Review Article

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The Effect of Vitamin C on Ischemia-Reperfusion Injury: A Systematic Review

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Abstract

Ischemia is one of the most common injuries that is usually caused by reduced blood flow to the tissues. Following this incident, the tissue becomes deficient in oxygen and nutrients, and energy production in the affected cells stops, eventually leading to cell damage, but there is also evidence that restoring blood flow to ischemic tissues can lead to extra tissue damage known as Ischemia Reperfusion Injury (IRI). In this study, we reviewed the relationship between vitamin C intake and ischemia/reperfusion injury to investigate the relationship between vitamin C intake and ischemia/reperfusion injury. The keywords "Vitamin C" or "Ascorbic Acid" and "Ischemic" or "Ischemia" and "Reperfusion" were used in this search. The results show that vitamin C has a positive effect on ischemia treatment in the renal tissue, brain, liver, intestine, lung, ovary, pancreas, and skin.

Keywords: Ascorbic acid, Ischemia, Reperfusion injury

Introduction

Ischemia is one of the most common injuries usually caused by reduced blood flow to the tissues. Following this incident, the tissue becomes deficient in oxygen and nutrients, and energy production in the affected cells stops, eventually leading to cell damage; however, there is also evidence that restoring blood flow to ischemic tissues can lead to extra tissue damage known as Ischemia Reperfusion Injury (IRI) (1). Ischemia reperfusion injury is a complex process involving various pathophysiological mechanisms; many neurochemicals such as neurotransmitters and ROS have been shown to be associated with ischemic processes (2). During ischemia-reperfusion, the balance between the production of free radicals and androgen antioxidants is upset by increasing the production of free radicals and decreasing the antioxidant capacity, which leads to severe oxidative stress. Eventually, organ function is lost and total antioxidant capacity decreases after ischemia-reperfusion (3,4). Efforts to reduce the incidence and severity of ischemia-reperfusion are based on three general principles: return of capillary blood flow, inhibition of the effects of oxygen radicals, inhibition of cell adhesion and inflammatory mediators, and ultimately regeneration of reperfusion tissue (5,6). After reperfusion, large amounts of reactive oxygen species are produced from various sources, such as mitochondrial electron transport chain reactions, reorganization of the enzymes NADPH oxidase, xanthine oxidase, lipoxygenase, cyclooxygenase, Induced Nitric Oxide Synthesis (INOS) and oxidation of catecholamines. Especially, in the case of lack of exposure to antioxidants such as vitamin C, it can damage proteins, membrane lipids, and DNA, causing necrotic cell death, apoptosis, and impaired cell and organ function (7). Antioxidants are substances that scavenge free radicals, prevent damage to cell membranes and DNA, and reduce cell death. The use of antioxidants is recommended to prevent free radical damage to cells, especially to reduce the damaging effects of ischemia (8). Since antioxidants can eliminate toxic oxygen metabolites, they can play an important role in counteracting ischemia-reperfusion damage (9). Ascorbic Acid (AA-vitamin C) is one of the types of antioxidants.

Vitamin C is a powerful antioxidant that is biosynthesized from glucose and galactose or their derivatives (10). The indole structure of vitamin C, by losing two electrons, turns it into an important antioxidant and free radical scavenger molecule (9). This vitamin is a water-soluble compound that is involved in preventing lipid peroxidation in cell membranes and refining hydroxyl radicals (11). Internal absorption *via* Saturated Vitamin C Transporter (SVCT1) and intestinal absorption during illness may be even more limited (12). It has also been suggested that injections of vitamin C through arteries or veins reduce oxidative stress (13,14). Due to the importance of this issue, the aim of this study was to investigate the effect of vitamin C on ischemia-reperfusion injury.

Previous study search strategy

To investigate the relationship between vitamin C intake and ischemia/reperfusion injury, we searched all the studies published up to January 2023 using the Web of Science, Science Direct, Scopus, PubMed, and Embase databases. The keywords “Vitamin C” or “Ascorbic Acid (AA)” and “Ischemic” or “Ischemia” and “Reperfusion” were used in this search. The search strategy in some of the searched databases is shown as an example in tables 1 and 2. No time limits were applied during the search.

266 articles were found in the initial search. In the next step, 30 articles were excluded due to lack of access to them and 7 articles due to lack of inclusion criteria and in the next step, a complete study of the remaining articles was performed. For this purpose, the articles were received and the quality of each of them was evaluated independently by two team members in terms of possible biases of quantitative studies, and in the end, 52 articles were used. The search results and selection process of the articles of this study are shown in figure 1.

Extraction of data

First, the articles were entered into Endnote X9 software, and after removing the duplicate titles and abstracts of the articles, based on a checklist agreed upon by the authors, the two authors reviewed the inclusion criteria. The data were charted in Microsoft Excel. Any disagreement was reviewed by another author, and a final agreement reached. Data included

Table 1. Search strategy

Search strategy	Number of papers	Data base	Number
'Vitamin c': ti AND ischemia: ti AND reperfusion: ti 'Ascorbic acid': ti AND ischemic: ti AND reperfusion: ti' 'Ascorbic acid': ti AND ischemia: ti AND reperfusion: ti' Vitamin c': ti AND ischemic: ti AND reperfusion: ti	64	Embase	1
TITLE (Vitamin AND c AND ischemic AND reperfusion) TITLE (Vitamin AND c AND ischemia AND reperfusion) TITLE (Ascorbic AND acid AND ischemic AND reperfusion) TITLE (Ascorbic AND acid AND ischemia AND reperfusion)	64	Scopus	2
TITLE: (Vitamin c AND ischemia AND reperfusion) TITLE: (Vitamin c AND ischemic AND reperfusion) TITLE: (Ascorbic acid AND ischemic AND reperfusion) TITLE: (Ascorbic acid AND ischemia AND reperfusion)	66	WoS	3
Title: Vitamin c AND ischemic AND reperfusion Title: Vitamin c AND ischemia AND reperfusion Title: Ascorbic acid AND ischemic AND reperfusion Title: Ascorbic acid AND ischemia AND reperfusion	18	Science direct	4
Vitamin c [Title AND ischemic [Title] AND reperfusion [Title] Vitamin c[Title] AND ischemia [Title] AND reperfusion [Title] Ascorbic acid [Title] AND ischemic [Title] AND reperfusion [Title] Ascorbic acid [Title] AND ischemia [Title] AND reperfusion [Title]	54	PubMed	5

Table 2. Effect of vitamin C on ischemia-reperfusion injury

Country	Study design	Characteristics of animal	Number of case	Weight of case (*g*)	I/R region	Intervention	Conclusion
Egypt	Experimental control trial	Albino rats	32	180–230	Ovary	Animals were divided into four main groups, each containing eight rats. Group I = control group. Group II= ischemia group. Group III= 4 *hr* ischemia was followed by reperfusion (I/R). Group IV = 4 *hr* ischemia was followed by vitamin C injection and then reperfusion (I/R+vitamin C)	Vitamin C treatment can help to protect the ovaries from ischemia–reperfusion injury after detorsion
Turkey	Experimental control trial	New Zealand rabbits	28	2,400–2,800	Suprarenal aortic	Group 1 (n=7) is the sham group. Group 2 (n=7) is the ischemia-reperfusion (IR) control group. Group 3 (n=7) is the iloprost group. Group 4 (n=7) is the iloprost + ascorbic acid group	Administered with iloprost and iloprost + vitamin C showed an attenuation of ischemia–reperfusion injury in distant organs
Japan	Experimental control trial	Male Wistar rat	20	230-260	Liver graft	The animals were divided into 2 groups, a control group (n=10), and an AA-2G[1] group (n=10)	The addition of AA-2G to the UW[2] solution attenuated 24 *hr* cold ischemia/reperfusion injury by inhibiting the apoptosis of hepatocytes

1. Ascorbic acid 2-glucoside
2. University of wisconsin solution

Contd. table 2.

