ISSN 1998 – 409X

REVIEW ARTICLE

Terpenoids in diabetes management: From molecular mechanisms to clinical translation and safety considerations

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Abstract

Diabetes mellitus is a multifaceted metabolic disorder that involves multiple pathological mechanisms, including insulin resistance, pancreatic β-cell dysfunction, chronic inflammation, oxidative stress, and dysregulated lipid metabolism, and requires a therapeutic strategy that can impact multiple mechanisms. One of the most structurally diverse and largest groups of secondary metabolites in plants is terpenoids, which have been reported to show extensive pharmacological properties and favorable therapeutic potential as multitarget agents. This review is a comprehensive overview of the current evidence regarding terpenoids and their classification, structure-activity relationship, molecular mechanisms, association with diabetes treatment, and safety profile. Experimental research has shown that terpenoids exert glycemic benefits by exerting coordinated effects on carbohydrate-digesting enzymes, insulin signaling pathways, preservation of pancreatic β-cells, antioxidant defense, inflammatory mediators, and lipid homeostasis. While these promising results are present, their use in clinical practice is limited due to inadequate aqueous solubility, low bioavailability upon oral administration, rapid metabolism, variability in phytochemical content, and a lack of long-term clinical evidence. Newly developed drug delivery technologies at the nanoscale, and the standardized developmental process of phytopharmaceuticals provide opportunities for resolving challenges between pre-clinical and clinical stages. This review also stresses the need for dose-dependent toxicological evaluation and highlights that therapeutic efficacy and safety need to be taken into account in drug development. Taken together, the evidence suggests terpenoids as potential promising candidates for the development of a new generation of antidiabetic drugs and highlights the importance of conducting extensive toxicological evaluation, regulatory standardization, and clinically well-designed studies to ensure successful clinical translation.

Key words: Clinical translation, diabetes mellitus, molecular mechanisms, nanotechnology, oxidative stress, phytotherapy, terpenoids

INTRODUCTION

Diabetes mellitus (DM) is one of the most common chronic metabolic diseases around the globe and is still a significant cause of mortality or morbidity due to its association with cardiovascular diseases, nephropathy, neuropathy, and retinopathy. Thus, in recent years, the race to develop novel, safer, multitarget therapeutics that control multiple metabolic pathways in diabetes has intensified. One major worldwide health concern is type 2 diabetes, a chronic metabolic illness. As a long-term metabolic disorder, type 2 diabetes is one of the biggest problems in world health today, affecting roughly 1/11 individuals worldwide.[1-3] In 2021, approximately 537 million adults between the ages of 20 and 79 were diagnosed with diabetes globally. Diabetes was responsible for 6.7 million deaths, and an additional 541 million persons exhibited poor glucose tolerance, a considerable risk factor for type 2 DM (T2DM).[4]

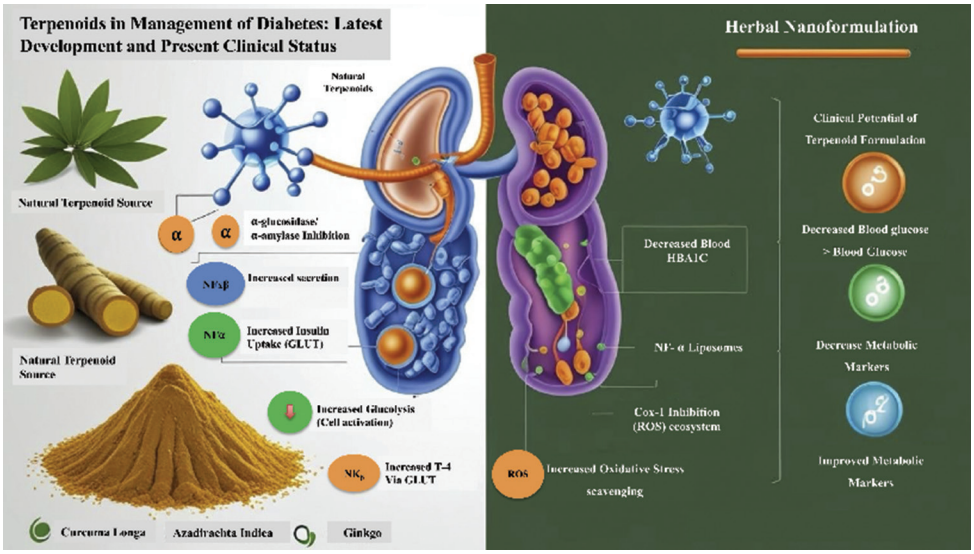
Terpenoidsor isoprenoidsare one of the largest and most structurally complex groups of naturally occurring

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Received: 05-07-2026
Revised: 11-09-2026
Accepted: 19-09-2026

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Graphical Abstract



compounds; over 80,000 molecules have been identified. The broad pharmacological diversity of terpenoids has prompted their wide interest as therapeutic candidates in cancer, inflammation, infectious diseases, and metabolic disorders. The multiple molecular targets of action of terpenoids on glucose metabolism, insulin signaling, modulation of oxidative stress, and inflammatory pathways indicate that these natural compounds have strong therapeutic potential for diabetes treatment as alternatives to one-target therapeutic strategies.[5,6]

While many studies have focused on the antidiabetic activity of individual terpenoids, there is a lack of understanding of the mechanisms, limitations, clinical applications, formulation strategies, safety considerations, and potential toxicities that underpin their antidiabetic activity. Thus, this review comprehensively discusses the recent advances and mechanisms on the antidiabetic potentials of terpenoids, and their future clinical implications, challenges, and safety concerns.

CLASSIFICATION OF TERPENOIDS

Terpenoids are the largest of all naturally occurring secondary metabolites and are the biosynthetic products of multiple repetitions of the isoprene (C_5) unit. Based on this amount, they are grouped into hemiterpenes, monoterpenoids, sesquiterpenoids, diterpenoids, triterpenoids, tetraterpenoids, and polyterpenoids. Of these subclasses, monoterpenoids, diterpenoids, triterpenoids, and tetraterpenoids have been extensively studied in the context of diabetes research due to their reported glucose-supporting effects, insulin signaling properties, antioxidant activity, anti-inflammatory activity, and lipid-modifying activity. They are structurally diverse; that is, their structures relate directly to their multitarget pharmacological properties, making them possible candidates for metabolic disease management (C_5H_8).[7-10] Terpenoids constitute one of the largest and most pharmacologically diverse classes of plant-derived natural products. Different classes of terpenoids are discussed and classified in Table 1.

STRUCTURE–ACTIVITY RELATIONSHIP OF TERPENOIDS IN DIABETES

Structural features such as the size, lipophilicity, pattern of hydroxylation, glycosylation, and oxidation state of terpenoids play an important role in determining their pharmacological and toxicological properties. The smaller terpenoids tend to have high membrane permeability and are quickly metabolized, whereas the larger ones have a high degree of target interaction but lower oral bioavailability. Usually, hydroxylated terpenoids have strong antioxidant properties, and glycosylation can increase solubility in water and intestinal absorption. Long-term exposures, in contrast, can raise the toxicological risk in the case of excessive lipophilicity and tissue accumulation. The rational design of safer, more effective therapeutic agents from terpenoid structures requires an understanding of these structure–activity relationships. The diversity of terpenoid structures ultimately leads to their molecular targets and biological responses. Thus, the knowledge of structural classification and structure–activity relationships is the basis for the understanding of the various molecular mechanisms by which terpenoids modulate glucose homeostasis and metabolic function.[19,20]

PLANTS CONTAINING TERPENOIDS

Terpenoids represent a highly diverse class of natural compounds predominantly encountered in various plant species. Among them, monoterpenoids are the principal constituents of essential oils, renowned for their characteristic aromas. These compounds represent

