with impaired glucose tolerance and a higher risk of hyperglycemia benefit from azelnidipine in recent research. It is thus predicted that human glucose intolerance and insulin levels may also be improved by this method.

CCB was shown to be more efficient than a thiazide diuretic in reducing the chance of acquiring diabetes in a clinical trial. By increasing the blood flow to the periphery, the vasodilatory properties of CCBs may reduce insulin resistance, and there is also some evidence that CCBs can increase insulin sensitivity.

Aldohexose tolerance has been studied in a number of clinical studies including CCBs. Aldohexose tolerance was shown to be improved in non-pregnant, non-diabetic individuals treated with calcium channel blockers **[Koyama et al.,2002]**. Diabetes patients with cardiovascular disease who used CCBs had decreased fasting glucose levels, according to a recent study. According to alternate research, aldohexose tolerance may be increased by drugs that interfere with the renin-angiotensin system, such as CCBs, whereas beta blockers and diuretics can aggravate it **[Mancia et al.,2006]**. CCBs were shown to have no effect on new-onset polygenic disorder in a recent network meta-analysis of medications to prevent it, while diuretics and beta blockers were. Ca2+-channel blocker inhibits aldohexose-stirred up internal secretion from islets in vitro models of internal secretion, which may correlate with post-nutrition hyperglycaemia **[Ramachandran et al.,2014]**. Using a calcium-channel blocker increases basal secretion and decreases endocrine secretion in intact islets, however. Calcium-channel blockers may also protect against ER stress and beta-cell apoptosis by reducing atomic number 20 flow throughout symptoms and drives **[Ma et al.,2013]**. Calcium channel blockers have been linked to better glucose management in non-pregnant people, according to study. These data support the use of CCBs as a GDM treatment option.

Combination therapies for T2D and GD

Sitagliptin and Metformin

Sitagliptin and Metformin are two different drugs having different mode of actions. These two are used basically as a Monotherapy. So, by using them together we can get better results in the treatment. Sitagliptin works by inhibiting the DPP-4 enzyme which leads to the elevation of GLP-1 and GIP up to 2-3 times **[Drucker et al.,2003**]It affects insulin secretion in different ways than sulfonylureas and apart from this it inhibits the production of glucagon which leads to lowering hepatic glucose output.

Metformin belongs to the member of the biguanides antidiabetic family of medicine. It is orally administered drug with bioavailability about 50-60%. It has few drug interactions apart from the well-known interaction seen with Cimetidine. When Cimetidine is given with metformin it increases the level of metformin by more than 40% [**Green J et al.,2008].**The mechanism of action isn't clearly outlined, however its result is especially through the liver.

Metformin, besides its result within the liver, has additionally been shown to extend the plasma concentrations of GLP-1 however not of GIP **[Migoya et al.,2010]**. The modest increase of GLP-1 by Glucophage might have Associate in Nursing additive result once given with sitagliptin, leading to an improved metabolic management among patients taking the mixture medication.

A number of studies have shown the effectiveness and superiority of combination therapy compared with most doses of monotherapy. Combination medical aid addresses the various pathophysiology's seen in patients with T2DM. They conjointly enable submaximal doses of the medicine used, so minimizing the probabilities of intolerable aspect effects of the medicine once used individually **[Bell et al.,2004]**. The use of antidiabetic drug and sitagliptin together is one in every of the popular first-line medication

agents within the treatment of T2DM. each agents act in numerous however complementary areas of defect seen in patients with polygenic disease. Thus, the utilization of the mixture medical aid in patients with suboptimal metabolic management provides another therapeutic plan. within the 1st study of sitagliptin-metformin combination medical aid, conducted among poorly controlled patients with polygenic disease, it absolutely was efficacious and well tolerated **[Charbonnel B et al.,2006].**It was observed that at week 24 of the combination therapy of these two drugs HbA1c was reduced by 0.65% in comparison with metformin monotherapy.

In a study it was observed that Initial treatment with a mixture of sitagliptin and antidiabetic drug showed superior outcomes once mistreatment the mix medical aid in poorly controlled patients with T2DM. The two medications have a complementary mechanism of action, resulting in the additive effects in the blood glucose control which is a lot of larger than the drug is employed alone. In addition it also showed an additive increase in postprandial active GLP-1 concentrations among patients mistreatment sitagliptin and metformin **[Migoya et al.,2010].**Also, the utilization of combination therapy, besides achieving optimum metabolic management, significantly improved beta-cell perform, improved markers of endocrine resistance and reduced hepatic glucose output.

Ertugliflozin and metformin

Some experts believe Ertugliflozin may be an SGLT-2-targeting drug. A reduction in plasma aldohexose concentrations may be achieved by decreasing the resorption of aldohexose from the kidney and increasing aldohexose excretion from the urine. Just over a hundred and eighty grams of aldohexose is filtered by the kidneys each day, and 90% of it is reabsorbed into the circulation through SGLT-2 and SGLT-1, respectively (10 percent). Thus, the water contains no aldohexose under normal circumstances.

When it comes to the mechanism of action for biguanides like metformin, no one knows exactly how it works. Among other planned methods, it is expected to prolong internal secretion like GLP-1 **[Rena et al., 2017]** secretion. The SGLT-2 inhibitors' mode of action does not explain these effects, which lead to an increase in plasma aldohexose concentrations.

