HASIL CEK_POTENTIAL PLANTS WITH ANTIDIABETIC ACTIVITY IN GLUT-4 TRANSLOCATION: A NARRATIVE REVIEW

by Sapto Yuliani, Nurkhasanah Potential Plants With Antidiabetic Activity

Submission date: 09-Oct-2023 11:22AM (UTC+0700)
Submission ID: 2189947447
File name: JIFKK_Unwahas.pdf (474.21K)
Word count: 5085
Character count: 27771

Jurnal Ilmu Farmasi dan Farmasi Klinik (JIFFK)
Supp. 1, No. 1, Juni 2023, Hal. 43-52
ISSN: 1693-7899 e-ISSN: 2716-3814

POTENTIAL PLANTS WITH ANTIDIABETIC ACTIVITY IN GLUT-4 TRANSLOCATION: A NARRATIVE REVIEW

Rabiatul Adawiyah*[1,4)], Ayu Shabrina [2)], Sapto yuliani [3)], Nurkhasanah [3)]

[1] *Postgraduate Student, Faculty of Pharmacy, Universitas Ahmad Dahlan*
[2] *Faculty of Pharmacy, Universitas Wahid Hasyim*
[3] *Faculty of Pharmacy, Universitas Ahmad Dahlan*
[4] *Medical School, Universitas Alkhairaat Palu*
Email: iyhaa.mariadjang@gmail.com

ABSTRACT

Diabetes Mellitus (DM) is a chronic disease caused by decreased pancreas activity in producing insulin. Insulin resistance is characterized by decreased synthesis and translocation of GLUT-4 to cell membranes, GLUT-4 can be found in several tissues, but mainly in muscle and adipose tissue. The purpose of this study was to identify plants that have antidiabetic activity in GLUT-4 translocation and further can be used as reference material in research. This research method is Article Review, by searching for articles published in 2013-2023 in the Pubmed, Google Scholar, Proquest, Springer Link, and Science Direct databases. The sample in this study was in the form of research articles that met the inclusion criteria and obtained 12 articles. The results of this study showed that there was significant antidiabetic activity from the administration of Ethanol Extract on 125 mg/kg BW of Salam Leaf, 200 mg/kg BW of Areca Nut, 200 mg/kg of Papaya Seed, 96 mg/kg of Black Cumin, Combination of Sambiloto Leaves and Gotu kola leaves 300 mg/kg BW, 400 mg/kg BW of Adem Ati Bark, 100 mg/kg BW of Artemisia Leaves, 250 mg/kg BW of Coffee Beans, 200 mg/kg BW of Tapak Dara Leaves, 300 mg/kg BW of Puguntano Leaves, 50 mg/kg BW of Ginger, and 200 mg/kg BW of Cinnamon. These plant extracts have antidiabetic activity as GLUT4 translocates to the plasma membrane of muscle cells. The bioactive compounds contained in them that act as antidiabetic activity are flavonoids, saponins and tannins.

Keywords: Blood Sugar Levels, Diabetes Mellitus, Extract, Glut-4 translocation

Name : Rabiatul Adawiyah
Institution : Master of Pharmacy, Universitas Ahmad Dahlan
Institution Adress: Jl. Prof. Dr. Soepomo, S.H. Janturan Yogyakarta
E-mail : iyhaa.mariadjang@gmail.com

INTRODUCTION

The International Diabetes Federation (IDF) in 2019 stated that the global estimate of diabetes mellitus prevalence worldwide was 9.3%, namely as many as 463 million and Indonesia was in 7 th place with 10.7 million sufferers. This number is projected to reach 13.7 million sufferers by 2030 (Atlas, 1955). In Indonesia, diabetes mellitus has the second highest prevalence rate after hypertension 8.5%. Further, 11.2 percent of people with diabetes 15 years live in rural areas, while 10.6 percent live in urban areas. The prevalence rate of people with diabetes mellitus in East Java Province is 2.02% (Kemenkes RI, 2018). Diabetes Mellitus (DM) is a chronic condition that occurs when the pancreas cannot produce any or enough insulin (a hormone that regulates blood glucose), or when the body cannot effectively use the insulin, it produces (Arania *et al*., 2021). Diabetes mellitus (type 1) is believed to result from the destruction of the insulin-producing β cells in the pancreas. Autoimmunity is considered the major factor in the pathophysiology of type 1 DM due to inflammation in β cells (Aren, G., *et al*. 2003). Whereas, diabetes (type 2) is defined as a group of

metabolic diseases characterized by chronic hyperglycemia, insulin resistance, and impaired insulin secretion (Ludwig *et al.*, 2020).

Type 2 DM is diagnosed by a situation termed 'insulin resistance' and deficiency of insulin secretion. Insulin resistance is identified as a condition associated with the impaired biologic response to hormone insulin stimulation of target organs. Insulin resistance is characterized by decreased synthesis and translocation of GLUT-4 to cell membranes. GLUT-4 can be found in several tissues, mainly in muscle and adipose tissue (Holloszy, 2017).

