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Research Article

Effect of Tender Coconut Water (TCW) on TNF-α, IL-1 and IL-6 in Streptozotocin (STZ) and Nicotinamid (NA) Induced Diabetic Rats

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ABSTRACT

Background: Diabetes Mellitus (DM) is characterized by an increase in blood sugar levels also known as hyperglycemia. Continuous hyperglycemia can increase the production of *Reactive Oxygen Species* (ROS). ROS causes oxidative stress and increases the formation of TNF-α expression as a marker of inflammation. Tender coconut water is rich in sources of free amino acids, L-arginine and vitamin C which can prevent oxidative stress. **Aim and Objectives:** This research to investigate the effect of tender coconut water on TNF-α, IL-1 and IL-6 in Streptozotocin (STZ) and Nicotinamid (NA) induced diabetic rats. **Material and Methods:** Experimental research design using *posttest control group design*. Twenty four male wistar strain rats were used in this study were divided randomly into 4 groups, which are group K1 (control); K2 (DM type 2); K3 (DM type 2+ Glibenclamid 0,18mg/200grBW); K4 (DM type 2+ tender coconut water 8mL/200gr BW). Type 2 Diabetes Mellitus were induced using Streptozotocin (STZ) 65mg/kg body weight and Nicotinamid 230 mg/kg body weight. The administration of tender coconut water were given on day 3 after DM condition is reached, given daily for 4 weeks with dose of 8 mL/200 gr BW. Data on of TNF-α , IL-1 and IL-6 levels were analyzed by *One Way Anova*. **Result:** Average TNF-α level, IL-1 level and IL-6 level in Group 2 increased compared to Group 1 , in Group 3 it decreased compared to Group 2 as well as in Group 4 .The results of the analysis has the p values <0.05. **Conclusion:** Administration of tender coconut water can be decreasing of TNF-α, IL-1 and IL-6 levels in wistar strain male rats with type 2 Diabetes Mellitus.

Key words: Diabetes mellitus, Tender coconut water, TNF-α, IL-1, IL-6.

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) globally is a health problem. It is estimated 6 people die every minutes worldwide[1]. According to the Basic Research in Health Science year 2013, the prevalence of DM in Indonesia ranked sixth of the most diseases in elderly with 4.8% percentage[2]. DM becomes very important due to the complications it causes. It can cause manifestations of diabetic retinopathy which can lead to blindness,in kidneys it can cause renal failure and also causing diabetic gangrene and vascular disease, one of which is coronary heart disease (CHD)[3]. There are many factors as the damage cause of pancreatic cell β, such as genetic factors, germinal infections, nutrition factor, diabetogenic substances and free radicals (oxidative stress)[4].

Pancreatic cell β damage can cause the inability of the body to produce insulin which cause the increase of blood glucose levels which results in hyperglycemia condition[4]. Hyperglycemia condition according to Robertson et al. can result in the formation of reactive oxygen species *(ROS=Reactive Oxygen Species)*. Excessive ROS in the body can cause oxidative stress and can worsen pancreatic beta cell damage[4]. Oxidative stress and inflammation happen unanimously as a result of hyperglycemia and increased ROS. ROS as a result of hyperglycemia damages / destroys nucleic acid, lipids and proteins[5]. Streptozotocin (STZ) can also cause damage to the heart and adipose tissue and increase oxidative stress, inflammation, endothelium dysfunction[6]. Based on studies, inflammation triggers the inflammatory cytokine inflammation which is *Tumor Necrosis Factor* α (TNF α), Interleukin-1 (IL-1), Inerleukin-6 (IL-6), and Interleukin 8 (IL-8)[7]. It is estimated that more than 25% of patients with a diagnosis of type 2 diabetes has been shown to experience systemic inflammation at the time of diagnosis, some studies show a strong correlation between TNF-alpha, IL-6, obese and and inflammation in type 2 diabetes mellitus, IL-6 can considered as the main marker for early detection of the risk of type 2 DM. Studies in humans showed that high IL 6 levels were associated with an increased incidence of type 2 DM, where people with high IL2 levels of 2.02 were at risk for type 2 DM (RR=2,02; 95%CI=1,14-3,58)[1]. High levels of IL-1 Beta are associated with hyperglycemia, insulin resistance, obesity and all factors that contribute to type 2 diabetes, increased IL-1 is associated with hyperglycemia[5]. Some studies show that type 1 or 2 DM is always accompanied by an increase in free radicals and decrease in antioxidants[8]. Low Magnesium (Mg) levels are associated with inflammation and increased production of ROS, this condition can be found in patients with type 2 diabetes due to the activity of damaged tyrosene kinases, post-receptorial decline

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in insulin action, and insulin resistance. Low Mg intake is associated with the development of type 2 DM, and Mg supplementation is a public health strategy to reduce the risk of diabetes[9].

Tender coconut water contains antioxidants, vitamin C, L-arginine vitamin C, polyphenols, selenium and minerals (Cu, Mg, Mn, K, Na, Zn)[10]. L-arginine contained in tender coconut water significantly can reduce free radicals levels in the body[11]. Antioxidant effects on coconut water can restore sensitivity from insulin and have antihypertensive effects[12]. Arginine also has the effect of regenerating pancreatic β cell which causes the activity of enzymes that regulate carbohydrate metabolism and pancreatic damage can return to normal[11]. Tender coconut water can prevent oxidative stress [13] and can increase SOD antioxidants, Catalase and GPx[14]. The aim of this study is to effect of tender coconut water on TNF α, IL-1 and IL-6 in Streptozotocin (STZ) and Nicotinamid (NA) induced diabetic rats.

MATERIAL AND METHODS

This study was designed as experimental research design with *Post-Test Control Group Design*.

Ethical clearance

This research received ethical clearance from the Medical / Health Bioethics Research Commission of the Faculty of Medicine, Unissula Semarang number 15/I/2019/Komisi Bioetik.

Tender coconut water

TCW used is from coconut water *viridis* (green coconut) variety aged 5-7 months old and obtained from the surrounding area of the research. By the time the coconut is 5-7 months old, it has soft, thin, jelly like endosperm and edible using spoon. The dosage administered is 8ml/200grBW/day for 4 weeks[10].

Experimental animal

Streptozotocin (STZ) dan Nicotinamide (NA) Induction

Rats were adapted for 7 days with the surroundings, intraperitoneally induced by STZ dosage 65 mg/kgBW and nicotinamide 230 mg/kgBW,wait for 3 days then assessed for glucose level using glucometer, if the glucose level ≥200mg/dL rats can be used as research material. Dosage of the drug glibenclamide used 0,18mg/200grBW.

Administration procedures

The rats used were Wistar male white rats that met the criteria of being 2 months old, weighing around 180-200g, healthy on the outside appearance, active motion, eating and drinking normally, no injuries and disabilities. The total of 24 rats were divided into 4 groups randomly and each group consisted of 6 rats.

Group 1 (K1)	Male white Wistar rats that with standard diet + drinking et libitum
Group 2 (K2)	Male white Wistar rats that with standard diet + drinking et libitum and were fed with Streptozotocin (STZ) dose 65mg/kg body weight and Nicotinamid 230 mg/kg body weight
Group 3 (K3)	Male white Wistar rats that with standard diet + drinking et libitum and induced with Streptozotocin (STZ) dose of 65mg/kg body weight and Nicotinamide dose 230mg/ kg body weight and glibenclamide drug 0.18mg/200gr body weight for 4 weeks
Group 4 (K4)	Male white Wistar rats that with standard diet + drinking et libitum and induced with Streptozotocin (STZ) dose of 65mg/kg body weight and Nicotinamide dose 230mg/ kg body weight and tender coconut water dose of 8mL/200gr body weight for 4 weeks

After 4 weeks blood was taken to measure TNF α, interleukin-1 (IL-1) and interleukin-6 (IL-6) levels.

Blood drawing prosedure

The equipment used is sterile microhematocrit tubes, blood storage bottles and sterile cotton. Blood is taken by inserting a microhematocrit tube in the ophthalmic vein in the corner of the eye of the mouse periorbital then rotating slowly until the blood comes out. Blood coming out is placed in Eppendorf as much as 2cc. Take the haematocrit tube when the required blood is sufficient, clean the remaining blood in the corner of the mouse's eye with sterile cotton. The examination of TNF-α, IL-1 and IL-6 levels using ELISA method.

Research location

The treatment of experimental animals and examination of TNF α, IL-1 and IL-6 levels were conducted at PAU Gadjah Mada Yogyakarta.

Statistical analysis

Data from TNF-α, IL-1 and IL-6 levels measurements were tested for normality using Shapiro-Wilk and homogeneity tests with Leuven's Test. Data on TNF α and IL-6 levels were normally distributed and homogenous so it is analysed using One Way Anova followed by Post Hoc LSD test to find out the differences between groups. Data IL-1 level was normally distributed but not homogenous, so it was analysed using One Way Anova followed by Tamhane Post Hoc test. The determination of analysis is according to alpha 5%.[15]

RESULT

The effect of tender coconut water on the average levels of TNF α, IL-1 and IL-6 is illustrated in Figure 1. The result analysis using ANOVA showed that administration of tender coconut water at a dose of 8mL/200gBW/day for 4 weeks can lower TNF-α, IL-1 and IL-6 ($p<0,05$). The average decrease of TNF α, IL-1 and IL-6 levels by Glibenclamide (K3) were higher compared to tender coconut water (K4).

TNF- α levels

Figure 1 illustrated that group K2 had the highest level of TNF α (80,77 ± 1,28 pg/dL) while K1 is the lowest (36,33 ± 0,68 pg/dL), K3 and K4 indicated the lower average levels (68,82 ± 1,00 pg/dL and 70,00 ± 0,95 pg/dL) compared to K2 but higher than K1, the decrease in the average of TNF-α between K2 and K3 is 11,94 pg/dL between K2 and K4 is 10,77 pg/dL.

IL-1 levels

The highest IL-1 level in the K2 group was highest (631.19 ± 4.31 pg/dL) while the K1 was the lowest (237.19 ± 3.29 pg/dL), K3 and K4 show lower average levels (587.39 ± 1.06 pg/dL and 605.79 ± 6.04 pg/dL) compared to K2 but higher than K1, the decrease in mean IL-1 level between K2 and K3 = 44.54 pg/dL, between K2 and K4 = 26.13 pg/dL.

IL-6 levels

The mean IL-6 level in group 2 was highest (628,19 ± 3,21 pg/dL) while K1 was the lowest (233,29 ± 2,79 pg/dL), K3 and K4 show lower average levels (577,09 ± 1,26 pg/dL and 601,99 ± 5,04 pg/dL) compared to K2 but higher than K1, the magnitude of the decrease in mean IL-1 level between K2 and K3 = 51.1 pg/dL, between K2 and K4 = 26.2 pg/dL.

