Therapeutic Potential of *Allium ampeloprasum* in the Management of Diabetic Nephropathy: A Comprehensive Review of Phytochemical and Pharmacological Evidence

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Abstract

Background: Diabetic nephropathy (DN) represents the leading cause of end-stage renal disease globally, characterized by progressive kidney damage driven by hyperglycemia-induced oxidative stress, inflammation, and fibrosis. *Allium ampeloprasum* L. (leek), a member of the *Amaryllidaceae* family, has demonstrated significant pharmacological potential through its diverse bioactive constituents, yet its therapeutic application in DN remains underexplored.

Objective: This comprehensive review systematically evaluates the phytochemical profile of *Allium ampeloprasum* and examines the pharmacological evidence supporting its potential nephroprotective effects in the context of diabetic kidney disease.

Methods: A systematic literature search was conducted across multiple electronic databases, including PubMed, Google Scholar, Crossref, and Europe PMC. Studies investigating the phytochemistry of *Allium ampeloprasum* and the pharmacological effects of Allium-derived compounds on diabetic nephropathy mechanisms were included. Data were synthesized to identify active constituents, molecular targets, and therapeutic pathways.

Results: *Allium ampeloprasum* contains a rich array of bioactive compounds, including organosulfur compounds (S-alkyl-L-cysteine sulfoxides, diallyl disulfide), flavonoids (quercetin, kaempferol), saponins (steroidal glycosides), and phenolic acids. These constituents exert

nephroprotective effects through multiple mechanisms: (1) antioxidant activity via Nrf2/Keap1/ARE pathway activation, (2) anti-inflammatory effects through NF-κB and NLRP3 inflammasome inhibition, (3) anti-fibrotic action via TGF-β/Smad pathway modulation, (4) anti-glycation effects reducing AGE formation, and (5) improvement of metabolic parameters, including glucose homeostasis and lipid profiles.

Conclusion: *Allium ampeloprasum* demonstrates substantial therapeutic potential for DN management through its multi-targeted phytochemical constituents. The available evidence supports further preclinical and clinical investigation to establish optimal dosing, formulation strategies, and therapeutic protocols for integration into DN treatment paradigms.

Keywords: *Allium ampeloprasum*, diabetic nephropathy, phytochemistry, organosulfur compounds, flavonoids, nephroprotection, oxidative stress.

1. INTRODUCTION

Diabetes mellitus has emerged as one of the most challenging global health crises of the 21st century, affecting approximately 537 million adults worldwide according to recent International Diabetes Federation estimates International Diabetes Federation, 2021 [1]. Diabetic nephropathy (DN) is one of the many potential complications of diabetes and the most common microvascular complication, and it is the primary cause of end-stage renal disease (ESRD) requiring dialysis or transplantation [2,3].

The pathophysiology of DN is a complex process involving metabolic changes, hemodynamic changes, and molecular changes that all play a role in the progressive kidney tissue damage [4]. The pathological changes consist of thickening of the glomerular basement membrane, expansion of the mesangial cells, damage to the podocytes, tubular atrophy and interstitial fibrosis [5]. Although there have been major improvements in the understanding of the pathogenesis of diabetes, there are only a few treatment classes currently available for use: renin-angiotensin-aldosterone system (RAAS) inhibitors, sodium-glucose cotransporter-2 (SGLT2) inhibitors, and glucagon-like peptide-1 receptor agonists (GLP-1RAs) [6].

Due to their increasing popularity as complementary therapeutic agents, the genus Allium has recently attracted research attention due to its several species having recognized therapeutic properties [7]. *Allium ampeloprasum* L., or wild leek, is one of these species with great potential for therapeutic use in metabolic diseases that has not been studied exhaustively [8].

Allium ampeloprasum L. is a member of the *Amaryllidaceae* family (formerly *Alliaceae*) that includes several botanical varieties, such as the cultivated leek (var. *porrum*), elephant garlic (var. *holmense*), and great-headed garlic (var. *ampeloprasum*) [9,10]. This biennial herb is native to the Mediterranean region and the Middle East, and has been used for thousands of years in both food and medicine [11].

A. ampeloprasum has been used in traditional medicine to treat different ailments in various cultures, such as gastrointestinal disorders, respiratory illness, cardiovascular diseases, and metabolic disturbances [12,13]. It is preferred for its very mild taste compared to the common garlic (*Allium sativum*) and yet has plenty of bioactive compounds [14].

Although there is a wealth of literature about the pharmacological activity of *A. sativum* and *A. cepa* in diabetes and its complications, *A. ampeloprasum* is relatively unstudied [15]. Although there is some evidence that *Allium ampeloprasum* possesses similar classes of bioactive compounds as other members of the genus *Allium*, such as organosulfur compounds, flavonoids, and saponins, investigations into the therapeutic potential of the plant to treat DN are remarkably few.

