ISSN: 2633-4828 Vol. 6 No.1, January, 2024

International Journal of Applied Engineering & Technology

THERAPEUTIC POTENTIAL OF MYRICETIN IN DIABETES ASSOCIATED COMPLICATIONS

Deepika[1], Dr. Abirami Arthanari[2]* and Dr. Parameswari R.P.[3]

[1]Under Graduate, Saveetha Dental College, Saveetha Institute of Medical and Technical Science, Saveetha University, Chennai 77, Tamil Nadu, India

[2]Senior Lecturer, Department of Forensic Odontology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Chennai - 600077

[3]Associate Professor, Department of Pharmacology, Saveetha dental college and hospitals, Saveetha institute of medical and technical sciences, Chennai - 600077

ABSTRACT

INTRODUCTION

Diabetes is a chronic metabolic disorder characterised by elevated blood glucose levels due to insulin deficiency or insulin resistance.Myricetin is a common plant derived flavonoids and is well recognised for its nutraceuticals value.This compound includes wide range of activities that includes strong antioxidant, diabetic and inflammatory activity

AIM AND METHODS

The aim of the study is to explore the therapeutic potential of myricetin in the context of diabetes- associated complications.

Evaluate the current evidence regarding the effects of myricetin on glucose metabolism and insulin sensitivity in individuals with diabetes.Assess the antioxidant properties of myricetin and its potential to mitigate oxidative stress- related damage in diabetes-associated complications such as nephropathy, retinopathy, and neuropathy.Investigate the anti inflammatory effects of myricetin and its role in reducing inflammation in diabetic individuals

MATERIALS AND METHODS

Chemicals and Reagents

Myricetin, Aminoguanidine hydrochloride, Metformin and was procured from TCI Chemicals, India. DL-glyceraldehyde, D-glucose, Fructose, lithium sulphate, NADPH, NADP, dimethyl sulphoxide (DMSO), sorbitol, bovine serum albumin, perchloric acid, ammonium sulphate, Tris-HCl, EDTA, sucrose and sorbitol dehydrogenase were purchased from Sigma aldrich (St Louis, MO, USA). All other chemicals of analytical grade were obtained from Himedia, India and SRL chemicals, India.

Advanced Glycation end product (AGE) assay (Harris et al., 2011)

Advanced glycation end products (AGEs) are formed by non-enzymatic glycosylation of proteins that enhance vascular permeability in both micro and macro vascular structures by binding to specific macrophage receptors

The compound Myricetin was evaluated for its activity on AGEs formation at different concentrations of 2.5-25µM. AGE reaction mixture was constituted as follows; 1 mg/mL bovine serum albumin in 50mM sodium phosphate buffer (pH 7.4) and 0.02% sodium benzoate into 0.2M fructose and 0.2M glucose.

DISCUSSION

The therapeutic potential of myricetin in diabetes-associated complications represents a promising avenue in the quest to alleviate the burden of diabetes-related organ damage. The compelling preclinical evidence supports myricetin's potential in mitigating diabetic nephropathy, retinopathy, neuropathy, and cardiovascular complications through its antioxidant, anti-inflammatory, and anti-diabetic properties

CONCLUSION

Myricetin shows promise as a potential therapeutic agent for diabetes-associated complications, it is necessary to continue expanding our knowledge through rigorous research. The exploration of myricetin's therapeutic potential may lead to the development of novel treatment strategies that can alleviate the burden of diabetes and improve the quality of life for affected individuals.

Keywords: Myricetin, metformin, sorbitol dehydrogenase, AGEs, potassium carbonate

INTRODUCTION

Diabetes mellitus, a global epidemic affecting millions worldwide, continues to pose significant challenges to public health systems. This chronic metabolic disorder results from impaired insulin secretion or insulin resistance, leading to chronic hyperglycemia. Beyond its primary consequences, diabetes is often accompanied by a range of debilitating complications affecting various organ systems. These complications can have severe implications on the quality of life for individuals living with diabetes and pose significant economic burdens on healthcare systems.(1)

