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The Effect of Patikan Kebo (*Euphorbia hirta*) Herbal Extract on Collagen Levels in the Kidney and Heart of Fibrotic Rats

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ABSTRACT

Noncommunicable diseases (NCDs) are the leading cause of death worldwide. There are around 36 million deaths every year. An example of NCD, a non-communicable disease, is hypertension. Excessive consumption of sodium chloride (NaCl) is the main factor that can cause hypertension and organ fibrosis. A natural ingredient that has the potential to act as an antifibrosis agent against fibrosis is quercetin by increasing PPAR-γ expression. Based on research, one of the plants that contains quercetin is the herb of Patikan Kebo (Euphorbia hirta Linn). Collagen is a protein biomarker of fibrosis synthesized via the PPAR-γ signaling pathway. The aim of this research was to determine the organ protective effect of administration of Patikan Kebo herbal extract against renal fibrosis and heart in Wistar rats (Rattus norvegicus) induced with 1.5% NaCl. The method involved 15 male Wistar rats aged 2.5 months with a body weight of 100-150 grams, which were divided into three groups (KI: control; KII: induced by 1.5% NaCl; KIII: induced by 1.5% NaCl + Patikan Kebo extract 200 mg/kg body weight. The induction was carried out for 8 consecutive weeks. On day 56, the kidneys and heart were removed in groups I and II, while in group III the treatment with the Patikan-Kebo extract from Patikan-Kebo at a dose of 200 mg/kg body weight was continued for 28 days in Group III. Specifically, for group III, kidneys and heart were collected on day 84 after treatment with Patikan kebo extract on day 84. Collagen was stained with Giemsa stain. Data were analyzed using a Kruskal-Wallis test. The difference is considered significant if the probability value is $p<0.05$. The result showed that there were significant differences between the control and treatment groups. Patikan

Kebo extract can reduce collagen in rats with induced fibrosis with 1.5% NaCl.

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ABSTRAK

Penyakit tidak menular (PTM) merupakan penyebab utama kematian di seluruh dunia. Ada sekitar 36 juta kematian setiap tahunnya. Contoh penyakit tidak menular yang merupakan penyakit tidak menular adalah hipertensi. Konsumsi natrium klorida (NaCl) berlebihan merupakan faktor utama yang dapat menyebabkan hipertensi dan fibrosis organ. Bahan alami yang berpotensi sebagai agen antifibrosis terhadap fibrosis adalah quercetin dengan meningkatkan ekspresi PPAR-γ. Berdasarkan penelitian, salah satu tanaman yang mengandung quercetin adalah ramuan Patikan Kebo (Euphorbia hirta Linn). Kolagen adalah biomarker protein fibrosis yang disintesis melalui jalur pensinyalan PPAR-γ. Penelitian ini bertujuan untuk mengetahui efek perlindungan organ pemberian ekstrak herbal Patikan Kebo terhadap fibrosis ginjal dan jantung pada tikus wistar (Rattus norvegicus) yang diinduksi NaCl 1,5%. Metode yang digunakan adalah 15 ekor tikus wistar jantan berumur 2,5 bulan dengan berat badan 100-150 gram yang dibagi menjadi tiga kelompok (KI: kontrol; KII: diinduksi NaCl 1,5%; KIII: diinduksi NaCl 1,5% + Ekstrak Patikan Kebo 200 mg/kg berat badan. Induksi dilakukan selama 8 minggu berturut-turut pada hari ke 56 dilakukan pengangkatan ginjal dan jantung secara berkelompok I dan II, sedangkan pada kelompok III perlakuan ekstrak Patikan-Kebo dari Patikan-Kebo dengan dosis 200 mg/kg berat badan dilanjutkan selama 28 hari. Pada kelompok III, khusus kelompok III diambil ginjal dan jantungnya pada hari ke 84 setelah perlakuan dengan ekstrak Patikan kebo pada hari ke 84. Kolagen diwarnai dengan pewarnaan Giemsa. Data dianalisis menggunakan uji Kruskal-Wallis p<0,05.Hasil: Hasil penelitian menunjukkan terdapat perbedaan bermakna antara kelompok kontrol dan perlakuan. Ekstrak Patikan Kebo dapat menurunkan kolagen pada tikus yang diinduksi fibrosis dengan NaCl 1,5%.

Kata Kunci: Euphorbia hirta; Quercetin; Kolagen, Fibrosis

1. Introduction

About 36 million deaths annually, or 6% of all deaths worldwide, are attributed to noncommunicable diseases (NCDs), which represent a serious threat to global health. Around 25–27 percent of these deaths, or roughly 9–1 million, are attributable to NCDs and happen before the age of 60. The three main risk factors for the three most prevalent noncommunicable diseases—cancer, heart disease, and diabetes—are inadequate physical activity, tobacco use, and hazardous alcohol consumption [1].

