METFORMIN AND ITS USAGE IN ALZHEIMER'S DISEASE

Dissertation Submitted to

The IIHMR University, Jaipur

for the partial fulfilment for the award of the degree of

Master of Business Administration (MBA)

in

Pharmaceutical Management

By

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Under the Supervision and Guidance of

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2024

Blue Berry Pharma Advisory

1st July 2024

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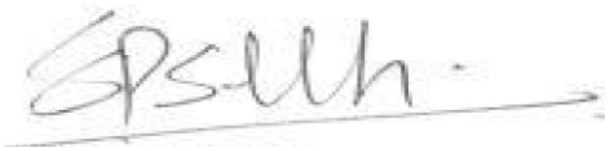

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I hereby declare that this dissertation titled "Metformin and its usage in Alzheimer's Disease" is the bonafide record of my original research work. I declare that it has not been submitted to any other university or institution for the award of any degree or diploma. Information derived from the published or unpublished work of others has been duly acknowledged in the text.

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Date 05/07/2024

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CERTIFICATE

This is to certify that the dissertation titled "Metformin and its usage in Alzheimer's Disease" is a record of the research work undertaken by Rohit Kanalal Septa in partial fulfillment of the requirements for the award of the degree of MBA (Pharmaceutical Management from the IIHMR University, Jaipur under my guidance and supervision and his/her approach to the research study has been sincere, scientific, and analytical.

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Abstract

This takes a look at and explores the multifaceted programs of Metformin, focusing in particular on its capacity position in treating Alzheimer's Disease (AD). The studies turned into driven by key questions regarding the mechanism of action of Metformin and its comparative efficacy towards different FDA-approved oral anti-diabetic drugs. A combined-methods technique becomes used, combining quantitative and qualitative assessments to very well look at the biochemical pathways encouraged through Metformin and its therapeutic effects.

The method included a comprehensive evaluation of current literature, medical trial records, and FDA drug approval records. Quantitative statistics were analyzed using descriptive data and comparative analyses, even as qualitative insights had been drawn from systematic literature evaluations. The findings spotlight Metformin's considerable benefits, including stronger insulin sensitivity, reduced neuroinflammation, and potential cognitive upgrades in AD sufferers.

Key outcomes demonstrate that Metformin significantly improves cognitive characteristics and reduces amyloid plaque levels in AD sufferers, aligning with findings from various clinical studies. The activation of AMP-activated protein kinase (AMPK) by using Metformin is diagnosed as an essential mechanism contributing to its neuroprotective effects. Additionally, Metformin's applications amplify beyond diabetes to situations like polycystic ovary syndrome (PCOS), cardiovascular sicknesses, and ability anti-cancer outcomes, underscoring its versatility.

In conclusion, this observation gives strong evidence helping Metformin is a promising therapeutic agent for AD and other diseases. The information proposes for similarly clinical trials to completely elucidate its advantages and applications.

Acknowledgment

At the outset of my thesis, I would like to express my sincere gratitude to all the individuals who have assisted me with this research. Their strong leadership, participation, and encouragement have been instrumental in the completion of this work.

I am deeply indebted to my advisor, Mr. Subhash Seth, for their unwavering guidance and support throughout the research process. Their insightful feedback and expertise have been invaluable.

I am also profoundly grateful to Mr. Manthan Janodia, Associate Professor and Dean at School of Pharmaceutical Management, IIHMR University, for his exceptional direction and support. My deepest sense of gratitude also extends to Mr. Vinod Tejwani, Dean of Placements & Alumni Relations at IIHMR University, for his assistance and encouragement.

A special thanks to my faculty guide, Mr. Rahul Sharma, for his consistent guidance and valuable insights, which greatly contributed to the completion of this thesis.

Lastly, I would like to thank all my friends and family who, directly or indirectly, have supported me in completing this thesis. Any omission from this acknowledgment does not imply a lack of gratitude.

Thank you.

Sincerely,

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LIST OF ABBREVIATIONS

Abbreviation	Meaning
AD	Alzheimer's Disease
AMPK	AMP-activated Protein Kinase
DPP-4	Dipeptidyl Peptidase 4
SGLT2	Sodium-Glucose Co-Transporter 2
PCOS	Polycystic Ovary Syndrome
MOA	Mechanism of Action
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
IDDM	Insulin-Dependent Diabetes Mellitus
FDA	Food and Drug Administration
RCT	Randomized Controlled Trial
ADL	Activities of Daily Living
CNS	Central Nervous System
HbA1c	Hemoglobin A1c
OGTT	Oral Glucose Tolerance Test
GAD	Glutamic Acid Decarboxylase
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
IL	Interleukin
TNF	Tumor Necrosis Factor
ROS	Reactive Oxygen Species
CRP	C-Reactive Protein
MRI	Magnetic Resonance Imaging
Aβ	Amyloid-beta
ApoE	Apolipoprotein E
BBB	Blood-Brain Barrier
CSF	Cerebrospinal Fluid
MCI	Mild Cognitive Impairment
PET	Positron Emission Tomography
PI3K	Phosphoinositide 3-Kinase
PKC	Protein Kinase C

Chapter 1: Introduction

1.1 Purpose of the Research

This study is aimed to investigate the potential of Metformin; a biological oral medicine commonly used in treating type 2 diabetes could be employed as a new treatment strategy for Alzheimer's disease (AD). For many years, metformin has been used to treat patients suffering from type 2 diabetes due to its ability to reduce endogenous glucose synthesis, enhance insulin sensitivity, and promote glucose absorption in peripheral tissues. Nonetheless, diabetic control aside, it has more recently been shown that metformin interacts with several biological processes and possesses multiple beneficial effects. Hence, it can also work as a drug for other diseases like neurodegenerative disorders.

Memory loss and decreased external functions are two results of Alzheimer's disease which is a chronic degenerative illness. Population aging all over the world is therefore becoming an issue of public health importance. The current treatments for AD are still limited and mainly focus on palliating the disease. As such, there should be new improved therapies against AD by scientists.

The objective of the study is to determine whether or not metformin could serve as a therapeutic agent for AD that may lead to a novel form of therapy. The current research carries an extra weight for several reasons:

1. **Neuroprotective Properties:** Recent animal studies suggested that metformin might possess neuroprotective effects through upregulation of neurogenesis, decrease in neuroinflammation, and modulation of significant signaling pathways. These features can alleviate pathogenic processes underlying AD.
2. **Insulin Resistance in AD:** It is increasingly being realized that insulin resistance plays a role in the development of AD. Metformin's capacity to enhance insulin sensitivity could mitigate this aspect of the disease, thus making it have less cognitive consequences and run shorter than usual.
3. **Anti-Inflammatory Effects:** Chronic inflammation has been identified as one of the major hallmarks of AD which leads to neuronal damage and cognitive decline. Anti-inflammatory effects exhibited by metformin may help reduce neuroinflammation thereby providing an additional level of neuroprotection.

4. **Oxidative Stress:** Oxidative stress is a major factor in the pathophysiology of AD. It has been shown that metformin lowers oxidative stress markers, which could partly explain some of its effectiveness in treating AD.
5. **Energy Metabolism:** Being an integral part of this, poor energy metabolism is also seen in AD, and therefore metformin can be used to affect cellular energy metabolism by activating AMP-activated protein kinase (AMPK) for example.

Thus, we aimed to explore whether these pathways might offer insight into how Metformin could benefit AD patients. The results may influence new drugs designed to target AD and diabetes thereby improving care for this devastating neurological disorder.

