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A NOVEL ANTIOXIDANT-DAPAGLIFLOZIN COMBINATION: COMBATING DIABETIC KIDNEY DISEASE AT THE CELLULAR LEVEL

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Keywords:

Dapagliflozin, Diabetic Kidney Disease, Diabetic Nephropathy, Antioxidant, Novel drug, Alpha-Lipoic Acid, Coenzyme Q10, N-Acetyl Cysteine, Taurine

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ABSTRACT: At present, the significant cause of chronic kidney disease (CKD) is said to be Diabetic Kidney Disease (DKD). This condition considerably impacts cost of healthcare, mortality and morbidity worldwide. Current treatment options for DKD basically focusses on Blood Pressure (BP) regulation, glycemic control along with suppression of Renin-Angiotensin-Aldosterone System (RAAS). The advancing nature of pathophysiology of DKD demands additional treatment options to reduce the ongoing chronic inflammation and oxidative stress as they are the key operators of renal dysfunction. In the current review, we put forward a novel, rationally designed antioxidant-Dapagliflozin combination as a single tablet formulation incorporating *N-Acetyl Cysteine (NAC)*, *Taurine*, *Alpha-Lipoic Acid (ALA)* and *Coenzyme Q10 (CoQ10)* with *Dapagliflozin* to boost renoprotection in DKD. In this review, we have explored the pathophysiological rationale underlying this novel drug combination, its mechanism, synergistic potential, efficacy in preventing development of DKD at the cellular level and challenges in drug formulation. This is the first article to propose this novel combination by incorporating SGLT-2 inhibitor with antioxidants based on scientific rationale to target multidimensional cellular mechanism in DKD progression. By addressing challenges in the formulation through innovative pharmaceutical techniques and rigorous clinical approval, this formulation might have a great success in clinical practice as it has an immense potential to improve patient outcome by reducing the stress of polypharmacy while simultaneously preventing the onset and progression of DKD in diabetic patients.

INTRODUCTION: At present, the significant cause of chronic kidney disease (CKD) is said to be Diabetic Kidney Disease (DKD). This condition considerably impacts cost of healthcare, mortality and morbidity worldwide [1]. Current treatment options for DKD basically focusses on Blood Pressure (BP) regulation, glycemic control along with suppression of Renin-Angiotensin-Aldosterone System (RAAS) [2]. While oral hypoglycemic agents like Dapagliflozin have shown significant nephroprotective effects apart from blood glucose regulation, the advancing nature of pathophysiology of DKD demands additional treatment options to reduce the ongoing chronic inflammation and oxidative stress as they are the key operators of renal dysfunction.

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The central pathophysiological mechanism in DKD is oxidative stress that causes endothelial injury, mitochondrial injury and podocyte dysfunction causing tubular and glomerular injury. Nevertheless, using multiple drugs often leads to polypharmacy which potentially decreases treatment compliance, efficacy and quality of life. In the current review, we put forward a novel, rationally designed antioxidant-*Dapagliflozin* combination as a single tablet formulation incorporating *N-Acetyl Cysteine (NAC)*, *Taurine*,

Alpha-Lipoic Acid (ALA) and *Coenzyme Q10 (CoQ10)* with *Dapagliflozin* to boost reno-protection in DKD [3-5]. This proposed formulation seeks to combat synergistically the ongoing inflammation, oxidative stress and mitochondrial dysfunction while concurrently harnessing the reno-protective effects of *Dapagliflozin*. The underlying aim of this combination is to target multiple pathways involved in pathophysiology of DKD with one rationally designed synergistic therapy. Implementing such therapy could decrease the pill burden, improve the patient treatment compliance and ultimately enhance the patient's quality of life.

In this review, we explore the pathophysiological rationale underlying this novel drug combination, its synergistic potential and efficacy in preventing development of DKD at the cellular level. Also, we will discuss its clinical applications, formulation, pharmaceutical challenges and future directions, in order to convert this proposed formulation into therapeutical practical drug.

METHODOLOGY:

Literature Search: A thorough search of literature was conducted by using various databases like SCOPUS, PubMed, Google Scholar, Cochrane and Web of Science to collect studies related to DKD, nephroprotective drugs and oxidative stress.

