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RESEARCH ARTICLE

Acute Kidney Injury: Current and Future Therapies Involving Antioxidants and Antioxidant Formulations

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ABSTRACT

Acute kidney injury is characterised by abrupt failure of kidney function, sometimes leading to chronic kidney disease, and is associated with significant morbidity and mortality. However, there is no clear effective therapeutic solution and treatment is mainly based on either alleviation or removal of the possible cause and/or renal replacement therapy. Oxidative stress has been indicated as one of the main pathophysiological pathways in the development of acute kidney injury. Various treatments including antioxidants, inflammatory mediators and genetic modifiers have been proposed to for the treatment of this condition. Epidemiological studies show lower incidence of kidney failure with higher consumption of antioxidants. However, the data is inconclusive due to their physicochemical properties, bioavailability or toxicity. Novel drug delivery systems such as liposomes and nanoparticles have been proposed to overcome the pharmacodynamic and pharmacokinetic barriers. This review provides a brief introduction to acute kidney injury and the different factors involved in its pathology, focusing on oxidative stress. It also covers details of antioxidant use as preventive and/or treatment option. It will summarise their limitations as free drugs and the possible improvement in their bioavailability by two main novel drug delivery systems: liposomes and polymeric nanoparticles. Other therapies such as inflammatory mediators and genetic modifiers are also discussed briefly.

Keywords: Acute kidney injury; antioxidants; ascorbic acid; curcumin; flavonoids; liposomes; nanoparticles; oxidant injury; oxidative stress; resveratrol; α-tocopherol

1. Introduction

One of the main functions of the kidney is to filter the blood and remove nitrogenous waste, excess fluids and excess electrolytes. Acute kidney Injury (AKI), formally known as acute renal failure, is a broad definition of a condition where the kidneys suddenly fail to function as an excretory organ[1,2]. Even if patients survive AKI, they are most likely to suffer chronic immune or cardiovascular diseases later and have a higher risk of developing chronic kidney disease (CKD, chronic renal failure)[1-7]. Although, there are no precise studies of the burden of AKI at an economic level, it clearly contributes to extended hospital stay, excess hospital costs and increased mortality[8].

This review article will give a brief introduction to the definitions and classifications of AKI including the different factors involved in the pathology of this disease focusing on oxidative stress. The review will also cover how antioxidants have recently been investigated as a preventative measure as well as a treatment option and their limitations as therapeutic agents. The possible improvement in their bioavailability using two main novel drug delivery systems: liposomes and polymeric nanoparticles is discussed. Other proposed therapies such as inflammatory mediators and genetic modifiers are discussed briefly.

2. Physiology of the Kidney

The function of the renal system is very complex, but its main function is to regulate body fluids and maintain homoeostasis. This is performed by three different steps; filtration, reabsorption and secretion. The filtrate is formed by filtering the blood entering the glomerulus from the afferent arteriole into the Bowman's capsule. This is done through three different layers of cells; firstly, through the endothelial cells, lining the capillaries of the glomerulus, followed by the glomerular basement membrane and finally through the epithelial cells of Bowman's capsule. The driving force at this point is only the pressure gradient within the glomerulus which is a combination of blood pressure and renal haemodynamics. Most of the water and solutes are reabsorbed back into the blood circulation at different points of the tubule via different mechanisms, including simple and facilitated diffusion, active transport, symport and osmosis. Solutes that are reabsorbed include amino acids, glucose, fructose, sodium, potassium, calcium, hydrogen carbonate and chloride ions. Urine formation also involves the secretion of non-filtered endogenous and exogenous substances from the blood into the urine along the proximal and distal tubule. Examples include ammonia which diffuses passively and hydrogen ions which diffuses actively by antiport in exchange of sodium ions[9-11] [Figure 1].

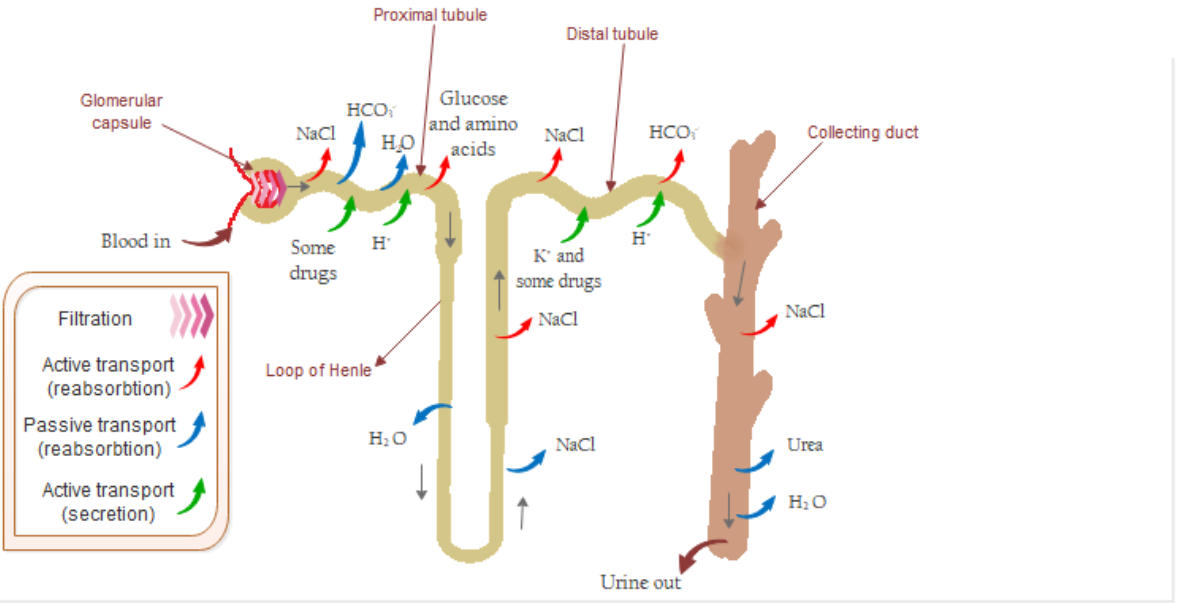

Figure 1: Reabsorption and secretion mechanisms at different sites of the renal tubule. Adapted from Hoenig and Zeidel[12].

Different hormones regulate kidney function. These include antidiuretic hormone (vasopressin) and aldosterone, which increase the reabsorption of water and sodium, respectively in the late distal tubule and collecting ducts. Natriuretic peptides, on the other hand, increase sodium excretion in different parts of the nephron. Parathyroid hormone and fibroblast growth factor 23 (FGF23),

both regulate phosphate excretion and vitamin D production. Other hormones produced by the kidneys are renin, an enzyme which helps regulate blood pressure through the renin-angiotensin-aldosterone hormonal system and erythropoietin, a hormone that is essential for the production of red blood cells[9].

3. Definitions of Acute Kidney Injury

Although, numerous attempts have been made to define AKI with many variations described, there is no one uniform definition used worldwide. This is the main cause for lacking precise statistical studies on its epidemiology[13-15]. In 2004, the Risk Injury Failure Loss of Kidney function End-stage kidney disease (RIFLE) classification was established to define and classify AKI[13-16]. This system was altered in 2007 to the Acute Kidney Injury Network (AKIN) classification to give more specificity and sensitivity to the concept[13-17]. The AKI is now defined by the abrupt decline (hours to days) in kidney function, leading to a rise in serum creatinine (SCr) and/or a decrease in urine output (UO)[1,13,18]. Electrolyte disturbance may also be observed during AKI as there may be reduction in the serum sodium and calcium ions with an increase in the serum potassium and phosphate levels compared to normal conditions. In addition, blood also may become more acidic, decreasing its pH value and hypervolaemia or hypovolaemia may be present according to severity of the injury[19]. As shown in Table 1, the SCr and UO are used according to the AKIN, to classify AKI into three stages. Stage 1, where SCr increases by 150-200%, Stage 2, where SCr increases by 200-300% and stage 3, where SCr increase by over 300%[13,18].

Table 1: The AKIN Classification. Adapted from Mendoza 2011[13]

Stage	SCr Criteria	UO Criteria
1	Increase in SCr of ≥0.3 mg/dl or increase to 150-200% (1.5 to 2-fold) from baseline	Less than 0.5 ml/kg/h (for >6 h)
2	Increase in SCr to >200-300% (2 to 3-fold) from baseline	Less than 0.5 ml/kg/h (for >12 h)
3	Increase in SCr >300% (>3-fold) from baseline or SCr≥4.0mg/dl with acute increase ≥0.5mg/dl	Less than 0.3 ml/kg/h (for 24 h) or anuria (for 12 h)

4. Epidemiology

As mentioned previously, epidemiology of AKI is very controversial. One specific study used the RIFLE classification and found the morbidity rate for AKI in hospitalized patients to be 9%[13,20]. Another specific review mentioned that the number of patients diagnosed with AKI in USA, Europe and Australia in 2010, was over one million patients with 2% of hospital admissions being referred for dialysis[21]. The AKI is agreed to be at its highest percentage in the intensive care unit and in seriously injured patients, where it ranges from 9% to 52%[4,22]. According to the RIFLE criteria, it may be as high as 66%. Mortality rate due to AKI is quite high with around 32% of AKI patients not surviving the condition[3,4]. Several researchers indicate the reason behind its wide epidemiology due its presentation as a multi-organ disease with overlapping causes[1]. For example, the incidence of AKI after angiography ranges from 1% to 38% according to different studies and population[13]. It should be mentioned that the diagnosis of AKI is increasing along with an increased awareness of its importance[20,23]. But still there is a significant amount of missing data, especially from developing countries where AKI is becoming a major cause of patient morbidity and mortality[4].

5. Classification and Aetiology of Acute Kidney Injury

The AKI is classified according to its aetiology as pre-renal, a functional response of structurally normal kidneys to hypoperfusion, intrinsic renal, involving structural damage to the renal parenchyma, or post-renal, e.g. due to urinary tract obstruction[18,24].

Pre-renal AKI occurs when the primary cause of injury is external to the kidneys, excluding an obstruction in the flow of urine, leading mainly to hypoperfusion[23]. Hypovolaemia due to excessive blood loss, diarrhoea, vomiting, burns or pancreatitis are all causes of pre-renal AKI[18]. A second cause is reduced cardiac output, as in myocardial infarction, stroke, trauma, sepsis and transplantation; all may lead to ischaemia and reperfusion injury leading to AKI[13]. Conditions affecting the main artery supplying the kidneys such as renal artery stenosis are another cause of pre-renal AKI[25]. Drugs such as, ciclosporin, tacrolimus, angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers can also cause AKI by specifically affecting renal haemodynamics[18].

Intrinsic AKI is when the main cause is located within the kidney, involving changes in the structure of the parenchyma renal cells[13]. Several diseases may

affect specific part of the kidneys including glomerulonephritis affecting the glomeruli, vasculitis affecting the vessels and acute tubular necrosis affecting the interstitium[18]. Radiocontrast agents, aminoglycosides, amphotericin, non-steroidal anti-inflammatory drugs, β-lactam antibiotics, sulphonamides, acyclovir, methotrexate and cisplatin have all been reported to be nephrotoxic[2,6,13]. The main cause of post-renal AKI is urinary tract obstruction, which may be due to an enlarged prostate gland, kidney, ureteral or bladder stones or a tumour within the kidney or bladder[18.26].

6. Reactive Oxygen and Nitrogen Species and their sources

Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) are highly reactive molecules with at least one unpaired electron located in their outer orbitals. It is a broad definition given to a group of oxygen and nitrogen species that can exist either as free radicals or as non-radical derivatives[27,28]. Production of free radicals increases due to the presence of inflammation, infection or ischaemia-reperfusion injury and may affect mitochondrial function, which according to recent studies, is the main cause of renal cell damage in AKI. Their damaging effect can be by different mechanisms including protein oxidation, lipid peroxidation and DNA damage and often involves a combination of effects collectively known as oxidant injury[13,24,27].

Bothe the ROS and RNS are the main source of free radicals that are responsible for majority of the free radical based reactions *in vivo*. When the free radical is present on an oxygen atom, it is called a ROS and examples include the superoxide anion ($O_2^{\bullet-}$), hydroxyl radical ($HO^{\bullet}$), hydroperoxyl radical ($HO_2^{\bullet}$) and peroxyl radical ($RO_2^{\bullet}$). But it should be noted that not all ROS are free radicals; examples include singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2), ozone (O_3) and hypochlorous acid (HOCl)[28-30]. In RNS the free radical is present on the nitrogen atom and examples include nitric oxide ($^{\bullet}NO$), dinitrogen trioxide (N_2O_3) and nitrogen dioxide radical ($^{\bullet}NO_2$). Other significant *in vivo* free radical species include reactive chlorine species (RCS) such as atomic chlorine and reactive bromine species (RBS) such as atomic bromine, where the radical is centred on the chlorine and bromine atoms, respectively. Peroxynitrite ($ONOO^-$) is a non-radical the breakdown products of which can lead to the generation of both RNS and ROS[28,30,31].

Superoxide and hydrogen peroxide can normally be formed in the mitochondria via the reduction of oxygen within the electron transport chain by complexes I, II and III or by oxidoreductase enzymes[28,30,32]. About 0.4-4% of oxygen is converted to superoxide via normal cell respiration, mainly in the mitochondria[33]. These ROS should normally be further reduced to water by cytochrome oxidase of complex IV to overcome their harmful effects[34,35]. Another source of hydrogen peroxide is a direct two electron reduction of oxygen by monoamine oxidase in the outer membrane of the mitochondria[34]. The hydroxyl radical is one of the main ROS produced *in vivo* that has attracted a lot of interest due to its high reactivity. It can be formed due to the oxidation-reduction reaction of redox active metals such as iron and copper within the mitochondrial membrane *via* the Fenton reaction or the Haber-Weiss reaction[28,31,34]. Additionally, ROS can also be produced intracellularly by NADPH oxidase (mainly in the neutrophils and macrophages), cytochrome P450 and nitric oxide synthase (NOS). Superoxide is produced in small amounts under normal physiological conditions during purine metabolism catalysed by xanthine oxidase (XO). This small amount seems to increase under certain pathological states such as ischaemia and reperfusion, due to the conversion of xanthine dehydrogenase to xanthine oxidase[27]. [Figure 2].

The NOS converts L-arginine into L-citrulline in the presence of oxygen to produce the nitric oxide radical[36,37]. Although, not reactive enough to cause cellular damage, it reacts with superoxide to form the highly reactive peroxynitrite, the breakdown products of which has many harmful effects[38-43]. Further, peroxynitrite can react with carbon dioxide *in vivo* to form nitrosoperoxycarbonate ($ONOOCO_2^-$), which can undergo homolytic fission leading to the formation of carbonate ($CO_3^{\bullet-}$) and nitrogen dioxide ($NO_2^{\bullet}$) radicals [Figure 3].

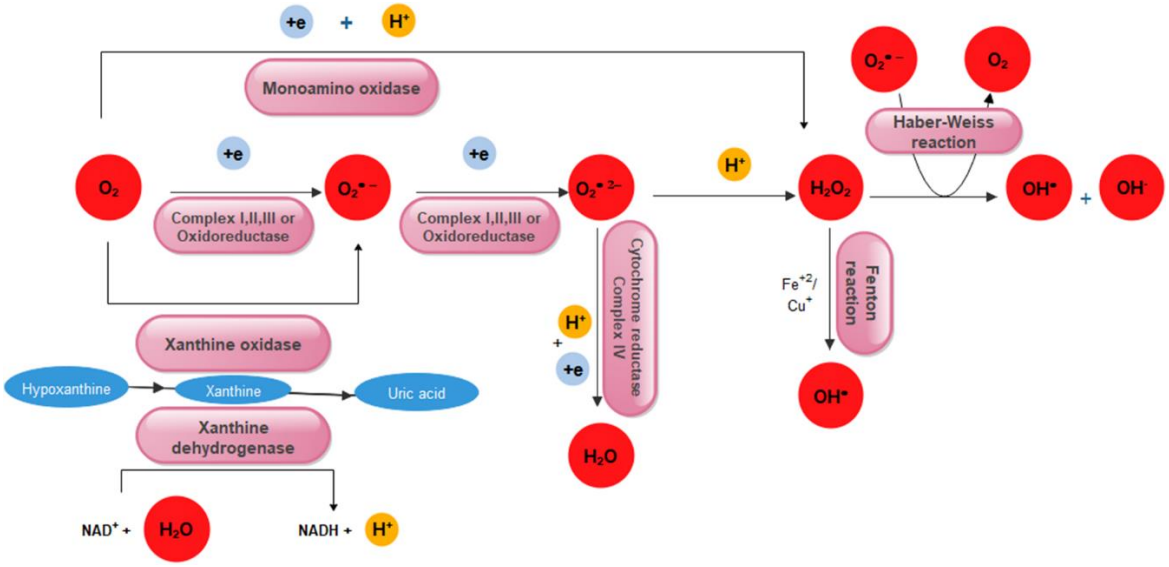

Figure 2: Production of reactive oxygen species *in vivo*. Adapted from Cadenas & Davies[34]. Oxygen is converted into superoxide anion and then into peroxide via complex I, II, III, xanthine oxidase and monoamine oxidase. This can be counterbalanced by complex IV, unless transformed into hydroxyl radicals by Fenton and Haber-Weiss reactions.

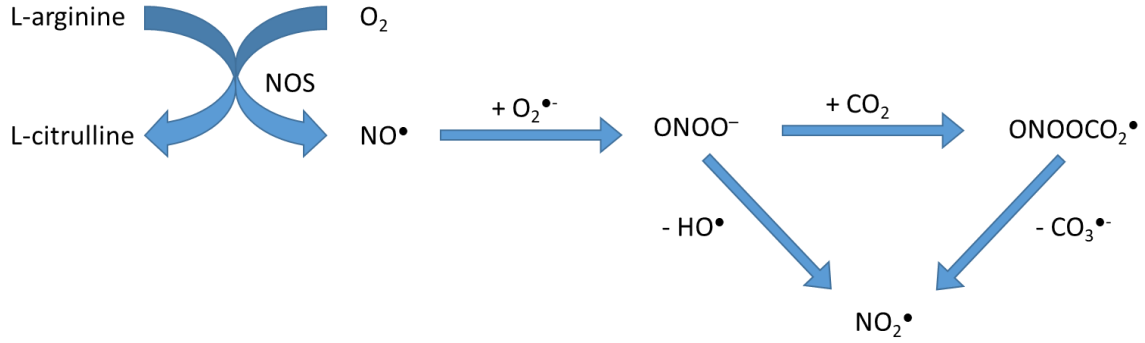

Figure 3: Production of reactive nitrogen species *in vivo*

The ROS in relatively low concentrations are believed to have an important function in regulating cellular signalling, facilitating normal growth and reproduction[29,31]. Higher levels of ROS are associated with defence against infection, as they have an important role in killing pathogens. This increase can be found in lymphocytes via 5-lipoxygenase (5-LO) and in endothelial cells via tumour necrosis factor (TNF). Compounds such as TNFα, interleukin-1, bacterial lipopolysaccharide and tumour promoter 4-O-tetradecanoylphorbol-13-acetate (TPA) are stimulators of cyclooxygenase-1 that may also lead to increased level of ROS during infection[27].

7. Mechanisms of Oxidative Stress

Due to the high reactivity of ROS, they are capable of reacting with a host of biological molecules including unsaturated fatty acids, proteins and nucleic acids to name a few leading to lipid peroxidation, protein oxidation, DNA strand breakage etc. Such reactions could result subsequent events including apoptosis.

7.1. PROTEIN OXIDATION BY THE REACTIVE OXYGEN SPECIES

Interaction of ROS such as •OH with the carbon backbone of the peptide linkages in a protein could lead to the formation of a carbon centred free radical on the protein. This in turn is highly reactive and can further react with O_2 and other ROS to form an alkylperoxyl radical intermediate, followed by the formation of an alkoxyl radical, leading to the formation of a hydroxylated protein or interaction with other amino acids to form new free radicals, which can undergo the same pathway. If oxygen is absent, the carbon centred free radical can cross-link with other carbon centred free radicals leading to the formation of dimers, thus modifying its structure and function [Figure 4]. The peptide chain may break down at the alkoxyl radical stage by either the diamide or α-amidation pathways. The ROS may also react with the

glutamyl, aspartyl and prolyl residue in a similar method, leading to protein fragmentation[38].

The side chains of the amino acids are also most likely to be oxidized by ROS with some more liable than others. Figures 5 and 6 below shows the most sensitive amino acids and their oxidation products[38]. Sulphur containing amino acids cysteine and methionine can be oxidized by ROS to form a disulphide (cystine) or a methionine sulfoxide, respectively. These residues can be converted back into their reduced state by disulphide reductases and methionine sulfoxide reductases, respectively, unless further oxidized[38]. Tyrosine and tryptophan are aromatic amino acids that are either oxidized to 3,4-dihydroxyphenylalanine and 2-, 4-, 5-, 6-, and 7-hydroxytryptophan, respectively, or nitrated by ONOO-. The nitration of these residues to form 3-nitro tyrosine and 5-nitro tryptophan, respectively, has been reported to obstruct enzyme activity and signal transduction pathways[38]. α-Amino acids such as lysine and arginine undergo oxidation in the presence of ROS to form semi-aldehydes while glutamic acid and threonine undergo oxidation to form oxalic acid and ketobutyric acid. Proline, a cyclic amino acid, undergoes oxidation in the presence of ROS leading to the formation of hydroxylated and oxidised products [Figure 6][38].