Table 1: Structural classification and pharmacological relevance of terpenoid subclasses in diabetes management

S. N.	Class	General formula	No. of monomeric isoprene units	No. of carbon atoms	Key biological activities	References
1.	Hemiterpenoids	C_5H_8	1	5	α-amylase and α-glucosidase inhibition	[11]
2.	Monoterpenoids	$C_{10}H_{16}$	2	10	Antioxidant, anti-inflammatory	[12]
3.	Sesquiterpenoids	$C_{15}H_{24}$	3	15	Antimicrobial, insulin sensitization	[13]
4.	Diterpenoids	$C_{20}H_{32}$	4	20	β-cell protection, glucose uptake	[14]
5.	Sesterterpenoids	$C_{25}H_{40}$	5	25	enhance glucose uptake, β-cell protection	[15]
6.	Triterpenoids	$C_{30}H_{48}$	6	30	α-glucosidase inhibition	[16]
7.	Tetraterpenoids (carotenoids)	$C_{40}H_{64}$	8	40	Enhancement of glucose and lipid metabolism regulation and insulin sensitivity	[17]
8.	Polyterpenoids	C_5H_8n	>8	>40	Diverse metabolic activities	[18]

substantial proportions of multiple botanicals, with notable examples including galbanum (80%), *Angelica* species (73%), *hyssop* (70%), *rose* (54%), *peppermint* (45%), *juniper* (42%), *frankincense* (40%), *spruce* (38%), *pine* (30%), *cypress* (28%), and *myrtle* (25%). Monoterpene hydrocarbons such as α-pinene, β-pinene, limonene, Δ3-carene, and myrcene are typically found as complex mixtures in essential oils, predominantly concentrated in the foliar components of these plants. Conversely, essential oils derived from flowers and seeds often display a wider variety of specialized monoterpenoids. The optical activity of these molecules results in the presence of different enantiomers sourced from distinct plant origins: (1)-α-pinene is derived from *Pinus palustris Mill*.; (2)-β-pinene comes from *Pinus caribaea Morelet* and *Pinus pinaster Aiton*; S-(1)-linalool is extracted from coriander (*Coriandrum sativum* L.); and R-(2)-linalool is isolated from *Cinnamomum camphora* (L.) *J. Presl*. Various Plants containing terpenoids and their usefulness in multiple diseases/disorders are discussed below in Table 2.[21,22]

MOLECULAR MECHANISM OF TERPENOIDS IN DIABETES MANAGEMENT

DM involves an interplay between insulin resistance, loss of β-Cell function, chronic inflammation, oxidative stress, disturbed lipid metabolism, and disturbed cellular energy homeostasis. Terpenoids have pleiotropic properties by modulating several interconnected signaling networks, in contrast to conventional antidiabetic agents, which control a single molecular pathway. The multitarget pharmacological activity allows for synergistic control of both glucose metabolism and insulin signaling, inflammatory pathways, oxidative stress, as well as mitochondrial function, providing the potential for a one-step pharmacologic therapy for diabetes.[53-56]

The antidiabetic effects of terpenoids arise from their ability to modulate multiple interconnected molecular pathways involved in glucose metabolism and metabolic homeostasis. These include regulation of insulin, oxidative stress, inflammatory responses, lipid metabolism, pancreatic beta cell function, and carbohydrate-digesting enzymes. Owing to this multitarget pharmacological profile, terpenoids have emerged as promising candidates for complementary diabetes therapy. A comprehensive discussion of these molecular mechanisms is presented in the methodology section [Figure 1] and below in Figure 2.[57-63]

METHODOLOGY

Pharmacological Profile of Different Terpenoids and Their Limitations

Terpenoids, categorized according to their isoprene unit count, demonstrate a wide array of pharmacological properties pertinent to the management of diabetes. Each subclass of terpenoids possesses distinct mechanisms of action and inherent limitations, which subsequently shape their therapeutic applications in clinical settings.[4]

Hemiterpenoids

Hemiterpenoids, composed of a single isoprene unit and including compounds such as isoprene and its derivatives such as prenol, exhibit subtle antioxidant and anti-inflammatory properties that may indirectly aid in regulating glucose homeostasis. Isoprene, for instance, serves as a precursor in the biosynthesis of coenzyme Q10, which is vital for mitochondrial energy production and the reduction of oxidative stress. However, their therapeutic application is limited by poor bioavailability due to their volatile nature and the lack of direct evidence supporting their efficacy in antidiabetic therapy.[64]

Table 2: List of some herbs containing terpenoids and their usefulness in various diseases

S. N.	Plant	Plant part with terpenoid	Class of terpenoids	Type of terpenoids	Useful in disease	References
1.	*Artemisia annua*	Leaves	Sesquiterpenes	Artemisinin	Malaria	[23]
2.	*Azadirachta indica*	Leaves	Limonoids	Azadirachtin	Antimicrobial, Insect repellent	[24]
3.	*Bacopa monnieri*	Whole plant	Triterpenoid saponins	Bacosides	Cognitive enhancement, Antioxidant	[25]
4.	*Boswellia serrata*	Resin	Triterpenes	Boswellic acids	Anti-inflammatory, Arthritis	[26]
5.	*Citrus limon*	Peel	Monoterpenes	Limonene	Antioxidant, Anticancer	[27]
6.	*Curcuma longa*	Rhizomes	Curcuminoids	Curcuminoids	Anti-inflammatory, Cancer	[28]
7.	*Foeniculum vulgare*	Seeds	Phenylpropanoids	Anethole	Digestive issues, Antimicrobial	[29]
8.	*Garcinia cambogia*	Fruit rind	Organic acids	Hydroxycitric acid	Weight loss, Metabolism booster	[30]
9.	*Ginkgo biloba*	Leaves	Terpenoids	Ginkgolides	Cognitive disorders	[31]
10.	*Glycyrrhiza glabra*	Root	Triterpenoid saponins	Glycyrrhizin	Anti-inflammatory, Antiviral	[32]
11.	*Mentha piperita*	Leaves	Monoterpenes	Menthol	Digestive issues, Headaches	[33]
12.	*Momordica charantia*	Fruits	Triterpenes	Charantin	Antidiabetic, Antioxidant	[34]
13.	*Moringa oleifera*	Leaves	Isothiocyanates	Isothiocyanates	Antioxidant, Anti-inflammatory	[35]
14.	*Ocimum sanctum*	Leaves	Phenylpropanoids	Eugenol	Antimicrobial, Anti-inflammatory	[36]
15.	*Origanum vulgare*	Leaves	Monoterpenes	Carvacrol	Antimicrobial, Antioxidant	[37]
16.	*Panax ginseng*	Roots	Ginsenosides	Ginsenosides	Adaptogen, Immune support	[38]
17.	*Rosmarinus officinalis*	Leaves	Phenylpropanoids	Rosmarinic acid	Antioxidant, Anti-inflammatory	[39]
18.	*Salvia officinalis*	Leaves	Monoterpenes	Thujone	Memory enhancement, Antioxidant	[40]
19.	*Silybum marianum*	Seeds	Flavonolignans	Silymarin	Liver health, Antioxidant	[41]
20.	*Sophora japonica*	Flowers	Flavonoids	Quercetin	Antioxidant, Anti-inflammatory	[42]
21.	*Stevia rebaudiana*	Leaves	Diterpenoid glycosides	Stevioside	Sweetener, Antioxidant	[43]
22.	*Syzygium aromaticum*	Flower buds	Phenylpropanoids	Eugenol	Antimicrobial, Anti-inflammatory	[44]
23.	*Tribulus terrestris*	Fruits	Steroidal saponins	Protodioscin	Libido enhancement, Muscle strength	[45]
24.	*Trigonella foenum-graecum*	Seeds	Steroidal saponins	Diosgenin	Hormonal balance, Anti-inflammatory	[46]
25.	*Withania somnifera*	Roots	Steroidal lactones	Withanolides	Adaptogen, Anti-inflammatory	[47]
26.	*Zanthoxylum armatum*	Fruits	Monoterpenes	Limonene	Digestive health, Antimicrobial	[48]
27.	*Zea mays*	Stigmas	Carotenoids	Zeaxanthin	Eye health, Antioxidant	[49]
28.	*Zingiber officinale*	Rhizomes	Phenylpropanoids	Gingerol	Anti-inflammatory, Nausea	[50]
29.	*Zingiber zerumbet*	Rhizomes	Sesquiterpenes	Zerumbone	Anti-inflammatory, Anticancer	[51]
30.	*Ziziphus jujuba*	Fruits	Triterpenes	Betulinic acid	Anticancer, Anti-inflammatory	[52]

