

Effect Of Extract Breadfruit Leaf (*Artocarpus altilis* (Park.) Fosberg) Toward Tumor Necrosis Factor (TNF- α) In Obese Rat (*Rattus norvegicus*) With Insulin Resistance

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ABSTRACT

Tumor necrosis factor- α (TNF- α) contributed to the insulin resistance which leads to type 2 diabetes. The *A. altilis* plant has traditionally been used by the Indonesian people to treat diabetes mellitus. The purpose of this study was to determine the parameter of TNF- α level in obese mice (*Rattus norvegicus*). This study was used experimental laboratory with Randomized Controlled Trial (RCT) design. It's divided into 5 groups, and each group consisted of 5 rats that have been given a 45% fat (open source) high fat diet for fattening itself. Measurement of body weight to assess obesity and examination of fasting blood sugar (GDP) were used of DR glucose test kits. Group I was negative control, group II as positive control using metformin HCl, group III using *A. altilis* 5%, group IV *A. altilis* with 10% and group V *A. altilis* with 15%. Treatment was carried out for 14 days in each group and TNF- α levels was assessed with ELISA test. Nonparametric test was used to see the differences between each groups with a 95% confidence level. There was a significant effect of *A. altilis* with 10% extract toward TNF- α levels, where the value of $p = 0.018$. While the administration of extracts of 5% and 15% did not show a significant effect. The administration of 10% *A. altilis* extract showed a significant decrease of TNF- α levels in obese mice who had hyperglycemia.

Keywords: *A. altilis*, obesitas, TNF- α , insulin resistance

Background

Obesity is health problem that affects hormones and cytokines in human ([Aeslan N. et.al, 2010](#)). It was identified as the most common caused of insulin resistance (IR). ([Romualdo MCdS, et.al, 2014](#), [Nuru H,et.al, 2017](#)). Insulin resistance is defined as inability of affront to apply its impacts on glucose, protein and lipid digestion system in target tissues ([Crescenzo R, et.al, 2015](#)), it has numerous hindering impacts on digestion system and is emphatically connected to testimony of lipids in non-adipose tissues.

A number of unremitting illnesses such as sort 2 diabetes, cardiovascular diseases, hypertension, a metabolic clutter of different etiology characterized by persistent hyperglycemia with unsettling influences of carbohydrate, fat, and protein digestion system coming about from abandons in affront discharge, disabled affront signaling, or both. Within the Joined together Expressed predominance of affront resistance portends a troubling slant for the burden of sort 2 diabetes in stout children ([Lee JM, et.al, 2006](#)). Previous

study mentioned the overall prevalence rates of IR in population-based studies of children was up to 68,4 % ([Aa MPvd, Farsani SF, et.al 2015](#)).

In corpulent people, fat tissue discharges a number of non-esterified greasy acids, glycerol, hormones, cytokines, proinflammation and other components included within the advancement of affront resistance ([Kahn SE, et.al, 2006](#)). Tumor necrosis factor-alpha (TNF-alpha) is a fat tissue determined proinflammatory cytokine incorporates a coordinate part within the improvement of affront resistance by improving adipocyte lipolysis and expanding the serine/threonine phosphorylation of IRS-1 (Affront Receptor Substrate-1) ([Chen L, et.al, 2015](#), [Hotamisligil GS, et.al, 1993](#), [Hotamisligil GS, et.al, 1996](#)). TNF-alpha can increment glucose take-up in both visceral and subcutaneous adipocytes by actuating the adenosine monophosphate enacted protein kinase (AMPK) pathway. It's basically delivered in adipocytes and / or fringe tissues and actuates tissue particular aggravation through the inclusion of era of receptive oxygen

species (ROS) and enactment of different transcriptional intervened pathways. The raised level of TNF alpha actuates affront resistance in adipocytes and fringe tissues by disabling the affront signaling through serine phosphorylation that leads to the improvement of T2DM (Akash MSH., et.al, 2018).