Japan	Experimental control trial	Male Sprague-Dawley rats	50	250–300	Heart	The hearts were randomly treated with 1 *mM* AA[1] or 0.1 *mM* NAC[2] (both obtained from Sigma) for 30 *min*	AA and NAC may be promising pharmacological tools in protecting the diabetic heart from I/R[3] injury
Brazil	Experimental control trial	Male Wistar rats		240 to 300	Hepatic	The animals were submitted to dissection of dorsal penile vein for injection of a 0.9% (1 *ml/kg*, IV) saline solution in group (SS) animals or an ascorbic acid solution diluted in 1 *ml* of saline (100 *mg/kg*, IV) in group AA animals	These results suggest that ascorbic acid reduces the morphological alterations of hepatic lysosomes induced by ischemia-reperfusion
Iran	Experimental control trial	Adult male Sprague–Dawley rats	30	250-300	Testicular	Group 1 (control) = which did not undergo any surgical procedure. Group 2 (TT-TD) = TT then testicular detorsion; TD) had 4 *hr* TT and then TD. Group 3 (TT-DO, TT and dopamine injection; DO) was the first treatment group in which animals had 4 *hr* TT and were then treated intramuscularly with 0.01 *mg kg*) dopamine (Tamin Pharmaceutical Co., Iran) just before TD. Group 4 (TT-VC, TT and vitamin C injection) was the second treatment group in which animals had 4 *hr* TT and were then treated intraperitoneally with 100 *mgkg*) 1 vitamin C (Darou Pakhsh Co., Tehran, Iran) just before TD. Group 5 (TT-DV, TT and dopamine and vitamin C injection) was the third treatment group in which animals had 4 *hr* TT and were then treated with dopamine (0.01 *mgkg*) 1, i.m) and vitamin C (100 *mgkg*) 1, i.p) just before TD. Group 6 (sham) was the sham operated group, which had all surgical procedures without TT and TD and treatment	Vitamin C was more effective than increasing blood flow by a vasodilator like dopamine on improving I-R injury following TT
Brazil	Experimental control trial	Male Wistar rats	12	Approximately 485	Brain	Sham (n=4), animals exposed to carotid arteries dissection without clamping; (ii) Control (n=4), animals that received an intraperitoneal injection of 0.9% saline solution (0.1 *ml/kg*) and underwent carotid arteries dissection with temporary clamping; (iii) Vitamin C (n=4), animals that received an intraperitoneal injection of vitamin C (750 *mg/kg*) and underwent carotid arteries dissection with temporary clamping	Vitamin C was associated with behavioral and motor preservation as well as decreased cerebral MDA levels after induced cerebral ischemia in rats

1. Ascorbic acid
2. N-acetyl cysteine
3. Ischemia-reperfusion

Contd. table 2.

Iran	Experimental control trial	Male adult Wistar albino rats	30	200-300	Intestine	Animals were divided into six equal groups. Group Sham: intact group, control group: IR group with 45 *min* of ischemia followed by 1 *hr* of reperfusion, group vitamin C: IR plus vitamin C (50 *mg/kg*, IV) treatment immediately after reperfusion, group vitamin E: IR plus vitamin E (20 *mg/kg*, IM) treatment 15 *min* before reperfusion, group hydrocortisone: IR plus hydrocortisone (50 *mg/kg*, IV) treatment immediately after reperfusion and group combination: IR plus combination of vitamin C, E, and hydrocortisone	Simultaneous administration of vitamin C, E, and hydrocortisone combination before reperfusion of blood flow to the ischemic tissue could improve the deleterious effects of IR injuries in intestinal mucosa
China	Experimental control trial	Male New Zealand white rabbits	40	-	Renal	-	Ischemic preconditioning may protect renal tissue against ischemia-reperfusion injury *via* use of extracellular ascorbic acid. *In vivo* microdialysis coupled with online electrochemical detection is effective for continuous monitoring extracellular ascorbic acid in the renal cortex
Korea	Experimental control trial	Dog (male Beagles)	6	12.4 *kg* (range: 11~13 *kg*)	Renal	The animals were divided into two groups, each of the groups contained 3 dogs randomly. Group 1 was the control group in which normal saline solution was given intravenously, and group 2 was the treated group in which ascorbic acid (100 *mg/kg*) was given intravenously	Administration of ascorbic acid for renal ischemic-reperfusion injury had influence on blood BUN level, but it was not revealed the influence on blood Cr and RI
Brazil	Experimental control trial	Male Wistar rats	58	-	Skin flap	Animals were divided into 4 groups of 12 animals. Group C (control): they received intravenously lactated Ringer's solution. Group T (treated): they received intravenously antioxidant solution made of lactated Ringer's solution (7.5 *ml/kg* body weight), mannitol (0.24 *ml/kg* body weight) and vitamin C (10 *ml/kg* body weight) with infusion speed of 0.5 *ml/min.* Group S1: received intravenously lactated Ringer's solution (7.5 *ml/kg* body weight) soon after simulation of ischemia period ended with infusion speed of 0.5 *ml/min.* Group S2: in the same way, the same solution as group T soon after simulation of ischemia period ended	In this experimental model, and in the doses used, the antioxidant solution made of mannitol and vitamin C diluted in lactated Ringer's solution did not prevent nor reduced the necrosis area in relation to control group treated only with lactated Ringer's solution

Contd. table 2.

