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EXPLORING THE THERAPEUTIC POTENTIALS FOR DIABETIC RETINOPATHY: A COMPREHENSIVE REVIEW

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Abstract: This integrative review aims to summarize recent advances in therapeutic approaches for diabetic retinopathy. A comprehensive literature search was performed in PubMed, covering publications from 2018 to 2024. Of the 167 articles initially identified, 7 were selected for final analysis. The selected articles highlighted promising therapeutic strategies: 1) Inhibition of NADPH oxidase (NOX), with NOX inhibitors showing potential in reducing oxidative stress and vascular damage; 2) Dietary polyphenols, which modulate oxidative and inflammatory pathways, suggesting their potential as preventive and therapeutic agents; 3) Stem cell therapies, indicating that stromal/mesenchymal cells can promote neurovascular repair in the diabetic retina. This review highlights the emerging therapeutic potential of addressing oxidative stress and neuroinflammation in DR, supporting further clinical investigations into NOX inhibitors, dietary polyphenols, and stem cell therapies.
Keywords: Diabetic retinopathy, oxidative stress, NADPH oxidase, polyphenols, stem cell therapy, neuroinflammation, early intervention.

INTRODUCTION

Diabetic retinopathy (DR) is one of the most common and devastating complications of diabetes mellitus, representing one of the main causes of preventable blindness worldwide. The global prevalence of diabetes is on the rise, making DR a growing public health concern. This ocular complication results from microvascular changes in the retina, leading to progressive visual damage and, eventually, irreversible vision loss (Lin et al., 2021).

In recent decades, DR management has evolved significantly. Notable advances include the use of anti-VEGF agents and the implementation of advanced imaging

technologies such as optical coherence tomography (OCT), which have revolutionized the diagnosis and early treatment of the disease (Tang et al., 2024). However, despite these advances, there remain considerable challenges in early diagnosis and effective treatment of DR, especially in regions with limited medical resources (Lin et al., 2021).

Recently, there has been an increase in interest in novel therapies that address the complex pathological mechanisms underlying DR, including oxidative stress, immune responses, and vascular endothelial dysfunction. Emerging research is exploring the potential of biomarkers, molecular and cellular therapies, antioxidant interventions, and gene therapy as promising strategies for treating DR (Tang et al., 2024). Furthermore, artificial intelligence is increasingly being incorporated into automated screening programs, improving early detection and monitoring of disease progression (Tan and Wong, 2023).

This integrative review article aims to analyze new emerging therapies for diabetic retinopathy. Drawing on recent discoveries and technological advances, we will discuss innovative therapeutic approaches that are being developed to address persistent challenges in treating DR. The review will also highlight the importance of automated screening and identification of specific biomarkers to improve early diagnosis and reduce the prevalence of blindness caused by DR.

METHODS

A systematic search was performed across several electronic databases, including PubMed for relevant articles published between 2018 and 2024. The search terms used were "diabetic retinopathy", "treatment" and "therapy". The search strategy included both keywords and MeSH terms (Medical Subject Headings) to ensure the comprehensiveness of the search. The inclusion criteria for selecting articles were: articles published in English; studies that address innovative therapies for diabetic retinopathy, with relevant clinical or preclinical data. The exclusion criteria were: articles of low methodological quality, according to critical evaluation.

Initially, 167 articles were identified through a database search. After removing the initial screening based on titles and abstracts, 45 articles were selected for full text evaluation. After complete reading and critical evaluation based on the inclusion and exclusion criteria, 7 articles were considered relevant and included in the final review.

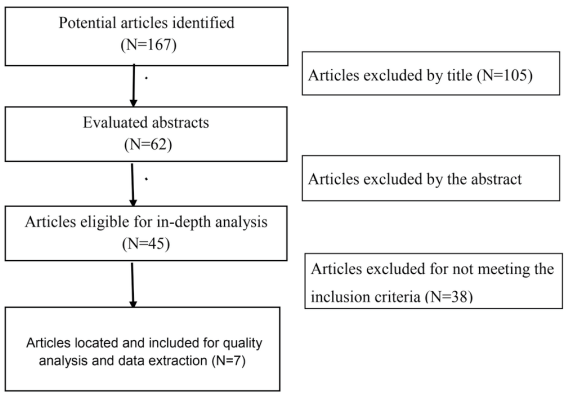

Figure 1.0 Flowchart of the distribution of articles found and selected.