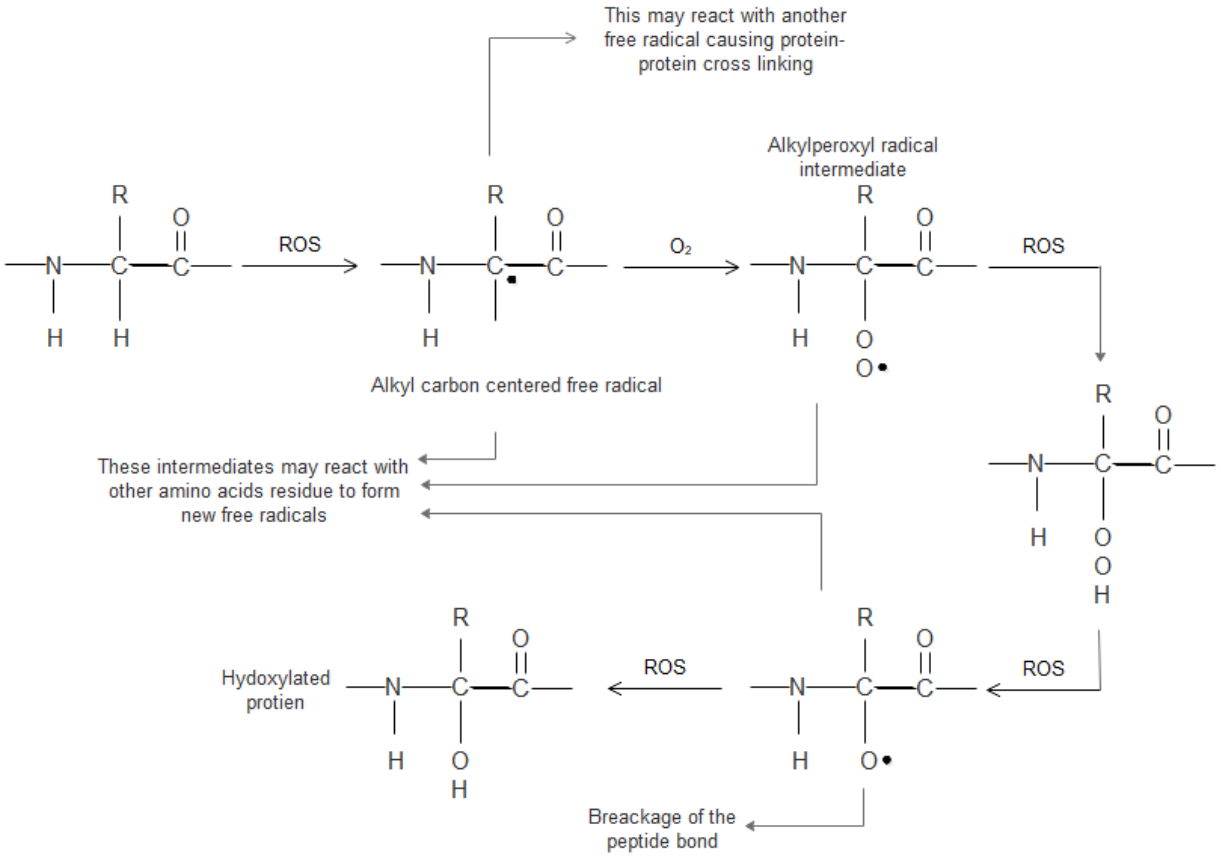

Figure 4: Different effects of ROS on amino acid residue. ROS may react with the amino acid forming a carbon centred carbonyl radical which can then form peroxyl radical and an oxyl radical. These products can lead to protein cross linking, form new free radicals, breakage of peptide chain and to hydroxylated proteins. Adapted from Berlett & Stadtman[38].

Furthermore, aldehydes produced by lipid peroxidation and reactive carbonyl derivatives produced by reducing sugar reactions (both will be discussed later), can react with proteins forming carbonyl derivatives. These can be used as oxidative stress biomarkers[38].

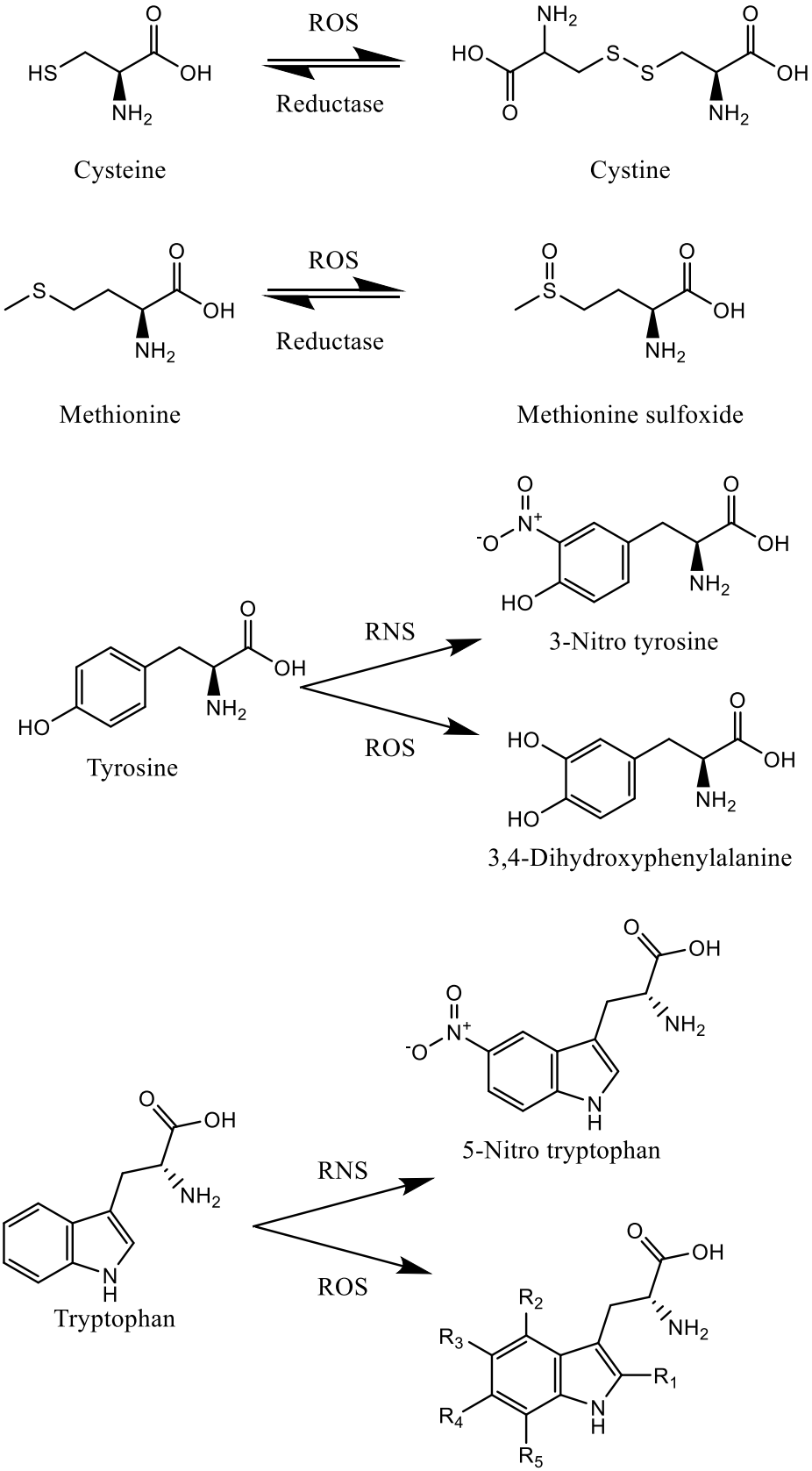

Figure 5: Oxidation products of aromatic and sulphur containing amino acids when exposed to ROS and RNS. Adapted from Berlett & Stadtman[38].

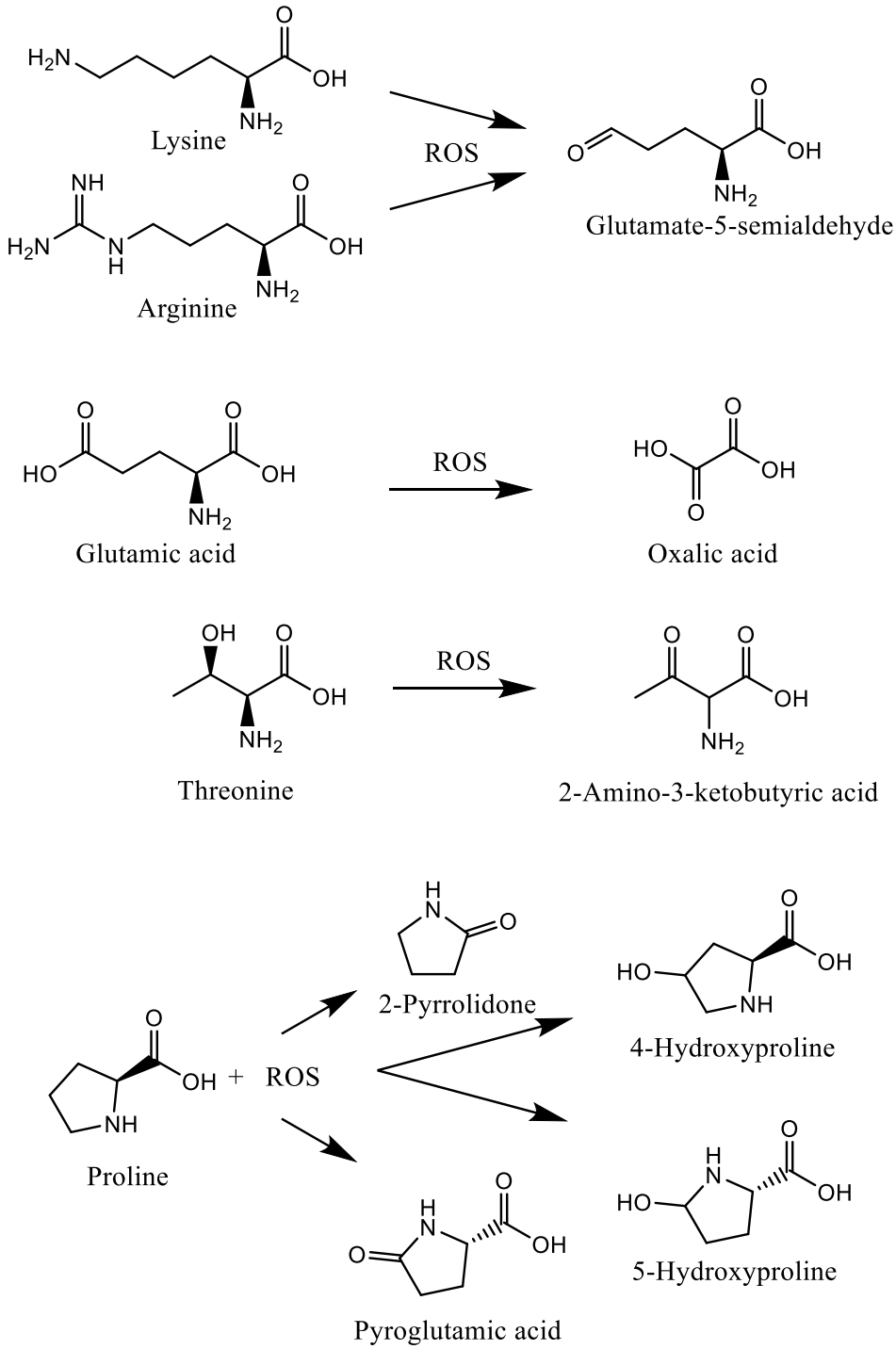

Figure 6: Oxidation products of some most sensitive amino acids to ROS. Adapted from Berlett & Stadtman[38].

7.2. LIPID PEROXIDATION

Lipid peroxidation is a process that involves oxidative deterioration of polyunsaturated fatty acids (PUFAs) that can be mediated by enzymes, ROS and RNS. They are considered most susceptible to peroxidation, due to their weak carbon-hydrogen bonds adjacent to the carbon-carbon double bonds. The reaction of a ROS, such as hydroxyl radical with a fatty acid led to the abstraction of hydrogen from the carbon leading to the formation of a fatty acid radical. This usually rearranges and reacts with oxygen to form a peroxyl radical, which can in turn react with a neighbouring fatty acid to form a peroxide and a new carbonyl radical, initiating a chain reaction[39] [Figure 7].

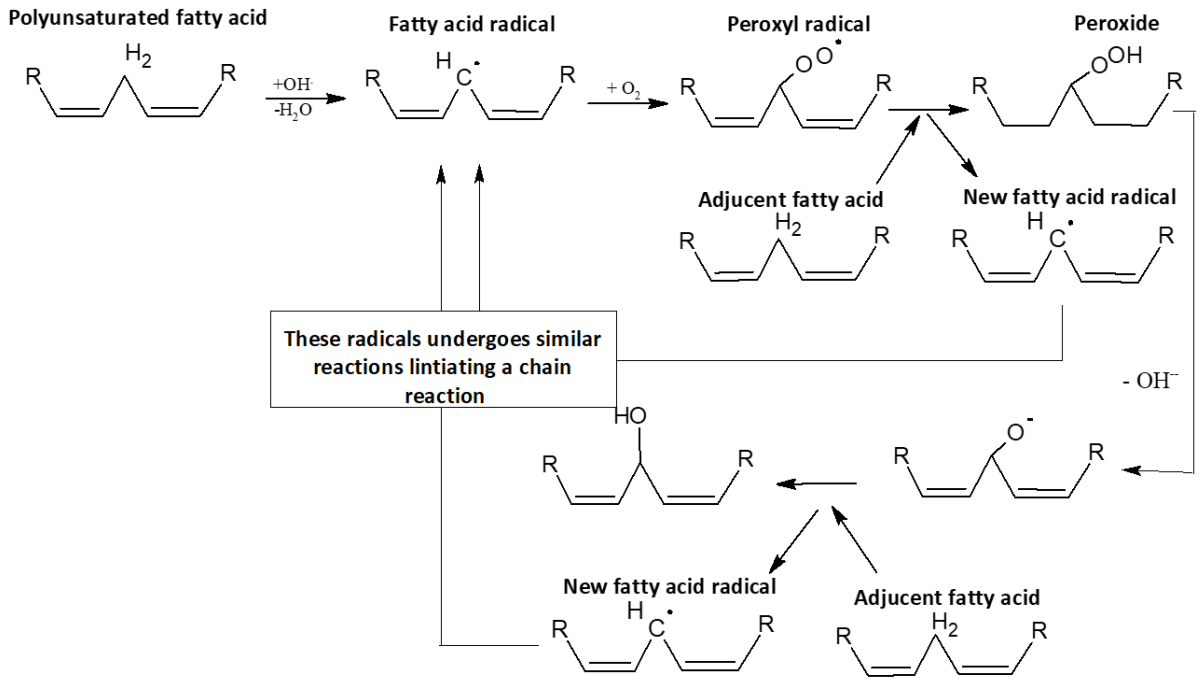

Figure 7: Lipid peroxidation chain reactions. Adapted from Spickett & Forma[39].

Products of these reactions include isoprostanes and malondialdehyde, which are used as markers of oxidative damage[33]. The addition of hydroxyl group to phospholipids in the bilayer membrane, may increases its water permeability, reducing its barrier function and initiate apoptosis. In addition to peroxidation, lipids such as oleic and linoleic acids can form nitrated products by reacting with nitric oxide or peroxynitrite in a manner similar to amino acids and proteins. An increase in oxidative stress is one of the main causative factors in complications associated with diabetes and as such an increase in the protein nitrotyrosylation was detected in the kidneys of patients suffering from diabetes[44]. Increased production of these nitrated lipids such as 9- and 10- nitro oleic acid was found in human plasma[45] and also in inflammation and ischaemia-reperfusion conditions[46]. Linoleic acid can further induce nitrative stress *in vivo* leading to protein nitrotyrosylation[47].

7.3. OXIDATION OF NUCLEIC ACIDS

Nucleic acids include are the biopolymers deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) comprising of the four nucleotide bases. Oxidation of nucleic acids can cause lead to strand breakage, abasic sites, sugar modifications and alterations to the nucleotide bases[33]. Hydroxyl radical is the major ROS responsible for oxidative stress to DNA. It either, abstracts hydrogen from the sugar structure or adds to the π-bond of the base, leading to strand breakage[48]. An important example of DNA base oxidation is the formation of 8-hydroxy-2'-deoxyguanosine (8-OHDG) from 2'-deoxyguanosine and 5-hydroxyuracil from uracil [Figure 8][49]. These can be repaired by base excision repair pathways. In conditions where the nucleus is unable to correct the alteration in the DNA strand, mutations may occur. If the oxidative stress is increased, cells undergo brief growth arrest and increased level of defensive protein expression. Further increase in the stress, induces permanent growth arrest, in which cells stop multiplying[49].

Poly (ADP-ribose) polymerase (PARP) is an enzyme present mainly in the cell nucleus. In addition to other functions, it is mainly responsible for signalling DNA damage and repair. Over activation of this enzyme has been linked to ischaemic injury to the brain, heart and kidneys. This has been attributed to the depletion of ATP, increased expression of proinflammatory agents and adhesion molecules[52]. There is some evidence that PARP inhibitors can provide protection against the ischaemia/ reperfusion injury, which contributes to the development of AKI[53,54].

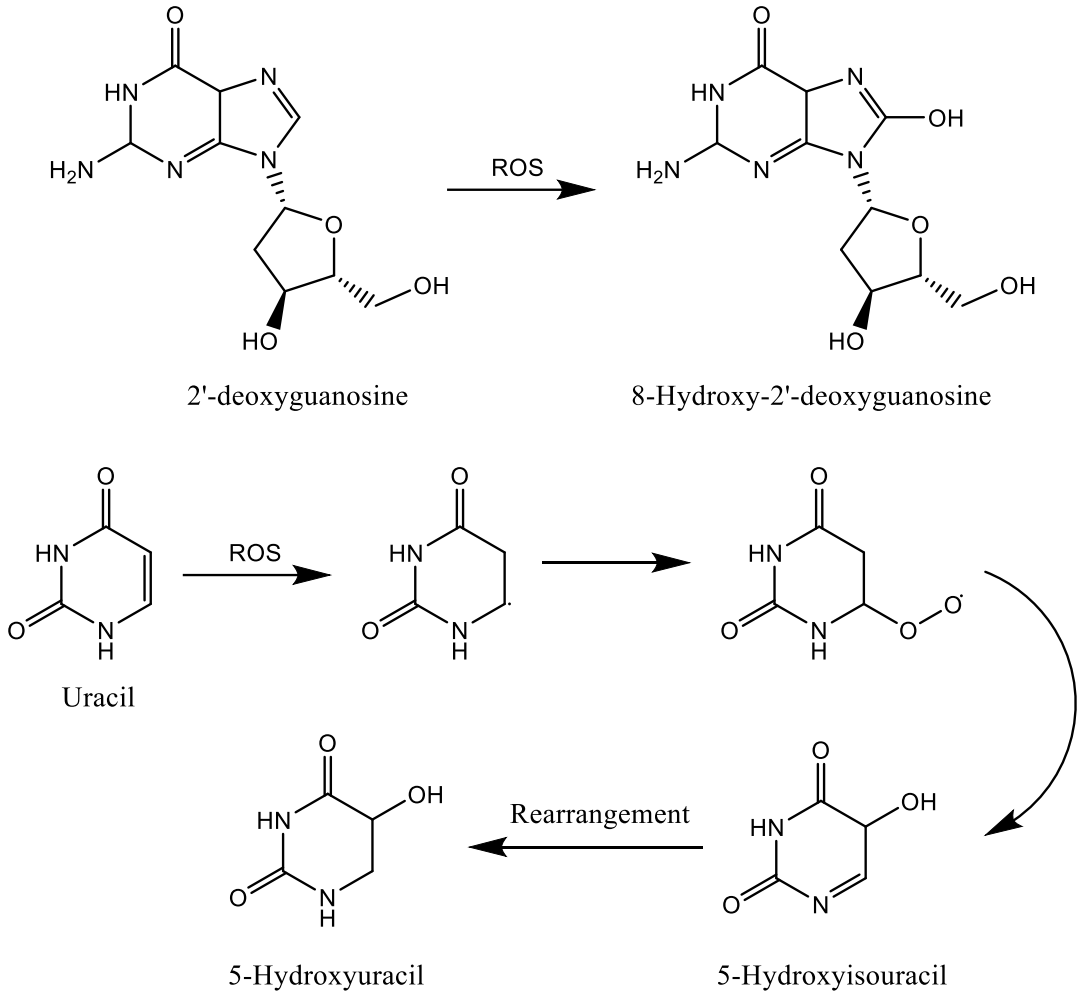

Figure 8: The formation of 8-hyroxy-2'-deoxyguanisine from 2'-deoxyguanosine and uracil oxidation pathway leading to the formation of 5-hydroxyuracil. Adapted from Valavanidis *et al.*[50] and von Sonntag[51].

