Journal of Phytonanotechnology and Pharmaceutical Sciences 3(3): 1-16, 2023

Online ISSN:2583-0376

http://jpps.ukaazpublications.com

DOI: http://dx.doi.org/10.54085/jpps.2023.3.3.1

Journal of Phytonanotechnology and Pharmaceutical Sciences

Review Article : Open Access

Diabetic nephropathy: An outline on molecular mechanism and protective pathways of phytoconstituents

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Article Info

Article history
Received 10 July 2023
Revised 12 August 2023
Accepted 13 August 2023
Published Online 30 September 2023

Keywords
Diabetes
Nephropathy
Inflammation
Phytochemicals
Flavonoids

Abstract

Diabetic nephropathy is a debilitating complication of diabetes mellitus characterized by progressive kidney damage. This review provides a comprehensive overview of the molecular pathways underlying its pathogenesis and explores the protective mechanisms offered by various phytobioactives. The pathogenetic mechanisms of diabetic nephropathy are multifaceted, encompassing the activation of key pathways such as the rennin angiotensin-aldosterone system (RAAS), the polyol pathway, protein kinase C (PKC) pathway, hexosamine pathway, and the formation of advanced glycation end products (AGEs). Understanding these pathways is crucial for developing effective therapeutic strategies to combat diabetic nephropathy. In parallel, this review sheds light on the role of phytobioactives, including alkaloids, flavonoids, tannins, and stilbenes, in mitigating the progression of diabetic nephropathy. These natural compounds exhibit a spectrum of protective properties, including antioxidative and anti-inflammatory effects. Their ability to modulate the molecular pathways implicated in diabetic nephropathy offers promising avenues for novel therapeutic interventions. This review of the pathogenetic mechanisms and the protective potential of phytobioactives underscore the importance of considering natural compounds as adjunctive therapies in managing diabetic nephropathy, potentially improving patient outcomes and quality of life.

1. Introduction

Due to its rising frequency and incidence, diabetes mellitus (DM) poses a major risk to the health of all people. In 2019, there were 463 million persons worldwide who had DM. By 2045, the International Diabetes Federation (IDF) predicts that this number would have surpassed 700 million (IDF, 2023; Kumaraswamy *et al.*, 2022). A chronic metabolic condition known as diabetes mellitus (DM) causes higher than normal blood sugar levels (hyperglycemia) as a result of impaired insulin secretion, cellular resistance to insulin, or both (Punthakee *et al.*, 2018). There are two main varieties of diabetes: type 1, in which the pancreas cannot generate insulin, and type 2, in which the body cannot effectively use the insulin that is produced (Latha and Vijaykumar, 2019). Microvascular consequences caused by DM include diabetic nephropathy (DN), diabetic retinopathy, and diabetic neuropathy in addition to macrovascular issues such stroke, cardiovascular disease (CVDs), and peripheral vascular disease (Adapa and Sarangi, 2015; Okur *et al.*, 2017).

Diabetic nephropathy, also known as diabetic kidney disease, is a persistent renal ailment that has the potential to impact individuals diagnosed with either type 1 or type 2 diabetes. About 40% of all cases of diabetes are affected by DN, and projections indicate that by 2023, there will be 382 million cases of diabetes worldwide, or 8-10% of the world's population (Lim, 2014). Diabetic nephropathy (DN) is characterized by a plethora of clinical manifestations, including heightened arterial blood pressure, a compromised glomerular filtration rate (GFR), the presence of diabetic glomerular lesions, and escalated urine albumin excretion levels surpassing the threshold of 300 mg/day (Gheith *et al.*, 2016). High blood sugar damages renal blood vessels, which leads to kidney dysfunction and is the underlying cause of DN (Gajjala *et al.*, 2015). There are five stages of kidney degeneration associated with DN, and stage 4 is typically when symptoms first appear. It is advised that diabetics have annual renal problems screenings because symptoms do not manifest until later stages. The swelling of ankles, legs, and hands due to water retention, blood in the urine, exhaustion from low oxygen levels in the blood, and nausea are the defining characteristics of the fourth stage of DN. If left unaddressed, this can progress to end-stage renal disease (ESRD), which is the fifth and final stage, where dialysis or kidney transplantation are the only viable treatment options as the kidneys can no longer function to meet daily needs. The risk factors associated with developing DN include hypertension dyslipidemia, smoking and poor glycemic control. A person's genetic makeup also has a significant impact on developing DN because those with a family history of the condition are more likely to do so (Ahmad *et al.*, 2013). According to current reports, DN accounts for 30 - 40% of ESRD cases in the US and is one of the main causes of ESRD (Ghaderian *et al.*, 2015).

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