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Oxidative Stress and Ischemia-Reperfusion Injury in Gastrointestinal Tract and Antioxidant, Protective Agents

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Summary **Exacerbation of hypoxic injury after reoxygenation is a crucial mechanism mediating organ injury in transplantation, and in myocardial, hepatic, gastrointestinal, cerebral, renal, and other ischemic syndromes. The occlusion and reperfusion of the splanchnic artery is a useful animal model to elucidate the mechanism of gastrointestinal injury induced by ischemia-reperfusion (I/R). Although xanthine oxidase is a major source of reactive oxygen species (ROS), which plays an important role in the I/R-induced intestinal injury, there are many other sources of intracellular ROS. Various treatment modalities have been successfully applied to attenuate the I/R injury in animal models. This review focuses on the role of oxidant stress in the mechanism of I/R injury and the use of antioxidant agents for its treatment.**

Key Words**: oxidant stress, ischemia-reperfusion, antioxidant**

Introduction

Oxidant stress, such as that due to free radicals and/or reactive oxygen species is known to cause organ injury. A growing body of evidence indicates that oxidative stress plays an important role in the pathogenesis of many clinical conditions [*1–3*] involving cardiovascular diseases [*4*, *5*], liver diseases [*6*, *7*], lung disease [*8*, *9*], gastrointestinal disorders [*10–12*], neurological disorders [*13*, *14*], muscle damage [*15*], diabetes [*16*], and aging [*17*]. The involvement of free radicals in gastrointestinal injury observed after ischemia-reperfusion (I/R) has also been reported [*18–20*]. Superoxide and hydrogen peroxide are considered to be the major free radicals contributing to gastrointestinal injury after I/R. Acute gastrointestinal mucosal lesions can be by abolishing these reactive oxygen species [*21*].

The present review focuses on the oxidant stress during ischemia and reperfusion injury in the gastrointestinal tract and the use of antioxidant agents in its treatment.

Oxidant Stress during Ischemia-Reperfusion Injury in the Gastrointestinal Tract

An important assumption that oxygen free radicals play a crucial role in the pathogenesis of I/R has been supported by many lines of evidence that superoxide dismutase (SOD)—a highly specific scavenger of superoxide—prevents I/R induced gastrointestinal injury [*18*, *22*]. Additionally, reperfusion-induced oxidant stress in the gastrointestinal tract is supported by reduced glutathione (GSH) consumption and concomitant formation of oxidized glutathione (glutathione disulfide: GSSG) in the gastrointestinal mucosa that is subjected to I/R [*23*, *24*]. These changes are signifi-

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cantly reversed by both SOD and allopurinol. Conversely, there are reports that the disappearance of most of the GSH occurs during the ischemic period and GSH is not oxidized during the I/R episode [*25*].

By using electron spin resonance spectrometry and low-level chemiluminescence, Nilsson and co-workers demonstrated that there is a burst of oxidant formation immediately after 2–5 min of reperfusion of the ischemic intestine [*26*, *27*]. This oxidant formation after reperfusion was supposedly derived from the electron transport chains of the mitochondria [*28*, *29*], xanthine oxidase (XO) metabolism [*30*, *31*], endothelial cells [*32*, *33*], prostaglandins [*34*], and activated neutrophils [*35*, *36*].

Since superoxide is more efficient as a reducing agent than as an oxidizing agent, its formation is not considered to induce high levels of cytotoxicity. Spontaneous or SOD-catalyzed dismutation of superoxide ($O_2^{\cdot -}$) produces hydrogen peroxide (H_2O_2). Additionally, superoxide—a relatively low-energy radical—is responsible for the production of highly reactive and harmful hydroxyl radicals ($HO^{\cdot}$) by the Haber-Weiss reaction.

$$O_2^{\cdot -} + H_2O_2 \rightarrow OH^- + HO^{\cdot} + O_2$$

Typically, $HO^{\cdot}$ causes biological damage by stimulating the free chain reaction of the lipid side chains of the membrane phospholipids and DNA strand breakage and causing organelle and cell disruption [*37*].

