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Role of plant based natural antioxidents on chronic kidney disease

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Abstract
Chronic kidney disease (CKD) is a prevalent global health issue that can lead to end-stage kidney disease and increased risk of cardiovascular disease. CKD is characterized by the progressive impairment of kidney function, which necessitates the exploration of novel therapeutic interventions. This article presents a comprehensive review of the current literature on the potential benefits of antioxidants in CKD patients, as well as the limitations and potential risks associated with antioxidant supplementation. Antioxidants are compounds known for their ability to neutralize free radicals and combat oxidative stress, a common occurrence in CKD. Research has shown that antioxidants hold promise in ameliorating CKD progression and associated complications. Neem, a traditional medicinal plant, has demonstrated improvements in kidney function in animal models with CKD. Bacopa monniera extract, another plant-derived compound, has shown potential in reducing oxidative stress and improving renal function in both animal models and human subjects with CKD. Furthermore, numerous other plants, foods, and spices, including Beta vulgaris, Camellia sinensis, Turmeric, Tulsi (Holy basil), Ginger, and Plums, possess antioxidant and anti-inflammatory properties that may benefit CKD patients. However, it is important to note that some studies have reported no significant effects of antioxidants in CKD patients. Additionally, the benefits of plant-based antioxidants appear to be more pronounced in the prevention of CKD rather than in the treatment of established CKD. While the potential benefits of antioxidants in CKD management are promising, more extensive research is necessary to fully understand their mechanisms of action and therapeutic potential and to establish the efficacy, optimal dosage, and long-term safety of antioxidant interventions in CKD patients.

Keywords: Antioxidants, oxidative stress, chronic kidney disease, cardiovascular disease

Introduction
The kidneys are vital organs that play a critical role in the body's overall health and well-being. They are responsible for filtering waste products and excess fluid from the blood, regulating electrolyte balance, and producing hormones that help to control blood pressure and red blood cell production. Chronic kidney disease (CKD) is a common condition that can occur when the kidneys are damaged or are not functioning properly. The kidneys are highly vascular organs, receiving approximately 20% of the cardiac output in resting adults [1]. Each kidney contains about a million nephrons, which are the functional units of the kidney. Nephrons consist of a glomerulus, which filters blood, and a tubule, which reabsorbs necessary substances and excretes waste products [2]. CKD is a major public health problem worldwide, affecting up to 10% of the global population [3]. It is a progressive condition that can lead to end-stage kidney disease (ESKD), where the kidneys are no longer able to function properly and dialysis or kidney transplantation is required. CKD is also associated with an increased risk of cardiovascular disease, which is a leading cause of morbidity and mortality in CKD patients [4]. In recent years, there has been growing interest in the potential role of antioxidants in CKD. Antioxidants are compounds that can neutralize free radicals and protect against oxidative stress, which is a common occurrence in CKD. This article will review the current literature on the potential benefits of antioxidants in CKD patients, as well as the limitations and potential risks of antioxidant supplementation.

Chronic kidney disease
Chronic kidney disease (CKD) affects a significant portion of the global population, with a prevalence ranging from 8% to 16%, and is often underdiagnosed by both patients and healthcare providers [6] CKD is defined by various criteria such as a decreased glomerular filtration rate (GFR), albuminuria, or markers of kidney damage that persist for more than 3 months.

The prevalence of CKD is higher in low- and middle-income countries, where factors such as diabetes, hypertension, glomerulonephritis, infections, and environmental exposures are common causes. Certain genetic factors, such as sickle cell trait and the presence of specific risk alleles, may also increase the risk of CKD. These risk factors are more prevalent in individuals of African ancestry [7] If tubular or overflow proteinuria is suspected, then urine protein electrophoresis or testing for the specific protein can be pursued (eg, immunoglobulin heavy and light chains, α1-microglobulin, and β2-microglobulin) [8]. Imaging by kidney ultrasound to assess morphology and to rule out urinary obstruction should be considered in all patients diagnosed as having CKD [8].

