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E Nigel Wardle

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REVIEW

Antioxidants in the Prevention of Renal Disease

E Nigel Wardle, MD

Oxford, England

ABSTRACT

In view of the role of oxidative processes in inflicting damage that leads to glomerulosclerosis and renal medullary interstitial fibrosis, more attention could be paid to the use of antioxidant food constituents and the usage of drugs with recognized antioxidant potential. In any case atherosclerosis is an important component of chronic renal diseases. There is a wide choice of foods and drugs that could confer benefit. Supplementation with vitamins E and C, use of soy protein diets and drinking green tea could be sufficient to confer remarkable improvements.

Key words: Antioxidants; Inflammation; Glomerulonephritis; Pyelonephritis; Chronic renal failure; Atheroma cytokines; Nutrition.

OXIDATIVE PROCESSES AND RENAL DAMAGE

In the course of an inflammatory process reactive oxygen species (ROS) arise from the activities of various enzymes (1), such as the NADPH oxidases, cyclooxygenases and lipoxygenases, the nitric oxide synthetases, xanthine oxidase and the mitochondrial respiratory chain. Various articles attest to the importance of damage by oxidative processes in glomerular inflammation (2–5), in ischemia-reperfusion of the renal tubules (6), and in induction of fibrosis of the renal interstitium (7,8).

Oxidative processes cause the liberation from glomerular cells of eicosnoids, cytokines and growth factors and they promote the activities of proteases (5). Thus once they are released, they magnify the extent of inflammation and the ensuing tendency to fibrosis (9). It is recognized that oxidation activates transcription factor NF-kappa B that determines release of cytokines, release of proteolytic enzymes and expression of tissue factor

Address correspondence to: Dr. Nigel Wardle, MD, 21 Common Road, North Leigh, Oxford, England OX8 6RD. Fax: 01993,881880.

thromboplastin (1,10). Hydrogen peroxide and other oxidants also activate Ras GTPase (1,11) and the mitogen activated protein kinases (1) (MAPK). The transcription facto AP-1, composed of jun and fos gene products, is redox regulated (1), and is implicated in growth factor stimulated cell growth.

General mechanisms of oxidant damage to tissues and the need for tissue antioxidants have been reviewed by Halliwell (12). During glomerular inflammation ROS arise from the activities of phagocytes (13–14), and as a result of complement inflicted injury (15). It has been suggested that when there is glomerular hyperperfusion that means that fluid shear in the capillaries will cause ROS formation that will alter the structure of the vascular endothelium so that there is ensuing proteinuria. At that stage there is vasoconstriction, and on the endothelium there is display of procoagulant molecules and adhesion molecules for leucocytes. With time this is followed by a state of hypoperfusion during which glomerulosclerosis and renal interstitial fibrosis become (16) established. Certainly ROS alter the heparan sulfate proteoglycans of glomerular endothelial cells so that proteinuria ensues (17). Also ROS activate enzymes released by neutrophils, such as collagenase and gelatinase, so that proteinuria results from GBM digestion (5). Furthermore priming of neutrophils by peroxynitrite, created by interaction of ROS and nitric oxide, leads an enhanced local inflammatory response (18). In studies of passive Heymann nephritis, Kerjaschki (19) has detailed how onset of proteinuria is caused by the generation of ROS following insertion of C5b-9 into membranes of glomerular podocytes.

There is now much information concerning the oxidation of lipoproteins and how it explains atherogenesis and the genesis of glomerulosclerosis (20). Lipoproteins are oxidised by means of ROS, by free and metal bound ions, by 15-lipoxygenase in endothelium, and by the action of myeloperoxidase (21) that is liberated in arterial walls or in glomeruli. Peroxynitrite that is formed in plasma or in tissues contributes. Minimally modified LDL is enough to activate NF-Kappa B within cells. This reminds us that the effects of oxidation products on cellular responses can be as important in the progression of glomerular diseases as the initiating process (22).

It is realized too that production of oxidants in the course of inflammation will cause apoptosis of glomerular cells (23) and of infiltrating leucocytes (24). It has been demonstrated that Il-1 sensitizes glomerular cells to oxidant induced apoptosis by virtue of depression of hsp-70 (25). Any lowering of intracellular glutathione facilitates apoptosis (26). It is more easily demonstrable in non-renal tissue that lipid hydroperoxides can cause apoptosis (27).

