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THE EFFECT OF MULBERRY IN RENAL, INFLAMMATION, OXIDATIVE STRESS AND GUT MICROBIOTA MARKERS: A REVIEW

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Abstract

Morus alba L. (white mulberry) is a multifunctional plant traditionally used in Asian medicine, increasingly recognized for its rich phytochemical profile and potential therapeutic applications. Its leaves, fruits, and roots are rich in bioactive compounds such as flavonoids, phenolic acids, alkaloids and polysaccharides, which exhibit antioxidant, anti-inflammatory, antidiabetic, and hypolipidemic activities. Chronic kidney disease (CKD), a growing global health concern, is closely associated with metabolic risk factors including diabetes, hypertension, obesity, and dyslipidemia. Recent studies suggest that *Morus alba* may contribute to renal protection by modulating these risk factors and acting directly on renal structures through anti-inflammatory, antioxidant, and gut microbiota-mediated mechanisms. This review **aims** to summarize the current scientific evidence regarding the potential nephroprotective effects of *Morus alba*, integrating data from in vitro, animal, and human studies. The findings highlight the role of *Morus alba* in improving metabolic parameters, attenuating renal inflammation and oxidative stress, and modulating the gut–kidney axis. Although promising, further clinical research is required to clarify its mechanisms, safety, and long-term effectiveness as a complementary dietary strategy for the prevention and management of CKD.

Resumen

Morus alba L. (morera blanca) es una planta multifuncional utilizada tradicionalmente en la medicina asiática y reconocida cada vez más por su perfil fitoquímico y sus posibles aplicaciones terapéuticas. Sus hojas, frutos y raíces son ricos en compuestos bioactivos como flavonoides, ácidos fenólicos, alcaloides y polisacáridos, los cuales presentan actividades antioxidantes, antiinflamatorias, antidiabéticas e hipolipemiantes. La enfermedad renal crónica (ERC), un problema creciente de salud global, está estrechamente relacionada con factores de riesgo metabólicos como la diabetes, hipertensión, obesidad y dislipemia. Estudios recientes sugieren que *Morus alba* puede contribuir a la protección renal mediante la modulación de estos factores de riesgo y a través de efectos directos sobre las estructuras renales, mediante mecanismos antioxidantes, antiinflamatorios y mediados por la microbiota intestinal. Esta revisión tiene como **objetivo** resumir la evidencia científica actual sobre los posibles efectos nefroprotectores de *Morus alba*, integrando resultados de estudios in vitro, en animales y en humanos. Los hallazgos destacan su papel en la mejora de parámetros metabólicos, la atenuación del estrés oxidativo e inflamación renal y la modulación del eje intestino–riñón. A pesar de sus prometedores efectos, se requieren más estudios clínicos para esclarecer sus mecanismos de acción, seguridad y eficacia a largo plazo como estrategia dietética complementaria en la prevención y manejo de la ERC.

1. Introduction

Chronic kidney disease (CKD) is a global health crisis, affecting approximately 9–13% of the global population, and over 25% of individuals aged 60 and older, with many cases likely underdiagnosis [1]. It is more prevalent in men and particularly common among individuals with comorbid conditions like obesity, hypertension, dyslipidemia, diabetes, and polypharmacy, where prevalence rates can reach 35–40% [2]. The burden of CKD is exacerbated by its high morbidity and mortality, particularly due to cardiovascular disease, which places a significant strain on healthcare systems [1,2]. CKD accounts for an estimated 7.6% of global mortality [1] and is projected to become one of the top five causes of years of life lost by 2040 [3]. In Spain, CKD affects around 15% of the population, surpassing the global average [4].

CKD is classified into six stages (G1–G5) based on estimated glomerular filtration rate (eGFR) thresholds and/or albuminuria levels (A1–A3) [5]. Both eGFR reduction and albuminuria are strong predictors of cardiovascular events and overall survival, and their coexistence considerably increases risk [6]. Among the stages, G3—subdivided into G3a and G3b (eGFR 30–59 mL/min/1.73 m^2)—is the most prevalent, representing over 90% of all CKD cases [7]. This stage increases the likelihood of cardiovascular complications and progression to end-stage renal disease (ESRD), requiring costly treatments such as dialysis or kidney transplantation, profoundly impacting patient well-being. Therefore, early preventive and therapeutic interventions are essential [2].

Current treatment strategies primarily focus on controlling modifiable risk factors through lifestyle changes, pharmacological therapy, and early diagnosis. Among these, nutritional management is a cornerstone in delaying CKD progression and improving patient outcomes [8,9]. Nutritional requirements vary across CKD stages; however, dietary interventions often become overly restrictive, particularly in stages G4–G5, and sometimes even in earlier stages [10]. Traditional guidelines recommend limiting protein, sodium, potassium and phosphorus intake. This often leads to the avoidance of health-promoting foods such as vegetables, fruits, legumes, and nuts due to fears related to their mineral content [10]. This paradoxically drives patients away from healthy dietary patterns and may worsen CKD outcomes [11].

To address this paradox, the 2020 KDOQI guidelines recommend plant-based dietary patterns such as the Mediterranean and DASH diets for patients with CKD stages 1 through 5 [10]. These diets emphasize whole foods including vegetables, fruits, whole grains, legumes, and nuts, offering multiple metabolic and cardiovascular benefits. A growing body of evidence indicates that such diets may not only reduce CKD progression, but also lower mortality risk and improve renal outcomes even in advanced stages [12-15].

Among various nutritional approaches, plant-derived compounds have attracted attention for their potential renoprotective effects. One such plant is *Morus alba* (white mulberry), traditionally used in Asian medicine and rich in flavonoids, anthocyanins, phenolic acids, polysaccharides, and the alkaloid 1-deoxynojirimycin (DNJ) [16]. These bioactive compounds may provide antioxidant, anti-inflammatory, antidiabetic, and nephroprotective actions, as supported by both in vitro and in vivo studies.

