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ANTIOXIDANTS AND THEIR ROLE IN THE PREVENTION AND TREATMENT OF CHRONIC KIDNEY DISEASE (CKD), PERSPECTIVE OF COMPLEMENTARY NURSING AND MEDICINE: A REVIEW

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ABSTRACT

BACKGROUND. Chronic kidney disease (CKD) is a progressive and irreversible disease that leads to end-stage renal disease. Many factors such as increased oxidative stress play a role in the occurrence of this complication. Due to the effective role of the antioxidant defense system in controlling many of the complications in which oxidative stress is involved, the present study was conducted to evaluate the role of antioxidants in the prevention and treatment of chronic kidney disease.

METHODS. In this review study, studies using standard keywords in internal and external databases including: SID, Magiran, IranDoc, Medlib, Science Direct, PubMed, Scopus, Embase, Web of Science, Medline and Google Scholar search engine, were retrieved and selected without time limit.

RESULTS. Among the selected articles, 14 articles were eligible for inclusion in the study, which was performed on more than 20,000 people and several animal models of rats from 2005 onwards. The results showed that there is an inverse relationship between the concentration of antioxidant enzymes in the body and the intensity and progression of CKD. In severe cases, a significant decrease in the concentration of antioxidant enzymes in the body, as well as cofactors such as selenium, iron and zinc in the progressive and severe course of CKD has been observed.

CONCLUSIONS. The positive and significant effect of antioxidant compounds in chronic kidney disease is evident. The use of these compounds in the diet in the form of fruits, vegetables and grains, as well as the supply of iron and zinc and other minerals elements as cofactors for the action of enzymatic antioxidants has an effective role in the prevention and treatment of diseases by controlling free radicals.

Keywords: *antioxidant, prevention, treatment, chronic kidney disease*

INTRODUCTION

Chronic diseases, including chronic kidney disease, are a global health problem and cause the death of millions of people (1). Approximately 10 percent of the adult population in the United States have been suffering from this complication, which, along with cardiovascular disease, has created significant economic costs for people and governments. CKD eventually causes damage to the nephrons and leads to chronic renal failure (2, 3). About one million people die each year in the end-stages of renal disease, also the death rate due to CKD continues to increase and will reach 14 per 100,000 people by 2030. For this reason, this complication is a global threat to health (4, 5). Global increase in the number of patients with chronic kidney disease is a reflection of those with chronic renal failure being treated. The end-stage of treatment for this complication is dialysis, transplantation and kidney replacement, and less developed countries have not been able to meet increasing demands for treatment of this complication due to the lack of adequate health care resources. Research indicates the low rate of CKD in developed countries and their inhabitants can afford to cover the costs of renal replacement therapy (6, 7).

Chronic kidney disease (CKD) is associated with chronic inflammation, oxidative stress, and glomerular scar. In diabetes, one of the leading causes of end-stage renal disease, enhanced generation of reactive oxygen species (ROS) and renin-angiotensin system (RAS), are considered to contribute to the development and progression of diabetic nephropathy (8).

Also, the structural similarity of renal mesenchymal cells and vascular smooth muscle cells and the confirmed role of vitamin E in coronary artery healing suggest that antioxidants may be beneficial in CKD (9).

Fatigue in dialysis patients, one of the causes of which is vitamin C deficiency also may indicate the role of antioxidants in CKD (10). Fruit, vegetables and grains have been proven to help prevent the progression of chronic diseases (10).

Finally an imbalance between free radical production and antioxidant defense in uremia caused by CKD lead to the production of reactive oxygen species (ROS) resulting from oxygen metabolism. The release of free radicals and overproduction is associated with a variety of clinical disorders, including CKD and the defense system that counteracts them is the antioxidant system (11). Oxidative stress, the pathogenic role of which has been proven in cardiovascular and renal diseases, reflects an imbalance of oxidative compounds and antioxidant systems.

Antioxidants are protective chemicals that counteract the oxidative damage caused by macromolecules (12). There are two sources of antioxidants: synthesis in the body and absorption through diet, and two types of antioxidant mechanisms: enzymatic and non-enzymatic. The non-enzymatic type includes vitamins, minerals, glutathione and antioxidants derived from medicinal plants. The enzymatic type includes superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase (CAT) (13). Antioxidant therapy is significant as an effective treatment approach in many diseases such as chronic renal failure (14, 15).

