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Herbal antioxidants and renal ischemic-reperfusion injury; an updated review

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ABSTRACT

Renal ischemia-reperfusion (RIR) is a pathological condition due to transient restriction of blood flow to the kidneys, which is followed by the subsequent recovery of perfusion and re-oxygenation. RIR injury contributes to the progression of renal dysfunction including acute kidney injury (AKI) in native and renal allograft transplant. The generation of reactive oxygen species (ROS) during oxidative stress contributes to the occurrence of RIR. Hence, the use of antioxidant compounds can improve oxidative stress due to RIR. This review highlights herbal antioxidant efficacy against RIR injury. The findings of this study indicate that antioxidant compounds with herbal origin could reduce complications due to oxidative stress related to RIR through diminishing lipid peroxidation, decreased production of malondialdehyde (MDA), apoptosis and increasing antioxidant enzymes activity. Reducing oxidative stress with the pharmacological approach of antioxidants can be a desirable target for ameliorating RIR.

Review

Implication for health policy/practice/research/medical education:
Antioxidants diminish the oxidative damage caused by renal ischemia-reperfusion (RIR) through inhibiting the lipid peroxidation and increasing the activity of antioxidant enzymes. Hence, targeting the oxidative stress pathway with antioxidants can be a pharmacological approach to ameliorate RIR injury.

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Introduction

Renal ischemia-reperfusion (RIR) is a pathological condition caused by transient restriction of blood flow to the kidneys that is followed by the subsequent recovery of perfusion and re-oxygenation. Under different conditions RIR injury may be caused by shock, cardiac arrest, sepsis, surgical interventions, and organ transplantation (1). Acute kidney injury (AKI) is recognized as a major complication of RIR, leading to a significant decrease in kidney function and a concomitant elevated serum creatinine level (2,3). The occurrence of RIR injuries involves various pathways such as apoptosis, the production of reactive oxygen species (ROS), activation of neutrophils, and inflammatory mediators including cytokines and adhesion molecules (4,5). Oxidative stress is one of the main events that occur during RIR, which induces cytotoxic effects; including DNA damage, proteins oxidation, lipids peroxidation, production of malondialdehyde (MDA) and induction of apoptosis (6,7).

Reperfusion following ischemia leads to re-oxygenation, re-warming and a throwback to aerobic metabolism. However, the increased renal oxygen concentration in reperfusion condition can contribute to the production of ROS (H_2O_2, $^{\bullet}O^{-2}$ and $^{\bullet}OH$), resulting in injury to the functional and cytoskeletal cellular components (8,9). RIR also has a significant role in early renal allograft dysfunction (10). Different strategies to reduce the complications of RIR injury through ROS scavenging is depicted in Figure 1 (11). The compounds extracted from medicinal plants including antioxidants have long been

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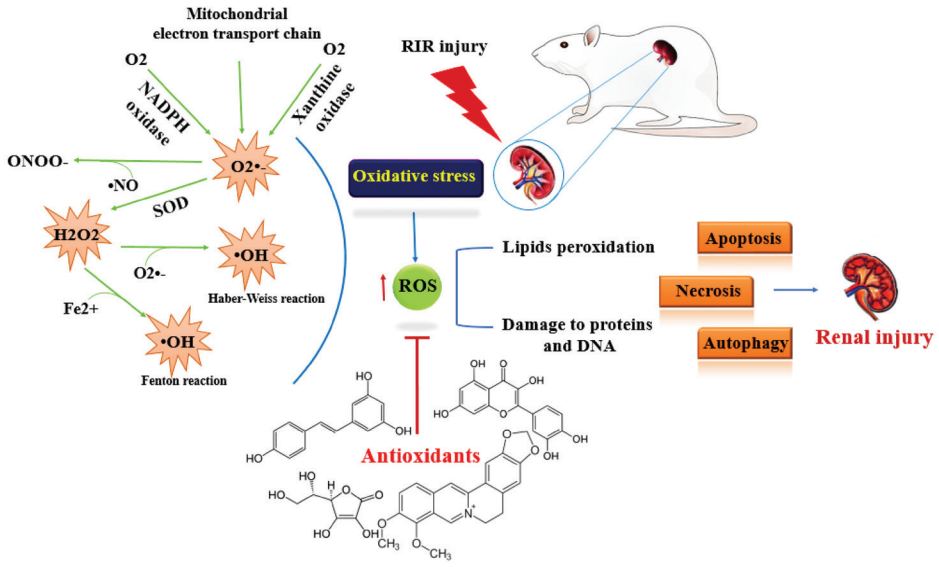

