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Effect Of Corn Silk Extract On Lithium Carbonate Induced Renal Toxicity In Rats

Miss. Dhanshri Nitin Patil*
Dr. Santosh B. Dighe
Prof. Rajashri . Ghogare Prof. Varsha. Tambe
Department Of Pharmacology,Pravara Rural College Of Pharmacy Loni

Abstract

This review manuscript examines the protective effects of corn silk extract (Zea mays) against lithium carbonate-induced renal toxicity in rats. Lithium carbonate, widely utilized as a mood stabilizer for bipolar disorder, has been associated with significant renal damage, manifesting as lithium-induced nephropathy. The review highlights the complex mechanisms underlying lithium nephrotoxicity, including oxidative stress, inflammation, and alterations in renal fluid balance, leading to chronic kidney disease. Given the potential adverse effects of long-term lithium use, there is an increasing interest in natural compounds that can mitigate these renal injuries. Corn silk, known for its diuretic, anti-inflammatory, and antioxidant properties, has shown promise in reducing kidney damage caused by nephrotoxic agents. The manuscript synthesizes existing research on the biochemical, histopathological, and molecular effects of corn silk extract, emphasizing its potential as a renoprotective agent. The findings suggest that corn silk extract could serve as a complementary treatment to reduce the risk of renal damage in patients undergoing prolonged lithium therapy. However, further clinical studies are required to validate its efficacy and safety in humans, as well as to explore optimal dosages and interactions with other nephrotoxic drugs. This review underscores the importance of investigating natural remedies in the context of pharmaceutical treatments, especially for vulnerable populations reliant on long-term medication.

Keywords : Corn Silk Extract ,Lithium Carbonate ,Nephrotoxicity , Oxidative Stress,Renal Protection

1. Introduction

Lithium carbonate, a mood stabiliser widely used for bipolar illness, has been linked to a variety of side effects, the most worrying of which is kidney damage[1].Lithium induced nephropathy has been observed in both humans and animal models, impairing renal function and causing long-term kidney damage. As a result, there is an increasing interest in developing protective medicines for lithium-induced renal injury[2]. For decades, lithium carbonate has served as the gold standard for treating bipolar disorder. Despite its efficacy, long-term lithium usage is frequently accompanied with a number of adverse effects, the most serious of which is kidney damage. Given the drug's continued use in bipolar disorder patients, lithium-induced nephropathy has emerged as a significant clinical concern. This nephropathy can manifest as renal tubular failure, glomerular damage, or, in severe cases, chronic kidney disease (CKD)[3]. The underlying processes of this toxicity are complicated, including oxidative damage, inflammation, and changes in renal fluid balance. Lithium salts, in the form of carbonate and, to a lesser extent, chloride, have previously been intensively studied for their reproductive and developmental toxicity. However, most studies did not follow regulatory criteria, did not include all of the parameters required for a thorough review, and were designed as exploratory research[3,4].

Long term usage of lithium could affect the functions of the kidney and cerebrum, in the light of fact they are the destinations where lithium has a tendency to accumulate. Generally, lithium toxicity had been

connected to disturbed cellular metabolism have suggested that the toxic effect of lithium on the cerebrum and kidney is due to its toxic effect on the endothelium of the blood vessels. Disturbed kidney function in patients taking lithium was reported as early as the 1970s. Checking of renal function is a standard care because of the known impact of lithium on the kidney. Lithium could influence tubular function resulting in nephrogenic diabetes insipidus[4]. Lithium could prompt tubulointerstitial nephritis which is characterized by the presence of cortical and medullary interstitial fibrosis and tubular atrophy. Different reviews suggested that the harmful impacts of lithium are caused by oxidative stress[5].

To address this issue, there has been growing interest in exploring natural compounds that may mitigate lithium induced renal toxicity. One such compound is corn silk (Zea mays), a natural product derived from the threads of the corn cob. Corn silk has been utilized in traditional medicine for its diuretic, anti inflammatory, and antioxidant properties.

