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Herbal supplementation improves clinical outcomes among diabetes mellitus patients

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ABSTRACT

Hyperglycemic conditions are still common in diabetes melllitus (DM) patients with routine therapy. Rural communities in the Special Region of Yogyakarta habitually consume herbal medicines. Herbal nutritional supplements (MHM) were developed as additional therapy to increase the success of achieving therapeutic targets for DM patients. This study aimed to identify the clinical picture of DM patients who were given MHM at public health center (PHC) in the rural areas of Bantul Regency, Yogyakarta Special Region. This retrospective study was conducted on 94 DM patients with routine therapy. Patients who met the inclusion and exclusion criteria and had agreed to the informed consent were divided into two groups. Patients in the treatment group were asked to consume herbal supplement preparations (MHM) for 20 days. On day 21, each group measured clinical outcome parameters (blood pressure, blood glucose levels, triglycerides, cholesterol, high density lipoprotein (HDL), low density lipoprotein (LDL), liver enzymes, urea, and creatinine). The mean difference test between the two groups (t-test) was carried out using a 95% confidence level. The results showed that the consumption of MHM herbal nutritional supplements for 20 days reduced blood sugar levels, Hb A1C levels, and urea levels ($p<0.05$). There were no differences in blood pressure, pulse, cholesterol, triglyceride, HDL, LDL, serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), and creatinine levels between the two groups ($p>0.05$). Administration of MHM for 20 days increased clinical outcomes in blood sugar, HbA1c, and urea levels in DM patients at PHC.

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1. INTRODUCTION

Diabetes mellitus (DM) is a disease that is a problem in most countries in the world [1]. The prevalence of DM in Indonesia has been increasing continuously [2]. Even though DM patients have received routine therapy, there are still many of them who experience hyperglycemia [3]. The incidence of hyperglycemia in DM patients is associated with non-adherence to therapy, lifestyle, genetic factors, and gut microbiota [4], [5]. Hyperglycemia conditions cause glucose auto-oxidation, protein glycation, and activation of glucose metabolism pathways that accelerate the formation of reactive oxygen compounds [6]. Free radicals initiate

inflammatory reactions and the emergence of various complications in DM, such as diabetic nephropathy, retinopathy, and cardiovascular [7]. Recent studies have strengthened the association between inflammation and the development of diabetes mellitus and exacerbation of cardiovascular disease in DM. It has been proven that there is a relationship between diabetes mellitus, inflammation, and cardiovascular complications [8], [9]. Levels of matrix metalloproteinases and proinflammation cytokines are elevated in patients with type 2 diabetes. They are associated with more severe atherosclerosis and an increased incidence of coronary heart events, nephropathy, and other microvascular complications [10]. Hypertension and poor glycemic control often precede diabetic nephropathy [9], [11]. A new strategy is needed for managing DM patients in PHC services to increase success in controlling blood sugar levels and preventing complications. The provision of antioxidant herbal nutritional supplements is thought to increase the success of therapy and prevent complications [12]. Recent scientific evidence shows that many herbs or active herbal compounds have a therapeutic effect on DM by modulating the gut microbiota to increase efficacy in controlling blood sugar levels and preventing complications [13], many plants have been shown to have antioxidant and anti-inflammatory activity [14], [15].

Herbal medicine is a source of natural antioxidants [16]. Plants that are widely used as antioxidants include moringa [17], gotu kola [18], and black cumin oil [19]. Black cumin seeds (BCS) are traditional medicines used as immunomodulators [20], antidiabetic mellitus [21], and hepatoprotectors [22]. Black cumin seeds oil (BCSO) contains unsaturated fatty acids (namely oleic and linolenic acids) and essential oils (thymoquinone, nigellin, and nigellon) [23]. Unsaturated fatty acids and thymoquinone in BCSO are strong antioxidants and immunomodulators [24]. The BCSO activity as an antioxidant and anti-inflammatory can prevent the occurrence of metabolic syndrome [25]. Black cumin oil administration for eight weeks can reduce inflammation and oxidative stress in patients with rheumatoid arthritis (RA) [26]. Thymoquinone can suppress proinflammatory cytokines and increase anti-inflammatory cytokines in inflamed test animals [27]. A combination of black cumin seed powder with anti-diabetic, anti-hypercholesterolemic, or anti-hypertension drugs has been shown to improve blood cholesterol profiles, reduce the percentage of hemoglobin A1c (HbA1C), and lower blood pressure in metabolic syndromes patients [28]. A preparation containing BCSO has been developed as an herbal nutritional supplement. The effect of consuming herbal nutritional supplements (MHM) herbal supplements on clinical outcomes in DM patients with routine therapy at PHC is not yet clear, so research is needed to clarify the effect of MHM.

