

Oxidative versus Recovery Therapeutics in Type 2 Diabetes Mellitus: An Immunometabolic Perspective

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ABSTRACT

Type 2 diabetes (T2DM) is a complex immunometabolic disorder characterized by insulin resistance, pancreatic β -cell dysfunction, oxidative stress, and persistent low-grade inflammation. Redox imbalance is exacerbated by advanced glycation, lipotoxicity, and endoplasmic reticulum stress, whereas persistent nutritional excess promotes the generation of mitochondrial and non-mitochondrial reactive oxygen species (ROS). Metabolic stress is linked to cytokine generation and tissue damage by ROS-sensitive pathways, including NF- κ B, JNK, and the NLRP3 inflammasome. The conceptual distinction between recovery therapies, which aim to maintain or restore cellular and tissue function, and oxidative treatments, which primarily minimize abnormal redox signaling and inflammatory damage, is developed in this study. Metformin, SGLT2 inhibitors, GLP-1 receptor agonists, and pioglitazone illustrate the overlap between these categories, whereas alpha-lipoic acid, curcumin, berberine, and other targeted phytochemicals exemplify more direct redox interventions. Extracellular vesicles, mitochondrial quality control, and mesenchymal stromal cells are examples of regenerative techniques that are still under research. Although there may be complementary immunometabolic benefits from nutritional treatments such as flaxseed, chia, and medicinal plants such as turmeric, berberine-containing botanicals, and cinnamon, their evidence base should be evaluated more cautiously than that of recognized pharmacotherapies. We suggest that progressive regulation of oxidative damage, immune activation, and tissue healing should replace a single-endpoint antioxidant paradigm in lasting therapy.

Keywords: immunometabolism; oxidative stress; reactive oxygen species; NLRP3 inflammasome; Nrf2; β -cell; tissue recovery; medicinal plants.

1. Introduction

Type 2 diabetes mellitus is one of the major chronic diseases. It is characterized by persistent hyperglycemia resulting from a combination of insulin resistance, impaired β -cell function, and progressive metabolic dysregulation. Diabetes has clinical effects on the cardiovascular, renal, retinal, and neural systems. Thus, diabetes is a multisystem condition, not a single malfunction of glucose processing.^{1, 2}

The conceptual framework of type 2 diabetes has expanded significantly over the past 20 years. Accumulating evidence suggests that chronic metaflammation results from a combination of cellular stress pathways, adipose tissue inflammation, innate immune activation, and excess food intake. In this context, immune cells are not just responding to metabolic derangement. Still, their metabolic state actively shapes inflammatory activity, and inflammatory signaling provides feedback that alters insulin action and tissue metabolism.^{3, 4} This network is dependent on oxidative stress. Physiological ROS are involved in redox signaling, host defense, and metabolic control, but excess or mislocalized ROS can damage proteins, lipids, and nucleic acids and cause inflammation.⁵ Therefore, a normal signaling system can be a chronic cause of cellular damage due to endoplasmic reticulum stress, lipotoxicity, mitochondrial dysfunction, and chronic hyperglycemia.⁶

This distinction raises an important therapeutic question. Should therapy focus on inhibiting the mechanisms that generate oxidative damage, or should it also repair tissue already damaged by metabolic stress? We refer to these complementary goals as oxidative therapeutics and recovery therapeutics. These categories are conceptual rather than mutually exclusive, and many successful antidiabetic agents have effects in both areas. Thus, this review explores the immunometabolic basis of oxidative injury, assesses pharmacological and nutritional interventions for oxidative stress, reviews recovery-oriented therapies, and proposes an integrated model that combines reducing ongoing injury with maintaining and restoring tissue function.