Preliminary studies have shown that corn silk extract may exert renoprotective effects, reducing kidney damage caused by nephrotoxic agents, including lithium carbonate. This review aims to synthesize available research on the potential of corn silk extract in mitigating lithium induced renal toxicity in rats, focusing on biochemical, histopathological, and molecular findings[6].

Corn silk (Zea mays), the threads found on the ears of corn, has been traditionally used in various cultures as a remedy for ailments like urinary tract infections, kidney stones, and hypertension. Recent studies suggest that corn silk extract may have renoprotective properties, potentially mitigating the toxic effects of various nephrotoxic agents, including lithium carbonate[7]. This review aims to explore the role of corn silk extract in alleviating lithium induced renal toxicity in rats, focusing on its biochemical and histopathological effects. Corn silk, the long, thread like styles found on maize ears, contains a variety of bioactive compounds such as flavonoids, alkaloids, saponins, and polysaccharides, which are believed to possess antioxidant, anti inflammatory, and diuretic properties. This paper reviews the pharmacological effects of corn silk extract in counteracting renal toxicity induced by lithium carbonate in rats, focusing on its biochemical, histopathological, and molecular mechanisms. Corn silk has immense potential in future research and commerce in the food industry[7,8]. It can be consumed as a tea, weight-loss remedy, and as an additive to improve the color and texture of various food products, such as meatballs . Additionally, corn silk fodder (corn scraps) has been successfully used to enhance the nutritional quality of chicken meat. Corn silk flavonoids have potential health benefits due to their antioxidant activity resulting from different conjugation and a varying number of hydroxyl groups present in their chemical structure[9]. Therefore, flavonoids can act as reducing agents, hydrogen- or electron-donating species, and as reactive oxygen species (ROS) scavengers . Positive effects of antioxidants correspond to their free radical scavenging ability and with the ability to interact with basic cellular processes found that specific CS flavonoid glycosides showed significant total antioxidant activity, DPPH radical scavenging activity and reducing power reported that corn silks varieties (yellow, green, pink, and purple colored silks) contained more phenolic and flavonoid compounds and had stronger antioxidant activity in comparison to medicinal herbs[10].

Since ancient times, maize silk (*Stigma maydis*) has been applied to cure a broad range of illnesses, counting oedema, kidney stones, diabetes, hyperuricemia, obesity, and many more. Corn silk may be employed as an antioxidant in both food and medication since it has high antioxidant properties both *in vitro* and *in vivo*. Corn silk is thought to have therapeutic qualities because of its abundance of phytochemicals, including flavonoids, alkaloids, and saponins. The diuretic, antioxidant, anti inflammatory, and antihypertensive properties of these substances have been demonstrated, that help explain the benefits of corn silk in renal health[11,12].

2. Mechanism of Lithium Induced Renal Toxicity

Lithium carbonate is widely used in the treatment of bipolar disorder, but its prolonged use can lead to renal toxicity, manifesting as nephrogenic diabetes insipidus, reduced glomerular filtration rate (GFR), and renal tubular dysfunction. Lithium affects kidney function by
interfering with water and electrolyte balance, particularly through the inhibition of the renal tubular ability to concentrate urine. Over time, this leads to sodium retention, polyuria, and potential kidney damage[13]. Lithium is primarily used as a mood stabilizer for treating
bipolar disorder, but it has a narrow therapeutic window, meaning that its plasma levels must be closely monitored to avoid toxicity. Renal toxicity is one of the most common adverse effects of lithium, with approximately 20 30% of patients on long term lithium therapy
developing some form of renal impairment. Lithium induced nephropathy encompasses several physiological changes in the kidneys, including the inhibition of renal tubular
function and electrolyte imbalances[14].
At the cellular level, lithium causes oxidative stress, inflammatory reactions, and
mitochondrial malfunction, which contribute to renal cell death and necrosis. Histologically,
lithium toxicity is defined by glomerular destruction, tubular necrosis, and interstitial fibrosis. Understanding these pathways is crucial to designing protective medicines[15].