The key words used for search are "Diabetes", "Diabetic Kidney Disease", "antioxidants", "Nephroprotective drugs", "Oxidative stress", "*Alpha-Lipoic Acid*", "*N-Acetlycysteine*", "*Taurine*", "*Coenzyme Q10*" and "*Dapagliflozin*". Inclusion criteria consist of clinical trial, meta-analysis, peer-reviewed article and experimental studies that are published in English. Those studies with lack of data and poor relevance were excluded.

Criteria for Selection: Studies that are relevant to DKD pathophysiology, effect of oxidative stress and therapeutic efficacy of nephroprotective antioxidant drugs and *Dapagliflozin* were selected.

Those articles which highlights mechanism, clinical efficacy and safety profile of these drugs were given priority. Studies which provide in-depth mechanistic evidence on renal protection and modulation of oxidative stress were considered.

Approach for Formulation Development: The rationale behind this formulation is combining nephroprotective anti-diabetic drug, *Dapagliflozin* with nephroprotective antioxidants like *NAC*, *Taurine*, *CoQ10* and *ALA*. With this formulation, we aim to target different pathways and cellular mechanism that contribute to development and progression of DKD. Hence, these drugs were also selected based on their capability to reduce the diabetes-related oxidative stress and inflammation.

Extraction and Analysis of Data: The extraction of data was done focussing on key parameters like mitochondrial dysfunction, oxidative stress, renal structural changes and clinical efficacy associated with development and progression of DKD. An evidence-based critical analysis was performed to assess the combined effects these drugs on these factors. All the relevant clinical and experimental studies were reviewed systematically to substantiate rationally this proposed formulation and to assess its therapeutic potential in preventing DKD at cellular level.

Pathophysiology of DKD: Diabetes is the major cause of chronic kidney disease (CKD) worldwide. Diabetic Kidney Disease (DKD) is exemplified by progressive form of renal dysfunction developing into CKD and ultimately to End Stage Renal Disease (ESRD). The Patho-mechanism of DKD is combinatorial and complex, encompassing hyperglycemia-induced inflammation, oxidative stress, endothelial dysfunction, mitochondrial damage, unregulated autophagy and podocyte injury [6].

The key element in pathophysiology of DKD is persistent hyperglycemia. This can lead to a state of glucotoxicity that evokes hemodynamic and metabolic changes, which cause kidney dysfunction. Chronic hyperglycemia enhances the polyol pathway by increasing aldose reductase activity. This causes accumulation of sorbitol leading to osmotic and oxidative stress in renal cells. It also causes increased formation of Advanced Glycation End Products (AGEs) that adhere to RAGE receptors fostering oxidative stress, inflammation and finally fibrosis. This also causes deviant post-translational changes due to enhanced hexosamine biosynthetic pathway causing renal fibrosis.

It could activate Protein Kinase C (PKC) that changes the normal renal hemodynamic, expands endothelial dysfunction and facilitates renal fibrosis [7, 8]. The second step is the mitochondrial dysfunction leading to enhanced production of Reactive Oxygen Species (ROS), compromised antioxidant system such as glutathione peroxidase and superoxide dismutase and eventually Endoplasmic Reticulum (ER) stress. The key attribute of DKD is ongoing chronic inflammation in diabetes. The inflammatory pathway involves excess release of pro-inflammatory cytokines like IL-6, TNF-α and IL-1β and induction of NLRP3 inflammasome which further facilitate the inflammation. Ultimately, this leads to renal tissue infiltration by macrophages, mediated by TGF- β1 and connective tissue growth factor (CTGF). This intensifies tubulointerstitial fibrosis [9].