The aim of the present review is to synthesize the existing information on the phytochemistry of *Allium ampeloprasum* and to extrapolate the possible mechanisms of nephroprotection from the mechanisms of related species of *Allium* and the identified bioactive constituents. This synthesis is crucial to focus future study in the direction of clinical validation of *Allium ampeloprasum* as a therapy for DN.

2. PHYTOCHEMISTRY OF *Allium ampeloprasum*

Allium ampeloprasum is rich in a wide range of bioactive phytochemicals, which are responsible for its pharmacological activities [16]. The phytochemical analysis has shown the presence of alkaloids, flavonoids, phenolic compounds, organosulfur compounds, saponins, and steroidal glycosides in various parts of the plant [8,17].

2.1. Organosulfur Compounds

The organosulfur compounds are the most pharmacologically important group of compounds found in *Allium* species such as *Allium ampeloprasum* [18]. These compounds are produced from the enzymatic decomposition of S-alk(en)yl-L-cysteine sulfoxides (ACSOs) on tissue breakdown by the enzyme alliinase [19].

2.1.1. Cysteine Sulfoxides: The main cysteine sulfoxides found in *Allium ampeloprasum* are:

- **Alliin (S-allyl-L-cysteine sulfoxide)**: It is the most abundant of the cysteine sulfoxides, which are the precursor of allicin and other bioactive compounds [20].
- **Isoalliin (S-trans-1-propenyl-L-cysteine sulfoxide)**: Found in high levels in onion-related *Allium* species and varieties [15].
- **Methiin (S-methyl-L-cysteine sulfoxide)**: Found in different amounts in different *Allium* species.

Some studies have compared elephant garlic (*Allium ampeloprasum* var. *holmense*) with common garlic and have shown that elephant garlic contains the same amount of alliin as common garlic and sometimes more of some cysteine sulfoxides [9].

2.1.2. Thiosulfinates and Derivatives: Cysteine sulfoxides (when enzymatically converted) give thiosulfinates and related compounds:

- **Allicin (diallyl thiosulfinate)**: The main thiosulfinate that gives allicin its smell and many biological properties [19].
- **Diallyl disulfide (DADS)**: A bio-stable metabolite of allicin that is nephroprotective [21].
- **Diallyl trisulfide (DATS)**: Among other important transformation products have strong anti-inflammatory and antioxidant properties.
- **S-allyl cysteine (SAC)**: Water-soluble and stable compound, which is formed during the aging process and is reported to have important therapeutic potential [22].
- **S-allyl mercaptocysteine (SAMC)**: Other stable compound with demonstrated pharmacological activities.

2.1.3. Hydrogen Sulfide Donors: One of the important means of activity of the organosulfur compounds is as hydrogen sulfide (H_2S) donors [19]. H_2S is a gasotransmitter that has been shown to play roles in vascular relaxation, anti-inflammatory responses, and protection

against oxidative stress in cells. The cardiovascular and renal protection is mainly due to the conversion of sulfur compounds derived from the *Allium* species to H_2S.

2.2. Flavonoids and Phenolic Compounds

In the composition of *Allium ampeloprasum*, there are significant amounts of flavonoids and phenolic compounds, which are responsible for the antioxidant effect and therapeutic properties [17].

2.2.1. Major Flavonoids:

- **Quercetin and its glycosides**: These are mainly found as quercetin-4'-glucoside and quercetin-3,4'-diglucoside and have strong antioxidant, anti-inflammatory, and antiglycation properties [23].
- **Kaempferol**: It is a flavonol that has been shown to have renoprotective effects via several mechanisms, such as the anti-inflammatory action and activation of the Nrf2 pathway [24].
- **Isorhamnetin**: A methylated flavonol with antioxidant properties.
- **Apigenin and luteolin**: Flavones with documented anti-fibrotic and anti-inflammatory activities.

2.2.2. Phenolic Acids: Caffeic acid, ferulic acid, p-coumaric acid, and chlorogenic acid are some of the phenolic acids found in *Allium ampeloprasum* [16]. The compounds are responsible for the overall antioxidant activity, and they can act synergistically with flavonoids and organosulfur compounds in order to improve therapeutic activity.

2.3. Saponins and Steroidal Glycosides

2.3.1. Steroidal Saponins: *Allium ampeloprasum* contains a considerable amount of steroidal saponins and glycosides, which are one of its distinguishing features from common garlic [25]. These compounds have been specifically investigated for their anti-inflammatory and gastroprotective effects.

Adão et al. [13] isolated a new steroidal saponin from *Allium ampeloprasum* var. *porrum* that demonstrated significant anti-inflammatory activity in experimental models. The compound, named as a furostanol glycoside, exhibited a dose-dependent inhibitory effect on inflammation and gastroprotection effect.

