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The Protective Role of Cinnamaldehyde in Kidney Injury: Modulation of NF-κB and PI3K/Akt Signaling Pathways

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ABSTRACT

Chronic renal disease is defined as the presence of kidney damage or impaired kidney function over a period of at least three months, regardless of the origin of the condition. Numerous factors, including oxidative stress, inflammation, and cell death, are frequently responsible for acute and chronic kidney injury, which is a significant issue in the field of global health. Because of the crucial functions that they play, the NF-κB and PI3K/Akt signaling pathways are potential therapeutic targets. These pathogenic processes are mediated by these pathways. cinnamonaldehyde, which is a naturally occurring bioactive component, has demonstrated encouraging nephroprotective properties. These properties are attributed to the fact that it contains anti-inflammatory, antioxidant, and anti-apoptotic properties. The purpose of this review is to investigate the molecular role of cinnamaldehyde in preventing kidney damage by modulating the NF-κB and PI3K/Akt pathways. Within this article, we examine the molecular pathways involved and highlight the potential of cinnamaldehyde as a treatment for renal disease. Although preclinical studies have demonstrated significant protective effects, additional research, including clinical trials, is required to validate its safety, effectiveness, and potential therapeutic uses in the management of renal illness in people.

Keywords- Cinnamaldehyde, Kidney Injury, NF-κB, PI3K/Akt pathway.

I. INTRODUCTION

Chronic kidney disease (CKD) affects between 8 to 16 percent of the world's population, yet it tends to go unnoticed by both patients and medical professionals[1]. Comparatively, countries with low and intermediate incomes have a higher prevalence of chronic kidney disease (CKD) than those with high incomes[2]. It is characterized by a glomerular filtration rate (GFR) that is lower than 60 mL/min/1.73 m2, albuminuria that is 30 mg per 24 hours or more, or signs of kidney damage (such as hematuria or structural abnormalities like polycystic or dysplastic kidneys) that continue for more than three months[3]. In spite of the fact that diabetes and hypertension are the most frequently cited causes of chronic kidney disease (CKD) all over the world, glomerulonephritis, infections, and environmental exposures (such as air pollution, herbal medicines, and pesticides) are prevalent in a great number of underdeveloped countries in Asia and sub-Saharan Africa[4-7]. The presence of genes that are predisposed to cancer could also be a factor. As an illustration, the risk of chronic kidney disease (CKD) can be increased by a factor of two in those who have sickle cell trait and two APOL1 risk alleles, both of which are more prevalent in Africans than in Europeans[8-10].

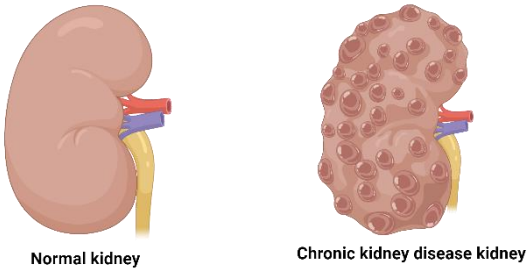

Fig.1 Difference between normal kidney and chronic kidney disease kidney

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II. ANATOMY OF KIDNEY

The kidneys, the urethra, and the ureters are the components that make up the renal system. It is the responsibility of the system as a whole to filter around 200 liters of fluid from the blood flow to the kidneys on a daily basis[11]. This allows for the expulsion of toxic substances, metabolic waste, and excess ions, while also ensuring that the blood's essential components are preserved. Through the regulation of blood volume, solute concentration, and electrolyte levels, the kidney is responsible for controlling the osmolarity of plasma[12]. Erythropoietin, which is responsible for stimulating the production of red blood cells, is produced by this organ. Additionally, it ensures that the acid-base balance is maintained over the long term. The production of renin and the conversion of vitamin D to its active form are both processes that it uses to control blood pressure[13]. The urogenital ridges are responsible for the development of the adult kidney, which occurs after three sets of kidneys expand in a sequential manner[14]. Initial renal tubules are referred to as the pronephros, which is the name given to this system. The development of the pronephros occurs during the fourth week of embryonic development; however, it quickly degenerates with the emergence of the mesonephros. When the metanephros develops, the remnants of the mesonephric kidney are incorporated into the male reproductive system. This occurs because the mesonephric kidney declines. During the fifth week of embryonic development, the metanephros begin to form as ureteric buds[15]. This occurs throughout the entire embryo. The maturation of the ureteric buds results in the production of nephrons. The renal pelvis, calyces, and collecting ducts all have their beginnings at the proximal end of the ureteric buds. This occurs along with the formation of the ureters at their distal locations[16]. A structure known as the cloaca is responsible for the formation of the rectum, the anal canal, and the urogenital sinus. During the third month of fetal development, the metanephric kidneys are able to produce urine that is discharged into the amniotic fluid. In the course of development, the urogenital sinus eventually gives rise to the urinary bladder and the urethra[17].