2. RESEARCH METHOD

2.1. Research design

A retrospective cohort research design was utilized to investigate the effect of MHM herbal preparation supplementation on the clinical outcomes of DM patients at PHC. We used data from a pilot study using herbal supplement preparations containing BCSO (MHM) as multi-nutrient supplementation for DM patients at the public health center (PHC) in a rural area in Bantul Regency, the Yogyakarta Special Region (YSR), Indonesia. A pilot trial of multi-nutrient supplementation containing BCSO was conducted in September–December 2016, involving 99 patients at risk of metabolic syndrome. The independent variable was MHM supplement preparation for 20 days. The dependent variables are blood pressure, pulse respiration, glucose levels, HbA1c, triglycerides, cholesterol, high density lipoprotein (HDL), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), urea, and creatinine.

2.2. Subject

The inclusion criteria were men and women aged >18 years with DM diagnosis or anti-diabetic drug, increased fasting blood glucose (fasting glucose level 100 mg/dL) [29], and willingness to be a research subject (filling in informed consent). Those who stopped out were recalcitrant while the trial was running, pregnant women, allergic to BCSO, using corticosteroids >10 mg/day, utilizing immune supplements, and patients with a history of malignancy, tuberculosis (TB), or diabetic ulcers were excluded. Calculation of the minimum sample size using the open epi program (www.openepi.com) using the two-group mean difference test formula. Suppose there is a difference in glucose levels of 15 mg/dl between the experimental and the control group, with a 95% confidence level and 90% power for a 2:1 comparison between groups. In that case, 27 and 54 samples are needed in the control and treatment groups, respectively. Based on the sample size calculation, the minimum total sample required for this study was 81 DM patients. This research has met the ethical feasibility with a certificate of research ethics feasibility number: 279/EP-FKIK- UMY/VIII/2016. The research team has also obtained a research permit from the local government of Bantul Regency.

2.3. Research instruments and materials

We used computer-based data and medical records of patients with diabetes mellitus and at risk of metabolic syndrome as a source of data collection for demographic, clinical, and medical characteristics at PHC. The data is recapitulated in the case form report. The MHM herbal supplement preparations in this study were preparations containing thymoquinone 2.72%, fatty acids 69%, caprylic 0.21%, capric 0.15%, lauric 0.1%, myristic 0.18%, palmitic 12.27%, palmitoleate 0.28%, heptadecanoate 0.1%, stearate 79.97%, oleic 0.07%, linoleic 2.85%, linolenic 0.1%, eicosanoate 3.15%, eicosanoate 0.15%, eicosadienoate 0.25 %, 0.03% arachidonate, 0.03% eicopentanoate, 0.06% bee % docohexanoate, and 0.02% terracanoate [30]. The traditional medicine industry provides MHM herbal nutritional supplements, which have received a certificate and are under the Food and Drug Supervisory Agency of the Republic of Indonesia.

2.4. Research and data collection procedures

2.4.1. Patient recruitment and grouping

This study was conducted on patients at risk of metabolic syndrome at PHC in a rural area in the Bantul district. Based on PHC data from January to October 2016, patients suffering from type 2 diabetes mellitus were 401 patients and 615 patients suffering from hypertension. Based on the doctor's recommendation, 120 patients met the inclusion criteria, 112 of whom had signed the informed consent. Ninety-nine patients in total met the eligibility requirements; 13 additional patients have turned away due to the following reasons: one patient had active TB; one patient's family objected; six patients failed to show up at the initial meeting; one patient had ulcers; one patient had a stroke; one patient had a low platelet count; one patient had a history of heart disease, and one patient was injured during blood collection. Ninety-nine patients were randomized using a simple manual method, but the number of volunteers who completed until the end of the study was 94.