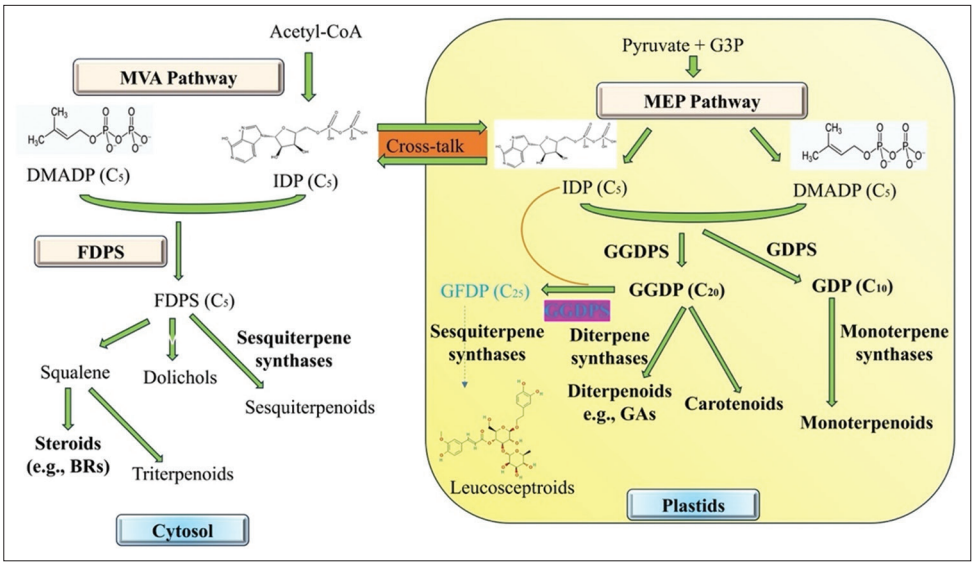


Figure 1: Schematic illustration of the prospective antidiabetic effects of terpenoids across many organs and metabolic targets

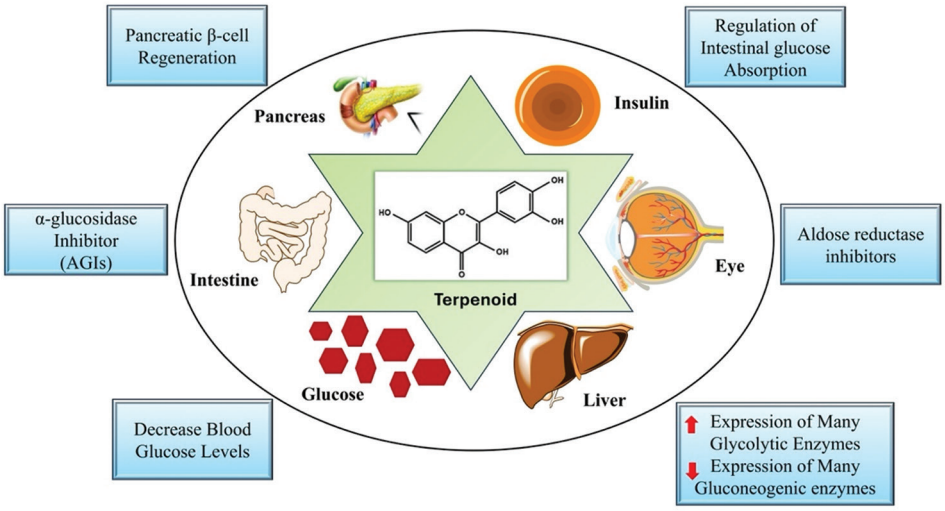


Figure 2: Comprehensive summary of the mevalonate (MVA) and methylerythritol phosphate (MEP) pathways pertinent to terpenoid biosynthesis

Monoterpenoids

Monoterpenoids, composed of two isoprene units and including compounds such as limonene, geraniol, and thymol, exhibit significant antioxidant, anti-inflammatory, and insulin-sensitizing activities. For example, geraniol has been shown to modulate lipid and glucose metabolism, enhance insulin sensitivity, and reduce oxidative stress. However, their therapeutic potential is constrained by instability under physiological conditions and poor aqueous solubility, which limits their systemic delivery.[65]

Sesquiterpenoids

Sesquiterpenoids, which consist of three isoprene units and include compounds such as artemisinin and farnesol, exhibit strong anti-inflammatory and insulin-sensitizing properties. Artemisinin, for instance, activates AMP-activated protein kinase (AMPK) signaling pathways, thereby enhancing glucose uptake in peripheral tissues and reducing hepatic glucose production. However, their clinical applicability is limited by rapid metabolism, leading to reduced bioavailability and the potential for toxicity at higher doses.[66]

Diterpenoids

Diterpenoids, composed of four isoprene units and represented by compounds such as forskolin, andrographolide, and tanshinone, exhibit β-cell protective effects, suppress oxidative stress, and reduce insulin resistance. Forskolin, for example, elevates cyclic AMP (cAMP) levels, thereby stimulating insulin secretion and supporting β-cell function. However, their therapeutic application is restricted by limited water solubility, rapid degradation in the gastrointestinal tract,

and potential interactions with other metabolic pathways that may lead to undesirable side effects.[67]

Triterpenoids

Triterpenoids, consisting of six isoprene units and including compounds such as ursolic acid, oleanolic acid, and lupeol, display a broad spectrum of antidiabetic activities, including α-glucosidase inhibition, activation of peroxisome proliferator-activated receptor gamma (PPAR-γ), and potent anti-inflammatory effects. Oleanolic acid, for instance, enhances insulin sensitivity and suppresses hepatic gluconeogenesis. However, their clinical effectiveness is limited by poor oral bioavailability resulting from low solubility, thereby necessitating formulation advancements such as nanoformulation to improve their therapeutic efficacy.[68]

Tetraterpenoids

Tetraterpenoids, composed of eight isoprene units and represented by carotenoids such as β-carotene, astaxanthin, and lutein, possess strong antioxidant properties that protect pancreatic β-cell*s* from oxidative stress-induced damage and improve insulin sensitivity. Astaxanthin, for example, has been shown to reduce oxidative stress and enhance glucose metabolism. However, their practical application is hindered by poor stability and rapid degradation upon exposure to light and oxygen, as well as high production costs that limit large-scale commercial utilization.[17]

Polyterpenoids

Polyterpenoids, containing more than eight isoprene units and encompassing compounds such as natural rubber and its derivatives, have been less extensively studied for their antidiabetic potential. Nonetheless, certain polyisoprenoid derivatives have shown promising bioactivity by enhancing glucose uptake in muscle cells and modulating glucose transporter (glucose transporter type 4) expression, thereby contributing to glucose homeostasis. However, their therapeutic relevance remains limited due to the lack of comprehensive studies evaluating their efficacy, mechanism of action, and safety in diabetes management.[69] A summary of various terpenoid classes and their antidiabetic activities is discussed below in Table 3.