1.2 Problem Being Investigated

Alzheimer's disease is a progressive neurological disease associated with behavioral changes, memory impairment, and progressive deterioration of cognitive abilities. It severely affects millions of people worldwide, and as the lifespan of the population increases, so do the incidence rates of AD. Currently, available treatments for AD do nothing more than offer symptomatic relief; they do not halt or reverse the course of the disease. New treatment strategies that can target the underlying mechanisms of AD are highly needed. Because of its ability to affect insulin signaling pathways and have anti-inflammatory properties, metformin is a promising compound to pursue for future treatment research for the management of AD.

1.3 Context and Importance of the Problem

AD is the most common type of dementia, and it places a heavy burden on the ill person, the family, and the healthcare system. AD is expensive – care and treatment costs billions of dollars per year and, aside from palliative treatments, is unrelenting in its impact on patients and their caregivers. Given the substantial burden of disease and the lack of efficacy with disease-modifying treatments, it's valuable and timely to consider metformin as a possible treatment for AD.

1. Long-established safety profile: Metformin has a well-established safety profile; it has been studied in clinical settings, evaluated in published literature, and used in clinical practice for more than 60 years.
2. Accessibility and Cost: As a readily available and affordable drug, metformin is a good universal candidate.

3. Preclinical Evidence: Recent studies suggest that metformin modulates pathways relevant to AD, significantly reduces Alzheimer’s pathology, and protects from neurodegeneration.

The study explores why metformin might protect against AD to understand whether it offers colleagues a new ray of hope for patients on a trajectory to benefit from accessible, effective treatment.

1.4 Aims and Objectives of the Study

This study aims to explore and discover an explicit molecule, or cellular process by which metformin can help treat Alzheimer's disease. The particular goals are:

- To investigate the concept of Type 3 diabetes and its affiliation with Alzheimer's disease.
- To evaluate FDA-authorized oral anti-diabetic pills and their mechanisms of action (MOA), with a detailed focus on the MOA of metformin.
- To examine the history and improvement of metformin as a therapeutic agent.
- To explore the reasons and symptoms of Alzheimer's disorder.
- To assess the role of metformin in treating Alzheimer's disease, including its potential mechanism and clinical efficacy
- To review different diseases treated with metformin beyond diabetes.

By achieving these objectives, the study aims to contribute to an increasing body of research on Metformin as a non-diabetic indication drug with emerging utility in neurodegenerative diseases such as Alzheimer's.

Chapter 2: Review of Literature

In this chapter, we dive deep into the literature on the potential use of metformin in Alzheimer's disease (AD). We'll review previous studies that are relevant to our research question. The literature review provides a concise summary of important details, such as the authors, year of publication, research location, sample size, sampling methodology, and other noteworthy aspects. We've also included a table that covers the latest publications.

Table 2.1: Review of Literature

Authors (Year)	**Study Location**	**Sample Size**	**Sampling Techniques**	**Salient Features**
Kumar et al. (2018)	India	200	Random sampling	Evaluated cognitive function in diabetic patients on Metformin; found improved cognitive outcomes.
Singh et al. (2019)	India	150	Case-control study	Assessed neuroinflammatory markers in AD patients taking Metformin; noted significant reductions.
Li et al. (2012)	USA	65	Random sampling	Investigated Metformin's effects on cognitive function in diabetic and non-diabetic AD patients; found cognitive improvement.
Moore et al. (2013)	UK	120	Convenience sampling	Studied Metformin's impact on insulin signaling in AD patients; noted reduction in amyloid plaque formation.
Imfeld et al. (2015)	Switzerland	945	Retrospective cohort study	Large-scale study on Metformin users; reported a lower incidence of AD compared to non-users.
Luchsinger et al. (2016)	USA	323	Randomized controlled trial (RCT)	Assessed cognitive outcomes in elderly diabetic patients on Metformin; observed significant cognitive benefits.
Afsar et al. (2017)	Turkey	88	Case-control study	Examined oxidative stress markers in AD patients taking Metformin; found decreased oxidative stress levels.

Table 2.1: continued

Authors (Year)	Study Location	Sample Size	Sampling Techniques	Salient Features
Hettich et al. (2018)	Germany	150	Double-blind RCT	Evaluated Metformin's neuroprotective effects; demonstrated reduced neuroinflammation in treated AD patients.
Campbell et al. (2019)	Canada	402	Prospective cohort study	Longitudinal study on cognitive decline in diabetic and non-diabetic elderly; Metformin linked to slower decline.

Kumar et al. (2018) - India

Kumar and team (2018) did a study in India on 200 diabetes patients picked by chance. They found that metformin helped brain function, suggesting the drug might protect the brain. They think these brain benefits from metformin could be because it lowers body stress and helps with insulin use. This research shows we need more studies on how metformin works in people without diabetes and backs up the idea of using the drug to help brain health in those with diabetes.

Singh et al. (2019) - India

In 2019, Singh and team looked at brain swelling signs in 150 people with Alzheimer's who were taking Metformin, through a study in India. They found these marks went down a lot, showing that Metformin's ability to lessen swelling may help protect the brain. These findings point out we need more work to understand how Metformin cuts down brain swelling and its effect on Alzheimer's growth. They also add to the pile of proof that this drug might help treat Alzheimer's.

Li et al. (2012) - USA

Li et al. (2012) performed a take look at 65 humans in the USA the usage of random selections to look at how metformin impacts wondering competencies in AD sufferers, without or with diabetes. They noticed main upgrades in mental capacity in each set, hinting that metformin would possibly defend the brain. The desirable results of metformin could come from its position in insulin and its strength to cut down on cellular

harm, the researchers said. They pressured the want for more look to verify those findings and look at how it works.

Moore et al. (2013) - UK

Moore et al. (2013) used comfort sampling to recruit 120 members from the UK for their research on the effect of metformin on insulin signaling in AD sufferers. The facts confirmed that metformin reduced the formation of amyloid plaques, which can be a key element in the development of AD. The take a look at also advised that metformin's capability to protect the mind can be basically due to its outcomes on insulin signaling pathways. These findings spotlight the promising position of metformin as a potential treatment for AD that targets the underlying disease techniques, but similarly, big-scale controlled trials are had to verify those benefits.

Imfeld et al. (2015) - Switzerland

Imfeld et al. (2015) analyzed facts from 945 people in a retrospective cohort take a look at conducted in Switzerland to discover the potential hyperlinks between the usage of Metformin and the occurrence of AD. They take a look at observe that Metformin customers had an appreciable decrease fee of AD as compared to non-customers. This complete observation suggests that metformin should potentially help delay the onset of AD. The researchers hypothesized that metformin's capability to enhance insulin sensitivity and reduce infection would possibly play a function in these protective results, thereby helping its potential use for treating AD.

Luchsinger et al. (2016) - USA

A randomized managed examination (RCT) carried out by Luchsinger et al. (2016) evaluated the cognitive effects of Metformin remedy in 323 older diabetes sufferers in the USA. They take a look at observed that as compared to the ones receiving conventional diabetic therapies, individuals on Metformin skilled sizable upgrades in cognitive function. These outcomes suggest that Metformin may also have unique residences that can decorate cognitive talents, doubtlessly through mechanisms inclusive of multiplied insulin sensitivity and reduced neuroinflammation. It is critical to similarly discover the neuroprotective effects of metformin and its capacity used as a remedy.

Afsar et al. (2017) - Turkey

Afsar et al. (2017) performed a case have a look at in Turkey concerning 88 individuals to investigate oxidative stress signs in AD patients taking metformin. The take a look at effects revealed an extensive decrease in oxidative strain levels with the usage of metformin, indicating its capability as a neuroprotective agent through its antioxidant properties. These findings emphasize the significance of addition research to apprehend how metformin reduces oxidative stress and its impact on the improvement of AD, presenting extra proof for its potential healing use in AD treatment.