In recent years, extensive research has been dedicated to finding novel therapeutic approaches to manage and prevent diabetes-associated complications. Among the plethora of natural compounds studied for their potential health benefits, myricetin, a flavonoid commonly found in fruits, vegetables, and medicinal herbs, has emerged as a promising candidate. Myricetin has garnered considerable attention due to its diverse biological properties, including antioxidant, anti-inflammatory, and anti-diabetic activities.(2)

In this comprehensive review, we explore the therapeutic potential of myricetin in mitigating diabetes-associated complications. We delve into the scientific evidence supporting its efficacy in addressing diabetic nephropathy, retinopathy, neuropathy, and cardiovascular complications. Additionally, we examine the molecular mechanisms underlying myricetin's beneficial effects and its impact on key pathways involved in diabetes pathogenesis(2,3)

In this comprehensive review, we explore the therapeutic potential of myricetin in mitigating diabetes-associated complications. We delve into the scientific evidence supporting its efficacy in addressing diabetic nephropathy, retinopathy, neuropathy, and cardiovascular complications. Additionally, we examine the molecular mechanisms underlying myricetin's beneficial effects and its impact on key pathways involved in diabetes pathogenesis.(4)

By shedding light on the remarkable properties of myricetin, this review aims to contribute to the growing body of knowledge on natural compounds that hold promise in combating the devastating consequences of diabetes. Understanding the potential of myricetin in diabetes management could pave the way for the development of targeted therapies and nutraceutical interventions to improve the lives of those affected by this prevalent and life-altering condition.(5)

As we delve into the fascinating world of myricetin and its therapeutic implications, we hope to inspire further research, clinical trials, and eventually, the integration of this bioactive compound into the armamentarium of diabetes management and prevention strategies.(5,6)

MATERIALS AND METHODS

Chemicals and Reagents

Myricetin, Aminoguanidine hydrochloride, Metformin and was procured from TCI Chemicals, India. DL-glyceraldehyde, D-glucose, Fructose, lithium sulphate, NADPH, NADP, dimethyl sulphoxide (DMSO), sorbitol, bovine serum albumin, perchloric acid, ammonium sulphate, Tris-HCl, EDTA, sucrose and sorbitol dehydrogenase were purchased from Sigma aldrich (St Louis, MO, USA). All other chemicals of analytical grade were obtained from Himedia, India and SRL chemicals, India.

Advanced Glycation end Product (AGE) assay (Harris et al., 2011)

Advanced glycation end products (AGEs) are formed by non-enzymatic glycosylation of proteins that enhance vascular permeability in both micro and macro vascular structures by binding to specific macrophage receptors. The compound Myricetin was evaluated for its activity on AGEs formation at different concentrations of 2.5-25µM. AGE reaction mixture was constituted as follows; 1 mg/mL bovine serum albumin in 50mM sodium phosphate buffer (pH 7.4) and 0.02% sodium benzoate into 0.2M fructose and 0.2M glucose. The reaction mixture (2.75mL) was treated with different concentrations of Myricetin (2.5-25µM). Amino guanidine was used as positive control. After incubating at 37°C for 3 days, the fluorescence intensity of the reaction was determined at excitation and emission wavelengths of 350 nm and 450 nm, respectively, using Biotek synergy multi-mode reader, USA. The percentage activity was calculated with respect to solvent control.

Determination of Aldose Reductase Inhibition (Reddy et al., 2011)

A total of 531µL of 0.1 M potassium buffer (pH 7.0), 90µL of NADPH solution (1.6 mM in potassium buffer), 90µL of recombinant human aldose reductase (AR) (6.5U/mg) (Sigma, USA - SRP6371-100UG), 90µL of ammonium sulphate solution (4 M in potassium buffer), and 90 µL of DL-glyceraldehyde (25 mM in potassium buffer) were mixed with 9µL of different concentrations of Myricetin (2.5-25µM) in a cuvette, and the activity of AR was assessed spectrophotometrically by measuring the decrease in NADPH absorbance at 340 nm for 3 min using a spectrophotometer (Biotek Synergy H4 multi mode reader, USA). Metformin was used as positive control. The inhibition of AR (%) was calculated using the following equation: (1 − (△A sample/min) – (△A blank/min)/(△A control/min) − (△A blank/min)) × 100%, where △A sample/min is the decrease in absorbance over 3 min with reaction solution, test sample, and substrate, and △A control/min without the test sample.

