AN OVERVIEW OF DIABETES MELLITUS COMPLICATION WITH COVID 19 AND ITS MANAGEMENT

Project Report submitted in partial fulfilment

For the award of the degree of

Bachelor of Pharmacy

Submitted By

SHIVAM KUMAR SINGH

1712102084

SCHOOL OF MEDICAL AND ALLIED SCIENCES

Under the Supervision of

RAKESH SAHU

Assistant Professor

GALGOTIAS UNIVERSITY

(Established under Galgotias University Uttar Pradesh Act No. 14 of 2011)

APRIL / MAY- 2021

SCHOOL OF MEDICAL AND ALLIED SCIENCES

BONAFIDE CERTIFICATE

Certified that this project report **"AN OVERVIEW OF DIABETES MELLITUS COMPLICATION WITH COVID 19 AND ITS MANAGEMENT"**is the bonafide work of **"SHIVAM KUMAR SINGH (1712102084)"**who carried out the project work under my supervision.

SIGNATURE   SIGNATURE

Dr.Pramod Kumar Sharma   **Rakesh Sahu**

Dean   **SUPERVISOR**

School of Medical and Allied Sciences   **Assistant Professor**

School of Medical and Allied Sciences

<u>Approval</u> <u>Sheet</u>

This thesis/dissertation/report entitled "AN OVERVIEW OF DIABETES MELLITUS COMPLICATION WITH COVID 19 AND ITS MANAGEMENT" by SHIVAM KUMAR SINGH is approved for the degree of BACHELOR OF PHARMACY.

Examiners

_____

_____

Supervisor (s)

_____

_____

_____

Chairman

_____

Date_____

Place_____

Statement of Project Report Preparation

1. Thesis title: AN OVERVIEW OF DIABETES MELLITUS COMPLICATION WITH COVID 19 AND ITS MANAGEMENT

1. Degree for which the report is submitted:BACHELOR OF PHARMACY

3 Project Supervisor was referred to for preparing the report.

4. Specifications regarding thesis format have been closely followed.

5. The contents of the thesis have been organized based on the guidelines.

6. The report has been prepared without resorting to plagiarism.

7. All sources used have been cited appropriately.

8 The report has not been submitted else where for a degree.

SHIVAM KUMAR SINGH

1712102084

TABLE OF CONTENTS

ABSTRACT

The coronavirus disease 2019 (covid-19) is a pandemic disease, originated in Wuhan city, China. it is caused by severe acute respiratory syndrome coronavirus 2 (sars-cov-2) and its biology is still poorly understood. there are many complications for diabetes mellitus patients in covid-19. there are enough data that indicate if a person doesn't have their blood glucose level in control then covid-19 surely affects that person. the mortality rate in this covid-19 diabetes patient is in large number. recent data also tell there are some complications with anti-diabetic drugs in this covid-19. further few ongoing trials for drugs related to covid-19 and diabetes which we surely help to control mortality rate and decrease the complication in diabetes mellitus in the future.

LIST OF TABLES

LIST OF FIGURES

Abstract

The coronavirus disease 2019 (COVID-19) is a pandemic disease, originated in Wuhan City, China. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its biology is still poorly understood. There are many complications for diabetes mellitus patients in covid-19. There are enough data that indicate if a person doesn't have their blood glucose level in control then covid-19 surely affects that person. The mortality rate in this Covid-19 diabetes patient is in large number. Recent data also tell there are some complications with anti-diabetic drugs in this covid-19. Further few ongoing trials for drugs related to Covid-19 and diabetes which we surely help to control mortality rate and decrease the complication in diabetes mellitus in the future.

Introduction

1. Covid 19 (Coronavirus)

The epic Covid (CoV) named '2019-nCoV' or '2019 novel Covid's or' Coronavirus' by the World Wellbeing Association (WHO) is responsible for the first lung outbreak in early December 2019 in Wuhan City, Hubei Area, China [1, 2, 3, 4]. Coronavirus is a pathogenic infection. Since the phylogenetic experiments have been completed with full-blown game techniques, bats have become a supply of Covid pollutants, but the most attractive (expensive) manager (s) are still unknown. Or three key areas of work are currently underway in China to teach our thinking about the onset of the outbreak pathogen. This is the first case-by-case trial that took place near Wuhan in December 2019, a live view from the Huanan Rebate Fish Market similar to other domain markets, as well as a compilation of preliminary reports and the biodiversity shown by the Huanan Market and the purpose of those creatures after the market closed [5, 6,7, 8].

Covid for the most part causes intestinal and respiratory pollution and is classified differently from four other important species: Gammacoronavirus, Deltacoronavirus, Betacoronavirus, and Alphacoronavirus [9, 10, 11]. The first two types are more polluted, while the last two contaminate the vertebrates. Six types of human CoV have been identified. These include HCoVHKU1, HCoV-OC43, Center East Respiratory Condition Covid (MERS-CoV), Serious Intense Respiratory Disorder Covid (SARS-CoV) Betacoronavirus, HCoV229E, and HCoV-NL6 which are materials from HOLV-NL63. Alphacoronavirus. Covid did not attract worldwide concern until the 2003 SARS epidemic [12, 13, 14], preceded by 2012 MERS [15,16,17] and the recent outbreak of COVID-19. SARS-CoV and MERS-CoV are known to be highly pathogenic and spread from bats to palm civets or camel camels and eventually to humans.

1.2 WHO Report (Table-1)

It is a report provided by WHO. Basically in this, there are a total no of people infected by covid-19 and mortality rate in the different-different region of the world.

WHO Region	New Cases in last 7 days (%)	Changes in new cases	Cumalativecases (%)	New deaths in lasts 7 days(%)	Change in new death	Cumulative deaths (%)

		in the last7 days			s in last 7 days	
Americas	804735 (35%)	6%	17794771	20509(48%)	-5%	588867(55%)
South East Aisa	575763 (25%)	-6%	7911036	7750(20%)	-8%	126917(12%)
Europe	694275(31%)	34%	6918265(19%)	6172(16%)	16%	246709(23%)
Eastern Mediterranean	138751(6%)	10%	2605478(7%)	3173(8%)	13%	66329(6%)
Africa	29169(1%)	11%	2605478(3%)	991(3%)	27%	2725599(3%)
Western Pacific	21996(1%)	6%	651841(2%)	633(2%)	26%	14265(1%)
Global	2268892	10%	37109851(100%)	39228(100%)	<1%	1070355(100%)

