Molecular mechanism of *Aloe vera* on modulating diabetes mellitus: a scoping review

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Abstract

Background By 2045, the global number of people living with diabetes is expected to reach 783 million; of these, 5–10% will have type 1 diabetes mellitus (T1DM), and 98% will have type 2 diabetes mellitus (T2DM). Drug treatments for T2DM often lead to adverse effects. Consequently, herbal ingredients such as Aloe vera may be used to regulate blood glucose levels and enhance pancreatic islet function. This review aims to provide a comprehensive explanation of the molecular mechanisms through which Aloe vera influences both T1DM and T2DM.

Methods This scoping review was based on the Preferred Reporting Items for Scoping Review protocol. Published experimental studies that explored the mechanisms of Aloe vera in cellular, animal and human modes were eligible for inclusion. Quality of studies was assessed with the EEQAT (in vitro) and the SYRCLE (in vivo) risk of bias instruments. Data were described in a narrative synthesis.

Results Out of the 3,210 articles obtained from the PubMed Central, Science Direct, and Scopus databases, six studies were included in this review. Multifaceted mechanisms were described including regeneration of pancreatic beta cells, glucose absorption and metabolism, insulin secretion and cellular sensitisation, antioxidant and anti-inflammatory pathways.

Conclusion The effects of Aloe vera in T1DM and T2DM require further investigation in human studies and in human trials. T1DM and T2DM have yet to be explored.

Introduction

Diabetes mellitus (DM) is a chronic condition resulting from either inadequate insulin production by the pancreas or inefficient utilisation of insulin. The International Diabetes Federation (IDF) estimates that in 2024, there were 589 million adults worldwide living with diabetes, representing 11.1% of the global population. Projections suggest that the number of people with diabetes will rise to 643 million by 2030 and to 783 million by 2045.[1] Most patients with DM can be categorised into two primary etiopathogenetic groups.[2] Type 1 DM (T1DM) results from insufficient insulin synthesis.[3] Type 2 DM (T2DM)

is characterised by compromised insulin sensitivity and impaired lipid, carbohydrate, and protein metabolism.[4] T1DM accounts for 5–10% of all cases, while T2DM is estimated to comprise 90-95% of global diabetes diagnoses, although this percentage varies by country.[2,5]

In developing nations, such as Indonesia, the prevalence of both T1DM and T2DM has rapidly increased.[6,7] Over the past decade, the incidence of T1DM has surged sevenfold.[7] In Indonesia, the prevalence of T2DM was estimated at 7% in 2016, impacting around 18 million people.[8]

Failing to manage diabetes mellitus can result in severe complications, including neuropathy, nephropathy (damage to the renal system), and retinopathy (damage to the eyes). Additionally, it can cause cardiovascular disease, stroke, and peripheral vascular disease.[9] Individuals with DM are especially vulnerable to depression, particularly those who lack adequate social support.[10] The widespread impact of DM on physical and mental health underscores the need for effective management.[11] T2DM can be managed through various approaches, including adopting a healthy lifestyle and utilising medications to decrease blood glucose levels.[3]

Pharmacological treatments for blood glucose management in T2DM include metformin, dipeptidyl peptidase IV inhibitors (DPP-4 inhibitors), GLP-1, dual glucagon-like peptide-1/gastric inhibitory polypeptide receptor agonists (GLP-1/GIP receptor agonists), sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors), sulfonylureas, and thiazolidinediones.[12] Nevertheless, the use of pharmacological medications is often constrained by various adverse reactions. For instance, metformin has been linked to vitamin B12 deficiency, which may result in anemia and neuropathy. While DPP-4 inhibitors may trigger nasopharyngitis, upper respiratory tract infections, and headaches.[13] Exploring herbal remedies as alternatives could offer a viable approach for managing blood glucose and mitigating side effects associated with existing pharmaceuticals.

Herbal remedies consist of plant-derived medicinal substances that may be used to treat various ailments. *Aloe vera*, a well-known traditional remedy across different cultures, contains a variety of bioactive compounds such as alkaloids, anthraquinones, and saponins. These components exhibit therapeutic properties such as anti-inflammatory, antioxidant, antibacterial, and antidiabetic effects.[14,15] These properties are explored in this review, underscoring on the molecular mechanisms of action.

Several studies indicate that *Aloe vera* is a promising alternative for improving glycemic control in individuals with prediabetes and T2DM. *Aloe vera* supplementation provides significant benefits regarding free fatty acids (FFA), hepatic transaminase levels, fasting total cholesterol (TC), triglycerides (TG), phospholipids, and reductions in fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), and blood glucose (FBG).[16–18] Moreover, the active compounds present in *Aloe vera* have been shown to notably elevate plasma insulin levels and inhibit the production of methylglyoxal and arginine, thereby suppressing the glycation process.[18,19] Despite this evidence, few reviews have focused on the molecular mechanisms by which *Aloe vera* alleviates diabetes. This scoping review aims to provide a comprehensive understanding of the molecular mechanisms through which *Aloe vera* influences diabetes, contributing to the advancement of knowledge in the field and potentially informing the development of novel therapeutic approaches for managing diabetes mellitus.

Methods

Study design

This scoping review was based on the Preferred Reporting Items for Scoping Review protocol (PRISMA-ScR). This scoping review aimed to scope of the evidence of the molecular mechanisms of *Aloe vera's* effect on type-1 or type-2 DM models. This question included information about the population (rats or humans with Type-1 or Type-2 DM), the concept (usage of *Aloe vera* in DM), and the context (the molecular mechanism of *Aloe vera* in DM).

This review was conducted in accordance with the PRISMA-ScR statement, which is an updated guideline for reporting scoping reviews. The method of summarising this review is conducted on the scoping review.