Figure 1. Oxidative stress and RIR injury, the role of antioxidants.

used as an alternative to synthetic drugs, due to their easy accessibility, fewer side effects and economic efficacy (12, 13). It has been documented that the administration of antioxidants leads to a protective effect against RIR Injury mediated oxidative injury (14). Although much progress has been made through the use of animal models, very few reviews have presented the quantitative synthesis of the effective antioxidants used against RIR injury (15-18). In the present review, we summarize the existing evidence found on the effects of the most important antioxidant compounds used for ischemia reperfusion (IR) induced renal injury (Figure 2). We also specifically highlighted some of lesser known antioxidants on this subject (Table 1).

Method of study

Relevant articles, published between 2004 to 2019, were searched from different databases such as the Google Scholar, PubMed/Medline, Web of Science, Scopus, Embase, EBSCO and Directory of Open Access Journals (DOAJ) using search terms of "renal ischemia-reperfusion", "antioxidant", "reactive oxygen species", "oxidative stress", "free radicals", and "medicinal plants".

Curcumin

Curcumin is a natural polyphenol derived from the dried rhizome of *Curcuma longa* (19). This compound is widely used in Asian countries due to its antimicrobial, anti-inflammatory, antimutagenic, anticancer and antioxidant properties (20). Curcumin can neutralize various types of free radicals including ROS and reactive nitrogen species (RNS), and also enhances the activity of antioxidant enzymes such as glutathione (GSH), catalase (CAT) and superoxide dismutase (SOD) (21). Furthermore, curcumin reduces the production of noxious oxidants and contributes to ameliorating tubular necrosis (22). It has been proven that curcumin exhibits remarkable protective effects against RIR injury (23, 24). It has been demonstrated that curcumin up-regulates adaptor protein (APPL1) and subsequently suppresses phosphorylation of Akt pathway thereby protecting kidneys from IR-induced AKI (25). Experimental studies in rats with RIR showed that curcumin can ameliorate renal tubular injury through inhibiting iNOS/NO/cGMP/PKG signaling pathway (26). In addition to this, curcumin-carrying nanoparticles showed protective effects in human renal proximal tubular (HK-2) cells exposed to RIR by decreasing apoptosis, ROS level, MDA content, inhibiting the expression of Bax protein and caspase-3 and enhancing the expression of Bcl-2 and SOD activity (27). Moreover, the renoprotective effect of curcumin in RIR injury is related to the suppression of NF-KB and activation of the JAK2/STAT3 signaling pathway (28).

Luteolin

Luteolin (3′, 4′, 5, 7-tetrahydroxyflavone) is a flavone compound present in fruits and vegetables. Luteolin biological activities include anti-inflammatory, anticancer and antioxidative activities (29). Several studies have indicated that treatment with luteolin ameliorates renal complications such as renal anemia, diabetic nephropathy and RIR injury (30, 31). In vivo and in vitro studies showed that luteolin inhibited xanthine oxidase (XO) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity during IR event (32). Luteolin, as an anti-inflammatory and antioxidant agent, showed nephroprotective effects in mice with RIR (33). These nephroprotective effects were evident by marked elevation in SOD and CAT levels and concomitant decrease in TNF-