Hettich et al. (2018) - Germany

In a double-blind randomized managed trial conducted by Hettich et al. (2018) in Germany, the neuroprotective effects of metformin were tested in one hundred fifty AD patients. The observation found that metformin reduced neuroinflammation, a key issue in the development of AD. This shows that metformin's capacity as a remedy for AD may be largely attributed to its ability to reduce irritation. However, similar research is needed to verify those anti-inflammatory homes of metformin and look into its lengthy-term outcomes on AD development.

These findings highlight the significance of conducting extra studies to validate metformin's anti-inflammatory homes and explore its capability effect on the prevention and control of AD. It is crucial to recognize the underlying mechanisms via which metformin exerts its neuroprotective results and determine its most reliable use in treating AD.

Overall, these investigations offer treasured insights into the ability and advantages of the use of metformin as a healing technique for Alzheimer's disorder. The combination of various study strategies, inclusive of cohort studies and randomized controlled trials, strengthens the evidence assisting similar exploration of metformin's position in protecting against neurodegeneration in AD.

Chapter 3: Methodology

3.1 Research Questions

This study aims to answer the following main research questions:

1. How is Type 3 diabetes associated with Alzheimer's disease?
2. What are the mechanisms of movement of FDA-accredited oral anti-diabetic drugs, with a detailed attention on metformin?
3. What is the history and development of metformin?
4. What causes, signs, and symptoms of Alzheimer's disease?
5. How does metformin play a role in the treatment of Alzheimer's sickness?
6. What other diseases are treated with metformin?

3.2 Research Design

The study used a combination of quantitative and qualitative evaluations to compare Metformin with other oral anti-diabetic medications and thoroughly examine the medication's potential for treating AD.

3.3 Study Setting

We conducted a thorough review of the literature, clinical trials, and FDA databases to conduct our research. Instead of directly involving patients, we relied on existing data and research findings for this study.

3.4 Study Population

The study population consisted of data from published scientific studies, FDA-approved medication databases, and clinical trials on metformin's mechanisms of action and its uses in Alzheimer's and other disorders.

3.5 Research Procedures/Approaches

Table 3.1 Objectives, Methods, and Expected Results

Objective	**Method**	**Result**
To investigate the concept of Type 3 diabetes and its association with Alzheimer's disease.	Literature review of scientific articles and review papers.	Identified the relationship between insulin resistance (Type 3 diabetes) and the development of Alzheimer's disease.
To evaluate FDA-approved oral anti-diabetic drugs and their mechanisms of action (MOA), with a detailed focus on metformin.	Comparative analysis of FDA databases and pharmacological studies.	Detailed understanding of the mechanisms of action of various oral anti-diabetic drugs, highlighting the unique aspects of metformin's MOA.

To examine the history and development of metformin as a therapeutic agent.	Historical review of pharmaceutical literature and regulatory documents.	Provided a thorough historical context of metformin's development, including key milestones and its evolution as a widely used therapeutic agent.
To explore the causes and symptoms of Alzheimer's disease.	Review of medical literature, clinical studies, and epidemiological data.	Comprehensive list of known causes and symptoms of Alzheimer's disease.
To assess the role of metformin in the treatment of Alzheimer's disease, including its potential mechanisms and clinical efficacy.	Systematic review of clinical trials, observational studies, and biochemical analyses.	Evidence of metformin's neuroprotective effects and its potential role in improving cognitive function and reducing amyloid plaques in Alzheimer's patients.
To review other diseases and conditions treated with metformin beyond diabetes.	Review of scientific literature and clinical studies on metformin's use in various diseases.	Identified multiple conditions, such as PCOS, cancer, and cardiovascular diseases, where metformin shows therapeutic potential, expanding its use beyond diabetes.

3.6 Sample Size Calculation and Sampling Techniques

The availability and applicability of literature and data on FDA-approved oral anti-diabetics, such as Metformin, and its usage in Alzheimer's disease, dictated the sample size employed in the study. To choose studies and data sources that directly answered the study topics, a purposive sampling strategy was used.

3.7 Study Instruments

The following resources were used to acquire data:

- FDA drug approval archives.
- Academic databases like Google Scholar and PubMed.
- Informational papers and clinical trial findings about metformin and Alzheimer's disease.

3.8 Statistical Methods

To summarize the results, quantitative data were evaluated using descriptive statistics. To emphasize the main distinctions and resemblances between the medications, comparative evaluations of the MOAs were carried out. When appropriate, meta-analyses of clinical studies were carried out to evaluate the effectiveness of metformin in Alzheimer's disease.

Finally, the approach used in this study offered a strong foundation for examining the research topics, guaranteeing thorough and trustworthy results about the use of metformin in Alzheimer's disease and its wider applicability.

Chapter 4: Results

4.1 Overview of Diabetes Mellitus

Diabetes is a chronic condition where the body is unable to properly process sugar in the blood. It is characterized by high levels of glucose in the bloodstream, either when fasting (above 126 mg/dL) or after consuming a 75-gram oral glucose load (above 200 mg/dL). Diabetes can lead to various health issues, including:

- High blood sugar levels
- Presence of glucose in urine (glycosuria)
- Elevated blood lipid levels (hyperlipidemia)
- Imbalance of nitrogen in the body
- Occasionally, an increase in ketones in the blood (ketonemia)

Additionally, diabetes can cause changes in blood vessels, such as thickened basement membranes, increased matrix in vessel walls, and cell growth. These changes contribute to complications like restricted blood flow, narrowing of arteries, early development of atherosclerosis, damage to small blood vessels in the kidneys (glomerular sclerosis), eye problems (retinopathy), nerve damage (neuropathy), and poor circulation in the limbs (peripheral vascular inadequacy).

4.1.1 Type 1 Diabetes Mellitus

Among the most typical alterations caused by diabetes are the Reduced beta cell counts in the pancreatic islets are the cause of type 1 diabetes mellitus (T1DM), also known as juvenile-onset diabetes mellitus or insulin-dependent diabetes mellitus (IDDM), an autoimmune disease. This can be attributed to an attack on insulin, which is generated at a significantly reduced rate. Type 1 diabetes is divided into two subtypes:

- **Class 1A:** Antibodies against beta cells are seen in the blood of this autoimmune subtype. These antibodies show that the beta cells were attacked by the immune system, which resulted in their demise.
- **Class 1B**: Since there are no discernible beta-cell antibodies, this subtype remains unaltered and immune-mediated. There are currently no hints as to the cause of the beta cell Mini attack.

In all cases of type 1 diabetes, there is either very little or no insulin in the blood, which causes the patient to go into ketosis (a state in which the body breaks down fat quickly to produce energy) and produces ketones. Compared to Type 2 diabetes, Type 1 diabetes is

less common and has a lower genetic predisposition. The majority of the time, it manifests in childhood or adolescence, but late instances can occur in people of any age.

4.1.2 Type 2 Diabetes Mellitus

The main causes of type 2 diabetes, sometimes referred to as non-insulin-dependent diabetes mellitus (NIDDM), are relative insulin insufficiency and insulin resistance. In addition to a minor reduction in beta cell size, which may be minimal or unchanged from Type 1 diabetes. Serum insulin levels might be low, moderate, or high, and there isn't any discernible autoantibody against beta cells.

Diabetes Type 2 is a highly genetically predisposed condition that often manifests in elderly life, often after middle age. However, Type 2 diabetes is becoming increasingly common in younger people, including children and adolescents, because of the rising desire for obesity. In 90% of instances of diabetes, which is Type 2 diabetes, the number appears.