2.3.2. Fistulosides and Related Compounds: The study of related *Allium* species has revealed that several steroidal glycosides showing biological activity have been discovered:

- **Fistulosides**: Steroidal saponins from *Allium fistulosum* with documented antifungal activity [25].
- **Chinenosides**: From *Allium chinense* with diverse pharmacological properties.
- **Porrigenin glycosides**: Characteristic steroidal sapogenins found in leek varieties.

2.4. Fructans and Prebiotic Compounds

Fructooligosaccharides (FOS) and inulin-type fructans are present in *Allium ampeloprasum* in significant amounts [10]. Such non-digestible carbohydrates are prebiotics and help to create a good balance of gut bacteria. There is growing evidence of the cross-talk between the gut and kidney, and manipulation of gut microbiota may be a future strategy for the management of DN.

2.5. Alkaloids and Other Constituents

Phytochemical studies have revealed the presence of alkaloids in *Allium ampeloprasum* extracts, although their structure has not been characterized [16]. Additional constituents include:

- Essential oils containing sulfur compounds
- Amino acids and peptides
- Vitamins (particularly vitamin C and B-complex)
- Minerals (selenium, germanium, zinc)
- Adenosine and related nucleosides

Table 1: Key Bioactive Compounds of *Allium ampeloprasum* and Their Molecular Targets in Diabetic Nephropathy.

Compound Class	**Specific Compounds**	**Molecular Targets**	**Therapeutic Mechanism**
Organosulfur Compounds [15,18-22,26]			
Cysteine Sulfoxides	Alliin	Alliinase	Precursor to bioactive thiosulfinates
	Isoalliin		Major compound in leek varieties

	Methiin		Contributes to sulfur compound diversity
Thiosulfinates & Derivatives	Allicin	NF-κB, MAPK, Nrf2	Anti-inflammatory, antioxidant, antimicrobial
	Diallyl disulfide (DADS)	Nrf2/Keap1/ARE, IKK	Antioxidant, anti-inflammatory, Phase-II enzyme induction
	Diallyl trisulfide (DATS)	NF-κB, AP-1, Nrf2	Potent antioxidant, anti-apoptotic
	S-allyl cysteine (SAC)	Nrf2, HO-1, GSH	Stable antioxidant, mitochondrial protection
	S-allyl mercapto cysteine (SAMC)	Caspases, Bcl-2 family	Anti-apoptotic, cell cycle regulation
H_2S Donors	Allium-derived sulfur compounds	Vascular smooth muscle, K-ATP channels	Vasodilation, anti-inflammatory, gaso-transmitter
Flavonoids [23,24]			
Flavonols	Quercetin & glycosides	Nrf2, NF-κB, AGE/RAGE	Antioxidant, anti-inflammatory, anti-glycation
	Kaempferol	Nrf2, HO-1, SIRT1	Antioxidant, anti-fibrotic, metabolic improvement
	Isorhamnetin	NF-κB, iNOS	Antioxidant, anti-inflammatory
Flavones	Apigenin	TGF-β/Smad, NF-κB	Anti-fibrotic, anti-inflammatory

	Luteolin	NLRP3, NF-κB	Anti-inflammatory, inflammasome inhibition
Phenolic Acids [16,17]			
Hydroxycinnamic acids	Caffeic acid	Nrf2, NF-κB, TGF-β	Antioxidant, anti-fibrotic
	Ferulic acid	Nrf2, HO-1, MMPs	Antioxidant, extra cellular matrix modulation
	p-Coumaric acid	NF-κB,COX-2	Anti-inflammatory
Hydroxybenzoic acids	Chlorogenic acid	AMPK, GLUT4	Glucose uptake, metabolic regulation
Saponins & Steroidal Glycosides [13,25]			
Steroidal saponins	Furostanol	COX-2, LOX, cytokines	Anti-inflammatory, gastroprotective
	Spirostanol	Cell membrane integrity	Antifungal, cytotoxic
	Diosgenin derivatives	TGF-β, collagen synthesis	Anti-fibrotic potential
Fructans & Prebiotics [10]			
Fructooligosaccharides	Fructans	GLP-1, PYY secretion	Metabolic improvement, satiety
Minor Constituents [11,17,18]			
Amino acids	S-methylcysteine, S-allycysteine	Glutathione synthesis	Detoxification, antioxidant support
Minerals	Selenium, Germanium	Selenoproteins, antioxidant enzymes	Catalytic antioxidant activity
Vitamins	Vitamin C, B-complex	Redox balance, metabolism	General antioxidant, metabolic cofactors

Nucleosides	Adenosine, Adenosine derivatives	Adenosine receptors	Vasodilation, anti-inflammatory

3. DIABETICNEPHROPATHY: PATHOPHYSIOLOGICAL MECHANISMS

The diabetic nephropathy progresses in a typical manner from early functional changes to irreversible structural changes [23]. The natural history will include the following:

Stage 1 (Hyperfiltration): Glomerular filtration rate (GFR) is up, and Albumin excretion is normal.

