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Comparative Review of Bioactive Molecules for Antidiabetic Properties

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This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Diabetes mellitus is a significant global health concern characterized by chronic hyperglycemia and associated metabolic dysfunctions that impact millions of lives. Despite advancements in its management, the need for safer, effective, and affordable antidiabetic therapies remains unmet. This review delves into the exploration of bioactive molecules derived from natural sources, such as phytochemicals and peptides, as well as synthetic compounds, presenting a comparative analysis of their therapeutic potential. It highlights their diverse mechanisms of action, including modulation of insulin secretion, glucose uptake, and reduction of oxidative stress. Additionally, the review discusses their efficacy, safety profiles, and future applications, emerging trends, emphasizing their role in addressing the challenges of diabetes management and improving patient outcomes. The study emphasizes the need for further research into synergistic effects and formulation strategies to improve their clinical use.

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Keywords: Bioactive; antidiabetic; polyphenol; flavonoid; alkaloid; terpenoid.

1. INTRODUCTION

Diabetes affects millions worldwide and poses significant healthcare challenges. While conventional treatments like insulin and oral hypoglycemic agents are effective, they come with limitations, including side effects and patient non-compliance (Khursheed et al., 2019). Bioactive molecules offer promising alternatives due to their diverse mechanisms of action and minimal adverse effects. This review consolidates current knowledge on various bioactive compounds with antidiabetic properties (Tran et al., 2020).

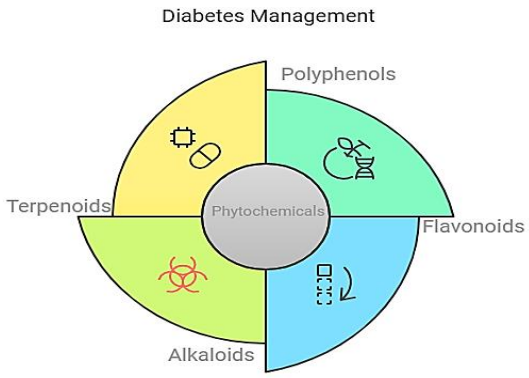

Fig. 1. Bioactive phytoconstituents responsible for antidiabetic activity

2. PHYTOCHEMICALS WITH ANTIDIABETIC POTENTIAL

Bioactive Phytoconstituents Responsible for Antidiabetic Activity includes Polyphenols, Flavonoids, Alkaloids, Terpenoids etc.

Phytochemicals, derived from plants, have shown significant promise in diabetes management:

1. **Polyphenols:** Found in tea, berries, and cocoa, polyphenols improve insulin sensitivity by modulating glucose metabolism and reducing oxidative stress (Paquette et al., 2017).

The role of polyphenols in insulin sensitivity:

Polyphenols are a diverse group of naturally occurring compounds found in various plant-based foods, including tea, berries, and cocoa. These compounds have garnered significant attention in recent years due to their potential health benefits, particularly in improving insulin sensitivity. This document explores how polyphenols modulate glucose metabolism and reduce oxidative stress, contributing to better insulin sensitivity and overall metabolic health (Paquette et al., 2017).

Understanding polyphenols:

Polyphenols are classified into several categories, including flavonoids, phenolic acids, polyphenolic amides, and other polyphenols. They are abundant in fruits, vegetables, whole grains, and beverages like tea and coffee. Their antioxidant properties are well-documented, which helps combat oxidative stress in the body (Roman et al., 2019).

Mechanisms of action:

Modulation of glucose metabolism (Nie & Cooper, 2021): Polyphenols influence glucose metabolism through various mechanisms:

a) **Enhancing Insulin Sensitivity:** Polyphenols can improve the action of insulin, allowing cells to take up glucose more effectively. This is crucial for maintaining normal blood sugar levels and preventing insulin resistance.
b) **Inhibition of Carbohydrate-Digesting Enzymes:** Certain polyphenols inhibit enzymes like alpha-glucosidase and alpha- amylase, which are responsible for breaking down carbohydrates into glucose. This results in a slower release of glucose into the bloodstream.
c) **Regulation of Glucose Transporters:** Polyphenols may enhance the expression and activity of glucose transporters, such as GLUT4, which facilitates glucose uptake in muscle and fat tissues.

Reduction of oxidative stress: Oxidative stress is a condition characterized by an imbalance between free radicals and antioxidants in the body, leading to cellular damage and inflammation. Polyphenols help reduce oxidative stress through (Srinivasan et al., 2019):

a) **Antioxidant activity:** Polyphenols scavenge free radicals, thereby protecting cells from oxidative damage. This is particularly important in tissues involved in

glucose metabolism (Srinivasan et al., 2019; Unuofin & Lebelo, 2020).

b) **Anti-inflammatory effects:** By reducing inflammation, polyphenols can help improve insulin sensitivity. Chronic inflammation is a known contributor to insulin resistance.

Sources of polyphenols:

To incorporate polyphenols into your diet, consider the following sources:

- **Tea:** Green tea and black tea are rich in catechins and flavonoids.
- **Berries:** Blueberries, strawberries, and blackberries are excellent sources of anthocyanins.
- **Cocoa:** Dark chocolate and cocoa powder contain high levels of flavonoids, particularly epicatechin.

