Antidiabetic Effects of Curcuma longa, Zingiber officinale, and Elettaria cardamomum : Scoping Review of the Family Zingiberaceae in Patients with Diabetes Mellitus

Sari Indah Kartika[1], Yunia Annisa[1], Yenni Bahar[1], Titik Kusumawinakhyu[1]

[1]*Faculty of Medicine, Universitas Muhammadiyah Purwokerto*

*) Correspondence Author
Sari Indah Kartika
Faculty of Medicine
Universitas Muhammadiyah Purwokerto, Purwokerto 53113, Indonesia
Email: sariindah230900@gmail.com

Abstract

Diabetes is a major problem affecting 387 million adults with a global prevalence of (8.3%) and is expected to increase to (10.1%) by 2035. The government recommends the use of herbal medicine as an effort to prevent and control diabetes mellitus. Potential herbal medicines that have antidiabetic effects are the family Zingiberaceae. Several in vitro studies on species of the Zingiberaceae showed antidiabetic activity by inhibiting the activity of the enzymes α-Amylase and α-Glucosidase. However, one problem related to the use of antidiabetic herbs from the Zingiberaceae is the lack of scientific studies showing the effects of the plants used. This scoping review aims to map clinical research evidence of the antidiabetic effects of Zingiberaceae in patients with diabetes mellitus. Using a scoping review methodology, article searches through computerized databases, namely: PubMed, Google Scholar, and Scopus, and search manually used English and Indonesian keywords. The initial search found 1239 articles, then filtered according to the inclusion and exclusion criteria such articles use the RCTs method that mentions the antidiabetic effect of Zingeberaceae family in English or Indonesian in the last 5 years (2017-2021). The results of the study showed 31 articles that met the requirements. 3 types of Zingiberaceae plants had antidiabetic effects, namely Curcuma longa (turmeric) with curcumin/nano-curcumin compounds, Elettaria cardamomum (cardamom), and Zingiber officinale (ginger) which can reduce HbA1c, fasting blood glucose, and insulin resistance in patients with diabetes mellitus with minimal side effects.

Keywords: Antidiabetic herbs; Clinical trials; Diabetes mellitus; Zingiberaceae

INTRODUCTION

Diabetes mellitus (DM), is a group of metabolic diseases characterized by an increase in blood sugar levels above normal[1]. Epidemiological research shows that DM is one of 10 triggers of mortality of ±400 million people globally in 2017[2]. The Indonesian government prioritizes diabetes through prevention and control of DM, one of which is by providing alternative herbal medicines[3]. People are starting to choose herbal medicine over conventional medicine because herbal medicine is considered natural, has few side effects, cheap, and widely available[4].

One of the potential herbal plants that have antidiabetic properties is the Zingiberaceae family [5]. The Zingiberaceae family or known as the ginger tribe has main genera including Amomum (16 spp.), Zingiber (49 spp.), Alpina (17 spp.), Kaempferia (17 spp.), Globba (42 spp.), Etlingera (12 spp.), Caulokaempferia (14 spp.), Curcuma (34 spp.), and Hedychium (22 spp.) [6]. The Zingiberaceae family has been used since ancient times as a plant that has medicinal properties and is widely consumed by the Indonesian people as a herbal medicine[7]

METHODS

The research was conducted using the scoping review method. The article search process used Harzing's Publish or Perish software, by entering specific filters that were consistently applied across all databases, the following keywords: *"*zingiberaceae *OR* alpinia calcarata *OR* alpinia galanga OR alpinia officinarum OR amomum villosum OR alpinia malaccensis OR amomum compactum OR boesenbergia rotunda OR boesenbergia pandurata OR curcuma aeruginosa OR curcuma heyneana OR curcuma longa OR curcuma

xanthorrhiza OR curcuma zedoaria OR cheilocostus speciosus OR etlingera elatior OR elettaria cardamomum OR globba pendula" OR Kaempferia galanga OR Kaempferia parviflora OR Hedychium coronarium OR roscoea purpurea OR zingiber montanum OR zingiber officinale OR curcumin OR Elettaria OR zingiber OR kunyit OR jahe OR kapulaga AND diabetes mellitus OR diabetes mellitus OR antihyperglycemic OR antihyperglycemic OR antidiabetes OR antidiabetic AND clinical trials OR clinical study OR clinical Test OR rct OR randomized controlled trial"

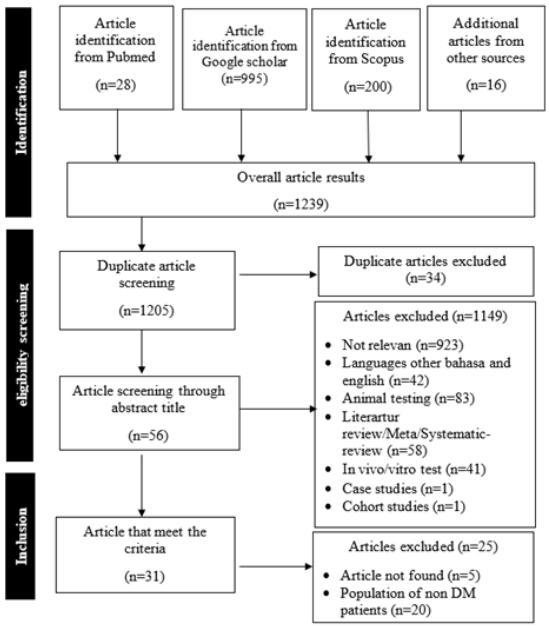

Figure 1. PRISMA ScR article search flowchart

The PRISMA ScR article search flowchart is shown in Figure 1. Identification from the initial search found 1239 articles from the Google Scholar database (n=995), PubMed (n=28), Scopus (n=200), and other sources (16 articles). Eligibility screening involves removing duplicate article titles by sorting them using Ms. Excel. The articles were then screened to meet the inclusion criteria (clinical research articles in English or Indonesian in the last 5 years (2017-2021), articles with RCT methods were selected for evidence-based clinical trial recommendations, and mentioned the effects of using the Zingiberaceae family for diabetes mellitus patients)) and exclusion criteria (articles using case studies/ case series/ case-control studies/ cohort studies/ systematic reviews /meta-analysis methods). Of the 1239 articles, 31 articles were found to meet the requirements.