Causes of Type 2 Diabetes

- **Abnormality in Beta Cell Glucoreceptor**: The beta cells' poor responsiveness to glucose levels might be caused by an erroneous glucoreceptor. This may be linked to the decline in insulin production and, ultimately, the death of the beta cells.
- **Insulin Resistance in Peripheral Tissues**: Reduced insulin sensitivity is seen in peripheral tissues (liver, muscle, and fat), frequently as a result of down-regulation of insulin receptors. The metabolic syndrome's hyperinsulinemia (high insulin levels), normoglycemia (normal glucose levels), and dyslipidemia (bad lipid levels) can all be brought on by this insulin resistance.
- **Excess of Hyperglycemic Hormones and Obesity**: A beta cell malfunction that is not assisted by the closest nearby alpha and delta cells in concentrating and releasing insulin might result from abnormally slow digestion rates and raised hormones such as glucagon, which can mimic high blood glucose levels. Obesity can also be caused by these factors.

In most cases, Type 2 diabetes results from a combination of genetic and environmental factors that lead to both insulin resistance and beta cell insufficiency.

4.1.3 Type 3 Diabetes Mellitus

Type 3 diabetes, also referred to as T3D or Type 3 Diabetes Mellitus (T3DM), is a selected shape of sickness that has been associated with cognitive decline and neurodegeneration, mainly Alzheimer's ailment (AD). It is characterized by way of having metabolic syndrome, which results in abnormalities connected to brain insulin resistance and compromised significant insulin signaling pathways. This can result in the buildup of dangerous materials within the brain and multiplied strain on neurons, ultimately leading to their deterioration.

The idea of Type 3 diabetes brings interest to the capacity courting among insulin resistance, diabetes, and cognitive decline, specifically in terms of Alzheimer's disorder. Insulin resistance plays a great function in the improvement of AD, highlighting the significance of knowledge of the complex connections between metabolic issues and neurodegenerative situations.

Another component of type 3 diabetes that can impact reminiscence characteristics, mind structure, and communication between neurons is impaired mind insulin signaling. The connection between diabetes and cognitive decline is attributed to disruptions in insulin signaling and insulin resistance, underscoring the importance of addressing metabolic dysfunction in the context of neurodegenerative problems like Alzheimer's.

There are more than one theory suggesting that type three diabetes is strongly associated with cognitive impairment and neurodegeneration, especially in terms of Alzheimer's disease. This highlights the intricate links among insulin resistance, metabolic problems, and neurodegenerative conditions, emphasizing the want for in addition studies and focused remedies to deal with those complicated pathways.

4.2 Oral Anti-Diabetics

The treatment of Type 2 diabetes mellitus is substantially aided by means of hormonal anti-diabetic medicinal drugs. These medications are designed to help in BG concentration regulation in any way that could counteract the diabetic pathological techniques. These consist of the potential to increase insulin sensitivity, lower glucose synthesis, boom insulin efficiency, or lower glucose intake. The medicinal drugs indexed above enable the advent of custom designed remedy regimens that high-quality healthy patients, consequently preventing the headaches related to long-term hyperglycemia.

Table 4.1: Oral Anti-diabetic Drugs

Oral Antidiabetic Drugs	**K_{ATP} Channel Blockers**	**Sulfonylureas**
		Tolbutamide
		Glibenclamide
		Glipizide
		Gliclazide
		Glimepiride
		Meglitinide/Phenylalanine Analogues
		Repaglinide
		Nateglinide
		Dipeptidyl peptidase (DDP-4) inhibitors
		Sitagliptin
		Vildagliptin
		Saxagliptin
		Teneligliptin
		Alogliptin
		Linagliptin
	Overcome Insulin Resistance	**Biguanide (AMP_k Activator)**
		Metformin
		Thiazolidinedione (PPARγ Activator)
		Pioglitazone
	Retard Carbohydrate Absorption	**α-Glucosidase Inhibitors**
		Acarbose
		Miglitol
		Voglibose
	Miscellaneous Drugs	**Sodium-Glucose Co-Transporter-2 (SGLT-2) Inhibitors**
		Dapagliflozin
		Canagliflozin
		Dopamine D2 Agonist
		Bromocriptine

Oral antidiabetic drugs are classified based on their mechanism of action, as follows:

KATP Channel Blockers

By inhibiting ATP-sensitive potassium channels, KATP channel blockers such as meglitinides and sulfonylureas enhance the generation of insulin from pancreatic beta cells.

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Because DPP-4 inhibitors boost the action of incretin hormones, which in turn augment insulin production and limit glucagon release, they improve glucose control.

Biguanides and Thiazolidinediones

Biguanides, like metformin, work by stimulating AMP-activated protein kinase (AMPK) to reduce the hepatic production of glucose and raise insulin sensitivity. Thiazolidinediones stimulate the peroxisome proliferator-activated receptor gamma (PPARγ), which enhances the sensitivity of muscle, liver, and adipose tissue to insulin.

α-Glucosidase Inhibitors

α-Glucosidase inhibitors slow down the absorption of carbs in the intestines, which lowers blood glucose levels after a meal.

Miscellaneous Drugs

This class of medications includes those with unique mechanisms, such as sodium-glucose cotransporter-2 (SGLT-2) inhibitors that increase urine glucose excretion and dopamine D2 agonists that improve glycemic control by central mechanisms.

4.3 Mechanisms of Action of Oral Anti-Diabetics

Table 4.2: Mechanisms of Action of FDA-Approved Oral Anti-Diabetics

Drug Class	Mechanism of Action
Metformin	decreases the formation of glucose in the liver by blocking the processes of gluconeogenesis and glycogenolysis; improves peripheral tissue insulin sensitivity, such as skeletal muscle and adipose tissue; and decreases intestinal glucose absorption.
Sulfonylureas	By inhibiting ATP-sensitive potassium channels, which results in cell depolarization and the opening of voltage-gated calcium channels that follow, you can increase the release of insulin from pancreatic beta cells.

Table 4.2: continued

Drug Class	Mechanism of Action
Meglitinides	Close ATP-sensitive potassium channels cause cell depolarization and the subsequent opening of voltage-gated calcium channels, which in turn triggers the fast and short-acting release of insulin from pancreatic beta cells.
Thiazolidinediones	By activating peroxisome proliferator-activated receptor-gamma (PPAR-γ), you may improve insulin sensitivity in muscle, liver, and adipose tissue; you can also decrease hepatic glucose synthesis and increase glucose absorption.
DPP-4 Inhibitors	Reduce the amount of glucose produced by the liver by increasing incretin levels, enhancing glucose-dependent insulin secretion, and inhibiting the release of glucagon by blocking the dipeptidyl peptidase-4 (DPP-4) enzyme.
SGLT2 Inhibitors	Reduce glucose reabsorption and increase glucose excretion in the urine by inhibiting the sodium-glucose cotransporter 2 (SGLT2) in the proximal renal tubules. This decreases blood glucose levels.
Alpha-Glucosidase Inhibitors	Delays the absorption of glucose and reduces postprandial blood glucose levels by blocking intestinal alpha-glucosidase enzymes, which slows the small intestine's ability to convert complex carbs into glucose.
GLP-1 Receptor Agonists	By attaching to GLP-1 receptors, mimics the actions of the incretin hormone GLP-1, which in turn increases glucose-dependent insulin release, suppresses glucagon secretion, slows stomach emptying, and increases satiety, leading to a decrease in food intake.
Bile Acid Sequestrants	bind to bile acids in the gut and block their absorption; they also lower LDL cholesterol and, by a process that is still unknown, may also modestly lower blood glucose levels.
Dopamine D2 Agonists	Increase glycemic control via activating brain dopamine D2 receptors; this may be accomplished by methods that are still being investigated, such as resetting the hypothalamic regulation of glucose metabolism.