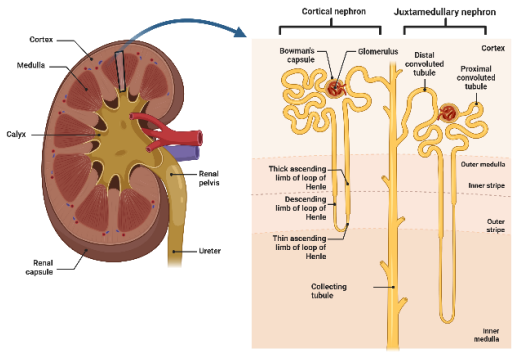

Fig.2 Anatomy of Kidney

III. EPIDEMIOLOGY

According to the Centers for Disease Control and Prevention (CDC) in the United States, it is estimated that over 37 million people in the United States are living with chronic kidney disease (CKD), which accounts for approximately 15% of the adult population[18]. Even among people with significantly impaired kidney function who are not receiving dialysis, fifty percent of adults are unaware that they have chronic kidney disease (CKD). This percentage is even higher among those who are not receiving dialysis[19]. In adults, the following are the two forms of high blood pressure and diabetes that are most commonly seen:

According to the Centers for Disease Control and Prevention (CDC), chronic kidney disease (CKD) is a potential complication in one out of every three instances of diabetes and one out of every five cases of hypertension in adults[20-22]. According to the most recent statistics from the Centers for Disease Control and Prevention (CDC), chronic kidney disease (CKD) is more prevalent in people aged 65 and older (38% vs 13% in those aged 45–64 and 7% in those aged 18–44), and it is slightly more prevalent in women (15%) than it is in men (12%). among addition, the prevalence of ESKD is nearly three times higher among African Americans compared to whites[23-25].

IV. PREVALENCE OF CKD

The problem of chronic kidney disease is a problem that affects public health on a global scale. According to the findings of a meta-analysis of observational studies that evaluated the prevalence of cholangitis, the condition is present in around 13.4 percent of the complete population of the world[26]. Despite the fact that 79% of patients were in severe stages of chronic kidney disease (stages 3-5), it is likely that the actual number of patients who are in early stages of the disease (stages 1 or 2) is significantly higher. This is because early stages of the disease do not exhibit any symptoms[27]. It would appear that chronic kidney disease (CKD) is being diagnosed in an increasing number of people in Western countries, including the United Kingdom.

According to the subnational demographic forecasts that were generated in 2012, by the year 2036, more than four million people in England would be suffering from chronic kidney disease (CKD) stages 3-5[28]. There are a number of factors that contribute to the development of chronic kidney disease (CKD), including obesity, hypertension, cardiovascular illness, and type 2 diabetes (T2DM). This is part of the reason why the incidence of CKD is increasing. Chronic kidney disease (CKD) is directly responsible for the deaths of between 5 and 10 million individuals per year, as stated by the World Health Organization

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(WHO)[29]. Comorbidities such as cardiovascular disease, type 2 diabetes, hypertension, HIV/AIDS, malaria, and COVID-19 all contribute to the mortality rate associated with chronic kidney disease in a fashion that is indirect when the condition is present. One of the factors that contributes to the high mortality and morbidity rates associated with chronic kidney disease (CKD) is the fact that patients and healthcare providers alike typically have a limited understanding of the condition[30].

