Review Article

A Novel, Rationally Designed Antioxidant Formulation to Prevent Diabetes-Related Complications

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(Received: 06-03-2025 Revised: 06-04-2025 Accepted: 14-04-2025)

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ABSTRACT

Diabetes is a well-known chronic disorder of metabolic origin that involves hyperglycaemia. It is said to affect around 451 million people all around the world. At current situation, this condition is found to be the leading cause of death due to complications associated with it. It ranges from neuropathy to nephropathy. The major mechanism behind this was found to be oxidative stress that is caused by rise of reactive oxygen species (ROS) and defective antioxidant defense mechanism.

To encounter this problem, antioxidants are being used as a therapy to target this problem of oxidative stress as a potential adjunctive treatment in diabetes. The current article explores the concept of targeted, novel formulation of antioxidant combination designed specifically to alleviate diabetes-associated oxidative stress, thereby delivering an effective solution to prevent development of complications and to enhance the patient outcomes.

Simultaneously, while managing the glucose metabolism it is crucial to regulate and mitigate the ongoing oxidative stress in diabetes to prevent the complications. Hence, development of a scientifically refined and potent antioxidant combination that could powerfully neutralize the oxidative stress is timely and necessary.

The proposed combination of antioxidants for diabetes comprises of Alpha-Lipoic Acid, N-Acetylcysteine, Curcumin, Vitamin E and Resveratrol. At present, this novel antioxidant formulation is a theoretical gem that needs real-world polish. The further steps should include laboratory testing and trials to confirm the efficacy, bioavailability variability, stability, dosage and safety of this novel combination.

Keywords: Antioxidant Formulation, Diabetes complications, Antioxidant therapy, Alpha-Lipoic Acid, Curcumin, Resveratrol, N-Acetyl Cysteine, Vitamin E.

1. INTRODUCTION

Diabetes is a well-known chronic disorder of metabolic origin that involves hyperglycaemia. It is said to affect around 451 million people all around the world. This statistic is expected to increase to 693 million by the year 2045 [1]. It comprises of both type 1 diabetes and types 2 diabetes. At current situation, this condition is found to be the leading cause of death due to complications associated with it. It ranges from neuropathy to nephropathy. The major mechanism behind this was found to be oxidative stress that is caused by rise of reactive oxygen species (ROS) and defective antioxidant defense mechanism [2-4].

High blood glucose increases the production of ROS by underlying mechanisms like glycation of proteins and autoxidation of glucose. This causes defective physiological function leading to cellular damage [5-7]. To encounter this problem, antioxidants are being used as a therapy to target this problem of oxidative stress as a potential adjunctive treatment in diabetes.

The conventional treatment approaches include adequate glycaemic control through appropriate lifestyle interventions and pharmacotherapy. In addition, antioxidant therapy is upcoming as it addresses the potential oxidative stress causing diabetic complications. Various antioxidants have shown efficacy in decreasing the oxidative

stress like polyphenols, vitamin C, vitamin E and herbal nano-formulations [8-13]. Despite these advances, the usage of antioxidant therapy is minimal because of prevailing challenges in personalizing treatments, optimizing formulations and increasing bioavailability.

Considering these limitations, there is an increasing requirement for a rationally designed formulation of antioxidant combination that works in a synergistic way to enhance the antioxidant effect maximally.

The current article explores the concept of targeted, novel formulation of antioxidant combination designed specifically to alleviate diabetes-associated oxidative stress, thereby delivering an effective solution to prevent development of complications and to enhance the patient outcomes.

Simultaneously, while managing the glucose metabolism it is crucial to regulate and mitigate the ongoing oxidative stress in diabetes to prevent the complications. Hence, development of a scientifically refined and potent antioxidant combination that could powerfully neutralize the oxidative stress is timely and necessary.

