A Combination Supplement of Bitter Melon Extract (momordica charantia l.) with Snakehead Fish (channa striata) Powder has no Effect as an Anti-glycation Agent in type 2 Diabetes Mellitus

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Abstract. Diabetes mellitus (DM) is characterized by hyperglycemia. Chronic hyperglycemia can cause interactions between vascular and inflammatory cells, resulting in advanced glycation end products (AGEs). This study aims to examine the combined supplement of bitter melon leaf extract with snakehead fish powder as an anti-glycation agent in Type 2 diabetes mellitus This study used a randomized, double-blinded, placebo-controlled trial. Eighty patients with Type 2 diabetes mellitus (DMT2) who met the criteria were divided into 2 groups, namely: 40 patients as the treatment group was given supplements of a combination of bitter melon leaf extract and snakehead fish powder, and the control group 40 patients received a placebo. This intervention was carried out for 4 weeks. AGEs levels were measured at baseline and the end of treatment. Data analysis using paired t-test and independent t-test, with a significance limit of $p < 0.05$. Supplements combined with bitter gourd leaf extract and snakehead fish powder have no effect as anti-glycation in Type 2 diabetes mellitus. This Supplements the combination of bitter gourd leaf extract and snakehead fish powder can used for further research in field of complementary therapy in diabetic treatment.

Keywords: Advanced Glycation End Products, Bitter Melon, Momordica Charantia L, Diabetes Melitus, Channa Striata.

1 Introduction

Diabetes Mellitus (DM) is a chronic and complicated condition that has had negative effects on both public health and the economy. Over 463 million persons globally have diabetes in 2019, according to the International Diabetes Federation (IDF). By 2045, there will be 700 million people worldwide who have diabetes if this trend continues [1]. Diabetes mellitus poses a hazard to health, ability to function, complications, and

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lifespan [2]. Nearly 70% of DM patients currently reside in underdeveloped and emerging nations, and it is predicted that this percentage will increase over the next 20 years [3]. About 90% of all diabetes cases worldwide are caused by Type 2 Diabetes Mellitus (T2DM), which has been dubbed a "twenty-first century calamity" [4] since it is usually linked to the metabolic syndrome.

Chronic hyperglycemia and inflammation are the hallmarks of Type 2 Diabetes Mellitus (T2DM), a metabolic condition that can lead to a variety of vascular problems. A collection of chemicals called AGEs, which are created by non-enzymatic interactions of reducing sugars with free amino groups from proteins, can be formed more quickly as a result of chronic hyperglycemia. Reactive oxygen species (ROS) production, interactions with certain receptors, and the development of cross-linked proteins that alter the extracellular matrix's structure and function are some of the processes through which AGEs can cause harm. Additionally, they are in charge of "metabolic memory" [5]. Free radicals may be produced as a result of hyperglycemia [6].

Chronic DM problems can start to manifest because of hyperglycemia and AGEs [7]. Through endothelial cell destruction and intracellular protein malfunction, AGEs can worsen diabetes symptoms and cause organ and cell damage. They are now seen as a measure that is increasingly important when evaluating diabetesn[8]. Due to the presence of phytochemicals and phytonutrients, dietary components have a crucial role in supporting health. This dietary element can aid in lowering the severity of issues brought on by diseases including diabetes, hypercholesterolemia, hyperlipidemia, and inflammation. A dietary pattern that incorporates nutritious foods into regular diet and exercise is a highly efficient method of halting the pathogenesis of diabetes mellitus. The usefulness of bitter melon as a diabetes preventative has been demonstrated in numerous research [9]. Due to the presence of numerous hypoglycaemic substances, including alkaloids, flavonoids, saponin, catechins, charantins, vicine, and polypeptides of fraction p, bitter melon has been shown to have a hypoglycaemic potential in numerous in vivo experiments [10]. In addition to being anti-inflammatory, bitter melon can regulate blood sugar levels and avoid problems from diabetes [11], [12].

The effectiveness of bitter melon in producing insulin has been demonstrated in numerous studies [13]. Although bitter melon has been touted as having potential up to this point, research on diabetic people has produced mixed results. The majority of earlier clinical investigations were non-randomized, had ambiguous product specifications, and were short-term [8]. Although there is still insufficient proof, it is widely believed that bitter melon lowers blood sugar levels [14]. According to Trakoon, Muscle, and colleagues, bitter melon can lower AGE levels in DM [8]. This study combines snakehead fish with bitter melon. Many healthy amino acids and fatty acids can be found in snakehead fish [15]. It acts as an antioxidant [16]. Considering no study on the combination of bitter melon with snakehead fish on glycaemic control in Type-2 diabetes patients. This pilot study aimed to investigate the effect of this herb in type 2 diabetes patients.