Eligibility criteria

To represent the current evidence regarding *Aloe vera* extract, we included original research papers. All included studies met several criteria, including all experiments related to type-1 or type-2 DM using *Aloe vera* extract, and were conducted on mice or cells. Studies were excluded if the paper was not written in English, or if the full text could not be found. Case reports and duplicate studies were also excluded from the analysis.

Search strategy

The PubMed Central, Science Direct, and Scopus databases were searched for articles published from January 2013 to January 2023. A flowchart of the study results is shown in Figure 1.1. Keywords were: "Diabetes Mellitus," "Aloe vera," "aloctin I," and "experimental." The PubMed search was supplemented with MeSH headings.

Study selection

Four authors (IL, GC, JD, and CJ) independently reviewed the abstracts, followed by a full-text assessment of studies that met the inclusion criteria. Discrepancies were resolved through discussion. The inclusion criteria were based on the population, concept, and context, specifically focusing on, *in vitro* and *in vivo* studies in animals (rats, mice) or clinical trials including humans with diabetes mellitus. The use of *Aloe vera* extract as the concept, and the context of this scoping review spans from January 2013 to January 2023 (Table 2).

Data extraction

Four authors (IL, GC, JD, and CJ) gathered data from all full-text articles that were approved for the final analysis. The collected information included the author's surname, study year, study location, research design, population demographics, intervention details, *Aloe vera* administration specifics, induction methods, outcomes, and the molecular mechanisms involved.

Risk of bias assessment

The risk of bias analysis for this scoping review was performed using two distinct instruments that were specific to the study-type. For *in vivo* studies, the SYRCLE's risk of bias tool was employed to assess the methodological quality and risk of bias. This tool systematically evaluates several domains, including selection, performance, detection, attrition, and reporting bias, to determine the rigor of animal research. For *in vitro* studies, the EEQAT (Expanded Experimental Quality Assessment Tool) was used. This tool provides a structured framework for evaluating the quality of laboratory-based experiments by scrutinising aspects such as cell culture methods, reagent validation, and data reporting to mitigate the risk of technical or methodological bias.

Result

A total of 3,210 articles were initially obtained from the PubMed Central, Science Direct, and Scopus database, of which 201 articles were duplicates. Title and abstract screening of 3,009 articles excluded 2,990. Reasons for exclusion of 1,827 articles was due to in the wrong population, 468 presented a different concept to diabetes models, 252 used a different study design, 430 were published outside the time period, and 12 were excluded as they were not published in English language. Ultimately, 19 full-text articles were evaluated for eligibility. From these 13 were excluded due to a lack of methodological description of the molecular mechanisms that were presented. This resulted in the inclusion of six studies in the qualitative synthesis (Figure 1).

Data were extracted from the six included articles and presented according to the author, country, study design (in vivo or in vitro), reference, population characteristics, and intervention (extract preparation).

Experimental methods

The most common method for inducing diabetes models in animal studies was with injection of streptozotocin (STZ) which is toxic to insulin-producing beta cells in the pancreas and consistently produces fasting blood glucose (FBG levels of 300-540 mg/dL).[24,26,32,34] Other methods included alloxan injection, which resulted in FBG of approximately 380 mg/dL in female mice,[23] and high fat diet (HFD) in male mice, which resulted in an FBG of 181.8 mg/dL.[25]

Study characteristics are presented in Table 3.

Risk of bias

For the included *in vivo* Studies, three studies used a random component for sequence generation, though the specific method was not detailed. Three studies did not randomly allocate animals, but they followed consistent guidelines. Four studies lacked blinding for outcome assessors. Notably, in all studies, the investigators were not blinded during intervention, the allocation was not concealed, and animals were not randomly selected for outcome assessment. No protocols were available for any of these studies. Additionally, two studies had authors with a financial interest in a pharmaceutical company. The quality assessment of *in vivo* studies is presented in Table 4.

Table 1. Search strategy

Database	Keywords and Queries
PubMed Central	Keywords: "Aloe vera," "diabetes mellitus type 2," "Aloe," "Aloe vera gel," "aloctin I" Query: (("diabetes mellitus, type 2"[MeSH Terms] OR diabetes mellitus type 2[Text Word]) AND (("aloe"[MeSH Terms] OR aloe[Text Word]) OR (aloctin[All Fields])))
Science Direct	Keyword: "Diabetes Mellitus Type 2," "Aloe," "Aloe vera gel," "aloctin I) Query: (Diabetes Mellitus, Type 2) AND (Aloe OR Aloe vera gel OR aloctin I)
Scopus	Keywords: "diabetes," "mellitus," "Aloe vera gel," "aloctin I" Query: ((Diabetes AND Mellitus) AND (Aloe OR (Aloe AND vera AND gel) OR (aloctin AND I)))

Table 2. Population, concept, and context of this scoping review

Population	We limited to *in vitro* and *in vivo* studies in animals (rats, mice) or clinical trials including humans with diabetes mellitus. A study that did not fulfill the population criteria will be excluded. There are no limitations on certain characteristics to ascertain the inclusion of all groups with diabetes mellitus.
Concept	Interventional strategies to treat diabetes mellitus using *Aloe vera* extract. *Aloe vera* extract may refer to any form of molecules and mechanism resulting from *Aloe vera* to treat diabetes mellitus.
Context	This scoping review included research that published between January 2013 and January 2023 to explore all the molecular mechanisms of *Aloe vera* extract in treating diabetes mellitus.
Type of Sources	Sources of included study were found in PubMed Central, ScienceDirect, and SCOPUS.

