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Hubungan *Selfcare* Terhadap Kualitas Hidup Pasien Diabetes Melitus Tipe 2 di RSUD Dr. Moewardi Surakarta

The Correlation of Self-care and Quality of Life Patients with Type 2 Diabetes Melitus at RSUD Dr. Moewardi, Surakarta

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Abstrak
Diabetes melitus (DM) adalah suatu kondisi yang ditandai dengan hiperglikemia yang apabila tidak ditangani dapat mengakibatkan komplikasi. Adanya komplikasi yang dialami pasien akan mengakibatkan menurunnya kualitas hidup pasien. Kualitas hidup pasien bisa terjaga apabila pasien melakukan *selfcare* dengan baik. Penelitian ini bertujuan untuk mengevaluasi korelasi antara tingkat *selfcare* dan kualitas hidup pasien diabetes melitus di instalasi rawat jalan RSUD Dr. Moewardi Surakarta. Penelitian ini menggunakan rancangan *cross-sectional*. *Selfcare* dinilai dengan menggunakan kuesioner DSMQ dan kualitas hidup pasien dengan menggunakan instrumen EQ-5D-5L. Hasil penelitian menunjukkan adanya hubungan yang signifikan antara *selfcare* dengan kualitas hidup pasien diabetes melitus tipe 2 yang ditandai dengan semakin baik tingkat *selfcare* maka semakin baik pula kualitas hidup pasien.

Kata kunci: Diabetes melitus; DSMQ; EQ-5D-5L; Kualitas hidup; *Selfcare*

Abstract
Diabetes mellitus (DM) is is a condition characterized by hyperglycemia, which, if left untreated, can lead to complications. Any complications experienced by the patient will result in a decrease in the patient's quality of life. The patient's quality of life can be maintained if the patient carries out good self-care. The aim of this study was to analyze the relationship between self-care and the quality of life of diabetes mellitus patients in the outpatient departement of RSUD Dr. Moewardi Surakarta. This research used a cross-sectional design. Selfcare was measured using the DSMQ questionnaire and patient quality of life using the EQ-5D-5L instrument. The results of the study showed that a significant association was observed between selfcare an quality of life in patient with type 2 diabetes mellitus, indicating that higher levels of selfcare contribute to better quality of life.

Keywords**:** *Diabetes mellitus; DSMQ; EQ-5D-5L; Selfcare; Quality of life*

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The Effect of Flaxseed (*Linum usitatissimum*) Ethanol Extract on LDL Cholesterol Levels and Foam Cell Number in the Aorta of Male Wistar Rats (*Rattus norvegicus*) Fed A High-Fat and High-Fructose Diet

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Abstract
A diet high in saturated fat and fructose leads to dyslipidemia, increasing atherosclerosis risk. Although lipid-lowering medications are available, they have certain limitations. Flaxseed, rich in ALA, lignans, and phytosterols, may improve lipid profiles and act as an antioxidant. This study evaluated the effectiveness of flaxseed in preventing LDL cholesterol elevation and aortic foam cell formation in male Wistar rats fed a high-fat, high-fructose (HFHF) diet. This actual experimental study used a post-test-only control group design for 35 days. Twenty-five male Wistar rats were randomly assigned to five groups: N (normal control, standard diet), K (negative control, HFHF diet), and three treatment groups (P1, P2, P3, HFHF diet) receiving flaxseed ethanol extract at doses of 200, 400, and 800 mg/kgBW/day. LDL cholesterol levels (mg/dL) and aortic foam cell counts (cells/HPF) were measured. Data were analyzed using Shapiro-Wilk and Levene tests for normality and homogeneity, followed by one-way ANOVA, Kruskal-Wallis, and Tukey-HSD post hoc tests. LDL cholesterol levels in groups N, P1, P2, and P3 were significantly lower than in group K ($p = 0.007$), with P2 showing the most significant inhibition ($p = 0.035$). Foam cell counts were lower in treatment groups than in group K ($p = 0.257$), but no significant differences were found among them. Flaxseed (*Linum usitatissimum*) ethanol extract at 400 mg/kgBW/day was the most effective in preventing an increase in LDL cholesterol. However, the extract at all three doses was ineffective in preventing an increase in aortic foam cells in male Wistar rats (*Rattus norvegicus*) fed an HFHF diet.

Keywords: Atherosclerosis; Dyslipidemia; Flaxseed; Foam cell; LDL

1. INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death worldwide, killing 17.9 million people, or 32% of all deaths. According to the WHO (2021), 85% of these deaths were caused by heart attacks and strokes (World Health Organization, 2021). Coronary heart disease (CHD) is the most common cardiac disease in adults in Indonesia. The number of people with it has grown from 0.5% in 2013 to 1.5% in 2018. Dyslipidemia, hypertension, diabetes, an unhealthy diet, a lack of exercise, an abnormal body mass index, smoking, and drinking too much alcohol are some of the things that can lead to CHD and atherosclerosis (Ministry of Health, Republic of Indonesia, 2018).

Atherosclerosis, which is when cholesterol, lipids, and/or calcium build up and harden along the walls of arteries, is a primary cause of coronary heart disease. The heart may not work as well because it does not get enough blood when this builds up. Atherosclerosis begins when small Apo-B particles, such as LDL cholesterol, clump together in the walls of arteries. This process causes foam cells to develop and plaque to accumulate through various cellular mechanisms (Juslim & Herawati, 2018; Li et al., 2022; Indonesian Heart Association, 2022). Foam cells, typically found in the tunica intima, are therefore considered an important indicator of worsening atherosclerosis (Maghfiroh et al., 2022). Dyslipidemia is a disorder characterized by abnormalities in lipid profiles, including aberrant levels of total cholesterol (TC), low-density lipoprotein (LDL), and triglycerides (TG), as well as reduced levels of high-density lipoprotein (HDL) (Ma'rufi & Rosita, 2014). Dyslipidemia causes one out of every three cases of cardiovascular disease and kills 2.6 million people. Throughout the world, LDL levels have increased, but the most significant rise has occurred in Indonesia. Because LDL contributes to atherosclerosis, this could lead to an increase in cases of the disease (Indonesian Endocrinology Association, 2021).

Modern diet habits often involve frequent consumption of food and drinks that are rich in sugar, fat, and calories. A diet high in saturated fat significantly increases LDL cholesterol levels. On the other hand, consuming a diet high in fructose disrupts the body's ability to use glucose and increases fat production through lipogenesis (Malik & Hu, 2015). Lipogenesis can lead to dyslipidemia, atherosclerosis, fatty liver, insulin resistance, and obesity (Handayani et al., 2021). Hardimarta et al. (2021) and Gileva et al. (2022) found that a diet high in saturated fat and fructose accelerates the rise in LDL cholesterol levels and foam cell formation in the aorta(Gileva et al., 2022; Hardimarta et al., 2020). A previous study by Veonika et al. (2024) reported that micronutrients could reduce lipid content (Veonika et al., 2024). Nevertheless, lipid-lowering medications are widely used despite their known limitations (Farida & Putri, 2016). The use of herbal therapy is an option due to its relatively lower cost, good efficacy, and low side effects. Flaxseed, known as linseed or by its scientific name *Linum usitatissimum*, is rich in polyunsaturated fatty acids (PUFA), phytosterols, and lignans. Flaxseed contains 41% fat (73% PUFA and 8% MUFA), 21% protein, and 28-40% fiber. It also contains vitamins, minerals, phytosterols, and lignans. The primary PUFA in flaxseed is alpha-linolenic acid (ALA) at 56.93%, followed by linoleic acid (LA) at 15.82%. Inside the body, ALA can be converted into eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which have anti-inflammatory properties, improve lipid metabolism, and support the myelination of neurons. The lignans, phytosterols, and fibers in flaxseed also contribute to better lipid profiles and help prevent atherogenic processes. Furthermore, the high levels of phytosterols and lignans in flaxseed act as antioxidants (Kanikowska et al., 2020; Shahidi et al., 2022).

Some studies have shown that flaxseed oil is effective in reducing small dense LDL (sd-LDL) levels while also significantly reducing LDL and total cholesterol (Kawakami et al., 2015). Flaxseed itself has also been linked to a reduction in the atherosclerotic process by reducing atheroma plaque formation and improving its contractility (Bujok et al., 2021). The research on the effects of commonly found flaxseed extracts on LDL cholesterol levels and the progression of atherosclerosis, particularly in Indonesia, is limited. There is a lack of specific studies investigating the effects of flaxseed extracts on LDL cholesterol levels and changes in the aortic lumen. This study aimed to investigate the effects of ethanolic flaxseed extract on LDL cholesterol levels and aortic foam cell counts in male Wistar rats fed a high-fat, high-fructose diet.

2. MATERIAL AND METHODS

2.1 Ethical clearance

This research received ethical approval from the Faculty of Medicine, University of Udayana Research Ethics Commission, with the number 2558 /UN 14.2.2.VII. 14/LT/2024.

2.2 Research design

This research is an actual experimental study with a randomized post-test-only control group design. Flaxseed extraction was conducted at the Integrated Biomedical Laboratory, Pharmacology Division, Faculty of Medicine, University of Udayana. The treatment and maintenance of the rats were carried out at the Integrated Biomedical Laboratory, Histology Division, Faculty of Medicine, University of Udayana. The phytochemical testing of flaxseed extract was conducted at the Integrated Research and Testing Laboratory of the University of Gadjah Mada. LDL cholesterol levels were measured at the Integrated Biomedical Laboratory, Biochemistry Division, Faculty of Medicine, Universitas Udayana. The histological specimens were prepared at the Anatomical Pathology Laboratory of the University of Udayana Hospital.

2.3 Flaxseed extraction and preparation of a high-fat, high-fructose diet

The flaxseed used in this study was registered with the Indonesian Ministry of Agriculture under the number KEMTAN RI PD 31.72-A.III.000-01-00634-10/21. The flaxseed extraction process began by grinding 9 kg of dried flaxseeds (Club Sehat; Jakarta, Indonesia) using a blender (Fomac; Jakarta, Indonesia). The flaxseed powder was placed in a maceration jar, and 18 L of 70% ethanol (Onemed; Sidoarjo, Indonesia) solvent was added until thoroughly soaked. The mixture was then stirred and left in a dark room for three days, with stirring performed twice daily, in the morning and evening. The residue and the maceration result were then separated using filter paper. Maceration was repeated three times, and all the maceration results obtained were combined and then evaporated using a rotatory evaporator (Hahnvapor; Gyeonggi-do, South Korea) until a thick extract was obtained (Putri, 2018).

A high-fat diet was formulated by mixing 300 grams of melted lard with 200 grams of duck egg yolk, then combining with 100 ml of distilled water to form a homogenous suspension. This suspension was administered to rats at a dose of 1 ml per day in the morning via oral gavage. The daily intake of the standard diet was monitored by weighing the food before and after feeding, allowing for the calculation of individual daily food consumption. A high-fructose diet was induced by providing a 30% fructose (Rose Brand; Bandar Lampung, Indonesia) solution in the drinking water. This high-fat, high-fructose diet was given to rats for 35 days (Harsa, 2014; Susanti et al., 2019).

2.4 Experimental animals

This study employed the Resource Equation Approach Formula to determine the minimum and maximum sample size. The minimal required sample was 3 per group (15 total), while the maximum was 5 per group (25 total). This study utilizes the maximum sample size, selecting 25 male Wistar rats bred at Laboratorium Biomedik Terpadu, Universitas Udayana, aged 2-3 months, weighing 180-200 grams, and in good health. Rats that were already ill, had died, or were not eating were excluded from the study (Kinanti et al., 2023). Samples were acclimated for one week in groups of 4-5 in a 40 x 30 x 20 cm cage with controlled ventilation, lighting, and temperature. A standard diet (feed 594) was given *ad libitum* throughout the experiment. After acclimatization, samples were divided into five groups: N (normal control) received a standard diet, K (negative control) was given a high-fat, high-fructose diet, while P1, P2, and P3 were administered a high-fat, high-fructose diet supplemented with 200, 400, and 800 mg/kg BW/day flaxseed ethanol extract for 35 days, respectively (Harsa, 2014; Rosmala et al., 2018). On the 36^{th} day, all rats were anesthetized with a mixture of 10% ketamine and 2% xylazine. Around 2 mL of blood was collected from the medial canthus of the orbital sinus for LDL cholesterol analysis. Euthanasia was performed with 2-3 times the anesthetic dose, followed by cervical dislocation. The thoracic aorta was then extracted, and the carcasses were buried.

2.5 Assessment of LDL cholesterol levels and histopathology

Blood samples of 2 ml were centrifuged using a Hettich EBA 3S (Tuttlingen, Germany) for 10-20 minutes at 3,000 rpm. Total cholesterol, HDL, and triglycerides were measured using a DiaSys Diagnostic System GmbH (Holzheim, Germany) CHOD-PAP enzymatic photometric test. LDL cholesterol levels were calculated using the Friedewald formula (LDL cholesterol (mg/dL) = Total cholesterol (mg/dL) – HDL cholesterol (mg/dL) – (Triglycerides (mg/dL)/5)). However, it has limitations and cannot be used for triglyceride levels greater than 400 mg/dL (Kumar et al., 2021).

Using a tissue processor (DEKO PATH Dk-TSM1; Shandong, China), the thoracic aorta was fixed in 10% neutral buffer formalin (Leica; Virginia, USA), dehydrated in 96% alcohol (JK Care; Jakarta, Indonesia), and cleared in xylene (Bratachem; Tangerang, Banten).

Subsequently, it was embedded in paraffin (Pro Histo; Jiangsu, China), sectioned into 4-5µm thick sections with a Leica microtome 820 (Bonn, Germany), and stained with hematoxylin and eosin (Kurniawan et al., 2022; ScyTek; Utah, USA). The prepared tissues were then examined under a microscope using the Olympus CX33 microscope with an EP50 camera (Guangzhou, China). Foam cell counts were conducted by observing under a microscope at 40x magnification to identify areas rich in foam cells and counting cells in five high-power fields (HPF) using 400x magnification (Han et al., 2015).

2.8 Statistical analysis

Data from this study were analyzed using SPSS software version 29.0.0. Descriptive analysis was presented as the mean, standard deviation (SD), minimum value (MIN), and maximum value (MAX). Data normality was assessed using the Shapiro-Wilk test, while variance homogeneity was evaluated using Levene's test. Since LDL cholesterol levels were normally distributed ($p \geq 0.05$) with homogenous variances, a one-way ANOVA was used to compare the means of three or more groups, followed by a Tukey-HSD post hoc test. The Kruskal-Wallis test was selected because the data on the number of aortic foam cells were not normally distributed ($p < 0.05$).

3. RESULTS AND DISCUSSION

A descriptive and comparative analysis of the lipid profiles (total cholesterol, triglycerides, HDL, and LDL) of rats was conducted after 35 days of a high-fat, high-fructose (HFHF) diet and flaxseed extract treatment (Table 1). Due to the prevalence of dropouts, the final analysis in this study only included 19 rats, with two rats from each treatment group (P1, P2, and P3) excluded. A descriptive analysis of LDL cholesterol levels (mean ± SD, mg/dL) across various experiments (Table 1) revealed that the normal control group (N) displayed a mean of 91.779 ± 29.780. In contrast, the negative control group (K) showed significantly elevated levels at 251.953 ± 91.111. The P1 group (200 mg/kgBW/day) exhibited a mean LDL cholesterol level of 145.788 ± 36.744, while the P2 (400 mg/kgBW/day) and P3 (800 mg/kgBW/day) groups exhibited mean levels of 112.209 ± 24.615 and 127.686 ± 56.043 mg/dL, respectively. The LDL cholesterol levels in all groups were normally distributed ($p \geq 0.05$) and showed homogeneity of variances ($p \geq 0.05$). The one-way ANOVA test yielded a p-value of 0.007 ($p < 0.05$), indicating a statistically significant difference between at least one group and all other groups compared.