8. Natural Antioxidant Activity in acute kidney injury

Antioxidants can be defined in general as any compound or system capable of donating an electron to a free radical to prevent its harmful effects[28,55]. Cells normally detoxify the harmful effect of free radicals by different mechanisms. These can be divided into two main categories: enzymes and small molecules. An important defensive mechanism in cells against oxidative stress is the nuclear E2-related factor 2 (Nrf2). It is a transcription factor that was found to be reduced in cisplatin induced AKI and plays an important role in upregulating detoxifying enzymes[56].

8.1. ENZYMES WITH ANTIOXIDANT ACTIVITY

Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and thioredoxin peroxidase (TRPx) are enzymes that have antioxidant activity[31]. Mammalian cells, and especially renal proximal tubular cells, have three different forms of SOD; SOD1 (CuZnSOD), SOD2 (MnSOD) and extracellular SOD3 (ecSOD)[57]. The SOD1 enzyme exists mainly in the cytoplasm and lysosomes while SOD2, on the other hand, is mainly present in the mitochondria and to some extent in the cytosol. All SODs dismutate superoxide to hydrogen peroxide. The enzyme CAT exists in the peroxisomes and GPx exists in the cytosol and mitochondria. Both enzymes catalyse the decomposition of hydrogen peroxide to water and oxygen. These antioxidant enzymes play an important role in protecting the kidney against oxidant injury of the kidney[58].

8.2. SMALL MOLECULES WITH ANTIOXIDANT PROPERTIES

Ascorbic acid (vitamin C), tocopherols (vitamin E), polyphenols, carotenoids and bioflavonoids are molecules from dietary sources that can act as antioxidants. Metallic nutrients such as selenium, copper, zinc, manganese and iron act as biofactors with an important role in maintaining enzyme antioxidant activity[59]. Compounds such as vitamin C and E act by donating electrons, therefore reducing highly reactive free radicals and becoming

themselves free radicals. However, the unpaired electrons in these compounds become delocalized by resonance leading to reduced activity and stability[28].

It is worth noting that the defence system of antioxidants works as a network. For example, when free radicals, oxidizes lipids forming lipid radicals, this can be neutralized by tocopherol, which itself is oxidized to tocopheroxyl radical. Ascorbic acid donates an electron to the later radical forming an ascorbyl radical. Glutathione (GSH) or thioredoxin(red) can be converted by GPx or TRPx, respectively to their oxidized forms glutathione disulphide (GSSG) or thioredoxin(ox), respectively, by increasing the lifespan of ascorbic acid. The latter can then be converted back by the NADPH cycle[48]. [Figure 9].

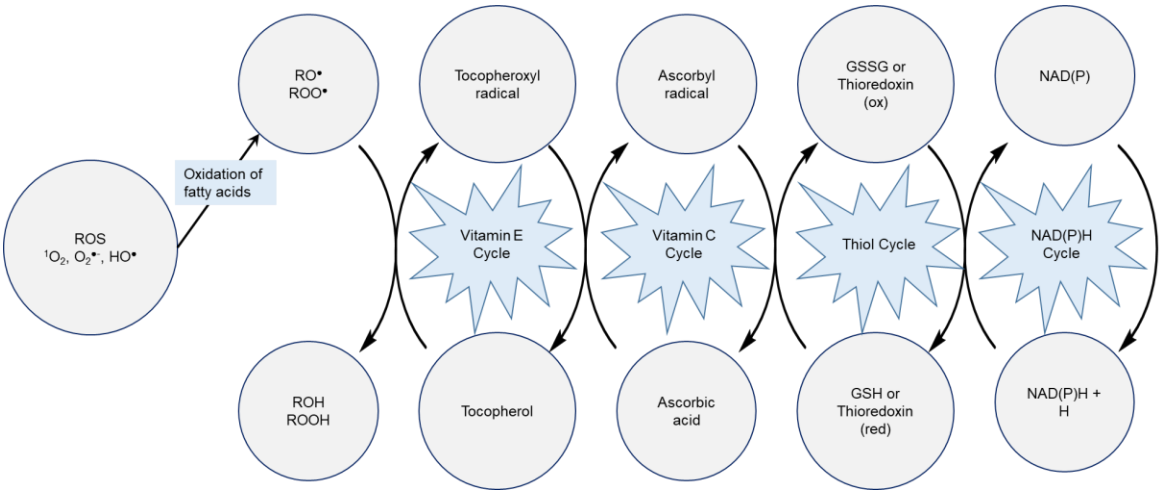

Figure 9: An example of antioxidants working as a network. Adapted[55].

9. Pathophysiology of acute kidney injury

It is important to understand the pathophysiology of AKI in order to determine the best treatment. The main mechanisms of developing AKI are vascular disruption leading to endothelial damage, direct reaction to an exogenous toxin, suppression of renal autoregulation and the release of inflammatory mediators[13,22]. A more recent study states that the pathophysiology of AKI includes inflammation, immune dysregulation, defective microcirculation and oxidative stress[24].

During ischaemia-reperfusion, the decreased blood flow to the kidneys leads to decreased oxygen and accumulation of metabolic products within cells. This in turn leads to reduced high-energy phosphate and imbalanced ion gradients across the cell membrane. Reperfusion of blood back to the renal cells is when the real injury occurs in the form of oxidant injury subsequent to oxidative stress. Free radicals are accumulated, which induce lipid peroxidation, polysaccharide depolymerization and DNA degradation[13]. The proximal tubules have been found to be most sensitive to hypoxia, ischaemia and toxic damage[13,57]. This may be due to the impairment of the mitochondrial function and proximal tubular cells contain an abundance of mitochondria by which they produce the metabolic energy required for tubular transport[60]. Injury to the proximal tubular cells has been found to lead to AKI[61]. The inflammatory state due to hypoxia is also induced by several factors as interleukin-1β (IL-1β), hypoxia inducible factor (HIF) and mitogen-activated protein kinase (MAPK)[13]. Moreover, the activation of NF-κB and its subsequent pathway is enhanced, which is also involved in inflammation due to oxidative stress[56].

Inflammation has a variety of contributions in developing AKI. It may lead to decreased blood flow to the cortex outer medulla affecting both function and viability of the renal tubules. This can be due to the innate as well as the adaptive immune responses, enhanced leukocyte-endothelial interactions and the generation of proinflammatory and chemotactic cytokines[23]. In a single nephron, microcirculation impairment can also be a cause of AKI. This is due the alteration in the trans-glomerular pressure gradient leading to insufficient filtration causing cell death due to reduced adenosine triphosphate (ATP)[24]. The reduced blood flow is more dominant in the medulla of the kidney[62,63]. These microvascular dysfunctions including impaired microvascular permeability have an important role in AKI[64].

Recently, the role of oxidative stress in AKI has been studied extensively[13,24]. Experiential as well as some clinical data shows that oxidative stress is the

main pathway of developing AKI in critically ill patients[65,66]. Oxidative stress is characterised by an increase in the production of ROS in contrast to endogenous antioxidants leading to cellular damage[29,31,67]. When the kidneys fail to compensate the increase in ROS, an imbalance in the homeostasis occurs leading to AKI[29,65] [Figure 10].

10. The Role of Oxidative Stress in acute kidney injury

As mentioned previously, oxidative stress plays an important role in AKI. Whatever the initial trigger for renal damage, the pathway leading to AKI is commonly characterised by ischaemic and nephrotoxic damage caused directly to the tubules or by activation of molecular mediators. In both pathways, ROS levels are raised above normal, leading to the development or progression of AKI [68]. One of the proposed mechanisms in which oxidative injury leads to cell death is by mitochondrial membrane permeability transition (MPT) where the mitochondria are the first organelle to be affected in the cells. During cell injury, ROS formation is increased in the mitochondria, leading to the oxidation of the dithiol groups in the membrane. This increases the permeability of the mitochondrial membrane thereby inducing MPT. The cells then either undergo apoptosis or necrosis according to ATP level[69-72]. Lipid peroxidation affects not only the mitochondrial membrane but also the lysosomal and plasma membranes[73]. Studies now target the mitochondria as a therapeutic approach for the treatment of AKI[74].

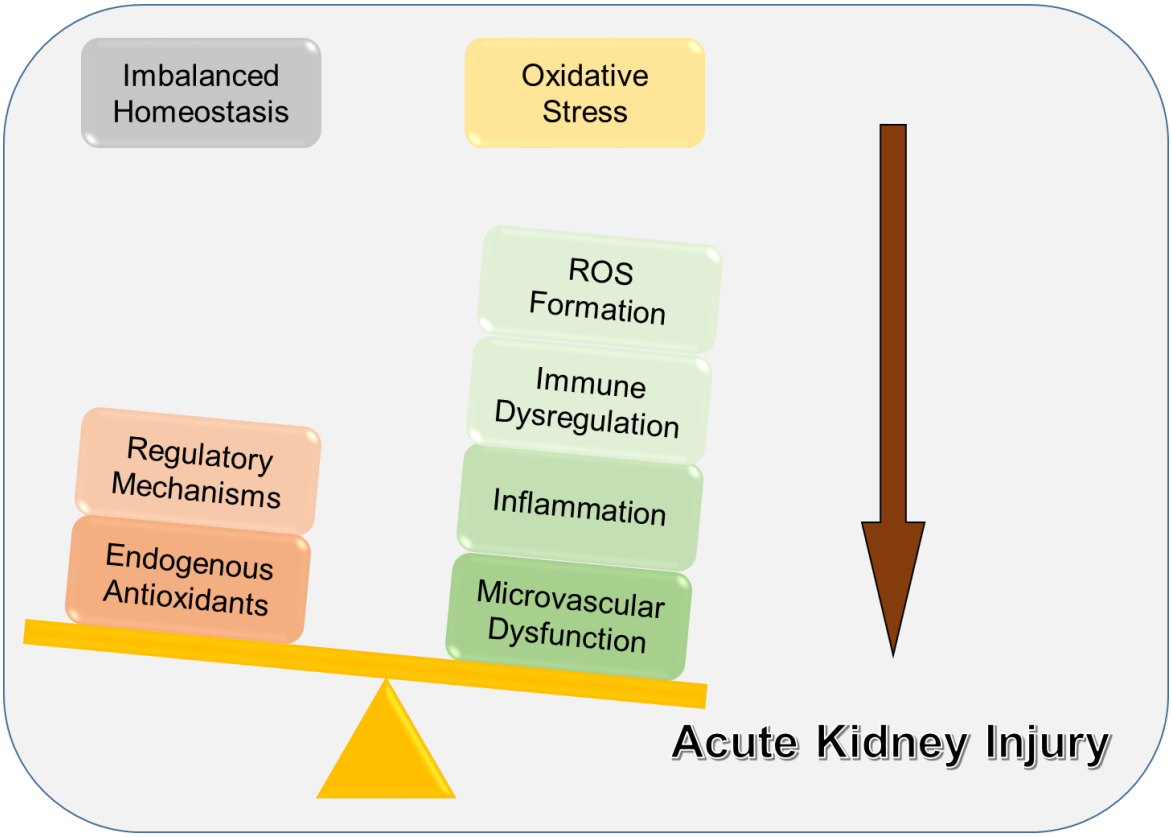

Figure 10: The AKI and Oxidative Stress, adapted[65]. When there is an imbalance between oxidative stress and antioxidant mechanisms in the renal cells, this may lead to AKI.

The ROS and RNS species $O_2^{\bullet-}$, H_2O_2, $HO^{\bullet}$, $^{\bullet}NO$ and $ONOO^-$ are among the most important free radicals involved in the development and progression of AKI [57]. Post injury, the cellular damage caused by these species is worsened due to the decreased activity of some antioxidant enzymes, alteration of xanthine oxidase, defective electron transport chain and increased levels of iron that may be released from storage points. The level of H_2O_2 was increased 1.5-fold after ischaemia and 4-fold after reperfusion[75]. Cisplatin, a widely used anticancer agent, is known to have nephrotoxicity as an adverse effect. It has been reported that it affects the electron transport chain where mainly the complexes I and IV are inhibited thereby increasing the formation of ROS[76]. Further, *in vitro* and *in vivo* studies suggested that redox cycling of iron lead to an increased production of hydroxyl radical in cisplatin induced cytotoxic effects, which were attenuated by the

administration of iron chelators deferoxamine and 1,10-phenanthroline[77]. Hydroxyl radical scavengers such as dimethylthiourea (DMTU) and N-acetyl-cysteine (NAC) attenuated cisplatin induced p53 gene activation leading to reduced tubular cell apoptosis and nephrotoxicity[78].

Several *in vivo* studies have shown that ischaemia and reperfusion results in reduced gene expression of antioxidant enzymes such as SOD, catalase and GPx. Oxidative stress, as a result, was increased leading to renal tissue damage[79,80]. Mice with SOD deficiency, specifically CuZnSOD, showed a more severe AKI after ischaemia and reperfusion compared to wild mice. In this study, AKI as more evident in aged mice compared to younger mice[81].

Nitric oxide induces programmed cell death in tubular epithelial cells *via* the activation of caspase-8, suggesting that caspase-8 inhibition could be an important therapeutic target for the treatment of AKI[82]. Pro-inflammatory cytokines released after kidney inflammation, regulate tubular epithelial cell apoptosis, which can be regulated by a caspase-8 inhibitor[83]. It is worth mentioning that nitric oxide in physiological levels has an important role in cell signalling. Also, some studies have shown that if obtained from exogenous sources, it can play a protective role against renal injury after ischaemia-reperfusion[84,85] Its main contribution to kidney damage is the formation of peroxynitrite, which is thought to cause both lipid peroxidation as well as inhibition of DNA synthesis[86]. However, a study also suggests that if the levels of nitric oxide are maintained at a physiological level, it can protect from kidney damage due to endotoxaemia[87].

11. Available and Future Treatments

Even with advanced technology treatment for AKI remains a major challenge[4,88]. The main reason that makes it difficult to treat AKI using a single set of pharmacological agents can be attributed to its complex pathogenesis and the fact that it is a multisystem disease[89]. Still renal replacement therapy is the main treatment approach for most of these patients after determining the main cause of the failure as being either pre-renal, intrinsic or post-renal[2,18,24,26,65]. Clinical trials now aim to target AKI at three different points. First, before the injury occurs as a prevention therapy, for example before surgery which may cause AKI. Second, at an early stage of AKI, which can be facilitated by the detection of novel biomarkers that can reveal kidney injury before there is an actual functional change. Third, is to treat the AKI after a significant raise in serum creatinine levels[4].

Antioxidants and anti-inflammatory mediators are now under investigation to evaluate their effect on AKI in patients. Anti-inflammatory agents, such as alkaline phosphatase, dipeptiylpeptidase-4 inhibitors and sphingosine 1 phosphate analogues are under clinical investigation to evaluate their efficacy in the treatment of AKI. Another group of drugs under investigation are genetic modifiers such as 5INP, an inhibitor of p53 tumour suppressor protein, which can extend the time available for DNA repair and therefore improve cell recovery. Angiotensin II and adenosine antagonists are renal flow modifiers that attempt to address microcirculation impairment associated with AKI. Administration of angiotensin II has been demonstrated to increase urine output and creatinine clearance. Theophylline, a non-selective adenosine antagonist, has been shown to prevent contrast induced nephropathy[24,90,91].

Several medicinal plants are known for their antioxidant activity and have been linked with prevention of different conditions such as Alzheimer's, cancer, cardiovascular conditions and diabetes to name a few. Carotenoids and phenolics are dietary antioxidants that derived from natural origins. Carotenoids are divided into two groups: molecules containing an oxygen atom, e.g. xanthophylls such as lutein and β-cryptoxanthin and hydrocarbons that are either cyclised such as α-carotene and β-carotene or linear, such as lycopene[92]. Phenolic compounds are mainly flavonoids, tannins and phenolic acids, including anthocyanidins such as pelargonidin, chalcones such as butein, flavonones such as taxifolin, flavones such as luteolin, flavonols such as quercetin, isoflavones such as genistein, hydroxybenzoic acids such as gallic acid and hydroxycinnamic acids such as caffeic acid[28,92]. These compounds and their metabolites are known for their antioxidant activity and may have the ability to ameliorate renal function against oxidative stress[93]. Such polyphenols have been shown to reduce AKI in animal models[68].

12. Animal Studies and Clinical Trials

Different *in vitro* and *ex vivo* studies have shown the advantages of exogenous antioxidants in renal injury, including vitamin E, vitamin C, edaravone, NAC, selenium, polyphenols and flavonoids such as curcumin, quercetin and resveratrol [94]. Tempol is an antioxidant with membrane permeable properties that acts by scavenging ROS. *In vivo* and *in vitro* studies showed possible protection of tempol against AKI induced by ischaemia/reperfusion injury[53,95].

Vitamin E shows some protection activity against lipid peroxidation, namely the oxidation of low-density lipoprotein (LDL)[43,96]. This has been demonstrated by the reduced oxidation of LDL due to iron treatment after the administration of vitamin E[97]. A systemic review conducted electronically using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials showed a potential benefit of using vitamin E plus hydration in reducing risk of contrast-induced AKI by 62% compared to hydration only. However, that review did not observe any significant effect on GFR after contrast treatment[98]. A separate clinical trial did not show any benefits of using vitamin E in preventing AKI after elective cardiac surgery[68]. Different mechanisms have been proposed for its "arguable" protective effect, including direct antioxidant activity by scavenging ROS, enhancing nitric oxide activity, reversing mitochondrial membrane depolarization and protecting lysosomal membrane integrity[99].

Troxerutin is a flavonoid found in tea, coffee, a variety of fruits, vegetables and also isolated from *Sophora japonica* flowers. It has been shown to have the ability to protect against AKI induced by d-galactose in mice and has both anti-inflammatory and antioxidant activity[100]. Its mechanism of action may involve restoration of antioxidant enzyme activity and reducing ROS formation, therefore decreasing DNA damage as shown by the reduction in 8-hydroxydeoxyguanosine formation[101]. Baicalein is also a natural flavonoid present in *Scutellaria baicalensis Georgi*. It has a slightly different mechanism of action, where it activates Nrf2, which has an important role in inhibiting cisplatin-induced AKI. Additionally, it inhibits MAP kinase activation and NF-κB signalling pathway[56].

Astaxanthin is a carotenoid, derived from algae and seafood, has both antioxidant and anti-inflammatory activities[102]. Its ability to quench ROS is much higher than β-carotene, ascorbic acid and α-tocopherol and can also reduce Fe^{3+} to Fe^{2+}. Additionally, it has the ability to prevent contrast induced AKI either *via* its antioxidant or anti-apoptotic properties[103]. There is significant evidence of its effect as an anticancer, antidiabetic and immune regulator. Studies also suggest its benefits in preventing oxidative stress in mercuric chloride induced AKI[102] and also due to its ability to reduce cisplatin-induced nephrotoxicity[103]. An animal study using a severe burn rat model, showed that astaxanthin provides a dose-dependent protection against AKI[104]. In another *in vivo* and *in vitro* study astaxanthin demonstrated its ability to reduce contrast-induced AKI[105].

Another group of flavonoids called proanthocyanidin oligomers are extracted mainly from red grape seeds, but are abundant in different fruit, chocolate and tea. Antioxidant activity of proanthocyanidins is fifty times higher than that of vitamins E and C. Studies have shown some evidence of potential pharmacological activity in protecting against AKI[106]. An *in vivo* study using both acetaminophen-induced kidney damage and genomic DNA kidney injury showed that treatment with grape extract can ameliorate kidney function after injury[107]. Animal studies on rats and mice have shown protection against cisplatin-induced AKI[108-110], rhabdomyolysis - induced AKI[111], cyclosporin-induced AKI[112] and exercise-induced AKI[113]. Furthermore, an *in vivo* study using a rat model showed both biochemical and histological improvements in kidney function after contrast-induced AKI[114]. Although the mechanism of action was not confirmed, it is believed to inhibit low-density lipoprotein peroxidation, protects DNA from oxidation, and increases the production of nitric oxide by reducing its reaction with superoxide. In addition to its antioxidant activity, it also shows anti-inflammatory activity by decreasing pro-inflammatory cytokines, e.g. interleukin-1 (IL-1), IL-12, and IL-18, tumour necrosis factor alpha (TNF-α)[106].