For *in vitro* Studies, all three had a clearly defined research question and used a new method. They all mentioned clear objectives, with one study focused on therapeutic efficacy, and two on evaluating chemical properties and composition. All studies used biological tissues with anonymity maintained, though one study did not specify whether the tissues were sterilised beforehand. All materials were biocompatible and approved by national bodies, but one study failed to mention proper waste disposal. The studies did not justify their sample size, mention randomisation methods, or implement blinding. While the results were not based on repeated readings, the analysis used appropriate statistical tests. All studies concluded that their objectives were met and that the research could be replicated in in vivo or clinical settings. The qualty assessment of *in vitro* studies is presented in Table 5.

Mechanisms of *Aloe vera* in diabetes models

Impaired insulin secretion

Aloe vera impacts insulin secretion was shown in diabetic animal models. A dose of 300 mg/kg BW increased insulin secretion in diabetic rats from 116.5 pmol/L to 146.1 pmol/L over three weeks, and associated with an increase in the number of pancreatic islet cells.[22] A separate study by Yimam et al. (2014) showed that administering UP780, an *Aloe vera* polysaccharide, at 2000 mg/kg to alloxan-induced T1DM model rats

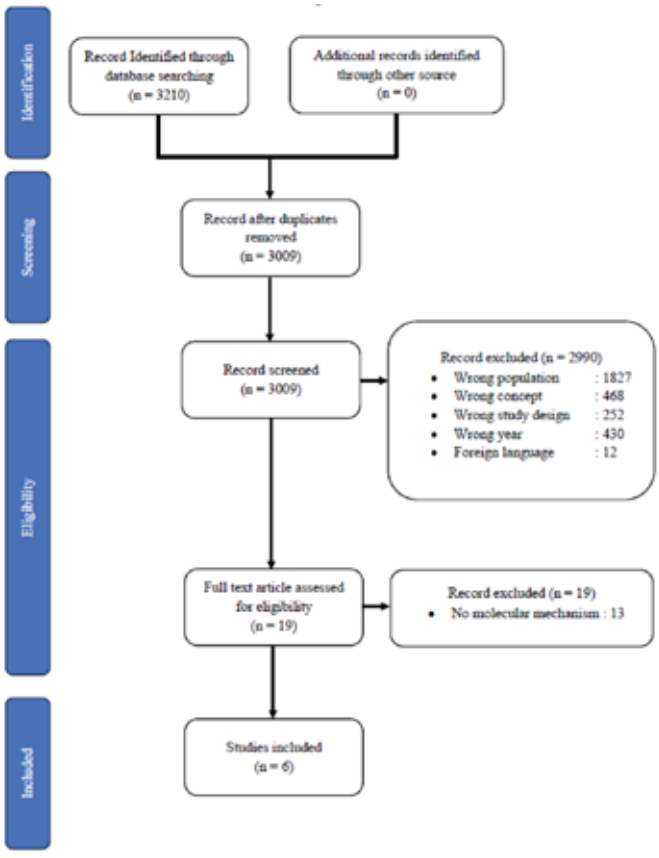

Figure 1. Result of data extraction

increased insulin levels by 60.1% after four weeks of treatment.[23] Govindarajan et al. (2021) also demonstrated that an *Aloe vera* derived carbohydrate fraction (AVCF), at concentrations of 20 and 60 µg/mL increased insulin levels by 40.2% and 58.5%, respectively, in streptozotocin (STZ)-treated cells[24]. However, a study by Yimam et al. (2013) showed a reduction in plasma insulin levels by 28.5% with UP780 (200 mg/kg) in mice consuming a high-fat diet (HFD).[25] Another study outlined a proposed mechanism of a peptide/polypeptide fraction (PPF) from *Aloe vera* enhancing plasma insulin levels by inhibiting the DPP-IV enzyme.[26]

Decrease in glucose absorption

Aloe vera was shown to decrease the rate of glucose absorption in the gastrointestinal tract. AVCF, which contains arabinose, rhamnose, and mannose, may inhibit the α-amylase and α-glucosidase enzymes, leading to decreased postprandial glucose levels in the range of 60.44 ± 1.02 µg and 82.85 ± 1.05 µg, respectively.[27] This was supported by another study demonstrating that *Aloe vera* methanol extract, at a concentration of 5 mg/mL. reduced α-glucosidase and α-amylase activity by 66% and 87%, respectively. However, at lower concentrations of 0.60 and 0.30 mg/mL, the methanol Aloe extract showed no inhibitory activity against these enzymes.[19]

Increased glucose uptake in cells

Aloe vera may enhance cellular glucose uptake. The use of AVCF in yeast cells was shown to enhance glucose uptake by facilitating the binding of various disaccharides to glucose molecules, activating glycolysis in skeletal muscle cells, and enhancing glucose storage in the liver.[24] In addition to AVCF, aloin, a bioactive compound in *Aloe vera*, enhanced glucose uptake by modulating the insulin receptor substrate-1 (IRS1)/phosphoinositide-3-kinase (PI3K) pathway.[28–30] Haghani et al. further supported this, showing that aloin enhances glucose tolerance by modulating the IRS1 and PI3K pathways.[31]

Antioxidant properties

Aloe vera possesses antioxidant properties. Tabatabei et al. (2017) observed that oral administration of *Aloe vera* gel at 100 mg/kg/day significantly reduced elevated malondialdehyde (MDA) levels in STZ-induced rats. The treated group showed significantly higher levels of superoxide dismutase (SOD) ($p = 0.009$) and catalase (CAT) ($p = 0.001$) activity compared to the STZ group.[32] Govindarajan et al. (2021) investigated the effect of AVCF on diabetic rats, showed similar results, with a significant increase in SOD levels in the liver (69.3%) and pancreas (50.8%), and CAT levels in the liver (50.1%) and pancreas (54.9%). Additionally, MDA levels in the kidneys of diabetic rats declined by 60.1% after AVCF treatment.[24]

