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Metformin: Optimal dosage, interactions, and efficacy. Exploring natural alternatives for diabetes management

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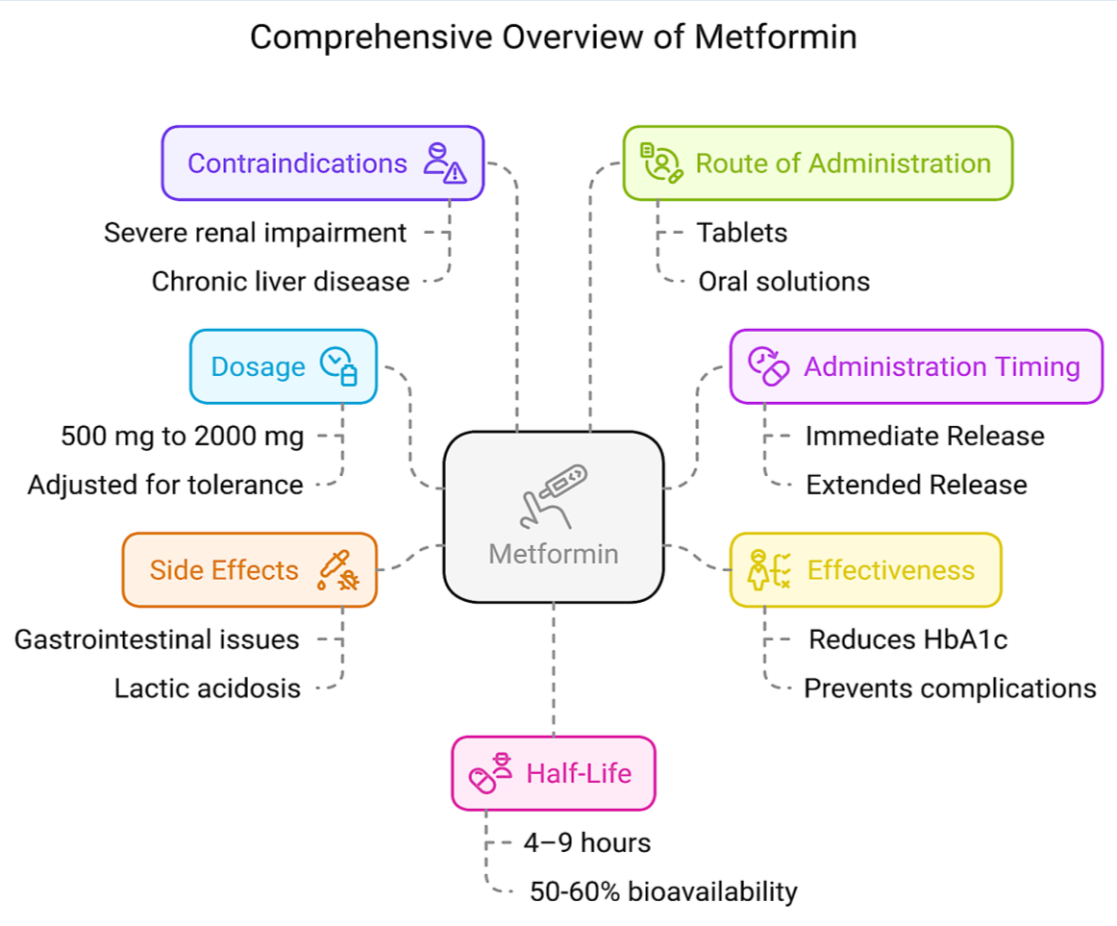
ABSTRACT

The foundation of functional food science is to improve health and wellness by validating foods that affect one's physical, behavioral, cognitive, psychological, or physiological function. Functional food science provides insight into foods that can be considered as "natural or processed foods that contain known or unknown biologically active compounds, which, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic diseases." This definition of functional foods is translatable to oral therapeutics, which can be defined as drugs taken orally that contain biochemically active compounds that combat diseases. Oral drug therapies have revolutionized modern medicine and patient health outcomes by ensuring accessible and effective treatments. Well-known drugs are established by their discrete drug usage indications based on clinical research that mimics real-world usage. These drug parameters act as a guideline for medication administration and patient education.

The Functional Food Center has introduced a novel system for validating functional foods. In a similar manner to Functional Food Center's multi-step classification of functional food, a comprehensive evaluation of oral therapeutic drugs can be formulated. When evaluating a drug, these criteria substantiate the reasonable usage and continuation of oral therapies. Metformin is one of the top ten oral drugs used in the United States. This review evaluates metformin under these guidelines and reports on its adherence or nuance to these criteria. Metformin has blood glucose-lowering properties that effectively treat chronic diseases, namely type 2 diabetes. As a first-line defense in hyperglycemic control, metformin is used to suppress hepatic gluconeogenesis, among other mechanisms of cell signaling in insulin uptake.

Focusing on the glucogenic breakdown properties of metformin, this review introduces fifteen key parameters of medicine performance and considerations for patient use.

Novelty: This review uniquely applies a functional food science framework to evaluate metformin, a widely used oral therapeutic for type 2 diabetes. By adapting the Functional Food Center's multi-step classification process, this work introduces fifteen key parameters for assessing medication performance and patient use, offering a novel perspective on optimizing oral drug therapies beyond traditional clinical research.



Graphical Abstract: Metformin: A review on optimal medication dosage, interactions, and efficacy. Exploring natural alternatives for diabetes management

INTRODUCTION

Advancements in modern medicine have created safer and more accessible treatments that can effectively combat and prevent the rise of chronic illnesses in the United States. Oral therapeutic agents were developed to ensure affordable and readily available solutions. The Food and Drug Administration (FDA) regulates the quality assurance and safety inspection of medication in the United States. Clinical research data and patient trials back oral medicines that make it to market to ensure their efficacy and proper use. When considering the practical use of medications, numerous factors tie into

patient history and livelihood. Drug adherence is a contributing factor to medication usage that directly affects health outcomes. Anti-diabetic drugs are prevalent in the pharmaceutical market due to over 10% of Americans having been diagnosed with diabetes, with over 20% of Americans having undiagnosed diabetes [1]. Commonly used anti-diabetic drugs are in the form of injectable peptide treatment that mimics the effects of the glucagon hormone [2]. Oral medications are a less well-known form of diabetes treatment, as metformin is the only oral anti-diabetic currently used in the United States. To evaluate a medication's effectiveness in facilitating patient adherence, this paper outlines the criteria for the drug metformin. Metformin is a blood glucose-lowering agent for treating individuals with type 2 diabetes [3]. The chemical structure of metformin is illustrated in Figure 1, which outlines its characteristic biguanide structure. Anti-diabetics aim to combat elevations in blood glucose levels when the body resists insulin. Insulin is a hormone secreted from the pancreas that works to lower blood sugar by enabling cell uptake of glucose [4]. Type 2 diabetics suffer from insulin inefficiency, where the body does not produce enough insulin or has become insensitive to the hormone, resulting in decreased glucose cell uptake and elevated blood sugar levels [3]. Anti-diabetic drug developments have produced an oral therapy to counter insulin resistance and address hyperglycemia in adults. Metformin enhances glycogenesis activated by insulin and reduces glucagon-enhanced gluconeogenesis [3].

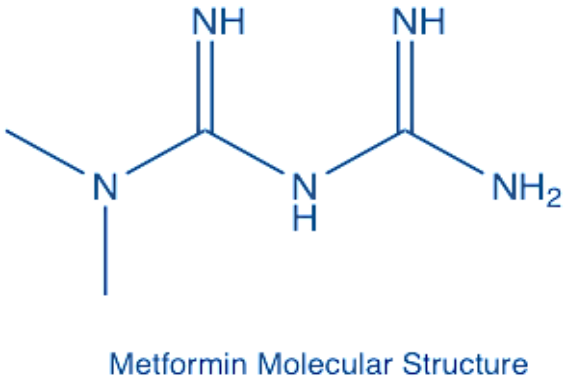


Figure 1. The molecular structure of Metformin is depicted above. The chemical name for metformin is 1,1-dimethylbiguanide hydrochloride, with the chemical formula $C_4H_{11}N_5$.

In recent years, multiple investigations have been conducted on the management of type 2 diabetes using specific functional food ingredients and bioactive compounds [5–10]. Many studies have also examined metformin, specifically in comparison to insulin-lowering food-based ingredients [11–13] and other drugs [14-15]. Additionally, there is a growing body of research focused on the insulin-lowering properties of food-derived bioactive compounds [16–17]. In this article, we focus on metformin's optimal dosage, interactions, and efficacy, while also exploring natural alternatives for diabetes management.

Research Strategy: A literature review was conducted using the PubMed, ScienceDirect, and www.FFHDJ.com databases. The search included studies on drug and plant therapeutics to understand the mechanisms of action of metformin in the context of its glucose-lowering metabolic treatment. Articles describing the metformin drug performance, efficacy, usage, indications, and mechanisms of action were included in this review paper. The included articles also pertained to plant ingredients with evidence of blood glucose-lowering capabilities. Keywords for this search: bioactive plant compounds,

squalene, amaranth oil, type 2 diabetes mellitus. Search results were limited to articles written between the years 1996 and 2025.

Characterization of Drug Performance Through Fifteen Key Parameters: Along with medication dosing and timing adherence, many vital parameters must be considered when evaluating the efficacy and safety of oral medications. These factors include but are not limited to: drug interactions and contraindications, bioavailability, absorption, tolerance, patient demographics, food interactions, and drug adherence. Below are fifteen guidelines pertinent to assessing a patient's medication efficacy.

1. Side Effects (Adverse Effects)

- Description: Unintended harmful effects caused by a drug. Side effects can range from mild (e.g., headaches, nausea) to severe (e.g., organ toxicity, allergic reactions). They may vary depending on the drug and individual patient factors. Side effects, or adverse effects, are unintended harmful consequences of drug use that can range in severity and vary depending on the specific drug and the individual patient [18]. Importance: Side effects are crucial in evaluating the drug's risk-to-benefit ratio. They influence treatment decisions and patient adherence. Researchers found that metformin modestly reduced the risk of pre-eclampsia and increased the risk of gastrointestinal side effects.

2. Contraindications

- Description: Conditions or situations in which a drug should not be used due to potential harm. This includes certain diseases (e.g., kidney failure), drug allergies, and possible interactions with other medications. Global pharmacovigilance data from the recent pandemic era highlights the ongoing relevance of understanding and adhering to contraindications as a critical measure to minimize adverse drug reactions and potential patient harm [19].
- Importance: Identifying contraindications ensures patient safety by preventing adverse reactions or worsening of pre-existing conditions.

3. Route of Administration

- Description: The method used to introduce a drug into the body (oral, intravenous, intramuscular, topical, etc.). The route determines how quickly and effectively the drug acts. Recent advancements in pharmaceutical manufacturing and drug delivery underscore the fundamental principle that the route of administration is a critical determinant of a drug's release profile and subsequent bioavailability, directly influencing how rapidly and effectively it can exert its therapeutic effects [20].
- Importance: Route of administration influences drug absorption, onset of therapeutic action, and patient compliance. For instance, intravenous administration offers rapid action, while oral drugs are more convenient but slower acting.

4. Half-Life

- Description: The time required for the concentration of the drug in the bloodstream to decrease by half. Recent literature in clinical pharmacy emphasizes that the half-life is a key pharmacokinetic parameter guiding effective and safe drug administration [21].

- Importance: The half-life determines dosing frequency and helps predict how long a drug stays effective in the body, which is vital for maintaining therapeutic levels.

5. Pharmacokinetics

- Description: Pharmacokinetics is the study of a drug's absorption, distribution, metabolism, and excretion (ADME). As highlighted in a recent update on the field, pharmacokinetics significantly influences a drug's therapeutic effectiveness and the duration of its action within the body [22].
- Importance: Pharmacokinetics helps understand how the body processes a drug, which is critical for dosing schedules and predicting interactions with other drugs.

6. Drug Interactions

- Description: How drugs interact with other drugs, foods, or supplements. Interactions can either enhance the drug's effect, reduce its effectiveness, or reduce its safety. Drug interactions with other drugs, food, or supplements can decrease effectiveness or increase safety risks [23].
- Importance: Managing drug interactions is essential for optimizing treatment and avoiding harmful consequences, especially in patients with multiple comorbidities.

