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Potential of medicinal plants to ameliorate neovascularization activities in diabetes: A systematic review

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Hyperglycemia in diabetes mediates the release of angiogenic factors, oxidative stress, hypoxia, and inflammation, which in turn stimulate angiogenesis. Excessive angiogenesis can cause diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy. All of these complications are debilitating, which may lead to an increased susceptibility to lower-limb amputations due to ulcerations and infections. In addition, microvascular alterations, segmental demyelination, and endoneurial microangiopathy may cause progressive deterioration ultimately leading to kidney failure and permanent blindness. Some medicinal plants have potent anti-angiogenic, antioxidant or anti-inflammatory properties that can ameliorate angiogenesis in diabetes. The purpose of this systematic review is to demonstrate the potential of medicinal plants in ameliorating the neovascularization activities in diabetes. Manuscripts were searched from PubMed, Science Direct, and Scopus databases, and Google Scholar was used for searching additional papers. From 1862 manuscripts searched, 1854 were excluded based on inclusion and exclusion criteria and 8 were included into this systematic review, whereas the required information was extracted and summarized. All identified medicinal plants decreased the high blood glucose levels in diabetes, except the aqueous extract of Lonicerae japonicae flos (FJL) and Vasant Kusumakar Ras. They also increased the reduced body weight in diabetes, except the aqueous extract of FL and total lignans from Fructus arctii. However, methanolic extract of Tinospora cordifolia and Vasant Kusumakar Ras were not tested for their ability to affect the body weight. Besides, all medicinal plants identified in this systematic review decreased the vascular endothelial growth factor (VEGF) protein expression and vasculature activity demonstrated by histopathological examination indicating promising anti-angiogenic properties. All medicinal plants identified in this systematic review have a potential to ameliorate neovascularization activities in diabetes by targeting the mechanistic pathways related to oxidative stress, inflammation, and angiogenesis.

Keywords: medicinal plants, neovascularization, diabetes, systematic review

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Diabetes mellitus (DM), characterized by a high blood glucose, is a metabolic disorder that can lead to several micro- and macro-vascular diseases. It has been indicated by World Health Organization (WHO) as one of the top four non-transmissible diseases (Cheng et al. 2018). WHO has estimated that there will be approximately 300 million diabetic patients in 2025 globally, especially in the developing countries. Presently, DM has become a worrisome problem in Malaysia, where its cases are rising up (Mahdi et al. 2013; Piero et al. 2015). The increasing prevalence of DM may contribute to significant morbidity and mortality risks leading to profound effects on the life quality, regional healthcare systems, the demand for health services, and economic costs. There are three types of DM stratified by causes and clinical manifestations. Type 1 DM (T1DM) is an autoimmune disease, which is caused by none or insufficient insulin production by pancreatic Langerhans insulin-producing β-cells islets. Type 2 DM (T2DM), also called insulin resistance, is a condition, in which target cells do not respond to insulin produced and account for majority of DM patients, especially in high income countries (Piero et al. 2015; Salehi et al. 2019). Type 3 DM (T3DM) is known as gestational DM, which occurs in some of the pregnant mothers, who have no DM history.

Neovascularization is a process of blood vessels formation consisting of angiogenesis and vasculogenesis (Cheng and Ma 2015). The major group of cells involved in angiogenesis is represented by endothelial cells (Tahergorabi and Khazaei 2012). In angiogenesis, the proliferation of pre-existing endothelial cells helps in the formation of new capillaries, whereas vasculogenesis is the process of *de novo* forming blood vessels from the endothelial progenitor cells (Risau and Flamme, 1995; Jin and Yang 2010; Cheng and Ma 2015). Angiogenesis is characterized by a vessel sprouting from pre-existing ones including endothelial cells activation, vascular destabilization, EC migration, and proliferation followed by the formation of patent vascular tubes (Potente et al. 2011; O'Leary et al. 2019). However, uncontrolled and persistent angiogenesis is one of the microvascular diabetic complications, due to hyperglycemia-induced oxidative stress, production of inflammatory factors and cytokines (Kim et al. 2013; Cheng and Ma 2015). Besides, angiogenic development is influenced by the angiogenic balance between endogenous angiogenic stimulators, e.g., erythropoietin, angiopoietins, transforming growth factor-β (TGF-β), fibroblast growth factor 2 (FGF2), vascular endothelial growth factors (VEGFs), and angiogenic inhibitors, e.g., pigment epithelium derived factor, angiostatin, thrombospondin-1, endostatin, and kallistatin (Tahergorabi and Khazaei 2012; Cheng and Ma 2015).

Although both exercise and dietary habits play a role in DM management, most diabetic patients are focused on the anti-diabetic pharmacological agents for their treatment (Salehi et al. 2019). Treatment of DM and its complications is expensive (Heinemann 2015). Recently, a new trend has appeared, in which immense use of medicinal plants or phytodrugs has been applied in the treatment of DM and its complications. In addition, cheap and easily accessible medicinal plants are also used for toxicity prevention, adverse side effects, and reduction of effectivity or drug resistance caused by conventional DM medicine, such as the oral hypoglycemic agents. The examples of oral hypoglycemic agents are sulfonylureas, α-glucosidase inhibitors, thiazolidinediones, biguanides, and non-sulfonylureas secretagogues (Salehi et al. 2019). According to WHO, for primary health care needs, 80% of the people around the world rely on medicinal plants, whereas the majority of them is resided in the developing countries. In industrialized countries, the public interest to use medicinal plants as natural therapies has also been increased including the United States. Therefore, if diabetes and its related complications can be controlled or treated effectively, the quality of life and life expectancy of diabetic patients can increase (El-Refaei et al. 2014; Piero et al. 2015).

This paper presents a detailed review to demonstrate the potential of medicinal plants in ameliorating the neovascularization activities in diabetes by using a systematic approach.

Methods

Preferred reporting items for systematic reviews and meta-analysis (PRISMA) (Moher et al. 2009) were used to present the flow of research strategy based on the including and excluding selection strategy of the relevant articles.

Briefly, the PRISMA checklist of items was employed to facilitate the reporting process and enhance the quality of the protocol. The study was explicitly identified as a systematic review in the title. Abstract has been provided to address the primary objectives, methods, and results of the review. The review objective was clearly and concisely stated. Inclusion and exclusion criteria for the review and the methods for grouping studies in the synthesis were specified. All databases, registers, websites,

organizations, reference lists, and other sources consulted to identify studies were documented. Comprehensive search strategies for all databases, registers, and websites, along with any filters and limits used were presented. The methods used to determine whether a study met the inclusion criteria of the review, including the number of reviewers screening each record and report retrieved, were explained. All outcomes, for which the data were sought, were listed and defined. The methods employed to assess the risk of bias in the included studies including details of the tools used, the number of reviewers assessing each study, and they working independency, were described.

Literature search. A systematic review of the literature was carried out to select the related studies about the application of medicinal plants in ameliorating the neovascularization activities in diabetes. PubMed, Science Direct, Scopus databases, and Google Scholar were used for the selection of relevant literature from January 2011 to April 2020. We searched the literature for the last 10 years. The searching strategy involved the relevant literature using the following key words: medicinal plants, diabetes-hyperglycemia, and neovascularization-angiogenesis.

Inclusion and exclusion criteria. Studies were included if: a) using animal model with rats or mice as sample models, b) blood glucose and body weight measurement were performed, c) VEGF protein expression was present, and d) histopathology of retinal tissue was done using hematoxylin and eosin (HE) staining. In contrast, review papers, conference proceedings, and those not relevant to the title were excluded.

The study design should include a minimum three groups: 1) control group, 2) diabetic group, and 3) group treated with medicinal plants. Papers that did not include the control group have been excluded. The control group plays a crucial role in balancing the baseline variables during the evaluation of the treatment effects with medicinal plants. The study included animal species, either rats or mice, and streptozotocin-induced diabetes to ensure maximum compatibility and minimize the likelihood of variations in the treatment outcomes across different animals.