Probucol is a superoxide anion scavenger that has both antioxidant activity and lipid lowering effects. *In vivo* studies showed that it has a prophylactic effect against contrast-induced AKI[115,116], which was confirmed by a randomized controlled clinical trial in humans[115,117,118]. *In vivo* investigations demonstrated that it also has protective effects against nephrotoxicity caused by gentamicin or ferric nitrilotriacetate, when given alone or in combination with vitamin E[119-121]. Rats which underwent bilateral ureteral obstruction showed improved kidney function when pre-treated with probucol; shown by the greater inulin and para-aminohippurate clearance, reduced level of GSSG and reduced lipid peroxidation compared to untreated rats with similar obstruction[122].

Gallic acid is a polyphenolic molecule, with the ability to break down the oxidation chain reactions by electron donation. It is found in tea leaves and blackberries and is also found in high amounts in Indian gooseberries (*Phyllanthus emblica*), in addition to vitamin C and quercetin. The plant extract demonstrated a protective role against contrast-induced AKI in rats[122]. Pomegranate flower extract contains around 10% gallic acid content. *In vivo* studies using a rat model demonstrated that gallic acid can ameliorate nephrotoxicity caused by

gentamicin in both the extract[124] and in pure form[125]. Gallic acid showed protection against oxidative injury and reduced renal function in rats caused by chemotherapeutic agents such as cyclophosphamide[126], cisplatin[127] and methotrexate[128]. Diazinon and lindane are pesticides that cause oxidative injury to various organs. Pre- and co-treatment with gallic acid in animal studies, showed correction of oxidative stress biomarkers in both cardiovascular, hepatic and renal systems[129-130]. AKI induced by ischaemia-reperfusion[131] and by sodium fluoride[132] was inhibited after pre-treatment and co-treatment with gallic acid, respectively.

Several studies including a meta-analysis showed the advantage of using vitamin C as a prophylactic treatment for contrast induced AKI. The mechanism of action has not been determined, but it is probably due to its strong antioxidant activity[133-135]. Animal studies demonstrated that high doses of vitamin C has better effect than vitamin E in protecting against oxidative damage to renal cells[68]. It is worth mentioning here that its effectiveness is still controversial, as some clinical trials have shown that its administration does not prevent contrast-induced AKI[136-137].

13. Relationship between diet and AKI

A recent investigation has shown that dietary vitamin A and vitamin E may lead to a reduced risk of AKI, with the latter being more effective[138]. Studies have also shown that tocotrienols (antioxidants in the vitamin E family) possess greater antioxidant activity than tocopherols and are effective in preventing AKI in mice[139]. Although α- and γ-tocopherols have shown a protective role against contrast-induced AKI[140], other studies showed that they do inhibit oxidative stress but do not necessarily reverse AKI induced by severe burns[141].

Dietary Approaches to Stop Hypertension (DASH) is a diet initially proposed to reduce the risk of hypertension mainly by reducing sodium intake. It recommends consuming more fruit, vegetables and nuts, which are a good source of natural antioxidants. Another recent investigation has shown that those on the DASH diet have a reduced risk of developing kidney disease[142]. Also due to its low sodium salt recommendations, people tend to use more spices such as turmeric, cinnamon, nutmeg etc. in their food, which are high in antioxidants and hence may be a contributing factor in reducing kidney diseases.

Green tea (*Camellia sinensis*), is consumed by many people as a hot or cold beverage, as part of their daily diet. It is rich in polyphenols with high antioxidant activity, mainly epicatechin, epicatechin-3-gallate (ECG), epigallocatechin (EGC) and epigallocatechin-3-gallate (EGCG), with EGCG having the highest activity. Several studies demonstrated the beneficial activity of green tea in preventing contrast-induced[143], gentamicin-induced[144,1445] and cyclosporin A-induced[164-148] AKI. It also prevented AKI in diabetic mice after cardiopulmonary bypass [149] and has been suggested for use as a prophylactic antioxidant prior to renal transplantation[150]. It should also be mentioned that although green tea extract is a natural product, there are still not enough studies to support its clinical safety and infrequent cases of hepatoxicity have been reported[151].

A meta-analysis has demonstrated some variations in the geographical epidemiology of AKI, showing that North America, Australia and Eastern Europe had a higher rate of AKI, compared to Asia and Africa. It also showed that North Africa and Central Asia had lower incidence compared to the rest of Africa and Asia, respectively[21]. These variations were explained by the limited reporting and resources of developing countries compared to developed countries. A different explanation could be the diet of these countries. Different spices, herbs and medicinal plants, which are high in antioxidant and anti-inflammatory activity, are consumed as part of a regular diet in greater amount in Asia and Africa. For example, turmeric (*Curcuma longa*), contains curcumin as an active ingredient. It is widely used as a colouring and flavouring spice in India and Africa and has been reported to possess a range of health benefits[152]. *Crocus sativus* (saffron) is originally grown in Iran is rich in carotenoids and is widely used in Asia and north Africa. Other plants that are traditionally used for the treatment of AKI, due to their anti-inflammatory and antioxidative activity include, *Panax ginseng* (ginseng), *Nigella sativa* (black seed), *Zingiber officinale* (Ginger), *Silybum marianum* (milk thistle), *Vitis vinifera* (grapes), *Punica granatum* (pomegranate), *Ginkgo biloba* (gingko) and *Allium sativum* (garlic). All these natural sources are rich in antioxidants[153].

14. Improving Bioavailability of Supplementary Antioxidants

The role of oxidative stress in AKI, although requires further investigations, is almost unquestionable. The real question concerns the effectiveness of antioxidants in the treatment/prevention of AKI. The principal drawback is their low solubility, permeability, instability, degradation during

metabolism and for some antioxidants, their toxicity. Novel drug delivery systems such as nanoparticles, liposomes, chemical modifications, coupling agents and gel-based systems may improve their bioavailability and safety profile[154,155].

Nanoparticles, as the name indicates, are particles within the nano-scale usually with an average size ranging between 1nm to 1000nm and at least one dimension that is less than 100 nm[156]. Nanotechnology has developed extensively during the recent years finding its way in medicine through novel drug delivery, either by tissue targeting or by improving drug pharmacokinetics[157]. Nanoparticle is a general term that applies to different shapes, sizes and composition including inorganic, polymeric and solid lipid nanoparticles, liposomes, nanotubes, nanocrystals and dendrimers [Figure 11]. In context of this review article, polymeric nanoparticles and liposomes are discussed in more detail in subsequent sections.

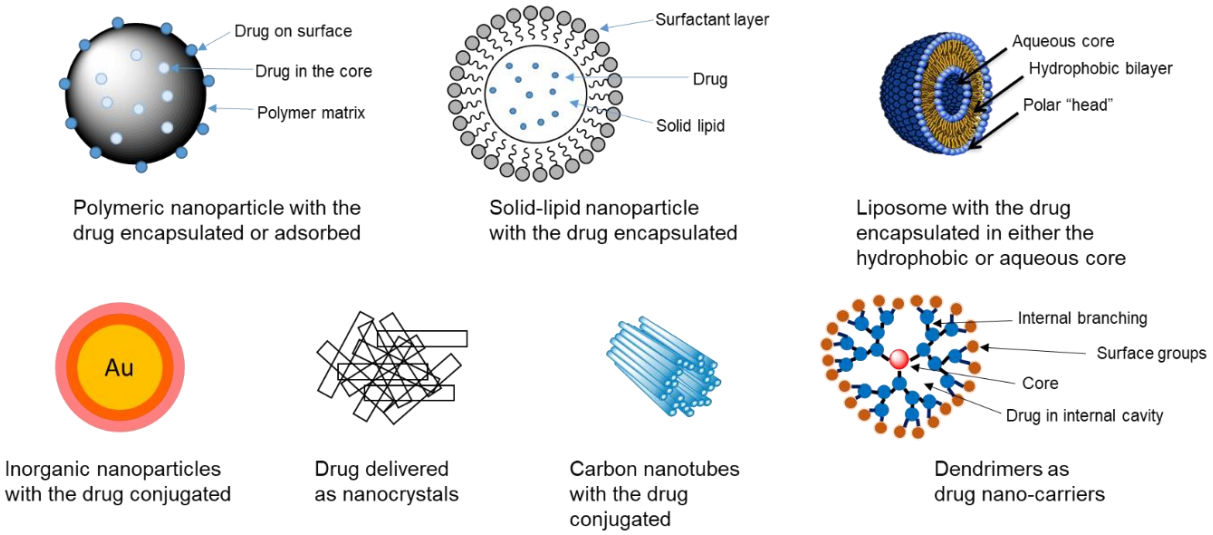

Figure 11: Different types of nanoparticles that can be used as drug delivery systems

14.1. Polymeric Nanoparticles

Polymeric nanoparticles are solid nano-scale drug carriers that can either have a matrix type structure made of a certain polymer, in which they are called nanospheres or can consist of a liquid core surrounded by a polymeric membrane where they are called nanocapsules. In both the types, drugs can either be embedded in the middle or adsorbed on the surface of the nanoparticle [Figure 12][158-160].

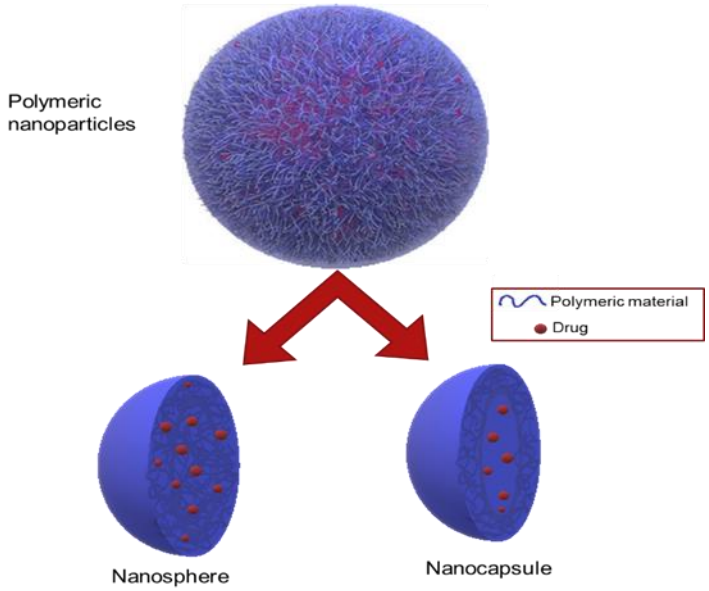

Figure 12: Types of nanocarrier systems – Nanospheres and nanocapsules

Biodegradable nanoparticles prepared from polymers are effective delivery systems that show many advantages over free drugs by providing excellent protection against degradation of the carried drug, hence improving its stability. They can act as good drug delivery devices to the site of action so less side effects may be observed and most importantly, they release the drug over a prolonged period giving a sustained drug release profile[157-159]. Polymeric nanoparticles can be derived from many different biodegradable and biocompatible polymers such as polylactic acid (PLA), poly (D, L-glycolide), polylactide-co-glycolide, polycyanoacrylate, poly (methylmethacrylate) and poly (butyl) cyanoacrylate[157]. The PLA is an aliphatic polyester of 2-hydroxypropionic acid [Figure 13]. It is a biodegradable compound derived from natural sources such as starch or sugar. The advantage of using a polymer such as PLA is its degradability in the body to lactic acid, which is a natural metabolite that can be removed by the normal citric acid cycle[161,162].

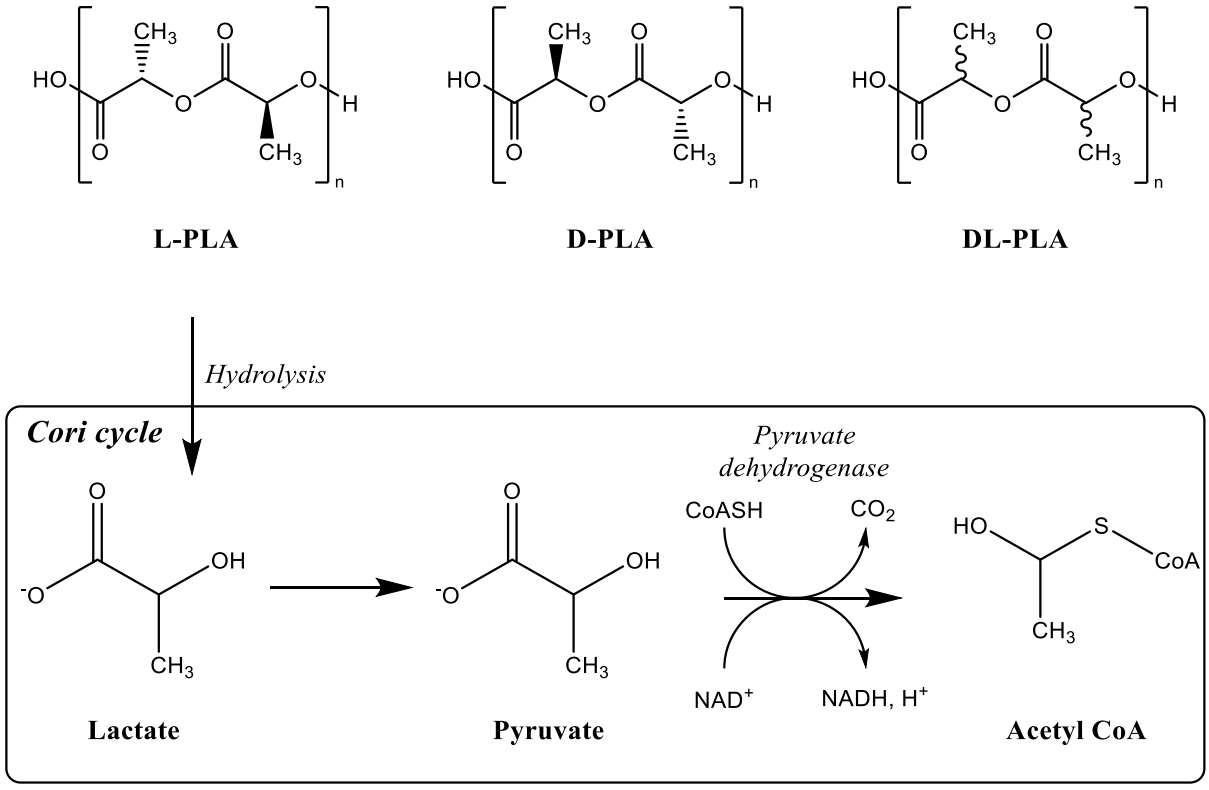

Figure 13: Isomers of poly(lactic acid): l-PLA, d-PLA, dl-PLA. The polymer hydrolyses to lactic acid *in vivo*, which then is metabolised in the Cori cycle, adapted[162].

14.2. Liposomes

Liposomes are vesicles within the nm to μm range. They consist of a liquid core surrounded with one or more bilayer phospholipids[163]. It is possible to manipulate the physical and chemical composition and characteristics of the liposomes to suit targeted applications[164]. They can be used to deliver both hydrophobic and hydrophilic drugs that are encapsulated in the lipid bilayer or the aqueous core, respectively. Due to their phospholipid composition, they have the advantage of being pharmacologically inactive and are relatively safe[165]. Different lipids have been used to formulate liposomes, including cholesterol, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC) and 1-myristoyl-2-stearoyl-sn-glycero-3-phosphocholine (MSPC)[166]. Gold encapsulated liposomal nanoparticles using DPPC, 2-dipalmitoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (DPPG) and 1,2-dipalmitoyl-3-trimethylammonium-propane (DPTAP) were developed as potential drug delivery systems[167].

The use of liposomes to deliver antioxidants is an extensively researched area. Several antioxidants such as vitamin E and vitamin C[168], curcumin[169], resveratrol[170,171], epicatechin[172] and ferulic acid[173] have all been developed as potential liposome formulations. These formulations have been investigated as potential drug delivery systems to treat different oxidative-stress related conditions such as pulmonary damage[168], liver injury[169], pathophysiological aging[170] and cancer[172] with varying degrees of success. Liposomal drug

delivery was developed to improve the antioxidant efficacy, increase cellular uptake, prolong clearance leading to reduced dosage, which directly results in reduced toxic effects. Antioxidants such as resveratrol and curcumin formulated as liposomes are already available as over the counter dietary supplements. However, their therapeutic application and safety assessments require further investigations.

15. Pharmacokinetics and Pharmacodynamics of External Antioxidants

As mentioned earlier, the pharmacokinetic and pharmacodynamic properties of supplementary antioxidants are one of the main obstacles for their effectiveness in AKI. Few examples of potential antioxidants that can be used for the treatment of AKI by developing as novel drug delivery systems are discussed below along with their sources, physiochemical properties, bioavailability, elimination and proposed mechanism of action.

15.1. ASCORBIC ACID (VITAMIN C)

Ascorbic acid is very water soluble and is present in high amounts in oranges, lemons, berries, mangos, broccoli and peppers[28]. Its bioavailability is almost 100% for doses up to 200mg. This percentage declines gradually, reaching 33% with higher doses (1.25g). It is mainly absorbed from the small intestine and it is not considered to be protein bound and therefore it is filtered into the glomerulus but reabsorbed back into the renal tubules by active transport. A 100mg dose of oral or IV vitamin C results in an excretion of 25% in urine, while higher IV doses are 100% excreted into the urine. Elimination half-life is around 10 hours[174] but it is mainly present as an ascorbate form at physiological pH levels. Due to its high aqueous solubility and high renal clearance ascorbate has the potential to be used for targeting the kidneys using oral drug delivery. A protective role for ascorbic acid in AKI has been suggested in ischaemia/reperfusion induced rat AKI models and in patients with low plasma vitamin C levels[175,176]. Critically ill patients have been shown to have low plasma ascorbic acid levels. While it has been reported that intravenous administration of ascorbic acid to critically ill patients can reduce the extent and duration of vasopressor support required as well as any mechanical ventilation, it has minimal effect on patients suffering from AKI[177].

15.2. VITAMIN E

Vitamin E is a collective term for eight different tocopherols and tocotrienols. α-Tocopherol, the most abundant isoform in tissues (90%), it is a fat-soluble compound available from natural sources in the R,R,R-stereoisomer form[174]. Wheat-germ, vegetable oils, nuts, grains and green vegetables are rich in vitamin E[28]. Due to its high lipophilicity, its absorption depends mainly on biliary secretions. Different forms of vitamin E are transferred into the blood stream *via* the lymph in chylomicrons. Only R,R,R-α-tocopherol is transferred *via* the liver in very low density lipoproteins[28,178]. Approximately 25-50% is absorbed from food (when the dose is less than 1 mg). Most of the drug at pharmacological doses is excreted in the faeces and about 10% is absorbed. Its peak plasma concentration is reached 12-14 hours after oral administration[48.178]. α-Tocopherol plays a major role in preventing lipid peroxidation by scavenging lipid peroxide radicals at a very fast rate. Furthermore, the α-tocopherol radical can react with a second peroxyl radical forming a non-radical product[28] and when scavenging reactive nitrogen species leads to the formation of α-tocopheroquinone[43]. □-Tocopherol, another naturally occurring tocopherol analogue of Vitamin E *in vivo*, on the other hand upon reaction with peroxynitrite leads to the formation of 5-nitro-□□-tocopherol and 5-hydroxy-□□-tocopherol, which react further leading to the formation of their corresponding quinones[178]. Vitamin E has been reported to possess protective properties against vancomycin-induced[179] and contrast-induced[180] nephrotoxicity leading to AKI. While it has been suggested that Vitamin E supplementation can act in a prophylactic function in vancomycin-induced nephrotoxicity[179], oral supplementation of α- and □□-tocopherol in combination with saline protects against contrast-induced AKI in patients with CKD[180]. Poly(Lactic-co-glycolic) acid (PLGA) nanoparticles and chitosan covered PLGA nanoparticles encapsulating α–tocopherol have been developed for oral drug delivery, where it has been shown that the entrapped antioxidant is protected against the harsh gastric environment by the polymers[181].

15.3. PHENOLIC COMPOUNDS

Most of the naturally occurring antioxidants can be classified under polyphenols. They cover a wide range of compounds and their pharmacokinetics and mechanism of action vary broadly, depending on their structure activity relationship. Most of these compounds act as antioxidants by either electron donation or undergoing substitution reactions when in contact with ROS and RNS[28].

15.3.1. trans-Resveratrol

Trans-Resveratrol is a stilbene antioxidant which is present in grapes produced as a defence

mechanism against fungi[28]. It is also present in blueberries, raspberries and mulberries[182]. Although it has a high absorption rate, its oral bioavailability is low (less than 1%) due to its fast metabolism in the intestine and liver[183,184]. Its main metabolites are due to conjugation reactions to form resveratrol glucuronides and resveratrol sulphates. Its main drawbacks are its low bioavailability, toxicity if given in high doses IP and instability. Further studies are needed to prove any benefit from IV infusion[182,186]. Efforts have been made in order to reduce its drawbacks by encapsulating the drug in liposomes[187], solid lipid nanoparticles (where oral bioavailability increased by more than 8-fold compared to drug suspension)[188] and dendrimers[189,190]. It has also been co-encapsulated with a novel NMDA receptor inhibitor (DAP5) and found to protect against ischaemia-reperfusion renal injury[191]. Studies show that it has both protective as well as recovery role from sepsis-induced AKI in mice, by activation of SIRT1/3[182,192,193]. Others demonstrated that its protection and treatment is due to the prevention of inflammation caused by macrophage and endoplasmic reticulum stress-activated NF-κB pathway[194,195]. Previous research has shown that its administration to ischaemia-reperfusion rat models reduces rate of mortality[68] and that it presents as potential treatment of cisplatin-induced AKI[196]. *In vivo* studies showed that it corrects AKI caused by arsenic trioxide by increasing its elimination and decreasing oxidative stress[197]. A more recent study demonstrated that its mechanism of action is by both blocking inflammatory pathways and decreasing oxidative stress, in addition to preventing cell death via the Nrf2/TLR4/NF-κB pathway[198]. An ongoing clinical trial is aiming to investigate the effect of resveratrol on inflammation and oxidative stress in CKD[74].