Source: Fernandes BMC et al. (2024)

RESULTS

The data extracted from the selected studies were organized in a summary table (Table 1.0), highlighting information about the main findings, evaluated therapies and mechanisms involved. A qualitative analysis was performed to identify recurring themes, gaps in knowledge, and implications for clinical practice and future research.

Author and year	Main findings	Therapies Evaluated	Mechanisms Involved
Liu & Wu (2021)	Nanotechnology offers new approaches to improve the bioavailability and minimize side effects of traditional therapies for diabetic retinopathy.	Nanotechnology	More efficient drug delivery, reduced side effects, improved nerve tissue regeneration.
Wang et al. (2024)	New receptor inhibitors and agonists show efficacy in delaying the progression of DR; advances in nanotechnology improve drug delivery systems.	Aldose reductase inhibitors, ACE inhibitors, PPAR-alpha agonists, nanotechnology	Improved drug solubility and penetration, reduced oxidative stress, neurodegeneration and inflammation.
Sun et al. (2023)	Early intervention in DR is crucial; early stages involve neurodegenerative and microvascular changes.	Therapies for non-proliferative stage, anti-VEGF agents, steroids	Microangiomas, hemorrhages, pericyte loss, neuronal death, polyol pathways, leukocyte adhesion, RNA regulation, ferroptosis, pyroptosis.
Fiori et al. (2018)	Mesenchymal stem cells (MSCs) show significant potential for cell therapy in DR by addressing neurovascular cell loss.	Cell therapy with MSCs	Repair of retinal microvasculature and neuroglia, diverse modes of action, including immunomodulation and tissue regeneration.
Lechner et al. (2022)	Stem cell therapies hold promise for replacing dying cells during the early and late stages of DR; the neurodegenerative phenotype needs to be addressed.	Cell therapy with vasoactive progenitors, induced pluripotent stem cells, retinal progenitor cells	Repair of damaged vasculature, replacement of neurons, treatment of neurodegeneration and vessel degeneration.
Peng et al. (2019)	NADPH oxidase (NOX) is an important source of reactive oxygen species in the retina and a potential target for DR therapy.	NADPH oxidase inhibitors	Reduction of oxidative stress, improvement of retinal functions, inhibition of neovascularization and oxidative damage.
Fanaro et al. (2023)	Dietary polyphenols reduce oxidative and inflammatory parameters in DR; further clinical studies are needed to validate its therapeutic efficacy.	Dietary polyphenols	Modulation of cellular signaling pathways, gene expression, reduction of cellular damage caused by inflammation and oxidative stress, improvement of neuroprotection and vascular health.

Table 1.0: Results Table of the Integrative Review on New Therapeutics for Diabetic Retinopathy

Source: Fernandes BMC et al. (2024)

DISCUSSION

Research reviewed by Liu and Wu (2021) highlights the emerging role of nanotechnology as an innovative approach to treating DR. Traditionally, clinical treatments for DR, such as laser photocoagulation, anti-VEGF injections, and vitrectomy, have been effective but have significant limitations, including low drug bioavailability and risks associated with surgical interventions. These challenges motivate the search for safer and more effective alternatives. Nanotechnology offers promising solutions to overcome these limitations, providing better drug delivery and minimizing side effects. Nanoparticles, for example, can be designed to release drugs in a controlled and targeted manner, improving therapeutic efficacy and reducing systemic toxicity.

Wang et al. (2024) emphasizes the complexity of DR as a neurovascular complication associated with type 1 and type 2 diabetes mellitus, and highlights the urgent need for more effective treatment strategies. Conventional treatments, such as anti-VEGF injections, steroids, laser photocoagulation, and vitrectomy, have been widely used, but not without significant limitations, including adverse effects and limited efficacy. The authors highlight the crucial role of new receptor inhibitors and agonists, such as aldose reductase inhibitors and peroxisome proliferator-activated receptor alpha agonists, which have shown potential in slowing the progression of DR. This progress could significantly improve therapeutic efficacy and reduce side effects.