Relative Contributions of Ischemia and Reperfusion to Mucosal Injury

The interruption of blood supply results in an ischemic injury. Paradoxically, restoration of the blood supply causes additional cell injury that is referred to as reperfusion injury. There are several lines of evidence in the oxygen radical hypothesis of gastrointestinal I/R injury that tend to support an important assumption that the tissue injury observed after reperfusion is due to the reintroduction of oxygen rather than a delayed manifestation of injury incurred during the ischemic period. Parks and Granger have demonstrated that the mucosal injury produced after 3 h ischemia followed by 1 h of reperfusion was significantly greater than that produced after 4 h of ischemia without reperfusion [*38*]. They also observed that 3 h of intestinal ischemia followed by 1 h of reperfusion with deoxygenated perfusate produced significantly less mucosal injury than that produced by reperfusion with oxygenated whole blood. Furthermore, the assumption that reoxygenation results in greater mucosal injury after reperfusion is supported by the consistent observation that antioxidants and inhibitors of oxy-radical formation (e.g., allopurinol) attenuate only that component of the mucosal injury that manifests after reperfusion [*39*]. Ates and co-workers demonstrated that the administration of antioxidants immediately before reperfusion is as effective in attenuating the mucosal injury as it would be if the antioxidant were to be administered before ischemia [*40*]. Oxy-radical production during the reperfusion period is largely responsible for the injury observed in intestinal models of I/R.

Xanthine Oxidase (XO)

The concept that XO-derived oxidants mediate the intestinal injury associated with I/R was first proposed in 1981 [*41*]. Subsequently, several studies have supported this concept and it is now considered that XO is a major source of oxidant generation during I/R injury in the gastrointestinal tract.

In comparison with the other organs, the intestine can generate high amounts of oxidants during I/R. The intestinal mucosa has tremendous capacity to oxidize hypoxanthine via the XO, which exists in normal healthy tissues predominantly as a NAD^+-reducing xanthine dehydrogenase (XD) [*42*]. Under ischemic conditions, XD rapidly converts to XO by ischemia-mediated protease, and XO is capable of reducing molecular oxygen to both $O_2^{\cdot -}$ and H_2O_2 (Fig. 1) [*39*]. However, there are also adverse reports that the activity of XO decreases during ischemia but increases subsequently following reperfusion [*43*].

Intestinal ischemia reduces cellular ATP levels rapidly and completely within 20 min while increasing the concentration of AMP and hypoxanthine [*23*, *44*, *45*]. Menguy *et al*. also reported that hemorrhagic shock resulted in a 75% reduction in ATP, a 27% reduction in ADP, and a 350% increase in AMP concentrations in the gastric mucosa within 15 min [*46*]. Therefore, 30-min of ischemia is sufficient to produce prolonged functional and structural changes in a rat intestine [*47*]. ATP depletion results in loss of ATP-dependent ion channel regulation, producing passive ion flux across the cell membrane. Increased intracellular Ca^{2+} is harmful, one of its important consequences being the activation of a calcium-dependent protease, which cleaves of XD to form

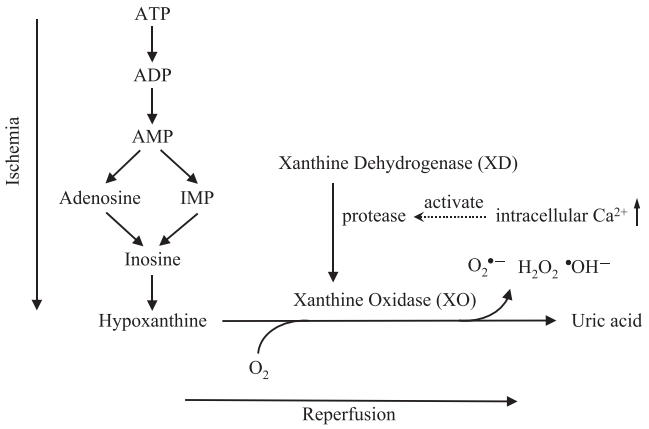

Fig. 1. Mechanism of xanthine oxidase-mediated free radical injury. Modified from Granger *et al* [*39*].

XO. Fructose-1,6-biphosphate (F16BP), which is a high-energy glycolytic intermediate [*48*], prevents the depletion of intracellular ATP during ischemia. Thus, it prevents the conversion of XD to XO [*49*] and inhibits free radical production, [*50*] thereby protecting the intestine during the I/R injury [*51*].