15.3.2. Curcumin

Several studies have demonstrated the activity of curcumin to ameliorate AKI in rats[152,199-207], while others demonstrated incomplete protection[208,209]. Despite the numerous *in vitro* and *in vivo* positive results of curcumin in preventing AKI[210], human clinical trials did not show any of its benefits[211]. In all the studies its potential as a prophylactic treatment for AKI is evident but incomplete, as the drug was administered to the animals intraperitoneally in dimethyl sulfoxide, orally dissolved in an oil or as a suspension. Animal and human studies have also shown that curcumin has very low oral bioavailability. This can be rationalised by its poor solubility and biodegradation through first-pass effect and intestinal metabolism. Its main degradation products include curcumin glucuronide and curcumin sulphate. Traces of di-, tetra- and hexa- hydrocurcumin, and hexahydrocurcuminol were found in the plasma after intraperitoneal injection[212]. Different attempts have been made, successfully, to improve its effectiveness such as incorporating it into liposomes[213] and nanoparticles[214]. Curcumin's antioxidant activity is due to the ability to scavenge ROS and RNS, upregulate haem oxygenase and glutathione transferase and downregulate xanthine oxidase. In addition to its antioxidant properties, studies have shown it ability to inhibit protein kinases, downregulate pro-inflammatory proteins, cytokines, growth factors and transcription factors[212].

15.3.3. Epicatechin

Epicatechin as well as catechin and epigallocatechin are available in red wine, cocoa and tea [28]. The oral bioavailability of epicatechin is around 4%. Although studies have showed minimal hepatic metabolism, the main reasons attributing this, was the efflux transport, low absorption and intestinal metabolism[215,216]. Epicatechin encapsulated in bovine serum albumin nanoparticles prepared using desolvation method had improved efficacy in cell culture models[217]. *In vivo* studies demonstrated limited renal injury via mitochondrial protection in cisplatin induced AKI [218, 219] and in lipopolysaccharides induced AKI[220].

15.3.4. Ferulic acid and Sinapic acid

Ferulic acid and sinapic acid are classified under hydroxycinnamates, which are small phenylpropanoids derived from plants. They are biosynthesised in plants from the amino acids L-tyrosine and L-phenylalanine, through the shikimic acid pathway. They are available in fruits, vegetables, cereal grains and oilseed crops, so they are high in normal human diet[221]. In addition to isoferulic, dihydroferulic and vanillic acids, ferulic acid is also one of the metabolic products of caffeic acid, which is present in high concentration in coffee beans[222-223]. Both ferulic and sinapic acids are available as free or as ester forms. In addition to their antioxidant action, they also possess antimicrobial, anti-inflammatory, anticancer and anti-anxiety activity[221].

Ferulic acid has good absorption (>60%) after oral administration. Its main metabolism is through conjugation with glucuronic acid, although 36-43% is excreted unchanged in the urine[223]. Minimal data is available on pure sinapic acid supplementation studies, but it has been shown that its main site of absorption is the small intestine through an active sodium gradient driven transport channel. Due to its poor solubility, its bioavailability after oral administration is very low, leading to reduced

bioactivity[223,224]. Sinapic acid undergoes phase I and II metabolism in the epithelium of intestinal cells[226]. *In vitro* and *in vivo* studies in cell culture models and in rats showed that sinapic acid ameliorates cisplatin induced nephrotoxicity[227]

There are no sources in the current document.

As discussed above, oxidative stress has a major role in the pathophysiological development of AKI. The use of dietary antioxidants such as curcumin and resveratrol has been studied intensively as a preventative and a treatment option for the injury with variable outcomes. Future research may be focused on using novel drug delivery systems to improve bioavailability, efficacy and drug targeting while minimising any toxic effects of these antioxidants that have potential beneficial properties in the treatment of AKI.

16. Conclusion

The AKI condition is a sudden loss of kidney function that has been linked to an increased rate of CKI and mortality. To date, there has not been a single approved pharmacological treatment for this. Current intervention, subsequent to identifying the cause, focuses on renal replacement. However, the original cause of injury has been classified into pre-renal, intrinsic and post-renal AKI. Different mechanisms have been proposed, including inflammation, immune dysregulation, defective microcirculation and oxidative stress. On this basis, a variety of future therapies is under clinical investigations.

As discussed in the review, oxidative stress has a major role in the pathophysiological development of AKI. The use of dietary antioxidants such as curcumin, gallic acid and resveratrol, has been studied extensively as a preventative and a treatment option for the injury with variable outcomes. A summary of various studies that have been reported in literature is summarised in Table 2. The main drawback of their activity is their pharmacokinetic and pharmacodynamics properties. Several studies have investigated in encapsulating antioxidants using nanotechnology, to improve bioavailability and reduce toxicity. However, due to their varying physico-chemical properties administration of these drugs as suitable therapeutic intervention is a challenge. Advances in the development of novel drug delivery systems should facilitate administering these compounds in a controlled dosage. Future research may be focused on using these novel drug delivery systems to improve their efficacy.

Declaration of interest

Authors declare that there is no conflict of interest.

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Table 2: A summary table of different antioxidants that have been investigated as potential treatments for AKI

Drug	Proposed activity	Type of animal	Method of stress	Marker	Results	References
Tempol	Radical scavenging and possible SOD activity	Male Wistar rats	bilateral renal pedicle clamping	Plasma concentrations of urea, creatinine, gamma-glutamyl transferase (γGT), aspartate aminotransferase (AST), and urinary N-acetyl-β-D-glucosaminidase (NAG)	Tempol reduced the increase in urea, creatinine, γGT, AST and NAG produced by renal ischaemia/reperfusion. Tempol reduced the histologic evidence of renal damage	[53]
Troxerutin (Vitamin P4)	Restoration of antioxidant enzyme activity and reducing ROS formation	male Kunming strain mice	Subcutaneous injections of d-galactose at dose of 50 mg/kg/day for 8 weeks.	Histological analysis Measurement of malondialdehyde (MDA) level. Measurement of Cu/Zn SOD, CAT GPx activity.	No significant histological improvement. Troxerutin improved d-galactose induced MDA increasing. No significant decrease in the activities of Cu/Zn SOD, CAT GPx enzymes.	[100]
Baicalein	Anti-inflammatory and antioxidant	Male Balb/C mice	Single intraperitoneal injection of cisplatin	Blood urea nitrogen (BUN) and creatinine Histopathological changes Oxidative stress level Mitochondrial activity TNF-a and IL-6 levels Myeloperoxidase activity NF-κB (p65)-DNA binding assay and other tests	Cisplatin significantly corrected the elevation of BUN and serum creatinine levels. Histological examination showed lesser tissue damage with baicalein. In general, baicalein shown to down regulate oxidative stress, apoptosis and inflammation via up regulation of Nrf2/HO-1 proteins and inhibition of MAPK activation and NF-κB signalling pathways.	[56]
Astaxanthin	Antioxidant	Rats	$HgCl_2$ nephrotoxicity	Lipid and protein oxidation Histological tests The increase in plasma creatinine δ-aminolevulinic acid dehydratase inhibition Antioxidant enzyme activity	Attenuated lipid and protein oxidation Corrected Not prevented Not prevented Changed	[102]
Astaxanthin	Antioxidant	Rats	Severe burns	Histological and biochemical assessments	Improved renal tubular injury Oxidative stress relieved	[104]

Drug	Proposed activity	Type of animal	Method of stress	Marker	Results	References
Astaxanthin	Inhibition of SIRT1/FOXO3a pathways	Male rats	Contrast media	Serum creatinine, BUN, oxidative stress markers and apoptosis-related proteins	Reduced	[105]
Grape seed extract	Antioxidant and anti-inflammatory	Male Wistar rats	Gentamicin	Histological changes Biochemical markers	Improved No significant corrections	[106]
Proanthocyanidin	Antioxidant	Rats	Cisplatin	DNA analysis Albumin, urea and Creatinine Tissue thiobarbituric acid Antioxidant enzyme activity	Absence of degradation and genotoxicity Increased level of albumin and a decreased level of urea and creatinine Reduced the increase in thiobarbituric acid Normalized antioxidant activity	[108]
Proanthocyanidin	Antioxidant	Rats	Contrast medium	BUN, creatinine and MDA levels Histopathological changes Oxidative stress parameters	Corrected Reduced Reduced	[114]
Probucol	Lowering renal oxidative stress	Wistar rats	Iopromide	Blood biochemistry MDA and SOD in renal tissue. Kidney histopathological examination.	Improved Corected Corrected	[116]
Pomegranate flower extract	Containing high amount of gallic acid	Male Wistar rats	Gentamicin	SCr and BUN Histopathological examination MDA	Decreased Reduced renal tissue damage Reduced	[124]
Gallic acid	Antioxidant and anti-inflammatory activity	Male Wistar rats	Gentamicin	SCr and BUN Histopathological examination MDA Antioxidant enzyme activity	Reduced Reduced kidney damage Reduced increased	[125]
Gallic acid	Free radical scavenging activity	Male Wistar rats	Cyclophosphamide	Urea, creatinine, bilirubin and enzymes in blood Vitamin C and GSH Antioxidant enzyme activity MDA	Reduced Increased Increased Attenuated	[126]
Gallic acid and tannic acid	Antioxidant	Rats	Cisplatin	Renal function test Oxidative stress biomarkers Histopathological examination of kidney	Reduced histological renal damage and suppressed the generation of ROS, lipid peroxidation, and oxidative stress in kidney tissues	[127]
Gallic acid	Anti-oxidant and anti-inflammatory effects	Male, Wistar Albino rats	Methotrexate	BUN, SCr and uric acid levels Oxidative stress markers	Ameliorated Reduced Normalized	[128]

Drug	Proposed activity	Type of animal	Method of stress	Marker	Results	References
				Histopathological examination Immuno-histochemical examination	Decreased expressions of inflammation parameters: TNF-α, CRP, and PGE-2	
Tocotrienols from palm oil	Antioxidants	Wistar male rats	Potassium dichromate	Renal functions, oxidative and nitrosative stress	Sustained	[139]
tert-butyl-bisphenol and vitamin E	Antioxidants	Male Sprague-Dawley rats	Rhabdomyolysis	Antioxidants level in blood, oxidative stress markers, gene regulation, immune-histochemistry, biochemistry of renal function, histochemistry, mitochondrial substructure in renal epithelial cells, measurement of total hemeoxygenase-1 activity and aortic function	Both drugs prevented lipid oxidation in both the vasculature and kidneys, corrected the reduction in aortic cGMP and down regulated hemeoxygenase-1. They also reduced oxidative stress markers but did not correct renal function.	[141]
Curcumin and resveratrol liposomes	Antioxidants with improved bioavailability	Male B6C3F1/J mice	PTEN knockout mice	Serum and prostate tissue level of curcumin and resveratrol Prostate cancer incidence	Increased when in liposomal form decreased prostatic adenocarcinoma *in vivo*	[187]
Resveratrol nanoparticles	Resveratrol encapsulated in solid lipid nanoparticles has increased bioavailability	Wistar male rats	No stress applied.	Pharmacokinetics parameters using HPLC	8-fold increase in oral bioavailability	[188]
Resvertrol-DAP5 nanoparticles	Resveratrol as antioxidant and DAP5 as an N-methyl-d-aspartate receptor inhibitor	Mice	renal ischaemia/reperfusion	SCr and BUN Histopathological examination Oxidative stress biomarkers	Decreased Corrected Reduced	[191]
Resveratrol	SIRT1 activator	Sprague-Dawley rats	Sepsis using the caecal ligation and puncture (CLP) technique	SIRT1 Activity Enzyme activity Renal function and survival time	Resveratrol corrected the decrease in SIRT1 Activity Restored Improved renal function and prolonged survival time	[192]
Resveratrol	Inhibiting endoplasmic reticulum stress-activated NF-κB pathway	Rats	Sepsis induced by CLP technique	Renal function Survival rate Serum and renal pro-inflammatory cytokines Expression and activation of NF-κB	Improved Increased Significant decrease Restored about 50% of the increase caused by sepsis Reduced	[195]

Drug	Proposed activity	Type of animal	Method of stress	Marker	Results	References
				Endoplasmic stress markers		
Resveratrol	Inactivation of the death receptor-mediated apoptotic pathway	Male Wistar rats	Cisplatin	Renal function Histopathological examination Apoptosis-associated proteins such as TNF-α and caspase-8	Improved Attenuated Corrected	[196]
Resveratrol	Antioxidant activity and increases arsenic elimination	Chinese Dragon-Li cats	Arsenic	SCr and BUN Antioxidants enzyme activity MDA Histopathological examination Arsenic level in kidneys Arsenic level in 24hour sample.	Reduced Corrected Reduced Reversed Attenuated Higher excretion	[197]
Resveratrol	Inhibiting inflammatory responses, reducing oxidative stress, and decreasing cell apoptosis	Male Sprague-Dawley rats	Kidney ischaemia-reperfusion injury	SCr and BUN Histopathological examination Proinflammatory cytokine expression assays Oxidative stress markers Apoptotic cells detection assay Caspase-3, -8, and -9 expression	Improved Corrected Inhibited Reduced Reduced Decreased	[198]
Curcumin, amifostine, and melatonin	ROS scavengers	Male Sprague-Dawley rats	Cisplatin	SCr and BUN Histopathological and electron microscopic examination Apoptotic cells detection assay Inflammation detection assay	All drugs improved kidney functions Corrected Reduced Decreased significantly	[204]
Curcumin	Modulating nitric oxide (NO) signalling pathway	Sprague Dawley rats	Renal ischaemia-reperfusion injury	β2-microglobulin, urinary albumin excretion rates, SCr and BUN Histopathological damage	Reduced decreased renal tissue damage Partially suppressed activation	[206]
Curcumin	Antioxidant	Rats	Renal ischaemia reperfusion injury	GFR Sodium levels in urine and plasma Tumour necrosis factor (TNF-α) in Serum Histopathological examination	No protection No effect Attenuated Mostly corrected	[208]
Curcumin liposomes	target delivery to renal tubular epithelial and	C57/B6 mice	renal ischaemia–reperfusion injury	SCr an BUN NF-κB activity Oxidative stress markers	Improved Reduced Reduced	[213]

Drug	Proposed activity	Type of animal	Method of stress	Marker	Results	References
	antigen-presenting cells			Cytokines and chemokines	Diminished	
Curcumin Nanoparticles	prolonged and constant drug release profile		Rhabdomyolysis induced by glycerol	Serum creatine phosphokinase, SCr and BUN Histopathological examination Oxidative stress and apoptosis markers	Reduced Less severe Reduced	[214]

References:

1. Kellum, JA, Ronco, C, Vincent, J-L. Controversies in Acute Kidney Injury. Contrib Nephrol. 2011;174. https://doi.org/10.1159/isbn.978-3-8055-9811-8
2. Bellomo, R, Kellum, JA, Ronco, C. Acute kidney injury. Lancet. 2012; 380 (9843): 756-766. https://doi.org/10.1016/S0140-6736(11)61454-2
3. Rangaswamy, D, Sud, K. Acute kidney injury and disease: Long-term consequences and management. Nephrology.2018; 23: 969–980. https://doi.org/10.1111/nep.13408
4. Mayer, B. Encyclopaedia of nephrology and acute kidney injury. Foster Academics; 2015. ISBN 978-1-63242-166-1.
5. Basile, DP, Donohoe, DL, Roethe, K, Mattson, DL. Chronic renal hypoxia after acute ischemic injury: effects of L-arginine on hypoxia and secondary damage. Am. J. Physiol. Renal Physiol. 2003; 284(2): 338-348. https://doi.org/10.1152/ajprenal.00169.2002
6. Wald, R, Quinn, RR, Luo, J, Li, P, Scales, DC, Mamdani, MM, Ray, JG. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. JAMA 2009; 302(11): 1179-85. https://doi.org/10.1001/jama.2009.1322
7. Coca, SG, Singanamala, S, Parikh, CR. Chronic kidney disease after acute kidney injury: A systematic review and meta-analysis. Kidney Int.2012; 81(5): 442-448. https://doi.org/10.1038/ki.2011.379
8. Chertow, GM, Burdick, E, Honour, M, Bonventre, JV, Bates, DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. J. Am. Soc. Nephrol. 2005;16(11): 3365-3370. https://doi.org/10.1681/ASN.2004090740
9. O'Callaghan, C. The Renal system at a glance. Fourth edition. John Wiley & Sons; 2017. ISBN: 978-1-118-39387-1.
10. Field, M, Pollock, C, Harris, D. The renal system. Second edition. Elsevier; 2007. ISBN: 978-0-7020-3371-1.
11. Seely, R, Van Putte, C, Regan, J, Russo, A. Seely's Anatomy and Physiology, Ninth edition. McGraw-Hill; 2010. ISBN: 978-0-07-352561-7.
12. Hoenig, MP, Zeidel, ML. (2014) Homeostasis, the milieu intérieur, and the wisdom of the nephron. Clin J Am Soc Nephrol. 2014; 9(7): 1272-1281. https://doi.org/10.2215/CJN.08860813
13. Mendoza, JD. Acute Kidney Injury: causes, diagnosis, and treatments. Nova Science Publishers; 2011. ISBN 987-1-61209-790-9.
14. Mehta, RL, Kellum, JA, Shah, SV, Molitoris, BA, Ronco, C, Warnock, DG, Levin, A. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit. Care. 2007; 11(2): R31. https://doi.org/10.1186/cc5713
15. Waikar, SS, Bonventre, JV. Creatinine kinetics and the definition of acute kidney injury. J. Am. Soc. Nephrol. 2008; 20(3). 672-679. https://doi.org/10.1681/ASN.2008070669
16. Hoste, EAJ, Clermont, G, Kersten, A, Venkataraman, R, Angus, DC, Bacquer, DD, Kellum, JA. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: A cohort analysis. Crit. Care. 2006; 10(3): R73. https://dx.doi.org/10.1186%2Fcc4915
17. Lopes, JA, Jorge, S. The RIFLE and AKIN classifications for acute kidney injury: A critical and comprehensive review. Clin. Kidney J. 2013; 6(1): 8–14. https://doi.org/10.1093/ckj/sfs160
18. Rahman, M, Shad, F, Michael, C. Acute kidney injury: A guide to diagnosis and management. Am Fam Physician. 2012; 86(7): 631-639.
19. Prowle, JP, Echeverri, JE, Ligabo, V, Ronco, C, Bellomo, R. Fluid balance and acute kidney injury. Nat Rev Nephrol. 2010; 6(2): 107-115. https://doi.org/10.1038/nrneph.2009.213
20. Thaker, CV. Perioperative acute kidney injury. Adv Kidney Dis Health. 2013; 20(1): 67-75. https://doi.org/10.1053/j.ackd.2012.10.003