Based on a research review conducted by Nizar (2021) it was explained that plant extracts containing antioxidant compounds that have been tested have functions as anti-diabetics including flavonoids, tannins, and saponins. The hypoglycemic effect of flavonoids works by increasing the process of insulin secretion and proliferation of pancreatic beta cells, reducing apoptosis and insulin resistance, and increasing the process of translocation of Glucose Transporter Type 4 (GLUT4) (Dewinta, 2020). Apart from flavonoids, the saponin content in elephant trunk leaves also has hypoglycemic activity which works by changing insulin signals, inhibiting disaccharide activity, activating the process of glycogen synthesis, inhibiting α-glucosidase activity and gluconeogenesis, and increasing GLUT4 expression (Barky, 2017). Further, the tannins activity in lowering blood glucose levels is carried out by increasing glucose uptake through GLUT4 translocation and activation of insulin signaling pathways such as phosphoinositide 3-kinase (PI3K) and p38 Mitogen Activated Protein Kinase (MAPK) (Kumari M, 2012).

Plants that have antidiabetic activity are widely examined to find drugs for diabetes mellitus treatment. This literature study aims to determine natural ingredients including bioactive compounds contained in plants that have potential as anti-diabetic activity in GLUT 4 translocation. Based on this background, the authors are interested in reviewing articles as a source of information for the community and further research to determine the potential for planting herbs that have antidiabetic activity in GLUT-4 translocation and can be used as reference material.

RESEARCH METHOD

This study employed literature review method on research journal databases and internet searches. The databases used were Pubmed, Google Scholar, Proquest, Springer Link, and Science Direct. The keywords used in finding references to articles from several relevant studies were "Extracts, Diabetes Mellitus, Glut-4 translocation, blood sugar levels". References obtained 50 articles. Furthermore, it was examined into 12 plant articles that have potential as anti-diabetic activity. The inclusion criteria included journal research articles, discussing the potential of herbal plants as antidiabetic activity in Glut-4 translocation. More, the articles were published in the last 10 years maximum, from 2013-2023. Of the 50 articles, 38 articles were excluded because they did not discuss the potential of herbal plants as antidiabetic activity in GLUT-4 translocations. It was found that a total of 12 articles were used regarding the potential of herbal plants as antidiabetic activity in GLUT-4 translocations according to Figure 1.

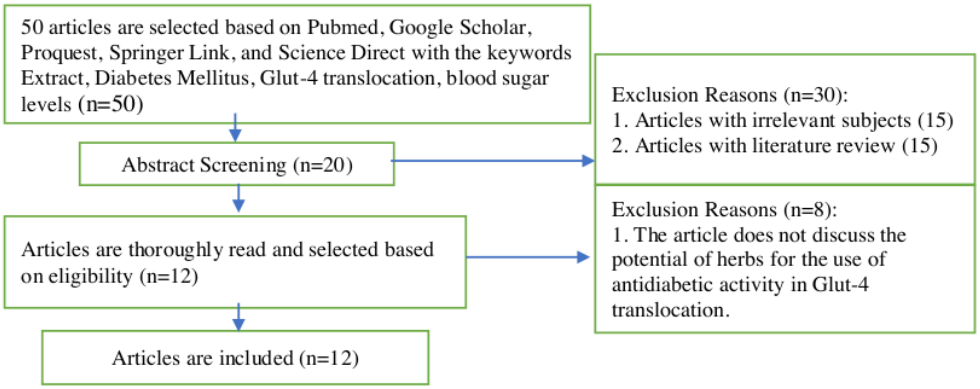

Figure 1. Flow of Research Methods

RESULTS AND DISCUSSION

Table 1. Article Search Results on Antidiabetic Activity in GLUT-4 Translocation containing Plant Extracts

No	Research Title, Year, Location	Intervention	Measurement Method	Results
1.	Effectiveness of Ethanol Extract in Bay Leaves (Eugenia polyantha) towards GLUT 4 in Adipose Tissue and Fasting Blood Sugar Levels in Male White Mice /2019/Palembang (Zanaria, *et al* 2019)	30 male white rats Group=1(normal) Provided standard food and given food and drink ad libitum. Group 2 (dose 62.5 mg/ kgBW) bay leaf extract Group 3 (dose 125 mg/ kgBW) bay leaf extract Group 4 (dose 250/ kgBW) bay leaf extract Group 5 (+) given 0.02-gram dose of Pioglithazone Group 6 (-) 2 ml of distilled water solution, The intervention was carried out for 35 days of treatment	Body weight was measured using an analytical balance and Fasting blood glucose was measured using a glucometer (Accu-Chek Performa), then mice intraperitoneally underwent an autopsy and adipose tissue was taken to examine GLUT 4 levels by ELISA.	Bay leaf ethanol extract was effective in lowering fasting blood sugar levels. The dose showed that there was different in the average GLUT 4 level between the control (-) compared to the treatment at dose 62.5, 125, 250 mg/kgbw and con14l (+). Meanwhile, the ethanol extract of bay leaves at a dose of 62.5 mg/kgbw compared to the control (+) showed no difference in mean GLUT 4 14vels, meaning that the ethanol extract of bay leaves (Eugenia polyantha) at a dose of 62.5 mg/kg and the control (+) had the same effectiveness in increasing GLUT 4 levels.

