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A Review on Dietary Poly Phenols: Herbal Neutraceuticals to Combat Nephrotoxicity

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Abstract

Acute kidney injury is a very common diagnosis, present in up to 60% of critical patients, and its third most main cause is due to drug toxicity. Nephrotoxicity defined as any injury in renal caused directly or indirectly by hepatotoxic drug, with acute renal failure, tubulopathies, and glomerulopathies as common clinical presentations**.** Dietary polyphenols are essential antioxidant agents have shown protective effects in nephrotoxicity. Polyphenols are the largest group of phytonutrients and derived from plant based food including fruits, vegetables, spices, herbs etc. In the present era, there has been a great interest towards the health benefits of dietary polyphenols against oxidative stress related diseases such as diabetes mellitus, cancer, chronic kidney disease etc. Here, the content presents an overview and recent information on dietary polyphenols in context of relevance to the nephrotoxicity.

Keywords: Nephrotoxicity, dietary polyphenols, antioxidant, oxidative stress

Introduction

The kidneys are paired and bean shaped organs, located on both sides of the vertebralcolumn. The kidney occurs about 0.5% of the total mass. Through renal artery kidney receives 20-25% of the total arterial blood and each kidney consists of about ten lakh nephrons[1]. It is theunit of the kidney. Nephron forms urine by filtering the blood. The small ions, watermolecules and other small molecules get reabsorbed back into the peritubular capillaries byreabsorption. After reabsorption the waste molecules, ions remain in the urine and they get eliminated throughurine. Acute kidney injury is cause mainly due to drugs. Most of the patients are subjected to thediagnostic and clinical procedures and they have more co morbidities with the potentialkidney failure. The drug induced nephrotoxicity is more common in patients receivingcertain medication and undergoing certain specific clinical conditions.

Nephrotoxicity is one of the most common kidney problemscause significant morbidity and mortality worldwide. The nephrotoxicity is occurs due to poisonous effect of some toxic chemicals and certain type of drugs on the kidneys[2]. Nephrotoxins are the agents displaying nephrotoxicity. Various nephrotoxicants, cancer therapeutics such as cisplatin, antibiotics such as aminoglycosides, metals such as mercury, arsenic and lead, and drugs of abuse such as cocainecauses nephrotoxicity like acute and chronic renal failure. The use of various drugs also leads to the development of nephrotoxicity. Once nephrotoxicity occurs, then the both kidneys fail to remove excess urine, and waste molecules. The kidneys are very important organs and involved in the excretion of waste products, toxic substances in the body. In kidney failure, the toxic metabolites retain in the body leading severe complications like edema, ascites, hepatomegaly, etc.[3] The nephrotoxic effect develops usually more in patients who are already suffering from the renal impairment.

Risk Factors

There are various factors that enhance a person 'susceptibility to a potentially nephrototoxic drug. Some of the nephrotoxic drugs are antibiotics (aminoglycosides, sulphonamides, amphotericin-B, neomycin, polymyxin, chlotetracyclines), rifampicin, bacitracin, trimethoprim, cephaloridine, methicillin, aminosalicyllic acid, oxy- and chlor-tetracyclines), analgesics(NSAIDs, ibuprofen, acetaminophen), contrast agents (sodium iodide), heavy metals (lead and mercury), anti-cancer drugs like cisplatin, cyclophosphamide, and cyclosporine, agents forming from methanoglobin, solvents and fuels like carbon tetrachloride(CCl_4), methanol, amylalcohol, glycol, herbicides, pesticides, and diseases that cause the nephrotoxicity. The preventive measures include alternative use of safer drugs wherever possible; and by correcting the risk factors of nephrotoxicity, by adjusting the dosage of drugs, by monitoring the renal function during the therapy by conducting the renal function, by observing the vital body function, renal function and by watching vital signs during therapy; and finally by avoiding nephrotoxic drug combination.