Enhancing insulin sensitivity

Several compounds in *Aloe vera* have been shown to enhance insulin sensitivity. UP780, for example, suppresses genes involved in lipid synthesis while

Table 3. Summary of included studies

Author	Country	Study Design	Reference	Population Characteristics	Intervention	Aloe vera Administration	Inducing Methods	Outcome	Molecular Mechanism
Yimam et al. (2014)[23]	USA	In vivo (mouse)	Blood glucose lowering activity of aloe-based composition, UP780, in alloxan induced insulin dependent mouse diabetes model	Female CD-1 mice	*Aloe vera* inner gel powder polysaccharide (Qmatrix) and chromone aloesin	UP780 at 2000 mg/kg and its constituents (aloesin at 80 mg/kg and Qmatrix at 1920 mg/kg) were given orally for 4 weeks	Single intraperitoneal injection of alloxan monohydrate at a dose of 150 mg/kg for 5 days	Increasing plasma insulin	UP780 increase plasma insulin by regeneration on of beta cell by protecting existing beta-cells, and stimulate the synthesis and/or release of insulin of beta-cells
Yimam et al (2013)[25]	USA	In vivo (mouse)	UP780, A chromone-enriched aloe composition improves insulin sensitivity	Male C57BL/6J mice	*Aloe vera* inner gel powder polysaccharide	UP780 at 200 mg/kg were given oral gavage for 4 weeks GW1929 at 5 mg/kg were given oral gavage for 10 weeks	HFD-induced diabetic animal model (45% kcal) for 8 weeks	Enhancing Insulin Sensitivity	UP780 could reduce the expression of lipid synthesis and increase expression of genes encoding fatty acid-binding proteins, while also inducing insulin signaling pathways
Tabatabaei et al. (2017)[32]	Iran	In vivo (mouse)	*Aloe vera* gel improves behavioral deficits and oxidative status in streptozotocin-induced diabetic rats	Male Wistar rats	*Aloe vera* gel extract	*Aloe vera* gel at 8 ml/kg volume were given oral gavage for 8 weeks	Single intraperitoneal injection of 60 mg/kg STZ dissolved in citrate buffer (0.1 M, pH 4.5) for 1 week	Antioxidant	*Aloe vera* gel have high amounts of flavonoids for enhancement of memory performance through regulating neurotrophins, stimulating neurogenesis, protecting neurons against oxidative and metabolic stresses
								Decreasing fasting blood glucose levels	*Aloe vera* gel preserves beta cells and stimulates insulin release, so it effectively lowers blood glucose levels
Govindarajan et al. (2021)[24]	India	In vitro (RIN-m5F cells)	*Aloe vera* carbohydrates play a role in regulating glucose metabolism by enhancing glycogen synthesis and reducing hepatic gluconeogenesis in diabetic rats.	N/A	*Aloe vera* carbohydrate fraction	N/A	RIN-m5F cells were given 5 mM STZ intraperitoneally along with treated with AVCF (20 and 60 µg/ml)	Antioxidant	Elevated insulin levels may occur due to the rejuvenation of pancreatic beta cells induced by AVCF, providing significant protection against STZ-induced damage to Rinm5F cells. The components arabinose, mannose, and rhamnose in AVCF demonstrate organoprotective effects against oxidative stress-induced tissue damage, as evidenced in pancreatic and liver sections.

Author	Country	Study Design	Reference	Population Characteristics	Intervention	Aloe vera Administration	Inducing Methods	Outcome	Molecular Mechanism
								Anti-Inflammatory	The rise in BrdU and insulin levels showed AVCF can lower NO and inflammatory cytokine levels AVCF protects pancreatic β-cells by reducing cytokine levels and suppressing apoptosis, restoring β-cell shape.
		In vivo (mouse)		Male Wistar rats		Group II: AVCF (27 mg/kg bw) Group III & IV: AVCF (54 mg/kg bw)	Intraperitoneal injection of STZ (40 mg/kg bw) dissolved in a freshly prepared citrate buffer (0,1 M pH 4.5) solution for 3 days	Lowering the postprandial glucose levels	In AVCF, arabinose, rhamnose, and mannose may aid in lowering postprandial glucose levels by postponing the hydrolysis of polysaccharides By enhancing gastrointestinal viscosity and gut microbial fermentability, dietary fibers and sugars in the AVCF may help in the restoration of gastrointestinal transit and reducing the rising postprandial glucose levels
								Increase glucose uptake	AVCF's rhamnose, arabinose, mannose, ribulose, and glucosamine may bind to glucose and transfer it across cell membranes, causing the skeletal muscle cells to begin glycolysis and produce more glycogen in liver