2	Effect of Papaya Seed Extract (Carica papaya Linn.) on Glucose Transporter 4 (GLUT 4) Expression of Skeletal Muscle Tissue in/Diabetic Mice Induced by High Fructose Diet/2017/Surabaya (Wulansariet al, 2017)	24 male white rats Group 1(-) No treatment Group 2 (dose 100/kgBW) papaya seed extract Group 3 (dose 200/ kgBW) papaya seed extract Group 3 (dose 300/ kgBW) papaya seed extract	GDP levels were examined using a spectrophotometer. Semiquantitative Immunoreactive score (IRS) method, with immunohistochemical staining using GLUT4 polyclonal antibodies was carried out.	Ethanol extract of papaya seeds was effective in reducing fasting blood sugar levels at all doses. The results of this data analysis showed that the GLUT4 protein expressed in immunohistochemical staining was a GLUT4 protein that translocated to the plasma membrane of skeletal muscle cells resulting in a decrease in blood glucose levels in hyperglycemic rats induced by a high-fructose diet.
3	Effectiveness of Ethanol Extract in Areca Seed towards Density GLUT4 in Mice Skeletal Muscle Cells Induced by Hyperglycemia/2017/ Bandung (Sari et al, 2017)	Male lab rats were divided into 8 groups, consisting of: Group 1 (normal) No treatment Group 2 (+) was given metformin Group 3 (-) without extract Group 4 (dose 50 mg/kgBW) areca seed extract Group 5 (dose 100 mg/kgBW) areca seed extract Group 6 (dose 150 mg/kgBW) areca seed extract Group 7 (dose 20 mg/kgBW) areca seed extract Group 8 (dose 250 mg/kgBW) areca seed extract. The intervention was carried out for 24 days.	Bradford method was applied and electrophoresis was used to detect β actin protein and GLUT4, then ImageJ software was used to quantify the band density of the two proteins. Furthermore, GLUT4 band density values were compared with β actin band density values in each group to obtain the GLUT4/β actin density ratio.	The effectiveness of the areca seed ethanol extract was proven by a better decrease in glucose levels in the treatment group given the areca seed ethanol extract at doses of 200 and 250 mg/kg BW. Areca seed ethanol extract gave significant role in increasing the density of GLUT4 in skeletal muscle cells of rats that were induced to become hyperglycemia under fasting conditions and one hour postprandial as well as may improve glucose tolerance.
4.	Effect of Black Seed (*Nigella sativa*) Extract for GLUT-4 Concentration on Wistar Strain of Albino Rat (*Rattus norvegicus*) as a Diabetes Mellitus Type 2 Model/ 2016/ Malang (Triastusi et al. 2016)	25 male white lab rats were divided into 5 groups Group 1 (-) was given 10% tween 80) Group 2 (+) was given metformin 75 mg/kg BW Group 3 (dose 24 mg/kg BW) black cumin seed extract Group 4 (dose 48 mg/kg BW) black cumin seed extract Group 5 (dose 96 mg/kg BW) black cumin seed extract The intervention was carried out for a month.	GLUT-4 concentration was measured using ELISA	Black cumin seed extract could improve blood glucose increasing insulin sensitivity, reducing oxidative stress so that it could maintain pancreatic β cells resulting in increased insulin levels, The group that had the highest average concentration of GLUT-4 in muscle tissue was Wistar white rats with type 2 DM