Risk of Bias Assessment

The risk of bias (ROB) assessment for the studies is presented in Figure. 2 (ROB graph) and Figure. 3 (ROB summary). Plotting was done with the help of *robvis*, a web application designed to visualize bias risk assessments[9]. Over 60% of the studies exhibited a low ROB in overall risk of bias. However, several studies showed an unclear ROB regarding deviations from intended intervention and missing outcome data.

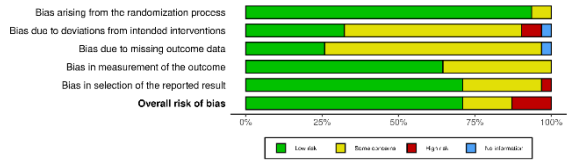

Figure 2. Risk of bias graph

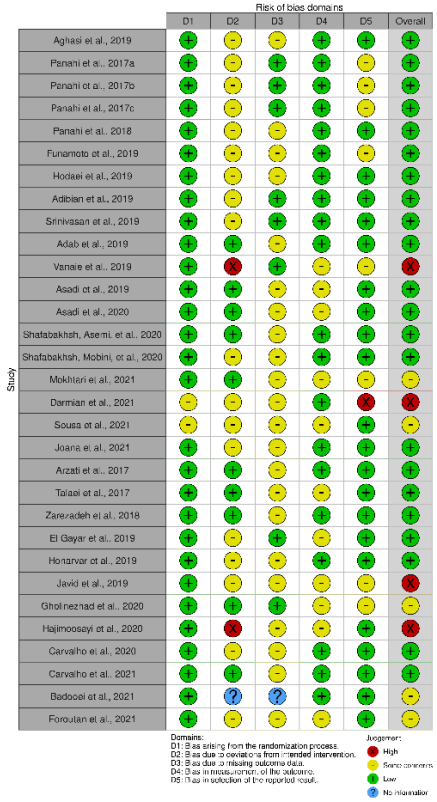

Figure. 3 Risk of bias summary

RESULTS AND DISCUSSION

A total of 31 articles with RCT research design were reviewed in this scoping review study. The publication year was between 2017-2021. The

articles were conducted in several countries: Brazil (4), India (1), Iran (24), Japan (1), and Egypt (1).

1. Elettaria cardamomum (Cardamom)

Research on the Elettaria cardamomum species in clinical trials of DM patients in 2017-2021, obtained 1 eligible article shown in **Table 1** List of studies using Elettaria cardamomum for the treatment of diabetes mellitus patients. The study was conducted by Aghasi et al., (2019) in Iran. In the cardamom group (n=41) given a dose of 3 grams/day for 10 weeks, a significant decrease in serum HbA1C (−0.4%), insulin (−2.8 **μ**IU dL−1), HOMA-IR (−1.7) and TG (−39.9 mg/dL), and an increase in SIRT1 (2.3 ng/mL). The side effects reported in the cardamom group were minimal, only 1 person had dysuria and 1 other person had mild skin inflammation. The author believes that the Elettaria cardamomum (cardamom) which is high in polyphenol content has components of quercetin, kaempferol, luteolin, pelargonidin, gallic acid, caffeic acid, and limonene. These components can increase insulin sensitivity and modulate gluconeogenesis by increasing SIRT1 levels, thereby affecting blood glucose [10].

Previous research by Kitada & Koya (2013) revealed that SIRT1 contributes to blood sugar homeostasis through several mechanisms including protection of pancreatic β cells, regulation of insulin secretion, improving insulin resistance, reducing inflammation, controlling fatty acid oxidation, adiponectin secretion, and regulating glucose production in liver cells[11].

2. Curcuma longa (Turmeric)

Curcuma longa has curcumin/nano-curcumin compounds that have promising antidiabetic properties. The side effects are minimal, 2 people were reported to have complained of an uncomfortable sensation in the stomach. The average dose of curcumin compounds that are quite effective is 500-2100 mg/day with a duration of administration of 8-24 weeks. Curcumin compounds have a low absorption rate, therefore nano-curcumin compounds are used or added with piperine. Research conducted by Asadi et al (2019) showed a significant decrease in glycaemic status in patients with HbA1c (-0.70%) and FBS (-14.80 mg/dl). In addition, research by Sousa et al (2021) showed a decrease in insulin resistance, with a reduction in HOMA-IR (-9.4%) and an increase in HOMA-β (+15.5%).

Curcumin exerts its antidiabetic effects through various mechanisms. The main mechanism involves increasing β-cell function due to its anti-inflammatory and antioxidant characteristics [12,13]. In addition, curcumin lowers fasting blood glucose by increasing the activity of peroxisome proliferator-activated receptors (PPARs), inhibiting hyperglycaemia, increasing glycolysis, reducing gluconeogenesis in the liver, stimulating insulin secretion from the pancreas, and promoting glucose uptake by increasing the expression of GLUT4, GLUT2, and GLUT3 genes. Furthermore, curcumin increases the expression of the adiponectin gene, which contributes to increased insulin sensitivity[14].

Curcumin as an antidiabetic effect also has other benefits which can be seen in **Table 2** List of studies using Curcuma longa for the treatment of diabetes mellitus patients as antioxidants, anti-hyperlipidaemia, nephroprotective effects, prevention of arterial stiffness, anti-depressant, and reduced anxiety. For instance, while many studies report positive effects of curcumin compounds, some show minimal or no significant results.

3. Zingiber officinale (Ginger)

Research has indicated that ginger exhibits antidiabetic properties across multiple studies. Additional research has proposed that the effectiveness of ginger's components varies based on the concentration of the dosage [15]. The main pharmacological actions of ginger shown in **Table 3** List of studies using Zingiber officinale for the treatment of diabetes mellitus patients include antidiabetic, anti-inflammatory, antioxidant, lipid-lowering effects, decreased symptoms and severity of xerostomia. The reported side effects are minimal, 2 people complained of an uncomfortable sensation in the stomach and experienced diarrhea. The average dose of Zingiber officinale administration is 500-3000 mg/day with a duration of administration of 6-12 weeks.