The marked hemodynamic alteration is glomerular hyperfiltration caused by high intraglomerular pressure due to dilation of afferent arteriole and constriction of efferent arteriole. It also causes defective nitric oxide (NO) production and enhanced levels of endothelin-1 (ET-1) levels. This leads to vasodilation further causing tissue hypoxia and damage. In addition, Angiotensin II causes glomerular hypertension. The chronic oxidative stress causes cytoskeletal disruption, diminution of Podocin and nephrin and dysregulation of autophagy and apoptosis. These effects lead to disrupted filtration barrier, detachment of podocyte which eventually leads to glomerular damage causing Proteinuria [10]. The cumulative effect of these combined alterations like pro-inflammatory cytokines, tubular atrophy and proteinuria-induced fibrotic pathways is tubulointerstitial damage. Due to chronic hyperglycemia, the normal autophagy flux is decreased leading to buildup of damaged proteins and organelles. This induces pro-inflammatory secretions which further exacerbates the kidney damage. Apart from these mechanisms, there occurs epigenetic modifications like histone alterations, DNA methylation and alterations in MicroRNAs (miRNAs), that causes progression of inflammatory and fibrotic pathways in DKD [11].

Studies have shown that dysbiosis of gut microbiota causes further activation of systemic inflammation due to defective production of Short-Chain Fatty Acid (SCFA) that aggravates DKD [12].

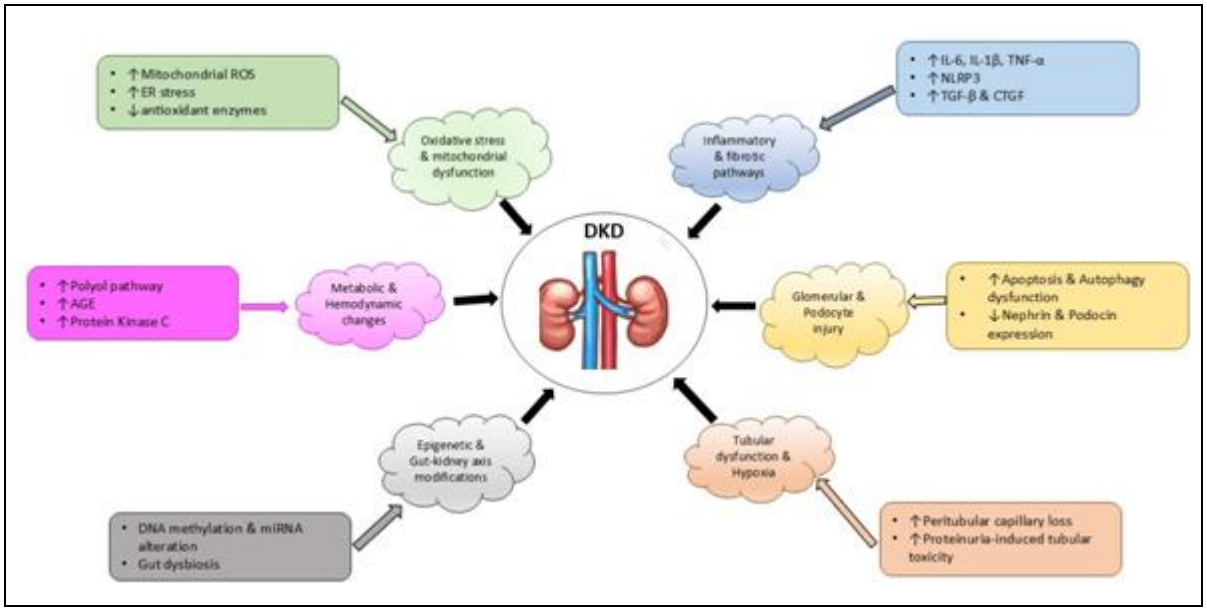

FIG. 1: PATHOPHYSIOLOGY OF DKD

Proposed Combination of *Dapagliflozin*-Antioxidants: The rationally designed novel formulation consists of *Dapagliflozin* with nephropotective antioxidants like *NAC*, *Taurine*, *ALA* and *CoQ10*. The basis of this formulation is to target specifically different cellular mechanisms related to oxidative stress that is involved in development of DKD. Each component of this combination plays a crucial role in alleviating diabetes-related oxidative stress, enhancing mitochondrial activity and thereby safeguarding renal function and structure.