1.3 Diabetes Mellitus

Diabetes mellitus (DM) is a metabolic disorder that occurs as a result of impaired insulin secretion, insulin function, or both. [18-21] Insulin insufficiency thus promotes progressive hyperglycemia by enhancing sugar, fat, and protein metabolism. [18- [21] As the disease develops tissue or vascular injury leads to exacerbation of diabetes, for example, retinopathy [22 - 23] neuropathy, [24-25] neuropathy [26,27] cardiovascular problems [28,29], and wound. [30 [31] In these lines, diabetes involves a wide range of different infections. Diabetes is a well-known endocrine problem and every year in 2010, it was estimated that more than 200 million people worldwide would have DM and 300 million would thus be infected by 2025. [32-34] References and diabetes status were first developed by the World Wellbeing Association (WHO) in 1965 [35] and then by Public Diabetes Information Gathering (NDDG)in 1979, [36] and this was followed by recommendations made by WHO. in 1980. [37] Theseare some of the unknown recommendations that were slightly revised in 1985. [38] The latest recommendations were published by the American Diabetes Affiliation (ADA) in 1997 and theWHO in 1999. The two circles agree with the proposals and the process. [39]

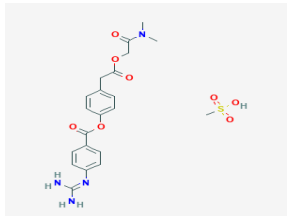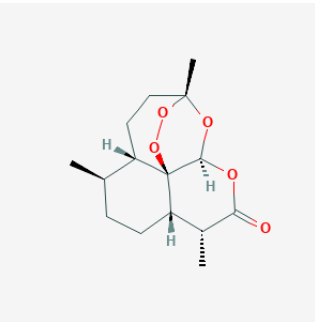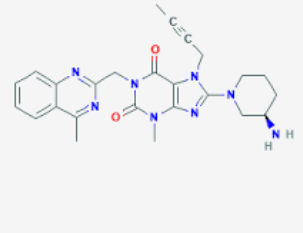## 1.4 Some facts and figures from the International 2020 Diabetes Association

• Around 463 million adults (20-79 years) are living with diabetes; by 2045 this will rise to 700 million

• The number of cases with type 2 diabetes is increasing in many countries

• 79% of grown-ups with diabetes live in low-and center pay nations.

• One in five people over the age of 65 has diabetes

• One in two people (232 million) with diabetes has not been diagnosed

• Diabetes has killed 4.2 million people

• Diabetes has created at least $ 760 billion in health care costs by 2019 - 10% of

• More than 1.1 million youngsters and youths are living with type 1 diabetes

• More than 20 million live births (one birth for every living person) are affected by diabetes during pregnancy

• 374 million people are at high risk of developing type 2 diabetes [40]

Development of drugs for Covid-19 and Diabetes mellitus.(Table-2)

There is some ongoing trial for the development of drugs that reduce the complication of covid-19 in diabetes mellitus. The main focus is to target Covid-19 and diabetes only. In the present time, there is no medicine for that. So these are the few drugs on which trial is going on and once they pass all their trail they will be launched in markets soon.

Development of drugs for Covid-19 and Diabetes mellitus

S.NO	Drugs	Development[ID]	Condition Target	Structure	Reference
1	Camostat Mesilate	Phase 2 NCT04 530617	Covid 19 Diabetes		https://clinicaltrials.gov/ct2/show/NCT04530617?cond=Drugs+for+diabetes+ and+covid+19&draw=2&rank=1 [41]
2	Artemisia Annua Leaf	Phase 2 NCT04 530617	Covid 19 Diabetes		https://clinicaltrials.gov/ct2/show/NCT04530617?cond=Drugs+for+diabetes+ and+covid+19&draw=2&rank=1 [42]
3	Linagliptin in 5MG	Phase 3 NCT04 371978	Covid 19 Coro David us Diabetes Mellitus, Type		**https://clinicaltrials.gov/ct2/show/NCT04371978?cond=Drugs+for+diab etes+and+covid+19&draw=2&rank=2[43]**

			2		

1.4 Causes Associated With Diabetes-Covid 19

A. **Family History** - If you have family members with diabetes, the chances of you getting them are very high. Anyone with a mother, father, sister, or relative with type 1 diabetes should be tested. A direct blood test can diagnose it.

B. **Infection or illness** - Few diseases and illnesses, especially, abnormalities, can damage your pancreas.

C. **Obesity**-Testing shows that this is type 2 diabetes. Due to rising power among U.S. youth, this type of influence affects many young people.

D. **Impaired glucose tolerance-** Prediabetes is a mild form of this condition. It may be decided that a basic blood test will be performed. If you happen to have it, there is a good chance that you will get type 2 diabetes.

E. **Insulin resistance** - Type 2 diabetes often begins with insulin-resistant cells. That means your pancreas needs to try to make enough insulin to deal with your body's problems

F. **Gestational Diabetes**- If you have diabetes while pregnant, you have had gestational diabetes. So that increases the chances of getting type 2 diabetes at some point.

G. **Age**- If you are over 45 and overweight or have a chance of getting symptoms of diabetes, talk to your primary care physician about a basic diagnostic test.

H. **Physical inactivity** - The real delay is another important risk factor for the development of type 2 diabetes. To some extent, these effects stem from the tendency of inactive people to incorporate fatty substances into their muscle cells and gain weight.

I. **Under the stellar diet system**- Any dietary intake that leads to overweight increases a person's risk of developing from HIV to diabetes.

J. **Foods high in starch increase glucose deficiency** - lowering the volume of a person with prediabetes and accelerating the development of type 2 diabetes.

K. High-fat, high-fiber foods, especially those that include saturated and trans fats, cause dyslipidemias, reduce insulin resistance, and promote the development of type 2 diabetes.

So there are many factors and including what are the causes associated with diabetes and covid-19.

1.5 Impact of COVID-19 on diabetes complications

The Coronavirus epidemic is driving a major shift in the medical care framework and the current disruptive procedures for the protection of diabetic resources, leaving a large number of patients untouched [44]. The effect of Coronavirus on the severity of diabetes is difficult to assess since details are not available as it progresses; however, a single study from the cardiovascular catheter tube inferred that there is a great post pension on schedule from the

beginning of STEMI coronary mediation indicators compared to the previous year, especially in the first clinical consultation program [45]. One of the most potentially unsafe complications of disruption in the planning of medical services is the protection of supplements in patients with progressive injury and coronary artery disease as there are many possible alternatives to consulting a specialist. A few creators set out to protect emergency structures that enable the reduction of clinic visits for non-life-threatening injuries, still dispersing patients with severe problems in-office visits or even telephone care and are far from sight [44]. Although not a guaranteed method, this can free up essential hospital supplies for those with emergency medical indications. Details of serious complications among epidemic-related problems (e.g. diabetic ketoacidosis, hypoglycemia) are almost non-existent, but hopefully, they will be developed after SARS-CoV-2, as this may allow them to plan for unparalleled future events. In a series of cases 10.3% (3/29) of patients suffered at least one episode of hypoglycemia (<70 mg / dl, i.e.<3.9mmol / l) [46]. Apart from the desire to achieve individual glucose and other metabolic purposes, there are currently no specific recommendations for people with diabetes regarding COVID-19 and its complications [47]

Thus few recorded cases show in some cases of diabetes that people suffer from pneumonia and other diseases but only in those cases where the blood sugar levels are very high.