The review by Sun et al. (2023) underlines the critical importance of early intervention in DR, highlighting that currently available pharmacological therapies, such as anti-VEGF agents and steroids, are primarily targeted at diabetic macular edema and do not address the disease in its early stages. Early identification and treatment of DR are essential to improving patients' quality of life and reducing costs associated with medical care. The article emphasizes that the initial non-proliferative phase of DR is characterized by pathological changes such as microangiomas, hemorrhages, loss of pericytes and neuronal cell death, in addition to interruptions in the functionality of the retinal neuronal vascular unit. These initial changes are driven by complex mechanisms, including polyol pathways, leukocyte adhesion, neutrophil extracellular traps, RNA regulation, and cell death processes such as ferroptosis and pyroptosis.

Fiori et al. (2018) and Lechner et al. (2022) discuss the use of mesenchymal stromal cells (MSCs) and other types of stem cells, such as retinal progenitor cells and pluripotent stem cell-derived photoreceptors, to treat DR. These treatments aim to replace dying cells and restore functionality to the damaged retina. In preclinical models, different types of stem cells have shown potential to repair the vasculature and neuroglial components of the retina, addressing both the vasculopathy and neurodegeneration associated with DR.

Fiori et al. (2018) explore the potential of cell replacement therapies, especially the use of stem and progenitor cells, to repair damage to the vascular and neuroglial compartments of the retina. Among the various stem cell populations studied, mesenchymal stromal cells (MSC) emerge as a promising option due to their ability to combine multiple modes of action (MoA), which can provide efficient repair of damaged retina. Although cell therapy is in its early stages of research, with many studies still in the preclinical phase, the potential of MSCs is significant. MSCs can act through various MoA, including secretion of trophic factors, immune modulation, and differentiation into retinal cells, which may contribute to retinal regeneration and improved visual function.

The study by Peng et al. (2019) highlights the crucial role of NADPH oxidase (NOX) in the development of DR and its potential usefulness as a therapeutic target. DR, a common complication of diabetes, is strongly influenced by oxidative stress induced by hyperglycemia. The resulting oxidative stress, caused by the accumulation of reactive oxygen species, triggers retinal damage, including leaky blood vessels and the induction of neovascularization, contributing to the microvascular symptoms of DR. NOX, an important enzymatic source of reactive oxygen species in the retina, plays a significant role in the early and advanced stages of DR. These findings suggest that NOX may represent a promising therapeutic target for the treatment of DR. By modulating NOX activity, it is possible to reduce oxidative stress in the retina, potentially slowing or stopping disease progression.

The study by Fanaro et al. (2023) offers new insights into the use of dietary polyphenols in the management of DR, a condition that represents a significant global burden of blindness associated with advanced diabetes mellitus (DM). Current therapies for DR mainly focus on alleviating clinical symptoms in the advanced stages of the disease by addressing specific microvascular changes. The study highlights the potential of dietary polyphenols to modulate the pathophysiological mechanisms involved in DR, especially those related to oxidative stress and neuroinflammation. Increasing evidence suggests that these bioactive compounds can

reduce oxidative and inflammatory parameters in several chronic conditions, including metabolic and neurodegenerative diseases. However, despite promising evidence from experimental studies, the review highlights the scarcity of clinical data, especially human studies, that evaluate the therapeutic potential of these substances in the management of DR.

FINAL CONSIDERATIONS

The studies reviewed highlight several promising approaches to treating DR. From the use of dietary polyphenol-based therapies, which have shown potential in reducing oxidative stress and neuroinflammation, to advances in nanotechnology and cellular therapies, such as the use of stem/progenitor cells to promote neurovascular regeneration, there are a variety of therapeutic options under development. However, it is crucial to recognize that the majority of the studies reviewed are based on evidence from preclinical models, and there is a substantial lack of data from robust clinical trials. Therefore, more clinical research is needed to validate the efficacy and safety of these therapeutic approaches in patients with DR.

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