5.	The Effect Of Combination From Purified Extract Of Sambiloto Herb (*Andrographis Paniculata* (Burm.F.) Nees) And Pegagan Herb (*Centella Asiatica* (L.) Urban) Of Translocation Of Glut-4 Protein In Type 2 Diabetes Mellitus-Insulin Resistance Rats/2014/ Yogyakarta (Lindawati et al, 2014)	40 male white rats were divided into 8 groups: group I: combination of purified extracts of bitter herbs and gotu kola (912.1 mg/kg BW: 300 mg/kg BW) group II: combination of purified extracts of bitter herbs and gotu kola (651.5 mg/kg BW: 500 mg/kg BW) Group III: combination of purified herbal extracts Sambiloto and gotu kola (390.9 mg/kg BW: 700mg/kg BW) group IV: extract single bitter herb purification with a dose of 1303 mg/kg BW group V: extract single dose of Centella asiatica herb purified 1000 mg/kg BW group VI: positive control (given metformin at a dose of 45 mg/kg BW) group VII: negative control, (given CMC-Na 0.5%) Group VIII: normal control (non-insulin resistant rats). Intervention was carried out for 70 days.	GLUT-4 protein translocation was analyzed using the Immunohistoch emistry (IHC) method on soleus muscles.	Purified extract combination containing of *Sambiloto* herb and Centella asiatica herb (dose 912.1 mg/kg BW: 300 mg/kg BW) on GLUT-4 protein translocation in type 2 diabetes mellitus insulin resistance rats was significantly better when compared to the effect of each extract ($p<0.05$).
6	Effect of *Litsea glutinosa* (Lour.) Bark Powder C.B. Rob. towards Postprandial Blood Glucose Levels and GLUT-4 Protein Translocation in Streptozotocin and Nicotinamide Induced Rats/2015/ Yogyakarta (Dwi Utami, et al. 2015)	5 groups of rats (each group consisted of 5 rats), namely normal rats and diabetic rats were exposed to 0.5% CMC Na, and Litsea glutinosa stem bark powder at a dose of 100 µg; 200; and 400 mg/kgBW. Toxicity was done orally. The intervention was carried out for 21 days	GLUT-4 protein activity was observed by applying immunohistoche mistry method.	The results showed that administration of *Litsea glutinosa* powder doses of 100 and 400 mg/kg for 7 days significantly reduced postprandial blood glucose levels ($p<0.05$) in STZ-nicotinamide induced rats. In addition, administration of *Litsea glutinosa* at a dose of 400 mg/kgBW significantly increased GLUT-4 protein translocation in STZ-nicotinamide induced rats.

7	*Artemisia annua* Leaf Extract Increases GLUT-4 Expression in Type 2 Diabetes Mellitus Rat/2019/Semarang (Kartikadewi et al., 2019)	Twenty 6-8 weeks-old-male Wistar rats weighed 150- 200 grams. The rats were divided into four groups, which each group consisted of five rats. All single rats were placed individually in separated cages. The groups consisting of healthy control group (C1 group) was given standard diet, and diabetic control group (C2 group) was administered with placebo. Then, diabetic treatment groups were supplemented with 50 mg/ kgBW of Artemisia annua leaf extract (T1 group) and 100 mg/kgBW of Artemisia annua leaf extract (T2 group).	GLUT-4 was analyzed by immunohistoche mistry method	Muscle cell's GLUT-4 in T1 and T2 group was expressed increasingly and significantly different compared to C2 group. HbA1C level in T2 group was slightly reduced although there was found no significant different compared to diabetic control.
8	The Effect of Coffee Arabica Gayo Leaf Extract (Coffea arabica L.) in Increasing Phosphoinositide 3-kinase and Glucose Transporter-4 Expression in the Skeletal Muscle/ 2021/Sumatera Utara (Martina et al., 2021)	Thirty-five male Wistar rats with Type 2 DM (T2DM) induced using a combination of a high-fat diet for 5 weeks followed by multiple intraperitoneal injections of low-dose streptozotocin (30 mg/kg). Divided into seven groups as such two groups that did not receive treatment and five groups that received treatment. The dosage administered was 150, 200, and 250 mg/kg/day through the nasogastric tube for 30 days.	GLUT-4 expression in the skeletal muscle membrane was evaluated by Immunohistoch emistry in their gastrocnemius muscles	Coffee Arabica Gayo leaves extract (*C. arabica* L) at a dose of 250 mg/kg/day can increase the expression of GLUT-4 in the skeletal muscle membrane greater than metformin.
9	Anti-diabetic potential of Catharanthus roseus Linn. and its effect on the glucose transport gene (GLUT-2 and GLUT-4) in streptozotocin induced diabetic wistar rats/2015/Saudi Arabia (Al-Shaqha et al., 2015)	A total of 30 rats were weighted before the experiment, and they were divided into 5 groups with 6 rats per group: group 1, normal untreated rats; group 2, diabetic control rats; group 3 and group 4, diabetic rats treated with c. roseus 100 mg/kg and 200 mg/kg; and group 5, diabetic rats treated with Metformin (100 mg/kg) for 4 weeks	Real-time polymerase chain reaction (PCR) amplifications for GLUT-4 (gene ID: 25139) were conducted using Light-Cycler 480 (Roche, USA) with the SyBr ® Inucleic acid stain (Invitrogen, USA)	The observed results showed a good positive correlation between intracellular calcium and insulin release levels in isolated islets of Langerhans. The supplementation of ethanolic extract of *C. roseus* significantly amplified the expression of GLUT gene mRNA by Real Time PCR in liver of diabetic rats.