2.4.2. Patient health check-up

DM patients at risk of metabolic syndrome in rural health centers in Bantul who stated that they were willing to be patients by signing informed consent were divided by simple manual randomization. Prospective volunteers are then subjected to a physical examination in the form of height, weight, respiratory rate (RR), and heart rate (HR), and laboratory examinations in the form of blood pressure, glucose levels, and fat levels to ensure health status. A doctor carries out a clinical examination of the patient with a license to practice accompanied by a certificate according to the results of the physical examination and blood laboratory.

2.4.3. Providing interventions and measuring outcomes

DM patients with routine therapy who signed the informed consent and were randomized were divided into two groups. The treatment group and routine therapy from PHC were also given MHM preparations for 20 days. The control group received routine therapy from PHC and then was given a placebo. Administration of MHM preparations or placebo was carried out for 20 days. On the 21st day, the clinical outcome parameters were measured, including checking weight, height, and vital signs, followed by taking blood for hematology and blood chemistry tests (blood sugar, cholesterol, triglyceride, HDL, SGPT, SGOT, urea, and creatinine and HbA1C) by trained health personnel. Determination of glucose, cholesterol, triglyceride, HDL, LDL, SGOT, SGPT, urea, and creatinine levels was carried out with the help of spectrophotometry. Calculation of HbA1C levels based on plasma glucose levels with the help of the formula HbA1C(%)=(Estimated average glucose(mg/dL)+46.7)/28.7 [31].

2.5. Data analysis

The research data were analyzed univariately to describe the demographic and clinical characteristics of the subjects. We performed a bivariate analysis of the mean difference test with an independent t-test to determine the significance of differences in blood glucose levels and other clinical parameters between the two groups. All statistical analyzes were performed at a 95% level of confidence. Data analysis was performed using the free edition statistical program for social science (SPSS) software.

3. RESULTS AND DISCUSSION

3.1. Subject characteristics

This research was conducted at a health center in a rural area in Bantul, YSR, for DM patients with routine therapy. Clinical descriptions of prospective subjects are presented in Table 1. The results of blood pressure, body weight, and body mass index (BMI) levels of glucose, triglyceride, and cholesterol between the treatment group and placebo before treatment are presented in Table 1. Examining clinical characteristics

before consuming preparations containing BCSO showed that most volunteers had abnormal BMI, systolic blood pressure, triglycerides level, and blood sugar levels. The statistical analysis of patient characteristics showed no differences in demographic or clinical characteristics between the two groups (p>0.05).

Table 1. Clinical characteristics of DM patients at PHC in rural areas in Bantul district, Special Region of Yogyakarta before consuming MHM herbal supplement preparations

Characteristic	Treatment group (n=66)	Control group (n=33)	p
Age (year)	55.65±8.93	57.45±11.15	>0.05
Systolic blood pressure (SBP) (mmHg)	142.68±17.64	142.48±16.42	>0.05
Diastolic blood pressure (DBP) (mmHg)	80.80±9.26	79.76±7.01	>0.05
Pulse (x/minutes)	90.08±10.94	89.39±9.99	>0.05
Body weight (Kg)	56.08±10.94	56.27±11.71	>0.05
BMI (Kg/m^2)	24.14±4.06	24.14±4.10	>0.05
Glucose level (mg/dl)	241.52±108.56	253.79±116.23	>0.05
Cholesterol total (mg/dl)	169.18±41.87	170.79±33.90	>0.05
Triglyceride (mg/dl)	196.92±117.67	220.12±67.23	>0.05
HDL (mg/dl)	45.44±10.31	43.79±8.05	>0.05

3.2. Examination of blood pressure, BMI, serum blood glucose, cholesterol, solid triglycerides treatment

Data on clinical outcomes of DM patients after consuming MHM preparations for 20 days are presented in Table 2. Table 2 shows no differences in blood pressure, cholesterol levels, triglyceride levels, SGOT, SGPT, HDL, LDL, and creatinine levels between the treatments and control group (p>0.05). The treatment group consuming MHM nutritional supplement preparations had lower glucose, HbA1C, and urea levels than those not consuming MHM preparations or the control group (p<0.05). Consumption of MHM preparations for 20 days was able to normalize blood glucose levels and reduce HbA1C and urea levels.

