

Chapter

Perspective Chapter: A Critical Overview of Metformin Use from Past to Present

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Abstract

Metformin, derived from *Galega officinalis* (Goat's rue), is a guanidine derivative. Its molecular formula is $C_4H_{11}N_5$, formed by the bonding of two guanidine groups *via* a carbon-nitrogen bridge. It is commercially available with the structural formula $C_4H_{11}N_5 + HCl$. It has an average molecular weight of 129.16 g/mol and is frequently preferred as a first-line treatment for type 2 diabetes. It is the most commonly prescribed oral antidiabetic agent to date and can be formulated in combination with GLP-1 agonists, SGLT-2 inhibitors, and DPP-4 inhibitors, in addition to being preferred as monotherapy. In addition to type 2 diabetes, it has been observed to have positive effects on diseases such as obesity, PCOS, neurodegenerative disorders, and cardiovascular system disorders, and studies are ongoing regarding its effects on cancer and aging. Common side effects observed with long-term treatment include gastrointestinal disorders, lactic acidosis, and a decrease in vitamin B12 levels. It is more economical than most antidiabetic agents and is one of the most readily available drugs worldwide. Due to its economic benefits, ease of access, clinical reliability, and being the preferred choice in various international treatment guidelines, metformin is becoming increasingly important and is being prescribed more frequently.

Keywords: diabetes mellitus, type-2 diabetes, insulin resistance, metformin, obesity, polycystic ovary syndrome (PCOS)

1. Introduction

Diabetes mellitus, whose prevalence is rapidly increasing worldwide and constitutes a serious economic burden, is getting worse day by day as a global public health problem, especially with the type-2 diabetes. According to the data obtained by the International Diabetes Federation in 2021, an average of 537 million adults worldwide have diabetes mellitus. As a result of the data and estimates, this number is thought to reach 783 million people by 2045 (**Figure 1**).

In individuals with diabetes, serious complications such as nephropathy, retinopathy, and cardiovascular disease are observed, which reduce the individual's quality of life and increase mortality in the community [1]. Type 2 diabetes, characterized

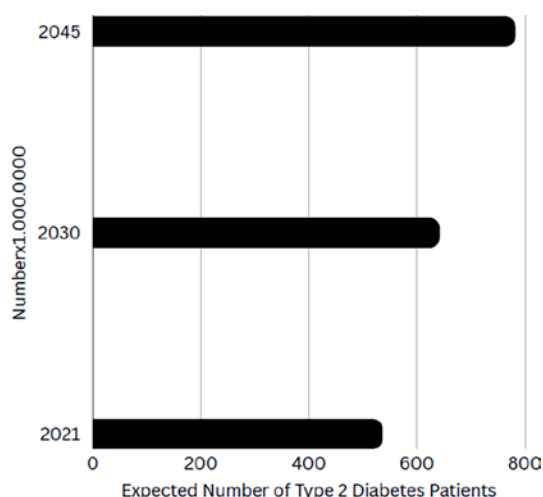


Figure 1.
Projected number of adult diabetes patients by year.

by multiple mechanisms, can generally be thought of as primarily involving β -cell dysfunction and insulin resistance. Due to its characterization by various biological system disorders, type 2 diabetes treatment is provided through multifaceted treatment methods and various pharmacological agents [2]. Among these treatment methods, the preferred first-line oral antidiabetic agent is metformin, which is known as the cornerstone of modern diabetes treatment [3].

Metformin, which entered clinical use in certain regions in 1950, is a biguanide derivative. It is widely used in combination with antidiabetic agents in the treatment of type 2 diabetes, as well as in monotherapy [4]. However, due to its neutral or mild weight-loss effect, its positive effect on cardiovascular disorders, and its low risk of hypoglycemia, it is recommended as the first-line treatment method in most international guidelines [2].

The importance of metformin is not limited to glycemic control; recent studies have shown that it has positive effects on the gut microbiota, oxidative stress, and inflammation [5, 6]. Additionally, there has been a significant amount of research in recent years on its cancer-preventive properties, potential anti-aging effects, and protective effects on the cardiovascular system [7]. Metformin, which is widely discussed in diabetes treatment, has also begun to be used off-label in various metabolic and endocrine disorders, particularly polycystic ovary syndrome (PCOS) [8]. Patient selection and dose adjustment are of great importance in treatment due to some observed side effects. These side effects can generally be listed as lactic acidosis, impaired kidney function, and gastrointestinal side effects [9]. Metformin, which is also used as monotherapy, can also be used in combination. Combination therapy is typically achieved with SGLT2 inhibitors, DPP-4 inhibitors, and GLP-1 agonists. The recent increase in its use makes it an important topic for discussion regarding its impact on health and economic considerations [10].

Detailed examinations to be conducted in this study on metformin are as follows:

1. Chemical structure, general pharmacological properties, and history;
2. Effect and efficacy on current treatment approaches;

3. Direct effects and side effects;
4. Synergistic and antagonistic effects observed when used in combination;
5. Regional usage rates and the increasing trend in its use over time;
6. Proper dosage and recommended regimens in treatment methods;
7. Comparison of effects with herbal drugs and synergistic/antagonistic effects observed when used in combination.

The topics will be explained in detail in a step-by-step manner.

2. Metformin

2.1 Structure and pharmacological effect

Metformin has the molecular formula $C_4H_{11}N_5$ and its chemical name is 1,1-dimethylbiguanide. The molecular weight of this antihyperglycemic agent is approximately 129.16 g/mol [11]. It has a pharmacological effect of increasing insulin sensitivity in the body and is formed by the bonding of two guanidine groups with a carbon-nitrogen bridge. It is available in oral tablet form as metformin HCl in 500 mg, 850 mg, and 1000 mg dosage forms. The molecular structure is highly soluble in water. The formulation is available in both conventional and extended-release preparations. The reason for preferring preparations prepared using extended-release technology is to improve patient compliance and reduce gastrointestinal side effects (Figure 2) [12].