Greece	Experimental control trial	Male Wistar Albino rats	18	250-300	Sciatic nerve	Rats were divided into three groups (N=6 per group). Group A Ischemic group. Group B Vitamin group. According to the literature, in order to produce stable levels of Vitamin E, its administration should start a few days prior to I/R [12]. Vitamin C (ascorbic acid) and Vitamin E (a-tocopherol) were administrated intraperitoneally 2 days before the ischemia and every day until the animals were euthanized, once a day, as o bolus injection. Ascorbic acid was dissolved in distilled water at a dose of 20 *mg/kg* and a-tocopherol was dissolved in 20% (v/v) ethanol in 0.15 *M* NaCl at a concentration of 25 *mg/ml*, at a dose of 50 *mg/kg*. Group C T-PA group	Both abnormalities reversed by vitamins and t-PA implying that these agents could effectively protect nerves from ischemic injury
Taiwan	Experimental control trial	Sprague-Dawley rats	40	250-300	Liver	The studies included four groups: group I, sham-operated controls (n=10); group II, operated with the Pringle maneuver without any treatment (n=10); and groups III and IV, orally treated with α -tocopherol (200 *mg/kg*/d; n=10) and L-ascorbic acid (60 *mg/kg*/d; n=10), respectively and 3 days prior to the study	L-ascorbic acid and α -tocopherol pretreatment 3 days prior to the Pringle maneuver attenuated myocardial injury and protected cardiac function by scavenging hydroxyl radical and reducing lipid peroxidation. L-ascorbic acid demonstrated better protection than α -tocopherol
Iran	Experimental control trial	Male NMRI mice	63	35–45	CA1 hippocampus	Pretreatment #1: were treated with ascorbic acid (100 *mg/kg*) 2 weeks before until 1 week after ischemia Post treatment #1: were treated with CPA, agonist of A1 receptor (1 *mg/kg*), 1 week after ischemia for 7 days Post treatment #2: were treated with DPCPX, A1 receptor antagonist (2.25 *mg/kg*) 1 week after ischemia for 7 days. Pre & post treatment #1: were treated with ascorbic acid 2 weeks before until 1 week after ischemia and agonist of A1 receptor for 7 days after ischemia. Pre & post treatment #2: were treated with ascorbic acid 2 weeks before until 1 week after ischemia and antagonist of A1 receptor for 7 days after ischemia	Vitamin C and CPA attenuated ischemic neuronal apoptosis mediated by upregulation Bcl-2 and down-regulation of Bax. Co-administration of vitamin c with the A1 adenosine receptor agonist (CPA) potentate effect exerted by the single administration of vitamin C
China	Experimental control trial	Adult male Sprague-Dawley rats	-	250-280	Cerebral	All rats were randomly divided into 6 groups: ischemia/reperfusion (I/R) for OECS recording, I/R + postconditioning for OECS, I/R for electrophysiological recording, I/R + postconditioning for electrophysiological recording, I/R for immunohistochemistry, and I/R + postconditioning for immunohistochemistry. Animals were maintained on a 12 *hr*-light/12 *hr*-dark schedule with food and water ad libitum	postconditioning treatment recovers the level of cortex ascorbic acid in the acute phase after cerebral ischemia. The fluctuation of cortex ascorbic acid occurs synchronously with cerebral blood flow recovery and accompanies the neural activity recovery as well as the decreased intracellular oxidative damage

Contd. table 2.

Japan	Experimental control trial	Sprague-Dawley Rats	-	120-140	Brain	The diabetic and nondiabetic groups were divided into 2 groups and were housed for an additional 6 weeks until stroke was induced by MCAO/Re. AA (L-Ascorbic acid, Wako Pure Chemicals Z Industries, Osaka, Japan) (100 *mg/kg*; nondiabetic and diabetic AA-supplemented groups) or distilled. Water (nondiabetic and diabetic control groups) was orally administered through nasogastric tube once daily for the last 2 weeks	Daily intake of AA attenuates the exacerbation of cerebral ischemic injury in a diabetic state, which may be attributed to anti-apoptotic and anti-inflammatory effects *via* the improvement of augmented oxidative stress in the brain. AA supplementation may protect endothelial function against the exacerbated ischemic oxidative injury in the diabetic state and improve AA transport through SVCT2 in the cortex
Korea	Experimental control trial	Male Sprague Dawley rats	-	270-300	Liver (Hepatic lobes)	L-Ascorbic acid (AA) sodium salt was dissolved in saline and administered to the rats *via* an intravenous injection of 100 *mg/kg* of body weight 5 *min* prior to the sustained ischemia. The animals were randomly assigned into the following groups: (a) vehicle-treated sham (sham), (b) AA-treated sham (AA), (c) vehicle-treated ischemic (I/R), (d) AA-treated ischemic (AA+I/R), (e) IPC/vehicle-treated ischemic (IPC + I/R), (f) IPC/AA-treated ischemic (IPC+ AA+I/R). Each experimental group was examined at 10 *min* and 5 *hr* posttreatment	AA might act synergistically with IPC to increase the tolerance of the liver to reperfusion injury. Therefore, IPC _ AA might be a promising strategy for preventing ischemic injury to the liver
Turkey	Experimental control trial	Sprague Dawley rats	40	253-360	Hind Limbs	Rats were split into 4 groups: group I as the control, group II as I/R, group III as I/R+erdosteine, and group IV as I/R+ vitamins C and E. In group III, animals were given oral erdosteine at 150 *mg/kg* daily, whereas in group IV, vitamins C and E were administered at 50 *mg/kg* IM and 20 *mg/kg* intraperitoneally starting in both groups 3 days prior to the procedure. Finally, the control and I/R group animals were given equal amounts of saline at the same time, for the same period, and in the exact same way	vitamins C and E and erdosteine improved the antioxidant levels in rat kidneys because of their inherent antioxidant features. Hence, we think that vitamins C and E and erdosteine may have potential as anti-ischemic agents for I/R-induced kidneys
Iran	Experimental control trial	Wistar strain male rats	30	280-300	Kidney	Thirty male rats were divided into six groups. Group Sham, Group I/R: (45 *min* of ischemia followed by 1 *hr* of reperfusion), Group I/R+Vit C: (50 *mg/kg* Vit C, IV, immediately after reperfusion), Group I/R+Vit E: (20 *mg/kg* Vit E, IM, 15 *min* before reperfusion), Group I/R+Hydrocortisone: (50 *mg/kg*, IV, immediately after reperfusion), and Group Combination: Ischemia-reperfusion plus combination of Vit C, E and hydrocortisone	vitamins C and E and erdosteine improved the antioxidant levels in rat kidneys because of their inherent antioxidant features. Hence, we think that vitamins C and E and erdosteine may have potential as anti-ischemic agents for I/R-induced kidneys

Contd. table 2.

India	Experimental control trial	Wistar rats	-	200-250	Kidney	Eleven groups were used in the present study, each comprising six rats. Group 1 (control): No surgery was performed on rats. Group 2 (sham operated): the rats were administered vehicle (olive oil, 2 *ml/kg*, i.p.), and surgery was performed on rats to expose both kidneys, but ischemia was not given. Group 3 (IRI): Both kidneys were occluded for 40 *min* in rats followed by reperfusion for 24 *hr*. Group 4 (progesterone low dose, PGL): progesterone (5 *mg/kg*) was dissolved in olive oil (1 *ml/kg*) and administered i.p. 1 *hr* before subjecting rats to IRI. Group 5 (Progesterone high dose, PGH): progesterone (10 *mg/kg*, i.p.) was administered 1 *hr* before subjecting rats to IRI. Group 6 (PGH þ mifepristone): mifepristone (5 *mg/kg*) was dissolved in olive oil (1 *ml/kg*) and administered 2 *hr* before IRI followed by treatment mentioned in group 5. Group 7 (AA perse): AA was dissolved in sterile distilled water and administered at dose of 500 *mg/kg*, i.p. once daily for 5 d. Group 8 (AA, 1 d): AA (500 *mg/kg*, i.p.) was administered 1 *hr* before subjecting rats to IRI. Group 9 (AA, 2 d): AA (500 *mg/kg*, i.p.) was administered once daily for 2 d, and surgery was performed on the second day after 1 *hr* of AA administration. Group 10 (AA, 5d): AA (500 *mg/kg*, i.p.) was administered once daily for 5 d, and surgery was performed on fifth day after 1 *hr* of AA administration. Group 11 (AA þ mifepristone): the rats were subjected to AA treatment as mentioned in group 10 along with mifepristone (5 *mg/kg*, i.p.) given 1 *hr* before AA administration	Exogenous administration of progesterone exerts significant antioxidant and renoprotective effect. Moreover, the progesterone receptors find their explicit involvement in AA-mediated renoprotection against ischemia-reperfusion reinduced AKI in rats
Chile	Experimental control trial	Sprague-Dawley neonatal rats	-	-	Heart	-	In conclusion, this is the first study where a pharmacological combination of Ascorbic acid, deferoxamine, and N-acetylcysteine (A/D/N), at low concentrations, protected cardiac fibroblast viability and function after simulated ischemia/reperfusion, and thereby represents a novel therapeutic approach for cardioprotection
Turkey	Experimental control trial	Sprague-Dawley rats	64	300-400	Left Leg	Animals were allocated to 4 randomized groups except for the control group. The animals received 50 *mg/kg* L-ascorbic acid sodium (Redoxon amp 500 *mg*/5 *ml*, Roche Diagnostics, Basel, Switzerland) intravenously *via* penile vein	Vitamin C can be used for the prevention of IRI for surgery with tourniquets. However, further experimental studies using different parameters with higher numbers of subjects should be carried out to determine the ideal dose and timing of vitamin C application

Contd. table 2.