Polyphenols play a significant role in improving insulin sensitivity by modulating glucose metabolism and reducing oxidative stress. Including polyphenol-rich foods in your diet can be a beneficial strategy for enhancing metabolic health and preventing conditions such as type 2 diabetes. As research continues to uncover the complexities of these compounds, their potential as functional foods in promoting health becomes increasingly evident (Testa et al., 2016; Ardalani et al., 2021; Ahangarpour et al., 2019).

2. **Flavonoids:** Present in citrus fruits, they inhibit α-glucosidase and enhance insulin secretion (Barber et al., 2021).

Flavonoids and their role in diabetes management:

Flavonoids, a diverse group of phytonutrients found abundantly in citrus fruits, have garnered attention for their potential health benefits, particularly in the context of diabetes management. This document explores the mechanisms by which flavonoids inhibit α-glucosidase activity and enhance insulin secretion, highlighting their significance in regulating blood sugar levels (Soares et al., 2017).

Flavonoids are a class of polyphenolic compounds that are widely distributed in the plant kingdom. They are known for their antioxidant properties and are found in various fruits, vegetables, and beverages. Citrus fruits, such as oranges, lemons, and grapefruits, are particularly rich in flavonoids, making them an important dietary source.

Table 1. Different sources of polyphenols

Polyphenol Source	Examples	Key Benefits	Mechanism of Action	Additional Notes
Tea	Green tea, Black tea, Oolong tea	Improves insulin sensitivity	Modulates glucose metabolism and reduces oxidative stress	Contains catechins (EGCG) known for strong antioxidant properties
Berries	Blueberries, Strawberries, Raspberries	Enhances glucose regulation	Combats oxidative stress and supports metabolic pathways	Rich in anthocyanins, which also support heart health
Cocoa	Dark chocolate, Cocoa powder	Promotes insulin sensitivity	Antioxidant activity and glucose metabolism modulation	Flavanols in cocoa improve endothelial function
Fruits	Apples, Grapes, Pomegranates	Regulates blood sugar levels	Polyphenols reduce post-meal glucose spikes	Resveratrol in grapes has additional anti-inflammatory benefits
Spices and Herbs	Cinnamon, Turmeric, Oregano	Improves insulin signaling	Contains bioactive compounds like curcumin and cinnamaldehyde	Regular consumption may reduce the risk of Type 2 Diabetes
Vegetables	Onions, Broccoli, Spinach	Supports metabolic health	High antioxidant activity to reduce oxidative stress	Also rich in vitamins and minerals that support overall health

Table 2. Flavonoid subclass and their biological activities

Flavonoid Subclass	Source	Biological Activity	Example
Flavanones	Citrus fruits (orange, lemon)	Antioxidant, enhance insulin secretion, anti-inflammatory	Naringin, Hesperidin
Flavonols	Onions, kale, broccoli	Antioxidant, anti-cancer, anti-inflammatory	Quercetin, Kaempferol
Isoflavones	Soybeans, chickpeas	Phytoestrogen activity, reduce menopausal symptoms	Genistein, Daidzein
Anthocyanins	Blueberries, cherries	Antioxidant, anti-diabetic, cardiovascular protection	Cyanidin, Delphinidin
Flavones	Parsley, celery	Anti-inflammatory, anti-cancer, antioxidant	Apigenin, Luteolin
Catechins (Flavanols)	Green tea, cocoa	Antioxidant, anti-cardiovascular, neuroprotective	Epicatechin, Epigallocatechin gallate (EGCG)
Chalcones	Apples, tomatoes	Anti-inflammatory, antimicrobial, antioxidant	Phloretin, Arbutin

Mechanism of action:

Inhibition of α-glucosidase: One of the key mechanisms by which flavonoids exert their effects on glucose metabolism is through the inhibition of α-glucosidase, an enzyme responsible for breaking down carbohydrates into glucose in the small intestine. By inhibiting this enzyme, flavonoids can slow down the absorption of glucose, leading to a more gradual increase in blood sugar levels after meals. This action can be particularly beneficial for individuals with diabetes, as it helps to prevent spikes in blood glucose (Hajiaghaalipour et al., 2015).

Enhancement of insulin secretion: In addition to their inhibitory effects on α-glucosidase, flavonoids have also been shown to enhance insulin secretion from pancreatic β-cells. Insulin is a crucial hormone that regulates blood sugar levels by facilitating the uptake of glucose into cells. By promoting insulin secretion, flavonoids can help maintain better glycemic control, further supporting their role in diabetes management (Baska et al., 2021).

The presence of flavonoids in citrus fruits offers a promising avenue for improving blood sugar regulation and enhancing insulin sensitivity. Their dual action of inhibiting α-glucosidase and promoting insulin secretion underscores their potential as a natural strategy for managing diabetes. Incorporating citrus fruits into the diet may provide not only a delicious source of nutrients but also a functional approach to supporting metabolic health (Bhambhani et al., 2021).