Studies were also excluded if evaluated only VEGF gene expression without protein expression or histopathology using wound tissue and staining other than HE. Since the majority of papers was primarily focused on VEGF protein expression rather than VEGF gene expression, we have chosen to include protein expression studies as a criterion to ensure optimal comparability among the selected studies.

Data extraction and management. The studies were included based on the inclusion and exclusion criteria. The selected data of the studies were extracted and summarized in a table. The extracted information included the last name of the first author, year published, sample model, medical plant used, treatment and estimated parameters: blood glucose level, body weight, VEGF protein expression and results of histopathological examination using HE staining (Table 1).

Systematic Review Center for Laboratory of Animal Experimentation (SYRCLE's) Risk of Bias tool was used for quality assessment of the studies involving animal intervention (Hooijmans et al. 2014). The article quality was evaluated by answering the following questions: 1) Was the allocation sequence adequately generated and applied? 2) Were the groups similar at baseline or were they adjusted for confounders in the analysis? 3) Were the animals randomly housed during the experiment? 4) Were the incomplete data adequately addressed? 5) Are reports of the study free of selective outcome reporting? Each question has been assigned a value as 'high,' 'low,' or 'unclear risk of bias' independently by three reviewers. Discrepancies among the reviewers were identified and resolved through consensus.

In summary, total 1862 papers were searched through four databases including PubMed, Science Direct, Scopus, and Google Scholar. Ten duplicated papers were discarded and titles and abstracts of the remaining 1852 papers were screened; 1818 papers were discarded, from which 1741 papers were irrelevant to the title and 77 were review papers. Full text papers of 34 studies were accessed for eligibility. Subsequently, 26 studies were further discarded according to the inclusion and exclusion criteria and 8 studies were included into the systematic review by the selection process as shown in Figure 1.

Results

Blood glucose levels and body weight measurements. All studies with animal models, where diabetes was induced by giving high-sugar-fat diet (HSFD) and/or streptozotocin (STZ) injection, were involved in this systematic review. Blood sugar levels and body weight were measured before and after diabetes induction to confirm the diabetic status of the animal models due to the fact that high blood glucose level and low body weight are the symptoms of DM.

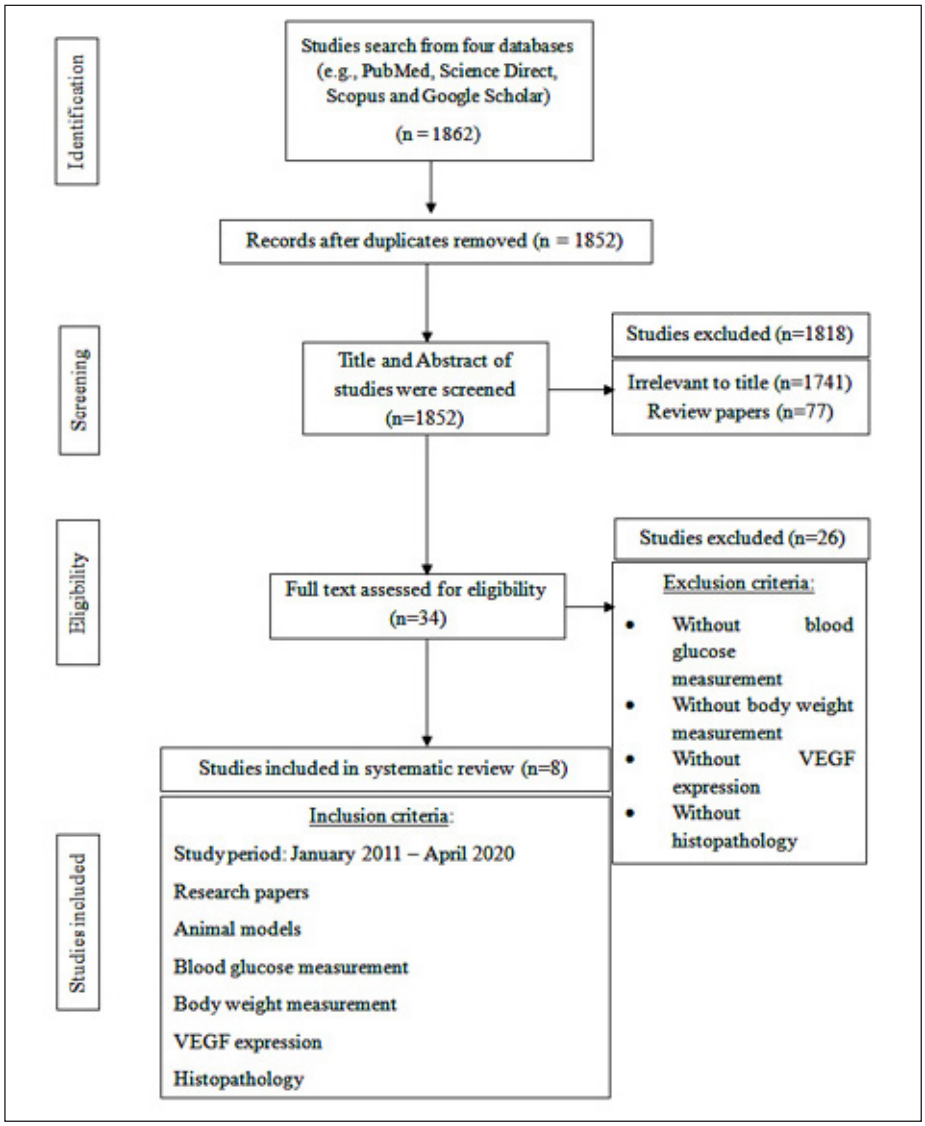


Figure 1. Literature search strategy.

The cut-off lines for blood glucose level set for each experiment included 13.88 mmol/L (250 mg/dL), 13.9 mmol/L (250 mg/dL), 16.5 mmol/L (297 mg/dL), 16.7 mmol/L (300.6 mg/dL), and 19.4 mmol/L (350 mg/dL) (Table 1). The blood glucose level higher than the cut-off value indicated that diabetes was successfully induced.

Dongare et al. (2016) (Zingiber officinale), Hong et al. (2016) (Zingiber zerumbet rhizomes), Lei et al. (2018) (Zhujing pill), and Dong et al. (2019) (resveratrol coated gold nanoparticles, AuNPs) have reported that medicinal plants applied showed positive effect in reducing blood glucose level and increasing body weight. Agrawal et al. (2012) (Tinospora cordifolia) have also reported that medicinal plant used showed positive effect on blood glucose reduction, but body weight was not measured in this study group. Tamoli et al. (2020) (Vasant Kusmakar Ras) have demonstrated that medicinal plant used showed no effect on blood glucose reduction; body weight was unknown in this study group. Zhang et al. (2020) (Fructus Arctii) have also shown a positive effect of this plant on blood glucose reduction but not on the body weight increment after treatment. However, Zhou et al. (2016) (Lonicerae japonicae flos) have discovered that medicinal plant used showed no effect either on the blood glucose level reduction or body weight increment.