***Dapagliflozin*:** *Dapagliflozin* is a nephroprotective anti-diabetic drug. It inhibits Sodium-Glucose co-Transporter-2 (SGLT2), thereby reduces reabsorption of glucose in the proximal tubule of kidney. This decreases chronic kidney damage caused by hyperglycemia in diabetes. This helps to attain adequate glycemic control, mitigates glomerular hyperfiltration. Additionally, it decreases chronic inflammation and oxidative stress related to progression of DKD. Also, this effect has been connected to enhanced mitochondrial efficiency and autophagy that are important in maintaining renal cell homeostasis [13-18].

***Alpha-Lipoic Acid (ALA)*:** *ALA* is said to be a dithiol compound that occurs naturally with potent anti-inflammatory and anti-oxidant capacity. It has a direct ROS scavenging property and helps in regeneration of other vital antioxidants like vitamin C and Glutathione. It also improves the mitochondrial function, hinders lipid peroxidation and decreases formation of AGE. All of which together promotes renal protection from oxidative stress in diabetes [19-21].

***N-Acetylcysteine (NAC)*:** It acts as an important precursor for synthesis of glutathione which is known as the body's master antioxidant. It safely decreases the level of oxidative stress, inhibits the release of pro-inflammatory cytokines and reduces apoptosis of renal tubular cells. Also, *NAC* has proven to alleviate renal fibrosis by decreasing the activation of TGF-β which is said to be the key driver of DKD progression [22-24].

***Taurine*:** *Taurine* is a sufur-containing amino acid that plays a crucial role in osmoregulation of cells and defense against oxidative stress. It shields against development of diabetic nephropathy by steadying mitochondrial membranes, alleviating oxidative damage and thereby mitigating inflammation. It also balances NO availability by which enhancing the function of endothelium and renal microcirculation [25].

***Coenzyme Q10 (CoQ10)*:** *CoQ10* is an essential component in the process of ATP production as it belongs to mitochondrial electron transport chain. Hence, it plays critical role in energy metabolism of cells. It executes a dual role in prevention of DKD by enhancing the mitochondrial energy production, thereby hold the role of potential lipid-soluble antioxidant. It can also alleviate the podocyte injury, decrease proteinuria and improve the renal cells function in DKD [26].