This study was conducted with the aim to understand the role of antioxidants and the antioxidant system in the prevention and treatment of chronic kidney disease (CKD).

MATERIALS AND METHODS

All studies examining chronic kidney disease and the role of antioxidants in this complication were eligible for inclusion in the study. For this purpose, using standard keywords such as; antioxidants, prevention, treatment and chronic kidney disease were retrieved in internal and external databases including: SID, Magiran, IranDoc, Medlib, Science Direct, PubMed, Scopus, Embase, Web of Science, Medline and Google Scholar search engine, without time limit. Articles based on compliance with the role of antioxidants on chronic kidney disease and eligible titles among articles such as the effect of diets and medications containing antioxidants, enzymatic antioxidants and cofactors on chronic kidney disease have been reviewed. Then, due to the duplication and lack of relevance of the content to the subject of the article, screening and required information were extracted and analyzed from approved articles.

RESULTS

Using the above keywords, 46 articles were found and 14 articles were included in the study according to the inclusion and exclusion criteria (Fig. 1).

In the cases where the articles were reviewed, most of the studies discussed the effects of antioxidants in humans, so only the human species was listed as the test population (Table 1).

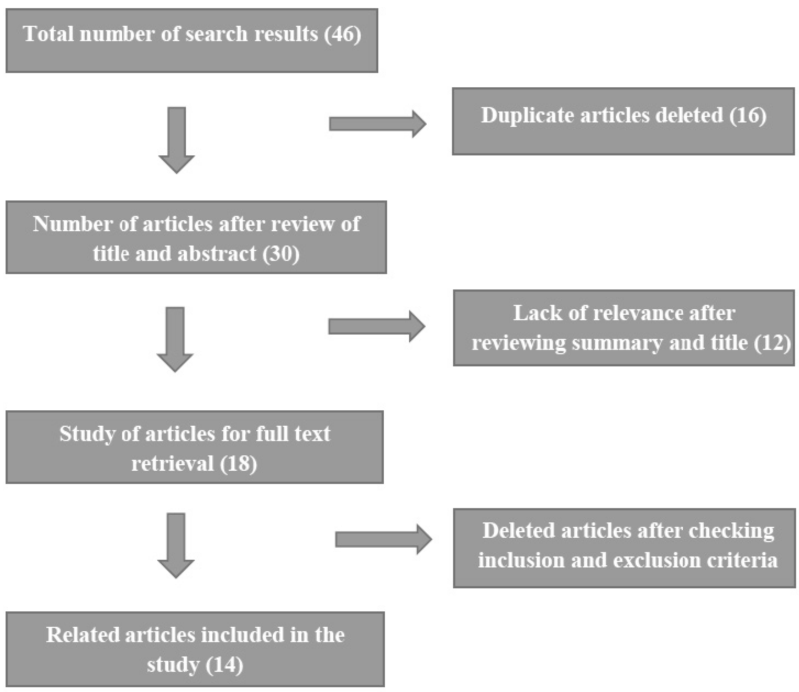

Figure 1. The process of selecting articles submitted for review

Table 1. Information on studies on antioxidants and their role in the prevention and treatment of chronic kidney disease (CKD)

