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A review on metformin and acarbose as anti-diabetic drugs with representative mechanisms

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Abstract:

Type 2 diabetes is a disease that happens to many people globally. But surprisingly, it is attacking more and more people like a tsunami over centuries of development of technology, and it even shows younger trends. It is still an issue that many patients lack awareness of type 2 diabetes. This paper mainly reviews two of the first-line anti-diabetic drugs used in the treatment of type 2 diabetes in these few years and aims to improve the perception of type 2 diabetes among the public. To begin with, the paper shows some overview of diabetes, including the symptoms and the pathogenesis, in order to explain why it is a disease with such a great impact on humans. Impacts like mortality are also mentioned to demonstrate the severity of type 2 diabetes in the world. Next, metformin and acarbose are used as two examples of the mainstream mode of therapy for type 2 diabetes. In this part, the paper discusses the history, the chemical properties, the manufacture, the mechanisms and the possibility of repurposing of these two drugs. Also, the paper makes a comparison between metformin and acarbose, and proposes some summative ideas.

Keywords: type 2 diabetes, metformin, acarbose, drug synthesis, gluconeogenesis, α-glucosidase inhibitor

1. Introduction

1.1 The pathogenesis of diabetes

Inside the pancreas, the hormone insulin is made in the beta cells, which are part of the islets of Langerhans. These islets also have alpha cells, which make glucagon, as well as delta cells. With each meal, beta cells release insulin to help the body use or store the blood glucose it gets from food. The principle of insulin is the combination of the insulin and the specific receptor on the target cell membrane, which distributes on a variety of cell membranes. The receptors become phosphorylated and continue to phosphorylate another protein substrate. That makes the metabolic reaction in cells to be modified, in order to lower the blood glucose concentration mainly by inhibiting gluconeogenesis and the decomposition

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of glycogen. All these are the metabolic reactions that happen in healthy people, but when the function of the pancreas in regulating blood glucose levels is aberrant, diabetes happens.

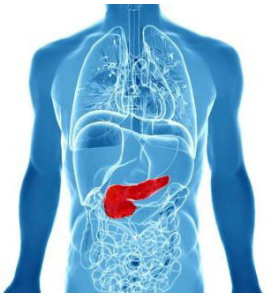

Figure 1. The position of the pancreas in human body [1].

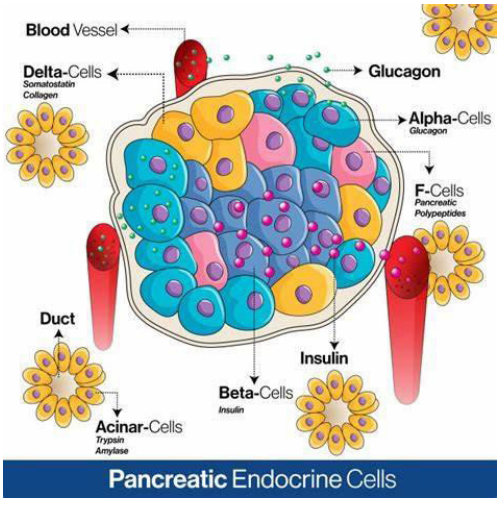

Figure 2. The structure of endocrine cells in pancreas [2]

Generally saying, there are mainly two types of diabetes, type 1 and type 2. They have different pathogenesis.

Type 1 diabetes are mostly cause by the disorder of immune system. The abnormal immunoreaction destroys the beta cells in pancreas. So the patients entirely lose the function of regulating blood glucose concentration by insulin, then the blood glucose would increase uncontrollably. Of note, the pathogenesis of type 1 diabetes is not completely explained even to this day. The reason of the abnormal immunoreaction still needs more study.

As for the other kind of diabetes, there are two typical reasons for the type 2 diabetes. First, the defect of the function of β cells may lead to a situation where there is inadequate insulin to lower the blood glucose concentration. Another reason is the organism cannot be affected by the insulin well due to the long-term maintenance of a surplus of blood sugar, and resistance of the organs against insulin arises [3]. Though their β cells can produce insulin regularly, their blood glucose concentration cannot be modified by insulin.

To make a comparison, patients with type 1 diabetes cannot produce insulin. However, patients of type 2 diabetes can produce insulin by themselves at the initial phase of the disease, and the ability to control hyperglycemia would decrease with the progression of the disease. What's more, type 2 diabetes has a much bigger inheriting factor than type 1 diabetes. Type 2 diabetes is very common in a family history.

1.2 The impact of type 2 diabetes

Type 2 diabetes is a serious disease besetting 537 million people around the world between 20 to 79 years old. This means about 10.5% of the adult population has diabetes, with almost half unaware that they are living with the condition. And it is estimated that the number of patients will grow up to 643 million by 2030 and 783 million by 2045. It is alarming data that there will be 1 in 8 adults will be living with diabetes [4].