When it is in its early stages, clinically silent chronic kidney disease does not exhibit any symptoms or indicators. It is possible for this stage of chronic kidney disease to progress to more advanced stages if it is not treated. At this point, patients may develop issues and/or ESKD, which is an acronym for emergent systemic effects associated to cardiovascular disease. The dissemination of information regarding chronic kidney disease (CKD) is of utmost importance in order to pave the way for early intervention, reduce the likelihood of complications, and ultimately save lives[31].

V. PATHOPHYSIOLOGY OF CHRONIC KIDNEY DISEASE

The severe chronic kidney disease (CKD) is a condition that can be caused by a number of different disease pathways. This condition causes the kidneys to undergo progressive and irreversible changes in their structure and function over the course of several months or years. For the purpose of making a diagnosis of chronic kidney disease (CKD), it is necessary to have evidence that chronic kidney function has been lowered and that renal structure has been damaged[32]. The estimation of glomerular filtration rate, also known as eGFR, is the most reliable method for determining kidney function. It is calculated by adding up all of the fluids that are filtered out by active nephrons in a specific amount of time. According to the most recent international standards, chronic kidney disease (CKD) is a serious condition that often worsens without the presence of any symptoms occurring[33]. It is characterized by a decrease in kidney function, which can be demonstrated by a glomerular filtration rate (GFR) that is below 60 mL/min per 1.73 m2, or by indicators of kidney damage, such as albuminuria (albumin: creatinine ratio ≥ 30 mg/g), or both. Furthermore, it must continue for a minimum of three months, regardless of the underlying cause[34].

An estimated 10–15 percent of the world's population is currently afflicted with chronic kidney disease (CKD), which has a negative impact on global health. Obesity, diabetes mellitus, and high blood pressure are the traditional risk factors for this disease, and the prevalence of these conditions is increasing all over the world[35]. The risk of mortality, major cardiovascular events, and hospitalization is increased in patients who have end-stage renal disease (ESRD) and modestly decreased kidney function because these individuals have a significant cardiovascular burden[36]. Inflammation is one of the non-traditional risk factors that are related with chronic kidney disease (CKD), and it is directly linked to an elevated risk of mortality from cardiovascular disease. On the other hand, when the immune system is unable to offer an adequate reaction, the likelihood of development of cancer and infections increases drastically[37]. It has been demonstrated that the mutually beneficial link that exists between the kidneys and other organs, particularly the stomach, has a significant influence on the immune and inflammatory responses produced by the body. Research into the relationship between renal disease and the gut microbiota system has been the subject of a significant amount of interest, as evidenced by the numerous recent publications and continuing clinical trials[38].

In a reciprocal connection that is referred to as "the gut-kidney axis," where metabolic and immunological pathways are interlaced, chronic kidney disease (CKD) and dysbiosis of the gut microbiota are related. Particularly noteworthy is the fact that recent studies have demonstrated that the microbiota-gut-kidney axis plays a significant part in salt-related osmoregulation, which assists desert-dwelling small animals in adapting to high salt loads. More recently, there has been a description of the microbiota that lives in the gut and its interactions with the key components of the brain-gut-kidney axis. These components include the neuronal, hormonal, bone marrow, and immune systems. The chronic kidney disease (CKD) and hypertension were both topics that were brought up in association with this network[39]. When it comes to renal disorders, it is feasible to enhance the prognosis by positively modifying the makeup and/or functionality of the microbiota that lives in the gut. This is due to the fact that alterations in the composition of the gut microbiota and/or the generation of metabolites include the potential to influence inflammation, oxidative stress (OS), and fibrosis. There is a complicated link between chronic kidney disease (CKD) and oral problems that involves a two-way interaction.

This interaction is based on common environmental and metabolic risk factors, and it includes immune responses and mineral metabolism. There is a correlation between weakened immunological responses and dysregulated mineral metabolism in persons who have chronic kidney disease (CKD). These factors can lead to an increase in oral infections and disturb tooth and bone homeostasis, respectively. This has the potential to exacerbate dental and periodontal problems, as well as have an impact on the microbiota in the gut[40].