2.2 History and development

Metformin is derived from guanidine derivatives obtained from *Galega officinalis*, a plant known as “goat’s rue.” Studies have shown that it was used in folk medicine during the Middle Ages to reduce symptoms observed in diabetic patients [13]. Although it was scientifically mentioned in the 1920s, it was not made available for clinical use due to toxicity observed in studies conducted at that time [14]. By the 1950s, Jean Sterne’s research led to the development of “Glucophage,” an agent that was better tolerated than other biguanides, which was made available for clinical use [11, 15]. In the 1960s and 1970s, the biguanide derivatives phenformin, buformin, and metformin were available on the market. However, shortly thereafter, phenformin

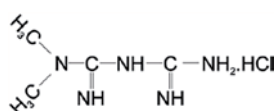


Figure 2.
 Metformin HCl Structural Formula.

and buformin were withdrawn from the market due to their high risk of lactic acidosis, and metformin remained the only biguanide derivative in clinical use [9, 13]. The United States, which began using metformin later than Europe, officially approved it by the FDA in 1995, and since then, metformin has become the most widely prescribed oral antidiabetic agent worldwide [16].

2.3 Pharmacokinetic properties

Metformin, which has a bioavailability of approximately 50–60%, is absorbed from the intestines when taken orally. Metformin, which shows a decrease in absorption depending on the dose, is absorbed from the body in a more controlled manner in extended-release forms [17]. Following absorption, tissue distribution is extensive, with high concentrations observed in the kidneys, liver, and intestines. The plasma protein binding rate is low [18]. It is not metabolized in the body and is excreted unchanged by the kidneys. In cases of renal insufficiency, the risk of lactic acidosis increases due to accumulation, and the elimination half-life is approximately 4–8 hours. Due to these dangerous effects, proper dosage adjustment and use are necessary, and monitoring of renal function is critical in clinical treatment [9, 11].

2.4 Pharmacodynamic properties and mechanism of action

The primary mechanism of action is associated with the activation of AMP-activated protein kinase (AMPK), which suppresses hepatic gluconeogenesis and reduces glucose production in the liver. It increases insulin sensitivity in tissues (particularly in muscles) and facilitates glucose uptake in the body. In the intestines, it reduces glucose absorption, regulates the intestinal microbiota, and may indirectly increase GLP-1 levels [6, 19]. Due to these effects, it reduces the risk of hypoglycemia and hyperglycemia and balances fasting and postprandial blood glucose levels.

2.5 Clinical significance

Metformin, a first-line antihyperglycemic agent, has been shown to reduce the risk of microvascular and macrovascular complications and to lower mortality in obese individuals [20]. Metformin, which is recommended as the first-line treatment following lifestyle change recommendations, is also used in combination with GLP-1 agonists, SGLT-2 inhibitors, and DPP-4 inhibitors. Due to its cardiovascular protective effect and low cost, it is the most commonly prescribed oral antidiabetic drug, particularly in developing countries [21]. It is also preferred for use in PCOS and certain endocrine disorders in addition to diabetes [8]. In recent years, studies have continued on its use for secondary prevention in diseases, slowing the biology of aging, and preventing cancer [22].

3. Side effects observed with metformin

3.1 Common side effects

The most common side effect observed is gastrointestinal. Approximately 20–30% of patients using this medication may experience side effects such as nausea, gas,

abdominal pain, diarrhea, and loss of appetite [11]. These effects are generally observed during the first few weeks of metformin use and may decrease over time. It has been noted that starting treatment with a low dose and gradually increasing the dose at specific intervals may lead to a reduction in such complaints [22]. It has been observed that the use of extended-release formulations may improve gastrointestinal tolerability [12].

3.2 Serious and rare side effects: Lactic acidosis

The most serious side effect observed, although rare, is lactic acidosis. Lactic acidosis is a type of metabolic acidosis that occurs as a result of increased lactate production and decreased clearance at the cellular level. Caution should be exercised regarding renal failure, hypoxia, septic conditions, and liver disease when metformin use is associated with lactate accumulation [23]. Meta-analyses and studies have also indicated that the risk of lactic acidosis is very low when metformin is used with appropriate patient and dose management [9]. According to 2016 data, the FDA has stated that metformin should not be used if the eGFR is <30 ml/min, and if used in the 30–45 ml/min range, the patient should be monitored at regular intervals [21].

3.3 Effect on vitamin B12 absorption

When metformin is used for a long time, vitamin B12 deficiency may be observed in patients. This condition may increase the risk of neuropathy in patients and make diagnosis difficult, especially in patients with diabetic neuropathy. Observations and studies have shown that approximately 10–30% of patients treated with metformin for 10 years or longer have experienced a decrease in vitamin B12 levels [24]. For this reason, it is of great importance for patients undergoing long-term metformin treatment to have their vitamin B12 levels measured at regular intervals for the sake of metabolic health and proper treatment.

3.4 Multifaceted effects

In addition to ensuring glycemic control in diabetic patients, metformin also provides general benefits in different systems. These can be summarized under the following subheadings:

3.4.1 Cardiovascular system

Studies have observed a 39% improvement in the cardiovascular system with metformin use [20]. Since this effect cannot be achieved with glycemic control alone, it is thought to also benefit anti-inflammatory and antithrombotic mechanisms in the body [25].

3.4.2 Anti-inflammatory effect

Metformin has an inhibitory effect on many markers of inflammation. For example, it reduces the production of cytokines such as TNF- α and IL-6 in the body [26]. In addition, certain studies suggest that it may slow the progression of atherosclerosis by preventing macrophages from transforming into inflammatory phenotypes [27].

3.4.3 Effect on microbiota

Metformin, which has been observed to have positive effects on the gut microbiota, supports the increase of certain bacteria in the flora. The best example of this is that it helps increase *Akkermansia muciniphila*, a bacterium that supports metabolic health. Thanks to such positive effects, it is seen as a positive effect independent of its effectiveness in maintaining glycemic control in the body [6, 28].

3.4.4 Cancer and aging

Although not entirely clear, some studies conducted in recent years have suggested that metformin has a slowing effect on aging and may prevent certain types of cancer. This effect is explained through AMPK-m TOR pathways, oxidative stress, and mitochondrial functions [7, 29]. Although not entirely clear, it is believed that metformin may reduce the risk of developing certain types of cancer, particularly breast, colon, and pancreatic cancer.

4. Combined use with metformin

4.1 Overview

Type 2 diabetes is a disease that progresses over time, so monotherapy is often insufficient. For this reason, treatment programs generally involve combination therapy. Metformin serves as the cornerstone of combination therapy [3]. Due to its lack of hypoglycemic effects, it can be used in combination with many oral antidiabetic agents or insulin preparations. In cases of combination therapy, it provides significant support in terms of reducing side effects and ensuring the appropriateness of treatment [30].