Zhujing pill extract (ZJPE) was given to male Sprague-Dawley (SD) rats to determine their ability in

Table 1
Summarized results for studies included

Reference	Experimental model	Medical plant	Experimental design		Findings
			Diabetes induction	Plant treatment	
Lei et al. 2018	Male Sprague-Dawley rats (140–150 g)	Zhujing pill extract (ZJPE) [56% (1000 g) of dried seed of Cuscuta Semen; 11% (200 g) of dried seed of Plantaginis Semen; 33% (600 g) of root of Radix Rehmanniae Praeoarata] (Medicinal Material Company, Shaanxi province, China)	• STZ i.p. injection (60 mg/kg b.w.) • Blood glucose (72 h after STZ injection): >16.7 mmol/L	Intragastric administration of ZJPE-L: 1.65 g/kg b.w., ZJPE-M: 3.33 g/kg b.w. and ZJPE: 6.66 g/kg b.w. for 12 weeks	• Decreased b.w. in STZ-induced DM rats compared to NC rats was slightly improved after the ZJPE treatment • ZJPE lead to a slight short-term fall in blood glucose levels compared to the DM group • Increased circulating levels of IL-6, TNF-α and hsCRP in DM group were attenuated by the ZJPE treatment
Zhou et al. 2016	C57BL/6 mice (20±2 g)	*Lonicerae Japonicae* Flos (FL) (Jin-Yin-Hua) - aqueous extract (Shanghai Kang-qiao Herbal Pieces Co. Ltd)	• STZ i.p. injection (55 mg/kg b.w.) for 5 days • Serum glucose (7 days after last STZ injection): >16.5 mmol/L	At 4 months after the STZ injection, oral administration of FL (100, 200 mg/kg per day) consecutively for 1 month	• FL had no obvious effect on blood glucose concentration • FL had no obvious effect on b.w. • Reduced the increased serum VEGF content • Decreased the increased number of retinal vessels in OPL and IPL
Dongare et al. 2016	Wistar albino male and female rats (200–250 g)	*Zingiber officinale* (ginger) rhizome extract [5% of 6 gingerol (6-G)]	• Single i.p. injection of STZ (45 mg/kg b.w.) • After 48 h of STZ administration, blood glucose concentration >300 mg/dl	75 mg/kg/day of ginger extract dispersed in 0.5% Tween-80 evenly by oral gavage in a volume of 0.5 mL/kg b.w.	• Reduced the blood sugar levels • Greater body weight was shown • VEGF levels were significantly lower • Observation of the retinal blood vessel (Ret BV) show a reduction in the thickness of vascular basement membrane after treatment with 6-G
Agrawal et al. 2012	Wistar male and female rats (200–225 g)	Methanol soluble extract of Tinospora cordifolia (TC) (Sanat Products Ltd., Delhi, India)	• STZ injection i.p. (45 mg/kg) • Blood glucose level of rats >250 mg/dl	Methanol soluble extract of TC: 250 mg/kg TC orally	• Oral administration of methanol soluble extract of TC suppressed the elevation of blood glucose level • Reduced the mean VEGF value • Showed no appreciable widening of vascular basement membrane
Tamoli et al. 2020	Wistar male rats (200–250 g)	Vasant Kusumakar Ras (VKR) (the ayurvedic text Yogratnakar Prameha chikit sanadhaya)	• After 12 h of fasting, a single i.p. injection of STZ (45 mg/kg) • Fasting blood glucose level > 250 mg/dL (> 13.88 mmol/L)	VKR treatment started from 4th week and continued to 8th week: 11.25 mg/kg p.o. of VKR	• No any changes were shown in blood glucose level • VEGF level in eye tissue significantly decreased • Decreased the formation of new blood vessels in the junction between GCL and IPL, and the junction between IPL and INL and vascularity of GCL

Abbreviations: b.w. – body weight; DM – diabetes mellitus; GCL - ganglion cell layer; IL-6 - interleukin-6; INL - inner nuclear layer; i.p. – intraperitoneal; IPL - inner plexiform layer; NC – normal control; ONL - outer nuclear layer; OPL - outer plexiform layer; STZ – streptozotocin; TNF-α - tumor necrosis factor-α; VEGF - vascular endothelial growth factor.

Table 1
Continued . . .

Reference	Experimental model	Medical plant	Experimental design		Findings
			Diabetes induction	Plant treatment	
Hong et al. 2016	Wistar male rats (200–250 g)	Ethanol extract of Zingiber zerumbet rhizomes (ZZR; EEZZR) (Wild ginger) [Dongshan, Dongshan Dist (Tainan City, Taiwan)]	• Single injection of STZ intravenously (60 mg/kg) • Non fasting blood glucose levels for rats >350 mg/dL	Rats were dosed with EEZZR by oral gavage for three consecutive months, - Once daily 200 or 300 mg/kg in a volume of 1.5 mL/kg distilled water	• Glucose levels in STZ-diabetic rats decreased • The b.w. reduction was not obvious • Retinal VEGF protein expression was downregulated by 300 mg/kg/day • Decreased the increased vessels in GCL, INL and ONL
Dong et al. 2019	Wistar male rats (200–250 g)	Resveratrol coated gold nanoparticles (AuNPs) (Sigma-Aldrich Chemicals, Shanghai)	• Sedation of single intravenous injection of STZ (60 mg/kg) • Non fasting blood glucose levels of > 350 mg/dL	Resveratrol coated AuNPs 200 in a volume of 1.5 mL/kg purified water (oral gavage for 3 months	• The levels of glucose were noticed to be decreased • No significant decrease in the b.w. • Protein level of VEGF was reduced
Zhang et al. 2020	Wistar male rats (100–120 g)	Total Lignans from Fructus Arctii (TLFA) (Pharmaceutical Co., Ltd., Xuzhou-Collected from Xuzhou, Jiangshu province)	• i.p. injections of STZ (30 mg/kg) • Fasting blood glucose level >16.7 mmol/L	Intragastric administration to all animals for 9 weeks, once daily: 1.38 (TLFA-H) or 0.69 (TLFA-M) or 0.35 (TLFA-L) g/kg/day of TLFA mixed with 30% polyethylene glycol 400	• Fasting blood glucose levels of rats were decreased • No significant difference was found in b.w. • VEGF expression was significantly weaker • Showed no abnormal blood vessel clusters and retinal status was completely continuous

Abbreviations: b.w. – body weight; DM – diabetes mellitus; GCL - ganglion cell layer; IL-6 - interleukin-6; INL - inner nuclear layer; i.p. – intraperitoneal; IPL - inner plexiform layer; NC – normal control; ONL - outer nuclear layer; OPL - outer plexiform layer; STZ – streptozotocin; TNF-α – tumor necrosis factor-α; VEGF - vascular endothelial growth factor.

lowering the blood glucose level and increasing the body weight. Treatment with ZJPE low- (250–500 g), middle- (250–500 g), and high-extracts (250–450 g) significantly decreased the blood glucose level in DM rats from 18 to 22 mmol/L, 18 to 22 mmol/L, and 16 to 22 mmol/L, respectively ($p<0.01$). The decreased body weight of STZ-induced DM rats was improved after treating with all ZJPE doses ($p<0.05$) (Lei et al. 2018) (Table 1).

Zingiber officinale (ginger) rhizome extract standardized to 5% of 6-gingerol (6-G), the major active constituent of ginger, was tested in Wistar albino rats of both sexes. Oral administration of 6-G reduced the blood sugar level to 361.33±93.44 mg/dl, which was significantly lower than in the diabetic control (DC) group (533.66±113.12 mg/dl) ($p<0.001$), but significantly higher than in normal control group (99.16±8.36 mg/dl) ($p<0.001$). Higher body weight (298.83±29.89 g) was shown in the 6-G-treated group as compared to the DC group (210.66±11.30 g) ($p<0.0001$) (Dongare et al. 2016) (Table 1).

Ethanol extract of Zingiber zerumbet rhizomes (EEZZR) (Hong et al. 2016) and resveratrol-coated AuNPs (Dong et al. 2019) were given to male Wistar rats before measuring blood sugar level and body weight. After treatment with EEZZR, the blood glucose level in STZ-diabetic rats was decreased and maintained at 290–350 mg/ml ($p<0.01$). The body weight reduction was not obvious in STZ-diabetic rats receiving EEZZR during the experimental period ($p<0.01$) (Hong et al. 2016) (Table 1). The blood glucose level in STZ-injected diabetic rats was decreased after treating with resveratrol coated AuNPs and sustained to 290–350 mg/ml. During the experiment period, no significant decrease in the body weight was observed in the

STZ-induced diabetic rats treated with resveratrol coated AuNPs alone (Dong et al. 2019) (Table 1).