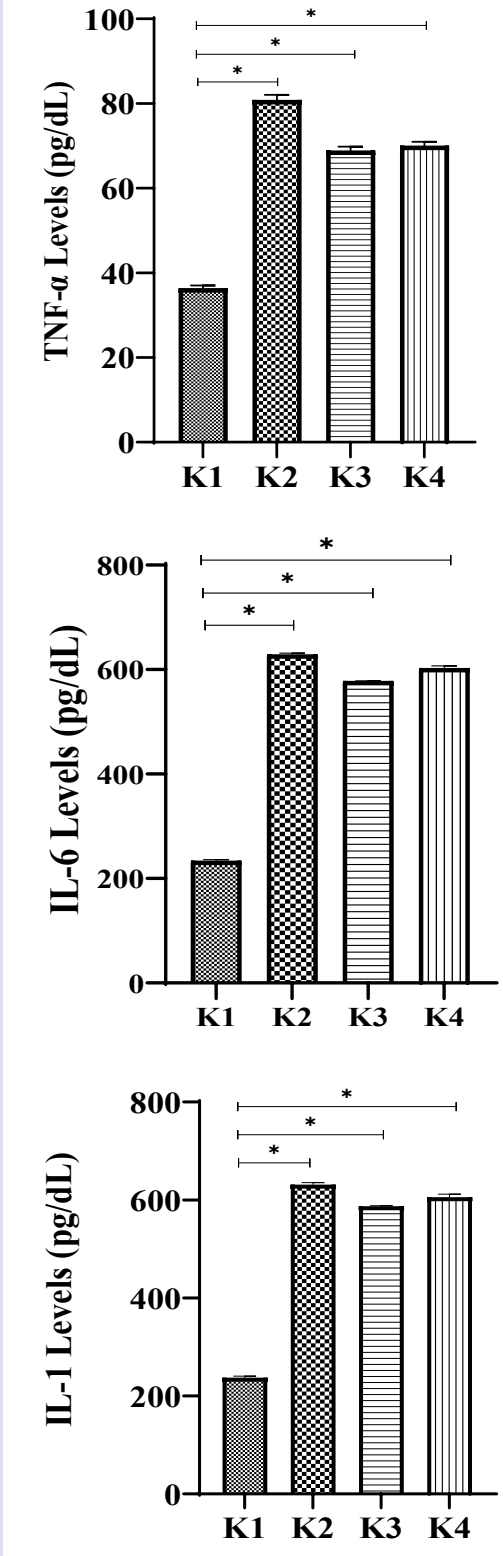

Figure 1: Average levels of TNF-α, IL-1 and IL-6 between groups (*p<0.05).

DISCUSSION

The results showed that the administration of tender coconut water dose 8mL/200grBW for 4 weeks is proven to prevent inflammation due to type 2 diabetes mellitus marked by decreasing levels of TNF α, IL-1 and IL-6. This study used male wistar strain rats induced with STZ and Na to make the rats experience type 2 DM. Group with type 2 DM there was increase in proinflammatory cytokines which are TNF α, IL-1 and IL-6, which signifies that type 2 DM is associated with inflammation. This research is relevant which indicated that proinflammatory cytokines such as TNF-α and Il-6 are increase during type 2 DM, the increase of IL-1 is associated with hyperglycemia with an increased risk of type 2 DM and with oxidative stress and inflammation[5]. The pathogenesis mechanism of type 2 DM is due to insulin resistance and β cell dysfunction. To obtain type 2 DM condition in male wistar strain rats was by injecting combination of STZ and NA, this administration is intended to cause hyperglycemia and insulin resistance to occur causing pancreatic damage. Blood sugar levels before and after injection of STZ and NA were measured, the increase of blood sugar levels after the administration of STZ +NA were indication of type 2 DM when blood sugar level is ≥ 200 mg/dL[16].

The STZ induction produces toxic effects on pancreatic β cells selectively and cause diabetes, it has the linkage of glucose in their chemical structure that allow STZ to enter pancreatic β cells through *Glucose transporter type 2* (GLUT-2) within plasma membrane, pancreatic β cells induced by STZ cause cell β death. There are three main pathways associated with cell death which are: (1) DNA methylation through the formation of carbonium ions (CH^{3+}) can produce activation of the poly enzyme *ADP-ribosesynthase* as part of cell repair mechanism and consequently, the decrease in *Nicotinamide Adenid Dinukeotida*(NAD^{+}); (2) NO Production; (3) ROS production in free radicals[6].

Oxidative stress is caused by prooxidant substances and the defense mechanism of bodily antioxidant imbalance as a result of ROS. Some reaction mechanisms that are considered to be involved in the oxidative stress genesis are glucose auto-oxidation, protein glycation, formation of advanced glycation products and *polyol* pathways. The involvement of ROS during STZ metabolism is the production of uric acid as the final product of ATP degradation by *xanthine oxidase* from *hypoxanthine.* This reaction will produce super-oxidant and hydroxyl radicals derived from H_2O_2 during hypoxanthine metabolism which will accelerate the process of destruction of pancreatic β cells. *Hidrogen peroksida* (H_2O_2) then produces free radicals such as superoxide anion (O_2^-) and hydroxyl radical (OH^-). These reactive compounds can cause lipid peroxidation, resulting in the formation of *hydroperoxyl* fatty acids and dan *endotoxides* [6]. The superoxide anion itself inhibits the key glycolytic enzyme glyceraldehyde-3phosphatedehydrogenase (GADPH), and consequently, glucose and glycolytic intermediates spill into the polyol and hexosamine pathways[17].