3. **Alkaloids:** Potential antidiabetic phytochemicals in Plants Compounds like berberine reduce hepatic glucose production and improve insulin sensitivity (Hajzadeh et al., 2011; Ardalani et al., 2021).

Alkaloids and their impact on hepatic glucose production and insulin sensitivity: Alkaloids are a diverse group of naturally occurring compounds that often exhibit significant pharmacological effects (Cui et al., 2016). Among these compounds, berberine has garnered attention for its potential to reduce hepatic glucose production and improve insulin sensitivity. This document explores the mechanisms through which berberine and similar alkaloids exert their effects on glucose metabolism and their implications for managing conditions such as type 2 diabetes.

Alkaloids are nitrogen-containing compounds that are primarily derived from plants. They are known for their wide range of biological activities, including analgesic, anti-inflammatory, and antidiabetic effects. Berberine, a prominent alkaloid found in several plants such as Goldenseal and Barberry, has been extensively studied for its role in glucose metabolism (Yang et al., 2022).

Mechanisms of action:

Reduction of hepatic glucose production: Berberine has been shown to inhibit

gluconeogenesis, the metabolic pathway that generates glucose from non-carbohydrate substrates in the liver. This action is primarily mediated through the activation of AMP-activated protein kinase (AMPK), a key regulator of energy homeostasis. By activating AMPK, berberine enhances the uptake of glucose by peripheral tissues and reduces the production of glucose in the liver (Tao et al., 2025).

Improvement of insulin sensitivity: In addition to its effects on glucose production, berberine also improves insulin sensitivity. It enhances the action of insulin in peripheral tissues, facilitating glucose uptake and utilization. This dual action not only helps in lowering blood glucose levels but also contributes to better overall metabolic health.

Clinical implications:

The ability of berberine to reduce hepatic glucose production and improve insulin sensitivity makes it a promising candidate for the management of type 2 diabetes and metabolic syndrome. Clinical studies have demonstrated that berberine supplementation can lead to significant reductions in fasting blood glucose and HbA1c levels, making it an attractive alternative or adjunct to conventional diabetes therapies (Li et al., 2022).

Alkaloids, particularly berberine, play a crucial role in modulating glucose metabolism through their effects on hepatic glucose production and insulin sensitivity. As research continues to unveil the mechanisms behind these effects, berberine may become an integral part of therapeutic strategies aimed at managing diabetes and improving metabolic health. Further studies are needed to fully understand the long-term implications and potential applications of alkaloids in clinical practice (Ghasemi-Gojani et al., 2022).

4. **Terpenoids:** Found in ginseng and other herbs, these compounds stimulate insulin secretion and have anti-inflammatory properties (Prakash, 2017).

Terpenoids: Their role in insulin secretion and anti-inflammatory properties:

Terpenoids, a diverse class of organic compounds found in various plants, including ginseng and other herbs, have garnered attention for their potential health benefits. This document explores the significance of terpenoids, particularly their ability to stimulate insulin secretion and their anti-inflammatory properties, highlighting their importance in herbal medicine and potential therapeutic applications (Szczuka et al., 2019).

Terpenoids, also known as isoprenoids, are a large and varied class of natural compounds derived from five-carbon isoprene units. They are primarily responsible for the aromatic qualities of many plants and play crucial roles in plant defence mechanisms. Beyond their ecological functions, terpenoids have been studied for their pharmacological properties, particularly in relation to metabolic health and inflammation.

Insulin secretion stimulation:

One of the notable effects of terpenoids is their ability to stimulate insulin secretion. Insulin is a vital hormone that regulates glucose metabolism, and its secretion is crucial for maintaining blood sugar levels. Certain terpenoids found in ginseng, such as ginsenosides, have been shown to enhance insulin sensitivity and promote insulin release from pancreatic beta cells. This action can be particularly beneficial for individuals with insulin resistance or type 2 diabetes, as it may help improve glycemic control (Xavier et al., 2024).

Anti-inflammatory properties:

In addition to their effects on insulin secretion, terpenoids exhibit significant anti-inflammatory properties. Chronic inflammation is linked to various health conditions, including metabolic syndrome, cardiovascular diseases, and autoimmune disorders. Terpenoids can modulate inflammatory pathways by inhibiting the production of pro-inflammatory cytokines and promoting the release of anti-inflammatory mediators. This dual action not only helps in reducing inflammation but also supports overall metabolic health (Yan et al., 2019).

Terpenoids are valuable compounds found in ginseng and other herbs, known for their ability to stimulate insulin secretion and exhibit anti-inflammatory effects. Their therapeutic potential makes them a subject of interest in the field of herbal medicine and metabolic health. Further research is essential to fully understand their mechanisms of action and to explore their applications in treating metabolic disorders and inflammatory conditions.