7. Tolerance and Dependence

- Description: Tolerance occurs when a drug's effectiveness diminishes over time with continued use, while dependence refers to physical or psychological reliance on the drug. Tolerance and dependence are key in long-term drug therapy, especially for substances with abuse potential [24].
- Importance: Understanding tolerance and dependence helps manage long-term treatments and avoids withdrawal symptoms when discontinuing a drug.

8. Cost and Accessibility

- Description: The affordability of the drug and its availability within various healthcare systems. This also includes whether the drug is available in generic forms.
- Importance: Cost and accessibility can significantly affect patient access to treatment and influence healthcare policies, especially for chronic conditions that require long-term therapy.

9. Indications (Therapeutic Uses)

- Description: The medical conditions or diseases for which a drug is prescribed [25].
- Understanding the drug's indications ensures that it is used appropriately for the right conditions and helps clinicians make informed treatment options.
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10. Efficacy vs. Safety Profile

- Description: This refers to the balance between how effective a drug is in treating a condition (efficacy) and the risk of side effects (safety). Evaluating the balance between a drug's effectiveness and its potential for adverse events is a critical aspect of clinical pharmacology, as demonstrated in studies assessing direct oral anticoagulants [26].
- Importance: This balance is key when comparing different treatment options, particularly when they offer similar therapeutic benefits but have differing safety profiles.

11. Patient Demographics

- Description: Patient-specific factors such as age, weight, gender, genetics, and pre-existing conditions affect how a drug is metabolized, alongside its therapeutic outcomes.
- Importance: Personalizing treatment based on demographic factors can enhance the drug's effectiveness and minimize adverse reactions.
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12. Bioavailability

- Description: The proportion of the drug that reaches the bloodstream after administration is available to have a therapeutic effect [27].
- Importance: Drugs with higher bioavailability require lower doses and/or less frequent administration to achieve therapeutic effects.
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13. Therapeutic Index

- Description: The ratio between a drug's toxic and effective doses. A higher therapeutic index indicates a safer drug. The therapeutic index is a crucial measure of its safety profile [28].
- Importance: An extensive therapeutic index offers a buffer against accidental overdose, reducing the risk of harmful effects.
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14. Drug and Food Interactions

- Description: Food and other substances can significantly impact the drug's absorption, metabolism, or effectiveness, potentially leading to altered therapeutic effects or safety profiles. Some foods or beverages may enhance or inhibit a drug's action [29].
- Importance: Managing drug-food interactions is essential to ensure the drug reaches its desired therapeutic effect and prevent unwanted side effects.
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15. Adherence and Compliance

- Description: Refers to how consistently and accurately patients follow the prescribed drug regimen. Non-compliance can lead to suboptimal therapeutic outcomes. Adherence and compliance are critical for achieving optimal therapeutic outcomes [30].
- Importance: Patient adherence is a critical factor in treatment success. Understanding barriers to compliance (e.g., side effects, dosing frequency) can help healthcare providers optimize therapy.

METFORMIN: Comprehensive Analysis of Metformin (Anti-diabetic Medication) Based on 15 Key Parameters

Dosage: Metformin is typically prescribed to be taken in dosages of 500 mg to 2,000 mg per day. Newly prescribed metformin recipients start at a low dose to minimize the adverse side effects of gastrointestinal upset. Dosing is subject to change based on the individual's blood glucose levels and renal function [3]. The recommended first dose for metformin therapy is 500 mg twice daily, or 850 mg once daily [5]. Its effectiveness in reducing HbA1c is significantly greater when administered in higher doses, demonstrating its value as a first-line pharmacologic.

Figure 2 illustrates the key points in optimizing metformin dosages.

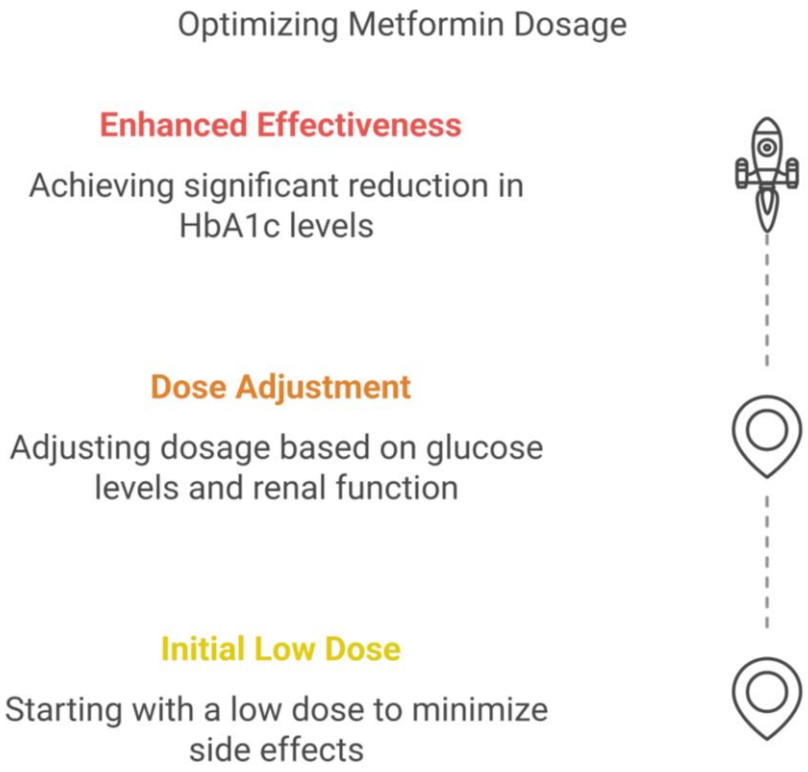

Figure 2. Key points in the establishment of Metformin dosing procedures. Optimization of Metformin dosage is outlined through reducing HbA1c levels, establishing a dosage procedure that effectively acts on lowering blood glucose and maintaining renal function to minimize negative lasting side effects.

Administration Timing: Metformin is most commonly prescribed to be taken once, twice, or thrice daily [31-35]. There are two formulations of metformin, immediate-release (IR) and extended-release (ER) [36]. The apt metformin formulation depends on the patient's blood glucose levels, medication tolerance, and whether they take other medications [3]. The onset of the full effect on blood glucose control may take several days to weeks. Dosing time management is a key component of drug efficacy, particularly applicable to the regular and extended-release formulations of metformin hydrochloride. The immediate-release form has indicated low gastrointestinal tolerability compared to doses of the extended-release form [37]. Metformin's immediate-release formulation can be prescribed once, twice, or thrice daily, and dosages can be taken at different mealtimes within the day [38]. This can be taxing for patient compliance with oral therapy and may not be suited for those with gastrointestinal intolerance. However, the immediate-release metformin can be used as a monotherapy, while the extended-release formulation is typically used in combination therapies. This expanded oral treatment prolongs drug absorption and allows for once-a-day dosing for patients with type 2 diabetes [39].

Effectiveness: Metformin is proven to reduce HbA1c and blood glucose levels significantly. Its long-term use effectively prevents diabetes complications, including cardiovascular disease [40]. Long-term use of metformin is typically associated with ER formulation, which reduces the severity of gastrointestinal discomfort or renal impairment that may occur with prolonged usage. With proven effectiveness as an anti-diabetic, studies show that Metformin can reduce the risk of cardiovascular events in type 2 diabetes patients [41]. The efficacy of metformin is derived from its mechanism of action, which changes the energy metabolism of the cell by inhibition of hepatic gluconeogenesis [42]. Metformin

works to deplete the metabolites involved in the tricarboxylic acid cycle to improve energetic systems that act on cellular metabolism. It hinders cancer cell growth by directly affecting energetic metabolism [43]. Metformin has anti-carcinogenic effects through AMP-activated protein kinase (AMPK) activation and inhibition of NADH-coenzyme Q oxidoreductase [44]. This mechanism limits the generation of reactive oxygen species, leading to hypoxic stabilization, a necessary component in reducing DNA damage [45]. Another aspect of metformin action is related to biological aging in combating age-related disorders related to lifespan. These aspects focus on the delay of stem cell aging, which helps regulate mitochondrial function and enhance intercellular communication [46]. Metformin's ability to activate the AMPK illustrates increased autophagic activity capable of restoring mitochondrial capacity and alleviating the hallmarks of cellular senescence [47]. The diversity of biochemical mechanisms that are affected through metformin therapy distinguishes its efficacy and novel treatment as an anti-diabetic and related health disorders.

Side Effects (Adverse Reactions): A common side effect experienced by patients taking metformin is gastrointestinal upset (nausea, diarrhea, abdominal pain) [48]. Metformin increases the absorption of glucose in the small intestine and the production of lactate. This also increases GLP-1 (glucagon-like peptide) and bile concentrations in the intestinal tract [49]. Kidneys are the primary organ in which metformin is absorbed and processed. Biguanide class drugs like metformin are known to increase blood plasma lactate levels by inhibiting liver mitochondrial respiration [50]. Patients with renal conditions or chronic renal failure are not recommended to take metformin due to their increased risk of lactic acidosis [51]. Severe adverse reactions include cases of lactic acidosis observed in patients who have preexisting renal or liver conditions [2]. Metformin therapy is typically used in long-term increments, taken daily for the rest of the patient's life. Vitamin B12 deficiency often results from the long-term use of metformin [52]. Figure 3 presents the side effects of metformin as observed in preclinical and clinical trials.

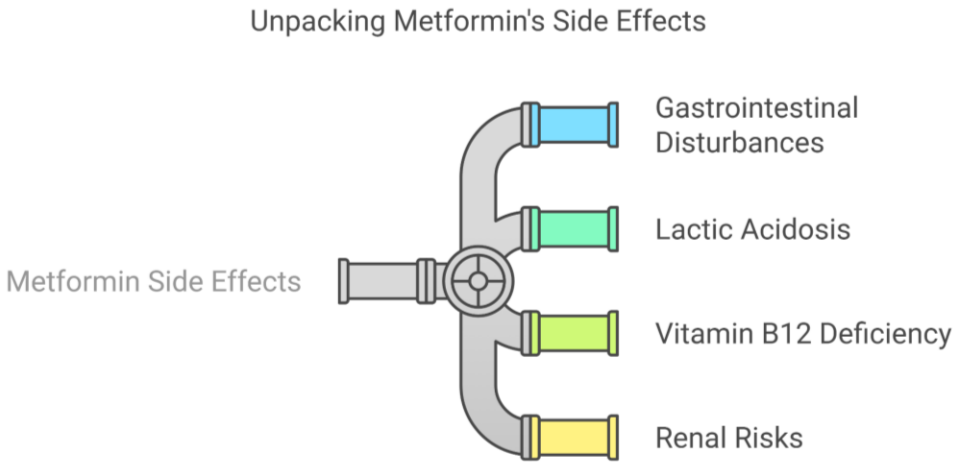

Figure 3. The main side effects experienced by metformin users, as observed in pre-clinical and clinical trials, are gastrointestinal discomfort and lactic acidosis. Some patients with prolonged usage of metformin experienced low vitamin B12 levels and mild impairment of renal function.

Contraindications: Metformin is not recommended in patients with severe renal impairment [3]. Metformin increases hepatic insulin sensitivity, increases peripheral glucose uptake and reducing basal glucose output and hepatic glucose concentrations. Since kidneys are the primary organ where metformin acts upon absorbing and

processing the medication, patients with renal conditions or chronic renal failure are not recommended to take metformin due to their increased risk of lactic acidosis. Metformin therapies for type 2 diabetic patients with chronic kidney disease showed a decline in their overall renal function, resulting in high serum LDL-C, high HbA1c, low baseline eGFR, high uric acid level, high UACR, and the use of ACEIs and/or ARBs. Patients with impaired renal and liver function may experience acute or chronic metabolic lactic acidosis as a result of continued usage [37].

In a retrospective cohort study involving patients with type 2 diabetes using metformin from January 1993 to June 1995, the risk of various contraindications was identified, including acute myocardial infarction, cardiac failure, renal impairment, and chronic liver disease. The population size was c, of whom 3.5% experienced acute myocardial infarction, 4.2% cardiac failure, 4.8% renal impairment, and 2.8% chronic liver disease. The recorded percentage of patients with contraindications taking metformin and observed contraindications was 24.5% and 6.4% of all patients with type 2 diabetes [53].

Route of Administration: Metformin is an oral tablet. It has two different formulations, the IR and the ER. Orally taken metformin solutions are also manufactured for those unable to take tablets [54].