Stage 2 (Silent phase): Normal/High GFR with intermittent microalbuminuria.

Stage 3 (Incipient DN): Microalbuminuria (30-300 mg/day), which is a persistent condition.

Stage 4 (Overt DN): Macroalbuminuria > 300mg/day and decreasing GFR.

Stage 5 (ESRD): End-stage renal disease (ESRD) is the final stage of kidney disease when renal replacement therapy (RRT) is needed.

3.1. Metabolic Pathways in DN Pathogenesis

3.1.1. Hyperglycemia-Induced Injury: The most important early event in the development of DN is chronic hyperglycemia [27]. Multiple downstream mechanisms mediate glucose-induced kidney damage:

Polyol Pathway Activation: When there is an excess of glucose, there is a pathway where aldose reductase converts glucose to sorbitol. This process will use NADPH, reduce glutathione and increase oxidative stress [28].

Advanced Glycation End Products (AGEs): Non-enzymatic glycation of protein, lipids and nucleic acids results in the accumulation of Advanced Glycation End Products (AGEs) in renal tissues [29]. AGEs have harmful effects by:

- Direct modification of extracellular matrix proteins
- Cross-linking of collagen molecules
- Interaction with RAGE (receptor for AGEs) triggering inflammatory signaling
- Quenching of nitric oxide, impairing vascular function

Protein Kinase C (PKC) Activation: Hyperglycemia increases diacylglycerol (DAG) synthesis, activating PKC isoforms that promote:

- Vascular endothelial growth factor (VEGF) expression
- Endothelin-1 production
- NF-κB activation
- Increased vascular permeability

Hexosamine Pathway Flux: Increased glucose flux through the hexosamine pathway modifies transcription factors via O-GlcNAcylation, altering gene expression patterns that contribute to diabetic complications.

3.1.2. Oxidative Stress: Oxidative stress is a major mechanism in DN pathogenesis that is caused by an imbalance between the production of reactive oxygen species (ROS) and the antioxidant mechanisms [30].

Sources of ROS in DN:

- Mitochondrial electron transport chain dysfunction
- NADPH oxidase (NOX) activation
- Xanthine oxidase upregulation
- Uncoupled nitric oxide synthase (eNOS)
- Advanced glycation end products

Consequences of Oxidative Stress:

- Lipid peroxidation and membrane damage
- Protein oxidation and dysfunction
- DNA damage and mutations
- Activation of pro-inflammatory pathways
- Stimulation of fibrotic signaling

3.1.3. Mitochondrial Dysfunction: The kidney is very metabolically active and is especially vulnerable to mitochondrial dysfunction [31]. Key features include:

- Mitochondrial fragmentation through Drp1-mediated fission.
- Impaired mitophagy leading to accumulation of damaged mitochondria.
- Reduced ATP production affects tubular transport functions.
- Release of mitochondrial DNA triggering inflammatory responses.

3.2. Inflammatory Pathways: Chronic low-grade inflammation is a hallmark of DN progression [32].

3.2.1. Immune Cell Infiltration

- **Macrophages**: Increase in number in glomeruli and interstitium and release pro-inflammatory cytokines and growth factors.
- **T lymphocytes**: Both CD4+ and CD8+ T cells contribute to kidney injury through direct cytotoxicity and cytokine production.
- **Dendritic cells**: Antigen presentation and immune response modulation.
- **Mast cells**: Release of histamine and proteases contributing to tissue remodeling.

3.2.2. Pro-inflammatory Cytokines and Chemokines: Key mediators involved in inflammatory responses in DN are:

- **Tumor necrosis factor-α (TNF-α)**: Induces insulin resistance, apoptosis, and inflammation.
- **Interleukin-1β (IL-1β)**: Activates endothelial cells and stimulates production of chemokines.
- **Interleukin-6 (IL-6)**: Causes systemic inflammation and fibrosis.
- **Interleukin-18 (IL-18)**: Promotes interferon-γ production and Th1 responses.
- **Monocyte chemoattractant protein-1 (MCP-1/CCL2)**: Recruits monocytes/macrophages to kidney tissues.
- **Transforming growth factor-β (TGF-β)**: Central mediator of fibrosis.

3.2.3. NLRP3 Inflammasome Activation: The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is an important factor in the pathogenesis of DN [33]. Hyperglycemia, AGEs, and oxidative stress cause activation, which results in:

- Caspase-1 activation
- IL-1β and IL-18 maturation and secretion
- Pyroptosis (inflammatory cell death)
- Amplification of inflammatory responses

3.3. Fibrotic Pathways: The progression to ESRD in DN is through renal fibrosis [34].

3.3.1. Transforming Growth Factor-β (TGF-β) Signaling: TGF-β is the master regulator of fibrosis, acting through:

- Smad-dependent pathways (canonical signaling)
- Smad-independent pathways (MAPK, PI3K/Akt)
- Epithelial-mesenchymal transition (EMT) induction
- Myofibroblast activation and proliferation
- Extracellular matrix (ECM) protein synthesis