Turkey	Experimental control trial	Wistar rats	34	180-200	Kidney	Animals were used and divided into five groups. In group I (normal group, n-6), the left kidney was excised immediately after laparotomy. In group II (sham group, n-6), after the exploration of the abdominal aorta neither ischemia nor treatment was given. Group III (n-6, control, I/R group) underwent 3 *hr* of ischemia and 1 *hr* of reperfusion without receiving any medication. Group IV (n-8) was given 20 *ng/kg/min* iloprost (Ilomedin, Schering AG) and group V (n-8) was given 100 *mg/kg* vitamin C (Redoxan, Roche) by constant intravenous infusion through the left jugular vein immediately before aortic cross clamping	Administered iloprost infusion during surgical interference of infrarenal abdominal aorta may prevent remote renal tissue injury resulting from lower extremity I/R damage, but vitamin C may be even more effective than iloprost
Turkey	Experimental control trial	Sprague-Dawley rats	32	200-250	Kidney	Animals were divided equally into four groups. In the control group (group 1), we dissected the right renal pedicle without performing a nephrectomy. Right nephrectomy was performed on all rats except group 1. The sham group (group 2) underwent right nephrectomy, but the left renal pedicle was not occluded.The animals in the I/R and AA+IR groups (groups 3 and 4, respectively) underwent right nephrectomy. All of the rats were allowed to recover for two weeks before groups 3 and 4 were subjected to I/R injury. Two weeks post-surgery, animals in the I/R group (group 3) were treated with 0.5 *ml* saline 1 *hr* prior to ischemia, and then the left renal pedicle was occluded for 45 *min* to induce ischemia followed by 3 *hr* of reperfusion. The AA-treated ischemic group (group 4) animals were treated with AA (250 *mg kg*-1 i.p.) in 0.5 *ml* saline 1 *hr* prior to ischemia. The rest of the protocol was the same as in group 3	AA was used to prevent short period of I/R injury in the kidney of male rats. It is important to inhibit oxidative stress to prevent renal I/R injury, and they suggest that acute administration of AA might be helpful in clinical practice, particularly transplantation and renal surgery
Korea	Experimental control trial	Rats	28	250-350	Hind-paw	The 4 treatment groups were control (no medication), group 1.0 (administration of 1 *mg/day* for vitamin C for 5 days), group 2.5 (administration of 2.5 *mg/day* vitamin C for 5 days), and group 7.5 (administration of 7.5 *mg/day* vitamin C for 5 days). The 50% mechanical withdrawal threshold and total blood antioxidant status (TAS) were measured before and after administration of vitamin C	The administration of a proper dose of vitamin C can reduce oxidative stress, increase antioxidant levels, and recover the threshold for mechanical allodynia in the CPIP model. These results suggested the possibility of a therapeutic effect of vitamin C in early-stage CRPS
US	Experimental control trial	Mongolian gerbils	-	55-65	Brain	-	In view of its comparatively high concentration and this apparent ability to tolerate depletion, ascorbic acid appears to be suited as a relatively expendable antioxidant in the CNS

Contd. table 2.

South Korea	Experimental control trial	Male sprague-dawley rats	58	270-300	Liver	Group 1 (control, n=8) underwent continuous perfusion for 120 *min*. The livers of groups 2–6 were perfused with Krebs–Henseleit bicarbonate buffer for 20 *min*. untreated (group 2, n=10), 60 *min* or 120 *min* of reperfusion with Krebs–Henseleit bicarbonate buffer; ascorbic acid was added to make total concentrations of 0.25, 0.5, 1 or 2 *mM*, respectively. These ascorbic acid concentrations were selected because they had been previously evaluated in an isolated perfused rat liver model of hypoxia and reoxygenation (Younes *et al*, 1992). The ascorbic acid concentrations used in the ascorbic acid treatment for 60 *min* or 120 *min* (groups 3–6) were as follows: the reperfusion of the liver with 0.25 *mM* (group 3, n=10), 0.5 *mM* (group 4, n=10), 1 *mM* (group 5, n=10), or 2 *mM* (group 6, n=10). The liver was weighed at the end of reperfusion and used for the experiments	Cold ischemia/ reperfusion injury is associated with a higher level of oxidative stress and ascorbic acid may act not only as an antioxidant but also as a prooxidant during cold ischemia/ reperfusion
Turkey	Experimental control trial	Wistar Albino rats	34	180-200	Lower extremities of rats	In the I/R group (n=6), the aorta was cross-clamped for 3 *hr*, followed by 1 *hr* of reperfusion. In the vitamin C group (n=8), animals were pretreated with 100 *mg/kg* ascorbic acid *via* the left jugular vein before aortic cross-clamping. In the iloprost group (n=8), animals were pretreated with 20 *ng/(kg Æ min*) iloprost by constant intravenous infusion *via* the left jugular venous cannula. In the sham group (n=6), the abdomen was left open at the same period and a jugular venous line was established. In the control group (n=6), lungs were removed and blood samples taken immediately after sternotomy. No treatment was given in this group	The results suggest that both vitamin C and iloprost are useful agents for attenuating the lung injury caused by increased oxidative stress and neutrophil accumulation after a period of I/R of the lower extremities
Japan	Experimental control trial	Male Wistar rats	132	250-300	Small intestines	Animals were divided into the following groups: (1) Controls (n=30); (2) AsA 2 *mmol/kg* (n=30), 0.5 *mmol*/kg (n=21), 0.1 *mmol/kg* (n=21); and (3) GSH: 2 *mmol/kg* (n=30)	Ascorbic acid (AA) acts as an antioxidant against peroxidative tissue injury, possibly by scavenging radicals, preserving reduced GSH, and reducing the peroxidative reaction
Korea	Experimental control trial	Adult beagle dogs of both genders	8	10-13 *kg*	Renal	The dogs were assigned randomly into a control group (n=4) and ascorbic acid treatment group (n=4). Three days after surgery, vitamin C (30 *mg/kg*) was injected intravenously in treatment group with the same amount of vehicle (physiological saline solution) being injected in the control group	-

Contd. table 2.