10	The Effect of Puguntano Leaf Extract (*Curanga Felterrae* Merr.) On P38 Mapk Levels and Glut-4 Expression in Type 2 Diabetic Rat Muscle /2019/Sumatera Utara (Syafril et al., 2019)	Forty-eight male Wistar rats had T2DM induced using a combination of feeding a high-fat diet for 5 weeks and multiple intraperitoneal injections of low-dose streptozotocin (30mg/kg). The diabetic rats were randomly divided into control and treatment groups, and 200 mg/kg/day *puguntano* extract was administered orally for 10 days to treatment group.	p38 MAPK levels were measured by Sandwich Elisa and plasma membrane GLUT-4 expression was evaluated by Immunohistochemistry in their gastrocnemius muscles.	There were significantly higher p38 MAPK levels and GLUT-4 expression in the treatment group than in the control group.
11	Ginger Extract Increases GLUT-4 Expression Preferentially Through AMPK Than PI3K Signalling Pathways in C2C12 Muscle Cells/2020/Iran (Kord et al., 2020)	C2C12 cells were seeded to four separate experimental groups; Control: treated with 50 mg/mL DMSO in the absence of any inhibitor; Treatment 1: treated with 50 mg/mL ethyl acetate ginger extract without any inhibitor; Treatment 2: treated with 50 mg/mL extract in the presence of 20 μM AMPK inhibitor; Treatment 3: treated with 50 mg/mL extract in the presence of 25 μM PI3K inhibitor. The amount of GLUT-4 protein (an important glucose transporter) was determined in cytosolic and membrane fractions using sodium dodecyl sulfate polyacrylamide gel electrophoresis and Western blotting.	Data were analyzed by the *Shapiro–Wilk* test and the *Kolmogorov–Smirnov* test for normality and equality of continuous distributions.	Ginger extract can affect glucose metabolism in muscle cells in vitro. The anti-diabetic effects of ginger may be by increasing GLUT-4 in the membrane fraction of differentiated C2C12 cells through AMPK and PI3K pathways, but the role of AMPK pathway is more important.
12	Effect of insulin and cinnamon extract on spatial memory and gene expression of GLUT1, 3, and 4 in streptozotocin-induced Alzheimer's model in rats/2023/ Iran (Sajadi et al., 2023)	Rats were indiscriminately separated into eight groups (n=8) including five groups of control and three experimental groups as follows: negative control (aCSF) (10 ml); insulin control (Ins); cinnamon control (Cinn); insulin and Cinn control (Cinn+Ins); STZ; treatment1 (STZ+Ins); treatment2 (STZ+Cinn); treatment3 (STZ+Ins+Cinn). aCSF was applied in all control groups. Cinn extract (orally by gavage) and Ins (icv) at doses of 200 mg/ kg and 5 mIU/5 μl for 14 days, respectively (18, 19); and STZ (icv) at a single dose of 4 mg/kg		The expression of GLUT4 mRNA in hippocampal tissue was significantly reduced in the STZ group compared with other experimental groups between treatment groups, GLUT4 mRNA expression was higher in the positive results were reflected in the MWM behavioral test.

The results of the research that articles have been reviewed showed that there is significant antidiabetic activity from the administration of 125 mg/kg BW doses of Ethanol Extract of Salam Leaves (*Eugenia Polyantha*), 200 mg/kg BW of Ethanol Extract of Areca Seeds (*Areca catechu* L),

200 mg/kg BW of Ethanol Extract of Papaya Seeds (*Carica papaya* Linn), 96 mg/kg BW of Ethanol Extract of Black Cumin (*Nigella Sativa*), Combination of *Sambiloto* Leaves Ethanol Extract (*Andrographis paniculata* (Burm. F)) and 300 mg/kg BW Ethanol Extract of Centella asiatica Leaves Extract, 400 mg/kg BW of Ethanol Extract of Adem Ati Stem Bark (*Litsea Glutinosa* (Lour.)), 100 mg/kg BW of Ethanol Extract of Artemisia (*Artemisia annua*) Leaf, 250 mg/kg BW of Ethanol Extract of Coffee Beans (*Coffea Arabica L.*), 200 mg/kg BW of Tapak Dara Leaf Ethanol Extract (*Catharanthus Roseus* L), 300 mg/kg BW Ethanol Extract of Purguntano Leaves (*Curanga fel-terrae* (Lour.) Merr), 50 mg/kg BW of Ginger Ethanol Extract (*Zingiber officinale*), and 200 mg/kg BW of Cinnamon Ethanol Extract (*Cinnamomum* sp). This effectively reduces fasting blood sugar levels and the GLUT4 protein which translocates to the plasma membrane of skeletal muscle cells resulting in a decrease in blood glucose level.