3.3.2. Epithelial-Mesenchymal Transition (EMT): Tubular epithelial cells undergo phenotypic transformation characterized by:

- Loss of epithelial markers (E-cadherin)
- Acquisition of mesenchymal markers (α-SMA, vimentin)
- Increased migratory capacity
- Enhanced ECM production

3.3.3. Other Fibrotic Mediators

- **Connective tissue growth factor (CTGF)**: Downstream mediator of TGF-β fibrotic effects.
- **Platelet-derived growth factor (PDGF)**: Stimulates mesangial cell proliferation.
- **Endothelin-1**: Potent vasoconstrictor with profibrotic properties.
- **Angiotensin II**: Hemodynamic and profibrotic effects through AT1 receptors.

3.4. Hemodynamic Alterations

3.4.1. Glomerular Hyperfiltration and Hypertension: Early DN is characterized by glomerular hyperfiltration driven by:

- Afferent arteriolar dilation (mediated by prostaglandins)
- Efferent arteriolar constriction (mediated by angiotensin II)
- Tubuloglomerular feedback dysregulation
- Increased intraglomerular pressure

3.4.2. RAAS Activation: The renin-angiotensin-aldosterone system is activated in diabetes, contributing to:

- Systemic and glomerular hypertension
- Podocyte injury
- Proteinuria
- Progressive fibrosis

3.5. Podocyte Injury: Podocytes are terminally differentiated cells essential for maintaining the glomerular filtration barrier [35].

Mechanisms of Podocyte Damage:

- Foot process effacement
- Slit diaphragm protein loss (nephrin, podocin)
- Podocyte detachment and loss
- Podocyte hypertrophy and dedifferentiation

Consequences:

- Proteinuria
- Glomerulosclerosis
- Progressive GFR decline

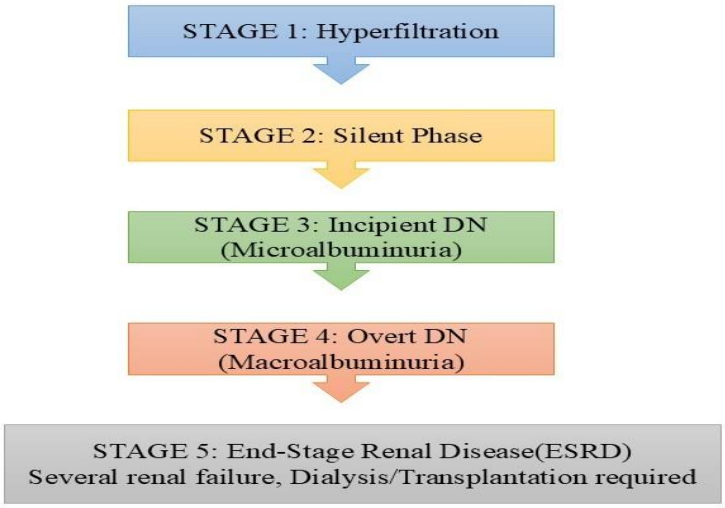


Figure 1: Pathophysiology of Diabetic Nephropathy.

4. PHARMACOLOGICAL EVIDENCE FOR *Allium* SPECIES IN NEPHROPROTECTION

4.1. Evidence from *Allium sativum* (Garlic)

4.1.1. Nephroprotective Effects in Diabetic Models: The protective effects of garlic on the kidneys in diabetic nephropathy models have been well documented [36].

Structural Protection: Al-Qattan et al. [37] showed that garlic and ginger were able to slow the progression of SN in STZ-induced diabetic rats. The serum glucose, creatinine, and blood urea nitrogen levels were significantly decreased, and the kidney histopathology improved with treatment.

Shiju et al. [38] reported that aqueous garlic extract was nephroprotective as it blocked the expression of VEGF and ERK-1. The diabetic rats in the garlic extract group had the following:

- Significantly reduced albuminuria
- Decreased mesangial expansion
- Attenuated glomerulosclerosis
- Reduced VEGF and ERK-1 immunohistochemical staining

Anti-glycation Effects: Al-Qattan et al. [37] have shown that garlic can reduce the glycation of the glomerulus in diabetic rats. Periodic acid-Schiff staining showed a decrease in the intensity and distribution of glycated proteins in renal corpuscles of the garlic-treated animals.

Oxidative Stress Modulation: Mariee and Abd-Allah [39] have studied the modulation of oxidative stress as well as nitric oxide production in the kidney tissue of diabetic nephropathy and have concluded that garlic is a NO production modulator and that it decreases the levels of oxidative stress markers in kidney tissues.