Given its diverse phytochemical profile, *Morus alba* has been studied for its potential nephroprotective effect. Experimental evidence suggests that extracts from different parts of the plant may contribute to improvements in metabolic parameters and renal outcomes across various disease models [16]. These potential benefits may be related to a combination of antioxidant, anti-inflammatory, antidiabetic, and lipid-lowering effects, as well as modulation of pathways implicated in kidney damage progression [17]. Among these mechanisms, the regulation of inflammatory responses has been particularly emphasized. Chronic low-grade inflammation is a key driver in the progression of CKD, contributing to structural damage such as glomerular sclerosis and interstitial fibrosis. Preclinical studies have reported that *Morus alba* extracts could downregulate the expression of pro-inflammatory cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), while promoting anti-inflammatory mediators such as interleukin-6 (IL-6) [18].

Furthermore, *Morus alba* has attracted scientific interest for its potential antioxidant capacity, which may be relevant in the context of chronic kidney disease. Its content in flavonoids and polyphenols has been associated with possible protective effects against oxidative stress [19]. Although mechanistic details remain under investigation, these compounds have been linked to improvements in redox balance and reductions in oxidative damage markers in animal models [20]. Such properties suggest that *Morus alba* could be considered a potential candidate for supporting renal function in conditions associated with oxidative stress [20].

The gut–kidney axis has also emerged as a relevant pathway in the progression of CKD. Dysbiosis, or imbalance in gut microbiota composition, is increasingly recognized as a contributing factor to systemic inflammation and uremic toxin production. Preliminary evidence suggests that *Morus alba* may influence gut microbial composition in beneficial ways [21,22]. In animal models, supplementation with *Morus alba* extracts has been associated with changes in gut bacterial populations and metabolic activity, with potential implications for intestinal and systemic homeostasis [22]. While more clinical research is needed, these findings open the possibility that *Morus alba* could indirectly support kidney health through modulation of the gut microbiota [22].

However, the renoprotective mechanisms of *Morus alba* remain poorly understood. These likely involve interactions with oxidative stress, systemic inflammation, and gut microbiota dysbiosis.

Clarifying these mechanisms is crucial to support its potential role as a complementary therapy to improve renal function.

Objective

Thus, this review aims to summarize the current scientific evidence on the effects of *Morus alba* on kidney health, with particular emphasis on its interaction with inflammation, oxidative stress, and gut microbiota as the key underlying mechanisms. By synthesizing data from both animal and human studies, this work seeks to explore the potential of *Morus alba* as a complementary dietary approach for the prevention and management of chronic kidney disease.

2. Methodology

2.1. Information sources and Search strategy

A comprehensive review of the literature published from the earliest available online indexing year to February 2025 was conducted by searching the MEDLINE-PubMed database and hand-searching the reference lists of the retrieved papers. With the use of Title/Abstract and keywords, 4 search subsets were used: the first subset included *Morus alba*-related keywords [*Morus alba*] OR [mulberry OR mulberry extract OR mulberries]; the second subset covered renal-related keywords [Kidney Diseases OR Renal Insufficiency OR renal disease OR kidney failure OR renal failure OR proteinuria OR Glomerular Filtration Rate OR egfr OR gfr OR kidney function OR chronic kidney disease OR Albuminuria OR cystatin c OR uacr OR albuminuria creatinine ratio OR acr]; the third subset involved inflammation and oxidative stress-related keywords [inflammation OR oxidative stress OR cytokines OR proinflammatory cytokines OR anti-inflammatory agents]; and the fourth subset included microbiota-related keywords [microbiome OR gut microbiome OR microbiote OR microbiota OR gastrointestinal microbiota OR gastrointestinal microbiome OR mycobiome]. The search was limited to studies published in English.

2.2. Eligibility criteria

The inclusion criteria of the literature were based on the PICO guidelines for evidence -based medicine (participants, interventions/exposures, comparators, outcomes and study design) to identify studies suitable for inclusion. The inclusion criteria were as follows: 1) participants: adults (>18 years old); 2) exposure: any form of *Morus alba* (Mulberry's) supplementation or extract; 3) outcomes of interest: renal pathology, microbiota, inflammation, or oxidative stress markers.

Exclusion criteria included: 1) studies with no mulberry exposure; 2) reviews, comments, editorials, or meeting abstracts. Other criteria were not applied due to the limited available evidence.

3. Chemical composition of *Morus alba*

Morus alba L., commonly known as white mulberry, is a plant that has garnered increasing scientific attention due to its rich phytochemical profile and broad spectrum of bioactivities. Different parts of the plant—leaves, fruits, bark, and roots—contain a variety of bioactive compounds, including flavonoids, phenolic acids, alkaloids, anthocyanins, polysaccharides, phytosterols, and other metabolites, which are responsible for its multiple pharmacological properties [17,23].

Among the most extensively studied phytochemicals in *Morus alba* are flavonoids, which are found abundantly in both the leaves and fruits. Notable compounds such as quercetin, kaempferol, rutin, and morin are known for their potent antioxidant, anti-inflammatory, and cytoprotective effects [23]. In addition to these common flavonoids, the plant also contains unique prenylated flavonoids, including kuwanon G, morusin, and sanggenon C, mainly found in the root bark. These have demonstrated antimicrobial, anticancer, and neuroprotective properties in various in vitro and in vivo studies [17,23]. Other flavonoid, such as chalcones (e.g., morachalcone A, morachalcone B, and chalcomoracin), are also considered promising bioactive molecules due to their anti-inflammatory and antimicrobial actions [23].