Importance of Herbs in Nephroprotection

The prolonged administration of nephrotoxic drugs will cause nephrotoxicity in patients who are receiving these drugs. Worldwide in recent years more attention and importance is given to the research on medicinal plants. Even in India, a large number of drugs obtained from plants are studied for their therapeutic applications. Currently the researchers are given more interest on studying at molecular levels to understand their mechanism of action by isolating the plant constituents. Numerous kidney protective herbs are prescribed for the nephrotoxicity by the ancient literature.

Polyphenols

Polyphenols are the largest group of phytonutrients that exert different biological activities that are beneficial to human health. Dietary polyphenols represent a group of secondary metabolites which widely occur in fruits, vegetables, cereals, and plant-derived beverages such as fruit juices, tea, coffee and red wine. Polyphenols are mostly derivatives, and/or isomers of flavones, isoflavones, flavonols, catechins, and phenolic acids. Dietary polyphenols exhibit many biologically significant functions, such as protection against oxidative stress, and degenerative diseases. Experimental data indicate that human consumption of polyphenols is, generally higher than any other phytonutrient or dietary antioxidant[4-6]. The scientific research interest in biological activities of polyphenols for maintaining human health approximately started in the year of 1980s and a tremendous progress has been made to date[7,8]. Polyphenols are widely distributed in the plant kingdom. Dietary polyphenols may act an indirect protection by activating endogenous defense systems and by modulating cellular signaling proliferation processes such as NF-κB activation, glutathione biosynthesis, AP-1 DNA binding, PI3-kinase/Akt pathway, MAPK proteins (ERK, JNK and P38) activation, and the translocation into the nucleus of Nrf2[9-11].

Classification of Dietary Polyphenols

Dietary polyphenols are one of the most importance antioxidants in human diets. Recently more than 8,000 structural variants are available; they are secondary metabolites of plants and provide many substances with aromatic ring(s) contains one or more hydroxyl moieties. They are subdivided into groups (Figure 1) by the number of phenolic rings and of the structural elements that link these rings [12]: (1) The phenolic acids with the subclasses synthesis from hydroxybenzoic acids (gallic acid) and from hydroxycinnamic acid, containing caffeic, ferulic, and coumaric acid; (2) the large flavonoid subclass, which includes the flavonols, flavones, flavanones, isoflavones, flavanols, and anthocyanidins; (3) the lignans and the polymeric lignins; and (4) the stilbenes.