Table 1. The statistical estimation of the number of patients of type 2 diabetes in 2021 in the US [5]

Characteristic	Diagnosed diabetes Number in Millions (95% CI)	Undiagnosed diabetes Number in Millions (95% CI)	Total diabetes Number in Millions (95% CI)
Total	**29.4 (26.7–32.0)**	**8.7 (7.0–10.5)**	**38.1 (34.2–42.0)**
Age in years			
18–44	3.5 (2.8–4.2)	2.2 (1.5–3.0)	5.8 (4.7–6.8)
45–64	12.0 (10.1–13.9)	3.8 (2.7–4.8)	15.8 (13.4–18.2)
≥65	13.8 (12.5–15.1)	2.7 (1.6–3.8)	16.5 (15.0–18.1)
Sex			
Men	16.1 (14.1–18.0)	3.7 (2.6–4.8)	19.8 (17.4–22.1)
Women	13.3 (11.5–15.1)	5.0 (3.3–6.7)	18.3 (15.3–21.3)
Race-Ethnicity			
White, non-Hispanic	17.8 (15.2–20.4)	4.3 (2.4–6.1)	22.1 (18.5–25.7)
Black, non-Hispanic	4.0 (3.3–4.6)	1.4 (1.0–1.9)	5.4 (4.7–6.1)
Asian, non-Hispanic	1.8 (1.5–2.1)	0.9 (0.5–1.2)	2.7 (2.2–3.1)
Hispanic	5.0 (4.3–5.7)	1.9 (1.4–2.4)	6.9 (6.2–7.6)

CI = confidence interval.

To Table 1, there are approximately 29.4 people in millions have diagnosed with diabetes in the US in 2021. Surprisingly, there are about 8.7 people in the millions who have diabetes that have not been diagnosed. It shows that 22.8% of people are not even aware of this painful disease they suffer from. Additionally, due to the statistics made by the IDF, there are even more patients who have not been diagnosed in undeveloped regions. The prevalence rate of people over 45 years old has a sharp increase compared to the people with age between 18 and 44. Of note, there was an increasing diabetes death rate of 3% be-

tween 2000 and 2019. In 2019, there were about 2 million of mortality caused by diabetes and kidney disease related to diabetes [6]. So, it is always a key point to focus on the therapy of type 2 diabetes.

Patients always have a high level of blood glucose concentration under the condition of type 2 diabetes. As for the normal value of fasting plasma glucose, it should be in the range of about 3.9mmol/L to 6.1mmol/L. However, the fasting plasma glucose of the people who suffer from diabetes is mostly above 7mmol/L. High levels of blood glucose concentration can lead to damage to the human body. It is reported by the WHO that diabetes is a major cause of blindness, kidney failure, heart attacks, stroke and lower limb amputation [6]. Too much glucose in the blood increases the osmotic pressure of the extracellular fluid. So, the water in the cells moves outwards the cell membrane. As the kidney excrete the excess of water, osmotic diuresis happens. Massive water carries electrolytes, and excess glucose in blood is excreted with urine. Then it results in the dehydration of the human body. What's even worse, as there is a deficiency of water in the brain cells, the metabolism in these cells cannot go properly, and serious central nervous system dysfunction may occur. And the loss of electrolytes also has a variety of impacts that cannot be ignored. Electrolyte disturbance can be a barrier for almost every organ to perform metabolic reactions. Furthermore, the alpha cells in the pancreas exhibit insensitivity to insulin, thereby failing to suppress glucagon release during meals. This results in heightened breakdown of fats in adipocytes, enhanced reabsorption of glucose by the kidneys, elevated production of new glucose (gluconeogenesis), and reduced effectiveness of incretin hormones. Additionally, there is a disruption in neural regulation within the brain, leading to an increase in appetite, a decrease in the morning surge of dopamine levels, and an elevation in sympathetic nervous system activity [7]. So depression and obesity can also happen to the patients.

Besides, not only can these lesions occur, but they also have an influence on patients' everyday lives. Obviously, it could become a really challenge thing for the patients to take care of their daily life under these conditions. For example, the increased sympathetic tone could make the patients find it hard to be calm, and it may lead to a lack of rest. What's more, men who have been diagnosed with type 2 diabetes face an increased likelihood of experiencing a decline in testosterone levels compared to those without diabetes. This can result in a decrease in sexual desire. However, many men have observed positive outcomes by addressing low testosterone through weight loss and/or hormone replacement therapy. Conversely, women living with diabetes may encounter more intricate obstacles concerning their sexual well-being. For instance, augmenting testosterone levels among post-menopausal women has the potential to enhance libido; nevertheless, there is limited long-term research available regarding its effects. Furthermore, experts propose that reduced sexual desire in diabetic women may arise from various factors, making it difficult to effectively identify and treat [8].

In that case, metformin and acarbose become parts of the efficient blood sugar lowering drugs that have been used globally.

2. Content

2.1 Metformin

2.1.1 The history of metformin

Since 1891, Galega officinalis has been used as a forage grass in the US. It is discovered that one of the compositions in Galega officinalis, called galegine, has a surprising effect in lowering the blood glucose concentration due to the guanidine group in its structure. However, its great poisonousness is a barrier for the galegine to be used as a drug to treat diabetes. So after modifying, metformin, a derivant of galegine with less toxicity is applied to clinical practice. Nowadays, there are more than 150 million patients worldwide taking metformin as a kind of anti-diabetic drug. Thus, metformin is also demonstrated by the market for its curative effect.