2. Potential Diabetes treatment in covid.

* Insulin

Insulin is a peptide product created by agitation neurons in the pancreatic Langerhans island that promotes glucose metabolism, glucose regulation, lipid and protein digestion, and cell proliferation and production via its mitogenic reactions.
Insulin sensitivity occurs when a usual or increased insulin rate induces a poor normal instinct; [48] historically, this corresponds to the curve of insulin sensitivity that results in decreased glucose depletion.[49]
Insulin Development In 1889, German researchers Minkowski and von Mering found that a successful pancreatectomy reduced the occurrence of diabetes in species. [50] They believed the pancreas was in charge of athleticism. Subsequent work developed the hypothesis, establishing a correlation between diabetes and the disappearance of the Langerhans Colonies. Whereas Minkowski, Zuelzer of Germany, and Scott of the United States attempted, with varying degrees of success, to locate and steer anything that isn't in the pancreatic island chain, a Belgian agent de Meyer and an English specialist Schaefer invented the phrase "insulin" in 1909 and 1916, respectively. After a decade, insulin was ultimately subdivided, refined, and transported to the structure that would house the upcoming organization in 1921.

Complications with covid – Insulin is a generally safe option and is the sole service for patients with type 1 diabetes mellitus. It can also be earned a master solution for the treatment of type 2 diabetes mellitus (T2DM) who have impaired insulin sensitivity. While insulin has not been shown to have a detrimental influence on ACE2, insulin therapy has been shown to decrease the expression of ADAM-17 (a disintegrin and metalloproteinase-17) in diabetic Akita mice (51). ADAM-17 cleaves ACE2 in natural physiology, infecting the enzyme. It is unknown if the same situation happened in individual pneumocytes. skeletal muscles that are not real (52,53).

Classification of insulin (Table-3)

Serial no	Drugs	Onset	Peak

1.	Ultra-short acting/Rapid-acting	15-30 min	30 min – 2 half hours
	*Lispro *Aspart *Glulisine		
2.	Long-acting * Glargine * Detemir * Degludec	3-4 hours	No peak +

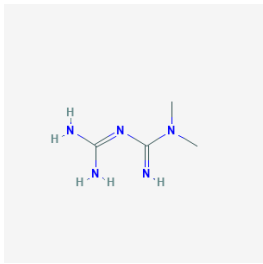## 2.1 Oralhyperglycemic drugs used can be used during covid -19

*Metformin

METFORMIN (dimethyl biguanide) is an oral medication used to lower blood sugar and is targeted at patients with low blood insulin (NIDDM). [54] It improves insulin sensitivity and in these lines reduces the insulin resistance that pervades NIDDM. The glycemic control content achieved with metformin is similar to that achieved with sulfonylureas, although their comparative methods are comparable. Metformin can be used as an initial treatment or as an additional medication when treatment for sulfonylurea alone is in short supply.

HISTORY-Metformin was first conceived as antidepressants, however, one of the results was glucose suppression [55]. Metformin's numerous pleiotropic impacts and common use in medical advances have prompted scientists to label it a "21st-century migraine" [56].

An issue with covid 19- We proposed that metformin will theoretically affect the supply of ACE2 in the respiratory system through the AMPK–phospho-ACE2 axis, thus promoting SARSCoV-2 contamination and aggravating COVID-19 infection. Additionally, individuals with COVID-19 have a heightened likelihood of kidney damage during illness,[57] that may result in lactic acidosis and exacerbate the condition when metformin is used. [58 and 59] At diagnosis, individuals in the metformin group were significantly elevated blood glucose and LDH concentrations than those in the non-metformin category. Increased blood glucose levels have been linked to a high risk of proinflammatory cytokines in the aftermath of viral infection,[60] which leads to the deterioration of COVID-19. (61) Additionally, an elevated LDH level has been linked to an increased risk of death and progression of the disease in individuals with COVID-19. [122,123] At induction, no discrepancy in diagnostic criteria or other laboratory parameters was observed between metformin and non-metformin instances. These findings suggest that the two events were in almost similar environments. Additionally, our findings indicated that metformin patients were likely to cause dangerous complications during inpatient.

Classification of biguanides (Table-4)

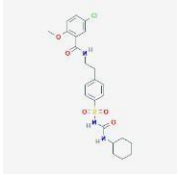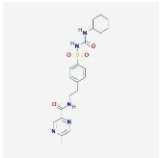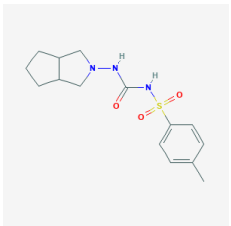| Serial No	Drug	Chemical structure	Mechanism of action
1.	Metformin		Metformin reduces hepaticglucose formation, reduces intestinal glucose intake, and improves insulin resistance by increasing fringe glucose uptake and utilization.[64]

* **Sulfonylureas**

Sulfonylureas have has been broadly utilized for the therapy of type 2 diabetes for almost 50 years and, even on our occasions, are generally utilized for the therapy of this staggering persistent sickness. Here, we audit a portion of the accessible information on sulfonylureas, assessing their component of activity and their impacts on glycemic control. We can infer that sulfonylureas are as yet the most utilized enemy of diabetic specialists: perhaps this is because of their lower cost, the chance of mono-dosing, and the presence of a relationship with metformin in the equivalent tablet.[65]

History - Sulfonylureas were found in 1942 when Janbon et al. seen that a few sulfonamides produced hypoglycemia in exploratory creatures. From this perception carbutamide (1-butyl-3-sulfonylurea) was integrated. Carbutamide was the principal sulfonylurea used to treat diabetes, however was consequently removed from the market due to its unfriendly consequences for bone marrow.[65]

The complication with covid – Sulfonylureas exhibits no interaction with either ACE2 orADAM-17 and can be safely continued.
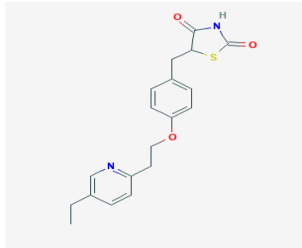
Classification of Sulfonylureas (Table-5)

