Supplementary Table S1. Organ-specific therapeutic landscape of quinones in diabetic complications: pathological targets, candidate compounds and translational gaps.

Diabetic complication	Dominant pathological processes	Candidate quinones	Proposed protective mechanisms	Relevant outcomes	Major translational gap	References
Diabetic nephropathy	Mitochondrial dysfunction, ROS accumulation, NF-κB activation, pyroptosis and fibrosis	CoQ10, PQQ, TQ	Restoration of electron transport, suppression of mitochondrial ROS and inhibition of NF-κB/pyroptosis signalling	Albuminuria, renal function, fibrosis, mitochondrial membrane potential and oxidative biomarkers	Lack of standardized renal exposure data and adequately powered renal-outcome trials	[1, 2]
Diabetic neuropathy	Oxidative injury, Schwann-cell apoptosis, demyelination and neuroinflammation	TQ, PQQ, CoQ10, vitamin K1	Reduction of COX-2, IL-1β, IL-6, TNF-α and lipid peroxidation; preservation of Schwann cells and nerve conduction	Neuropathic pain, nerve-conduction velocity, demyelination and inflammatory markers	Limited human evidence beyond adjunctive supplementation	[3, 4]
Diabetic retinopathy	Endothelial injury, mitochondrial ROS, vascular leakage, VEGF signalling and retinal neurodegeneration	CoQ10, short-chain mitoprotective quinones, aloe-emodin	Mitochondrial stabilization, Nrf2/NQO1/HO-1 activation, NF-κB inhibition and VEGF suppression	Retinal leakage, MMP-9, retinal thickness, ganglion-cell survival and visual function	Ocular pharmacokinetics, retinal exposure and long-term safety remain poorly defined	[5, 6]
Diabetic cardiovascular injury	Endothelial dysfunction, NLRP3 activation, myocardial fibrosis and impaired mitochondrial bioenergetics	CoQ10, PQQ, tanshinones, embelin, plumbagin, aloe-emodin	Nrf2 activation; NF-κB/NLRP3 inhibition; mitochondrial preservation and improved NO signalling	Endothelial function, myocardial fibrosis, cardiac function, oxidative stress and inflammation	Few diabetes-specific cardiovascular endpoint trials	[7, 8]
Diabetic wounds and skin injury	Persistent M1 macrophage activation, infection, impaired angiogenesis, ECM loss and oxidative stress	Rhein, emodin, TQ, plumbagin, lawsone, juglone, shikonin	M1-to-M2 macrophage transition, antimicrobial and antibiofilm activity, collagen deposition, keratinocyte migration and re-epithelialization	Wound-closure rate, microbial burden, collagen organization, angiogenesis and inflammatory markers	Formulation heterogeneity and scarcity of randomized human wound trials	[9, 10]

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Supplementary Table S2. Barrier-driven formulation strategies for translating quinone pharmacology into diabetes-directed therapy.

Quinone/candidate	Principal developability barrier	Suitable formulation strategy	Intended route or target	Expected pharmaceutical gain	Critical requirement before translation	References
CoQ10	High molecular weight, extreme lipophilicity and oral bioavailability below 5%	Ubiquinol formulations, nanoemulsions, phytosomes, cyclodextrin complexes and TPGS conjugation	Oral systemic delivery; retina, heart and kidney	Improved dissolution, intestinal absorption and tissue exposure	Demonstration that improved exposure produces clinically meaningful metabolic outcomes	[1-3]
PQQ	Hydrophilicity, rapid systemic elimination and limited cellular retention	Liposomes, polymeric carriers or food-matrix incorporation	Oral systemic and mitochondria-directed delivery	Longer circulation and improved intracellular delivery	Exposure–response and renal-clearance characterization	[4, 5]
TQ	Poor water solubility, first-pass metabolism and sensitivity to pH and light	Lipid nanoparticles, nanoemulsions, liposomes and protected polymeric systems	Oral delivery or topical wound application	Increased stability, controlled release and tissue-specific exposure	Standardized loading, photostability, dose and chronic safety	[6-8]
Embelin	BCS class II behaviour and poor aqueous solubility	Liposomes, transfersomes, lipid nanospheres and chitosan nanoparticles	Oral or topical delivery	Improved dissolution, permeability and localized delivery	Comparative safety of metallic versus biodegradable carriers	[9]
Lapachol	Poor absorption and inadequate activity despite high systemic doses	Oil-in-water nanoemulsion or microemulsion	Oral delivery	Sustained release and improved apparent solubility	Proof that enhanced exposure overcomes previous clinical inefficacy	[10-12]
Emodin and related anthraquinones	Poor solubility, rapid glucuronidation/sulfation and chemical degradation	Nanocapsules, lipid carriers and Pluronic F-127 hydrogels	Oral or topical wound delivery	Protection from degradation, reduced first-pass loss and localized release	Control of hepatic and renal toxicity during repeated administration	[13, 14]
Vitamin K derivatives	Variable dietary absorption and	Mixed micelles, emulsions	Oral systemic or wound-	Improved stability, absorption	Monitoring coagulation-related effects	[15, 16]

	acid-related instability	and lipid nanocarriers	directed delivery	and sustained tissue distributio n	and drug interactions	
MitoQ/idebeno ne	Need for controlled mitochondrial accumulation and avoidance of excess redox cycling	Organelle-targeted conjugates or controlled-release systems	Pancreas, kidney, retina and heart	Direct mitochond rial delivery with lower systemic exposure	Definition of the mitochondrial therapeutic window	[17]

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