Author	Year of publication	Study place	Population or species studied	Antioxidant
Jing Chen and colleague (16)	2015	United States of America	Human species 19,461 people CKD	Diet containing antioxidants
Bronislaw A. Zachara (17)	2015	Poland	Human species 454 people CKD	Glutathione peroxidase and selenium
Sudhir V. Shah (18)	2007	United States of America	Animal model and human CKD	Superoxidase catalase, vitamin E and selenium
A Meguid El Nahas and colleagues (19)	2005	England	Human species CKD	Diet containing antioxidants
Jorge Rojas-Rivera and colleagues (20)	2012	Spain	Human species CKD	Drugs with antioxidant and anti-inflammatory properties (such as: Bardoxolone methyl)
Minglei Lu and collegues (21)	2019	China and United States	Animal model	Nrf2 antioxidant response
Vassilios Liakopoulos and colleagues (22)	2019	Greece	Human species	Omega-3 fatty acids, statins, coenzyme Q10, curcumin, trace elements, vitamins B and D, green tea, flavonoids and polyphenols, NAC and α-tocopherol
Hadja Fatima Tbahriti and colleagues (23)	2013	Algeria	167 men and women CKD	Superoxide desmutase, catalase, glutathione peroxidase, glutathione reductase, vitamin E and iron and bilirubin
Hamid Nasri (24)	2007	Iran	Human species	Superoxide desmutase, catalase, glutathione peroxidase, N-acetylcysteine, vitamins E, C and selenium and herbs
Yu-Jie Zhang and colleagues (25)	2015	China	Human species and animal model	Medicinal plants, vegetables, fruits and grains
Mohammad Nasiruddin Rana and colleagues (26)	2020	Thailand	Human species	Xanthones from a tropical fruit of Garcinia mangostana L.
Mohamad Reza Tamadon and colleagues (27)	2015	Iran	Human species	Antioxidant enzymes, N-acetylcysteine, vitamins C, E.
David J. Kennedy and colleagues(28)	2019	United States of America	Human species	Vitamin E
Stefanos Roumeliotis and colleagues (29)	2019	Greece	Animal model	Vitamins E, C, polyphenols, flavonoids, tea, probiotic compounds, arginine, N-acetylcysteine

CKD – chronic kidney disease

DISCUSSION

In this study, 14 articles on antioxidants and chronic kidney disease were reviewed. The findings showed that a higher oxidative balance score (OBS), reflecting higher antioxidant levels, was associated with a lower prevalence of CKD and that OBS was inversely related to mortality. These findings provide a good approach to oxidative balance in predicting the risk of chronic kidney disease. Also, controlling and modifying external oxidants through diet in individuals with reduced renal clearance, especially when combined with antioxidant therapy, is effective in controlling CKD (16).

In chronic kidney disease, the antioxidant efficiency decreases directly with the progression of the disease and is minimal in the final stage of kidney disease. There are four dominant antioxidant enzymes. These include superoxide dismutases (SODs), catalase (CATs), glutathione peroxidases (GSH-Px), and possibly selenoprotein (SePP). Selenium, as a cofactor and part of some proteins, plays an important role in the activity of many of these enzymes and its deficiency plays a role in the development of disorders such as cancer, cardiovascular and kidney disease. A significant negative correlation was demonstrated between plasma selenium and creatinine concentrations in CKD. In healthy people, selenium supplementation increases the synthesis of GSH-Px activity in the blood and other tissues, which is reduced in people with CKD, so the disease progresses to end-stage renal disease (ESRD). GSH-Px are the important cellular components in balancing and eliminating ROS in patients with CKD, and Se has an integral role in maintaining this balance, so selenium supplementation should be considered as a suitable nutritional option in CKD (17).

Chronic kidney disease tends to progress to the final stage of kidney disease, which suggests common mechanisms for further loss of nephrons. Among the mechanisms involved in this process are active oxygen metabolites – reactive oxygen intermediates (ROMs) and oxidants. Superoxide and H2O2 are the primary species produced to be involved in the production of additional and more active oxidants, including highly reactive hydroxyl radicals, in which metals such as iron act as catalysts in the reaction. Iron can also be involved in the formation of ROMs. In many cases, administration of hydroxyl radical scavengers or iron chelators significantly reduces proteinuria. Several other animal and human studies have shown that reduction in proteinuria due to iron chelator significantly slows the progression of chronic kidney disease. Thus in CKD, both in animal and human studies, an iron-deficient diet or iron chelator provides functional and histological protection against disease progression (18).

CKD is more common in families with the genetic or familial predisposition and that suggested the mechanisms involved in renin-angiotensin system. A high prevalence of CKD has also been reported in hypertension, diabetes, or both. Some studies have linked the use of analgesics, particularly paracetamol and nonsteroidal anti-inflammatory drugs, to a higher risk of developing CKD. Control of proteinuria and inhibition of the renin-angiotensin system are important factors in slowing the progression of diabetic and non-diabetic CKD. Limits on salt and diets rich in fruits and vegetables and low in saturated fat have also been recommended. Managing high blood pressure, improving the education of the public regarding losing too much weight, regular exercises and dietary approaches containing antioxidants should lead to a long-term reduction in the number of people with diabetes and high blood pressure, the main reservoir of CKD cases (19).