Chronic kidney disease surveillance has significantly increased, currently growing at a rate of about 8% per year, as a result of the rising prevalence of non-communicable diseases (NCDs) like obesity, diabetes mellitus, and hypertension. Nowadays, chronic kidney disease is regarded as one of the biggest global health issues, and research is being done to identify practical ways to prevent it from progressing to

its final stages. With diabetes mellitus accounting for half of cases, hypertension for 27%, glomerulonephritis for 13%, and other causes for the remaining 10%, these conditions are the main causes of end-stage renal disease [2].

One of the biggest issues facing public health is essential hypertension. In 2005, about one billion people, or 14% of the global population, suffered from hpertension. The heart, kidneys, liver, and blood vessels can all develop fibrosis as a result of this condition, which is a major risk factor for cardiovascular, cerebrovascular, and renal disorders [3,4].

There are several factors that contribute to the rise in blood pressure. According to epidemiological data, environmental factors, physical activity, stress, and genetic predisposition all play a significant role in raising blood pressure [5]. On a global scale, however, excessive consumption of mineral salts—particularly sodium chloride (NaCl)—contributes significantly to the rise in hypertension, cardiovascular diseases, and kidney diseases [6]. Uncertainty surrounds the mechanism underlying high blood pressure, which is impacted by excessive consumption of mineral salts. The kidneys' inability to adequately and efficiently eliminate sodium chloride, however, may be the cause [7]. There is still uncertainty regarding the relationship between high blood pressure and mineral salt intake, and some communities continue to deny it. Collagen accumulation in these processes, the role of sympathetic nerve activity (SNA) through the baroreflex mechanism, and the contribution of sodium chloride to kidney injury have all received a lot of attention recently [3].

Prior research on animals demonstrated that both spontaneously hypertensive rats (SHRs) and normotensive Wistar-Kyoto rats (NWKYs) could experience an increase in blood pressure when exposed to an 8 percent NaCl solution [8]. The goal of the stimulation techniques is to use sodium to activate angiotensin II, which will then produce aldosterone and endogenous ouabain (EO) [9]. Vasoconstriction and the adrenal gland's release of aldosterone are both triggered by angiotensin II. After that, aldosterone stimulates the distal tubules, which facilitates the reabsorption of water and sodium [10,11]. Furthermore, angiotensin II stimulates the transformation of fibroblasts into myofibroblasts through the signaling pathway of transforming growth factor beta1 (TGF-β1). Myofibroblasts are in charge of producing extracellular matrix (ECM), which causes it to build up in the tubules' interstitial space [12].

In society, telmisartan and other angiotensin receptor blockers (ARBs) are the most widely used antihypertensive drugs. Telmisartan stimulates PPAR-γ activity by acting as a partial agonist for peroxisome proliferator-activated receptor-γ (PPAR-γ) in addition to blocking angiotensin receptors [13,14]. TGF-β1 expression may be inhibited by the synthesis of a corepressor that results from the heterodimerization of PPAR-γ with retinoid X receptors (RXRs) [15].

Numerous herbal medications are now available to treat fibrosis. Due to the presence of quercetin as an active ingredient, Patikan Kebo is one of them. The herb Patikan Kebo is anticipated to demonstrate antifibrotic effects when given to rats that have been exposed to 1.5% sodium chloride. The amount of collagen in kidney and heart tissue, which is stained with Giemsa stain, is measured to determine this.

2. Method

In this procedure, 15 male Wistar rats weighing between 100 and 150 grams at 2 months of age were split into three groups (KI: control; KII: induced by 1 percent NaCl; KIII: induced by 1 percent NaCl + 200 mg/kg BW Patikan Kebo extract). For eight weeks in a row, 1.5% NaCl induction was performed. On day 56, the kidneys and hearts of

groups I and II were removed, and on day 84, kidneys and hearts from group III III were collected following treatment with Patikan Kebo extract at a dose of 200 mg/kg body weight for 28 days. Giemsa stain was applied to collagen.

The data were examined using either the Kruskal-Wallis test or a one-way parametric ANOVA test. A significant difference is defined as one where the probability value is $p<0.05$

3. Results and Discussion

According to Figure 1 and Tables 1 and 2, the collagen proportions of the kidney and heart organs in the Wistar rat group under plant extract treatment were lower than those in the control group ($p<0.05$).