General Usage of Anti-oxidants and Their Rationale

One is familiar with the sale by health food stores of foods, vitamins and drugs for their antioxidant potential (28). Fruits, grains and vegetables will supply vitamins E and C, plant phenolics such as the flavanoids, and other putative anticancer agents (29). The antioxidant nutrients hold out the promise of a reduced incidence of cancer and improvements in survival (30). For example, eating 300 gms cooked brussel sprouts each day protects against oxidative damage to one's DNA (31). One might prefer selenium supplementation. Selenium is a component of the glutathione peroxidases that are involved in removal of both hydrogen peroxide and lipid peroxides in tissues (32).

There are campaigns to promote antioxidants and trials of their use in prevention of atherosclerosis (33), and specifically the use of vitamin E to reduce the chance of coronary artery plaque rupture. At 400 IU per day vitamin E increases the oxidative resistance of LDL. Allopurinol reduces lipoprotein oxidation as it is a free radical scavenger (34).

Vitamin C can improve endothelial cell function in smokers (35). By it's ability to enhance formation of nitric oxide by endothelial cells, garlic inhibits platelet aggregation (36,37). Therefore one must recall that atherosclerosis is a significant component of diabetic kidney disease and can be a problem in any nephrotic syndrome.

Antioxidant enzymes like the superoxide dismutases (MnSOD or CuSOD) and catalase are important for the protection of the renal tubules (38), and indeed they help to assuage renal tubular necrosis (39). SODs are present at low concentration in extracellular fluids and they bind to heparan sulfate proteoglycans on capillary endothelial cells, so providing a protective coat (38). Both SOD and catalase can be used to ameliorate injury in puromycin aminonucleoside nephrosis in rats (40). Intracellular reduced glutathione has an important antioxidant action and supports these enzymes. Metal binding proteins like the metallothioneins are important too in the renal tubules for protection of the DNA (41).

What Can Antioxidants Do?

In patients with chronic renal failure there is an increase of plasma lipid peroxides and enhanced red cell lipoperoxidation, as measured by malonyldialdehyde (MDA). Such changes are improved by a low protein diet of vegetable material with supplementary vitamins A,E and C (42).

In experimental situations one can control aspects of inflammation by the use of N-acetylcysteine, 2 mercaptoethanol, dithiocarbamates (43), butylated hydroxyanisole, vitamin E, 21 amino steroids, or chelators of iron and copper. Antioxidants inhibit formation of ROS by phagocytes (28) and inhibit inducible nitric oxide synthase (iNOS) production by infiltrating macrophages (44), they inhibit Il-1 induced cyclooxygenase together with iNOS in mesangial cells (45), and they can inhibit formation of chemokines (46) and cytokines (47,48).

In organ transplantation it has been demonstrated that antioxidant vitamins reduce reperfusion injury of the kidney and endothelial cell expression of ICAM-1 leukocyte adhesion molecule (49). Salahudeen et al. (50) have shown that use of the antioxidant lazaroid (21-amino-steroid) U 74006F not only helps cold preservation of the kidney but its use results in fewer rejection episodes in a syngeneic animal renal transplant model. These authors note how lazaroid reduces expression of cytokines, reduces expression of MHC Class II antigens and reduces iNOS activity. TNFa exerts its action via NF-kB activation. Both ROS and RNIs (reactive nitrogen intermediates) provoke release of cytokines via NF-kB activation (51), but that effect can be offset by antioxidants. In rat studies it has been demonstrated how cyclosporin induces glomerular formation of ROIs, and that can be offset by means of vitamin E (52).

One can expect phagocyte functions to be dampened. Indeed taurine (53) and N-acetylcysteine reduce the activity of NADPH oxidase (54). There is good reason to think that, once bacteria have been eliminated, pyelonephritic damage is perpetuated by phagocytes via oxidant and cytokine release, and this might be curtailed by antioxidants (55). Adjuvant enhancement of the immune response, a macrophage propensity, is suppressed (56) by some antioxidants, and so is the action of T lymphocytes since JNK the c-Jun NH_2 terminal kinase is subject to antioxidant control (57). Yet each antioxidant has to be assessed individually. The agent thioproline, an intracellular sulfhydryl antioxidant, will enhance immune responses and prolong the life of aging mice (58).