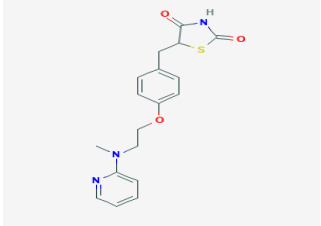| S No.	Drug Name	Chemical Structure	Mechanism of action
1.	Glibenclamide		Part of the drug's function contains a barrier to ATP-touchy K + channels, which cause cell proliferation and insulin secretion. Because of the same iron as well as the increased pancreatic function of the liver, bone

			marrow, heart muscle, and smooth muscleareas[66]
2.	Glipizide		The atomic management of glipizide incorporates the intermediate square of potassium diverts in beta cells of the pancreatic islands. This bar of potassium digestion leads to cell breakdown, which broadens up strong calcium gateways, leading to insulin discharge from the pancreatic beta cells.[67]
3.	Gliclazide		Gliclazide increases insulin release via the beta-cell sulphonylurea receptors, likely by directly affecting calcium transfer throughout cells. It stimulates the levels of first-line insulin particularly in type 2 diabetes and affects the 2nd layer.[68]

*Pioglitazone- Pioglitazone is a diabetes medication (of the thiazolidinedione class, also known as "glitazones") that is used in conjunction with a healthier food regimen and workout schedule to help people with type 2 diabetes regulate their blood glucose levels. It functions by aiding the system in restoring a normal insulin response, thus lowering your blood glucose. Regulating high blood glucose prevents kidney damage, vision impairment, nerve damage, appendage loss, and reproductive ability complications. [70]It belongs to the thiazolidinedione (TZD) family of drugs and functions by increasing the tissue's response to insulin. Pioglitazone was approvedfor medicinal use in 1999 after being licensed in 1985. (71) It is a standard drug.

A potential problem with covid 19 – It has been demonstrated that pioglitazone increases ACE2 expression in insulin-sensitive groups of rats and decreases ADAM-17 therapeutic potential muscle tissue. (72,73).

Classification of thiazolidinediones (Table-6)

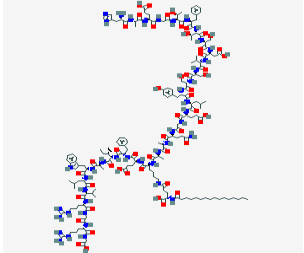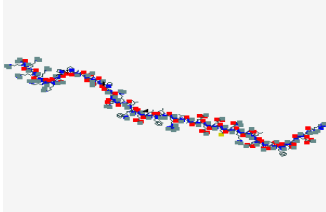| Serial no	Drug	Chemical Structure	Mechanism of action
1.	Pioglitazone		Pioglitazone improves blood circulation in patients with Type 2 diabetes by activating PPAR gamma 1 and PPAR gamma 2 and by manipulating lipid breakdown via alpha PPAR alpha.74]

2.	Rosiglitazone		Rosiglitazone, an anti-diabetic practitioner in the thiazolidinedione category, increases glucose control by reducing insulin sensitivity. Rosiglitazone is a highly selective and active stimulant of the peroxisome proliferator-induced receptor-gamma (PPAR-gamma). [75]

Liraglutide * Liraglutide is a glucagon-like peptide-1 (GLP-1) receptor agonist, also known as an incretin mimic. It functions by raising pancreatic insulin secretion and decreasing unnecessary glucagon secretion. [106]
Liraglutide was authorized for clinical use during 2009 in the European Union and 2010 in the United States[77,78].

 A complication with covid 19–Liraglutide analog improves cardiac and pulmonary ACE2 output. (79). Therefore it will be dangerous to use in humans during covid 19.

Classification of GLP-1 receptor agonists (Table-7)

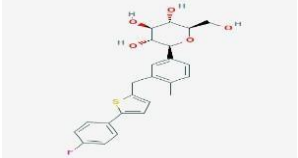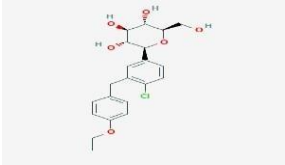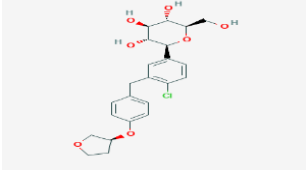| Serial no	Drugs	Chemical Structure	Mechanism of action.
1.	Liraglutide		Victoza comprises liraglutide, a simple individual GLP-1 receptor,and behaves as a GLP-1 receptor agonist. Liraglutide enhances intracellular cyclic AMP (cAMP) causing insulin to be segregated within the glucose uptake.[80]
2.	Lixisenatide		Lixisenatide is a component of the Glucagon-like peptide-1 receptoragonist sedates, each of which activates the GLP-1 receptor. GLP-1 is a chemical that helps pancreatic beta cells by releasing insulin into high glucose levels. As a general chemical, insulin may be released when glucose is high. Like GLP-1, it similarly reduces back pain.[81]

* **SGLT2 inhibitors**- SGLT2 inhibitors are a class of expertly endorsed solutions that are FDA-attested for use with healthy eating and workout to cut down glucose in individuals with type 2 diabetes. Prescriptions in the SGLT2 inhibitor class join canagliflozin, dapagliflozin, and

empagliflozin. They are open as single-fixing things and besides in mix with other diabetes remedies like metformin. SGLT2 inhibitors lower glucose by causing the kidneys to dispose of sugar from the body through the pee. [82]

History - **SGLT2 inhibitors,** also called **gliflozins**, In the United States, the Food and Drug Administration (FDA) has approved three medications: dapagliflozin, canagliflozin, and empagliflozin. Canagliflozin was the primary SGLT-2 antagonist that the FDA recommended, as noted in Stroll 2013. In 2014, dapagliflozin and empagliflozin were approved. (83)

Complications associated with covid 19 – Several studies have indicated that oral hypoglycemic substances, such as Sodium-Glucose-Transporter-2 inhibitors (SGLT-2i), can prove disastrous to COVID-19 patients with diabetes [84,85]. Information likewise upholds the advancement of ACE2 action by sodium-glucose carrier 2 inhibitors.