OXIDATIVE STRESS AND ANTIOXIDANTS IN DIABETES:

Diabetes is a condition of chronic hyperglycaemia leading to imbalance between antioxidant defenses and production of ROS [14]. ROS includes generation of free radicals like hydroxyl and superoxide radicals. These are normally produced as a by-product of cellular metabolism during oxidation of glucose in the mitochondria. In chronic diseases like diabetes, this production of ROS is amplified through various pathways like activation of protein kinase C, polyol pathway and formation of advanced glycation end-product (AGE). This overpowers the body's antioxidant defense system, contributing to oxidative damage to proteins, lipids and DNA within cells [15-17].

The ramifications of this imbalance are huge leading to associated complications like neuropathy, nephropathy and retinopathy. For example, excess ROS may contribute to damage of endothelial cells which causes cardiovascular diseases as it may cause chronic inflammation and atherosclerosis. These complications emphasize the pressing requirement to reduce the oxidative stress in management of diabetes [18-21].

Antioxidants are a group of compounds that helps to neutralize the formed ROS, thereby preventing cellular damage [22,23]. The commonly studies antioxidants are vitamin E (tocopherol) and vitamin C (ascorbic acid). Vitamin C is said to be a water-soluble compound that scavenges the free radicals and helps to regenerate antioxidants such as tocopherol. This helps to prevent damage to lipid membranes from peroxidation. Previous studies have shown that antioxidants like vitamin C helps to enhance the glycaemic control and decrease the oxidative stress markers [24-26]. Even though some studies have reported that vitamin E can decrease the level of lipid peroxidation, large studies have shown limited evidence in diabetic patients, emphasizing limited efficacy [27-29].

Another potent antioxidant is *Alpha-Lipoic Acid (ALA)*, that has the capability to chelate metal ions catalysing the formation of ROS and can generate other antioxidants. Studies have found that ALA supplementation can reduce the neuropathic signs and symptoms and increase the insulin sensitivity in diabetes [30,31]. Likewise, other antioxidants like *selenium*, *curcumin* and polyphenols have been investigated widely regarding it efficacy and dosing in diabetes [32-34].

Regardless of these theoretical assurances, conventional antioxidants often fail to meet their efficacy in clinical settings. Their history shows that involvement of challenges such as poor tissue penetration, limited solubility and inefficiency to meet the multifaceted oxidative stress in diabetic patients. Often monotherapy with these antioxidants lacks complete capacity to neutralize the formed ROS. This often leads to failure in tackling primary metabolic disruption or the total damage across organ systems.

This gap between the antioxidants and effective antioxidant therapy can be met by formulating a effective antioxidant combinations that involves synergistically targeting various pathways, thereby increasing the overall antioxidant effect. This provides a comprehensive protection

against oxidative stress in diabetes. This can optimize the antioxidant therapy by advanced formulations which could shape the wellness of diabetic patients.

2. METHODOLOGY:

Literature Search:

A literature search was conducted comprehensively using SCOPUS, Google Scholar, PubMed and Web of Science to recognize studies relevant to antioxidants and their mechanism in hindering diabetes-associated complications. The published studies were included up to the year 2025, with the help of key words "Diabetes-related oxidative stress", "antioxidants in diabetes", "antioxidant therapy", "novel antioxidant formulations" and "oxidative stress and complications of diabetes. In addition, the references of these articles were also studied.

Criteria for Selection:

The studies that explain mechanism and potential role of antioxidants in inhibiting complications associated with diabetes, clinical and preclinical studies that determines the antioxidant interventions in diabetes, mechanism of prevailing chronic inflammation induced oxidative stress in diabetes causing complications and published in English journals that do peer-review. Exclusion criteria include studies that has poor scientific evidence, not done peer-review and are unrelated to complications of diabetes.

Approach for Formulation development:

The criteria behind selecting the antioxidant combinations include compatibility with tablet form, Synergistic and complementary effects, targeting multiple pathways of inflammation, stability, potent antioxidant effect in diabetes, tolerability, potential interactions, evidence-based, dosage and safety.

The idea behind these criteria is to formulate a potential antioxidant combination that is capable of targeting multiple pathways of chronic inflammation in diabetes, thereby completely addressing the ongoing oxidative stress that is responsible for development of complications in diabetes.