Metformin is one of treatments that has positive effect to improve inflammatory activity in obese adolescents with IR (Evia-Viscarra, et.al.2012). However, in modern era herbal medicine more considerable in the community. A World Health Organisation overview shown that approximately 70-80% of the world populaces depend on non-conventional medication basically (Chan K, 2003). The foremost common reasons for utilizing conventional pharmaceutical are that it is more reasonable, more closely compares to the patient's belief system, eases concern almost the antagonistic impacts of chemical (manufactured) drugs, fulfills a want for more personalized wellbeing care, and permits more prominent open get to to wellbeing data (Wachtel-Galor S, et.al.2003). *Artocarpus altilis* (Park.) Fosberg is a plant that lives in the tropics and is spread throughout most parts of Indonesia. Essentially *Artocarpus* species comprises of phenolic compounds which incorporate flavonoids, stilbenoids, arylbenzofurans and Jacalin, alectin (Sikarwar MS, et.al. 2014). It has traditionally been used by the Indonesian people to treat liver cirrhosis, hypertension, and diabetes mellitus. In other countries, *A. altilis* leaf extract is used for antiinflammatory, antioxidant, antifungal, sexual behavior, immunomodulatory effect, antidiabetic effect and antibacterial effect (Sikarwar MS, et.al. 2014). This study aimed to analyze the benefit of *artocarpus altilis* in improving insulin resistance throughout identification the concentration of TNF alpha in obese rats (*Rattus norvegicus*).

Materials dan Methods

Artocarpus altilis (Park.) Fosberg plant is utilized as primary fabric macerated with 90% ethanol. The ethanol extricate was gotten and after that concentrated employing a rotational evaporator (BuchiLabortechnik AG, Switzerland) to get a fluid extricate. The fluid extricate was at that point vanished until thickened. Along these lines, the ethanol extricate of *A. altilis* was arranged into suspensions with concentrations of 5, 10 and

15% w/v. Solid wistar male rats utilized as test creatures with 4-month-old, weighing 150-200 g. The rats were partitioned into five bunches and bolstered a high-fat count calories of 45% fat rat eat less (open source) until their weight come to 300 g. Increments within the blood glucose level were evaluated by checking the fasting blood sugar (GDP) of the rats utilizing the GlucoDR instrument (HimedicalCo., LTD, South Korea). Gather I was the negative control bunch, the rats in gather II shaped the positive control bunch and were managed metformin HCl and bunches III, IV and V were signified the 5, 10 and 15% *A. altilis* test bunches, separately. After 14 days of treatment, each bunch were evaluated through a quantitative sandwich chemical safe test (ELISA). The noteworthiness of the contrasts among the bunches was evaluated through nonparametric tests with a 95% certainty level. All measurable examination were performed utilizing the Factual Bundle for Social Science (SPSS) adaptation 21.0 for windows (SPSS Inc., Chicago, IL, USA).

Finding

In this study, the effects of the *A. altilis* extracts on the TNF alpha levels were analyzed statistically using nonparametric tests and are presented in Table 1. The most significant differences presented between the negative control and the 10% *A. altilis* extract test group, whereas TNF alpha levels as 136.92 ± 0.53 and 124.67 ± 2.51 ng/mL. The mean TNF alpha levels of the 15 and 5% *A. altilis* extract groups, were 129.92 ± 5.69 and 133.61 ± 9.29 ng/mL, separately, which were moreover essentially distinctive from the levels identified within the negative control.

Table 1: Average TNF alpha levels in each group after treatment

Groups	N	Mean	SD
Negative	5	136.92	0.53
Control	5	126.80	8.12
Positive Control	5	133.61	9.29
<i>A. altilis</i> Extract	5	124.67	2.51
5%	5	129.92	5.69
<i>A. altilis</i> Extract			
10%			
<i>A. altilis</i> Extract			
15 %			

Table 2: Inter-group differences in the post-treatment TNF alpha levels

Groups	Variance level	SD	P
Negative Control – Positive Control	10.11	3.91	0.018
Negative Control – <i>A. altilis</i> 5%	3.30	3.91	0.408
Negative Control – <i>A. altilis</i> 10%	12.25	3.91	0.005
Negative Control – <i>A. altilis</i> 15%	7.00	3.91	0.089
Positive Control – <i>A. altilis</i> 5%	-6.81	3.91	0.097
Positive Control – <i>A. altilis</i> 10%	2.13	3.91	0.591
Positive Control – <i>A. altilis</i> 15%	-3.11	3.91	0.435
<i>A. altilis</i> 5% - <i>A. altilis</i> 10%	8.94	3.91	0.033
<i>A. altilis</i> 5% - <i>A. altilis</i> 15%	3.69	3.91	0.356
<i>A. altilis</i> 10% - <i>A. altilis</i> 15%	-5.25	3.91	0.194