The herbal plants that have been studied aforementioned contain active compounds, namely flavonoids, saponins, and tannins which can reduce blood glucose levels. It contains active compounds called flavonoids that maintain blood glucose homeostasis and reduce insulin resistance in several ways. Flavonoids can inhibit the process of gluconeogenesis, liver glucose release, and activate the processes of glycogenesis and glycolysis so that they can regulate the body's carbohydrate metabolism, reduce serum and pancreatic islet cells thereby increasing the function of pancreatic beta cells and insulin action (Anggraeny, 2021). Flavonoids can also act as alpha-glucosidase inhibitors. The glucosidase enzyme is located in the brush border of the small intestine which breaks down carbohydrates into monosaccharides to be absorbed (Retnaningsih, 2021). If the glucosidase enzyme is inhibited, the absorption of carbohydrates obtained from food will be delayed, so that it can lower blood glucose levels after eating. Flavonoids also have a role in antioxidant activity by suppressing the apoptotic process of pancreatic Langerhans beta cells thereby improving the activity of beta cells in producing insulin (Abdullah, 2017). Flavonoids can increase muscle and liver glycogen, glucokinase and synthesis glycogen increases expression of GLUT 4 mRNA and GLUT 4 protein in striated muscle (Daisy 2009).

Further, saponins reduce blood glucose levels by activating glycogen synthesis, inhibiting disaccharide activity, modulating insulin signaling, inducing insulin regeneration, and inhibiting the process of gluconeogenesis (Barky, 2017). Meanwhile, tannins work by inducing the regeneration of pancreatic beta cells in producing insulin, increasing insulin activation through adipose cell action, and increasing glucose uptake through GLUT-4 translocation and activation of insulin signaling pathways. GLUT4 works as the main glucose transporter in skeletal muscle and adipose tissue (Kumari, 2012). Glucose uptake by muscle tissue at rest requires insulin, so it is referred to as insulin-dependent tissue. While when the muscles are active, even though there is an increase in glucose demand, insulin levels do not increase (Amar, 2009).

Skeletal muscle cells do not depend on insulin to absorb glucose, even though they need it at rest, but contracting muscles can trigger the insertion of GLUT-4 into the plasma membrane of active muscle cells even in the absence of insulin (Sherwood, 2011). Contracting muscles increase blood glucose uptake, although blood glucose levels are usually maintained by glucose production through liver glycogenolysis and gluconeogenesis and mobilization of alternative fuels, such as free fatty acids (FFA) (Yunir, 2009).

CONCLUSION

This review demonstrates the limitations in published articles on human clinical trials for medicinal plants' intervention for diabetes. In conclusion, extracts from 12 plants above can be an alternative for antidiabetic activity in GLUT-4 translocation due to the present of components for antidiabetics. The extract content of these plants can increase the expression of GLUT4 messenger ribonucleic acid (mRNA) profiles. Hence, further testing and standardization of the methods in the studies can be suggested for human clinical trials for reliable data collections such as methods of extract preparation, duration of intervention, and conditions set for the study design.

REFERENCES

Amar, M. (2009) *Insulin: mekanisme sekresi dan aspek metabolisme*. *Dalam:* 5th edn. Edited by Buku ajar ilmupenyakitdalamJilid. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam FK UI.

Abdullah N, K.K. (2017) 'In-Vitro Antidiabetic Activity of Clinacanthus nutans Extracts', *Int J Pharmacogn Phytochem*, 9(6), pp. 846–52.

Al-Shaqha, W.M.. (2015) 'Anti-diabetic potential of *Catharanthus roseus* Linn. and its effect on the glucose transport gene (GLUT-2 and GLUT-4) in streptozotocin induced diabetic wistar rats', *BMC Complementary and Alternative Medicine*, 15(1), pp. 1–8. Available at: https://doi.org/10.1186/s12906-015-0899-6.

Anggraeny EN, Cahyani IM, Retnaningsih C, Kristina V, Prahasiwi MS, N.B. (2021) 'The Effect of Aqueous Fraction of *Clinacanthusnutans* (Burm . F .) Extract Microcapsules on Rat Blood Glucose Level', 1(31), pp. 126–31.

Arania, R.. (2021) 'Hubungan Antara Pekerjaan Dan Aktivitas Fisik Dengan Kejadian Diabetes Mellitus Di Klinik Mardi Waluyo Kabupaten Lampung Tengah', *Jurnal Medika Malahayati*, 5(3), pp. 163–169. Available at: https://doi.org/10.33024/jmm.v5i3.4110.

Aren, G., Sepet, E., Ozdemir, D., Dinccag, N., Guvener, B., Firatli, E. (2003) 'Periodontal health, Saliva Status, and Metabolic Control in Children with Type 1 Diabetes mellitus', *J. Periodontol,* 12(74), pp. 1789–1795.

Atlas, I.D.F.D. (1955) *International Diabetes Federation*, *The Lancet*. Available at: https://doi.org/10.1016/S0140-6736(55)92135-8.