MOLECULAR MECHANISM OF TERPENOIDS IN DIABETES MANAGEMENT

The pathogenesis of DM is a multifactorial process involving insulin resistance, impaired β-cell function, chronic inflammation, oxidative stress, dysregulated lipid metabolism, and stromal cell energy derangement. Terpenoids act on multiple and interconnected pathways, unlike the action of conventional antidiabetic agents, which normally focus on just a single pathway. The multitarget pharmacological spectrum allows simultaneous adjustment of glucose metabolism, insulin signaling, inflammatory pathways, oxidative stress, and mitochondrial function for a more holistic therapeutic strategy for diabetes care.

Inhibition of α-Glucosidase and α-Amylase

The enzyme inhibition of carbohydrate-digesting enzymes, such as α-glucosidase and α-amylase, is one therapeutic approach to control postprandial hyperglycemia. A number of terpenoids have been found to have inhibitory activity on these enzymes, which slows carbohydrate hydrolysis, decreases intestinal glucose absorption, and dampens postprandial glucose spikes. It acts in a similar way to clinically approved α-glucosidase inhibitors, but also may have antioxidant and anti-inflammatory effects.[76]

Enhancement of Insulin Secretion

Certain terpenoids exert their antidiabetic effects by stimulating pancreatic β-cells, thereby enhancing insulin

Table 3: Summary of terpenoid classes and their antidiabetic activities

Class	Example	Key activities	Limitations	References
Hemiterpenoids	Prenol	Antioxidant, metabolic precursor	Poor bioavailability	[70]
Monoterpenoids	Limonene	Antioxidant, anti-inflammatory	Instability, poor solubility	[71]
Sesquiterpenoids	Artemisinin	AMPK activation, glucose uptake	Rapid metabolism, potential toxicity	[72]
Diterpenoids	Forskolin	β-cell protection, insulin secretion	Limited solubility, rapid degradation	[14]
Triterpenoids	Oleanolic acid	Insulin sensitization, gluconeogenesis inhibition	Poor oral bioavailability, formulation challenges	[73]
Tetraterpenoids	Astaxanthin	Oxidative stress reduction, β-cell protection	Unstable, costly	[74]
Polyterpenoids	Polyisoprenoid	GLUT4 modulation, glucose homeostasis	Limited research	[75]

AMPK: AMP-activated protein kinase, GLUT4: Glucose transporter type 4

secretion and restoring glycemic control. The diterpenoid forskolin increases cAMP levels, which activate protein kinase A and promote insulin exocytosis, whereas the sesquiterpenoid artemisinin protects β-cells from apoptosis, improving their insulin-secreting capacity. This mechanism is particularly relevant for type 2 diabetes patients with compromised β-cell function. However, its therapeutic applicability is limited in advanced stages of diabetes where β-cell mass and functionality are severely diminished, reducing the effectiveness of such insulin-secretagogue actions. Besides stimulating insulin secretion, some terpenoids maintain the integrity of pancreatic β-cells through reducing oxidative stress, blocking inflammatory mediators, and inhibiting apoptosis. The dual action could play a role in maintaining the production of endogenous insulin in the early stages of diabetes.[77]

Antioxidant Activity

Terpenoids play a vital role in reducing oxidative stress by neutralizing reactive oxygen species, which are major contributors to pancreatic β-cell dysfunction and the onset of insulin resistance. The tetraterpenoid astaxanthin effectively scavenges free radicals and enhances the activity of endogenous antioxidant enzymes such as superoxide dismutase (SOD) and catalase, whereas the monoterpenoid geraniol modulates oxidative stress pathways, decreases lipid peroxidation, and preserves β-cell integrity. This antioxidant mechanism is crucial in preventing the progression of diabetic complications such as neuropathy, nephropathy, and retinopathy. However, the therapeutic potential of many antioxidant terpenoids is limited by their low bioavailability, necessitating advanced formulation approaches such as nanoencapsulation to improve their stability and systemic delivery. In addition to their direct antioxidant activity as free radical scavengers, several terpenoids can induce endogenous antioxidant defense mechanisms by regulating the activation of the transcription factor involved in such pathways, such as Nrf2, which leads to upregulation of antioxidant enzymes such as SOD, catalase, and glutathione peroxidase. Thus, oxidative damage to β-cells, to the vascular endothelium, and to peripheral tissues is significantly decreased, reducing the occurrence of diabetic complications.[60]

Modulation of Lipid Metabolism

Terpenoids regulate lipid metabolism by modulating critical enzymes and signaling pathways, thereby reducing lipotoxicity and enhancing insulin sensitivity. Triterpenoids such as oleanolic acid activate PPAR-γ, which promotes lipid uptake and adipocyte differentiation. At the same time, diterpenoids such as andrographolide suppress hepatic lipogenesis by downregulating sterol regulatory element-binding protein 1 (SREBP-1c). This regulation of lipid metabolism not only improves overall metabolic balance but also decreases the risk of cardiovascular complications commonly associated with diabetes. However, achieving optimal therapeutic outcomes often requires higher doses of terpenoids, which may elevate the risk of off-target interactions and potential side effects. Another crucial pathway in which terpenoids contribute to metabolic homeostasis is the control of lipid metabolism. Activation of PPAR-γ stimulates adipocyte differentiation and insulin sensitivity, and inhibition of SREBP-1c lowers hepatic lipogenesis and ectopic lipid accumulation. These effects work together to lower lipotoxicity, enhance insulin responsiveness in the periphery, and reduce the cardiovascular risk associated with diabetes.[78] Various mechanism-focused approaches at the molecular target level in diabetes management are shown in Table 4, and a classification-based mechanistic overview of terpenoids in DM is discussed in Table 5.

Molecular pathways are explained [Figure 1] here in isolation for simplicity, but there are many crossroads between these pathways. The activation of AMPK simultaneously inhibits inflammatory signaling by blocking nuclear factor-kappa B (NF-κB) and improves insulin action through enhancing phosphoinositide 3-Kinase (PI3K)/Akt signaling. Likewise, reducing oxidative stress aids in the maintenance of pancreatic β-cell function and thus indirectly enhances insulin secretion. Hence, the therapeutic benefits of the terpenoids are more a result of an orchestrated regulation of the interplay of interconnected molecular pathways than as a result of their individual pharmacological actions. While the molecular pathways outlined above are well established by a great wealth of experimental data, most of the discoveries have been made *in vitro* and in animal models. There is still poor clinical validation, and variations in absorption, distribution,

Table 4: Mechanism-focused at the molecular target level in diabetes management

Mechanism	Terpenoid example	Molecular target/pathway	References
α-Glucosidase inhibition	Oleanolic acid	α-Glucosidase enzyme	[79]
α-Amylase inhibition	Limonene	α-Amylase enzyme	[80]
Insulin secretion enhancement	Forskolin	cAMP/PKA signaling	[81]
Antioxidant activity	Astaxanthin	ROS scavenging, upregulation of SOD	[82]
Lipid metabolism modulation	Oleanolic acid	PPAR-γ activation	[83]
Lipogenesis inhibition	Andrographolide	SREBP-1c pathway	[84]

PKA: Protein kinase A, ROS: Reactive oxygen species, SOD: Superoxide dismutase, PPAR-γ: Peroxisome proliferator-activated receptor gamma, SREBP-1c: Sterol regulatory element-binding protein 1

and formulation have the potential to have a marked impact on human therapeutic response. Thus, investigating mechanistic effectiveness should be performed with due care for translation.

CHALLENGES ASSOCIATED WITH THE USE OF TERPENOIDS IN DIABETES MANAGEMENT

Despite their promising pharmacological potential, terpenoids face several challenges in their application for diabetes management. These limitations, if addressed, could enhance their therapeutic efficacy and commercial viability. Challenges associated with, and corresponding solutions for, the use of terpenoids in diabetes management are illustrated in Figure 3.