Source: Primary Data 2016 One Way Anova Test

Table 2 explain that the extract concentration of *A. altilis* 10% was significantly decreased TNF alpha level in obese mice that have insulin resistance when compared to the negative and positive control group about 12.25 SD 3.91 with p value 0.005. *A. altilis* with 5% and 10% was significantly decreased TNF alpha level 8.94 SD 3.91 with p value 0.033. Even though this result affected the TNF alpha level in obese mice that have insulin resistance but it's not greater than the negative and positive groups.

Metformin was used as positive control in this study, metformin is an agent that able to repair the hepatic insulin-resistance through improved fatty liver diseases, reversing hepatomegaly, steatosis, aminotransferase abnormalities and inhibited hepatic expression of TNF alpha (Lin HZ, et.al. 2006). Metformin not as it were repressing the basal lipolysis recreated by tall glucose, but too smothers the tall glucose-enhanced lipolysis reaction to TNF-alpha or isoproterenol. The anti-lipolytic activity in adipocytes may well be the instrument by which cellular activity by metformin diminishes systemic free greasy corrosive (FFA) concentration and hence makes strides affront affectability in corpulent patients and the hyperglycemic conditions of NIDDM (Ren T,et.al. 2006). Therefore, in this study found that metformin has significant influence to decrease the concentration of TNF alpha in obese rat with insulin resistance as mentioned in table 2.

As shown in table 2 that breadfruit leaf extracts with 10% concentration have significant effect to reduce TNF alpha in obese mice with IR compare with other groups. It means that breadfruit leaf extracts with 10% concentration is effective concentration to treat

the obese mice with IR. Previous study mentioned that *A. altilis* extract traditionally used for the treatment of many diseases (Nguyen MT, et.al. 2015). *A. altilis* extracts has active compound that function in the homeostasis of blood glucose. Flavonoids is one of the active compounds that act as antioxidants to inhibit TNF alpha and prevent free radicals (Gerritsen ME, et.al. 1995). TNF alpha is an inflammatory cytokine that plays a major part within the pathogenesis of obesity-induced affront resistance, which results from interactions with insulin signaling pathways (Hotamisligil GS, et.al. 1999). Decreasing TNF-alpha in obese animals and humans will induce insulin sensitivity by up directing the tyrosine kinase movement of the affront receptor and expanding the expression of GLUT-4 glucose transporters (Dalziel B, et.al. 2002, Halle M, et.al. 1998). Another active compounds of the *A. altilis* extracts is ethanolic which acts to encourage communication within cells diminished the level of blood glucose and expanded the affront expression in pancreas beta-cells (Indrowati M, et.al. 2017). Therefore *A. altilis* extracts has significant effect to decrease the level of TNF alpha in obese rat with IR.

However, less and higher than 10% concentration of breadfruit leaf extracts were not significantly affect to decrease the level of TNF alpha. Most of the ponders appeared no contrasts in impact when half or one-quarter of the regular measurements, or indeed a littler sum, was utilized. Within the considers that appeared a distinction in reaction between measurements, the lower dosages or still ordinarily delivered a clinically imperative reaction. In other words, these so also effective lower dosages likely don't reflect the lower

portion of the dose–response bend. Indeed lower measurements would likely have created a clinical reaction in a sensible number of patients. So, in spite of the fact that prove from randomized controlled trials is accommodating in appearing that certain moo or exceptionally low doses work, this sort of prove isn't absolutely required to embrace an approach of beginning with exceptionally moo dosages (McCormack JP,et.al. 2011).

Conclusion

The best concentration of *A. altilis* extract can reduce TNF- α levels in obese mice with IR is 10%, so it can be taken into though to utilize of *A. altilis* within the avoidance of insulin resistance

Conflict-of-Interest Statement

No conflict of interest

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