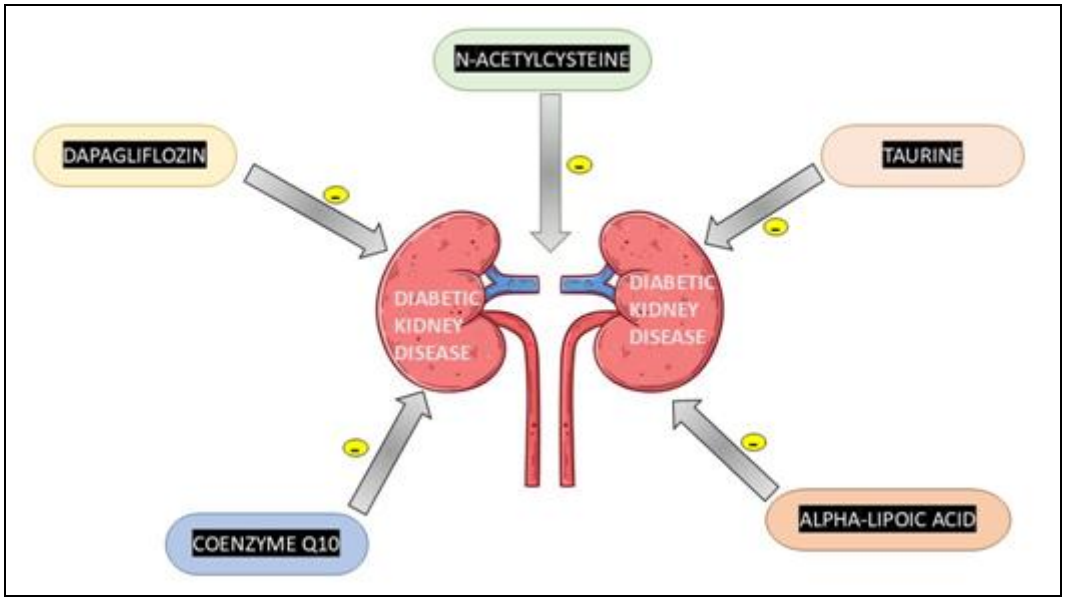

FIG. 2: PROPOSED COMBINATION OF *DAPAGLIFLOZIN* AND ANTIOXIDANTS

Mechanism of Action of *Dapagliflozin*-Antioxidants Combination: DKA is basically fuelled by chronic hyperglycemia in diabetes, that causes various metabolic and hemodynamic modifications. This leads to chronic oxidative stress, mitochondrial insufficiency, chronic inflammation and ultimately ending in renal fibrosis. The current study formulates a novel

combination of *Dapagliflozin*, *ALA*, *NAC*, *Taurine* and *CoQ10* in such a way that this combination targets specifically the pathological pathways, thereby prevents the progression of DKD synergistically.

Reduction of Hyperglycemia-Induced Oxidative Stress and Mitochondrial Dysfunction: In diabetes, uncontrolled hyperglycemia increases the polyol pathway, causing excess accumulation of sorbitol and high generation of mitochondrial ROS. *Taurine*, *NAC*, *ALA* and *CoQ10* are efficient antioxidants that scavenges these excess ROS. Also, they improve the endogenous antioxidant enzymes, by which they help to decrease ER stress and mitochondrial injury. Addition of Dapagliflozin to this antioxidant combination can enhance their effect by its glucose lowering effect, thereby reducing mitochondrial overload induced oxidative stress [27-49].

Protection against Glomerular Injury and Endothelial Dysfunction: Chronic hyperglycemia induces AGE-RAGE signaling and PKC, which leads to glomerular hypertension and endothelial dysfunction.*ALA* and *CoQ10* enhance the mitochondrial function and decreased AGE-related oxidative stress. *Taurine* prevents glomerular injury by controlling CTGF and TGF-β pathways. Addition of *Dapagliflozin* with this combination might help to preserve nephrin, protect expression of podocin, safegaurd podocytes and thereby maintains the glomerular filtration barrier [50-64].

Anti-inflammatory and Anti-fibrogenic Effects: Diabetes is a chronic condition characterized by chronic inflammation. It is marked by increased activity of inflammatory cytokines like IL-1β, IL-6, TNF-α and activation of NLRP3 inflammasome which accelerates the process of renal fibrosis. *NAC*, *ALA* and *Taurine* are antioxidants that alleviates the inflammation by supressing these inflammatory cytokines and thereby curbing fibrotic pathways. Addition of *Dapagliflozin* with *CoQ10* helps to regulate the inflammatory signalling, thereby decreasing the mesangial expansion and alleviates interstitial fibrosis [65-86].

Protection against Tubular Hypoxia and Dysfunction: The progression of DKD is characterized by impaired autophagy, tubular apoptosis and proteinuria-driven tubular toxicity. Taurine and NAC improve the detoxification mechanisms of cells, thereby alleviating the oxidative damage of renal tubules. Addition of *Dapagliflozin* along with *CoQ10*, reduces the peritubular capillary depletion, maintaining renal oxygenation and slowing the process of hypoxia-induced tubular damage [87-97].

Gut-Kidney Axis and Epigenetic Modulation: Diabetes is also characterized by SCFA deficiency and gut dysbiosis, further aggravating the ongoing systemic inflammation and renal insult. *CoQ10* and *ALA* are capable of influencing miRNA expression and DNA methylation, thereby protecting against persistent renal injury. *NAC* and *Taurine* helps to regain the gut microbiota balance, thereby decreasing the inflammatory overload on kidneys [98-107].

Hence, this combination consisting of *Dapagliflozin*, *ALA*, *NAC*, *CoQ10* and *Taurine* offers a multidimensional nephroprotection that addresses the underlying inflammation, oxidative load, mitochondrial injury and fibrosis at the cellular level. This novel, rationally-designed treatment strategy provides a synergistic effect and offers a promising effect to halt the development and progression of DKD, thereby prevents ESRD.