Bioavailability

Terpenoids frequently face the challenge of low oral bioavailability owing to their poor water solubility, rapid metabolic degradation, and limited gastrointestinal absorption. For instance, triterpenoids such as oleanolic acid possess strong antidiabetic potential but suffer from low solubility, resulting in reduced systemic availability, whereas the tetraterpenoid astaxanthin encounters absorption and distribution limitations due to its highly lipophilic nature. To address these challenges, advanced drug delivery strategies such as nanotechnology-based formulations, including liposomes and polymeric nanoparticles, have been developed to enhance solubility, stability, and targeted delivery. In addition, the use of natural bioenhancers such as piperine has shown promise in improving intestinal absorption and systemic exposure. Future research should focus on the incorporation of terpenoids into polymeric nanoformulations designed for sustained release and site-specific delivery, thereby maximizing therapeutic efficacy while minimizing systemic side effects. Nanotechnology-based delivery systems for enhancement of terpenoid bioavailability are shown in Figure 4.[85]

Table 5: Classification-based mechanistic overview of terpenoids in diabetes mellitus

S. N.	Terpenoids	Mechanism of action	Example of compounds
1.	Hemiterpenoids	AMPK activation, insulin sensitization, enzyme inhibition, antioxidant.	Isoprene, isovaleric acid.
2.	Monoterpenoids	Inhibition of α-glucosidase and α-amylase	Limonene, menthol
3.	Sesquiterpenoids	Antioxidant activity, anti-inflammatory	β-Caryophyllene
4.	Diterpenoids	Enhancement of insulin secretion	forskolin
6.	Triterpenoids	Modulation of lipid metabolism	Oleanolic acid
7.	Tetraterpenoids (carotenoids)	Inhibition of enzymes, regulation of gene expression, antioxidant	Astaxanthin, lutein, lycopene, β-carotene
8.	Polyterpenoids	Inhibition of enzymes, regulation of gene expression, antioxidant	Natural rubber, Gutta-percha

AMPK: AMP-activated protein kinase

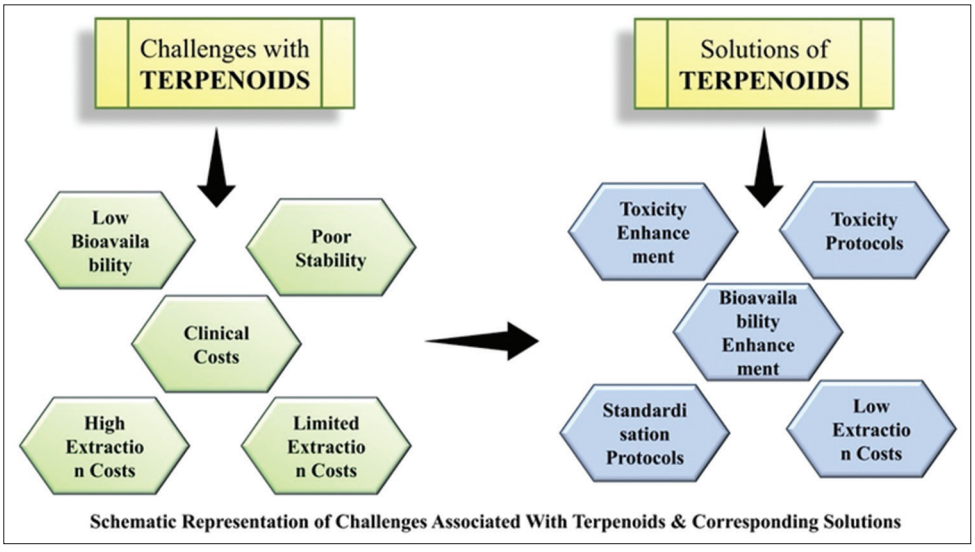


Figure 3: Challenges associated with terpenoids and the corresponding solutions

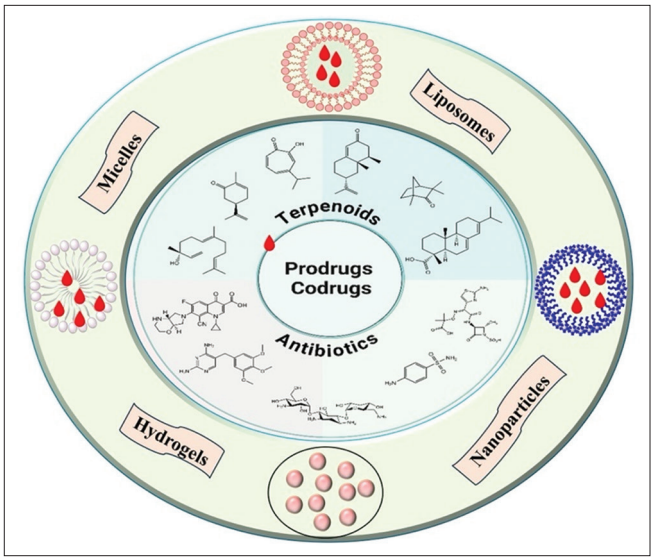


Figure 4: Nanotechnology-based delivery systems for enhancement of terpenoid bioavailability

Toxicity

Although terpenoids are generally regarded as safe, higher doses or prolonged use can lead to toxicity concerns. Sesquiterpenoids such as artemisinin have been reported to cause hepatotoxicity and neurotoxicity at elevated concentrations, whereas diterpenoids like forskolin may interact with other metabolic pathways, resulting in off-target effects. To mitigate these risks, current research emphasizes establishing clear dose–response relationships through comprehensive pre-clinical and clinical studies to define safe therapeutic windows. In addition, combining terpenoids with synergistic bioactive compounds can enhance therapeutic efficacy, allowing for reduced dosage requirements and lower toxicity risks. Future investigations should focus on detailed toxicological profiling of individual terpenoids to identify, characterize, and minimize potential adverse effects, ensuring their safe and effective integration into antidiabetic therapy.

Standardization

The heterogeneity in terpenoid content and composition, arising from differences in plant species, cultivation conditions, and extraction methodologies, poses a major challenge to their clinical translation. For example, the concentration of ursolic acid can vary significantly depending on the plant part used and the extraction method employed, leading to inconsistencies in potency and efficacy. This variability, coupled with the lack of standardized procedures for preparing terpenoid-rich formulations, hinders reproducibility and compliance with regulatory standards. Current strategies to address these challenges involve the application of advanced analytical techniques such as high-performance liquid chromatography (HPLC), gas chromatography, mass spectrometry (GC-MS), and nuclear magnetic resonance (NMR) spectroscopy for precise quantification and molecular characterization. Furthermore, the adoption of standardized extraction and processing protocols is being encouraged to ensure batch-to-batch uniformity. Future research should prioritize the establishment of global regulatory frameworks and good manufacturing practice (GMP) guidelines for terpenoid-based formulations to promote their consistency, safety, and clinical reliability.