3. Pharmacological Properties of Corn Silk

Corn silk is rich in bioactive compounds, including flavonoids, saponins, alkaloids, and polysaccharides, all of which contribute to its medicinal properties. Corn silk is known for its diuretic, antioxidant, anti inflammatory, and antidiabetic activities, making it a promising candidate for protecting against nephrotoxic agents. Corn silk, the long, thread like styles found on corn cobs, has been used for centuries in folk medicine. It has a range of
pharmacological properties, which include antioxidant, anti inflammatory, diuretic, and
hepatoprotective activities. These properties make it a promising candidate for mitigating lithium induced renal toxicity[16].
Corn silk has been demonstrated in studies to have strong antioxidant capabilities that may help reduce oxidative stress in the kidneys. It also has anti-inflammatory properties, which
may reduce inflammation linked with kidney injury. Furthermore, maize silk contains modest diuretic effects that may help improve kidney function and fluid balance in people exposed to nephrotoxic drugs such as lithium.

1. Diuretic Effect: Corn silk is well-known for its diuretic effects, which promote urine production and can help with problems such as water retention, kidney stones, and urinary tract infections.
2. Anti inflammatory: It contains chemicals that have anti-inflammatory properties, which may help reduce inflammation and pain in disorders like arthritis or urinary tract difficulties.
3. Antioxidant Activity: The presence of polyphenols and flavonoids gives corn silk
antioxidant properties, helping to neutralize free radicals and reduce oxidative stress, which could help in preventing chronic diseases.
4. Antimicrobial: Corn silk has been found to possess antimicrobial activity, which can help protect against bacterial and fungal infections, especially in the urinary system.
5. Blood Sugar Regulation: Some studies suggest that corn silk might help in lowering blood glucose levels, thus being beneficial for people with diabetes.
6. Cholesterol Regulation: It has been shown to have potential in lowering cholesterol levels, contributing to better cardiovascular health.
7. Kidney Health: Corn silk is often used in traditional medicine for kidney health, including for the treatment of kidney stones and promoting overall renal function.
8. Hepatoprotective Effects: Some research indicates that corn silk may have protective effects on the liver, helping detoxify the body and prevent liver damage.

Phytochemical Constituents:

Corn silk has a number of bioactive chemicals, including:

Flavonoids: These chemicals, including quercetin and kaempferol, are powerful antioxidants that scavenge free radicals and minimise oxidative stress. Flavonoids also have anti-inflammatory characteristics, which may help relieve renal irritation caused by lithium.

-Alkaloids: Corn silk contains alkaloids, such as zea maysine, which have been demonstrated to have mild diuretic effects, potentially improving renal function and fluid balance.

-Saponins: These chemicals have anti-inflammatory and antioxidant properties and may help prevent kidney injury by modifying inflammatory pathways and lowering oxidative stress.

Polysaccharides: These molecules, known for their immunomodulatory and anti- inflammatory properties, may help avoid renal inflammation and fibrosis[7,8].

Renoprotective Properties:

Several investigations have proven that maize silk extract has renoprotective properties. It has been found to reduce oxidative stress by enhancing antioxidant enzyme activity (e.g., superoxide dismutase, catalase) and decreasing lipid peroxidation.

-Control inflammation by lowering the expression of pro-inflammatory cytokines and mediators.

- Enhance kidney function by reducing indicators of renal injury such serum creatinine and blood urea nitrogen (BUN).

4. Animal Models of Renal Toxicity

Rats are frequently used in preclinical studies to investigate renal toxicity and the effects of potential therapeutic agents. These animal models help simulate the human condition and assess the efficacy of natural extracts, such as corn silk, in mitigating kidney damage. In studies of lithium induced renal toxicity, rats are given lithium carbonate, which induces nephropathy, and various biomarkers (e.g., serum creatinine, blood urea nitrogen) and histological assessments are used to evaluate kidney damage[.

Corn silk extract has been tested in several rat models, where it has shown promise in reducing the renal damage caused by lithium. This makes it a valuable tool for further investigating the renoprotective effects of natural substances[19,20].