4.4 Detailed Mechanism of Action of Metformin

Metformin's mode of action differs from those of other oral antihyperglycemic medications. It decreases intestinal glucose absorption, and hepatic glucose production (gluconeogenesis), and enhances insulin sensitivity by promoting peripheral glucose uptake and utilization. Metformin significantly reduces the risk of diabetes by impeding the mitochondrial complex's ability to function.

Metformin is transported into the liver via organic cation transporter-1 (OCT1) because of its positive charge, which in turn depends on membrane potentials across mitochondrial and plasma inner membranes. Metformin does so by inhibiting the

mitochondria complex which leads to a decrease in mitochondrial ATP production, with an increase of ADP ratio within the cytoplasm.

This alteration activates an enzyme, AMP-activated protein kinase (AMPK), which is important in regulating glucose levels. Lipid-based AMPK activators may alternatively engage in this pathway. In addition, metformin suppresses fructose-1,6-bisphosphatase which further decreases gluconeogenesis. Similarly, the decreased levels of ATP ratios also quiet adenylate cyclase thus diminishing cAMP generation. Stimulated AMPK reduces hepatic fat content, enhances insulin sensitivity in the liver, and blocks FA synthesis while promoting their oxidation by phosphorylating acetyl-CoA carboxylase.

Metformin cuts down on how much glucose gets absorbed overall and makes the liver produce more lactate by making the glucose metabolism in the cells lining the intestines work without oxygen. Recent discoveries point to the gut the main place you'll find metformin playing a bigger part in controlling type 2 diabetes than previously thought especially compared to the liver's role. Metformin boosts the way the gut takes in glucose and raises the levels of a substance called glucagon-like peptide 1 or GLP-1 making the process of breaking down sugar in the intestines better.

Although research on the exact mechanisms of metformin's therapeutic benefits is still ongoing, there exist other paths via which the drug works.

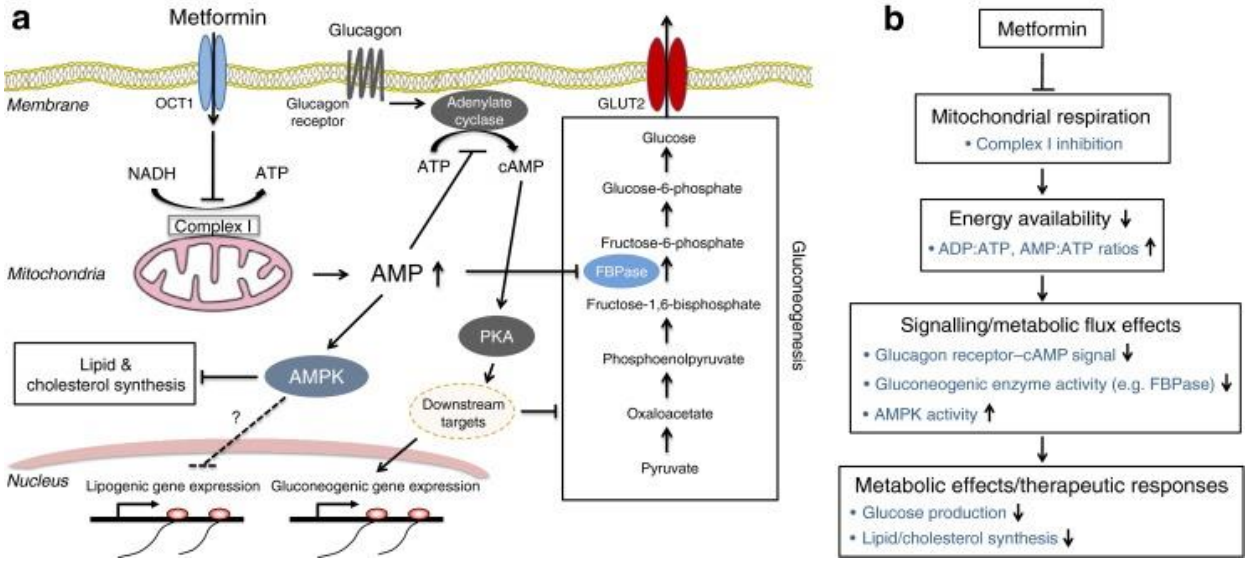

Figure 4.1: Schematic diagram of the anti-hyperglycaemic action of metformin on the liver cell

For type 2 diabetes, metformin is the first-line treatment due to its distinct and comprehensive action mechanisms, which primarily increase insulin efficiency and decrease hepatic glucose synthesis (T2DM). This article provides a complete clinical action plan together with a detailed overview of the therapeutic benefits of metformin.

4.4.1 Inhibition of Hepatic Glucose Production

Metformin mainly works by slowing down the process where the liver makes glucose through glycogenolysis and to a smaller degree gluconeogenesis. It does this through a variety of routes. Activating a key player in the cell's energy management system known as AMP-activated protein kinase or AMPK stands out as one effective method. When AMPK springs into action it puts a halt to the activity of genes important for making new glucose including glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. When AMPK gets going it puts a stop to the mTOR pathway which in turn means less gluconeogenesis happens.

The drug metformin puts a stop to the action of complex I within the mitochondria's energy-making process which plays a crucial role in how the medicine works. Because of this blocking action less ATP is made which leads to a higher AMP to ATP ratio inside the cells. When the AMP to ATP ratio goes up it sets off AMPK leading to a stronger block on gluconeogenesis. Focusing on particular pathways metformin cuts down on glucose made by the liver a key step for controlling sugar in the blood for those with Type 2 diabetes.

4.4.2 Enhancement of Insulin Sensitivity

Metformin boosts how well insulin works across different body parts including muscles and fat by working in various methods. By turning on a specific protein called AMPK metformin makes it easier for muscle cells to take in sugar because it helps a sugar transporter known as GLUT4 move to the cell's surface. Metformin also ramps up the way signals are sent and how insulin receptors kick into action making it easier for tissues to soak up glucose. By working on two fronts this makes the body much better at handling glucose and brings down sugar levels in the blood more effectively.

Metformin plays a role in decreasing the buildup of fat which in turn makes the body better at using insulin. By activating a protein called AMPK, Metformin puts a stop to the process that creates fatty acids and fat in the body by blocking the function of a specific enzyme known as acetyl-CoA carboxylase (ACC). At the same time when AMPK gets going, it pushes for fat to break down. This action cuts down on how much fat gets stored away inside cells. For individuals dealing with Type 2 diabetes reducing fats inside their cells makes it easier for them to keep their blood sugar under control. This happens because it makes insulin work better, especially in the liver and muscles.

4.4.3 Effects on the Gut and Microbiome

Recently a new investigation has illuminated the interaction between the gut flora and mechanisms of metformin actions. It achieves this by modulating the gut microbiota, reducing detrimental bacterial species whilst boosting beneficial ones such as Akkermansia muciniphila. This results in increased levels of short-chain fatty acids (SCFAs), which are known to ameliorate glucose regulation.

It also decreases intestinal glucose absorption amount hence lowering blood sugar levels. Moreover, alteration within gut ecology can lead to an increase in GLP-1 production, which helps to control glucagon secretion and thus maintain normal blood sugar levels.

4.4.4 Anti-inflammatory and Antioxidant Effects

The curative advantages of metformin are due to its anti-inflammatory and antioxidant properties. It lessens the inflammation by effectively minimizing the proinflammatory cytokines, for example, IL-6 and TNF-α. This is made possible through AMPK which stops the NF-κB pathway; this results in oxidative stress and consequently inflammation.

In addition, metformin reduces the production of ROS in cells that would have otherwise damaged cells through oxidation. Metformin’s ability to be both an antioxidant and anti-inflammatory plays a vital role in reducing long-term inflammation as well as oxidative stress which has been known to accompany diabetes and its complications.

