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The Role of Antioxidant Therapy in the Management of Type 2 Diabetes Mellitus: A Literature Review

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a metabolic disease and has become a global problem due to the rapid increase in the number of cases. This disease is characterized by chronic hyperglycemia caused by insulin resistance and pancreatic beta cell dysfunction. The occurrence of oxidative stress is known to play a central role in the development of T2DM complications, through increased reactive oxygen species (ROS) that worsen insulin resistance, worsen beta cell function, and trigger complications such as cardiovascular complications, nephropathy, and neuropathy. **Objectives:** This literature review aims to evaluate the scientific evidence supporting the use of antioxidant therapy as an additional approach in the management of T2DM, focusing on the effectiveness and mechanism of action of antioxidant compounds on glycemic parameters, oxidative stress, and diabetes complications. **Methods:** A literature search was conducted through databases on ScienceDirect, PubMed, and Google Scholar, with the keywords “antioxidant therapy”, “type 2 diabetes mellitus”, “oxidative stress”, and “diabetes management”. The selected articles included in vitro, in vivo studies, and clinical trials published in the period 2013-2023. Literature review focused on the biochemical mechanisms of antioxidant compounds and clinical outcomes related to glycemic parameters and diabetes complications. The literature extraction process was carried out from January to March 2024. **Results:** Supplementation of vitamin D, vitamin E, vitamin C, polyphenols, saponins, and flavonoids has been proven to reduce blood glucose levels and increase insulin sensitivity in type 2 diabetes mellitus. The mechanism involves increasing antioxidant activity, regulating glucose homeostasis, as well as modulating signaling pathways such as AMPK, PPAR, and GLUT4. **Conclusions:** This bioactive compound has potential as an adjunct therapy in the management of type 2 diabetes mellitus by targeting oxidative stress and insulin resistance. Further research is needed to determine optimal dosage and long-term effectiveness.

Keywords: *Adjuvant therapy; antioxidants; diabetic complications; oxidative stress; type 2 diabetes mellitus*

BACKGROUND

Type 2 diabetes mellitus (T2DM) is a chronic metabolic condition characterized by persistent hyperglycemia due to insulin resistance and/or pancreatic beta cell dysfunction. This disease has become a global disease with a prevalence that increases sharply every year. The prevalence of type 2 DM increased to 9.3% among the adult population in 2019, and is expected to continue to increase if no effective intervention is carried out¹.

Oxidative stress plays a central role in the pathophysiology of type 2 DM. The mechanism of oxidative stress is activated by increased glucose levels, which triggers excessive production of reactive oxygen species (ROS). Accumulation of ROS causes cellular damage to pancreatic, liver, and skeletal muscle tissues, which further worsens insulin resistance and other diabetic complications. Therefore, interventions that can reduce oxidative stress are potential strategies for controlling type 2 DM^{2,3}.

In recent decades, antioxidant therapy has attracted attention as an innovative approach to reduce oxidative stress in patients with type 2 DM. Antioxidants work by neutralizing ROS, thereby protecting body cells from oxidative damage. Several studies have shown that antioxidant supplements can improve glycemic parameters and reduce diabetic complications^{4,5}. This quote supports the therapeutic approach that “Addressing oxidative stress through antioxidant therapy may pave the way for innovative treatment strategies in managing type 2 diabetes mellitus.”

Through this literature review, an analysis of scientific evidence regarding the role of antioxidants in the management of type 2 DM, as well as the underlying molecular mechanisms, will be carried out, especially on the effects of antioxidants on glycemic parameters and related complications. This analysis is expected to provide deeper and evidence-based insights to develop antioxidant

therapy as part of the management of type 2 DM.

RESEARCH METHODS

This study is a systematic literature review aimed to evaluate the role of antioxidant therapy in the management of type 2 diabetes mellitus (type 2 DM), especially in the mechanism of reducing oxidative stress, improving glycemic parameters, and preventing related complications.