4.2 Synergistic effects

4.2.1 Combination with insulin

As mentioned above, metformin suppresses hepatic glucose production and enhances the peripheral effects of insulin. Insulin resistance is generally high in patients with type 2 diabetes. At a certain point, insulin is added to the treatment regimen in the form of basal or bolus doses. Studies have shown that the use of metformin in conjunction with insulin preparations results in a reduction in insulin requirements and limits weight gain in patients [20, 31]. When used in combination with insulin preparations, metformin has resulted in an additional 0.6–1.0% decrease in HbA1c. Additionally, observations have shown a 15–25% reduction in daily insulin dosage. At the same time, good glycemic control has been observed without the risk of hypoglycemia [32].

4.2.2 Combination with SGLT-2 inhibitors

SGLT2 inhibitors generally increase glucose uptake by the kidneys, thereby exerting their effect independently of insulin. Observations have shown that their use in combination with metformin produces a synergistic effect and provides protective benefits for the cardiovascular system [33]. The clinical data observed as a result of combined use generally show: an additional 0.7–1.2% decrease in HbA1c, an

approximate weight loss of 2–3 kg in patients, and positive improvements in the renal and cardiovascular systems [34].

4.2.3 Combination with GLP-1 receptor agonists

GLP-1 agonists reduce appetite and increase glucose-dependent insulin secretion in the body. When used in combination with metformin, weight loss has been observed in patients, along with stronger glycemic control [35]. The clinical data obtained from combined use include an additional 1–1.5% decrease in HbA1c, an average weight loss of 3–5 kg in patients, and a reduction in the risk of hypoglycemia.

4.2.4 Combination with DPP-4 inhibitors

When used in combination with metformin, DPP-4 inhibitors generally have good gastrointestinal tolerance and work by increasing GLP-1 levels in the body [36]. The clinical advantages of combined use include an additional reduction of approximately 0.7% in HbA1c, a neutral effect on weight, and a reduction in the risk of hypoglycemia.

4.3 Antagonistic effects and possible interactions

Although metformin generally has low drug interactions, it should be used with caution in certain situations. These include:

1. In individuals who are to be administered contrast agents, metformin treatment should be temporarily discontinued before and after drug administration. This is because it may cause acute kidney damage and predispose to lactic acidosis [1].
2. Metformin is not recommended in patients with excessive alcohol consumption due to the risk of lactic acidosis [9].
3. Metformin is not recommended in cases of respiratory failure or heart failure, and if used, it requires careful monitoring [23].

4.4 Clinical recommendations

Guidelines based on international studies and observations clearly recommend combination therapy with metformin. The ADA/EASD 2022 report outlines the treatment approach for patients with type 2 diabetes as follows [30]:

1. Upon diagnosis, the first-line treatment method is metformin combined with lifestyle changes (diet, exercise, etc.).
2. If the desired reduction in HbA1c is not achieved with the initial treatment method, GLP-1 agonists and SGLT-2 inhibitors are added alongside metformin, taking into account any chronic kidney disease or cardiovascular disorders in the patient.
3. Depending on the progression of the disease and the patient's condition, sulfonylureas, DPP-4 inhibitors, and insulin preparations may also be added.

5. Treatment approaches and new strategies with metformin

5.1 Current treatment practices in type 2 diabetes

All guidelines developed by organizations such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD), which focus on diabetes research and treatment methods, recommend metformin as the first-line treatment for type 2 diabetes [1, 30]. A gradual increase in dosage is recommended to improve gastrointestinal tolerance. Treatment is initiated with an initial dose of 500 mg/day, which is gradually increased according to the patient's condition. However, in general, the maximum daily dose should be 2000–2550 mg [11]. Extended-release formulations may also be preferred according to the patient's condition to reduce gastrointestinal side effects [22].

5.2 Response to treatment and follow-up

The effects and response observed in patients as a result of metformin use should be monitored. Studies have shown that the maximum effect of metformin use occurs within 2–4 months, reducing the average HbA1c by 1–1.5%. The benefits on the cardiovascular system have also been clearly observed [20]. For patients using metformin: It is recommended that HbA1c levels be measured every 3–6 months, eGFR levels be measured at least once a year, and B12 vitamin levels be checked at least once a year after 5 years of use.

5.3 Uses other than diabetes treatment

5.3.1 Polycystic ovary syndrome (PCOS)

Metformin is the most commonly used pharmaceutical agent in the treatment of PCOS, which is characterized by hyperandrogenism, ovulatory dysfunction, and polycystic ovary morphology [37]. Its effects generally include: reducing insulin resistance, lowering serum insulin levels, regulating menstrual cycles, improving ovulation, and bringing the LH/FSH ratio to an acceptable level [38]. It has also been reported to reduce the number of acne lesions associated with hyperandrogenism. Randomized controlled trials have observed an increase in pregnancy rates when used in combination with ovulation induction agents such as clomiphene [39]. The treatment plan involves a daily dose of 1000–2000 mg, which can be gradually increased.

5.3.2 Metformin in obesity

Obesity may also be observed in patients with diabetes. Metformin use may prevent weight gain in patients and may even result in slight weight loss [40]. However, it has been observed that it may cause weight loss even at low doses in obese individuals without diabetes. The mechanism of action involves reducing appetite through its effect on hypothalamic AMPK pathways, breaking insulin resistance, positive changes in gut hormones such as GLP-1, and improvement in gut microbiota

profile [6]. Clinical observations have shown that it reduces the development of type 2 diabetes in prediabetic individuals by up to 30% (Diabetes Prevention Program Research Group, 2002) and causes an average weight loss of 2–5 kilograms in patients who use it [41].

5.3.3 Use in cancer prevention and treatment support

Studies on the effects of metformin, which is frequently mentioned, on cancer biology have increased significantly in recent years. Epidemiological data have shown that metformin use is associated with lower incidence and mortality rates in certain types of cancer [29, 42]. The proposed mechanisms are:

1. Reducing inflammation in the tumor microenvironment,
2. Decreasing proliferative signals through reduced insulin/IGF-1 levels,
3. Inhibiting mTOR through AMPK activation,
4. Inhibiting cell-based proliferation [26].

The types of cancer frequently studied are: Breast, colon, pancreatic, and prostate cancer. Although there is no fully established clinical treatment protocol, research on this topic is ongoing.

5.3.4 Neuropathic pain and neurological diseases

In addition to vitamin B12 deficiency observed as a result of long-term metformin use, experimental studies have also observed the neuroprotective effects of metformin [24]. The mechanism of action generally involves: reducing oxidative stress, suppressing inflammation through AMPK activation, and improving neuronal mitochondrial function [26, 27]. In experimental studies: potential protection in Parkinson's disease and reduction of hyperalgesia in neuropathic pain models. However, it is not yet fully recommended for clinical use.