Methanolic extract of Tinospora cordifolia (TC) was also tested on the Wistar rats in both sexes. Its oral administration suppressed the elevation of blood glucose levels to 352.22±47.78 mg/dL, which was significantly lower than in DC animals (423.15±49.28 mg/dL) ($p<0.001$), but was significantly higher ($p<0.0001$) than in normal rats (96.07±2.76 mg/dL). Body weight was not measured in this study group (Agrawal et al. 2012) (Table 1). To check for blood glucose level, Vasant Kusumakar Ras (VKR) was given to adult male Wistar rats. There was a significant change in blood glucose level after VKR treatment ($p<0.01$). Body weight measurement was not done in this study group (Tamoli et al. 2020) (Table 1).

The blood sugar level and body weight were also measured in male Wistar rats treated with total lignans of Fructus arctii (TLFA). Free blood glucose levels in the rats treated with high-TLFA, middle-TLFA, and low-TLFA were decreased to 22.5–30 mmol/L, 22.5–30 mmol/L and 22.5–30 mmol/L, respectively, compared to rats in model group (27.5–35 mmol/L). No significant difference was found in the body weight in diabetic rats treated with any of the total lignans of Fructus arctii (Zhang et al. 2020) (Table 1). The aqueous extract of Lonicerae japonicae flos (LJF) was tested on C57BL/6 mice to determine their potential in reducing blood glucose level and increasing body weight. The result showed that 100 and 200 mg/kg of aqueous extract of LJF had no obvious effect on blood glucose concentration and body weight ($p<0.001$) (Zhou et al. 2016) (Table 1).

Vascular endothelial growth factor (VEGF) protein expression. VEGF protein expression was determined to assess the amount of angiogenic factors leading to angiogenesis. All study groups have reported a decrease in VEGF protein expression after treatment, whereas, five studies of them (Agrawal et al. 2012; Dongare et al. 2016; Zhou et al. 2016; Lei et al. 2018; Tamoli et al. 2020) have performed enzyme-linked immunosorbent assay (ELISA) to determine VEGF protein expression. Dongare et al. (2016) have found a significant ($p<0.0001$) potential treatment with Zingiber officinale in inhibiting the neovascularization. Agrawal et al. (2012) (TC, Tinospora cordifolia), Zhou et al. (2016) (LJF, Lonicerae japonicae flos) and Tamoli et al. (2020) (VKR, Vasant Kusmakar Ras) have found a significant ($p<0.001$) and potential treatment to decrease the neovascularization. However, Lei et al. (2018) (ZJPE, Zhujing pill) have reported a significant ($p<0.01$), but lower potential effect in inhibiting neovascularization (Table 1). Zhou et al. (2016) (LJF, Lonicerae japonicae flos) have indicated a significant ($p<0.05$) and the lowest treatment potential that can inhibit the neovascularization - opakuje sa. Besides, Hong et al. (2016) (EEZZR, Zingiber zerumbet rhizomes) and Dong et al. (2019) (resveratrol coated AuNPs) have performed Western blot analysis to determine VEGF protein expression using arbitrary units (Table 1). Zhang et al. (2020) (TLFA, Fructus Arctii), which is the last group, have performed immunohistochemistry (IHC) to examine VEGF protein expression (Table 1).

Amongst study groups performed ELISA, in the very significant and highly potential treatment group, VEGF level in Wistar albino rats of either sex in 6-G-treated group was 6.6±0.85 pg/ml, which was significantly lower than DC rats (14.10±1.8 pg/ml) but higher than normal control rats (4.71±0.8 pg/ml) ($p<0.0001$) (Dongare et al. 2016). In the moderate significant and moderate potential treatment groups, 100 mg/kg of aqueous extract of LJF reduced the increased VEGF serum content to less than 40 ng/L on C57BL/6 mice ($p<0.001$) (Zhou et al. 2016). Methanolic extract of TC significantly reduced the mean VEGF value in the treatment group to less than 10 pg/mg as compared to DC group of Wistar rats of either sex (less than 15 pg/mg) ($p<0.001$) (Agrawal et al. 2012). Furthermore, VKR treatment significantly decreased ($p<0.001$) VEGF level to 3030.77±299.16 pg/mg in the eye tissue of adult male Wistar rats (Tamoli et al. 2020). Next, in the less significant and lower potential treatment group, ZJPE-L-treated group (less than 10 pg/mg), ZJPE-M-treated group (less than 10 pg/mg) and ZJPE-H-treated group (5 pg/mg) lowered the retinal VEGF expression in comparison to DM group male SD rats ($p<0.01$) (Lei et al. 2018). Lastly, in the least significant and the lowest potential treatment group, 200 mg/kg of aqueous extract of LJF was shown to reduce the increased VEGF serum content to less than 60 ng/L in C57BL/6 mice ($p<0.05$) (Zhou et al. 2016) (Table 1).

In the study groups applied the Western blot analysis, the retinal VEGF protein expression was downregulated to 300 mg/kg/day of EEZZR treatment (less than 2.0 arbitrary units) as compared to vehicle-treated normal male Wistar rats (1.0 arbitrary unit) and STZ-diabetic male Wistar rats (less than 3.0 arbitrary units) ($p<0.05$) (Hong et al. 2016). The VEGF protein level in resveratrol coated AuNPs 300-treated group was reduced to less than 2.0 arbitrary units as compared to vehicle-treated normal rats (1.0 arbitrary unit) and STZ-diabetic rats

(less than 3.0 arbitrary units). However, the significance level was not stated (Dong et al. 2019) (Table 1).

In the study performing IHC, the VEGF expression was significantly lower than in the model group ($p<0.05$, $p<0.01$) after treatment with TLFA-low, TLFA-middle, and TLFA-high (Zhang et al. 2020) (Table 1).

Histopathology of hematoxylin and eosin staining. Histopathological examination of tissue using HE staining was used to visualize the tissue structure and formation or proliferation of new blood vessels. All study groups showed decreased vasculature activity after treatment. Zhou et al. (2016) (LJF, Lonicerae japonicae flos), Hong et al. (2016) (EEZZR, Zingiber zerumbet rhizomes), and Dong et al. (2019) (resveratrol coated AuNPs) have reported decreased blood vessels in the retina. Two study groups Dongare et al. (2016) (Zingiber officinale) and Agrawal et al. (2012) (TC, Tinospora cordifolia) have demonstrated a decreased of vascular membrane thickness. Vascularity reduction has also been shown by Tamoli et al. (2020) (VKR, Vasant Kusmakar Ras). Zhang et al. (2020) (TLFA, Fructus Arctii) have reported no abnormal blood vessel clusters and the retinal status was completely continuous, while Lei et al. (2018) (ZJPE, Zhujing pill) have reported a rare vascularization.

In the study groups reporting decreased vessels in the retina, 100 and 200 mg/kg of aqueous extract of LJF decreased the increased number of retinal vessels in both the outer (OPL) and inner plexiform layer (IPL) in C57BL/6 mice (Zhou et al. 2016). EEZZR (300 mg/kg) decreased the increased vessels in ganglion cell layer (GCL), inner nuclear layer (INL), and outer nuclear layer (ONL) in STZ-diabetic male Wistar rats (Hong et al. 2016). After treating with 300 mg/kg of resveratrol coated AuNPs, the increased vessels in the ONL, INL, and GCL of the STZ-induced diabetic Wistar male rats were decreased (Dong et al. 2019) (Table 1).

A decreased vascular membrane thickness and a thinner vascular basement membrane have been observed after 6-G treatment as compared to DC group of Wistar albino rats of either sex (Dongare et al. 2016). Besides, methanolic extract of TC-treated Wistar rats of both sexes also showed no appreciable vascular basement membrane widening (Agrawal et al. 2012). One study group has reported a decrease in the vascularity. VKR decreased the formation of new blood vessels in the junction between GCL and IPL and the junction between IPL and INL, as well as the vascularity of GCL in adult male Wistar rats (Tamoli et al. 2020). In addition, it has been reported that there were no abnormal blood vessel clusters and the retinal status was completely continuous. The rats in TLFA-M and TLFA-H groups showed no abnormal blood vessel clusters and retinal status was completely continuous on male Wistar rats (Zhang et al. 2020). The last study group reported that vascularization implicating degenerative changes in the INL and OPL was seldom found in the ZJPE groups. These results suggest that treatment with ZJPE was likely to provide protective effects against retinal damage in DM rats (Lei et al. 2018) (Table 1).