Iran	Experimental control trial	Bulb-c mice	56	20-30	Global brain ischemia	Mice were assigned to 8 experimental groups (n=7/group) as follows: 1) Intact group: no ischemia, no treatment; 2) Ischemia control group: ischemia without any treatment; 3) Vehicle group: received treatment with vehicle from one week after ischemia to the end (second week after ischemia). 4) Pretreatment group: received vitamin C (100 *mg/kg*) from one week before ischemia to the end; 5. A1 receptor agonist treatment: received CPA (1 *mg/kg*); 6) Combination treatment with vitamin C/CPA: received vitamin C (100 *mg/kg*)/A1receptor agonist (1 *mg/kg*); 7) A1 receptor antagonist (DPCPX) treatment: received DPCPX (2.25 *mg/kg*); 8) Combination treatment with vitamin C and DPCPX: received vitamin C (100 *mg/kg*)/DPCPX (2.25 *mg/kg*). Animals in groups 5 to 8 received their treatments from one week after ischemia to the end	Concurrent treatment with vitamin C and adenosine A1 Receptor agonist (CPA) can be tested as a pharmaceutical approach to lessen destructive effects of ischemia reperfusion on hippocampus
Egypt	Experimental control trial	Adult Wistar rats of both sexes	50	150-200	Renal	Animal were divided in 5 groups: I: Control group, receive daily intraperitoneal (i.p.) saline for 3 days. II: Renal I/R group, received i.p saline for 3 days and subjected to renal I/R. III: L-arginine Pretreated, 400 *mg/kg*/day i.p. for 3 days prior to I/R. IV: Vitamin C Pretreated, 500 *mg/kg*/day i.p. 24 *hr* prior to I/R. V: combined L-arginine and Vitamin C Pretreated, exposed to Renal I/R group	Oxidative stress is the primary element involved in renal I/R injury. Thus, antioxidants could play an important role than NO donors in amelioration of renal I/R injury
India	Experimental control trial	Rat	21	200-300	Renal	Wistar albino rats were divided into Group I, II & III (the group II is experimental group) were subjected to ischemia for 60 *min* followed by 24 *hr* of reperfusion. The Gr.III was pre-treated with vitamin C (20 *mg/kg*.bw) for 30 days followed by 60-*min* ischemia & 24 *hr* of reperfusion. After the experimental procedure was over; the kidneys were removed and homogenized. The homogenized tissue was used for biochemical estimation of lipidperoxidation & ceruloplasmin	The results of the present study suggest that administration of vitamin C prior to renal ischemia reperfusion protect the renal tissue from the free radical induced reperfusion injury
Turkey	Experimental control trial	Male adult New Zealand type rabbit	48	2500-3000 (2610± 1122)	Skeletal muscle	They were separated into four groups. Group I was the control group without any drugs. The other groups were treatment groups (groups II, III, and IV). Group II rabbits administrated 50 *mg/kg* ascorbic acid and 100 *mg/kg* alpha-tocopherol 3 days prior to ischemia, group III rabbits received 50 *mg/kg* allopurinol 2 days prior to ischemia, and group IV rabbits were administrated both 50 *mg/kg* ascorbic acid, 100 *mg/kg* alpha tocopherol 3 days prior to ischemia and 50 *mg/kg* allopurinol 2 days prior to ischemia	Antioxidant medication may help lower ischemia reperfusion injury. In our study, all drug medications are shown to be able to have an effective role for preventing ischemia reperfusion injury. Moreover, ascorbic acid +alpha tocopherol +allopurinol group (group IV) may have a beneficial effect to decrease the local and systemic damage due to ischemia-reperfusion injury

Contd. table 2.

Turkey	Experimental control trial	Rat	40	250-352	Pancreatic	Animals were divided into four experimental groups (10 rats in each group) as follows: control; ischemia/reperfusion; erdosteine administration before ischemia/reperfusion; vitamin C and E administration before ischemia/reperfusion. In the erdosteine group, animals received erdosteine per orally at a daily dose of 150 *mg/kg* for 3 days before ischemia/reperfusion. In the vitamin C and E group, animals received intraperitoneal vitamin C 200 *mg/kg*/d and intramuscular vitamin E 150 *mg/kg*/d for 3 days before ischemia/reperfusion. Animals in the control and ischemia/reperfusion groups received saline solution intraperitoneally for 3 days	The administration of erdosteine and vitamins C and E had a modest protective effect on the oxidative stress and pancreatic injury induced ischemia/reperfusion
China	Experimental control trial	Male Sprague–Dawley rats	-	225-350	Brain	-	The results obtained with the on-line electrochemical method suggest that the change in the extracellular ascorbic acid during the acute period of different cerebral ischemia/reperfusion models could be the synergic consequences of the neurochemical processes involved in the cerebral ischemia/reperfusion processes and is essentially dependent on the ischemic models
Iran	Experimental control trial	Rat	-	270-220	Brain	Rats were divided into 7 groups: group 1 for ascorbic acid niosomal formulation, group 2 for α-tocopherol niosomal formulation, group 3 for free ascorbic acid (as α-tocopherol was not water soluble there was no treated group with iv administration of free α-tocopherol), group 4 for normal saline (negative control), group 5 for blank niosomes, group 6 for a mixture of α-tocopherol and ascorbic acid niosomes in a ratio of 1: 1 (w/w), and group 7 for sham-operated rats	*In vivo* studies showed that ST60/Chol 35:35:30 niosomes had more neuroprotective effects against cerebral ischemic injuries in male rats than free ascorbic acid
South Korea	Experimental control trial	Male Sprague–Dawley rats,	-	250-300	Liver	Five *min* prior to ischemia, the animals were administered either vehicle or ascorbic acid (AA) (30, 100, 300, and 1000 *mg/kg*) intravenously. l-Ascorbic acid sodium salt was dissolved in saline (vehicle) and administered by intravenous injection of 30, 100, 300, and 1000 *mg/kg* of body weight 5 *min* prior to ischemia. Four treatment groups were studied: (a) AA-treated ischemic, (b) vehicle-treated ischemic, (c) AA-treated control; (d) vehicle-treated control	Ischemia/reperfusion diminishes the hepatic secretory and microsomal functions. AA has both antioxidant and pro-oxidant effects, depending upon the dose

Contd. table 2.

Brazil	Experimental control trial	Male Wistar rats	50	250-300	Intestinal	Animals were divided in 5 groups (n=10 in each group): sham (S), ischemia (I); ischemia/ reperfusion (IR), ischemia/ ascorbic acid (IA) and ischemia/ reperfusion/ascorbic acid (IRA). Animals in the ischemia and ischemia/ reperfusion groups received 2 *ml* of sterile saline solution (0.9% NaCl) into the peritoneal cavity one *hr* before the surgical procedure. The ischemia/ ascorbic acid and ischemia/reperfusion/ ascorbic acid groups underwent the same experimental procedure but with an intraperitoneal injection of 2 *mmol*/kg of ascorbic acid	Ascorbic acid pretreatment has a protective effect against the intestinal morphological lesions induced by ischemia reperfusion injury in rats
Turkey	Experimental control trial	Adult male Sprague–Dawley rats	36	250-300	Hind Limb	The animals were divided randomly into four groups as nine rats each as follows: control, I/R, I/R plus erdosteine, and I/R plus VCE combination. The animals received orally erdosteine once a day and 3 days before I/R in the erdosteine group. In the VCE group, the animals VCE combination received one time in a day and 3 days before I/R, although placebo was given to control and I/R group animals. In the erdosteine (Ilsan, Turkey) with I/R group, animals received erdosteine150 *mg/kg* [10] orally, once a day and 3 days before the I/R. In the vitamin C (Redoxon; Roche, Basel, Switzerland) and vitamin E (Evigen; Aksu Farma, Istanbul, Turkey) with I/R group, animals received vitamin C 200 *mg/kg* [13,14] intraperitoneally and vitamin E 150 *mg/kg* [12,13] by intramuscularly once a day and 3 days before the I/R. The control and I/R group animals received equal amount of saline at the same time, along the same period and *via* the same route	It is important to inhibit lipid peroxidation to prevent lung I/R injury, and we suggest that acute administration of erdosteine may be helpful in clinical practice, *e.g.*, at reconstructive lung surgery and transplantation. Taken together, our data support a role for erdosteine in attenuation lung damage after I/R injury of the lung
China	Experimental control trial	Male Sprague-Dawley (SD) rats	35	250–300	Myocardium	Male SD rats (250-300 *g*) were randomly divided into 7 groups (n=5): 1) Control group: isolated hearts were perfused without I/R; 2) I/R group: hearts underwent 30 *min* global ischemia followed by 120 *min* of reperfusion; 3) VC group: hearts were post-treated with 2 *μM* VC for 30 *min* after global ischemia; 4) VC+5-hydroxydecanoate (5-HD) group: hearts were perfused for 20 mins with 100 *μM* 5-HD before global ischemia and then treated with 2 *μM* VC for 30 *min* before reperfusion; 5) VC+Ionidamine (LND) group: hearts were treated with 2 *μM* VC for 30 *min* after global ischemia and exposed to 30 *μM* LND for 20 *min* at the beginning of reperfusion; 6) 5-HD group: hearts were first perfused for 20 *min* with 100 *μM* 5-HD and then perfused with K–H buffer for 30 *min* before global ischemia; 7) LND group: hearts were exposed to 30 *μM* LND for 20 *min* at the beginning of reperfusion	The results of the current studies have shown that VC protects the myocardium from I/R-induced injury. This cardioprotective effect may be mediated by the activation of mitoK ATP channels, a reduction in both+ overload and reactive oxygen species generation, the inhibition of mPTP opening and the maintenance of ΔΨm. Furthermore, mitoKATP channels may act upstream of mPTP. Vitamin C mediates cardioprotection *via* activation of the PI3K-Akt signaling pathway. This result may contribute towards the development of novel strategies for clinical cardio protection against I/R injury