Arzati et al (2017) revealed that giving ginger to people with diabetes mellitus significantly reduced FBS (-26.30 ± 35.27), and HbA1c (-0.38 ± 0.35), this is also supported by clinical trials conducted by Gholinezhad et al (2020). Research by Carvalho et al (2020) with the administration of ginger to people with diabetes mellitus for a longer duration, showed an average decrease in FBS which was almost the same FBS (-29.55 ± 53.76 mg/dl) compared to research conducted by Arzati et al (2017). Research by Foroutan et al., 2021 with a longer research duration, by administering ginger 500mg/day for 12 weeks, there was a significant decrease in HbAIc levels (-

0.42%). In addition, research by El Gayar et al (2019) showed the effect of reducing insulin resistance by increasing HOMA-β levels, which indicates increased β cell function.

Rani et al. (2010) proposed that the phenolic compounds in ginger, namely gingerol, and shoagol, inhibit important enzymes associated with the management of type 2 diabetes, specifically α-glucosidase and α-amylase, improve insulin-sensitive glucose absorption in adipocytes, and boost glycogen storage in both muscle and liver[16].

The evidence indicates that a moderate amount of ginger, easily incorporated through dietary adjustments, can alter glycaemic levels. The significance of dietary components and changes in diet in managing diabetes[17]. It can be said that ginger has an antidiabetic effect so it can be used as an adjuvant in the treatment of diabetes mellitus.

LIMITATIONS

The process of searching for articles using Harzing's Publish or Perish software has a maximum of 1000 articles per search on 1 database. To overcome the limitations of covering all articles that meet the research criteria, the scoping review process adds articles from other sources including searching with keywords for each plant species, through meta/systematic review articles, clinical trial registration websites, and manual searches.

Thirty-one articles in this scoping review took data sources from different studies, which makes it possible for the results of each study to be inconsistent because the effects of the drug depend on each individual's response, variations in the duration of diabetes, the specific dosing used, time of intervention, type of supplement administered, and individual compliance in taking the drug.

CONCLUSION

Based on the scoping review research that has been conducted to map clinical trial evidence on the Zingiberaceae family to evaluate their antidiabetic efficacy and identify compounds, it can be concluded that in 2017-2021, 31 clinical studies have been conducted that tested the effects of Zingiberaceae family species on patients with diabetes mellitus. The newly tested species are Curcuma longa (Turmeric) with curcumin/nano-curcumin compounds, Elettaria Cardamomum (Cardamom), and Zingiber officinale (Ginger). These species have the potential as antidiabetics with minimal side effects.

Recommendations for future research include studying underrepresented species within the Zingiberaceae family, exploring long-term effects, or conducting trials in diverse populations with a longer duration, and variable doses are needed to evaluate.

REFERENCE

1. PERKENI. Pedoman pengelolaan dan pencegahan diabetes melitus Tipe 2 dewasa di Indonesia. PB PERKENI; 2019.
2. IDF. Eighth edition 2017. IDF Diabetes Atlas, 8th edition. International Diabetes Federation; 2017. 1–150 p.
3. IDAI. Konsesus nasional pengelolaan diabetes melitus tipe 1 [Internet]. 2015. 6–36 p. Available from: http://www.idai.or.id/wp-content/uploads/2016/06/Konsensus Endokrin DM tipe 1 (2015).pdf
4. Skalli S, Hassikou R, Arahou M. An ethnobotanical survey of medicinal plants used for diabetes treatment in Rabat, Morocco. Heliyon. 2019;(September 2018): e01421.
5. Rachkeeree A, Kantadoung K, Suksathan R, Puangpradab R, Page PA, Sommano SR. Nutritional compositions and phytochemical properties of the edible flowers from selected zingiberaceae found in Thailand. 2018;5(February):1–10.
6. Rachkeeree A, Kantadoung K, Suksathan R, Puangpradab R, Page PA, Sommano SR. Nutritional Compositions and Phytochemical Properties of the Edible Flowers from Selected Zingiberaceae Found in Thailand. 2018;5(February):1–10.
7. Lianah. Biodiversitas Zingiberaceae: Mijen Kota Semarang. 2020.
8. Arumugam G, Manjula P, Paari N. A review: Anti diabetic medicinal plants used for diabetes mellitus. Journal of Acute Disease. 2013;2(3):196–200.
9. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods [Internet]. n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/jrsm.1411