4.1.2. Key Bioactive Compounds and Their Mechanisms

Allicin: Arellano Buendía et al. [26] documented the immunomodulatory effects of allicin in diabetic nephropathy progression. The study demonstrated that allicin treatment:

- Reduced pro-inflammatory cytokine production
- Modulated immune cell infiltration
- Improved kidney function parameters
- Showed comparable efficacy to losartan in chronic kidney disease models

S-allyl cysteine (SAC): As the primary stable organosulfur compound in aged garlic extract, SAC has demonstrated significant therapeutic potential [22]. Key mechanisms include:

- Free radical scavenging activity
- Metal chelation
- Inhibition of lipid peroxidation
- Modulation of glutathione metabolism

Diallyl Disulfide (DADS): This compound has shown specific benefits for diabetic complications through:

- Activation of Nrf2 antioxidant response
- Inhibition of inflammatory cytokine production
- Improvement of mitochondrial function
- Enhancement of insulin sensitivity

4.2. Evidence from *Allium cepa* (Onion)

4.2.1. Nephroprotective Mechanisms: Pradeep et al. [40] demonstrated that dietary onion (3%) attenuates diabetic nephropathy through the suppression of glucose transporters (GLUT2, SGLT2) and the renin-angiotensin system. The study revealed:

- Reduced renal glucose reabsorption
- Attenuated angiotensin II-mediated injury
- Decreased podocyte damage
- Reduced leaching of renal enzymes

Ahmed et al. [41] reported hepato-nephroprotective effects of phenolic-rich extracts from red onion peels against CCl4-induced oxidative stress. The protection was attributed to:

- High quercetin content
- Strong antioxidant capacity
- Anti-inflammatory activity
- Preservation of antioxidant enzyme activities

4.2.2. Hypoglycemic and Metabolic Effects: Clinical studies have demonstrated the antidiabetic potential of onion. Eldin et al. [42] reported hypoglycemic effects of red onion in Type 1 diabetic patients, with significant reductions in fasting blood glucose following consumption.

Onion's hypoglycemic, antioxidant, and hepatoprotective effects in alloxan diabetic rabbits have been evaluated by Ogunmodede et al. [43], and they showed that:

- Significant blood glucose reduction
- Improved serum lipid profiles
- Enhanced antioxidant enzyme activities
- Reduced liver enzyme leakage

4.3. Comparative Analysis of *Allium* Species: Table 2 provides a comparative overview of the phytochemical composition and pharmacological activities of major *Allium* species relevant to diabetic nephropathy.

Table 2: Comparative Phytochemical and Pharmacological Profile of *Allium* Species.

Species	**Key Phytochemicals**	**Nephroprotective Evidence**	**Notable Characteristics**
A. sativum (Garlic)	High allicin, SAC, DADS, DATS, Flavonoids	Extensive in vitro and in vivo studies; reduced proteinuria, improved kidney histology, anti-inflammatory	Most researched; strong antimicrobial activity; pungent odor
A. cepa (Onion)	High quercetib glycosides, isoalliin, phenolic acids	Moderate evidence; suppression of glucose transporters, antioxidant protection	Milder flavor; high flavonoid content especially in outer scales

A. ampeloprasum (Leek)	Moderate allicin, high steroidal saponins, kaempferol, alliin	Limited evidence; direct related species data suggestive	Milder than garlic; unique steroidal saponin content; underexplored
A. ursinum (Wild garlic)	High alliin, methiin, flavonoids	Limited specific studies on nephroprotection	Native to Europe; distinct aroma profile
A. fistulosum (Welsh onion)	Fistulosides, quercetin, organosulfur compounds	Antifungal saponins studied; limited nephroprotection data	Popular in Asian cuisine; unique saponin profile

5. MECHANISM OF NEPHROPROTECTION: POTENTIAL ROLE OF *Allium ampeloprasum* CONSTITUENTS

Considering the phytochemical profile of *Allium ampeloprasum* and known mechanisms of related *Allium* species, we suggest a multi-targeted concept for nephroprotection against diabetic nephropathy.

5.1. Antioxidant Mechanisms

5.1.1. Nrf2/Keap1/ARE Pathway Activation: Nuclear factor erythroid 2-related factor 2 (Nrf2) is a master antioxidant defence regulator in cells [44]. Compounds present in *Allium ampeloprasum* that may activate this pathway include:

S-allyl cysteine (SAC):

- Induces nuclear translocation of Nrf2
- Upregulates antioxidant response element (ARE)-driven genes
- Enhances expression of glutathione S-transferases (GSTs)
- Increases NAD(P)H:quinone oxidoreductase 1 (NQO1) activity

Diallyl disulfide (DADS):

- Modifies Keap1 cysteine residues, preventing Nrf2 degradation
- Induces phase II detoxification enzymes
- Enhances cellular glutathione levels

Quercetin and kaempferol:

- Direct Nrf2 activators through phosphorylation-mediated mechanisms
- Modulation of mitogen-activated protein kinases (MAPKs)
- Enhanced expression of heme oxygenase-1 (HO-1)