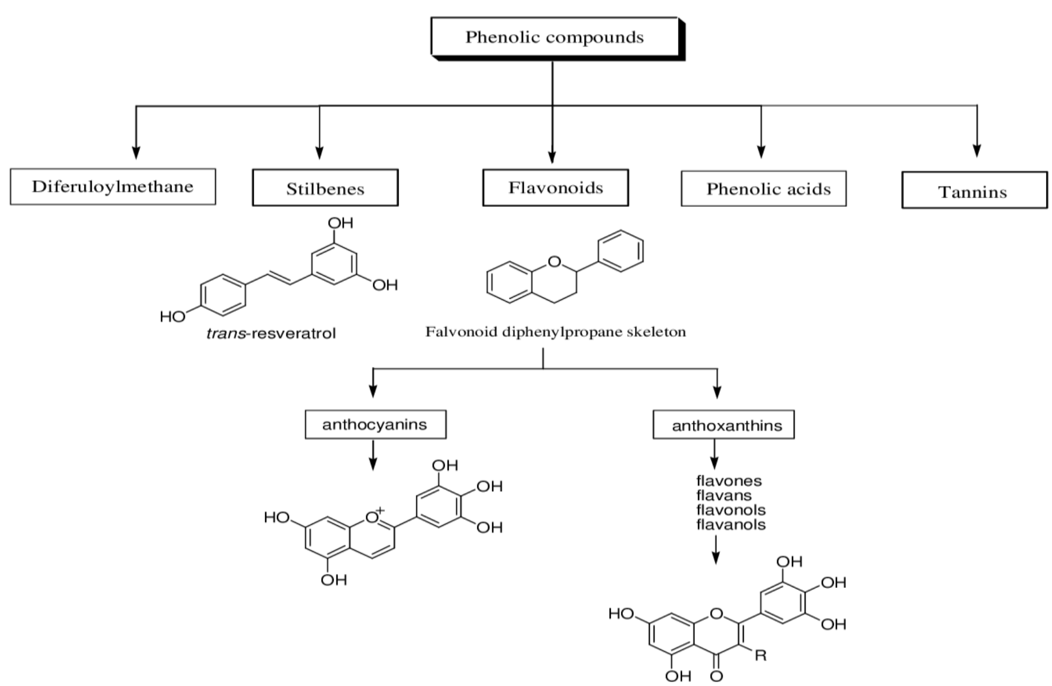

Figure 1: Classification of Dietary Polyphenols

Phenolic Acids

A major class within the phenolic compounds is the hydroxycinnamic acids, which are widely available in plant kingdom. The major hydroxycinnamic acid is caffeic acid, which occurs in foods mainly as an ester with quinic acid called chlorogenic acid (5-caffeoylquinic acid). Chlorogenic acid and caffeic acid are antioxidants *in vitro* and they might inhibit the formation of mutagenic and carcinogenic *N*-nitroso compounds for the inhibitory effect on the *N*-nitrosation reaction *in vitro*.

Flavonoids

Flavonoids are one of the most abundant polyphenols in human diets, and are mainly divided into: (a) anthocyanins, glycosylated derivative of anthocyanidin, present in colorful flowers and fruits; (b) anthoxanthins, a group of colorless compounds further divided in several categories, including flavones, flavans, flavonols, flavanols, isoflavones, and their glycosides. Flavonols are mainly represented by myricetin, fisetin, quercetin and kaempferol.

Stilbenes

Stibenes are structurally characterized by the presence of a 1,2-diphenylethylene nucleus with hydroxyls substitued on the aromatic rings, and exist in the form of monomers or oligomers. Stilbenes are best known compound is trans-resveratrol, possessing a trihydroxystilbene skelelton.

Tannins

Tannins are a group of water-soluble polyphenols having molecular weights from 500 to 3,000 which are subdivided into condensed and hydrolisable tannins, and commonly found complexed with alkaloids, polysaccharides and proteins, particularly the latter. On the basis of structural characteristics there are two groups, gallotannins and ellagitannins of hydrolysable tannins.

Diferuloylmethanes

Diferuloylmethanes are one of the small groups of phenolic compounds with containing two aromatic rings substituted with hydroxyls, and linked by aliphatic chain containing carbonyl groups. There are also some other polyphenols such as hydroxytyrosol, a simple polyphenol presenting in olive fruits and olive oil[13,14].

Sources of Dietary Polyphenols

The main dietary sources of polyphenols include some common fruits, vegetables and beverages. Phenolic acids account for about one third of the total intake and flavonoids account for the remaining two thirds. The most abundant and importance flavonoids in the diet are flavanols (catechins plus proanthocyanidins), anthocyanins and their oxidation products. The main polyphenol dietary sources present in fruit and beverages (fruit juice, wine, tea, coffee, chocolate and beer) and, to a lower extent vegetables, dry legumes and cereals.

Table 1: Classification and Sources of Dietary Polyphenols

Class and Subclass	**Dietary Polyphenol**	**Foods or Beverages**
Flavonoids Anthocyanidins	Cyanidin 3 galactoside Cyanidin 3-glucoside Cyanidin 3-arabinoside Cyanidin 3-xyloside Malvidin Delphinidin Pelargonidin	**Fruits**: blackberries, black currant, blueberries, black grape, elderberries, strawberries, cherries, plums, cranberry, pomegranate juice, raspberry **Others**: red wine
Anthoxanthins Flavonols	Myricetin Fisetin Quercetin Kaempferol Isorhamnetin	**Vegetables**: capers, celery, chives, onions, red onions, dock leaves, fennel, hot peppers,cherry tomatoes, spinach, sweet potato leaves, lettuce, celery, broccoli, Hartwort leaves, kale **Cereal**: buckwheat, beans(green/yellow) **Fruits**: apples, apricots, grapes, plums, bilberries, blackberries, blueberries, cranberries, olive elderberries, currants, cherries, black currant juice, apple juice, ginkgo biloba **Spices and herbs**: dill weed **Others**: red wine, tea (green, black), tea (black beverage), cocoa powder, turnip (green), endive, leek