Discussion

The effects of medicinal plants on blood glucose levels, body weight, and angiogenesis. DM, which is characterized by an increased blood glucose level and decreased body weight, is a metabolic disorder and a non-contagious disease (Piero et al. 2015; Cheng et al. 2018). Medicinal plants, which are composed of antidiabetic potential, particularly hypoglycemic or antihyperglycemic one, can be used to treat diabetes, so DM symptoms can be controlled (Kalra et al. 2013).

Based on Table 1, Zingiber officinale rhizome extract (standardized to 5% of 6-G), ZJPE, EEZZR and resveratrol coated AuNPs could decrease the blood glucose level and increase body weight (Dongare et al. 2016; Hong et al. 2016; Lei et al. 2018; Dong et al. 2019). Moreover, methanol soluble extract of TC could reduce blood glucose level, but body weight was unknown (Agrawal et al. 2012). VKR did not decrease the blood sugar level and body weight measurement was unknown (Tamoli et al. 2020). TLFA showed positive effect on the blood glucose level reduction, but the body weight increment is unknown (Zhang et al. 2020). The aqueous extract of LJF had no effect on the blood glucose and body weight (Zhou et al. 2016).

It is known that hyperglycemia in DM induces the release of inflammatory cytokines, angiogenic factors such as VEGF, and mediate oxidative stress and hypoxia, which in turn stimulates angiogenesis. This will lead to pathological or excessive angiogenesis resulting in microvascular complications such as diabetic retinopathy, diabetic neuropathy, and diabetic nephropathy (Kota et al. 2012; Tahergorabi and Khazaei 2012; Cheng and Ma 2015). Thus, abovementioned medicinal plants exerted their antidiabetic effects by regulating the neovascularization via targeting these mechanistic pathways.

Angiogenesis is a process of blood vessel formation for pre-existing vessels. Increased angiogenesis leads to an increased blood vessel formation (Ucuzian et

al. 2010). Histopathology of tissue using HE staining allows to examine the overview of tissue structure in order to differentiate normal from the pathological tissue (Leung and Jensen 2013). Studies evaluating the anti-angiogenic potential of medicinal plants to ameliorate neovascularization activity in diabetes are scarce. Therefore, published studies are very important in reporting the potential of medicinal plants in this activity. Recently, medicinal plants become increasingly popular in the developing and developed countries due to their affordability, less occurrence of side effects, and natural origin properties (Lordani et al. 2018).

According to the results showed in Table 1, the increased VEGF protein expression in diabetic animal models decreased after the treatment with all medicinal plants. Moreover, all the medicinal plants have shown decreased vasculature activity using histopathological examinations (Agrawal et al. 2012; Dongare et al. 2016; Hong et al. 2016; Zhou et al. 2016; Lei et al. 2018; Dong et al. 2019; Tamoli et al. 2020; Zhang et al. 2020).

Zhujing pill/ZJPE, known as Zhujing wan or preserve vistas pill, is a formulation that consist of several medicinal plants, for example semen cuscutae and semen plantaginis. In this systematic review, only one study has reported that ZJPE could decrease the blood glucose level and increase the body weight. ZJPE has been reported to have an ability to decrease protein expression of VEGF in dose-dependent manner. Vascularization that indicates degenerative changes in the INL and OPL was rare in the ZJPE-treated groups. These results have suggested that treatment with ZJPE may provide protective effects against retinal damage in DM rats (Lei et al. 2018).

6-G is one of the major bioactive constituents and the most abundant and pungent gingerol in fresh roots of the ginger. It has been reported to possess physiological and pharmacological effects of anti-hyperglycemic and anti-diabetic levels (Ghareib et al. 2015; Samad et al. 2017; Han et al. 2019; Teng et al. 2019). 6-G can decrease the blood glucose concentration and increase the body weight on diabetic Wistar albino rats of both sexes (Dongare et al. 2016). Sukalingam et al. (2013) have, however, reported that 6-G significantly reduced blood glucose level, but it did not induce significant difference in body weight in STZ-induced diabetic rats after post treatment. 6-G also reduced the increased inflammatory cytokines, such as interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), serum levels in myocardial ischemia/reperfusion (I/R) injured rats (Xu et al. 2014). Antioxidant activities are also supported by data of Dugasani et al. (2010), in which 6-G induced substantial scavenging potential toward 1,1-diphenyl-2-picryl-hydrazyl (DPPH) radical, superoxide radical, and hydroxyl radical in antioxidant assays. Angiogenesis can be lowered through its anti-inflammatory and antioxidant properties (Giacco and Brownlee 2010; Kota et al. 2012; Kim et al. 2013; Huang and Nan 2019). Furthermore, 6-G can decrease the increased VEGF protein expression and reduce the thickness of vascular basement membrane (Dongare et al. 2016). This indicates that excessive angiogenesis has been controlled (Nakuda 2014).

Zingiber zerumbet also called bitter ginger or Asian ginger is found in tropical and sub-tropical countries including Malaysia and India. Zingiber zerumbet rhizomes (ZZR) has therapeutic effects at anti-hyperglycemic and anti-diabetic levels (Yob et al. 2011; Koga et al. 2016; Chaudhuri et al. 2018; Samad et al. 2019). EEZZR has been demonstrated to have an ability to lower blood glucose level, but the body weight reduction in STZ-diabetic rats is not obvious (Hong et al. 2016), which is supported by another study after the 8-week of treatment with 300 mg/kg EEZZR in STZ-diabetic rats (Tzeng et al. 2016). Besides, it has therapeutic effects at anti-inflammatory and antioxidant levels (Yob et al. 2011; Koga et al. 2016; Chaudhuri et al. 2018; Samad et al. 2019). Zakaria et al. (2010) have demonstrated that all dosages of methanolic extract of Zingiber zerumbet (MEZZ) induced a significant anti-oedema activity when assessed using the carrageenan-induced paw oedema test for acute inflammation and the cotton-pellet-induced granuloma test for chronic inflammation. Antioxidant potential is supported by Nag et al. (2013) who have shown that ZZR has a significant hydroxyl radical scavenging and DPPH activities. In this systematic review, EEZZR was potentiated to decrease the increased VEGF protein expression and the increased vessels in GCL, INL and outer nuclear layer (ONL) in STZ-diabetic male Wistar rats (Hong et al. 2016). Tzeng et al. (2016) have discovered that ZER, a bioactive compound found in ZZR, could reduce VEGF overexpression in the retinas of STZ-diabetic rats. These findings have suggested that ZZR and ZER have anti-angiogenic potential.

Resveratrol is a polyphenol and phytochemical found in plants. It can be used to treat T2DM by decreasing insulin resistance or increasing glycemic control. Based on the results shown in Table 1, resveratrol coated AuNPs decreased blood glucose concentration, but the body weight reduction was insignificant (Dong et al. 2019). This is supported

by another study showing that 60 days resveratrol supplementation significantly reduced full blood sugar and glycated hemoglobin (HbA1c) levels in T1DM patients by comparing with the baseline values, but no significant change in body weight (Movahed et al. 2020). Chang et al. (2012) have also shown that resveratrol significantly reduced the protein expression of superoxide anion, manganese-superoxide dismutase (Mn-SOD), and protein carbonyl levels as well as the expression of NF-κB p65 and IL-1β in hepatic tissues of diabetic rats. Dong et al. (2019) have reported that resveratrol coated AuNPs could decrease VEGF protein expression, and in addition, the vessels in the ONL, INL, and GCL were decreased after treating with resveratrol coated AuNPs. Other studies have shown that resveratrol treatment attenuated the increased VEGF in diabetic kidney of SD male rats and STZ-diabetic retinopathy rats (Chen et al. 2019). Therefore, increased angiogenesis can be ameliorated (Giacco and Brownlee 2010; Kota et al. 2012; Kim et al. 2013; Huang and Nan 2019).