Table 2. Clinical characteristics of DM patients at PHC in rural areas in the Bantul district, Special Region Yogyakarta after 20 days of consuming the MHM herbal supplement preparations

Characteristic	Treatment group (n=61)	Control group (n=33)	p
Systolic blood pressure (SBP) (mmHg)	137.95±16.79	138.66±13.17	>0.05
Diastolic blood pressure (SBP) (mmHg)	80.19±13.87	75.31±8.47	>0.05
Pulse (x/minutes)	92.21±1.62	82.42±2.51	>0.05
Body weight (Kg)	57.47±11.34	56.65±12.04	>0.05
BMI (Kg/m2)	24.67±4.161	24.55±4.36	>0.05
Blood glucose level (mg/dl)	188.84±87.92	264.72±80.48	<0.00*
Cholesterol total level (mg/dl)	193.92±49.33	178.81±47.59	>0.05
Triglyceride level (mg/dl)	174.73±111.80	184.34±116.33	>0.05
SGOT (mg/dl)	21.32±6.80	21.47±5.43	>0.05
SGPT (mg/dl)	19.66±7.14	21.50±8.40	>0.05
HDL level (mg/dl)	45.23±6.76	44.25±5.41	>0.05
LDL level (mg/dl)	113.74±43.24	97.72±42.67	>0.05
HbA1C (%)	7.64±2.50	9.76±2.25	<0.05*
Ureum (mg/dl)	33.56±13.05	39.94±16.16	<0.05*
Creatinine (mg/dl)	1.22±0.31	1.36±0.31	>0.05

Increased blood pressure, BMI, LDL, and glucose levels can increase risk factors for metabolic syndrome [32]. Metabolic syndrome is associated with increased risk factors for cardiovascular disease. One of the therapy goals for DM patients at PHC is to control blood sugar levels and prevent DM patients from developing metabolic syndrome, thereby reducing the risk of cardiovascular disease. According to the eighth joint national committee (JNC 8), the target blood pressure of hypertensive patients with diabetes mellitus is 140 mmHg (systolic blood pressure), 90 mmHg (diastolic blood pressure). The results of blood pressure measurements showed that both study groups had controlled systolic and diastolic blood pressure, which was less than 140/90 mmHg. The one-year nonrandomized clinical trial research of 114 patients with type 2 diabetes mellitus showed that Nigella sativa dose of 2 g/day administration for six months did not affect systolic and diastolic blood pressure, blood pressure in the control and the treatment group were not significantly different (p>0.05); while diastolic blood pressure at the 9th and 12th months showed a significant difference (p<0.05) [33]. The factors that cause DM patients to experience hypertension include oxidative stress, endothelial dysfunction, insulin resistance, and an increase in inflammatory mediators. Monitored systolic and diastolic blood pressure will reduce risk factors for atherosclerosis in type 2 DM patients [34].

The results showed that both groups had a body mass index (BMI) classification of fat. There was no significant difference in BMI between the treatment and control groups (p>0.05). The results of this study are in line with previous research. A nonrandomized clinical trial study on 114 patients with type-2 diabetes

mellitus for one year showed no difference in BMI between the control group and the treatment group Nigella sativa at a dose of 2 g/day ($p>0.05$). BMI in patients with diabetes mellitus who were given Nigella sativa for eight weeks showed no significant difference between the treatment group and the control group in pre- and post-treatment [35].

The results of the examination of serum glucose levels and HbA1C showed that the treatment group had normal glucose levels (<200 mg/dl), which was 188.84±87.92 mg/dl when compared to the control group (264.72±80.48 mg/dl) ($p<0.01$). The treatment group also had lower HbA1C levels (7.64±2.50%) than the control group (9.76±2.25%) ($p<0.05$). This study confirms the results of clinical trials of the effect of preparations containing *Nigella sativa* on previous blood glucose levels. Previous clinical trials showed that administering *Nigella sativa* preparations to both DM patients and healthy volunteers were proven to reduce blood glucose levels [28]. The hypoglycemic effect of *Nigella sativa* is attributed to its activity as an antioxidant. Thymoquinone is the primary antioxidant component of *Nigella sativa* which has antioxidant potential that can scavenge free radicals, reduce oxidative stress and promote pancreatic cell proliferation, thereby leading to increased insulin secretion [36]. Thymoquinone decreased gluconeogenic enzyme expression and inhibited intestinal absorption of glucose. Thymoquinone also inhibited gluconeogenesis in muscle and liver by activating adenosine monophosphate-activated protein kinase (AMPK) [37].