Fast and postprandial aldohexose and overall glycaemic control have been significantly improved when they are used simultaneously. After six months of therapy, ertugliflozin reduced A1C in patients with a goal A1C of 7.0 percent who were taking an antidiabetic alone or in combination with other glucose-lowering medicines by 0.7 percent to 0.9 percent. Additionally, this decrease was maintained in studies with six-month extensions and coincided with both weight loss and improved blood pressure. One year of ertugliflozin medication produced identical A1C management to that of the anti-diabetic glimepiride, but with fewer symptoms, weight reduction (as hostile weight increase with the sulfonylurea), and improvements in pressure **[Hollander et al.,2018]**. Anti-diabetic treatment may benefit from the positive effects of SGLT-2 substances, which are obviously beneficial for patients. As a consequence, patients using drugs that might cause hypoglycaemia (such as sulfonylureas and meglitinides) should be re-educated about the diagnosis and management of hypoglycaemia, and the dosage of these medications should be considered depending on the SGLT-2 inhibitor.

Ertugliflozin and metformin have been shown to be safe and effective in improving glycaemic management, as well as providing other advantages beyond A1C, such as weight reduction, reduced blood pressure, and a very low risk of hypoglycaemia.

Glibenclamide and metformin

Glibenclamide is a sulfonylurea second-generation antidiabetic medication that increases insulin production to help regulate blood sugar levels. ATP-sensitive K channels in beta cells of the pancreas are inhibited, resulting in an increase in insulin production. The cell membrane is depolarized, and calcium channels are opened as a result **[Luzi et al.,1997].** The rise in intracellular calcium causes insulin to be produced. It has been discovered that glibenclamide raises the levels of glycogen phosphorylase alpha and fructose 2,6-biphosphate in the liver, which results in decreased gluconeogenesis and increased glycolysis **[LopezAlacron et al.,1995]**.

Biguanide-type anti-hyperglycaemic agent Metformin Reduced hepatic gluconeogenesis is thought to be the primary mechanism by which glucose levels are decreased **[Stumvoll M et al.,1995]**. Reduced gluconeogenic gene expression is the result of phosphorylation of the CREB proteins, which also reduces the availability of free fatty acids as a source of gluconeogenic substrate. Additionally, insulin-mediated aldohexose absorption in peripheral tissues will be increased by antidiabetic medication. GLP-1 and GLP-1 receptor gene expression may be increased by anti-diabetic medicines in order to enhance the

insulinsecreting actions of GLP-1 and GLP-1 **[Cho YM et al.,2011**].

Type 2 diabetes can benefit from the use of metformin and glibenclamide together.

Metformin's effectiveness was proven in a randomised, double-blind, controlled research. On the basis of random selection, those patients were given metformin or placebo in the experiment **[DeFronzo et al,1995]**. People in the metformin group saw their FPG levels fall an average of 52±5 mg/dL, whereas those in the placebo group saw their FPG levels rise by 6 5 mg/dL, to 244 ±6 mg/dL ($p<0.001$). Metformin reduced HbA1c by 1.4 ±0.1 percent, but placebo raised it by 0.4 ±0.1 percent ($p <0.001$). Additional research has shown that Glibenclamide-metformin medication can help those with type 2 diabetes who are unable to regulate their condition by diet and exercise **[Garber et al., 2003]**. They had glibenclamidemetformin 1.25/250, metformin 500 mg, or glibenclamide 2.5 as alternatives for treatment. In the glibenclamide-metformin group, the mean HbA1c decreased by 2.3% from baseline (8.8%± 1.5), while in the metformin and glibenclamide groups, the mean HbA1c dropped by 1.5% from baseline (8.5% ±1.4 and 8.7%± 1.4, respectively) ($p = 0.003$). When compared to either monotherapy, the combination of FPG and 2-hour PPG concentration reductions were considerably larger in the combination treatment pill. In comparison to the monotherapy groups, the glibenclamide and metformin doses in the fixed-dose pill group were lower (3.7 mg/735 mg) (glibenclamide: 7.6 mg; metformin 1796 mg). These medicines may have a synergistic impact if they operate together to increase insulin production and improve peripheral tissue insulin sensitivity. As glibenclamide in the combination tablet is more accessible than metformin alone, this is also likely to have a role. When glibenclamide and metformin are used together, patient compliance is better than when either drug is used alone. **[Blonde et al., 2003]**. In addition, patients' adherence improves statistically (71 vs. 87 percent, $p < 0.001$) when they convert from dual monotherapy to combination glibenclamidemetformin.
Ultimately, it was shown that Glibenclamide-metformin treatment was much more helpful and successful in improving blood sugar levels than diet and exercise alone, metformin alone, or glibenclamide alone.

Conclusion

Even by the use of Drug repurposing techniques and combinational therapy we still have not found a proper and productive drugs and there is still a long way to go.But,it is in progressive and right direction because the drug formed are showing higher efficacy in comparison to monotherapy and other traditional drug. So, there needs to be more research work in both dry and wet labs.

Although there is major advancement in medicines and wet lab techniques but we still have not found a productive and most effective treatment for Type 2 diabetes and Gestational diabetes. So, there is a requirement for exploring of various other approaches for drug formation like drug repurposing from other drugs. By using computational data,AI,Big Data analytics, molecular dynamics stimulation and other approaches in Dry lab. Maybe in recent future by the use of modern technology and computer science based drug repurposing techniques we will certainly have a better drug and treatment available for the T2D and GD.

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