Flavanones	Naringenin Eriodictyol Hesperetin	**Citrus fruits and juices**: lemon, lemon juice, lime juice, orange, orange juice, grapefruit, tangerine juice **Spices and herbs**: peppermint
Flavones	Apigenin Luteolin	**Fruits**: celery, olives **Vegetables**: hot peppers, celery hearts, fresh parsley **Spices and herbs**: oregano, rosemary, dry parsley, thyme
Flavanols (Flavan-3-ols)	(+)-Catechin (-)-Epicatechin (-)-Epicatechin 3-gallate Morin (-)-Epigallocatechin (-)-Epigallocatechin-3-gallate (+)-Gallocatechin Procyanidins Prodelphinidins	**Fruits**: apples, apricots, grapes, peaches, nectarines, pears, plums, raisins, raspberries, cherries, blackberries, blueberries, cranberries **Others**: red wine, tea (green, black), chocolate (dark, milk), white wine, cocoa
Isoflavones (Flavans)	Genistein Daidzein Equol	**Fruits**: grape seed/skin **Others**: soybean, soy nuts, soy flour/bread, tofu, miso, soy milk, tofu yogurt, soy cheese/sauce/hot dog
Flavonoid glycoside	Rutin Hesperidin Naringin	**Fruits**: lemon, orange, orange juice, grapefruit, tangerine juice

Phenolic acids Hydroxycinnamic acids	Caffeic acid Chlorogenic acid Ferulic acid Neochlorogenic acid P-coumaric acid Sinapic acid Caftaric acids	**Fruits**: bluberry, cranberry, pear, cherry(sweet), apple, orange, grapefruit, cherry juice, apple juice, lemon, peach, **Vegetables**: potato, lettuce, spinach **Others**: coffee beans, tea, coffee, cider
Hydroxybenzoic acids	Ellagic acid Gallic acid Corilagin	**Fruits**: strawberry, raspberry grape juice(black/green), longan seed, pomegranate juice
Tannins	Catechin polymers Epicatechin polymers Ellagitannins Proanthocyanidins Casuarictin Sanguin H6 Tannic acids	**Fruits**: grape (dark/light) seed/skin, apple juice, strawberries, longan, raspberries, pomegranate, walnuts, muscadine grape, muscadine grape, peach, blackberry (juices/jams/jellies), olive, plum, **Vegetables**: chick pea, black-eyed peas, lentils, **Cereal**: haricot bean, **Others**: red wine, white wine, cocoa, chocolate, oak-aged red wine, tea, cider, tea, coffee, immature fruits
Diferuloylmethane	Curcumin	herbal remedy, dietary spice turmeric

Bioactivities of Dietary Polyphenols

Dietary intake of plant polyphenols can vary considerably and be quite high. However, ultimately the nutritional impact and subsequent systemic effects depend on the fate of polyphenols in the human digestive tract[15,16]. Physicochemical characteristics of polyphenols appear to dictate absorption and metabolism and are determined primarily by the chemical structures[17,18]. Relatively small molecular weight phenolic acids, such as gallic acid and isoflavones are easily absorbed through the gut followed by flavanones, catechins, and quercetin glucosides. Larger polyphenols such as proanthocyanidins are very poorly absorbed. The main difficulty with incorporating polyphenols into existing products is to present them in a form that is bioavailable[19]. Accordingly, the total polyphenol metabolite content in plasma or in urine after intake of dietary polyphenols is generally low[20]. It was further noted that bioavailability is differed greatly from one polyphenol to another and the most abundant dietary polyphenol was not necessarily the one leading to the highest levels of active metabolites in plasma. The maximum plasma concentrations of polyphenol metabolite content are <10 µmol/L[21]. The characteristics of polyphenols in physicochemical mechanism contribute to the disparity in results between the epidemiological studies and *in-vitro* data, which may affect, in part, relatively poor bioavailability, rapid metabolism, and excretion of polyphenols[22].