A systematic literature search was conducted through online databases, namely PubMed, ScienceDirect, and Google Scholar. The keywords used included “antioxidant therapy,” “type 2 diabetes mellitus,” “oxidative stress,” and “diabetes management.” In addition, combinations of keywords such as “antioxidant therapy,” “type 2 diabetes mellitus,” and “oxidative stress management” were also used to expand the search results. The search focused on articles published between 2013-2023 to ensure the latest and relevant data.

Studies that met the inclusion criteria were original articles (in vitro, in vivo, and clinical) that reported the effects of antioxidants on glycemic parameters or complications related to type 2 DM. Articles discussing the molecular mechanisms of antioxidants, such as their effects on the AMPK, PPAR- α , and Nrf2 pathways, were also included. Irrelevant articles, such as non-systematic reviews, editorial comments, and conference abstracts, were exclusion criteria. Articles that did not have full access or were not available in English or Indonesian were also excluded from the analysis.

The article selection process was carried out in stages. Articles that met the inclusion criteria were screened based on the title and abstract, then reviewed in full. Data extraction was carried out by recording information on the research method (in vitro, in vivo, or clinical design), the type of antioxidant used, the main results including the effect of antioxidants on glycemic parameters (such as HbA1c levels, fasting glucose) and other diabetic complications, and the molecular mechanisms reported in the article.

The extracted data were analyzed descriptively and thematically. Particular emphasis was placed on the mechanism of action of antioxidants in reducing oxidative stress and their effects on glycemic parameters and diabetic complications. In addition, this review examines the successes and limitations of each study as well as the potential application of antioxidant therapy in the clinic.

RESULTS

Of the total of 30 articles identified, there were 15 studies that met the inclusion criteria, consisting of 3 in vitro studies, 7 in vivo studies using animal models, and 5 clinical trials. The types of antioxidants that have been most researched include vitamin E, vitamin C, polyphenols (such as resveratrol and flavonoid compounds). Results can be seen in Table 1.

High glucose levels in type 2 diabetes cause the accumulation of ROS, which damages pancreatic beta cells and peripheral tissues. Antioxidants capture ROS, reduce

oxidative stress, and protect cells from oxidative damage⁶. Antioxidants activate the transcription factor NRF2, which induces the expression of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, strengthening cellular defense against ROS³. Antioxidants suppress the activation of NF- κ B, a major inflammatory signaling pathway, reducing inflammation that worsens insulin resistance. This increases insulin sensitivity and glucose uptake in target tissues⁷. Antioxidants inhibit the formation of advanced glycation products (AGEs), which damage tissue and contribute to chronic complications of diabetes⁸.

Vitamin D supplementation was proven to significantly reduce fasting blood glucose levels in type 2 diabetes patients in a 12-week clinical trial⁹. In research with rat, it shows that administration of vitamin D can reduce insulin resistance in rat with prediabetes¹⁰ one that received vitamin D3 at 100 IU/kg BW, and one group that received vitamin D3 at 1000 IU/kg BW. The high-fat and high-glucose diets were continuously given throughout the twelve weeks of treatment. At the end of the supplementation period, glucose control parameters, inflammatory markers, and the expressions of IRS1, PPAR γ , NF- κ B, and IRS1 were measured. Results: Vitamin D3 dose-dependently improves glucose control parameters, as shown by the reduction of fasting blood glucose (FBG). In research on diabetic rat, a combination of vitamin E and resveratrol showed a significant reduction in blood glucose levels and improved glycemic control compared to the control group¹¹. Vitamin E and its combination with vitamin C can reduce blood glucose and HbA1C levels in patients with type 2 diabetes mellitus¹². A study in diabetes patients suggests ascorbic acid may be a useful therapeutic adjunct in preventing or managing long-term complications of diabetes, particularly related to kidney function¹³ Renal function, Albumin Creatinine Ratio (ACR). Other research in diabetes patients shows that ascorbic acid has been shown to reduce oxidative stress in skeletal muscle, which is one of the mechanisms that plays a role in insulin resistance in type 2 diabetes¹⁴.