1. Rodent Models

-Rats and Mice: These are the most commonly used animals in renal toxicity research due to their well characterized genetics, physiology, and relatively low cost. Rodent models are used for both acute and chronic kidney injury studies.

-Acute Kidney Injury (AKI): Often induced by nephrotoxic agents like cisplatin, gentamicin, or ischemia reperfusion injury (IRI).

-Chronic Kidney Disease (CKD): Induced by conditions like diabetic nephropathy, hypertension, or by toxins such as adriamycin or 5/6 nephrectomy (removal of part of the kidney).

2. Non-Rodent Models: Larger animals, such as dogs and pigs, are occasionally utilised due to their similarity to human renal physiology. They are commonly employed in preclinical safety assessment, particularly during drug development.

-Primates: Non-human primates are occasionally used in kidney toxicity research, particularly when more genetic and physiological similarities to humans is desired.

3. Mechanisms Induced in Models

-Nephrotoxins: Substances such as medications (e.g., gentamicin, cyclosporine, and cisplatin), environmental toxins (e.g., cadmium), and contrast agents (e.g., iodine-based contrast agents) are given to animals to cause kidney injury.

-Ischaemia Reperfusion Injury: A situation in which blood flow is temporarily reduced and then restored, resulting in kidney injury; frequently used to imitate events such as kidney transplantation or trauma[21].

-Diabetic Nephropathy: Induced in rodents to examine kidney damage caused by prolonged high blood sugar levels and its consequences on renal shape and function.

4. Key Endpoints for Renal Toxicity

Renal histology examines kidney tissue for pathology such as tubular necrosis, glomerular injury, fibrosis, and inflammatory infiltrates.

-Blood Markers: Serum creatinine, blood urea nitrogen (BUN), and electrolyte abnormalities are used to assess kidney function.

- Urinary Biomarkers: Urinary protein, albumin, and tubular biomarkers such as kidney injury molecule 1 (KIM 1) and cystatin C can assist detect kidney injury early.

-Functional Assessment: GFR and urine output measurements are critical for understanding renal function[22].

5. Genetically Modified Models

-Transgenic and Knockout Mice : These models are used to study specific genes that are involved in kidney function and toxicity. For example, knockout mice lacking certain transporters may have altered drug handling, making them ideal for studying nephrotoxic drug effects.

6. Advantages of Animal Models in Renal Toxicity

-They provide a controlled environment for studying the impact of specific toxins and mechanisms of kidney damage.

-They help to evaluate the efficacy and safety of new drugs and therapies.

-Animal models are essential for understanding dose response relationships and the long term effects of kidney toxicity.

7. Limitations

-Species differences may limit the translation of results from animals to humans.

-Ethical considerations regarding animal use require adherence to strict guidelines and regulations.

Lithium Induced Renal Toxicity Models:

Acute Toxicity model: In this paradigm, rats are given a single high dosage of lithium carbonate, which causes fast renal failure. This animal is excellent for investigating short-term renal injury and determining the acute protective effects of therapies such as maize silk extract.

Chronic Toxicity Model: Rats are given lithium carbonate over time, simulating the chronic kidney impairment seen in human patients on long-term lithium medication. This model allows researchers to assess maize silk's long-term protective effects as well as its ability to prevent or correct existing kidney damage[23].

5. Effect of Corn Silk Extract on Lithium Induced Renal Toxicity in Rats

Several research have looked into the preventive properties of maize silk extract against lithium-induced nephrotoxicity in rats. In these experiments, rats are usually separated into control and experimental groups, with the latter receiving lithium carbonate followed by maize silk extract.

Corn silk extract has been found to lower serum levels of BUN and creatinine, which are high due to kidney impairment caused by lithium. This shows that maize silk extract could improve kidney function by avoiding lithium-induced damage[24].

-Histopathological Effects:

The histopathological study of rat kidneys treated with lithium alone often reveals glomerular destruction, tubular degeneration, and interstitial fibrosis. However, administering maize silk extract results in a significant reduction in these histological abnormalities, with less tubular damage and intact glomerular structure. This histological improvement is consistent with the biochemical findings, providing more support for maize silk's renoprotective effect.