The Tukey-HSD post hoc test (Table 2) revealed a significant decrease in LDL cholesterol levels between the normal control group (N) and the negative control group (K), as well as between the negative control group (K) and P2 at a dose of 400 mg/kg BW/day. There was no significant decrease in LDL cholesterol levels between the negative control and P1 ($p = 0.14$) or P3 ($p = 0.069$). A descriptive and comparative analysis of HDL levels and foam cell counts in control and treatment groups following 35 days of a high-fat, high-fructose (HFHF) diet and flaxseed extract treatment (Table 3) revealed a statistically significant difference in HDL levels ($p < 0.05$). In contrast, no significant difference was observed in foam cell counts ($p \geq 0.05$). A quantitative analysis of the phytochemical composition of the flaxseed ethanol extract, measured by spectrophotometry and gas chromatography (Table 4).

Table 1. Descriptive and comparative analysis of the lipid profiles (total cholesterol, triglycerides, HDL, and LDL) in rats after 35 days of HFHF diet and flaxseed extract treatment. *Description*: n = sample size; SD = standard deviation; p value = significance; * = significant value; N = normal control group; K = negative control group; P1 = 200 mg/kg BW/day; P2 = 400 mg/kg BW/day; P3 = 800 mg/kg BW/day.

Variable	Group	n	Mean ± SD	Minimal	Maximal	p
Total cholesterol (mg/dL)	N	5	265.745 ± 34.418	231.92	313.83	0.006*
	K	5	425.745 ± 94.325	302.13	560.64	
	P1	3	301.773 ± 55.994	243.62	355.32	
	P2	3	261.347 ± 26.368	242.55	291.49	
	P3	3	301.418 ± 38.421	259.57	335.11	
Triglycerides (mg/dL)	N	5	343.575 ± 45.956	298.32	411.17	0.16
	K	5	385.251 ± 75.146	289.94	498.88	
	P1	3	380.447 ± 110.682	272.07	493.30	
	P2	3	277.467 ± 17.366	257.54	289.39	
	P3	3	321.787 ± 49.918	281.56	377.65	
LDL (mg/dL)	N	5	91.779 ± 29.780	57.64	117.31	0.007*
	K	5	251.953 ± 91.111	120.48	372.11	
	P1	3	145.788 ± 36.744	107.02	180.10	
	P2	3	112.209 ± 24.615	96.97	140.61	
	P3	3	127.686 ± 56.043	64.60	171.70	

There were significant differences in LDL cholesterol levels among the treatment groups. The normal control group (N) had lower levels compared to the negative control group (K). In comparison, the P2 (400 mg/kg BW/day) also showed significantly lower levels compared to the negative control group (K). Descriptive analysis of foam cell counts (mean ± SD, mg/dL) across different experiments found that the normal control group (N) exhibited 0.40 ± 0.89. In contrast, the negative control group (K) showed higher levels at 1.40 ± 1.52. Among the treatment groups, P1 had foam cell counts of 0.33 ± 0.58, P2 had 0,00 ± 0.00, and P3 had 0.00 ± 0.00. The foam cell counts in all groups were not normally distributed ($p < 0.05$) but exhibited homogeneity of variances ($p \geq 0.05$). The Kruskal-Wallis test yielded a p-value of 0.15, indicating no significant difference between any of the groups compared. The histopathological features of the thoracic aorta lumen are shown in Figure 1, while those of foam cells in the tunica intima of the thoracic aorta are shown in Figure 2.

A high-fat, high-fructose (HFHF) diet consisting of duck egg yolk, lard, and 30% fructose was administered. Previous research demonstrates that these diets increase LDL-cholesterol, total cholesterol, and triglycerides, while reducing HDL-cholesterol (Harsa, 2014). This high-fat diet contains many saturated fats, which can increase LDL cholesterol levels and lead to the formation of foam cells in the aorta (Han et al., 2015). The high-fructose diet further exacerbates these effects by promoting de novo lipogenesis and impairing glucose metabolism. The diet can lead to oxidative stress, insulin resistance, and endothelial dysfunction, ultimately contributing to the development of atherosclerosis (Febrianingsih, 2019; Malik & Hu, 2015; Susanti et al., 2019). Flaxseed (Linum usitatissimum) is a good source of lignans, omega-3 fatty acids, flavonoids, and fiber. It has been shown to work to lower LDL cholesterol levels. Omega-3 fatty acids, especially alpha-linolenic acid (ALA), help cholesterol get to the liver, increase the number of LDL receptors in the liver, and change how the body uses HDL. Alpha-linolenic acid (ALA), an omega-3 polyunsaturated fatty acid (PUFA), reduces foam cell formation by inhibiting the expression of CD36 and ACAT1 while facilitating cholesterol efflux through the PPARγ/LXRα/ABCA1 pathway (Moss et al., 2016; Pizzini et al., 2017; Poznyak et al., 2021). Lignans also act as antioxidants by preventing the oxidation and absorption of LDL. Flavonoids and isoflavones also help lower cholesterol by inhibiting the body's production of cholesterol and increasing the availability of LDL receptors. Flaxseed contains phenolic compounds that work as antioxidants by neutralizing ROS and making the endothelium work better by making nitric oxide (NO). Lignans and flavonoids alter the oxidative stress pathway and reduce the number of foam cells by decreasing oxidized LDL and inhibiting the secretion of adhesion molecules. Fiber in flaxseed also helps reduce cholesterol and prevents the body from producing more cholesterol.

Table 2. Post hoc test results for total cholesterol and LDL cholesterol levels among control and treatment groups after 35 days of flaxseed ethanol extract administration in rats fed a HFHF diet. *Description*: p value = significance; * = significant value; N = normal control group; K = negative control group; P1 = 200 mg/kg BW/day; P2 = 400 mg/kg BW/day; P3 = 800 mg/kg BW/day.

Variable	Group	p
Total Cholesterol	N vs K	0.007*
	N vs P1	0.92
	N vs P2	1.00
	N vs P3	0.923
	K vs P1	0.086
	K vs P2	0.016*
	K vs P3	0.084
	P1 vs P2	0.95
	P1 vs P3	0.99
	P2 vs P3	0.99
LDL	N vs K	0.005*
	N vs P1	0.71
	N vs P2	0.99
	N vs P3	0.91
	K vs P1	0.14
	K vs P2	0.035*
	K vs P3	0.069
	P1 vs P2	0.95
	P1 vs P3	0.99
	P2 vs P3	0.99

Phytochemicals in flaxseed ethanol extract were analyzed by spectrophotometry and gas chromatography (Fadli et al., 2024). The phytochemical analysis revealed that the extract contained elevated concentrations of total phenols (4.57%) and flavonoids (0.36%). Previous studies found a high amount of omega-3, but this extract contained more omega-6 (linoleic acid, 27.53%) and less omega-3, as will be explained later. The low omega-3 concentration may be due to its susceptibility to oxidation, as it contains multiple double bonds. It can also be affected by the extraction method and the maturity of the seeds (Kauser et al., 2024; Mercola & D'Adamo, 2023). Omega-6 fatty acids in moderate amounts promote cholesterol metabolism by enhancing LDL receptor activity and affecting CYP7A1 activity through LXRα activation (Djuricic & Calder, 2021). Although omega-6 can reduce foam cells by downregulating ox-LDL uptake and cholesterol accumulation, excessive intake may induce pro-inflammatory effects and increase cardiovascular risk (Bruen et al., 2017).

Table 3. Descriptive and comparative analysis of HDL levels and foam cell counts in control and treatment groups following 35 days of flaxseed ethanol extract administration in rats fed a HFHF diet. *Description*: n = sample size; SD = standard deviation; p value = significance; N = normal control group; K = negative control group; P1 = 200 mg/kg BW/day; P2 = 400 mg/kg BW/day; P3 = 800 mg/kg BW/day.

Variable	Group	n	Median	Minimal	Maximal	p
HDL (mg/dL)	N	5	109.063	81.25	124.06	0.006*
	K	5	91.250	88.13	105.00	
	P1	3	80.938	75.56	82.19	
	P2	3	95.938	85.63	99.38	
	P3	3	112.813	81.56	133.75	
Aortic Foam Cell (cell/HPF)	N	5	0.000	0.00	2.00	0.15
	K	5	1.000	0.00	3.00	
	P1	3	0.000	0.00	1.00	
	P2	3	0.000	0.00	0.00	
	P3	3	0.000	0.00	0.00	

Our research showed that flaxseed ethanol extract significantly lowered LDL cholesterol levels ($p = 0.035$), especially at a dose of 400 mg/kg BW/day (P2) compared to the negative control (K) after 35 days. The phenolic compounds (lignans and flavonoids) and omega-6 in flaxseed extract prevented the elevation of LDL cholesterol levels. However, there were no significant differences between the negative control group (K) and the treatment groups (P1 and P3) because the dose in P1 was too low (200 mg/kg BW/day) and the dose in P3 was too high (800 mg/kg BW/day). This result aligns with that of Yang et al. (2021), who found that excessive flaxseed supplementation does not enhance its lipid-lowering effect (Yang et al., 2021). Group P2 had the lowest levels of LDL cholesterol among the treatment groups, but the differences were not statistically significant. This result suggests that increasing flaxseed extract does not offer additional benefit in lowering LDL cholesterol. The extract's higher omega-6 and lower omega-3 content may have reduced its effectiveness in lowering LDL (Yang et al., 2021). The LDL cholesterol levels in the negative control group (K) were still significantly higher ($p = 0.005$) than in the normal control group (N), indicating an adverse effect of consuming a diet high in fat and sugar. Moreover, the persistence of higher LDL cholesterol levels in the treatment groups compared to the normal control group (N) suggests that doses of 200, 400, and 800 mg/kg body weight per day were insufficient to reduce LDL levels effectively. This outcome may be related to variations in bioactive compound content (influenced by extraction method, flaxseed variety, and seed maturity), individual variability in lipid metabolism, or the relatively short duration of treatment.

The negative control and treatment groups of rats were fed a high-fat diet in addition to a standard diet (type 594) containing at least 3% fat. This diet had 300 g of lard (43.95% saturated fat) and 200 g of duck egg yolks (31.85% saturated fat) (Polat et al., 2013; Xu et al., 2016). Similar formulations in previous studies have led to substantial elevations in total cholesterol, LDL cholesterol, and triglycerides, accompanied by diminished HDL cholesterol levels (Juslim & Herawati, 2018; Harsa, 2014). Saturated fatty acids stimulate hepatic triglyceride synthesis, which in turn increases LDL and VLDL levels, thereby contributing to the development of atherosclerosis (Chan et al., 2015). The high-fructose diet (30% fructose in drinking water) increased small dense LDL (sdLDL) levels even further in three weeks, which contributed to atherosclerosis (Sanches et al., 2015). Fructose disrupts glucose and lipid metabolism, promotes visceral fat accumulation, and induces insulin resistance, leading to increased hepatic triglycerides and an increased risk of cardiovascular disease (Malik & Hu, 2015; Sanches et al., 2015).

Table 4. Quantitative analysis of the phytochemical composition of flaxseed ethanol extract, measured by spectrophotometry and gas chromatography. *Description*: % (w/w) = percent weight by weight.

Type	Parameter	Result	Unit
Phenolic content	Total Phenol	4.57	% (w/w)
	Total Flavonoid	0.36	% (w/w)
Saturated fat	Methyl arachidate	25.99	%Relative
	Methyl heneicosanoate	29.68	%Relative
	Methyl tricosanoate	0.16	%Relative
	Methyl lignocerate	0.15	%Relative
Unsaturated fat	Methyl palmitoleate	12.25	%Relative
	Methyl cis-9-oleate	4.08	%Relative
	Methyl linolelaidate	27.53	%Relative
	Methyl cis-11-eicosenoate	0.16	%Relative

Descriptive analysis revealed variations in median foam cell counts among groups, although the comparative test showed no statistically significant differences ($p = 0.26$). The negative control group (K) had the highest foam cell count in the aorta (seven cells/HPF; median=1), followed by the normal control group (N), with two cells/HPF; median=0), and the treatment group (P1) (one cell/HPF; median=0). The treatment group (P2 and P3) showed no foam cells (median = 0). The high-fat, high-fructose (HFHF) diet in K likely contributed to foam cell formation, as saturated fats and fructose promote LDL cholesterol production and lipogenesis by bypassing the phosphofructokinase enzyme (Indonesian Endocrinology Association, 2021). Foam cell formation is influenced by oxidized LDL (ox-LDL) levels, triglycerides, and smaller LDL particle size (sd-LDL). Small, dense LDL is readily recognized by macrophage scavenger receptors, enhancing foam cell development. HDL cholesterol facilitates the removal of LDL, but elevated ox-LDL impairs hepatic LDL receptor activity, thereby contributing to the formation of foam cells.

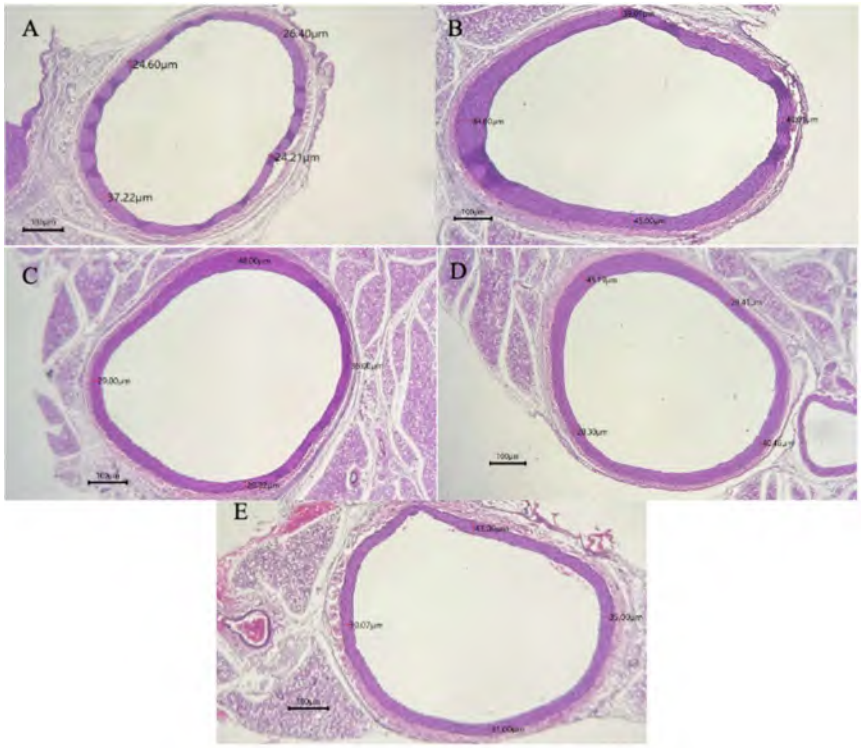

Figure 1. Histopathological features of the thoracic aorta lumen stained with Hematoxylin & Eosin (x40). (A) N; (B) K; (C) P1; (D) P2; (E) P3.