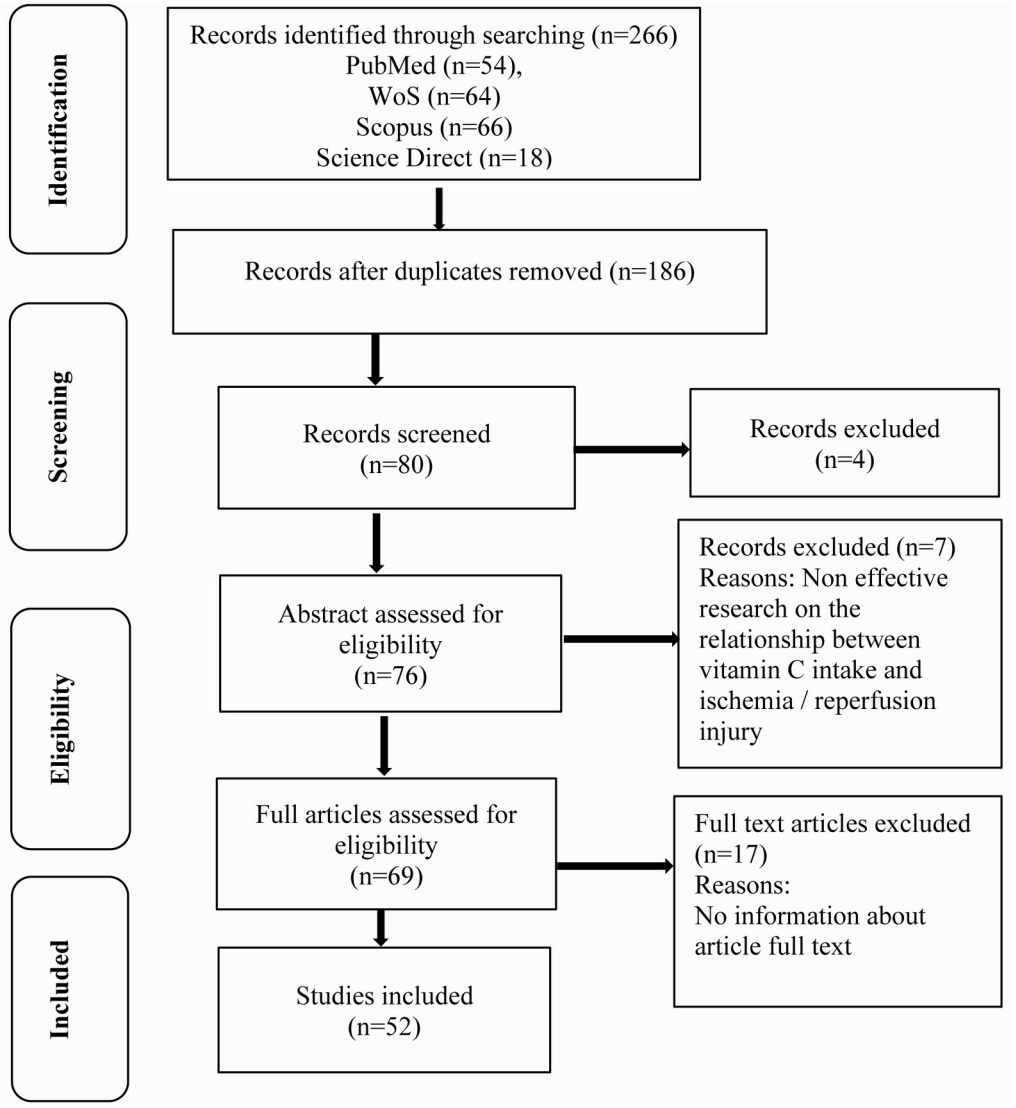

Figure 1. Prisma chart data analysis of the present study.

the first author of the study, year of publication, type of study, country, type of animals, number and weight of animals, location of ischemia and reperfusion, intervention, and important findings of the study. In terms of location, 2 studies in Egypt (15,16), 10 in Turkey (15-24), 4 in Japan (25-28), 4 in Brazil (29-32), 6 in Iran (33-38), 6 in China (39-44), 5 in South Korea (45-49), 1 in Greece (50), 1 in Taiwan (51), 2 in India (52,53), 1 in the United States (54), and 1 study were conducted in Chile (55). All studies were performed on animal specimens, including 36 studies on rats, 13 on rabbits, 2 on dogs and one study on Mongolian gerbils.

In this study, ischemia-reperfusion area was reviewed in 11 studies on the kidney (4,16,19,24,36,39,45,52,53,56,57), 6 on the liver (25,29,46,48,51,58), 5 on the heart (26,42,55,59,60), 10 on the brain (27,30,35,37,38,40,41,43,44,54), 1 on the ovaries (61), one on the aortic suprarenal (17), 3 on the intestine (28,32,34), 1 on the testes (33), 1 on the skin flap (31), 1 on the sciatic nerve (50), 6 on the limbs (15,18,20-22,47), and one study on the pancreas (23).