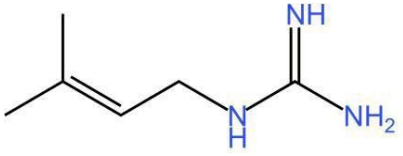

Figure 3. The structure of the galegine

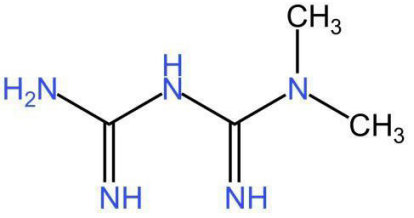

Figure 4. The structure of the metformin

2.1.2 One of the ways of synthesis of metformin

The metformin is synthesised from ethanolic solutions of MeNH2·HCl and cyanoguanidine, and with the association of microwave, irradiating the raw material with an interval of 40 seconds in 5 minutes at 540 W. As the TLC confirmed the quantity of the raw material that has been reacted, the product can be extracted. Besides, the process only takes 5 minutes and can reach 92% yield, which is remarkable and economically beneficial[9].

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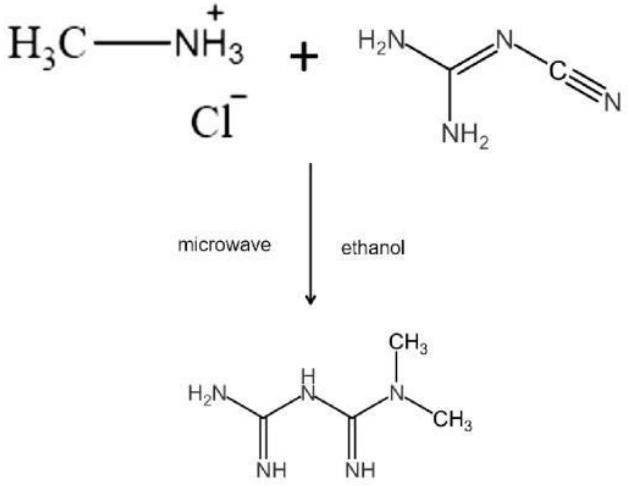

Figure 5. The process of synthesis of metformin

2.1.3 The mechanism of metformin

2.1.3 .1. Mitochondrial respiratory chain complex

The respiratory chain is a system constituted by hydrogen transfer reactions and electron transfer reactions followed by specific steps. It takes off pairs of hydrogen atoms and gives them to oxygen to form water, with the formation of ATP. The respiratory chain actually represents the basic function of mitochondria. It contains hydrogen carriers and electron carriers, which are enzymes made by the protein complex on the inner membrane of mitochondria. There are two kinds of complexes related to the function of metformin: complex I and complex IV.

Complex I is a complex of enzymes in the redox reaction of nicotinamide adenine dinucleotide(NADH) and coenzyme Q. Complex I has a series of redox centers arranged in affinity and gradient according to different electron affinities. It gains two electrons from NADH, the reducing power of the TCA cycle(tricarboxylic acid cycle), which it passes to Coenzyme Q via ferrithione. Ferrothionein contains non-heme iron and acid-unstable sulfur, and its iron is complex with the sulfur atom of peptide cysteine. The valence change of iron transfers electrons from FMNH2 to Coenzyme Q. A small amount of energy is released in the electron transport process, and with this energy, complex I can co-function as a proton pump.

The complex IV is Cytochrome C oxidase complex, the final acceptor of the electron. Here transfers the electron to one molecule of oxygen to make two molecules of water. In order to synthesize water, the proton concentration here is strengthened, half the number of protons are synthesized into the water, and the other half is pumped into the membrane space by a proton pump. In the absence of oxygen, the associated ATP synthesis is also stopped, a process known as oxidative phosphorylation.

2.1.3 .2. Glucagon-like pipetide-1(GLP-1)

GLP-1 is a kind of incretin, which can stimulate the insulin to be released. The insulin secretion capacity caused by incretin accounts for about 50-70% of the total insulin secretion, and the effect of insulin secretion stimulation is characterized by glucose concentration dependence. Patients with type 2 diabetes always do not have an abundant secretion of GLP-1. So, it is an effective way of controlling the blood glucose level of patients with type 2 diabetes.

2.1.3 .3. The way of metformin works

There are mainly 3 ways of mechanism of metformin in regulating the blood glucose level. And the targets are mainly located in two organs, the liver and the intestine.