Comparative tests revealed significant differences in total cholesterol (p = 0.006) but not in triglycerides (p = 0.16) or HDL cholesterol (p = 0.06), which may partly explain the lack of differences between the K and treatment groups (Wahyuni, 2015). The LDL cholesterol measurement method used did not specifically assess ox-LDL levels, which are more relevant to foam cell formation. Additionally, the 35-day duration may have been inadequate to observe significant differences, as prolonged exposure is recognized to intensify lipid profile abnormalities, oxidative stress, and foam cell formation (Febrianingsih, 2019; Bujok et al., 2021; Malik & Hu, 2015).

The bioactive components of the flaxseed ethanol extract (phenols, flavonoids, and omega-3 alpha-linolenic acid (ALA)) may have been insufficient to prevent foam cell formation. The lower levels of ALA compared to linoleic acid (LA) and the variability in extract composition due to seed variety, farming practices, and extraction methods (Kauser et al., 2024; Mueed et al., 2022). Groups P2 and P3 did not reveal any foam cells; however, this could be attributed to the rat's overall health rather than the extract itself. Physiological factors, including genetic predisposition, oxidative stress, and chronic inflammation induced by gavage feeding and fructose water, may also contribute (Chahirou et al., 2018; Juszczyk et al., 2021). Foam cell findings could also be influenced by staining methods, such as Oil Red O and Sudan Black (Gurina & Simms, 2025).

These findings underscore the need for more extended intervention periods and optimized extract formulations to elucidate better the mechanisms by which flaxseed prevents foam cell formation.

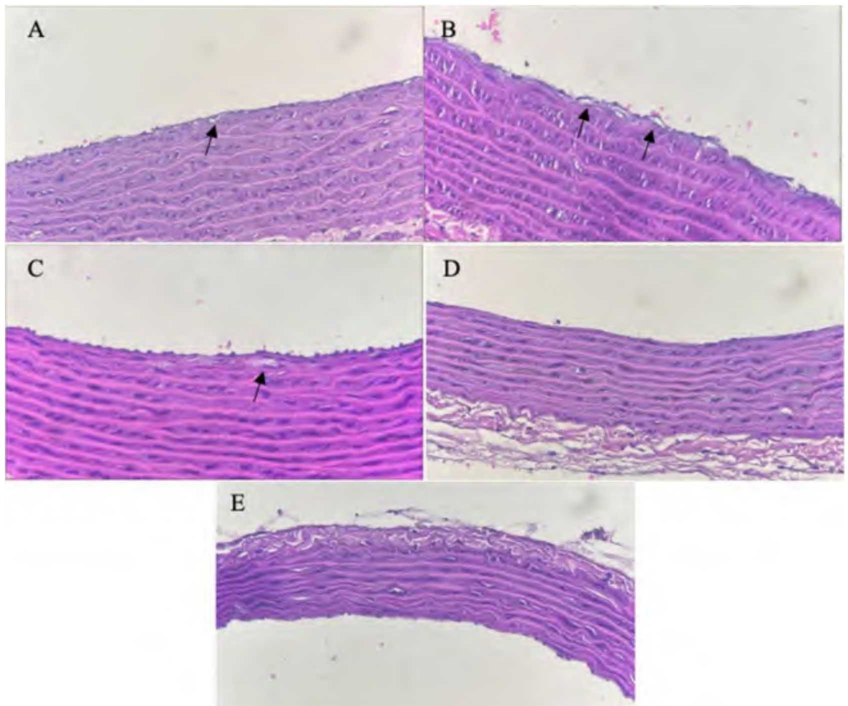

Figure 2. Histopathological features of foam cells in the thoracic aorta tunica intima stained with Hematoxylin & Eosin (x400). (A) N; (B) K; (C) P1; (D) P2; (E) P3. Arrows indicate foam cells (foamy cytoplasm and eccentric nuclei).

This study has several limitations. During the study, six rats (two from each treatment group) dropped out of the study. A statistical analysis remained feasible, as each group retained at least three rats, which is the minimum required for the sample size. The mortalities were likely associated with complications related to the oral gavage procedure, not the extract itself, as there were no signs of toxicity, changes in behavior, or unusual findings. However, other factors, including individual variability or dietary stress, cannot be completely ruled out. Oral gavage can cause aspiration pneumonia, perforation of the esophagus or stomach, and esophageal impaction. According to the Institutional Animal Care and Use Program, gavage was performed twice a day, with at least a four-hour break in between, to maintain stable cortisol levels (Institutional Animal Care and Use Program, 2023). Oral gavage method and fructose water may cause stress, which could lower 5-HT(1A) receptor levels and lead to sudden cardiac death (Chahirou et al., 2018). Flaxseed extract was not toxic, as previous studies had indicated adverse effects solely at significantly elevated doses (>5 g/kg body weight/day)

(Es-said et al., 2022). The lack of quantitative measurement of oxidized LDL (ox-LDL), a critical component in foam cell formation, coupled with the absence of phytochemical analysis of lignans and phytosterols, hinders the understanding of their roles in cholesterol metabolism. Subsequent research should encompass extended study durations, incorporate phytochemical analyses of lignans and phytosterols, and utilize comprehensive lipid profiling, particularly ox-LDL measurements, to enhance the evaluation of flaxseed extract's influence on atherosclerosis progression.

4. CONCLUSION

This study found that flaxseed extract lowered LDL cholesterol levels in Wistar rats on a high-fat, high-fructose (HFHF) diet, particularly at a dose of 400 mg/kg body weight per day. This effect was caused by the bioactive compounds in flaxseed, including phenolics, flavonoids, and omega-6 fatty acids. However, both lower and higher doses failed to offer additional benefits, suggesting a dose-dependent threshold for efficacy. Although LDL cholesterol levels decreased, there were no significant differences in foam cell formation among the treatment groups; this may be attributed to the relatively short study duration and variations in the bioactive components of the flaxseed ethanol extract. In addition, the high-fat, high-fructose (HFHF) diet also significantly elevated LDL cholesterol, confirming its role in promoting dyslipidemia and atherosclerosis.

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CONFLICT OF INTEREST

All authors declared that this study was carried out without any commercial or financial associations that could be perceived as a potential conflict of interest.

DECLARATION OF GENERATIVE AI IN SCIENTIFIC WRITING

All authors declared that generative AI and AI-assisted technologies were used in preparing this manuscript only to improve language, grammar, and readability. The authors have reviewed and approved the final version of the manuscript and take full responsibility for its content.

REFERENCES

Bruen, R., Fitzsimons, S., & Belton, O. (2017). Atheroprotective effects of conjugated linoleic acid. *British Journal of Clinical Pharmacology*, *83*(1), 46–53. https://doi.org/10.1111/bcp.12948

Bujok, J., Mista, D., Wincewicz, E., Kroliczewska, B., Dzimira, S., & Zuk, M. (2021). Atherosclerosis Development and Aortic Contractility in Hypercholesterolemic Rabbits

Supplemented with Two Different Flaxseed Varieties. *Bioactive/Nutraceutical Compounds in Plant Foods*, *10*(3), Article 534. https://doi.org/10.3390/foods10030534

Chahirou, Y., Lamtai, M., Mesfioui, A., Ouichou, A., Coulibaly, M., Boussekkour, R., & El Hessni, A. (2018). Impact of the Association of a High Fructose Diet and Chronic Mild Stress on Metabolic and Affective Disorders in Male Rat. *Journal of Behavioral and Brain Science*, *08*(04), 157–170. https://doi.org/10.4236/jbbs.2018.84010

Chan, J., Karere, G. M., Cox, L. A., & VandeBerg, J. L. (2015). Animal Models of Diet-induced Hypercholesterolemia. InTech. https://doi.org/10.5772/59610

Djuricic, I., & Calder, P. C. (2021). Beneficial Outcomes of Omega-6 and Omega-3 Polyunsaturated Fatty Acids on Human Health: An Update for 2021. *Nutrients*, *13*(7), Article 2421. https://doi.org/10.3390/nu13072421

Es-said, S., Lafhal, K., Elkhiat, A., Hammoud, M., Regbaoui, N., Ezoubeiri, A., Makbal, R., Sbyea, S., Elhiba, O., Sellami, S., Rais, H., Karim, A., Gamrani, H., Rada, N., Bouskraoui, M., & Fdil, N. (2022). Flaxseed extract reduces tissue accumulation and enhances urinary excretion of chondroitin sulphate in the rat: a possible new path in substrate reduction therapy for mucopolysaccharidosis. *Pharmaceutical Biology*, *60*(1), 879–888. https://doi.org/10.1080/13880209.2022.2068618

Fadli, J. C., Guntarti, A., Salamah, N. (2024). Autentikasi Minyak Biji Jagung *Zea mays* L.: Pengaruh Metode Ekstraksi dan Analisis Komposisi Menggunakan Metode Gas Cromatography-Mass Spectrometry (GC-MS). *Journal of Pharmaceutical Science and Clinical Research*, *9*(2), 256-267. https://doi.org/10.20961/jpscr.v9i2.85367

Farida, Y., Putri, C.I.P. (2016). Efek Penggunaan Simvastatin terhadap Kenaikan Gula Darah Puasa Pasien Diabetes Melitus Tipe 2. *Journal of Pharmaceutical Science and Clinical Research*, *1*(1), 58-65.

Febrianingsih, E. (2019). Pengaruh Pemberian Diet High Fat High Fructose terhadap Jumlah Sel Busa dan Ketebalan Dinding pada Aorta Tikus Sprague Dawley Jantan Model Obesitas Pengaruh Pemberian Diet High Fat High Fructose terhadap Jumlah Sel Busa dan Ketebalan Dinding pada Aorta Tikus Sprague Dawley Jantan Model Obesitas (Thesis). Universitas Brawijaya, Malang.

Gileva, O. G., Butolin, E. G., Tereshchenko, M. V., & Ivanov, V. G. (2022). Evaluation of indicators of carbohydrate and lipid metabolism in rats depending on the type of high-calorie diet. *Obesity and Metabolism*, *19*(1), 47–52. https://doi.org/10.14341/omet12712

Gurina, T. S., & Simms, L. (2025). *Histology, Staining*. Florida: StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557663/

Han, H., Yan, P., Chen, L., Luo, C., Gao, H., Deng, Q., Zheng, M., Shi, Y., & Liu, L. (2015). Flaxseed Oil Containing α-Linolenic Acid Ester of Plant Sterol Improved Atherosclerosis in ApoE Deficient Mice. *Oxidative Medicine and Cellular Longevity*, *2015*, 1–17. https://doi.org/10.1155/2015/958217

Handayani, D., Febrianingsih, E., Desi Kurniawati, A., Kusumastuty, I., Nurmalitasari, S., Widyanto, R. M., Oktaviani, D. N., Maghfirotun Innayah, A., & Sulistyowati, E. (2021). High-Fructose Diet Initially Promotes Increased Aortic Wall Thickness, Liver Steatosis, and Cardiac Histopathology Deterioration, but Does Not Increase Body Fat Index. *Journal of Public Health Research*, *10*(2), Article 2181. https://doi.org/10.4081/jphr.2021.2181

Hardimarta, F. P., Ikawati, K., & Yuniarti, C. A. (2020). Perbaikan Gambaran Lesi Aterosklerotik Dengan Pemberian Ekstrak Beta Vulgaris Pada Tikus Model Diet Atherogenik. *Media Farmasi Indonesia*, *15*(1), 1571-1577. https://doi.org/10.53359/mfi.v15i1.140

Harsa, I. M. S. (2014). Efek Pemberian Diet Tinggi Lemak terhadap Profil Lemak Darah Tikus Putih (Rattus novergicus). *Jurnal Ilmiah Kedokteran*, *3*(1), 21-28.

Indonesian Endocrinology Association. (2021). *Pedoman Pengelolaan Dislipidemia di Indonesia*. Available from: https://pbperkeni.or.id/wp-content/uploads/2022/02/23-11-21-Website-Panduan-Dislipidemia-2021-Ebook.pdf. [Accessed April 5, 2024]

Indonesian Heart Association. (2022). *Panduan Tata Laksana Dislipidemia*. Available from: https://www.inaheart.org/storage/guideline/7f75cffa237e402536f3d425012d985d.pdf. [Accessed April 5, 2024]

Institutional Animal Care and Use Program. (2023). Oral Gavage in Mice and Rats IACUC Standard Procedure. Available from: https://iacuc.ucsf.edu/sites/g/files/tkssra16261/files/wysiwyg/STD%20PROCEDURE%20-%20Misc%20Rodent%20Procedures%20-%20Oral%20Gavage%20In%20Mice%20and%20Rats.pdf. [Accessed 10th January 2025]

Juslim, R. R., & Herawati, F. (2018). *Penyakit Kardiovaskular*. Yogyakarta: Graha Ilmu.

Juszczyk, G., Mikulska, J., Kasperek, K., Pietrzak, D., Mrozek, W., & Herbet, M. (2021). Chronic Stress and Oxidative Stress as Common Factors of the Pathogenesis of Depression and Alzheimer's Disease: The Role of Antioxidants in Prevention and Treatment. *Antioxidants*, *10*(9), Article 1439. https://doi.org/10.3390/antiox10091439

Kanikowska, D., Korybalska, K., Mickiewicz, A., Rutkowski, R., Kuchta, A., Sato, M., Kreft, E., Fijałkowski, M., Gruchała, M., Jankowski, M., Breborowicz, A., & Witowski, J. (2020). Flaxseed (Linum Usitatissimum L.) Supplementation in Patients Undergoing Lipoprotein Apheresis for Severe Hyperlipidemia—A Pilot Study. *Nutrients*, *12*(4), Article 1137. https://doi.org/10.3390/nu12041137

Kauser, S., Hussain, A., Ashraf, S., Fatima, G., Ambreen, Javaria, S., Abideen, Z. U., Kabir, K., Yaqub, S., Akram, S., Shehzad, A., & Korma, S. A. (2024). Flaxseed (Linum usitatissimum); phytochemistry, pharmacological characteristics and functional food applications. *Food Chemistry Advances*, Article 100573. https://doi.org/10.1016/j.focha.2023.100573

Kawakami, Y., Yamanaka-Okumura, H., Naniwa-Kuroki, Y., Sakuma, M., Taketani, Y., & Takeda, E. (2015). Flaxseed oil intake reduces serum small dense low-density lipoprotein concentrations in Japanese men: a randomized, double blind, crossover study. *Nutrition Journal*, *14*(1), Article 39. https://doi.org/10.1186/s12937-015-0023-2

Kinanti, A. P., Lestari, A., Nabilah, Z. M., Maulida, R., Widiastuti, T. C., Kiromah, N. Z. W. (2023). Uji Aktivitas Antidiabetes Ekstrak Etanol Daun Ganitri (Elaeocarpus ganitrus Roxb.) Pada Tikus Wistar Jantan (Rattus norvegicus) Yang Diinduksi Streptozotocin. *Journal of Pharmaceutical Science and Clinical Research*, *8*(1), 139-151. https://doi.org/10.20961/jpscr.v8i1.64771

Kumar, N., Aithal, A. P., & Verma, S. (2021). Morphohistological analysis of the prevalence and distribution of atheroma in the abdominal aorta and its branches: a cadaveric study.