5.1.2. Direct Free Radical Scavenging: The phenolic compounds and organosulfur compounds in *Allium ampeloprasum* possess direct antioxidant capacity:

- **Hydrogen atom donation**: Neutralizing hydroxyl radicals (·OH) and peroxynitrite (ONOO−)
- **Electron donation**: Scavenging superoxide anion ($O_2 \cdot -$)
- **Metal chelation**: Binding transition metals (Fe2+, Cu2+) that catalyze Fenton reactions
- **Lipid peroxidation inhibition**: Protecting membrane phospholipids from oxidative damage

5.1.3. Mitochondrial Protection: Organosulfur compounds may protect mitochondrial function through:

- Preservation of mitochondrial membrane potential
- Inhibition of mitochondrial ROS production
- Enhancement of mitochondrial biogenesis (via PGC-1α activation)
- Promotion of mitophagy for clearance of damaged mitochondria

5.2. Anti-Inflammatory Mechanisms

5.2.1. NF-κB Pathway Inhibition: The transcription factor NF-κB plays a central role in DN-associated inflammation [5]. *Allium ampeloprasum* constituents may inhibit this pathway through:

Allicin and related compounds:

- Inhibition of IκB kinase (IKK) phosphorylation
- Prevention of NF-κB nuclear translocation
- Reduced expression of adhesion molecules (ICAM-1, VCAM-1)
- Decreased production of pro-inflammatory cytokines

Quercetin:

- Inhibition of NF-κB DNA binding
- Modulation of upstream kinases (IKK, PI3K)
- Synergistic effects with other anti-inflammatory compounds

5.2.2. NLRP3 Inflammasome Modulation: Targeting the NLRP3 inflammasome represents a promising therapeutic strategy for DN [33]. Potential mechanisms include:

- Inhibition of NLRP3 oligomerization
- Blockade of ASC speck formation
- Reduction of caspase-1 activation
- Decreased IL-1β and IL-18 maturation

5.2.3. Cytokine and Chemokine Modulation: *Allium ampeloprasum* constituents may reduce inflammatory mediator production:

- **TNF-α inhibition**: Reduced gene expression and protein secretion
- **IL-6 suppression**: Modulation of JAK/STAT signaling
- **MCP-1 reduction**: Decreased monocyte recruitment to kidney tissues
- **TGF-β modulation**: Context-dependent regulation of fibrotic signaling

5.3. Anti-Fibrotic Mechanisms

5.3.1. TGF-β/Smad Pathway Modulation: Transforming growth factor-β represents the primary driver of renal fibrosis. Potential inhibitory mechanisms include:

Direct TGF-β inhibition:

- Blockade of TGF-β receptor binding
- Inhibition of Smad2/3 phosphorylation
- Enhancement of inhibitory Smad7 expression

Epithelial-mesenchymal transition (EMT) prevention:

- Maintenance of E-cadherin expression
- Inhibition of α-SMA induction
- Preservation of epithelial phenotype in tubular cells

5.3.2. Extracellular Matrix Regulation

- Reduced collagen I and III synthesis
- Inhibition of fibronectin expression
- Modulation of matrix metalloproteinase (MMP) activity
- Reduced tissue inhibitor of metalloproteinase (TIMP) expression

5.4. Anti-Glycation and Metabolic Effects

5.4.1. AGE Formation Inhibition: *Allium ampeloprasum* constituents may reduce AGE formation through:

- **Carbonyl trapping**: Quercetin and other flavonoids react with reactive carbonyl species
- **Metal chelation**: Preventing metal-catalyzed glycation reactions
- **Antioxidant effects**: Reducing oxidative pathways of AGE formation
- **Amadori product inhibition**: Blocking early glycation reactions

5.4.2. RAGE Expression Modulation: The receptor for AGEs (RAGE) is the main mediator of the toxic effects of advanced glycation end products. Potential interventions include:

- Downregulation of RAGE gene expression
- Competitive inhibition of AGE-RAGE binding
- Blockade of downstream signaling pathways

5.4.3. Glucose Homeostasis Improvement: Organosulfur compounds may improve metabolic control through:

- Enhanced insulin secretion from pancreatic β-cells
- Improved peripheral insulin sensitivity
- Increased glucose uptake in skeletal muscle
- Reduced hepatic glucose production
- Inhibition of intestinal glucose absorption (α-glucosidase inhibition)

5.5. Endothelial and Hemodynamic Protection

5.5.1. Nitric Oxide Bioavailability: Hydrogen sulfide (H_2S) donors from Allium-derived compounds enhance NO bioavailability through:

- Stabilization of eNOS cofactors (BH4)
- Reduction of eNOS uncoupling

- Scavenging of ROS that degrade NO
- Direct H2S-mediated vasodilation

5.5.2. RAAS Modulation: Potential effects on the renin-angiotensin-aldosterone system include:

- ACE inhibitory activity (peptide fractions)
- AT1 receptor modulation
- Aldosterone secretion inhibition
- Improved intraglomerular hemodynamics

6. PROPOSED MECHANISTIC FRAMEWORK FOR *Allium ampeloprasum* IN DIABETIC NEPHROPATHY

6.1. Multi-Targeted Action Model

Given the phytochemical profile and based on the findings in other *Allium* species, we suggest that the nephroprotective activity of *Allium ampeloprasum* might be mediated by multiple modes of action in the main pathophysiological mechanisms of DN (Figure 2).