Half-Life: The half-life for IR metformin is 4–9 hours in healthy individuals, supporting once or twice daily dosing. The extended-release form has a longer half-life that is suitable for once-daily dosing. Following oral administration, the bioavailability is reportedly 50-60%. Completion of metformin absorption is estimated at 6 hours following administration, occurring primarily in the upper intestine. Following intravenous metformin administration, most was excreted in the urine after 8 hours. In oral administrations of 500 mg metformin, half of the dose was recovered in urine, while a quarter was present in feces [55]. Table 1 presents the drug distribution of metformin, which can be characterized as a two-compartment system. Distribution through blood circulation occurs from absorption and processing in the kidneys. Complete elimination from both compartments occurs between approximately 12 and 14 hours [56].

Table 1. Metformin pharmacokinetics via intravenous administration.

N	Dose (mg)	Infusion time (min)	t1/2 plasma (h)	t1/2 urine (h)	Plasma clearance (L/h)	Renal clearance (L/h)	Reference
5	1000	<1	1.52 ± 0.13	N/A	26.5 ± 2.4	20.1 ± 2.8	[57]
3	500	5	1.74 ± 0.11	9.29 ± 0.48	27.5 ± 0.36	27.2 ± 2.8	[58]
4	250	15	4.50 ± 1.0	19.0 ± 5.0	42.4 ± 0.96	32.6 ± 1.8	[59]
N = sample size t1/2 = terminal elimination half-life N/A = not available							

Metformin half-life after single-dose intravenous administration in healthy volunteers (means ± SEM)

Pharmacokinetics: Metformin acts on the body through absorption in the small intestine, where its maximal plasma concentration is reached 2-3 hours following administration. Metformin is not metabolized in the liver; instead, it leaves the body unchanged by the kidneys through excretion [60].

Table 2 presents metformin absorption and elimination during multiple-dosing regimens in healthy subjects (HS) or patients with type 2 diabetes mellitus (DM) with good renal function [60].

Table 2. Immediate-Release Metformin Pharmacokinetic Variation

Immediate release metformin pharmacokinetic variation						
Dosage (mg)	**n**	**Cav, ss (mg/L)**	**CL/F (mL/min)**	**Vd/F (L)**	**t1/2 (h)**	**Reference**
HS, 250 mg bid	24	0.35 ± 0.06	780 ± 139	N/A	N/A	[61]
DM, 850 mg tid	9	1.35 ± 0.50	1118 ± 325	1952 ± 1519	19.8 ± 15.9	[62]
HS, 850 mg tid	9	1.34 ± 0.35	1130 ± 457	1211 ± 690	13.0 ± 7.8	[62]
DM, 1000 mg bid	13	1.23 ± 0.30	881 ± 215	N/A	N/A	[63]
values are expressed as mean ± standard deviation						
Vd/F (L) and t1/2 (h) are determined through terminal log-linear phase elimination following treatment termination; these pharmacokinetic parameters do not represent a dosage interval.						
qd = once daily, **bid** = twice daily, **tid** = thrice daily, **Cav,ss** = average plasma concentration steady state over dosage interval, **CL/F** = total clearance after oral administration, **t1/2** = elimination half-life, **Vd/F** = volume of distribution after oral administration, **N/A** = not available,						

Table 3 presents metformin absorption and elimination during single-dosing regimens in healthy subjects (HS) or patients with type 2 diabetes mellitus (DM) with good renal function [60].

Table 3. Extended-Release Metformin Pharmacokinetic Variation

Extended-release metformin pharmacokinetic Variation						
Dosage (mg)	**n**	**Cav,ss (mg/L)**	**CL/F (mL/min)**	**Vd/F (L)**	**t1/2 (h)**	**Reference**
HS, 500 qd	16	0.26 ± 0.08	1029 ± 325	463 ± 204	5.2 ± 1.6	[64]
HS, 1000 mg qd	16	0.52 ± 0.13	1033 ± 260	402 ± 123	4.5 ± 0.8	[128]
HS, 1500 mg qd	15	0.70 ± 0.17	1159 ± 287	481 ± 129	4.8 ± 0.5	[65]
HS, 2000 mg qd	14	0.85 ± 0.17	1271 ± 256	572 ± 175	5.2 ± 1.2	[65]
values are expressed as mean ± standard deviation						
Vd/F (L) and t1/2 (h) are determined through terminal log-linear phase elimination following treatment termination; these pharmacokinetic parameters do not represent a dosage interval						
qd = once daily, bid = twice daily, tid = thrice daily, Cav,ss = average plasma concentration steady state over dosage interval, CL/F = total clearance after oral administration, t1/2 = elimination half-life, Vd/F = volume of distribution after oral administration, N/A = not available						

Tables 2 and 3 depict a pharmacokinetic comparative analysis between the immediate-release and extended-release metformin dosage forms. The overall blood plasma concentrations of metformin indicate no significant accumulation in varying dosage amounts and frequencies. The average concentration per dosage interval (Cav, ss) describes the time course of metformin in the patient's plasma concentration [66]. In subjects with good renal function (HS), the average half-life is 5 hours. Patients with slightly impaired renal function (DM) show a similar half-life time for the extended-release form [67]. A comparison between the absorption of metformin in the immediate-release versus extended-release formulation shows that metformin plasma concentrations are, on average, lower but sustained longer in the extended-release tablet. The CL/F values increased, slightly increasing metformin's daily dosing (QD) [68].

Drug Interactions: Monitoring potential drug interactions is integral to medication review. Understanding the various biochemical outcomes when using metformin in combination therapies is crucial to proper dosage and timing. H_2 inhibitors like cimetidine may increase plasma concentrations of metformin. [48]. Cimetidine decreases the renal clearance of metformin

by inhibiting renal tubular cation transport [69]. The intracellular accumulation of cimetidine after administration to the basal compartment was considerably higher in MDCK-OCT2 cells than in all other cells. The presence of MATE1 in the apical membrane caused a pronounced translocation of cimetidine in both single- and double-transfected cells. Transcellular, basal-to-apical metformin net transport was reduced by 89.1, 74.5, and 91.0% in MDCK-OCT2-MATE1 cells after the addition of cimetidine (100 µM) to the basal, the apical, or both compartments [69]. Severe side effects regarding metformin usage are lactic acidosis, which is an increased risk when the patient is also taking diuretics or steroids [41]. Alcohol consumption also increases the risk of lactic acidosis [2]. Drugs that directly affect renal function or cause insulin sensitivity should not be used in combination therapy with metformin [3].

Figure 4 presents the significant factors regarding metformin use: drug interactions and contraindications.

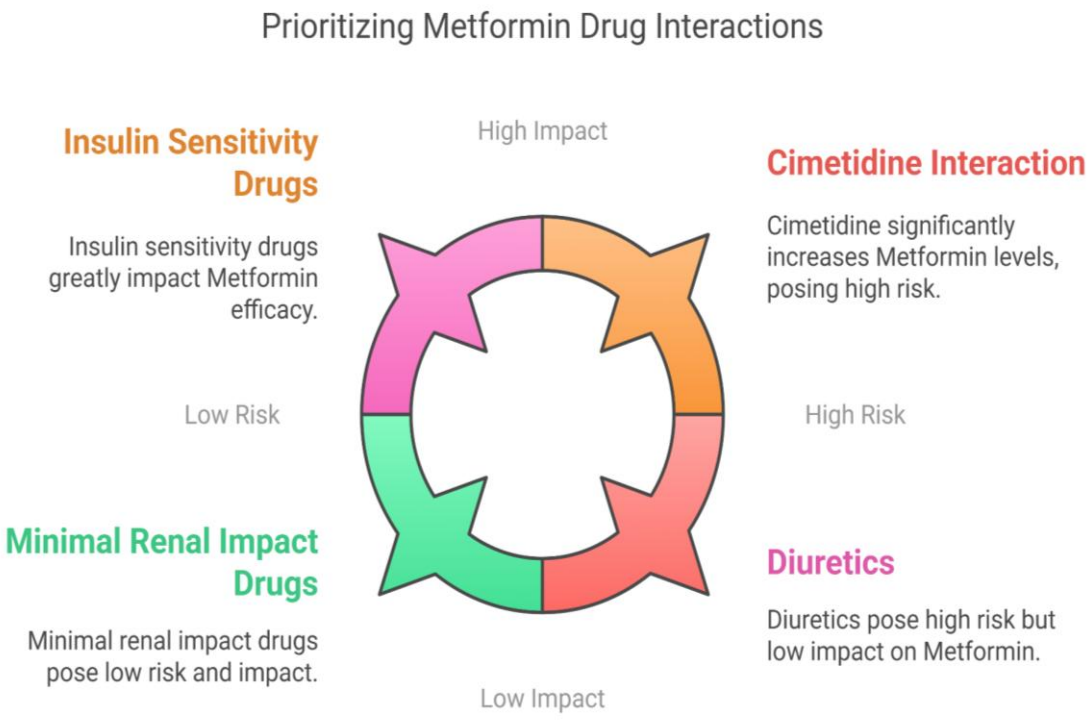

Figure 4. The significant factors regarding metformin use are drug interactions and contraindications. Drug interactions with metformin impact its efficacy and safety of use, specifically medications that affect insulin sensitivity and medicines used to treat stomach acid buildup, like Cimetidine.

Tolerance and Dependence: Due to metformin's hypoglycemic effects, tolerance development was not observed. There were no physical dependence or withdrawal symptoms linked to metformin. Medication adherence is essential to ensure the drug can act as intended. Inadequate medication usage can lead to worsened conditions of increased thirst, impaired kidney function, fatigue, and prolonged hyperglycemia [41].

Cost and Accessibility: Metformin is available under its generic name, making it widely available in most community pharmacies and generally affordable. Different biguanide-based medications are marketed in other countries, but the United States only offers metformin as an oral anti-diabetic agent.

Indications (Therapeutic Uses): Metformin is most commonly prescribed to treat type 2 diabetes and insulin

resistance [54]. Other prescribed uses include the treatment of polycystic ovary syndrome and gestational diabetes.

Therapeutic Index: The therapeutic index is the concentration comparing the toxic dose to its maximally effective dose. The breadth of its therapeutic index determines drug safety; the larger the index, the safer the drug is. Metformin has a broad therapeutic index for patients with normal kidney function. Metformin may pose the risk of lactic acidosis in patients with impaired renal function [2].

Drug and Food Interactions: This section explores the interactions between metformin, a common medication for type 2 diabetes, and various foods and substances. It highlights how these interactions can affect the drug's absorption and efficacy and the potential need for dietary adjustments and supplementation during long-term use.

Metformin Absorption and Dietary Considerations: Metformin absorption occurs primarily in the small intestine, which is crucial for food and nutrient absorption [54]. It is important to note that the absorption of metformin may be diminished when taken with high-fat meals, potentially decreasing the drug's efficacy. Therefore, while it is recommended that metformin be taken with meals, high-fat meals should be avoided to ensure optimal absorption.

Alcohol and Lactic Acidosis Risk: The use of metformin is associated with increased lactic acid levels in the blood. Consequently, alcohol intake is advised against in individuals taking metformin, as it can heighten the risk of lactic acidosis [2]. This risk underscores the importance of monitoring alcohol consumption while on this medication.

Carbohydrate Intake Monitoring: When taking metformin, it is essential to monitor carbohydrate intake. Excessive levels of simple sugars can counteract the medication's blood glucose-lowering effects [41]. A balanced approach to carbohydrate consumption can help maintain the drug's effectiveness in managing blood sugar levels.

Long-term Use and Vitamin Absorption: Long-term use of metformin may reduce the absorption of specific vitamins, particularly vitamin B12 and folic acid. In prolonged metformin usage, supplementation of these vitamins may be necessary to prevent deficiencies [2].

Recommended Diet for Optimal Effectiveness: To optimize metformin's effectiveness, a balanced diet rich in whole grains, fruits, vegetables, and lean proteins is recommended [48]. Such a diet supports overall health and enhances the medication's ability to manage blood glucose levels effectively.

In conclusion, understanding the interactions between metformin and various foods and substances is crucial for maximizing its therapeutic benefits while minimizing potential risks. Careful dietary management and monitoring can significantly contribute to the successful management of type 2 diabetes for individuals taking this medication.

In Figure 5, we presented dietary and substance interactions with metformin.