Journal Vascular Brasileiro, *20*, Article e20210014. https://doi.org/10.1590/1677-5449.210014

Kurniawan, D. W., Lestari, N. D., Sulistyo, H., Cacu. (2022). Pengaruh Pemberian Kombinasi Ekstrak Etanol Brotowali, Sambiloto, Meniran dan Kayu Manis Terhadap Histopatologi Glomerulus Tikus Model Hiperglikemia. *Journal of Pharmaceutical Science and Clinical Research*, *7*(3), 294-306. https://doi.org/ 10.20961/jpscr.v7i3.51501

Li, M. Q., Jiao, Q. Z., Xin, W. Q., Niu, S. L., Liu, M. M., Song, Y. X., Wang, Z. G., Yang, X. Y., & Liang, D. G. (2022). The Emerging Role of Rho Guanine Nucleotide Exchange Factors in Cardiovascular Disorders: Insights into Atherosclerosis: A Mini Review. *Frontiers Cardiovascular Medicine*, *8*, Article 782098. https://doi.org/10.3389/fcvm.2021.782098

Maghfiroh, R. M., Hariani, D., & Khaleyla, F. (2022). Efektivitas Ekstrak Daun Pepaya Jepang (Cnidoscolus aconitifolius) terhadap Kadar Kolesterol dan Histologi Aorta Mencit Hiperkolesterolemia. *LenteraBio*, *11*(1), 89–100. https://doi.org/10.26740/lenterabio.v11n1.p89-100

Malik, V. S., & Hu, F. B. (2015). Fructose and Cardiometabolic Health. *Journal of the American College of Cardiology*, *66*(14), 1615–1624. https://doi.org/10.1016/j.jacc.2015.08.025

Ma'rufi, R., & Rosita, L. (2014). Hubungan Dislipidemia dan Kejadian Penyakit Jantung Koroner. *JKKI*, *6*(1), 48–52.

Mercola, J., & D'Adamo, C. R. (2023). Linoleic Acid: A Narrative Review of the Effects of Increased Intake in the Standard American Diet and Associations with Chronic Disease. *Nutrients*, *15*(14), Article 3129. https://doi.org/10.3390/nu15143129

Ministry of Health, Republic of Indonesia. (2018). *Laporan Riset Kesehatan Dasar*. Available from: https://repository.badankebijakan.kemkes.go.id/id/eprint/3514/1/Laporan%20Riskesdas%202018%20Nasional.pdf. [Accessed April 24, 2024].

Moss, J. W. E., Davies, T. S., Garaiova, I., Plummer, S. F., Michael, D. R., & Ramji, D. P. (2016). A Unique Combination of Nutritionally Active Ingredients Can Prevent Several Key Processes Associated with Atherosclerosis In Vitro. *PLoS ONE*, *11*, Article e0151057. https://doi.org/10.1371/journal.pone.0151057

Mueed, A., Shibli, S., Korma, S. A., Madjirebaye, P., Esatbeyoglu, T., & Deng, Z. (2022). Flaxseed Bioactive Compounds: Chemical Composition, Functional Properties, Food Applications and Health Benefits-Related Gut Microbes. *Foods*, *11*(20), Article 3307. https://doi.org/10.3390/foods11203307

Pizzini, A., Lunger, L., Demetz, E., Hilbe, R., Weiss, G., Ebenbichler, C., & Tancevski, I. (2017). The Role of Omega-3 Fatty Acids in Reverse Cholesterol Transport: A Review. *Nutrients*, *9*(10), Article 1099. https://doi.org/10.3390/nu9101099

Polat, E. S., Citil, O. B., & Garip, M. (2013). Fatty acid composition of yolk of nine poultry species kept in their natural environment. *Animal Science Papers and Reports*, *31*(4), 363–368.

Poznyak, A. V., Nikiforov, N. G., Starodubova, A. V., Popkova, T. V., & Orekhov, A. N. (2021). Macrophages and Foam Cells: Brief Overview of Their Role, Linkage, and Targeting Potential in Atherosclerosis Macrophages and Foam Cells: Brief Overview of

Their Role, Linkage, and Targeting Potential in Atherosclerosis. *Biomedicines*, *9*(9), Article 1221. https://doi.org/10.3390/biomedicines9091221

Putri, D. A. (2018). Pengaruh Pemberian Ekstrak Etanol Biji Rami (Linum usitatissimum L.) dengan Fibroblast Growth Factor (FGF) Dari Telur Ayam Terfertilisasi Terhadap Kadar Glukosa Darah Mencit Putih Jantan Hiperglikemia (Thesis). STFI Yayasan Perintis, Padang.

Rosmala, A. Z., Asmara, I. G. Y., & Widiastuti, I. A. E. (2018). Perbedaan Hasil Pengukuran Kadar Kolesterol LDL antara Metode Direk dan Indirek dengan Menggunakan Rumus Friedewald pada Tikus Putih (Rattus norvegicus). *Unram Medical Journal*, *7*(3), 1-4. https://doi.org/10.29303/jku.v7i3.178

Sanches, S. C. L., Ramalho, L. N. Z., Augusto, M. J., da Silva, D. M., & Ramalho, F. S. (2015). Nonalcoholic Steatohepatitis: A Search for Factual Animal Models. *BioMed Research International*, *2015*, 1–13. https://doi.org/10.1155/2015/574832

Shahidi, S., Mahmoodi, M. S., Komaki, A., & Sadeghian, R. (2022). The comparison of omega-3 and flaxseed oil on serum lipids and lipoproteins in hyperlipidemic male rats. *Heliyon*, *8*(6), Article e09662. https://doi.org/10.1016/j.heliyon.2022.e09662

Susanti, N., Rahmawati, E., & Aprinda, R. K. (2019). Efek Diet Tinggi Fruktosa terhadap Profil Lipid Tikus Rattus Rattus norvegicus Strain Wistar. *Journal of Islamic Medicine*, *3*(2), 26–35.

Veonika, D. A., Wiboworini, B., Muthmainah. (2024). Cholecalciferol Effects on Lipid Profile of Experimental Animals: A Scoping Review. *Journal of Pharmaceutical Science and Clinical Research*, *9*(1), 33-44. https://doi.org/10.20961/jpscr.v9i1.73400

Wahyuni, S. (2015). *Dislipidemia* (1st ed., Vol. 1). Denpasar: Udayana University Press.

World Health Organization. (2021). *Cardiovascular diseases (CVDs)*. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds). [Accessed July 24, 2024].

Xu, L. Z., Gao, F., Yang, Z. L., Han, L. J., & Liu, X. (2016). Discriminant analysis of terrestrial animal fat and oil adulteration in fish oil by infrared spectroscopy. *International Journal of Agricultural and Biological Engineering,* *9*(3), 179–185. https://doi.org/10.3965/j.ijabe.20160903.2239

Yang, C., Xia, H., Wan, M., Lu, Y. F., Xu, D. F., Yang, X., Yang, L. G., & Sun, G. J. (2021). Comparisons of the effects of different flaxseed products consumption on lipid profiles, inflammatory cytokines and anthropometric indices in patients with dyslipidemia related diseases: systematic review and a dose–response meta-analysis of randomized controlled trials. *Nutrition & Metabolism*, *18*(1), Article 91. https://doi.org/10.1186/s12986-021-00619-3

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Eksplorasi Potensi Antidiabetes *Gynura procumbens*: Analisis Bibliometrik Berbasis Data Scopus

Exploration of the Antidiabetic Potential of Gynura procumbens: A Bibliometric Analysis Based on Scopus Data

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Abstrak
Gynura procumbens (Lour.) Merr., tumbuhan tropis dari famili Asteraceae, telah lama digunakan dalam pengobatan tradisional untuk berbagai penyakit. Studi praklinis menunjukkan potensi *G. procumbens* sebagai agen antidiabetes, yang relevan dengan tren peningkatan kasus diabetes melitus (DM) secara global. Penelitian ini bertujuan mengevaluasi perkembangan riset praklinis *G. procumbens* sebagai agen antidiabetes melalui analisis bibliometrik berbasis data Scopus. Sebanyak 23 artikel terpilih (2000–2024) dianalisis menggunakan perangkat lunak VOSviewer. Analisis meliputi pemetaan tren publikasi, jaringan keterkaitan kata kunci (*keyword co-occurrence*), distribusi negara dan institusi, artikel paling berpengaruh, hubungan referensi bersama (*bibliographic coupling*), dan kutipan bersama (*co-citation*). Hasil menunjukkan peningkatan tren publikasi sejak tahun 2000, dengan Malaysia sebagai kontributor utama, khususnya Universiti Sains Malaysia. Tema utama mencakup efek hipoglikemik, mekanisme molekuler, identifikasi senyawa aktif, serta potensi unik dalam meningkatkan fertilitas pada kondisi DM—suatu arah riset yang jarang ditemukan pada agen antidiabetes lain. Perkembangan penelitian bergerak dari studi ekstrak kasar menuju formulasi inovatif seperti nanopartikel. Analisis *bibliographic coupling* dan *co-citation* mengungkap keterkaitan antar tema, membentuk empat klaster utama yang saling beririsan. Studi ini mengidentifikasi celah penting, termasuk kurangnya data toksikologi kronis dan profil farmakokinetik. Temuan pada penelitian ini menegaskan *G. procumbens* sebagai kandidat terapi antidiabetes berbasis bukti ilmiah, dengan peluang pengembangan pada terapi komplikasi reproduksi akibat DM. Temuan ini menyediakan peta tematik yang dapat dimanfaatkan peneliti untuk merancang studi multidisiplin, mempercepat pemahaman mekanisme kerja, dan mendorong pengembangan formulasi *G. procumbens* yang efektif dan aman untuk aplikasi klinis.

Kata kunci: Antidiabetes; Bibliometrik; Farmakologi; *Gynura procumbens*; Profertilitas

Abstract
Gynura procumbens (Lour.) Merr., a tropical plant from the Asteraceae family, has long been used in traditional medicine for various ailments. Preclinical studies highlight its potential as an antidiabetic agent, aligning with the global rise in diabetes mellitus (DM). This study evaluates the development of preclinical research on G. procumbens through a bibliometric analysis using Scopus data. Twenty-three articles (2000–2024) were analyzed with VOSviewer to map publication trends, keyword co-occurrence, productive countries and institutions, most

influential articles, bibliographic coupling, and co-citation networks. Results show an increasing publication trend since 2000, with Malaysia—particularly Universiti Sains Malaysia—as the main contributor. Major research themes include hypoglycemic effects, molecular mechanisms, active compound identification, and a distinctive potential to improve fertility in diabetic conditions—a unique feature among other antidiabetic agents. The research trajectory progressed from crude extract studies to innovative formulations such as nanoparticles. Bibliographic coupling and co-citation analyses revealed thematic linkages, forming four interconnected clusters. Key research gaps include limited chronic toxicology and pharmacokinetic data. These findings reinforce G. procumbens as an evidence-based candidate for antidiabetic therapy, with promising applications in managing diabetes-related reproductive complications. This bibliometric mapping provides a thematic roadmap to guide future multidisciplinary studies, deepen mechanistic insights, and accelerate the development of effective and safe G. procumbens formulations for clinical use.

Keywords: *Antidiabetic; Bibliometric; Pharmacology; Gynura procumbens; Profertility*

1. PENDAHULUAN

Gynura procumbens (Lour.) Merr., anggota famili *Asteraceae* yang dikenal dengan nama "Sambung Nyawa," merupakan tumbuhan yang tumbuh subur di negara-negara beriklim tropis dan subtropis seperti Indonesia, Malaysia, Vietnam, dan China (Septaningsih et al., 2022). Tumbuhan ini telah lama dimanfaatkan secara tradisional untuk mengobati berbagai penyakit. Beberapa klaim khasiatnya telah dibuktikan melalui penelitian farmakologi, antara lain aktivitas antibakteri (Amin et al., 2021), antihiperlipidemia (Ahmad Nazri et al., 2019; Nath et al., 2023) antihiperglikemik (Choi et al., 2016; Sathiyaseelan et al., 2021), dan antihipertensi (Abrika et al., 2013). Saat ini, *G. procumbens* semakin mendapat perhatian sebagai kandidat terapi antidiabetes karena efektivitasnya yang telah dibuktikan secara ilmiah dengan berbagai penelitian praklinis (Tahsin et al., 2022). Hal ini sejalan dengan meningkatnya prevalensi diabetes melitus (DM) secara global, yang diperkirakan mencapai 693 juta penderita pada tahun 2045 (Cho et al., 2018).

Penelitian praklinis terkait aktivitas antidiabetes *G. procumbens* telah mencakup berbagai pendekatan. Studi *in vivo* melaporkan aktivitas antihiperglikemik tumbuhan ini (Algariri et al., 2013), sedangkan penelitian *in vitro* menunjukkan penghambatan enzim α-glukosidase dan α-amilase yang berperan dalam metabolisme glukosa (Choi et al., 2016). Selain itu, studi molekuler mengungkap mekanisme perbaikan sensitivitas insulin (Guo et al., 2021a). Namun, aspek analisis terhadap tren riset, pemetaan fokus penelitian, serta identifikasi gap penelitian masih belum banyak dikaji.

Analisis bibliometrik dapat menjawab kebutuhan tersebut. Metode ini mampu mengidentifikasi pola publikasi, tema dominan, serta kolaborasi institusional dan geografis dalam suatu bidang riset, berdasarkan data publikasi ilmiah yang dapat diperoleh dari berbagai basis data seperti *Scopus* atau *Web of Science* (Bamel et al., 2020). Studi-studi sebelumnya telah memanfaatkan analisis bibliometrik untuk tumbuhan obat lain, seperti *Tinospora crispa* (Arifah et al., 2023) dan *Piper betel* (Mandal et al., 2024), guna melihat dinamika riset dan arah pengembangan ke depan. Perkembangan penggunaan bibliometrik dalam eksplorasi herbal mencerminkan urgensi pendekatan ini dalam merumuskan prioritas riset, termasuk dalam konteks pengembangan fitofarmaka (Bamel et al., 2020).

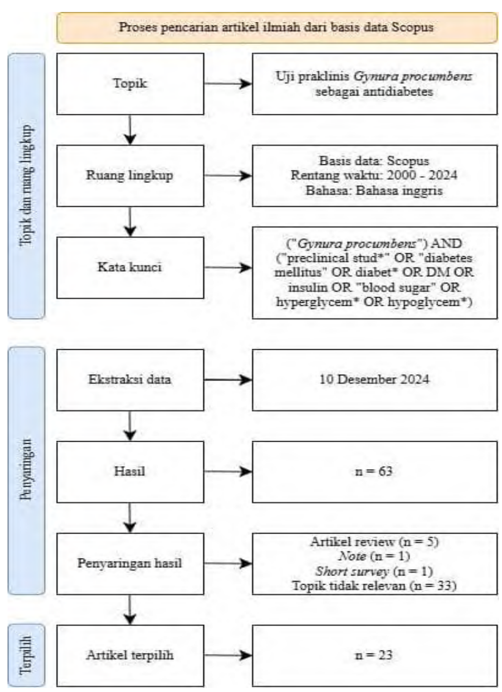
Oleh karena itu, penelitian ini bertujuan untuk melakukan analisis bibliometrik terhadap riset praklinis *G. procumbens* sebagai antidiabetes. Melalui pemetaan tren publikasi dan jaringan keterkaitan ilmiah, studi ini diharapkan dapat memberikan gambaran komprehensif mengenai perkembangan riset serta mengidentifikasi potensi celah yang penting untuk ditindaklanjuti dalam penelitian masa depan.

