Plant-Derived Compounds for Antidiabetic Drug Development

Dr Anna L Wagner [1*], Dr Maximilian F Müller [2], Dr Clara S Richter [3]
[1] Institute of Pharmaceutical Nanotechnology, Ludwig Maximilian University, Munich, Germany
[2] Department of Drug Delivery, University of Heidelberg, Heidelberg, Germany
[3] Center for Nanomedicine, Technical University of Berlin, Berlin, Germany

* Corresponding Author: **Dr Anna L Wagner**

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Abstract
Diabetes mellitus represents one of the most significant global public health challenges of the twenty-first century, with an estimated 537 million adults currently affected worldwide and projections indicating a dramatic rise in disease burden over the coming decades. Despite substantial pharmacological advances, existing therapeutic regimens—including metformin, sulfonylureas, thiazolidinediones, and sodium-glucose cotransporter-2 (SGLT2) inhibitors—remain limited by adverse effect profiles, inadequate glycaemic control in a proportion of patients, and the progressive nature of the underlying disease. Plant-derived compounds have attracted considerable scientific interest as potential sources of novel antidiabetic agents owing to their structural diversity, multi-target pharmacological properties, and extensive ethnobotanical history. This article provides a comprehensive review of the major classes of phytochemicals—including flavonoids, alkaloids, terpenoids, glycosides, and polyphenols—that have demonstrated antidiabetic activity, with emphasis on their biochemical mechanisms of action. These mechanisms encompass enhancement of insulin receptor signalling, inhibition of carbohydrate-digesting enzymes, upregulation of glucose transporters, activation of AMP-activated protein kinase (AMPK), and attenuation of oxidative stress and systemic inflammation. The article further examines preclinical and clinical evidence supporting their therapeutic potential, challenges in pharmacokinetic optimisation and standardisation, recent advances in drug delivery systems, and regulatory considerations in the translation of plant-based molecules into approved pharmaceuticals. It is argued that a rigorous, mechanism-driven approach to the investigation of phytochemicals offers a promising pathway for the development of safer and more effective antidiabetic therapies.

Keywords: Plant-derived compounds, Antidiabetic agents, Phytochemicals, Glucose metabolism, Insulin resistance, Drug development

1. Introduction

The global prevalence of diabetes mellitus has reached epidemic proportions, affecting individuals across all socioeconomic strata and imposing an enormous burden on healthcare systems [1]. The International Diabetes Federation estimates that, without decisive intervention, the number of affected adults will exceed 783 million by 2045, accompanied by disproportionate increases in low- and middle-income countries [2]. Diabetes mellitus is characterised by chronic hyperglycaemia arising from defects in insulin secretion, insulin action, or both, and is broadly classified into type 1, which is autoimmune in aetiology, and type 2, which accounts for approximately 90 to 95 percent of all cases and is strongly associated with obesity and sedentary lifestyle [7]. A third category, gestational diabetes mellitus, poses additional risks to maternal and neonatal health and frequently predisposes affected women to subsequent development of type 2 diabetes [8].

The chronic complications of diabetes, including nephropathy, retinopathy, peripheral neuropathy, and macrovascular disease,

are responsible for substantial morbidity, premature mortality, and diminished quality of life [9]. Current pharmacological management, while effective in many patients, does not address the full spectrum of pathophysiological events underlying the disease. Metformin, the most widely prescribed first-line agent, acts primarily by reducing hepatic glucose output, but is contraindicated in patients with significant renal impairment and may cause gastrointestinal intolerance [10]. More recently introduced drug classes, including glucagon-like peptide-1 receptor agonists and SGLT2 inhibitors, have demonstrated cardioprotective and nephroprotective benefits but are associated with high costs and specific side-effect concerns [11]. Against this background, plant-derived compounds offer a potentially attractive source of new chemical entities for antidiabetic drug development, as they may act through complementary or novel mechanisms and possess favourable safety profiles shaped by millennia of human use [4, 5].