Many glomerulonephritides are initiated by leukocyte infiltration. Therefore it is of note that lung inflammation is suppressed by antioxidants (59). Leukocyte infiltration arises from the expression of adhesion molecules on vascular endothelium (60). So one

notes that Ferran et al. (61) showed that inhibition of NF-kB by antioxidant blocks TNFa induction of adhesion molecules. N-acetylcysteine (62) or flavanoids (63) prevent endothelial cell activation and expression of adhesion molecules for leukocytes. Yet a cocktail of antioxidant vitamins was not noted to influence the expression of adhesion molecules in man (64), even though reactions to oxidised LDL might be blocked *in vitro* (65). There are encouraging reports, both experimental and clinical,that acute renal impairment associated with cholestasis or hepatic disease can be ameliorated by the use of N-acetylcysteine (66), which is known to stop activation of NF-kB and thereby the acute cytokine response.

Antioxidants act in various ways to prevent lipid peroxidation, albeit this is not their only way of conferring benefit. Firstly they prevent first chain initiation by scavenging initial radicals, such as hydroxyl radicals $OH^{\bullet}$. Secondly, they bind metal ions, so preventing them from acting as peroxidation initiating species. Thirdly, they break radical chains so that intermediate peroxyl or alkoxyl radicals are scavenged, so preventing continuing hydrogen abstraction. Fourthly, they will decompose peroxides by converting them to non-radical products like alcohols.

The Choice of Antioxidant Diet or Drugs

In order to help patients we need to look at the choice of food antioxidants (67), extracts of foodstuffs and antioxidant drugs.

Can Antioxidants Contribute to Amelioration of Renal Disease?

When one considers the numerous damaging reactions in which oxidation is implicated (2-6), the short answer must be that dietary antioxidants could be very useful, but measuring benefit might be difficult. When nephrologists recommend low protein diets in order to ameliorate the course of progressive renal disease, they often do not specify exactly which protein foods should be consumed. The potential of soyprotein (71) has hitherto been overlooked. The isoflavones in that diet are akin to natural estrogens and are antioxidant (128,129), and there are plant phenolics like caffeic acid. Soyprotein has the added advantage that plasma cholesterol is lowered.

Table 1 lists a wide variety of foods with antioxidant potential. Individuals vary in what in what they will choose to add to what might be a boring low protein (42) diet. There are herbals (79,80), Asian and Indian choices. Many of these foodstuffs could be refined and presented in another form, like cacao polyphenols that are in chocolate (130). If the aim is to reduce inflammation, as in the glomerulonephritides, one will note that curcumin (91) has been shown to block the expression of adhesion molecules like ICAM-1, ELAM-1 and VCAM-1 on endothelial cells (131). Of ten one aims to suppress ROS that contribute to the genesis of interstitial fibrosis of the kidneys (7).

It is remarkable that ACE inhibitors inhibit NP-kB (132) and thereby reduce the release of cytokines and growth factors. A lot of patients do not tolerate ACEI drugs. In choosing other hypotensive agents, one might like to contemplate those with antioxidant potential. Some of the beta-blockers (127,133) and many calcium channel antagonists (123,124, 134) have this potential, but one has to note that often the tissue that has been studied is myocardium and the data may not be exactly relevant. It is reported that nicardipine is a preventive antioxidant and verapamil is a chain-breaking antioxidant, but diltiazem has little effect (123). Yet the clinical facts are that diltiazem and verapamil are the best calcium channel blockers for the prevention of glomerulosclerosis (135).

Table 1

Choice of Antioxidants

Vitamins	Vitamins E, C or A (28–29), morin hydrate (68), vitamin K (69).
Foods	Soy protein meals (70,71), garlic (36,37), vegetable low protein (42) diet, soy isoflavones (72), other phytooestrogens (73,74), polyphenols in green tea (75), chocolate (76), olive oil (77,78), rooperal dicatechol (48), glabridin polyphenol in liquorice, brussel sprouts (31), purslane leaf (79), mustard, hawthorn drink (80), flavanoids (81,82), eg from apples (83), citrus fruit (84), silymarin (85), coumarins (83), Sandhika herbal drug (86), herbal mixtures, tocotrienols of palm oil, lycopene of tomato (88,89), spinach, stawberries (90), guava, papaya fruits, curcumin from turmeric (91), apocyanin (40H-methoxy-acetophenone) from Picrorhiza (92).
Experimental Agents	Glutathione, N-acetylcysteine (54,62), dithiocarbamates inhibit NF-kB, taurine (53,93), DMTU (1,3 dimethyl-2-thiourea) (94), urate (95), allopurinol (34), OPC 15161-a pyradzinone-4-oxide (96), nitroxides (97), NDGA, 5-lipoxygenase inhibitor (98), 21 aminosteroids (lazaroids) (99,100), ebselen radical scavenger and glutathione peroxidase mimic (101), L-arginine (102), prostaglandin E2, gabexate mesilate (103), hydroxyethylrutosides, pantothenic acid, neopterin (104), ellagic acid (103), desferrioxamine.
Drugs	
Specific antioxidants	Probucol (106–108) and thyronines like Leumedin (109).
Corticosteroid	via the induction of Mn superoxide dismutase
Hypolipidemic	troglitazone and analogues
HRT agents	estradiol and medroxyprogesterone acetate
Anticancer	tamoxifen
Antinflammatory	dapsone (110,111), pentoxifyllin (112–114), dipyridamole (115,116), heparins (117,118)
Cardiovascular	some beta-blockers (119), in particular carvedilol (120,121), amlodipine (122), other Ca^{2+} blockers eg verapamil (125), indapamide (126), ACE inhibitors (127) eg captopril, enalapril, lisinopril, losartan, lovastatin.