It can be estimated (assuming a tissue PaO_2 of 20 mmHg) that the XO activity measured in a cat intestine subjected to I/R injury produced superoxide and hydrogen peroxide fluxes of 1 and 40 $nmol \cdot min^{-1} \cdot g^{-1}$, respectively [*39*]. These rates of oxidant production are cytotoxic to cells in culture [*52*] and exceed the fluxes required to increase microvascular permeability. Parks *et al*. have demonstrated that intra-arterial infusion of XO (to achieve a plasma activity of ~2 mU/ml) in nonischemic intestines produced an increase in microvascular permeability that is comparable to that observed after I/R [*53*]. Furthermore, the cytotoxicity is largely prevented by SOD and dimethyl sulfoxide (DMSO), a hydroxyl radical scavenger, which supports the assumption that these oxidants mediate the increased microvascular permeability induced by arterial XO infusion.

Previous research supports the hypothesis that the intestine appears to be the most sensitive to I/R injury among the other internal organs [*39*, *54*]. The intestine is composed of labile enterocytes that are easily injured by episodes of ischemia, and subsequent reperfusion results in further damage to the intestinal mucosa. Enterocytes that are located at the microvilli tips are more sensitive to the effect of ischemia than those present in the crypts. This is because of the their location at the end of the distribution of a central arteriole and a relative lack of collateral blood flow, which can result in a lower PaO_2 in the distal enterocytes as when compared with that in the crypts [*55*]. Intestinal XO activity, which is one of the major sources of free radicals, is found primarily in the mucosal layer with an increasing gradient of activity from the villus base to the tip. This is an additional reason for the increased sensitivity of the villus tip to I/R injury as compared to that of the base [*54*]. Additionally, the differentiated enterocytes—located at the tip of the microvilli—are inherently more sensitive to ischemia-induced injury than their undifferentiated counterparts that are located at the base [*56*].

Nitric Oxide (NO)

The role of nitric oxide (NO) in I/R injury is still controversial. Inhibition of NO in certain models of I/R injury causes tissue dysfunction, whereas it proves beneficial in others.

NO is synthesized from L-arginine by a family of enzymes known as NO synthase (NOS). The constitutive forms of NOS (neural NOS: nNOS and endothelial NOS: eNOS) are critical to normal physiology, and the inhibition of these enzymes causes tissue injury [*57*]. However, the inducible form of NOS (iNOS), which is only expressed in the response to cytokines and growth factors, produces a large amount of NO that contributes to the pathophysiology of I/R injury. Therefore, while the use of selective inhibitors of iNOS, namely, N(6)-(iminoethyl)-L-lysine (L-NIL) and ONO-1714 has been shown to be beneficial [*58–60*], the use of non-selective inhibitors, namely, N(G)-nitro-L-arginine methyl ester (L-NAME) has been shown to be deleterious in gastrointestinal I/R injury [*61*]. Additionally, iNOS knockout mice are more resistant to intestinal I/R-induced bacterial translocation and mucosal injury, further supporting the role of iNOS as an important mediator of I/R injury in the intestine [*62*]. The nonselective NO inhibitors such as NG-monomethyl-L-arginine (L-NMMA) and L-NAME aggravate the gastric mucosal injury due to I/R, and this effect is blocked by L-arginine [*63*].

Using an NO-sensitive electrode, Wada and his co-workers measured the NO concentrations in the gastric mucosa and concluded that NO has an important pathological role in acute gastric mucosal injury induced by I/R [*64*]. They state that the NO concentration in the gastric mucosa increases during the ischemic period; subsequently, reperfusion causes a rapid decrease to normal levels. NOS inhibitors prevent both the increase in NO concentration during the ischemic episode and the mucosal injury induced by I/R.

NO has many beneficial effects in the I/R injury scavenging of oxygen free radicals, reduction of leukocyte adhesion to the mesenteric endothelium, and maintenance of normal vascular permeability [*65–67*]. During the early phase of reperfusion, after ischemia, an increase in $O_2^{\cdot -}$ limits the accumulation of NO and prevents any of the beneficial effects of NO; as a result, the leukocytes tend to adhere to the endothelium [*68*]. Supplementation of NO using NO donors such as FK-409, molsidomine, and nitroprusside have been shown to attenuate gastrointestinal I/R injury [*58*, *69–71*].

