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Review

The Role of SGLT2 Inhibitors in the Management of Diabetic Retinopathy: A Literature Review

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Abstract

Diabetic retinopathy (DR) remains a leading cause of blindness among individuals with diabetes mellitus (DM), with a continuously rising global prevalence. While anti-vascular endothelial growth factor (anti-VEGF) therapy, corticosteroids, laser photocoagulation, and vitreoretinal surgery have improved outcomes, none can permanently prevent disease progression. The complex pathophysiology of DR, which includes inflammation, oxidative stress, and neurodegeneration, highlights the need for additional systemic strategies. This narrative review was informed by a structured search of PubMed, Scopus, and Web of Science covering the period from January 2000 to September 10, 2025. Original studies, systematic reviews, and meta-analyses were included, whereas case reports and editorials were excluded. Findings were synthesized qualitatively. Preclinical models suggest that sodium–glucose cotransporter 2 (SGLT2) inhibitors exert neuroprotective, anti-inflammatory, and antioxidant effects on the retina, preserve the blood–retinal barrier, and reduce vascular endothelial growth factor (VEGF) expression. However, whether these retinal effects are only partially independent of glycemic control remains speculative, as clinical studies have not adequately controlled for changes in glycated hemoglobin (HbA1c) or for differences in concomitant glucose-lowering therapies. Observational clinical studies have associated SGLT2 inhibitor use with a lower risk of DR progression, a reduced incidence of proliferative DR, and fewer vision-threatening interventions compared with some other antihyperglycemic agents. Owing to the established indications in heart failure and chronic kidney disease associated with SGLT2 inhibitors, these agents appear promising for DR prevention and risk modification. However, current clinical evidence is based mainly on observational and retrospective studies and remains vulnerable to confounding and selection bias. Prospective randomized studies with ophthalmic endpoints are needed before firm conclusions can be drawn.

Keywords: diabetic retinopathy; SGLT2 inhibitors; microvascular complications; retina; diabetes mellitus

1. Introduction

Diabetic retinopathy (DR) is one of the most significant causes of new cases of blindness among individuals with diabetes mellitus (DM) [1]. According to data from 2020, more than 103 million people worldwide with DM had a diagnosis of DR, and this number is projected to reach approximately 160 million by 2045 [2]. Unlike other leading causes of blindness, DR is the only condition that did not show a decline in age-standardized prevalence between 1990 and 2020 (Global Burden of Disease 2019). In the absence of timely preventive and therapeutic measures, a further rise in prevalence is expected, exposing a large number of patients to the risk of severe complications that can result in profound and permanent vision loss, including diabetic macular edema (DME) and proliferative diabetic retinopathy.

The pathophysiological mechanisms of DR include processes of inflammation, neurodegeneration, and oxidative stress. Although currently available treatment options, such as vascular endothelial growth factor (VEGF) inhibitors (anti-VEGF therapy), corticosteroids, laser photocoagulation, and pars plana vitrectomy have significantly improved treatment outcomes, their use remains limited by adverse effects and the inability to permanently halt disease progression, underscoring the need for innovative and more effective therapeutic strategies [3].

According to the most recent American Diabetes Association (ADA) *Standards of Care* from 2024, achieving and maintaining target levels of glycemia, blood pressure, and lipids represents the cornerstone of DR prevention and slowing its progression [1]. Results from large prospective randomized trials have shown that intensive diabetes management aimed at near-normoglycemia can significantly delay disease onset and progression, reduce the need for later ophthalmic interventions, and contribute to preserving patients' quality of life and visual function (The Diabetes

Control and Complications Trial Research Group 1993) [4]. However, reports from certain clinical trials indicate that newer therapies, such as glucagon-like peptide-1 receptor agonist (GLP-1) (liraglutide, semaglutide, dulaglutide), may be associated with an increased risk of rapid worsening of retinopathy, particularly in the context of abrupt reductions in glycated hemoglobin (HbA1c) levels [5]. These findings emphasize the need for careful monitoring of patients and further studies to better assess the long-term impact of modern antihyperglycemic drugs on the course of DR.

