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REVIEW ARTICLE

Effect of antioxidants on kidney damage repair in - diabetes-induced animal: a literature study

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ABSTRACT

Diabetes mellitus is a disease characterized by hyperglycemia. Chronic hyperglycemia in diabetes mellitus can cause various complications, one of which is diabetic nephropathy, which affects the kidney. Chronic hyperglycemia causes an increase in free radicals and a decrease in antioxidant activity resulting in oxidative stress conditions. This study aims to determine kidney damage caused by oxidative stress and the role of antioxidants in reducing this damage through literature studies. The literature used comes from Google search results such as PubMed, Google Scholar, ResearchGate, and ScienceDirect. From the search results, ten journals meeting the inclusion and exclusion criteria were selected for review and comparison so that a conclusion could be drawn. The results of this literature study have demonstrated that biochemical parameters, such as increased levels of creatinine, urea, malondialdehyde (MDA), and decreased antioxidant enzymes, as well as kidney histological parameters, such as changes in the shape of tubules, glomeruli, and increased kidney expression, are indicators of kidney damage caused by oxidative stress. The mechanism of antioxidants in reducing kidney damage is through DNA cutting, binding to phenolic OH groups, down-regulation of the oxidase expression of nitrogen oxides 4 nicotinamide adenine dinucleotide phosphate (Nox4 NADPH), antioxidant enzyme systems, activation of the activated protein kinase pathway - silent mating type information regulation 2 homolog 1-peroxisome proliferator-activated receptor-γ coactivator 1α (AMPK-SirT1- PGC-1 α), protein glycation reactions, and inhibition of protein 53 (P53) so that erythroid nuclear factor 2-related factor 2 (Nrf2) can activate antioxidant gene transcription.

Keyword: Antioxidants, diabetes mellitus, kidney damage , diabetic rats, oxidative stress

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INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease that occurs as a result of abnormalities in insulin secretion, insulin resistance, or both, which is characterized by an increase in high blood glucose levels (hyperglycemia).[1,2] According to the International Diabetes Federation (IDF), Indonesia has the second-highest population of diabetics among 7 countries, , at 10.7 million.[3] Chronic hyperglycemia in DM can cause various chronic complications, one of which is chronic progressive diabetic nephropathy (ND) or diabetic kidney disease (DKD), affecting the kidney.[4,5]

Diabetic nephropathy occurs due to chronic hyperglycemia, which will trigger a condition of oxidative stress, a condition where the number and reactivity of free radicals are more dominant than the body's antioxidants.[6] Persistent hyperglycemia causes an increase in the production of reactive oxygen species (ROS). This leads to the emergence of oxidative stress, which can interfere with the function and structure of the kidney, specifically the function of the proximal tubule in reabsorbing glucose from glomerular filtration, as well as thickening of the glomerular base membrane (GBM), endothelial dysfunction, and tubulointerstitial fibrosis.[7]

Oxidative stress causes progressive damage to tubular and glomerular cells, resulting in glomerulosclerosis and contributing to diabetic nephropathy.[8] To reduce the damaging effects of free radicals, several antioxidants have evolved as cellular defences.[9] Antioxidants are substances that can counter the harmful effects of free radicals formation due to oxidative metabolism.[10] Increased antioxidant activity and its levels usually reduce kidney injury caused by oxidative stress.[11] Antioxidants work by inhibiting the occurrence of auto-oxidation reactions of free radicals to prevent the appearance of oxidative stress.[12,13] With the evidence that oxidative stress conditions cause kidney damage that requires antioxidants, the researchers are interested in conducting a literature study on the effect of antioxidants on repairing kidney damage in diabetic rats.

METHOD AND SUBJECT

This research employed a literature study method or literature review. The object of this study is to use secondary data, such as books, notes, reports on previous research results, newspapers, scientific journals, case studies, and proceedings of the results conferences, articles, government publications, journal reviews, annual reports, documents, and other literature related to the effect of antioxidants on the repair of diabetes-induced kidney damage in experimental animals.