2. BAHAN DAN METODE

2.1. Sumber data

Bahan penelitian ini diperoleh dengan menggunakan basis data Scopus. Pencarian artikel dilakukan pada tanggal 10 Desember 2024 dengan kata kunci sebagai berikut: ("*Gynura procumbens*") AND ("*preclinical stud**" OR "*diabetes mellitus*" OR diabet* OR DM OR insulin OR "*blood sugar*" OR *hyperglycem** OR *hypoglycem**). Kriteria inklusi yang digunakan dalam studi ini adalah artikel ilmiah yang bersumber dari basis data Scopus, dengan tipe dokumen berupa *original article* atau *conference paper*, ditulis dalam bahasa Inggris, dan memiliki topik yang relevan dengan *G. procumbens* sebagai agen antidiabetes pada tingkat praklinis.

Adapun kriteria eksklusi meliputi dokumen yang bertipe *review article*, *note*, *short survey*, buku, dan bab dalam buku, serta artikel yang tidak memiliki relevansi langsung terhadap aktivitas antidiabetes *G. procumbens*. Artikel-artikel tersebut dikeluarkan dari dataset akhir pada tahap penyaringan, sebagaimana ditampilkan dalam diagram alir proses pencarian literatur (Gambar 1).



Gambar 1. Diagram alir proses pencarian artikel dari basis data Scopus (2000–2024) mengenai potensi antidiabetes *G. procumbens* (Arifah et al., 2023).

2.2. Ekstraksi dan analisis data

Pada proses awal pencarian artikel, ditemukan 63 artikel yang terbit antara tahun 2000 hingga 2024. Sejumlah 63 artikel tersebut disimpan dalam format ".CSV". Setelah melalui proses seleksi berdasarkan kriteria inklusi dan eksklusi, diperoleh 23 artikel yang memenuhi syarat untuk dianalisis lebih lanjut. Kemudian dilakukan *data cleaning* menggunakan perangkat lunak *Open Refine*. *Data cleaning* bertujuan untuk meningkatkan kualitas data dengan menghapus duplikasi data, deteksi dan koreksi kesalahan ketik, dan standardisasi format data (Mozzherin et al., 2024).

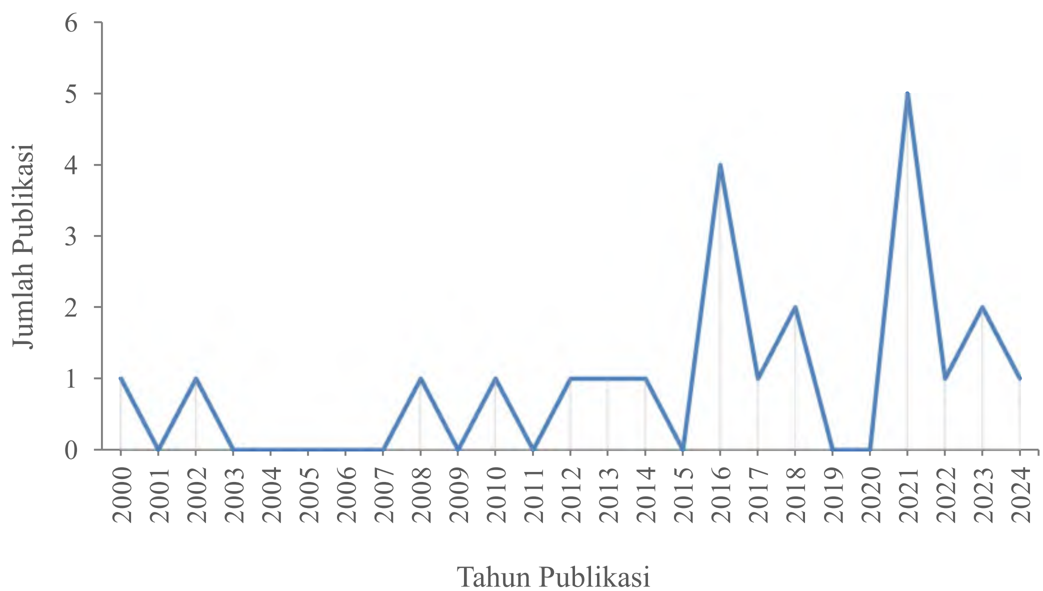
Setelah proses *data cleaning*, dataset dianalisis menggunakan VOSviewer 1.6.20. Jenis analisis yang dilakukan mencakup tiga analisis bibliometrik utama, yaitu *keyword co-occurrence*, *bibliographic coupling*, dan *co-citation* (Yeung et al., 2018)**.** Pada analisis *keyword co-occurrence*, kata kunci yang dianalisis adalah yang memenuhi kriteria *minimum number of occurrences sebesar* 2, artinya setiap kata kunci muncul sedikitnya dua kali dalam kumpulan data. Analisis *bibliographic coupling* dilakukan pada tingkat unit dokumen dengan metode *fractional counting*, yaitu metode pembobotan yang memberikan kontribusi proporsional pada setiap dokumen untuk mengurangi bias dari dokumen dengan jumlah referensi atau penulis yang besar. Pada analisis ini tidak ditetapkan minimum *number of citations per document*, sehingga seluruh dokumen yang memenuhi kriteria awal dimasukkan dalam pemetaan. Pada *co-citation analysis*, referensi yang diikutsertakan adalah yang memiliki minimum 2 sitasi di dalam dataset, sehingga hanya referensi dengan keterkaitan kutipan yang cukup kuat yang divisualisasikan dalam jaringan (Alshar et al., 2022).

Pada semua visualisasi jaringan (*network visualization*) yang dihasilkan oleh VOSviewer, setiap simpul (*node*) merepresentasikan elemen-elemen seperti kata kunci, dokumen, atau referensi tertentu. Ukuran simpul menunjukkan frekuensi kemunculan atau pengutipan, sedangkan jarak antar simpul mencerminkan tingkat kedekatan atau hubungan antar elemen. Warna klaster pada visualisasi menunjukkan kelompok elemen yang saling berkaitan secara tematik, yang dihasilkan melalui analisis keterkaitan intensitas hubungan antar elemen dalam jaringan (Bamel et al., 2020; Yeung et al., 2018).

3. HASIL DAN PEMBAHASAN

3.1. Tren publikasi

Artikel pertama yang membahas potensi *G. procumbens* sebagai antidiabetes diterbitkan pada tahun 2000 oleh Singapore Medical Journal, menyoroti efek ekstrak etanol daun ini terhadap kadar glukosa darah pada tikus model diabetes (Zhang & Tan, 2000). Setelahnya, terjadi fase jeda hingga tahun 2002, di mana *Pharmaceutical Biology* mempublikasikan studi terkait identifikasi flavonoid dalam fraksi butanol dan aktivitas hipoglikemiknya (Akowuah et al., 2002). Setelah itu, terjadi fase jeda tanpa publikasi pada tahun 2003 hingga 2007. Periode 2008 hingga 2014 masih menunjukkan tren yang lambat, dengan hanya satu artikel per tahun yang diterbitkan pada 2008, 2010, dan 2012–2014, serta tidak ada publikasi pada 2009 dan 2011. Meskipun terbatas secara kuantitas, artikel-artikel yang muncul pada periode ini mulai mengeksplorasi mekanisme farmakologis dan keamanan penggunaan *G. procumbens*. Studi oleh Hassan et al. (2008, 2010) menunjukkan bahwa aktivitas hipoglikemik tumbuhan ini dapat terjadi melalui mekanisme ekstra-pankreatik, termasuk peningkatan ambilan glukosa di jaringan otot. Pada tahun 2012, *Sains Malaysiana* mempublikasikan studi yang menunjukkan inaktivasi GSK3β secara tidak langsung oleh fraksi daun *G. procumbens*, sehingga meningkatkan sintesis glikogen hati dan membantu kontrol glukosa darah (June et al., 2012). Selanjutnya, studi tahun 2013 yang diterbitkan di *Asian Pacific Journal of Tropical Biomedicine* mengeksplorasi efek antidiabetes dari ekstrak etanol daun *G. procumbens* pada hewan uji. Studi ini menyoroti kemungkinan kontribusi senyawa aktif seperti flavonoid dan fenolik terhadap aktivitas tersebut, meskipun tanpa mengkaji secara spesifik mekanisme atau efek sinergistik antar senyawa (Algariri et al., 2013). Pada tahun 2014, fokus penelitian bergeser pada aspek keamanan, dengan studi yang menunjukkan bahwa ekstrak etanol 25% daun *G. procumbens* tidak menimbulkan efek toksik dan mendukung dosis harian sebesar 700 mg/kg (Algariri et al., 2014). Periode ini menjadi fondasi penting bagi arah riset di tahun-tahun berikutnya.



Gambar 2. Tren publikasi riset *G. procumbens* sebagai antidiabetes pada tingkat penelitian praklinis.

Lonjakan signifikan publikasi terjadi pada tahun 2016, dengan 4 artikel yang menandai titik balik penting dalam perkembangan riset *G. procumbens* (Gambar 2). Pada tahun ini, penelitian mulai mengeksplorasi potensi tumbuhan ini dalam mengurangi dampak negatif diabetes pada sistem reproduksi. Studi oleh Pusparanee et al. (2016) menunjukkan peningkatan signifikan jumlah sperma, motilitas, dan kadar testosteron plasma pada tikus diabetes tipe 1 setelah pemberian ekstrak air dan etanol. Hasil ini diperkuat oleh Khaidatul Akmar & Mahanem (2016) melalui analisis histologi testis yang mengungkap regenerasi lapisan sel germinal dan peningkatan densitas spermatogenik. Selain itu, riset oleh Choi et al. (2016) memperluas fokus ke mekanisme antidiabetes, menunjukkan bahwa *G. procumbens* dapat meningkatkan sensitivitas insulin sekaligus menghambat aktivitas enzim α-glukosidase dan α-amilase untuk mengontrol hiperglikemia postprandial.

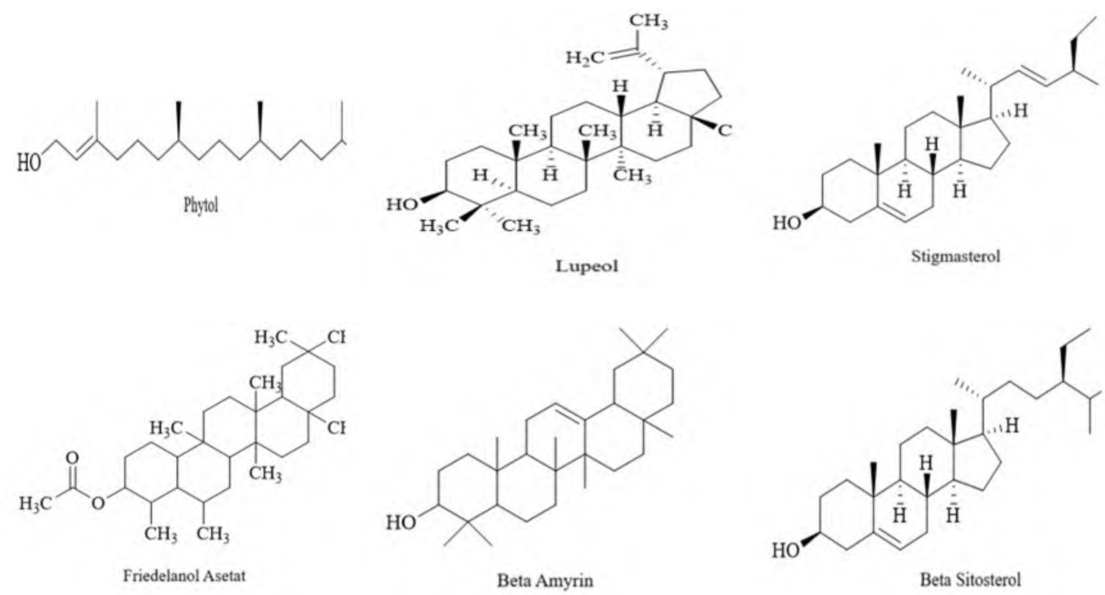
Tren positif ini berlanjut pada 2017–2018 dengan riset yang semakin menajamkan pemahaman tentang efek profertilitas pada kondisi diabetes. Studi yang dipublikasikan oleh *Sains Malaysiana* menegaskan aktivitas ekstrak air daun *G. procumbens* untuk menurunkan kadar glukosa darah, meningkatkan fertilitas, dan libido pada tikus diabetes (Kamaruzaman & MatNoor, 2017). Hal ini diperkuat dengan studi di tahun 2018, yang membuktikan ekstrak air tumbuhan ini memulihkan fertilitas melalui peningkatan ekspresi protein sperma yang berperan dalam maturasi dan interaksi sperma-ovum pada tikus diabetes (Kamaruzaman et al., 2018). Studi lain di tahun 2018, membahas tentang faktor metode pengeringan dan konsentrasi pelarut dapat memengaruhi efek inhibitor α-glukosidase (Hashim et al., 2018).

Pada rentang tahun 2000 sampai 2024, tahun 2021 merupakan tahun dengan jumlah publikasi riset terbanyak untuk topik ini yaitu 5 artikel (Gambar 2). Penelitian pada tahun ini semakin memperluas eksplorasi manfaat *G. procumbens*. Studi pertama menunjukkan bahwa ekstrak air dan etanol *G. procumbens* dapat menurunkan glukosa darah pada tikus obesitas, melalui jalur AMPK-*mediated signaling* yang meningkatkan transpor GLUT4 pada otot dan jaringan adiposa (Aung et al., 2021). Studi lainnya mengungkap potensi *G. procumbens* dalam mempercepat penyembuhan luka pada tikus diabetes melalui aplikasi topikal, dengan meningkatkan ekspresi faktor pertumbuhan seperti VEGF dan TGF-β serta mempercepat neovaskularisasi (Sutthammikorn et al., 2021). Selain itu, pendekatan *network pharmacology* dan metabonomik mengungkap mekanisme molekuler antidiabetes *G. procumbens* dengan mengaktifkan jalur PI3K/Akt dan AGE-RAGE untuk memperbaiki resistensi insulin dan metabolisme glukosa (Guo et al., 2021a; Guo et al., 2021b). Studi terakhir fokus pada evaluasi senyawa bioaktif dan fraksinya. Fraksi etil asetat terbukti memiliki kandungan fenolik dan flavonoid tertinggi serta aktivitas penghambatan enzim α-glukosidase dan α-amilase, yang berperan penting dalam mengontrol hiperglikemia postprandial (Sathiyaseelan et al., 2021).

Penelitian dari tahun 2022 hingga 2024 menunjukkan variasi yang makin beragam dalam mengeksplorasi manfaat *G. procumbens* sebagai antidiabetes. Studi yang diterbitkan *Evidence-Based Complementary and Alternative Medicine* mengombinasikan dua pendekatan, yaitu *in vivo* dan *in silico*. Pada *in vivo, G. procumbens* memiliki aktivitas antihiperglikemik dengan efektivitas yang sebanding dengan metformin pada tikus yang diinduksi aloksan, sedangkan uji *in silico*, ditemukan bahwa senyawa aktif dalam ekstrak diprediksi memiliki afinitas tinggi terhadap enzim regulator metabolisme glukosa (Tahsin et al., 2022). Pada tahun 2023, penelitian mengarah ke pengembangan nutraseutikal berbasis daun *G. procumbens* dan identifikasi senyawa aktif. Studi menunjukkan bahwa konsumsi makanan berbasis daun tumbuhan ini secara signifikan memperbaiki kadar glukosa darah, profil lipid, dan mineral pada tikus diabetes. Selain itu, enam senyawa aktif utama yang teridentifikasi (Gambar 3), yaitu phytol, lupeol, stigmasterol, friedelanol asetat, β-amyrin, dan β-sitosterol, dilaporkan memiliki aktivitas antioksidan dan antidiabetes yang kuat. Senyawa-senyawa ini berperan dalam mengurangi stres oksidatif yang berkontribusi terhadap perkembangan komplikasi diabetes

(Jobaer et al., 2023; Nath et al., 2023). Pada tahun 2024, pendekatan inovatif menggunakan kombinasi ekstrak etanol *G. procumbens* dengan nanopartikel kitosan menunjukkan peningkatan efikasi antihiperglikemik pada tikus diabetes (Badsha et al., 2024).