Supplementation of polyphenols such as resveratrol associated with a significant reduction in HbA1c in type 2 diabetes patients. Clinical trials showed that 24 weeks of resveratrol reduced HbA1c by 5.6% in diabetes patients¹⁵. Giving quercetin for 7 days can also reduce blood glucose levels by 14.78% in mice with diabetes¹⁶. The combination of quercetin and resveratrol also demonstrated reduced HbA1c and improved fasting blood glucose levels in a 14 days in rat with diabetes¹⁷. Research on mice given a diet high in sucrose shows that administration of saponin can reduce postprandial blood glucose levels¹⁸. Saponin from *Stauntonia chinensis* was also found to have significant hypoglycemic and hypolipidemic activity in diabetic rats¹⁹. Research in mice with diabetes shows that wogonin can also improve glucose tolerance through activation of PPAR α ²⁰.

Monomeric catechin (cocoa flavanol fraction rich in monomeric catechin) demonstrated increased glucose-stimulated insulin secretion in INS-1 832/13 β cells and cultured primary rat islets, indicating improved β cell function²¹. Cocoa procyanidins (a type of flavanol found in cocoa), especially the larger ones (oligomeric and

polymeric), have significant antidiabetic potential through mechanisms involving increased glucose utilization and glycogen synthesis independent of insulin, and open the possibility of utilizing this strategy to manage glucose metabolism disorders²². Another study showed that the cocoa-flavanol epicatechin has a protective effect on hepatic lipid metabolism, thereby offering a potential preventive and therapeutic approach for hepatic steatosis in type 2 diabetes. This effect is most likely due to the modulation of key signaling pathways (AMPK, AKT, PKC ζ) that regulate synthesis and oxidation of fatty acids in the liver²³.

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TABLE 1. IN VITRO, IN VIVO STUDIES AND CLINICAL TRIALS REGARDING THE BENEFITS OF ANTIOXIDANTS

Name of antioxidant	Model used	Result	Reference
Vitamin D	Clinical trial	↓ fasting blood glucose	Nikooyeh et al., 2014 ^[9]
Vitamin D	In vivo	↓ Insulin resistance	Krisnamurti et al., 2023 ^[10]
Vitamin E and resveratrol combination	In vivo	↓ fasting blood glucose, improve glyemic control	Rehman et al., 2018 ^[11]
Vitamin E and C combination	Clinical trial	↓ blood glucose, ↓ HbA1C levels	El-Aal et al., 2018 ^[12]
Vitamin C	Clinical trial	Preventing or managing long-term complications of diabetes	Gillani et al., 2017 ^[13] Renal function, Albumin Creatinine Ratio (ACR)
Vitamin C	Clinical trial	↓ oxidative stress in skeletal muscle	Mason et al., 2016 ^[14]
Resveratrol	Clinical trial	↓ HbA1C levels	Mahjabeen et al., 2022 ^[15]
Quercetin	In vivo	↓ blood glucose	Srinivasan et al., 2018 ^[16]
Quercetin and resveratrol combination	In vivo	↓ fastin blood glucose, ↓ HbA1C levels	Yang et al., 2018 ^[17]
Saponin	In vivo	↓ postprandial blood glucose levels	Luyen et al., 2018 ^[18]
Saponin	In vivo	hypoglycemic and hypolipidemic activity	Xu et al., 2018 ^[19]
Wogonin	In vivo	improve glucose tolerance	Bak et al., 2014 ^[20]
Catechin	In vitro	↑ glucose-stimulated insulin secretion	Rowley et al., 2017 ^[21]
Procyanidins	In vitro	↑ glucose utilization and glycogen synthesis independent of insulin	Bowser et al., 2016 ^[22]
Epicatechin	In vitro	protective effect on hepatic lipid metabolism	Cordero-Herrera et al., 2015 ^[23]

DISCUSSION

The results of this study indicate that supplementation with various bioactive compounds has significant potential in managing type 2 diabetes mellitus through various molecular mechanisms that play a role in the regulation of glucose metabolism and insulin sensitivity.

Vitamin D plays a role in increasing insulin sensitivity through activation of the vitamin D receptor (VDR) which is expressed in pancreatic β cells and insulin target tissues. Activation of VDR can increase the expression of genes related to glucose homeostasis as well as reduce the production of proinflammatory cytokines that contribute to insulin resistance²⁴. Clinical studies show that vitamin D supplementation reduces fasting blood glucose levels in type 2 diabetes patients, most likely through increasing insulin secretion and reducing insulin resistance.