CLINICAL TRANSLATION AND THERAPEUTIC CHALLENGES

Although there is a huge amount of pre-clinical evidence on the antidiabetic potential of terpenoids, so far their application in the clinic has been limited in success. The pharmacological activity of most terpenoids is promising in experimental models, but their therapeutic potential is still hindered by several drawbacks such as low oral bioavailability, rapid metabolism, formulation instability, phytochemical variability, and lack of sufficient clinical validation. Thus, optimal translation must be achieved simultaneously with respect to the pharmacokinetics, formulation, toxicological safety, and regulatory standardization.[86,87]

Pharmacokinetic Limitation[88]

Nanotechnology-based strategies have emerged as a pivotal advancement in overcoming the pharmacokinetic limitations of terpenoids by improving their solubility, stability, and bioavailability. Advanced nanocarriers such as nanoparticles, liposomes, and micelles facilitate targeted and sustained delivery of these compounds. For instance, liposomal encapsulation of oleanolic acid markedly enhances its bioavailability and therapeutic performance, whereas solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) have proven effective in improving gastrointestinal absorption, as demonstrated with astaxanthin. In addition, prodrug approaches where terpenoids are chemically modified into more hydrophilic derivatives have shown promise; glycosylated triterpenoid derivatives, in particular, exhibit superior intestinal transport and absorption. Another complementary strategy involves the use of natural bioenhancers such as piperine and quercetin, which increase intestinal permeability and overall systemic exposure of terpenoids. The pharmacokinetic properties of terpenoids are not only due to their poor water solubility. Therapeutic exposure after oral administration is often diminished due to extensive first-pass metabolism, limited intestinal permeability, rapid clearance from the systemic circulation, and chemical instability. Hence, there is often a gap between laboratory efficacy and clinical effectiveness, the latter of which is usually lower. Nanotechnology-based delivery systems for enhancement of terpenoid bioavailability in Figure 4.

Clinical Evidence[89]

Dose optimization, targeted delivery, and combination therapy represent key strategies for enhancing the safety and efficacy of terpenoid-based antidiabetic treatments. Pre-clinical and clinical investigations have established safe therapeutic thresholds, demonstrating that lower doses of terpenoids such as artemisinin, when used alongside adjunctive agents, can effectively reduce hepatotoxicity while maintaining therapeutic potency. Targeted drug delivery systems, including polymeric nanoparticles and antibody-drug conjugates, enable site-specific administration of terpenoids, thereby minimizing systemic exposure and off-target effects. For example, diterpenoid-loaded nanoparticles have been shown to preferentially localize within pancreatic β-cells, significantly reducing toxicity while enhancing insulin-regulating activity. Furthermore, combination therapy integrating terpenoids with conventional antidiabetic agents or synergistic phytochemicals can amplify therapeutic outcomes at reduced dosages, decreasing the risk of adverse effects.

Formulation Strategies[90]

Advanced analytical methods

HPLC, GC-MS, and NMR spectroscopy are essential techniques for assessing the integrity and quality of terpenoid formulations. These methods enable precise quantification and comprehensive characterization of terpenoids, which are vital for rigorous quality control and compositional analysis. For example, HPLC is frequently utilized to quantify ursolic acid and various triterpenoids in herbal extracts, ensuring accurate profiling.

Good agricultural and manufacturing practices (GAP and GMP)

Consistency in cultivation, harvesting, and processing methods is critical for minimizing variability in terpenoid content. A pertinent example is the implementation of standardized extraction protocols for *Andrographis paniculata*, which guarantees uniform levels of diterpenoids across production batches, thus enhancing reproducibility.

International regulatory frameworks

Harmonizing global regulatory standards for terpenoid-based formulations is imperative to facilitate their translation into clinical applications and commercial markets.

Novel Drug Formulations[91-93]

The hybrid systems are combinations of synthetic pharmacological agents with naturally occurring terpenoids that can lead to synergistic interactions that enhance therapeutic outcomes while alleviating the limitations associated with each component. For example, concurrent administration of synthetic PPAR-γ agonists in conjunction with triterpenoids has been shown to significantly improve the modulation of lipid metabolism. The controlled-release systems are an advancement of sustained-release formulations, including hydrogels and biodegradable implants, enabling prolonged bioavailability of terpenoids. This strategy effectively decreases dosing frequency and optimizes therapeutic regimens, allowing for more consistent and effective treatment delivery. In order to resolve pharmacokinetic limitations, much effort has been committed to the development of advanced drug delivery systems. The nanoparticles, liposomes, nanoemulsions, SLNs, NLCs, and polymeric micelles have superior properties for increasing the aqueous solubility of the terpenoids, preventing premature degradation of chemically labile terpenoids, increasing intestinal absorption, prolonging systemic circulation, and targeted delivery to metabolically relevant tissues. In experimental diabetes, these formulation strategies have led to a marked improvement in therapeutic effectiveness, albeit limited clinical efficacy has been demonstrated.

Status of Clinical Trials

Recent years have witnessed a significant increase in clinical investigations focused on terpenoids as potential antidiabetic agents. A multitude of studies are currently evaluating their safety, therapeutic efficacy, and the biochemical mechanisms by which they regulate glucose homeostasis and insulin sensitivity. This overview highlights notable terpenoid-derived compounds that are presently undergoing clinical trials, underscoring their promise in the realm of diabetes management.

Triterpenoids in Clinical Trials

Oleanolic acid

The clinical investigation focused on evaluating the hypoglycemic and antihyperlipidemic effects of terpenoid-based interventions in individuals with T2DM. The results demonstrated statistically significant reductions in fasting plasma glucose levels, along with notable improvements in lipid profiles, indicating effective metabolic regulation. Moreover, the treatment displayed a favorable safety profile, with minimal adverse events reported throughout the study period. The Phase II clinical trials have been completed, validating both the efficacy and safety of the terpenoid formulation for potential therapeutic application in diabetes management.

Ursolic acid

The study focused on evaluating the efficacy of the terpenoid compound in enhancing insulin sensitivity and alleviating oxidative stress in diabetic subjects. The results demonstrated notable improvements in glycemic control, accompanied by

a marked decrease in oxidative stress biomarkers, suggesting a dual benefit in metabolic regulation and cellular protection. The investigation is presently in the early-phase clinical trial stage, with ongoing studies aimed at further validating its therapeutic potential and establishing long-term safety and efficacy profiles.

Diterpenoids in Clinical Trials

Andrographolide

The clinical trial evaluated the therapeutic potential of the terpenoid compound in reducing inflammation and improving glycemic regulation among individuals with prediabetes. The results revealed significant decreases in glycated hemoglobin levels, accompanied by marked reductions in inflammatory cytokines, particularly tumor necrosis factor-alpha, indicating both metabolic and anti-inflammatory benefits. The study is presently in Phase II clinical trials, focusing on further validating its efficacy, safety, and potential role in delaying the progression from prediabetes to T2DM.

Forskolin

The clinical trial investigated the efficacy of the terpenoid-based intervention in enhancing insulin secretion among individuals with early-stage T2DM. The findings demonstrated a significant improvement in pancreatic β-cell function and overall glycemic regulation, confirming the compound's potential in restoring endogenous insulin activity. Moreover, the intervention exhibited a strong safety profile, with no severe adverse events reported during the study. Phase-II clinical trials have been completed, supporting the therapeutic promise of terpenoids as effective agents in early diabetes management.

Tetraterpenoids in Clinical Trials

Astaxanthin

The clinical trial examined the antioxidant potential of the terpenoid compound and its effects on oxidative stress–related complications in diabetic patients. The results revealed substantial reductions in oxidative stress biomarkers, coupled with notable improvements in microvascular function, particularly among individuals with diabetic retinopathy. These findings highlight the compound's role in mitigating oxidative damage and supporting vascular health in diabetic conditions. The study is currently in Phase III clinical trials, aiming to further validate its long-term efficacy, safety, and clinical applicability in managing diabetes-associated complications.

Polyterpenoids in Clinical Trials

Paclitaxel derivatives

The study focused on evaluating the terpenoid compound's ability to modulate lipid metabolism and reduce insulin resistance. Promising pre-clinical findings demonstrated significant improvements in lipid regulation and insulin sensitivity, prompting the initiation of early-phase human clinical trials. Preliminary results indicate measurable reductions in insulin resistance, supporting its potential as a metabolic modulator in diabetes management. The investigation is currently in Phase I clinical trials, with ongoing assessments to establish its safety, tolerability, and optimal therapeutic dosage.

Various data from clinical trials of terpenoids in diabetes management are discussed in Table 6; global progress in clinical trials of terpenoids, highlighting different trial phases and geographical distributions, is shown in Figure 5.