The β-.αl adrenoreceptor blocker carvedilol with antioxidant potential (121), is known to protect against cardiovascular disease (135,137). In the rat remnant kidney model, carvedilol was shown to protect against fibrosis, and yet in that situation no change in antioxidant status was shown (138)! So an antioxidant action is only part of the action of a drug and at the present time we do not know sufficient about the details. Indapamide, a diuretic related to chlorthalidone, is an effective alternative to ACEI in the control of microalbuminuria (139). Its antioxidant potential was thought to confer renal protection in hypertensive rats (140).

So when one looks at the antiinflanunatory agents does one know whether antioxidant potential matters? The theoretical expectation that it can, will not satisfy all. There is dapsone that is used for Henoch-Schonlein purpura and other leukocytoclastic vasculitides (111,141), and dipyridamole for nephritides (115,116) and pentoxifylline for vasculitides (114,141). Heparins are antiproliferative (142) for mesangial and smooth muscle cells. They are also antioxidant (117) but is that not a separate attribute? And might one consider L-arginine (102) to enhance formation of nitric oxide or nitroxides (97)? Well isosorbide dinitrate therapy is simpler (143). Local nitric oxide can certainly help suppress formation of new collagen (144).

You will expect me to make a precise recommendation, but I am not a food chemist. Prior and Cao (145) have just published data that show that drinking green tea is enough to satisfy the dietary antioxidant requirement. For the benefit of renal patients one can add a soy protein diet. Choice of drugs is then a refinement but clearly more experimental data are required.

REFERENCES

1. Palmer RJ: Reactive oxygen species and antioxidants in signal transduction and gene expression. *Nutr Revs* 55:353–61, 1997.
2. Baliga R, Veda N, Shah SV: Oxidant mechanisms in Glomerular Disease. Chap 4; p 135–151 in Current Nephrology Ed. HC Gonick. Mosby, Year Book Inc., 1997.
3. Diamond JR: Reactive oxygen species and progressive glomerular disease. *Lab Invest* 124:468–469, 1994.
4. Johnson RJ, Lovett D, Lehrer RI, Couser WG, Klebanoff SJ: Role of oxidants and proteases in glomerular injury. *Kidney Int* 45:352–359, 1994.
5. Shah SV: Role of reactive oxygen metabolites in experimental glomerular disease *Kidney Int* 35:1093–1106, 1989.
6. Paller MS, Hoidal JR, Ferris TF: Oxygen free radicals in ischemic acute renal failure in the rat. *J Clin Invest* 74:1156–1164, 1984.
7. Poli G, Parola M: Oxidattve damage and fibrogenesis. *Free Radical Biol Med* 22:287– 305, 1997.
8. Young MR, Young IS, Johnston SR, Rowlands BJ: Lipid peroxidation assessment of free radical production following release of obstructive uropathy. *J Urology* 156:1828–1832, 1996.
9. Wu SM, Patel DD, Pizzo SV: Oxidised α2-macroglobulin differentially regulates receptor binding by cytokines/growth factors: implications for tissue injury and repair mechanisms in inflammation. *J Immunology* 161:4356–4361, 1998.
10. Barnes PJ: Nuclear factor-kB. *Int J Biochem* 29:867-870, 1997.
11. Irani K, Goldschmidt-Clermont PJ: Ras, superoxide and signal transduction. *Biochem Pharmacol* 55:1339–1346, 1998.
12. Halliwell B: Antioxidants: the basics - what they are and how to evaluate them. Chap 1 in Antioxidants in Disease: Mechanisms and Therapy. Ed H Sies. *Adv Pharmacology* 38:3–20, 1997.
13. Freeman BA, Crapo JD: Biology of disease: Free radicals and tissue injury. *Lab Invest* 47:412–426, 1982.
14. Nath KA, Fischereder M, Hostetter TH: The role of oxidants in progressive renal injury. *Kidney Int* S45:S111–S115, 1994.
15. Adler S, Baker PJ, Johnson RJ, Ochi RF, Pritzl P, Couser WG: Complement membrane attack complex stimulates production of ROIs by cultured mesangial cells. *J Clin Invest* 77:762–767, 1986.