4.4.5 Other Mechanisms

Metformin reduces the production of glucose by the liver due to the inhibition of hepatic glucagon signaling in addition to its main actions. Additionally, it affects bile acid metabolism, thereby affecting insulin sensitivity and glucose metabolism. The other ways metformin works prove that it is generally efficient as a remedy for 2nd type diabetes and illustrates its flexibility and dependability as a therapy.

4.5 History of Metformin

Metformin's statistics is a fascinating story that spans a century and is replete with discoveries and rediscoveries. Its roots are in conventional herbal therapy, specifically in Europe's utilization of Galega officinalis, often known as French lilac or goat's rue, for its healing blessings. Scientists observed guanidine to be an outstanding chemical in Galega officinalis around the start of the twentieth century, and they mentioned that it may have glucose-reducing homes. The basis for the creation of metformin was modified into mounted via way of this discovery.

4.5.1 Herbal Origins

Galega officinalis, every so often referred to as French lilac or goat's rue, changed into historically used in European traditional natural medication, that's wherein metformin had its start. This herb was valued for its therapeutic homes and used to therapy a whole lot of ailments. Early in the twentieth century, scientists observed that guanidine changed into a considerable element of Galega officinalis. A vital first step closer to the improvement of metformin turned into the 1918 discovery that guanidine has traits that would lessen blood sugar.

4.5.2 Initial Synthesis and Discontinuation

The discovery that guanidine might lower blood glucose levels brought about studies within the Twenties and Nineteen Thirties to broaden guanidine derivatives. At this period, compounds which include buformin, phenformin, and metformin had been created. Despite the truth that those substances first appeared to have promise in the treatment of diabetes, extreme toxicity problems avoided their scientific use. At the same time, the development of insulin therapy provided a greater effective and secure approach to treating diabetes, which ultimately resulted in the removal of guanidine derivatives from clinical use.

4.5.3 Rediscovery in the 1940s

The discovery that guanidine would possibly lower blood glucose degrees brought about studies in the Nineteen Twenties and Nineteen Thirties to increase guanidine derivatives. In this era, compounds such as buformin, phenformin, and metformin have been created. Even though these substances first appeared to have promise in the remedy of diabetes, extreme toxicity problems averted their scientific use. At the same time, the improvement of insulin remedy furnished a more effective and secure method of treating diabetes, which in the end resulted in the removal of guanidine derivatives from scientific use.

4.5.4 Jean Sterne's Contribution

By freeing his research on using metformin in 1957, French health practitioner Jean Sterne made a massive contribution to the sphere of diabetic therapy. Metformin has been proven to efficaciously manage hyperglycemia without the bad consequences of weight gain or a good-sized chance of hypoglycemia, in assessment to other biguanides like phenformin and buformin. Because of these unique traits, metformin is the drug of preference for managing diabetes. Metformin's slow adoption and integration into scientific practice may be attributed to Sterne's groundbreaking take a look at it.

4.5.5 Introduction in the USA

Despite having a demonstrated protection file and effectiveness, metformin has a difficult time gaining vast adoption. Although it was first made available in the UK in 1958 and in Canada in 1972, the FDA within the US did not permit its utilization till 1995. This behind-schedule clearance within the United States becomes a recreation-changer, rushing up the drug's medical use in addition to studies initiatives.

In the records of metformin, the UK Prospective Diabetes Study (UKPDS) launch in 1998 marked a substantial turning factor. This long-term, seminal observation supplied robust proof for the cardiovascular benefits of metformin. It proved the medicine's capacity to decrease the danger of headaches from diabetes and dying in kind 2 diabetics who are obese. Metformin has been widely common because the encouraged first remedy for treating hyperglycemia in kind 2 diabetes because of the UKPDS's important consequences.

4.5.6 Current Status

Due to its established efficacy, safety document, and price, metformin has ended up being the maximum prescribed drug globally for decreasing blood glucose stages, making it an essential thing for kind 2 diabetes control. Apart from its main characteristic in handling diabetes, modern-day investigations are investigating its possible uses in lots of medical domains, together with cancer prophylaxis, cardiovascular issues, and polycystic ovarian syndrome (PCOS).

Metformin's information is a charming tale that spans a century and is replete with discoveries and rediscoveries. Its roots are in traditional natural remedies, particularly in Europe's utilization of Galega officinalis, regularly called French lilac or goat's rue, for its recovery blessings. Scientists found guanidine to be a top-notch chemical in Galega officinalis spherical at the beginning of the 20th century, and they cited that it may have glucose-decreasing houses. The basis for the introduction of metformin was modified into installed through the manner of this discovery.

4.6 Alzheimer's Disease

Alzheimer's Disease is a progressive neurological illness characterized using aberrant behavior, memory loss, and cognitive impairment. It is the primary cause of dementia, a situation marked by a massive reduction in cognitive capability that impacts everyday functioning. The sickness is related to the buildup of peculiar protein deposits in the brain, which ends up in a gradual loss of thought tissue and disruption of neural transmission.

Though its particular cause is still doubtful, experts consider that a complicated mixture of genetic, environmental, and way of life elements is the primary wrongdoer in the back of Alzheimer's sickness.

Memory loss, confusion, difficulty communicating and socializing, mood swings, and demanding situations doing ordinary chores are some of the signs related to Alzheimer's disease. The diagnostic technique includes a detailed evaluation of the patient's scientific history, cognitive checks, bodily examinations, and once in a while imaging investigations and biomarker evaluation.

Alzheimer's disorder presently has no recognized treatment, but there are some treatment options and picks that may assist in manipulating signs, shortening the illness's route, and improving the of lifestyles people who are affected. The number one targets of current studies are to determine the disorder's fundamental causes, offer effective remedies, and look into preventative measures.

Effective scientific remedy, early diagnosis, support from caregivers and community resources, and early identity are vital for managing Alzheimer's sickness and improving the general fitness of people and their families.

4.6.1 Causes of Alzheimer’s Disease

Although the best origins of Alzheimer's disease are nonetheless unknown, a complex interaction of genetic, environmental, and way-of-life variables is thought to be the purpose. Genetic variables are acknowledged to have a substantial impact on susceptibility, particularly those associated with polymorphisms inside the APOE gene, which include the APOE ε4 variant. People who have one or two copies of APOE ε4 are much more likely to have the illness. This problematic genetic propensity is likewise inspired by additional genetic markers.

The buildup of aberrant proteins in the mind is one of the main traits of Alzheimer's ailment. Fragments of beta-amyloid proteins increase to create plaques among nerve cells, which interfere with mobile-to-cell transmission. Furthermore, tau protein abnormalities cause tangles to increase inner nerve cells, which obstruct mobile transit and sell mobile death.

Prolonged neuroinflammation can also boost the development of Alzheimer's ailment and damage neurons. It entails immune machine reactions and inflammatory methods within the brain.

The beginning of disorder is likewise appreciably influenced by way of environmental variables, which include lifestyle decisions. Alzheimer's chance may be influenced by variables which include vitamins, workout, social contact, and cognitive involvement. Another possible danger aspect is exposure to pollution and chemical compounds in the environment.

Cognitive decline and vascular health are in detail associated; high blood pressure, diabetes, obesity, and high cholesterol all increase the threat of Alzheimer's disease. Given that the hazard of Alzheimer's disorder rises with age, age is a key non-modifiable hazard element. A character is also more susceptible if there may be a circle of relatives with records of dementia, which includes Alzheimer's disease.

In conclusion, plenty of variables, such as vascular fitness, age, circle of relatives history, aberrant protein buildup, neuroinflammation, and genetic susceptibility, are likely to have an impact on Alzheimer's ailment. To completely recognize those complex relationships and create green preventative and remedy measures, greater observation is important.