Phenolic acids are another important group of compounds found in *Morus alba*, including chlorogenic acid, caffeic acid, gallic acid, ferulic acid, and p-coumaric acid, which are predominantly found in the leaves and fruits [17,23]. These molecules function as efficient free radical scavengers, reducing oxidative stress and modulating inflammatory pathways [24]. Their presence supports the traditional use of *Morus alba* in treating chronic diseases related to oxidative damage [17].

A distinctive chemical constituent of *Morus alba* is the alkaloid 1-deoxynojirimycin (DNJ), which is primarily concentrated in the leaves. DNJ acts as a potent α-glucosidase inhibitor, delaying carbohydrate digestion and absorption, thereby improving postprandial glycemic control [23]. This mechanism underpins the antidiabetic applications of *Morus alba* in both traditional and modern therapeutic contexts. Other alkaloids, such as calystegines B2 and C1, found in the root bark, have also been reported to inhibit glycosidase activity, further enhancing the plant's hypoglycemic potential [17].

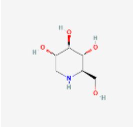
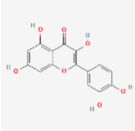
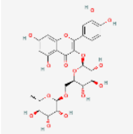
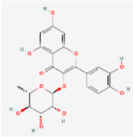
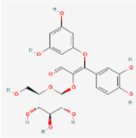
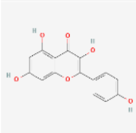
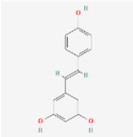
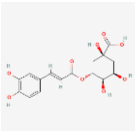
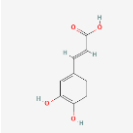
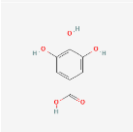
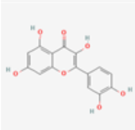
The fruits of *Morus alba* are a rich source of anthocyanins, particularly cyanidin-3-glucoside and cyanidin-3-rutinoside, which contribute to the deep coloration of ripe berries [23]. These compounds exhibit strong antioxidant activity and are implicated in cardiovascular and neuroprotective effects [25]. The anthocyanin content increases with fruit maturity, and its bioactivity is influenced by environmental conditions and harvesting time [26].

Polysaccharides extracted from different parts of the plant, including leaves and fruits, have shown immunomodulatory and antioxidant properties. These complex carbohydrates enhance innate immune responses and protect cells against oxidative damage [23]. Although the precise molecular mechanisms remain under investigation, they represent a promising group of bioactive macromolecules in *Morus alba* [17].

Additionally, the plant contains various fatty acids and phytosterols. The predominant fatty acids found in the seeds and fruits include linoleic acid, oleic acid, and palmitic acid, which contribute to lipid metabolism regulation and cardiovascular protection [17]. Phytosterols such as β-sitosterol further supports its hypocholesterolemic properties [23]. Furthermore, other bioactive secondary metabolites such as coumarins, stilbenes (e.g., resveratrol), terpenoids, and lectins have been identified in different plant parts and are associated with anti-inflammatory, antimicrobial, and metabolic regulatory effects [27].

Overall, the chemical complexity of *Morus alba* aligns with its broad therapeutic potential. The synergistic interaction among its various phytochemicals likely contributes to its effectiveness in modulating multiple physiological pathways, including oxidative stress, inflammation, glucose metabolism, and gut microbiota composition. Given this multifaceted phytochemical profile, *Morus alba* remains an key focus of current research aimed at identifying natural compounds with clinical applicability.

Table 1. Main bioactive compounds identified in *Morus alba* and their reported biological activities.

No.	***Category***	***Compound***	***Plant Part***	***Main Bioactivity***	***Molecular Formula***	***Structure (link)***	***Reference***
1	Alkaloid	DNJ (1-Deoxynojirimycin)	Leaves	α-glucosidase inhibitor, hypoglycemic	$C_6H_{13}NO_4$		[28]
2	Flavonoid	Quercetin	Leaves, fruits	Antioxidant, anti-inflammatory, cytoprotective	$C_{15}H_{10}O_7$		[20]
3	Flavonoid	Rutin	Leaves, fruits	Antioxidant, metabolic regulation	$C_{27}H_{30}O_{16}$		[26]
4	Flavonoid	Quercitrin	Leaves	Antioxidant, anti-inflammatory	$C_{21}H_{20}O_{11}$		[29]
5	Flavonoid	Isoquercitrin	Leaves	Antioxidant, anti-inflammatory	$C_{21}H_{20}O_{12}$		[30]
6	Flavonoid	Kaempferol	Leaves, fruits	Antioxidant, anti-inflammatory	$C_{15}H_{10}O_6$		[30]
7	Phenol	Resveratrol	Fruits	Antioxidant, anti-inflammatory, metabolic regulation	$C_{14}H_{12}O_3$		[29]
8	Phenolic acid	Chlorogenic acid	Leaves, fruits	Antioxidant, anti-inflammatory	$C_{16}H_{18}O_9$		[24]
9	Phenolic acid	Caffeic acid	Leaves	Antioxidant, anti-inflammatory	$C_9H_8O_4$		[24]
10	Phenolic acid	Gallic acid	Leaves, fruits	Antioxidant	$C_7H_6O_5$		[31]
11	Anthocyanin	Cyanidin-3-glucoside	Fruits	Antioxidant, cardiovascular protection	$C_{21}H_{21}O_{11}^+$		[32]

4. *Morus alba* and principal risk factors for renal dysfunction

4.1. Diabetes and hyperglycemia

Diabetes mellitus is a chronic metabolic disorder characterized by elevated blood glucose levels due to impaired insulin secretion, resistance to insulin, or both [33]. Type 2 diabetes mellitus (T2DM), the most prevalent form, is a significant risk factor for the development of CKD, primarily through prolonged hyperglycemia that causes glomerular and tubular damage via hemodynamic, oxidative, and inflammatory pathways [34].