10. Aghasi M, Koohdani F, Qorbani M, Nasli-esfahani E, Ghazi-zahedi S, Khoshamal H. Beneficial effects of green cardamom on serum SIRT1, glycemic indices and triglyceride levels in patients with type 2 diabetes mellitus: a randomized double-blind placebo controlled clinical trial. 2019;(March).
11. Kitada M, Koya D. SIRT1 in type 2 diabetes: mechanisms and therapeutic potential. Diabetes Metab J. 2013;37(5):315–25.
12. Rivera-Mancía S, Lozada-García MC, Pedraza-Chaverri J. Experimental evidence for curcumin and its analogs for management of diabetes mellitus and its associated complications. Eur J Pharmacol. 2015 Jun 5; 756:30–7.
13. Hodaei H, Adibian M, Nikpayam O, Hedayati M, Sohrab G. The effect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: A randomized, double-blind clinical trial. Diabetol Metab Syndr [Internet]. 2019;11(1):1–8. Available from: https://doi.org/10.1186/s13098-019-0437-7
14. Na LX, Li Y, Pan HZ, Zhou XL, Sun DJ, Meng M, et al. Curcuminoids exert glucose-lowering effect in type 2 diabetes by decreasing serum free fatty acids: a double-blind, placebo-controlled trial. Mol Nutr Food Res [Internet]. 2013 Sep [cited 2024 Dec 10];57(9):1569–77. Available from: https://pubmed.ncbi.nlm.nih.gov/22930403/
15. El Gayar MH, Aboromia MMM, Ibrahim NA, Abdel Hafiz MH. Effects of ginger powder supplementation on glycemic status and lipid profile in newly diagnosed obese patients with type 2 diabetes mellitus. Obes Med. 2019 Jun 1; 14:100094.
16. Rani MP, Padmakumari KP, Sankarikutty B, Cherian OL, Nisha VM, Raghu KG. Inhibitory potential of ginger extracts against enzymes linked to type 2 diabetes, inflammation and induced oxidative stress. Int J Food Sci Nutr. 2011;62(2):106–110.
17. Arzati MM, Honarvar NM, Saedisomeolia A, Anvari S, Effatpanah M, Arzati RM, et al. The effects of ginger on fasting blood sugar, hemoglobin A1c, and lipid profiles in patients with type 2 diabetes. Int J Endocrinol Metab. 2017;15(4):0–6.
18. Panahi Y, Khalili N, Sahebi E, Namazi S, Simental-Mendía LE, Majeed M, et al. Effects of curcuminoids plus piperine on glycemic, hepatic and inflammatory biomarkers in patients with type 2 diabetes mellitus: a randomized double-blind placebo-controlled trial. Drug Res. 2018;68(7):403–9.
19. Asadi S, Gholami MS, Siassi F, Qorbani M, Khamoshian K, Sotoudeh G. Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: A randomized double-blind placebo- controlled clinical trial. Complement Ther Med [Internet]. 2019;43(August):253–60. Available from: https://doi.org/10.1016/j.ctim.2019.02.014
20. Shafabakhsh R, Asemi Z, Reiner Ž, Soleimani A, Aghadavod E, Bahmani F. The effects of nano-curcumin on metabolic status in patients with diabetes on hemodialysis, a randomized, double blind, placebo-controlled trial. Iran J Kidney Dis. 2020;14(4):290–9.
21. Mokhtari M, Razzaghi R, Momen-Heravi M. The effects of curcumin intake on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Phytotherapy Research. 2021;35(4):2099–107.
22. Darmian MA, Hoseini R, Amiri E, Golshani S. How combined and separate aerobic training and turmeric supplementation alter lipid profile and glycemic status? A clinical trial in middle-aged females with type 2 diabetes and hyperlipidemia. Int Cardiovasc Res J. 2021;15(3):111–8.
23. Sousa DF De, Flávio M, Araújo M De, De VD, Maria M, Damasceno C, et al. Cost-effectiveness of passion fruit albedo versus turmeric in the glycemic and lipaemic control of people with type 2 diabetes: randomized clinical trial. J Am Coll Nutr [Internet]. 2021;40(8):679–88. Available from: https://doi.org/10.1080/07315724.2020.1823909

24. Joana N, Figueiredo F De, Saraiva VV, De SDF, Maria C, Maria Q, et al. Effectiveness of the piperine-supplemented Curcuma longa L. in metabolic control of patients with type 2 diabetes: a randomised double-blind placebo-controlled clinical trial. Int J Food Sci Nutr [Internet]. 2021;0(0):1–10. Available from: https://doi.org/10.1080/09637486.2021.1885015
25. Panahi Y, Khalili N, Sahebi E, Namazi S, Atkin SL, Majeed M, et al. Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial. Inflammopharmacology. 2017;25(1):25–31.
26. Shehzad A, Ha T, Subhan F, Lee YS. New mechanisms and the anti-inflammatory role of curcumin in obesity and obesity-related metabolic diseases. Eur J Nutr [Internet]. 2011 Apr [cited 2024 Dec 10];50(3):151–61. Available from: https://pubmed.ncbi.nlm.nih.gov/21442412/
27. Panahi Y, Khalili N, Sahebi E, Namazi S, Atkin SL, Majeed M, et al. Curcuminoids plus piperine modulate adipokines in type 2 diabetes mellitus. Curr Clin Pharmacol. 2017;12(4):253–258.
28. Shafabakhsh R, Mobini M, Raygan F, Aghadavod E, Ostadmohammadi V, Amirani E, et al. Curcumin administration and the effects on psychological status and markers of inflammation and oxidative damage in patients with type 2 diabetes and coronary heart disease. Clin Nutr ESPEN. 2020 Dec 1; 40:77–82.
29. Panahi Y, Khalili N, Sahebi E, Namazi S, Atkin SL, Majeed M, et al. Curcuminoids modify lipid profile in type 2 diabetes mellitus: a randomized controlled trial. Complement Ther Med. 2017 Aug 1; 33:1–5.
30. Adibian M, Hodaei H, Nikpayam O, Sohrab G, Hekmatdoost A, Hedayati M. The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Phytother Res. 2019;33(5):1374–1383.
31. Adab Z, Eghtesadi S, Vafa MR, Heydari I, Shojaii A, Haqqani H, et al. Effect of turmeric on glycemic status, lipid profile, hs-CRP, and total antioxidant capacity in hyperlipidemic type 2 diabetes mellitus patients. Phytotherapy Research. 2019;33(4):1173–81.
32. Srinivasan A, Selvarajan S, Kamalanathan S, Kadhiravan T, Lakshmi NCP, Adithan S. Effect of Curcuma longa on vascular function in native Tamilians with type 2 diabetes mellitus: A randomized, double-blind, parallel arm, placebo-controlled trial. Phytother Res. 2019;33(7):1898–1911.
33. Vanaie A, Shahidi S, Iraj B, Siadat ZD, Kabirzade M, Shakiba F, et al. Curcumin as a major active component of turmeric attenuates proteinuria in patients with overt diabetic nephropathy. Journal of Research in Medical Sciences. 2019;24(1).
34. Asadi S, Gholami MS, Siassi F, Qorbani M, Sotoudeh G. Beneficial effects of nano-curcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: A randomized, double-blind, placebo-controlled clinical trial. Phytotherapy Research. 2020;34(4):896–903.
35. Funamoto M, Shimizu K, Sunagawa Y, Katanasaka Y, Miyazaki Y, Kakeya H, et al. Effects of Highly Absorbable Curcumin in Patients with Impaired Glucose Tolerance and Non-Insulin-Dependent Diabetes Mellitus. J Diabetes Res. 2019;2019.
36. Gholinezhad H, Bazyar H, Rashidi H, Salehi P, Haghighi-zadeh MH, Zare Javid A. Using ginger supplement in adjunct with non-surgical periodontal therapy improves metabolic and periodontal parameters in patients with type 2 diabetes mellitus and chronic periodontitis: A double-blind, placebo-controlled trial. J Herb Med. 2020 Apr 1; 20:100315.
37. Hajimoosayi F, Sadatmahalleh SJ, Kazemnejad A, Pirjani R. Effect of ginger on the blood glucose level of women with gestational diabetes mellitus (GDM) with impaired glucose tolerance test (GTT): a randomized double- blind placebo-controlled trial. 2020; 5:1–7.