TC, categorized under Menispermaceae family, has been reported with hypoglycemic and anti-diabetic medicinal properties (Sivakumar and Rajan 2011; Saha and Ghosh 2012; Mishra and Kaur 2013). Agrawal et al. (2012) have reported that methanol soluble extract of TC had a positive effect on the blood glucose level reduction, but body weight data were unknown. Hypoglycemic properties of TC were supported by the study, in which oral administration of alcoholic and/or methanolic TC extracts significantly decreased the blood sugar level in alloxan-treated albino rats (Kinkar and Patil 2015). Ethanolic extract of TC increased the body weight in STZ-induced diabetic rats (Ruchita et al. 2016). Further, TC has been shown to have antioxidant and anti-inflammatory properties (Sivakumar and Rajan 2011; Saha and Ghosh 2012; Mishra and Kaur 2013). Aqueous extract of TC downregulated *TNF-α* and *IL-1β* gene expression in mouse macrophage RAW 264.7 cell line (Ghatpande et al. 2019). TC ethyl acetate stem and methanolic leaf extracts showed the highest DPPH, 2, 2'-azino-bis (3- ethylbenzothiazoline-6-sulfonic acid) (ABTS) radical, ferric reducing antioxidant power (FRAP), and hydroxyl radical scavenging effects when compared to other extracts (Ilaiyaraja and Khanum 2011). Agrawal et al. (2012) have reported that methanolic extract of TC reversed the increased VEGF protein expression. No appreciable widening of vascular basement membrane was observed under histopathological examination indicating an increased angiogenesis (Nakuda 2014).

VKR is an ayurvedic medicine that can be used to treat diabetes and the relevant symptoms (Sachin and Akhilesh 2016). In this systematic review, VKR did not reduce the blood sugar level and its effect is unknown on the body weight (Tamoli et al. 2020). However, one study has shown that 8-week treatment of 50 mg/kg of VKR reversed the increased FBG and post prandial glucose level in STZ-induced diabetic nephropathy non-insulin-dependent diabetes mellitus (NIDDM) rats and no body weight change was observed when compared to the diabetic group (Gandhi 2014). VKR also possesses anti-angiogenic and anti-inflammatory properties by reducing proinflammatory cytokines (Panda et al. 2018). For example, plasma levels of TNF- α and nitric oxide (NO) in STZ-induced diabetic nephropathy NIDDM rats were decreased significantly after VKR treatment (Gandhi 2014). Based on the findings in Table 1, VKR could reduce VEGF protein expression and the formation of new blood vessels in the junction between ganglion cell layer (GCL) and IPL, and the junction between IPL and inner nuclear layer (INL), as well as vascularity of GCL (Tamoli et al. 2020). This is supported by another study, in which VKR treatment significantly decreased VEGF plasma concentration in diabetic nephropathy of STZ-induced NIDDM rats (Gandhi 2014).

Fructus arctii, a dried ripe fruit of Arctium lappa L, is belonging to the Asteraceae family. In China, it is known as "Niubangzi" and mainly used for T2DM due to its satisfactory hypoglycemic effect (Gao et al. 2018). Total ligands from Fructus arctii (TLFA) also possess an anti-diabetic activity (Xu et al. 2014). In this systematic review, TLFA had the ability to decrease the blood glucose level, but not the body weight increment (Zhang et al. 2020). A similar finding has been found by Xu et al. (2014) who have shown that HbA1c level in spontaneously diabetic Goto-Kakizaki rats could be controlled significantly by TLFA, but not the final body weight of diabetic Goto-Kakizaki rats. Besides, Fructus arctii has also been reported to have antioxidant and anti-inflammatory properties by inhibiting oxidative stress and proinflammatory factors including NF-κB and inducible nitric oxide synthase (iNOS) (Shin et al. 2015). Treatment with arctigenin, a lignan from Fructus arctii, significantly reduced the levels of TNF-α, IL-6, interleukin-10 (IL-10), and c-reactive protein (CRP) in a rat model of gastric ulcers when compared to the vehicle group (Li et al. 2016). Zhang et al. (2020) have reported that VEGF protein expression was reduced after TLFA treatment. Moreover, in the TLFA-middle group and the TLFA-high group, no abnormal blood

vessel clusters were found and the retinal status was completely continuous. In diabetic retinopathy, macular oedema, a type of angiogenesis-related eye disorder, can occur. In the proliferative phase, angiogenesis occurs and cluster of high permeable vessels are formed when compared to non-proliferative phase. These conditions were reversed after treating with TLFA showing that TLFA exerted a protective effect on the retina (Tahergorabi and Khazaei 2012). Anti-angiogenic potential of TLFA was also supported by another study, in which after treatment with arctiin, a lignan isolated from dry seeds of Arctium lappa L, retinal VEGF expression in STZ-induced diabetic retinopathy of male SD rats was ameliorated (Lu et al. 2012).

Lonicerae japonicae flos (LJF), which is known as Japanese honeysuckle, is classified under Caprifoliaceae family. The pharmacological effect of LJF includes both hypoglycemic and anti-diabetic impacts (Shang et al. 2011; Yuan et al. 2012; Wang et al. 2016; He et al. 2019). However, aqueous extract of LJF did not show any effect on blood glucose reduction and body weight increment (Zhou et al. 2016). Han et al. (2019) have shown that LJF reduced high blood glucose level and restored body weight after four weeks of oral administration of 100 mg/kg of LJF in both high-fat diet-fed and low-dose STZ-induced male SD rats. LJF also possesses anti-inflammatory, antioxidant and anti-angiogenic properties (Shang et al. 2011; Yuan et al. 2012; Wang et al. 2016; He et al. 2019). Different doses of green bud of LJF and aqueous extract of LJF significantly inhibited the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) production induced by TNF-α on HEK 293 cells (Jiang et al. 2014). LJF also displayed a potent scavenging activity on ABTS and DPPH (Fan et al. 2019). It has also been reported that both 100 mg/kg and 200 m/kg of aqueous extracts of LJF could reduce VEGF protein expression to less than 40 ng/L and 60 ng/L, respectively. The increased number of retinal vessels in OPL and IPL were also reduced significantly (Zhou et al. 2016) have suggested that increased angiogenesis was alleviated.

Limitations of this review

The animal species used were not identical and the treatment methods for diabetic animals were not standardized. Additionally, the parts of the medicinal plants used were not consistent across all studies, which could potentially lead to varying effects. These differences in treatments and sources may result in varying effects on blood glucose levels or body weight, making it challenging to generalize results and outcomes. Furthermore, the results were constrained by the small number of papers.

On the other hand, this review has provided an overview of the usefulness of medicinal plants in combating diseases for clinical researchers. It can be inferred that if sufficient information regarding the potential of medicinal plants against diabetes complications in preclinical studies is established more effective types of potential treatments could be employed, which could be more beneficial to the healthcare system and the socio-economy of the community.

However, the sparse information on different dosages or combinations of medicinal plants, as well as their validity, and the need for well-controlled clinical trials is still missing and therefore, there is a real need for further research.

Conclusion

All the medicinal plants described in this systematic review have a potential to decrease the blood glucose level, except the aqueous extract of LJF and VKR. However, other studies have reported that LJF and VKR can reduce the increased blood glucose in diabetes. Moreover, these medicinal plants also increased the body weight in diabetes, except the aqueous extract of LJF and TLFA. However, the body weight increment potential of LJF has been reported. Methanolic extract of TC and VKR have not been tested for their potential to increase the body weight. These medicinal plants also showed anti-angiogenic properties by downregulating VEGF protein expression and inhibiting vasculature activity as observed by histopathological HE staining. Based on the significance, 6-G seems to be the most powerful medicinal plant to ameliorate angiogenesis in diabetes. However, different studies may yield different results due to different extraction methods, associated compound, and doses of medicinal plants used. Therefore, additional preclinical studies should be conducted to confirm their anti-neovascularizing activities before translation into clinical settings.