Endothelial Cells and Polymorphonuclear Neutrophils (PMNs)

Both endothelial cells and polymorphonuclear neutrophils (PMNs) are another potential source of oxidants in the gastrointestinal tract. NADPH oxidase is found in both these cells, and reoxygenation promotes oxidant generation by NADPH [*32*, *33*]. Moreover, activated PMNs secrete a variety of enzymes such as myeloperoxidase (MPO) and elastase that can injure parenchymal cells and the microvasculature [*72*].

Intravital microscopic studies of tissue exposed to I/R injury reveal an acute inflammatory response that is characterized by increased adhesion and emigration of PMNs in postcapillary venules, microvascular permeability, and

mucosal injury [*73*]. Reduced PMNs and monoclonal antibodies that interfere with the adhesion and emigration of the PMNs across venules provide significant protection against I/R injury [*74*, *75*]. Determination of tissue-associated MPO activity showed that the infiltration of PMNs in the mucosal layer during the reperfusion period is significantly more than that during ischemia [*35*]. The increased mucosal MPO activity after reperfusion can be significantly attenuated by the use of antioxidants. However, this attenuation of MPO activity is reflective of the blockage of the recruitment of PMNs into the mucosal layer rather than the inhibition of MPO catalytic activity [*39*]. These observations suggest that the adhesive interaction between PMNs and endothelial cells plays a crucial role in I/R injury and this process mainly depends on the oxidant stress.

Antioxidants: Protective Agents against Ischemia-Reperfusion Injury

Under normal conditions, the oxygen molecule undergoes a tetravalent reduction by the cytochrome system in the mitochondria to form water. However, one to two percent of the oxygen molecules that escape this pathway undergoes univalent reduction and generates oxygen-derived free radicals. Under normal conditions, these radicals are neutralized by endogenous antioxidant enzymes such as SOD and GSH, thereby having no deleterious effect on the cells [*76*]. However, oxidative stress occurs when the production of oxidants exceeds the capacity of the antioxidant defense systems of the cell, or when the effectiveness of the antioxidant defense system decreases. The human body has many natural antioxidants; however, not all of them are capable of protection against the attack of oxidants induced by the I/R condition.

Many animal studies have shown that antioxidant agents are useful in protection against I/R-induced gastrointestinal injury. XO inhibitors such as allopurinol, significantly reduce the severity of intestinal mucosal lesions and gastric lesions induced by I/R, [*18*, *19*, *22*, *77–80*]. Enteral administration of XO inhibitors such as pterin aldehyde or folic acid also attenuates the I/R-induced increase in microvascular permeability [*81*]. Although XO plays a crucial role in mucosal damage during reperfusion, it is also provoke the injury caused during the ischemic episodes [*22*].

Table lists antioxidant agents that have been reported to be helpful in reducing I/R-induced tissue damage in the intestine and stomach separately. The agents that have been used are acetaminophen [*82*], allopurinol [*18*, *19*, *22*, *23*, *77–80*, *83–87*], astragalus membranaceus [*88*], anti-thrombin III [*89*], bilirubin [*90*, *91*], captoprile [*92*], cimetidine [*93*], 5-(2-amino-ethylamino)-1-phenyl-2-pentanone (compound IA) [*94*], CV-6209—a platelet-activating factor antagonist [*95*], cystathionine [*96*], cyclosporine [*97*, *98*], desferrioxamine [*99–101*], dimethyl sulfoxide (DMSO) [*19*, *83*, *102–104*], edaravone [*105*], epidermal growth factor (EGF) [*106*, *107*, *108*], ellagic acid—one of the polyphenols [*109*], fullerenol [*110*], glutamine [*103*, *111–113*], honey [*102*, *114*], IT-066—a novel histamine H_2-receptor antagonist (H_2RA) [*115*], mannitol [*116*, *117*], melatonin and its precursor L-tryptophan [*40*, *118–127*], methylprednisolone [*116*], N-acetylecysteine (NAC) [*117*, *128–131*], nitroglycerine [*132*, *133*], pyrrolidine dithiocarbamate (PDTC) [*134*, *135*], pyruvate [*136*], rapamycin [*97*], rebamipide [*100*, *103*, *137*, *138*], rotenone [*139*], selenium [*140*, *141*], SOD [*18*, *19*, *22*, *77–79*, *85*, *142*], sofalcone [*143*, *144*], sucralfate [*79*, *145–148*], T-593—an H_2RA [*149*, *150*], 2,2,6,6-tetramethylpiperidine-1-oxyl (TPL) [*151*], trimetazidine [*152*, *153*], verapamil [*87*, *154*, *155*, *156*], vitamin C [*116*, *117*, *157–159*], vitamin E [*116*], and zinc N-(3-aminopropionyl)- L-histidine (Z-103) [*21*].