In recent years, sodium-glucose cotransporter 2 (SGLT2) inhibitors have gained increasing importance as systemic antihyperglycemic therapy. In addition to their primary glucose-lowering effect, these drugs also exert numerous pleiotropic effects, including anti-inflammatory and antioxidant actions, which may provide additional protection against diabetes-related microvascular damage [6–8]. Preclinical studies support this hypothesis, showing that SGLT2 inhibitors can slow or prevent DR progression in its early stages [9]. Furthermore, data from observational real-world studies indicate that treatment with SGLT2 inhibitors may be associated with a lower risk of developing advanced stages of retinopathy compared with other antihyperglycemic therapies [9], while systematic review and meta-analysis data suggest that SGLT2 inhibitors do not appear to significantly increase the overall risk of eye disorders during treatment [10]. Based on these findings, it can be assumed that SGLT2 inhibitors may have a potential role in the prevention and modification of the course of DR.

Therefore, the objective of this review is to present and analyze the available evidence on the mechanisms of action and clinical effects of SGLT2 inhibitors, and to evaluate their potential role in current therapeutic strategies for the management of diabetic retinopathy.

2. Systemic Effects of SGLT2 Inhibitors

SGLT2 inhibitors have multifaceted systemic effects beyond glucose lowering, influencing cardiovascular, renal, and metabolic pathways. There are several pharmacological approaches to the treatment of type 2 diabetes mellitus (T2DM). Strict glycemic control with metformin, thiazolidinediones, sulfonylureas, meglitinides, and dipeptidyl peptidase-4 (DPP-4) inhibitors reduces the risk of microvascular complications, but does not have a significant effect on macrovascular outcomes. SGLT2 inhibitors have been associated with cardioprotective effects and reduced cardiovascular events [11].

This drug class acts by blocking sodium-glucose transporters in the proximal renal tubules, thereby reducing their reabsorption and enabling glucose excretion in the urine, which lowers glycemia. Renal glucose elimination does not induce the adverse metabolic consequences associated with removal of endogenous glucose and also contributes to weight loss through caloric deficit. At the same time, SGLT2 inhibition enhances sodium excretion, which lowers arterial blood pressure. Favorable cardiovascular effects may also be partly related to reduced sympathetic activity in the heart and blood vessels [12].

SGLT2 uses one sodium ion to transport a glucose molecule, whereas SGLT1 requires two sodium ions, making SGLT2 more energy-efficient. Increased renal SGLT2 expression has been confirmed in both humans with T2DM and in experimental T1DM and T2DM models. Inhibition of this transporter lowers HbA1c, uric acid levels, and body weight, thereby improving several risk factors associated with adverse cardiovascular outcomes [13].

Large cardiovascular outcome trials have demonstrated favorable cardiovascular effects of SGLT2 inhibitors in patients with type 2 diabetes mellitus (T2DM), including reductions in cardiovascular and renal events with canagliflozin and reduced cardiovascular mortality with empagliflozin [14,15]. Real-world data analyses have reported an association between SGLT2 inhibitor use and lower cardiovascular disease risk in patients with T2DM [16]. These drugs have also been shown to slow the progression of chronic kidney disease progression by reducing intraglomerular pressure via natriuresis and restoring tubuloglomerular feedback, thereby alleviating glomerular hyperfiltration [17].

This drug class is generally well tolerated. The most common adverse events, related to their mechanism of action, are glycosuria and consequently increased risk of genital and urinary infections, which are typically mild to moderate and respond well to treatment. Orthostatic hypotension due to hyponatremia and fluid loss may occur, and in severe cases can cause circulatory disturbances in peripheral tissues. Some trials have also reported an increased risk of lower-limb amputations and bone fractures, particularly with canagliflozin [18]. These drugs are not recommended during pregnancy [19].

Four SGLT2 inhibitors are approved by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for T2DM therapy: canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin. Notably, empagliflozin and dapagliflozin, based on demonstrated cardiovascular and nephroprotective benefits, have been granted extended indications for heart failure and chronic kidney disease, irrespective of T2DM status [20]. Beyond their systemic and cardiovascular benefits, increasing attention has been directed toward the possible microvascular and ocular protective effects of SGLT2 inhibitors.

2.1 Pharmacological and Pharmaceutical Properties of SGLT2 Inhibitors

SGLT2 inhibitors represent a distinct class of orally active antihyperglycemic agents characterized by selective blockade of glucose reabsorption in the proximal renal tubules [21,22]. All members of this class share a com-

Table 1. Comparative pharmacokinetic and pharmacodynamic properties of approved SGLT2 inhibitors.