Morus alba (white mulberry) has shown promising hypoglycemic activity, largely attributed to its content of 1-deoxynojirimycin (DNJ), a potent competitive inhibitor of α-glucosidase that slows carbohydrate digestion and glucose absorption, thereby reducing postprandial glycemic peaks [35]. In both preclinical and clinical studies, *Morus alba* leaf and root extracts have demonstrated the ability to maintain β-cell function, reduce fasting blood glucose, HbA1c, and insulin levels [34,36].

Beyond enzyme inhibition, *Morus alba* enhances insulin sensitivity and modulates glucose transporter expression, particularly GLUT4, improving peripheral glucose uptake through AMPK activation [37,38]. These effects contribute not only to glycemic control but also to renal protection, as chronic hyperglycemia promotes oxidative stress, advanced glycation end-products (AGEs), and inflammation—key mediators of diabetic nephropathy [34].

An experimental study in streptozotocin-induced diabetic rats revealed that *Morus alba* polysaccharides exhibit hypoglycemic activity by significantly reducing serum insulin and glucose. These findings suggested that *Morus alba* improved insulin sensibility and protected the pancreas [39]. Furthermore, histopathological benefits in pancreas tissues were observed. In human trials, *Morus alba* supplementation improved postprandial glycemic response and reduced HbA1c in individuals with impaired glucose tolerance, supporting its utility as a dietary adjunct in prediabetes and T2DM management [40]. This same trial also showed an improvement in insulin resistance after the 12-week intervention.

Given the strong association between hyperglycemia and renal deterioration, incorporating *Morus alba* into dietary strategies may offer therapeutic value for preventing or delaying diabetic kidney complications.

4.2. High blood pressure

Hypertension, is a major risk factor for heart disease, stroke, and is well-established as a key contributor to the onset and progression of CKD [41]. It occurs when the force of blood against artery walls remains consistently high, often due to poor diet, lack of exercise, or genetic factors. Hypertension is the second cause of end-stage renal disease, after diabetes [42]. Persistent high blood pressure leads to glomerular hyperfiltration, endothelial dysfunction, fibrosis, vascular remodeling, and eventual nephron loss [43]. Recently, natural remedies, such as *Morus alba* have gained interest for their potential role in managing hypertension.

Studies have shown that *Morus alba* can improve vascular health because of the presence of GABA in water extracts from *Morus alba* leaves [44]. *Morus alba* also helps reduce oxidative stress and inflammation, both of which contribute to hypertension. Some research suggests that mulberry extracts can inhibit the angiotensin-converting enzyme (ACE), which plays a crucial role in blood pressure regulation, similar to how pharmaceutical ACE inhibitors work [44].

Morus alba has demonstrated antihypertensive effects in experimental models, particularly in high-fat diet-induced hypertensive rats. Administration of mulberry leaf extract significantly lowered systolic and diastolic blood pressure, likely via enhancement of nitric oxide bioavailability and attenuation of oxidative stress [45]. However, the mechanisms responsible for blood pressure reduction in chronic diabetic rats remain unclear.

Although human clinical data on *Morus alba* for hypertension are currently limited, existing research suggests that its inclusion in dietary strategies could benefit patients with CKD and comorbid hypertension.

4.3. Obesity

Obesity is a chronic, multifactorial condition characterized by excessive adipose tissue accumulation, which increases the risk of developing a wide range of comorbidities, including type 2 diabetes, cardiovascular disease, metabolic bone disorder, anemia, and acid-base and fluid imbalance [33]. Importantly, obesity also significantly contributes to the development and progression of CKD [46]. The mechanisms linking obesity to renal damage include glomerular hyperfiltration, increased renal plasma flow, insulin resistance, low-grade systemic inflammation, and ectopic lipid accumulation in renal tissues, which can lead to glomerular hiperfiltration and tubular injury [46,47].

In this context, *Morus alba* has emerged as a promising candidate for mitigating obesity-related metabolic disturbances through its complex composition of flavonoids, polyphenols, alkaloids (notably DNJ) and other bioactive compounds. In vivo studies in high-fat diet rats support its anti-obesity effects, with mechanisms involving both inhibition of adipocyte hypertrophy and reduced body weight gain [48].

In adipocyte cell lines such as 3T3-L1, *Morus alba* leaf extract significantly inhibited adipogenesis, fat accumulation, and the expression of adipogenesis-related factors [49]. These key factors included CCAAT/enhancer-binding protein alpha (C/EBPα) and peroxisome proliferator-activated receptor gamma (PPARγ), which are essential for initiation and maintenance of adipogenesis [49].

In animal models, particularly rodents subjected to high-fat diets, supplementation with *Morus alba* extracts has consistently resulted in reduced body weight gain, reduced blood glucose, decreased liver fat, fewer immature adypocytes, and improved histological features of liver steatosis [48,50]. Mechanistically, these effects could be attributed to the activation of AMP-activated protein kinase (AMPK), a cellular energy sensor that plays a central role in regulating lipid metabolism and energy homeostasis. Activation of AMPK by *Morus alba* leads to increased fatty acid oxidation, inhibition of lipogenesis, and improved mitochondrial function [50]. Additionally, anti-inflammatory effects in adipose tissue have been observed, including decreased expression of proinflammatory cytokines, which contribute to insulin resistance and metabolic dysfunction in obesity [48].

4.4. Dyslipidemia

Dyslipidemia refers to abnormal concentrations of lipids in the blood, including elevated levels of total cholesterol, low-density lipoprotein (LDL), and triglycerides, or reduced levels of high-density lipoprotein (HDL-C). It is a key component of the metabolic syndrome and a well-established risk factor for cardiovascular disease [51]. In the context of kidney health, dyslipidemia contributes to endothelial dysfunction, vascular calcification, and glomerular injury, thereby accelerating the progression of CKD [47]. Furthermore, some studies have shown a positive linear correlation between CKD and total cholesterol, triglycerides and LDL, as well as a negative correlation with HDL-C [52,53,54].