Intravenous administration of N-acetylcysteine (NAC), which is a free radical scavenger, has been proved to be beneficial in protection against I/R injury of intestine [*117*, *128*]; however, there are some controversial reports in this regard [*147*, *160*]. Some reports have demonstrated that NAC treatment resulted in significant aggravation of the gastric mucosal injury after I/R injury [*147*, *161*]. Although intraluminal perfusion of NAC increased the hexosamine concentration, gastric mucus was significantly decreased. This resulted in the exacerbation of the mucosal injury.

Some types of H_2RA, which inhibit acid secretion by parietal cells, are potent antioxidants and it has been suggested that these exert a protective effect on I/R-induced gastric mucosal injury. Although the luminal acid was completely neutralized by NaOH instead of T-593 (an H_2RA), no reduction in the mucosal clearance was observed. This indicated that the endogenous luminal acid does not play an important role in gastric injury induced by localized I/R stress [*149*]. Kitano demonstrated that compared to luminal perfusion with an HCl solution alone, the luminal perfusion with a solution containing HCl and H_2RA, cimetidine (3 mmol/l) significantly reduced the total area of erosions. Additionally, cimetidine (3 mmol/l) inhibited hydroxyl radical-induced lipid peroxidation of human erythrocyte membranes by 60% *in vitro*; this indicated that cimetidine possesses a protective effect against acute gastric mucosal injury induced by I/R not only due to the suppression of gastric acid secretion but also due to its antioxidant properties when it is present at high concentrations in the intragastric environment [*93*]. Furthermore, Naito *et al.* [*115*] showed that IT-066 (an H_2RA) scavenged the superoxide and hydroxyl radicals generated by the hypoxanthine-XO system and the hydrogen peroxide-ferrous iron system, respectively, by a spin trapping method using 5,5-dimethyl-1-pyrroline-N-oxide.

Mucoprotective agents such as sofalcon, sucralfate, and rebamipide have also been suggested to have antioxidant

Table. A list of antioxidant agents used agints ischemia-reperfusion injury in the intestine and stomach