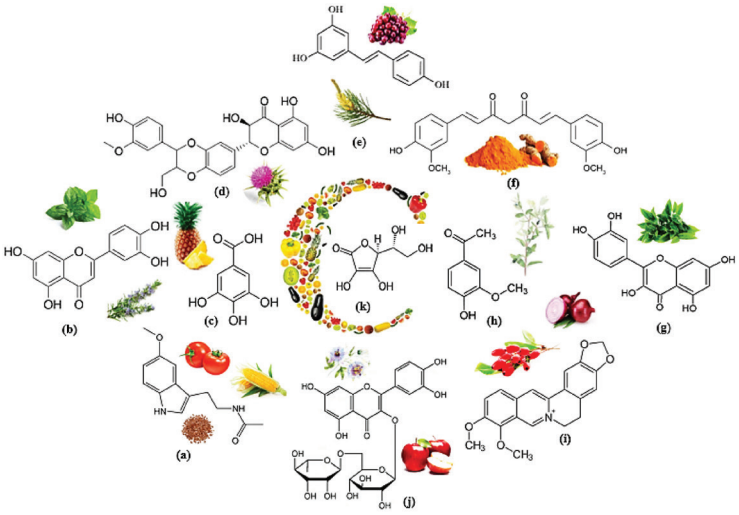

Figure 2. Chemical structure of studied antioxidants; (a) Melatonin, (b) Luteolin, (c) Gallic acid, (d) Silymarin, (e) Resveratrol, (f) Curcumin, (g) Quercetin, (h) Apocynin, (i) Berberine, (j) Rutin, (k) Vitamin C.

α, IL -1β, IL-6 levels (33). Further, treatment with luteolin upregulated Bcl-2 expression and reduced Bax expression, indicating that luteolin reduced the level of apoptosis in renal tissue (34).

Melatonin

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous hormone with multiple physiological and cellular functions. Several lines of evidence indicate the presence of melatonin in plants as an antioxidant (35). Melatonin plays a major role in several pathological conditions; including cardiovascular diseases, neurodegenerative diseases, metabolic syndrome, infection and others (36). Different studies have illustrated that melatonin, as an attractive therapeutic agent, can ameliorate ischemic/reperfusion (IR)-induced disorders in membrane structure, biogenesis, mitochondrial redox state, mitophagy and related dynamics (37-39). Melatonin protects against RIR injury through its antioxidative effects as evidenced by the increased levels of antioxidative enzymes such as glutathione peroxides (GPX, GSH), CAT, SOD and neutralizing hydroxyl radicals. Interestingly, it scavenges free radicals more effectively than vitamin E (40). It has been presented that melatonin as a key modulator of cell survival, greatly increases activation of AMP-activated protein kinase (AMPK) that stimulates antioxidative enzymes and contributes to antioxidant defense (41). In addition to this, melatonin therapy improved RIR injury by preventing cell apoptosis, oxidative stress and histopathological lesions in diabetic rats with RIR injury (42). Furthermore, melatonin reduced expressions of nuclear factor erythroid 2-related factor 2 (Nrf2), silent information regulator 2 associated protein 1 (SIRT1) and heme oxygenase-1 (HO-1) by activating SIRT1/Nrf2/HO-1 signaling pathway (42). Melatonin also reduced cell injury due to RIR via reducing endoplasmic reticulum stress and Akt pathway (43).

Resveratrol

Resveratrol (3,5,4′-trihydroxystilbene) is a plant-derived molecule with potent antioxidant properties. Treatment with this polyphenol ameliorated diabetic nephropathy and renal dysfunction by reducing creatinine, urea, albumin levels and albumin to creatinine ratio (44). Studies using animal models showed that resveratrol, through its antioxidant effect or SIRT1 activation, ameliorated IR induced AKI (45). A recent study suggested that resveratrol administration at a dose of 60 mg/kg for three weeks improved levels of GSH and MDA as well as renal tissue injury in rats with RIR (46). Although the nephroprotective mechanisms of resveratrol in RIR injury are not fully clarified, some studies indicate that the resveratrol in combination with leptin, modulate the JAK/STAT signaling pathway and ameliorates RIR injury (47). Additional studies suggest that the combination of resveratrol and N-methyl-d-aspartate receptor inhibitor (DAP5) may prevent RIR injury by suppressing inflammation processes and apoptosis via NF-κB and CaMK/DAPK/AKT/NMDA pathways (48). In this context, resveratrol has been demonstrated to be involved in the recovery of renal function after RIR injury through the Nrf2/TLR4/NF-κB pathway (49).