Morus alba has demonstrated consistent hypolipidemic effects by root or leaves extract in rats with high-fat diet-fed [55]. In animal studies, mulberry extracts have been shown to reduce total cholesterol, triglycerides, and LDL-C levels while increasing HDL-C [56,57]. Additionally, *Morus alba* has been found to significantly improve hepatic fatty degeneration [56]. Notably, *Morus alba* extract inhibits de novo synthesis and promote cholesterol elimination in rats in induced nonalcoholic fatty liver disease [58].

Clinical evidence also supports these findings. In a randomized, double-blind, placebo-controlled trial involving hyperlipidemic individuals, daily supplementation with *Morus alba* leaf extract for several weeks resulted in significant reductions in total cholesterol, LDL-C, and triglycerides, along with a modest increase in HDL-C levels [59]. A systematic review of studies on *Morus* species, including *Morus alba*, further corroborated the lipid-lowering effects observed in both human and animal models [60]. The antioxidant activity of *Morus alba* also contributes to cardiovascular protection by preventing LDL cholesterol oxidation—a key step in the development of atherosclerotic plaques—and by reducing markers of oxidative stress and inflammation.

5. Evidence about *Morus alba* and renal function

Recent experimental studies have demonstrated that *Morus alba* and its bioactive components exert direct protective effects on renal tissue, extending beyond their systemic impact on metabolic risk factors. These studies have been conducted in vitro, as well as in animals models and humans trials [61,62,63].

In a well-established model of renal fibrosis, *Sang-Bai-Pi* extract, along with its major component regiafuran C, suppressed the TGF-β/Smad and Wnt/β-catenin signaling pathways. This treatment reduced the expression of α-smooth muscle actin (α-SMA) and fibronectin, helping preserved renal tissue integrity and histological structure, highlighting its antifibrotic potential in CKD [61].

The administration of *Morus alba*-derived alkaloids (SZ-A) in a model of diabetic nephropathy resulted in improved glomerular morphology, including reduced blood urea nitrogen level (BUN) and serum creatinine levels. SZ-A also downregulated key profibrotic and inflammatory mediators such as TGF-β1, collagen IV, fibronectin, TNF-α, and IL-6, confirming its role in mitigating renal inflammation and fibrosis [62].

In another model of induced renal fibrosis mice, *Morus alba* leaf extract combined with chlorogenic acid reduced serum creatinine excretion and improved the urinary protein-to-creatinine ratio. This treatment preserved Bowman's capsule integrity, reduced tubular epithelial injury, and improved glomerular architecture, reinforcing its protective role against obstructive renal injury [64].

Additional studies in diabetic mice studies showed that *Morus alba* reduced urinary albumin levels and serum creatinine excretion compared with the control animals [65]. It also significantly increased total urine volume, urine flow, and creatinine clearance, while preventing oxidative stress-induced renal fibrosis [34,65]. These findings were accompanied by improvements in blood glucose levels and liver histopathological damage.

In a randomized controlled trial involving patients with diabetic nephropathy, *Morus alba* extract supplementation improved oxidative stress and inflammatory markers, including glutathione, malondialdehyde, and high-sensitivity C-reactive protein (hs-CRP) [63]. These results support the clinical potential of *Morus alba* in modulating factors contributing to the progression of diabetic kidney disease and underline the need for further research on its renal effects.

Altogether, these studies provide compelling evidence that *Morus alba* exhibits direct renoprotective mechanisms. By modulating fibrotic pathways (e.g., TGF-β signaling), reducing oxidative and inflammatory damage, preserving glomerular architecture, and improving biochemical markers of renal function, *Morus alba* emerges as a promising candidate in the management and prevention of CKD. Importantly, these effects appear not merely secondary to glycemic or lipid control but rather reflect targeted actions within renal tissue.

Table 2. Summary of Experimental and Clinical Evidence on the Renal Effects of Morus alba and Its Bioactive Components

Model / Study Type	***Main Renal Effect***	***Mechanism Involved***	***Reference***
HK-2 cells and male rats with induced renal fibrosis	▼ Renal fibrosis ▼ α-SMA and fibronectin expression	Inhibition of TGF-β/Smad and Wnt/β-catenin signaling	[61]
Male diabetic rats	▼ BUN ▼ Serum creatinine ▼ TGF-β1, collagen IV, fibronectin, TNF-α, IL-6	Downregulation of profibrotic and inflammatory cytokines; cytokine–NO modulation	[62]
Mice with induced renal fibrosis	▼ Serum creatinine ▼ Protein-to-creatinine ratio ▼ Tubular damage ▼ Glomerular injury	Activation of Nrf2/HO-1 and inhibition of NF-κB pathways	[64]
Streptozotocin-induced diabetic nephropathy mice	▼ Urinary albumin ▼ Serum creatinine ▲ 24-h urine volume and flow ▲ Creatinine clearance ▼ Oxidative stress-induced fibrosis	Antioxidant action via modulation of MDA and GSH levels	[65]
Diabetic mice	▼ Urinary microalbumin ▼ Renal fibrosis	TGF-β/Smad signaling pathway	[34]
Humans with diabetic nephropathy (RCT)	▼ Serum triglycerides ▼ hs-CRP ▼ Malondialdehyde (MDA) ▲ Glutathione	Improvement of oxidative stress and inflammatory biomarkers	[63]

The table includes in vitro assays, animal models, and human clinical trials assessing changes in renal function markers, structural integrity, and molecular signaling pathways. ▼ indicates a decrease; ▲ indicates an increase. Abbreviations: BUN, blood urea nitrogen; α-SMA, alpha-smooth muscle actin; TGF-β, transforming growth factor-beta; NO, nitric oxide; MDA, malondialdehyde; GSH, glutathione; hs-CRP, high-sensitivity C-reactive protein; PCR, protein-to-creatinine ratio.