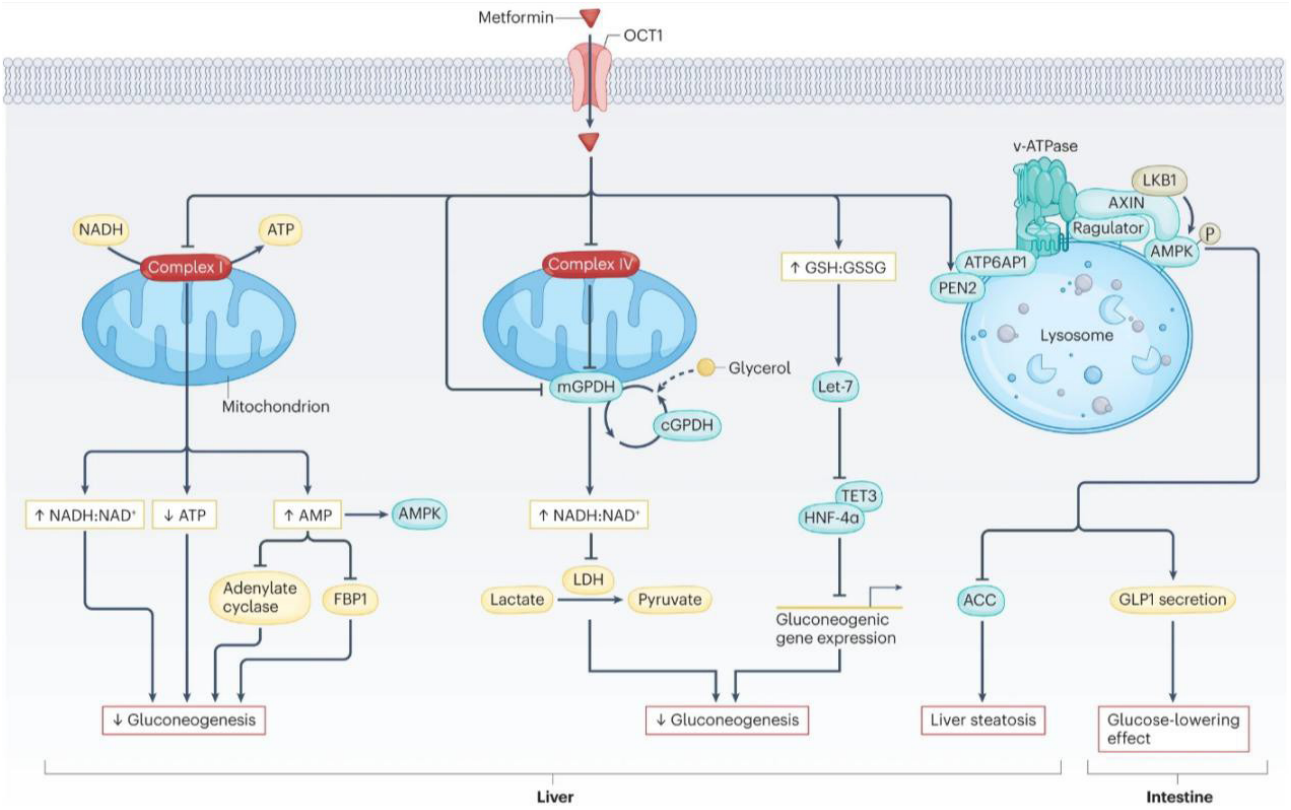

Figure 6. The mechanism of metformin in lowering the blood glucose level[10]

(1) Complex I inhibition-dependent mechanisms: Metformin induces a mild reduction in the activity of mitochondrial respiratory chain complex I in liver cells. This leads to a moderate decline in ATP synthesis and an accompanying rise in AMP levels within the cells. The decrease in hepatic gluconeogenic flux, which is an ATP-dependent metabolic process, may be attributed to this decline in ATP production caused by metformin. Furthermore, elevated levels of AMP inhibit enzymes involved in gluconeogenesis that are regulated by AMP, such as adenylate cyclase and fructose-1-6-bisphosphatase (FBP1), contributing to a decrease in glucose output. It is worth noting that although metformin also activates AMP-activated protein kinase (AMPK) through an increase in the ratio of AMP to ATP, this activation does not directly impact glucose regulation. Additionally, alongside inhibiting complex I, metformin results in an increasing of cellular redox potential (NADH:NAD+).[9]

(2) Mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH)-dependent and complex IV inhibition-dependent mechanisms: Metformin acts by directly inhibiting mGPDH, resulting in a raised cytosolic redox state (NADH:NAD+ ratio), decreased gluconeogenesis from lactate, and reduced activity of the glycerol-phosphate shuttle (which transfers NADH from the cytosol to mitochondria). This leads to a reduction in the availability of raw materials for gluconeogenesis, thereby lowering its rate. Additionally, metformin enhances hepatic redox state by increasing the ratio of glutathione to oxidized glutathione (GSH:GSSG), which subsequently inhibits genes responsible for encoding enzymes involved in gluconeogenesis through a let-7-TET3-HNF-4α pathway [10].