The data was obtained from the research findings that previous researchers had carried out. The research started from August 2022 to January 2023. The objects of the research used in this study were selected based on inclusion and exclusion criteria. The inclusion criteria for this study were the source of the literature for this study, using Indonesian and English journals and articles published over the past ten years (2012-2022), the library data used was ready mode, and a secondary source. Exclusion criteria from this study included a literature that could not be accessed in text, unrelated to the seven key research topic words (diabetes mellitus, antioxidants, renal, diabetic rats, oxidative stress, alloxan or streptozotocin, diabetic nephropathy or diabetic kidney disease) papers.

A literature search using Google on the internet with four keywords: diabetes mellitus, antioxidants, renal, diabetic rats, was carried out in stages. First, do a literature search with the first keyword, for example, diabetes mellitus. After collecting the articles or journals, do a screening using the second keyword: antioxidant, on all articles found based on

the first keyword. Continue with the same procedure until the last keyword. The articles that had been collected were then selected based on the first inclusion criteria.

The researcher selected ten articles based on the inclusion criteria and three articles based on the exclusion criteria. Other keywords were oxidative stress, alloxan or streptozotocin, and diabetic nephropathy or diabetic kidney disease simultaneously in each article found. The results were grouped using the synthesis matrix method to identify similarities or dissimilarities, compare, and summarize in order to get conclusions, and were analyzed using descriptive analysis methods. The sources of articles used in this literature were articles published by PubMed, Google Scholar, ResearchGate, and ScienceDirect.

RESULT AND DISCUSSION

An Overview of Kidney Damage Caused by Oxidative Stress

Diabetic nephropathy occurs due to increased oxidative stress caused by uncontrolled hyperglycemia. Oxidative stress causes an increase in the formation of ROS, which leads to decreased kidney function. The literature search have found three of ten journals: the effect of lipoic acid (α-LA) on mitochondria, the effect of traditional Chinese medicine DSS on AGE, and the effect of GSPE on podocyte injury. According to these journalsthe biochemical parameters of oxidative stress include an increase in malondialdehyde (MDA) levels, lipid peroxidation, and carboxymethyl-lysine (CML), but a decrease in antioxidant enzymes such as SOD, CAT, and GSH-Px.[14–16]

In addition, six out of ten pieces of literature were found, showing that the signs of diabetic nephropathy were identified in increased levels of creatinine and blood urea nitrogen (BUN), protein (nephrin and PCX), urinary albumin excretion (UAER), and protein (P53), but a decreased urinary Alb/Cre ratio. [14–16,20–22]

Furthermore, from ten studies, nine showed that signs of diabetic nephropathy could be seen from the histopathological appearance of the kidney in addition to biochemical parameters. This occurred because the conditions of oxidative stress caused not only disturbances in kidney function but also damage to the kidney structure. [7,11,23–25]

The signs of renal histopathology were found to be tubular cell swelling, modification of endothelial permeability in the Glomerulus, leukocyte infiltration, apoptosis and necrosis of proximal tubular epithelial cells, capillary and tubular dilatation, interstitial bleeding, glomerular lobulation, loss of brush border membrane, glomerular hypertrophy, increased mesangial expansion due to accumulation of ECM matrix in the Glomerulus, mesangial damage, increased glomerulosclerosis ratio/ glomerulus, increased OPN expression in the Glomerulus, increased renal expression (TGF-β, SirT1, NF-κB, collagen type IV, RAGE), but decreased VDAC expression and mtDNA content. [14–20,22,26]