The renin-angiotensin-aldosterone system (RAAS) is a major pathway involved in the pathogenesis and progression of chronic kidney disease, and RAAS blockade is an effective therapeutic strategy to reduce proteinuria and slow the progression of diabetic and non-diabetic CKD. Bardoxolone methyl, a new synthetic triterpenoid with antioxidant and anti-inflammatory properties, has been shown to improve renal function in patients with chronic kidney disease who previously received RAAS blockers with few side effects (20). Transmission of acute kidney injury (AKI) to chronic kidney disease (CKD) is one of the major causes of kidney failure. The conversion of AKI to CKD leads to interstitial fibrosis and atrophy of renal tubular cells, permanent damage to the renal tubules with persistent oxidative stress associated with abnormal Nrf2 antioxidant defense (Nrf2 – NF-E2-related factor, a cap-n-collar basic-region leucine zipper nuclear transcription factor that mediates the primary cellular defense against the cytotoxic effects of oxidative stress). In damaged kidney Nrf2 response was impaired and was associated with decreased antioxidant production. Inhibition of GSK3β (glycogen synthase kinase, a key modulator of the Nrf2 regulation) in renal tubules restored the antioxidant response of Nrf2 in the kidney through weekly treatment (with low-dose lithium) and prevented the transfer of AKI to CKD. Thus, the findings suggest that GSK3β-mediated regulation of Nrf2 may serve as a practical therapeutic target for correcting the long-term consequences of AKI and the development of CKD (21).

Disruption of the balance between the production of reactive oxygen species and antioxidant systems in favor of oxidants is called oxidative stress (OS). OS is present in the early stages of chronic kidney disease, gradually increasing as kidney function deteriorates and is exacerbated by renal replacement therapy. End-stage renal disease patients undergoing hemodialysis (HD) suffer from OS, which is associated with an increased risk of mortality and cardiovascular disease. The beneficial antioxidant effects of omega-3 fatty acids, statins, coenzyme Q10, curcumin, trace elements, vitamins B and D, green tea, flavonoids and polyphenols remain controversial and the most promising results in these patients seem to have N-acetylcysteine and α-tocopherol (22).

In another study prooxidant status was assessed by measuring the reactants of thiobarbituric acid, hydroperoxides and protein carbonyls (23). The antioxidant defense was assessed by analysis of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, vitamin E, iron and bilirubin. Antioxidant enzymes were previously reduced in the severe stage of CKD and were significantly reduced in HD patients. Also for vitamin E, Fe and bilirubin a significant decrease was observed in most of the groups studied, especially in HD patients, and the progression of CKD was associated with an increase in oxidative stress (23).

Oxidative stress is caused by an imbalance between the production of free radicals and antioxidant defense, therefore, antioxidants are effective in improving chronic renal failure due to oxidative stress. There are several endogenous antioxidant enzymes including superoxide dismutase, catalase, glutathione peroxidase and non-enzymatic defense such as glutathione, melatonin, N-acetylcysteine, urate and plasma protein thiols. Studies have shown that oxidative damage is mainly due to decreased levels of endogenous antioxidants. The presence of antioxidants in the cell or the administration of herbal medicines with antioxidant properties can improve the oxidative stress caused by kidney damage (24). Consumption of vegetables and fruits is inversely related to the risk of many chronic diseases, and the antioxidant phytochemicals in vegetables and fruits are responsible for these health benefits. Antioxidant phytochemicals can be found in many foods and herbs and play an important role in the prevention and treatment of chronic diseases caused by oxidative stress. They often have strong antioxidant and free radical scavenging abilities as well as anti-inflammatory effects, which are also the basis of other biological activities and health benefits such as anti-cancer, anti-ageing and protective function for kidney, cardiovascular disease and diabetes mellitus. For example, epigallocatechin gallate (EGCG) is an antioxidant compound in plant and fruit compounds in a study of an animal species, by reducing liver and kidney damage and improving age-related inflammation and oxidative stress by inhibiting NF-κB signalling, and increasing the length of the life of healthy mice (25).