(3) AMPK activation-dependent mechanisms in lysosomes: Metformin at low concentrations binds presenilin enhancer 2 (PEN2), which is recruited to ATPase H+ transporting accessory protein 1 (ATP6AP1) independent of changes in AMP levels, leading to inhibition of v-ATPase and phosphorylation and/or activation of AMPK in lysosomes through the formation of a supercomplex containing the v-ATPase, Ragulator, AXIN, liver kinase B1 (LKB1) and AMPK. Thereafter, metformin-activated AMPK from lysosomes reduces lipid accumulation in the liver via acetyl-CoA carboxylase (ACC) inhibition and increases glucagon-like peptide 1 (GLP1) secretion in the gut, inducing reductions in blood levels of glucose [10]. It is a new discovery of the mechanism of the metformin in regulating the hyperglycemia. However, the detailed process of how the AMPK affects the steatosis of fat in the liver and increases the secretion of GLP1 is not being explained nowadays. But one thing that can be convinced is the adjustment of liver steatosis by AMPK can reduce the quantity of fat tissue on the surface of the organs. To

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a great extent, the fat tissue acts as a barrier to a combination of insulin and the receptors on the cell membrane. So it lowers insulin resistance by reducing fat steatosis. (cGPDH, cytosolic glycerol-3-phosphate dehydrogenase; HNF-4α, hepatocyte nuclear factor 4α; LDH, lactate dehydrogenase; OCT1, organic transporter 1; TET3, Tet methylcytosine dioxygenase 3)

To summarize the mechanism, the inhibition in mitochondria is very direct against the influence at lysosome. But further experiment has shown that the concentration of metformin in the hepatic portal vein is much lower than it was expected, so this recently discovered mechanism might have a significant influence in controlling the blood glucose level.

2.1.4 Mode of delivery

Metformin is mainly absorbed by the small intestine, and it moves into the bloodstream straightly. So it can be taken orally. It is excreted through urine after it has done its work, just as the waste product in metabolic reactions in other organs.

2.1.5 Repurposing of metformin

There are more and more targets that metformin can combine with being discovered nowadays. So it is an interesting thing to think about the repurposing of metformin. One of the examples is the use of metformin in treating cancer.

Numerous studies have been conducted to demonstrate the direct impact of metformin on cancer cells, both in laboratory settings and animal models. Metformin has been found to influence various characteristics of cancer cells, including their proliferation, metastasis potential, cell-cycle progression, apoptosis induction, and ability to undergo anoikis. Additionally, metformin enhances the sensitivity of cancer cells toward other treatment approaches like chemotherapy drugs, immunotherapy, and radiotherapy. The effectiveness of metformin on target cells depends on factors such as its transportation mechanism within the body. For instance, hepatocellular carcinoma cells are significantly affected by metformin due to the expression of organic cation transporter 1 (OCT1), mainly a crucial protein responsible for transporting metformin into hepatocytes. Organs with abundant metformin transporters, like the intestine and liver, hold great promise for clinical efficacy. However, it is worth noting that experimental models have shown that the effective dosage required for treating cancer is considerably higher (measured in millimoles) than the therapeutic dose commonly used for diabetes management in clinical practice. In vitro studies indicate that inhibitory effects on cancer cells necessitate approximately ten times more metformin compared to what diabetic patients with normal kidney function typically receive as part of their treatment regimen [11].

2.2 Acarbose

2.2.1 The history of acarbose

Nowadays, acarbose has become a widely used antidiabetic drug. At first, the acarbose is extracted from the *Actinoplanes* in the soil. It is discovered that this genus of bacteria can secret acarbose to inhibit the growth of other bacteria in the nearby areas. So scientists realized that acarbose might have the potential to be applied to treat human disease. In the later research, it shows that acarbose is a kind of a α-glucosidase inhibitor. That shows the possibility for acarbose to treat type 2 diabetes.

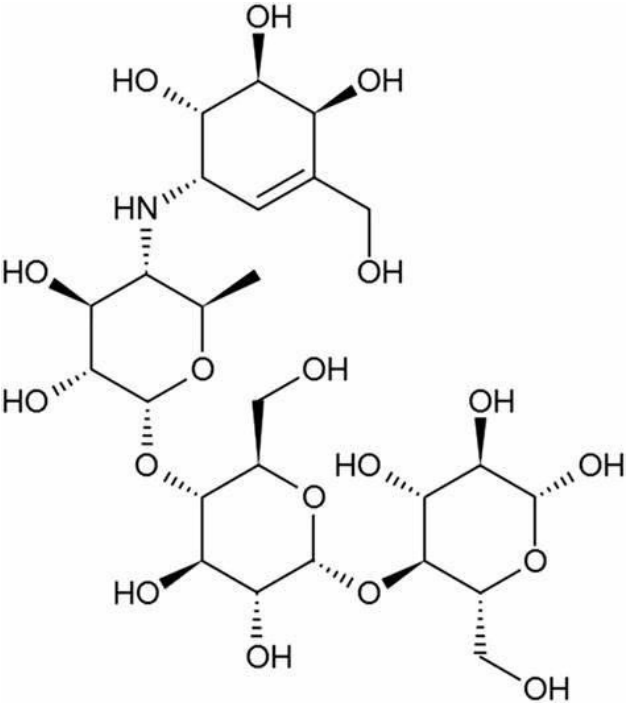

Figure 7. The structure of acarbose

2.2.2 The synthesis of acarbose

One way of obtaining acarbose is the fermentation of the bacteria *Actinoplanes* sp. SE50/110, the process of the synthesis is shown below.