Table 1 Kidney Damage Caused by Oxidative Stress

No	Author, Year	Biochemical parameters	Histological parameters
1.	Arifah et al, 2015	↑ creatinine and BUN	Have inflammation
2.	Joni et al, 2017	↑ creatinine and BUN	Tubular cells undergo necrosis
3.	Manel et al, 2018	↑ creatinine and BUN	Modification of glomerular endothelial permeability, leukocyte infiltration, apoptosis and necrosis in proximal tubular epithelial cells, capillary and tubular dilatation, interstitial bleeding, lobulation the glomerulus, loss of the brush border membrane
4.	Kamal et al, 2013	-	Dilation of glomerular capillaries, dilatation tubular and interstitial bleeding
5.	Weiying et al, 2018	↑ protein (P53), ↑ MDA levels	-
6.	Sang pil yoon et al, 2014	Proteinuria, ↑ BUN and creatinine	↑ mesangial matrix, ↑ OPN expression in Glomerulus
7.	Lei et al, 2014	↑ MDA levels, ↓ SOD and CAT	↑ kidney expression, i.e., RAGE, ↓ mtDNA content
8.	Xiang et al, 2019	↑ ratio Alb/Cre urin	↑ glomerulosclerosis/glomerulus ratio, ↑ renal expression (TGF-β, SirT1)
9.	Li et al, 2013	↑ creatinine and BUN, ↓ SOD, ↑ MDA, ↑ UAER	Damage to the glomerulus and mesangial cells ↓ VDAC expression
10.	I-Min et al, 2012	↑ creatinine and BUN, ↑ UAER, ↓ SOD, ↑ lipid peroxidation, ↑ CML	Mesangial expansion due to accumulation of extracellular matrix (ECM) in the glomerulus, ↑ renal expression (NF-κB, TGF- β1, Collagen Type IV)

information:
↑: Upgrade
↓: Decrease
-: Without explanation

The Role of Antioxidants in Repairing Kidney Damage

The classification of antioxidants based on this source was divided into two categories: endogenous and exogenous antioxidants.[12] Nine out of ten literatures discovered that exogenous antioxidants were used to repair kidney damage caused by diabetic nephropathy. Six of the nine types of literatures investigated natural antioxidants, while the other three reviewed synthetic antioxidants. The first included black rice bran ethanol extract (EEBBH), red gondola leaf ethanol extract, spirulina platensis green-blue algae, green tea extract, grape seed proanthocyanidin extract, and epigallocatechin 3-O-gallate (EGCG). [14,17–20,26] The examples of synthetic antioxidants were resveratrol, lipoic acid (α-LA), and Danggui-Shaoyao San (DSS). [15,16,22]

According to six literatures reviewing natural antioxidants, five reviewed non-enzymatic antioxidants. They were the effect of EEBBH on plasma glucose, the effect of ethanol extract of red gondola leaves on creatinine, urea, and renal tubular histology, the role of green tea extract in reducing pathological changes in DM rats, the effect EGCG against diabetic nephropathy, and the effects of lipoic acid (α-LA) on mitochondria.[15,17,18,20,26] While the other examined enzymatic antioxidants: the effects of Spirulina platensis on lipid peroxidation and antioxidant defenses and the effects of grape seed proanthocyanidin extracts (GSPE) in repairing injured podocytes, which have various mechanisms for

repairing, inhibiting or preventing damage to the kidney parenchyma. [14,19]

The non-enzymatic antioxidants contain anthocyanins (cyanidin-3-glucoside and pelargonidin-3-galactoside), which can prevent the cutting of supercoiled DNA strands triggered by ROS so as to reduce oxidative stress and reduce urea levels. [17] By creating bonds with phenolic OH groups, they can also capture or neutralize free radicals, donating hydrogen ions and causing ion stability. This process increases GFR, allowing nephrotoxic substances entering the kidney to be excreted quickly. [18] Epigallocatechin gallate (EGCG) can reduce kidney injury by inhibiting oxidative stress and lowering the amount of Nox4 NADPH oxidase. [26] In addition, EGCG can inhibit the proliferation of mesangial cells, and induce apoptosis in renal interstitial fibroblast cells, reduce serum creatinine and proteinuria, and inhibit increased expression of OPN.[20] The enzymatic antioxidants contain CAT and SOD, which turn superoxide anion into hydrogen peroxide, as well as GSH-Px, which detoxifies hydrogen peroxide and converts lipid hydroperoxides to non-toxic alcohols. The antioxidant enzymatic system can accelerate the damage of oxygen radicals, and the removal of organic compounds and hydroxides. [16,19]