2. Immunometabolic Basis of Oxidative Injury

Oxidative stress occurs when the production of oxidants surpasses the antioxidant systems' ability to neutralize them. In T2DM, this imbalance results from multiple interacting processes rather than a single metabolic defect. Hyperglycemia boosts substrate flow to mitochondria and activates alternative glucose pathways, while free fatty acids, inflammatory cytokines, and endoplasmic reticulum stress further elevate cellular redox pressure.²

Mitochondrial electron transport is a key source of superoxide. When nutrients are abundant, increased electron leakage from the respiratory chain produces more superoxide, which can then be transformed into hydrogen peroxide and other reactive molecules.⁷ Brownlee's model positions mitochondrial superoxide as an early factor that activates multiple traditional hyperglycemia-related pathways, including AGE formation, PKC activation, polyol metabolism, and flux through the hexosamine pathway.^{8,9}

AGEs serve as another link connecting metabolic and inflammatory damage. AGE-RAGE interaction activates NF- κ B and NADPH oxidase pathways, promoting inflammation in blood vessels and tissues.¹⁰ Simultaneously, hyperglycemia-induced activation of diacylglycerol and protein kinase C (PKC) can activate NADPH oxidases, thereby amplifying the production of reactive oxygen species (ROS).¹¹

The immune system detects and enhances this redox imbalance. ROS and products from damaged cells can trigger inflammasome activation, with NLRP3 signaling aiding in the maturation of IL-1 β and IL-18. These cytokines contribute to β -cell dysfunction and insulin resistance, creating a cycle in which metabolic stress and inflammation reinforce each other.¹²

Metabolic factors also influence macrophage phenotype. Obesity and diabetes promote the buildup of inflammatory macrophages in adipose tissue, leading to higher levels of TNF- α , IL-6, and other mediators that disrupt insulin signaling. In contrast, reparative macrophages are involved in tissue remodeling and the resolution of inflammation.^{13,14}

Pancreatic β -cells are especially vulnerable to oxidative damage due to their relatively limited antioxidant defenses. Ongoing oxidative stress and endoplasmic reticulum stress can disrupt insulin gene expression, reduce mitochondrial ATP production, impair insulin secretion, and eventually trigger cell death pathways.^{15,16}

Together, these mechanisms position oxidative stress as an immunometabolic regulator rather than merely a consequence of hyperglycemia. They link excess nutrients to inflammatory signaling, mitochondrial dysfunction, and continuous tissue damage.

3. Oxidative Therapeutics: Interrupting the Cycle of Injury

Oxidative therapies involve reducing harmful ROS production, boosting the body's antioxidant defenses, or targeting redox-sensitive inflammatory pathways. Their goal is to restore a stable redox balance, supporting normal insulin signaling and tissue repair rather than just neutralizing chemicals.¹⁷

These therapies work by scavenging radicals, activating Nrf2-ARE signaling, enhancing glutathione metabolism, inhibiting NF- κ B and NLRP3 pathways, and supporting mitochondrial function. Nrf2 is especially important because it regulates the expression of numerous cytoprotective and antioxidant genes, rather than focusing on a single ROS species.¹⁸

One example of an indirect oxidative approach is metformin. Although glucose reduction is its main therapeutic activity, actions related to mitochondria and AMPK can also reduce metabolic stress and influence inflammatory and antioxidant pathways.¹⁹ Although its redox activities link glycemic management to broader cellular defense, its proven therapeutic advantages should not be attributed solely to antioxidant activity.

SGLT2 inhibitors also reduce oxidative stress, primarily by lowering glucose levels and altering renal and systemic metabolism. Clinical trials focusing on cardiovascular and renal outcomes show benefits that extend beyond lowering glycated hemoglobin, while experimental studies suggest they may influence mitochondrial function and inflammatory signaling.^{20,21}

A more direct antioxidant intervention is alpha-lipoic acid. Although its role should be viewed as complication-specific rather than comparable to disease-modifying glucose-lowering therapy, its reduced form contributes to the regeneration of endogenous antioxidant systems, and clinical trials and meta-analyses support symptomatic benefit in diabetic peripheral neuropathy.^{22,23}

Coenzyme Q10 aids mitochondrial electron transport and acts as a lipid-phase antioxidant.²⁴ While small clinical studies indicate potential benefits for oxidative stress and metabolic markers, the evidence remains less conclusive than that for well-established glucose-lowering medications.²⁵

Sulforaphane and related Nrf2 activators represent a targeted nutritional approach. Rather than broadly neutralizing ROS, activating Nrf2 boosts the body's internal protective mechanisms.²⁶ Human research offers initial signs of metabolic improvement, though factors such as dosage, bioavailability, and the significance of long-term effects require further investigation.