Results and Discussion

Renal

The results showed that the combination of vitamin C and E, and hydrocortisone may be sufficient to efficiently prevent subsequent oxidative stress in renal I/R injury and improve their function after I/R. The histopathology finding in the current study has shown that intravenous injection of single dose of vitamin C (50 *mg/kg*) immediately after reperfusion

of blood flow noticeably reduces I/R injuries in the renal tissue. Lee *et al* revealed that vitamin C (AA), as an exogenous antioxidant, appears to reduce ischemia-reperfusion lesions (49). In a study by Mohamed Abd *et al*, pretreatment with vitamin C resulted in a significant improvement in renal function, manifested by a dramatic decrease in plasma urea and creatinine and renal MDA levels. Similar findings have been demonstrated in other studies (19,53,56). In a study by Lee Jae-il *et al*, the results of the functional parameters, histopathological changes, and antioxidant enzyme activity suggest that AA alone may play a role in attenuating ischemia-reperfusion injury and assist in the recovery of the renal function after the renal transplant. Pretreatment with AA reduced serum creatinine, BUN, and LDH levels, most likely as a result of the protective effect of ROS inhibition. Similarly, administration of AA (100 $mg\ kg^{-1}$) has been shown to reduce the serum BUN levels in ischemic/renal reperfusion injury in dogs (45). A similar group of researchers also suggested that in all dogs AA may play a role in attenuating ischemia-reperfusion injury and assist in the recovery of the renal function after a renal transplant (49). Also, in the study of Mohamed Abd *et al*, in the group treated with vitamin C, improvements were observed in ischemia/reperfusion in the form of significant regression of histopathological changes caused by ischemia. Glomeruli and tubules appeared apparently healthy, and most of the tubules showed less necrosis and infiltration (56). The more apparent role of vitamin C observed in the current study when compared to NO donor was in the same line with Miloradović *et al*'s study, but reduction of tubular injury promoted vitamin C as an effective chemoprotectant against I/R tubular injury in hypertension (62). However, the apparent effect of vitamin C on L-arginine in the present study was contrary to the findings of the studies by Unal *et al* (62). Mahfoudh-Boussaid *et al* showed that ischemia and vitamin C preconditions improved the ischemic testicular function parameters (57). However, the protective effects are attenuated when the two treatments are combined. They also demonstrated that a potent antioxidant like vitamin C was found to be more effective than increasing blood flow by a vasodilator like dopamine on improving I/R injury following testicular ischemia (56). Another study group examined the effects of AA on kidney as a remote organ after ischemia/reperfusion following abdominal aortic surgery. Their findings suggest that AA reduces MDA levels in the kidney after ischemia-infrarenal renal reperfusion in a rat model. According to the results, they showed that AA treatments, before and during abdominal aortic ligation, reduce renal tissue damage due to ischemia/reperfusion injury. Therefore, it can be stated that AA can prevent remote kidney damage after ischemia/reperfusion as well as ischemia/gram-renal reperfusion injury in rats (16). Previous studies in laboratory animals and young individuals have reported that serum ceruloplasmin levels have decreased with high vitamin C intake (63,64). However, the findings of the study by Vinodini *et al* do not agree with the previous study, which may be due to differences in the dose levels. In this study, 20 *mg/kg* body weight per week was used. It plays an important role in protecting antioxidants against organic and mineral oxygen radicals from iron and ascorbate (53).

In laboratory animals, preventive administration of AA and sodium selenite caused protective effects against acute kidney damage (24). AA ameliorates renal injury caused by ischemia-reperfusion injury and has therapeutic effects (66).

Brain

AA has been shown to inhibit necrotic cell death and apoptosis following hypoxic ischemia in the brain of immature mice (35). A study reveals the protective effects of CPA/Vitamin C co-administration for the first time. The results of this study represented that improvement of memory status in treatment groups has been closely correlated with the effects of therapeutic strategy on neuronal death. This study showed that vitamin C and CPA, as protective and/or therapeutic agents, can increase the survival of the hippocampal neurons in the brain, thus improving the hippocampal function by reducing damage to the neurons caused by free radicals in stressful conditions. However, CPA/vitamin C is introduced as a successful approach containing both vitamin C and CPA positive effects.

Thus, using a combination of these two components can be more favorable than taking each medication alone. This can be due to the fact that vitamin C

decreases the neuronal vulnerability to ischemia and if it fails and neurons are damaged, adenosine A1 receptor agonist postpones the onset of apoptosis and gives them time to repair which results is reducing ischemic complications. In conclusion, concurrent treatment with vitamin C and adenosine A1 Receptor agonist (CPA) can be tested as a pharmaceutical approach to lessen destructive effects of ischemia reperfusion on the hippocampus (38). Due to the common pathophysiological pathway of sepsis and ischemia/reperfusion injury, the potential role of vitamin C for ischemia/reperfusion injury is further supported by the results of preliminary sepsis studies, showing earlier recovery from organ failure and higher survival rates (7). One study confirmed that the STZ-evoked diabetic state aggravates the neuronal damage caused by a transient cerebral ischemia and subsequent reperfusion in rats. They found that diabetes enhanced the production of O2−, activated caspase-3, and induced the expression of proinflammatory cytokines (TNF-α and IL-1β) in the brain. These detrimental effects are markedly potentiated by cerebral ischemia and reperfusion, leading to greater infarct growth and aggravation of apoptosis and inflammation. Their results show that chronic supplementation with AA inhibits the apoptotic changes and proinflammatory responses and attenuates the exacerbation of cerebral injury and neurological deficits in the diabetic state. These beneficial effects of AA could be attributed to its antioxidant and anti-inflammatory properties. Of course, Iwata *et al* acknowledged that the relative low dose of AA (100 *mg/kg*) which they used in this study might not be efficacious against the severe inflammatory responses induced by the combination of stroke and diabetes (27). However, in a study by Mehrooz *et al*, they reported that vitamin C supplementation did not improve performance in patients with ischemic stroke (35,66). Aly *et al* showed that a regimen of combined ibuprofen and AA did not improve neurological outcomes of the infants with hypoxic ischemic encephalopathy (67).

Intravenous administration of vitamin C significantly improves neurological deficits and reduces cerebral infarction and cerebral edema by reducing transient Middle Cerebral Artery Occlusion (tMCAO) caused by nitrosative stress, inflammatory responses, and blood-brain barrier disorders and its reduction. In other words, it is effective as an auxiliary agent with intravenous thrombolysis or endovascular thrombectomy in the acute treatment of ischemic stroke (7); it is also effective on hypoxic ischemic encephalopathy by regulating immunity and functional processes related to inflammation and signaling pathways (44).

Liver

The results of studies by Taha *et al* demonstrated that AA reduced the morphological changes of hepatic lysosomes caused by ischemia/reperfusion (29). In another study that examined the *in vivo* effects of Ischemic Preconditioning (IPC), AA, or a combination (IPC _ AA) on the level of mitochondrial injury caused by hepatic Ischemia/Reperfusion (I/R), it was suggested that IPC and AA synergistically reduced the level of mitochondrial damage during I/R as a result of decreased post-ischemic oxidant stress. The results show that the ALT and AST activities increased significantly after 5 *hr* reperfusion. This hepatoprotective effect against a warm I/R injury was clearly demonstrated in the rats pretreated with IPC or AA alone. Interestingly, IPC_AA had an additional protective effect (46).

Parra-Flores *et al*'s preliminary studies revealed that A, D, and N separately increased the viability of CF (Cardiac Fibroblast**)** exposed to sI/R (Simulated Ischemia/Reperfusion) in a concentration-dependent manner, at high concentrations (≥100 μM) (55). However, 10 *mmol* of AA was lethal due to peroxidant activity at higher concentrations, as shown in mouse tumors (68). In addition, these antioxidants alone did not protect against ischemia/reperfusion injury simulated at 1 and 10 μM, but when combined with dual or triple compounds in every 10 μM, they showed synergistic cell protection (69-72).