Conflict of interest. *The authors declare no conflict of interest.*

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References

Agrawal SS, Naqvi S, Gupta SK, Srivastava S. Prevention and management of diabetic retinopathy in STZ diabetic rats by Tinospora cordifolia and its molecular mechanisms. Food Chem Toxicol 50, 3126–3132, 2012.

Chang CC, Chang CY, Huang JP, Hung LM. Effect of resveratrol on oxidative and inflammatory stress in liver and spleen of streptozotocin-induced type 1 diabetic rats. Chin J Physiol 55, 192–201, 2012.

Chaudhuri A, Sharma SC, Khan F. An overview on the advances of Zingiber zerumbet. Pharmaceut Biosci J 6, 24–27, 2018.

Chen Y, Meng J, Li H, Wei H, Bi F, Liu S, Tang K, Guo H, Liu W. Resveratrol exhibits an effect on attenuating retina inflammatory condition and damage of diabetic retinopathy via PON1. Exp Eye Res 181, 356–366, 2019.

Cheng R, Ma JX. Angiogenesis in diabetes and obesity. Rev Endocr Metab Disord 16, 67–75, 2015.

Cheng LS, Aagaard-Hansen J, Mustapha FI, Christensen UB. Malaysian diabetes patients' perceptions, attitudes and practices in relation to self-care and encounters with primary health care providers. Malaysian J Med Res 2, 1–10, 2018.

Dong Y, Wan G, Yan P, Qian C, Li F, Peng G. Fabrication of resveratrol coated gold nanoparticles and investigation of their effect on diabetic retinopathy in streptozotocin induced diabetic rats. J Photochem Photobiol B 195, 51–57, 2019.

Dongare S, Gupta SK, Mathur R, Saxena R, Mathur S, Agarwal R, Nag TC, Srivastava S, Kumar P. Zingiber officinale attenuates retinal microvascular changes in diabetic rats via anti-inflammatory and antiangiogenic mechanisms. Mol Vis 22, 599–609, 2016.

Dugasani S, Pichika MR, Nadarajah VD, Balijepalli MK, Tandra S, Korlakunta JN. Comparative antioxidant and anti-inflammatory effects of [6]-gingerol, [8]-gingerol, [10]-gingerol and [6]-shogaol. J Ethnopharmacol 127, 515–520, 2010.

El-Refaei MF, Abduljawad SH, Alghamdi AH. Alternative medicine in diabetes - Role of angiogenesis, oxidative stress, and chronic inflammation. Rev Diabet Stud 11, 231–244, 2014.

Fan Z, Li L, Bai X, Zhang H, Liu Q, Zhang H, Fu Y, Moyo R. Extraction optimization, antioxidant activity, and tyrosinase inhibitory capacity of polyphenols from Lonicera japonica. Food Sci Nutr 7, 1786–1794, 2019.

Gandhi S. Investigation of new pharmacological interventions for diabetic nephropathy in experimentally induced NIDDM in rats. Shodhganga, 1–35, 2014.

Gao Y, Gu C, Wang K, Wang H, Ruan K, Xu Z, Feng Y. The effects of hypoglycemia and weight loss of total lignans from Fructus Arctii in KKAy mice and its mechanisms of the activity. Phytoter Res 32, 631–642, 2018.

Ghareib SA, El-Bassossy HM, Elberry AA, Azhar A, Watson ML, Banjar ZM. 6-Gingerol alleviates exaggerated vasoconstriction in diabetic rat aorta through direct vasodilation and nitric oxide generation. Drug Des Devel Ther 9, 6019–6026, 2015.

Ghatpande NS, Misar AV, Waghole RJ, Jadhav SH, Kulkarni PP. Tinospora cordifolia protects against inflammation associated anemia by modulating inflammatory cytokines and hepcidin expression in male Wistar rats. Sci Rep 9, 10969, 2019.

Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res 107, 1058–1070, 2010.

Han X, Zhang Y, Liang Y, Zhang J, Li M, Zhao Z, Zhang X, Xue Y, Zhang Y, Xiao J, Chu L. 6-Gingerol, an active pungent component of ginger, inhibits L-type Ca2+ current, contractility, and Ca2+ transients in isolated rat ventricular myocytes. Food Sci Nutr 7, 1344–1352, 2019.

He H, Zhang D, Gao J, Andersen TR, Mou Z. Identification and evaluation of Lonicera japonica flos introduced to the Hailuogou area based on ITS sequences and active compounds. PeerJ 7, e7636, 2019.

Heinemann L. Biosimilar insulin and costs: What can we expect? J Diabetes Sci Technol 10, 457–462, 2015.

Hong TY, Tzeng TF, Liou SS, Liu IM. The ethanol extract of Zingiber zerumbet rhizomes mitigates vascular lesions in the diabetic retina. Vascul Pharmacol 76, 18–27, 2016.

Hooijmans CR, Rovers MM, De Vries RBM, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. BMC Med Res Methodol 14, 43, 2014.

Huang YJ, Nan GX. Oxidative stress-induced angiogenesis. J Clin Neurosci 63, 13–16, 2019.

Ilaiyaraja N, Khanum F. Antioxidant potential of Tinospora cordifolia extracts and their protective effect on oxidation of biomolecules. Pharmacognosy J 3, 56–62, 2011.

Jiang M, Han YQ, Zhou MG, Zhao HZ, Xiao X, Hou YY, Gao J, Bai G, Luo GA. The screening research of anti-inflammatory bioactive markers from different flowering phases of Flos Lonicerae Japonicae. PloS One 9, e96214, 2014.

Jin K, Yang G. Experimental stroke, Sharjah, Bentham Science Publishers, 2010.