A key challenge with direct antioxidant therapy is its lack of specificity. ROS are not always damaging; they play roles in normal redox signaling that support insulin function, adaptation, and immune response. Therefore, widespread suppression of ROS can lead to unpredictable outcomes, which helps explain why antioxidant supplements have not consistently replicated the benefits observed in experimental models.²⁷

4. Recovery Therapeutics: Restoring Biological Resilience

The goal of recovery therapies is to restore functional capacity following metabolic damage. Improved mitochondrial quality control, tissue remodeling, immune resolution, and, when possible, regeneration of injured cell populations are all included in this strategy.

One of the main factors contributing to the worsening of T2DM is progressive β -cell dysfunction. Oxidative stress, inflammatory cytokines, lipotoxicity, and glucotoxicity all affect the survival and secretory activity of β -cells.²⁸ Therefore, recovery-oriented therapies aim to preserve surviving β -cells and create favorable conditions for functional restoration.

GLP-1 receptor agonists demonstrate this more general idea. Large cardiovascular outcome trials have demonstrated significant clinical advantages beyond glucose reduction, and GLP-1 signaling has cytoprotective and anti-inflammatory effects in experimental systems in addition to increasing glucose-dependent insulin secretion.^{29, 30}

Pioglitazone increases insulin sensitivity by modifying adipose tissue and activating PPAR γ . Additionally, PPAR γ regulates inflammatory gene expression and macrophage phenotype, linking immune regulation and metabolic remodeling.³¹ A recognized adverse-effect profile limits its therapeutic application; therefore, recovery-oriented effects should be addressed alongside safety and patient selection. Because SGLT2 inhibitors preserve organ function by protecting the kidneys and heart, they can also be viewed in terms of recovery. Rather than relying on a single antioxidant pathway, the molecular foundation is complex and encompasses hemodynamic, metabolic, mitochondrial, and inflammatory effects.

The concept of recovery is expanded by regenerative medicine. Exosomes, extracellular vesicles, and mesenchymal stromal cells can all provide paracrine signals that affect tissue remodeling, angiogenesis, inflammation, and survival.^{31, 32} These techniques are still under development and should not be compared to existing diabetic treatments, but they show how future therapy might shift from metabolic correction to tissue restoration.

Immune resolution is central to recovery. Resolution is a dynamic biological program that includes altered leukocyte trafficking, macrophage reprogramming, cellular debris clearance, and restoration of tissue homeostasis.³³ Thus, recovery treatments may be differentiated from basic immunosuppression by their emphasis on restoring a reparative immune milieu.

5. Nutritional Oxidative and Recovery Therapeutics: Medicinal Plants

Nutritional oxidative and recovery therapeutics involve the strategic use of dietary components, antioxidants, and micronutrients to maintain redox homeostasis, regulate excessive oxidative stress and inflammation, and support tissue repair and metabolic recovery.³⁴ Functional seeds and therapeutic plants serve as a good bridge between oxidative and recovery principles. Chia (*Salvia hispanica*) contains viscous fiber, α -linolenic acid, and polyphenols, whereas flaxseed (*Linum usitatissimum*) has α -linolenic acid, lignans, and fiber. Their biological effects are most likely pleiotropic and cannot be attributed to a single molecule.^{35, 36}

Human data for chia are encouraging but varied and should be viewed in light of nutritional background. A randomized study in overweight or obese persons with T2DM assessed Salba-chia during a calorie-restricted diet, and following controlled studies have looked at chia-containing therapies in people receiving conventional therapy.^{37, 38} These studies indicate the viability of chia as a dietary supplement, but they do not prove it as a substitute for pharmaceuticals.