21. Mehta, RL, Cerda, J, Burdmann, EA, Tonelli, M, García-García G, Jha V, Susantitaphong P, Rocco M, Vanholder R, Sever MK, Cruz D, Jaber B, Lameire NH, Lombardi R, Lewington A, Feehally J, Finkelstein F, Levin N, Pannu N, Thomas B, Aronoff-Spencer E, Remuzzi G. International society of nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology. The lancet commissions. 2015; 385(9987): 2616-2643. https://doi.org/10.1016/S0140-6736(15)60126-X
22. Thaker, CV, Chrisianson, A, Freyberg, R, Almenoff, P, Render, ML. Incidence and outcomes of acute kidney injury in intensive care units: A Veterans Administration study. 2009; Crit. Care Med. 37(9):2552. https://doi.org/10.1097/CCM.0b013e3181a5906f
23. Ronco, C, Bellomo, R, Kellum, JA. Acute kidney injury. Contributions to Nephrology. Vol. 156. Karger Publishers; 2007. ISBN: 978-3-8055-8271-1
24. Chen, H, Busse, LW. Novel therapies for acute kidney injury. Kidney Int Rep. 2017; 2(5): 785-799. https://dx.doi.org/10.1016%2Fj.ekir.2017.06.020
25. Yang J, Lu C, Yan L, Tang X, Li W, Yang Y, Hu D. The association between atherosclerotic renal artery stenosis and acute kidney injury in patients undergoing cardiac surgery. PLoS One. 2013; 8(5): e64104. https://doi.org/10.1371/journal.pone.0064104
26. Finlay, S, Jones, MC. Acute Kidney Injury. Acute Med. II. 2017; 45(3): 173-176. https://doi.org/10.1016/j.mpmed.2016.12.010
27. Agarwal, A, Sharma, R, Gupta, S, Harlev, A, Ahmad, G, du Plessis, SS, Esteves, SC, Wang, SM, Durairajanayagam, D. Oxidative stress in human reproduction. Springer; 2017. Date accessed 9/12/2018. https://doi.org/10.1007/978-3-319-48427-3_1
28. Halliwell, B, Gutteridge, J. Free radicals in biology and medicine. Oxford University Press; 2015. Date accessed 12/12/2018. https://doi.org/10.1093/acprof:oso/9780198717478.001.0001
29. Ray, PD, Haung, BW, Tisuji, Y. Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signalling. Cell Signal. 2012; 24(5): 981-990. https://doi.org/10.1016/j.cellsig.2012.01.008
30. Chandrasekaran, A, Idelchik, MDPS, Melendez, JA. Redox control of senescence and age-related disease. Redox Biol. 2016; 11: 91-102. https://doi.org/10.1016/j.redox.2016.11.005
31. Newsholme, P, Cruzat, VF, Keane, KN, Carlessi, R, de Bittencourt, PI Jr. Molecular mechanisms of ROS production and oxidative stress in diabetes. Biochem. J. 2016; 4(24): 4527-4550. https://doi.org/10.1042/BCJ20160503C
32. Vakifahmetoglu-Norberg, H, Ouchida, AT, Norberg, E. The Role of mitochondria in metabolism and cell death. Biochem Biophys Res Commun . 2016; 482(3): 426-431. https://doi.org/10.1016/j.bbrc.2016.11.088
33. Preedy, V. Aging: Oxidative stress and dietary antioxidants. Academic Press. Elsevier; 2014. ISBN 978-0-12-405933-7.
34. Cadenas, E, Davies, KJ. Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med. 2000; 29(3-4): 222–230. https://doi.org/10.1016/s0891-5849(00)00317-8
35. Brand, M. Mitochondrial generation of superoxide and hydrogen peroxide as the source of mitochondrial redox signalling. Free Radic Biol Med. 2016; 100: 14-31. https://doi.org/10.1016/j.freeradbiomed.2016.04.001
36. Gelpi R., Boveris A., Poderoso J. Biochemistry of Oxidative Stress. Advances in Biochemistry in Health and Disease. Springer, Cham; 2016. Date accessed 13/4/2020. https://doi.org/10.1007/978-3-319-45865-6_5.
37. Bartesaghi, S, Radi, R. Fundamentals on the biochemistry of peroxynitrite and protein tyrosine nitration. Redox Biol. 2018; 14: 618-625. https://doi.org/10.1016/j.redox.2017.09.009
38. Berlett, B, Stadtman, E. Protein oxidation in aging, disease, and oxidative stress. J. of Biol Chem. 1997; 272(33): 20313-20316. https://doi.org/10.1074/jbc.272.33.20313
39. Spickett, CM, Forman, HJ. Lipid Oxidation in Health and Disease. CRC Press, Taylor & Francis Group; 2015. ISBN: 978-1-4822-0285-4.
40. Radi, R, Beckman, JS, Bush, KM, Freeman, BA. Peroxynitrite-induced membrane lipid peroxidation: the cytotoxic potential of superoxide and nitric oxide. Arch Biochem Biophys .1991; 288(2): 481-487. https://doi.org/10.1016/0003-9861(91)90224-7
41. Pannala, AS, Rice-Evans, CA, Halliwell, B, Singh, S. Inhibition of peroxynitrite- mediated tyrosine nitration by catechin polyphenols. Biochem.

Biophys. Res. Commun. 1997; 232(1): 164-168. https://doi.org/10.1006/bbrc.1997.6254

42. Pannala, AS, Razaq, R, Halliwell, B, Singh, S, Rice-Evans, CA. Inhibition of peroxynitrite-mediated tyrosine nitration by hydroxycinnamates: Nitration or electron donation? Free Radic Biol Med. 1998; 24(4): 594-606. https://doi.org/10.1517/17425247.2014.919253
43. Pannala, AS, Rice-Evans, CA, Sampson, J, Singh, S. Interaction of peroxynitrite with carotenoids and tocopherols within low density lipoprotein. FEBS Lett. 1998; 432(3). 297-301. https://doi.org/10.1016/S0014-5793(98)00108-2
44. Drel, VR, Pacher, P, Stevens, MJ, Obrosova, IG. Aldose reductase inhibition counteracts nitrosative stress and poly(ADP-ribose) polymerase activation in diabetic rat kidney and high-glucose-exposed human mesangial cells. Free Rad. Biol. Med. 2006; 40: 1454–1465. https://doi.org/10.1016/j.freeradbiomed.2005.12.034
45. Trettin, A, Böhmer, A, Zoerner, A A, Gutzki, FM, Jordan, J, Tsikas, D. GC-MS/MS and LC-MS/MS studies on unlabelled and deuterium-labelled oleic acid (C18:1) reactions with peroxynitrite (O=N-O-O$^-$) in buffer and hemolysate support the pM/nM-range of nitro-oleic acids in human plasma. J. Chromatogr. B Analyt Technol Biomed Life Sci. 2014; 964: 172–179. https://doi.org/10.1016/j.jchromb.2014.01.016
46. Kansanen, E. Lipid oxidation and nitration products as activators of cytoprotective Nrf2 signaling in the endothelium. Publications of the University of Eastern Finland Dissertations in Health Sciences; 2012. ISBN: 978-952-61-0644-1.
47. Zhang H-M, Dang H, Yeh C-K, Zhang B-X. Linoleic Acid-Induced Mitochondrial Ca2+ Efflux Causes Peroxynitrite Generation and Protein Nitrotyrosylation. PLoS ONE. 2009; 4(6): e6048. https://doi.org/10.1371/journal.pone.0006048
48. Baskin, S, Salem, H. Oxidants, antioxidants, and free radicals. 1st edition. CRC Press. Taylor and Francis Group; 1997.
49. Barzilai, A, Yamamato, K-I. DNA damage responses to oxidative stress. DNA Repair (Amst). 2004; 3 (8-9): 1109-1115. https://doi.org/10.1016/j.dnarep.2004.03.002
50. Valavanidis, A, Vlachogianni, T, Fiotakis, C. 8-hydroxy-2-deoxyguanosine (8-OHdG): A critical biomarker of oxidative stress and carcinogenesis. J Environ Sci Health C. 2009; 27:120–139. https://doi.org/10.1080/10590500902885684
51. von Sonntag, C. Free Radical-Induced DNA Damage and Its Repair: A Chemical perspective. Springer Science & Business Media; 2006. ISBN: 978-3-540-30592-7.
52. Devalaraja-Narashimha, K, Singaravelu, K, Padanilam, BJ. Poly (ADP-ribose) polymerase-mediated cell injury in acute renal failure. Pharmacol Res.2005; 52(1): 44-59. https://doi.org/10.1016/j.phrs.2005.02.022
53. Chatterjee, Pk, Zacharowski, K, Cuzzocrea, S, Otto, M, Thiemermann, C. Inhibitors of poly (ADP-ribose) synthetase reduce renal ischemia-reperfusion injury in the anesthetized rat *in vivo*. FASEB J. 2000; 14(5): 641-651. https://doi.org/10.1096/fasebj.14.5.641
54. Chatterjee, PK, Chatterjee, BE, Pedersen, H, Sivarajah, A, McDonald, CM, Mota-Filipe, H, Brown, PAJ, Stewart, KN, Cuzzocrea, S, Threadgill, MD, Thiemermann, C. 5-Aminoisoquinolinone reduces renal injury and dysfunction caused by experimental ischemia/reperfusion. Kidney Int. 2004; 65(2): 499-509. https://doi.org/10.1111/j.1523-1755.2004.00415.x
55. Surh, Y-J. Oxidative Stress, Inflammation, and Health. CRC Press. Taylor & Francis Group; 2005 ISBN 978-0-8247-2733-8.
56. Sahu, BD, Mahesh Kumar, J, Sistla, R. (2015). Baicalein, a bioflavonoid, prevents cisplatin-induced acute kidney injury by up-regulating antioxidant defences and down-regulating the MAPKs and NF-κB pathways. PloS one. 2015; 10(7): e0134139. https://doi.org/10.1371/journal.pone.0134139
57. Basile, DP, Anderson, MD, Sutton, TA. Pathophysiology of acute kidney injury. Compr Physiol.2012; 2(2): 1303–1353. https://dx.doi.org/10.1002%2Fcphy.c110041
58. Ichikawa, I, Kiyama, S, Yoshioka, T. Renal antioxidant enzymes: their regulation and function. Kidney Int. 1994; 45(1): 1-9. https://doi.org/10.1038/ki.1994.1
59. Salmonowicz, B, Krzystek-Korpacka, M, Noczyńska, A. Trace elements, magnesium, and the efficacy of antioxidant systems in children with type 1 diabetes mellitus and in their siblings. Adv Clin Exp Med. 2014; 23(2):259-68. https://doi.org/10.17219/acem/37074

60. Funk, J, Odejinmi, S, Schnellmann, R. SRT1720 Induces mitochondrial biogenesis and rescues mitochondrial function after oxidant injury in renal proximal tubule cells. J Pharmacol Exp Ther. 2010; 333(2): 593–601. https://doi.org/10.1124/jpet.109.161992
61. Nowak, G, Aleo, MD, Morgan, JA, Schnellmann, RG. Recovery of cellular functions following oxidant injury. Am J Physiol. 1998; 274(3): 509-515. https://doi.org/10.1152/ajprenal.1998.274.3.F509
62. Karlberg, L, Norlén, BJ, Ojteg, G, Wolgast, M. Impaired medullary circulation in postischemic acute renal failure. Acta Physiol. 1983; 198(1):11-17. https://doi.org/10.1111/j.1748-1716.1983.tb07234.x
63. Bonventre, JV, Yang, L. Cellular pathophysiology of ischemic acute kidney injury. J Clin Investig. 2011; 121(11): 4210–4221. https://dx.doi.org/10.1172%2FJCI45161
64. Sutton, T. Alteration of microvascular permeability in acute kidney injury. Microvasc Res. 2009; ***77***(1): 4–7. https://dx.doi.org/10.1016%2Fj.mvr.2008.09.004
65. Pavlakou, P, Zhang, H, O'Connor, Z, Chertow, M, Crowley, T, Choudhury, D, Finkel, K, Kellum, A, Paganini, E, Schein, M, Smith, W, Swanson, M, Thompson, T, Vijayan, A, Watnick, S, Star, A, Peduzzi, P. Intensity of renal support in critically ill patients with acute renal injury. N Engl J Med. 2008; 359: 7-20. https://doi.org/10.1056/NEJMoa0802639
66. Tomsa, AM, Alexa, AL, Junie, ML, Rachisan, AL, Ciumarnean, L. Oxidative stress as a potential target in acute kidney injury. Peer J. 2019; **7:** e8046. https://doi.org/10.7717/peerj.8046
67. Pavlakou, P, Liakopoulos, V, Elftheriadis, T, Mitsis, M, Dounousi, E. Oxidative stress and acute kidney injury in critical illness: Pathophysiologic mechanisms-biomarkers-interventions, and future perspectives. Oxid Med Cell Longev. 2017; 6193694. https://doi.org/10.1155/2017/6193694
68. Rodrigo, R. Oxidative stress and antioxidants: their role in human diseases. Nova Biomedical publishers, Inc; 2009. ISBN: 978-1-60741-554-1.
69. Lemasters, JJ, Nieminen, AL, Qian, T, Trost, LC, Elmore, SP, Nishimura, Y, Crowe, RA, Cascio ,WE, Bradham, CA, Brenner, DA, Herman, B. The mitochondrial permeability transition in cell death: a common mechanism in necrosis, apoptosis and autophagy. Biochim Biophys Acta. 1998; 1366(1–2):177-196. https://doi.org/10.1016/s0005-2728(98)00112-1
70. Kim, J-S, He, L, Lemasters, JJ. Mitochondrial permeability transition: A common pathway to necrosis and apoptosis. Biochem Biophys Res Commun. 2003; 304(3): 463-470. https://doi.org/10.1016/s0006-291x(03)00618-1
71. Kim, J-S, Jin, Y, Lemasters, JJ. Reactive oxygen species, but not Ca2+ overloading, trigger pH- and mitochondrial permeability transition-dependent death of adult rat myocytes after ischemia-reperfusion. Am J Physiol Heart Circ Physiol. 2006; 290(5): 2024-2034. https://doi.org/10.1152/ajpheart.00683.2005
72. Takeyama, N, Miki, S, Hirakawa, A, Tanaka, T. Role of the mitochondrial permeability transition and cytochrome C release in hydrogen peroxide-induced apoptosis. Exp Cell Res. 2002; 274(1): 16-24. https://doi.org/10.1006/excr.2001.5447
73. Paller, MS, Hoidal, JR, Ferris, TF. Oxygen free radicals in ischemic acute renal failure in the rat. J Clin Investig. 1984; 74(4): 1156–1164. https://dx.doi.org/10.1172%2FJCI111524
74. Ishimoto, Y, Inagi, R. Mitochondria: A therapeutic target in acute kidney injury. Nephrol Dial Transplant. 2016; 31(7): 1062-1069. https://doi.org/10.1093/ndt/gfv317
75. González-Flecha, B, Boveris, A. Mitochondrial sites of hydrogen peroxide production in reperfused rat kidney cortex. Biochim Biophys Acta. 1995; 1243(3): 361-366. https://doi.org/10.1016/0304-4165(94)00160-y
76. Kruidering, M, Van de Water, B, de Heer, E, Mulder, GJ, Nagelkerke, JF. Cisplatin-induced nephrotoxicity in porcine proximal tubular cells: mitochondrial dysfunction by inhibition of complexes I to IV of the respiratory chain. J Pharmacol Exp Ther. 1997; 280(2): 638-49.
77. Baliga, R, Zhang, Z, Baliga, M, Ueda, N, Shah, V. *In vitro* and *in vivo* evidence suggesting a role for iron in cisplatin-induced nephrotoxicity. Kidney Intern. 1998; 53(2): 394-401. https://doi.org/10.1046/j.1523-1755.1998.00767.x
78. Jiang, M, Wei, Q, Pabla, N, Dong, G, Wang, CY, Yang, T, Smith, SB, Dong, Z. Effects of hydroxyl radical scavenging on cisplatin-induced p53 activation, tubular cell apoptosis and nephrotoxicity. Biochem Pharmacol. 2007; 73(9): 1499-510. https://doi.org/10.1016/j.bcp.2007.01.010
79. Dobashi K, Ghosh B, Orak JK, Singh I, Singh AK. Kidney ischemia-reperfusion: modulation of

antioxidant defences. Mol Cell Biochem. 2000; 205(1-2): 1-11. https://doi.org/10.1023/a:1007047505107

80. Leach, M, Frank, S, Olbrich, A, Pfeilschifter, J, Thiemermann, C Decline in the expression of copper/zinc superoxide dismutase in the kidney of rats with endotoxic shock: Effects of the superoxide anion radical scavenger, tempol, on organ injury. Br J Pharmacol. 1998; 125(4): 817–825. https://doi.org/10.1038/sj.bjp.0702123
81. Yamanobe, T, Okada, F, Iuchi, Y, Onuma, K, Tomita, Y, Fujii, J. Deterioration of ischemia/reperfusion-induced acute renal failure in SOD1-deficient mice. Free Radic Res. 2007; 41(2): 200-207. https://doi.org/10.1080/10715760601038791
82. Du, C, Guan, Q, Diao, H, Yin, Z, Jevnikar, AM. Nitric oxide induces apoptosis in renal tubular epithelial cells through activation of caspase-8. American Journal of Physiology. Renal Physiol. 2006; 290(5): 1044-1054. https://doi.org/10.1152/ajprenal.00341.2005
83. Du, C, Guan, Q, Yin Z, Zhong, R, Jevnikar, AM IL-2-mediated apoptosis of kidney tubular epithelial cells is regulated by the caspase-8 inhibitor c-FLIP. Kidney Int. 2005; 67(4): 1397-1409. https://doi.org/10.1111/j.1523-1755.2005.00217.x
84. Garcia-Criado, FJ, Eleno, N, Santos-Benito, F, Valdunciel, JJ, Reverte, M, Lozano-Sánchez, FS, Ludeña, MD, Gomez-Alonso, A, López-Novoa, JM. Protective effect of exogenous nitric oxide on the renal function and inflammatory response in a model of ischemia-reperfusion. Transplant. 1998; 66(8): 982-990. https://doi.org/10.1097/00007890-199810270-00003
85. Hegarty, NJ, Young, LS, Kirwan, CN, O'Neill, AJ, Bouchier-Hayes, DM, Sweeney, P, Watson, RW, Fitzpatrick, JM. Nitric oxide in unilateral ureteral obstruction: effect on regional renal blood flow. Kidney Int. 2001; 59(3): 1059-1065. https://doi.org/10.1046/j.1523-1755.2001.0590031059.x
86. Noiri, E, Nakao, A, Uchida, K, Tsukahara, H, Ohno, M, Fujita, T, Brodsky, S, Goligorsky, MS. Oxidative and nitrosative stress in acute renal ischemia. American Journal of Physiology. Renal Physiol. 2001; 281(5): 948-957. https://doi.org/10.1152/ajprenal.2001.281.5.F948
87. Wang, W, Jittikanont, S, Falk, SA, Li, P, Feng, L, Gengaro, PE, Poole, BD, Bowler, RP, Day, BJ, Crapo, JD, Schrier, RW. Interaction among nitric oxide, reactive oxygen species, and antioxidants during endotoxemia-related acute renal failure. Am J Physiol. Renal Physiol. 2003; 284(3): F532-537. https://doi.org/10.1152/ajprenal.00323.2002
88. Wu, J, Pan, X, Fu, H, Zheng, Y, Dai, Y, Yin, Y, Chen, Q, Hao, Q, Bao, D, Hou, D. Effect of curcumin on glycerol-induced acute kidney injury in rats. Sci Rep. 2017; 7: 10114.
89. Kyung Jo, S, Rosner, M, Okuso, M. pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon. Clin J Am Society Nephrol. 2007; 2: 356-365. https://doi.org/10.2215/CJN.03280906
90. Wan, L, Langenberg, C, Bellomo, R, May, CN. Angiotensin II in experimental hyperdynamic sepsis. Crit Care. 2009; 13(6): R190. https://doi.org/10.1186/cc8185
91. Okusa, MD, Linden, J, Macdonald, T, Huang, L. Selective A2A adenosine receptor activation reduces ischemia-reperfusion injury in rat kidney. Am J Physiol. 1999; 277(3): 404–412. https://doi.org/10.1152/ajprenal.1999.277.3.F404
92. Palipoch, S. A Review of oxidative stress in acute kidney injury: Protective role of medicinal plants-derived antioxidants. Afr J Tradit Complement Altern Med. 2013; 10(4): 88–93. https://doi.org/10.4314/ajtcam.v10i4.15
93. Miyake, Y, Shimoi, K, Kumazawa, S, Yamamoto, K, Kinae, N, Osawa, T. Identification and antioxidant activity of flavonoid metabolites in plasma and urine of eriocitrin-treated rats. J Agric Food Chem. 2000; 48(8): 3217–3224. https://doi.org/10.1021/jf990994g
94. Dennis, JM, Witting, PK. Protective role for antioxidants in acute kidney disease. Nutrients. 2017; 9(7): 718. https://dx.doi.org/10.3390%2Fnu9070718
95. Chatterjee PK, Cuzzocrea S, Brown PA, Zacharowski K, Stewart KN, Mota-Filipe H, Thiemermann C. Tempol, a membrane-permeable radical scavenger, reduces oxidant stress-mediated renal dysfunction and injury in the rat. Kidney Int. 2000; 58(2): 658-673. https://doi.org/10.1046/j.1523-1755.2000.00212.x
96. Meydani, M. Vitamin E and atherosclerosis: Beyond prevention of LDL oxidation. J Nutrition. 2001; 131(2): 366S-368S. https://doi.org/10.1093/jn/131.2.366S
97. Roob, JM, Khoschssorur, G, Tiran, A, Horina, JH, Holzer, H, Winklhofer-Roob, BM. Vitamin E attenuates oxidative stress induced by

intravenous iron in patients on hemodialysis. J Am Soc Nephrol. 2000; 11(3): 539–549.