Vitamin C

Vitamin C or ascorbic acid is one of the water-soluble vitamins, that has the ability to protect cell membranes against lipid peroxidation by acting as a ROS scavenger (50). Vitamin C can neutralize $\bullet O^{-2}$ in the cytosol and extracellular matrix and scavenge peroxynitrite to inhibit the formation of nitrotryphophan, nitrotyrosine and

Table 1. The renoprotective effects of specific antioxidants against RIR injury

Antioxidant compounds	Model	Ischemia time	Reperfusion time	Outcomes	Reference
Oleanolic acid	Wistar rat	45 min	6 h	• Stabilization of Nrf2/GCLc signaling • Preservation of the GSH level	(15)
Astaxanthin	Mice	45 min	-	• Reduction of tubular injury, apoptosis, necrosis and inflammation via scavenging free radicals	(16)
Naringin	Sprague-Dawley rat	45 min	24 h	• Improvement of morphological alterations and renal dysfunction • Reduced TBARS levels and • Increased renal antioxidant enzymes	(87)
Ligustrazine	C57BL/6 mice	50 min	-	• Reduction of ROS generation • Inhibition of neutrophils infiltration and apoptosis • Reduction of TNF- α and ICAM-1 expression	(88)
Magnolol	Sprague-Dawley rat	60 min	24 h	• Prevention of apoptosis • Diminution of TNF-α	(89)
Protocatechuic acid	Sprague-Dawley rat	45 min	3 h	• Reduction of kidney and serum MDA, TNF-α level • Improvement of total antioxidant status in serum and kidney	(90)
Syringic acid	Wistar-Albino rat	30 min	1 h	• Prevention of apoptosis • Reduction of TOS, OSI and MDA • Amelioration of GPX activity	(91)
Ukrain	Sprague-Dawley rat	30 min	2 h	• Reduction of apoptosis and oxidative stress • Regulation of the TOS/TAS activity	(92)
Tyrosol	Sprague–Dawley rat	45 min	6 h	• Inhibition of iNOS-mediated oxidative stress	(93)
Salvianolic acid A	Sprague-Dawley rat	45 min	-	• Improvement of histopathology alteration and renal dysfunction • Reduction of oxidative stress and apoptosis through the Akt/mTOR/4EBP1 pathway	(94)
	Sprague-Dawley rat	60 min	-	• Prevention of peritubular capillary endothelium damages • Improvement of the renal hypoxia	(95)
Salvianolic acid B	Sprague-Dawley rat	50 min	48 h	• Reduction of the inflammatory process and oxidative stress via PI3K/Akt signaling pathway	(96)
Apigenin	Sprague-Dawley rat	45 min	-	• Prevention of apoptosis in vitro and in vivo through PI3K/Akt pathway • Improvement of histopathology alteration of kidney	(97)
Baicalin	Wistar rat	45 min	-	• Decreased oxidative stress • Inhibition of proinflammatory responses and apoptosis through mitochondrial stress and TLR2/4 pathway	(98)
Lycopene	Wistar-Albino rats	45 min	6 h	• Decreased MDA, blood urea nitrogen creatinine and NO levels, • Improvement of histopathology alteration of kidney	(99, 100)

nitrated lipids (51). This antioxidant compound reduces oxidative stress and improves cellular function by inhibiting inflammation due to IR injury (52). Furthermore, vitamin C supplementation promoted renal nitric oxide (NO), GSH and SOD, leading to the preservation of kidney function and renal arterial reactivity against RIR (53). It has been revealed that the administration of vitamin C reduced RIR-induced renal injury in rats by reversing elevated serum creatinine and blood urea nitrogen (54).