2 Method

2.1 Making the combination of snakehead fish powder and bitter melon extract

Bitter melon extract was macerated with ethanol solution. Once filtered, the solution on the bitter melon extract was evaporated. For the snakehead fish, its head and dirt were removed prior to be steamed, drained and dried. After drying, it was blended and sieved. The capsules of the combination of bitter melon extract and snakehead fish powder were made at the Clinical Pharmacy Laboratory, UMS (Universitas Muhammadiyah Surakarta).

2.2 Clinical trial

This study used a randomized control trials design with a control group in Public Health Centers in Purwosari, Pajang, Nusukan and Banyuanyar in Surakarta City. The protocol of this study protocol has been approved by the Health Research Ethics Committee Dr. Moewardi General Hospital/School of Medicine, Universitas Sebelas Maret Surakarta, Indonesia.

2.3 Patients

Patients who met the criteria included those with Type 2 Diabetes Mellitus (T2DM) between the ages of 25 and 65 who visited the Surakarta City, Central Java, Indonesia, Health Centers of Purwosari, Pajang, Nusukan, and Banyuanyar. The T2DM patients chosen from medical records were diagnosed with DM using metformin, a type of biguanide medicine, and had fasting blood glucose levels between 126 mg/dL and 200 mg/dL. They also agreed to sign an informed consent form. Patients who were excluded from the study included those who had tested positive for pregnancy and lactation in pregnant women and those whose renal function had been compromised by laboratory tests. more than 1.5 mg/dL on a creatinine test, poor liver function: Serum glutamate oxaloacetate transaminase (SGOT) enzyme value of 40U/L and serum glutamate pyruvate transaminase (SGPT) of 35U/L are twice over the normal range, drop out, and allergic to snakehead fish powder and bitter melon leaf extract, respectively.

2.4 Study procedure

The patients were given a written and verbal explanation before the trial began. Each patient then provided their informed permission. Patients were assessed for research eligibility at the initial appointment. The eligible patients were then randomly assigned to 2 groups: the treatment group and the control group. For four weeks, the treatment group consumed a concoction of snakehead fish powder and bitter melon extract, while the control group took a placebo. By monitoring the number of pills taken and interviewing patients in each control group, this study's adherence to using herbal remedies was assessed.

2.5 Outcome measurement

The results of primary efficacy refer to the changes in fasting blood glucose levels analyzed by enzymatic technique. Glycated albumin, insulin and AGEs were analyzed by ELISA method. Meanwhile, the fasting blood glucose, glycated albumin, AGEs and insulin levels were measured at baseline and at the end of fourth 4 in both groups.

2.6 Statistical analysis

Data were analyzed based upon the protocol principles (PP) and expressed as the number of patients (N), mean ± SD or mean difference ± SE difference. The difference between baseline and after intervention was expressed as the change value (Δ) in fourth week. Discrete data were evaluated by Pearson's Chi-square test or Fisher Exact. Two factors of Repeated Measurement - Analysis of Variance (RM-ANOVA) with multiple comparisons with the Bonferroni or Friedman test was used to assess treatment effects, timing, and interaction. Independent t-test or ManneWhitney test was used to compare the effects between the 2 groups at each time point. The paired t-test or Wilcoxon Signed Rank test was used to compare the change value after 4 weeks of treatment in the groups. The two-side hypothesis was used in all tests and $P < 0.05$ here was considered statistically significant.

3 Result and Discussion

3.1 Results

In this study there were 80 DM patients who participated. All DM patients were randomized, then divided into 2 groups, namely: the treatment group (n = 40) were given supplementation of a combination of bitter melon extract with snakehead fish powder in people with Type 2 diabetes mellitus and the control group (n = 40) were given a placebo. Baseline characteristics data between the 2 groups showed no difference (Table 1). There was no difference in all baseline parameters in the treatment and control groups. Age, gender, education, occupation, body weight, body mass index (BMI), duration of DM, antidiabetic drugs, fasting plasma glucose levels, systolic and diastolic blood pressure did not differ between groups and did not change during the experiment.

Laboratory assessments at baseline and mean change from baseline at week 4 are shown in Table 2. The results showed that the average AGEs after treatment did not change significantly from baseline in each group. None of the participants experienced signs and symptoms of hepatitis. No adverse effects were found in any of the subjects and no participants dropped out of the study.

Table 1. Baseline characteristics of patients

Variable	Treatment Group (n = 45)	Control Group (n = 45)	*p-value*[a]
Age (year)	58.97±9.25	55.67±10.49	0.157
Sex			0.169
Male (%)	18 (45)	12 (30)	
Female (%)	22 (55)	28 (70)	
Education			0.358
Primary School (%)	7 (17.5)	13 (32.5)	
Junior High School (%)	8 (20)	5 (12.5)	
Senior High School (%)	18 (45)	15 (37.5)	
University (%)	7 (17.5)	7 (17.5)	
Occupation			0.185
Midwife (%)	15 (37.5)	21 (52.5	
Entrepreneur (%)	18 (45)	13 (32.5)	
Civil Servants (%)	1 (2.5)	2 (5)	
Retired (%)	6 (15)	4 (10)	
Weight (kg)	64.80±13.32	63.42±10.06	0.441
Body Mass Index (kg/m2)	26.14±4.50	24.15±4.08	0.053
Duration of diabetes mellitus (Year)	5.87±6.90	4.27±5.43	0.244
Antidiabetic drugs (OAD)			1.00
Yes (%)	40 (100)	40 (100)	
No (%)	0	0	
Fasting plasma glucose level (mg/dL)	178.17±90,59	178.52±66.77	0.283
Blood Pressure (Systolic) (mmHg)	129.75±14.23	128.50±14.59	0.221
Blood Pressure (Systolic) (mmHg)	83.25±9.44	82±7.91	0.925