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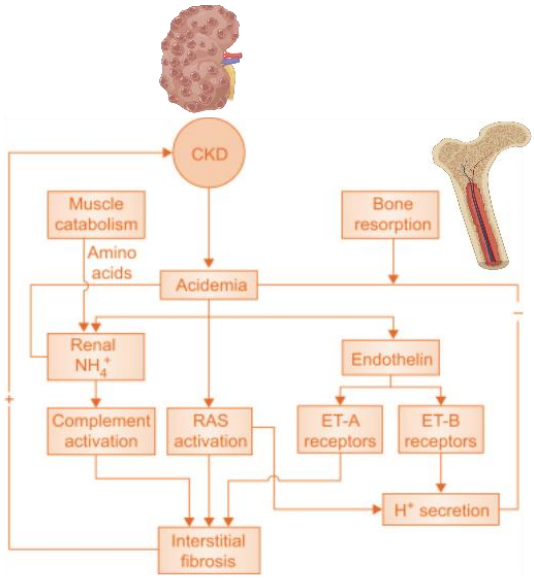

Fig.3 Pathophysiology of CKD

VI. CINNAMALDEHYDE

One of the most prevalent food additives, cinnamonaldehyde can be found in cinnamon and other products that contain cinnamon. As an α, β-unsaturated aldehyde, it is also utilized in the production of ice cream, beverages, candies, chewing gum, and also in the production of sauces. In addition, CA is a type of traditional Chinese medicine that has been utilized for the treatment of a variety of conditions, including inflammation, gastritis, indigestion, and issues related to blood circulation. There are two types of fungus that are responsible for the deterioration of food: Phytophthora capsici in peppers and Geotrichum citri-aurantii in citrus fruits. According to research, CA is able to inhibit both of these types of fungi. Catecholamine (CA) is a natural active component that is safe, has an excellent safety profile, and is well accepted by both people and animals. Both the Food and Drug Administration (FDA) and the European Council have concurred with this concept, recommending that 1.25 mg/kg be taken on a daily basis. Furthermore, it has been discovered that CA is capable of eliminating both chemical and natural toxins, including ochratoxin A, in addition to safeguarding human health[41]. The antioxidant and anti-cerebral thrombosis properties of CA in mice have already been demonstrated to be strong. There have been discoveries that indicate that CA has the capability of causing damage to the mitochondrial membranes of Penicillium expansum and causing the production of reactive oxygen species (ROS). When it comes to traveling and storing food, everyone is in agreement that CA is an excellent preservative to bring along. A recent study discovered that CA, in addition to its capacity to induce apoptosis in cancer cells, can also inhibit A. flavus at lower concentrations. In spite of the fact that one study discovered that CA causes oxidative stress in A. flavus, another study discovered that it just observed changes in the activity of antioxidant enzymes. Furthermore, the precise method by which ROS in A. flavus induce subsequent damage is not fully understood. Despite this, it is acknowledged that it would be beneficial to understand the mechanism by which CA inhibits A. flavus.

VII. CINNAMALDEHYDE IN CHRONIC KIDNEY DISEASE

It is possible that cinnamon, in general, has some beneficial effects based on the salutogenic effects that have been documented in the literature. This is the case even if there are not many studies that particularly investigate the impact that cinnamon has on the kidneys[42]. Chronic kidney disease (CKD) is the largest cause of death across the globe, and it is becoming increasingly prevalent in countries with low and intermediate incomes as a result of the multiplicative effect of social deprivation[43]. The contemporary movement to consider "food as medicine" emphasizes the exploitation of bioactive chemicals found in nature as potential therapies for the growing aging pandemic. This movement takes a page out of Hippocrates' playbook and supports the utilization of these substances[44]. The inclusion of cinnamon as a tool in the toolkit of medical experts and dietitians would be both prudent and beneficial.

Common processes are responsible for the favorable benefits of cinnamon on chronic kidney disease (CKD)[45]. One of these mechanisms is the suppression of the ERK/JNK/p38 MAPK pathway, which in turn lowers the proliferation and hypertrophy of renal interstitial fibroblasts. Cinnamon has been shown to have a positive impact on CKD[46]. In addition, this mechanism is dependent on the Nrf2 pathway, which is a crucial component in minimizing kidney damage and preserving renal function[47]. Cinnamon is said to have a number of benefits, some of which include the ability to influence the formation of NO and PGE2, the inhibition of peroxynitrite-induced nitration and lipid peroxidation, and other advantageous properties. Cilantro has the potential to slow down the cellular aging process, which is accelerated in people with chronic kidney disease (CKD), who already age more rapidly[48]. Cinnamaldehyde's ability to diminish kidney cellular senescence through the downregulation of microRNA-155 and the autophagy that is mediated by the PI3K/AKT pathway gives credibility to this concept[49]. Cinnamon has the potential to be an effective dietary component for the treatment of chronic kidney disease (CKD) due to its capacity to lower the risk of developing diabetes and dyslipidemia. Studies suggest that an improvement in kidney function may be possible through the implementation of dietary regimens that boost antioxidant and anti-inflammatory defenses[50].