2. Pathophysiology of Diabetes Mellitus

An understanding of the pathophysiological processes underpinning diabetes mellitus is essential for identifying rational molecular targets for pharmacological intervention. In type 2 diabetes, the predominant pathological events are peripheral insulin resistance—primarily affecting skeletal muscle, hepatic, and adipose tissue—and progressive dysfunction and loss of pancreatic beta cells [12]. In the early stages of the disease, compensatory hyperinsulinaemia maintains near-normal glucose levels, but as beta-cell secretory capacity declines, overt hyperglycaemia supervenes [13]. Insulin resistance arises through multiple interconnected mechanisms, including impaired tyrosine phosphorylation of insulin receptor substrate proteins, dysregulation of the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) signalling cascade, and enhanced serine phosphorylation of insulin receptor substrates mediated by inflammatory kinases [14].

Chronic low-grade inflammation, driven by adipokine dysregulation and activation of innate immune pathways including the nuclear factor kappa B (NF-kB) and c-Jun N-terminal kinase (JNK) pathways, contributes substantially to the perpetuation of insulin resistance [15]. Oxidative stress, characterised by excessive generation of reactive oxygen species (ROS) and inadequate antioxidant defences, exacerbates beta-cell damage and impairs insulin signalling at multiple steps [16]. Mitochondrial dysfunction in skeletal muscle reduces glucose oxidative capacity and promotes ectopic lipid accumulation, further worsening insulin sensitivity [17]. These interconnected pathways provide multiple molecular targets at which plant-derived compounds may exert beneficial effects, highlighting the potential value of phytochemicals with pleiotropic pharmacological activities.

3. Major Classes of Plant-Derived Antidiabetic Compounds

Phytochemicals relevant to antidiabetic research may be grouped into several broad structural and biosynthetic classes, each characterised by distinct chemical features and pharmacological properties. Flavonoids constitute one of the most extensively studied groups, comprising polyphenolic compounds characterised by a C6-C3-C6 carbon skeleton. Quercetin, kaempferol, and rutin are among the most biologically active members of this class and have been identified in diverse plant sources including onions (Allium cepa), apples (Malus domestica), green tea (Camellia sinensis), and buckwheat (Fagopyrum esculentum) [18]. Alkaloids represent another pharmacologically rich class; berberine, derived from Berberis aristata and related species, has emerged as a particularly promising compound owing to its AMPK-activating and glucose-lowering properties that are mechanistically comparable to metformin [19]. Trigonelline, present in fenugreek (Trigonella foenum-graecum), has been reported to enhance pancreatic beta-cell regeneration and improve glucose tolerance in experimental models [20].

Terpenoids, encompassing mono-, di-, tri-, and sesquiterpenoids, are biosynthetically derived from isoprene units and display considerable structural diversity. Oleanolic acid and ursolic acid, pentacyclic triterpenoids found in olive (Olea europaea) and rosemary (Rosmarinus officinalis) respectively, have demonstrated insulin-sensitising and anti-inflammatory activities [21]. Gymnemic acid, a mixture of triterpenoid saponins from Gymnema sylvestre, has long been used in Ayurvedic medicine for glycaemic management and has been shown to suppress intestinal glucose absorption and stimulate insulin secretion [22]. Cardiac and steroidal glycosides, including phlorizin from apple root bark and stevioside from Stevia rebaudiana, have provided important templates for the development of SGLT inhibitors and have demonstrated direct pancreatic and extrapancreatic antidiabetic effects [23]. Polyphenols such as resveratrol, present in grape skin and red wine, and curcumin from turmeric (Curcuma longa) have attracted considerable attention for their antioxidant, anti-inflammatory, and insulin-sensitising properties [24].