Berberine

Berberine is an isoquinoline alkaloid present in some medicinal plants, including barberry, golden thread, Oregon grape, tree turmeric and Amur cork tree (55). In vitro and in vivo studies have demonstrated that berberine possesses protective effects in IR injury (56, 57). According to a recent study, berberine administration at the doses of 100 and 150 mg ameliorated RIR in diabetic rats via its anti-apoptotic, anti-inflammatory and antioxidant

properties (58). Further, this compound improved histopathological lesions and kidney dysfunction through decreased creatinine and blood urea nitrogen levels and normalized intracellular ion levels via enhancing the Ca^{2+}-ATPase and Na^{+}/K^{+}-ATPase levels (58). In addition, in rats with RIR injury, berberine effectively improved renal function by exhibiting anti-apoptotic response through down-regulating Bax expression and upregulating Bcl-2 expression (59). Anti-apoptotic effect of berberine is also associated with the activation of the phosphatidylinositol 3-kinase/Akt signaling pathway and induction of Nrf2 that results in the protection of renal tubular cells (60).

Quercetin

Quercetin is a bioflavonoid compound with a high antioxidant property that has a protective effect against IR injury. This compound scavenges free radicals and inhibits lipid peroxidation (61). It has been noted that quercetin, in rats with RIR injury, mitigated oxidative stress by reducing MDA level and increasing GSH level as well as inhibiting endothelial nitric oxide synthase (eNOS) and NF-κB (62). Additionally, this flavonoid can stimulate AMPK activation by AMPK-regulated autophagy pathway and protect renal cells against IR injury *in vivo* and *in vitro* (63).

Rutin

Rutin is a flavonol found in plants such as apples, tea, passion flower and buckwheat (64). Several studies in experimental models have illustrated that the rutin has potent nephroprotective activity (65,66). It has been demonstrated that rutin suppresses the pathogenesis of RIR through its radical scavenging activity. This antioxidant can remarkably prevent MDA production, enhance GSH content and manganese superoxide dismutase (MnSOD) activity in the RIR rats (67). Pretreatment with rutin showed beneficial effects against RIR by improving the oxidative status and diminishing cGMP level in the kidneys. Moreover, rutin prevents kidney dysfunction during RIR, through its potent inducible NOS (iNOS) inhibiting activity (68).

Silymarin

Silymarin is a polyphenolic compound extracted from *Silybum marianum* plant. Several in vivo experimental models of diabetes and drug induced nephrotoxicity have investigated the effects of silymarin (69,70). Treatment with silymarin could reduce NO level, protein carbonyl and serum and tissue MDA in RIR rats indicating its antioxidant property against RIR (11). During RIR injury, silymarin pretreatment improved kidney function by reducing creatinine and blood urea nitrogen levels, inflammatory cytokines and necrosis of renal tubular cells (71). Further, treatment with silymarin increased Bcl-2 expression and decreased Bax expression during the recovery from RIR injury. In addition to this, a combination of silymarin and palmitoylethanolamide significantly decreased renal failure due to IR via suppressing NF-κB and apoptosis pathways (72).

Rosmarinic acid

Rosmarinic acid is a polyphenol compound present in plants of *Rosmarinus officinalis L*, *Origanum vulgare, Ocimum basilicum*, *Salvia officinalis* and *Melissa officinalis* (73). Different studies have revealed the pharmacological and biological activities of rosmarinic acid including anticancer, anti-inflammatory, antidiabetic, antibacterial, immunomodulatory and antioxidant (73,74). Rosmarinic acid has been illustrated to have a beneficial impact against nephrotoxicity (75). However, very few studies are available concerning rosmarinic acid's effect on IR injury. For instance, Ozturk et al, one of the few available, found that rosmarinic acid diminishes both the tubular and the glomerular injury in kidney of IR rats through reduction of oxidative stress and increase of antioxidant enzyme activities such as SOD and GPX (76).