Vitamin E and resveratrol have strong antioxidant effects that can reduce oxidative stress, a major factor in the development of insulin resistance and diabetes complications. Resveratrol is known to activate the AMPK (AMP-activated protein kinase) pathway, which plays a role in increasing glucose utilization and inhibiting fat synthesis²⁵ with consequent high blood glucose levels. Permanently increased blood glucose tends to lead to an increase in reactive oxygen species (ROS). Vitamin E in diabetic rat showed a decrease in blood glucose levels and improved glyemic control through increasing GLUT4 expression and AKT phosphorylation in muscle and liver tissue²⁶.

Ascorbic acid (vitamin C) has a protective effect against diabetes complications through its ability to reduce oxidative stress and systemic inflammation. In the context of diabetic nephropathy, vitamin C contributes to the

protection of renal function by reducing the accumulation of advanced glycation end products (AGEs) and increasing enzymatic antioxidant activity. In addition, ascorbic acid reduces oxidative stress in skeletal muscle, which is a key mechanism in improving insulin sensitivity²⁷.

Polyphenols such as resveratrol and quercetin work by inhibiting enzymes in the gluconeogenesis pathway and increasing glucose transport through GLUT4 activation. Resveratrol induces SIRT1 expression, which plays a role in the regulation of energy metabolism and improves insulin sensitivity²⁸ indicating that SIRT1 may be a novel therapeutic target for T2DM prevention. In the present study, a T2DM rat model was established by administering a high fat diet and streptozotocin (STZ). Quercetin also has anti-inflammatory effects that contribute to improved glucose metabolism. Quercetin can reduce blood glucose levels through increasing AMPK phosphorylation and modulating the PPAR γ pathway²⁶.

Saponins play a role in lowering postprandial blood glucose levels by inhibiting the α -glucosidase enzyme in the intestine, thereby slowing glucose absorption¹⁸. Wogonin, a flavonoid compound from medicinal plants, improves glucose tolerance by activating PPAR α , which contributes to increased fatty acid oxidation and insulin sensitivity²⁹.

Cocoa flavonoids, such as monomeric catechins and procyanidin, play a role in the regulation of insulin secretion and glucose metabolism. Monomeric catechins increase insulin secretion in pancreatic β cells through activation of the AKT pathway and increased expression of key enzymes in insulin biosynthesis³⁰. Cocoa procyanidins show antidiabetic potential by increasing glucose utilization in muscle and liver through activation of AMPK³¹. In addition, epicatechin from cocoa has a protective effect on hepatic lipid metabolism by inhibiting fat accumulation through the regulation of AMPK, AKT, and PKC ζ pathways³².

Based on this evidence, supplementation with various bioactive compounds such as vitamin D, vitamin E, vitamin C, polyphenols, saponins, and flavonoids works through complex mechanisms in managing type 2 diabetes mellitus, including increasing insulin sensitivity, reducing blood glucose levels and HbA1c, and protecting against metabolic complications. Further studies are needed to optimize dosage and understand the long-term effects of this compound in the clinical therapy of diabetes.

CONCLUSIONS

Supplementation of vitamin D, vitamin E, vitamin C, polyphenols, saponins, and flavonoids shows potential in improving insulin sensitivity, lowering blood glucose levels, and reducing metabolic complications in type 2 diabetes mellitus through various molecular mechanisms. These positive effects involve the regulation of glucose homeostasis, increased antioxidant activity, reduced oxidative stress, and modulation of signaling pathways such as AMPK, PPAR, and GLUT4. Taking into account the existing scientific evidence, this bioactive compound may be an additional therapeutic strategy in the management of type 2 diabetes mellitus. However, further research is

needed to confirm its long-term effectiveness and safety in humans.

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Availability of Data and Material

Data and material can be accessed via corresponding author.

Conflicts of Interest

The researchers did not have a conflict of interest in this study.

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