Table 3. Alkaloids and their antidiabetic activities

Alkaloid	Source	Mechanism of Antidiabetic Activity	Example(s)
Berberine	Berberis species, goldenseal	Reduces hepatic glucose production, improves insulin sensitivity	Berberine chloride
Caffeine	Coffee, tea, cocoa	Enhances energy expenditure, modulates glucose metabolism	Methylxanthine
Vincamine	Periwinkle plant	Improves cerebral glucose utilization	Vincamine
Matrine	Sophora flavescens	Enhances insulin secretion, protects pancreatic β-cells	Matrine, Oxymatrine
Harmine	Peganum harmala, Passiflora	Promotes β-cell proliferation, improves insulin production	Harmine
Ephedrine	Ephedra species	Increases glucose uptake via adrenergic pathways	Ephedrine
Quinidine	Cinchona bark	Modulates insulin secretion, improves glucose tolerance	Quinidine sulfate
Reserpine	Rauwolfia serpentina	Lowers blood pressure, indirectly affecting glucose metabolism	Reserpine

Table 4. Terpenoids and their antidiabetic activities

Terpenoid	Source	Mechanism of Antidiabetic Activity	Example(s)
Ginsenosides	Ginseng (Panax species)	Stimulate insulin secretion, enhance glucose uptake, anti-inflammatory	Rg1, Rb1, Rd
Limonene	Citrus fruits (lemon, orange)	Improves insulin sensitivity, reduces oxidative stress	Limonene
Carnosol	Rosemary, sage	Activates AMPK pathway, reduces blood glucose levels	Carnosol
Beta-Caryophyllene	Black pepper, cloves	Modulates glucose metabolism via CB2 receptor activation	Beta-Caryophyllene
Ursolic acid	Apple peel, rosemary	Enhances insulin secretion, promotes pancreatic β-cell function	Ursolic acid
Oleanolic acid	Olive leaves, holy basil	Improves insulin sensitivity, inhibits α-glucosidase	Oleanolic acid
Menthol	Peppermint, spearmint	Enhances glucose uptake, anti-inflammatory	Menthol
Linalool	Lavender, coriander	Reduces oxidative stress, improves glucose metabolism	Linalool

5. **Peptides with Antidiabetic Properties:** Explores the role of bioactive peptides derived from food proteins and synthetic sources in exhibiting antidiabetic effects. With the rising prevalence of diabetes worldwide, the search for effective therapeutic agents has led to the investigation of peptides as potential candidates. This overview will delve into the mechanisms by which these peptides exert their antidiabetic properties, their sources, and their implications for diabetes management (Manandhar & Ahn, 2015).

Diabetes mellitus is a chronic metabolic disorder characterized by high blood sugar levels due to insulin resistance or insufficient insulin production. The management of diabetes often involves lifestyle changes, medication, and in some cases, insulin therapy. Recent research has highlighted the potential of bioactive peptides, which are short chains of amino acids, in regulating blood glucose levels and improving insulin sensitivity (Manandhar & Ahn, 2015).

Sources of bioactive peptides:

Bioactive peptides can be derived from various sources, including:

a) **Food Proteins (Manandhar & Ahn, 2015):**

- Dairy products (e.g., casein, whey)
- Meat and fish
- Plant proteins (e.g., soy, legumes, grains)

b) **Synthetic Sources:**

- Chemically synthesized peptides
- Recombinant DNA technology to produce specific peptide sequences

Mechanisms of antidiabetic action:

Bioactive peptides exhibit their antidiabetic properties through several mechanisms (Belfiore et al., 2009):

a) **Inhibition of dipeptidyl peptidase-4 (DPP-4):** Some peptides can inhibit the DPP-4 enzyme, which is responsible for the degradation of incretin hormones. By prolonging the action of these hormones, peptides can enhance insulin secretion and reduce blood glucose levels.
b) **Enhancement of insulin sensitivity:** Certain peptides may improve the sensitivity of cells to insulin, facilitating better glucose uptake and utilization.
c) **Regulation of glucose metabolism:** Peptides can influence glucose metabolism by modulating the expression of key enzymes involved in gluconeogenesis and glycolysis.

Anti-inflammatory effects:

Chronic inflammation is a contributing factor to insulin resistance. Some bioactive peptides possess anti-inflammatory properties that may help mitigate this issue.

Potential applications:

The incorporation of bioactive peptides into functional foods and dietary supplements presents a promising avenue for diabetes management (Jensen et al., 2007). These peptides can be utilized in:

- Nutraceuticals aimed at improving glycemic control.
- Functional foods designed to enhance overall metabolic health.
- Therapeutic agents in the development of new diabetes medications.

Bioactive peptides derived from food proteins and synthetic sources hold significant promise in the fight against diabetes. Their ability to modulate blood glucose levels and improve insulin sensitivity makes them valuable candidates for further research and application in diabetes management. As the understanding of these peptides expands, they may play a crucial role in developing innovative strategies to combat this global health challenge (Jensen et al., 2007).

Synthetic sources exhibit antidiabetic effects:

1. **GLP-1 analogs:** Mimicking glucagon-like peptide-1, these peptides enhance insulin secretion and reduce glucagon levels (Teixeira & Fussenegger, 2017).
2. **Insulin mimetics:** Synthetic peptides that mimic insulin action by activating insulin receptors (Lutz, 2012).