A few terpenoids have advanced into early clinical trial phases, but the clinical evidence is not coherent and cannot be categorized into any specific type. However, most human studies are limited in size, treatment length, use of surrogate biochemical endpoints, and in formulating the study characteristics, thus making direct comparisons across studies difficult. Thus, no therapeutic that uses terpenes is widely used in clinical practice as a diabetes treatment.

Challenges in Clinical Translation

- Limited large-scale trials: Most terpenoid studies are in early phases or on small cohorts
- Lack of long-term safety data: Extended use of terpenoid-based drugs needs further evaluation

Table 6: Clinical trials of terpenoids in diabetes management

Terpenoid	Trial phase	Key focus	Outcome
Oleanolic acid	Phase-II	Glycemic and lipid control	Improved fasting glucose and lipid profiles
Ursolic acid	Early phase	Insulin sensitivity	Reduced oxidative stress markers
Andrographolide	Phase-II	Anti-inflammatory effects	Decreased *HbA1c* and *TNF-α* levels
Forskolin	Phase-II	Insulin secretion enhancement	Improved β-cell function
Astaxanthin	Phase-III	Antioxidant activity	Reduced oxidative stress in retinopathy
Paclitaxel derivatives	Phase-I	Lipid metabolism modulation	Reduced insulin resistance

HbA1c: Glycated hemoglobin, TNF-α: Tumor necrosis factor-alpha

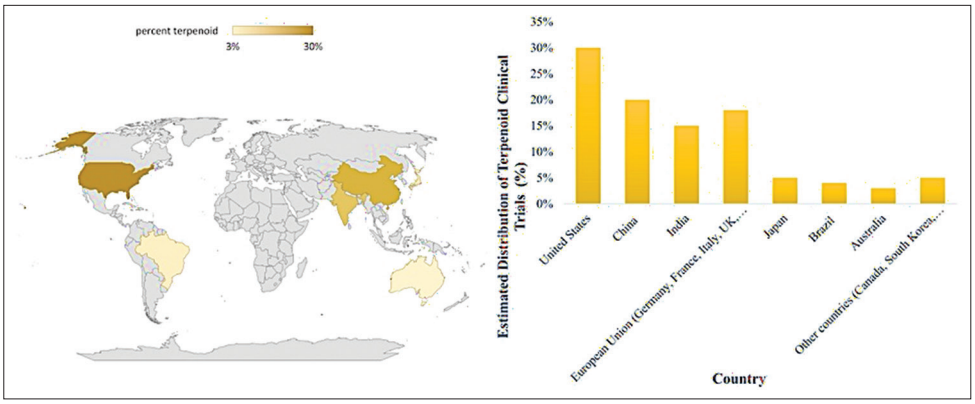


Figure 5: Global progress in clinical trials of terpenoids, highlighting different trial phases, and geographical distribution

- Variable efficacy: Differences in outcomes may result from non-standardized formulations or patient heterogeneity.

Although randomized controlled clinical trials make up a small portion of the literature, the current evidence hierarchy starts with mechanistic investigations and then moves on to pre-clinical animal studies, leaving very few clinical trials at the bottom. Therefore, the conclusions drawn for long-term efficacy and safety should be interpreted with caution pending completion of multicenter clinical studies with high numbers of patients.

Regulatory Consideration

For therapeutic development to be successful, compliance with internationally recognized regulations and guidelines for botanical products and phytopharmaceuticals is crucial. Botanical sources must be standardized, with a quantitative phytochemical profile, batch-to-batch consistency, characterization of impurities, stability assessment, and GMP must be satisfied. In addition, detailed toxicological studies, pharmacokinetic studies, and well-designed clinical trials are required before terpenoid formulations can be used in routine clinical practice.

SAFETY, TOXICOLOGICAL CONSIDERATIONS, AND RISK ASSESSMENT OF TERPENOIDS

Terpenoids have been considered as natural compounds with great therapeutic potential, but their use must be evaluated in light of a well-conducted safety analysis. Not all natural compounds are harmless, and a few terpenoids have dose-dependent experimental and clinical toxicological effects. Thus, the understanding of the safety of the terpenoids is crucial and essential for the rational development of terpenoid-based antidiabetic therapeutics. A summary of the toxicological profiles of representative terpenoids, including their therapeutic benefits, reported toxicities, target organs, dose dependency, and levels of evidence, is presented in Table 7.

Dose-responsive Relationship

Terpenoids have a high biological activity, which varies according to dose. Terpenoids demonstrate anti-inflammatory, insulin sensitizing, cytoprotective, and antioxidant activity when taken at therapeutically optimized concentrations. But manifesting over-exposure can lead to disruption of membrane integrity, organ-specific toxicity, oxidative stress, and impaired mitochondrial function. Hence, the determination of the therapeutic window is an important factor during drug development.

Occupational Toxicology

In addition to therapeutic use, terpenoids find wide-ranging applications in the pharmaceutical industry, essential oil extraction, pharmaceutical herbal processing, cosmetics, and nutraceuticals formulation. Exposure can be via inhalation, dermal absorption, and/or accidental ingestion during extraction, purification, and drug formulation. Exposure to terpenoids in the workplace is usually low, but repeated exposure to concentrated terpenoid preparations can lead to sensitization of the eyes or skin, allergic reactions, or chronic systemic effects. Industrial hygiene practices, engineering controls, and personal protective equipment are still important in controlling the risk in the workplace.

Regulatory Toxicity

Toxicity evaluation should be conducted according to internationally agreed-upon guidelines, including recommendations of the Organization for Economic Co-operation and Development for chronic, repeated-dose, reproduction and developmental, genotoxicity, and carcinogenicity testing. Pre-clinical safety evaluation for

potential clinical translation should involve a pharmacokinetic evaluation, impurity profiling, and exposure measurements.

While the evidence suggests that most terpenoids have relatively safe toxicities within therapeutic dose limits, several compounds have not been tested. Therefore, long-term exposure studies and standardized approaches to safety assessment protocols and well-designed clinical investigations are needed prior to general therapeutic use.

The Strengths and Limitations of Existing Evidence

Evidence presented is sufficient to support a mechanism for terpenoid-mediated metabolic regulation. There are still significant obstacles, however, such as small randomized controlled trials (RCTs), inconsistent formulation approaches, lack of pharmacokinetic profile, lack of uniformity of phytochemicals, and experimental animal models. The therapeutic potential for terpenoids should always be interpreted in light of these limitations.

DISCUSSION

DM is a complex metabolic disease that is multifactorial, with a complex interaction between insulin resistance, β-cell dysfunction, chronic inflammation, oxidative stress, dysregulated lipid homeostasis, and altered cellular energy homeostasis. Therapeutic strategies that target a single molecular pathway often only give partial metabolic control and can fail to sufficiently halt the progression of the disease and associated complications. Terpenoids have been identified as a class of natural bioactive compounds that are able to act on several interconnected signaling pathways directly involved in the pathogenesis of diabetes, making them promising therapeutic agents. The present review showed that terpenoids have antidiabetic effects through various mechanisms such as inhibiting carbohydrate-digesting enzymes, increasing insulin secretion, maintaining the function of pancreatic beta-cells, reducing oxidative stress and inflammatory responses, improving insulin sensitivity, and regulating lipid metabolism. The multitarget pharmacological profile sets terpenoids apart from numerous traditional antidiabetic drugs which target a single pathway.

Terpenoids' ability to modulate a number of pathways simultaneously is one of their strongest assets, as they are not single-enzyme inhibitors. All of these pathways lead to improvement in metabolic homeostasis, including activation of AMPK, modulation of PI3K/Akt and PPAR-γ signaling, suppression of NF-κB-mediated inflammation, enhancement of the endogenous antioxidant defense systems, and preservation of mitochondrial function. More importantly, these molecular pathways do not act without interacting with other molecular pathways in substantial biological crosstalk. Thus, activation of AMPK improves insulin sensitivity, while the inhibition of oxidative stress maintains the integrity of pancreatic β-cells and indirectly contributes to insulin secretion. The coordinated regulation offers a mechanistic argument to view terpenoids as potential multitarget therapeutic agents to target the complex DM pathophysiology.