Author	Country	Study Design	Reference	Population Characteristics	Intervention	Aloe vera Administration	Inducing Methods	Outcome	Molecular Mechanism
Zhong et al. (2022)[34]	China	In vitro (IR-HepG2 cells)	The anti-diabetic impact of aloin through the JNK-IRS1/PI3K pathways and modulation of gut microbiota.	N/A	Aloin at 1, 10, 100, 200, 250, 500, 750, and 1000 μg/mL were used to treat HepG2 cells.	HepG2 cells were cultured in DMEM supplemented with 1% penicillin-streptomycin and 10% FBS at 37°C, 5% CO2, and 95% humidity. Upon reaching 95% confluence, the cells were subcultured using trypsin-EDTA digestion.	IR-HepG2 cells was determined using 1.5 μmol/L dexamethasone for 72h	Enhancing insulin sensitivity	Aloin can alleviate insulin resistance, due to inhibit JNK protein expression
		In vivo (mice)		Male Kunming mice		Mice was treated with aloin (90 mg/kg body weight)	Mice was administrated with 50mg/kg of STZ intraperitoneally, dissolved in 4.5 pH citrate buffer	Increase glucose uptake	Aloin can increase glucose uptake by increasing IRS1/PI3K/AKT protein expression
Babu et al. (2021)[26]	India	In vitro (Rin-m5f cells)	The involvement of zonulin and GLP-1/DPP-IV in mitigating diabetes mellitus using the peptide/polypeptide fraction of *Aloe vera* in streptozotocin-induced diabetic Wistar rats.	N/A	30% trichloroacetic acid (TCA) precipitation was used to extract the peptide/polypeptide fraction	Inoculation with varying concentrations of PPF (5, 10, 15, 20, 25, 30 μg/mL).	Rin-m5f cells were cultured and subcultured in Dulbecco's Modified Eagle Medium supplemented with 10% FBS, 0.4% penicillin, and streptomycin, and maintained in a CO2 incubator at 37°C with 5% CO2.	Increasing insulin levels	By delaying the activation of GLP-1, inhibiting the DPP-IV enzyme enhances postprandial insulin production. Inhibiting glucose diffusion is often linked to the potential for hypoglycemia.
		In vivo (mouse)		Male Wistar rats		Oral gavage was used to administer PPF extract at 0.45 and 0.22 mg/kgbw for a duration of 21 days	Rats were injected with 40 mg/kgbw of STZ	Decreasing blood glucose	
					95% ethanol was used to make *Aloe vera* extract	Oral gavage of an *Aloe vera* extract 300 mg/kgbw was administered for 21 days			

Table 4. Risk of bias analysis of *in vivo* using SYRCLE's risk of bias tool

SYRCLE's Risk of Bias Tool20		Yimam et al 2014[23]	Yimam et al 2013[25]	Tabatabaei et al 2017[32]	Govindarajan et al 2021[24]	Zhong et al 2022[34]	Babu et al 2021[26]
Was the allocation sequence adequately generated and applied?	Did the investigators describe a random component in the sequence generation process such as: referring to a random number table or using a computer random number generator	No	No	No	Yes	Yes	Yes
Were the groups similar at baseline or were they adjusted for confounders in the analysis?	Was the distribution of relevant baseline characteristics balanced for the intervention and control groups?	Yes	Yes	Yes	Yes	Yes	Yes
	If relevant, did the investigators adequately adjust for unequal distribution of some relevant baseline characteristics in the analysis?	Yes	Yes	Yes	Unclear	Unclear	Unclear
	Was the timing of disease induction adequate?	No	No	Yes	Yes	Yes	Yes
Was the allocation to the different groups adequately concealed during?	Could the investigator allocating the animal to intervention or control group not foresee assignment due to one of the following or equivalent methods?	No	No	No	No	No	No
Were the animals randomly housed during the experiment?	Did the authors randomly place the cages or animals within the animal room/facility?	No	No	No	Yes	Yes	Yes
	Is it unlikely that the outcome or the outcome measurement was influenced by not randomly housing the animals?	No	No	No	No	No	No
Were the caregivers and/or investigators blinded from knowledge which intervention each animal received during the experiment?	Was blinding of caregivers and investigators ensured, and was it unlikely that their blinding could have been broken?	No	No	No	No	No	No
Were animals selected at random for outcome assessment?	Did the investigators randomly pick an animal during outcome assessment, or did they use a random component in the sequence generation for outcome assessment?	No	No	No	No	No	No
Was the outcome assessor blinded?	Was blinding of the outcome assessor ensured, and was it unlikely that blinding could have been broken?	No	Yes	Yes	No	No	No
	Was the outcome assessor not blinded, but do review authors judge that the outcome is not likely to be influenced by lack of blinding?	Yes	Yes	Yes	Yes	Yes	Yes
Were incomplete outcome data adequately addressed?	Were all animals included in the analysis?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
	Were the reasons for missing outcome data unlikely to be related to true outcome?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
	Are missing outcome data balanced in number across intervention groups, with similar reasons for missing data across groups?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
	Are missing outcome data imputed using appropriate methods?	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Are reports of the study free of selective outcome reporting?	Was the study protocol available and were all of the study's pre-specified primary and secondary outcomes reported in the current manuscript?	No	No	No	No	No	No
	Was the study procotol not available, but was it clear that the published report included all expected outcomes?	Yes	Yes	Yes	Yes	Yes	Yes
Was the study apparently free of other problems that could result in high risk of bias?	Was the study free of contamination?	Yes	Yes	Yes	Yes	Yes	Yes
	Was the study free of inappropriate influence of funders?	No	No	Yes	Yes	Yes	Yes
	Was the study free of unit analysis errors?	Yes	Yes	Yes	Yes	Yes	Yes
	Were design-specific risks of bias absent?	Yes	Yes	Yes	Yes	Yes	Yes
	Were new animals added to the control and experimental groups to replace drop-outs from the original population?	No	No	No	No	No	No

increasing genes for fatty acid-binding proteins, leading to a reduction in free fatty acids.[25] This is supported by Misawa et al., who showed that *Aloe vera* phytosterols decreased free fatty acid levels.[33] Zhong et al. also found that aloin reduced insulin resistance by inhibiting *c-Jun NH2-terminal kinase* (JNK) protein expression.[34] Feng et al. (2023) demonstrated significant JNK inhibition at varying doses of aloin (10, 20, and 40 mg/kg).[28]

Anti-inflammatory properties

Aloe vera was shown to exhibit anti-inflammatory properties. In STZ-treated pancreatic beta cells, AVCF at concentrations of 20 and 60 µg/mL reduced tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) levels, and increased bromo deoxy uridine (BrdU) levels.[24,35] A PPF caused a reduction in IL-6 and TNF-α levels, 54.9% and 61.6%; and 56.8% and 59.5% respectively, equivalent to the effects of sitagliptin.[26] These mechanisms are summarised in Figure 2.