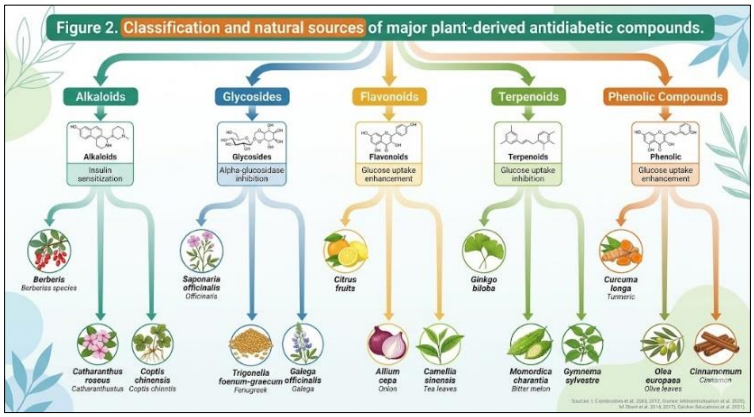

Fig 2: Classification and natural sources of major plant-derived antidiabetic compounds

4. Molecular Mechanisms of Antidiabetic Action

The antidiabetic effects of plant-derived compounds operate through several interconnected molecular mechanisms, providing a rationale for their therapeutic relevance and supporting their investigation as drug leads. Inhibition of carbohydrate-digesting enzymes, specifically alpha-amylase and alpha-glucosidase, is among the most well-characterised mechanisms. Flavonoids and phenolic acids competitively and non-competitively inhibit these enzymes in the small intestinal brush border, thereby slowing the rate of carbohydrate hydrolysis and attenuating postprandial hyperglycaemia [25]. This mechanism forms the basis of the approved antidiabetic drug acarbose, lending pharmacological credibility to phytochemical compounds acting via analogous pathways.

Enhancement of insulin signalling represents another major mechanistic category. Quercetin and resveratrol have been shown to activate the PI3K/Akt pathway, stimulate GLUT4 translocation to the plasma membrane of skeletal muscle cells, and increase glucose uptake *in vitro* and *in vivo* [26]. Berberine activates AMPK through inhibition of mitochondrial complex I, a mechanism shared with metformin, thereby reducing hepatic glucose production, promoting fatty acid oxidation, and improving peripheral insulin sensitivity [19]. Curcumin exerts its insulin-sensitising effects in part through inhibition of the inflammatory kinases JNK and IkB kinase beta (IKKbeta), which phosphorylate insulin receptor substrate-1 on serine residues and attenuate downstream insulin signalling [27].

Antioxidant mechanisms are of particular importance given the central role of oxidative stress in beta-cell apoptosis and insulin resistance. Polyphenols such as ellagic acid and epigallocatechin gallate (EGCG) upregulate the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, inducing expression of antioxidant enzymes including superoxide dismutase, catalase, and haem oxygenase-1, thereby reducing ROS-mediated cellular damage [28]. Gymnemic acid modulates the peroxisome proliferator-activated receptor gamma (PPARgamma) pathway, improving adipocyte differentiation and glucose homeostasis [22]. Phlorizin and stevioside act on SGLT2 and SGLT1 transporters respectively, reducing renal glucose reabsorption and intestinal glucose absorption, mechanisms directly translatable to clinical drug targets [23].

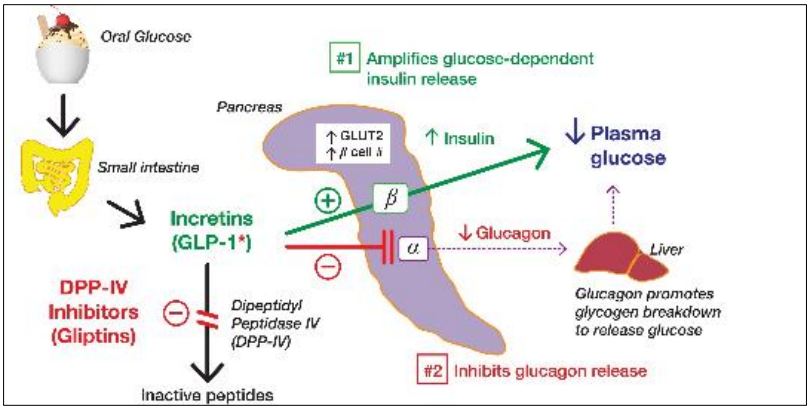

Fig 1: Key metabolic pathways involved in diabetes and molecular points of intervention by plant-derived compounds