Also, a study reported by Nikas *et al* revealed that in this experimental pig model, the antioxidants AA, desferrioxamine, and NAC administered alone or in combination did not reduce the deleterious effects of reperfusion injury and specifically the extent of myocardial necrosis. The infusion of all drugs was started 15 *min* before and completed 5 *min* after reperfusion, except for the administration of NAC, which was terminated 60 *min* postreperfusion (73). In another study, treatment with A/D/N reduced

the anti-apoptotic effects of ischemia/reperfusion-exposed cardiac fibroblasts by reducing p38 and JNK phosphorylation, which play an important role in apoptosis in cardiac ischemia-reperfusion (74). In another study carried out by Hsu and Wang, it was shown that pretreatment with either L-AA or Alpha-tocopherol protected cardiac function and myocardial cells through decreasing systemic hydroxyl radicals and cardiac lipid peroxidation while the former was somewhat more effective (51).

Intestine

The findings of Nakamura *et al* suggest that AA acts as an antioxidant in the small intestine and reduces the damage caused by reperfusion (28). In one study, co-injection of vitamin C (50 *mg/kg*) with reperfusion showed that this antioxidant had a protective effect on the intestinal mucosa. In summary, systemic therapy with antioxidants like vitamins C, vitamin E, and HC, either separately or in combination, can protect the intestinal tissues against the local and systemic injuries following intestinal ischemia reperfusion. Their data indicate that the combination therapy, synergistically, can be developed as a new therapeutic method for intestinal IRI and subsequent remote organ injury (34). In one study conducted by Higa *et al*, it was found that necrotizing changes after small intestine ischemia and reperfusion, without AA protection, were associated with increased villous necrosis and hemorrhagic infarct. Thus, for instance, villous necrosis extension was significantly related to small intestine ischemia and reperfusion, and AA treatment reduced the extension of necrosis, and this was also significantly related to most of the contramesenteric intestinal border. Most interesting was the quantitative relationship found between AA treatment and mucosal hemorrhagic infarct. AA caused a significant reduction of antimesenteric villous hemorrhagic infarction of the small intestine after ischemia followed by reperfusion. The lesions found in the small intestine were more prominent along the antimesenteric margin (32).

Lung

Sirmah *et al* showed that Erdosteine had an antioxidant role and had a greater protective effect than vitamins C and E in reducing ischemia-reperfusion lesions in the lungs of mice (22).

Ovary, testicular

Vitamin C is a safe and easy drug that can protect the ovaries from ischemia-reperfusion damage caused by detour, which is the main conservative method for managing ovarian torsion (61). Sagsoz *et al*, who studied the effects of antioxidants on the ovaries, reported that vitamin C reduced ischemia-reperfusion of the ovaries in its early stages, which is better than verapamil, a calcium channel blocker (75).

Pancreas

Lu *et al* showed that AA significantly reduced the concentration of MDA in the pancreatic tissue (76). In the study by Koçkar *et al*, their histological parameters supported the biochemical parameters. The tissues of the ischemia/reperfusion group showed significantly histopathological changes including edema, vacuolization, Polymorphonuclear Neutrophil (PMN) infiltration, and necrosis. On the other hand, in the erdosteine group edema and PMN infiltration was significantly decreased when compared with the ischemia/reperfusion group. In the vitamin C and E combination group, the edema significantly decreased when compared with the ischemia/reperfusion group. In the erdosteine group, the damage was less severe than the ischemia/reperfusion and vitamin C and E groups. Erdosteine seems to have more protective effect on ischemia/reperfusion injury of the pancreas (23).

Skin

Matsuda *et al* showed the beneficial effects of high-dose vitamin C (14 *mg/kg/hr*) in reducing premature lipid peroxidation after burns and reducing capillary leakage of fluid and protein from the intravascular to interstitial space in mongrel dogs (77-79).

Human

Contrary to the disappointing results of chronic administration of antioxidants to prevent cardiovascular events, administration of antioxidants may have beneficial effects in the reperfusion phase of an acute event (80). Endothelial dysfunction during reperfusion is a common finding in animal

studies (81,82) and has recently been reported in humans as well (83). Ischemia/reperfusion injury reduces arterial sensitivity to acetylcholine expansion function in patients with Peripheral Arterial Disease (PAD) (84,85). Vitamin C augmented the vasodilation to Ach (ACh; endothelium-dependent agonist) under basal conditions and prevented IR-induced endothelial dysfunction in this high-risk cohort, consistent with increased oxidative stress as a determinant of endothelial function before and after IR (86).

Bailey *et al*'s findings suggest that ascorbate prophylaxis may have promoted iron-induced oxidative lipid damage *via* a Fenton-type reaction initiated during the ischemic phase of surgery (87). Although many studies have shown a positive effect of high-dose IV vitamin C on ischemia/reperfusion, this was not the case. Various factors could influence this issue. First, specific laboratory conditions can have a major effect on the effect of vitamin C on ischemia/ reperfusion injury. Dosage, route, and duration of use varied widely between studies. Doses ranged widely from 500 *mg* to 1 *g* of vitamin C per *kg* body weight. The route of administration can be IV, IP, oral, or intra-coronary (88). AA has many drugs in different doses ranging from 30 $mgkg^{-1}$ to 1,000 $mgkg^{-1}$. In ischemia/reperfusion studies, the protective effects of the liver against ischemia/reperfusion injury were demonstrated only in low-dose rats (30–100 $mgkg^{-1}$). High doses (1000 $mgkg^{-1}$) increased ischemia/reper-fusion-induced liver damage by increasing lipid peroxidation (19). Also in another study, improvement in hepatic hemodynamics was shown only in the liver treated with low concentrations of AA (0.25 and 0.5 *mM*). The high concentrations used in these experiments exacerbated cold ischemia/reperfusion-induced changes in hepatic hemodynamics (48). Similarly, the effects of hepatic protection against warm ischemia/ reperfusion were shown only in the rats treated with low doses of AA (30 or 100 *mg/kg*). High doses (1000 *mg/kg*) increased ischemia/reperfusion due to hepatic perfusion by increasing lipid peroxidation (89). In fact, low concentrations of AA have a protective effect against liver cell damage. The significant increase in bile production in the group with low AA concentration indicates that AA treatment improves hepatocyte integrity. Bile production has been used as a valid and accurate measure of liver integrity (90). In addition, the results of Seo *et al*'s study revealed that AA primarily acts as an antioxidant in low doses and has pro-oxidating effects in high doses, thus it should be used with caution in pharmaceutical doses (58). In vector-treated ischemic mice, cytochrome P450 levels remained unchanged for up to 1 *hr* after reperfusion but were significantly lower 5 *hr* after reperfusion. This decrease was inhibited by low doses of AA. High doses of AA reduced total cytochrome P450 levels. Loss of cytochrome P450 is most likely due to microsomal lipid peroxidation due to ischemia/ reperfusion (91). Unlike previous studies, one study showed that the direct purifying activity of vitamin C was only achieved with a plasma concentration of 1 to 10 *mmol/L* or higher. In addition, the timing of vitamin C intake is very important in studies (88). Numerous clinical and pre-clinical studies have also shown that high-dose injectable vitamin C can reduce systemic ischemia/reperfusion and myocardial damage (7).

In another study, the combined effects of magnesium (Mg) and high-dose AA on cardiac Ischemia Perfusion (IP) damage were investigated; it was determined that to reduce IP, Mg with a high dose of AA can be effective in patients undergoing heart surgery, and it is effective to improve the disease outcomes (60,92).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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