Sorbitol Accumulation Inhibition Assay (Malone et al., 1980)

5 ml of blood was collected into heparinized tubes from healthy volunteers after an overnight fast. The blood was immediately centrifuged at 2000 rpm for 5 min, 4ºC to separate the erythrocytes from the plasma. After discarding the plasma and buffy coat, add isotonic saline (0.9% NaCl) equal to twice the volume of the erythrocytes and centrifuged at 2000 rpm for 10 min. Washed RBCs were suspended in Hank's balanced salt solution [HBSS] (pH 7.4) to a ratio of 1:10. Samples were incubated at 37°C for 3 h under normal (5.5mM) and high glucose (55mM) conditions. The effect of Myricetin on sorbitol accumulation was evaluated by incubating the RBC with different concentrations of the Myricetin. At the end of incubation periods, RBC were centrifuged, washed with saline and again centrifuged. Red cell was precipitated with cold 6% perchloric acid to the ratio of 1:3. The homogenate was centrifuged at 2000 rpm at 4°C for 10 min and the pH of the supernatant was adjusted to 3.5 with 0.5M potassium carbonate. The sorbitol content of the supernatant was measured by fluorometric method. In brief, the reaction mixture contained the appropriate protein-free supernatant, 50mM glycine buffer (pH 9.4), 0.2mM NAD+, and 1.28U/ml sorbitol dehydrogenase. The mixture was incubated at 37°C for 30 min, and the relative fluorescence due to NADH was measured by a fluorescence spectrometer at an excitation wavelength of 366 nm and an emission wavelength of 452 nm.

Statistical Analysis

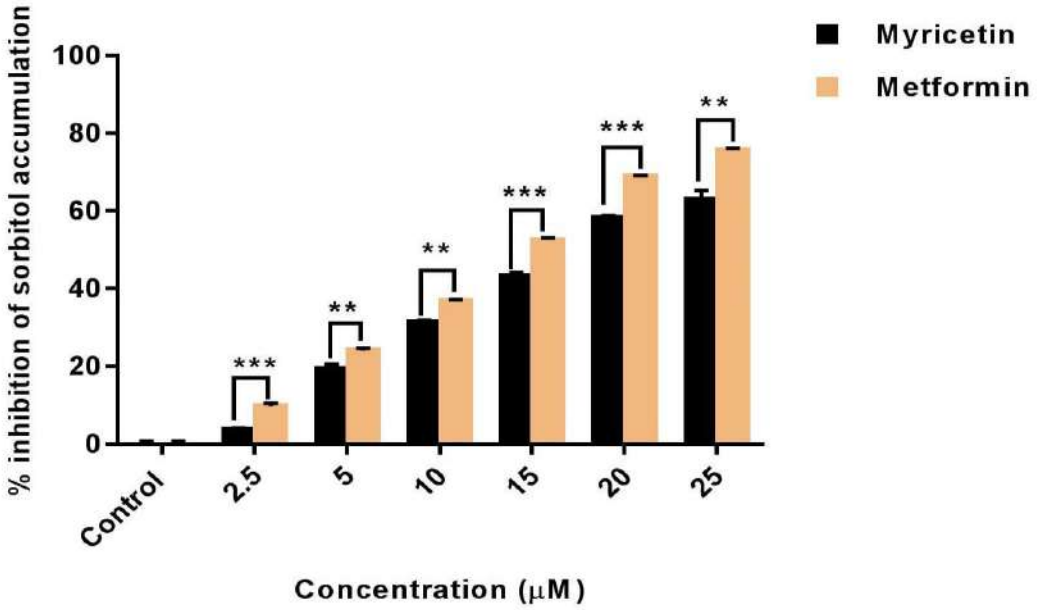
Data were analysed using Graphpad prism (version 7.0). The results were expressed as Mean±SEM and the IC_{50} values were obtained from the linear regression plots. Two-way ANOVA was used to assess differences between means at $p<0.001$ level of significance. The means were compared with standards groups using the Holm-Sidak Test.