Kalra S, Mukherjee JJ, Venkataraman S, Bantwal G, Shaikh S, Saboo B, Das AK, Ramachandran A. Hypoglycemia: The neglected complication. Indian J Endocrinol Metab 17, 819–834, 2013.
Kim YW, West XZ, Byzova TV. Inflammation and oxidative stress in angiogenesis and vascular disease. J Mol Med (Berl) 91, 323–328, 2013.
Kinkar SB, Patil KG. Antidiabetic activity of Tinospora cordifolia (Fam: Menispermaceae) in Alloxan treated Albino rats. Appl Res J 1, 316–319, 2015.
Koga AY, Beltrame FL, Pereira AV. Several aspects of Zingiber zerumbet: a review. Revista Brasileira de Farmacognosia 26, 385–391, 2016.
Kota SK, Meher LK, Jammula S, Kota SK, Krishna SVS, Modi KD. Aberrant angiogenesis: The gateway to diabetic complications. Indian J Endocrinol Metab 16, 918–930, 2012.
Lei X, He J, Ren C, Zhou Y, Chen X, Dou J. Protective effects of the Chinese herbal medicine prescription Zhujing pill on retina of streptozotocin-induced diabetic rats. Biomed Pharmacother 98, 643–650, 2018.
Leung WY, Jensen MB. Histological quantification of angiogenesis after focal cerebral infarction: a systematic review. ISRN Neurol 2013, 853737–853737, 2013.
Li XM, Miao Y, Su QY, Yao JC, Li HH, Zhang GM. Gastroprotective effects of arctigenin of Arctium lappa L. on a rat model of gastric ulcers. Biomed Rep 5, 589–594, 2016.
Lordani TVA, de Lara CE, Ferreira FBP, de Souza Terron Monich M, Da Silva CM, Lordani CRF, Bueno FG, Teixeira JJV, Lonardoni MVC. Therapeutic effects of medicinal plants on cutaneous wound healing in humans: A systematic review. Mediators Inflamm 2018, 7354250, 2018.
Lu LC, Zhou W, Li ZH, Yu CP, Li CW, Luo MH, Xie H. Effects of arctiin on streptozotocin-induced diabetic retinopathy in Sprague-Dawley rats. Planta Med 78, 1317–1323, 2012.
Mahdi HJ, Hassan Y, Aziz NA, Abdulrazzaq HA, Jirjees FJ, Abduelkarem AR. Diabetes knowledge and practice in Malaysian and the United Arab Emirates diabetic patients. Res J Pharmaceut Biol Chem Sci 4, 653–665, 2013.
Mishra R, Kaur G. Aqueous ethanolic extract of Tinospora cordifolia as a potential candidate for differentiation based therapy of glioblastomas. PLoS One 8, e78764, 2013.
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6, e1000097, 2009.
Movahed A, Raj P, Nabipour I, Mahmoodi M, Ostovar A, Kalantarhormozi M, Netticadan T. Efficacy and safety of resveratrol in type 1 diabetes patients: A two-month preliminary exploratory trial. Nutrients 12, 161, 2020.
Nag A, Bandyopadhyay M, Mukherjee A. Antioxidant activities and cytotoxicity of Zingiber zerumbet (L.) smith rhizome. J Pharmacognosy Phytochem 2, 102–108, 2013.
Nakuda H. Ischemia and diabetic neuropathy. Handb Clin Neurol 126, 469–487, 2014.
O'Leary C, Mcgahon MK, Ashraf S, McNaughten J, Friedel T, Cincola P, Barabas P, Fernandez JA, Stitt AW, McGeown JG, Curtis TM. Involvement of TRPV1 and TRPV4 channels in retinal angiogenesis. Invest Ophthalmol Vis Sci 60, 3297–3309, 2019.
Panda AK, Ratha KK, Dighe D, Bhuyan GC. Successful switch over from insulin therapy to ayurveda medication in a newly diagnosed diabetic patient: A case study. Int J Res Ayurveda Pharm 9, 42–45, 2018.
Piero MN, Nzaro GM, Njagi JM. Diabetes mellitus – a devastating metabolic disorder. Asian J Biomed Pharmaceut Sci 5, 1, 2015.
Potente M, Gerhardt H, Carmeliet P. Basic and therapeutic aspects of angiogenesis. Cell 146, 873–887, 2011.
Risau W, Flamme I. Vasculogenesis. Annu Rev Cell Dev Biol 11, 73–91, 1995.
Ruchita FF, Nandy KK, Haque SMN, Naznin T, Chouwdhury Z, Faroque ABM, Hannan JMA. Hypoglycemic and hypolepidemic effects of the ethanolic extract of Tinospora cordifolia in streptozotocin induced diabetic rats. J Diabetes Metab 7, 67, 2016.
Sachin C, Akhilesh S. Clinical effect of Ras Aushadhi (Vasant Kusumakar Ras) on diabetic foot (Case Presentation). Int J Appl Ayurved Res 2, 1019–1023, 2016.
Saha S, Ghosh S. Tinospora cordifolia: One plant, many roles. Anc Sci Life 31, 151–159, 2012.
Salehi B, Ata A, Kumar NVA, Sharopov F, Ramirez-Alarcon K, Ruiz-Ortega A, Ayatollahi SA, Fokou PVT, Kobarfard F, Zakaria ZA, Iriti M, Taheri Y, Martorell M, Sureda A, Setzer WN, Durazzo A, Lucarini M, Santini A, Capasso R Ostrander EA, Atta-ur-Rahman, Choudhary MI, Cho WC, Sharifi-Rad J. Antidiabetic potential of medicinal plants and their active components. Biomolecules 9, 551, 2019.
Samad MB, Mohsin NMAB, Razu BA, Hossain MT, Mahzabeen S, Unnoor N, Muna IA, Akhter F, Kabir AU, Hannan JMA. [6]-Gingerol, from Zingiber officinale, potentiates GLP-1 mediated glucose-stimulated insulin secretion pathway in pancreatic β-cells and increases RAB8/RAB10-regulated membrane presentation of GLUT4 transporters in skeletal muscle to improve hyperglycemia in Lepr(db/db) type 2 diabetic mice. BMC Complement Altern Med 17, 395, 2017.

Samad NA, Abdul AB, Rahman HS, Abdullah R, Tengku Ibrahim TA, Othman HH. Antiproliferative and antiangiogenic effects of zerumbone from Zingiber zerumbet L. Smith in sprague dawley rat model of hepatocellular carcinoma. Pharmacognosy Magazine 15, 277–282, 2019.

Shang X, Pan H, Li M, Miao X, Ding H. Lonicera japonica Thunb.: ethnopharmacology, phytochemistry and pharmacology of an important traditional Chinese Med J Ethnopharmacol 138, 1–21, 2011.

Shin HS, Jung SY, Back SY, Do JR, Shon DH. Arctigenin from Fructus Arctii (Seed of Burdock) reinforces intestinal barrier function in Caco-2 cell monolayers. Evid Based Complement Alternat Med 2015, 368105, 2015.

Sivakumar V, Rajan MD. Hypoglycemic and antioxidant activity of Tinospora cordifolia in experimental diabetes. Int J Pharmaceut Sci Res 2, 608–613, 2011.

Sukalingam K, Ganesana K, Gani SB. Hypoglycemic effect of 6-gingerol, an active principle of ginger in streptozotocin induced diabetic rats. Research and Reviews: J Pharmacol Toxicol Stud 1, 23–30, 2013.

Tahergorabi Z, Khazaei M. Imbalance of angiogenesis in diabetic complications: the mechanisms. Int J Prev Med 3, 827–838, 2012.

Tamoli SM, Kohli KR, Kaikini AA, Muke SA, Shaikh AA, Sathaye S. Vasant Kusmakar Ras, an ayurvedic herbomineral formulation prevents the development of diabetic retinopathy in rats. J Ayurveda Integr Med 11, 270–276, 2020.

Teng H, Seuseu KT, Lee WY, Chen L. Comparing the effects of microwave radiation on 6-gingerol and 6-shogaol from ginger rhizomes (Zingiber officinale Rosc). PLoS One 14, e0214893, 2019.

Tzeng TF, Liou SS, Tzeng YC, Liu IM. Zerumbone, a phytochemical of subtropical ginger, protects against hyperglycemia-induced retinal damage in experimental diabetic rats. Nutrients 8, 449, 2016.

Ucuzian AA, Gassman AA, East AT, Greisler HP. Molecular mediators of angiogenesis. J Burn Care Res 31, 158–175, 2010.

Wang L, Jiang Q, Hu J, Zhang Y, Li J. Research progress on chemical constituents of Lonicerae japonicae flos. Biomed Res Int 2016, 8968940, 2016.

Xu Z, Ju J, Wang K, Gu C, Feng Y. Evaluation of hypoglycemic activity of total lignans from Fructus Arctii in the spontaneously diabetic Goto-Kakizaki rats. J Ethnopharmacol 151, 548–555, 2014.

Yob NJ, Jofrry SM, Affandi MMRMM, Teh LK, Salleh MZ, Zakaria ZA. Zingiber zerumbet (L.) Smith: A review of its ethnomedicinal, chemical, and pharmacological uses. Evid Based Complement Alternat Med 2011, 543216, 2011.

Yuan Y, Song L, Li M, Liu G, Chu Y, Ma L, Zhou Y, Wang X, Gao W, Qin S, Yu J, Wang X, Huang L. Genetic variation and metabolic pathway intricacy govern the active compound content and quality of the Chinese medicinal plant Lonicera japonica thunb. BMC Genomics 13, 195, 2012.

Zakaria ZA, Mohamad AS, Chear CT, Wong YY, Israf DA, Sulaiman MR. Antiinflammatory and antinociceptive activities of Zingiber zerumbet methanol extract in experimental model systems. Med Princ Pract 19**,** 287–294, 2010.

Zhang H, Gao Y, Zhang J, Wang K, Jin T, Wang H, Ruan K, Wu F, Xu Z. The effect of total lignans from Fructus Arctii on streptozotocin-induced diabetic retinopathy in Wistar rats. J Ethnopharmacol 255, 112773, 2020.

Zhou L, Zhang T, Lu B, Yu Z, Mei X, Abulizi P, Ji L. Lonicerae Japonicae Flos attenuates diabetic retinopathy by inhibiting retinal angiogenesis. J Ethnopharmacol 189, 117–125, 2016.