Free radicals

The current advancements in the understanding of free radicals and reactive oxygen species (ROS) in the field of biology are bringing about a medical revolution, which holds the promise of a new era in the management of health and disease. Oxygen, an essential element for life, paradoxically can have harmful effects on the human body in certain circumstances, mostly due to the production and action of ROS, which donate oxygen to other molecules. The terms free radicals and antioxidants have become commonplace in discussions regarding the mechanisms of diseases [9]. A free radical is a molecular species that has an unpaired electron in an atomic orbital, which results in certain common properties shared by most radicals. These properties make many radicals highly reactive and unstable, allowing them to either donate or accept electrons from other molecules, behaving as oxidants or reductants [10]. In several disease states, the most important oxygen-containing free radicals are hydroxyl radical, superoxide anion radical, hydrogen peroxide, oxygen singlet, hypochlorite, nitric oxide radical, and peroxynitrite radical. These species can damage biologically relevant molecules such as DNA, proteins, carbohydrates, and lipids, and thus disrupt cellular homeostasis. Free radicals can attack all kinds of molecules in the body, but lipids, nucleic acids, and proteins are the major targets [11].

Formation of ROS

Free radicals and other ROS are derived either from normal essential metabolic processes in the human body or from external sources such as exposure to X-rays, ozone, cigarette smoking, air pollutants, and industrial chemicals [12]. Free radical formation occurs continuously in the cells as a consequence of both enzymatic and nonenzymatic reactions. Enzymatic reactions, which serve as source of free radicals, include those involved in the respiratory chain, in phagocytosis, in prostaglandin synthesis, and in the cytochrome P-450 system [13]. Free radicals can also be formed in nonenzymatic reactions of oxygen with organic compounds as well as those initiated by ionizing reactions. When the balance between the production of free radicals and the protective functions of antioxidants is disrupted, it results in oxidative damage, which is known as oxidative stress. This kind of stress can harm various molecular structures, including proteins, nucleic acids, and lipids [14].

Antioxidants

An antioxidant is a stable molecule that can give an electron to a free radical, which then neutralizes it and reduces its ability to cause damage. Antioxidants are primarily responsible for delaying or inhibiting cellular damage by scavenging free radicals [15]. These low-molecular-weight antioxidants can safely interact with free radicals and stop the chain reaction before important molecules are harmed. Some antioxidants, like glutathione, ubiquinol, and uric acid, are naturally produced during the body's metabolism. [16] Other antioxidants are found in food. Although the body has several enzyme systems that can scavenge free radicals, the main micronutrient (vitamins) antioxidants are vitamin E (α-tocopherol), vitamin C (ascorbic acid), and beta-carotene. Since the body cannot synthesize these micronutrients, they must be supplied through the diet [17].

There are two main ways in which antioxidants work, as suggested by researchers [18]. The first way is through chain-breaking, where the main antioxidant gives an electron to the free radical in the system. The second way involves removing the catalysts that initiate the chain reaction of reactive oxygen or nitrogen species by using secondary antioxidants. Antioxidants can have an impact on biological systems in various ways such as donating electrons, chelating metal ions, acting as co-antioxidants, or regulating gene expression [19].

The defense mechanisms of antioxidants operate at various levels, including preventive, radical scavenging, repair, and de novo synthesis, as well as adaptation, which is the fourth line of defense. Preventive antioxidants act as the first line of defense by inhibiting the formation of free radicals. Although the exact mechanism and location of radical formation *in vivo* are still unclear, metal-induced decomposition of hydroperoxides and hydrogen peroxide is likely a significant source. To prevent these reactions, some antioxidants reduce hydroperoxides and hydrogen peroxide to alcohols and water, respectively, without generating free radicals, while certain proteins sequester metal ions [9]. The second line of defense involves antioxidants that scavenge active radicals to suppress chain initiation and propagation reactions. Endogenous radical-scavenging antioxidants come in various forms, such as hydrophilic and lipophilic antioxidants. Hydrophilic antioxidants, like vitamin C, uric acid, bilirubin, albumin, and thiols, scavenge radicals, while lipophilic antioxidants, such as vitamin E and ubiquinol, are potent scavengers of radicals. Repair and de novo antioxidants constitute the third line of defense. Proteolytic enzymes, such as proteinases, proteases, and peptidases, found in the cytosol and mitochondria of mammalian cells, recognize, degrade, and eliminate oxidatively modified proteins to prevent the accumulation of oxidized proteins [9].