Extraction and Analysis of Data:

Based on the criteria, a group of antioxidants were selected and their information like mechanism, dosage, bioavailability and safety profile were extracted. In addition, key findings from previous clinical and preclinical studies were summarized that supports the formulated combination of antioxidants for diabetes. The research gap and crucial limitations were determined to identify future directions.

3. PROPOSED ANTIOXIDANTS COMBINATION:

The proposed combination of antioxidants for diabetes comprises of *Alpha-Lipoic Acid*, *N-Acetylcysteine*, *Curcumin*, Vitamin E and *Resveratrol*.

1. *Alpha-Lipoic Acid (ALA)*:

- Function: It is a potent antioxidant that reduces oxidative stress and enhance the insulin sensitivity. It helps to regenerate production of other forms of antioxidants such as *glutathione* [35,36].
- Targeting pathway: *ALA* inhibits NF-κB, thereby decreasing formation of ROS [37-39].
- Dosage: As per clinical studies, the evidence-based range is between 300-600mg/day [40]
- Rationale: In solid form, it is highly stable that is compatible in tablet form. It is extensively been administered as an antioxidant in management of diabetic neuropathy [41,42].

2. *N-Acetylcysteine (NAC):*

- Function: It helps to reduce the load of oxidative damage by acting as a precursor for a crucial cellular antioxidant called *glutathione*.
- Targeting pathway: It plays a critical role in modulating the production of cytokines like IL-6, TNF-α & thereby targeting ROS [43-46].
- Dosage: As per trials, the commonly administered dosage is 600-1200mg/day [47,48].
- Rationale: It is usually stable as tablet form and tolerable. It works synergistically with *ALA* by amplifying the production of the powerful antioxidant, *glutathione* [49-51].

3. *Curcumin*:

- Function: It specifically hinders lipid peroxidation and nullifies the free radicals formed. Hence, it acts as an anti-oxidant and anti-inflammatory.
- Targeting pathway: It attacks multiple pathways of inflammation such as NF-κB, COX-2 and LOX and enhances glucose metabolism [52-56].
- Dosage: Along with bioavailability enhancer, *piperine* it is given at a dose of 500-1000mg/day [57,58].
- Rationale: It harmonizes with *ALA* and *NAC*, as it helps to address the inflammation broadly. During formulation as a tablet, its bioavailability is enhanced by adding *piperine* and is generally considered stable in dry form [59,60].
- Vitamin E (Tocopherol/ Tocotrienol):
- Function: It functions as a lipid-soluble antioxidant and shields the cell membrane from damage due to oxidative stress.
- Targeting pathway: It targets lipid peroxidation which is said to be the key culprit in diabetes complication [61-65].
- Dosage: Mixed form that consists of tocopherols α, β, γ and δ are commonly used in a dosage of 200-400IU/day [66,67].
- Rationale: It is found to be stable and is commonly made in tablet form. Studies supports its task in mitigating oxidative stress that is related to diabetes [68].
- *Resveratrol*:
- Function: It belongs to polyphenol group that has anti-inflammatory and antioxidant properties. It ignites SIRT1 for metabolic advantages.
- Targeting pathway: It minimizes inflammation through IL-6 and IL-1β and boosts the mitochondrial function [69-72].
- Dosage: As per clinical trials, it is administered at a dose of 150-300mg/day [73-75].
- Rationale: It is usually well-tolerable and is stable in tablet form. It works as an add on supportive mechanism in the formulation by targeting the mitochondrial oxidative stress [76].

Formulation Basis and Criteria Alignment:

1. Consistency as Table Form:

The selected antioxidants in this formulation are stable in arid condition and solid at ambient temperature and hence can be formulated together as a tablet supplement. Adding stabilizers such as magnesium stearate and microcrystalline cellulose can secure proper stability and compression [77].