Barky A El, Hussein SA, Alm-Eldeen A-E, Hafez YA, M.T. (2017) 'Saponins-and-Their- Potential-Role-in-Diabetes-Mellitus', 1(7), pp. 148–58.

Dewinta NR, Mukono IS, M.A. (2020) 'Pengaruh Pemberian Ekstrak Dandang Gendis (*Clinacanthus nutans)* Terhadap Kadar Glukosa Darah pada Tikus Wistar Model Diabetes Melitus', *J Med Vet*, 3(1), p. 26.

Holloszy, J. (2017) 'Regulation by exercise of skeletal muscle content of mitochondria and GLUT4.', *Journal of Physiology and Pharmacology*, 5, p. 18.

Kartikadewi, A. (2019) '*Artemisia annua* leaf extract increases GLUT-4 expression in type 2 diabetes mellitus rat', *Indonesian Biomedical Journal*, 11(1), pp. 78–84. Available at: https://doi.org/10.18585/inabj.v11i1.531.

Kemenkes RI (2018) 'Hasil Riset Kesehatan Dasar Tahun 2018', *Kementrian Kesehatan RI*, 53(9), pp. 1689–1699.

Kord, M.T., Pourrajab, F. and Hekmatimoghaddam, S. (2020) '*Ginger* extract increases GLUT-4 expression preferentially through AMPK than PI3K signalling pathways in C2C12 muscle cells', *Diabetes, Metabolic Syndrome and Obesity*, 13, pp. 3231–3238. Available at: https://doi.org/10.2147/DMSO.S260224.

Kumari M, J.S. (2012) 'Tannins : An Antinutrient with Positive Effect to Manage Diabetes.', *Res J Recent Sci*, 1(12), pp. 70–3.

Ludwig, B. (2020) 'Large Animal Models of Diabetes', *Methods in Molecular Biology*, 2128, pp. 115–134. Available at: https://doi.org/10.1007/978-1-0716-0385-7_9.

Martina, S.J. (2021) 'The effect of coffee arabica gayo leaf extract (*Coffea arabica* L.) in increasing phosphoinositide 3-kinase and glucose transporter-4 expression in the skeletal muscle', *Open Access Macedonian Journal of Medical Sciences*, 9, pp. 906–910. Available at: https://doi.org/10.3889/oamjms.2021.5985.

Nizar, R.Z.E., Andriane, Y. and Trisnadi, S. (2021) 'Scoping Review : Efek Daun Belalai Gajah (Clinacanthus nutans) terhadap Penurunan Kadar Glukosa Darah pada Tikus Model Diabetes', *Bandung Conference Series: Medical Science*, pp. 810–819.

Olaokun, O.O. *et al*. (2014) 'The potential role of GLUT4 transporters and insulin receptors in the hypoglycaemic activity of Ficus lutea acetone leaf extract', *BMC Complementary and Alternative Medicine*, 14(1), pp. 1–12. Available at: https://doi.org/10.1186/1472-6882-14-269.

Retnaningsih C, Ananingsih VK, Anggraeny EN, Cahyani IM, Nugraheni B, E.R. (2021) 'The Effect of Clinacanthus nutans (Burm.f.) Lindau Water Fraction Addition on Hypoglycemia The Effect of Clinacanthus nutans (Burm.f.) Lindau Water Fraction Addition on Hypoglycemia.', 1, p. 292.

Sajadi, E. (2023) 'Effect of insulin and cinnamon extract on spatial memory and gene expression of GLUT1, 3, and 4 in streptozotocin-induced Alzheimer's model in rats', *Iranian Journal of Basic Medical Sciences*, 26(6), pp. 680–687. Available at: https://doi.org/10.22038/IJBMS.2023.68568.14957.

Sari, M.S. (2020) 'Skrining Potensial Pinang Aceh (Areca catechu L .) Sebagai Elevator Transporter GLUT4 dan Fitokonstituen Antiproliferatif Sel Kanker', *Herbal Medicine Journal*, 3(1), pp. 6–9.

SARI, M.S. and RIDWAN, A. (2017) 'Efektivitas Ekstrak Etanol Biji Pinang Terhadap Densitas GLUT4 pada Sel-Sel Otot Rangka Mencit yang Terinduksi Hiperglikemia', *Jurnal Sumberdaya Hayati*, 2(2), pp. 52–58. Available at: https://doi.org/10.29244/jsdh.2.2.52-58.

Sherwood L. (2011) *fisiologimanusia: dari sel kesistem*. 6th edn. Edited by EGC. Jakarta.

Sri Astutik , Endang Susantini, Madladzim, M.N. (2017) 'Digital Repository Universitas Jember Digital Repository Universitas Jember Editorial Board', *Journal of Health and Environmental Science*, 5(2), pp. 41–47.