Parameter	Canagliflozin	Dapagliflozin	Empagliflozin	Ertugliflozin
Chemical class/core structure	C-arylglucoside derivative	C-arylglucoside derivative	C-arylglucoside derivative	C-arylglucoside derivative
Molecular weight (Da)	444.5	408.9	450.9	436.9
Oral bioavailability (%)	≈65	≈78	≈60	≈100
Tmax (h)	1–2	1–2	1.5	1
Elimination half-life (h)	10–13	12–13	12.4	16.6
Protein binding (%)	99 (mainly albumin)	91	86	93.6
Volume of distribution (L)	83.5	118	74	85.5
Main metabolic pathway	UGT1A9, UGT2B4 (glucuronidation)	UGT1A9 (glucuronidation)	UGT2B7 (minor CYP3A4)	UGT1A9 (glucuronidation)
SGLT2:SGLT1 selectivity ratio	≈260:1	≈1200:1	≈2500:1	≈2200:1
Main route of excretion	Urine (40–50%), feces (rest)	Urine (~75%)	Urine (~55%)	Urine (~50%)
Approved indications (FDA/EMA)	T2DM; CV risk reduction	T2DM; HF; CKD	T2DM; HF; CKD	T2DM
Distinctive features/remarks	Slight SGLT1 inhibition → ↑ GI AEs; ↓ AUC (~51%) with rifampin	High renal selectivity; well tolerated	Highest selectivity; strong CV/renal evidence	Longest half-life; QD dosing possible

Data compiled from [21–24], and FDA Drug Labels (2013–2017).

Abbreviations: SGLT1, sodium-glucose cotransporter 1; SGLT2, sodium-glucose cotransporter 2; FDA, United States Food and Drug Administration; EMA, European Medicines Agency; T2DM, type 2 diabetes mellitus; CV, cardiovascular; HF, heart failure; CKD, chronic kidney disease; QD, once daily; GI, gastrointestinal; UGT, UDP-glucuronosyltransferase; AEs, adverse events; AUC, area under the plasma concentration–time curve. Arrows indicate direction of change: ↑, increase; ↓, decrease; →, indicates leads to or results in.

mon *C-arylglucoside* scaffold but differ in physicochemical properties, metabolic pathways, and selectivity toward SGLT2 versus SGLT1 transporters, which contribute to differences in their pharmacokinetic and pharmacodynamic profiles [23].

After oral administration, SGLT2 inhibitors are rapidly absorbed, exhibit high plasma protein binding (>85%), and undergo extensive glucuronidation via hepatic and renal UDP-glucuronosyltransferases (UGT1A9, UGT2B4, UGT2B7) with minimal CYP450 involvement, resulting in a low potential for metabolic drug–drug interactions [24] (FDA Invokana Review, 2013; FDA Farxiga Review, 2014; FDA Jardiance Label, 2014; FDA Steglatro Label, 2017). Their relatively long elimination half-lives (10–16 h) allow once-daily dosing and stable systemic exposure.

Although they share a similar mechanism of action, individual agents differ in SGLT2/SGLT1 selectivity, bioavailability, and distribution volume, which may influence both their systemic pharmacological effects and potential microvascular or ocular benefits [25,26]. For example, empagliflozin shows approximately 2500-fold selectivity for SGLT2 over SGLT1, while dapagliflozin and canagliflozin display ratios of about 1200:1 and 260:1, respectively [21]. These pharmacological differences may be relevant to tissue penetration, endothelial function, and downstream antioxidant and anti-inflammatory effects. The pharmacokinetic characteristics of approved SGLT2 inhibitors are summarized in Table 1 (Ref. [21–24]). These agents also differ in bioavailability, selectivity, metabolic pathways, and elimination profiles, which may influence their pharmacological activity and safety.

These pharmacokinetic and pharmacodynamic characteristics indicate that SGLT2 inhibitors have predictable systemic exposure and low potential for CYP-mediated drug interactions. Beyond their metabolic effects, experimental findings suggest that SGLT2 transporters may also be expressed in retinal pericytes and endothelial cells, providing a molecular rationale for exploring their actions in the eye. The following section summarizes current evidence on the mechanisms through which SGLT2 inhibition may modulate the pathophysiology of diabetic retinopathy.