RESULTS

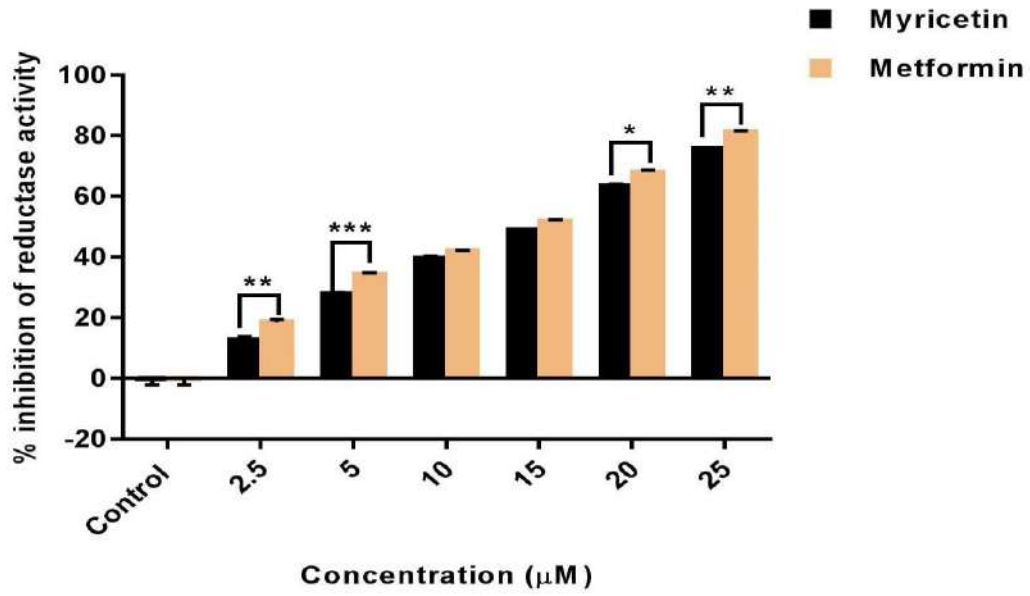
Results shows that Graph 1, Myricetin shows 70-75 % of inhibition level that metformin has against sorbitol accumulation. As concentration level increases, inhibition levels also increase.Graph:2, Myricetin shows 80-85 % of inhibition level that metformin has against reductase activity . As concentration level increases, inhibition levels also increase.

Graph 3, Myricetin shows 90% of the inhibition level that metformin has against AGEs. As concentration level increases, inhibition levels also increase. Results show that even if there is no equal level of inhibition, it shows nearby inhibition levels and also it has significant inhibition levels against sorbitol accumulation, reductase activity and AGEs.

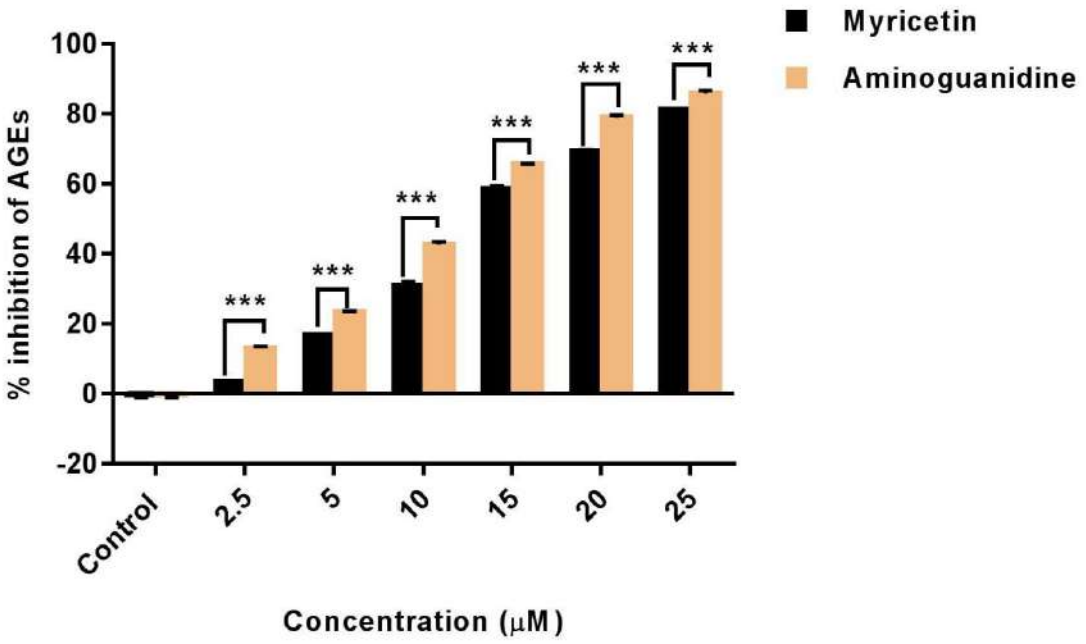
Graph:1-It represents % inhibition of sorbitol accumulation