The results of the examination of cholesterol, triglyceride, LDL, and HDL levels in both groups were within normal limits. There was no difference in cholesterol, triglyceride, HDL, and LDL levels between the two groups ($p>0.05$). The effect of giving preparations containing BCSO in various clinical trials gave varied results. In a randomized, double-blind, controlled trial, giving black cumin seeds for eight weeks to 20 patients with diabetes mellitus on triglyceride and cholesterol levels, there was no significant difference between the placebo and the treatment group. However, there was a significant difference in HDL and LDL levels. Black cumin seeds can reduce HDL, triglyceride, and cholesterol levels in patients with diabetes mellitus [38].

The provision of MHM nutritional supplement preparations is proven to reduce urea levels. The results showed that the treatment group had lower urea levels than the control group (33.56±13.05 mg/dl vs. 39.94±16.16 mg/dl) ($p<0.05$). This study's results align with previous studies, where preparations containing black cumin seeds could reduce urea and creatinine levels in chronic kidney disease (CKD) patients on hemodialysis [39]. Thymoquinone has an activity to inhibit cyclooxygenase and lipoxygenase enzymes in arachidonic metabolism. In addition, thymoquinone can increase antioxidant enzyme activity. Thymoquinone can inhibit the expression of vascular endothelial growth factor (VEGF) through the VEGFR2/PI3K/Akt pathway, potentially improving asthma [40]. The superoxide dismutase (SOD) activity increased significantly after the administration of thymoquinone injection [41].

We recognize that this study has many weaknesses. One of the weaknesses is that the research design used is a retrospective cohort and the duration of treatment is still relatively short in community settings, so many confounding variables cannot be controlled. Research with a randomized clinical control trial design with a longer duration of treatment needs to be carried out at a later stage.

4. CONCLUSION

Blood sugar levels and systolic blood pressure of DM patients at PHC before treatment were abnormal. Consumption of MHM herbal preparations as herbal supplements containing BCSO for 20 days by DM patients with standard therapy at PHC has the potential to increase clinical outcomes, especially in reducing blood sugar levels, decreasing HbA1C percentage, and decreasing urea levels. It is necessary to educate DM patients in PHC the importance of consuming nutritional supplements to increase the achievement of therapeutic goals.

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REFERENCES

[1] R. Hinkel *et al.*, "Diabetes Mellitus–Induced Microvascular Destabilization in the Myocardium," *Journal of the American College of Cardiology*, vol. 69, no. 2, pp. 131–143, 2017, doi: 10.1016/j.jacc.2016.10.058.

[2] A. Rudijanto, M. R. Saraswati, E. Yunir, P. Kumala, H. H. Puteri, and V. V Mandang, "Indonesia Cohort of IO HAT Study to Evaluate Diabetes Management, Control, and Complications in Retrospective and Prospective Periods Among Insulin-Treated Patients with Type 1 and Type 2 Diabetes," *Acta Med. Indonesia*, vol. 50, no. 1, pp. 26–37, 2018.