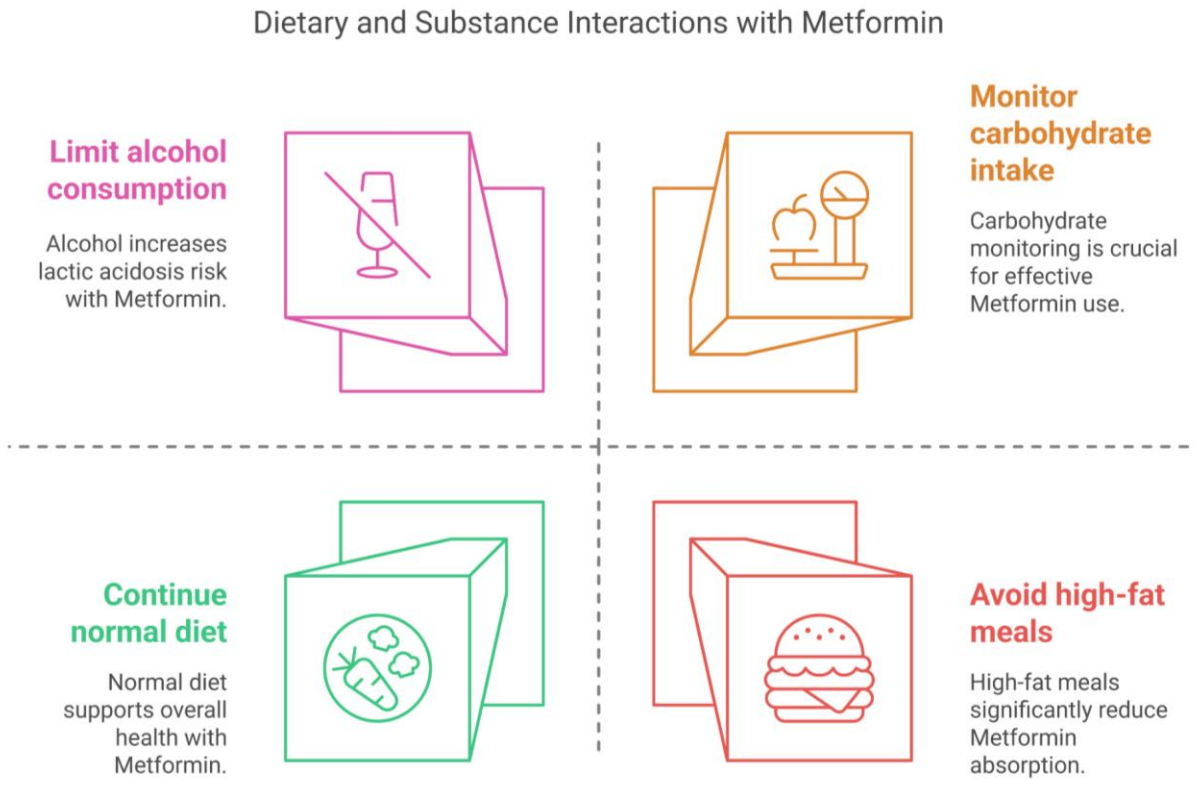

Figure 5. Key reminders for metformin users to maximize drug efficacy are to limit alcohol consumption to minimize the risk of lactic acidosis and to monitor dietary and lifestyle factors, especially carbohydrate, fat, and sugar intake.

Adherence and Compliance: Adherence to the drug regimen is necessary to see accurate and effective results. Metformin-based treatments for type 2 diabetes consider various factors regarding the physical and psychological effects of taking oral medication, especially with metformin's large tablet size and possible gastrointestinal side effects. Prescribed metformin is a strict self-management medication that is taken for the rest of a patient's life [61].

Functional Food Significance: In the discussion of functional food products, discovering plant-based resources as therapeutic agents is a foundational component to accessible and sustainable health. These innovative practices can supplement medication regimens as a dietary alternative to support nutritional and lifestyle routines. Current treatments for type 2 diabetes include the development of glucagon-like peptide 1 (GLP-1) receptor agonists, which act on cellular glucagon receptors to enable a prolonged release of insulin into the bloodstream [70]. This effect inhibits the release of the blood sugar-raising hormone glucagon while prompting the pancreatic cells to release insulin, maintaining blood glucose levels. As an effective type 2 diabetes medication, these GLP-1 drugs are marketed at high value as both for diabetes maintenance and weight loss medication. Even though the efficacy of GLP-1 drugs is well supported, various limitations hinder their widespread usage and availability. Its injectable formulation and high market cost limit its accessibility for diabetes patients. As GLP-1 drugs are also marketed for weight loss, a recent rise in their popularity caused shortages of GLP-1 injectables to be available for patient use [71]. The significance of functional foods is that they create an accessible and cost-efficient method to treat chronic illnesses through a safe and available approach. The need to establish and create functional foods is to address the limitations of modern medicine and make advancements that target dietary and nutritional processes. This metformin evaluation provides insight

into an oral therapeutic connected to a plant bioactive compound in *Galega officinalis*. In the progression of functional food discovery, there is a present need for compounds that can effectively lower blood glucose levels. A discussion of plant sources that act as natural alternatives to chemical drug formulations provides an advancement towards the future of combination therapies that incorporate functional foods into medical practice.

Diabetes Therapeutics: Plant Sources Exploring Natural Alternatives for Diabetes Management: This section delves into the potential of plant sources as alternatives to metformin in managing type 2 diabetes. Characterized formally as a chemically synthesized drug, metformin's biguanide structure is derived from a plant ingredient in goat's rue, or *Galega officinalis*. Early reports of treatments to lower blood glucose using *Galega officinalis* extract are recorded in the early 1930s in Europe [72]. Plant-based therapeutic alternatives minimize the risk of discomforting side effects, while generating an accessible resource for many populations. With the increasing incidence of type 2 diabetes mellitus, it is necessary to explore all safe and effective treatment plans [73]. Exploring these natural remedies emphasizes the importance of integrating traditional knowledge with modern medical practices, paving the way for innovative treatments in diabetes care. In Figure 6, an illustration of *Gallega officinalis*, commonly known as goat's rue, is depicted. *G. officinalis* is the source from which metformin's biguanide structure originates.

Figure 6. Illustration of *Galega officinalis*. *Galega officinalis*, commonly known as goat's rue, is the plant source from which the metformin biguanide ingredient is derived. (https://www.herbalreality.com/herb/goats-rue/)

In functional food science, research fueled by interest in medicinal herbs has shown that plant alternatives can produce blood glucose-lowering or antihyperglycemic effects. These alternatives belong to a class of compounds known as secondary metabolites. Secondary metabolites function as protective agents for

plants and produce various flavors, aromas, and colors. Terpenoids are promising for potential use as functional foods, as they are found in almost all natural foods. They are derived from terpenes, which are simple hydrocarbons that are the most significant secondary metabolites [74]. Abundant and chemically diverse, terpenoids are differentiated into subclasses based on their isoprene structures and carbon molecules. Specific to their bioavailability and their therapeutic effects on type 2 diabetes, terpenoids have the potential to be introduced as a functional food product [75].

Therapeutic Agents in Natural Products: Putative therapeutic agents in natural products complement medical interventions. Herbal alternative medicine therapies, including chromium, garlic, ginseng, and α-lipoic acid, are natural for type 2 diabetes prevention [68]. Plant metabolites are an active research area for the clinical use of digestive enzyme inhibitors from bacterial secondary metabolites. Classes of plant metabolites that potentiate effective treatment are flavonoids, terpenoids, and glycosides [76].

Herbal medications have been widely explored in Eastern medicine, using medicinal plants to inspire Indigenous remedies and ethnomedicinal practices. Various plants may possess anti-diabetic properties among this historically dense ethnobotanical collection. *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum* have been observed to be responsive in lowering blood glucose [77]. These medicinal plants can act as an alternative therapy for type 2 diabetes management, presenting a non-invasive treatment with minimal side effects [78]. The antidiabetic potential of natural products can exhibit insulin-mimetic properties. To name a few, plants in the *Liliaceae*, *Caesalipiniaceae*, *Theaceae*, *Cucurbitaceae*, *Myrtaceae*, and *Fabaceae* families have phytoconstituents with bioactivity in hypoglycemic control. Glucose-lowering mechanisms vary within each plant's active constituents in stimulating glucose uptake through insulin secretagogues.

Characterizing bioactive compounds is central to determining a plant's functionality in antidiabetic treatments. Premier pharmacological therapeutics can be derived from plant ingredients to treat diabetes related conditions, such as glucolipotoxicity and insulin insensitivity. Aguerd et al. detail a comprehensive list of plant bioactive compounds that have potential in mimicking the blood sugar-lowering capabilities of metformin [79]. The specific component of the glucose uptake mechanism in the body categorizes the outlined plant compounds. Bioactive compounds that produce in vitro α-glucosidase and α-amylase inhibitory activity alter one's glucose metabolism, insulin sensitivity, and incretin secretion [79]. Involved in the GLUT-4 pathway responsible for insulin secretion and glucose uptake is the dipeptidyl peptidase-4 (DPP-4) enzyme, which breaks down GLP-1. DPP-4 inhibitory activity helps slow gastric motility and increases cell glucose uptake [80-81]. Protein tyrosine phosphatase 1B (PTP1B) is a regulatory phosphatase used in cell signaling for insulin and leptin hormones [82-83]. Plant ingredients containing PTP1B inhibitory activity negatively regulate leptin and allow insulin secretion to persist. These bioactive compounds propose a promising facet in type 2 diabetes treatment using natural sources. Table 4, shown below, lists key plant and animal sources of metformin-like compounds and their effect as a type 2 diabetes treatment.

Table 4. Natural resources (plants and animals) with bioactive food ingredients, which can be used to manage symptoms of diabetes.

Source	Bioactive ingredient	Effect on Diabetes symptoms	References
Amaranth seed oil (*Amaranthus viridis*), Shark liver oil	Squalene	Promotes synthesis of anti-inflammatory cytokines. Lowers LDL cholesterol and triacylglycerol levels	[84-87]
Melicope latifolia	β-Sitosterol, Halfordin, Methyl p-coumarate, Protocatechuic acid,	α-amylase inhibition	[80], [88]
Moringa (*Moringa Oleifera*)	Stevioside, Stigmasterol	α-amylase inhibition	[98], [99]
Citrus (*Citrus sps.*)	Narirutin	α-glucosidase inhibition	[90], [91]
Smooth Wendlandia (*Wendlandia glabrata)*	Procyanidin A2	α-glucosidase inhibition	[90], [92]
Garlic bulb (*Allium sativum*)	Galangin	DPP-4 inhibition	[93-95]
Indian rennet (*Withania coagulans*)	Sitoindoside, Withanolide B, Withanolide D	DPP-4 inhibition	[95], [96]
Yellow Cow Wood (*Cratoxylum cochinchinense*)	Cratoxanthone A	PTP1B inhibition	[97-99]
Banana peel (*Musa*)	Urolithin A, Chrysin, Naringenin	PTP1B inhibition	[100-102]

Integrating Natural Remedies with Conventional Treatments: While metformin is primarily a synthetic medication used to manage type 2 diabetes, some studies have suggested that certain plants may contain compounds with similar hypoglycemic effects. Research into these natural sources has highlighted various herbs and botanical extracts that have shown promise in supporting glucose metabolism and could serve as complementary options alongside conventional treatments.

Exploring these natural alternatives not only broadens the therapeutic options available for managing diabetes but also emphasizes the importance of integrating traditional knowledge with modern medical practices to create a more holistic approach to health. The potential benefits of these natural remedies are essential, as they encourage collaboration between researchers, healthcare professionals, and traditional healers to validate their efficacy and safety through rigorous scientific studies.

Investigating these natural sources further could lead to the discovery of new compounds that enhance insulin sensitivity and improve overall metabolic health, potentially paving the way for innovative treatments in diabetes care. Such collaborative efforts may also foster a greater understanding of the underlying mechanisms by which these natural remedies operate, ultimately contributing to more personalized and effective management strategies for individuals living with diabetes. This integrative approach also seeks to bridge the gap between conventional medicine and alternative therapies, ensuring that patients receive comprehensive care tailored to their unique health needs.

Figure 7 identifies a few metformin-like plants that exhibit similar blood glucose-lowering properties.