In type 2 DM, the inflammatory process is the result of systemic etiological factors, such as central obesity and insulin resistance. Eventually, the inflammatory mediator activates several receptors and transcription factors such as *nuclear factor-κβ, toll-like receptors* (TLRs), *c-jun amino terminal kinases* and receptors for glycation end products which cause cell dysfunction and apoptosis,tissues insulin sensitive signaling disorders, systemic endothelial dysfunction and changes in vascular flow[18].

It is estimated that more than 25% of patients diagnosed with type 2 DM have systemic inflammation. High levels of TNF alpha are

associated with insulin resistance and type 2 diabetes, or by an increase in pancreatic beta cell apoptosis. Several studies have shown that there is a strong relationship between TNF alpha and DM type 2. High levels of IL 6 are associated with metabolic abnormalities of insulin resistance and IL-6 can be considered a major marker for early detection of risk for type 2 DM. Human studies have shown that High IL 6 levels are associated with an increased incidence of type 2 DM, where people with high IL 6 levels are 2.02 times at risk of type 2 DM (RR = 2,02; 95% CI = 1,14-3,58) [1]. Some studies indicated that patients with type 2 DM have high levels of interleukin-6 (IL-6) levels and high TNF alpha[8].

Tender coconut water contains Flavonoid, L-arginin, selenium, vitamin C and other minerals such as Cu, Zn, Mn, Mg which are beneficial for the body. Epidemiology studies suggested that most diabetics have low Mg levels. Insulin and glucose are important compounds in Mg metabolism. Low levels of intracellular Mg will cause damage in tyrosine kinase activity, decrease post-receptorials in insulin actions and the disruption of insulin resistance in diabetic patients. Low Mg intake is associated with the development of type2 diabetes. Mg deficiency can trigger the development of proinflammation which cause excessive interleukin production and release[9].

The Mg supplementation is public health strategy to decrease the risk of diabetes. A prospective Trudy of 85 000 women for 18 months found that women who consumed the highest Mg had a protective factor against type 2 DM compared to the women who consumed the lowest Mg (RR=0,68)[9].

The results showed that the mean Mg serum levels of DM patients were lower when compared to non-DM (DM patients = 1.88 ± 0.28 mg/dL and non DM = 2.10 ± 0.29 mg/dL). There was a significant difference in mean serum Mg levels between DM and non-DM patients ($P < 0.003$)[19].

The high nutrients contents in tender coconut water can be used as one of the sources and important minerals for the body, one of which is a natural antioxidant SOD cofactor found in the body. The Cu, Zn and Mn mineral deficiencies can lower the activities of Cu-Zn SOD and Mn-SOD which triggering oxidative stress[14].

Other studies stated that antioxidants supplementations (vitamin C, E) and minerals (Cu, Zn, Mg) can reduce the risk of DM complications, vitamin C helps reducing capillary fragility which also contributes to complications from DM. Evidence from experimental, epidemiological and clinical studies have proven the utility of antioxidants which might therefore be helpful for treating diabetes and its complication , vitamin C administration has beneficial effects on glucose and lipid metabolism in T2DM patients[20].

Nwangwa and Aloamaka (2011) reported the hypoglycemic and regenerative effects on pancreatic cells from the administration of yellow/mature coconut water for 14 and 28 days in diabetic rats. Preetha *et al*. (2012) reported decrease in blood glucose levels and decreased oxidative stress in diabetic sprague dawley rats. L-arginine has been reported to protect rat β-cells against the diabetogenic effects, It follows that increasing NO synthesis by L-arginine could prevent oxidative stress and inflammation by restoring the regulatory axis of NO that controls glucose metabolism via AR and the downstream activation of PKC and ROS production. Treatment with L-arginine markedly prevented tissue sorbitol accumulation, ROS generation, and PKC activation-three critical biochemical abnormalities associated with hyperglycemic injury[21].