2. Complementary and Synergistic effects:

NAC and *ALA* work synergistically to amplify glutathione production and to neutralize the formed ROS [78]. Additionally, *Resveratrol* and *Curcumin* targets specifically the inflammatory cascades like cytokines and NF-κB [79]. Simultaneously, Vitamin E constructs a multi-tiered defense against the oxidative stress and helps to mitigate the chronic inflammation in diabetes.

3. Targeting various pathways of inflammation:

This combination covers different inflammatory pathways in diabetes. *ALA* and *Curcumin* acts on NF- κB while *Resveratrol* and *NAC* modulates production of inflammation associated cytokines. In addition, *Curcumin* targets COX and LOX pathway while Vitamin E prevents lipid peroxidation which is the crucial driver of inflammation in diabetes.

4. Stability & Bioavailability:

Further, formulating a bioavailable and stable antioxidants combination holds a crucial challenge. Antioxidants like *NAC*, *ALA* and Vitamin E are generally stable in tablet form when properly stored in cool and dry area. *Resveratrol* and *Curcumin* require protective antioxidants or coatings like ascorbic acid to deter degradation from oxygen or light exposure as they have poor bio-availability due to low solubility and rapid metabolism. Also, the stability of this combination in long-term under storage conditions needs a proper evaluation. Methods like use of bio-enhancers (Eg: adding *Piperine* for *Curcumin*), nano-formulation or liposomal delivery systems could be opted to improve both bioavailability and stability with proper evaluation.

5. Powerful antioxidant effect in diabetes:

Each of the antioxidant have been shown to prevent oxidative stress in diabetes. For example,

ALA been used in diabetic neuropathy, *NAC* acts to replenish glutathione stores in diabetes, *Curcumin* helps regulate glucose metabolism, Vitamin E controls vascular health in diabetes and *Resveratrol* prevents mitochondrial oxidative stress.

6. Tolerability:

These antioxidants are generally safe and well-tolerated. *ALA* can cause subtly GI upset, *Curcumin* requires *piperine* that is safe and found in black pepper, *NAC* may produce sulfur odour and *Resveratrol* and Vitamin E exhibits good tolerability [80].

7. Potential Drug Interactions:

Curcumin at high doses might affect CYP450 enzymes and therefore used cautiously along with anticoagulants, statins and can cause liver injury at high doses [81]. *ALA* could increase the insulin sensitivity and might produce hypoglycemia at high doses when given with antidiabetic drugs. Vitamin E at strong doses of >800 IU can increase the risk of bleeding, especially when used along with warfarin.

8. Research Evidence-Based:

Previous studies have shown significant antioxidant effect these drugs in diabetes.

9. Dosage and safety profile:

Within evidence based and safe ranges, it is safe to administer with minor adverse effects. Total tablet size could be compatible and proposed dose is 1tablet/ day.

POTENTIAL DRUG INTERACTIONS BETWEEN COMPONENTS:

While this novel combination of *NAC*, *ALA*, *Curcumin*, *Resveratrol* and Vitamin E holds a great potential due to their overall strong anti-inflammatory and antioxidant benefits, the possible pharmacokinetic and pharmacodynamic drug interactions among them must be considered. For example, ALA might influence the Vitamin E bioavailability and the metabolic pathways of *Resveratrol* could possibly be affected by *Curcumin*. These possible interactions might either antagonize or potentiate the final efficacy of the formulation, underscoring the need for studies to evaluate their interaction before proper clinical application.