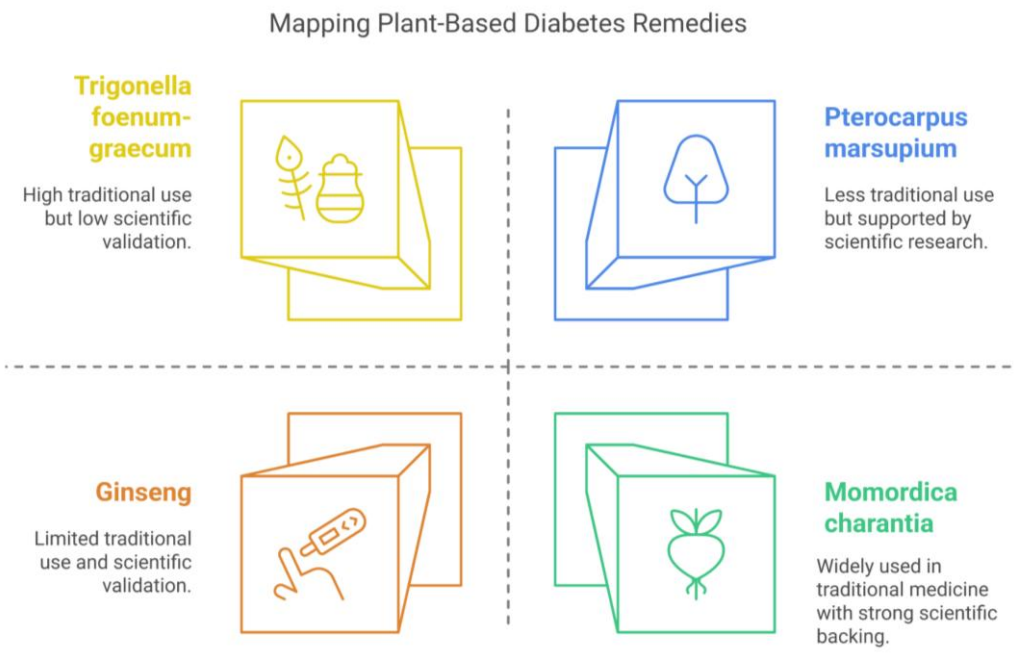

Figure 7. Identification of a few metformin-like plants that exhibit similar blood glucose-lowering properties. As most herbal treatments have limited scientific evidence, historical use of these plant remedies has reported effects akin to metformin indications.

Fruit fiber components, fermentability, and their role in type 2 diabetes management: Whole fruits contain a variety of fibers, sugars, and energy-rich components that contribute to their nutritional value. During ripening, the hydrated cell wall structures, comprising pectin, hemicellulose, and cellulose, gradually disassemble, increasing microbial accessibility and enhancing fiber fermentability [103]. Mastication and upper gastrointestinal digestion further disrupt the fruit matrix, breaking down cell walls and allowing colonic bacteria to ferment the material more effectively. Starchy fruits, such as bananas and plantains, offer fermentable fiber both from cell walls and intracellular resistant starch [104]. While soluble fibers were traditionally considered more readily fermentable, recent insights suggest that even the partially disassembled “insoluble fibers” of ripe fruits exhibit increased fermentability [105]. Distinguishing soluble from insoluble fibers remains difficult due to methodological limitations. Nonetheless, whole fruits are recognized as rich sources of fermentable fibers that support prebiotic activity in the colon and may contribute to improved health outcomes when consumed regularly.

Importantly, the fermentable fibers and associated bioactive compounds in fruits may play a significant role in the dietary management of type 2 diabetes by improving gut microbiota balance, enhancing glycemic control, and reducing systemic inflammation.

Functional Food Center’s Evaluation of Metformin: The Functional Food Center aims to implement new approaches in the assessment of functional foods, using a standardized guideline informed by scientific research. In recognition of oral drug therapeutics, their classification in the lens of functional food science can help inform and guide the various principles of nutrition, dietary health, and the treatment of chronic diseases. In alignment with the Functional Food Center, this paper has outlined fifteen key parameters about drug performance for the anti-diabetic medication metformin. The regulation system proposed by the Functional Food Center is a seventeen-step process that accounts for specific criteria concerning the biological and physical

validity of a functional food [106-108]. The Functional Food Center, under the leadership of Dr. Martirosyan, has established a groundbreaking definition of functional foods, along with a comprehensive set of principles and developmental steps for their formulation and commercialization [109-111]. This innovative framework provides a scientific and practical foundation for identifying and validating functional food products based on their bioactive components, health benefits, safety, and mechanisms of action.

Utilizing this model, the Functional Food Center has effectively applied its criteria to assess whether various food products truly meet the standards of functional foods. If a product falls short, the framework outlines specific actions required to advance it into a fully recognized functional food category [112-121]. This systematic approach ensures scientific credibility and supports the development of evidence-based functional foods in the marketplace.

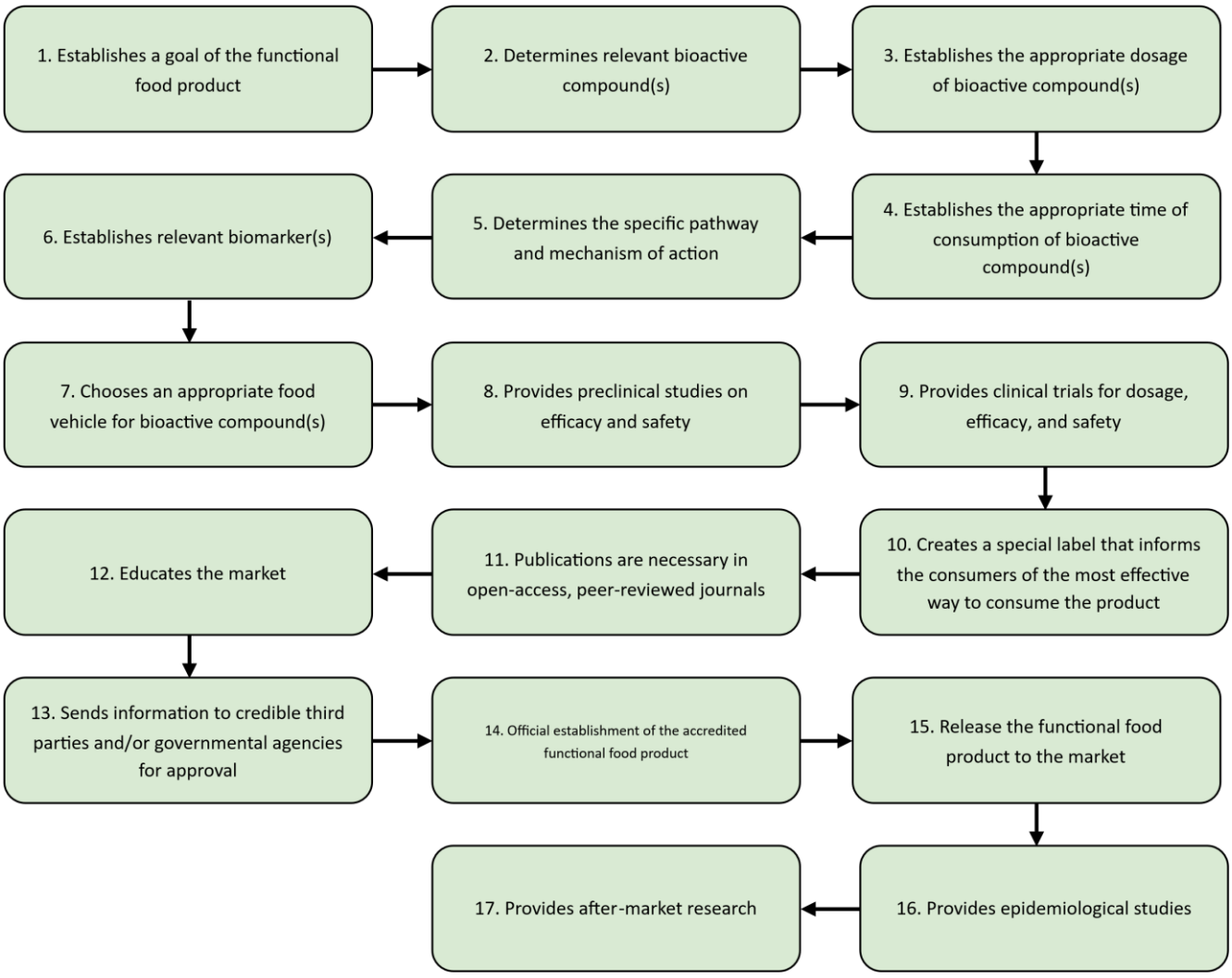

Figure 8. The flowchart identifies the multi-step process outlined by the Functional Food Center in the proposed regulatory paradigm for establishing functional foods [106].

These guidelines consider biochemical aspects, nutritional assessment, clinical data, and epidemiological studies. Evaluation of metformin through these guidelines establishes the drug in alignment with the necessary components of a functional food. As functional foods are deemed nutritionally enriched products that provide a clinically proven or documented health benefit for preventing, managing, or treating chronic diseases,

drug therapies fit this definition. Derived from the plant *Galega officinalis*, metformin is a chemically synthesized drug used to treat type 2 diabetes. While metformin itself is not a naturally occurring product, it matches some qualities about functional foods, as found in the seventeen-step classification scheme established by the Functional Food Center.

Step 1 establishes therapeutic indications of the proposed compound. Metformin is used as a blood glucose-lowering agent for treating type 2 diabetes. Step 2 describes the unique properties of the proposed compound and its effective use. Metformin is the active ingredient responsible for the medication's anti-diabetic treatment mechanism. Step 3 is the establishment of appropriate dosing, which is crucial in the drug development process for medication. This guideline matches the drug parameter listed above regarding Metformin dosage. However, the characterization of metformin as a drug does not explicitly outline its mode of bioactive compound containment. In this regard, the bioactive compounds in metformin have not been established. Step 4 is summarized as administration timing, another significant component of medication usage. Steps 5 and 6 are the determination of relevant biomarkers and the bioactive compound's specific pathway and mechanism of action, which is established for Metformin in the Effectiveness section. Step 7 is not directly applicable to metformin, since it does not require a food vehicle as a pharmacologic drug. Steps 8-10 are comparable to the FDA's guidelines in developing new medicines. However, this evaluation is translated to the assessment of bioactive compounds. Drug development requires a pre-clinical trial, a clinical trial phase, and the inclusion of a medication guide. Metformin meets these criteria from a drug development standpoint. Step 11 requires that publications of the bioactive compound are accessible through open-access, peer-reviewed journals, a criterion metformin thoroughly meets. Step 12 asserts that the market must be informed about the functional food before it meets consumers. Metformin studies have been used to medical professionals about its use as a maintenance medication. As metformin is an FDA-approved medication in the United States, steps 13-17 must be satisfied due to this rigorous procedure.

Evaluation of Metformin using the Functional Food Center's seventeen-step process in the designation of bioactive compounds as functional foods reveals that the Metformin drug fulfills these criteria. Functional foods are "natural or processed foods that contain known or unknown biologically active compounds, in defined, effective, and non-toxic amounts, provide a clinically proven and documented health benefit for the prevention, management, or treatment of chronic diseases." Metformin is a pharmacologic product established as a first-line oral therapeutic for treating type 2 diabetes [122-127]. Definitive connections can be drawn between functional foods and metformin. However, metformin is formally regarded as a medication instead of a "food."

Future Directions: Areas of improvement are applicable for steps 16 and 17, which are the evidence of epidemiological studies and after-market research. As metformin is used globally, a diverse array of epidemiological evidence supports its use and outcomes. Post-clinical usage data of metformin can be collected in studies. This can help understand the practical application of this daily medication and assess the quality of life of patients who are taking metformin or are taking metformin. Plant resources are another facet of exploration that can supplement these objectives. With growing global interest in functional foods, the development can be furthered through investigating plant sources to create low-cost, accessible alternatives. Generating novel anti-diabetic treatments initiates sustainable methods for chronic disease maintenance.

Scientific Innovation and Practical Implications: This review presents a significant innovation by bridging

the gap between functional food science and pharmaceutical drug evaluation. By adapting the Functional Food Center's established multi-step process for functional food development, we have created a novel framework for assessing oral therapeutic drugs, specifically demonstrated through the comprehensive evaluation of Metformin. This approach introduces fifteen key parameters that extend beyond traditional clinical research, incorporating patient adherence, real-world usage, and optimal dosage considerations.