38. Carvalho GCN, Lira-Neto JCG, de Araújo MFM, de Freitas RWJF. Effectiveness of ginger in reducing metabolic levels in people with diabetes: a randomized clinical trial *. 2020;
39. Foroutan M, Yarmohamadi M, Ghorbani R, Movahhed H. The effect of ginger on blood sugar and urine protein in patients with type 2 diabetes mellitus; a clinical trial. 2021;10(x).
40. Talaei B, Mozaffari-khosravi H, Bahreini S. The effect of ginger on blood lipid and lipoproteins in patients with type 2 diabetes: a double-blind randomized clinical controlled trial. 2017;2(1):87–95.
41. Mozaffari-Khosravi H, Talaei B, Jalali BA, Najarzadeh A, Mozayan MR. The effect of ginger powder supplementation on insulin resistance and glycemic indices in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial. Complement Ther Med. 2014 Feb 1;22(1):9–16.
42. Carvalho GCN, Neto JCGL, Nunes LCC, Alencar AMPG, Marques RLL, Damasceno MM. Effectiveness of ginger in the treatment of type 2 diabetes mellitus: A pilot study of the randomized clinical trial type *. 2021; 21:1–14.
43. Honarvar MN, Zarezadeh M, Khorshidi M, Makhdoomi Arzati M, Yekaninejad MS, Abdollahi M, et al. The effect of an oral ginger supplementation on NF-κB concentration in peripheral blood mononuclear cells and anthropomorphic data of patients with type 2 diabetes: A randomized double-blind, placebo-controlled clinical trial. Complement Ther Med. 2019 Feb 1; 42:7–11.
44. Zarezadeh M, Saedisomeolia A, Khorshidi M, Kord Varkane H, Makhdoomi Arzati M, Abdollahi M, et al. Asymmetric dimethylarginine and soluble inter-cellular adhesion molecule-1 serum levels alteration following ginger supplementation in patients with type 2 diabetes: A randomized double-blind, placebo-controlled clinical trial. J Complement Integr Med. 2018;16(2).
45. Javid AZ, Bazyar H, Gholinezhad H, Rahimlou M, Rashidi H, Salehi P, et al. The effects of ginger supplementation on inflammatory, antioxidant, and periodontal parameters in type 2 diabetes mellitus patients with chronic periodontitis under non-surgical periodontal therapy. A double-blind, placebo-controlled trial. 2019;1751–61.
46. Badooei F, Imani E, Hosseini-Teshnizi S, Banar M, Memarzade MR. Comparison of the effect of ginger and aloe vera mouthwashes on xerostomia in patients with type 2 diabetes: A clinical trial, triple-blind. Med Oral Patol Oral Cir Bucal. 2021;26(4): e408–13.

Table 1. List of studies using Elettaria cardamomum for the treatment of diabetes mellitus patients

Author	Country	Article Title	Name of plant/compound	Administration details	Results
Aghasi et al., 2019 [10]	Iran	Beneficial effects of green cardamom on serum SIRT1, glycemic indices, and triglyceride levels in patients with type 2 diabetes mellitus: a randomized double-blind placebo-controlled clinical trial	Elettaria cardamomum	83 patients with type 2 DM and overweight/obesity, were divided into 2 groups. cardamom group (n=41) and placebo group (n=42) were given a dose of 3 g/day for 10 weeks.	Cardamom administration significantly reduced HbA1c, insulin, HOMA-IR, TG levels, and increased SIRT-1

Abbreviations: SIRT1: sirtuin (silent mating type information regulation 2 homolog) 1, HOMA-IR: homeostasis model assessment as an index of insulin resistance, HbA1c: Hemoglobin A1c

Table 2. List of studies using Curcuma longa for the treatment of diabetes mellitus patients

Author	Country	Article Title	Name of plant/compound	Administration details	Results	Discussion
2.A Antidiabetic						
Panahi et al., 2018[18]	Iran	Effects of Curcuminoids Plus Piperine on Glycemic, Hepatic and Inflammatory Biomarkers in Patients with Type 2 Diabetes Mellitus: A Randomized Double-Blind Placebo-Controlled Trial	Curcuma longa/ curcuminoid	100 patients with type 2 DM. were divided into 2 groups. The curcuminoid group (n=50) received 500 mg/day + 5 mg piperine and the placebo group (n=50) 500 mg/day. Both groups were treated for 3 months.	The curcuminoid group experienced a significant decrease in serum levels of glucose (-9 ± 16 mg/dL), C-peptide (-0.6 ± 0.8 ng/mL), and HbA1c levels (-0.9 ± 1.1 %) compared to the placebo group.	**Antidiabetic** The antidiabetic properties of curcuminoids may be linked to their ability to decrease hepatic glucose production by activating AMP kinase and inhibiting the activities of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase. Administration of curcuminoids showed a modest increase in HOMA-β, indicating improvement in β-cell function. In this context, there is evidence that curcuminoids can effectively protect pancreatic islets from oxidative damage by neutralizing free radicals, which may improve β-cell function.
Hodaei et al., 2019[13]	Iran	The efect of curcumin supplementation on anthropometric indices, insulin resistance and oxidative stress in patients with type 2 diabetes: a randomized, double-blind clinical trial	Curcumin	44 patients type 2 DM. Curcumin capsules (n=21) and placebo (n=23) at a dose of 500 mg 3x/day for 10 weeks	The group given curcumin experienced significant changes in fasting blood sugar (FBS) (− 7 ± 2 vs. 3 ± 0.2 $p < 0.05$). However, it was not significant in HbA1c, HOMA-IR, and HOMA-β levels.	
Asadi et al., 2019[19]	Iran	Nano curcumin supplementation reduced the severity of diabetic sensorimotor polyneuropathy in patients with type 2 diabetes mellitus: A randomized double-blind placebo-controlled clinical trial	nano-curcumin	80 patients type 2 DM were divided into 2 groups. Nano-curcumin group (n=40) and placebo group (n=40) with a dose of 80 mg/day for 8 weeks	The group given nano-curcumin experienced a significant decrease in HbA1c (-0.70 %) and FBS (-14.80 mg/dl).	
Shafabakhsh, Asemi, et al., 2020V[20]	Iran	The effects of nano-curcumin on metabolic status in patients with diabetes on hemodialysis, a randomized, double-blind, placebo-controlled trial	Curcuma longa / nano-curcumin	53 patients type 2 DM with hemodialysis were divided into 2 groups. Nano-curcumin (n=26) and placebo group (n=27) with a dose of 80 mg/day for 12 weeks	The group was given nano-curcumin significantly decreased FBS (-19.68 mg/dl) and serum insulin levels (-1.70 µIU/mL), TG, VLDL-c, total cholesterol, LDL-c, hs-CRP, and MDA. There was also an increase in TAC levels and total nitrite levels.	
Mokhtari et al., 2021[21]	Iran	The effects of curcumin intake on wound healing and metabolic status in patients with diabetic foot	Curcuma longa/ nano-curcumin	50 patients with grade 3 diabetic foot ulcers. The nano-curcumin group (n=25)	The nano-curcumin group experienced a significant decrease in FBS (-15.54 mg/dl), insulin (-1.35 µIU/ml), HOMA-IR (-0.66),	