Gallic acid

Gallic acid (GA) or 3,4,5 -trihydroxybenzoic acid is a phenolic acid compound with antioxidant characteristics and is found in natural products including green tea, grapes, pineapple and other plants (77). It has been demonstrated that GA pretreatment mitigates renal tubular damage in RIR rats by affecting antioxidant enzymes (78). It is also noted that GA offered renoprotective effect against RIR induced AKI through the activation of peroxisome proliferator-activated receptor gamma (PPAR-γ) (79).

Apocynin

Apocynin was first extracted from the roots of *Apocynum cannabinum* and was used as a medicine for cardiovascular diseases (80). Recently, it has been presented that apocynin has a nephroprotective potential in many models of IR (81, 82). Treatment with apocynin ameliorates renal function and antioxidant status in RIR rats via modulating the level of zinc and enhancing expression of metallothionein, which leads to a reduction of the level of IL-6, MDA, TNF-α and increment the SOD activity (83). Apocynin alone, or in combination with allopurinol, can reduce the IR induced renal dysfunction through inhibition of NADPH oxidase. In fact, inhibition of NADPH oxidase diminishes the formation of $^{\bullet}O^{-2}$, thereby reducing oxidative stress during IR (84). Furthermore, apocynin contributes to mitigating histological lesions of RIR through glomerular damage, tubular necrosis and apoptosis as well as levels of blood urea nitrogen, creatinine and myeloperoxidase (85). Moreover, apocynin stimulates expression of Srchomology-2 domain-containing phosphatase-1 and ameliorates nitroso-redox unbalance to protect the kidney against IR injury (86).

Discussion

Oxidative stress is identified as one of the important pathophysiological factors in IR injury. Free radicals produced during the oxidative stress process play a vital role in the stimulation of IR injury in different organs, including the kidney (101). Increased oxidative markers such as RNS and ROS may lead to deleterious impacts on the cellular structure through induction of necrosis or apoptosis (102). Moreover, inflammation pathways intensify oxidative stress, therefore the over-generation of pro-inflammatory cytokines induce tissue and cellular injury via inflammatory cell infiltration (103).

Recently, medicines such as diuretics and atorvastatin have been used to improve RIR, however, these medications don't have considerable suppressive effects against renal injury (104). It has presented that potent antioxidant ingredients with herbal origin can positively protect the kidney against IR injury (105). In fact, antioxidants such as alkaloids, vitamins, phenolics and flavonoids can significantly scavenge free radicals and ameliorate the function of antioxidant enzymes and lipid peroxidation in oxidative stress-related RIR (106).

Antioxidants diminish damage due to RIR through different mechanisms. For instance, Jiang et al reported that pretreatment with oxymatrine, an alkaloid compound, up-regulated the expression of HO-1 through the stimulation of the Nrf2 pathway and thereby protected kidney by improving RIR injury (107). The protective effect of N-acetylcysteine on RIR may also be related to the Nrf2 pathway (108). Li et al in a recent study investigated the renoprotective effect of tea polyphenols on IR-induced renal injury, as well as its renoprotective mechanism. Their results demonstrated that pretreatment with tea polyphenols before induction of ischemia, reduce inflammatory cell infiltration and renal tubular injury through suppressing the TLR4/NF-κB p65 signaling pathway in RIR rats (109). In addition, PI3K/Akt, JAK/STAT signaling (47,96) and other pathways related to the regulation of apoptosis and NF-κB pathways were considered in many studies (49,72). Even some herbs, such as Allium sativum (garlic), have been shown to decrease inflammatory markers in dialysis patients, and might be appropriate interventions in future studies in RIR (110).

Conclusion

Altogether, this review adds further evidence to ongoing discussion on the benefits of herbal antioxidants in the treatment of renal injury. The evidence from this study implies that different antioxidants diminish the oxidative damage caused by RIR through inhibiting the lipid peroxidation and increasing the activity of antioxidant enzymes. Therefore, targeting the oxidative stress pathway with antioxidants can be a pharmacological approach to ameliorate RIR injury. However, it is recommended to carry out future studies in this field.

Authors' contribution

MA, NM and AT searched the literature. MA, and AT prepared the manuscript. BVKSL and RT edited the paper. All authors critically revised and approved the final manuscript.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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