The practical implications of this framework are substantial. It provides a structured methodology for healthcare professionals to evaluate and optimize the use of oral medications, enhancing patient outcomes and adherence. By shifting the focus from mere efficacy to a broader understanding of medication performance within a patient's lifestyle, this review offers a valuable tool for improving patient education and treatment strategies. This novel application of functional food science principles to pharmaceutical drugs has the potential to revolutionize how medications are evaluated and utilized, ultimately leading to more personalized and effective healthcare.

Future Directions: The Functional Food Center (FFC) is initiating a special project to develop a comparative framework that aligns the stages of functional food development with the clinical phases of drug development (Phases I–IV). This structured comparison is intended to clarify how functional foods are scientifically validated and how their assessment can mirror pharmaceutical standards, offering greater context for evaluating their progression and credibility. While this vital topic is highly relevant to the current study, it falls beyond its immediate scope and will be explored in detail in future work.

CONCLUSION

Functional food science is an expanding research field that encompasses the discovery of bioactive compounds for treating or maintaining chronic diseases. The Functional Food Center has established a seventeen-step scheme to qualify functional foods scientifically and practically. These guidelines can be adopted for the comprehensive analysis of pharmacologic drugs. The widespread application of medications requires clear parameters to assess the medication performance through biochemical efficacy and practical patient use. This paper provides a definitive approach to the qualification of medication performance through fifteen parameters that account for effectiveness, safety, and optimized healthcare.

List of Abbreviations: FDA: Food and Drug Administration, IR: immediate release, ER: extended release, AMPK: adenosine monophosphate activated protein kinase, GLP-1: glucagon-like peptide, LDL: low density lipoprotein, Hb: hemoglobin, eGFR: estimated glomerular filtration rate, UACR: urine albumin-to-creatinine ratio, ACEis: angiotensin-converting enzyme inhibitors, ARBs: angiotensin II receptor blockers, QD: once daily, BID: twice daily, TID: thrice daily, HS: healthy subjects, DM: diabetes mellitus

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REFERENCES

1. Centers for Disease Control. National Diabetes Statistics Report. *Diabetes*, https://www.cdc.gov/diabetes/php/data-research/index.html. Retrieved on May 17, 2025
2. Bailey, C. J., and Turner, R. C. Metformin. *The New England Journal of Medicine*, 1996. 334(9), 574-579. DOI: https://doi.org/10.1056/NEJM199602293340906

3. Marathe, P. H., Gao, H. X., and Close, K. L. American Diabetes Association Standards of Medical Care in Diabetes. *Journal of Diabetes*, 2017. 9(4), 320-324. DOI: https://doi.org/10.1111/1753-0407.12524
4. Home P. The evolution of insulin therapy. *Diabetes Research and Clinical Practice*, 2021. 175, 108816. DOI: https://doi.org/10.1016/j.diabres.2021.108816
5. Rejali L., Ozumerzifon S., Nayeri H., Williams S., Asgary S. Risk Reduction and Prevention of Cardiovascular Diseases: Biological Mechanisms of Lycopene. Bioactive Compounds in Health and Disease 2022; 5(10): 202-221. DOI: https://www.doi.org/10.31989/bchd.v5i10.975
6. El-Khouly N., Bayoumy E. S. M., Ali W. E., Eid A. M. M. A., Sofy M. R., Fakhrelden S. M., et al. Vitamin D Levels in Non-alcoholic Fatty Liver Disease in type II diabetic and non-diabetic Patients. Bioactive Compounds in Health and Disease 2023; 6(9):202-214, DOI: https://www.doi.org/10.31989/bchd.v6i9.1128
7. Ghods M., Karimi S., Salari S., Alem E., Bahmani P., Karimi A., Saeedpour A., Noormohamadi M., Jahromi S. R. Anti-diabetic effect of a combination of black seed (Nigella sativa) and Cumin (Cuminum cyminum), a two-step study from bench to bed. Functional Food Science. 2023; 4(2):55-68. DOI: https://doi.org/10.31989/ffs.v4i2.1295
8. 304: Komolkriengkrai M., Matsathi U., Jangchart R., Sirinupong N.,Radenahmad N., KhimmaktongW. The efficacy of an edible bird's nest in the restoration and enhancement of kidney glomeruli and peritubular capillaries in induced diabetic rats by increasing TGF-β and CD 31. Functional Foods in Health and Disease 2025; 15(5): 241-256. DOI: https://doi.org/10.31989/ffhd.v15i5.1591
9. Babiker R., Ali I. A., Merghani T. H., Banaga A. S., Hashim N. T., Seed Ahmed M., Saeed A. M. Gum Acacia supplementation improves adiponectin levels and HbA1c/adiponectin ratio in women with type 2 diabetes: A randomized controlled trial. Functional Foods in Health and Disease 2025; 15(3): 176-190. DOI: https://doi.org/10.31989/ffhd.v15i3.1568
10. Rithi A. T., Mitra A., Banerjee A., Ilanchoorian D., Marotta F., Radhakrishnan A. K. Effect of prebiotics, probiotics, and synbiotics on gut microbiome in diabetes among coastal communities. Functional Food Science 2023; 4(1): 11-28. DOI: https://doi.org/10.31989/ffs.v4i1.1271
11. Nakatake R., Iida H., Ishizaki M., Matsui K., Nakamura Y., Kaibori M., Nishizawa M., Okumura T., Metformin inhibits expression of the proinflammatory biomarker inducible nitric oxide synthase in hepatocytes. Functional Foods in Health and Disease 2018; 8(3): 175-192. DOI: https://doi.org/10.31989/ffhd.v8i3.423
12. Shali K. S., Soumya N. P., Mondal S., Mini S. Hepatoprotective effect of morin via regulating the oxidative stress and carbohydrate metabolism in STZ induced diabetic rats. Bioactive Compounds in Health and Disease 2022; 5(3): 53-66. DOI: https://www.doi.org/10.31989/bchd.v5i2.893
13. Soumya S., Soumya N. P., Mondal S., Mini S. Menthol confers neuroprotection through Nrf2/ARE pathway in diabetic encephalopathy. Bioactive Compounds in Health and Disease 2023; 6(6): 108-125. DOI: https://www.doi.org/10.31989/bchd.v6i7.1113
14. Wang, X., Liu, W., Chen, H., & Chen, Q. (2021). Comparison of Insulin, Metformin, and Glyburide on Perinatal Complications of Gestational Diabetes Mellitus: A Systematic Review and Meta-Analysis. *Gynecologic and obstetric investigation*, *86*(3), 218–230. DOI: https://doi.org/10.1159/000515893
15. Kelly, F. A., de Oliveira Macena Lôbo, A., Cardoso, J. H. C. O., and de Moraes, F. C. A.. Comparison of metformin with inositol versus metformin alone in women with polycystic ovary syndrome: a systematic review and meta-analysis of randomized controlled trials. *Endocrine*, 2025; *87*(2), 389–399. DOI: https://doi.org/10.1007/s12020-024-04052-3
16. Mofolorunso A.M., Oyebanji K. E., Ndubuisi C. N., Samuel T. A., Morakinyo A. O. Beneficial effect of Cellgevity® on metabolic indices, lipid profile, and antioxidant enzymes in cold-restraint stress rat model. Dietary Supplements and Nutraceuticals 2023; 2(10): 41-54. DOI: https://www.doi.org/10.31989/dsn.v2i10.1223
17. Lim W.X.J., Gammon C.S., von Hurst P.R., Chepulis L., Mugridge O., Page R.A. Hypoglycaemic effects of antioxidant-rich plant extracts on postprandial glycaemic responses in participants with prediabetes (GLARE study). Functional Foods in Health and Disease 2021; 11(11): 604-626. DOI: https://www.doi.org/10.31989/ffhd.v11i11.829
18. Miura K., Hasumura M., Kitahara Y., Nishitani S., Yamada Y. A novel amino acid mixture containing isoleucine, glycine, and cystine improves insulin sensitivity with restoring mitochondrial oxygen consumption in C2C12 myotubes. Functional Foods in Health and Disease; 2025; 15(4): 205 - 216. DOI: https://doi.org/10.31989/ffhd.v15i4.1582
19. TadevosyanA., HakobjanyanA., TovmasyanA., AsatryanA., RoostaH.R., Daryadar M. Hypoglycemic and Hypolipidemic

Activity of Moringa Grown in Hydroponics and Soilin Ararat Valley. Functional Foods in Health and Disease 2023;13(8):398 - 408.
DOI: https://www.doi.org/10.31989/ffhd.v13i8.1158

20. Adebodun G. O., Kayode A. A. A., Adebodun S. A., A Review on Alternative Treatments of Gestational Diabetes Mellitus: Focus on Phytotherapy. Functional Food Science 2023; 3(9): 179-192. DOI: https://www.doi.org/10.31989/ffs.v3i9.1137
21. Takano S., Yoshizumi K., Kobayashi H., Iwamoto N., Taga M. Suppression of blood glucose level elevation and promotion of GLP-1 secretion by ingestion of Undaria pinnatifida sporophylls (Mekabu): Open-label crossover design. Functional Foods in Health and Disease 2022; 12(2): 93-102. DOI: https://www.doi.org/10.31989/ffhd.v12i2.891
22. Alshakrah, M. A., & Alotaibi, N. M. Artificial intelligence in predicting and preventing adverse drug events: A systematic review. *Expert Opinion on Drug Safety*, 2024; *23*(1), 1-15. DOI: https://doi.org/10.1080/14740338.2023.2292283
23. Sarker, A., Hobbiger, S. F., and Danielyan, A. Global trends of adverse drug reactions reported during the COVID-19 pandemic: A pharmacovigilance study. *Drug Safety*, 2023; *46*(3), 249-260.
DOI: https://doi.org/10.1007/s40264-022-01280-w
24. Alhalaweh, A., Laffleur, F., & Khinast, J. G. Continuous manufacturing of solid oral dosage forms: Understanding drug release and bioavailability. *European Journal of Pharmaceutics and Biopharmaceutics*, 2023; *188*, 153-167. DOI: https://doi.org/10.1016/j.ejpb.2023.05.013
25. Silva, A. Clinical Efficacy: The Major Role of Drug Half-Life in Pharmacotherapy. *Journal of Basic and Clinical Pharmacy*, 2024; *15*(4), 369.
26. Pelkonen, O., and Turpeinen, M. Pharmacokinetics and drug metabolism: an update. *Clinical Pharmacology & Therapeutics*, 2023; *113*(6), 1265-1287.
DOI: https://doi.org/10.1002/cpt.2871
27. Zhou, T. H., Jin, T. Y., Wang, X. W., & Wang, L. Drug-Drug interactions prediction calculations between cardiovascular drugs and antidepressants for discovering the potential co-medication risks. *PLoS ONE*, 2025; *20*(1), e0316021.
DOI: https://doi.org/10.1371/journal.pone.0316021
28. Kosten, T. R., and George, T. P. The neurobiology of opioid use disorder: Implications for treatment. *Molecular Psychiatry*, 2023; *28*(1), 9-22.
DOI: https://doi.org/10.1038/s41380-022-01886-x
29. Thayer, K. Navigating the Label: Understanding Drug Indications and Usage. *Pharmacy Times*, 2023; *89*(10), 45-46.
30. Tadrous, M. Z., Abdel-Qader, D. H., & Alsabbagh, M. Q. Efficacy and safety of direct oral anticoagulants in patients with atrial fibrillation and valvular heart disease: A systematic review and meta-analysis. *Pharmacology Research and Perspectives*, 2024; *12*(1), e01217.
DOI: https://doi.org/10.1002/prp2.1217
31. Chaudhary, S., and Kulkarni, A. (2024). Metformin: Past, Present, and Future. *Current Diabetes Reports*, *24*(6), 119-130. DOI: https://doi.org/10.1007/s11892-024-01539-1
32. American Diabetes Association. *Standards of Medical Care in Diabetes***,** 2024. Retrieved from https://diabetes.org/standards (The ADA updates these annually, with the 2024 Standards being the most current as of early 2024).
33. Medscape. *Metformin, 2024***.** Retrieved from https://reference.medscape.com/drug/glucophage-metformin-342717 (Medscape drug monographs are continuously updated; the latest content reflects 2024 information).
34. Drugs.com. *Metformin Dosage Guide***.** 2024, Retrieved from https://www.drugs.com/dosage/metformin.html (This page was last updated on April 23, 2024, as per the site).
35. National Institutes of Health (NIH). *Metformin***.** In StatPearls, 2025. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK518983/
36. Bhansali, A., and Masoodi, S. R. Efficacy of once- or twice-daily extended-release metformin compared with thrice-daily immediate release metformin in type 2 diabetes mellitus. *The Journal of the Association of Physicians of India*, 2005. 53, 441-445
37. Jabbour, S. and Ziring, B. Advantages of extended-release metformin in patients with type 2 diabetes mellitus. *Postgraduate Medicine*, 2011. 123(1), 15-23. DOI: https://doi.org/10.3810/pgm.2011.01.2241
38. Chacra A. R. Evolving metformin treatment strategies in type-2 diabetes: from immediate-release metformin monotherapy to extended-release combination therapy. *American Journal of Therapeutics*, 2014. 21(3), 198-210. DOI: https://doi.org/10.1097/MJT.0b013e318235f1bb
39. Blonde, L., Dailey, G. E., Jabbour, S. A., Reasner, C. A., and Mills, D. J. Gastrointestinal tolerability of extended-release metformin tablets compared to immediate-release metformin tablets: results of a retrospective cohort study. *Current Medical Research and Opinion*, 2004. 20(4),