2.2 Mechanisms of Action of SGLT2 Inhibitors Relevant to DR

DR can be divided into two clinical forms: nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR). NPDR develops in earlier stages and is characterized by structural damage and occlusion of retinal capillaries due to chronic hyperglycemia. By contrast, PDR represents an advanced stage, in which chronic retinal hypoxia stimulates neovascularization, with newly formed vessels showing fragility and leakage tendency [27]. During the progression of both NPDR and PDR, DME may develop, defined as interstitial fluid accumulation in the macula due to compromised blood-retinal barrier [28]. DME is consid-

ered the most important and clinically severe complication of DR due to its direct and pronounced impact on central visual acuity loss.

Recent preclinical studies suggest that SGLT2 transporters may not be limited to renal proximal tubules and may also be expressed in human retinal pericytes and endothelial cells [29,30]. These transporters facilitate sodium-coupled glucose uptake under physiological conditions. In hyperglycemia, upregulation of SGLT2 expression enhances intracellular sodium and glucose influx, leading to osmotic imbalance, mitochondrial dysfunction, and altered calcium signaling. Excessive sodium accumulation results in pericyte swelling, contraction, and apoptosis, ultimately contributing to microvascular instability and capillary dropout, key early events in DR [31]. Pharmacological inhibition of SGLT2 may attenuate these abnormalities by limiting glucose entry into pericytes, restoring ionic homeostasis, and helping preserve endothelial barrier integrity.

The physiology of SGLT2 receptors in human retinal pericytes is not fully elucidated. One of the first studies highlighting SGLT2 inhibitors' role in the retina was conducted on bovine retinal pericyte cultures by Wakisaka *et al*. [32]. The authors hypothesized that the Na^{+}/Ca^{2+} pump, which regulates intracellular calcium concentration, partially participates in SGLT2 physiology. Retinal pericytes also express SGLT2 receptors, which enable sodium and glucose entry into cells. At high extracellular glucose concentrations, SGLT2 receptor activation increases glucose and sodium influx. Excessive intracellular sodium accumulation leads to receptor dysfunction, cell swelling, contraction, and pericyte loss [30].

The role of sorbitol in DR pathogenesis remains under investigation. It is thought that glucose is converted intracellularly into sorbitol by aldose reductase, present in retinal epithelium, while sorbitol may subsequently be transformed into fructose by sorbitol dehydrogenase (SDH). Since retinal cells have limited SDH expression, sorbitol accumulates, leading to osmotic damage and cell necrosis in hyperglycemia [33–35]. Excess intracellular glucose thus drives the formation of fructose and reactive intermediates such as fructose-3-phosphate and 3-deoxyglucosone, potent glycating agents that accelerate advanced glycation end-product (AGE) formation. Their accumulation enhances oxidative stress and activates protein kinase C, contributing to tissue injury and blood–retinal barrier (BRB) dysfunction [36]. By reducing glucose uptake through SGLT2 inhibition, these downstream deleterious pathways can be attenuated.

Experimental models further support the mechanistic rationale for SGLT2 inhibition in DR. In diabetic rodents treated with luseogliflozin or ipragliflozin, retinal ganglion cell preservation, improved microcirculation, and downregulation of VEGF-A expression were observed, even at non-hypoglycemic doses [37]. Similarly, empagliflozin reduced pericyte swelling, oxidative stress markers, and abnormal extracellular matrix deposition, suggesting a potential direct microvascular protective effect in preclinical models [31]. These findings suggest a broader pharmacodynamic potential of SGLT2 inhibitors beyond glycemic regulation, although the clinical relevance of these effects remains to be established.

Collectively, available preclinical evidence suggests that SGLT2 inhibition may act through multiple mechanisms, including reduction of intracellular glucose and sodium overload, limitation of polyol-pathway flux, modulation of oxidative and inflammatory mediators (IL-6, TNF-α, ICAM-1, VEGF), and support of tight-junction proteins such as occludin, claudin-1, and zonula occludens-1(ZO-1). These integrated effects may contribute to blood-retinal barrier stabilization, improved retinal perfusion, and potential vasculoprotective and neuroprotective actions. These interrelated mechanisms are summarized in Table 2 (Ref. [14,16,29–31,33,34,36–38]).