		ulcer: A randomized, double-blind, placebo-controlled trial		and placebo group (n=25) received a dose of 80 mg/day for 12 weeks	LDL-c levels, and an increase in TAC levels compared to the placebo group. But no significant effects on ulcer length	
Darmian et al., 2021[22]	Iran	How Combined and Separate Aerobic Training and Turmeric Supplementation Alter Lipid Profile and Glycemic Status? A Clinical Trial in Middle-Aged Females with Type 2 Diabetes and Hyperlipidemia	Curcuma longa	42 female patients type 2 DM with hyperlipidemia. Divided into 4 groups, including: Aerobic + turmeric (n=11), aerobic + placebo (n=10), turmeric (n=11), and control + placebo (n=10). The dose of turmeric or placebo was 2100 mg/day for 8 weeks.	The group given turmeric supplements for 8 weeks significantly decreased, insulin, HOMA-IR, FBS, HbA1c, BMI, TG, total cholesterol, LDL-c, ApoB, GDP, and increased HDL-c and ApoA1.	
Sousa et al., 2021[23]	Brazil	Cost-Effectiveness of Passion Fruit Albedo versus Turmeric in the Glycemic and Lipaemic Control of People with Type 2 Diabetes: Randomized Clinical Trial	Curcuma longa	Group 1 (n=33) was given capsules containing 500 mg turmeric + 5 mg piperine every day. Group 2 (n=28) was given capsules containing 1500 mg passion fruit peel flour/day. Group 3 was given capsules containing placebo. The treatment was carried out for 120 days.	The group given turmeric showed a significant decrease in FBS, HbA1c (-0.8%) , HOMA-IR (-9.4%), and total cholesterol levels compared to before treatment. There was an increase in HOMA-β(+15.5%) although not significant	
Joana et al., 2021[24]	Brazil	Effectiveness of the piperine-supplemented Curcuma longa L. in metabolic control of patients with type 2 diabetes: a randomised double-blind placebo-controlled clinical trial	Curcuma longa	61 patients type 2 DM were divided into 2 groups. Curcumin + 5mg piperine (n=33) and placebo (n=28) with a dose of 500 mg/day turmeric + 5mg piperine for 120 days.	The group given curcumin capsules significantly decreased FBS, HbA1c, HOMA-IR, LDL-C and TG.	
2.B Other effect						
Panahi et al., 2017a[25]	Iran	Antioxidant effects of curcuminoids in patients with type 2 diabetes mellitus: a randomized controlled trial	Curcuma longa /curcuminoid	100 patients type 2 DM, was divided into 2 groups. The curcumin group (n=50) received 1000 mg/day + 10mg piperine and the placebo group (n=50) 1000 mg/day. Both groups were treated for 12 weeks	This study shows the antioxidant effects of curcuminoid supplementation in T2DM patients, by decreasing MDA levels and increasing TAC and SOD levels compared to the placebo group.	**Antioxidants** Curcuminoids are natural antioxidants that can provide protective effects through free radical scavenging and enhancing the biological antioxidant defense system. curcumin inhibits genes expression of inflammatory cytokines like 1, 2, 6, 8, 12 Interleukins and Tumor necrosis factor alpha (TNF-α) by inactivate Nuclear Factor Kappa Beta (NF-ƙB)[26]
Panahi et al., 2017b[27]	Iran	Curcuminoids Plus Piperine Modulate Adipokines in Type 2 Diabetes Mellitus	Curcuma longa /curcuminoid	100 patients type 2 DM, The curcumin group (n=50) received 1000 mg/day + 10mg piperine and the placebo group (n=50) 1000 mg/day. Both groups were treated for 12 weeks	Curcumin administration increased adiponectin levels compared to the placebo group and between groups showed a significant decrease in leptin levels, TNF-α, leptin: adiponectin ratio.	
Shafabakhsh, Mobini, et al., 2020[28]	Iran	Curcumin administration and the effects on psychological status and markers of inflammation and oxidative damage in patients with type 2 diabetes and coronary heart disease	Curcumin	60 patients type 2 DM with coronary heart disease (CHD). The curcumin group (n=30) and placebo group (n=30) were given a dose of 1000 mg/day of curcumin for 12 weeks.	The curcumin group experienced decreased MDA and increased TAC levels compared to the placebo group.	
Panahi et al., 2017c[29]	Iran	Curcuminoids modify lipid profile in type 2 diabetes mellitus: A randomized controlled trial	Curcuma longa /curcuminoid	100 patients type 2 DM, was divided into 2 groups. The curcumin group (n=50) received 1000 mg/day + 10mg piperine and the placebo group (n=50) 1000	The intervention group given curcumin showed significant results in decreasing total cholesterol, lipoprotein levels, and increasing HDL-c levels compared to the control group.	**Anti-hyperlipidaemia** Curcumin inhibits the replication of proteins from the pathway of adipogenesis as well as curcumin leads to