6. Underlying mechanisms involved: inflammation, oxidative stress, and gut microbiota

Emerging studies have explored the role of *Morus alba* in the preserving kidney function, particularly in models of diabetic nephropathy and renal fibrosis. Current evidence emphasizes its direct renoprotective effects through mechanisms involving modulation of gut microbiota, attenuation of oxidative stress, and anti-inflammatory actions.

Mechanistic investigations in diabetic models have demonstrated that *Morus alba* modulates renal oxidative stress and inflammatory pathways—most notably by activating Nrf2-dependent antioxidant systems and downregulation of oxygen species (ROS)-producing enzymes [2]. Collectively, these findings support the nephroprotective potential of *Morus alba* in diabetic kidney disease and fibrosis. Its multifactorial effects—including antioxidant, anti-inflammatory, and antifibrotic actions—underscore its value as a promising candidate for complementary renal therapies, especially in metabolic and inflammatory conditions.

6.1. Antioxidant activity and oxidative stress regulation

Oxidative stress is a central pathological mechanism in the development and progression of chronic CKD, particularly in the context of metabolic disorders such as diabetes mellitus, obesity and hypertension. It is characterized by an excessive generation of reactive ROS that surpasses the neutralizing capacity of endogenous antioxidant systems, leading to cellular and molecular damage. At the renal level, this redox imbalance contributes to lipid peroxidation, oxidative modification of proteins, and DNA damage, which collectively promote glomerular and tubular injury, endothelial dysfunction, inflammatory responses, and interstitial fibrosis—hallmarks of CKD pathophysiology [19,31].

Morus alba has demonstrated notable antioxidant properties, largely attributed to its rich content of bioactive phytochemicals. Key compounds such as flavonoids (including quercetin, rutin, and isoquercitrin), anthocyanins, phenolic acids, and polysaccharides exert antioxidant effects via multiple mechanisms: direct scavenging of ROS, inhibition of lipid peroxidation, metal ion chelation, and enhancement of enzymatic antioxidant defenses [17,31]. Both in vitro and in vivo studies have consistently reported increased activity of major antioxidant enzymes—including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx)—following administration of *Morus alba* extracts [30,61].

Robust evidence from experimental models supports the antioxidant-mediated renoprotective effects of *Morus alba*. S Alanazi et al. [66], in a streptozotocin (STZ)-induced diabetic rat model, observed a significant reduction in renal malondialdehyde (MDA) levels and a joint increase in antioxidant enzyme activity upon administration of *Morus alba* extract, indicating an improvement in oxidative status. Similarly, Nguyen et al. [65] demonstrated that supplementation with mulberry leaf extract in mice subjected to a high-fat diet resulted in reduced oxidative damage and improved renal histopathological outcomes. These effects were mechanistically linked to activation of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway, a key regulator of antioxidant gene expression and phase II detoxification.

Beyond renal tissues, *Morus alba* has demonstrated systemic antioxidant effects. A recent pharmacological investigation reported that anthocyanins isolated from *Morus alba* enhanced intestinal epithelial barrier integrity and significantly reduced ROS and MDA levels in a murine colitis model, underscoring the systemic redox-modulating capacity of these compounds [67]. Additionally, *Morus alba* polysaccharides have been shown to attenuate oxidative stress in STZ-induced diabetic rats by increasing SOD, CAT, and GPx activities while reducing oxidative DNA damage [66]. These effects were further associated with the activation of the AMP-activated protein kinase (AMPK)/peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) signaling pathway, a critical regulator of mitochondrial biogenesis and metabolic homeostasis [37].

In summary, current evidence supports that *Morus alba* exerts antioxidant effects via both direct ROS neutralization and modulation of intracellular signaling pathways. These findings suggest that *Morus alba* may serve as a promising nutritional and therapeutic strategy for the prevention and mitigation of oxidative stress-induced renal damage, particularly in individuals with metabolic comorbidities that predispose to CKD.

6.2. Anti-inflammatory mechanisms

Chronic low-grade inflammation is a key driver in the development and progression of metabolic and renal diseases [1]. Recent studies have shown that *Morus alba* leaf extract significantly downregulates inflammatory cytokines such as TNF-α and IL-6 in diabetic models, leading to improved insulin sensitivity and reduced hepatic inflammation [68].

An in vivo study reported that aqueous extract of *M. alba* suppressed the TLR2/MyD88/NF-κB signaling pathway, thereby reducing systemic inflammation in high-fat diet-induced type 2 diabetic mice [69]. Moreover, polyphenols and polysaccharides from *M. alba* modulate the gut microbiota and reduce systemic inflammatory burden through microbiota–immune system interactions [22]. These anti-inflammatory effects may contribute to slowing the progression of chronic kidney disease by reducing renal inflammation and fibrosis [61].

Chronic low-grade inflammation is widely recognized as a major contributor to the initiation and progression of CKD, promoting structural damage such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis, which are closely associated with functional decline [19]. Elevated levels of inflammatory markers including TNF-α, IL-6, and C-reactive protein (CRP) have been associated with worse renal outcomes and higher cardiovascular risk among individuals with CKD [19].

Morus alba appears to possess bioactive compounds—such as flavonoids (e.g., quercetin, rutin), phenolic acids, and alkaloids like DNJ—that may exert anti-inflammatory effects relevant to renal health [16]. These compounds have been shown to modulate inflammatory signaling pathways, particularly nuclear factor kappa B (NF-κB) and mitogen-activated protein kinases (MAPKs), which are key regulators of cytokine expression [70].