Berdasarkan linimasa publikasi, tren riset praklinis *G. procumbens* sebagai antidiabetes menunjukkan pola pertumbuhan yang konsisten sejak 2016, dengan peningkatan substansial setelah 2020. Lonjakan ini selaras dengan meningkatnya minat global terhadap terapi herbal dalam manajemen diabetes, khususnya yang berbasis antioksidan dan mekanisme molekuler baru (Badsha et al., 2024). Dominasi kontribusi artikel berasal dari negara-negara Asia Tenggara, terutama Malaysia menunjukkan bahwa tumbuhan ini menjadi perhatian lokal yang kuat. Namun demikian, terdapat peluang besar untuk eksplorasi lanjutan, khususnya pada uji toksikologi jangka panjang, farmakokinetik senyawa aktif, serta translasi dari model hewan ke uji klinis. Kombinasi pendekatan *in vivo*, *in silico*, dan formulasi lanjutan seperti nanopartikel menunjukkan bahwa riset *G. procumbens* sedang bergerak menuju fase aplikasi terapetik yang lebih rasional dan terstandar.



Gambar 3. Struktur kimia dari beberapa senyawa aktif dalam *G. procumbens* (Jobaer et al., 2023).

3.2. Analisis negara dan institusi paling berdampak

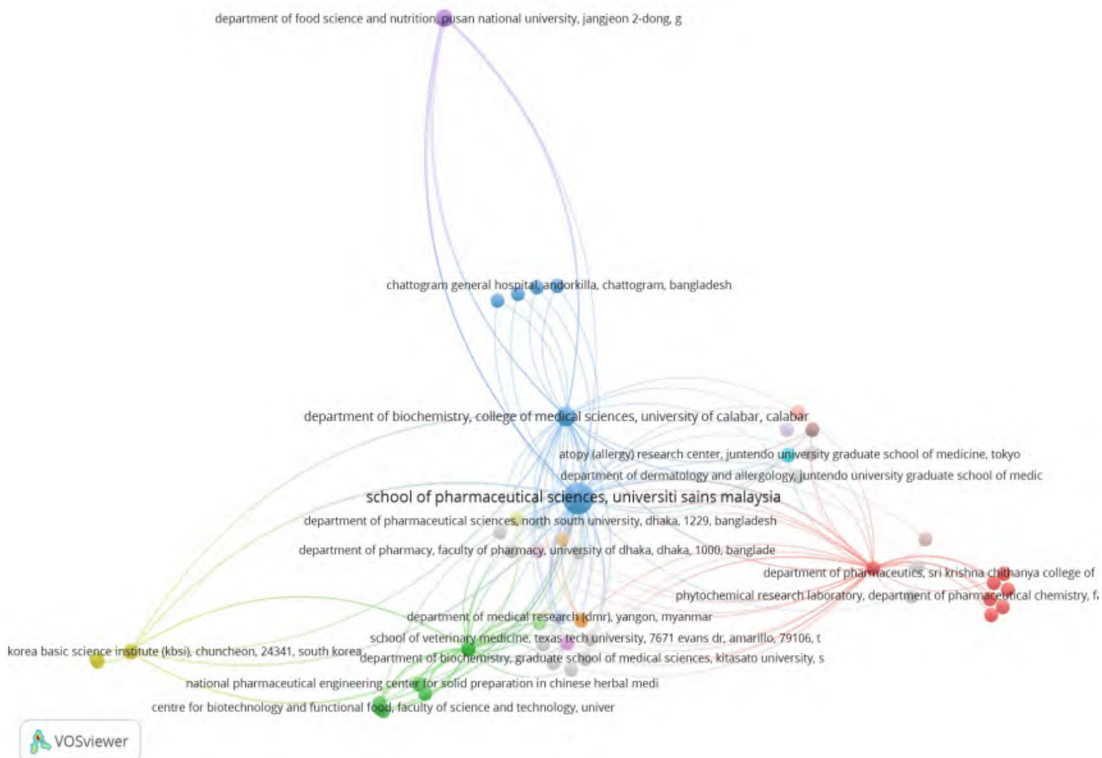
Malaysia adalah negara dengan kontribusi paling signifikan terhadap penelitian *G. procumbens* sebagai antidiabetes, dengan 11 dokumen, 354 sitasi, dan 35 *total link strength* (Tabel 1). *Total link strength* pada analisis ini menunjukkan kekuatan hubungan suatu negara atau institusi dengan negara atau institusi lain dalam jaringan berdasarkan jumlah sitasi bersama (*shared citations*) yang mereka miliki (Alshater et al., 2022). Nilai ini mencerminkan intensitas keterkaitan ilmiah, di mana semakin tinggi *total link strength*, semakin kuat posisi negara atau institusi tersebut dalam jejaring pengetahuan pada topik yang diteliti (Alshater et al., 2022). Dengan demikian, tingginya nilai *total link strength* Malaysia menunjukkan bahwa negara ini tidak hanya produktif dalam jumlah publikasi, tetapi juga berperan sentral dalam menghubungkan berbagai penelitian lintas negara. Posisi ini memperkuat peran Malaysia sebagai pusat rujukan global dalam studi *G. procumbens* sebagai agen antidiabetes.

Tabel 1. Daftar negara paling berdampak dalam penelitian praklinis *G. procumbes* sebagai antidiabetes berdasarkan basis data Scopus.

Negara	Dokumen	Sitasi	Total *Link Strength*
Malaysia	11	354	35
Singapura	1	114	18
Nigeria	2	88	21
Korea Selatan	3	50	8
Cina	3	31	7

Universiti Sains Malaysia (USM) menjadi institusi yang paling berkontribusi dalam topik penelitian ini, dengan 5 dokumen, 298 sitasi, dan 81 *total link strength*. USM dengan *total link strength* 81 menempati posisi sentral, seperti yang ditunujukkan pada Gambar 3, menandakan kontribusi dan keterhubungan riset yang tinggi dengan institusi lain di bidang penelitian *G. procumbens* sebagai agen antidiabetes. Analisis *co-authorship* mengungkap bahwa USM membentuk jejaring kolaborasi dengan berbagai institusi, antara lain *Sri Krishna Chithanya College of Pharmacy* (India), *Department of Pharmacy Island College of Technology* (Malaysia), *Department of Biochemistry University of Calabar* (Nigeria), *College of Health Sciences*, *Masterskill University* (Malaysia), dan *Department of Human Anatomy Faculty of Medicine and Health Sciences Universiti Putra Malaysia* (Malaysia). Pola kolaborasi ini menunjukkan bahwa USM tidak hanya menjadi pusat produktivitas riset, tetapi juga menjadi penghubung lintas institusi dan negara dalam penelitian *G. procumbens*, yang berpotensi memperluas jangkauan dan dampak ilmiah studi di bidang ini.

Alasan yang mendasari dominasi Malaysia dan salah satu institusinya, yaitu USM dalam penelitian *G. procumbens* sebagai antidiabetes dapat dijelaskan melalui dua faktor utama. Yang pertama, *G. procumbens* secara turun-temurun oleh masyarakat Malaysia telah dimanfaatkan sebagai tumbuhan pangan dan obat tradisional untuk penyakit seperti diabetes, hipertensi, dan inflamasi (Kaewseejan et al., 2015; Tan et al., 2016). Yang kedua, komitmen dan dukungan pemerintah Malaysia untuk penelitian terkait tumbuhan obat. Komitmen ini diejawantahkan pada kebijakan strategis dalam *National Health Policy* yang mengatur keamanan, kualitas, dan praktik yang sesuai dalam penggunaan obat tradisional dan komplementer dan pengaturan peredaran produk herbal di bawah *Drug Control Authorithy*. Selain itu, program *Entry Point Project* 1 (EPP1) menempatkan industri herbal sebagai salah satu prioritas ekonomi nasional. Dukungan ini diperkuat dengan regulasi keamanan produk, pengawasan pasca-pasar, dan insentif riset melalui skema pendanaan pemerintah (Ismail et al., 2020). Kombinasi antara biodiversitas, potensi farmakologis *G. procumbens*, dan ekosistem riset yang terstruktur menjadikan Malaysia dengan institusi pendidikan di dalamnya, sebagai negara yang paling berdampak dalam penelitian *G. procumbens* sebagai antidiabetes.



Gambar 3. Visualisasi jaringan institusi paling berdampak dalam penelitian praklinis *G. procumbens*.

3.3. Analisis artikel yang paling berdampak

Sepuluh artikel paling berdampak berdasarkan jumlah sitasi dalam penelitian *G. procumbens* sebagai antidiabetes (Tabel 2) bersumber dari data Scopus. Secara umum, mayoritas artikel berdampak tersebut terbit pada periode 2000–2014, yang merepresentasikan fase awal pembentukan basis pengetahuan ilmiah mengenai *G. procumbens*. Benang merah di antara artikel-artikel ini terletak pada kemampuannya mengaitkan aktivitas biologis *G. procumbens* dengan mekanisme molekuler yang relevan dalam patofisiologi diabetes. Studi-studi tersebut tidak hanya menyajikan bukti efektivitas, tetapi juga memberikan dasar ilmiah bagi eksplorasi lebih lanjut terkait optimasi dosis, pengembangan system penghantaran, serta evaluasi keamanan jangka panjang. Tingginya jumlah sitasi menunjukkan bahwa artikel-artikel tersebut sering dijadikan rujukan utama dalam penelitian lanjutan, baik pada studi eksperimental maupun tinjauan sistematis. Pola ini mengindikaksikan bahwa kontribusi konseptual dan metodologis berperan penting dalam meningkatkan visibilitas dan dampak ilmiah suatu publikasi. Selain itu, artikel dengan dampak ilmiah besar umumnya memiliki kombinasi antara desain eksperimental yang kuat, data yang komprehensif, dan keterkaitan yang jelas dengan potensi aplikasi klinis. Temuan ini dapat menjadi acuan strategis dalam perancangan penelitian farmasi selanjutnya agar memiliki relevansi ilmiah yang kuat dan potensi aplikasi klinis yang lebih luas, khususnya dalam pengembangan dan optimasi kandidat antidiabetes berbasis bahan alam.

Tabel 2. Sepuluh artikel paling berdampak berdasarkan jumlah sitasi dalam penelitian antidiabetes *G. procumbens* bersumber dari basis data Scopus.

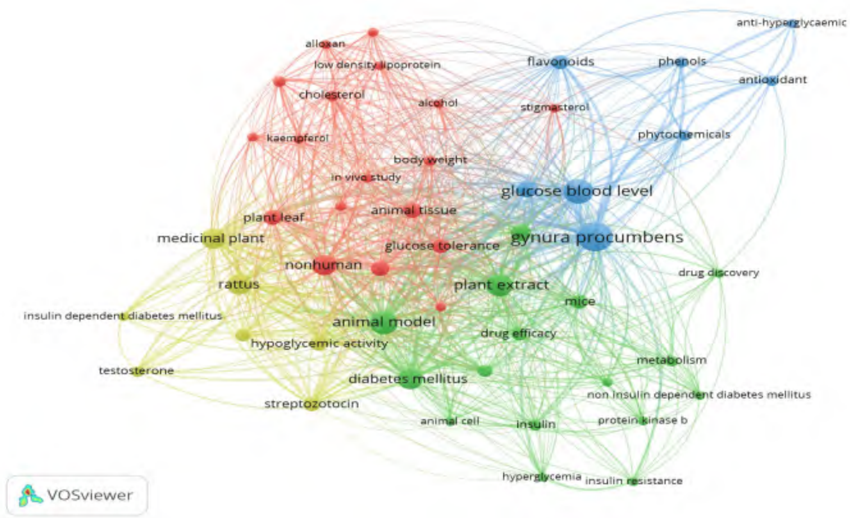
Penulis	Judul	Jurnal	Jumlah sitasi
Zhang & Tan, 2000	*Effects of an ethanollic extract of Gynura procumbens on serum glucose, cholesterol and triglyceride levels in normal and streptozotocin-induced diabetic rats*	Singapore Medical Journal	114
Hassan et al., 2010	*Antidiabetic properties and mechanism of action of Gynura procumbens water extract in streptozotocin-induced diabetic rats*	Molecules	109
Akowuah et al., 2002	*Flavonoid identification and hypoglycaemic studies of the butanol fraction from Gynura procumbens*	Pharmaceutical Biology	92
Algariri et al., 2013	*Hypoglycemic and anti-hyperglycemic study of Gynura procumbens leaf extracts*	Asian Pacific Journal of Tropical Biomedicine	65
Sathiyaseelan et al., 2021	*Evaluation of phytochemicals, antioxidants, and antidiabetic efficacy of various solvent fractions of Gynura procumbens (Lour.) Merr*	Process Biochemistry	26
June et al., 2012	*Hypoglycemic effects of Gynura procumbens fractions on streptozotocin- induced diabetic rats involved phosphorylation of GSK3β (Ser-9) in liver*	Sains Malaysiana	25
Algariri et al., 2014	*Antihyperglycaemic and toxicological evaluations of extract and fractions of Gynura procumbens leaves*	Tropical Life Sciences Research	23
Guo et al., 2021a	*Exploring the protective effect of: Gynura procumbens against type 2 diabetes mellitus by network pharmacology and validation in C57BL/KsJ db/db mice*	Food and Function	13
Choi et al., 2016	*Gynura procumbens extract alleviates postprandial hyperglycemia in diabetic mice*	Preventive Nutrition and Food Science	12
Choi et al., 2016	*Gynura procumbens extract improves insulin sensitivity and suppresses hepatic gluconeogenesis in C57BL/KsJ-db/db mice*	Nutrition Research and Practice	12

3.4. Analisis *keyword co-occurrence network and overlay*

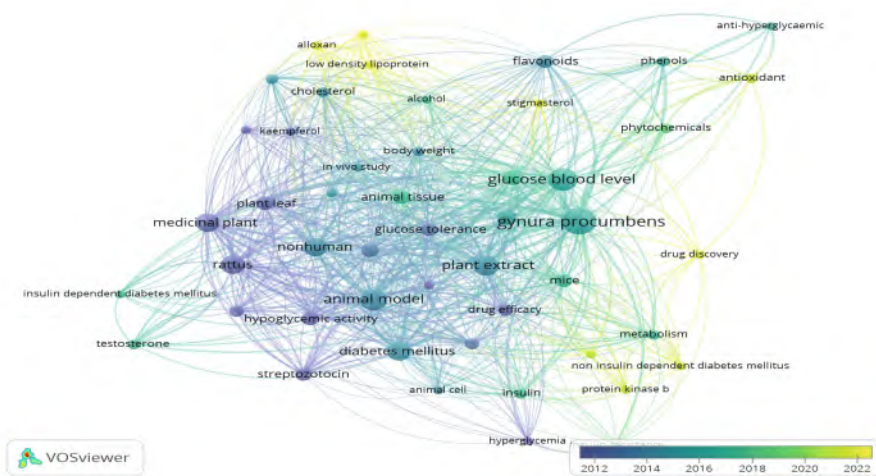
Analisis *keyword co-occurrence* bertujuan untuk mengungkap hubungan antara kata kunci yang diekstraksi dalam rentang waktu tertentu, di mana kata kunci berkumpul menjadi satu klaster yang mewakili tema penelitian yang serupa (Mukherjee et al., 2022). Kami menggunakan semua kata kunci, yaitu gabungan antara *author* dan *indexed keywords* sebagai unit analisis. *Author keywords* adalah kata kunci yang diberikan langsung oleh penulis untuk menggambarkan fokus utama penelitian, sehingga mencerminkan perspektif subjektif penulis terhadap penelitiannya. Oleh sebab itu, kata kunci ini berpotensi bias karena penulis cenderung memilih kata tertentu untuk meningkatkan visibilitas artikel mereka (Vargas-Quesada et al., 2017). Di sisi lain, *indexed keywords* adalah kata kunci yang diberikan oleh basis data, dalam hal ini adalah Scopus, berdasarkan konten artikel, sehingga bersifat lebih objektif (Vargas-Quesada et al., 2017). Dengan menggabungkan *author* dan *indexed keywords*, dapat diperoleh kata kunci yang representatif dari penelitian-penelitian *G. procumbens* sebagai antidiabetes. Untuk memastikan keakuratan data, kami menggunakan dokumen thesaurus dalam proses analisis untuk mengeliminasi pengulangan kata kunci yang memiliki makna serupa (Arifah et al., 2023).