-Oxidative Stress and Inflammatory Response:

Corn silk extract has been proven to reduce oxidative stress indicators, such as malondialdehyde (MDA) levels, while increasing antioxidant enzyme activity including superoxide dismutase (SOD) and catalase. Corn silk extract lowers pro-inflammatory cytokines including TNF and IL 6, which are increased after lithium-induced kidney damage. These findings indicate that maize silk extract reduces kidney damage via its antioxidant and anti-inflammatory characteristics.

-Renal Function Improvement:

Corn silk's diuretic effects may help to improved renal function. Corn silk extract, by increasing urine production and decreasing fluid retention, may help to reduce the polyuric symptoms of lithium toxicity.

6. Mechanisms of Renoprotection by Corn Silk Extract

The renoprotective effects of corn silk extract may be attributed to several mechanisms:

1. Antioxidant Activity: Corn silk extract has dominant antioxidant capabilities due to its high flavonoid and phenolic component concentration. By scavenging free radicals, it decreases oxidative stress in the kidneys, which is a significant cause of renal injury. Corn silk extract includes a number of antioxidants, including flavonoids and phenolic substances, which can scavenge free radicals and prevent oxidative damage to kidney cells. This helps to maintain cellular integrity and function in the face of lithium-induced toxicity.
2. Anti inflammatory Effects: Corn silk inhibits the activation of inflammatory pathways, including the NF-κB pathway. This reduces the production of pro-inflammatory cytokines, which alleviates kidney inflammation. Corn silk extract reduces inflammation by inhibiting NF κB activation and pro-inflammatory cytokine production. This helps to minimise renal inflammation and avoid fibrosis.
3. Modulation of Apoptosis: Corn silk extract has been shown to modulate apoptotic pathways, reducing renal cell death and promoting cell survival. This could help in preventing the irreversible damage caused by lithium. Corn silk has been shown to reduce apoptosis (programmed cell death) in renal cells by modulating pro apoptotic and anti apoptotic proteins. This helps prevent the loss of kidney cells and tissue damage.
4. Diuretic Action: Corn silk promotes diuresis, which could help in the excretion of excess lithium and reduce its nephrotoxic effects. This action may also support overall kidney function by improving fluid and electrolyte balance.

7. Toxicity and Safety Profile of Corn Silk

Corn silk extract has been used successfully in traditional medicine for generations, with few reports of side effects. Corn silk has been shown in animal experiments to have a low toxicity profile, even at high dosages. However, as with any herbal extract, long-term safety and potential interactions with other drugs warrant additional investigation. It is critical to ensure that maize silk extract does not cause toxicity or other negative effects when used in conjunction with other nephrotoxic medications such as lithium. Orn silk has traditionally been used as a safe treatment, with a low toxicity profile. Corn silk extract has been demonstrated in animal experiments to have no notable detrimental effects, even at larger doses. However, like with any herbal therapy, long-term safety and potential

8. Conclusion

Corn silk extract holds significant potential as a renoprotective agent against lithium induced nephrotoxicity. Its antioxidant, anti inflammatory, and diuretic properties contribute to its ability to reduce renal damage caused by lithium. While current studies in rats have shown promising results, further clinical studies and trials are necessary to confirm the efficacy and safety of corn silk extract in humans. The integration of corn silk extract into therapeutic protocols could offer a natural, complementary treatment option for individuals undergoing long term lithium therapy, reducing the risk of renal damage associated with this essential drug. Corn silk extract demonstrates significant promise as a renoprotective agent against lithium induced renal toxicity in rats. Through its antioxidant, anti inflammatory, and diuretic effects, corn silk extract mitigates oxidative stress, reduces inflammation, and improves kidney function. While current studies in animal models are promising, further research, including clinical trials, is needed to fully understand its potential as a therapeutic option for patients undergoing long term lithium therapy. Future studies should also investigate the optimal dosage, safety profile, and potential interactions with other nephrotoxic drugs.

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