Bioavailability of *Aloe vera*

Studies on the bioavailability of *Aloe vera* extracts show that it may enhance the absorption of other compounds. In vitro studies using Caco-2 cells demonstrated that both *Aloe vera* gel and extracts of the whole-leaf decreased transepithelial electrical resistance (TEER), indicating the opening of tight junctions.[36,37] Both extracts also increased the apparent permeability coefficient (Papp) for FITC-dextran (FD-4) across the Caco-2 cells, though not for larger molecules[37].

A randomised, double-blind, crossover trial in humans found that *Aloe vera* gel increased the bioavailability of vitamin C by 3.04-fold and vitamin E by 3.69-fold, while whole-leaf extract increased the AUC of vitamin E by 1.98-fold[38,39].

Comparison of *Aloe vera* Dosage and Outcome

The studies showed that different *Aloe vera* compounds and dosages had varied effects on FBG. Yimam et al. (2013) found that oral administration of UP780 at 200 mg/kg to HFD mice significantly lowered FBG.[25] A later study by Yimam et al. (2014) showed a 10-fold higher dose of UP780 (2000 mg/kg) in alloxan-induced diabetic mice also significantly reduced FBG, outperforming glyburide.[23] PPF at 0.45 mg/kgbw in STZ-induced rats decreased FBG from 387.6 mg/dL to 135.1 mg/dL in three weeks.[26] An AVCF at 54 mg/kgbw in STZ-induced rats significantly reduced FBG by 74.8%, while a 27 mg/kg dose showed no significant effect.[24] *Aloe vera* gel at 100 mg/kg/day in STZ-induced rats lowered blood glucose from 536.7 mg/dL to 255.4 mg/dL over eight weeks.[32] Finally, aloin at 90 mg/kg in a T2DM mouse model resulted in an FBG of 199.9 mg/dL after two weeks, a level comparable to that of metformin.[34]

Discussion

The findings from this review indicate that *Aloe vera* may modulate the pathophysiology of diabetes mellitus through multifaceted mechanisms. These include the regeneration of pancreatic beta cells, glucose absorption and metabolism, insulin secretion and sensitivity, and antioxidant and anti-inflammatory protection. However, results of some studies were conflicting and bioavailability may be dose related.

The conflicting results of Aloe vera's effects on insulin concentrations varied due to the type of diabetes being investigated. In T1DM, the aim of therapy is to restore and/or supplement insulin production, whereas in T2DM (often augmented by HFD), the goal is to improve insulin sensitivity, and lower plasma insulin levels. *Aloe vera* reduced postprandial hyperglycemia by acting as a non-competitive inhibitor of key digestive enzymes α-amylase and α-glucosidase,[27] and delaying carbohydrate breakdown, glucose absorption and reducing post-prandial insulin concentrations. These findings, revealed in HFD mice models, suggested that glucose absorption from the gastrointestinal tract is a pathway for lowering glycemic concentration after meals. The dose-dependent nature of this effect, highlighted by lower doses of the methanol extract with no observed inhibitory effects, underscores the importance of sufficient concentrations for affecting insulin sensitivity.

In addition to regulating glucose absorption, *Aloe vera* may enhance cellular glucose uptake via two mechanisms; the AVCF facilitation of glucose transport and through Aloin enhancing core insulin signaling pathways. While the study on yeast cells provides insight into the potential of an AVCF to enhance glucose transport, it is important to note the difference in cellular mechanisms between yeast and human cells. A significant finding relevant to human use, is the role of aloin in activating the IRS1/PI3K pathway.[28–30] This pathway is key in insulin signaling, and may lead to increased glucose uptake in muscle and liver cells. Aloin may mimic or amplify the effects of insulin, thereby increasing cellular glucose utilisation and contributing to lowered glycemic levels. The mechanism of action for PPF, which inhibits the DPP-IV enzyme to elevate GLP-1 levels, mirrors the effects of conventional anti-diabetic drugs like sitagliptin[26,43], highlighting a powerful pathway for managing diabetes.

The research also suggests that *Aloe vera* compounds, particularly UP780 and aloin, may directly address insulin resistance, a central feature of T2DM pathogenesis.[25,34] UP780's ability to regulate lipid synthesis and reduce free fatty acids is a crucial contributor, as excess free fatty acids are a primary cause of insulin resistance in adipose and muscle tissue.[25,33] Furthermore, aloin's action on the JNK-IRS1/PI3K pathway provides a detailed molecular explanation for its anti-diabetic effects. By inhibiting the JNK protein expression, leading to the inactivation of the insulin receptor, aloin maintains cellular responsiveness to insulin, thereby addressing the underlying pathology of insulin resistance and helping to control blood sugar levels.[28,41]

The antioxidant and anti-inflammatory effects of *Aloe vera* are also important and consistent with findings that flavonoids with a similar chromone structure can protect