Scientists are being taking efforts to increase the bioavailability of polyphenols but several considerations, and potential impediments, exist including solubility, permeability, metabolism, excretion, target tissue uptake using nanoparticle based approaches and disposition[22]. Initial strategies for improving bioavailability of dietary polyphenol supplements include changes to polyphenol structure, which may affect the solubility and dissolution, and the use of pharmaceutical recipients[23]. An additional consideration is that degradation and absorption of polyphenols within the gastrointestinal tract depend on the intestinal microflora and gut enzymes, which may significantly change bioavailability[24].

Metabolism of Polyphenols

Dietary polyphenols are initially metabolized, within the gastrointestinal tract. Glycosides are hydrolyzed to their corresponding aglycones prior to the absorption, aglycones and low molecular weight polyphenols molecules are absorbed directly. Polyphenols that are not absorbed are transported to the colon where they can be readily hydrolyzed by colonic microflora to simpler chemical compounds and eliminated in the feces or further modified. Bacterial fermentation of the glycones effectively releases the polyphenol from fiber permitting subsequent metabolism similar to other aglycones[25].

Polyphenols and Human Diseases

Correlations between the intake of polyphenols and reduced incidence of chronic diseases have been firmly established using different *in-vivo* models in the past decades. The in cooperation of polyphenols in the prevention and management of inflammation and oxidative stress related pathologies is emerging (Figure 2). Epidemiological studies have repeatedly shown an inverse association between the occurrence of chronic diseases and the consumption of polyphenolic rich diet[26,27]. Various experimental data suggested that polyphenol-rich foods and beverages may increase plasma antioxidant capacity. This increase in the antioxidative capacity of plasma and following the consumption of polyphenol-rich food may be explained either by the presence of reducing polyphenols and their metabolites in plasma, by their effects upon concentrations of other reducing agents *via* sparing effects of polyphenols on other endogenous antioxidants, or by their effect on the absorption of pro-oxidative food components, such as iron[28]. Consumption of antioxidants has been associated with reduced levels of oxidative damage to lymphocytic DNA[29]. Numerous increasing evidences that as antioxidants, polyphenols may protect cell constituents against oxidative stress and therefore, limit the risk of various degenerative diseases associated with oxidative stress[30,31].

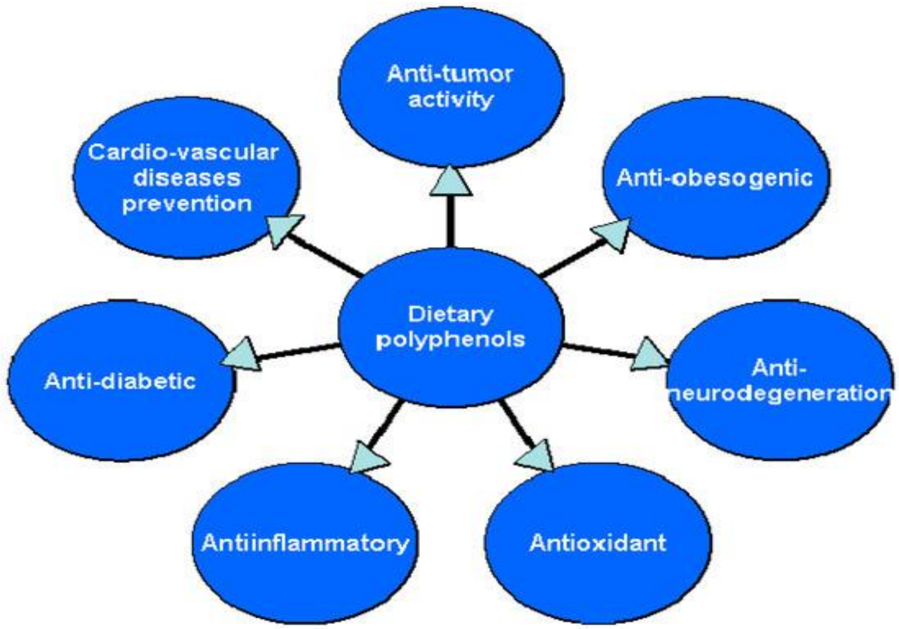

Figure 2. Biological Properties of Dietary Polyphenols Prevention on Lifestyle Diseases