565-572.
DOI: https://doi.org/10.1185/030079904125003278

40. Stolar M: Review of pharmacology, pharmacokinetics, and clinical efficacy of metformin. *Journal of Clinical Endocrinology & Metabolism*. 2010; 95(3): 1448-1456
41. Inzucchi, S. E., Bergenstal, R. M., Buse, J. B., Diamant, M., Ferrannini, E., Nauck, M., et. al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*, 2015. 38(1), 140-149. DOI: https://doi.org/10.2337/dc14-2441
42. Pernicova, I., and Korbonits, M. Metformin -- mode of action and clinical implications for diabetes and cancer. *Nature Reviews Endocrinology*, 2014. 10(3), 143-156. DOI: https://doi.org/10.1038/nrendo.2013.256
43. Janzer, A., German, N. J., Gonzalez-Herrera, K. N., Asara, J. M., Haigis, M. C., and Struhl, K. Metformin and phenformin deplete tricarboxylic acid cycle and glycolytic intermediates during cell transformation and NTPs in cancer stem cells. *Proceedings of the National Academy of Sciences (PNAS)*, 2014. 111(29), 10574-10579. DOI: https://doi.org/10.1073/pnas.1409844111
44. Wheaton, W. W., et al. Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. *eLife*, 2014. 3, e02242.
DOI: https://doi.org/10.7554/eLife.02242
45. Algire, C., et al. Metformin reduces endogenous reactive oxygen species and associated DNA damage. *Cancer Prevention Research (Philadelphia, Pa.)*, 2012. 5(4), 536-543. DOI: https://doi.org/10.1158/1940-6207.CAPR-11-0536
46. Kulkarni, A. S., Gubbi, S., and Barzilai, N. Benefits of Metformin in Attenuating the Hallmarks of Aging. *Cell Metabolism*, 2020. 32(1), 15-30.
DOI: https://doi.org/10.1016/j.cmet.2020.04.001
47. Bang, S., Kim, D. E., Kang, H. T., and Lee, J. H. Metformin restores autophagic flux and mitochondrial function in late passage myoblast to impede age-related muscle loss. *Biomedicine and Pharmacotherapy*, 2024. 180, 116981. DOI: https://doi.org/10.1016/j.biopha.2024.116981
48. Moin, T., Schmittdiel T., Flory J.A., Yeh J.H., Karter J, Andrew J. et al. A Review of Metformin Use for Type 2 Diabetes Prevention. *American Journal of Preventive Medicine*, 2018. 55(4), 565-574.
DOI: https://doi.org/10.1016/j.amepre.2018.04.038
49. McCreight, L. J., Bailey, C. J., and Pearson, E. R. Metformin and the gastrointestinal tract. *Diabetologia*, 2016. 59(3), 426-435.
DOI: https://doi.org/10.1007/s00125-015-3844-9
50. DeFronzo, R., Fleming, G. A., Chen, K., and Bicsak, T. A. Metformin-associated lactic acidosis: Current perspectives on causes and risk. *Metabolism: Clinical and Experimental*, 2016. 65(2), 20-29.
DOI: https://doi.org/10.1016/j.metabol.2015.10.014
51. Yi, Y., et al. Impact of metformin on cardiovascular and kidney outcome based on kidney function status in type 2 diabetic patients: a multicentric, retrospective cohort study. *Scientific Reports*, 2024. 14(1), 2081. DOI: https://doi.org/10.1038/s41598-024-52078-4
52. Tung, M. L., and Tan, L. K. Long-term use of metformin leading to vitamin B12 deficiency. *Diabetes Research and Clinical Practice*, 2014. 104(3), e75-e76. DOI: https://doi.org/10.1016/j.diabres.2013.12.054
53. Emslie-Smith, A. M., Boyle, D. I., Evans, J. M., Sullivan, F., Morris, A. D., and DARTS/MEMO Collaboration. Contraindications to metformin therapy in patients with Type 2 diabetes -- a population-based study of adherence to prescribing guidelines. *Diabetic Medicine*, 2001. 18(6), 483-488.
DOI: https://doi.org/10.1046/j.1464-5491.2001.00509.x
54. Sanchez-Rangel, E., and Inzucchi, S. E. Metformin: clinical use in type 2 diabetes. *Diabetologia*, 2017. 60(9), 1586-1593. DOI: https://doi.org/10.1007/s00125-017-4336-x
55. Scheen A. J. Clinical pharmacokinetics of metformin. *Clinical Pharmacokinetics*, 1996. 30(5), 359-371.
DOI: https://doi.org/10.2165/00003088-199630050-00003
56. Schwartz S, Fonseca V, Berner B, Cramer M, Chiang YK, Lewin A. Novel extended-release metformin in type 2 diabetes. *Diabetes Care*. 2006;29(4):759-64.
DOI: https://doi.org/10.2337/diacare.29.04.06.dc05-1967
57. Sambol, N. C., Chiang, J., O'Conner, M., Liu, C. Y., Lin, E. T., Goodman, A. M., et al. Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *Journal of Clinical Pharmacology*, 1996. 36(11), 1012-1021.
DOI: https://doi.org/10.1177/009127009603601105
58. Herman, G. A., Bergman, A., Yi, B., Kipnes, M., and Sitagliptin Study 012 Group. Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase-4 inhibitor

sitagliptin when co-administered in patients with type 2 diabetes. *Current Medical Research and Opinion*, 2006. 22(10), 1939-1947.
DOI: https://doi.org/10.1185/030079906X132587

59. Hong, Y., Rohatagi, S., Habtemariam, B., Walker, J. R., Schwartz, S. L., and Mager, D. E. Population exposure-response modeling of metformin in patients with type 2 diabetes mellitus. *Journal of Clinical Pharmacology*, 2008. 48(6), 696-707.
DOI: https://doi.org/10.1177/0091270008316884
60. Raigon P, Kaunda B, Sood A, Devi S, Dutt S, Singh B. Quantification of biguanide and related compounds (anti-diabetic) in vegetables and fruits. *Journal of Food Composition and Analysis*, 2018; (74):82-88, DOI: https://doi.org/10.1016/j.jfca.2018.09.001
61. Rao N, Chou T, Ventura D, Abramowitz W. Investigation of the pharmacokinetic and pharmacodynamic interactions between memantine and glyburide/metformin in healthy young subjects: a single-center, multiple-dose, open-label study. *Clinical Therapeutics*. 2005;27(10):1596-1606.
DOI: https://doi.org/10.1016/j.clinthera.2005.10.006
62. Sambol NC, Chiang J, O'Conner M, Liu CY, Lin ET, Goodman AM, et al. Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *Journal of Clinical Pharmacology*. 1996;36(11):1012-21.
DOI: https://doi.org/10.1177/009127009603601105
63. Herman GA, Bergman A, Yi B, Kipnes M, Sitagliptin Study 012 Group. Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase-4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes. *Current Medical Research and Opinion*. 2006;22(10):1939-47.
DOI: https://doi.org/10.1185/030079906X132587
64. Pentikainen PJ, Neuvonen PJ, Penttila A. Pharmacokinetics of metformin after intravenous and oral administration to man. *European Journal of Clinical Pharmacology*. 1979;16(3):195-202.
DOI: https://doi.org/10.1007/BF00562061
65. Timmins P, Donahue S, Meeker J, Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clinical Pharmacokinetics*. 2005;44(7):721-9.
DOI:https://doi.org/10.2165/00003088-200544070-00004
66. Timmins P, Donahue S, Meeker J, Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clinical Pharmacokinetics*, 2005. 44(7), 721-729.
DOI: https://doi.org/10.2165/00003088-200544070-00004
67. Müller, F., Weitz, D., Mertsch, K., König, J., and Fromm, M. *Molecular Pharmaceutics*, 2018. 15 (8), 3425-3433. DOI: https://doi.org/10.1021/acs.molpharmaceut.8b00416
68. Mahabaleshwarkar, R., and DeSantis, A. Metformin dosage patterns in type 2 diabetes patients in a real-world setting in the United States. *Diabetes Research and Clinical Practice*, 2021. 172, 108531.
DOI: https://doi.org/10.1016/j.diabres.2020.108531
69. Scarpello JH. Review: Optimal dosing strategies for maximising the clinical response to metformin in type 2 diabetes. *The British Journal of Diabetes and Vascular Disease*. 2001. 1(1):28-36,
DOI: https://doi.org/10.1177/14746514010010010501
70. Centers for Disease Control. National Diabetes Statistics Report. *CDC*. 2024. Retrieved from: https://www.cdc.gov/diabetes/php/data-research/index.html
71. Marathe PH, Gao HX, Close KL. ADA Standards of Medical Care. *Journal of Diabetes*. 2017;9(4):320-4.
DOI: https://doi.org/10.1111/1753-0407.12524
72. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use. *Diabetologia*. 2017;60(9):1586-93.
DOI: https://doi.org/10.1007/s00125-017-4336-x
73. Moin T, Schmittdiel T, Flory JA, Yeh JH, Karter J, Andrew J, et al. Metformin use for type 2 diabetes prevention. *American Journal of Preventive Medicine*. 2018;55(4):565-74.
DOI: https://doi.org/10.1016/j.amepre.2018.04.038
74. Bailey CJ, Turner RC. Metformin. *New England Journal of Medicine*. 1996;334(9):574-9.
DOI: https://doi.org/10.1056/NEJM199602293340906
75. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes. *Diabetes Care*. 2015;38(1):140-9.
DOI: https://doi.org/10.2337/dc14-2441
76. Bailey CJ, Flatt PR, Conlon JM. Peptide-based therapies for type 2 diabetes. *Peptides*. 2023; 161:170939.
DOI: https://doi.org/10.1016/j.peptides.2023.170939
77. Bhansali A, Masoodi SR. Extended vs immediate release metformin. *Journal of the Association of Physicians of India*. 2005;53:441-5
78. Blonde L, Dailey GE, Jabbour SA, Reasner CA, Mills DJ. Tolerability of extended-release vs immediate-release metformin. *Current Medical Research and Opinion*. 2004;20(4):565-72.
DOI: https://doi.org/10.1185/030079904125003278
79. Chacra AR. Evolving metformin treatment strategies. *American Journal of Therapeutics*. 2014; 21(3): 198-210.
DOI: https://doi.org/10.1097/MJT.0b013e318235f1bb