5. Preclinical Evidence and Translational Research

The preclinical investigation of plant-derived antidiabetic compounds typically begins with *in vitro* enzyme inhibition assays and cell-based models of insulin resistance or beta-cell dysfunction, before progressing to rodent models of diabetes mellitus [29]. Streptozotocin-induced diabetic rats and mice represent the most commonly employed experimental systems, offering reproducible hyperglycaemia suitable for evaluating glucose-lowering efficacy, although they primarily model absolute insulin deficiency rather than the insulin-resistant phenotype of type 2 diabetes [30]. High-fat diet-induced and genetically obese models such as db/db mice and Zucker fatty rats more faithfully recapitulate the metabolic syndrome context relevant to type 2 diabetes and have been used to evaluate compounds including berberine, quercetin, and curcumin [26, 27].

Pharmacokinetic profiling in preclinical models has revealed significant challenges associated with many phytochemicals. Resveratrol, despite impressive *in vitro* activity, undergoes rapid Phase II conjugation in the intestinal epithelium and liver, resulting in low systemic bioavailability of the free aglycone form and necessitating high doses to achieve pharmacological plasma concentrations [24]. Similarly, curcumin exhibits poor aqueous solubility, rapid metabolism, and limited tissue distribution, constraining its translational prospects unless formulation strategies are employed [31]. Berberine faces efflux by P-glycoprotein at the intestinal barrier, reducing oral bioavailability to below five percent in some studies, although its pharmacodynamic activity at the gastrointestinal level may partially compensate for poor systemic absorption [19]. These pharmacokinetic limitations underscore the importance of integrating formulation science early in the preclinical development pathway.

6. Clinical Evidence

Clinical evidence for plant-derived antidiabetic compounds remains heterogeneous in quality, with most trials characterised by small sample sizes, short follow-up durations, inadequate blinding, and significant variability in the composition and dose of test preparations [32]. Berberine has yielded the most robust clinical data; several randomised controlled trials have demonstrated reductions in fasting plasma glucose, postprandial glucose, and glycated haemoglobin (HbA1c) comparable to those achieved with metformin in patients with type 2 diabetes, with a generally favourable safety profile [33]. A meta-analysis of fourteen trials found that berberine significantly reduced HbA1c by approximately 0.9 percent compared to placebo, an effect size clinically comparable to established oral hypoglycaemic agents [34].

Clinical data for curcumin suggest benefits in reducing inflammatory biomarkers and improving insulin sensitivity in pre-diabetic and diabetic populations, although methodological heterogeneity limits definitive conclusions [31]. Gymnema sylvestre extracts have demonstrated modest but consistent reductions in fasting blood glucose and HbA1c in several trials, consistent with its proposed mechanism of enhancing beta-cell regeneration [22]. Fenugreek seed supplementation has shown reductions in postprandial glucose in both type 1 and type 2 diabetic patients, attributed to the soluble fibre content and trigonelline activity of the seeds [20]. The primary limitations across the available clinical literature include lack of standardisation of plant extracts, absence of pharmacokinetic data in trial populations, variable outcome measures, and inadequate assessment of drug interactions, particularly relevant for patients receiving polypharmacy.

7. Formulation and Delivery Advancements

Addressing the pharmacokinetic limitations inherent to many phytochemicals has become a central theme in contemporary plant-based drug development research. Nanoparticle-based delivery systems—including polymeric nanoparticles, solid lipid nanoparticles, and self-nanoemulsifying drug delivery systems—have been extensively investigated as strategies to enhance solubility, protect active compounds from presystemic metabolism, and promote intestinal permeability [35]. Curcumin encapsulated within poly(lactic-co-glycolic acid) (PLGA) nanoparticles has demonstrated substantially improved bioavailability and sustained plasma concentrations compared to unformulated curcumin in animal studies [36]. Phospholipid complexation, as exemplified by Meriva®, a curcumin-phosphatidylcholine complex, has been translated into commercially available dietary supplement formulations with improved clinical bioavailability data, providing a proof-of-concept for this approach [31].

Liposomal encapsulation of quercetin and resveratrol has been explored to overcome the dual challenges of poor water solubility and rapid metabolic inactivation, with several *in vitro* and *in vivo* studies demonstrating enhanced cellular uptake and pharmacological activity [26, 35]. Cyclodextrin inclusion complexes represent another well-established strategy applicable to poorly water-soluble phytochemicals, offering improved dissolution rates with minimal toxicological concerns. Mucoadhesive and sustained-release oral formulations have been investigated for compounds such as berberine, aiming to prolong gastrointestinal residence time and maximise local enzyme-inhibitory activity alongside systemic absorption [37]. The integration of these delivery innovations with standardised, well-characterised phytochemical preparations represents a critical bridge between the pharmacological promise identified in preclinical research and the clinical performance required for regulatory approval.

8. Regulatory, Safety, and Commercialisation Challenges

The regulatory landscape for plant-derived antidiabetic compounds is complex and varies considerably across jurisdictions. In the United States, botanical drugs may be reviewed under the Food and Drug Administration (FDA) Botanical Drug Guidance, which provides a regulatory pathway for plant-based preparations provided that chemistry, manufacturing, and control standards and clinical safety data meet defined thresholds [38]. The European Medicines Agency (EMA) operates comparable frameworks for herbal medicinal products, with well-established herbal medicines benefiting from simplified registration procedures based on documented traditional use [39]. In jurisdictions such as India, Ayurvedic preparations are governed by distinct legislative frameworks under the Ministry of AYUSH, although increasing alignment with international good manufacturing practice standards is occurring.

Safety concerns associated with plant-derived compounds include herb-drug interactions mediated through cytochrome P450 enzyme induction or inhibition—a property documented for compounds including quercetin, which inhibits CYP3A4 and may affect co-administered drugs with narrow therapeutic indices [40]. Berberine inhibits CYP2D6 and has been shown to increase plasma concentrations of cyclosporine and metformin in clinical studies, necessitating caution in polypharmacy settings [33]. Hepatotoxicity, while less common than with synthetic agents, has been documented with certain botanical preparations, underlining the need for rigorous toxicological characterisation. The absence of strong intellectual property protection for naturally occurring compounds creates a significant commercial disincentive for full-scale clinical development by pharmaceutical industry sponsors, a structural barrier that may be partially addressed through patenting of novel formulations, delivery systems, or synthetic derivatives inspired by natural product scaffolds.

9. Conclusion and Future Perspectives

Plant-derived compounds represent a scientifically compelling and pharmacologically diverse resource for antidiabetic drug development. The multi-target mechanisms of action exhibited by flavonoids, alkaloids, terpenoids, glycosides, and polyphenols align well with the complex, multifactorial pathophysiology of type 2 diabetes mellitus, and several compounds—most notably berberine—have accrued sufficient clinical evidence to justify further investigation in large, rigorously designed randomised controlled trials. The historical success of plant-derived templates in generating approved pharmaceuticals, exemplified by the development of SGLT2 inhibitors from phlorizin and the influence of galegine from Galega officinalis on the development of metformin, provides strong precedent for this research strategy [10, 23].