Dietary Polyphenols and Nephrotoxicity

The nephrotoxicity is occurs due to poisonous effect of some toxic chemicals and complications include lower glomerular filtration rate, higher serum creatinine, and reduced serum magnesium or potassium levels. Nephrotoxin-induced kidney injury is associated with increased kidney vascular resistance and histological damage to proximal tubular cells resulting in decreased blood flow and ischemic injury of the kidneys, contributing to a decline in glomerular filtration rate. The nephrotoxin caused cytotoxicity has multiple intracellular effects, including regulating genes, causing direct cytotoxicity with reactive oxygen species (ROS), apoptosis, activating MAPKs, stimulating inflammation and fibrogenesis. These events cause tubular damage and tubular dysfunction with sodium, potassium, and magnesium wasting. It is due to a combination of cell membrane peroxidation, mitochondrial dysfunction, inhibition of protein synthesis, and DNA injury. These events conclude the loss of renal function during nephrotoxicity, and acute renal failure[32,33].

Nephrotoxin increases ROS production via the disrupted respiratory chain and induce mitochondrial dysfunction. Nephrotoxin induces ROS formation in the microsomes via the cytochrome P450 system. This drug causes break down of nuclear and mitochondrial DNA and production of ROS lead to activation of both mitochondrial and non-mitochondrial pathways of apoptosis and necrosis. ROS in renal epithelial cells reduce the activity of antioxidant enzymes and deplete intracellular concentrations of glutathione (GSH). Nephrotoxicity of drug is amassing of it in the tubular epithelial cells of proximal kidney tubule and is characterized by morphological destruction of intracellular organelles and cellular necrosis[34]. Oxidative stress plays an important role in development of kidney disease including glomerular injury or promoting hypertension and kidney ischemia.

In addition, it consequences decrease of natural cell antioxidant capacity or increase in quantity of ROS in kidney. A growing amount of results provide evidence that toxic drugs are capable of interacting with nuclear proteins and deoxyribonucleic acid (DNA) causing oxidative deterioration of biological macromolecules[35]. Numerous studies have focused on the role of antioxidants in nephrotoxicity. Also the oxidative stress induced nephrotoxin in the kidney was partially inhibited by antioxidant therapy using antioxidants such as vitamin C or E, flavonoids, superoxide dismutase, glutathione and selenium, as well as plants antioxidants[36]. The antioxidants are bioactive molecules which are capable of decreasing or preventing the oxidation of substrate molecules. The oxidation reactions can produce free radicals, which start chain reactions and subsequently can cause a large number of diseases in humans. Antioxidant from natural products has attracted a lot of attentions, nowadays. The natural product antioxidants may detoxify ROS in kidneys. Hence, antioxidants have potential therapeutic applications.

Antioxidant compounds remove free radical intermediates, and inhibit other oxidation reactions by being oxidized themselves. Antioxidants trap free radicals, terminating the chain reaction by chelating metal ion and preventing the reaction with ROS or by chelating metal and protecting against metal toxicity[37]. Chelating metal has ability of binding to toxic metal ions to form complex structures which are easily excreted from the body removing them from intracellular or extracellular spaces. The concept of cisplatin therapeutic is based on simple coordination of herbal plants, evolution of an ideal chelator and chelation therapy that completely removes specific toxic metal from desired site in the body which involves an integrated drug design approach. Some herbal medicines have also been shown to protect kidney injury. Natural products from herbal plants have capacity to ameliorate oxidative stress. Phytochemicals play an important role as natural antioxidants and immunomodulators[38].