Agent	Intestine			Stomach		
	Author	Outcome	Reference	Author	Outcome	Reference
Acetaminophen				Nakamoto	↓ mucosal lesion	82
Allopurinol	Parks	↓ histological damage, ↑ blood flow	38	Itoh	↓ mucosal lesion, ↓ XO	18
	Schoenberg	↓ mucosal damage	23	Perry	↓ mucosal permeability	19
	Haglund	↓ mucosal damage	77	Laudanno	↓ mucosal lesion	79
	Bilbao	↓ histological damage, ↓ mortality	78	Alarcon de la Lastra	↓ mucosal lesion, ↓ mucosal neutrophils	84
	Boros	↓ histological damage, ↑ blood flow	80	Zollei	↓ mucosal permeability, ↓ mucosal lesion, ↓ histological damage	85
	Horne	↓ mucosal damage	83			
	Hakguder	↑ motility	86			
	Kulah	↓ histological damage, ↓ MDA, ↑ GSH, ↓ LDH	87			
Astragalus membranaceus	Hei	↓ histological damage, ↑ NO, ↓ Endothelin-1, ↑ SOD, ↑ GSH	88			
Anti-thrombin III	Ozden	↓ histological damage, ↓ MPO, ↓ MDA	89			
Bilirubin	Ceran	↓ histological damage, ↓ MDA	90			
	Hammerman	↓ histological damage, ↓ thiobarbituric acid-reducing substances	91			
Captopril	Buyukgebiz	↓ histological damage, ↓ MDA	92			
Cimetidine				Kitano	↓ mucosal lesion	93
Compound IA	Poussios	↓ histological damage, ↓ MDA	94			
CV-6209				Yoshikawa	↓ mucosal lesion, ↓ TBARS	95
Cystathionine				Wada	↓ mucosal lesion, ↓ TBARS	96
Cyclosporine	Puglisi	↓ histological damage	97, 98			
Desferrioxamine	Balogh	↓ MDA, ↓ TBARS, ↓ 4-hydroxy-alkenals	101	Andrews	↓ histological damage	99
				Kurokawa	↓ mucosal permeability	100
DMSO	Horne	↓ mucosal damage	83	Perry	↓ mucosal permeability	19
	Kojima	↓ apoptosis	103	Ali	↓ mucosal lesion, ↓ vascular permeability, ↑ NP-SH	102
	Dabareiner	↓ microvascular permeability, ↓ edema	104			
Edaravone	Tomatsuri	↓ mucosal damage, ↓ histological damage, ↓ TBARS, ↓ MPO, ↓ CINC-1	105			
EGF	Berlanga	↓ intraluminal bleeding, ↓ MPO, ↓ MDA	106			
	Villa	↓ intestinal permeability, ↓ histological damage	107			
	Martin	↓ mucosal damage	108			
Ellagic acid				Iino	↓ mucosal lesion, ↓ lipid peroxidation	109
Fullerenol	Lai	↓ histological damage, ↓ MDA, ↑ GSH	110			
Glutamin	Harward	↑ GSH, conjugated diene (a by-product of lipid peroxidation)	112	Stein	↓ mucosal lesion	111
	Basoglu	↓ NO, ↑ GSH	113			
	Kojima	↓ apoptosis	103			
Honey	Koltuksuz	↓ mucosal damage, ↓ MDA	114	Ali	↓ mucosal lesion, ↓ vascular permeability, ↑ NP-SH	102
IT-066				Naito	↓ mucosal lesion, ↓ O2, ↓ OH, ↓ lipid peroxidation	115
Mannitol	Gunel	↓ histological damage, ↓ MDA, ↑ GSH	116			
	Byrka-Owczarek	↓ histological damage, ↑ blood flow	117			
Melatonin (L-tryptophan)	Kazez	↓ histological damage, ↓ MDA	121	Konturek	↓ histological damage, ↑ blood flow	118, 119
	Ustundag	↑ GSH-Px, ↑ SOD, ↑ selenium	122	Brzozowski	↓ mucosal lesion	120
	Sileri	↓ bacterial translocation	126	Cabeza	↓ histological damage, ↓ XO, ↑ SOD, ↑ GSH, ↑ PGE2	123, 124
	Ates	↑ catalase, ↑ SOD, ↑ GSH-Px, ↓ MDA	40	Bulbuller	↓ mucosal lesion, ↓ histological damage	125
	Ozacmak	↓ MDA, ↑ contraction, ↓ histological damage, ↑ GSH	127			
Methylprednisolone	Gunel	↑ GSH	116			
NAC	Cuzzocrea	↓ nitrosine, ↓ PARS, ↓ MPO, ↓ MDA, ↓ P-selectin, ↓ ICAM-1	128			

Table. A list of antioxidant agents used agints ischemia-reperfusion injury in the intestine and stomach (continued)