80. Huang XM, Wang GZ, He BB, Gao T, Long P, Zhang BK. Bioequivalence of metformin hydrochloride tablets. *Clinical Pharmacology and Drug Development*. 2020;9(8):910-7. DOI: https://doi.org/10.1002/cpdd.849
81. Jabbour S, Ziring B. Advantages of extended-release metformin. *Postgraduate Medicine*. 2011;123(1):15-23. DOI: https://doi.org/10.3810/pgm.2011.01.2241
82. Türk D, Scherer N, Selzer D, Dings C, Hanke N, Dallmann R, et al. Time-of-day variation on metformin pharmacokinetics. *Diabetologia*. 2023;66(6):1024-34. DOI: https://doi.org/10.1007/s00125-023-05898-4
83. Yi Y, Kwon EJ, Yun G, Park S, Jeong JC, Na KY, et al. Metformin's impact on cardiovascular and kidney outcomes. *Scientific Reports*. 2024;14(1):2081. DOI: https://doi.org/10.1038/s41598-024-52078-4
84. Stolar M. Review of the pharmacology, pharmacokinetics, and clinical efficacy of metformin. *Journal of Clinical Endocrinology & Metabolism*. 2010;95(3):1448-1456
85. Martirosyan D.M., Christopher S. The benefits of terpenoids as functional foods for the management of type 2 diabetes mellitus. *Bioactive Compounds in Health and Disease* 2024; 7(7): 345-348. DOI: https://doi.org/10.31989/bchd.v7i7.1426
86. Perveen S, Al-Taweel A. Terpenes and Terpenoids [Internet]. IntechOpen; 2018
87. An H, He L. Current understanding of metformin effect on the control of hyperglycemia in diabetes. *Journal of Endocrinology*. 2016;228(3):R97-106. DOI: https://doi.org/10.1530/JOE-15-0447
88. Foretz M, Guigas B, Viollet B. Understanding the glucoregulatory mechanisms of metformin in type 2 diabetes mellitus. *Nature Reviews Endocrinology*. 2019;15(10):569-589. DOI: https://doi.org/10.1038/s41574-019-0242-2
89. Graham GG, et al. Clinical pharmacokinetics of metformin. *Clinical Pharmacokinetics*. 2011;50(2):81-98. DOI: https://doi.org/10.2165/11534750-000000000-00000
90. Raigon P, Kaunda B, Sood A, Devi S, Dutt S, Singh B. Quantification of biguanide and related compounds (anti-diabetic) in vegetables and fruits. *Journal of Food Composition and Analysis*. 2018;74:82-88. DOI: https://doi.org/10.1016/j.jfca.2018.09.001
91. Timmins P, Donahue S, Meeker J, Marathe P. Steady-state pharmacokinetics of a novel extended-release metformin formulation. *Clinical Pharmacokinetics*. 2005;44(7):721-9. DOI: https://doi.org/10.2165/00003088-200544070-00004
92. Rao N, Chou T, Ventura D, Abramowitz W. Investigation of the pharmacokinetic and pharmacodynamic interactions between memantine and glyburide/metformin in healthy young subjects: a single-center, multiple-dose, open-label study. *Clinical Therapeutics*. 2005;27(10):1596-1606. DOI: https://doi.org/10.1016/j.clinthera.2005.10.006
93. Sambol NC, Chiang J, O'Conner M, Liu CY, Lin ET, Goodman AM, et al. Pharmacokinetics and pharmacodynamics of metformin in healthy subjects and patients with noninsulin-dependent diabetes mellitus. *Journal of Clinical Pharmacology*. 1996;36(11):1012-21. DOI: https://doi.org/10.1177/009127009603601105
94. Herman GA, Bergman A, Yi B, Kipnes M, Sitagliptin Study 012 Group. Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase-4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes. *Current Medical Research and Opinion*. 2006;22(10):1939-47. DOI: https://doi.org/10.1185/030079906X132587
95. Hong Y, Rohatagi S, Habtemariam B, Walker JR, Schwartz SL, Mager DE. Population exposure-response modeling of metformin in patients with type 2 diabetes mellitus. *Journal of Clinical Pharmacology*. 2008;48(6):696-707. DOI: https://doi.org/10.1177/0091270008316884
96. Müller F, Weitz D, Mertsch K, König J, Fromm M. Metformin transport by the organic cation transporter OCT1: a pharmacogenetic perspective. *Molecular Pharmaceutics*. 2018;15(8):3425-33. DOI: https://doi.org/10.1021/acs.molpharmaceut.8b00416
97. Mahabaleshwarkar R, DeSantis A. Metformin dosage patterns in type 2 diabetes patients in a real-world setting in the United States. *Diabetes Research and Clinical Practice*. 2021;172:108531. DOI: https://doi.org/10.1016/j.diabres.2020.108531
98. Scarpello JH. Optimal dosing strategies for maximising the clinical response to metformin in type 2 diabetes. *British Journal of Diabetes and Vascular Disease*. 2001;1(1):28-36. DOI: https://doi.org/10.1177/14746514010010010501
99. Pernicova I, Korbonits M. Metformin -- mode of action and clinical implications for diabetes and cancer. *Nature Reviews Endocrinology*. 2014;10(3):143-56. DOI: https://doi.org/10.1038/nrendo.2013.256
100. Kulkarni AS, Gubbi S, Barzilai N. Benefits of metformin in attenuating the hallmarks of aging. *Cell Metabolism*. 2020;32(1):15-30. DOI: https://doi.org/10.1016/j.cmet.2020.04.001
101. Bang S, Kim DE, Kang HT, Lee JH. Metformin restores autophagic flux and mitochondrial function in late passage myoblast to impede age-related muscle loss. *Biomedicine and Pharmacotherapy*. 2024;180:116981. DOI: https://doi.org/10.1016/j.biopha.2024.116981

102. Algire C, Moiseeva O, Deschênes-Simard X, Amrein L, Petruccelli LA, Birman E, et al. Metformin reduces endogenous reactive oxygen species and associated DNA damage. *Cancer Prevention Research (Philadelphia)*. 2012;5(4):536-43. DOI: https://doi.org/10.1158/1940-6207.CAPR-11-0536
103. Janzer A, German NJ, Gonzalez-Herrera KN, Asara JM, Haigis MC, Struhl K. Metformin and phenformin deplete TCA cycle and glycolytic intermediates during cell transformation. *Proceedings of the National Academy of Sciences (PNAS)*. 2014;111(29):10574-9. DOI: https://doi.org/10.1073/pnas.1409844111
104. Wheaton WW, Weinberg SE, Hamanaka RB, Soberanes S, Sullivan LB, Anso E, et al. Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. *eLife*. 2014;3:e02242. DOI: https://doi.org/10.7554/eLife.02242
105. McCreight LJ, Bailey CJ, Pearson ER. Metformin and the gastrointestinal tract. *Diabetologia*. 2016;59(3):426-35. DOI: https://doi.org/10.1007/s00125-015-3844-9
106. Martirosyan, D. M., Stratton, S. Quantum and Tempus theories of functional food science in practice. *Functional Food Science* 2023; 3(5): 55-62. DOI: https://doi.org/10.31989/ffs.v3i5.1122
107. Marecek S., Martirosyan D. An assessment of clinical trials used in functional food science. *Functional Foods in Health and Disease* 2023; 13(2): 22-35. DOI: https://www.doi.org/10.31989/ffhd.v13i2.1077
108. Martirosyan D.M., Sanchez S.S. Quantum Theory of Functional Food Science: Establishment of dosage of bioactive compounds in functional food products. *Functional Food Science* 2022; 3(2): 79-93. DOI: https://doi.org/10.31989/ffs.v2i3.915
109. Dutka P., Martirosyan D. The effectiveness of resveratrol in the management of childhood obesity. *Functional Food Science* 2023; 3(10): 193-216. DOI: https://www.doi.org/10.31989/ffs.v3i10.1244
110. Son J., Martirosyan D. Salient Features for GRAS Status Affirmation. *Functional Food Science* 2024; 4(8): 299-308. DOI: https://doi.org/10.31989/ffs.v4i8.1417
111. Baghdasaryan A., Martirosyan D. Economic implications of functional foods. *Functional Food Science* 2024; 4(6): 216-227. DOI: https://www.doi.org/10.31989/ffs.v4i6.1379
112. Melyan G., Barseghyan A., Dangyan K., Sahakyan N., Vardanyan A., Martirosyan Y. Impact of aeroponic cultivation and plant growth regulators on the biochemical composition of grapevine leaves. *Functional Food Science* 2024; 4(10): 359-269. DOI: https://www.doi.org/10.31989/ffs.v4i10.1458
113. Daryadar M., Tadevosyan A., Roosta H. R., Ghorbanpour M., Ghahramanyan A., Stepanyan A., Matevosyan A. A preliminary study of the domestication of *Falcaria vulgaris* Bernh. in the Ararat Valley of Armenia. *Bioactive Compounds in Health and Disease* 2025; 8(4): 144 - 155. DOI: https://www.doi.org/10.31989/bchd.8i4.1613
114. Tadevosyan A., Martirosyan G., Tovmasyan G., Terteryan H., Gasparyan N. Evaluation of several lettuce varieties based on economically valuable traits and nutritional value under vertical hydroponic cultivation conditions. *Bioactive Compounds in Health and Disease* 2025; 8(3): 104-113. DOI: https://www.doi.org/10.31989/bchd.8i3.1595
115. Beglaryan I., Gasparyan G., Khachatryan S., Yeritsyan S., Eloyan A., Jhangiryan T. The change in functional components in mulberry fruits (*Morus alba* L.) through the development of an optimal land transformation scheme for different land types. *Bioactive Compounds in Health and Disease* 2025; 8(3): 113-129. DOI: https://www.doi.org/10.31989/bchd.8i3.1583
116. Yargatti R., Deshmane A. R. Sensory impacts and consumer acceptability of using dates as an alternative functional sweetener in traditional Indian sweets. *Functional Food Science* 2025; 5[1]: 30-45 DOI: https://www.doi.org/10.31989/ffs.v5i2.1522
117. Pilevar Z., Martirosyan D., Ranaei V., Taghizadeh M., Balasjin N. M., Ferdousi R., Hosseini H. Biological activities, chemical and bioactive compounds of *Echinophora platyloba* DC: A systematic review. *Bioactive Compounds in Health and Disease* 2024; 7(2):95-109. DOI: https://doi.org/10.31989/bchd.v7i2.1283
118. Zhou J. V ., Martirosyan D. Functional foods for cholesterol management: A comparison between the United States and Japan. *Functional Food Science* 2024; 4(6): 228-250. DOI: https://www.doi.org/10.31989/ffs.v4i6.13
119. Trachtenberg T., Martirosyan D. Addressing vitamin D deficiency through nutritional strategies. *Bioactive Compounds in Health and Disease* 2024; 7(6): 289-301, DOI: https://www.doi.org/10.31989/bchd.v7i6.1364
120. Rodwal I., Shinwari H. R., Naizi M. H., Sherzada H., Gopi M. Lactoferrin: Structure, biological functions as functional food and maintaining health. *Functional Food Science* 2024; 4(12): 495-507. DOI: https://www.doi.org/10.31989/ffs.v4i12.1407

121. Salman, I., Martirosyan, D. Migraine management: a review of healthy diets and bioactive compounds. *Functional Food Science* 2023; 3(8): 129-153. DOI: https://www.doi.org/10.31989/ffs.v3i8.1149
122. Shiri S., Gharanjig K., Heidari H., Tahghighi A. Plant Sources Containing Berberine with Potential of Control Type 2 Diabetes Mellitus: A Brief Literature Review. *Functional Food Science* 2024; 4(12): 466-478. DOI: https://doi.org/10.31989/ffs.v4i12.1461
123. Chan, J. C. N., Yang, A., Chu, N., and Chow, E. Current type 2 diabetes guidelines: Individualized treatment and how to make the most of metformin. *Diabetes, Obesity and Metabolism*, 2024; 26 Suppl 3, 55-74. DOI: https://doi.org/10.1111/dom.15700
124. Bailey C. J. Metformin: Therapeutic profile in the treatment of type 2 diabetes. *Diabetes, Obesity and Metabolism*, 2024; 26 Suppl 3, 3-19. DOI: https://doi.org/10.1111/dom.15663
125. Petrie J. R. Metformin beyond type 2 diabetes: Emerging and potential new indications. *Diabetes, Obesity and Metabolism*, 2024; 26 Suppl 3 31-41. DOI: https://doi.org/10.1111/dom.15756
126. Xie, C., Iroga, P., Bound, M. J., Grivell, J., Huang, W., Jones, K. L., et al. Impact of the timing of metformin administration on glycaemic and glucagon-like peptide-1 responses to intraduodenal glucose infusion in type 2 diabetes: a double-blind, randomised, placebo-controlled, crossover study. *Diabetologia*, 2024; 67(7), 1260-1270. DOI: https://doi.org/10.1007/s00125-024-06131-6
127. Chaudhary, S., and Kulkarni, A. Metformin: Past, Present, and Future. *Current Diabetes Reports*, 2024; 24(6), 119-130. DOI: https://doi.org/10.1007/s11892-024-01539-1
128. Noel DS. Kinetic study of normal and sustained release dosage forms of metformin in normal subjects. J Int Biomed Inform Data 1980; 1:9-20.