Together, these data suggest that SGLT2 inhibition may have potential as a pharmacological approach targeting the metabolic, vascular, and neuroinflammatory components of diabetic retinopathy in an integrated manner.

2.3 Preclinical Models

An increasing number of preclinical studies suggest that SGLT2 inhibitors may exert neuroprotective and vasculoprotective effects relevant to DR. Beyond their primary role in glycemic control, experimental evidence suggests possible direct effects on retinal structure and function.

Takakura *et al*. [39], demonstrated the effect of ipragliflozin on diabetic retina in spontaneously diabetic Torii fatty rats. Treated rats showed reduced oscillatory potentials on electroretinography, abnormalities in the outer nuclear layer, and inhibition of cataract progression [40]. In DR mice treated with dapagliflozin, significant metabolic benefits were observed—including stable body weight and improved glucose tolerance [41]. Dapagliflozin was associated with reduced microvascular and neuronal retinal damage, and increased fibroblast growth factor 21 (FGF21), which has protective roles in metabolism and central nervous system (CNS) function [41].

In a 2025 experimental study by Chen *et al*. [41], the effects of empagliflozin were investigated in db/db diabetic mice. Animals were divided into three groups: db/db mice treated with empagliflozin for 8 weeks, untreated db/db controls, and healthy C57 controls. Parameters such as body weight, fasting glucose, serum VEGF, inflammatory cytokines, and retinal barrier proteins (Claudin-1, Occludin-1, ZO-1) were evaluated, alongside ultrastructural retinal changes by electron microscopy. Empagliflozin significantly reduced fasting glucose and serum VEGF levels, lowered TNF-α and IL-6, increased BRB protein expression, and reduced adhesion molecules (ICAM-1, fibronectin), thereby preserving microvascular integrity. It also reduced endothelial junction damage,

Table 2. Proposed mechanisms of SGLT2 inhibitors in the prevention and progression of diabetic retinopathy.

Level/Target	Mechanism of SGLT2 inhibition	Pharmacological consequence	Retinal/Clinical outcome	Supporting references
Retinal pericytes and endothelial cells	Blockade of sodium-glucose cotransport (↓ SGLT2 activity) → reduced intracellular Na^+ and glucose accumulation	Restored ionic and osmotic homeostasis; ↓ pericyte swelling and apoptosis	Preservation of microvascular stability and capillary integrity	[29–31]
Oxidative stress pathways	↓ Polyol pathway flux; ↓ sorbitol and fructose accumulation	↓ ROS formation; ↓ AGE and PKC activation	Attenuation of oxidative injury and BRB dysfunction	[33,34,36]
Inflammatory response	↓ IL-6, TNF-α, ICAM-1, fibronectin, and VEGF expression	↓ Inflammatory signaling; ↓ vascular leakage	Preservation of blood–retinal barrier and reduced edema	[31,38]
Tight-junction proteins	↑ Expression of ZO-1, occludin, and claudin-1	Strengthened endothelial junctions	Improved barrier integrity and microvascular resistance	[31]
Retinal neurons (ganglion cells)	Improved mitochondrial efficiency and ↓ oxidative stress	↓ Apoptosis; enhanced neuroprotection	Preservation of visual function	[37]
Systemic/indirect effects	↓ Hyperglycemia, ↓ blood pressure, ↓ oxidative and hemodynamic load	Improved retinal perfusion and metabolic stability	Reduced risk of DR onset and progression	[14,16]

Abbreviations: SGLT2, sodium-glucose cotransporter 2; Na^+, sodium ion; ROS, reactive oxygen species; AGE, advanced glycation end-product; PKC, protein kinase C; BRB, blood–retinal barrier; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; ICAM-1, intercellular adhesion molecule-1; VEGF, vascular endothelial growth factor; ZO-1, zonula occludens-1; DR, diabetic retinopathy. Symbols: ↑ indicates increase or upregulation; ↓ indicates decrease or downregulation; → indicates leads to or results in.

basement membrane thickening, and retinal SGLT2 expression, suggesting direct retinal transporter effects. Overall, empagliflozin showed metabolic, anti-inflammatory, anti-angiogenic, and structural effects in preclinical model, supporting its potential relevance for early DR prevention.