Xanthones of a tropical fruit of *Garcinia mangostana L*. have a wide range of medicinal properties, including antioxidant, antibacterial, anti-inflammatory and anti-diabetic activities. The study by Rana et al. aimed to evaluate the possible protective effects of xanthones against chronic kidney disease (CKD) (26). The results showed that xanthones potentially kill free radicals due to its effectiveness in activating Nrf2, regulate the intracellular [Ca2+], as well as NF-κB pathway depletion, MAPK (mitogen-activated protein kinases) pathway. Thus, current findings suggest that xanthones may be a potential candidate for the management of heavy metal toxicity by suppressing oxidative stress in renal injury. Further studies are also needed to isolate abundant plant compounds and evaluate mechanical pathways (26).

Cardiovascular accidents are one of the leading causes of death in chronic kidney patients, especially chronic dialysis patients. Increased peroxidation products as well as decreased antioxidants are effective factors in atherosclerosis in these patients undergoing hemodialysis. Antioxidant compounds in foods have been suggested to play a beneficial role in chronic kidney disease or high blood pressure (27).

In patients with CKD, decreased PON-1 (Paraoxonase-1) enzyme activity associated with the antioxidant HDL was demonstrated which was predictive of increased risk of adverse cardiac events, including non-fatal myocardial infarction, non-fatal stroke, or death. Oxidative stress is an important mediator in the progression of kidney disease and points to the compensatory role of the potential antioxidant role of HDL and its associated protein PON-1. Further studies aimed at modulating PON-1 activity for both cardiac protective effects and potential protection of the kidney against disease progression in this population of patients may provide more knowledge (28).

Glomerular hypertension, ischemia, and interstitial inflammation and subsequent increase in OS have been linked to uric acid, hypertension, and CKD. As a result of hyperuricemia, changes in systemic and renal hemodynamics occur, resulting in loss of renal self-regulation and inflammation in rats. Hyperuricemia in rats causes accumulation of free radicals and significantly increases an oxidative stress, activates RAAS, and ultimately causes cell apoptosis, severe structural damage to the kidneys, and chronic kidney disease (CKD). Probiotics, arginine, and acetylcysteine are mentioned as antioxidant compounds that protect cell membrane integrity by eliminating ROS and blocking the chain of oxidative reactions (29).

CONCLUSIONS

As shown in various studies, there are the direct and indirect effects of antioxidants and compounds with antioxidant properties in CKD. The direct effect of antioxidants is to inhibit ROS metabolism, as well reduce the progression of chronic kidney disease by blocking the RAAS pathway. Antioxidant inflammation modulators potently induce the antioxidant and cytoprotective transcription factor Nrf2 and this is the basis of biological activities of pharmaceutical compounds such as Bardoxolone methyl and fruits and vegetables containing antioxidant compounds. Reducing underlying diseases such as hypertension and tissue damage has an indirect effect on reducing chronic kidney disease. Finally, it is essential the adoption and development of a comprehensive treatment protocol containing antioxidant compounds in chronic kidney disease.