Three literatures that have revealed synthetic antioxidants are the studies on the effects of ramipril and resveratrol in overcoming glomerulosclerosis, the effect of α-LA on mitochondria, and the effect of traditional Chinese medicine DSS on AGE.[15,16,22] In these three studies, synthetic antioxidants include resveratrol, which can improve oxidative stress induced by hyperglycemia in the kidney tubules of diabetic nephropathy rats by increasing FoxO3a phosphorylation via SirT1 pathway activation, increasing the expression of connective tissue growth factor (CTGF), and inducing angiogenesis. Ramipril exerts a regulatory effect on CTGF. The combination of ACEi (ramipril) and antioxidant (resveratrol) treatment can reduce proteinuria, prevent the deregulation of CTGF expression, and improve the fibrotic effect of CTGF.[22] DSS can reduce excessive expression of AGEs, reduce levels of CML and lipid peroxidation products in the kidney, and downregulate the NF- pathway κB-TGF-β1 in the kidney through a protein glycation reaction, resulting in reduced expression of type IV collagen in the renal cortex and decreased kidney damage. Danggui-Shaoyao San can prevent or inhibit the development of diabetic nephropathy by not only correcting hyperglycemia and antioxidant enzymatic systems, but also protecting against histopathological changes in the kidney.[16]

One study explained that the activity of endogenous antioxidants or antioxidants originating from within the body is regulated by Nrf2. Nuclear factor erythroid 2-related factor 2 (Nrf2)is the main regulator of cellular antioxidant activity and activates the transcription of antioxidant genes, such as heme oxygenase-1(Ho1) and NAD(P)H dehydrogenase quinone 1 (Nqo1). It is assisted by the mouse double minute 2 (MDM2) which increases antioxidants in the body and can cause a reduction of free radicals. There is an increase in P53, which causes glomerular hypertrophy and the accumulation of fibrosis, induces the loss of podocytes, and affects mesangial cell injury, which can inhibit the expression and function of Nrf2, resulting in increased oxidative stress in the kidney. In this study, both types of mice were given the same two substances:nutlin3a and pifithrin-α (PFT -α). Nutlin3a can reduce kidney antioxidant activity by inhibiting Nrf2 expression, while PFT-α can inhibit P53, thereby increasing Nrf2 expression and function.[21]

The study on the effect of GSPE in repairing podocyte injury has found that GSPE is a natural antioxidant, which can restore mtDNA content and increase expression of NRF-1 and TFAM mRNA through activation of activated protein

kinase-silent mating type information.

CONCLUSION

Based on the analysis and discussion of the various research results used in this literature study, it can be concluded that signs of kidney damage caused by regulation of two homologs 1-peroxisome proliferator-activated receptor-γ coactivator 1α (AMPK-SIRT1-PGC-1α) in podocytes can inhibit the expression of PGC-1 α and oxidative stress, which causes a decrease in the number of mitochondria and changes in mitochondrial morphology, allowing the podocyte injury to be repaired. The study on the effect of lipoic acid (α-LA) on mitochondria has found that α-LA is a synthetic antioxidant, which provides a protective role for the kidneys by preventing the formation of oxidants, protecting mitochondrial function, and regulating VDAC protein expression. Lipoic acid (α-LA) can reduce levels of BUN, SCr, UAR, and MDA, reduce glomerular and mesangial cell injury, and induce an increase in SOD activity so that the formation of ROS can be reduced. All of these mechanisms lead to a collapse of the mitochondrial membrane potential, a weakening of Ca2+-induced mitochondrial swelling, and a decrease in the VDAC signal. Oxidative stresses can be identified from the biochemical and histological parameters of the kidney, as well as the antioxidant mechanisms for preventing, inhibiting, and repairing kidney damage, which vary widely. It requires further research to determine the effect of antioxidants on the repair of kidney damage in humans.

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DECLARATION OF INTEREST

We hereby declare that there is no conflict of interest in the scientific articles we write.

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