[a]No difference (comparable) $p > 0,05$

Table 2. Laboratory examination for treatment group and control group

Variable	Baseline	Δ at week 4	*p within group*[a]	*p between groups*[b]
AGEs (ng/L)				
Treatment Group	47.94±11.08	93.34±23.26	0.629	0.974
Control Group	46.30±89.28	83.26±30.13	0.621	

Data are stated with mean ± SD.

The change values of fasting plasma glucose level showed a significant difference for time or treatment effects (Independent t Test) at $p < 0.05$.

[a] $p < 0.05$ significant different of change values between treatment group and control group at the same period of time (Paired t-test)

[b] $p < 0.05$ significant different of change values after 4 weeks (Independent t test)

3.2 Discussion

GA and fasting blood glucose levels can both be decreased by two grams of a bitter melon extract and snakehead fish powder combination taken twice daily. In T2DM patients with poor control, glycated albumin can be utilized to monitor blood glucose levels [17]. Blood glucose levels have been known to be lowered by bitter melon extract

[18]. The existence of numerous hypoglycaemic substances in bitter melon, including alkaloids, flavonoids, saponins, catechins, charantins, vicine, and polypeptides of fraction p, has been demonstrated in numerous in vivo experiments [19]. Bitter melon can regulate blood sugar levels and shield DM sufferers from problems[11]. According to pre-diabetes experiment findings, eating bitter melon can lower postprandial glucose levels in 50% of patients [20]. Additionally, aRCT in 52 individuals with pre-diabetes shown that eating bitter melon could dramatically lower the level of fasting blood glucose[21]. Therefore, bitter melon will have a better hypoglycaemic effect on diabetics. Another observational study established the hypoglycaemic effects of bitter melon [22].

This study's findings also indicated a rise in insulin. This research is consistent with that of Rosyid y et al., 2018 [17] which found that diabetic rats fed with bitter melon had significantly higher insulin levels than those in the diabetes control group. Similar to this, Fernandes et al., 2007 [23] discovered that bitter melon extract had a favorable impact on serum insulin levels. Bitter melon supplementation may have caused the Langerhans beta cells in diabetic rats to heal, increasing their insulin levels [23], [24]. Another investigation revealed that include bitter melon in the diet can boost beta cell production [24]. Several researchers have claimed that bitter melon can boost beta cell activity [25]. Several theories contend that bitter melon can operate as an insulin secretagogue in vivo [26], [27], enhancing the elimination of glucose. Others hypothesized that the hypoglycaemic effect is brought on by an increase in the metabolism of glucose, a corresponding increase in tissue sensitivity to glucose, and/or an induction of the translocation of the glucose transporter isoform 4 (GLUT4) [10], [28]. Additionally, bitter melon can reduce the small intestine's -glucosidase activity, which lessens the digestive tract's ability to digest and absorb glucose [28]. One of the bitter melon's primary chemical constituents, polypeptide-p, has demonstrated insulin-mimetic hypoglycemic effects [26], [27], [29].

The amounts of AGEs, a class of chemicals produced by the non-enzymatic interaction of reducing sugars with free amino groups from proteins, appeared to be unaffected by this study's efforts to do so. Reactive oxygen species (ROS) generation, interactions with certain receptors, and the synthesis of cross-linked proteins that change the extracellular matrix's structure and function are just a few of the processes through which AGEs can have negative consequences [30]. The various lives of the members in each group can be the cause of this. The levels of AGEs may then be impacted by this.

This study's primary shortcoming is connected to the non-random sample. Due to the low drop-out rate, research subjects were those who were willing to take part in the intervention. The Covid-19 epidemic made it challenging to assign random samples for interventions. Additionally, a lot of diabetes people still do not trust herbal remedies since they think that they can make their situation worse. The various lives of the study participants represent another drawback. This condition undoubtedly has an impact on AGEs, GA, insulin, and blood glucose levels. The participants were divided into a treatment group and a control group, which was the study's principal strength.

4 Conclusion

This study presents the initial clinical evidence showing that the combination of bitter melon extract and snakehead fish powder have no effect as anti-glycation in Type 2 diabetes mellitus However, a larger clinical test needs to be done to confirm the results of this pilot study.

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