Classification of SGLT2 inhibitors (Table -8)

Serial no	Drugs	Chemical Structure	Mechanism of action
1.	Canagliflozin		Invokana belongs to the family of medicines known as sodium-glucose transport protein 2 (or SGLT2) inhibitors. These drugs function by increasing the amount of glucose excreted in the urine.[86]
2.	Dapagliflozin		Dapagliflozin inhibits sodium-glucose transporter subgroup 2 (SGLT2), which is responsible for at least 90% of glucose uptake in the kidneys. Impairing this carriage device results in the evaporation of bloodglucose from the pee. In drug testing, dapagliflozin reduced HbA1c by 0.6 points when combined with metformin.[87]
3.	Empagliflozin		Empagliflozin functions byimpairing the sodium-glucose cotransporter-2 (SGLT-2) enzyme present in the kidney's proximal tubules. Empagliflozin decreases glucose reabsorption in thekidneys and improves glucose detoxification in the urine by inhibiting SGLT2**.** [88]

* **DPP4 inhibitors**- DPP-4 inhibitors are a relatively new form of dental diabetes medications. Known colloquially as gliptins, they are typically prescribed to patients with type 2 diabetes
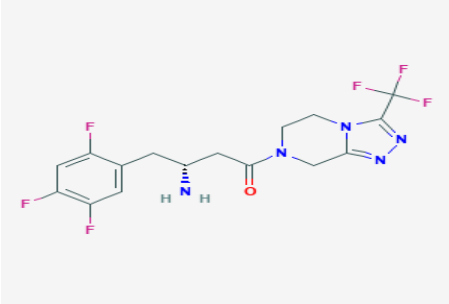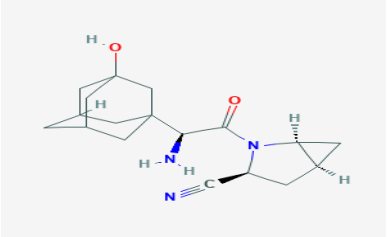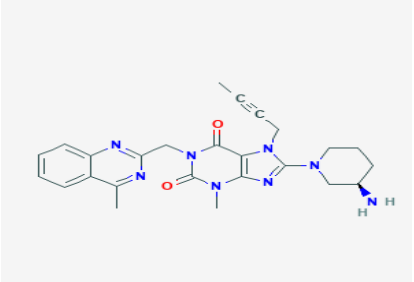
who have not responded well with the metformin or sulphonylureas. While DPP-4 inhibitors
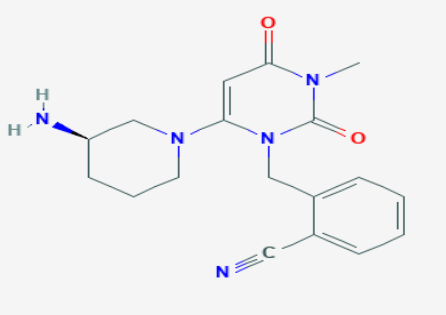
can aid in losing weight and diabetes control, they have been linked to an increased risk of pancreatitis. [90]

The formulation of the DPP-4 inhibition hypothesis for type 2 diabetes glucose-lowering treatment was based on the incretin theory. Starling invented the word incretin in the early 1900s to refer to a gut hormone that activates the pancreas's inner secretion (90). Likewise, La Barre and Still (91) and Heller (92) demonstrated in the 1930s that organizing gut focuses to trial beings resulted in a decrease in flowing glucose.

Complications involved with COVID-19 - In theory, DPP4 regulation may help mitigate thecytokine-mediated acute respiratory problems associated with COVID-19.

Classification of DPP4 inhibitors(Table-10)

S.No	Drugs	Chemical Structure	Mechanism of action
1.	Sitagliptin		Sitagliptin directly captures the activity of DPP- 4, an important catalyst that suppresses incretin, allowing peptide-1 and low-glucose peptide-1 to work under glucose in light at the banquet.[93]
2.	Saxagliptin		Saxagliptin, a flexible, sensitive dipeptidyl peptidase-4 inhibitor, is similar to the previously accepted specialist in the treatment of T2DM. It works by preventing glucagon-like peptide - 1 and thus builds insulin secretion and reduces glucagon release.[94]
3.	Linagliptin		Linagliptin is an inhibitor of DPP-4, a protein-damaging protein incretin glucagon-like peptide-1 (GLP-1) and glucose-subordinate insulinotropic polypeptide (GIP)[95]

4.	Alogliptin		Nesina contains a dipeptidyl peptidase (DPP) IV inhibitor, which lowers glucagon and glucose levels in the blood. Medications increase insulin secretion and incretin levels, and in addition reduce gastric emptying as blood glucose levels.

2.6 - Complication of Covid 19 with Anti-Diabetic Drugs(Table-11)

Anti-Diabetic Medicine	Information from animal research	Information from human Research	Problems for use during COVID-19
Insulin	Diminishes renal ADAM-17 impression in diabetic mice thereby diminishing urinary ACE2 shedding and enhancing intrarenal ACE2 impression	-	No individual information to aid vulnerable result[96]
Metformin	-	-	No problem
Sulfonylureas	-	-	No issue
Pioglitazone	Overexpression of ACE2 in insulin-delicate tissues of rats	Deregulation of ADAM 17 in human skeletal muscles	Conceptual peril of Bad result, although, no information on human pulmonary ACE2 impression [96]

Liraglutide	Overexpression ACE2 in cardiac and pulmonary tissues of diabetic rats	-	Conceptual peril of Bad result, although, no information on human pulmonary ACE2 impression [96]
SGLT2 inhibitors	-	Enhancement of renal ACE2 activities	Conceptual peril of Bad result, although, no information on human pulmonary ACE2 impression[96]
DPP4 inhibitors	DPP4H/M mice promote acute infections with MERS-CoV DPP4i do not change ACE2 activities in diabetic mice	DPP4i might deploy universal antiinflammatory part	Conceptually, DPP4 regulation might aid offset The cytokine mediated Acute respiratory problems of COVID-19[96]

According to the given data, several tests are performed which tell us till now there is no such complication found in human being from anti-diabetic drugs in covid-19. On the other hand same test done on mice there, some complication has to be seen but in humans, there is no such evidence which shows any complication in humans.

Conclusion

As we have proper evidence which shows there is surely complication with diabetes mellitus in covid-19. The complication is mostly seen in those people whose blood glucose level is not in control before or during covid-19. There are several diseases just like bacterial pneumonia and other diseases impact that patient only. As we know covid-19 is a new disease so we don't have any particular drug to treat and reduce the complication but the doctor advice us to use regular anti-diabetic drugs only. Few data indicate maybe these drugs have some complication with covid-19 but as such to evidence found till now. Few trials are going to develop the drugs targeting these two factors and reduce complications in the future.

REFERENCE

1. Hui, David S., Esam I. Azhar, Tariq A. Madani, Francine Ntoumi, Richard Kock, Osman Dar, Giuseppe Ippolito et al. "The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health—The latest 2019 novel coronavirus outbreak in Wuhan, China." *International journal of infectious diseases* 91 (2020): 264-266.