Hanaguri *et al.* [38] found that tofogliflozin improved glycemic control and preserved retinal neurovascular function in db/db mice. Normalization of retinal blood flow responses to flicker stimulation and hyperoxia was observed, alongside shortened implicit times of oscillatory potentials, indicating improved neuronal function. Reduced expression of glial activation marker glial fibrillary acidic protein (GFAP) and VEGF suggested decreased early neuroinflammation and angiogenic activity. These findings suggest a potential protective role of tofogliflozin in early DR-related changes.

These experimental findings provide a rationale for further exploration of the translational potential of SGLT2 inhibitors in clinical settings.

2.4 Clinical Studies

In recent years, multiple observational cohort studies have suggested potential associations between SGLT2 inhibitor use and more favorable DR outcomes. A large population-based analysis showed that patients treated with these agents had a significantly lower risk of developing sight-threatening retinopathy compared with those using other antihyperglycemics such as DPP-4 inhibitors, pioglitazone, and sulfonylureas [9].

These findings have also prompted recent commentary on diabetic retinopathy as a potential additional target for SGLT2 inhibition [42]. Systematic review and meta-analysis data have evaluated ocular outcomes associated with SGLT2 inhibitor use, including retinopathy-related events, although the available evidence remains heterogeneous and does not yet establish a causal protective effect [43].

In addition, prospective clinical trials are underway using advanced imaging methods such as optical coherence tomography angiography (OCT-A) to evaluate the effects of SGLT2 inhibitors on retinal microcirculation, including parameters such as the foveal avascular zone and vessel density [44]. Collectively, these findings suggest a potential role of SGLT2 inhibitors in DR risk modification; however, current clinical evidence is derived predominantly from observational and retrospective studies and requires confirmation in prospective randomized trials with predefined ophthalmic endpoints.

3. Discussion

The available preclinical and clinical studies suggest that, beyond their primary glucose-lowering effect, SGLT2 inhibitors may exert pleiotropic actions relevant to the pathophysiology of DR. Preclinical models, particularly those based on db/db diabetic mice, have suggested neuroprotective, vasculoprotective, and anti-inflammatory retinal effects of these agents. In the study by Chen *et al.* [41], empagliflozin was shown to reduce levels of inflammatory cytokines and angiogenic factors while simultaneously enhancing the expression of blood-retinal barrier proteins, suggesting a potential role in preventing early microvascular changes. Similarly, Hanaguri *et al.* [38] re-

ported that tofogliflozin improved neurovascular regulation and reduced glial activation, further supporting the hypothesis that SGLT2 inhibitors may exert direct neuroprotective effects in preclinical settings.

The importance of these findings lies in the complex pathophysiological mechanisms of DR, which involve oxidative stress, inflammation, growth factor dysregulation, and blood–retinal barrier breakdown. Unlike currently available treatments that are mainly directed at VEGF inhibition, SGLT2 inhibitors may offer a broader mechanistic profile by targeting multiple pathogenic pathways simultaneously. Of particular note, several preclinical studies have reported beneficial retinal effects even at non-hypoglycemic doses. However, whether these actions are partly independent of glycemic control remains hypothetical, as available clinical studies have not adequately controlled for HbA1c changes or differences in concomitant glucose-lowering therapy.

From a clinical perspective, observational studies have reported findings broadly consistent with preclinical investigations. Patients treated with SGLT2 inhibitors appear to have a lower incidence of advanced stages of retinopathy and a reduced need for invasive ophthalmologic interventions; however, these associations should be interpreted cautiously. However, these data are predominantly derived from retrospective and observational analyses and remain susceptible to selection bias, confounding, and inadequate adjustment for HbA1c changes and background glucose-lowering therapy, whereas prospective randomized clinical trials remain limited. Observed differences in outcomes across sex and age groups highlight the need for individualized interpretation and personalized therapeutic decision-making.

Considering the high prevalence and functional consequences of DR, as well as the limitations of current therapeutic options, evaluation of SGLT2 inhibitors as a potential adjunctive strategy warrants further investigation. Further clinical trials with clearly defined ophthalmologic endpoints and biomarkers of retinal damage are necessary to clarify the potential clinical role of this drug class in routine practice.