Flaxseed has a significantly larger clinical literature. A meta-analysis of 25 randomized studies reported decreases in blood glucose, insulin, and HOMA-IR, with benefits more pronounced with whole flaxseed than with isolated oil or lignan preparations.³⁹ A flaxseed-derived lignan intervention has also been investigated for inflammatory biomarkers in persons with T2DM, suggesting that lignan-related benefits may extend beyond glucose metabolism.⁴⁰

The same nutritional oxidative-recovery paradigm has been extended to a broader class of botanicals beyond functional seeds, with numerous medicinal plants and isolated phytochemicals studied for combined oxidative and glycemic benefits in type 2 diabetes. In experimental models, curcumin, the main polyphenol of turmeric (*Curcuma longa*), suppresses NF- κ B-mediated inflammatory transcription and stimulates Nrf2-dependent antioxidant signaling. In a randomized, double-blind, placebo-controlled trial in patients with type 2 diabetes,

curcumin supplementation improved markers of oxidative stress and conferred modest benefits in anthropometric measures and insulin resistance; however, poor oral bioavailability and inconsistent dosing continue to limit translational certainty.⁴¹

Berberine, an isoquinoline alkaloid found in *Berberis* and *Coptis* species, improves insulin sensitivity, modulates gut microbial metabolism, and reduces fasting and postprandial glucose levels via AMPK activation. Mechanistic studies have also shown that berberine has anti-inflammatory and antioxidant properties. Although the methodological quality of the underlying studies was typically poor, a comprehensive review and meta-analysis of randomized trials revealed that berberine, when paired with lifestyle modification, provided substantial glucose-lowering and lipid-modifying benefits.⁴²

Numerous randomized trials have assessed the effects of cinnamon (*Cinnamomum* spp.) on lipid profiles and fasting plasma glucose. According to a meta-analysis of 10 randomized controlled trials, cinnamon supplementation reduced fasting plasma glucose, total cholesterol, LDL cholesterol, and triglycerides, but did not consistently affect glycated hemoglobin. This mirrors the variation in dose, preparation, and trial duration that restricts interpretation across nutritional oxidative therapies more generally.⁴³

However, the differentiation among these nutritional therapies should continue to generate hypotheses. Flaxseed's lignans, α -linolenic acid, and fiber offer multiple potential pathways for modulating inflammation, lipid metabolism, and redox biology; chia's viscous fiber and seed matrix may primarily affect postprandial metabolism and gastrointestinal nutrient handling; and medicinal plants such as curcumin, berberine, and cinnamon act through more clearly defined molecular targets (Nrf2, NF- κ B, and AMPK, respectively), yet they still lack standardized dosing, formulations, and long-term safety data available for pharmacotherapy. These agents are best positioned as supplementary elements of a more comprehensive immunometabolic approach, as there is currently insufficient data to designate any of them as a definitive oxidative or recovery therapy in isolation.

6. Comparative Immunometabolic Framework

It is better to view the oxidative-versus-recovery dichotomy as a therapeutic continuum. While recovery therapies focus on preservation, remodeling, and repair, oxidative interventions primarily target ongoing molecular damage. In practice, individual agents may span both domains.

To limit ROS formation, prioritize reducing metabolic drivers, suppressing excessive inflammation, preserving viable β -cells and susceptible organ tissues, and promoting reparative processes. This sequence is not rigid because metabolic management and tissue healing occur concurrently, but it does provide a framework for aligning treatment aims with disease stage.

7. Biomarkers for an Integrated Therapeutic Strategy

The absence of a widely recognized clinical diagnosis for abnormal oxidative load is a significant barrier to precision redox treatment. Malondialdehyde, 8-hydroxy-2'-deoxyguanosine, F2-isoprostanes, total antioxidant capacity, glutathione status, and the activity of SOD, catalase, and GPx are examples of potential oxidative biomarkers.^{44, 45} Tissue specificity, nutrition, renal function, inflammation, and analytical variability should all be considered during interpretation. Redox measures can be supplemented with immunological indicators. While NLRP3-related indicators and caspase-1-associated pathways provide mechanistic insight in research settings, circulating TNF- α , IL-6, and IL-1 β reflect inflammatory activity.⁴⁶ Fasting insulin, HOMA-IR, β -cell function, organ-specific imaging or histology in experimental models, and functional outcomes in clinical research should all be included in recovery-oriented evaluation. Therefore, rather than treating oxidative stress as a separate laboratory variable, future studies should include metabolic outcomes alongside redox and immunological indicators. Using multidimensional phenotyping can help identify which patients are most likely to benefit from specific antioxidant or recovery methods.