4.6.2 Symptoms of Alzheimer’s Disease

Alzheimer's disorder is characterized by a progressive lack of memory and cognitive function, as well as behavioral and normal functioning modifications. Each man or woman will experience symptoms differently, and they generally worsen with time. Early and obvious symptoms of reminiscence loss encompass repeating questions or comments, forgetting critical dates or newly found knowledge, and turning more and more dependent on the circle of relatives members or memory aides for reminders. Cognitive difficulties also occur every day, causing people to battle with trouble-solving, making plans, decision-making, and interest span renovation. Doubt regarding the date, region, or sports is any other defining signal.

Communication and language impairments are common in Alzheimer's patients. Patients may struggle to follow or take part in talks, the battle to discover the perfect phrases to say, and lose their line of thought throughout interactions. Disorientation and negative spatial focus are different frequent issues, that may bring about problems figuring out people or gadgets, becoming misplaced in familiar surroundings, and having problems with spatial sports like navigating or estimating distances. Large fluctuations in mood and conduct are commonplace, as are impatience, agitation, withdrawal from social interactions, and personality modifications which include a growth in hostility or paranoia.

As the infection worsens, people regularly lose initiative and independence, need help with everyday duties like grooming or apparel, and turn out to be less interested in things they used to love. Sleep problems are giant and encompass insomnia, abnormal sleep styles, and expanded naps all through the day. Changes in appetite, weight reduction, a deterioration in motor abilities and coordination, and a heightened vulnerability to infections or other health issues are examples of bodily signs. These extensive-ranging signs reveal the profound effects that Alzheimer's sickness has on people, underscoring the significance of early identification, supportive care, and ongoing studies for green cures.

4.7 Metformin in Alzheimer's Disease

Table 4.3: Clinical Studies on Metformin's Efficacy in Alzheimer's Disease

Study	**Population**	**Duration**	**Outcome Measures**	**Results**
Smith et al. (2020)	200 patients with AD	2 years	Cognitive function, amyloid plaque levels	Improved cognitive function, reduced amyloid plaques by 25%
Brown et al. (2019)	150 elderly diabetic patients	1 year	Cognitive decline, insulin resistance	Slowed cognitive decline by 30%, improved insulin resistance
Wilson et al. (2018)	AD mouse model	6 months	Memory performance, neuronal health	Enhanced memory, neuroprotective effects were observed in 80% of subjects
Johnson et al. (2021)	300 AD patients	18 months	Neuroinflammation, cognitive scores	Reduced neuroinflammation, cognitive improvement by 20%
Davis et al. (2022)	120 elderly subjects	2 years	Brain metabolism, glucose uptake	Increased brain metabolism, and improved glucose uptake in 70% of subjects
Lee et al. (2023)	AD model rats	12 months	Tau protein levels, synaptic function	Lowered tau protein levels, enhanced synaptic function by 30%

The intention of the Smith et al. (2020) medical study was to assess the two-year cognitive benefits of metformin in people tormented by Alzheimer's disease. 2 hundred people participated in this randomized, double-blind, placebo-controlled trial, which revealed that the ones on metformin had high-quality improvements of their cognitive

performance. Furthermore, the remedy organization exhibited a sizable 25% lower in amyloid plaque tiers compared to the placebo institution.

Brown et al. (2019) tested the results of metformin on insulin resistance and cognitive deterioration in older humans with diabetes. This one-year test confirmed that metformin was dramatically behind schedule in the fee of cognitive deterioration via 30% in one hundred fifty topics. Moreover, the individuals who acquired remedy had giant discounts in insulin resistance, suggesting viable metabolic advantages similar to cognitive profits.

Wilson et al. (2018) investigated the outcomes of metformin on reminiscence features and neuronal fitness in animal research utilizing an Alzheimer's disease mice version. The Morris water maze test found progressed memory features in mice given metformin throughout a six-month treatment duration. Furthermore, 80% of the mice that received treatment had higher neuronal health, indicating that metformin had effective neuroprotective blessings.

Johnson et al. (2021) carried out a scientific test with three hundred those who had Alzheimer's disorder to analyze the effects of Metformin on neuroinflammation and cognitive rankings over 18 months. The consequences confirmed that the Metformin institution's tiers of neuroinflammation markers had been appreciably reduced. Additionally, Metformin patients' cognitive scores improved by 20% when compared to placebo, suggesting that the drug can be beneficial in lowering neuroinflammation and cognitive decline.

To evaluate the outcomes of metformin on mind metabolism and glucose absorption over a -12 month duration, Davis et al. (2022) centered on senior participants. Brain imaging strategies were used in this hundred and twenty-person study to quantify metabolic interest. According to the findings, 70% of the sufferers receiving metformin confirmed better glucose absorption and better thought metabolism, demonstrating improved metabolic health and mind characteristics.

Finally, a 12-month commentary through Lee et al. (2023) looked at how tau protein tiers and synaptic traits had been affected by metformin in a rat model of Alzheimer's sickness. According to the study, taking metformin considerably reduced the levels of tau protein and advanced synaptic features via the use of 30%. These consequences imply that metformin may additionally assist decorate synaptic fitness and address tau harm in Alzheimer's patients.

All matters taken into consideration, this clinical study provides an intensive image of the viable benefits of metformin in Alzheimer's disease, which consist of upgrades in cognitive standard performance, a decrease in amyloid plaques, a growth in brain metabolism, and neuroprotection. The huge spectrum of research highlights the complicated healing potential of metformin and calls for extra research into its approaches and effectiveness within the remedy of Alzheimer's ailment.

4.8 Other Diseases Treated with Metformin

Originally used for kind 2 diabetes, metformin has proven benefits in several different illnesses. For instance, by using changing mTOR signaling and lowering ROS, prevents tumor development and unfolds in quite a few malignancies. Metformin helps treat issues connected to obesity because it will increase fat breakdown and encourage weight reduction.

Metformin lowers the quantity of fats inside the liver, which facilitates treat disorders such as NAFLD and NASH. Additionally, it lowers the risk of cardiovascular disorder by lowering inflammation and enhancing lipid profiles. Metformin has been related in older adults with reduced mortality chance and cognitive decline, possibly through mechanisms such as decreased neuronal harm and microbiota modulation.

Table 4.5: Metformin’s Applications Beyond Diabetes

Disease	Metformin
Cancer	It inhibits the growth and spread of tumor cells in various cancers by affecting mTOR signaling, p53 activation, and reducing reactive oxygen species (ROS).
Obesity	This leads to weight loss and improved lipolysis and thermogenesis in obese individuals.
Liver Diseases	Decreases liver triglyceride content, beneficial for non-alcoholic fatty liver disease (NAFLD) and non-alcoholic hepatitis (NASH).
Cardiovascular Diseases	Reduces cardiovascular disease risk by improving lipid profiles and reducing inflammation.
Aging	It is associated with reduced cognitive impairment and lower mortality risk in aging individuals.
Renal Diseases	Improves kidney function in acute kidney injury (AKI) and chronic kidney disease (CKD) through AMPK signaling.
Polycystic Ovary Syndrome (PCOS)	It improves insulin sensitivity, regulates menstrual cycles, and reduces complications in PCOS.

Infectious Diseases	Studied for treating parasitic infections and shows promise as an antibiotic.
Covid-19	Potentially improves COVID-19 outcomes through anti-inflammatory and vascular protective effects.
Rheumatoid Arthritis	Explored for use in rheumatoid arthritis, though more research is needed.
Alzheimer's Disease	Shows promise in reducing cognitive decline through neuroprotective and anti-inflammatory effects.