TABLE 1: EVIDENCE-BASED CRITICAL ANALYSIS OF THE FORMULATION

S. no.	Mechanism of action	Drugs	Individual effects	References
1.	Reduction of hyperglycemia-induced oxidative stress and mitochondrial dysfunction	*Dapagliflozin, ALA, Taurine, NAC, CoQ10*	*Dapagliflozin:* glucose lowering effect, thereby reducing mitochondrial overload- induced oxidative stress	27-31
			ALA: reduce ROS, improves antioxidant enzymes	32-34
			NAC: mitigates ER stress and mitochondrial injury	35-39
			Taurine: improves mitochondrial function and decrease oxidative load	40-44
			CoQ10: enhances mitochondrial bioenergetics and prevents oxidative injury	45-49

2.	Protection against glomerular injury and endothelial dysfunction	*Dapagliflozin, ALA, CoQ 10, Taurine*	*Dapagliflozin*: maintains podocin and nephrin expression amd preserves glomerular filtration barrier.	50,51
			CoQ10: Alleviates AGE-related oxidative injury and enhances mitochondrial function	52-54
			ALA: Supresses oxidative stress and enhances endothelial function	55-62
			Taurine: Modulate CTGF and TGF-β and prevents glomerular injury.	63,64
3.	Anti-inflammatory and anti-fibrogenic effects	*Dapagliflozin, ALA, NAC, CoQ10, Taurine*	*Dapagliflozin*: Controls inflammatory signalling and decreases interstitial fibrosis	65-70
			ALA: reduces pro-inflammatory cytokines	71-74
			NAC: supresses fibrosis-associated pathways	75-80
			Taurine: Decreases NLRP3activation	81-84
			CoQ10: reduces mesangial expansion and fibrosis	85,86
4.	Protection against tubular hypoxia and dysfunction	*Dapagliflozin, Taurine, CoQ10, NAC*	*Dapagliflozin*: Reduces peritubular capillary depletion and slows down the hypoxia-induced damage	87-89
			NAC: improves cellular detoxification and protects renal tubules	90,91
			Taurine: Decreases proteinuria associated renal toxicity	92-94
			CoQ10: Preserves renal oxygenation and decreases oxidative stress	95-97
5.	Gut-Kidney Axis and Epigenetic modulation	*NAC, ALA, Taurine, CoQ10*	*ALA*: controls DNA methylation and prevents underlying renal injury	98-100
			CoQ10: modulates miRNA expression and decreases inflammation	101,102
			Taurine: Regains gut microbiota balance and decreases systemic inflammation	103-105
			NAC: preserves the healthy gut-kidney axis	106,107