Experimental studies suggest that *Morus alba* extracts could reduce the expression of pro-inflammatory mediators such as TNF-α, IL-6, and inducible nitric oxide synthase (iNOS) in both in vitro and in vivo models [70]. Additionally, the suppression of the NF-κB pathway observed in animal models may contribute to a reduced systemic inflammatory response, particularly under metabolic stress conditions such as obesity or diabetes [71]. These findings point to a potential for *Morus alba* in mitigating inflammation-associated renal damage by downregulating key pro-inflammatory signals and supporting a more favorable inflammatory profile.

Given the central role of inflammation in CKD progression, these anti-inflammatory properties suggest that *Morus alba* could represent a supportive strategy to counteract chronic inflammatory activity in renal tissue.

6.3. Modulation of gut microbiota

The gut–kidney axis is increasingly recognized as a key modulator of chronic kidney disease (CKD) progression. Dysbiosis, or the imbalance in gut microbiota composition, has been associated with increased production of uremic toxins, intestinal barrier dysfunction, and systemic inflammation, all of which contribute to renal injury and functional decline [21].

Morus alba contains bioactive compounds—such as polyphenols, flavonoids, and polysaccharides—that seem to interact with the gut microbiota in ways that may help restore microbial balance and reduce inflammatory and metabolic disturbances. In a study using obese mouse models, supplementation with *Morus alba* extract appeared to shift the microbial composition toward beneficial species, increase the abundance of short-chain fatty acid (SCFA)-producing bacteria, and improve energy expenditure [72]. Similar findings were reported by Li et al., who observed that a mixture of *Morus alba* polyphenols and fiber enhanced brown adipose tissue activity and simultaneously modulated the gut microbiota [22].

Recent findings suggest that *Morus alba* polyphenols and dietary fibers reshape the gut microbiota, increasing microbial diversity and abundance of beneficial genera such as *Lactobacillus* and *Akkermansia* [72]. These shifts in microbial communities were associated with reduced markers of inflammation and improved intestinal barrier function. The production of SCFAs, promoted by these changes, has been linked to improved mucosal integrity and regulation of immune signaling pathways. These effects may contribute indirectly to renal protection by limiting systemic inflammation and oxidative stress—both key contributors to CKD progression [22].

Although further studies are needed to confirm the nephroprotective role of microbiota modulation, current evidence suggests that *Morus alba* might act on the gut–kidney axis through microbiota-mediated mechanisms that support renal health, especially in individuals with metabolic disorders such as obesity or diabetes.

7. Conclusions and prospects

This narrative review provides a comprehensively synthesis to the current scientific evidence regarding the potential renoprotective effects of *Morus alba* (white mulberry), with special emphasis on its interaction with inflammation, oxidative stress, and gut microbiota—three interrelated mechanisms increasingly recognized as key drivers in the onset and progression of CKD. The evidence gathered suggests that *Morus alba*, owing to its diverse and bioactive phytochemical composition, exerts both direct and indirect benefits on renal health. These effects span a broad spectrum of metabolic and renal parameters, including improvements in glomerular structure, oxidative status, and inflammatory signaling, as well as modulation of pathways implicated in fibrosis and endothelial dysfunction.

A central finding of this review is the potential of *Morus alba* **to modulate major modifiable risk factors for CKD**, such as type 2 diabetes mellitus, sustained hyperglycemia, hypertension, dyslipidemia, and obesity. These comorbidities not only contribute to the onset of CKD but also exacerbate its progression and heighten the risk of cardiovascular events. Through a range of mechanisms—including α-glucosidase inhibition, enhancement of insulin sensitivity, reduction of systemic and renal inflammation, activation of mitochondrial biogenesis, and modulation of gut microbial composition—*Morus alba* emerges as a promising candidate for integrative and preventive strategies targeting CKD and its associated complications (see **Figure 1**).