Graph:2-It represents% of inhibition of reductase activity



Graph:3-It represents %of inhibition of AGEs



DISCUSSION

It's important to note that while preclinical and some clinical studies have shown positive effects of myricetin in diabetes- associated complications, further research is needed to fully understand its mechanisms of action, optimal dosage, and long- term effects in humans. Additionally, myricetin should not be considered a standalone treatment but rather as a potential adjunct therapy alongside standard diabetes management approaches.(7)

The therapeutic potential of myricetin in diabetes-associated complications is a topic of significant scientific interest and has implications for the management and prevention of various complications arising from diabetes mellitus. In the discussion section, we will delve deeper into the findings presented in the review and address the implications, limitations, and future prospects of utilising myricetin as a therapeutic agent for diabetes-related complications.(8)

The therapeutic potential of myricetin is just one facet of a broader field of research into natural compounds and their applications in diabetes management. Continued investigations into other flavonoids and plant-derived compounds may yield additional therapeutic candidates for diabetes-associated complications. In Discussion, the therapeutic potential of myricetin in diabetes-associated complications represents a promising avenue in the quest to alleviate the burden of diabetes-related organ damage.(9) The compelling preclinical evidence supports myricetin's potential in mitigating diabetic nephropathy, retinopathy, neuropathy, and cardiovascular complications through its antioxidant, anti-inflammatory, and anti-diabetic properties. However, translating these findings into clinical applications requires further investigation and validation. As research in this field progresses, myricetin and other natural compounds hold great promise in augmenting diabetes care and enhancing the quality of life for individuals living with this chronic metabolic disorder(10)

Studies examining the effects of myricetin on diabetic nephropathy have demonstrated its ability to attenuate renal damage, reduce oxidative stress, and ameliorate inflammation, all of which are key contributors to the progression of kidney complications in diabetes.(11) Similarly, in diabetic retinopathy, myricetin has shown potential in preserving retinal function, inhibiting neovascularization, and protecting against retinal cell death. These findings are particularly promising for diabetic patients, as retinopathy is a leading cause of vision loss and blindness.(12)

CONCLUSION

In conclusion, the exploration of myricetin as a potential therapeutic agent in diabetes-associated complications has unveiled a promising avenue in the battle against the detrimental effects of this pervasive metabolic disorder. The body of evidence presented in this review supports the notion that myricetin possesses remarkable antioxidant, anti-inflammatory, and anti-diabetic properties, making it an attractive candidate for managing and preventing complications arising from diabetes.(10)

Furthermore, the neuroprotective effects of myricetin have been highlighted in the context of diabetic neuropathy, with evidence suggesting its ability to mitigate nerve damage and alleviate neuropathic pain. Additionally, the compound's cardiovascular benefits have been evident in studies that demonstrate its capacity to improve endothelial function, reduce atherosclerosis, and enhance cardiac performance in diabetic subjects.(11,12)

The mechanistic insights provided in this review shed light on myricetin's impact on critical pathways involved in diabetes pathogenesis, including the modulation of insulin signalling, regulation of inflammation-related molecules, and inhibition of oxidative stress-induced damage. Such mechanisms contribute to its overall protective effects against diabetes-associated complications.(13)