Dietary Polyphenols: A natural Antioxidants

Antioxidant compounds including tocopherols, flavonoids, carotenoids, and phenolic compounds can inhibit Fe^{3+} induced oxidation and scavenge free radicals. Also they act as reductants spices and are used in medicine. It is notable that phenolic compounds have strong H-donating activity. Antioxidants protect biomolecules from free radical damage induced by both ROS and reactive nitrogen species (RNS)[39]. The plant phenolic antioxidants are divided into four general groups: phenolic diterpenes (carnosol and carnosic acid), phenolic acids (gallic, protocatechuic, caffeic, and rosmarinic acids), flavonoids (quercetin and catechin), and volatile oils (menthol). Generally phenolic acids act as antioxidants by trapping free radicals and flavonoids can scavenge free radicals and chelate metals as well and biological aspects of antioxidants are particularly related to their chelating properties. Also flavonoids with multiple hydroxyl groups are more effective antioxidants than the other ones with only one.

Role of Dietary Polyphenols in Antioxidant Activities and Free Radical Scavenging Properties

In order to combat and neutralize the deleterious effects of ROS, various antioxidant strategies have evolved either by increasing the endogenous antioxidant enzyme defenses or by enhancing the non-enzymatic defenses through dietary or pharmacological means. Dietary polyphenols have been reported to possess potent antioxidant activity by regulating endogenous and exogenous mechanisms. Dihydrocaffeic acid was able to scavenge free radicals (superoxide anion, hydroxyl and peroxyl radicals) in human EA.hy926 endothelial cells[40]. Curcumin and quercetin increased enzymatic and non-enzymatic antioxidant activities such as superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase (CAT) or glutathione reductase (GR) *in vivo* and *in vitro* and activatedendogenous defense systems *in vitro.* Hydroxytyrosol could increase CAT and SOD activities in rats fed a cholesterol-rich diet[41]. The transcription factor Nrf2 regulates the basal and inducible expression of numerous detoxifyingand antioxidant genes. The Nrf2–Kelch-like ECH-associated protein 1 (Keap1)-ARE system is now recognized as one of the major cellular defence mechanisms against oxidative and xenobiotic stresses[42].

Role of Dietary Polyphenols in Protective Effect on Immune Cell Functions

Dietary polyphenols appear to have a protective role on immune cell functions. Alvarez *et al*. suggested that leukocyte functions were improved in prematurely aging mice after supplementation of polyphenol-rich cereals for five weeks. They may increase macrophage chemotaxis, phagocytosis, activity of microbicidal, and natural killer function, and increase lymphoproliferation and IL-2 release in response to lipopolysaccharide and concanavalin A. Curcumin could prevent tumor-induced T cell apoptosis by downregulating Bax level and augmenting Bcl-2 expression and restore cytokine-dependent Jak-3/Stat-5a signaling pathway in T cells of tumor bearer. Caffeic acid, ferulic acid, and ellagic acid could inhibit apoptosis through the independent mechanism of Bcl-2 in normal human peripheral blood mononuclear cells[43]. Thus, regular intake of these compounds in diet will protect and improve quality of life.

Anti-Inflammatory Effect of Dietary Polyphenols

Since low-grade, chronic inflammation is a key factor in the development and progression of lifestyle diseases and beneficial effects of dietary polyphenols towards inhibition and reduction of any form of inflammation may be crucial in prevention and treatment of this type of disorders. Several experimental studies revealed positive role of tea polyphenols considering inhibition of different mechanisms of inflammation.

Conclusion

Dietary polyphenols is a group of phytonutrients that exert different biological activities that are beneficial to human health. Considering the significant amounts of compounds consumed in this class and the multitude of their activities, it should be noted that they can play an important role in the prevention of numerous disorders, including kidney diseases. Dietary polyphenols are beneficial against the development and progression of many chronic oxidative stress related pathological conditions. The role of polyphenols in human health and disease is still an interesting area of research and more research of this type is needed to better understand the real value of dietary polyphenols in the context of their ability to prevent the progress of kidney diseases.

Conflict of Interest

None declared

Reference

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