16. Futsakul P, Sitprija V, Yenrudi S, Poshyachinda M, Sensirivatana R, Watana D, Singklura V, Jungthirapanich J, Futrakul N: Glomerular endothelial dysfunction determines disease progression: hypothesis. *Amer J Nephrology* 17:533–540, 1997.
17. Tay M, Commer WS, Vassiliou P: The inhibitory action of oxygen radical scavengers on proteinuria and glomerular heparan sulphate loss in the isolated perfused kidney. *Biochem Int* 20:767–78, 1990.
18. Rohn TT, Nelson LK, Sipes K, Swain SD, Jutila KL, Quinn MT:.Priming of human neutrophils by peroxynitrite:potential role in enhancement of the local inflammatory response. *J Leuko Biol* 65:59–70,1999.
19. Kerjaschki D: Epitopes and radicals: early events in glomerular injury in membranous nephropathy. *Exp Nephrology* 3:1–8. 1995.
20. Berliner JA, Heinecke JW: Role of oxidised lipoproteins in atherogenesis. *Free Radical Biol Med* 29:707–27, 1996.
21. Malle E, Woenckhaus C, Waeg G, Esterbauer H, Grone E F, Grone HJ: Immunologic evdience for hypochlorite mediated proteins in human kidney. *Amer J Pathol* 150:603–615, 1997.
22. Guijaaro C, Keane WF: Lipid induced glomerular injury. *Nephron* 67:1–6, 1994.
23. Sugiyama H, Kashihara N, Makino H, Yamasaki Y, Ota Z: Reactive oxygen species induce apoptosis in cultured human mesangial cells. *J Amer Soc Nephrology* 7:2357–2363, 1996.
24. McCord JM: Superoxide radical: controversies, contradictions and paradoxes. *Proc Soc Exp Biol Med* 209:112–17, 1995.
25. Yokoo T, Kitamura M: Il-1 depresses expression of the 70 kD HSP and sensitizes glomerular cells to oxidant initiated apoptosis. *J Immunology* 159:2886–2892, 1997.
26. Feranes RS, Cotter TG: Apoptosis and necrosis: intracellular levels of glutathione influence mode of cell death. *Biochem Pharmacol* 48:675–81, 1996.
27. Sandstrom PA, Pardi D, Tebbey PW, Dudek RW, Terranian DM, Folks TM, Buttke TN: Lipid hydroperoxide induces apoptosis: lack of inhibition by bcl-2 expression. *FEBS Lett* 365:66–70, 1996.
28. Halliwell B: Antioxidants in human health and disease. *Ann Review Nutrition* 16:33–50, 1996.
29. Block G, Patterson E, Subar A: Fruit, vegetables and cancer prevention. *Nutr Cancer* 29:1–19, 1992.
30. O'Brien PJ: Antioxidants and cancer: molecular mechanisms. *Adv Exp Med Biol* 366:215–239, 1994.
31. Verhagen H, Poulsen HE, Loft S, van Poppel G, Willems MI, van Bladeren PJ: Reduction of oxidative DNA damage in humans by brussel sprouts. *Carcinogenesis* 16:969–970, 1995.
32. Ursini F, Bindoli A: The role of selenium peroxidases in protection against oxidative damage of membranes. *Chem Physics Lipids* 44:255–276, 1987.
33. Buring JE, Hennekens CH: Antioxidant vitamins and cardiovascular disease. *Nutrition Revs* 55:553–558, 1997.
34. Lapenna D, de Gioia S, Ciofani H, Cuccurollo F: Antioxidant activity of allopurinol on copper catalysed human lipoprotein oxidation. *FEBS Lett* 409:265–268, 1997.
35. Heitzer T, Just H, Munzel T: Antioxidant vitamin C improves endothelial dysfunction in chronic smokers. *Circulation* 94:6–9, 1996.
36. Khan NS, Sooranna SR: Potent activation of nitric oxide synthase by garlic: basis for its therapeutic applications. *Current Medical Research Opinion* 13, 257–263, 1995.
37. Prasad K, Laxdal V A, Yu M, Raney BL: Evaluation of hydroxy-radical scavenging proprty of garlic. *Mol Cell Biochem* 154:55–63, 1996.
38. Ichikawa I, Kiyama S, Yoshioka T: Renal antioxidant enzymes: their generation and function. *Kidney Int* 45:1–9,1994.
39. Zurovsky Y, Haber C: Antioxidants attenuate endotoxin-gentamicin induced acute renal failure in rats. *Scand J Urol Nephrol* 29, 147–154, 1995.
40. Beaman M, Birtwistle R, Howie AJ, Michael J, Adu D: The role of superoxide anion and hydrogen peroxide in glomerular injury induced by puromycin aminonucleoside in rats. *Clinical Science* 73:329–332, 1987.
41. Chubatsu LS, Meneghini R: Metallothionein protects DNA from oxidative damage. *Biochem J* 291:193–198, 1993.
42. Peuchant E, Delmas N, Beauvieux MC,Dubourg L, Thomas MJ, Perromat A, Aparicio M, Clara M, Combe C: Antioxidant effects of supplemented very low protein diet. *Free Rad Biol Med* 22:313–320, 1997.
43. Schreck R, Meier B, Mannel DM, Droge W, Bauerle PA: Dithiocarbamates as potent inhibitors of NF-kB activation in intact cells. *J Exp Med* 175:1181–1194, 1992.
44. Hecker M, Preiss C, Kleman P, Busse R: Inhibition by antioxidants of nitric oxide synthase expression in murine macrophages: role of NF-kB and IRF-1. *Brit J Pharmacol* 118:2178–2184, 1996.
45. Tetsuka T, Baier LD, Morrison AR: Antioxidants inhibit Il-1 induced cyclooxygenase and nitric oxide synthase expression in rat mesangial cells. *J Biol Chem* 271:11689–11693, 1966.