Future research should prioritise the development of robust standardisation protocols and analytical quality assurance frameworks to ensure compositional reproducibility of plant-based preparations used in clinical trials. The integration of systems pharmacology approaches, including network analysis of phytochemical-target interactions and multi-omics profiling of treated patient populations, offers the potential to identify synergistic compound combinations and predict interindividual variability in therapeutic response. Advanced formulation technologies should be systematically applied to address the pharmacokinetic limitations of the most promising phytochemical candidates, with bioavailability-enhancing strategies incorporated from the earliest stages of the development pipeline. Collaborative frameworks bringing together academic researchers, clinical

trialists, regulatory agencies, and industry partners will be essential for overcoming the translational barriers that have historically limited the progression of phytochemical leads to approved medicines. With appropriate investment in rigorous mechanistic and clinical research, plant-derived compounds hold genuine promise as a source of next-generation antidiabetic therapies.

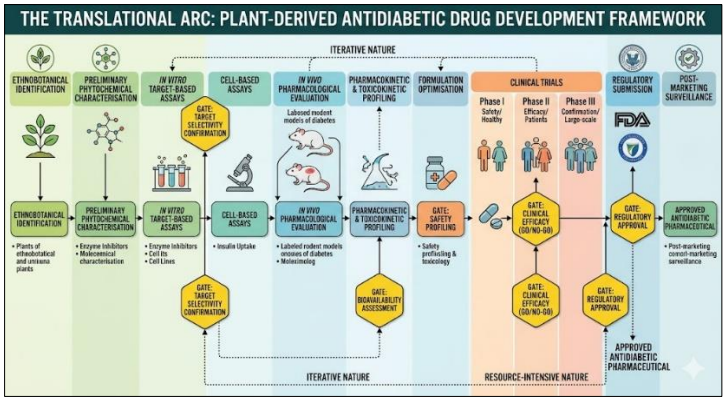

Fig 3: Translational pathway from experimental studies to clinical application in antidiabetic drug development.

Tables

Table 1: Classes of Plant-Derived Compounds, Their Natural Sources, and Mechanisms of Antidiabetic Action

Compound Class	Representative Examples	Natural Sources	Mechanism of Antidiabetic Action
Flavonoids	Quercetin, Kaempferol, Rutin	Onion, apple, green tea, buckwheat	Inhibition of alpha-glucosidase; GLUT4 upregulation; improvement of insulin secretion
Alkaloids	Berberine, Trigonelline, Vincamine	Barberry, fenugreek, periwinkle	AMPK activation; inhibition of gluconeogenesis; enhancement of insulin receptor signaling
Terpenoids	Oleanolic acid, Ursolic acid, Gymnemic acid	Olive leaf, rosemary, gymnema	PPARgamma activation; insulin mimetic activity; inhibition of intestinal glucose absorption
Glycosides	Phlorizin, Stevioside, Salicin	Apple root bark, stevia, willow bark	SGLT2 inhibition; modulation of pancreatic beta-cell function; reduction of postprandial glucose
Polyphenols	Resveratrol, Curcumin, Ellagic acid	Grape skin, turmeric, pomegranate	Antioxidant activity; NF-kB inhibition; improvement of mitochondrial function; reduction of systemic inflammation

Table 2: Advantages, Limitations, and Clinical Considerations of Plant-Based Antidiabetic Therapies

Aspect	Advantages	Limitations	Clinical Considerations
Therapeutic Profile	Multi-target mechanisms; complementary to existing drugs; potential for synergistic use	Variable potency; mechanism often poorly characterised in humans	May serve as adjunctive rather than primary therapy
Safety	Generally lower toxicity; long ethnobotanical history; fewer severe adverse effects reported	Herb-drug interactions; hepatotoxicity risk with some compounds; lack of long-term safety data	Thorough drug interaction screening required before clinical use
Standardisation	Advances in phytochemical profiling improve batch consistency	Natural variability in plant composition; no universal standardisation protocols	Standardised extracts essential; certificate of analysis required for trials
Bioavailability	Improved by novel delivery systems such as nanoparticles and liposomes	Poor oral bioavailability of many active compounds; extensive first-pass metabolism	Formulation strategy must be defined early in development pipeline
Regulatory Status	Growing regulatory frameworks in EU, US, and India for botanical drugs	Absence of exclusive IP; limited commercial incentive for full clinical development	Early engagement with regulatory agencies recommended; combination product strategies may be viable