PROPOSED ANTIOXIDANT SUPPLEMENT TABLET FORMULA:

Ingredient	**Function**	**Quantity per Tablet (mg)**
Alpha-Lipoic Acid	Antioxidant	300mg
N-Acetylcysteine	Powerful detoxifier and antioxidant	600mg
Curcumin (along with 5mg *Piperine*)	Anti-inflammatory	500mg
Vitamin E (comprising mixed Tocopherols)	Prevent oxidative stress	200IU (~134mg)
Resveratrol	Cardio protective and antioxidant	150mg
Microcrystalline cellulose	Binder, Filler	Added accordingly to adjust weight
Magnesium Stearate	Lubricant	~5-10mg
Silica	Stabilizer and glidant	~5-15mg
Total tablet weight		~1.5-2g

EVIDENCE-BASED CRITICAL ANALYSIS OF THE FORMULATED COMPOSITION:

Table 1. Compatibility for Tablet form

Factor	**Analysis**
Chemical and Physical stability	The antioxidants that are chosen for combination are stable at atmospheric arid condition. *Curcumin* and *Resveratrol* needs protective coating to hinder oxidation.
Excipient choice	Microcrystalline cellulose and magnesium stearate are needed for tablet integrity and compression. Addition of silica prevents moisture.

Table 2. Synergistic effect

Antioxidant combination	**Synergistic effect**
Curcumin and *Resveratrol*	Mitigates NF-κB and release of pro-inflammatory cytokines, thereby decreasing inflammation
ALA and *NAC*	Enhances levels of Glutathione and decreases oxidative stress
Vitamin E and *NAC*	Suppresses the ongoing lipid peroxidation due to oxidative damage and enhances antioxidant defense

Table 3. Targeting pathway of inflammation

Pathway	Targeting mechanism
Suppression of NF-Kb	*Curcumin* and *ALA* hinders NF-κB, thereby decreasing inflammation
Modulation of cytokine	*NAC* and *Resveratrol* reduces the levels of IL-6 and TNF-α
Hindering lipid peroxidation	Vitamin E shields lipid membrane against lipid peroxidation

Table 4. Antioxidant benefit in Diabetes

Antioxidant	Therapeutic efficacy
ALA	Enhances the sensitivity to insulin and decreases the symptoms of neuropathy. It also boosts other antioxidants like Vitamin E and Glutathione
NAC	Replenishes glutathione, thereby mitigating oxidative stress
Curcumin	Improves glucose metabolism and decreases inflammation
Resveratrol	Improves mitochondrial function by reducing its oxidative stress load
Vitamin E	Shields against vascular complications

Table 5. Safety and Tolerability

Antioxidant	Tolerability profile
ALA	At high doses, minimal gastrointestinal upset
NAC	Minimal sulfur odor, but usually tolerated better
Curcumin	The maximum daily intake is 3mg/Kg body weight. Other side effects include elevated liver enzymes, diarrhea and nausea.
Resveratrol	Usually well tolerated at dose of 150mg/day. At high doses, it can cause mild diarrhea, nausea and anal pruritus.
Vitamin E	In routine use, safe at a moderate dose of <400 IU/day with mild GI upset.

Table 6. Possible drug interactions

Antioxidant	Tolerability profile	References
ALA	Increases risk of hypoglycemia when used with anti-diabetic drugs, as it increases sensitivity of insulin. It boosts other antioxidants like Vitamin E	82
Vitamin E	At dose of >800 IU, can increase the risk of bleeding when given along with warfarin	83
Curcumin	Has potential to affect CYP450 metabolism, thereby alter actions of statins and anticoagulants	84-87

Table 7. Possible Administration and dosage

Components	Analysis
Tablet size	~1.5-2g that can be orally administered
Total Daily Dose	Effective and safe clinical range is 1-2tablets per day
Modified-Release option	Can be modified as enteric coating for increased absorption

Table 8. Key aspects of formulation

Key aspects	Analysis
Clinical Rationale	Multiple evidences on anti-inflammatory and antioxidant effect in diabetes
Synergistic mechanism	Previous studies show the synergistic role between the individual aniti-oxidant
Pharmaceutical feasibility	Tablet formulation is highly possible, practical, manufacturable and chemically stable
Safety	Within clinical doses, usually well-tolerated. But need rigorous drug monitoring to known any other interactions and adverse effects