Table 5. GLP-1 analog and their antidiabetic activities

GLP-1 Analog	Mechanism of Action	Clinical Benefits	Example(s)
Exenatide	Mimics GLP-1 to enhance insulin secretion, suppress glucagon	Reduces postprandial glucose, promotes weight loss	Byetta®, Bydureon®
Liraglutide	Activates GLP-1 receptors to stimulate insulin release	Improves glycemic control, supports cardiovascular health	Victoza®, Saxenda®
Dulaglutide	Long-acting GLP-1 receptor agonist	Reduces HbA1c, promotes weight reduction	Trulicity®
Semaglutide	Stimulates insulin secretion, delays gastric emptying	Superior glycemic control, cardiovascular protection	Ozempic®, Rybelsus®
Albiglutide	GLP-1 receptor activation, prolongs GLP-1 activity	Lowers HbA1c, enhances post-meal glucose regulation	Eperzan® (discontinued in some regions)
Eperzan	Extended half-life GLP-1 analog	Reduces fasting and postprandial glucose levels	Albiglutide (formerly)
Efpeglenatide	Long-acting GLP-1 receptor agonist	Improves glycemic control, provides potential CV benefits	Experimental in some regions

Insulin mimetics: Synthetic peptides that mimic insulin action:

Insulin mimetics represent a groundbreaking area of research in diabetes treatment, focusing on synthetic peptides designed to activate insulin receptors and replicate the effects of natural insulin (Mehanna, 2013). This document delves into the mechanisms, potential benefits, and challenges associated with insulin mimetics, highlighting their significance in managing diabetes and improving metabolic health.

Insulin is a crucial hormone that regulates glucose metabolism, and its deficiency or resistance leads to diabetes mellitus. Traditional insulin therapy, while effective, has limitations such as the need for injections and potential side effects. Insulin mimetics offer a promising alternative by providing a means to stimulate insulin receptors without the need for exogenous insulin administration.

Mechanism of action:

Insulin mimetics are synthetic peptides engineered to bind to insulin receptors, thereby activating the signaling pathways typically triggered by natural insulin (Torres-Piedra et al., 2010). These peptides can mimic the conformational changes that occur when insulin binds to its receptor, leading to glucose uptake in cells, inhibition of gluconeogenesis, and promotion of glycogen synthesis (Bhaskarachary & Joshi, 2018).

Advantages of insulin mimetics:

a. **Oral administration:** Many insulin mimetics can be formulated for oral delivery, which is a significant advantage over traditional insulin injections.
b. **Reduced side effects:** By specifically targeting insulin receptors, these peptides may minimize the risk of hypoglycemia and other side effects associated with insulin therapy.
c. **Improved patient compliance:** The convenience of oral administration can lead to better adherence to treatment regimens among patients.

Challenges and considerations: Despite their potential, the development of insulin mimetics faces several challenges:

- **Stability:** Synthetic peptides must be stable in the gastrointestinal tract to be effective when taken orally.
- **Efficacy:** Ensuring that these peptides can effectively mimic all the actions of insulin is crucial for their success.
- **Regulatory approval:** As with any new therapeutic agent, insulin mimetics must undergo rigorous testing and regulatory scrutiny before they can be widely used in clinical practice.

Insulin mimetics represent a promising frontier in diabetes management, offering the potential for more convenient and effective treatment options. Continued research and development in this area may lead to innovative therapies that improve the quality of life for individuals with diabetes, making it an exciting field to watch in the coming years.

2. **Amylin analogs:** Regulate glucose homeostasis by slowing gastric emptying and promoting satiety.

Emerging trends in bioactive molecule for antidiabetic activity:

Nanotechnology in antidiabetic drug delivery: Nanotechnology has emerged as a transformative approach in drug delivery, especially in the context of diabetes management. The use of nanocarriers, such as nanoparticles, liposomes, micelles, and dendrimers, offers several advantages:

1. Improved Bioavailability: Many bioactive molecules derived from natural sources have poor solubility and stability, which limits their therapeutic potential. Nanocarriers enhance solubility, protect against enzymatic degradation, and facilitate targeted delivery, thereby improving bioavailability.
2. Controlled Release: Nanoparticles enable sustained and controlled release of antidiabetic drugs, reducing the frequency of administration and enhancing patient compliance.
3. Targeted Delivery: Functionalized nanocarriers can be engineered to target specific tissues, such as pancreatic beta cells, liver, or adipose tissues, reducing off- target effects and enhancing therapeutic efficacy.
4. Examples of Nanotechnology Applications:

- Curcumin-loaded nanoparticles have demonstrated improved glucose-lowering effects compared to free curcumin.
- Insulin-loaded nanospheres have been developed to mimic physiological insulin release patterns.

Personalized medicine in diabetes management: Personalized medicine leverages advances in genomics, proteomics, and metabolomics to tailor therapies to individual patients based on their unique genetic, metabolic, and lifestyle profiles. This approach is particularly promising in diabetes, given the heterogeneity of the disease.