Despite the growing body of evidence suggesting the potential relevance of SGLT2 inhibitors in DR, several limitations prevent firm conclusions and evidence-based clinical recommendations. A key issue is the lack of prospective, randomized controlled trials designed specifically with DR outcomes as primary endpoints. Most existing studies have focused primarily on cardiovascular and renal endpoints, with retinal outcomes being reported only as secondary observations, often without detailed methodological standardization. In addition, many studies have relatively short follow-up durations-typically no longer than two to three years - which may be insufficient to detect structural and functional retinal changes, particularly in the early stages of disease. Furthermore, few studies provide adequate stratification by retinopathy stage (nonproliferative, proliferative, or macular edema), making it difficult to accurately assess therapeutic responses across different clinical scenarios.

To improve the current understanding and to formulate clear clinical guidelines, it is essential to conduct long-term, multicenter, and prospectively designed studies utilizing standardized ophthalmologic imaging techniques such as OCT and fluorescein angiography, with well-defined retinal outcome parameters and rigorous control of known risk factors. Only through such comprehensive approaches can the potential role of SGLT2 inhibitors in diabetic retinopathy prevention and risk modification be more accurately defined.

Pharmaceutical Perspectives

From a pharmaceutical perspective, the expanding evidence on SGLT2 inhibitors highlights the potential relevance of systemically administered agents to ocular microcirculation and retinal homeostasis. Their well-characterized pharmacokinetic profile, marked by high oral bioavailability, extensive protein binding, and minimal CYP-mediated metabolism, is consistent with predictable systemic exposure and a low risk of pharmacokinetic interactions.

Ocular formulations of SGLT2 inhibitors are currently in the preclinical and early development stages, primarily as potential topical solutions (eye drops) for the non-invasive management of diabetic eye diseases such as diabetic retinopathy and diabetic macular edema. To date, no FDA-approved SGLT2 inhibitor eye drops are available; all marketed agents (e.g., dapagliflozin, empagliflozin, canagliflozin, and ertugliflozin) are formulated for oral systemic use. However, advances in ocular drug delivery systems, such as nanocarriers, microemulsions, and permeability enhancers, may support the future development of SGLT2-based topical therapies with improved blood-retinal barrier penetration and localized pharmacological activity. These features, together with the growing understanding of SGLT2-related pathways in retinal tissues, may provide a rationale for further targeted drug optimization.

Future pharmaceutical research may explore the development of next-generation SGLT2 modulators with enhanced blood-retinal barrier permeability or tissue selectivity, as well as formulation approaches enabling controlled ocular delivery. Such innovations may broaden future therapeutic strategies by linking systemic glucose-lowering pharmacology with locally targeted retinal drug delivery.

4. Conclusion

SGLT2 inhibitors represent a modern class of orally active antihyperglycemic agents with pleiotropic benefits extending beyond glycemic control. Initially developed for the treatment of type 2 diabetes mellitus, they are now approved for heart failure and chronic kidney disease ir-

respective of diabetic status, reflecting their broad cardiometabolic clinical utility. Increasing experimental and clinical evidence suggests that these agents may also have potential relevance for microvascular protection, including possible effects on the retina. Experimental evidence suggests anti-inflammatory, antioxidant, and vasculoprotective actions that may be relevant to diabetic retinopathy pathophysiology. However, current clinical evidence is based mainly on observational and retrospective studies and remains vulnerable to confounding and selection bias. Future prospective randomized studies with clearly defined ophthalmic endpoints are needed to clarify the potential clinical role of SGLT2 inhibitors in diabetic retinopathy.

Author Contributions

ND conceived the study concept and design, coordinated the literature search, performed data extraction and synthesis, integrated all manuscript sections, and finalized the manuscript. NM participated in the literature search, data extraction, synthesis of results, and preparation of the manuscript. SB contributed to the conception and design of the review, ophthalmological interpretation of the evidence, analysis of clinical relevance, and critical revision of the manuscript. MPK and AR contributed to the pharmacological design of the review, interpretation of pharmacological and pharmaceutical data, analysis of drug-related mechanisms, and critical revision of the manuscript. DZ contributed to the interpretation and contextualization of cardiovascular and systemic evidence related to SGLT2 inhibitors and critically revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was conducted as a narrative literature review of previously published literature and did not involve any new studies with human participants or animals performed by the authors. Therefore, ethical approval and informed consent were not required.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

The detailed search strategy used to inform this narrative review is provided in the Supplementary Material. Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/Pharmazie51803.

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