5.3.5 Cardiovascular protective use

Studies have shown that it reduces myocardial infarction by 39% due to its positive effects on improving glycemic control, improving endothelial function, anti-inflammatory and antithrombotic effects [25], and lipid profile [20].

5.4 Future treatment strategies

Future treatment options include response prediction based on gene polymorphisms such as OCT1, MATE1, and ATM [43–45], personalized treatment algorithms, improvements in the microbiome due to beneficial bacteria such as *Akkermansia muciniphila*, and combined probiotic treatments. New formulation forms being developed include: extended-release formulations that are better tolerated, or dose combinations created with GLP-1 agonists and SGLT2 inhibitors.

6. Metformin usage rates by year

6.1 Introduction: Global significance

Due to its low cost, effectiveness, and safety, it is the most commonly prescribed oral antihyperglycemic drug worldwide [46]. It has been included in the World Health Organization's List of Essential Medicines [47].

6.2 Historical growth and initial approvals

It first entered the market in France [11]. With its approval by the FDA in the USA in 1995, the volume of prescriptions increased significantly over time. The rates by year are as follows: In 1995, following its approval, the number of prescriptions in the USA was less than 1 million. By the early 2000s, this figure had risen to 30 million [43]. By the 2010s, the figure in the United States had reached 80–90 million boxes [48]. These increases were not solely related to diabetes; combined treatment methods also significantly increased its use [49].

6.3 Current usage statistics

6.3.1 United States

According to the National Ambulatory Medical Care Survey (NAMCS) and CDC data, approximately 70% of adults with type 2 diabetes in the United States were using metformin in 2015 [50]. By 2021, prescription data indicated that this rate had risen to approximately 85 million [49]. The data indicate that it is the most commonly covered antidiabetic agent, primarily due to its cost-effectiveness [48].

6.3.2 Europe

According to 2021 NHS data, approximately more than 80% of patients with type 2 diabetes in the UK use metformin [51]. This rate indicates that more than 4 million metformin prescriptions have been issued [51]. In Germany, metformin was prescribed to 88% of type 2 diabetes patients in 2013, while this figure rose to 89.4% in 2023 [52]. One reason for these rates may be that National Health Authorities and the European Association for the Study of Diabetes (EASD) recommend it as the first line of treatment in diagnosed cases.

6.3.3 Asia-Pacific

Diabetes is increasing significantly, particularly in Asia. China and India have the largest diabetic populations. In China, the usage rate of metformin, which is the first-line treatment of choice, is approximately 85% [53]. In India, this rate exceeded 60 million in 2019 [54]. Due to its low cost and availability of local generics, it is the most commonly prescribed oral antidiabetic agent. When examining South Korea and Japan, this reality remains unchanged, with metformin being the preferred first-line treatment method [55]. In India, this rate exceeded 60 million in 2019 (**Figure 3**) [54].

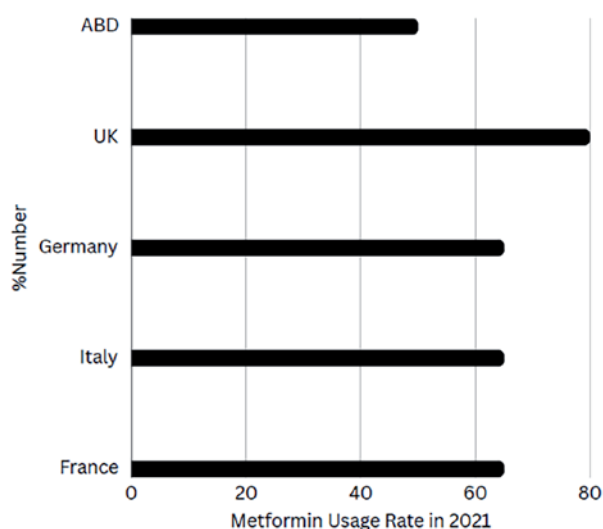


Figure 3.
Metformin usage rate in 2021.

6.4 Reasons for increased use

The factors contributing to the increase in use are as follows:

1. Neutral or reduced effect on weight,
2. Protective effect on the cardiovascular system,
3. Low cost and multiple generic examples,
4. Being considered a first-line treatment method by strong health authorities,
5. Creating a low risk of hypoglycemia,
6. Having strong evidence-based foundations [20],
7. The serious increase in the number of diabetic patients globally can be cited as reasons.

At the same time, estimates and calculations show that there are approximately over 500 million adult diabetic patients worldwide [56].

6.5 Health economics and accessibility

Metformin is increasingly being prescribed due to its various generic formulations, low cost, and combination formulations. It is even included in the reimbursement programs of developing countries such as India (Jan Aushadhi program). Such factors have been observed to reduce costs and alleviate the economic burden on the health-care system due to the presence of metformin in treatment plans [57].

6.6 Prediabetes and off-label uses

Studies conducted on patients with prediabetes as a result of metformin use have shown that it reduces the transition from prediabetes to diabetes by approximately 30% in the USA [58]. This leads to an increase in the number of prescriptions written for individuals with prediabetes. At the same time, it is also frequently prescribed off-label for the management of PCOS and obesity.

6.7 International diabetes federation (IDF)

Based on the data and estimates reviewed, it is estimated that there will be approximately 643 million people with diabetes worldwide by 2030 [56] and that this number will reach approximately 783 million by 2045. Given these expected rates, it is noted that the use of metformin will increase and continue to be used as a first-line treatment method. Additionally, formulations obtained through fixed-dose combinations are also supporting this trend. With the increase in pharmacogenetic testing due to OCT1, ATM, and MATE1 polymorphisms, individualized treatment methods will become more widespread, enabling direct, personalized metformin dose adjustments [45].

7. Use in treatment methods and dose calculations

7.1 General principles

Due to its advantages, such as a reduction of approximately 1–1.5% in HbA1c, neutral effect or loss in weight, protective effect on the cardiovascular system, absence of hypoglycemia risk, and low cost, it is used as a first-line treatment method in patients with type 2 diabetes [1, 2]. The primary goal is to maximize efficacy while increasing tolerability and minimizing observed side effects [11].

7.2 Pharmacokinetic and pharmacodynamic properties

When administered orally, the bioavailability rate is approximately 50–60%. Absorption may vary in the small intestine depending on the dose. Distribution is characterized by low plasma protein binding, and the drug is excreted unchanged by the kidneys. The half-life is 4–6 hours in the normal form and approximately 8–12 hours in the extended-release form [22].