Genetic Profiling: Identifying genetic polymorphisms associated with diabetes risk and drug metabolism can guide the selection of bioactive molecules and therapies. For instance, patients with specific genetic variants in the SLC30A8 gene may benefit from zinc-enhanced therapies.

Metabolomic Insights: Analyzing metabolic biomarkers can help stratify patients into subtypes of diabetes, such as Type 1, Type 2, or latent autoimmune diabetes in adults (LADA), enabling targeted interventions.

Bioactive Molecules and Personalization:

- Resveratrol has shown differential effects in patients based on their gut microbiome composition.
- Omega-3 fatty acids may be more effective in individuals with specific lipid profiles.

Integration with Digital Health: Combining wearable devices, continuous glucose monitoring, and AI-driven analytics can enhance the application of personalized medicine in real-world settings.

Combinatorial approaches: Diabetes often requires a multifaceted treatment strategy due to its complex pathophysiology. Combinatorial approaches involving bioactive molecules and conventional drugs have gained attention for their synergistic effects.

Table 6. Insulin mimetic and their antidiabetic activities

Insulin Mimetic	Mechanism of Action	Clinical Benefits	Example(s)
Prandial Insulin Mimetics (Insulin Glulisine, Insulin Lispro)	Mimic rapid-acting insulin, activate insulin receptors to facilitate glucose uptake	Quick onset and short duration of action, used for meal-time control	Insulin Lispro (Humalog®), Insulin Glulisine (Apidra®)
Insulin Detemir	Long-acting insulin analog, activates insulin receptor	Provides basal insulin coverage with prolonged action	Levemir®
Insulin Degludec	Ultra-long-acting insulin, mimics basal insulin function	Stable and extended release for glucose regulation	Tresiba®
Afrezza	Inhaled insulin mimetic, rapidly activates insulin receptors	Rapid action for meal-time insulin management	Afrezza® (Inhaled insulin)
Insulin Glargine	Long-acting insulin analog that mimics basal insulin	Constant, steady release of insulin for 24 hours	Lantus®, Toujeo®
Peglispro	Engineered insulin analog with longer half- life	Improved basal glucose control with reduced injections	Experimental (clinical trials)

Table 7. Amylin analog and their antidiabetic activities

Amylin Analog	Mechanism of Action	Clinical Benefits	Example(s)
Pramlintide	Slows gastric emptying, reduces postprandial glucose spikes, promotes satiety	Improves glycemic control, reduces insulin doses needed, supports weight loss	Symlin® (Pramlintide)

Synergy in Mechanisms of Action: Combining bioactive molecules with standard antidiabetic drugs can target multiple pathways, such as glucose absorption, insulin sensitivity, and beta-cell function.

- Example: Berberine, when combined with metformin, has demonstrated enhanced efficacy in lowering blood glucose levels and improving lipid profiles.

5. **Reducing Side Effects:** Combinatorial therapies can lower the required doses of conventional drugs, reducing their associated side effects.

- Example: Quercetin combined with sulfonylureas reduces oxidative stress and mitigates drug-induced toxicity.

Potential Combinations:

- Polyphenols like catechins combined with DPP-4 inhibitors.
- Flavonoids like luteolin with SGLT2 inhibitors for enhanced glucose excretion.

Advances in Formulation Science: Developing co-formulations, such as nanoparticles carrying both a bioactive molecule and a synthetic drug, is a cutting- edge approach in this domain.

These emerging trends highlight the potential of integrating advanced technologies and innovative approaches to revolutionize diabetes management. By addressing challenges such as bioavailability, patient variability, and polypharmacy, they pave the way for more effective and personalized therapies.

3. SYNTHETIC COMPOUNDS AS ANTIDIABETIC AGENTS

This document explores the various synthetic molecules that have been developed as antidiabetic agents. With the rising prevalence of diabetes globally, the need for effective treatments has led to significant advancements in the field of synthetic chemistry. This overview will highlight some of the key synthetic compounds that have shown promise in managing blood glucose levels and improving insulin sensitivity.

Overview of synthetic antidiabetic agents:

Synthetic antidiabetic agents are designed to mimic or enhance the body's natural mechanisms for regulating blood sugar levels. These compounds can be classified into several categories based on their mechanisms of action, including:

1. **Insulin secretagogues:** These compounds stimulate the pancreas to release more insulin. Examples include sulfonylureas and meglitinides.
2. **Biguanides:** Metformin, the most well-known biguanide, decreases hepatic glucose production and increases insulin sensitivity in peripheral tissues.
3. **Thiazolidinediones (TZDs):** These agents improve insulin sensitivity by acting on adipose tissue, muscle, and the liver. Pioglitazone and rosiglitazone are notable examples.
4. **Dipeptidyl peptidase-4 (DPP-4) inhibitors:** These drugs enhance the body's incretin hormones, which help to regulate insulin secretion. Sitagliptin and saxagliptin are commonly used DPP-4 inhibitors.
5. **Sodium-glucose cotransporter-2 (SGLT2) inhibitors:** This class of drugs promotes the excretion of glucose through urine, thereby lowering blood sugar levels. Canagliflozin and empagliflozin are examples of SGLT2 inhibitors.