Agent	Intestine			Stomach		
	Author	Outcome	Reference	Author	Outcome	Reference
	Sun	↓ endothelial and epithelial permeability, ↓ MPO, ↓ IL-1beta	129			
	Montero	↓ histological damage	130			
	Olanders	↓ endothelial permeability,	131			
	Byrka-Owczarek	↑ blood flow	117			
Nitroglycerine	Dun	↓ histological damage, ↓ MDA, ↓ LDH	132			
	Khanna	↓ intestinal permeability, ↓ histological damage,	133			
PDTC	Mallick	↑ blood flow, ↑ HO, ↓ LDH, ↓ histological damage	134	El Eter	↓ vascular permeability, ↓ LDH, ↓ TNF-alpha, ↓ TBARS, ↓ NF-kappaB, ↑ GSH	135
Pyruvate	Cicalese	↓ histological damage, ↓ free radical	136			
Rapamycin	Puglisi	↓ histological damage	97			
Rebamipide	Kojima	↓ apoptosis	103	Kim	↓ MPO, ↓ MDA, ↑ SOD, ↑ NOS	137
				Kurokawa	↓ mucosal permeability	100
				Hiratsuka	↓ histological damage, ↓ COX2	138
Rotenone	Ichikawa	↓ mucosal damage, ↓ TBARS, ↓ CINC-1, ↓ TNF-alpha	139			
Selenium	Yoshida	↓ histological damage, ↑ blood pressure	140			
	Ozturk	↓ histological damage, ↓ bacterial translacation, ↓ MDA	141			
SOD	Parks	↓ histological damage, ↑ blood flow	22	Itoh	↓ mucosal lesion	18
	Haglund	↓ mucosal damage	77	Perry	↓ mucosal permeability	19
	Bilbao	↓ histological damage	78	Laudanno	↓ mucosal lesion	79
	Riaz	↓ MDA, ↓ neutrophil rolling & adhesion	142	Zollei	↓ mucosal permeability, ↓ mucosal lesion, ↓ histological damage	85
Sofalcone				Yoshikawa	↓ mucosal lesion, ↓ lipid peroxidation	143
				Momo	↓ mucosal lesion, ↓ MDA	144
Sucralfate	Sencan	↓ histological damage, ↓ enterocyte apoptosis	148	Laudanno	↓ mucosal lesion	79
				al-Swayeh	↓ mucosal lesion, ↓ vascular permeability, ↓ superoxide, ↑ NP-SH	145
				Wada	↓ mucosal lesion, ↓ TBARS	146
				Mojzis	↓ mucosal lesion, ↑ mucus	147
T-593 (H2RA)				Seno	↓ mucosal permeability	149
				Naito	↓ mucosal lesion	150
TPL	Udassin	↓ intestinal permeabitily	151			
Trimetazidine	Tsimoyiannis	↓ peritoneal adhesion	152			
	Tetik	↓ histological damage, ↓ MDA, ↓ MPO	153			
Verapamil	Mocan	↓ histological damage	155	Sato	↓ mucosal lesion, ↓ lipid peroxidation	154
	Kulah	↓ histological damage, ↓ MDA, ↓ GSH	87	al-Dohayan	↓ mucosal lesion	156
Vitamin C	Nakamura	↓ histological damage, ↓ lipid peroxides, ↓ GSSH/GSH	159	Ekman	↓ mucosal bleeding, ↑ vascular patency	157, 158
	Gunel	↓ histological damage, ↓ MDA, ↓ GSH	116			
	Byrka-Owczarek	↓ histological damage, ↑ blood flow	117			
Vitamin E	Gunel	↑ GSH	116			
Z-103				Yoshikawa	↓ mucosal lesion	21

Compound IA: 5-(2-amino-ethylamino)-1-phenyl-2-pentanone
DMSO: dimethyl sulfoxide
EGF: epidermal growth factor
NAC: N-acetylecysteine
PDTC: pyrrolidinedithiocarbamate
SOD: superoxide dismutase
TPL: 2,2,6,6-tetramethylpiperidine-1-oxyl
Z-103: zinc N-(3-aminopropionyl)-L-histidine

properties; thus, they may prevent I/R-induced mucosal injury. High concentrations of sucralfate (3–10 mg/ml) reduced the superoxide radicals generated by leukocytes or xanthine-XO, and protected erythrocyte membrane ghosts against lipid peroxidation induced by hydrogen peroxide and Fe^{2+} *in vitro* [*146*]. The administration of sucralfate, either before ischemia or before reperfusion, prevented the gastrointestinal mucosal injury due to I/R stress [*79*, *145–148*]. Rebamipide also reduced gastrointestinal damage by the pretreatment of ischemic changes [*100*, *103*, *137*, *138*]. Only intraluminal administration of sofalcon before the onset of ischemia has been proven to be effective in providing gastric mucosal protection against I/R injury [*143*, *144*].

Conclusion

Oxygen-derived free radicals play a major role in the pathophysiological mechanism of ischemia-reperfusion injury of the intestine. The sources of reactive oxygen species are abundant, and the attenuation of oxidant stress minimizes the extent of the ischemia-reperfusion injury. Therefore, antioxidant agents play an important role in the treatment of intestinal injury induced by ischemia-reperfusion.

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