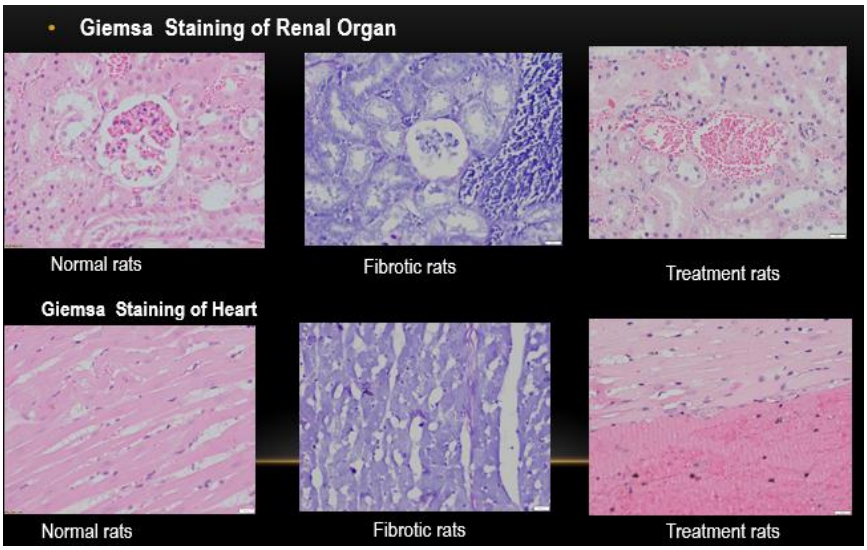

Figure 1. Microscopic image of kidney and heart organ slide for groups I, II, and III using Giemsa stain (pale blue color → shows collagen) at 200x magnification.

Cox et al. based on two cohort studies carried out in human populations, explained how mineral salts can promote fibrosis in the heart, kidneys, and cardiovascular system. Since then, Yu et al. Mineral salts were also found to promote fibrosis in the kidneys, left ventricle, and myocardial artery of Wistar-Kyoto rats (WKYs) and spontaneously hypertensive rats (SHRs) [8]. Chronic kidney disease is brought on by this kidney fibrosis and progressively worsens kidney function. Furthermore, renal fibrosis raises blood pressure and can lead to acute and chronic kidney disease.

Table 1. Percentage of renal collagen volume fraction (CVF).

Group	CVF	p
Aquades-control group	0.12	0.000
NaCl-control group	18.78	
Treatment group	14.28	

Based on the findings of the earlier study, male Wistar rats given drinking water containing 1.5% NaCl for eight weeks showed elevated CHOP gene expression in kidney tissue. Researchers looked at Sprague-Dawley rats weighing 250–300 grams in a related study conducted in 2015. For three days, these rats were not allowed to drink any water in order to cause osmotic stress. Following this withdrawal, they were given drinking

water containing 2% NaCl for seven days. Additionally, regardless of the water deprivation and 2 percent NaCl intake conditions, the hypothalamic tissue of these rats exhibited significantly higher expression of the CHOP gene than the normal control group [16].

Table 2. Percentage of heart collagen volume fraction (CVF).

Group	CVF	p
Aquades-control group	0.05	0.000
NaCl-control group	20.16	
Treatment group	12.53	

It was noted in earlier research that rats given 1.5% NaCl in their drinking water for eight weeks developed mild renal fibrosis. In a comparative study conducted in 2015, mice that had 5/6 nephrectomy were included. A low-salt diet (0.02 percent NaCl), a normal diet (0.4 percent NaCl), and a high-salt diet (4 percent NaCl) with hydralazine were given to the mice in three groups.) during a two-week span. According to the results, which supported our findings, eating salt causes stable kidney and heart fibrosis.

As a result, long-term high-salt diets, regardless of blood pressure, cause renal tissue fibrosis and chronic progressive kidney disease. Dahl rats (DSS) that are sensitive to salt were split into two groups and given diets containing 2 percent and 8 percent NaCl for five weeks in a 2017 study. This study found no discernible kidney tissue fibrosis or significant variations in serum creatinine and urea levels between the two groups, which is in contrast to our findings. After 15 weeks, however, there were notable variations in the groups' serum creatinine and urea levels in addition to notable kidney tissue fibrosis. In line with our findings, at the end of the fifteenth week, the kidney tissue of the rats fed an 8 percent NaCl diet had substantially more KIM-1 gene expression than that of the group fed a 2 percent NaCl diet. Additional research on male Wistar albino rats in 2017 and 2018 supported our findings, demonstrating that the group fed an 8 percent NaCl diet for 8 weeks had renal tissue fibrosis and tubular degeneration that was significantly worse than that of the normal control group [17, 18, 19, and 20].

Increased renal collagen formation was a result of elevated TGF-β1 levels. A solution of 8% sodium chloride was found to increase collagen levels, blood pressure, lumen diameter, media stiffness, media to lumen ratio, and proliferating cellular nuclear antigen (PCNA) expression in the arterial organs of Wistar rats. greatly raised. the control group ($p<0.05$) [21]. Finally, Patikan Kebo extract reduces TGF-β1 expression and consequently leads to a reduction in collagen content.

4. Conclusion

The administration of Patikan Kebo (*Euphorbia hirta*) herbal extract demonstrated protective effects against kidney and heart fibrosis in male Wistar rats induced with 1.5% NaCl. This study revealed that the extract significantly reduced collagen levels in kidney and heart tissues compared to the negative control group. The antifibrotic effect is likely attributed to the presence of quercetin, which reduces TGF-β1 expression and modulates the PPAR-γ signaling pathway. These findings support the potential of Patikan Kebo as a natural therapeutic agent for managing organ fibrosis induced by high salt intake and provide new insights into the development of plant-based medical therapies. However, further research on other models and clinical trials is necessary to validate its efficacy and safety in humans.

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