Antioxidants have a wide range of applications, including their use as additives in fats, oils, and food processing industries to prevent food spoilage. Spices and herbs are known to be good sources of antioxidants and are added to foods that contain unsaturated fatty acids to increase their shelf life and prevent them from going rancid due to oxidation. To reduce oxidation, antioxidants are being added to foods more frequently. Synthetic phenolic antioxidants such as butylated hydroxyanisole (BHA), butylated hydroxytoluene (BHT), and propyl gallate have been found to inhibit oxidation, while chelating agents such as ethylene diamine tetra acetic acid (EDTA) bind metals and reduce their participation in the reaction. Some vitamins (ascorbic acid [AA] and alpha-tocopherol), as well as many herbs, spices, and plant extracts (such as rosemary, thyme, oregano, sage, basil, pepper, clove, cinnamon, nutmeg, tea,

and grapeseed) contain antioxidant components that impart antioxidant properties to the compound. Natural phenolic antioxidants act as reducing agents, terminate free radical chain reactions, absorb UV light in the 100-400 nm range, and chelate transition metals, thus inhibiting oxidation reactions. They also prevent the production of off-odors and tastes [20] Significant immunostimulant, anti-inflammatory, and anti-carcinogenic effects can be achieved by taking high doses of nutritional antioxidants such as selenium, vitamins E, and C, which are also beneficial in protecting the structural integrity of tissues that experience oxygen deprivation. Furthermore, these antioxidants may have useful anti-thrombotic effects. Taking high doses of nutritional antioxidants could potentially improve the management of cancer, cardiovascular disease, infections, inflammatory conditions, and certain complications associated with diabetes, whether through prevention, treatment, or palliation [21].

Table 1: Some of the plants commonly used as the potential source of antioxidants.

Name of plant	English name	Family	Plant part used	Clinical significance
Aegle marmelos	Bengal quince	Rutaceae	Fruit pulp, leaves extract	Natural antioxidants, has nephroprotective properties [22]
Allium cepa	Onion	Amaryllidacea	Bulb	Nephroprotective, antioxidant [23]
Aloe vera	Indian aloe	Xanthorrhoeaceae	Leaf	No proven benefits on kidneys, causes toxicity [24].
Asparagus	Satavar	Liliaceae	Shoot	antioxidant, anti-inflammatory, and antihepatotoxic [25]
Azadirachta indica	Neem	Meliaceae	Leaf	Nephroprotective activity is present [26, 27]
Bacopa monniera	Brahmi	Plantaginaceae	Leaf	Nephroprotective, cognitive function, reduce anxiety [28]
Beta vulgaris	Beet root	Amaranthaceae	Root	Nephroprotective [29]
Camellia sinensis	Green tea	Theaceae	Green tea	Reduce oxidative stress in CKD patients [30]
Cinnamomum tamala	Tejpat	Lauraceae	Tejpat	anti-inflammatory on kidneys [31]
Curcuma longa	Turmeric	Zingiberaceae	Turmeric	Antioxidant [32]
Cuscuta reflexa	Akashabela	Convolvulaceae	Stem	Antioxidants and anti-inflammatory [33]
Daucus carota	Carrot	Apiaceae	Root	Antioxidants [34]
Emblica officinalis	Amla/Emblic	Euphorbiaceae	Fruit	Antioxidants and anti-inflammatory [35]
Eucalyptus camaldulensis	River red gum	Myrtaceae	Leaf	Antioxidants and anti-inflammatory [36]
Foeniculum vulgare	Saunf	Apiaceae	Fruit oil	Reduce oxidative stress and antioxidant [37]
Lavandula angustifolia	Lavender	Lamiaceae	Aerial parts	Inflammatory [38]
Mangifera indica	Aam/mango	Anacardiaceae	Root/fruit	Reduce oxidative stress, anti-inflammatory and antioxidant [39]
Murraya koenigii	Curry tree	Rutaceae	Leaf	Antioxidants and anti-inflammatory [40]
Ocimum sanctum	Tulsi	Lamiaceae	Leaf	Antioxidants and anti-inflammatory [41]
Piper nigrum	Black pepper	Piperaceae	Fruit	Antioxidants, Reduce oxidative stress, and anti-inflammatory [42]
Prunus domestica	Plums	Rosaceae	Fruit	Antioxidants and low potassium [43]
Solanum tuberosum	Potato	Solanaceae	Tuber	low phosphorus diet in CKD [44]
Solanum nigrum	Black nightshade	Solanaceae	Leaf	antioxidants and has anti-inflammatory [45]
Santalum album	Sandalwood	Santalaceae	Heartwood, bark	anti-inflammatory [46]
Zingiber officinale	Ginger	Zingiberaceae	Rhizome	antioxidants and has anti-inflammatory [47]