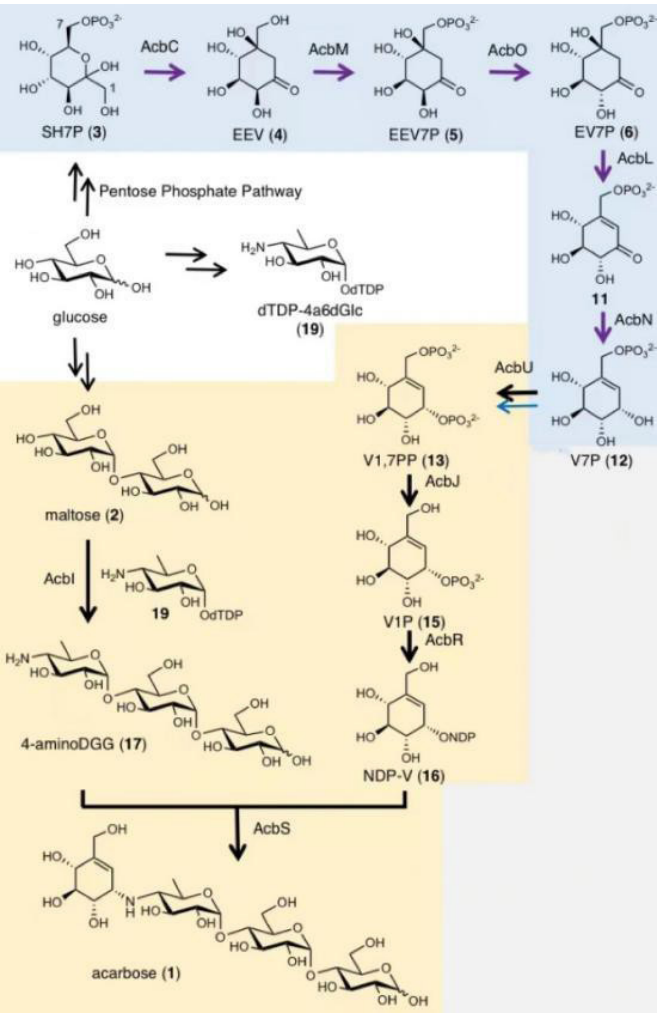

Figure 8. The process of bio synthesis of acarbose in Actinoplanes sp. SE50/110 [12]

Table 2. the explaination of the enzymes participate in the reaction[13]

enzyme in the figure 8	function as
AcbC	2-*epi*-5-*epi*-valiolone synthase
AcbM	2-*epi*-5-*epi*-valiolone-7-kinase
AcbO	2-*epi*-5-*epi*-valiolone-7-phosphate 2-epimerase
AcbL	2-*epi*-valiolone-7-phosphate 1-reductase
AcbN	Cyclitol oxidoreductase
AcbJ	Hydrolase
AcbR	Valienol-1-phosphate guanylyltransferase
AcbI	Glycosyltransferase
AcbS	Glycosyltransferase

The chemical structure of acarbose consists of a pseudo-sugar (C7-cyclitol), which is attached to an amino-deoxy-hexose through a C-N bond, and maltose.

The C7-cyclitol unit of acarbose originates from 2-epi-5-epi-valiolone (EEV), a cyclization product of the pentose phosphate pathway intermediate sedoheptulose 7-phosphate (SH7P). Then EEV undergoes phosphorylation to become 5-epi-valiolone 7-phosphate(EV7P). After the reduction catalyzed by AcbL and AcbN, it forms valienol1,7-diphosphate(V7P). Recent work by scientists showed that V7P is one of the intermediates in acarbose biosynthesis. On the basis of its resemblance to a hexose 6-phosphate, V7P is predicted to be either phosphorylated to valienol 1,7-diphosphate (V1,7PP) or directly converted to valienol 1-phosphate (V1P). Then it is nucleotidylated to NDP-valienol (NDP-V). The other part of acarbose

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is synthesized by the derivative product of glucose, which is maltose and dTDP-4-amino-4,6-dideoxyglucose (dTDP4a6dGlc).

Then, AcbI was able to catalyze the coupling between dTDP4a6dGlc and maltose to give 4-aminoDGG. At last, NDP-V and dTDP4a6dGlc are combined by AcbS to give the final product, the acarbose [12].

2.2.3 The target of acarbose:

It is known that the main target of acarbose is α-glucosidase as an inhibitor. α-glucosidase is a kind of hydrolytic enzyme works at the intestinal epithelial cells. As for the mechanism of this glucosidase, it is used to degrade the oligosaccharide and the disaccharide into glucose by cutting the α-1,4 glycosidic bond at the non-reducing end group. Then the glucose can be absorbed to the blood, which straightly increases the level of postprandial blood glucose. Another enzyme that acarbose also target on is pancreatic α-amylase, an enzyme related to producing glucose as well.