2. Read, Jonathan M., Jessica RE Bridgen, Derek AT Cummings, Antonia Ho, and Chris P. Jewell. "Novel coronavirus 2019-nCoV: early estimation of epidemiological parameters and epidemic predictions." *MedRxiv* (2020).

3. Corman, Victor M., Olfert Landt, Marco Kaiser, Richard Molenkamp, Adam Meijer, Daniel KW Chu, Tobias Bleicker et al. "Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR." *Eurosurveillance* 25, no. 3 (2020): 2000045.

4. Fong, Simon James, Gloria Li, Nilanjan Dey, Rubén González Crespo, and Enrique Herrera-Viedma. "Composite Monte Carlo decision making under high uncertainty of novel coronavirus epidemic using hybridized deep learning and fuzzy rule induction." *Applied soft computing* 93 (2020): 106282.

5. Fong, Simon James, Nilanjan Dey, and Jyotismita Chaki. "An introduction to COVID-19." In *Artificial intelligence for coronavirus outbreak*, pp. 1-22. Springer, Singapore, 2021.

6. Fong, Simon James, Nilanjan Dey, and Jyotismita Chaki. "An introduction to COVID-19." In *Artificial intelligence for coronavirus outbreak*, pp. 1-22. Springer, Singapore, 2021.

7. Standaert, Michael. "Coronavirus closures reveal vast scale of China's secretive wildlife farm industry." *The Guardian* 25 (2020).

8. Fong, Simon James, Nilanjan Dey, and Jyotismita Chaki. "An introduction to COVID-19." In *Artificial intelligence for coronavirus outbreak*, pp. 1-22. Springer, Singapore, 2021.

9. Woo, Patrick CY, Susanna KP Lau, Carol SF Lam, Candy CY Lau, Alan KL Tsang, John HN Lau, Ru Bai et al. "Discovery of seven novel Mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus." *Journal of virology* 86, no. 7 (2012): 3995-4008.

10. Fong, Simon James, Gloria Li, Nilanjan Dey, Rubén González Crespo, and Enrique Herrera-Viedma. "Finding an accurate early forecasting model from small dataset: A case of 2019-ncov novel coronavirus outbreak." *arXiv preprint arXiv:2003.10776* (2020).

11. Fong, Simon James, Nilanjan Dey, and Jyotismita Chaki. "An introduction to COVID-19." In *Artificial intelligence for coronavirus outbreak*, pp. 1-22. Springer, Singapore, 2021.

12 Can We Learn Anything from the SARS Outbreak to Fight COVID-19? https://www.healthline.com/health-news/has-anything-changed-since-the-2003-sars-outbreak Access on 10/04/2021.

13 Huang, Yanzhong. "The SARS epidemic and its aftermath in China: a political perspective." *Learning from SARS: Preparing for the next disease outbreak* (2004): 116-36.

14. Hung, Lee Shiu. "The SARS epidemic in Hong Kong: what lessons have we learned?." *Journal of the Royal Society of Medicine* 96, no. 8 (2003): 374-378.

15. Rajinikanth, V., Nilanjan Dey, Alex Noel Joseph Raj, Aboul Ella Hassanien, K. C. Santosh, and N. Raja. "Harmony-search and otsu based system for coronavirus disease (COVID-19) detection using lung CT scan images." *arXiv preprint arXiv:2004.03431* (2020).

16. Kim, K. H., T. E. Tandi, Jae Wook Choi, J. M. Moon, and M. S. Kim. "Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in South Korea, 2015: epidemiology, characteristics and public health implications." *Journal of Hospital Infection* 95, no. 2 (2017): 207-213.

17. Sikkema, R. S., E. A. B. A. Farag, Mazharul Islam, Muzzamil Atta, C. B. E. M. Reusken, Mohd M. Al-Hajri, and M. P. G. Koopmans. "Global status of Middle East respiratory syndrome coronavirus in dromedary camels: a systematic review." *Epidemiology & Infection* 147 (2019).

18. Kumari, M. Sujatha, M. Kiran Babu, Rehana Sulthana, M. Srinivas, and Ch Prasanthi. "Diabetes Mellitus: Present status and Drug therapy Updates." *Research Journal of Pharmacy and Technology* 7, no. 1 (2014): 84-94.

19. Lindberg, G., U. Lindblad, and A. Melander. "Sulfonylureas for treating type 2 diabetes mellitus." *Cochrane Database Systemic Reviews* 3 (2004): 254.

20. Bearse, Marcus A., Ying Han, Marilyn E. Schneck, Shirin Barez, Carl Jacobsen, and Anthony J. Adams. "Local multifocal oscillatory potential abnormalities in diabetes and early diabetic retinopathy." *Investigative ophthalmology & visual science* 45, no. 9 (2004): 3259-3265.

21. Hove, Marianne N., Jette K. Kristensen, Torsten Lauritzen, and Toke Bek. "The prevalence of retinopathy in an unselected population of type 2 diabetes patients from Århus County, Denmark." *Acta Ophthalmologica Scandinavica* 82, no. 4 (2004): 443-448.

22. Seki, Masaaki, Takayuki Tanaka, Hiroyuki Nawa, Tomoaki Usui, Takeo Fukuchi, Kazuhito Ikeda, Haruki Abe, and Nobuyuki Takei. "Involvement of brain-derived neurotrophic factor in early retinal neuropathy of streptozotocin-induced diabetes in rats: therapeutic potential of brain-derived neurotrophic factor for dopaminergic amacrine cells." *Diabetes* 53, no. 9 (2004): 2412-2419.

23. Moran, Andrew, Walter Palmas, Lesley Field, Jyoti Bhattarai, Joseph E. Schwartz, Ruth S. Weinstock, and Steven Shea. "Cardiovascular autonomic neuropathy is associated with microalbuminuria in older patients with type 2 diabetes." *Diabetes care* 27, no. 4 (2004): 972-977

24. Huang, Chunmei, Youngki Kim, Maria Luiza A. Caramori, Alfred J. Fish, Stephen S. Rich, Michael E. Miller, Gregory B. Russell, and Michael Mauer. "Cellular basis of diabetic

nephropathy: II. The transforming growth factor-β system and diabetic nephropathy lesions in type 1 diabetes." *Diabetes* 51, no. 12 (2002): 3577-3581.

25. Shukla, N., G. D. Angelini, and Jamie Y. Jeremy. "—to: Looker HC, Fagot-Campagna A, Gunter EW et al.(2003) Homocysteine as a risk factor for nephropathy and retinopathy in Type 2 diabetes. Diabetologia 46: 766–772." *Diabetologia* 47, no. 1 (2004): 140-141.