Due to the growing risks of deadly diseases, people are turning to natural substances found in medicinal and dietary plants as therapeutic antioxidants. Many herbs and spices, such as Eugenia caryophyllus, Piper brachystachyum, Elettaria cardamomum, Terminalia bellerica, and Zingiber officinale, have been found to have antioxidant properties. This global trend towards natural remedies is aimed at promoting better health and preventing diseases [20]. (Table 1 provides further information on these substances).

Azadirachta indica, commonly known as neem, is a plant that has been used in traditional medicine for various ailments, including kidney diseases. Chronic kidney disease (CKD) is a progressive condition that affects the function of the kidneys, and there is some evidence to suggest that neem may have benefits for people with CKD. One study published in the Journal of Medicinal Food in 2012 investigated the effects of neem leaf extract on kidney function in rats with CKD. The researchers found that treatment with neem leaf extract led to improvements in kidney function, including a reduction in proteinuria (excessive protein in the urine) and an increase in creatinine clearance (a measure of how well the kidneys are functioning) [26]. Another study published in the Journal of Renal Nutrition in 2013 looked at the effects of neem seed oil on oxidative stress and inflammation in patients with CKD. The study found that treatment with neem seed oil led to a significant reduction in markers of oxidative stress and inflammation, which are both thought to play a role in the progression of CKD [27]. It is important to note, however, that more research is needed to fully understand the potential benefits of neem for CKD.

Bacopa monniera, also known as Brahmi, has been used in traditional medicine to enhance cognitive function, reduce anxiety, and improve memory. There is some evidence to suggest that Bacopa monniera may have benefits for people with chronic kidney disease (CKD) as well. One study published in the Journal of Ethnopharmacology in 2010 found that Bacopa monniera extract improved renal function in rats with CKD. The extract was found to reduce the levels of serum creatinine and urea nitrogen, which are markers of kidney function, and increase the levels of antioxidants in the kidneys, which can help to protect against further damage. A systematic review and meta-analysis published in the Journal of Evidence-Based Integrative Medicine in

2018 evaluated the available evidence on the use of Bacopa monniera in the management of CKD. The review concluded that Bacopa monniera supplementation may improve kidney function and reduce oxidative stress in patients with CKD [28].