Although the mechanistic results are encouraging, clinical translation is limited. Most of the evidence available is *in vitro*, obtained from experimental animals, but is limited with respect to long-term efficacy, safety, and therapeutic reproducibility. In addition, there are studies that are already available that have relatively small sample sizes, and the patient populations are heterogeneous with varying formulations and intervention time periods. So, despite the fact that some terpenoids such as oleanolic acid, andrographolide, forskolin, and astaxanthin have shown encouraging pharmacological effects, existing evidence is not enough to support their use as a well-established antidiabetic drug.

One of the biggest hurdles of clinical development for many terpenoids is their poor PK profile. Oral bioavailability and therapeutic exposure are significantly diminished due to low aqueous solubility, low intestinal uptake, extensive first-pass metabolism, rapid systemic elimination, and chemical instability. Hence, the potent biological effect seen in the laboratory rarely translates into a similar clinical effect. Great progress has been made, and advanced drug delivery systems such as nanoparticles, liposomes, nanoemulsions, polymeric micelles, SLNs, and NLCs with enhanced solubility, stability, controlled drug release, and tissue-specific delivery have been developed. However, such formulation strategies are still mostly limited to pre-clinical research, and further clinical validation is required prior to clinical use in therapy.

One of the most significant problems is standardization of products containing terpenoids. Botanical source material, growing conditions, harvesting methods, extraction methods, purification techniques, and storage conditions can all affect the phytochemical composition and biological activity. This variation makes it difficult to understand the results from one experiment to another, and it poses significant regulatory hurdles for the development of new drugs. Standardized manufacturing protocols are therefore required to ensure batch-to-batch consistency, product quality, and product regulatory compliance, which are supported by advanced analytical technologies like HPLC, LC-MS, GC-MS, and NMR spectroscopy.

Another important factor is the toxicity of terpenoids. These compounds are commonly thought to be safe due to their natural origin, but there is evidence available suggesting there is a strong dose/response relationship for the effectiveness of these compounds as a therapy. While terpenoids have antioxidant, anti-inflammatory, insulin sensitizing, and cytoprotective properties at optimal

Table 7: Toxicological profile of representative terpenoids

Terpenoid	Therapeutic effect	Reported toxicity	Target organ	Dose dependency	Evidence level
Artemisinin	β-cell protection	Hepatotoxicity (high dose)	Liver	Yes	Pre-clinical
Forskolin	Insulin secretion	Hypotension	Cardiovascular	Yes	Experimental
Astaxanthin	Antioxidant	Generally well tolerated	—	Low	Clinical
Oleanolic acid	α-glucosidase inhibition	Mild hepatotoxicity at high doses	Liver	Yes	Experimental
Andrographolide	AMPK activation	Gastrointestinal irritation	GI	Dose dependent	Clinical/ experimental

AMPK: AMP-activated protein kinase

concentrations, they may induce oxidative imbalance, mitochondrial dysfunction, destabilization of membranes, and organ-specific toxicity at higher levels of exposure. High-dose or long-term exposure experiments have shown hepatotoxicity, gastrointestinal disturbances, cardiovascular and neurotoxicity for some terpenoids. Besides, another often neglected point of terpenoid safety is occupational exposure during pharmaceutical production, extraction from herbs, and phytochemical processing. Therefore, extensive toxicology testing should be performed in conjunction with pharmacological studies, including acute, repeated-dose, reproductive and developmental, and genotoxicity testing, to define proper therapeutic windows and safe clinical translation.

The unique advantage of terpenoids is their multitarget pharmacological activity, which may enable them to simultaneously modulate two or more pathological processes involved in diabetes progression, with respect to conventional antidiabetic drugs. However, conventional treatments have proven superior clinical evidence, known pharmacokinetics, standardized manufacturing, and have been approved by regulatory agencies. Hence, terpenoids are more desirable to be used as a therapeutic agent in addition to the present drugs than as alternatives to the available drugs and are better suited as lead compounds for the development of new antidiabetic drugs. Chemical modification of the structure in a rational manner, use of nanoparticles for drug delivery, and combination therapy with other available drug molecules for diabetes can further improve their clinical use and reduce the side effects.

This current review also identifies some key gaps in the current literature. The evidence for most of the mechanisms is experimental, while the quality of randomized controlled clinical trials is limited. There is a great degree of variance in the purity of terpenoids, their formulations, dosing schedules, experimental procedures, and measures of outcome, which limit the comparability of the published studies. Furthermore, the long-term pharmacokinetic and toxicological studies are not available for many subclasses of terpenoids. These restrictions highlight the importance of standardized experimental protocols and well-designed multicenter clinical studies to make proof-of-concept therapeutic recommendations.

Hence, it is suggested that future research will need to be an integrated multidisciplinary effort involving medicinal chemistry, systems pharmacology, nanotechnology, toxicology, pharmacokinetics, and precision medicine. The identification of reliable biomarkers, the use of artificial intelligence to assist in drug discovery, the optimization of structure–activity relationships, and the development of standardized phytopharmaceutical formulations are all anticipated to speed up the translation of terpenoids from laboratory to the clinic as therapeutic agents. At the same time, the process of harmonizing the international regulatory standards, as well as the implementation of GMP principles, will be crucial for maintaining product quality, safety, and reproducibility.

Overall, the available evidence in this review suggests that the terpenoids are one of the most promising classes of naturally occurring multitarget drugs for diabetes management. However, their clinical success in the future will be as much dependent on further understanding of the molecular mechanisms as it will be on the resolution of pharmacokinetic challenges, the development of a full understanding of their toxicological safety, formulation standardization, and the generation of strong clinical data that will support regulatory approval and routine clinical use.

FUTURE PERSPECTIVE

Future studies should concentrate on the rational modification of terpenoids, nano-enabled drug delivery, and targeted formulation approaches to enhance the pharmacokinetics of the molecules. More focus should be given to long-term efficacy and safety assessment of therapeutic uses of phytochemicals as well, using biomarker-guided precision medicine, artificial intelligence-assisted phytochemical screening, systems pharmacology, and multicenter RCTs.

Although many experimental advances have been made in the field of pharmacology, the use of terpenoids in therapeutics is still in early stages of clinical translation. A range of different

future developments will hinge on optimized drug efficacy, drug safety, drug formulation, drug regulation, and clinical proof of efficacy. This interdisciplinary approach will help achieve successful integration of terpenoids into the new generation of drug therapies for diabetes.

CONCLUSION

The terpenoids are a class of multitarget bioactive natural products that show great potential for managing diabetes as key regulators in insulin signaling, oxidative stress, inflammation, lipid metabolism, and pancreatic β-cell function all at once. They can be used to control more than one molecular pathway at a time, making them different from traditional strategies that aimed to target individual molecules. While promising pre-clinical and emerging clinical data exist, there are challenges to their translation to routine clinical use, including limitations in the bioavailability of the drug, formulation problems, inadequate long-term clinical safety data, and the absence of large-scale randomized clinical trials. These constraints can be overcome by improving drug delivery systems, standardizing the development of phytopharmaceutical formulated products, conducting extensive toxicological studies, and validating and approving products through thorough clinical trials.

ACKNOWLEDGMENTS

The authors sincerely acknowledge the competent authorities of Guru Ghasidas Vishwavidyalaya (A Central University), Bilaspur, Chhattisgarh, India, 495009, for providing the necessary facilities.

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Source of Support: Nil. **Conflicts of Interest:** None declared.