Visualisasi pada Gambar 4 dan 5 terdiri dari 337 kata kunci, dari jumlah tersebut, sebanyak 59 kata kunci memenuhi kriteria. Beberapa kata kunci yang tidak relevan dengan topik ini dihapus, sehingga didapat 49 kata kunci. Gambar 4 menunjukkan *Network Visualization* yang menampilkan hubungan antar kata kunci berdasarkan frekuensi kemunculan bersama (*co-ocurrence*) dalam kumpulan data penelitian, sehingga memungkinkan identifikasi tema utama pada tiap klaster (Alshater et al., 2022). Setiap simpul mewakili kata kunci dan ukurannya menunjukkan frekuensi kemunculan kata kunci, sedangkan garis penghubung memperlihatkan hubungan kemunculan kata kunci tersebut secara bersamaan (Donthu et al., 2021). Kata kunci yang memiliki simpul besar adalah "*Gynura procumbens*", "*glucose blood level*", "*plant extract*", "*animal model*", dan "*diabetes mellitus*". Lima kata kunci tersebut merupakan simpul sentral yang menunjukkan frekuensi kemunculan yang tinggi. Hal ini relevan dengan topik penelitian yang dianalisis yaitu terkait aktivitas *G. procumbens* sebagai antidiabetes pada tingkat praklinis. Jarak antar simpul dalam *Network Visualization* mencerminkan kedekatan tematik antar kata kunci (Donthu et al., 2021). Kata kunci "*Gynura procumbens*" dan "*glucose blood level*" memiliki jarak dekat dan garis penghubung tebal, menandakan banyak penelitian mengevaluasi tanaman ini terhadap kadar glukosa darah.

Sementara itu, kata kunci "*plant extract*" juga berdekatan dengan "*Gynura procumbens*", menunjukkan penggunaan ekstrak tanaman ini sebagai bahan uji dalam studi praklinis. Kata kunci dengan jarak sedang, seperti "*Gynura procumbens*" dan "*insulin*", mengindikasikan bahwa meski mekanisme kerja terkait insulin sering muncul, topik ini tidak selalu menjadi fokus utama. Terdapat pula kata kunci yang tidak saling terhubung, seperti "*flavonoids*" dan "*drug discovery*". "*Flavonoids*" lebih sering muncul dalam konteks aktivitas farmakologis seperti "*antioxidant*" atau "*anti-hyperglycaemic*" pada klaster biru, sedangkan "*drug discovery*" berada di klaster hijau yang lebih dekat ke topik mekanisme molekuler, metabolisme, dan uji efikasi. Hal ini menunjukkan bahwa penelitian penemuan obat belum secara spesifik mengaitkan flavonoid sebagai target utama, yang dapat menjadi potensi gap penelitian untuk eksplorasi lebih lanjut.



Gambar 4. Visualisasi jaringan *keyword co-occurrence* pada publikasi terkait potensi antidiabetes *G. procumbens* berdasarkan basis data Scopus



Gambar 5. Visualisasi *Keyword co-occurrence overlay* yang menunjukkan perkembangan temporal penelitian antidiabetes *G. procumbens* berdasarkan basis data Scopus

Pada *Overlay visualization* terdapat penambahan dimensi waktu dengan memberikan spektrum warna pada simpul untuk menunjukkan periode kemunculan kata kunci, sehingga perkembangan tren penelitian dapat diamati dari waktu ke waktu *(*Mandal et al., 2024). Gambar 5 menunjukkan tiga klaster warna, yaitu ungu, biru-hijau, dan kuning. Klaster ungu (sekitar 2012-2014), terdapat kata kunci "*rattus*", "*animal model*", "streptozotocin", "*hypoglyclemic activity*", "*medicinal plant*", dan "*drug efficacy*". Kata kunci pada periode tersebut menunjukkan bahwa fokus penelitian terletak pada studi praklinis berbasis hewan model diabetes. Klaster warna biru-hijau (sekitar 2014-2018), muncul kata kunci "*insulin*", "*animal tissue*", "*flavonoids*", "*phenols*", hingga "*testosterone*". Munculnya kata kunci tersebut memperlihatkan bahwa penelitian mulai bergeser menuju eksplorasi mekanisme antidiabetes, identifikasi senyawa aktif, dan pencarian efek *G. procumbens* pada kesehatan reproduksi dalam konteks komplikasi diabetes.

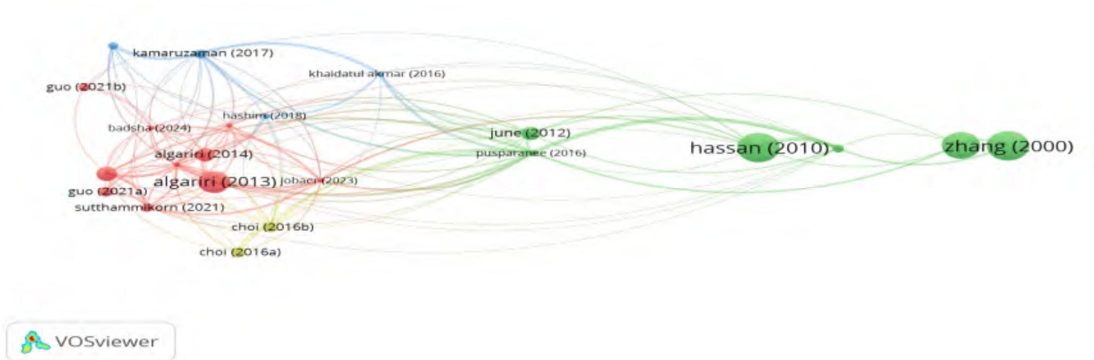
Klaster kuning (sekitar 2018–2020) memuat kata kunci seperti "*stigmasterol*", "*protein kinase b*", "*non insulin dependent diabetes mellitus*", "*low density lipoprotein*", dan "*drug discovery*". Kata kunci pada periode ini menunjukkan arah penelitian yang semakin beragam, dengan fokus pada identifikasi senyawa aktif dan pemanfaatan *G. procumbens* untuk mengatasi diabetes serta komplikasinya. Stigmasterol sebagai senyawa fitosterol memiliki potensi antidiabetes dan penurun *low density lipoprotein* (LDL). Senyawa ini mampu melindungi sel β pankreas dari glukolipotoksisitas, yaitu kondisi peningkatan kadar glukosa dan asam lemak bebas yang merusak sel β, sehingga membantu memperbaiki resistensi insulin (Ward et al., 2017). Relevansinya semakin jelas ketika dikaitkan dengan protein kinase b yang berperan penting dalam modulasi resistensi insulin, salah satu tantangan utama pada *non insulin dependent diabetes mellitus* (Lee et al., 2022).

3.5. Analisis *bibliographic coupling*

Bibliographic coupling adalah metode dalam analisis bibliometrik yang mengukur hubungan antar dokumen berdasarkan referensi yang dikutip oleh dokumen-dokumen tersebut (Öztürk et al., 2024). Jika dua dokumen mengutip satu atau lebih referensi yang sama, maka kedua dokumen tersebut memiliki hubungan *bibliographic coupling*. Gambar 6 memperlihatkan visualisasi *bibliographic coupling network*, di mana simpul mewakili dokumen, ukuran simpul menunjukkan seberapa kuat keterhubungan (jumlah referensi bersama) dengan dokumen lain, dan garis yang menghubungkan simpul menunjukkan kekuatan hubungan tersebut; semakin tebal garisnya, semakin banyak referensi yang sama (Donthu et al., 2021; Alshater et al., 2022). Analisis *bibliographic coupling* ini mengungkap referensi bersama membentuk jaringan penelitian dengan menghubungkan studi-studi dengan fokus serupa (Mukherjee et al., 2022).

Hasil analisis menunjukkan terbentuknya empat klaster utama. Klaster hijau terdiri dari Zhang (2000), Hassan (2010), dan June (2012), yang terhubung kuat melalui referensi terkait mekanisme antidiabetes berbasis model hewan, khususnya jalur kerja ekstrapancreatik dan regulasi glukosa darah. Klaster merah dipusatkan pada Algariri (2013) dan Algariri (2014), yang banyak digunakan sebagai rujukan untuk penelitian terkait keamanan dan aktivitas antihiperglikemik, termasuk efeknya pada komplikasi diabetes. Klaster biru dengan pusat Kamaruzaman (2017) dan Khaidatul Akmar (2016) lebih fokus pada aspek kesehatan reproduksi terkait diabetes, sementara klaster kuning yang dipimpin oleh Choi (2016a, 2016b) mengangkat topik mekanisme molekuler spesifik, seperti penghambatan enzim pencernaan karbohidrat.

Tinjauan keterkaitan antarklaster memperlihatkan bahwa klaster hijau dan merah memiliki koneksi referensi yang cukup tebal, menunjukkan adanya irisan sumber pustaka antara penelitian mekanisme dasar serta studi keamanan dan aktivitas biologis. Sementara itu, klaster biru berperan sebagai penghubung antara klaster merah dan kuning, menandakan adanya integrasi topik mekanisme molekuler dengan penelitian terkait efek reproduksi. Klaster kuning memiliki hubungan paling tipis dengan hijau, menunjukkan bahwa studi mekanisme spesifik seperti penghambatan α-glukosidase berkembang relatif terpisah dari riset mekanisme dasar awal. Perbedaan fokus ini mengindikasikan adanya alur pengembangan riset yang bergerak dari studi dasar, ke keamanan dan khasiat, hingga eksplorasi mekanisme spesifik dan manfaat tambahan.



Gambar 6. Visualisasi jaringan *bibliographic coupling* antar dokumen pada publikasi potensi antidiabetes *G. procumbens* berdasarkan basis data Scopus

3.6. Analisis *co-citation*

Analisis *co-citation* merupakan metode dalam bibliometrik yang mengidentifikasi hubungan antara dua dokumen yang sering dikutip bersama oleh dokumen lain (Cheng et al., 2022). Tujuan dari analisis *co-citation* adalah untuk memetakan keterkaitan referensi yang membentuk kelompok atau klaster sesuai tema yang sama (Mukherjee et al., 2022). Visualisasi *co-citation network* (Gambar 7) dibangun dengan mengidentifikasi dokumen-dokumen yang paling sering dikutip bersama dalam dataset. Dari total 792 referensi yang dikutip, hanya 20 dokumen yang memenuhi kriteria minimum 2 sitasi dan dilibatkan dalam analisis. Dari 20 referensi, hanya 16 referensi yang membentuk jaringan yang saling terhubung. Dokumen yang sering dikutip bersama akan digambarkan sebagai simpul besar dengan garis antar klaster. Garis penghubung antar klaster menunjukkan bahwa terdapat dokumen dalam dataset yang mengutip referensi dari lebih dari satu klaster secara bersamaan, membentuk hubungan kutipan bersama (*co-citation*) (Cheng et al., 2022).

Gambar 7. Visualisasi jaringan *co-citation* (sitasi bersama) antar referensi pada publikasi terkait potensi antidiabetes *G. procumbens* berdasarkan basis data Scopus

Hasil analisis menunjukkan adanya empat klaster utama. Klaster 1 (merah) berfokus pada aktivitas farmakologis *G. procumbens*, meliputi efek antidiabetes, antihipertensi, dan antioksidan, serta membahas mekanisme molekuler resistensi insulin sebagai landasan teori penting. Klaster 2 (hijau) menegaskan potensi *G. procumbens* sebagai agen antidiabetes sekaligus profertilitas, sehingga menjadi penghubung tematik antara penelitian pengendalian glukosa dan kesehatan reproduksi. Klaster 3 (biru) berisi referensi terkait protokol penelitian pada perilaku tikus jantan dan pengujian semen manusia, menandakan pergeseran riset ke arah topik reproduksi. Klaster 4 (kuning) berpusat pada identifikasi senyawa aktif dan pengujian aktivitas biologis spesifik seperti inhibitor α-glukosidase, antioksidan, dan antiinflamasi, yang mengaitkan kajian fitokimia dengan aplikasi terapeutik.

Keterkaitan antar klaster dapat diamati dari garis lintas warna pada visualisasi. Hubungan antara klaster merah dan kuning menunjukkan bahwa penelitian farmakologis sering mengaitkan efek biologis dengan senyawa aktif tertentu. Sementara hubungan antara klaster hijau dan biru mencerminkan integrasi riset profertilitas dengan protokol eksperimen hewan. Pola ini mengindikasikan bahwa meskipun tiap klaster memiliki fokus tematik berbeda, terdapat tumpang tindih yang menghubungkan riset dasar, mekanisme, dan potensi aplikasinya. Makna penting analisis *co-citation* terhadap perkembangan riset *G. procumbens* terletak pada kemampuannya memetakan lanskap referensi kunci yang menjadi rujukan utama para peneliti (Mukherjee et al., 2022). Analisis ini membantu mengidentifikasi tema riset dominan, titik temu lintas bidang kajian, dan celah penelitian yang masih terbuka (Cheng et al., 2022). Dengan demikian, hasilnya dapat menjadi panduan strategis untuk merancang studi lanjutan yang relevan, sinergis, dan berpeluang memberikan kontribusi signifikan pada pengembangan terapi antidiabetes berbasis *G. procumbens*

4. KESIMPULAN

Studi ini merupakan analisis bibliometrik pertama yang memetakan lanskap penelitian praklinis *Gynura procumbens* sebagai antidiabetes. Hasil analisis menunjukkan tren publikasi yang berfluktuasi sejak 2000, dengan peningkatan signifikan setelah 2016 dan puncaknya pada 2021. Malaysia menjadi negara paling produktif, dengan Universiti Sains Malaysia, jurnal *Molecules*, dan penulis Zurina Hassan sebagai kontributor utama. Analisis *keyword co-occurence*, *co-citation*, dan *bibliographic coupling* mengungkap fokus penelitian pada efektivitas antihiperglikemik, mekanisme molekuler, identifikasi senyawa aktif, serta manfaat tambahan seperti efek profertilitas pada kondisi diabetes—suatu temuan yang jarang dilaporkan pada tumbuhan obat antidiabetes. Temuan ini menegaskan kontribusi penting studi ini dalam memetakan penelitian yang komprehensif, mengidentifikasi tema dominan, keterkaitan antar topik, serta celah riset yang masih terbuka. Ke depan, penelitian *G. procumbens* berpotensi diarahkan pada penentuan dosis terapeutik berbasis profil farmakokinetik, uji keamanan jangka panjang, serta pengembangan formulasi dan sistem penghantaran berbasis nanopartikel. Selain itu, eksplorasi aspek profertilitas *G. procumbens* berpotensi membuka peluang pengembangan terapi komplementer yang menargetkan komplikasi reproduksi pada penderita diabetes.