Beta vulgaris Contains nitrates which can lower blood pressure and improve endothelial function in CKD patients [29] *Camellia sinensis* Contains antioxidants that may help reduce oxidative stress in CKD patients [30]. Tejpat (Cinnamon leaf) - Has anti-inflammatory properties and can help reduce inflammation in the kidneys of CKD patients [31] Turmeric - Contains curcumin, which has anti-inflammatory and antioxidant properties that may benefit CKD patients. = Akashabela (Cassia siamea) - Contains antioxidants and can help reduce inflammation in the kidneys of CKD patients. [33] Carrot - Contains antioxidants and has a low potassium content, making it a good food option for CKD patients. [34] Amla/Emblic (Indian gooseberry) - Contains antioxidants and can help reduce inflammation and improve kidney function in CKD patients [35]. River red gum - Contains antioxidants and has anti-inflammatory properties that may benefit CKD patients. [36] Saunf (Fennel) - Contains antioxidants and can help reduce oxidative stress in CKD patients [37]. Lavender - Has anti-inflammatory properties and can help reduce inflammation in the kidneys of CKD patients [38]. Aam/mango - Contains antioxidants and can help reduce oxidative stress and inflammation in the kidneys of CKD patients [39]. Curry tree - Contains antioxidants and can help reduce inflammation in the kidneys of CKD patients [40]. Tulsi (Holy basil) - Contains antioxidants and can help reduce inflammation and improve kidney function in CKD patients [41]. Black pepper - Contains antioxidants and can help reduce oxidative stress and inflammation in CKD patients [42]. Plums - Contains antioxidants and has a low potassium content, making it a good food option for CKD patients [43]. Potato - Has a low phosphorus content, making it a good food option for CKD patients [44]. Black nightshade - Contains antioxidants and has anti-inflammatory properties that may benefit CKD patients [45]. Sandalwood - Has anti-inflammatory properties and can help reduce inflammation in the kidneys of CKD patients [46] Ginger - Contains antioxidants and can help reduce inflammation and improve kidney function in CKD patients. [47]

Safety and efficacy of antioxidants in chronic kidney disease

A study conducted by [Jun M, Venkataraman V, Razavian M, *et al*. Antioxidants for chronic kidney disease. *Cochrane Database Syst Rev*.] aimed to evaluate the effectiveness and safety of antioxidant therapy for people with chronic kidney disease (CKD). The researchers conducted a systematic review of randomized controlled trials that investigated the effects of antioxidant therapy on kidney function and cardiovascular outcomes in people with CKD. A total of 67 trials involving 3,109 participants were included in the review. The results showed that antioxidant therapy did not significantly improve kidney function or reduce the risk of cardiovascular events in people with CKD [20]. Additionally, there was no evidence of any harmful effects of antioxidant therapy. In conclusion, the study did not find any evidence to support the use of antioxidant therapy for people with CKD. While antioxidants may have potential benefits, further research is needed to determine their safety and effectiveness in this population. Clinicians should exercise caution when recommending antioxidant therapy for CKD patients, and individualized treatment decisions should be based on a thorough assessment of each patient's medical history and overall health [48].

Conclusion

The consumption of various substances through food, drinks, and inhalation, as well as exposure to exogenous materials like UV radiation, can be harmful to human health and shorten lifespan. Free radicals generated in the body can cause damage and ultimately lead to death. Lipid peroxidation, caused by the continuous use of improperly stored and reused vegetable oil, can generate free radicals. Smoking and chronic alcoholism are also social problems that reduce important antioxidants in the body, leading to negative health effects. Proper intake of antioxidants can help reduce the risk of diseases such as cancer, protect the skin from sun damage, and improve overall health. To address these issues, there is a need for education on balanced diet intake to provide the necessary antioxidants. By meeting the recommended dietary allowances (RDA), people can reduce their health risks and live longer with fewer disabilities. Several plants and foods may have potential benefits for people with chronic kidney disease (CKD). Neem, a plant used in traditional medicine, has been found to improve kidney function in rats with CKD, while Bacopa monniera extract may improve renal function and reduce oxidative stress in both rats and humans with CKD. Other plants and foods, including Beta vulgaris, Camellia sinensis, Tejpat (Cinnamon leaf), Turmeric, Akashabela (Cassia siamea), Carrot, Amla/Emblic (Indian gooseberry), River red gum, Saunf (Fennel), Lavender, Aam/mango, Curry tree, Tulsi (Holy basil), Black pepper, Plums, Potato, Black nightshade, Sandalwood, and Ginger, contain antioxidants and anti-inflammatory properties that may benefit CKD patients. However, more research is needed to fully understand the potential benefits of these plants and foods for CKD.

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