Despite the promising findings, it is important to acknowledge that the clinical application of myricetin as a therapeutic agent requires further investigation and validation through rigorous clinical trials. Dosing, safety, and potential interactions with existing medications must be thoroughly evaluated to ensure its efficacy and safety in human subjects.(14)

Nonetheless, the compelling evidence accumulated thus far encourages the continued exploration of myricetin and other natural compounds as potential adjuvant therapies in diabetes management. Incorporating these bioactive agents into a comprehensive diabetes care strategy holds the potential to enhance patient outcomes, reduce the burden of complications, and improve the overall quality of life for individuals living with diabetes.(15)

CONFLICT OF INTEREST

There is no conflict of interest

ACKNOWLEDGEMENT

We extend our gratitude to Saveetha dental college and hospital for their constant support and encouragement and hereby helping in successful completion of this research work.

FUNDING:

1. Saveetha institute of medical and technical sciences
2. Saveetha dental college and hospital
3. Saveetha university
4. Sri Srinivasa Clinic

ETHICAL CLEARANCE

Since it is an in vitro study, ethical clearance is not required.

REFERENCE

1. Watson RR, Dokken B. Glucose Intake and Utilisation in Pre-Diabetes and Diabetes: Implications for Cardiovascular Disease. Elsevier; 2014. 442 p.
2. Mérillon JM, Ramawat KG. Bioactive Molecules in Food. Springer; 2019. 2370 p.
3. Hrelia S, Angeloni C. New Mechanisms of Action of Natural Antioxidants in Health and Disease. MDPI; 2020. 168 p.
4. Grosso G. Effects of Polyphenol-Rich Foods on Human Health: Volume 1. MDPI; 2018. 441 p.

5. Wen J, Dridi S, Gilbert ER. Fat Metabolism and Deposition in Poultry: Physiology, Genetics, Nutrition and Interdisciplinary Research, Volume I. Frontiers Media SA; 2022. 158 p.
6. Hussain A, Behl S. Treating Endocrine and Metabolic Disorders With Herbal Medicines. IGI Global; 2020. 489 p.
7. Strobel P, Allard C, Perez-Acle T, Calderon R, Aldunate R, Leighton F. Myricetin, quercetin and catechin-gallate inhibit glucose uptake in isolated rat adipocytes. Biochem J. 2005 Mar 15;386(Pt 3):471–8.
8. Wang H, Fowler MI, Messenger DJ, Ordaz-Ortiz JJ, Gu X, Shi S, et al. Inhibition of the intestinal postprandial glucose transport by gallic acid and gallic acid derivatives. Food Funct. 2021 June 21;12(12):5399–406.
9. Sankar S. In silico design of a multi-epitope Chimera from Aedes aegypti salivary proteins OBP 22 and OBP 10: A promising candidate vaccine. J Vector Borne Dis. 2022 Oct-Dec;59(4):327-336. doi: 10.4103/0972-9062.353271.
10. Inflammatory Disorders - Part B. Academic Press; 2020. 436 p.
11. Devi SK, Paramasivam A, Girija ASS, Priyadharsini JV. Decoding The Genetic Alterations In Cytochrome P450 Family 3 Genes And Its Association With HNSCC. Gulf J Oncolog. 2021 Sep;1(37):36-41.
12. Chen Y, Li D, Tang D, Abalo R. Herbal medicine for the treatment of chronic metabolic diseases. Frontiers Media SA; 2023. 268 p.
13. Lee YS, Choi EM. Myricetin inhibits IL-1beta-induced inflammatory mediators in SW982 human synovial sarcoma cells. Int Immunopharmacol. 2010 Jul;10(7):812–4.
14. Rani V, Yadav UCS. Functional Food and Human Health. Springer; 2018. 694 p.
15. Watanabe T, Kondo K, Oishi M. Induction of in vitro differentiation of mouse erythroleukemia cells by genistein, an inhibitor of tyrosine protein kinases. Cancer Res. 1991 Feb 1;51(3):764–8.