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DAFTAR PUSTAKA

Abrika, O. S. S., Yam, M. F., Asmawi, M. Z., Sadikun, A., Dieng, H., & Hussain, E. A. (2013). Effects of extracts and fractions of *Gynura procumbens* on rat atrial contraction. *JAMS Journal of Acupuncture and Meridian Studies*, *6*(4): 199–207. https://doi.org/10.1016/j.jams.2013.01.020.

Ahmad Nazri, K. A., Fauzi, N. M., Buang, F., Mohd Saad, Q. H., Husain, K., Jantan, I., & Jubri, Z. (2019). *Gynura procumbens* standardised extract reduces cholesterol levels and modulates oxidative status in postmenopausal rats fed with cholesterol diet enriched with repeatedly heated palm oil. *Evidence-Based Complementary and Alternative Medicine*, *2019*. https://doi.org/10.1155/2019/7246756.

Akowuah, G. A., Sadikun, A., & Mariam, A. (2002). Flavonoid identification and hypoglycaemic studies of the butanol fraction from *Gynura procumbens*. *Pharmaceutical Biology*, 40(6): 405–410. https://doi.org/10.1076/phbi.40.6.405.8440.

Algariri, K., Atangwho, I. J., Meng, K. Y., Asmawi, M. Z., Sadikun, A., & Murugaiyah, V. (2014). Antihyperglycaemic and Toxicological Evaluations of Extract and Fractions of *Gynura procumbens* Leaves. *Tropical Life Sciences Research*, 25(1): 75-93.

Algariri, K., Meng, K. Y., Atangwho, I. J., Asmawi, M. Z., Sadikun, A., Murugaiyah, V., & Ismail, N. (2013). Hypoglycemic and anti-hyperglycemic study of *Gynura procumbens* leaf extracts. *Asian Pacific Journal of Tropical Biomedicine*, 3(5): 358–366. https://doi.org/10.1016/S2221-1691(13)60077-5.

Alshater, M. M., Hassan, M. K., Rashid, M., & Hasan, R. (2022). A bibliometric review of the Waqf literature. *Eurasian Economic Review*, 12(2): 213–239. https://doi.org/10.1007/s40822-021-00183-4.

Amin, M. Z., Afrin, M., Meghla, N. S., Nur, M. A., Rahman, M. M., & Uddin, M. J. (2021). Assessment of antibacterial, anti-inflammatory, and cytotoxic effects of different extracts of *Gynura procumbens* leaf. *Current Therapeutic Research - Clinical and Experimental*, *95*. https://doi.org/10.1016/j.curtheres.2021.100636.

Arifah, F. H., Endro Nugroho, A., Rohman, A., & Sujarwo, W. (2023). A Bibliometric Analysis to Preclinical Studies of *Tinospora Crispa* (L.) Hook. F. & Thomson as An Antidiabetic. Indonesian Journal of Pharmacy, 34(1): 24-35. https://doi.org/10.22146/ijp.123456.

Aung, C. L., Kawakami, F., Imai, M., Lwin, T. T., Kanzaki, M., Mar, O., Phyu, K. P., Thwin, M. M., & Maruyama, H. (2021). Blood glucose-lowering effect of water and ethanolic extracts of *Gynura procumbens* (Lour.) Merr. *Traditional and Kampo Medicine*, 8(2): 138–147. https://doi.org/10.1002/tkm2.1277.

Badsha, S. A., Islam, R., Parvez, M. M., Rashid, M. B., Hasan, M. M., Kulkarni, V., & Sarkar, S. (2024). Effect of *Gynura procumbens* leaf extract with biological nanoparticles on streptozotocin-induced hyperglycemia in a rat model. *Journal of Advanced Biotechnology and Experimental Therapeutics*, 7(1): 255–265. https://doi.org/10.5455/jabet.2024.d21.

Bamel, U. K., Pandey, R., & Gupta, A. (2020). Safety climate: Systematic literature network analysis of 38 years (1980-2018) of research. *Accident Analysis and Prevention*, *135*. https://doi.org/10.1016/j.aap.2019.105387.

Cheng, K. H., Tang, K. Y., & Tsai, C. C. (2022). The mainstream and extension of contemporary virtual reality education research: Insights from a co-citation network analysis (2015–2020). *Educational Technology Research and Development*, 70(1): 169–184. https://doi.org/10.1007/s11423-021-10070-z.

Cho, N. H., Shaw, J. E., Karuranga, S., Huang, Y., da Rocha Fernandes, J. D., Ohlrogge, A. W., & Malanda, B. (2018). IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Research and Clinical Practice*, *138*, 271–281. https://doi.org/10.1016/j.diabres.2018.02.023.

Choi, S. I., Park, M. H., & Han, J. S. (2016). *Gynura procumbens* extract alleviates postprandial hyperglycemia in diabetic mice. *Preventive Nutrition and Food Science*, 21(3): 181–186. https://doi.org/10.3746/pnf.2016.21.3.181.

Donthu, N., Kumar, S., Mukherjee, D., Pandey, N., & Lim, W. M. (2021). How to conduct a bibliometric analysis: An overview and guidelines. *Journal of Business Research*, *133*, 285–296. https://doi.org/10.1016/j.jbusres.2021.04.070.

Fadhilah Ismail, S., Madieha Abd Ghani Azmi, I., Daud, M., Abd Jalil, J., & Safuan, S. Regulatory control of herbal and traditional medicines in Malaysi. *International Journal of Business and Society*, 21(1): 192-204.

Guo, S., Ouyang, H., Du, W., Li, J., Liu, M., Yang, S., He, M., & Feng, Y. (2021). Exploring the protective effect of: *Gynura procumbens* against type 2 diabetes mellitus by network pharmacology and validation in C57BL/KsJ db/db mice. *Food and Function*, 12(4): 1732–1744. https://doi.org/10.1039/d0fo01188f.

Guo, W., Ouyang, H., Liu, M., Wu, J., He, X., Yang, S., He, M., & Feng, Y. (2021). Based on Plasma Metabonomics and Network Pharmacology Exploring the Therapeutic Mechanism of *Gynura procumbens* on Type 2 Diabetes. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.674379.

Hashim, H., Embong, F. A., Yee, C. K., Daud, N. M., & Rahman, H. A. (2018). Effect of different drying methods and ethanol concentrations on antioxidant and anti-hyperglycaemic properties of Gynura procumbens leaves extract. *Malaysian Applied Biology*, 47(5): 157–164. https://doi.org/10.1234/mab.v47i5.123456.

Hassan, Z., Ahmad, M., Pauzi, M. Y., Naidu, S. R., Kumar, G. S., & Umachigi, S. P. (2008). Hypoglycaemic effects of aqueous extract of *Gynura procumbens*. *Pharmacologyonline*, 1, 30–50.

Hassan, Z., Yam, M. F., Ahmad, M., & Yusof, A. P. M. (2010). Antidiabetic properties and mechanism of action of *Gynura procumbens* water extract in streptozotocin-induced diabetic rats. *Molecules*, 15(12): 9008–9023. https://doi.org/10.3390/molecules15129008.

Ismail, S. F., Azmi, I. M. A. G., Daud, M., Jalil, J. A., & Safuan, S. (2020). Regulatory control of herbal and traditional medicines in Malaysia: Issues and concerns. *International Journal of Business and Society*, 21(S1), 192–204.

Jobaer, M. A., Ashrafi, S., Ahsan, M., Hasan, C. M., Rashid, M. A., Islam, S. N., & Masud, M. M. (2023). Phytochemical and Biological Investigation of an Indigenous Plant of Bangladesh, *Gynura procumbens* (Lour.) Merr.: Drug Discovery from Nature. *Molecules*, 28(10). https://doi.org/10.3390/molecules28104186.

June, C. C., Wen, L. H., Sani, H. A., Latip, J., Gansau, J. A., Chin, L. P., Embi, N., & Sidek, H. M. (2012). Hypoglycemic effects of *Gynura procumbens* fractions on streptozotocin-induced diabetic rats involved phosphorylation of GSK3β (Ser-9) in liver. *Sains Malaysiana*, 41(8), 969–975.

Kaewseejan, N., Sutthikhum, V., & Siriamornpun, S. (2015). Potential of *Gynura procumbens* leaves as source of flavonoid-enriched fractions with enhanced antioxidant capacity. *Journal of Functional Foods*, 12: 120–128. https://doi.org/10.1016/j.jff.2014.11.001.

Kamaruzaman, K. A., Aizat, W. M., & Mat Noor, M. (2018). *Gynura procumbens* Improved Fertility of Diabetic Rats: Preliminary Study of Sperm Proteomic. *Evidence-Based Complementary and Alternative Medicine*, *2018*. https://doi.org/10.1155/2018/9201539.

Kamaruzaman, K. A., & MatNoor, M. (2017). *Gynura procumbens* leaf improves blood glucose level, restores fertility and libido of diabetic-induced male rats. *Sains Malaysiana*, 46(9): 1471–1477. https://doi.org/10.17576/jsm-2017-4609-16.

Khaidatul Akmar, K., & Mahanem, M. N. (2016). Profertility and antidiabetic properties of *Gynura procumbens* on streptozotocin induced male rats. *AIP Conference Proceedings*, *1784*. https://doi.org/10.1063/1.4966737.

Lee, S. H., Park, S. Y., & Choi, C. S. (2022). Insulin Resistance: From Mechanisms to Therapeutic Strategies. *Diabetes and Metabolism Journal*, 46(1): pp.15–37. Korean Diabetes Association. https://doi.org/10.4093/DMJ.2021.0280.

Mandal, V., Mukherjee, S., Khan, A., Nathani, M., Majhi, S., Bhushan Singh Chouhan, K., Septya Kusuma, H., Dhobi, M., & Sahidul Ali, M. (2024). A Deeper Insight into Research on *Piper betel* Essential Oil from 1991-2021: A Critical Bibliometric Analysis based Appraisal. *J, Biotechnology and Bioprocessing*, 5(2). https://doi.org/10.31579/2766-2314/137.

Mozzherin, D., Paul, D., & Whitmire, A. (2024). Can We Standardize Name Reconciliaton via OpenRefine? *Biodiversity Information Science and Standards*, *8*. https://doi.org/10.3897/biss.8.134910.

Mukherjee, D., Lim, W. M., Kumar, S., & Donthu, N. (2022). Guidelines for advancing theory and practice through bibliometric research. *Journal of Business Research*, *148*, 101–115. https://doi.org/10.1016/j.jbusres.2022.04.042.

Nath, M., Adhikary, K., Ahamed, M. T., Devnath, H. S., & Islam, M. M. (2023). Effects of *Gynura procumbens* leaf-based meal on glucose level, lipid profile and mineral content of alloxan-induced diabetic mice. *Food Research*, 7(2): 332–340. https://doi.org/10.26656/fr.2017.7(2).818.

Öztürk, O., Kocaman, R., & Kanbach, D. K. (2024). How to design bibliometric research: an overview and a framework proposal. *Review of Managerial Science*. https://doi.org/10.1007/s11846-024-00738-0.

Sathiyaseelan, A., Park, S. J., Saravanakumar, K., Mariadoss, A. V. A., & Wang, M. H. (2021). Evaluation of phytochemicals, antioxidants, and antidiabetic efficacy of various solvent fractions of *Gynura procumbens* (Lour.) Merr. *Process Biochemistry*, *111*, 51–62. https://doi.org/10.1016/j.procbio.2021.08.028.

Septaningsih, D. A., Putra, C. A., Suparto, I. H., Achmadi, S. S., Heryanto, R., & Rafi, M. (2022). Phytochemical Profiling of *Gynura procumbens* (Lour.) Merr. Leaves and Stem Extracts Using UHPLC-Q-Orbitrap HRMS. *Indonesian Journal of Chemistry*, 22(6): 1553–1565. https://doi.org/10.22146/ijc.74236.

Sutthammikorn, N., Supajatura, V., Yue, H., Takahashi, M., Chansakaow, S., Nakano, N., Song, P., Ogawa, T., Ikeda, S., Okumura, K., Ogawa, H., & Niyonsaba, F. (2021). Topical *Gynura procumbens* as a novel therapeutic improves wound healing in diabetic mice. *Plants*, 10(6): https://doi.org/10.3390/plants10061122.

Tahsin, M. R., Tithi, T. I., Mim, S. R., Haque, E., Sultana, A., Bahar, N. B., Ahmed, R., Chowdhury, J. A., Chowdhury, A. A., Kabir, S., Aktar, F., Uddin, M. S., & Amran, M. S. (2022). In Vivo and in Silico Assessment of Diabetes Ameliorating Potentiality and Safety Profile of *Gynura procumbens* Leaves. *Evidence-Based Complementary and Alternative Medicine*, *2022*. https://doi.org/10.1155/2022/9095504.

Tan, H. L., Chan, K. G., Pusparajah, P., Lee, L. H., & Goh, B. H. (2016). *Gynura procumbens*: An overview of the biological activities. In *Frontiers in Pharmacology* (Vol. 7, Issue MAR). Frontiers Media S.A. https://doi.org/10.3389/fphar.2016.00052.

Vargas-Quesada, B., Chinchilla-Rodríguez, Z., & Rodriguez, N. (2017). Identification and Visualization of the Intellectual Structure in Graphene Research. *Frontiers in Research Metrics and Analytics*, *2*. https://doi.org/10.3389/frma.2017.00007.

Pusparanee, H., Lee, H. W., Halimah, A. S., & Mahanem, M. N. (2016). Effects of *Gynura procumbens* on sperm quality and testosterone level in streptozotocin-induced Type 1 diabetic rats. International Journal of Pharmacognosy and Phytochemical Research, 8(1): 22–30.

Ward, M. G., Li, G., Barbosa-Lorenzi, V. C., & Hao, M. (2017). Stigmasterol prevents glucolipotoxicity induced defects in glucose-stimulated insulin secretion. *Scientific Reports*, 7(1). https://doi.org/10.1038/s41598-017-10209-0.

Yeung, A. W. K., Heinrich, M., & Atanasov, A. G. (2018). Ethnopharmacology-A bibliometric analysis of a field of research meandering between medicine and food science? *Frontiers in Pharmacology*, *9*(MAR). https://doi.org/10.3389/fphar.2018.00215.

Zhang, X. F., & Tan, B. K. (2000). Effects of an ethanolic extract of *Gynura procumbens* on serum glucose, cholesterol and triglyceride levels in normal and streptozotocin-induced diabetic rats. *Singapore Medical Journal*, 41(1): 9–13. http://europepmc.org/abstract/MED/10783673.