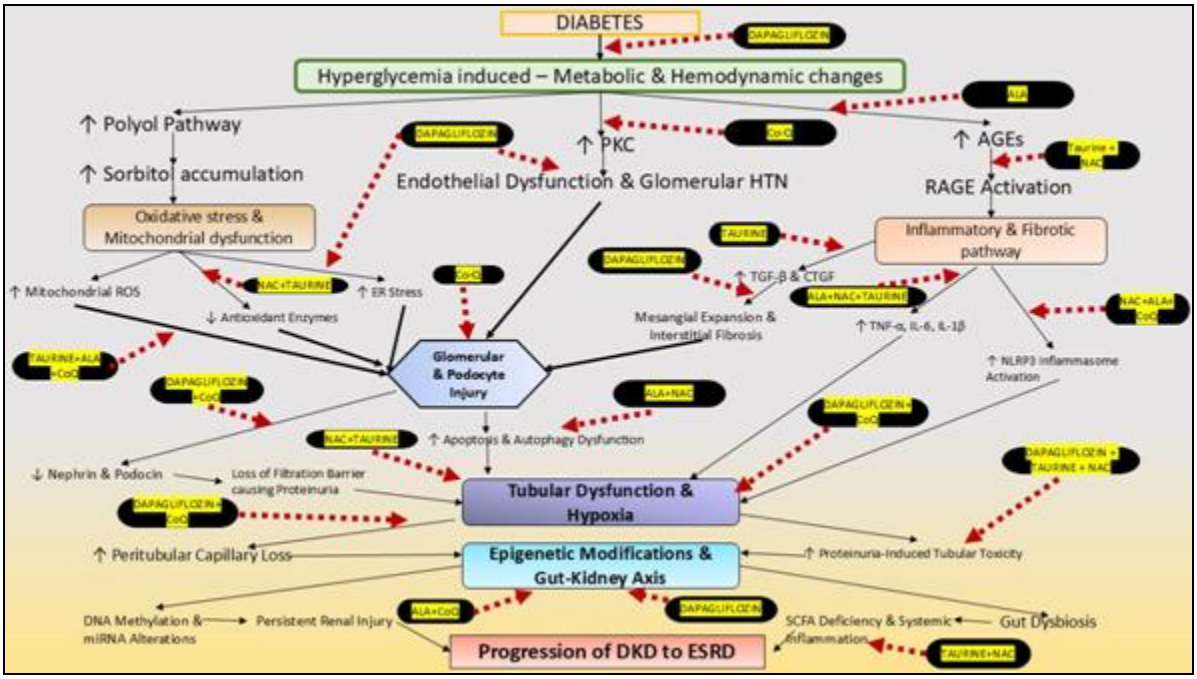

FIG. 3: MECHANISM OF *DAPAGLIFLOZIN*-ANTIOXIDANT COMBINATION IN COMBATING DKD

Figure Legend: This figure depicts the multidimensional pathophysiology of DKD, highlighting the key pathways such as inflammatory, metabolic and hemodynamic pathways that are involved in development and progression of DKD. Hyperglycemia activated metabolic alterations causes mitochondrial dysfunction, oxidative stress, endothelial

dysfunction and glomerular injury, that contribute to podocyte damage, proteinuria and ultimately renal fibrosis. The complex interplay of AGE-RAGE signalling, activation of polyol pathway, excess mitochondrial ROS formation and release of inflammatory cytokines exacerbates renal dysfunction. The synergistic effect of this novel combination (*Dapagliflozin*, *NAC*, *Taurine*, *ALA* and *CoQ10*) is shown by targeting various pathological pathways to reduce oxidative stress, chronic inflammation and prevent fibrosis, thereby aiming prevent DKD development and progression.

Challenges: These are few challenges in development of a combination consisting of *Dapagliflozin* with nephroprotective antioxidants namely *NAC*, *Taurine*, *CoQ10* and *ALA* as a single-tablet formulation. This includes pharmaceutical compatibility, optimal drug release profile, absorption and bioavailability, dosing, manufacturing possibility, adverse effects, drug regulatory approval, cost and accessibility. These challenges must be addressed effectively for a successful clinical validation and practical formulation.

Future Perspectives: The future directions in this formulation could be incorporating innovative drug delivery technologies, fixed-ratio dosing strategies, integrating other anti-fibrotic and anti-diabetic drugs, large-scale studies to prove its efficacy, scalability and commercialization.

CONCLUSION: The present study on a rationally-designed single tablet formulation, by combining nephroprotective anti-diabetic drug, *Dapagliflozin* with nephroprotective antioxidants provides an innovative and novel strategy to prevent DKD at cellular level. This article underscores the evidence-based potential of this combination to mitigate the oxidative stress and mitochondrial dysfunction, which are the key driving factors for development and progression of DKD along with achieving adequate glycemic control. This is the first article to propose this novel combination by incorporating SGLT-2 inhibitor with antioxidants based on scientific rationale to target multidimensional cellular mechanism in DKD progression. This points its strength and credibility for a successful formulation. If this formulation is clinically validated and successfully developed, it has an immense potential to create a prominent impact in the diabetic population by enhancing the renal outcomes, improving the treatment compliance and thereby improving the overall quality of life. Also, it has a greater potential to pave way for formulation of similar drugs in future. By addressing challenges in the formulation through innovative pharmaceutical techniques and rigorous clinical approval, this formulation might have a great success in clinical practice as it has an immense potential to improve patient outcome by reducing the stress of polypharmacy while simultaneously preventing the onset and progression of DKD in diabetic patients.

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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 final approval. All authors have read the manuscript and approved its final version.

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