[3] A. M. Schmidt, "Highlighting Diabetes Mellitus," *Arteriosclerosis, Thrombosis, and Vascular Biology*, vol. 38, no. 1, pp. e1–e8, 2018, doi: 10.1161/ATVBAHA.117.310221.
[4] A. Berbudi, N. Rahmadika, A. I. Tjahjadi, and R. Ruslami, "Type 2 Diabetes and its Impact on the Immune System," *Current Diabetes Reviews*, vol. 16, no. 5, pp. 442–449, 2020, doi: 10.2174/1573399815666191024085838.
[5] H. Vargas-Uricoechea and L. Á. Casas-Figueroa, "An Epidemiologic Analysis of Diabetes in Colombia," *Annals of Global Health*, vol. 81, no. 6, pp. 742–753, 2015, doi: 10.1016/j.aogh.2015.11.001.
[6] O. Tabatabaei-Malazy, B. Larijani, and M. Abdollahi, "A novel management of diabetes by means of strong antioxidants' combination," *Journal of Medical Hypotheses and Ideas*, vol. 7, no. 1, pp. 25–30, 2013, doi: 10.1016/j.jmhi.2012.12.002.
[7] M. McGill, L. Blonde, J. C. N. Chan, K. Khunti, F. J. Lavalle, and C. J. Bailey, "The interdisciplinary team in type 2 diabetes management: Challenges and best practice solutions from real-world scenarios," *Journal of Clinical & Translational Endocrinology*, vol. 7, pp. 21–27, 2017, doi: 10.1016/j.jcte.2016.12.001.
[8] E. McCracken, M. Monaghan, and S. Sreenivasan, "Pathophysiology of the metabolic syndrome," *Clinics in Dermatology*, vol. 36, no. 1, pp. 14–20, 2018, doi: 10.1016/j.clindermatol.2017.09.004.
[9] B. Bikbov *et al.*, "Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017," *The Lancet*, vol. 395, no. 10225, pp. 709–733, 2020, doi: 10.1016/S0140-6736(20)30045-3.
[10] Y.-C. Lin, Y.-H. Chang, S.-Y. Yang, K.-D. Wu, and T.-S. Chu, "Update of pathophysiology and management of diabetic kidney disease," *Journal of the Formosan Medical Association*, vol. 117, no. 8, pp. 662–675, 2018, doi: 10.1016/j.jfma.2018.02.007.
[11] N. Marissa, M. Marlinda, M. Maulidar, V. Wilya, N. Ramadhan, and Z. Hadifah, "Interferon gamma concentration in diabetes mellitus and dyslipidemia patient," *Health Science Journal of Indonesia*, vol. 12, no. 2, pp. 74–80, 2021, doi: 10.22435/hsji.v12i2.4290.
[12] M. Rudrapal *et al.*, "Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights Into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action," *Frontiers in Pharmacology*, vol. 13, pp. 1–15, 2022, doi: 10.3389/fphar.2022.806470.
[13] L. Liu *et al.*, "Gut microbiota: A new target for T2DM prevention and treatment," *Frontiers in Endocrinology*, vol. 13, pp. 1–19, 2022, doi: 10.3389/fendo.2022.958218.
[14] M. Dhibi, Z. Amri, A. M. Bhouri, S. Hammami, and M. Hammami, "Comparative study of the phenolic profile and antioxidant activities of Moringa (Moringa oleifera Lam.) and Jujube (Ziziphus lotus Linn.) leaf extracts and their protective effects in frying stability of corn oil," *Measurement: Food*, vol. 7, p. 100045, 2022, doi: 10.1016/j.meafoo.2022.100045.
[15] P. Prakash *et al.*, "Evidence-based traditional Siddha formulations for prophylaxis and management of respiratory symptoms in COVID-19 pandemic-a review," *Biocatalysis and Agricultural Biotechnology*, vol. 35, p. 102056, 2021, doi: 10.1016/j.bcab.2021.102056.
[16] E. Darmawan, A. Akrom, E. F. Lerebulan, and A. Adnan, "Jamu Reduce Oxidative Stress from Active Smokers in a Rural Area of Yogyakarta," *IOP Conference Series: Earth and Environmental Science*, vol. 810, no. 1, p. 12039, 2021, doi: 10.1088/1755-1315/810/1/012039.
[17] M. Yang *et al.*, "Recent developments in Moringa oleifera Lam. polysaccharides: A review of the relationship between extraction methods, structural characteristics and functional activities," *Food Chemistry: X*, vol. 14, p. 100322, 2022, doi: 10.1016/j.fochx.2022.100322.
[18] Akrom, F. A. Hastanto, and L. H. Nurani, "Hepatoprotective effect of chewable tablet of Centella asiatica (L.) Urb extractin Wistar rats induced by high fat diets," *Indonesian Journal of Pharmacology and Therapy*, vol. 2, no. 1, 2021, doi: 10.22146/ijpther.1128.