Flavonoids in the tender coconut water components are responsible for potent anti inflammatory effect as they inhibit the synthesis of prostaglandins (PGs). Synthesis of PGs, i.e. prostaglandin F2 alpha, prostaglandin E2 and synthesis of free radicals along with interleukin-1 (IL-1), IL-2 and tumor necrosis factor-alpha induces nociception and inflammation via stimulation of nociceptors. Young and mature coconut water both possess significant anti-inflammatory activity[22]. Coconut water called "water of life in various place in the world because of efficacy treatment. TCW can be used as ready to drink food product having natural health beneficial nutrients[23-26]. This study could serve as a positive finding in using tender coconut water for for their anti-inflammatory properties.

CONCLUSION

The administration of tender coconut water at a dose of 8mL/200g body weight/day for 4 weeks can has the effect of decreasing levels of TNF-α, IL-1 and IL-6 in Streptozotocin (STZ) and Nicotinamide (NA) induced diabetic rats.

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CONFLICTS OF INTEREST

There is no conflicts of interest.

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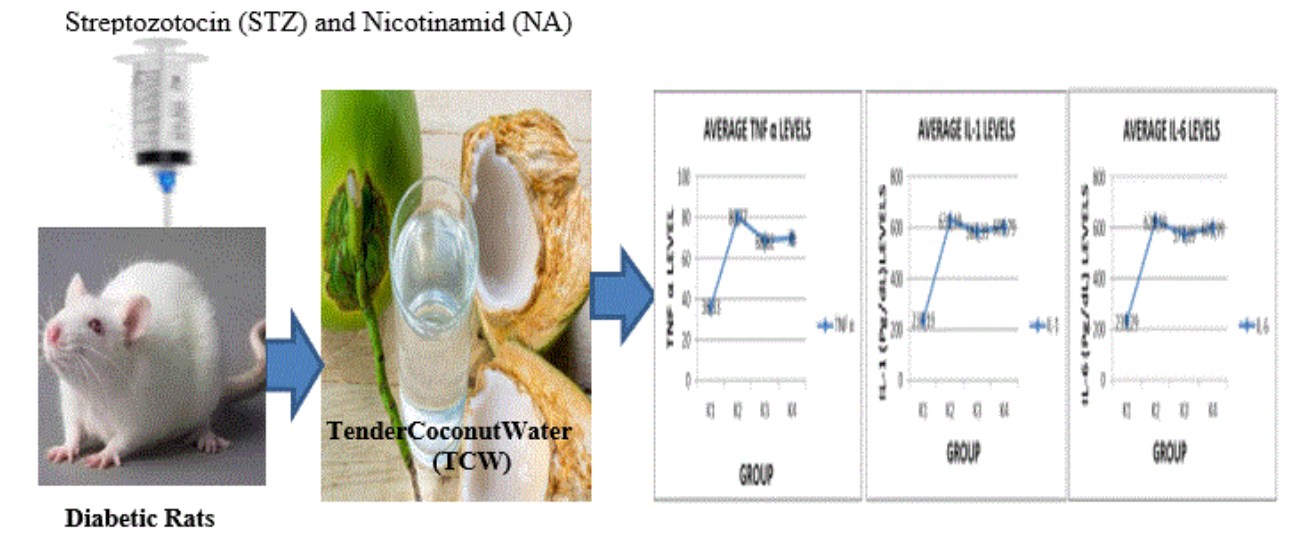
GRAPHICAL ABSTRACT



SUMMARY

- Tender coconut water significantly decreasing the level of TNF α in Diabetic Rats.
- Tender coconut water significantly decreasing the level of IL-1 in Diabetic Rats.
- Tender coconut water significantly decreasing the level of IL-6 in Diabetic Rats.

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