98. Cho, MH, Kim, SN, Park, HW, Chung, S, Kim, KS. Could Vitamin E Prevent Contrast-Induced Acute Kidney Injury? A Systematic Review and Meta-Analysis. J Korean Med Sci. 2017. 32(9): 1468–1473. https://doi.org/10.3346/jkms.2017.32.9.1468
99. Liu, P, Feng, Y, Wang, Y, Zhou, Y, Zhao, L. Protective effect of vitamin E against acute kidney injury. Biomed Mater Eng. 2015; 26(1) S2133–S2144. https://doi.org/10.3233/BME-151519
100. Fan, S, Zhang, Z, Zheng, Y, Lu, J, Wu, D, Shan, Q, Hu, B, Wang, Y. Troxerutin protects the mouse kidney from d-galactose-caused injury through anti-inflammation and anti-oxidation. Int Immunopharmacol. 2008; 9(1): 91-96. https://doi.org/10.1016/j.intimp.2008.10.008
101. Liu, C-M, Ma, J-Q, Lou, Y. Chronic administration of troxerutin protects mouse kidney against d-galactose-induced oxidative DNA damage. Food Chem Toxicol. 2010; 48(10): 2809-2817. https://doi.org/10.1016/j.fct.2010.07.011
102. Augusti, PR, Conterato, GMM, Somacal, S, Sobieski, R, Spohr, PR, Torres, JV, Charão, MF, Moro, AM, Rocha, MP, Garcia, SC, Emanuelli, T. Effect of astaxanthin on kidney function impairment and oxidative stress induced by mercuric chloride in rats. Food Chem Toxicol. 2008; 46(1): 212-219. https://doi.org/10.1016/j.fct.2007.08.001
103. Gao, D, Li, W. Research progress of astaxanthin on contrast agent induced acute kidney injury. J Cardiol Cardiovasc Med. 2018; 2(3): 6-9. https://doi.org/10.29245/2578-3025/2018/3.1123
104. Guo, S-X, Zhou, H-L, Huang, C-L, You, C-G, Fang, Q, Wu, P, Wang, X-G, Han, C-M. Astaxanthin attenuates early acute kidney injury following severe burns in rats by ameliorating oxidative stress and mitochondrial-related apoptosis. Mar Drugs. 2015; 13(4): 2105–2123. https://doi.org/10.3390/md13042105
105. Liu, N, Chen, J, Gao, D, Li, W, Zheng, D. Astaxanthin attenuates contrast agent-induced acute kidney injury *in vitro* and *in vivo* via the regulation of SIRT1/FOXO3a expression. Int J Nephrol Urol. 2018; 50(6): 1171–1180. https://doi.org/10.1007/s11255-018-1788-y
106. Safa, J, Argani, H, Bastani, B, Nezami, N, Ardebili, BR, Ghorbanihaghjo, A, Kalagheichi, H, Amirfirouzi, A, Mesgari, M, Rad, JS. Protective Effect of grape seed extract on gentamicin induced acute kidney injury. Iran J Kidney Dis. 2010; 4(4): 285-291.
107. Bagchi, D, Bagchi, M, Stohs, SJ, Das, DK, Ray, SD, Kuszynski, CA, Joshi, SS, Pruess, HG. Free radicals and grape seed proanthocyanidin extract: importance in human health and disease prevention. Toxicol. 2000; 148(2-3): 187-197. https://doi.org/10.1016/s0300-483x(00)00210-9
108. Saad, AA, Youssef, MI, El-Shennaway, LK. Cisplatin induced damage in kidney genomic DNA and nephrotoxicity in male rats: The protective effect of grape seed proanthocyanidin extract. Food Chem Toxicol. 2009; 47(7): 1499-1506. https://doi.org/10.1016/j.fct.2009.03.043
109. Hasan, HA, Edrees, GM, El-Gamel, EM, El-Sayed, EA. Amelioration of cisplatin-induced nephrotoxicity by grape seed extract and fish oil is mediated by lowering oxidative stress and DNA damage. Cytotechnology. 2014; 66(3): 419–429. https://doi.org/10.1007/s10616-013-9589-8
110. Sayed, AAR. Proanthocyanidin protects against cisplatin-induced nephrotoxicity. Phytother Res. 2009; 23(12): 1738-1741. https://doi.org/10.1002/ptr.2833
111. Ulusoy, S, Ozkan, G, Alkanat, M, Mungan, S, Yuluğ, E, Orem, A. Perspective on rhabdomyolysis-induced acute kidney injury and new treatment options. Am J Nephrol. 2013; 38(5): 368-378. https://doi.org/10.1159/000355537
112. Ulusoy, S, Ozkan, G, Yucesan, FB, Ersöz, S, Orem, A, Alkanat, M, Yuluğ, E, Kaynar, K, Al, S. Anti-apoptotic and anti-oxidant effects of grape seed proanthocyanidin extract in preventing cyclosporine A-induced nephropathy. Nephrol. 2012; 17(4): 372-379. https://doi.org/10.1111/j.1440-1797.2012.01565.x
113. Zhang, H, Sun, X-Q, Cao, J-M, Zhou, H-T, Guo, X, Wang, Y. Protective effect of epimedium combined with oligomeric proanthocyanidins on exercise-induced renal ischemia-reperfusion injury of rats. Int J Clin Exper Med. 2014; **7**(12): 5730–5736. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4307546/
114. Ozkan, G, Ulusoy, S, Orem, A, Ersöz, S, Alkanat, M, Yucesan, FB, Kaynar, K, Al, S. Protective effect of the grape seed proanthocyanidin extract in a rat model of contrast-induced nephropathy. Kidney Blood Press Res. 2012; 35(6): 445–453. https://doi.org/10.1159/000337926
115. Li, G, Yin, L, Liu, T, Zheng, X, Xu, G, Xu, Y, Yuan, R, Che, J, Liu, H, Zhou, L, Chen, X, He, M, Li, Y, Wu, L, Liu, E. Role of probucol in preventing

contrast-induced acute kidney injury after coronary interventional procedure. Am J Card. 2009; 103(4): 512-514. https://doi.org/10.1016/j.amjcard.2008.10.009

116. Wang, N, Wei, RB, Li, QP, Yang, X, Li, P, Huang, MJ, Wang, R, Cai, GY, Chen, XM. Renal protective effect of probucol in rats with contrast-induced nephropathy and its underlying mechanism. Med Sci Monit. 2015; 21: 2886–2892. https://dx.doi.org/10.12659%2FMSM.895543

117. Yin, L, Li, GP, Liu, T, Liu, M, Chen, X, He, M, Zheng, X-T, Liu, E-Z, Zhou, L-J. Role of probucol in preventing contrast induced acute kidney injury after coronary interventional procedure: a randomized trial. Zhonghua Xin Xue Guan Bing Za Zhi. 2009; 37(5):385-388.

118. Yin, L, Li, G, Liu, T, Yuan, R, Zheng, X, Xu, G, Xu, Y, Che, J, Liu, X, Ma, X, Li, F, Liu, E, Chen, X, Wu, L, Fan, Z, Ruan, Y, He, M, Li, Y. Probucol for the prevention of cystatin C-based contrast-induced acute kidney injury following primary or urgent angioplasty: A randomized, controlled trial. Int J Cardiol. 2013; 167 (2): 426-429. https://doi.org/10.1016/j.ijcard.2012.01.017

119. Abdel-Naim, AB, Abdel-Wahab, MH, Attia, FF. Protective effects of vitamin E probucol against gentamicin-induced nephrotoxicity in rats. Pharmacol Res. 1999; 40(2): 183-187. https://doi.org/10.1006/phrs.1999.0494

120. Kumar, K, Naidu, M, Shifow, A, Ratnakar, A. Probucol protects against gentamicin-induced nephrotoxicity in rats. Indian J Pharmacol. 2000; 32(2): 108-113.

121. Qin, X, Zhang, S, Zarkovic, M, Yamazaki, Y, Oda, H, Nakatsuru, Y, Ishikawa, T, Ishikawa, T. Inhibitory effect of probucol on nephrotoxicity induced by ferric nitrilotriacetate (Fe-NTA) in rats. Carcinog. 1995; 16(10): 2549–2552. https://doi.org/10.1093/carcin/16.10.2549

122. Modi, KS, Morrisey, J, Shah, SV, Schreiner, GF, Klahr, S. Effects of probucol on renal function in rats with bilateral ureteral obstruction. Kidney Int. 1990; 38(5): 835-850. https://doi.org/10.1038/ki.1990.280

123. Tasanarong, A, Kongkham, S, Itharat, A. Antioxidant effect of Phyllanthus emblica extract prevents contrast-induced acute kidney injury. BMC Complement Altern Med. 2014; 14: 138. https://doi.org/10.1186/1472-6882-14-138

124. Sadeghi, F, Nematbakhsh, M, Noori-Diziche, A, Eshraghi-Jazi, F, Talebi, A, Nasri, H, Mansouri, A, Dehghani, A, Saberi, S, Shirdavani, S, Ashrafi, F. Protective effect of pomegranate flower extract against gentamicin-induced renal toxicity in male rats. J Renal Inj Prev. 2015; 4(2): 45–50. https://dx.doi.org/10.12861%2Fjrip.2015.10

125. Ghaznavi, H, Fatemi, I, Kalantari, H, Tabatabaei, SMTH, Mehrabani, M, Gholamine, B, Kalantar, M, Mehrzadi, S, Goudarzi, M. Ameliorative effects of gallic acid on gentamicin-induced nephrotoxicity in rats. J Asian Nat Prod Res. 2017; 20(12): 1182-1193. https://doi.org/10.1080/10286020.2017.1384819

126. Olayinka, ET, Ore, A, Ola, AS, Adeyemo, OA. Ameliorative effect of gallic acid on cyclophosphamide-induced oxidative injury and hepatic dysfunction in rats. Med Sci. 2015; 3(3): 78-92. https://dx.doi.org/10.3390%2Fmedsci3030078

127. Akomolafe, SF, Akinyemi, AJ, Anadosie, SO. Phenolic Acids (Gallic and Tannic Acids) modulate antioxidant status and cisplatin induced nephrotoxicity in rats. Int Sch Res Notices. 2014; 984709. https://doi.org/10.1155/2014/984709

128. Asci, H, Ozmen, O, Ellidag, HY, Aydin, B, Bas, E, Yilmaz, N. The impact of gallic acid on the methotrexate-induced kidney damage in rats. J Food Drug Anal. 2017; 25(4): 890-897. https://doi.org/10.1016/j.jfda.2017.05.001

129. Ajibade, TO, Oyagbemi, AA, Omobowale, TO, Asenuga, ER, Afolabi, JM, Adedapo, AA. Mitigation of diazinon-induced cardiovascular and renal dysfunction by gallic acid. Interdiscip Toxicol. 2016; 9(2): 66–77. https://dx.doi.org/10.1515%2Fintox-2016-0008

130. Padma, VV, Sowmya, P, Felix, TA, Baskaran, R, Poornima, P. Protective effect of gallic acid against lindane induced toxicity in experimental rats. Food Chem Toxicol. 2011; 49(4): 991-998. https://doi.org/10.1016/j.fct.2011.01.005

131. Ahmadvand, H, Yalameha, B, Adibhesami, G, Nasri, M, Naderi, N, Babaeenezhad, E, Nouryazdan, N. The Protective Role of Gallic Acid Pretreatment on Renal Ischemia-reperfusion Injury in Rats. Rep Biochem Molecul Biol. 2019; 8(1): 42–48. https://www.ncbi.nlm.nih.gov/pubmed/31334287

132. Nabavi, SM, Habtemariam, S, Nabavi, SF, Sureda, A, Daglia, M, Moghaddam, AH, Amani, MA. Protective effect of gallic acid isolated from Peltiphyllum peltatum against sodium fluoride-induced oxidative stress in rat's kidney. Molecul Cell Biochem. 2013; 372(1-2): 233-239. https://doi.org/10.1007/s11010-012-1464-y

133. Sadat, U, Usman, A, Gillard, JH, Boyle, JR Does Ascorbic acid protect against contrast-induced acute kidney injury in patients undergoing coronary angiography. A systematic review with meta-analysis of randomized, controlled trials. JACC. 2013; 62(23): 2167-2175. https://doi.org/10.1016/j.jacc.2013.07.065

134. Frei, B, England, L, Ames, B. Ascorbate is an outstanding antioxidant in human blood plasma. Proceedings of the National Academy of Sciences of the United States of America. 1989; 86(16): 6377-6381. https://dx.doi.org/10.1073%2Fpnas.86.16.6377

135. Hamdi, S, Selmi, W, Hraiech, A, Jomaa, W, Hamda KB, Maatouk, F CRT-66 Prevention of contrast induced nephropathy in patients undergoing coronarography with ascorbic acid. J Am Coll Card: Cardiovascul Interven. 2012; 6(2): 84. https://doi.org/10.1016/j.jcin.2012.12.084

136. Li, R, Chen, H. Prevention of contrast-induced nephropathy with ascorbic acid. Internal Med. 2012; 51(6): 531-535. https://doi.org/10.2169/internalmedicine.51.6260

137. Brueck, M, Cengiz, H, Hoeltgen, R, Wieczorek, M, Boedeker, R, Scheibelhut, C, Boening, A. Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: a single-center, prospective, randomized, double-blind, placebo-controlled trial. J Invasive Cardiol. 2013; 25(6): 276-228.

138. Rezaei, Y, Hemilä, H. Vitamins E and C may differ in their effect on contrast-induced acute kidney injury. Am J Kidney Dis. 2017; 69(5): 708–709. https://doi.org/10.1053/j.ajkd.2016.12.022

139. Khan, MR, Siddiqui, S, Parveen, K, Javed, S, Diwakar, S, Siddiqui, WA. Nephroprotective action of tocotrienol-rich fraction (TRF) from palm oil against potassium dichromate (K 2 Cr 2 O 7)-induced acute renal injury in rats. Chemico-Biologic Interact. 2010; 186(2): 228-238. https://doi.org/10.1016/j.cbi.2010.04.025

140. Tasanarong, A, Vohakiat, A, Hutayanon, P, Piyayotai, D. New strategy of α- and γ-tocopherol to prevent contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. Nephrol Dial Transplant. 2013; 28(2): 337–344. https://doi.org/10.1093/ndt/gfs525

141. Kim, HB, Shanu, A, Wood, S, Parry, SN, Collet, M, McMahon, A, Witting, PK. Phenolic antioxidants tert-butyl-bisphenol and vitamin E decrease oxidative stress and enhance vascular function in an animal model of rhabdomyolysis yet do not improve acute renal dysfunction. Free Radic Res. 2011; 45(9): 1000-1012. https://doi.org/10.3109/10715762.2011.590137

142. Rebholz, CM, Crews, DC, Grams, ME, Steffen, LM, Levey, AS, Miller, ER 3rd, Appel, LJ, Coresh, J. DASH (Dietary Approaches to Stop Hypertension) Diet and Risk of Subsequent Kidney Disease. Am J Kidney Dis. 2016; 68(6): 853–861. https://doi.org/10.1053/j.ajkd.2016.05.019

143. Nasri, H, Ahmadi, A, Baradaran, A, Nasri, P, Hajian, S, Pour-Arian, A, Kohi, G, Rafieian-Kopaei, M. A biochemical study on ameliorative effect of green tea (Camellia sinensis) extract against contrast media induced acute kidney injury. J Renal Inj Preven. 2014; 3(2): 47–49. https://doi.org/10.12861/jrip.2014.16

144. Khan, SA, Priyamvada, S, Farooq, N, Khan, S, Khan, MW, Yusufi, AN. Protective effect of green tea extract on gentamicin-induced nephrotoxicity and oxidative damage in rat kidney. Pharmacol Res. 2009; 59(4): 254–262. https://doi.org/10.1016/j.phrs.2008.12.009

145. Veljković, M, Pavlović, DR, Stojiljković, N, Ilić, S, Petrović, A, Jovanović, I, Radenković, M. Morphological and morphometric study of protective effect of green tea in gentamicin-induced nephrotoxicity in rats. Life Sci. 2016; 147: 85-91. https://doi.org/10.1016/j.lfs.2016.01.035

146. Rehman, H, Krishnasamy, Y, Haque, K, Thurman, RG, Lemasters, JJ, Schnellmann, RG, Zhong, Z. Green tea polyphenols stimulate mitochondrial biogenesis and improve renal function after chronic cyclosporin a treatment in rats. PLOS ONE. 2013; 8(6): 1–12. https://doi.org/10.1371/journal.pone.0065029

147. Ryu, HH, Kim, HL, Chung, JH, Lee, BR, Kim, TH, Shin, BC. Renoprotective effects of green tea extract on renin-angiotensin-aldosterone system in chronic cyclosporine-treated rats. Nephrol Dialysis Transplant. 2011; 26(4): 1188–1193. https://doi.org/10.1093/ndt/gfq616

148. Shin, BC, Kwon, YE, Chung, JH, Kim, HL. The antiproteinuric effects of green tea extract on acute cyclosporine-induced nephrotoxicity in rats. Transplant Proceedings. 2012; 44(4): 1080-1082. https://doi.org/10.1016/j.transproceed.2012.03.047

149. Funamoto, M, Masumoto, H, Takaori, K, Taki, T, Setozaki, S, Yamazaki, K, Minakata, K, Ikeda, T, Hyon, S-H, Sakata, R. Green tea polyphenol

prevents diabetic rats from acute kidney injury after cardiopulmonary bypass. Ann Thorac Surg. 2015; 101(4): 1507-1513. https://doi.org/10.1016/j.athoracsur.2015.09.080

150. Rah, DK, Han, DW, Baek, HS, Hyon, SH, Park, BY, Park, JC. Protection of rabbit kidney from ischemia/reperfusion injury by green tea polyphenol pre-treatment. Arch Pharmaceut Res. 2007; 30(11): 1447-1454. https://doi.org/10.1007/bf02977370

151. Molinari, M, Watt, KD, Kruszyna, T, Nelson, R, Walsh, M, Huang, WY, Nashan, B, Peltekian, K. Acute liver failure induced by green tea extracts: Case report and review of the literature. Liver Transplant. 2006; 12(12): 1892-1895. https://doi.org/10.1002/lt.21021

152. Kaur, A, Kaur, T, Singh, B, Pathak, D, Buttar, HS, Singh, AP. Curcumin alleviates ischemia reperfusion-induced acute kidney injury through NMDA receptor antagonism in rats. Renal Failure. 2016; 38(9): 1462-1467. https://doi.org/10.1080/0886022X.2016.1214892

153. Boozari, M, Hosseinzadeh, H. Natural medicines for acute renal failure: A review. Phytother Res. 2017; 31(12): 1824-1835. https://doi.org/10.1002/ptr.5943

154. Venkat Ratnam, D, Ankola, DD, Bhardwaj, V, Sahana, DK, Ravi Kumar, MNV. Role of antioxidants in prophylaxis and therapy: A pharmaceutical perspective. J Control Release. 2006; 113(3): 189-207. https://doi.org/10.1016/j.jconrel.2006.04.015

155. Pangeni, R, Sahni, JK, Ali, J, Sharma, S, Baboota, S. Resveratrol: review on therapeutic potential and recent advances in drug delivery. Expert Opin Drug Deliv. 2014; 11(8): 1285-1298. https://doi.org/10.1517/17425247.2014.919253

156. Soppimath, KS, Aminabhavi, TM, Kulkarni, AR, Rudzinski, WE. Biodegradable polymeric nanoparticles as drug delivery devices. J Control Release. 2001; 70(1–2):1-20. https://doi.org/10.1016/S0168-3659(00)00339-4

157. Faraji, AH, Wipf, P. (2009). Nanoparticles in cellular drug delivery. Bioorganic & Medicinal Chemistry **17**(8): 2950-2962. https://doi.org/10.1016/j.bmc.2009.02.043

158. Reis, CP, Neufeld, RJ, Ribeiro, AJ, Veiga, F. Nanoencapsulation I. Methods for preparation of drug-loaded polymeric nanoparticles. Nanomed. 2006; 2(1): 8-21. https://doi.org/10.1016/j.nano.2005.12.003

159. Parveen, S, Misra, R, Sahoo, SK. Nanoparticles: A boon to drug delivery, therapeutics, diagnostics and imaging. Nanomed. 2012; 8(2): 147-166. https://doi.org/10.1016/j.nano.2011.05.016

160. Rao, JP, Geckeler, KE. (2011). Polymer nanoparticles: Preparation techniques and size-control parameters. Prog Polym Sci. 2011; 36(7): 887-913. https://doi.org/10.1016/j.progpolymsci.2011.01.001

161. da Silva, D, Kaduri, M, Poley, M, Adir, O, Krinsky, N, Shainsky-Roitman, J, Schroeder, A. Biocompatibility, biodegradation and excretion of polylactic acid (PLA) in medical implants and theranostic systems. Chem Engin J. 2018; 340: 9-14. https://doi.org/10.1016/j.cej.2018.01.010

162. Buhecha, MD, Lansley, AB, Somavarapu, S, Pannala, AS. (2019) Development and characterization of PLA nanoparticles for pulmonary drug delivery: Co-encapsulation of theophylline and budesonide, a hydrophilic and lipophilic drug. J Drug Delivery Sci Techn. 2019; 53: 101128. https://doi.org/10.1016/j.jddst.2019.101128

163. Rai, M, Kon, K. Nanotechnology in Diagnosis, Treatment and Prophylaxis of Infectious Diseases. 1st Edition. Academic Press; 2015. ISBN 9780128013175.