[19] S. Tabassum, N. Rosli, S. J. A. Ichwan, and P. Mishra, "Thymoquinone and its pharmacological perspective: A review," *Pharmacological Research - Modern Chinese Medicine*, vol. 1, p. 100020, 2021, doi: 10.1016/j.prmcm.2021.100020.
[20] T. HIdayati, "Effect of ethanol extract of black cumin on phagocytic activity of macrophages of Swiss P. berghei infected mice in vitro," in *Proceedings of the National Seminar on Pharmacotherapy*, 2006.
[21] N. M. P. Maideen, "Antidiabetic Activity of Nigella sativa (Black Seeds) and Its Active Constituent (Thymoquinone): A Review of Human and Experimental Animal Studies," *Chonnam Medical Journal*, vol. 57, no. 3, pp. 169–175, 2021, doi: 10.4068/cmj.2021.57.3.169.
[22] G. O. Adam *et al.*, "Hepatoprotective effects of Nigella sativa seed extract against acetaminophen-induced oxidative stress," *Asian Pacific Journal of Tropical Medicine*, vol. 9, no. 3, pp. 221–227, Mar. 2016, doi: 10.1016/j.apjtm.2016.01.039.
[23] A. S. Dehyab, M. F. A. Bakar, M. K. AlOmar, and S. F. Sabran, "A review of medicinal plant of Middle East and North Africa (MENA) region as source in tuberculosis drug discovery," *Saudi Journal of Biological Sciences*, vol. 27, no. 9, pp. 2457–2478, 2020, doi: 10.1016/j.sjbs.2020.07.007.
[24] I. I. Severina *et al.*, "In search of novel highly active mitochondria-targeted antioxidants: Thymoquinone and its cationic derivatives," *FEBS Letters*, vol. 587, no. 13, pp. 2018–2024, 2013, doi: 10.1016/j.febslet.2013.04.043.
[25] D. R. Fajar, Akrom, and E. Darmawan, "The influence of black cumin seed oil therapy with dosage of 1.5 mL/day and 3 mL/day to interleukin-21 (IL-21) expression of the patients with metabolic syndrome risk," *IOP Conference Series: Materials Science and Engineering*, vol. 259, p. 12012, 2017, doi: 10.1088/1757-899X/259/1/012012.
[26] S. Bourgou, A. Pichette, B. Marzouk, and J. Legault, "Bioactivities of black cumin essential oil and its main terpenes from Tunisia," *South African Journal of Botany*, vol. 76, no. 2, pp. 210–216, 2010, doi: 10.1016/j.sajb.2009.10.009.
[27] A. Ahmad *et al.*, "A review on therapeutic potential of Nigella sativa: A miracle herb," *Asian Pacific Journal of Tropical Biomedicine*, vol. 3, no. 5, pp. 337–352, 2013, doi: 10.1016/S2221-1691(13)60075-1.
[28] G. P. Widodo, R. Herowati, J. M. Perangin-angin, and J. E. Y. Kamlasi, "Antihyperglycemic, antioxidant, and pancreas regeneration activities of black cumin (Nigella sativa L.) seeds ethanol extract in alloxan-induced diabetic rats," *International Journal of Pharmacy and Pharmaceutical Science*, vol. 8, no. 5, pp. 37–40, 2016.
[29] V. Panda, A. Deshmukh, S. Singh, T. Shah, and L. Hingorani, "An Ayurvedic formulation of Emblica officinalis and Curcuma longa alleviates insulin resistance in diabetic rats: Involvement of curcuminoids and polyphenolics," *Journal of Ayurveda and Integrative Medicine*, vol. 12, no. 3, pp. 506–513, 2021, doi: 10.1016/j.jaim.2021.05.005.
[30] A. Akrom and E. Darmawan, "Tolerability and safety of black cumin seed oil (Bcso) administration for 20 days in healthy subjects," *Biomed. Res.*, vol. 28, no. 9, pp. 4196–4201, 2017.
[31] A. Kumar *et al.*, "Formulation and evaluation of SGLT2 inhibitory effect of a polyherbal mixture inspired from Ayurvedic system of medicine," *Journal of Traditional and Complementary Medicine*, vol. 12, no. 5, pp. 477–487, 2022, doi: 10.1016/j.jtcme.2022.03.003.
[32] J. E. Villena, "Diabetes Mellitus in Peru," *Annals of Global Health*, vol. 81, no. 6, pp. 765–775, 2015, doi: 10.1016/j.aogh.2015.12.018.
[33] H. Shaterzadeh-Yazdi, M.-F. Noorbakhsh, S. Samarghandian, and T. Farkhondeh, "An Overview on Renoprotective Effects of