Table 5. EEQAT risk of bias tools

EEQAT Risk of Bias Tools[21]		Govindarajan et al 2021[24]	Zhong et al 2022[34]	Babu et al 2021[26]
Rational and Need	Is there a clearly defined research question?	Yes	Yes	Yes
	Is a new method/technique/material under investigation?	Yes	Yes	Yes
	Is there a previously done similar in vitro study?	No	No	No
	Is yes, is this study warranted in terms of overcoming flaws/limitaion/supperior technique/superior material?	Yes	-	Yes
	Can this in vitro study be translated into an in vivo study?	Yes	Yes	Yes
	Is in vitro method the only plausible method to answer the given research question?	No	No	No
Statement of Purpose/ Objectives of the Study	Are the objectives of the study clearly mentioned?	Yes	Yes	Yes
	Is the study related to ascertaining efficacy, dosage/concentration of drug, or therapeutic agent (e.g., as in microbial assay)?	No	Yes	No
	Is the study related to the evaluation of physical/biological/chemical properties?	Yes	Yes	No
	Is the study related to the assessment of nutritional or chemical composition?	Yes	No	No
Ethical Considerations	Are any biological tissues used?	Yes	Yes	Yes
	If Yes			
	a. Is anonymity and confidentiality maintained?	Yes	Yes	Yes
	b. Is information provided on approvals and permissions where anonymity cannot be maintained?	Yes	-	Yes
	c. Are the tissues subjected to the standard protocol for streilization/disinfection before handling?	Yes	Not clear	Yes
	Are the material used biocompatible?	Yes	Yes	Yes
	Are the materials used, approived by National/International regulatory bodies?	Yes	Yes	Yes
	Are the materials used, disposed according to the biomedical waste disposal guidelines of the country?	Yes	Not clear	Yes
	Are the methods/techniques used acceptable to patients/subjects in case, the study needs to replicated in human subjects in the future?	Yes	Yes	Yes
	Is the study approved by Institutional Ethics Committe?	Yes	Yes	Yes
Methodology	Is the sample size estimation justified?	Not sure	Not sure	Not sure
	Is the sample selection based on inclusion and exclusion criteria?	Yes	Yes	Yes
	Is the method of randomation mentioned?	No	No	No
	Is blinding done?	No	No	No
	If Yes			
	a. Single blinding	No	-	No
	b. Double bliding	No	-	No
	c. Triple blinding	No	-	No
Methodology	Are the machinery/ equipment used for resting, certified for quality, accuracy, dan precision?	Yes	Not mentioned	Yes
	Are the techniques and methods used in the study, standard methods as per the current evidence?	Yes	Yes	Yes
	Is any artificial environment/agent/simulator is used, does it closely mimic the physiological or clinical scenario?	Yes	Yes	Yes
	Do the chemicals used in the study have a certificate of purity as provided by the manufacturer?	Yes	Not clear	Yes
	Is the laboratory personnel trained and experienced to perform the analysis?	Not sure	Not clear	Not sure
	If the primary investigator is involved in carriying out the study, is he trained and calibrated angainst a reference expert?	Yes	Not clear	Yes

EEQAT Risk of Bias Tools[21]		Govindarajan et al 2021[24]	Zhong et al 2022[34]	Babu et al 2021[26]
Result	Are the result based on repeated readings?	No	No	No
	Is the analysis based on appropriate statistical test?	Yes	Yes	Yes
	Do the resuls throw light on statistically significant findings?	Yes	Yes	Yes
Conclusion	Does the conclusion mention whether the objectives of the study were met?	Yes	Yes	Yes
	Does it mention the scope for further research or any obvious recommendations?	Yes	No	No
Relevance of the study w.r.t evidence-based medicine/ dentistry	Are there parameters or performance as reported in the study subject to change in a clinical/community setting or conditions?	Yes	Yes	Yes
	Based on the result of the in vitro study, can the study be replicated as in vivo/ clinical research?	Yes	Yes	Yes
	Is there any important new information obtained which is a valuable addition to existing literature of worth recommendation through guidelines (e.g., nutritional information and recommendations, etc.)?	Yes	Yes	Yes

beta cells from oxidative damage.[40] Complications in diabetes are often associated with excessive reactive oxygen species (ROS) and oxidative stress,[42] with damage to pancreatic beta cells. By increasing antioxidant enzymes such as SOD and CAT, and reducing MDA levels, *Aloe vera* may support neutralisation of ROS and cellular protection.[24,32] Additionally, its anti-inflammatory effects may mitigate beta-cell destruction. [24,35] Both AVCF and PPF from *Aloe vera* were shown to reduce pro-inflammatory cytokines, including TNF-α and IL-6.

The bioavailability of *Aloe vera* extracts is an important consideration. Results from both in vitro and human studies demonstrate that *Aloe vera* may enhance the absorption of digestive compounds by increasing the permeability of the intestinal wall, likely by modulating tight junctions.[36,37] This suggests that *Aloe vera* could improve the bioavailability of its own bioactive compounds as well as co-administered drugs. However, the studies also highlight the effect of molecular weight, or size on absorption, and that various preparation methods and resultant viscosity may influence overall absorption.[37]

The human trial data, which showed enhanced vitamin C and E absorption with the gel compared to the whole-leaf extract, suggests that the specific type of extract and its preparation are contributory factors that should be considered in both research and practical applications.[38,39]

These mechanisms collectively suggest that *Aloe vera* has a multifaceted approach to enhancing insulin sensitivity, making it a promising natural agent for blood glucose management in T2DM.

Finally, the variability in induction models of diabetes used in the animal models across the studies (STZ, alloxan, and HFD),[23–26,32,34] may present results from different forms of diabetes, which limits direct comparisons and emphasises the need for standardised protocols. The dose-dependent effects of *Aloe vera* compounds[24] underscore the importance of accurate dosage. The apparent inconsistency in the UP780 studies[23,25] can be attributed to the different diabetic models, emphasising that the underlying pathology of the disease dictates the effectiveness of the treatment. These findings collectively suggest that effective treatment requires a careful consideration of the specific *Aloe vera* compound, its optimal dosage, and the type of diabetes it is intended to treat.

Limitations and strengths

This review's primary strength lies in its transparent, systematic approach and adherence to the PRISMA-ScR protocol. The search was comprehensive across three major databases, screening for inclusion criteria was independently conducted by four authors. The use of specific tools, SYRCLE for *in vivo* and EEQAT for *in vitro* studies, allowed for a structured risk of bias assessment, adding a layer of critical appraisal. The resulting synthesis provides a comprehensive overview of the multifaceted molecular mechanisms by which *Aloe vera* may modulate diabetes.