26. Svensson, Maria, Jan W. Eriksson, and Gisela Dahlquist. "Early glycemic control, age at onset, and development of microvascular complications in childhood-onset type 1 diabetes: a population-based study in northern Sweden." *Diabetes care* 27, no. 4 (2004): 955-962.

27. Saely, C. H., S. Aczel, T. Marte, P. Langer, and H. Drexel. "Cardiovascular complications in Type 2 diabetes mellitus depend on the coronary angiographic state rather than on the diabetic state." *Diabetologia* 47, no. 1 (2004): 145-146.

28. Wallace, Carolyn, Gayle E. Reiber, Joseph LeMaster, Douglas G. Smith, Katrina Sullivan, Shane Hayes, and Christy Vath. "Incidence of falls, risk factors for falls, and fall-related fractures in individuals with diabetes and a prior foot ulcer." *Diabetes care* 25, no. 11 (2002): 1983-1986.

29. Centers for Disease Control and Prevention (CDC. "History of foot ulcer among persons with diabetes--United States, 2000-2002." *MMWR. Morbidity and mortality weekly report* 52, no. 45 (2003): 1098-1102.

30. King, Hilary, Ronald E. Aubert, and William H. Herman. "Global burden of diabetes, 1995–2025: prevalence, numerical estimates, and projections." *Diabetes care* 21, no. 9 (1998): 1414-1431.

31. Zimmet P. Globalization, coca-colonization and the chronic disease epidemic: can the Doomsday scenario be   averted? J Med 2000; 247: 301-310 Access on 10/05/2021.

32. World Health Organization Expert Committee on Diabetes Mellitus. Second WHO Technical Report, Series 310. Geneva: World Health Organization, 1965 Access on 10/04/2021.

33. National Diabetes Data Group. Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes 1979; 18: 1039-1057 Access on 10/04/2021.

34. World Health Organization Expert Committee on Diabetes Mellitus. Second WHO Technical Report, Series 646. Geneva: World Health Organization 1980 Access on 10/04/2021.

35. World Health Organization Study Group. Diabetes Mellitus: WHO Technical Report, Series 727. Geneva: World Health Organization, 1985 Access on 10/04/2021.

36. World Health Organization Consultation. Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications, Part 1: Diagnosis and classification of Diabetes Mellitus. Report of a WHO Consultation. Geneva: World Health Organization, 1999 Access on 10/04/2021.

37. Zimmet, Paul, Catherine Cowie, Jean-Marie Ekoe, and Jonathan Shaw. "Classification of diabetes mellitus and other categories of glucose intolerance." *International textbook of diabetes mellitus* (2003).

38. Gupta, Ritesh, Amerta Ghosh, Awadhesh Kumar Singh, and Anoop Misra. "Clinical considerations for patients with diabetes in times of COVID-19 epidemic." *Diabetes & metabolic syndrome* 14, no. 3 (2020): 211.

39. Yang, Jing, Y. A. Zheng, Xi Gou, Ke Pu, Zhaofeng Chen, Qinghong Guo, Rui Ji, Haojia Wang, Yuping Wang, and Yongning Zhou. "Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis." *International Journal of Infectious Diseases* 94 (2020): 91-95.

40. https://www.diabetesatlas.org/en/sections/worldwide-toll-of-diabetes.html Access on 10/04/2021.

41. https://clinicaltrials.gov/ct2/show/NCT04530617?cond=Drugs+for+diabetes+and+covid+19&draw=2&rank=1 Access on 10/04/2021.

42. https://clinicaltrials.gov/ct2/show/NCT04530617?cond=Drugs+for+diabetes+and+covid+19&draw=2&rank=1 Access on 10/04/2021.

43. **https://clinicaltrials.gov/ct2/show/NCT04371978?cond=Drugs+for+diabetes+and+covid+19&draw=2&rank=2** **Access on 10/04/2021.**

44. https://meridian.allenpress.com/japma/article/doi/10.7547/20-051/436248/All-Feet-On-Deck-The-Role-of-Podiatry-During-the Access on 10/04/2021.
45. Tam, Chor-Cheung Frankie, Kent-Shek Cheung, Simon Lam, Anthony Wong, Arthur Yung, Michael Sze, Yui-Ming Lam et al. "Impact of coronavirus disease 2019 (COVID-19) outbreak on ST-segment–elevation myocardial infarction care in Hong Kong, China." *Circulation: Cardiovascular Quality and Outcomes* 13, no. 4 (2020): e006631.

46. Zhou, Jun, and Jie Tan. "Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China." *Metabolism* 107, no. 107 (2020): 154216.

47. ÖDG. InformationzuCovid-19undMenschenmitDiabetes mellitus. Access on 10/04/2021.

48. World Health Organization. Obesity: Preventing and Managing the Global Epidemic Report of a WHO Consultation Technical Report Series. World Health Organization, Geneva 2000 Access on 10/04/2021.

49. Wilcox, Gisela. "Insulin and insulin resistance." *Clinical biochemist reviews* 26, no. 2 (2005): 19.

50. Bliss, Michael. "The history of insulin." *Diabetes care* 16, no. Supplement 3 (1993): 4-7.

51. Salem, Esam SB, Nadja Grobe, and Khalid M. Elased. "Insulin treatment attenuates renal ADAM17 and ACE2 shedding in diabetic Akita mice." *American Journal of Physiology-Renal Physiology* 306, no. 6 (2014): F629-F639.

52. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med [Internet]. 2020 [cited 2020 Mar 20]; Available from: https://linkinghub.elsevier.com/retrieve/pii/S2213260020301168 Access on 24/04/2021.

53. Pal, Rimesh, and Sanjay K. Bhadada. "Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?." *Diabetes research and clinical practice* 163 (2020).

54. Bailey CJ. Biguanides and NIDDM. Diabetes Care 1992;15:755-72 Access on 24/04/2021.

55. Sharma, Swati, Avik Ray, and Balakrishnan Sadasivam. "Metformin in COVID-19: a possible role beyond diabetes." *Diabetes research and clinical practice* 164 (2020): 108183.

56. Romero, Roberto, Offer Erez, Maik Hüttemann, Eli Maymon, Bogdan Panaitescu, Agustin Conde-Agudelo, Percy Pacora, Bo Hyun Yoon, and Lawrence I. Grossman. "Metformin, the aspirin of the 21st century: its role in gestational diabetes mellitus, prevention of preeclampsia and cancer, and the promotion of longevity." *American journal of obstetrics and gynecology* 217, no. 3 (2017): 282-302.