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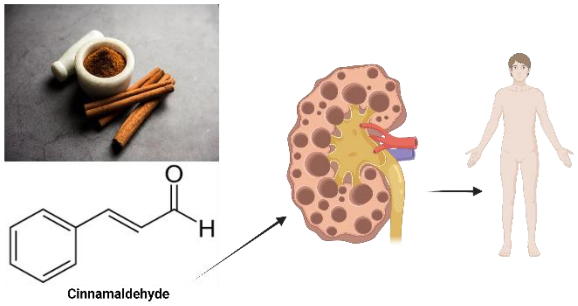

Fig.4 Cinnamaldehyde in chronic kidney disease

VIII. MECHANISMS OF NF-KB MODULATION BY CINNAMALDEHYDE

Those who survive acute kidney injury (AKI) are at risk for developing chronic renal disease in the future[51]. This is because AKI is associated with a considerably higher incidence of morbidity and mortality than other types of kidney injuries. Ischemia-reperfusion frequently causes the kidneys to enter a hypoxic condition, which results in a reduction in the amount of blood that flows to the kidneys, which ultimately results in acute kidney injury (AKI)[52]. Reduced inflammation has been proven to help minimize kidney injury and speed up the healing process. Acute kidney injury (AKI) inflammation is a primary contributor to kidney injury, and lowering inflammation has been demonstrated to help reduce kidney injury[53]. The transcription factor NF-κB is believed to play a crucial role in the regulation of inflammation, and its activation occurs in tandem with the occurrence of kidney injury caused by ischemia-reperfusion. In animal models, it has been proven that NF-κB inhibitors have the ability to diminish the initiation of renal inflammation and damage when administered[54]. Based on the findings of inhibitor experiments, it is possible that NF-κB plays a role in the regulation of renal damage that is induced by aldosterone and salt[55]. The impact of a smaller interfering RNA (siRNA) for IKKβ on kidney injury was investigated in a study that was conducted by researchers not too long ago. Through the administration of IKKβsiRNA into the renal arteries of rats with a kidney injury model, the reduction of inflammation and kidney injury caused by ischemia-reperfusion is achieved[56]. This is achieved by suppressing the expression of IKKβ and activating NF-κB.

A recently published study has established a correlation between the presence of elevated levels of NF-κB members, such as RelA and NF-κB2, and the occurrence of acute renal damage in cases when folic acid doses are high[57]. Pyrrolidine dithio-carbamate ammonium (PDTC), which is an inhibitor of nuclear factor κB, was found to alleviate renal dysfunction. This finding suggests that NF-κB plays a role in the development of kidney injury. It has also been hypothesized that NF-κB has a role in the development of kidney injury that is caused by hypertension, which is a chronic health problem that is characterized by consistently high blood pressure[58]. The elevated levels of angiotensin II, which are specifically associated with hypertension, serve as a catalyst for the activation of NF-κB and the subsequent development of inflammatory responses. By transgenically expressing endothelium cells with a degradation-resistant IκBα mutant, IκBαΔN, in order to suppress NF-κB, it was shown that the renal damage induced by hypertension in a mouse model was improved. The reduction of NF-κB does not have any impact on the development of hypertension. However, hypertension does prevent the generation of proinflammatory cytokines and cell adhesion molecules, both of which contribute to kidney injury. PDTC, which is an inhibitor of NF-κB, was found to minimize the inflammatory kidney damage caused by angiotensin II in a rat model of hypertension. This result was comparable to the findings observed in the previous study.