8. Integrated Therapeutic Model

This review's main argument is that oxidative damage and tissue repair are reciprocally related. While restoring tissue and mitochondrial function can mitigate oxidative stress, persistent ROS production can prevent regeneration. Therefore, a combined approach could make more sense than either focusing solely on metabolic outcomes or indiscriminately supplementing with antioxidants.

Evidence-based glucose-lowering medication is still essential in established type 2 diabetes. Individual risk and comorbidity profiles should be considered when selecting agents for which cardiovascular and renal outcome data are available. While regenerative and mitochondrial treatments should remain within well-controlled research programs until more robust clinical data are available, targeted antioxidant therapy may then be considered for

specific issues. The model further explains why nutritional interventions, such as whole flaxseed, chia, and medicinal compounds like curcumin, berberine, and cinnamon, may be better positioned as adjunctive elements of a broader metabolic strategy. The potential effects of fiber on fiber-mediated glucose handling, lipid metabolism, inflammation, and redox balance are biologically relevant; however, clinical claims should be proportional to the available evidence.

9. Future Directions

Future studies should focus on tissue-specific redox biology regulation rather than the idea of a general antioxidant. Systemic radical scavenging may not offer as much mechanistic precision as mitophagy-enhancing therapies, specific Nrf2 activators, and antioxidants targeting mitochondria.⁴⁷⁻⁴⁹ Because inflammasome activity establishes a direct link between metabolic stress and immunological disease, suppression of NLRP3 is another viable approach. The majority of highly selective NLRP3 inhibitors remain in the research stage, and translation requires careful consideration of patient selection, tissue distribution, and safety.⁵⁰⁻⁵²

Regenerative medicine may someday complement existing approaches through cell-based therapies, extracellular vesicles, synthetic tissues, and alteration of endogenous repair processes. The primary goal will be to ensure that regeneration occurs in a metabolically and immunologically stable environment, rather than attempting to rebuild tissue while the underlying inflammatory damage persists.^{32, 53}

The gut microbiota and precision diet are also important. Alkaloids, fiber, polyphenols, lignans, and omega-3 fatty acids may affect host redox signaling and microbial metabolism, potentially forming a gut-immune-mitochondrial axis. For medicinal plant therapies such as curcumin and berberine, where formulation variations across studies likely account for much of the reported variability, standardization of extract composition, dosage, and bioavailability would be crucial. Dietary composition, microbial profiles, metabolic phenotypes, and redox biomarkers should all be included in future studies to identify which patients actually benefit.⁵⁴⁻⁵⁸

10. Conclusion

T2DM is best conceptualized as a chronic immunometabolic disease in which hyperglycemia, oxidative stress, inflammation, and defective tissue recovery constitute a self-reinforcing network. Oxidative therapeutics can decrease ongoing molecular injury, but direct ROS scavenging alone has important biological and clinical limitations. Recovery therapeutics target the complementary problem of restoring cellular and tissue function post-injury.

An integrative approach is therefore the most promising direction in therapy. Upstream reduction of glucotoxic and lipotoxic stress should be combined with modulation of oxidative pathways, immune resolution, and, where appropriate, tissue repair. Metabolic treatment with established drugs such as metformin, SGLT2 inhibitors, and GLP-1 receptor agonists exemplifies the potential of organ-protective effects. Targeted antioxidants and regenerative therapies are more specific or in development.

Flaxseed, chia, and medicinal herbs such as curcumin, berberine, and cinnamon demonstrate how dietary therapies might contribute to this paradigm; however, available human research suggests they should be used as adjuncts rather than alternatives to evidence-based pharmacotherapy. Finally, the shift from oxidative harm to biological recovery should be a key goal of next-generation T2DM therapies.

Conflicts of Interest

The authors declare no conflict of interest.

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