				mg/day. Both groups were treated for 12 weeks		increase resting metabolic rate (RMR). This component of turmeric have direct effects on lipid metabolism such as as reducing TG synthesis and increasing in beta oxidetion of free fatty acids with increasing metabolic rate and releases some kind of cytokines which are effective in weight loss[26].
Adibian et al., 2019 [30]	Iran	The effects of curcumin supplementation on high-sensitivity C-reactive protein, serum adiponectin, and lipid profile in patients with type 2 diabetes: A randomized, double-blind, placebo-controlled trial	Curcumin	44 patients type 2 DM, was divided into 2 groups. The curcumin and placebo groups were given a dose of 1500 mg/day for 10 weeks.	The curcumin group experienced a decrease in TG levels and a significant increase in adiponectin	
Adab et al., 2019[31]	Iran	Effect of turmeric on glycemic status, lipid profile, hs-CRP, and total antioxidant capacity in hyperlipidemic type 2 diabetes mellitus patients	Curcuma longa	75 patients type 2 DM with hyperlipidemia. Turmeric rhizome powder grup (n=36) and placebo group (n=39) with a dose of 3x700mg (2100 mg/day) for 8 weeks.	Turmeric showed a significant decrease in measurements weight, BMI TG, and LDL-c, but was not significant in levels of glycemic status.	
Srinivasan et al., 2019[32]	India	Effect of Curcuma longa on vascular function in native Tamilians with type 2 diabetes mellitus: A randomized, double-blind, parallel arm, placebo-controlled trial	Curcuma longa	114 patients type 2 DM Divided into two groups, the turmeric and placebo groups, which were given treatment for 3 months.	Treatment with turmeric significantly reduced arterial blood vessel stiffness compared to the placebo group.	**Prevent arterial stiffness** Curcumin's antioxidant and anti-inflammatory properties can activate Sirtuin 1 (SIRT1) and NRF2, which may help protect against blood vessel stiffness
Vanaie et al., 2019[33]	Iran	Curcumin as a major active component of turmeric attenuates proteinuria in patients with overt diabetic nephropathy	Curcuma longa/ curcumin	46 patients type 2 DM with albuminuria ≥300 mg/24hours and eGFR ≥30 mL/min/1.73 m^2. Divided into two groups, the curcumin group (n=27) received 3x500 mg/day capsules and the placebo group (n=19) for 16 weeks.	The curcumin group experienced a significant decrease in albuminuria levels from 900.42 ± 621.91 at the baseline to 539.68 ± 375.16 at the end of the study, but was not significant in levels of glycemic status.	**Nephroprotective effects** Curcumin, a type of polyphenol, reduces renal inflammation and fibrosis in experimental models of diabetic nephropathy (DN) and inflammatory responses, while also playing a role in oxidative stress in end-stage renal disease (ESRD).
Asadi et al., 2020[34]	Iran	Beneficial effects of nano-curcumin supplement on depression and anxiety in diabetic patients with peripheral neuropathy: A randomized, double-blind, placebo-controlled clinical trial	nano-curcumin	80 patients with type 2 DM. Divided into two groups, the nano-curcumin (n=40) and placebo group (n=40) with a dose of 80 mg/day for 8 weeks	The group given nano-curcumin experienced a significant decrease in levels of depression and anxiety score.	**Anti-depressant and reduce anxiety** The mechanism underlying the observed effects of nano-curcumin on depression may be through its potent anti-inflammatory properties targeting nuclear factor κB.
2. C The study results did not show any significant effect.						
Funamoto et al., 2019[35]	Jepang	Effects of Highly Absorbable Curcumin in Patients with Impaired Glucose Tolerance and Non-Insulin-Dependent Diabetes Mellitus	Curcumin (Theracurmin)	33 patient pre-diabetes/type 2 DM were divided into 2 groups. Curcumin capsules (n=15) and placebo (n=18) at a dose of 180 mg/day for 6 months	There was no significant change in HbA1c in either group.	

Abbreviations: FBS: fasting blood sugar, HOMA-β: Homeostatic Model Assesment of Beta Cell Function, MDA: Malondialdehyde, SOD: superoxide dismutase, TAC: total antioxidant capacity, hs-CRP: high sensitivity C-reactive protein, TG: Triglycerides, HDL: High Density Lipoprotein, VLDL: Very-low-density lipoprotein, LDL: low-density lipoprotein, BMI: Body Mass Index, PPAR-γ: peroxisome proliferator-activated receptor gamma

Table 3 List of studies using Zingiber officinale for the treatment of diabetes mellitus patients