Thymoquinone," *Kidney Diseases*, vol. 4, no. 2, pp. 74–82, 2018, doi: 10.1159/000486829.
[34] F. S. Ahmad, H. Ning, J. D. Rich, C. W. Yancy, D. M. Lloyd-Jones, and J. T. Wilkins, "Hypertension, Obesity, Diabetes, and Heart Failure–Free Survival," *JACC: Heart Failure*, vol. 4, no. 12, pp. 911–919, 2016, doi: 10.1016/j.jchf.2016.08.001.
[35] S. Safi *et al*., "The effect of Nigella sativa on appetite, anthropometric and body composition indices among overweight and obese women: A crossover, double-blind, placebo-controlled, randomized clinical trial," *Complementary Therapies in Medicine*, vol. 57, p. 102653, 2021, doi: 10.1016/j.ctim.2020.102653.
[36] F. Li, P. Rajendran, and G. Sethi, "Thymoquinone inhibits proliferation, induces apoptosis and chemosensitizes human multiple myeloma cells through suppression of signal transducer and activator of transcription 3 activation pathway," *British Journal of Pharmacology*, vol. 161, no. 3, pp. 541–554, 2010, doi: 10.1111/j.1476-5381.2010.00874.x.
[37] N. Chehl, G. Chipitsyna, Q. Gong, C. J. Yeo, and H. A. Arafat, "Anti-inflammatory effects of the Nigella sativa seed extract, thymoquinone, in pancreatic cancer cells," *HPB*, vol. 11, no. 5, pp. 373–381, 2009, doi: 10.1111/j.1477-2574.2009.00059.x.
[38] J. V Thomas, M. E. Mohan, P. Prabhakaran, S. Das S, B. Maliakel, and K. I.M., "A phase I clinical trial to evaluate the safety of thymoquinone-rich black cumin oil (BlaQmax®) on healthy subjects: Randomized, double-blinded, placebo-controlled prospective study," *Toxicology Reports*, vol. 9, pp. 999–1007, 2022, doi: 10.1016/j.toxrep.2022.04.020.
[39] N. M. Dinar, S. Pratiwi, R. Kihara, N. G. Paramita, N. R. Fathurrahman, and J. Levita, "Hepato-Nephroprotective Activity of Nigella Sativa Oil on Paracetamol-Induced New Zealand Rabbits (Oryctolagus Cuniculus)," *International Journal of Pharmacy and Pharmaceutical Sciences*, vol. 9, no. 10, p. 225, Nov. 2017, doi: 10.22159/ijpps.2017v9i11.21854.
[40] H. Rahma, I. W. A. Indrawan, M. Nooryanto, Rahajeng, and K. Keman, "Effect of a black cumin (Nigella sativa) ethanol extract on placental angiotensin II type 1-receptor autoantibody (AT1-AA) serum levels and endothelin-1 (ET-1) expression in a preeclampsia mouse model," *Journal of Taibah University Medical Sciences*, vol. 12, no. 6, pp. 528–533, 2017, doi: 10.1016/j.jtumed.2017.06.002.
[41] F. Alghamdi, M. N. Al-Seeni, and M. A. Ghoneim, "Potential synergistic antioxidant effect of thymoquinone and vitamin E on cisplatin-induced acute nephropathy in rats," *Clinical Nutrition Experimental*, vol. 32, pp. 29–37, 2020, doi: 10.1016/j.yclnex.2020.05.002.

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Arif Budi Setianto is medicine formulator and crystallography analysis researcher and good attention about the interaction between drug and drug or drug and conformer when both combined in formulation as like the solubility, stability and transformation phase are highlight in concern as well as manufacture problem in solid dosage form. The identification and characterization on analysis of manufacture process to good quality product are important. The potential phase transformations that can occur during common pharmaceutical processing operations, the underlying mechanisms, anticipation/prevention, and impact on product quality are important to consider when manufacturing dosage forms. These are attention in his research. He can be direct contact via email: arif.setianto@pharm.uad.ac.id.