57. Naicker, S., C. Yang, S. Hwang, C. Liu, and V. Jha. "The 2019 Coronavirus epidemics and kidney disease." *Kidney Int* (2020).

58. Katulanda, P. *et al*. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. *Diabetologia* 63, 1440–1452 (2020). https://doi.org/10.1007/s0012 5-020-05164 -x Access on 24/04/2021.

59. Bornstein, S.R. *et al*. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol.* 8, 546–550 (2020). https://doi.org/10.1016/S2213 -8587(20)30152 -2 Access on 24/04/2021

60. Wang, Qiming, Peining Fang, Rui He, Mengqi Li, Haisheng Yu, Li Zhou, Yu Yi et al. "O-GlcNAc transferase promotes influenza A virus–induced cytokine storm by targeting interferon regulatory factor–5." *Science Advances* 6, no. 16 (2020): eaaz7086.

61. Huang, Chaolin, Yeming Wang, Xingwang Li, Lili Ren, Jianping Zhao, Yi Hu, Li Zhang et al. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." *The lancet* 395, no. 10223 (2020): 497-506.

62. Ballard, Clive, Janet Grace, I. MCREITH, and Clive Holmes. "Neuroleptic sensitivity in dementia with Lewy bodies and Alzheimer's disease." *Lancet (British edition)* 351, no. 9108 (1998): 1032-1033 Access on 24/04/2021.
63. Guan, Wei-jie, Zheng-yi Ni, Yu Hu, Wen-hua Liang, Chun-quan Ou, Jian-xing He, Lei Liu et al. "Clinical characteristics of coronavirus disease 2019 in China." *New England journal of medicine* 382, no. 18 (2020): 1708-1720.

64. https://go.drugbank.com/drugs/DB00331 Access on 24/04/2021.

65. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4548036 Access on 24/04/2021.

66.https://pubmed.ncbi.nlm.nih.gov/9451465/#:~:text=The%20mechanism%20of%20action%20of,muscle%20and%20smooth%20muscle%20sites Access on 24/04/2021.

67.https://www.ncbi.nlm.nih.gov/books/NBK459177/#:~:text=The%20molecular%20mechanisms%20of%20glipizide,from%20the%20pancreatic%20beta%20cells Access on 24/04/2021.

68.https://pubmed.ncbi.nlm.nih.gov/1794262/#:~:text=Gliclazide%20stimulates%20insulin%20secretion%20through,effect%20on%20the%20second%20phase. Access on 24/04/2021.

69. https://www.webmd.com/drugs/2/drug-17406/pioglitazone-oral/details Access on 24/04/2021.

70. *British national formulary: BNF 76 (76 ed.). Pharmaceutical Press. 2018. p. 694. ISBN 9780857113382.*Access on 24/04/2021.

71. *Fischer J, Ganellin CR (2006). Analog-based Drug Discovery. John Wiley & Sons. p. 450. ISBN 9783527607495 Access on 24/04/2021.*

72. Fang, L., G. Karakiulakis, and M. Roth. "Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?." *The Lancet. Respiratory Medicine* 8, no. 4 (2020): e21-e21.
73. Pal, Rimesh, and Sanjay K. Bhadada. "Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?." *Diabetes research and clinical practice* 163 (2020).

74.https://pubmed.ncbi.nlm.nih.gov/11594239/#:~:text=Pioglitazone%20improves%20glycaemic%20control%20in,through%20action%20at%20PPAR%20alpha Access on 24/04/2021.

75. https://www.fda.gov.in Access on 24/04/2021.

76. *Drugs.com*. American Society of Health-System Pharmacists. Access on 24/04/2021.

77. *"Liraglutide"* European Medicines Agency *Access on 24/04/2021*.

78. *"DailyMed - liraglutide injection"*. dailymed.nlm.nih.gov *Access on 24/04/2021*.

79. Pal, Rimesh, and Sanjay K. Bhadada. "Should anti-diabetic medications be reconsidered amid COVID-19 pandemic?." *Diabetes research and clinical practice* 163 (2020).

80. https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/4395-victoza Access on 24/04/2021.

81. https://en.wikipedia.org/wiki/Lixisenatide Acess on 24/04/2021

82. [https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/sodium-glucose-cotransporter-2-sglt2-

inhibitors#:~:text=SGLT2%20inhibitors%20are%20a%20class,canagliflozin%2C%20dapagli
flozin%2C%20and%20empagliflozin] Acess on 24/05/2021 Access on 24/04/2021.

83. https://en.wikipedia.org/wiki/Discovery_and_development_of_gliflozins Access on
24/04/2021.

84. Pal, Rimesh, and Sanjay K. Bhadada. "Should anti-diabetic medications be reconsidered
amid COVID-19 pandemic?." *Diabetes research and clinical practice* 163 (2020).

85. Sharma, Swati, Avik Ray, and Balakrishnan Sadasivam. "Metformin in COVID-19: a
possible role beyond diabetes." *Diabetes research and clinical practice* 164 (2020): 108183.

86. https://www.diabetes.co.uk/diabetes-medication/invokana-
canagliflozin.html#:~:text=Mechanism%20of%20action,passed%20out%20in%20the%20uri
ne Access on 24/04/2021.

87. https://en.wikipedia.org/wiki/Dapagliflozin Access on 24/04/2021.

88. https://www.ncbi.nlm.nih.gov/books/NBK532925/#:~:text=Go%20to%3A-
Mechanism%20of%20Action,increases%20urinary%20excretion%20of%20glucose Access
on 24/04/2021.

89. https://www.diabetes.co.uk/diabetes-medication/dpp-4-inhibitors.html Access on
24/04/2021.

90. Moore, Benjamin, Edward S. Edie, and John Hill Abram. "On the treatment of Diabetus
mellitus by acid extract of Duodenal Mucous Membrane." *Biochemical Journal* 1, no. 1
(1906): 28.

91. Rehfeld, Jens F. "The origin and understanding of the incretin concept." *Frontiers in
endocrinology* 9 (2018): 387.

92. Ahrén, Bo. "DPP-4 inhibition and the path to clinical proof." *Frontiers in
endocrinology* 10 (2019): 376.

93.https://www.medscape.com/viewarticle/584860_1#:~:text=Sitagliptin%20selectively%20i
nhibits%20the%20action,in%20response%20to%20a%20meal Access on 24/04/2021.

94. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3198516ion%20n Access on 24/04/2021.

95. https://www.clinicaltrialsarena.com/projects/nesina-alogliptin-for-the-treatment-of-type-
2-diabetes-mellitus Access on 24/04/2021.

96. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151403/ Access on 24/04/2021.