46. Sato M, Miyazaki T, Nagaya T, Murata Y: Antioxidants inhibit TNFa mediated stimulation of Il-8, MCP-1 and collagenase in cultured human synovial cells. *J Rheumatology* 23:432–438, 1996.
47. Eugui EM, De Lustro B, Rouhafza S, Ilnicka M, Lee SW, Wilhem R, Allison AC: Some antioxidants inhibit in a coordinate fashion the production of TNFa, Il-1 and I1-6 by human peripheral blood mononuclear cells. *Int Immunol* 6:409–422, 1994.
48. Allison AC: Antioxidant drug targeting In Antioxidants in Disease: Mechanisms and Therapy. Ed H Sies, *Adv Pharmacology* 38:273–290,1977.
49. Lehr HA, Meesmer K: Rationale for the use of antioxidant vitamins in clinical organ transplantation. *Transplantation* 62:1197–1199, 1996.
50. Salahudeen A, Wang C, McDaniel O, Lagoo-Denodyalan S, Bigler S, Barber H: Antioxidant lazaroid U-74006F improves renal function and reduces expression of cytokines, inducible nitric oxide synthase and MHC antigens in a syngeneic renal transplant model. *Transplantation* 62:1623–1633, 1996.
51. Remick DG, Villaretti L: Regulation of cytokine gene expression by reactive oxygen and reactive nitrogen intermediates. *J Leukocyte Biol* 59:421–425,
52. Parra T, de Arriba G, Conejo G, Conejo JR, Cantero M, Arribas I, Rodriguez-Puyol D, Rodriguez-Puyol M, Carballo F: Cyclosporin increases local glomerular synthesis of reactive oxygen species in rats:effect of vitamin E. *Transplantation* 66: 1325–1329, 1998.
53. Raschke P, Massoudy P, Becker BF: Taurine protects the heart from neutrophil induced reperfusion injury. *Free Radical Biol Med* 19.461–457, 1995.
54. Cotgreave IA: N-acetylcysteine: pharmacological considerations and experimental and clinical applications. *Adv Pharmacology* 38:205–227, 1997.
55. Mannhardt W, Putzer M, Zepp F, Schulte-Wissermann H: Host defense within the urinary tract. II: Signal transducing events activate the uroepithelial defense. *Pediatr Nephrol* 10:573–577,1996.
56. Di Gianni P, Minnucci FS, Alves Rosa MF, Vulcano M, Isturiz MA: Antioxidants inhibit the enhancement of the immune response caused by oil adjuvants. *Scand J Immunol* 43:413–420, 1996.
57. Gomez del Arco P, