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Hypoglycemic potential of *Aloe vera* in diabetes mellitus induced by diabetogenic substances and high fat diet: A systematic meta-analysis review

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Abstract
Diabetes mellitus is a chronic disease that has always been the primary health concern worldwide. A few herbal plants showed anti-diabetic potential, *Aloe* is among these few species, and the pharmacological effects may vary for Aloe leaf preparations. We carried out a systematic and meta-analysis review to evaluate the hypoglycemics property of *Aloe vera* in Diabetes Mellitus Condition to develop its therapeutic benefit information and knowledge. The search used the following medical subject headings (MeSH): Aloe, aloe spp, diabetes mellitus, and hyperglycemia. This was followed by keyword search using *Aloe vera* or aloe gel or aloe polysaccharide or acemannan or aloe phytosterols or aloe elements. The historical search of relevant articles and personal contact with experts in the area were also undertaken. Twelve articles discuss the hypoglycemia effect of *Aloe vera* or Barbaloin or acemannan based *in vivo* study. Ten articles discuss the hypoglycemia effect of *Aloe vera extract*, and two articles discuss the hypoglycemia effect of the component of *Aloe vera*. In contrast, one article discusses the beneficial effect of polysaccharide equivalent *Aloe vera* gel on blood glucose levels *in vivo* and Yiman using Chromones based on *Aloe vera*. Several articles have been reviewed and concluded about the anti-diabetic effect of *Aloe vera* on animal studies with the favorable properties and ability of this material, such as the antioxidant and anti-inflammatory ability.

Keywords: diabetes, glycemic control, hypoglycemic potential, *Aloe vera*

Introduction
Diabetes mellitus is a chronic disease that has always been the primary health concern worldwide [1]. According to American Diabetes Association (ADA) and World Health Organization (WHO), diabetes mellitus is a metabolic disturbance characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both due to the pancreas' failure to produce insulin or insulin resistance [2, 3].
There are approximately 422 million diabetics worldwide, and most of them live in low- and middle-income countries. Each year around 1.6 million deaths due to diabetes, prevalence, and incidence of diabetes show a steady escalation over the past few decades [4]. Indonesia is a developing country with one of reported by the International Diabetes Federation (IDF) to have over a 1 million adults population suffer from diabetes representing a prevalence of around 6.2% [5]. it has been reported that from 2013 to 2018, the four Indonesian provinces with the highest prevalence of diabetes were DI Yogyakarta, DKI Jakarta, Sulawesi Utara and Kalimantan Timur [6].
There are three known main types of diabetes mellitus (DM), i.e., type 1 associated with total insulin deficiency, type 2 is a progressive insulin deficiency problem, and gestational DM, which is early diagnosed in the second or third semester of pregnancy [7]. Type 1 DM cannot be prevented, but type 2 can be prevented with regular exercise, low glucose, and a fat diet. Type 2 DM has been affecting a vast population leading to more complications in nerves, eyes, heart, etc [8].
DM is a significant chronic metabolic disorder characterized by decreasing or cessation of insulin secretion caused by physiological stimuli response or increased resistance of peripheral tissues to the insulin [9].

The pathological metabolic of diabetes affects mitochondrial superoxide excessive production in endothelial cells in both large and small vessels and the myocardium. As a result, oxidative stress plays an essential role in establishing diabetes complications, both microvascular and macrovascular complications [10].

The economic load and unfavorable health side effects of anti-diabetic drug therapy alert us to seek former times and give more observation to function the herbal products and other alternative therapy [11] For a long-time, plants have played a significant role in maintaining the quality of life and improving human health. Herbal products have been proven to help prevent and treat diseases [12]. Recently, there is renewed attention to plant-based medicines [13], especially in the search for natural and essential anti-hyperglycemic material that has only slight to no side effects [14]. Approximately 1200 plant species have been known to be used as traditional medicines to treat many diseases, including diabetes mellitus.

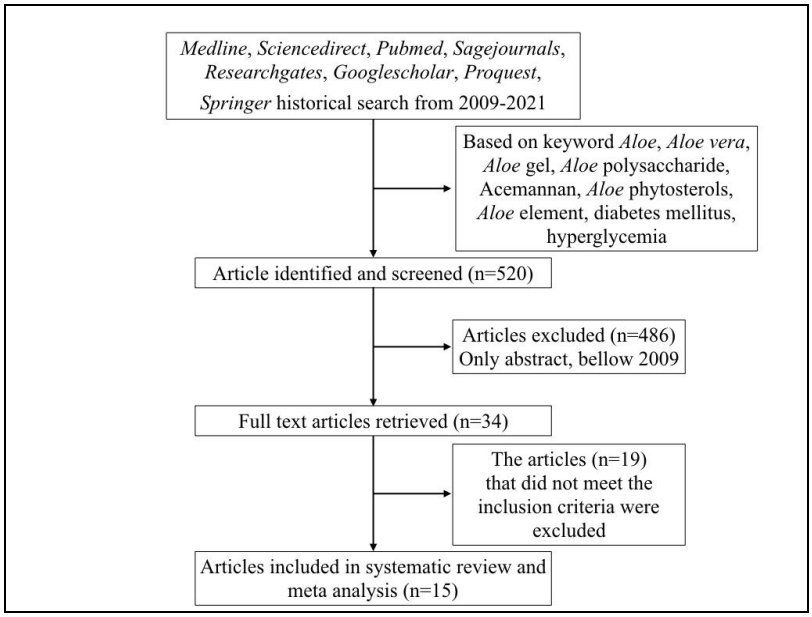
A few herbal plants showed anti-diabetic potential, *Aloe* is among these few species, and the pharmacological effects may vary for Aloe leaf preparations [15] *Aloe vera spp* has been known in traditional medicine practices for its curative properties. It is commonly used to treat many injuries such as burns and wounds. The juice, gel or formulated products have been used for health and esthetic purposes [16]. *Aloe vera* (Aloe Barbadensis belongs to the Liliaceae family) is an herbal material used to control blood glucose levels in type 2 DM in adults [17]. and as an anti-inflammatory agent.[18] The *Aloe vera*'s hypoglycemic activity has been reported to decrease glucose level directly and decrease cells and tissues insulin resistance [19]. We carried out a systematic and meta-analysis review to evaluate the hypoglycemics property of *Aloe vera* in Diabetes Mellitus Condition to develop its therapeutic benefit information and knowledge.

Methods

The first step in this systematic review article was to create PICOT Framework (P: *In vivo* research on induced diabetes condition, I: Hyperglycemia interventions using *Aloe vera* spp, C: Alternative anti-diabetic agents, O: Effectiveness in decreasing blood glucose level, T: Duration of the intervention to lower blood glucose level). The research question of this study is "What is the hypoglycemics potential of *Aloe vera* in diabetes Mellitus condition induced by diabetogenic substances and high-fat diet?

Reports of relevant clinical trials were searched and identified through search engines in the following bibliographic databases: Science direct, Pubmed, Sage journals, Research gates, Google scholar, Proquest. These databases were searched for relevant articles published from 2010 until January 2021 without language restriction. The search used the following medical subject headings (MeSH): Aloe, aloe spp, diabetes mellitus, and hyperglycemia. This was followed by keyword search using *Aloe vera* or aloe gel or aloe polysaccharide or acemannan or aloe phytosterols or aloe elements. The historical search of relevant articles and personal contact with experts in the area were also undertaken.

Inclusion and exclusion criteria were determined before the literature search started. The inclusion criterion was full-text primary research articles about using *Aloe vera in vivo* intervention for DM in animal models induced by diabetogenic substances and a high-fat diet. Exclusion criteria were (a) articles not written in English, (b) articles on intervention for DM induced by diabetogenic substances and high-fat diet using other than *Aloe vera*, (c) articles containing only abstract (d) articles containing on intervention for DM not induced by diabetogenic substances and high-fat diet and (e) articles on DM clinical trials to patient. Articles were searched in each electronic database using the keywords, and then the researchers determine whether the inclusion criterion is met. Articles were collected and selected according to the inclusion criterion. A total of 520 articles were found, 486 articles were found to cover intervention of using herbal plants. The number of articles that met the inclusion criterion was 15. The scheme of the article's selection process is shown in the following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA diagram):



Articles Selection Process

Data Extraction and Quality Assessment of The Articles

Two reviewers independently extracted the data and assessed the quality of the research. A third reviewer resolved discrepancies. Data extracted were study design, country,

sample, number of samples, intervention, duration of intervention, blood glucose level resulting, and detail of result/ notes.

Result

Twelve articles discuss the hypoglycemia effect of *Aloe vera* or Barbaloin or acemannan based *in vivo* study. Ten articles discuss the hypoglycemia effect of *Aloe vera extract*, and two articles discuss the hypoglycemia effect of the component of *Aloe vera*. In contrast, one article discusses the beneficial effect of polysaccharide equivalent *Aloe vera* gel on blood glucose levels *in vivo* and Yiman using Chromones based on *Aloe vera*.

Table 1: Meta-Analysis Data

No	Study	Published year	Country	Design	Sample	Intervention	Result (Blood Glucose Level)
1	Kamel [2]	2011	Egypt	POCD	40 male albino alloxan-induced	Diabetic rats fed on pellet diet plus *Aloe vera* gel extract (0.5 ml/day) for five weeks	Group I (Healthy rats "normal control") 82.58 ± 9.8 Group II (Diabetic rats) 202.43 ± 7.31 Group III (Healthy rats with *Aloe vera* gel "positive control") 83.45 ± 4.59 Group IV 96.23 ± 9.05 (Diabetic rats with *Aloe vera* gel)
2	Mourad [9]	2011	Egypt	POCD	24 male albino streptozotocin-induced diabetic rats	Diabetic rats were given *Aloe vera* (10 ml/kg) daily using an intragastric tube for 14 days	(Blood Glucose Level) Group I (Healthy rats "Normal Control") 82.24 ± 5.17 Group II (Diabetics rats) 331.88 ± 29.72 Group III (Diabetic rats with glimepiride "Positive control") 117.43 ± 21.96 Group IV (Diabetics rats with *Aloe vera*) 93.66 ± 26.92
3	Sethi *et al.* [20]	2012	India	POCD	24 Albino alloxan-induced diabetic rabbits of either sex	Diabetic rabbits received *Aloe vera* leaf gel extract (300mg/Kg) in an aqueous solution for 21 days	(Blood Glucose Level) Group I (Healthy rabbits "Normal Control") 150 ± 16.08 Group II (Diabetic rabbits) 266.17 ± 14.08 Group III (Diabetic rabbits with *Aloe vera*) 182 ± 12.26 Group IV (Diabetic rabbits with glibenclamide "Positive Control." 160 ± 13.84
4	Vherma *et al.* [21]	2016	India	POCD	24 male Charles Foster alloxan-induced diabetic rats	Diabetic rats received *Aloe vera* extract (500mg/kg) for 30 days	(Blood Glucose Level) Group I (Control rats with normal saline) 91.22 ± 7.31 Group II (Alloxan induced diabetic rats with normal saline) 340.48 v 22.60 Group III (Alloxan induced diabetic rats with *Aloe vera* extract) 256.27 ± 21.93 Group IV (Alloxan induced diabetic rats with glibenclamide) 238.77 ± 21.14
5	Manjunath *et al.* [22]	2016	India	POCD	30 Albino alloxan-induced diabetic rats either sex	Diabetic rats received *Aloe vera* Leaf extract in three graded doses of 100, 200, and 400 mg/kg, respectively, for five weeks	(Blood Glucose Level) Group I (Control rats with 1ml distilled water) Group II (Control positive with metformin 50 mg/kg) Group III (Alloxan-induced diabetics rats with 100 mg/kg) Group IV (Alloxan induced diabetics rats with 200 mg/kg) Group V (Alloxan-induced diabetics rats with 300 mg/kg)
6	Kim *et al.* [23]	2009	South Korea	POCD	108 male C57BL High fat-diet-induced	Diabetics rats received 25, 50, and 100 mg/kg processed *Aloe vera* Gel for eight weeks	(Blood Glucose Level) Group I (Normal condition rats) 7.6 ± 0.7 Group II (Negative control

							diabetic rats with Phosphate buffered saline) 14.8 ± 0.1 Group III (Diabetic rats with processed *Aloe vera* Gel 25 mg/kg) 7.1 ± 0.7 Group IV (Diabetic rats with processed *Aloe vera* Gel 50 mg/kg) 7.2 ± 0.7 Group V (Diabetic rats with processed *Aloe vera* Gel 100 mg/kg) 7.1 ± 0.6 Group VI (Positive control Diabetic rats with pioglitazone 2.5 mg/kg) 6.8 ± 0.7
7	Kumar *et al.* [24]	2011	India	POCD	40 Swiss albino streptozotocin-induced diabetic Mice either sex	Diabetic mice received an oral dose of *Aloe vera* extract (130mg/kg) for 21 days	Group I (Control Group rats with sodium citrate buffer) Group II (Diabetic rats induced with streptozotocin) Group III (Diabetic rats induced with treptozotocin, with an oral dose *Aloe vera* extract (130 mg/kg) Group IV (Diabetic rats with metformin 50 mg/kg)
8	Atanu *et al.* [25]	2018	Nigeria	POCD	40 male Albino Alloxan-induced diabetic rats	Diabetic rats treated with 300 mg/kg Polysaccharide equivalent *Aloe vera* gel orally for 21 days	Group I (Normal untreated control rats) 130 mg/dl Group II (Diabetic untreated rats) >500 mg/dl Group III (Diabetic rats treated with 300 mg/ kg Polysaccharide equivalent *Aloe vera* gel orally) 145 mg/dl Group IV (Diabetic rats treated with 2 mg/kg metformin Orally) 120 mg/dl Group V (Diabetic rats co-administered with 300 mg/kg PE *Aloe vera* gel and 2 mg/kg Metformin orally 155 mg/dl
9	Sharma [26]	2014	India	POCD	24 Swiss albino alloxan-induced diabetic mice either sex	Diabetic mice received *Aloe vera* 300 mg/kg and 500 mg/kg for 21 days	Group I (Normal Control "saline") 77.24 ± 6.78 mg/dl Group II (Alloxan treated control) 226.4 ± 8.88 mg/dl Group III (*Aloe vera* extract 300 mg/kg) 117.2 ± 12.17 mg/dl Group IV (*Aloe vera* extract 500 mg/kg) 98.06 ± 5.06 mg/dl
10	Mahabady *et al.* [27]	2011	Iran	POCD	40 Wistar male streptozotocin-induced diabetic rats	Diabetic rats received 8 ml/kg *Aloe vera* extract for eight weeks	Group I (Control Group, Healthy rats not in diabetic condition with normal saline) 109.7 ± 3 Group II (*Aloe vera* Group, Healthy rats with 8ml/ kg *Aloe vera* extract) 107.2 ± 3.7 Group III (Diabetic rats with normal saline) 541 ± 20.5 Group IV (Diabetic rats with *Aloe vera* extract 8ml/kg) 255.4 ± 32.5 Group V (Diabetic rats with human NPH insulin 10 IU/kg) 204.7 ± 44.2
11	Yiman [28]	2014	USA	POCD	105 female CD-1 alloxan-induced mice	Diabetic mice received UP780 2000 mg/kg and UP 394 80 mg/kg for 4 weeks	Group I (Healthy mice without alloxan injection) 98.3 ± 5.4 Group II (Healthy mice without alloxan injection with UP780 administered) 85.3 ± 3.3

							Group III (Alloxan-induced diabetic rats) 431.9 ± 21.2 Group IV (Alloxan-induced diabetic rats with glyburide administered) 398.7 ± 19.1 Group V (Alloxan-induced diabetic rats with UP780 administered) 315.1 ± 34.9 Group VI (Alloxan-induced diabetic rats with UP394 administered) 442.1 ± 48.0 Group VII (Alloxan-induced diabetic rats administered with Qmatrix) 443.2 ± 42.0
12	Rajasekaran *et al.* [29]	2014	India	POCD	24 Wistar male albino streptozotocin-induced diabetic rats	Diabetic rats treated with *Aloe vera* Extract (300 mg/kg) for 21 days	Group I (Control rats received 0.1 M citrate buffer) 85.3 ± 5.8 Group II (Diabetic controls, streptozotocin-induced diabetic rats) 270 ± 13 Group III (Streptozotocin-induced diabetic rats treated with *Aloe vera* extract 300 mg/kg) 102.5 ± 10.5 Group IV (Streptozotocin-induced diabetic rats treated with glibenclamide 600mg/kg) 128.5 ± 12
13	Riyanto *et al.* [30]	2018	INA	POCD	18 Wistar male alloxan-induced diabetic rats	Diabetic rats received 400 IU/day/adult Instant *Aloe vera* for five weeks	Group I (Normal Control) Around >50mg/dl Group II (Diabetic rats) Around >200 mg/dl Group III (Diabetic rats with Vitamin E) <100 mg/dl Group IV (Diabetic rats with instant *Aloe vera*) >100mg/dl
14	Wariyah [31]	2020	INA	POCD	18 alloxan induced diabetic male Wistar rats	Diabetic rats received *Aloe vera* Powder 600 IU for four weeks	Group I (Diabetic rats) > 200 mg/dl Group II (Diabetic rats with gel drink) <150 mg/dl Group III (Diabetic rats with *Aloe vera* Powder) >100 mg/dl
15	Mohamed *et al.* [32]	2012	India	POCD	34 Long Evans Female streptozotocin-induced diabetic rats	Diabetic rats received Gel-Et, Gel-C, Skin-Et 1.25 g/kg for 28 days	Group I (Water treated Control Rats) >9 mmol/L Group II (glibenclamid Control Rats) <8 mmol/L Group III (Gel-Et treated rats) >8 mmol/L Group IV (Gel-C treated rats) ≥ Eight mmol Group V (Skin-Et treated rats) >8 mmol

Notes: *POCD (Post Test Only Control Group Design)

Kamel (2011) [2] investigated the anti-diabetic Effect of *Aloe vera* Gel extract in 40 Alloxan-induced diabetic rats divided into four groups. The blood glucose level improved to near normal after the intervention was done orally using *Aloe vera* gel extract (0.5 ml/day) for five weeks. The significant decrease in blood glucose level in the diabetic group was accompanied by a significant decrease in serum cholesterol and triacylglycerols levels compared to the control group by 31% and 20.61%, respectively ($p< 0.05$).

Mourad (2011) [9] reported that treatment of streptozotocin-induced diabetes among 24 male albino rats using *Aloe vera* extract in a dosage of 10 ml/kg, and glimepiride administered with an intragastric tube for fourteen days, significantly reduced blood glucose level to near normal and significantly increased serum insulin level.

Sethi *et al.* (2012) [20], investigated the antioxidant and anti-diabetic effect on 24 Alloxan-induced diabetic rabbits using *Aloe vera* extract gel (300 mg/kg, in aqueous solution) for 21 days significantly reversed the blood glucose level near to normal level after treatment with glibenclamide and *Aloe vera* compared to control group.

Vherma *et al.* (2016) [21] investigated anti-diabetic properties of *Aloe vera* in 24 alloxan-induced diabetic rats fed with its extract (500 mg/kg) for 30 days. The result showed that the

hypoglycemic potential of *Aloe vera* extract was less compared to glibenclamide.

Manjunath *et al.* (2016) [22] investigated the effect of *Aloe vera* extract toward blood glucose level in 30 alloxan-induced diabetic rats fed with *Aloe vera* leaf extract in three graded doses of 100, 200, and 400 mg/kg, respectively for five weeks. Administration of alloxan monohydrate (50 mg/kg i.p.) produced hyperglycemia that was stable around five weeks in Group I (control) treated with distilled water. At the end of five weeks, *Aloe vera* leaf extract significantly reduced the blood glucose level in Groups IV and V (at 200 mg/kg and 400 mg/kg doses, respectively) ($p < 0.0001$) when compared to the control (Group I). But, not in Group III (at 100 mg/kg), which did not show a significant decrease in blood glucose levels compared to the same control (Group I).

The standard drug metformin (50 mg/kg) significantly decreased ($p < 0.0001$) blood glucose levels in Group II in comparison to control (Group I) at the end of five weeks. However, there is no significant difference in blood glucose level decrease between metformin group groups (II), IV, and V after five weeks (50 mg/kg) of feeding with *Aloe vera* leaf extract at 200 mg/kg 400 mg/kg, respectively.

Kim *et al.* (2009) [23] showed the hypoglycemic effects of the processed *Aloe vera* gel in 108 high-fat diets in induced diabetic rats, treated with 25, 50, and 100 mg/kg *Aloe vera* gel for eight weeks. The mice that exhibited fasting blood glucose levels above 180 mg/dl were chosen then randomly grouped into experimental and treatment groups with orally administered PAG with different doses for eight weeks, with continued free access to a high-fat diet. The mean fasting of the blood glucose level of the DIO mice before PAG administration was 199.77±21.7 mg/dl, while the regular diet-fed mice were 131.57±13.4 mg/dl. The fasting blood glucose levels are increased gradually in the untreated DIO mice over the 8-week treatment period and reached 266.57±0.7 mg/dl. However, when the PAG was administrated orally, the fasting blood glucose levels are decreased significantly. The anti-hyperglycemic effects of PAG were apparent from week two treatments and continued throughout the experimental period. The mean fasting blood glucose level of the DIO mice that were treated with the 100 mg/kg PAG for eight weeks was 127.7711.4mg/dl, which was not significantly different from the regular diet-fed mice. The plasma glucose-lowering activities of the PAG at 100 mg/kg were closely comparable to the PGZ, which was administrated to the DIO mice at 2.5 mg/kg daily. There is no difference in either food intake or body weights in the treatment period in the PAG-treated and the untreated DIO mice.

Kumar *et al.* (2011) [24] showed *Aloe vera*'s hypoglycemics activity on 40 streptozotocin-induced diabetic mice given an oral dose of *Aloe vera* extract (130mg/kg) for 21 weeks. Diabetic mice administered with Aloe extract for four weeks showed highly significant improvement in FBG compared to untreated diabetic mice. The blood glucose reducing the potential of *Aloe vera* extract is comparable closely to metformin-treated mice. FBG levels in Aloe extract and metformin-treated groups were significantly lower compared to the control streptozotocin-induced group. After Oral GTT, postprandial blood glucose in control, Aloe, and the metformin-treated group showed a significant change after glucose (1g/kg BW). The anti-hyperglycemic property of *Aloe vera* extract is possibly mediated by a mechanism other than insulin since streptozotocin selectively destroyed beta cells of the pancreas.

Atanu *et al.* (2018) [25] reported an anti-diabetic effect of combined treatment with *Aloe vera* gel and metformin among 40 male alloxan-induced diabetic rats treated with 300 mg/kg Polysaccharide equivalent *Aloe vera* gel orally for 21 days. The FBG concentration in diabetic animals treated with 300 mg/kg BW PE of *Aloe vera gel* decreased by 40.5, 47.6, and 65.5% as of the 7th, 14th, and 21st days of the study. The animal group treated with the standard drug decreased by 33.4, 43.4, and 76.0% at day 7, 14, and 21, respectively, while FBG concentration in the diabetic animal group administered a combination of both *Aloe vera* extract and metformin decreased by 28.4, 38.0 and 69.0% at day 7, 14 and 21, respectively.

Sharma (2014) [26] investigated an anti-diabetic effect of processed *Aloe vera* gel among 24 alloxan-induced diabetic mice treating them with Aloe 300 mg/kg and 500 mg/kg for 21 days. At the start of the study, the mean blood glucose level in the control group of mice was evaluated to be 77.24 ± 6.78 mg/dl (range 70-89 mg/dl). Whereas in the treatment group, it was 226.4 ± 8.88 mg/dl, with the treatment of mice with *Aloe vera*, with a dosage of 300mg/kg, the glucose level decreased significantly ($p<0.05$) to 117.2 ± 12.17 mg/dl, ranging 102-132 mg/dl. The dose of 500 mg/kg, the level of glucose also significantly ($p<0.05$) decreased to 98.06 ± 5.06 mg/dl, ranging 89-103 mg/dl.

Mahabady *et al.* (2021) [27] showed the beneficial effect of *Aloe vera* among 40 Streptozotocin-induced diabetic rats that received 8 ml/kg body weight *Aloe vera* extract for eight weeks. At the end of the eighth week, the blood sugar levels decreased significantly compared to the diabetic control group ($p <0.05$) following daily intake of *Aloe vera* gel at a dose of 400 mg/kg in diabetic rats and the diabetic group treated with insulin at the end of the eighth week. At the same time, blood sugar levels increased in diabetic control rats at the end of the eighth week.

Yiman (2014) [28] investigated the anti-diabetic effect of *Aloe vera*-based component (Chromones UP780) on 105 Alloxan-induced mice received UP 780 2000 mg/kg and UP 394 80 mg/kg for four weeks. Fasting blood glucose levels were decreased compared to base treatment following two weeks of oral administration with glyburide (39.1% reduction), UP780 (39.1% reduction), aloesin (14.5% reduction), and Qmatrix (19.6% reduction). Following 4-weeks of oral treatment with Glyburide, UP780, UP394, and Qmatrix decreased the fasting blood glucose level by 21.4%, 35.9%, 11.6%, and 17.2%, respectively, compared to the base control group. Only UP780 and glyburide showed blood glucose level statistically significant decreased in both weeks-2 ($p = 0.00001$, $p = 0.003$, respectively) and week-4 ($p= 0.0001$, $p = 0.01$, respectively). Qmatrix administered mice showed significant blood glucose level reduction in week 2 ($p = 0.01$). Fasting blood glucose levels of the control groups were unaffected at each time point.

Rajasekaran *et al.* (2014) [29] reported the hypoglycemic effect of *Aloe vera* Gel on 24 streptozotocin-induced diabetic rats, treated with *Aloe vera* Extract (300 mg/kg) for 21 days. The result showed the *Aloe vera* and glibenclamide administration decreased blood glucose levels and urea levels and increased serum protein levels compared to the diabetic rats. The effect was higher group treated with *Aloe vera*.

Riyanto (2018) [30] Investigated about Hypoglycemic effect of instant *Aloe vera* on 18 Alloxan induced diabetic rats treated with an instant *Aloe vera* 400 Iu/kg for five weeks. The result showed that the diabetic rats fed without an instant *Aloe vera* showed high stable blood glucose (>200 mg/dl) during the four weeks of treatment. Whereas normal fasting blood

glucose was <110mg/dl and 140 mg/dl after meals

Wariyah (2020) [31] showed Hypoglycemic activity of *Aloe vera* Powder among 18 Alloxan-induced diabetic rats, which are received *Aloe vera* powder 600 IU for four weeks. At the end of the four weeks, diabetic rats without *Aloe vera* treatment showed stable significantly higher blood glucose (>200 mg/dl), and the blood glucose level (<150mg/dl) in diabetic rats with *Aloe vera* treatment decreased significantly.

Mohamed *et al.* (2012) [32] investigated the anti-diabetic effect of Aloe Barbadensis Miller extract on 34 Streptozotocin-induced diabetic rats, which are received concentrated gel extract (Gel-C), gel extract (Gel-Et), skin extract (Skin-Et) based Aloe 1,25 g/kg for 28 days. At the baseline, there was no significant difference in the fasting serum glucose (FSG) levels of the rats among the five experimental groups, and the FSG levels decreased in the rats of all the groups except those of the WC (water) group after the oral administration of the five different treatments over 28 days. However, this decrease was not statistically significant. The group administered with the ethanolic extract of *Aloe vera* gel showed a statistically significant (p = 0.047) decrease in their FSG levels on days 14 and 28 compared to the baseline values. As expected, glibenclamide showed a statistically significant (p = 0.026) decrease of the FSG levels on day 28 of the experiment.

Discussion

This meta-analysis review discusses the anti-diabetic effect of *Aloe vera* on animal models. Nine articles using standard golden medicine as a positive control are four articles using glibenclamide, three articles using Metformin, one article using glimepiride, and one article using human NPH Insulin. *Aloe vera* showed a positive effect on decreasing blood glucose level near to control level on diabetic rats with no significant differences even compared with positive medicine control; this is due to the antioxidant ability of *Aloe vera* [32, 33].

Aloe vera extract contained natural antioxidant components, such as total phenol, flavonoid, vitamin C and E. These antioxidant components are direct in scavenging reactive oxidants. They are hypothesized to constitute a strong endogenous defense against the oxidative cell and against tissue injury.[34] Therefore, these natural antioxidants contained in a plant may contribute to antioxidant activity and straight towards the total or even partial alleviation of some clinical disorder, especially in diabetes [34].

Trace elements analysis show that *Aloe vera* extract contained more appreciable amounts of Cr, Zn, and Mn, which may be responsible for potentiating the insulin action.[16] These trace elements may be present in *Aloe vera* gel extract and play a crucial role in controlling and managing diabetes since diabetes is associated with marked alteration of the concentration in these trace elements. These elements are also known as hypoglycemic elements because they have a crucial role in glucose metabolism.[35] Chromium facilitated insulin binding and adequate uptake of glucose to the cell. Supplement chromium has shown a decrease in fasting glucose levels, improve blood glucose tolerance, lower insulin levels, and reduced total cholesterol and triacylglycerols [36].

Studies confirmed that *Aloe vera* gel contains Zn, Cr, and Mn and vitamins as vitamin E and vitamin C.[35,36] Many explanations suggested these components contribute to the anti-diabetic effect of this plant. The first explanation is the potent antioxidant effect of the aloe extract. Aloe is very long known to have an antioxidant potential via suppressing the free radical formation and enhancement of the cellular thiol status. It is also reported that it stimulates glutathione-S-transferase enzyme activity [34]. Our results supported the antioxidant potentials of Aloe, where it was found to be suppressing elevated serum of MDA levels and increase the blood GSH and SOD levels. Recent approaches focused on the role of oxidative stress in pancreatic beta-cell damage. Hence, oxidative stress has involved the pathogenesis of diabetes, and antioxidants like Aloe might have an actual anti-diabetic effect via antioxidant potential [32].

The anti-inflammatory potential of Aloe may be the second property that explains its anti-diabetic effect. Diabetes may be considered as an inflammatory disease where inflammation participates in the progression of diabetes, where the tumor necrosis factor was found to reduce peripheral insulin sensitivity [37]. Many authors claim that the anti-inflammatory potential of Aloe is due to its components like emodin and mannose-6-phosphate. It was reported that the anti-inflammatory effect of the aloe extract is comparable to hydrocortisone [38].

The activity of this Aloe as a glucose-lowering agent may be affected by processing, parts of the Aloe that are used, animal models selected, and structure and content of active components [39]. Likewise, some bioactive components such as chromones of the Aloe, which are limited to the rinds of the plant and the manufacturing processes, usually remove as well with them and other anthraquinone compounds. Hence, the current study was conducted to evaluate the glucose-lowering activity of a defined composition (UP780) of *Aloe vera* inner leaf gel powder (Qmatrix) with aloe chromones (aloesin) in insulin-dependent alloxan-induced type-1 diabetes model and non-diabetic healthy CD-1 mice [40].

UP780 could incur its activity by protecting stimulation in existing beta-cells to produce increased insulin levels. An unexpected synergy was observed through the combination of aloesin with aloe polysaccharide, and that the beneficial effects were seen with UP780 treatment exceeding the sum of the known effects for each of its constituents [41]. The decrease in fasting blood glucose level of the diabetic mice in the present investigation is shown to reveal UP780 possessing potential anti-diabetic activities. UP780, containing 4% aloesin and 96% *Aloe vera*, may have assisted surviving β-cells to resist oxidative damage or prevent further damage caused by the alloxan. Alloxan is a cytotoxic agent to the insulin-secreting β cells of the pancreas, especially effective in inducing insulin-dependent phenotypes that are similar to type 1 diabetes or post-beta cell "burnout" type 2 diabetes. Nevertheless, the daily administration of UP780 may lead to the presence of known antioxidants such as aloesin and aloe polysaccharides. These antioxidants provide a shield to provide antioxidant activity to the β-cells of the islet of Langerhans from the destruction caused by the superoxide radicals derived from alloxan [42]. In addition, the possibilities of glyburide enhancing β-cells responsiveness to the glucose has also been reported [43]. This action mechanism might also be another potential property of UP780 that alleviates hyperglycemia. However, a further detailed investigation must focus on the mode of action of UP780 to obtain a better understanding of how the composition is better used in targeting the pathogenesis of diabetes. Some have suggested that hypoglycemic activities of Aloe observed in the alloxan-induced insulin-dependent mouse model could also be associated with its radical-scavenging activities or stimulate the synthesis or release of insulin from beta-cell of pancreases [44].

Conclusion

Several articles have been reviewed and concluded about the anti-diabetic effect of *Aloe vera* on animal studies with the favorable properties and ability of this material, such as the antioxidant and anti-inflammatory ability.

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