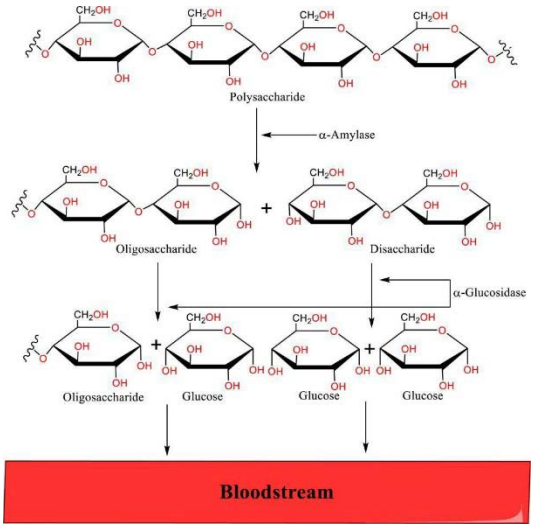

Figure 9. The degradation of sugar[14]

When it come to the function of acarbose as an α-glucosidase inhibitor, it works by competing with the substrates at the active sites. Acarbose is a complex oligosaccharides, so it has similar structure comparing to other kinds of sugar. So after mixing with food, the concentration of normal oligosaccharide is decreased. Therefore, the rate of enzymatic reaction of alpha glucosidase and alpha amylase is reduced. As the figure shows, the absorption of glucose in the intestine is delayed. So the postprandial blood glucose level would not increase that quickly, then there is more time for the small amount of insulin to play a role in lowering blood glucose level. It can be summarized that acarbose treating hyperglycemia in a great extent by affect the absorption of glucose.

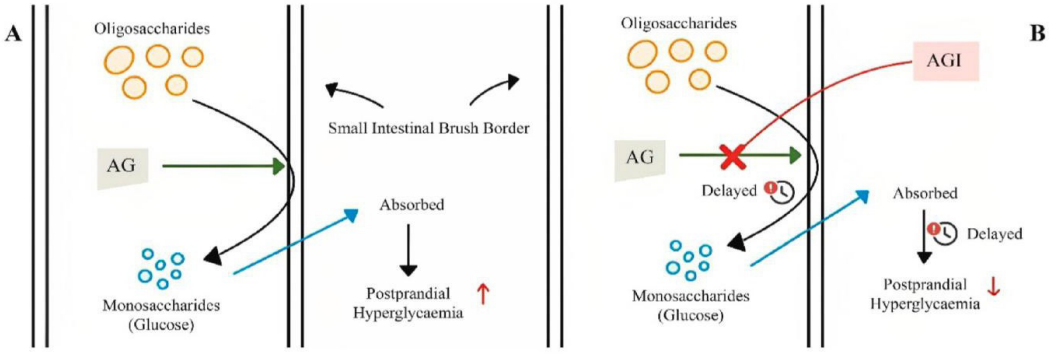

Figure 10. The mechanism of the α glucosidase inhibitor[15]

The residue of the alpha glucosidase Gln322, Thr301, Arg312, Thr307, Glu304, Ser308 and Asn241, they combine with acarbose by hydrogen bonds. The His239 and Val305 bond with acarbose by C-H bonds. Additionally, there is a hydrophobic interaction with His279 and unfavourable interactions with Thr307 and Arg312. It is also shown by the figure that there are a variety of alcohol groups in the structure of acarbose, which is the benefit of solubility and bioavailability.

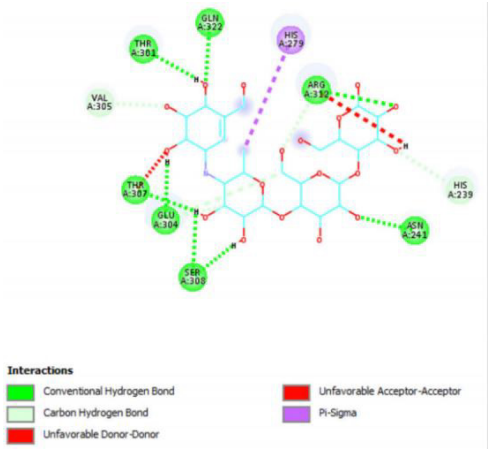

Figure 11. The combination of acarbose with the active sites[14]

2.2.4 Mode of delivery

The target of acarbose is the intestinal epithelial cell. So, taking acarbose orally can easily make the drug access the small intestine in the alimentary canal. After being used, it is egested through the anus.

2.2.5 Repurposing of acarbose

It is shown by vitro test that acarbose could inhibit the interaction between death-associated protein kinase 1(DAPK1) and p53. And it can also avoid the incapacitation of mitochondria and lysosome. Additionally, it may modify the gene expression which helps the cell to survive, to fight against inflammation and self-repairment. These discoveries have explained the potential of acarbose for promoting neuronal survival and regeneration following ischemia-reperfusion injury. Especially for the cerebral apoplexy, it offers a new pathway in rehabilitation [16].