Recent developments in synthetic antidiabetic compounds:

Recent research has focused on developing novel synthetic compounds that offer improved efficacy and safety profiles. Some of the promising developments include:

- **Dual-acting agents:** These compounds target multiple pathways involved in glucose metabolism, potentially leading to better glycemic control with fewer side effects.
- **Long-acting formulations:** Innovations in drug delivery systems have led to the development of long-acting synthetic agents that require less frequent dosing, improving patient compliance.
- **Combination therapies:** The use of synthetic compounds in combination with other antidiabetic agents is being explored to enhance therapeutic outcomes and minimize the risk of adverse effects.

The development of synthetic compounds as antidiabetic agents represents a significant

advancement in diabetes management. Ongoing research and innovation in this field continue to provide new options for patients, improving their quality of life and health outcomes. As the understanding of diabetes and its underlying mechanisms grows, the potential for even more effective synthetic therapies remains promising.

Several synthetic molecules have been developed as antidiabetic agents:

1. **Sulfonylureas:** Stimulate pancreatic insulin secretion.
2. **Thiazolidinediones:** Improve insulin sensitivity by activating PPAR-γ.
3. **DPP-4 Inhibitors:** Prolong the action of incretin hormones, enhancing insulin secretion.

Mechanisms of action: Bioactive molecules act through diverse mechanisms, including:

1. **Insulin sensitization:** Enhancing insulin action at cellular levels.
2. **Glucose uptake stimulation:** Facilitating glucose transport into cells.
3. **Enzyme inhibition:** Reducing carbohydrate digestion and glucose absorption.
4. **Antioxidant effects:** Mitigating oxidative stress-related complications.

Comparative analysis: comparative study of bioactive phytoconstituents responsible for antidiabetic activity (Table 9).

Challenges and strategies to overcome challenges:

The bioavailability and pharmacokinetics of bioactive molecules used in antidiabetic therapy are critical aspects that determine their therapeutic efficacy and safety. Here's an overview of the key challenges and considerations:

Bioavailability challenges: Bioavailability refers to the fraction of an administered dose of a drug that reaches the systemic circulation in its active form. For antidiabetic bioactive molecules, common challenges include:

- **Poor solubility**: Many antidiabetic molecules, such as some plant-derived bioactives, are poorly water-soluble, limiting their absorption in the gastrointestinal tract (GIT).
- **Low permeability**: Bioactives may face challenges crossing the intestinal epithelium due to their chemical structure or molecular size.
- **First-pass metabolism**: Extensive hepatic metabolism can significantly reduce the amount of bioactive compound reaching systemic circulation.
- **Instability in GIT**: Many bioactives are unstable in the acidic environment of the stomach or are degraded by digestive enzymes.

Table 8. Different synthetic compounds

Class of Drug	Mechanism of Action	Clinical Benefits	Examples	Side Effects
Sulfonylureas	Stimulate pancreatic β-cells to secrete more insulin	Effective for lowering blood glucose, used for Type 2 diabetes management	Glibenclamide, Glimepiride, Gliclazide	Hypoglycemia, weight gain, gastrointestinal issues
Thiazolidinediones (TZDs)	Activate PPAR-γ receptors to improve insulin sensitivity	Reduce insulin resistance, lower fasting blood glucose, cardiovascular benefits	Pioglitazone, Rosiglitazone	Weight gain, fluid retention, edema, risk of fractures
DPP-4 Inhibitors	Inhibit DPP-4 enzyme, prolonging the action of incretin hormones, which increase insulin secretion	Improve postprandial glucose control, weight- neutral	Sitagliptin, Saxagliptin, Linagliptin	Nasopharyngitis, headache, gastrointestinal issues

Table 9. Different Phytoconstituent and their Mechanism of Action

Phytoconstituent	Sources	Mechanism of Action	Examples of Compounds	References
Polyphenol	Green tea, berries, grapes	Inhibit α-glucosidase, delay glucose absorption, reduce oxidative stress, improve insulin sensitivity	Resveratrol, Epigallocatechin gallate (EGCG)	(Testa et al., 2016)
Flavonoid	Citrus fruits, onions	Inhibit α-amylase and α-glucosidase, enhance insulin secretion, protect β-cells from oxidative stress	Quercetin, Kaempferol	(Barber et al., 2021; Soares et al., 2017)
Alkaloid	Fenugreek, bitter melon	Enhance glucose uptake in cells, inhibit glycogen phosphorylase, stimulate insulin release, mimic insulin action	Berberine, Trigonelline	(Hajzadeh et al., 2011; Cui et al., 2016; Yang et al., 2022; Unuofin & Lebelo, 2020)
Terpenoid	Ginseng, Salacia species	Improve glucose uptake, inhibit glucose absorption, modulate insulin sensitivity	Ginsenosides, Mangiferin	(Prakash, 2017; Szczuka et al., 2019; Yan et al., 2019; Xavier et al., 2024; Unuofin & Lebelo, 2020)

- **Efflux by P-glycoprotein (P-gp):** Some molecules are substrates for P-gp, which actively transports them out of intestinal cells, reducing absorption.
- **Interaction with food and gut microbiota:** Co-administration with food or interaction with gut microbiota can alter the stability or absorption of bioactives.