IX. ACTIVATION OF PI3K/AKT PATHWAY BY CINNAMALDEHYDE

In the early 1980s, a significant amount of research was conducted on insulin receptor signaling, which ultimately led to the discovery of the PI3K-PKB/Akt pathway and the activation of receptor tyrosine kinases (RTKs)[59]. From these humble beginnings, the components and manner of insulin receptor signaling have been identified. This signaling process involves insulin receptor substrate (IRS) proteins, PI3K, and the subsequent activation of 3-phosphoinositide-dependent protein kinase 1 (PDK1) through PKB/Akt. Following the discovery that PI3K and PKB/Akt activation are key contributors to the development of tumors, researchers dived deep into the task of figuring out how to regulate this pathway[60]. In the end, they discovered the negative regulators PP2A, PTEN, and PHLPP1/2. We have recently finished our model of the PI3K-PKB/Akt pathway. This was accomplished by locating the DNA-dependent protein kinase (DNA-PK), the mammalian target of rapamycin (mTOR), and the elusive PKB/Akt hydrophobic motif kinases, also known as mTORC2 and mTOR[61]. Moreover, we have demonstrated that Ras has the ability to exert an influence on the PI3K-PKB/Akt pathway by means of PI3K.
It is a multi-step mechanism that carefully controls the activation of the PI3K-PKB/Akt pathway, which is a route that is well conserved[62]. An example of an adapter molecule or regulatory subunit that activated receptors employ to stimulate binding class 1A PI3Ks is insulin receptor substrate (IRS) proteins[63]. These proteins are a substrate for insulin receptors. The catalytic domain of the protein kinase PI3K is responsible for the conversion of the lipids that contain phosphatidylinositol (3,4)-bisphosphate (PIP2) to

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phosphatidylinositol (3,4,5)-trisphosphate (PIP3) when this occurs. PKB/Akt binds to PIP3 at the plasma membrane, which then causes PDK1 to be released. This allows PDK1 to access and phosphorylate T308 across the "activation loop," which ultimately results in a partial activation of PKB/Akt. Direct phosphorylation and inactivation of PRAS40 and TSC2, two proteins that are components of the PKB/Akt complex, are the means by which mTORC1 is activated. This is accomplished through the utilization of the PKB/Akt complex. When mTORC1 phosphorylates ribosomal protein S6 (S6/RPS6), which is a substrate of eukaryotic translation initiation factor 4E binding protein 1 (4EBP1) and ribosomal protein S6 kinase, 70 kDa, polypeptide 1 (S6K1), it leads to an increase in the production of proteins and the proliferation of cells[64].