References

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels: International Diabetes Federation; 2021.
2. Sun H, Saeedi P, Karuranga S, Pinkepank M, Ogurtsova K, Duncan BB, *et al*. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res Clin Pract. 2022;183:109119.
3. Blonde L, Umpierrez GE, Reddy SS, McGill JB, Berga SL, Bush M, *et al*. American Association of Clinical Endocrinology clinical practice guideline: Developing a diabetes mellitus comprehensive care plan. Endocr Pract. 2022;28(10):923-1049.
4. Alam S, Sarker MMR, Afrin S, Richi FT, Zhao C, Zhou JR, *et al*. Traditional antidiabetic plants: a concise review of phytochemistry, antidiabetic potential, and safety profile. Front Pharmacol. 2022;13:1063886.
5. Governa P, Baini G, Borgonetti V, Cettolin G, Giachetti D, Magnano AR, *et al*. Phytotherapy in the management of diabetes: a review. Molecules. 2018;23(1):105.
6. Patel DK, Kumar R, Laloo D, Hemalatha S. Natural medicines from plant source used for therapy of diabetes

mellitus: An overview of its pharmacological aspects. Asian Pac J Trop Dis. 2012;2(3):239-50.
7. American Diabetes Association Professional Practice Committee. Classification and diagnosis of diabetes: Standards of medical care in diabetes. Diabetes Care. 2023;46(Suppl 1):S19-S40.
8. Zhu Y, Zhang C. Prevalence of gestational diabetes and risk of progression to type 2 diabetes: a global perspective. Curr Diab Rep. 2016;16(1):7.
9. Standl E, Khunti K, Hansen TB, Schnell O. The global epidemics of diabetes in the 21st century: Current situation and perspectives. Eur J Prev Cardiol. 2019;26(2_suppl):7-14.
10. Bailey CJ. Metformin: historical overview. Diabetologia. 2017;60(9):1566-76.
11. Zelniker TA, Wiviott SD, Raz I, Im K, Goodrich EL, Bonaca MP, *et al*. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet. 2019;393(10166):31-9.
12. DeFronzo RA, Ferrannini E, Groop L, Henry RR, Herman WH, Holst JJ, *et al*. Type 2 diabetes mellitus. Nat Rev Dis Primers. 2015;1:15019.
13. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest. 1999;104(6):787-94.
14. Samuel VT, Shulman GI. Mechanisms for insulin resistance: common threads and missing links. Cell. 2012;148(5):852-71.
15. Hotamisligil GS. Inflammation, metaflammation and immunometabolic disorders. Nature. 2017;542(7640):177-85.
16. Bhatti JS, Bhatti GK, Reddy PH. Mitochondrial dysfunction and oxidative stress in metabolic disorders—A step towards mitochondria based therapeutic strategies. Biochim Biophys Acta Mol Basis Dis. 2017;1863(5):1066-77.
17. Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev. 2018;98(4):2133-223.
18. Eid HM, Haddad PS. The antidiabetic potential of quercetin: underlying mechanisms. Curr Med Chem. 2017;24(4):355-64.
19. Yin J, Xing H, Ye J. Efficacy of berberine in patients with type 2 diabetes mellitus. Metabolism. 2008;57(5):712-7.
20. Nagulapalli Venkata KC, Swaroop A, Bagchi D, Bishayee A. A small plant with big benefits: Fenugreek (Trigonella foenum-graecum Linn.) for disease prevention and health promotion. Mol Nutr Food Res. 2017;61(6):1600950.