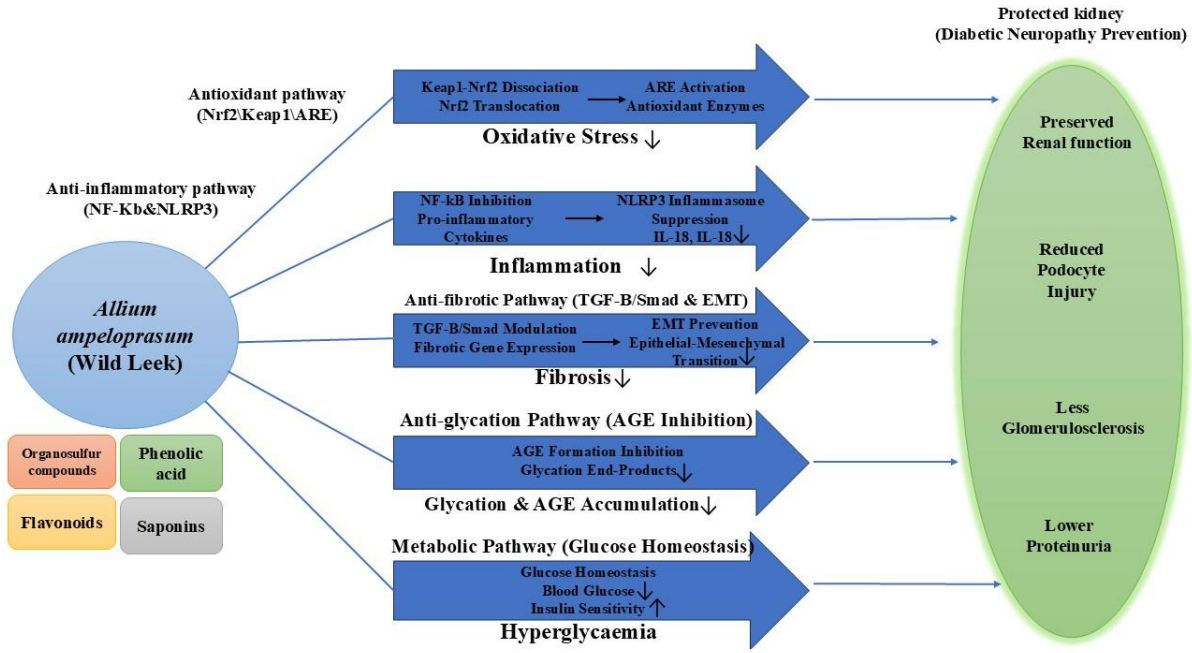


Figure 2: Multi-Targeted Nephroprotective Mechanism of *Allium ampeloprasum* Constituents in Diabetic Nephropathy.

6.2. Integration with Current Therapeutic Paradigms

The potential integration of *Allium ampeloprasum* into current DN management strategies should be considered in the context of:

- **Complementary to RAAS inhibition**: Different mechanisms may provide additive benefits.
- **Adjunct to SGLT2 inhibitors**: Potential synergy in glucose-lowering and kidney protection.
- **Combination with GLP-1 RAs**: Complementary metabolic and protective effects.
- **Supportive to lifestyle interventions**: Natural product approach aligning with dietary modifications.

7. CONCLUSION

Allium ampeloprasum is a potential and yet understudied target for the management of diabetic nephropathy. The molecular basis of multi-targeted nephroprotection is its rich phytochemical profile, including organosulfur compounds, flavonoids, saponins, and phenolic acids with their antioxidant, anti-inflammatory, anti-fibrotic, and metabolic properties. Considering the proven effectiveness of the related species of *Allium*, such as garlic and onion, in experimental diabetic nephropathy models and the commonality and distinctiveness of the constituents of *Allium ampeloprasum*, further research should be pursued. The biological plausibility and safety profile provide reason for moving forward with thorough preclinical and clinical investigation; at present, evidence is mostly mechanistic and extrapolated. However, further studies should focus on direct assessment of *Allium ampeloprasum* in DN models, standardization of the profile of bioactive compounds, and the design of clinical trials to demonstrate efficacy, dosage, and their incorporation in the existing therapeutic approaches. *Allium ampeloprasum* has great potential for being a safe, natural, complementary medicine for the treatment of diabetic nephropathy, which has great potential to develop an evidence-based phytotherapy.

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