164. Banerjee, R. Liposomes: Application in medicine. J Biomat App. 2001; 16(1): 3-21. https://doi.org/10.1106/RA7U-1V9C-RV7C-8QXL

165. Sercombe, L, Veerati, T, Moheimani, F, Wu, SY, Sood, AK, Hua, S. Advances and challenges of liposome assisted drug delivery. Front Pharmacol. 2015; 6: 286. https://doi.org/10.3389/fphar.2015.00286

166. Bulbake, U, Doppalapudi, S, Kommineni, N, Khan, W. Liposomal formulations in clinical use: An updated review. Pharm. 2017; 9(2): 12. https://doi.org/10.3390/pharmaceutics9020012

167. Dichello, GA, Fukuda, T, Maekawa, T, Whitby, RLD, Mikhalovsky, SV, Alavijeh, M, Pannala, AS, Sarker, DK. Preparation of liposomes containing small gold nanoparticles using electrostatic interactions. European J Pharm Sci. 2017; 105: 55-63. https://doi.org/10.1016/j.ejps.2017.05.001

168. Galvão, AM, Wanderley, MS, Silva, RA, Filho, CA, Melo-Junior, MR, Silva, LA, Streck, EL, Dornelas de Andrade, AF, Souza Maia, MB, Barbosa de Castro, CM. Intratracheal co-administration of antioxidants and ceftriaxone reduces pulmonary injury and mortality rate in

an experimental model of sepsis. Respirol. 2014; 19(7): 1080–1087. https://doi.org/10.1111/resp.12363

169. Alhusaini, A, Fadda, L, Hassan, I, Ali, HM, Alsaadan, N, Aldowsari, N, Aldosari, A, Alharbi, B. Liposomal Curcumin Attenuates the Incidence of Oxidative Stress, Inflammation, and DNA Damage Induced by Copper Sulfate in Rat Liver. Dose-Response. 2018; 16(3): 1559325818790869. https://doi.org/10.1177/1559325818790869

170. Csiszár, A, Csiszar, A, Pinto, JT, Gautam, T, Kleusch, C, Hoffmann, B, Tucsek, Z, Toth, P, Sonntag, WE, Ungvari, Z. Resveratrol encapsulated in novel fusogenic liposomes activates Nrf2 and attenuates oxidative stress in cerebromicrovascular endothelial cells from aged rats. The Journals of Gerontology. Series A, Biol Sci Med Sci. 2015; 70(3): 303–313. https://doi.org/10.1093/gerona/glu029

171. Bonechi, C, Martini, S, Ciani, L, Lamponi, S, Rebmann, H, Rossi, C, Ristori, S. Using liposomes as carriers for polyphenolic compounds: the case of trans-resveratrol. PloS One. 2012; **7**(8): e41438. https://doi.org/10.1371/journal.pone.0041438

172. Fang, JY, Hwang, TL, Huang, YL, Fang, CL. Enhancement of the transdermal delivery of catechins by liposomes incorporating anionic surfactants and ethanol. Int J Pharm. 2006; 310(1-2): 131–138. https://doi.org/10.1016/j.ijpharm.2005.12.004

173. Qin, J, Chen, D, Lu, W, Xu, H, Yan, C, Hu, H, Chen, B, Qiao, M, Zhao, X. Preparation, characterization, and evaluation of liposomal ferulic acid *in vitro* and *in vivo*. Drug Dev Ind Pharm. 2008; 34(6): 602–608. https://doi.org/10.1080/03639040701833559

174. Schwedhelm, E, Maas, R, Troost, R, Bogar, R. Clinical pharmacokinetics of antioxidants and their impact on systemic oxidative stress. Clin Pharmacok. 2003; 42(5):437. https://doi.org/10.2165/00003088-200342050-00003

175. Ergin, B, Zuurbier, CJ, Bezemer, R, Kandil, A, Almac, E, Demirci, C, Ince, C. Ascorbic acid improves renal microcirculatory oxygenation in a rat model of renal I/R injury. J Transl Int Med. 2015; 3(3): 116–125. https://doi.org/10.1515/jtim-2015-0011

176. Dennis, JM, Witting, PK. Protective Role for Antioxidants in Acute Kidney Disease. Nutrients. 2017; 9(7): 718. https://doi.org/10.3390/nu9070718

177. Wang, Y, Lin, H, Lin, BW, Lin, JD. Effects of different ascorbic acid doses on the mortality of critically ill patients: a meta-analysis. Ann Intensive Care. 2019; 9(1): 58. https://doi.org/10.1186/s13613-019-0532-9

178. Christen, S, Woodall, AA, Shigenaga, MK, Southwell-Keely, PT, Duncan, MW, Ames, BN. gamma-tocopherol traps mutagenic electrophiles such as NO(X) and complements alpha-tocopherol: physiological implications. Proceedings of the National Academy of Sciences of the United States of America. 1997; 94(7): 3217–3222. https://doi.org/10.1073/pnas.94.7.3217

179. Soltani, R, Khorvash, F, Meidani, M, Badri, S, Alaei, S, Taheri, S. Vitamin E in the prevention of vancomycin-induced nephrotoxicity. Res Pharm Sci. 2020; 15(2): 137–143. https://doi.org/10.4103/1735-5362.283813

180. Tasanarong, A, Vohakiat, A, Hutayanon, P, Piyayotai, D. New strategy of α- and γ-tocopherol to prevent contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. Nephrol Dial Transpl. 2013; 28(2): 337–344. https://doi.org/10.1093/ndt/gfs525

181. Simon, LC, Stout, RW, Sabliov, C. Bioavailability of Orally Delivered Alpha-Tocopherol by Poly(Lactic-Co-Glycolic) Acid (PLGA) Nanoparticles and Chitosan Covered PLGA Nanoparticles in F344 Rats. Nanobiomedicine. 2016; 3: 8. https://doi.org/10.5772/63305

182. Holthoff, JH, Wang, Z, Seely, KA, Gokden, N, Mayeux, PR. Resveratrol improves renal microcirculation, protects the tubular epithelium, and prolongs survival in a mouse model of sepsis-induced acute kidney injury. Kidney Int. 2012; 81(4): 370-378. https://doi.org/10.1038/ki.2011.347

183. Rotches-Ribalta, M, Andres-Lacueva, C, Estruch, R, Escribano, E, Urpi-Sarda. Pharmacokinetics of resveratrol metabolic profile in healthy humans after moderate consumption of red wine and grape extract tablets. Pharmacol Res. 2012; 66(5): 375-382. https://doi.org/10.1016/j.phrs.2012.08.001

184. Walle, T. Bioavailability of resveratrol. Ann N Y Acad Sci. 2011; 1215: 9-15. https://doi.org/10.1111/j.1749-6632.2010.05842.x

185. Wenzel, E, Somoza, V. Metabolism and bioavailability of trans-resveratrol. Mol Nutr Food Res. 2005; 49(5): 472-481. https://doi.org/10.1002/mnfr.200500010

186. Crowell, JA, Korytko, PJ, Morrissey, RL, Booth, TD, Levine, BS. Resveratrol-associated renal toxicity. Toxicol Sci. 2004; 82(2): 614-619. https://doi.org/10.1093/toxsci/kfh263

187. Narayanan, NK, Nargi, D, Randolph, C, Naryanan, BA. Liposome encapsulation of curcumin and resveratrol in combination reduces prostate cancer incidence in PTEN knockout mice. Int J Cancer. 2009; 125(1): 1-8. https://doi.org/10.1002/ijc.24336

188. Pandita, D, Kumar, S, Poonia, N, Lather, V. Solid lipid nanoparticles enhance oral bioavailability of resveratrol, a natural polyphenol. Food Res Int. 2014; 62: 1165-1174. https://doi.org/10.1016/j.foodres.2014.05.059

189. Chauhan, AS. Dendrimer nanotechnology for enhanced formulation and controlled delivery of resveratrol. Ann N Y Acad Sci. 2015; 1384(1): 134-140. https://doi.org/10.1111/nyas.12816

190. Pentek, T, Newenhouse, E, O'Brien, BO, Chauhan, AS. Development of a topical resveratrol formulation for commercial applications using dendrimer nanotechnology. Molecules. 2017; 22(1): 137. https://dx.doi.org/10.3390%2Fmolecules22010137

191. Xu, Y, Zhang, B, Xie, D, Hu, Y, Li, H-L, Zhong, L-L, Wang, H-W, Jiang, W, Ke, Z-P, Zheng, D-H. Nanoparticle-mediated dual delivery of resveratrol and DAP5 ameliorates kidney ischemia/reperfusion injury by inhibiting cell apoptosis and inflammation. Oncotarget. 2017; 8(24): 39547–39558. https://doi.org/10.18632/oncotarget.17135

192. Xu, S, Gao, Y, Zhang, Q, Wei, S, Chen, Z, Dia, X, Zeng, Z, Zhao, K-S. SIRT1/3 Activation by resveratrol attenuates acute kidney injury in a septic rat model. Oxi Med Cell Longev. 2016; 7296092. https://doi.org/10.1155/2016/7296092

193. Gan, Y, Tao, S, Cao, D, Xie, H, Zeng, Q. Protection of resveratrol on acute kidney injury in septic rats. Hum Exp Toxicol. 2017; 36(10): 1015-1022. https://doi.org/10.1177/0960327116678298

194. Chen, L, Yang, S, Zumbrun, EE, Guan, H, Nagarkatti, PS, Nagarkatti, M. Resveratrol attenuates lipopolysaccharide-induced acute kidney injury by suppressing inflammation driven by macrophages. Mol Nutr Food Res. 2015; 59(5): 853-864. https://doi.org/10.1002/mnfr.201400819

195. Wang, N, Mao, L, Yang, L, Zou, J, Liu, K, Liu, M, Zhang, H, Xiao, X, Wang, K. Resveratrol protects against early polymicrobial sepsis-induced acute kidney injury through inhibiting endoplasmic reticulum stress-activated NF-κB pathway. Oncotarget. 2017; 8(22): 36449–36461. https://doi.org/10.18632/oncotarget.16860

196. Hao, Q, Xiao, X, Zheng, J, Feng, J, Song, C, Jiang, B, Hu, Z. Resveratrol attenuates acute kidney injury by inhibiting death receptor-mediated apoptotic pathways in a cisplatin-induced rat model. Mol Med Rep. 2016; 14(4): 3683-3689. https://doi.org/10.3892/mmr.2016.5714

197. Yu, M, Xue, J, Li, Y, Zhang, W, Ma, D, Liu, L, Zhang, Z. Resveratrol protects against arsenic trioxide-induced nephrotoxicity by facilitating arsenic metabolism and decreasing oxidative stress. Ach Toxicol. 2013; 87(6): 1025-1035. https://doi.org/10.1007/s00204-013-1026-4

198. Li, J, Li, L, Wang, S, Zhang, C, Zheng, L, Jia, Y, Xu, M, Zhu, T, Zhang, Y, Rong, R. Resveratrol alleviates inflammatory responses and oxidative stress in rat kidney ischemia-reperfusion injury and H2O2-induced NRK-52E Cells via the Nrf2/TLR4/NF-κB pathway. Cell Physiol Biochem. 2018; 45(4): 1677-1689. https://doi.org/10.1159/000487735

199. Nabavi, SF, Moghaddam, AH, Eslami, S, Nabavi, SM. Protective effects of curcumin against sodium fluoride-induced toxicity in rat kidneys. Biol Trace Elem Res. 2011; 145(3): 369-374. https://doi.org/10.1007/s12011-011-9194-7

200. Hismiogullari, AA, Hismiogullari, SE, Karaca, O, Sunay, FB, Paksoy, S, Can, M, Kus, I, Seyrek, K, Yuvuz, O. The protective effect of curcumin administration on carbon tetrachloride (CCl4)-induced nephrotoxicity in rats. Pharmacol Rep. 2015; 67(3): 410-416. https://doi.org/10.1016/j.pharep.2014.10.021

201. Fan, Y, Chen, H, Peng, H, Haung, F, Zhong, J, Zhou, J. Molecular mechanisms of curcumin renoprotection in experimental acute renal injury. Front Pharmacol. 2017; 8: 912. https://doi.org/10.3389/fphar.2017.00912

202. Ugur, S, Ulu, R, Dogukan, D, Gurel, A, Yigit, IP, Gozel, N, Aygen, B, Ilhan, N. The renoprotective effect of curcumin in cisplatin-induced nephrotoxicity. Ren Fail. 2015; 37(2): 332-336. https://doi.org/10.3109/0886022X.2014.986005

203. Najafi, H, Ashtiyani, SC, Sayedzadeh, SA, Yarijani, ZM, Fakhri, S. Therapeutic effects of curcumin on the functional disturbances and oxidative stress induced by renal

ischemia/reperfusion in rats. Avicenna J Phytomed. 2015; 5(6): 576–586. http://www.ncbi.nlm.nih.gov/pmc/articles/pmc4678503/

204. Mercantepe, F, Mercantepe, T, Topcu, A, Yilmaz, A, Tumkaya, A. Protective effects of amifostine, curcumin, and melatonin against cisplatin-induced acute kidney injury. Naunyn Schmiedebergs Arch Pharmacol. 2018; 391(9): 915–931. https://doi.org/10.1007/s00210-018-1514-4

205. Tapia, E, Sánchez-Lozada, LG, García-Niño, WR, García, E, Cerecedo, A, García-Arroyo, FE, Osorio, H, Arellano, A, Cristóbal-García, M, Loredo, ML, Molina-Jijón, E, Hernández-Damián, J, Negrette-Guzmán, M, Zazueta, C, Huerta-Yepez, S, Reyes, JL, Madero, M, Pedraza-Chaverrí, J. Curcumin prevents maleate-induced nephrotoxicity: relation to hemodynamic alterations, oxidative stress, mitochondrial oxygen consumption and activity of respiratory complex I. Free Radic Res. 2014 48(11): 1342–1354. https://doi.org/10.3109/10715762.2014.954109

206. Liu, F, Ni, W, Zhang, J, Wang, G, Li, F. Ren, W. Administration of curcumin protects kidney tubules against renal ischemia-reperfusion injury (RIRI) by modulating nitric oxide (NO) signaling pathway. Cell Physiol Biochem. 2017; 44(1): 401–411. https://doi.org/10.1159/000484920

207. Topcu-Tarladacalisir, Y, Sapmaz-Metin, M, Karaca, T. Curcumin counteracts cisplatin-induced nephrotoxicity by preventing renal tubular cell apoptosis. Ren Fail. 2016; 38(10): 1741-1748. https://doi.org/10.1080/0886022X.2016.1229996

208. Hammad, FT, Al-Salam, S, Lubbad, L. Curcumin provides incomplete protection of the kidney in ischemia reperfusion injury. Physiol Res. 2012; 61(5): 503-511. https://doi.org/10.33549/physiolres.932376

209. Vlahović, P, Cvetković, T, Savić, V, Stefanović, V. Dietary curcumin does not protect kidney in glycerol-induced acute renal failure. Food Chem Toxicol. 2007; 45(9): 1777-1782. https://doi.org/10.1016/j.fct.2007.04.004

210. He, L, Peng, X, Zhu, J, Liu, G, Chen, X, Tang, C, Liu, H, Liu, F, Peng, Y. Protective effects of curcumin on acute gentamicin-induced nephrotoxicity in rats. Can J Physiol Pharmacol. 2015; 93(4): 275-282. https://doi.org/10.1139/cjpp-2014-0459

211. Garg, AX, Devereaux, PJ, Hill, A, Sood, M, Aggarwal, B, Dubois, L, Hiremath, S, Guzman, R, Iyer, V, James, M, McArthur, E, Moist, L, Ouellet, G, Parikh, CR, Schumann, V, Sharan, S, Thiessen-Philbrook, H, Tobe, S, Wald, R, Walsh, M, Weir, M, Pannu, N, and Curcumin AAA AKI Investigators. Oral curcumin in elective abdominal aortic aneurysm repair: a multicentre randomized controlled trial. Can Med Assoc J. 2018; 190(43): E1273-E1280. https://doi.org/10.1503/cmaj.180510

212. Sharma, RA, Steward, WP, Gescher, AJ. Pharmacokinetic and pharmacodynamics of curcumin. Adv Exp Med Biol. 2007; 595: 453-470. https://doi.org/10.1007/978-0-387-46401-5_20

213. Rogers, NM, Stephenson, MD, Kitching, AR, Horowitz, JD, Coates, PTH. Amelioration of renal ischaemia–reperfusion injury by liposomal delivery of curcumin to renal tubular epithelial and antigen-presenting cells. Br J Pharmacol. 2012; 166(1): 194–209. https://doi.org/10.1111/j.1476-5381.2011.01590.x

214. Chen, X, Sun, J, Li H, Wang, H, Lin, Y, Hu, Y, Zheng, D. Curcumin-loaded nanoparticles protect against rhabdomyolysis-induced acute kidney injury. Cell Physiol Biochem. 2017; 43(5): 2143–2154. https://doi.org/10.1159/000484233

215. Chen, Y-A, Hsu, K-Y. Pharmacokinetics of (-)-epicatechin in rabbits. Arch Pharm Res. 2009; 32(1): 149-154. https://doi.org/10.1007/s12272-009-1129-x

216. Lee, SYH, Munerol, B, Pollard, S, Youdim, KA, Pannala, AS, Kuhnle, GC, Debnam, ES, Rice-Evans, C, Spencer, JPE. The reaction of flavanols with nitrous acid protects against N-nitrosamine formation and leads to the formation of nitroso derivatives which inhibit cancer cell growth. Free Rad Biol Med. 2006; 40(2), 323-334. https://doi.org/10.1016/j.freeradbiomed.2005.08.031

217. Yadav, R, Kumar, D, Kumari, A, Yadav, SK. Encapsulation of catechin and epicatechin on BSA NPS improved their stability and antioxidant potential. EXCLI J. 2014; 13: 331–346. https://www.ncbi.nlm.nih.gov/pubmed/26417264

218. Tanabe, K, Tamura, Y, Lanaspa, MA, Miayzaki, M, Suzuki, N, Sato, W, Maeshima, Y, Schreiner, GF, Villarreal, FJ, Johnson, RJ, Nakagawa, T. Epicatechin limits renal injury by mitochondrial protection in cisplatin nephropathy. Am J Physiol. Ren Physiol. 2012; 303(9): F1264-1274. https://doi.org/10.1152/ajprenal.00227.2012

219. Malik, S, Suchal, K, Bhatia, J, Gamad, N, Dinda, AK, Gupta, YK, Arya, DS. Molecular mechanisms underlying attenuation of cisplatin-induced acute kidney injury by epicatechin gallate. Lab Inves. 2016; 96(8): 853-861. https://doi.org/10.1038/labinvest.2016.60

220. Prince, PD, Fischerman, L, Toblli, JE, Fraga, CG, Galleano, M. LPS-induced renal inflammation is prevented by (−)-epicatechin in rats. Redox Biol. 2017; 11: 342-349. https://dx.doi.org/10.1016%2Fj.redox.2016.12.023

221. Nićiforović, N, Abramovič, H. Sinapic acid and its derivatives: natural sources and bioactivity. Compr Rev Food Sci Food Saf. 2013(1): 34-51. https://doi.org/10.1111/1541-4337.12041

222. Rechner, AR, Spencer, JP, Kuhnle, G, Hahn, U, Rice-Evans, CA. Novel biomarkers of the metabolism of caffeic acid derivatives *in vivo*. Free Rad Biol Med. 2001; 30(11): 1213–1222. https://doi.org/10.1016/s0891-5849(01)00506-8

223. Rechner, AR, Pannala, AS, Rice-Evans, CA. Caffeic acid derivatives in artichoke extract are metabolised to phenolic acids *in vivo*. Free Rad Res. 2001; 35(2): 195–202. https://doi.org/10.1080/10715760100300741

224. Kern, SM, Bennett, RN, Mellon, FA, Kroon, PA, Garcia-Conesa, M-T. Absorption of hydroxycinnamates in humans after high-bran cereal consumption. J Agric Food Chem. 2003; 51(20): 6050-6055. https://doi.org/10.1021/jf0302299

225. Shakeel, F, Raish, M, Anwar, MK, Al-Shdefat, R. Self-nanoemulsifying drug delivery system of sinapic acid: *In vitro* and *in vivo* evaluation. J Mol Liq. 2016; 224(A): 351-358. https://doi.org/10.1016/j.molliq.2016.10.017

226. Chen, C. Sinapic acid and its derivatives as medicine in oxidative stress-induced diseases and aging. Oxid Med Cell Longev. 2016; 3571614. https://doi.org/10.1155/2016/3571614

227. Ansari, MA. Sinapic acid modulates Nrf2/HO-1 signaling pathway in cisplatin-induced nephrotoxicity in rats. Biomed Pharmac. 2017; 93: 646-653. https://doi.org/10.1016/j.biopha.2017.06.085