7.3 Initial and maintenance doses

7.3.1 Standard release (IR form)

Standard-release medications are typically started at 500 mg/day, preferably with dinner. Gradual dose increases are made at a rate of 500 mg per week or 500 mg every 2 weeks. The target maintenance dose is 1500–2000 mg/day. In highly sensitive patients, this rate can be reduced to 250 mg/day. The most common dosing regimens are 500 mg twice daily or 850 mg twice daily, with a maximum daily dose of 2550 mg/day. It is recommended that the maximum dose be divided into three doses.

7.3.2 Extended release (XR/ER form)

In extended-release formulations, the initial treatment dose is generally 500 mg/day taken with dinner. The dose is then increased to 500 mg weekly or 500 mg every 2 weeks, and the maintenance dose is adjusted to 1500–2000 mg/day. The maximum dosage is 2000–2500 mg/day. The use of extended-release formulations results in better gastrointestinal tolerance and higher patient compliance.

7.4 Renal function and dosage adjustment

In patients with renal failure due to lactic acidosis, metformin should be used with caution and monitored closely in critically ill patients. If $\text{eGFR} \geq 60$, no restrictions are necessary and treatment may be continued. If the eGFR value is between 45 and 59, treatment may be initiated or continued if already underway, but annual creatinine monitoring is required. If the eGFR value is between 30 and 44, it is not recommended for new patients, but if treatment is being administered, the current treatment should be less than 1000 mg/day, and creatinine monitoring should be performed every 3–6 months. If the eGFR is <30 , it is contraindicated and its use is definitely not recommended [1].

7.5 Recommended use in special patient categories

7.5.1 Elderly patients

Considering the risks of malnutrition and dehydration, low starting doses are recommended. Generally, the dose is 250–500 mg/day, and the patient's eGFR value should be closely monitored.

7.5.2 Recommended use in children and adolescents

FDA approval is for ages 10 and older, with a general dosage of 500×2 mg/day. It is recommended to start with an initial dose of 500 mg/day, with a maintenance dosage range of 1000–2000 mg/day.

7.5.3 Pregnancy

Metformin is classified as FDA category B during pregnancy, and its use is not recommended in gestational diabetes. Instead, insulin is recommended as the first choice for the treatment of gestational diabetes. It has also been observed to reduce the risk of spontaneous abortion in the first trimester of pregnant women with PCOS.

7.5.4 Polycystic ovary syndrome (PCOS)

An initial dose of 500 mg/day is recommended to induce ovulation and reduce insulin resistance. A maintenance dose of 1000–2000 mg/day is recommended after gradual increases. Combination use with pharmacological agents such as clomiphene citrate is also possible, but there is no indication information available on this subject [38].

7.5.5 Obesity

It is prescribed off-label for increasing insulin sensitivity and suppressing appetite. Observations have shown that a weight loss of 2–5 kg has been observed when used at a dose of 1500–2000 mg/day.

7.5.6 Liver disease

It is contraindicated in patients with active progressive liver disease and should be used with caution in patients with mild to moderate liver disease who are stable.

7.6 Dosage adjustment in combination therapies

The dosage of metformin used in combination with DPP-4, SGLT-2 inhibitors, and GLP-1 agonists is generally 500–1000 mg per tablet, and a combined dosage of 1000–2000 mg/day is recommended.

7.7 Pharmacogenetic approaches and the future

Different polymorphisms alter the effects of metformin. For example, OCT1 polymorphisms cause differences in absorption and hepatic uptake. ATM can alter the HbA1c response. MATE1/2 can cause differences in renal elimination [44, 59].

8. Some herbal drugs used in the treatment of type 2 diabetes

8.1 *Gymnema sylvestre*

Gymnema sylvestre, known by its Hindi name Gurmar, is a woody climber belonging to the Asclepiadaceae family. The family to which it belongs is commonly referred to as “milkweed” [60]. This plant, whose history in diabetes treatment dates back 2000 years, exhibits this effect primarily due to the high concentration of gymnemic acid in its leaves. Its effects include anti-inflammatory, hypoglycemic, and antidiabetic properties. It is claimed to have properties such as reducing/inhibiting glucose reabsorption from the intestines, increasing insulin secretion in the body, and improving peripheral glucose uptake [61]. In an animal experiment using a high-fat diet and streptozotocin, animal groups were administered gymnemic acid (600 mg/day) and metformin (200 mg/day) separately, and a group was administered a dual combination (200 mg/day metformin + 600 mg/day gymnemic acid). After 28 days, the greatest decrease in HbA1c levels was observed in the group that received only metformin (200 mg/day). A decrease was also observed in the group receiving the combination therapy (200 mg/day metformin + 600 mg/day gymnemic acid), while the smallest decrease was observed in the group receiving only gymnemic acid (600 mg/day). The study concluded that gymnemic acid does not have a synergistic effect on metformin but may provide additional benefits [62].

8.2 *Berberis vulgaris*

The main component is berberine, an isoquinoline alkaloid [63, 64]. Berberine is solid, yellow in color, and has a bitter taste. It is insoluble in water [65]. It has been

used for many years in traditional Chinese medicine to treat diabetes. It is believed to have antiviral, antihypertensive, hypolipidemic, antibacterial, and anti-inflammatory effects (same as the reference above). In a study, 36 individuals with type 2 diabetes were administered 0.5 grams of metformin and berberine separately three times daily. Additionally, a combined dose of 0.3 grams of berberine plus 0.5 grams of metformin was administered. No significant difference was observed in the effects on HbA1c levels between the separate administrations, and no antagonistic effects were observed with combined use [65].

8.3 *Trigonella foenum-graecum* L.

Fenugreek, which is mainly used for its leaves and seeds, is a plant belonging to the Fabaceae (legume) family [66]. The soluble fiber galactomannan found in its seeds has a slowing effect on the passage and absorption of carbohydrates in the gastrointestinal system. Additionally, it contains 4-hydroxyisoleucine and diogenin in its seeds, and it is argued that these active compounds may exhibit antidiabetic properties [67]. Its effect on diabetes can be described as stimulating insulin release from β cells, increasing insulin sensitivity, and selectively reducing glucose absorption [68]. Thirty randomly selected individuals with type 2 diabetes were divided into two different groups. The first group was given only 500 mg of metformin twice daily. The second group was given 500 mg of metformin twice daily and 1 gram of fenugreek powder three times daily. After 12 weeks of treatment, the change in HbA1c levels was more significant in the second group, where combined use was involved [69].