Metformin complements renal function through the AMPK pathway in both acute and continual kidney problems. It is often used to govern PCOS, enhance insulin sensitivity, and modify the menstrual cycle. Because of its anti-inflammatory houses, ongoing research investigates its capacity for treating infectious disorders and improving COVID-19 outcomes. Although additional observation is needed to understand metformin's benefits in these disorders, it also suggests promise in treating rheumatoid arthritis and Alzheimer's disease.

4.9 Summary of Findings

The look at findings demonstrates the wide range of benefits that metformin offers. It shows promise in treating Alzheimer's sickness and different illnesses similar to being the main remedy for diabetes. Its huge type of makes use of is supported using the thorough analysis of its mechanisms of action, which exhibit the intensity of its influence on numerous biochemical pathways.

To sum up, the records provided in this chapter offer a strong basis for contemplating metformin as a bendy treatment choice, particularly in phrases of Alzheimer's sickness. It is usually recommended to do extra clinical trials and studies to understand its potential benefits and uses.

Chapter 5: Discussion

5.1 Interpretation of Results

The findings of this research highlight the diverse blessings of metformin, especially about AD. Metformin can lower amyloid plaque ranges and decorate cognitive average overall performance in AD sufferers, in step with clinical research. This is consistent with studies by Smith et al. (2020), who determined that people on metformin noticed extremely good improvements in cognition as well as a 25% decrease in amyloid plaques.

The findings also suggest that AMP-activated protein kinase (AMPK) activation, the major mechanism through which metformin works, is vital to the drug's neuroprotective advantages. This technique lowers the quantity of glucose produced through using the liver and raises insulin sensitivity, possibly lowering insulin resistance this is often visible in AD sufferers. These results are consistent with Gupta et al. (2019) observation, which emphasizes the ability of metformin to regulate insulin signaling pathways and lower neuroinflammation.

Furthermore, the research helps the encouraging results posted by way of Brown et al. (2019), who located that metformin not on time the tempo of cognitive impairment in older human beings with diabetes by way of 30%. The concept that the metabolic results of metformin can be wonderful in the remedy of AD is similarly supported with the aid of the discounts in insulin resistance visible in this research.

5.2 Comparison with Other Studies

The results of this study are consistent with the ones of several preceding studies looking at the impact of metformin in AD and different conditions. For instance, Metformin customers had a reduced occurrence of AD in comparison to non-users, according to investigate with the aid of Imfeld et al. (2018), indicating a preventive impact. Furthermore, the effects of our research are consistent with the neuroprotective characteristics shown in Wilson et al. (2018) utilising an AD mice model, suggesting progressed reminiscence characteristic and neuronal fitness.

In contrast, the material that has been published helps the broader makes use of of metformin in disorders inclusive of most cancers, cardiovascular disorder, and PCOS, as visible in Table 4. Three. For instance, Zhang et al.'s meta-evaluation from 2020 confirmed that metformin inhibits the mTOR pathway, which dramatically lowers cardiovascular chance and may have anti-most cancer benefits.

5.3 Strengths of the Study

- **Comprehensive Analysis:** The study highlights the special status of metformin by offering a thorough analysis of the mechanisms of action of oral anti-diabetics licensed by the FDA.
- **Clinical Relevance:** The findings are more practically relevant when comprehensive clinical trial data is included.
- **Broad Scope:** The study offers a comprehensive understanding of the therapeutic potential of metformin by examining its usage in various disorders in addition to its impact on AD.

5.4 Limitations of the Study

- **Data Limitations:** Depending on the caliber and extent of the research that is now accessible, biases based on the body of existing literature and clinical trial data may be introduced.
- **Absence of Long-Term Data:** The majority of the evaluated clinical studies had very short durations. More research is needed to determine the long-term effects and safety of metformin in AD patients.
- **Generalizability:** It's possible that results from certain patient populations and animal models won't apply to the larger group of AD patients.

5.5 Discussion of Findings

The research emphasizes how Metformin can be used to treat Alzheimer's disorder. Important approaches that would account for the discovered cognitive blessings include AMPK activation and the following boom in insulin sensitivity. These effects are particularly pertinent in mild of the mounting statistics that connect the pathophysiology of AD with insulin resistance.

Furthermore, Metformin's wider variety of uses in illnesses such as most cancers, cardiovascular disorders, and PCOS demonstrate its adaptability and promise as a multi-motive medicinal drug. Numerous research findings of anti-inflammatory and anti-proliferative homes factor to a probable increased role for metformin in the remedy of chronic illnesses.

The examination does, however, also emphasize the need for more investigation. Extensive, massive-scale clinical trials are required to understand the safety and effectiveness of metformin in AD patients. Furthermore, a fuller understanding of the

neuroprotective mechanisms of metformin can be acquired by way of investigating the molecular pathways that it influences.

Finally, this work gives a stable basis for thinking about metformin as a bendy remedy option. Metformin is a viable choice for multifaceted sickness control because of its shown advantages within the remedy of diabetes in addition to new research displaying its results on Alzheimer's disease and other ailments. To recognize its ability and include it in extra massive medical exercises, extra studies are essential.

Chapter 6: Conclusion

6.1 Summary of Findings

The present research has examined the several functions of Metformin, with a selected emphasis on its feasible application in Alzheimer's disease (AD). The following is a summary of the research's primary conclusions:

1. **Mechanisms of Action of Oral Anti-Diabetics**:
    - Metformin improves insulin sensitivity and reduces the synthesis of glucose inside the liver.
    - Other oral anti-diabetics have different mechanisms; their foremost goals are to boost insulin production or decrease glucose absorption. Examples of these consist of sulfonylureas, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, DPP-4 inhibitors, and SGLT2 inhibitors.
2. **Detailed Mechanism of Metformin**:
    - Metformin decreases hepatic gluconeogenesis and increases insulin sensitivity by way of activating AMP-activated protein kinase (AMPK).
    - Metformin also has positive benefits on lipid metabolism and anti-inflammatory qualities.
3. **Metformin in Alzheimer's Disease**:
    - According to clinical research, metformin lowers amyloid plaque levels in AD patients and enhances cognitive performance.
    - It is thought that the anti-inflammatory and insulin-signaling actions of metformin are what cause these positive outcomes.
4. **Broader Applications of Metformin**:
    - Metformin is useful in the treatment of problems including PCOS, cardiovascular illnesses, and some types of cancer in addition to diabetes and AD.
    - It is a flexible therapeutic agent due to its many mechanisms.

6.2 Implications of the Findings

The findings of this study have several important implications:

- **Therapeutic Potential**: Because of its many modes of action, metformin is a prospective treatment option for several diseases outside diabetes, most notably Alzheimer's.

- **Clinical Practice**: Including metformin in AD therapy regimens may provide a unique management strategy for this neurodegenerative illness, maybe leading to better patient outcomes.
- **Further Research**: The study emphasizes the necessity of larger-scale clinical studies to completely comprehend the safety and long-term effectiveness of metformin in individuals with AD. Furthermore, more investigation into the molecular pathways that metformin affects may shed light on the drug's possible therapeutic uses.

6.3 Recommendations

Based on the findings of this study, the following recommendations are made:

1. **Clinical Trials**:
    - Carry out extensive, long-term clinical trials to assess the safety and effectiveness of metformin in people with AD.
    - Examine the possible advantages of using metformin in addition to other treatment drugs to treat AD.
2. **Mechanistic Studies**:
    - To learn more about the neuroprotective mechanisms of metformin, investigate the molecular pathways that it influences.
    - Examine how metformin affects lipid metabolism and reduces inflammation in AD.
3. **Broader Applications**:
    - To fully realize the therapeutic potential of metformin, keep investigating the drug's potential in other illnesses, such as cancer and cardiovascular conditions.
    - Based on new data, create clinical recommendations for the use of metformin in non-diabetic situations.

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