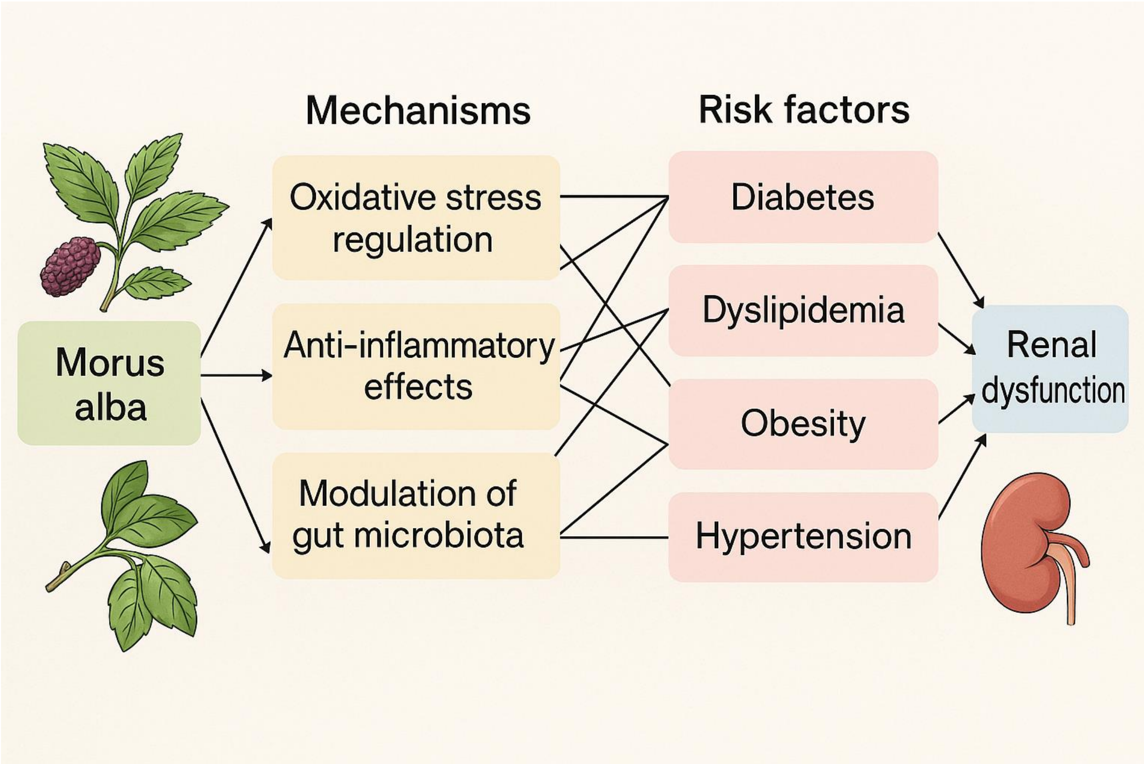


Figure 1. Mechanistic pathways and metabolic risk factors through which *Morus alba* may modulate renal dysfunction

The hypoglycemic effect of *Morus alba*, particularly through its main alkaloid 1-deoxynojirimycin (DNJ), has been well-documented in both preclinical and clinical settings. DNJ slows the digestion of carbohydrates, blunts postprandial glucose excursions, and reduces glycation-mediated tissue damage. In diabetic models, *Morus alba* extracts have shown the ability to attenuate hyperglycemia-induced oxidative stress and inflammation in renal tissues, thereby protecting glomerular and tubular structures. Additionally, studies have demonstrated improvements in serum creatinine and urea levels, decreased urinary albumin excretion, and modulation of fibrotic markers, supporting its potential nephroprotective effects.

Moreover, *Morus alba* displays **anti-obesity and antihypertensive properties**, which are of particular relevance given their close association with renal injury. Obesity contributes to glomerular hyperfiltration, lipotoxicity, and systemic inflammation, all of which compromise kidney function. Experimental data show that *Morus alba* can inhibit adipogenesis, enhance fatty acid oxidation via AMPK activation, and improve adipokine profiles (e.g., increasing adiponectin, reducing TNF-α). Its flavonoids and polyphenols have been shown to suppress key regulators of lipid synthesis, while also upregulating mitochondrial biogenesis and thermogenesis. In hypertensive models, *Morus alba* leaf extract has been shown to lower blood pressure through nitric oxide-mediated vasodilation and inhibition of the renin–angiotensin–aldosterone system (RAAS), with additional reductions in vascular oxidative stress and inflammation.

Another novel area of interest is *Morus alba*'s effect on the **gut–kidney axis**, a bidirectional communication system wherein gut dysbiosis exacerbates systemic inflammation, uremic toxin production, and renal deterioration. Preclinical studies indicate that *Morus alba* polyphenols and polysaccharides may increase microbial diversity and promote the growth of beneficial genera such as *Akkermansia* and *Lactobacillus*, while also enhancing the production of short-chain fatty acids (SCFAs). These changes have been associated with reduced intestinal permeability, lower endotoxemia, and improved systemic immune homeostasis—factors that collectively benefit renal health.

Despite this broad array of positive findings, it is important to critically examine the **limitations of the existing evidence**. First, the majority of data are derived from animal studies or in vitro experiments. While these models provide mechanistic insights, they cannot fully replicate the complexity of human pathophysiology. Human clinical trials are still scarce, and among those available, most focus on metabolic outcomes (e.g., glucose or lipid levels) rather than renal-specific endpoints. Moreover, the heterogeneity in extract composition (due to differences in plant part used, geographic origin, and preparation methods) poses challenges for reproducibility and dose standardization. The lack of longitudinal studies and the absence of large, placebo-controlled trials in CKD patients further limit our ability to draw definitive conclusions regarding clinical efficacy and safety.

In addition, the **bioavailability and pharmacokinetics** of *Morus alba* compounds remain insufficiently understood. While many of its bioactive constituents show promising activity in vitro, their absorption, metabolism, and distribution in human tissues require further investigation. Similarly, the potential for herb–drug interactions, especially in polymedicated CKD patients, must be carefully considered. Safety data, although reassuring in animal models, must be validated through long-term human trials, especially in vulnerable populations such as those with advanced renal insufficiency.

From a clinical standpoint, the integration of *Morus alba* into therapeutic strategies for CKD would ideally occur within **dietary frameworks** that align with nephrological guidelines. Plant-based diets such as the Mediterranean or DASH diets, which emphasize fruits, vegetables, legumes, whole grains, and healthy fats, are associated with improved renal outcomes and reduced cardiovascular risk. *Morus alba* could serve as a functional ingredient within these dietary patterns, offering an additional layer of metabolic and inflammatory modulation. Its use could be particularly valuable in early CKD stages or in patients with metabolic syndrome at risk of renal deterioration.

Looking forward, **future research** should focus on:

- Conducting randomized controlled trials in CKD patients to assess the efficacy of standardized *Morus alba* preparations on renal function markers (eGFR, albuminuria, cystatin C) and clinical outcomes.
- Exploring its role in combination therapies, including with antihypertensive or antidiabetic medications.
- Investigating microbiota-mediated mechanisms using metagenomics and metabolomics to better understand its impact on the gut–kidney axis.
- Evaluating the long-term safety and tolerability of chronic *Morus alba* supplementation.
- Defining optimal doses, treatment durations, and patient populations that may benefit the most.

In summary, *Morus alba* emerges as a multifunctional plant with potential to contribute to CKD prevention and management through its antioxidant, anti-inflammatory, antidiabetic, antihypertensive, hypolipidemic, and microbiota-modulating properties. While the current body of evidence is encouraging, it remains largely exploratory. Advancing from experimental promise to clinical application will require robust, multidisciplinary research efforts aimed at validating its efficacy, ensuring its safety, and establishing evidence-based guidelines for its use in nephrology.

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