9. Conclusion

Metformin, which is more commonly associated with type 2 diabetes, is a pharmacological agent that is frequently used in monotherapy and combination therapies [3]. Due to its economic affordability, reliable sources, and easy availability, it is becoming increasingly effective [48]. Metformin, which is used at various doses, can also cause various side effects such as kidney failure and lactic acidosis if not used with caution [9]. Due to the observed vitamin B12 deficiency with long-term use, it should be measured at least once for patients, especially after the fifth year [24]. Metformin, which is frequently prescribed in obesity and PCOS treatments, is also the subject of serious studies on cancer biology and anti-aging effects [8, 40]. However, the synergistic and antagonistic effects of some commonly used herbal drugs on metformin have been thoroughly investigated, and studies have not shown that fenugreek and gymnemic acid provide additional benefits to metformin, nor that berberine has an antagonistic effect [62, 65, 69]. Additionally, combined use with DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 agonists is also being considered [70]. This molecule, supported by various international guidelines, will continue to maintain its place in the healthcare sector with the appropriate dosage forms and necessary follow-ups, and it is anticipated that it will be prescribed in the future for various cancer diseases and to slow down aging [7, 22, 29].

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Additional notes

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References

- [1] American Diabetes Association. Standards of medical care in diabetes. *Diabetes Care*. 2024;**47**(Supplement 1):S1-S350. DOI: 10.2337/dc24-S001
- [2] Joseph JJ, Deedwania P, Acharya T, Aguilar D, Bhatt DL, Chyun DA, et al. Comprehensive management of cardiovascular risk factors in adults with type 2 diabetes: A scientific statement from the American Heart Association. *Circulation*. 2022;**145**(9):e722-e759. DOI: 10.1161/CIR.0000000000001040
- [3] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in type 2 diabetes: A patient-Centered approach. Update to the position statement of the American Diabetes Association and the European Association for the Study of diabetes. *Diabetes Care*. 2015;**38**(1):140-149. DOI: 10.2337/dc14-2441
- [4] Rena G, Hardie DG, Pearson ER. Mechanisms of action of metformin. *Diabetologia*. 2017;**60**(9):1577-1585. DOI: 10.1007/s00125-017-4342-z
- [5] Prattichizzo F, Giuliani A, Mensà E, Sabbatinelli J, De Nigris V, Rippo MR, et al. The pleiotropic effects of metformin: Shaping the microbiome to manage type 2 diabetes and prevent aging. *Reviews in Aging Research*. 2018;**48**:87-98. DOI: 10.1016/j.arr.2018.10.003
- [6] Wu H, Esteve E, Tremaroli V, Khan MT, Caesar R, Mannerås-Holm L, et al. Metformin contributes to the therapeutic effects of the drug by altering the gut microbiome of untreated type 2 diabetic individuals. *Nature Medicine*. 2017;**23**(7):850-858. DOI: 10.1038/nm.4345
- [7] Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA. Metformin as a tool targeting aging. *Cell Metabolism*. 2016;**23**(6):1060-1065. DOI: 10.1016/j.cmet.2016.05.011
- [8] Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: A systematic review and meta-analysis. *BMJ*. 2003;**327**(7421):951-953. DOI: 10.1136/bmj.327.7421.951
- [9] Salpeter SR, Greyber E, Pasternak GA, Salpeter EE. Risk of fatal and non-fatal lactic acidosis with metformin use in type 2 diabetes mellitus: A systematic review and meta-analysis. *Archives of Internal Medicine*. 2010;**170**(10):831-839. DOI: 10.1001/archinternmed.2010.109
- [10] Tuersun A et al. Combination therapy with SGLT-2 inhibitors and GLP-1 receptor agonists effectively reduces HbA1c, APG, and SBP without increasing the risk of hypoglycemia. *Diabetes Treatment*. 2024. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S000296292401348X>
- [11] Bailey CJ, Turner RC. Metformin. *New England Journal of Medicine*. 1996;**334**(9):574-579. DOI: 10.1007/s00125-017-4318-z
- [12] Garber AJ, Handelsman Y, Grunberger G, Einhorn D, Abrahamson MJ, Barzilay JI, et al. Joint statement of the American Association of Clinical Endocrinologists and the American College of Endocrinology on a comprehensive type 2. *Diabetes Management Algorithm*. 2019;**25**(1):69-100. DOI: 10.4158/CS-2018-0535
- [13] Bailey CJ, Day C. Metformin: Botanical background. *Practical Diabetes*

International. 2004;**21**(3):115-117.
DOI: 10.1002/pdi.615

[14] Marongiu F, Cauli C, Mariotti S. Tiroid, hemostaz ve tromboz. Journal of Endocrinological Investigation. 2004;**27**:1065-1071. DOI: 10.1007/BF03345311

[15] Bailey CJ. Metformin: A historical overview. Diabetologia. 2017;**60**(9):1566-1576. DOI: 10.1007/s00125-017-4318-z

[16] Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of Hyperglycemia in type 2 diabetes: A patient-Centered approach: An update to the ADA and EASD position statement. Diabetes Care. 2015;**38**(1):140-149. DOI: 10.2337/dc14-2441

[17] Scheen AJ. Clinical pharmacokinetics of metformin. Clinical Pharmacokinetics. 1996;**30**(5):359-371. DOI: 10.2165/00003088-199630050-00003

[18] Graham GG, Punt J, Arora M, et al. Clinical pharmacokinetics of metformin. Clinical Pharmacokinetics. 2011;**50**:81-98. DOI: 10.2165/11534750-000000000-00000

[19] Downes NL, Laham-Karam N, Kaikkonen MU, Ylä-Herttuala S. Differential but complementary HIF1 α and HIF2 α transcriptional regulation. Molecular Therapy. 2018;**26**(7):1735-1745. DOI: 10.1016/j.ymthe.2018.05.004

[20] Jeong I-K, Yoon KH, Lee MK. Diabetes and COVID-19: Global and regional perspectives. Diabetes Research and Clinical Applications. 2020;**16**:108303. DOI: 10.1016/j.diabres.2020.108303

[21] FDA Drug Safety Update. The FDA is Updating its Warnings Regarding the Use of the Diabetes Drug Metformin in some

Patients with Reduced Kidney Function. U.S. Food and Drug Administration; 2016. Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-revises-warnings-regarding-use-diabetes-medicine-metformin-certain>