3. Conclusion

To make a summary, this paper is an overview of type 2 diabetes and two of the effective drugs in treating the disease, which have a wide influence globally, metformin and acarbose. By comparison in the target, metformin mainly focuses on the impact on the receptors in mitochondria and lysosomes in the liver and intestine, while acarbose targets the alpha glucosaccharase in the gut. When it comes to the mechanisms, there are some similarities and differences. As for the similarities, both of them can act as an inhibitor at the target, and both of them do not contain toxic components against the liver. So they can be used by a wide range of type 2 diabetes patients whether they suffer from hepatic injury. About the differences, it is obvious that metformin works on multiple targets to enhance the ability to regulate the blood glucose level. But acarbose almost works on one kind of target. Due to the inhibition of the digestive enzymes, the side effects could depend on the gastrointestinal function of the patients and the regional diets. Thus, acarbose has a more limiting factor in clinical use compared with metformin. In addition, the foundational principles of these two drugs are different as well. Briefly, metformin controls the blood glucose level by modifying gluconeogenesis and insulin resistance, which are both effective ways of regulating the metabolic reaction in the human body related to the formation of glucose, while acarbose directly reduces the absorption of glucose to decrease the blood glucose concentration. For further consideration, both metformin and acarbose have great potential for repurposing. The exhaustive mechanism of these drugs still needs more experiment and clinical test to demonstrate and expand. Last but not least, type 2 diabetes still has a lot of pathogenesis beyond imagination, like defects in genes; figuring out more factors that lead to type 2 diabetes is always beneficial for new thinking of precaution and treatment to develop.

References

[1] Upper GI Surgery. Pancreatic cancer. https://uppergisurgery.com.au/procedures/oncology/pancreatic-cancer.

[2] https://www.veer.com/illustration/386182393.html?sign=es/.

[3] Banday, M.Z., Sameer, A.S., Nissar, S. (2020) Pathophysiology of diabetes: An overview. Avicenna J Med. 10(4): 174-188.

[4] International diabetes federation. Facts & figures. https://idf.org/about-diabetes/diabetes-facts-figures/.

[5] U.S. Centers For Disease Control And Prevention. (2024) National Diabetes Statistics Report. https://www.cdc.gov/diabetes/php/data-research/index.html.

[6] World Health Organization. (2023) Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes.

[7] Taiwona L. Elliott DO, Kim M. Pfotenhauer DO., (2022). Classification and Diagnosis of Diabetes, Primary Care: Clinics in Office Practice, 49. 2: 191-200.

[8] Lauren Panoff, MPH, RD. (2022) How Type 2 Diabetes Affects Your Daily Life. https://www.verywellhealth.com/type-2-diabetes-daily-life-6751664.

[9] Hernández-Velázquez, E.D., Alba-Betancourt, C., Alonso-Castro, A.J., Ortiz-Alvarado, R., López, J.A., Meza-Carmen, V., Solorio-Alvarado, C.R. (2023) Metformin, a biological and synthetic overview, Bioorganic & Medicinal Chemistry Letters, 86: 129241.

[10] Foretz, M., Guigas, B., Viollet, B. (2023) Metformin: update on mechanisms of action and repurposing potential. Nat Rev Endocrinol, 19: 460–476.

[11] Saengboonmee, C., Sanlung, T., Wongkham, S. (2021) Repurposing Metformin for Cancer Treatment: A Great

ISSN 2959-409X

Challenge of a Promising Drug. Anticancer Research, 41 (12): 5913-5918.

[12] Tsunoda, T., Samadi, A., Burade, S. et al. (2022) Complete biosynthetic pathway to the antidiabetic drug acarbose. Nat Commun, 13: 3455.

[13] Wang, Y.L., Xu, N., Ye, C. (2015) Reconstruction and in silico analysis of an Actinoplanes sp. SE50/110 genome-scale metabolic model for acarbose production. Front Microbiol, 6: 632.

[14] Fallah, Z., Tajbakhsh, M., Alikhani, M., Larijani, B., Faramarzi, M.A., Hamedifar, H., Mohammadi-Khanaposhtani, M., Mahdavi, M. (2022) A review on synthesis, mechanism of action, and structure-activity relationships of 1,2,3-triazole-based α-glucosidase inhibitors as promising anti-diabetic agents, Journal of Molecular Structure, 1255: 132469.

[15] Benjamin, M.A.Z., Mokhtar, R.A.M., Iqbal, M., Abdullah, A., Azizah, R., Sulistyorini, L., Mahfudh, N., Zakaria, Z.A. (2024) Medicinal plants of Southeast Asia with anti-α-glucosidase activity as potential source for type-2 diabetes mellitus treatment, Journal of Ethnopharmacology, 330: 118239.

[16] Das, J., Mahammad, F.S., Krishnamurthy, R.G. (2022) An integrated chemo-informatics and in vitro experimental approach repurposes acarbose as a post-ischemic neuro-protectant. 3 Biotech. 12: 71.