A comparative evaluation of these molecules reveals their advantages and limitations:

Pharmacokinetics challenges: Pharmacokinetics involves the study of absorption, distribution, metabolism, and excretion (ADME) of drugs. Key challenges for antidiabetic bioactive molecules include:

- **Absorption:**
  - Variability in absorption rates due to patient-specific factors (e.g., gastric emptying time, pH).
  - Interference by dietary components or other medications.
- **Distribution:**
  - Limited ability to cross cell membranes or penetrate target tissues, such as pancreatic β-cells.
  - Binding to plasma proteins like albumin, reducing the free drug available for action.
- **Metabolism:**
  - Rapid hepatic or intestinal metabolism by enzymes (e.g., cytochrome P450 enzymes), leading to short half-lives.
  - Formation of inactive or toxic metabolites that may impact efficacy or cause adverse effects.
- **Excretion:**
  - Rapid renal clearance may reduce the drug's duration of action, necessitating frequent dosing.
  - Accumulation risks in patients with compromised kidney function.

Strategies to overcome challenges: Efforts to enhance the bioavailability and pharmacokinetics of antidiabetic bioactive molecules include:

- **Formulation approaches:**
  - Nanoformulations (e.g., nanoparticles, liposomes) to improve solubility and stability.

- Use of permeability enhancers or co-solvents.
- Sustained-release or targeted delivery systems to prolong action and reduce side effects.

- **Chemical modifications:**
  - Structural modifications to improve lipophilicity or reduce metabolic degradation.
  - Prodrug strategies to enhance absorption or bypass first-pass metabolism.
- **Inhibition of efflux pumps and enzymes:**
  - Co-administration of inhibitors of P-gp or metabolic enzymes.
- **Novel delivery routes:**
  - Non-oral routes, such as transdermal, buccal, or pulmonary, to bypass first-pass metabolism.
- **Combination therapies:**
  - Using bioactives in combination with other drugs to achieve synergistic effects and improved pharmacokinetics.

4. RESULTS

The comprehensive review of bioactive molecules for antidiabetic therapy highlights their immense potential in complementing or replacing conventional treatments. Key findings from the analysis include:

Diversity in sources and mechanisms of action:

Bioactive molecules from natural sources such as polyphenols, flavonoids, alkaloids, terpenoids, and peptides demonstrate diverse mechanisms of action, including:

1. Enhanced insulin secretion from pancreatic β-cells.
2. Improved glucose uptake by peripheral tissues through modulation of GLUT4 expression.
3. Reduction of oxidative stress and inflammatory markers, which are critical in diabetes-related complications.

Efficacy across models:

1. Clinical trials on compounds such as berberine and resveratrol indicate promising results in lowering blood glucose and HbA1c levels.

Safety and tolerability:

1. Bioactives often present better safety profiles compared to synthetic antidiabetic drugs, with fewer side effects like hypoglycemia or gastrointestinal disturbances.However, challenges remain in standardizing dosages and ensuring consistent bioavailability.

Synthetic analogues and combination therapies:

1. Synthetic analogues of bioactive molecules, designed to enhance stability and activity, it helpful to improved pharmacokinetics.
2. Combining bioactives with existing antidiabetic drugs may offer synergistic effects, optimizing glycemic control while minimizing adverse effects.

Table 10. A comparative evaluation of phytochemicals, peptides and synthetic compounds

Category	Advantages	Limitations
Phytochemicals	Natural, minimal side effects	Variable potency, bioavailability
Peptides	Specific targets, multifunctional	Expensive, administration challenges
Synthetic Compounds	Well-studied, predictable effects	Side effects, resistance development

5. CONCLUSION

In conclusion, the exploration of bioactive molecules offers a transformative approach to addressing the global challenge of diabetes mellitus. With their diverse mechanisms of action, these molecules provide a promising avenue for safer and more effective antidiabetic therapies. Advances in nanotechnology, personalized medicine, and genetic engineering further enhance their potential, paving the way for innovative solutions to overcome limitations in existing treatments. The integration of bioactive molecules into functional foods, targeted drug delivery systems, and combination therapies underscores their versatility in both preventive and therapeutic contexts.

The study emphasizes the need for further research into synergistic effects and formulation strategies to improve their clinical use. By fostering interdisciplinary collaboration and leveraging emerging technologies, the scientific community can accelerate the development of personalized, sustainable, and impactful diabetes management strategies. Such efforts will not only improve patient outcomes but also contribute to global efforts in reducing the burden of diabetes and enhancing quality of life for millions worldwide.

6. FUTURE DIRECTIONS

1. Identification of novel bioactives through high-throughput screening of natural product libraries.
2. Genomic and metabolomic studies to personalize bioactive-based therapies.
3. Regulatory frameworks to ensure quality and efficacy of bioactive-based formulations.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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