[22] Silverii GA. Optimizing metformin therapy in practice: Tailoring therapy in specific patient groups to improve tolerability, efficacy and outcomes. Diabetes, Obesity and Metabolism. 2024;**26**(Suppl. 3):42-54. DOI: 10.1111/dom.15749

[23] Rossetti P, Ampudia-Blasco FJ, Ascaso JF. Old and new basal insulin formulations: Understanding pharmacodynamics is still relevant in clinical practice. Diabetes, Obesity and Metabolism. 2014;**16**(8):695-706. DOI: 10.1111/dom.12256

[24] de Jager J, Kooy A, Leheret P, Wulffelé M, van der Kolk J, Bets D, et al. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: Randomized placebo controlled trial. BMJ. 2010;**340**:c2181. DOI: 10.1136/bmj.c2181

[25] Foretz M, Guigas B, Viollet B. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. Nature Reviews. Endocrinology. 2019;**15**:569-589. DOI: 10.1038/s41574-019-0242-2

[26] Viollet B, Guigas B, Garcia NS, Leclerc J, Foretz M, Andreelli F. The cellular and molecular mechanisms of metformin: An overview. 2012;**122**(6):253-270. DOI: 10.1042/CS20110386

[27] Feng X, Chen W, Ni X, Little PJ, Xu S, Tang L, et al. Metformin, macrophage dysfunction and atherosclerosis. Frontiers in Immunology.

2021;12:682853. DOI: 10.3389/fimmu.2021.682853

[28] Zhu X et al. Metformin-enriched Akkermansia muciniphila in the gut modulates host inflammation-related pathways and improves cognitive function by reducing the proinflammatory cytokine IL-6 in aged mice. *Microbiome*. 2023;11(1):1-16. DOI: 10.1186/s40168-023-01567-1

[29] Pollak M. The insulin and insulin-like growth factor receptor family in neoplasia: An update. *Nature Reviews. Cancer*. 2012;12(3):159-169. DOI: 10.1038/nrc3215

[30] Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of diabetes (EASD). *Diabetes Care*. 2022;45(11):2753-2786. DOI: 10.2337/dci22-0034

[31] Wulffelé MG, Kooy A, Lehert P, Bets D, Ogterop JC, van der Burg BB, et al. Combination of insulin and metformin in the treatment of type 2 diabetes. *Diabetes Care*. 2002;25(12):2133-2140. DOI: 10.2337/diacare.25.12.2133

[32] United Kingdom Prospective Diabetes Study (UKPDS) Group. Intensive Blood Glucose Control with Sulfonylureas or Insulin Versus Conventional Therapy and the Risk of Complications in Patients with Type 2 Diabetes (UKPDS 33)1998. DOI: 10.1016/S0140-6736(98)07019-6

[33] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *New England Journal of Medicine*.

2015;373(22):2117-2128. DOI: 10.1056/NEJMoa1504720

[34] Neuen BL, Young T, Heerspink HJL, Neal B, Perkovic V, Billot L, et al. SGLT2 inhibitors for the prevention of kidney failure in patients with type 2 diabetes: A systematic review and meta-analysis. *The Lancet Diabetes and Endocrinology*. 2019;7(11). DOI: 10.1016/S2213-8587(19)30256-6

[35] Rao AD, Kuhadiya N, Reynolds K, Fonseca VA. Is the combination of sulfonylureas and metformin associated with an increased risk of cardiovascular disease or all-cause mortality?: A meta-analysis of observational studies. *Diabetes Care*. 2008;31(8):1672-1678. DOI: 10.2337/dc08-0167

[36] Nauck M, Frid A, Hermansen K, Thomsen AB, Düring M, Shah N, et al. Long-term efficacy and safety comparison of liraglutide, glimepiride and placebo, all in combination with metformin in type 2 diabetes: 2-year results from the LEAD-2 study. *Diabetes, Obesity and Metabolism*. 2013;15(3):204-212. DOI: 10.1111/dom.12012

[37] Teede HJ, Misso ML, Costello MF, Dokras A, Laven J, Moran L, et al. International PCOS network, recommendations from the international evidence-based guideline for the assessment and management of polycystic ovary syndrome. *Human Reproduction*. 2018;33(9):1602-1618. DOI: 10.1093/humrep/dey256

[38] Legro RS, Barnhart HX, Schlaff WD, Carr BR, Diamond MP, Carson SA, et al. Cooperative Multicenter reproductive medicine network. Clomiphene, metformin, or both for infertility in the polycystic ovary syndrome. *The New England Journal of Medicine*. 2007;356(6):551-566. DOI: 10.1056/NEJMoa063971