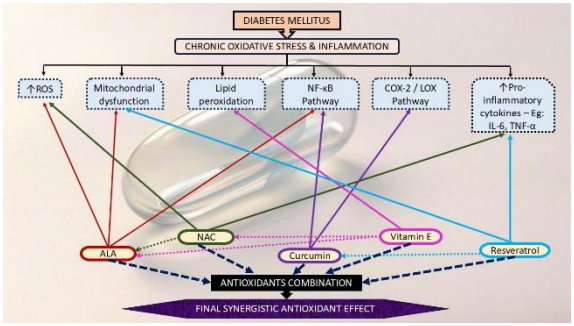

Figure 1: Mechanism of Synergistic Antioxidant effect by Antioxidant formulation

Figure Legend: The rationally designed combination of antioxidants consisting of *Alpha-Lipoic Acid* (*ALA*), *N-Acetylcysteine (NAC)*, *Curcumin*, Vitamin E and *Resveratrol* specifically targets chronic inflammation and oxidative stress in diabetes. Solid lines show the direct action of these antioxidants on various

inflammatory pathways such as COX-2, LOX, NF-κB and lipid peroxidation, leading to decreased reactive oxygen species (ROS), enhanced mitochondrial function and mitigated pro-inflammatory cytokines (e.g., IL-6, TNF-α). Dotted lines connecting the antioxidants depicts their enhancing effects on each other, further intensifying antioxidant capacity and synergistically decreasing diabetes-associated oxidative damage.

4. LIMITATIONS AND CHALLENGES:

While this rationally designed antioxidant formulation looks promising, several challenges need to be addressed. The overall stability of tablet form must be checked and may require additional protective coating in order to avoid oxidation. Also, possible interactions among active components and excipients might affect the stability and bioavailability with time. The designed synergistic efficacy must be optimized by further clinical trials. Even though studies have shown that antioxidants have potential benefit in diabetes, large-scale randomized controlled trials are lacking to prove its efficacy.

It is crucial to consider the key aspects like tolerability and safety, especially with high doses. This necessitates careful scrutinizing of adverse effects during its administration. Other possible challenges are drug interactions and tablet size. This may affect patient compliance.

It is essential to check for pharmaceutical feasibility to produce a bioavailable and stable table with proper regulatory approval. In addition, strict post-marketing surveillance is essential to ensure safety.

5. FUTURE DIRECTIONS:

In spite of mechanistic and preclinical data supporting the synergistic potential of this novel combination of antioxidants to prevent diabetes-related complications, there is a need for robust clinical evidence and validation. Further, large-scale double-blinded RCTs are required to evaluate and validate this current formulation for its real-world tolerability, long term efficacy and safety. These clinical trials must target evidences on decrease in oxidative markers and prevention of diabetes-related complications on long-term basis.

PLANNED RESEARCH STEPS:

In view of importance of a proper testing of the current novel formulation, our future works will be on in-vitro evaluation and validation followed by in-vivo studies, with reference from the theoretical framework of the current review. Furthermore, a clinical trial protocol evaluating the synergistic efficacy, bioavailability and safety among diabetic populations will be aimed. The ultimate goal of this current review is to translate this novel formulation from bench to bedside.

6. CONCLUSION:

At present, this novel antioxidant formulation is a theoretical gem, that needs real-world polish. The further steps should include laboratory testing and trials to confirm the efficacy, bioavailability variability, stability, dosage and safety of this novel combination.

CONFLICT OF INTEREST:

The authors declare no conflicts of interest.

FUNDING:

No specific grant from any funding agency was obtained for this study.

ACKNOWLEDGEMENT:

The authors sincerely acknowledge and express their gratitude to all the scientists and researchers whose pioneering work in the fields of diabetes, antioxidants, and complications related to diabetes and diabetic therapy has laid the foundation for this novel drug formulation. Their invaluable contributions to scientific literature and innovation have been instrumental in shaping the rationale behind this combination therapy.

AUTHOR CONTRIBUTION:

Dr.B.Dharani conceptualized the study, conducted the literature review and drafted the manuscript. Dr.Suba.A contributed to data analysis, manuscript revision and approval of final manuscript. All authors have read the manuscript and approved its final version

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