However, the review is constrained by limitations inherent in the body of evidence. The most critical being that findings are derived exclusively from preclinical (*in vitro* and *in vivo* (animal)) models, and the applicability of these mechanisms to patients with diabetes remains speculative. The small number of studies (six) that met the final inclusion criteria restricts indicates the need for replication of the findings. Moreover, the included research exhibited substantial heterogeneity in the types, dosages and constituents of *Aloe vera* , the methods for inducing diabetes (STZ, alloxan, HFD), and the derived outcomes, made comparisons difficult. Finally, the review's own bias assessment revealed significant methodological weaknesses in the primary studies, such as a lack of blinding and randomisation, which inherently limits the quality of this review's conclusions.

Guide for future research

The extent and applicability of *Aloe vera* in the treatment of T1DM and T2DM in humans is yet to be explored. Further research is needed, particularly clinical trials in human patients. Aloe vera is a traditional medicine frequently used in traditional medicine systems around

the globe, areas where diabetes prevalence is predicted to grow. Further studies may reveal an effective adjunct or treatment for people with diabetes, with ready accessibility low costs and high acceptability ultimately benefitting patients with diabetes.

Conclusion

In this study, *Aloe vera* and its constituents demonstrated numerous beneficial mechanisms in T1DM and T2DM pre-clinical models, including decreased blood glucose levels, antioxidant activity, enhanced insulin sensitivity, and anti-inflammatory effects. Further research of regarding the use of *Aloe vera* in humans clinical trials is warranted to determine the clinical efficacy of treatment in T1DM and T2DM.

Conflict of interest

The researchers have no conflict of interests to declare.

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Supplementary information

All supplementary data can be found at journals.cambridgemedia.com.au/ajhnm

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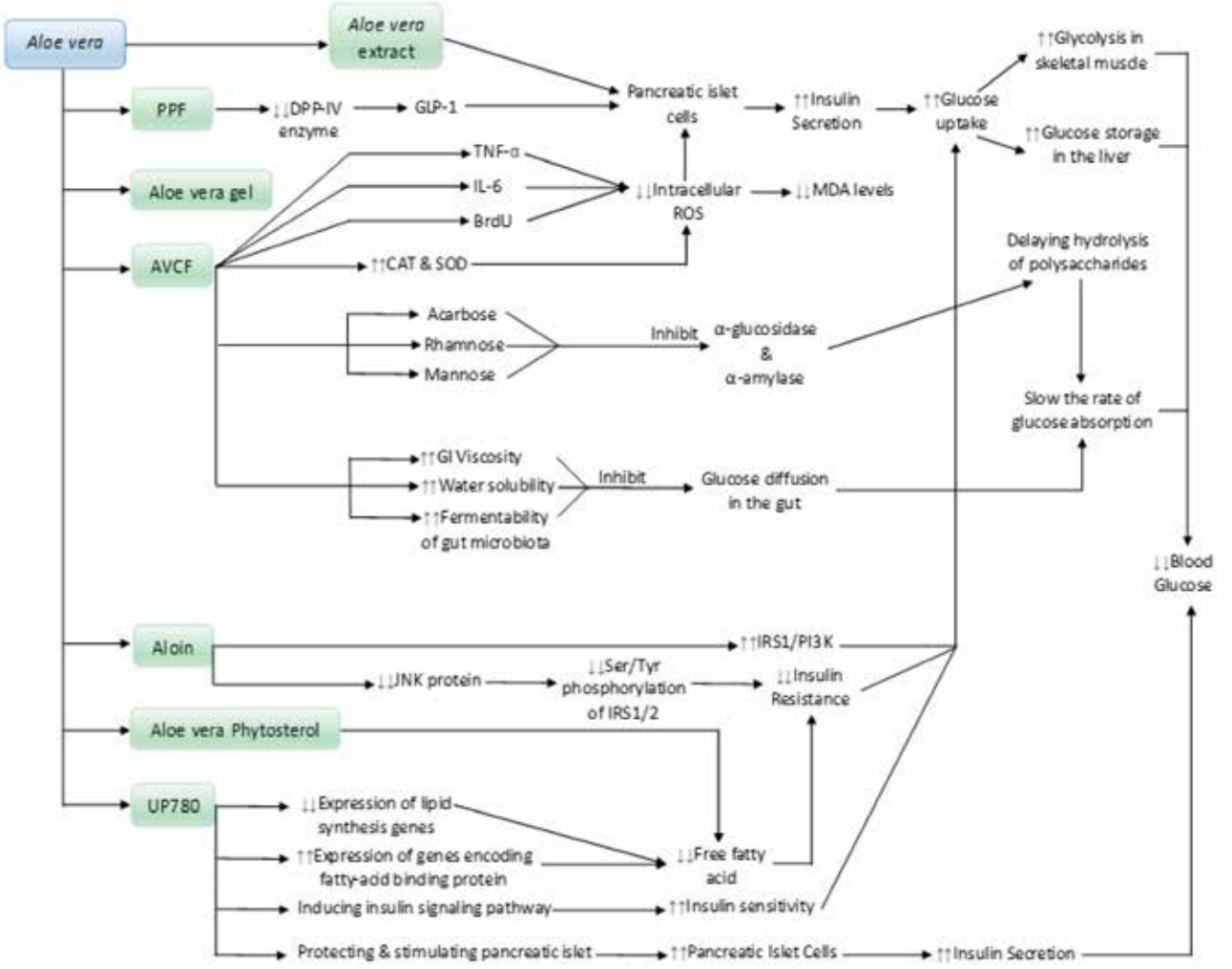

Figure 2

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