- [39] Palomba S, Falbo A, Orio F, Russo T, Tolino A, Sarno M, et al. Clomiphene citrate and metformin as treatments for infertility in polycystic ovary syndrome. *Fertility and Sterility*. 2009;**92**(5):1766-1774. DOI: 10.1016/j.fertnstert.2008.09.032
- [40] Sánchez-Guerrero J, Liang MH, Karlson EW, Hunter DJ, Colditz GA. Postmenopausal estrogen therapy and the risk for developing systemic lupus erythematosus. *Annals of Internal Medicine*. 1995;**122**(6):430-433. DOI: 10.7326/0003-4819-122-6-199503150-00005
- [41] Bray GA, Frühbeck G, Ryan DH, Wilding JP. Management of obesity. *Lancet*. 2016;**387**(10031):1947-1956. DOI: 10.1016/S0140-6736(16)00271-3
- [42] Angus L, Beije N, Jager A, Martens JWM, Sleijfer S. ESR1 mutations: Moving towards guiding treatment decision-making in metastatic breast cancer patients. *Cancer Treatment Reviews*. 2017;**52**:33-40. DOI: 10.1016/j.ctrv.2016.11.001
- [43] Shu Y, Sheardown SA, Brown C, Owen RP, Zhang S, Castro RA, et al. Effect of genetic variation in the organic cation transporter 1 (OCT1) on metformin pharmacokinetics. *Clinical Pharmacology & Therapeutics*. 2007;**81**(3):303-310. DOI: 10.1038/sj.clpt.6100209
- [44] Zhou K, Donnelly LA, Kimber CH, Donnan PT, Doney AS, Leese G, et al. Reduced-function SLC22A1 polymorphisms encoding organic cation transporter 1 and glycemic response to metformin: A GoDARTS study. *Diabetes*. 2009;**58**(6):1434-1439. DOI: 10.2337/db08-0896
- [45] Chen P, Cao Y, Chen S, Liu Z, Chen S, Guo Y. Association of SLC22A1, SLC22A2, SLC47A1, and SLC47A2 polymorphisms with metformin efficacy in type 2 diabetic patients. *Biomedicine*. 2022;**10**(10):2546. DOI: 10.3390/biomedicines10102546
- [46] Scarpello JH, Howlett HC. Metformin therapy and clinical uses. *Diabetic Medicine*. 2008;**25**(5):460-467. DOI: 10.1111/j.1464-5491.2008.02427.x
- [47] Rojas LBA, Gomes MB. Metformin: Tip 2 diyabet için eski ama hala en iyi tedavi2013. DOI: 10.1186/1758-5996-5-6
- [48] Syafhan NF, Donnelly R, Harper R, Harding J, Mulligan C, Hogg A, et al. Adherence to metformin in adults with type 2 diabetes: A combined method approach. *Journal of Pharmaceutical Policy and Practice*. 2022;**15**(1):61. DOI: 10.1186/s40545-022-00457-5
- [49] Kitten AK, Kamath M, Ryan L, Reveles KR. Trends in national outpatient non-insulin antidiabetic drug prescribing in the United States, 2009-2015. *PLoS One*. 2019;**14**(8):e0221174. DOI: 10.1371/journal.pone.0221174
- [50] Corcoran C, Jacobs TF. Metformin. 2025. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK518983/>
- [51] Tang Y, Weiss T, Liu J, Rajpathak S, Khunti K. Metformin adherence and discontinuation among patients with type 2 diabetes: A retrospective cohort study. *Journal of Clinical & Translational Endocrinology*. 2020;**20**(100):225. DOI: 10.1016/j.jcte.2020.100225
- [52] Robert Koch-Institut. DMP-Qualitätszielerreichung Typ-2-Diabetes –Erwachsene (Ergebnisse der Diabetes-Surveillance 2015-2024)2024. DOI: 10.25646/12297
- [53] Cai XL, Shen J, Ye BQ, Li Q, Clark DAS, Ji LN. Characteristics,

treatment patterns, and glycemic control of older type 2 diabetes mellitus patients in China. *Chinese Medical Journal*. 2021;**134**(23):2893-2895. DOI: 10.1097/CM9.0000000000001674

[54] Agarwal AA, Jadhav PR, Deshmukh YA. Prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients. *Journal of Basic and Clinical Pharmacy*. 2014;**5**(3):79-83. DOI: 10.4103/0976-0105.139731

[55] Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type 2 diabetes and kidney disease: A systematic review. *JAMA*. 2014;**312**(24):2668-2675. DOI: 10.1001/jama.2014.15298

[56] International Diabetes Federation (IDF). *IDF Diabetes Atlas*. 10th ed. International Diabetes Federation; 2021. Available from: <https://diabetesatlas.org>

[57] Herman WH, Hoerger TJ, Brandle M, Hicks K, Sorensen S, Zhang P, et al. Diabetes prevention program research group. The cost-effectiveness of lifestyle modification or metformin in preventing type 2 diabetes in adults with impaired glucose tolerance. *Annals of Internal Medicine*. 2005;**142**(5):323-332. DOI: 10.7326/0003-4819-142-5-200503010-00007

[58] Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *New England Journal of Medicine*. 2002;**346**(6):393-403. DOI: 10.1056/NEJMoa012512

[59] Shu Y, Yu Y, Yang J, McCormick DA. Selective control of cortical axonal spikes by a slowly inactivating K⁺ current. *Proceedings of the National Academy of Sciences of the United States of America*.

2007;**104**(27):11453-11458. DOI: 10.1073/pnas.0702041104

[60] Kanetkar P, Singhal R, Kamat M. *Gymnema sylvestre*: A Memoir. *Journal of Clinical Biochemistry and Nutrition*. 2007;**41**(2):77-81. DOI: 10.3164/jcbn.2007010

[61] Mukherjee PK, Maiti K, Mukherjee K, Houghton PJ. Leads from Indian medicinal plants with hypoglycemic potentials. *Journal of Ethnopharmacology*. 2006;**106**(1):1-28. DOI: 10.1016/j.jep.2006.03.021

[62] Kodiyatar A, Rai N, Mishra A, Roy V. Evaluation of antidiabetic potential of *Gymnema Sylvestre* and metformin combination in Streptozotocin-induced diabetic rats. *Qeios*. 2025. DOI: 10.32388/FNUVKI.3

[63] Neag MA, Mocan A, Echeverría J, Pop RM, Bocsan CI, Crişan G, et al. Berberine : Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. *Frontiers in Pharmacology*. 2018;**9**:557. DOI: 10.3389/fphar.2018.00557

[64] Zhang SW, Zhou J, Gober HJ, Leung WT, Wang L. Effect and mechanism of berberine against polycystic ovary syndrome. *Biomedicine & Pharmacotherapy*. 2021;**138**:111468. DOI: 10.1016/j.biopha.2021.111468

[65] Gaba S, Saini A, Singh G, Monga V. An insight into the medicinal attributes of berberine derivatives: A review. *Bioorganic & Medicinal Chemistry*. 2021;**38**:116143. DOI: 10.1016/j.bmc.2021.116143

[66] Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. *Metabolism*. 2008;**57**(5):712-717. DOI: 10.1016/j.metabol.2008.01.013

[67] Nagulapalli, Venkata KC, Swaroop A, Bagchi D, Bishayee A. A small plant with big benefits: Fenugreek (*Trigonella foenum-graecum* Linn.) for disease prevention and health promotion. *Molecular Nutrition & Food Research*. 2017;**61**(6). DOI: 10.1002/mnfr.201600950

[68] Gong J, Fang K, Dong H, Wang D, Hu M, Lu F. Etkili Etnofarmakoloji Dergisi. 2016;**194**:260-268. DOI: 10.1016/j.jep.2016.08.003

[69] Chehregosha F, Maghsoumi-Norouzabad L, Mobasser M, Fakhr L, Tarighat-Esfanjani A. The effect of fenugreek seed dry extract supplement on glycemic indices, lipid profile, and prooxidant-antioxidant balance in patients with type 2 diabetes: A double-blind randomized clinical trial. *Journal of Cardiovascular and Thoracic Research*. 2024;**16**(3):184-193. DOI: 10.34172/jcvtr.33231

[70] Wang GY, Bellringer ME. Social connectedness and its relationship with gambling risk in New Zealand. *Journal of Clinical Medicine*. 2022;**11**(23):7123. DOI: 10.3390/jcm11237123