REFERENCES

1. Wetmore JB, Collins AJ. Global challenges posed by the growth of end-stage renal disease. Ren Replace Ther 2016;2(1):1-7.
2. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 Suppl 1):S1-S266.
3. Xue JL, Ma JZ, Louis TA, et al. Forecast of the number of patients with end-stage renal disease in the United States to the year 2010. J Am Soc Nephrol 2001;12(12):2753-8.
4. Hamer RA, El Nahas AM. The burden of chronic kidney disease. BMJ 2006;332(7541):563:564.
5. Webster AC, Nagler EV, Morton RL, et al. Chronic kidney disease. Lancet 2017;389(10075):1238-52.
6. Collins AJ, Foley R, Herzog C, et al. United States Renal Data System 2007 Annual Data Report Abstract. Am J Kidney Dis 2008;51(1):A6-A7.
7. De Vecchi AF, Dratwa M, Wiedemann M. Healthcare systems and end-stage renal disease (ESRD) therapies – an international review: costs and reimbursement/funding of ESRD therapies. Nephrol Dial Transplant 1999;14(suppl_6):31-41.
8. Centers for Disease Control and Prevention (CDC). Prevalence of chronic kidney disease and associated risk factors – United States, 1999-2004. MMWR Morb Mortal Wkly Rep 2007;56(8):161-5.
9. Mune M, Otani H, Yukawa S. Effects of antioxidants on kidney disease. Mech Ageing Dev 2002;123(8):1041-6.
10. Kruk J. Association between vegetable, fruit and carbohydrate intake and breast cancer risk in relation to physical activity. Asian Pac J Cancer Prev 2014;15(11):4429-36.
11. Yu BP. Cellular defenses against damage from reactive oxygen species. Physiol Rev 1994;74(1):139-62.
12. Radák Z, Apor P, Pucsok J, et al. Marathon running alters the DNA base excision repair in human skeletal muscle. Life Sci 2003;72(14):1627-33.
13. Wu S, Li S, Xu X-R, et al. Sources and Bioactivities of Astaxanthin. Int J Mod Biol Med 2012;1(2):96-107.
14. Shahreza FD. Oxidative stress, free radicals, kidney disease and plant antioxidants. Immunopathol Persa 2017;3(2):e11.
15. Modaresi A, Nafar M, Sahraei Z. Oxidative stress in chronic kidney disease. Iran J Kidney Dis 2015;9(3):165-79.
16. Chen J, Siriki R. Antioxidants Therapy for Patients with Chronic Kidney Disease: A Question of Balance. Am J Nephrol 2015;42(4):318-319.
17. Zachara BA. Selenium and selenium-dependent antioxidants in chronic kidney disease. Adv Clin Chem 2015;68:131-51.
18. Shah SV, Baliga R, Rajapurkar M, et al. Oxidants in chronic kidney disease. J Am Soc Nephrol 2007;18(1):16-28.
19. El Nahas AM, Bello AK. Chronic kidney disease: the global challenge. Lancet 2005;365(9456):331-40.
20. Rojas-Rivera J, Ortiz A, Egido J. Antioxidants in kidney diseases: the impact of bardoxolone methyl. Int J Nephrol 2012;2012:321714.
21. Lu M, Wang P, Qiao Y, et al. GSK3β-mediated Keap1-independent regulation of Nrf2 antioxidant response: A molecular rheostat of acute kidney injury to chronic kidney disease transition. Redox Biol 2019;26:101275.
22. Liakopoulos V, Roumeliotis S, Bozikas A, et al. Antioxidant Supplementation in Renal Replacement Therapy Patients: Is There Evidence? Oxid Med Cell Longev 2019;2019:9109473.
23. Tbahriti HF, Kaddous A, Bouchenak M, et al. Effect of different stages of chronic kidney disease and renal replacement therapies on oxidant-antioxidant balance in uremic patients. Biochem Res Int 2013;2013:358985.
24. Nasri H. Antioxidant therapy to ameliorate chronic kidney disease induced by oxidative stress; an updated mini-review. J Prev Epidemiol 2017;2(1):e04.
25. Zhang Y-J, Gan R-Y, Li S, et al. Antioxidant Phytochemicals for the Prevention and Treatment of Chronic Diseases. Molecules 2015;20(12):21138-56.
26. Rana MN, Tangpong J, Rahman MA. Xanthones protects lead-induced chronic kidney disease (CKD) via activating Nrf-2 and modulating NF-kB, MAPK pathway. Biochem Biophys Rep 2020;21:100718.

27. Tamadon MR, Zahmatkesh M, Mousavi SSB. Administration of antioxidants in chronic kidney disease. J Nephropharmacol 2015;4(1):9-11.
28. Kennedy DJ, Wilson Tang W, Fan Y, et al. Diminished antioxidant activity of high-density lipoprotein–associated proteins in chronic kidney disease. J Am Heart Assoc 2013;2(2):e000104.
29. Roumeliotis S, Roumeliotis A, Dounousi E, et al. Dietary Antioxidant Supplements and Uric Acid in Chronic Kidney Disease: A Review. Nutrients 2019;11(8):1911.

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