21. Khanna K, Kohli SK, Handa N, Kaur H, Ohri P, Bhardwaj R, *et al*. Ursolic acid and oleanolic acid—chemistry and therapeutic perspectives. In: Atta ur Rahman, editor. Studies in Natural Products Chemistry. Amsterdam: Elsevier; 2020. p. 455-97.
22. Tiwari P, Mishra BN, Sangwan NS. Phytochemical and pharmacological properties of Gymnema sylvestre: an important medicinal plant. Biomed Res Int. 2014;2014:830285.
23. Ehrenkranz JR, Lewis NG, Kahn CR, Roth J. Phlorizin: a review. Diabetes Metab Res Rev. 2005;21(1):31-8.
24. Bhatt JK, Thomas S, Nanjan MJ. Resveratrol supplementation improves glycemic control in type 2 diabetes mellitus. Nutr Res. 2012;32(7):537-43.
25. Cheng AYY, Fantus IG. Oral antihyperglycemic therapy for type 2 diabetes mellitus. CMAJ. 2005;172(2):213-26.
26. Bi X, Lim J, Henry CJ. Spices in the management of diabetes mellitus. Food Chem. 2017;217:281-93.
27. Chuengsamarn S, Rattanamongkolgul S, Luechapudiporn R, Phisalaphong C, Jirawatnotai S. Curcumin extract for prevention of type 2 diabetes. Diabetes Care. 2012;35(11):2121-7.
28. Baur JA, Sinclair DA. Therapeutic potential of resveratrol: the *in vivo* evidence. Nat Rev Drug Discov. 2006;5(6):493-506.
29. Srinivasan K, Ramarao P. Animal models in type 2 diabetes research: an overview. Indian J Med Res. 2007;125(3):451-72.
30. King AJ. The use of animal models in diabetes research. Br J Pharmacol. 2012;166(3):877-94.
31. Prasad S, Tyagi AK, Aggarwal BB. Recent developments in delivery, bioavailability, absorption and metabolism of curcumin: the golden pigment from golden spice. Cancer Res Treat. 2014;46(1):2-18.
32. Suksomboon N, Poolsup N, Boonkaew S, Suthisisang CC. Meta-analysis of the effect of herbal supplement on glycemic control in type 2 diabetes. J Ethnopharmacol. 2011;137(3):1328-33.
33. Dong H, Wang N, Zhao L, Lu F. Berberine in the treatment of type 2 diabetes mellitus: a systemic review and meta-analysis. Evid Based Complement Alternat Med. 2012;2012:591654.
34. Liang Y, Xu X, Yin M, Zhang Y, Huang L, Chen R, *et al*. Effects of berberine on blood glucose in patients with type 2 diabetes mellitus: a systematic literature review and a meta-analysis. Endocr J. 2019;66(1):51-63.
35. Dang Y, Guan J. Nanoparticle-based drug delivery systems for cancer therapy. Smart Mater Med. 2020;1:10-19.
36. Anand P, Kunnumakkara AB, Newman RA, Aggarwal BB. Bioavailability of curcumin: problems and promises. Mol Pharm. 2007;4(6):807-18.
37. Xu X, Yi H, Wu J, Kuang T, Zhang J, Li Q, *et al*. Therapeutic effect of berberine on metabolic diseases: Both pharmacological data and clinical evidence. Biomed Pharmacother. 2021;133:110984.
38. US Food and Drug Administration. Botanical Drug Development Guidance for Industry. Silver Spring: FDA; 2016.
39. European Medicines Agency. Guideline on the Assessment of Clinical Safety and Efficacy in the Preparation of Community Herbal Monographs/Entries to the Community List for Well-Established Use and Traditional Herbal Medicinal Products. London: EMA; 2010.
40. Maaike JP, Timmers M, Rietjens IM, Alink GM, Koeman JH. Quercetin: mechanisms of action and pharmacokinetics. Chem Biol Interact. 2004;152(1):1-17.