Syafril, S. (2019) 'The effect of puguntano leaf extract (Curanga Fel - Terrae Merr.) on P38 Mapk levels and glut-4 expression in type 2 diabetic rat muscle', *Open Access Macedonian Journal of Medical Sciences*, 7(4), pp. 521–525. Available at: https://doi.org/10.3889/OAMJMS.2019.165.

Triastusi, E., Auli, M.T. and Yunita, E.P. (2016) 'Efek Pemberian Ekstrak Biji Jintan Hitam (*Nigella sativa*) Terhadap Konsentrasi GLUT-4 Pada Tikus Putih (Rattus Norvegicus) Strain Wistar Model Diabetes Melitus Tipe 2', *Jurnal Ilmiah Kesehatan Media Husada*, 5(1), pp. 01–10. Available at: https://doi.org/10.33475/jikmh.v5i1.84.

Wulansari, D.D., Basori, A. and Suhartati, S. (2017) 'Effect of Papaya Seed Extract (*Carica papaya* Linn.) on Glucose Transporter 4 (GLUT 4) Expression of Skeletal Muscle Tissue in Diabetic Mice Induced by High Fructose Diet', *Majalah Obat Tradisional*, 22(2), p. 131. Available at: https://doi.org/10.22146/tradmedj.27926.

Yety Lindawati, N., Endro Nugroho, A. and Pramono, S. (2014) 'The Effect Of Combination From Purified Extract Of Sambiloto Herb (*Andrographis paniculata* (Burm.f.) Nees) And Pegagan Herb (*Centella asiatica* (L.) Urban) Of Translocation Of Glut-4 Protein In Type 2 Diabetes Mellitus-Insulin Resistance Rats Pengaruh Komb', *Traditional Medicine Journal*, 19(2), p. 2014.

Yunir, E. (2009) *Terapinon farmakologis pada diabetes melitus*. III. Edited by ilmu penyakit dalam. Jakarta: Pusat Penerbitan Ilmu Penyakit Dalam FK UI.

Zanaria, R., Kamaluddin, M. and Theodorus, T. (2019) 'Efektivitas Ekstrak Etanol Daun Salam (*Eugenia polyantha*) terhadap GLUT 4 di Jaringan Adiposa dan Kadar Gula Darah Puasa pada Tikus Putih Jantan', *Biomedical Journal of Indonesia*, 3(3), pp. 145–153. Available at: https://doi.org/10.32539/bji.v3i3.8605.

HASIL CEK_POTENTIAL PLANTS WITH ANTIDIABETIC ACTIVITY IN GLUT-4 TRANSLOCATION: A NARRATIVE REVIEW

ORIGINALITY REPORT

9%	6%	8%	4%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Kanika Verma, Ritika Jaiswal, Sarvesh Paliwal, Jaya Dwivedi, Swapnil Sharma. "An insight into PI3k/Akt pathway and associated protein–protein interactions in metabolic syndrome: A recent update", Journal of Cellular Biochemistry, 2023 Publication	1%
2	Submitted to Trinity College Dublin Student Paper	1%
3	Mona Alaee, Ahmad Akbari, Hadi Karami, Zahra Salemi, Jamal Amri, Mitra Panahi. "Antidiabetic and protective effects of Scrophularia striata ethanolic extract on diabetic nephropathy via suppression of RAGE and S100A8 expression in kidney tissues of streptozotocin-induced diabetic rats", Journal of Basic and Clinical Physiology and Pharmacology, 2020 Publication	1%
4	www.coursehero.com Internet Source	

		1 %
5	C Retnaningsih, V K Ananingsih, Meiliana, E N Anggraeny, I M Cahyani, B Nugraheni, R Efendi. " The Effect of (Burm.f.) Lindau Water Fraction Addition on Hypoglycemia ", IOP Conference Series: Earth and Environmental Science, 2019 Publication	1 %
6	Edible Medicinal and Non Medicinal Plants, 2014. Publication	1 %
7	Efta Triastusi, Meutia Tamimi Auli, Ema Pristi Yunita. "Efek Pemberian Ekstrak Biji Jintan Hitam (Nigella Sativa) Terhadap Konsentrasi GLUT-4 Pada Tikus Putih (Rattus Norvegicus) Strain Wistar Model Diabetes Melitus Tipe 2", Jurnal Ilmiah Kesehatan Media Husada, 2016 Publication	1 %
8	www.publikasiilmiah.unwahas.ac.id Internet Source	1 %
9	Submitted to University of Wollongong Student Paper	1 %
10	www.ijnrd.org Internet Source	1 %
11	ijstm.inarah.co.id Internet Source	1 %

12	Submitted to Universiti Teknologi Petronas Student Paper	1 %
13	Submitted to Higher Education Commission Pakistan Student Paper	1 %
14	journal.stikesdrsoebandi.ac.id Internet Source	1 %

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		