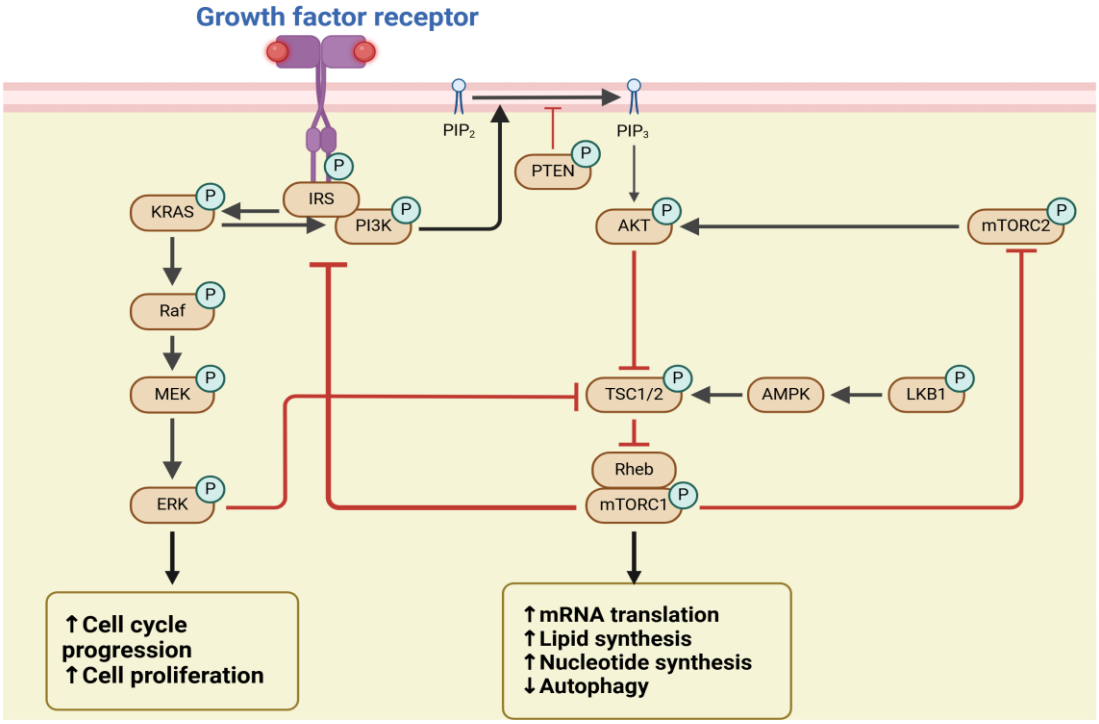

Fig.5 PI3K/AKT pathway

In addition to its organoleptic properties, cinnamon has been used as a flavoring component in cooking for hundreds of years, and many different civilizations all over the world have relied on it. The potential health advantages of this substance have been the subject of a significant amount of investigation, and it has a lengthy history of application as a treatment for gastrointestinal and respiratory conditions[65]. These substances have a wide range of advantageous benefits, including the reduction of inflammation, the elimination of bacteria, the prevention of diabetes, the battle against cancer, and the reduction of cholesterol. The anti-inflammatory properties of cinnamon may be attributed, at least in part, to the fact that it reduces the levels of proinflammatory cytokines such as tumor necrosis factor (TNF), C-reactive protein (CRP), and interleukin (IL) 6. The inhibition of nuclear factor kappa B (NF-κB) expression is the means by which this objective is accomplished. Additionally, cinnamon increases the activation of Nrf2, which in turn upregulates various cytoprotective defenses and improves the synthesis of antioxidant enzymes such as CAT, HO-1, GPx-1, and NAD(P)H dehydrogenase [quinone]. Cinnamon is a powerful antioxidant. 1. Patients who have chronic illnesses, such as chronic kidney disease (CKD), are more likely to have cardiovascular disease (CVD). Patients who have chronic disorders frequently exhibit systemic inflammation, oxidative stress, dysregulated glucose and lipid metabolism, changes in blood pressure, and other symptoms. Additionally, these patients may display changes in the composition of their gut flora, which can result in increased levels of uremic toxin in the blood, which in turn makes oxidative and inflammatory stresses even more severe[66]. Through the utilization of the concept of food as medicine, the goal of enhancing health and reducing the impact of lifestyle-related chronic diseases has been accomplished. The reason for this is because nutrients and bioactive compounds are obtained from the food that we eat. It has been demonstrated that patients suffering from chronic kidney disease (CKD) may benefit from consuming particular foods. Ingredients such as turmeric, propolis, Brazil nuts, beetroot, cruciferous vegetables, and berries are included in this category of foods. Foods like these

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have the potential to reduce inflammation, oxidative stress, and dysbiosis in the gut. A limited number of studies have been conducted to investigate the effects that cinnamon has on people who suffer from chronic renal disease. To further investigate cinnamon's medicinal potential for high-risk populations, including those with chronic kidney disease (CKD), we present a narrative review that summarizes cinnamon's positive effects and suggests its potential role as a nonpharmacologic adjuvant treatment for complications related to cardiovascular disease (CVD), diabetes, obesity, and gut dysbiosis.

X. CONCLUSION AND FUTURE DIRECTION

Cinnamaldehyde, due to its ability to exert an influence on the NF-κB and PI3K/Akt signaling pathways, exhibits a significant amount of potential as a potential therapeutic agent for kidney injury. In models of acute and chronic renal sickness, it preserves the kidneys by lowering inflammation, increasing antioxidant defenses, and preventing cell death. This is accomplished through the use of compounds. Despite the fact that preliminary evidence is encouraging, additional study, which should include clinical studies that are carefully managed, is necessary in order to confirm its safety, effectiveness, and therapeutic value in the management of renal illness in humans. It is feasible that the molecular mechanisms and pharmacological features of cinnamaldehyde might be further investigated, which would lead to the development of novel medicines that could reduce kidney injury and improve renal health.

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