Author	Country	Article Title	Name of plant/compound	Administration details	Results	Discussion
3.A Antidiabetic						
Arzati et al., 2017[17]	Iran	The Effects of Ginger on Fasting Blood Sugar, Hemoglobin A1c, and Lipid Profiles in Patients with Type 2 Diabetes	Zingiber officinale	45 patients type 2 DM were divided into 2 groups. Ginger powder group (n=23) and placebo group (n=22) with a dose of 2000 mg/day for 10 weeks	The ginger supplement group experienced significant reductions in FBS (-26.30 ± 35.27), HbA1c (-0.38 ± 0.35), LDL-c/HDL-c ratio, compared to the placebo group.	The antidiabetic effects of gingerol include inhibiting important enzymes associated with the management of type 2 diabetes, particularly α-glucosidase and α-amylase, increasing insulin-sensitive glucose uptake in adipocytes, and increasing glycogen storage in muscle and liver.
El Gayar et al., 2019[15]	Mesir	Effects of ginger powder supplementation on glycemic status and lipid profile in newly diagnosed obese patients with type 2 diabetes mellitus	Zingiber officinale	80 patients new-onset type 2 DM were divided into 2 groups. Ginger and placebo groups received capsules taken 3x600mg/day (1800 mg/day) for 8 weeks. Both groups were accompanied by diet, physical activity, and metformin 850 mg 2x/day	The ginger group experienced a significant decrease in FBS, HbA1c, total cholesterol, LDL-c, TG, insulin, HOMA-IR levels, and a significant increase in HDL-c, HOMA-β compared to the placebo group.	
Gholinezhad et al., 2020[36]	Iran	Using ginger supplement in adjunct with non-surgical periodontal therapy improves metabolic and periodontal parameters in patients with type 2 diabetes mellitus and chronic periodontitis: A double-blind, placebo-controlled trial	Zingiber officinale	50 patients type 2 DM with chronic periodontitis. The ginger group and placebo group were given 500 mgx4 (2 g) tablets per day for 8 weeks.	The group given ginger tablets significantly decreased HbA1c, FBS, MDA levels and increased HDL levels compared to before the intervention	
Hajimoosayi et al., 2020[37]	Iran	Effect of ginger on the blood glucose level of women with gestational diabetes mellitus (GDM) with impaired glucose tolerance test (GTT): a randomized double-blind placebo-controlled trial	Zingiber officinale	70 pregnant women aged 24-28 weeks with gestational diabetes were divided into 2 groups. The ginger group (n=37) and placebo group (n=33) were given 3x500 mg/day (1500 mg/day) for 6 weeks.	The ginger group experienced a significant decrease from baseline in FBS, insulin, and HOMA levels.	
Carvalho et al., 2020[38]	Brazil	Effectiveness of ginger in reducing metabolic levels in people with diabetes: a randomized clinical trial	Zingiber officinale	The ginger group (n=47) and placebo group (n=56) were given 2x600 mg/day (1200 mg/day) for 90 days.	The ginger group experienced decreased FBS (-29.55 ± 53.76 mg/dl) and total cholesterol levels (-11.62 ± 30.55) compared to the placebo group.	
Foroutan et al., 2021[39]	Iran	The effect of ginger on blood sugar and urine protein in patients with type 2 diabetes mellitus; a clinical trial	Zingiber officinale	The ginger group (n=48) and placebo group (n=50) were given 2x250 mg/day capsules (500 mg/day) for 12 weeks.	Ginger capsule administration significantly decreased HbA1c (-0.42%) compared to pre-treatment values and the placebo group.	
3.B Other effect						
Talaei et al., 2017[40]	Iran	The Effect of Ginger on Blood Lipid and Lipoproteins in Patients with Type 2 Diabetes: A Double-Blind Randomized Clinical Controlled Trial	Zingiber officinale	81 patients type 2 DM were divided into 2 groups. Capsules containing ginger powder (n=40) and placebo group (n=41) with a dose of 3000 mg/day for 8 weeks	Consumption of capsules containing ginger powder significantly reduced LDL-c, LDL-c/HDL-c ratio, and ApoA1 compared to before treatment.	**Lipid-lowering effects** One potential effect of ginger is the suppression of hepatic phosphorylase, which can lower hepatic glycogenolysis and enhance the activity of the enzymes responsible for advancing glycogenesis [41].
Carvalho et al., 2021[42]	Brazil	Effectiveness of Ginger in the Treatment of Type 2 Diabetes Mellitus: A Pilot Study of the Randomized Clinical Trial Type	Zingiber officinale	The ginger group (n=9) and placebo group (n=12) were given 2x600 mg/day (1200 mg/day) for 90 days.	Administration of ginger capsules did not significantly reduce blood glucose levels, but it could reduce body weight, BMI, waist circumference, and LDL	
Honarvar et al., 2019[43]	Iran	The effect of an oral ginger supplementation on NF-κB concentration in peripheral blood mononuclear cells and anthropomorphic data	Zingiber officinale	The intervention group was given capsules containing 2 grams of ginger powder/day, and the placebo group was given capsules containing	The ginger group experienced significant effects on anthropometric evaluations	

		of patients with type 2 diabetes: A randomized double-blind, placebo-controlled clinical trial		2 grams of wheat flour/day. Both groups consumed the capsules for 10 weeks		
Zarezadeh et al., 2018[44]	Iran	Asymmetric dimethylarginine and soluble inter-cellular adhesion molecule-1 serumlevels alteration following ginger supplementation in patientswith type 2 diabetes: a randomized double-blind, placebo-controlled clinical trial	Zingiber officinale	The ginger group (n=23) received 2 g of ginger powder and the placebo group (n=22) received 2 g of wheat flour for 10 weeks.	The ginger group experienced a significant decrease ADMA and ICAM-1 compared to before treatment.	**Anti-inflammatory** Gingerols are one of the ginger active components that inhibit the production of inflammation-causing prostaglandins. ADMA–NF-κB–ICAM-1 axe is a considerable process in which any interruption strongly prevents CV consequences in DM patients.
Javid et al., 2019[45]	Iran	The effects of ginger supplementation on inflammatory, antioxidant, and periodontal parameters in type 2 diabetes mellitus patients with chronic periodontitis under non-surgical periodontal therapy. A double-blind, placebo-controlled trial	Zingiber officinale	42 patients type 2 DM with chronic periodontitis. The ginger group (n=21) and placebo group (n=21) were given 500 mg (2 g) tablets per day for 8 weeks.	The group given ginger tablets significantly decreased the levels of IL-6, hs-CRP, TNF-α, and increased SOD and GPx compared to before treatment.	**Antioxidant** These findings indicate that Z. officinale may protect against oxidative damage in diabetes patients by decreasing oxidative stress and preventing antioxidant depletion.
Badooei et al., 2021[46]	Iran	Comparison of the effect of ginger and aloe vera mouthwashes on xerostomia in patients with type 2 diabetes: A clinical trial, triple-blind	Zingiber officinale	105 patients DM with xerostomia. The ginger group (n=35), aloe vera group (n=35), and placebo group (n=35) were given mouthwash 3x2 cc/day for 14 days.	The ginger and aloe vera groups significantly decreased symptoms and severity of xerostomia.	**Decreased symptoms and severity of xerostomia** Ginger in the oral cavity can increase saliva production and stimulate the salivary glands to produce more saliva.

Abbreviations: ApoA1: Apolipoprotein A1, ADMA: asymmetric dimethylarginine, BS2hpp: Blood Sugar 2 h post-prandial, ICAM-1: inter-cellular adhesion molecule-1, IL: interleukin, GPx: glutathione peroxidase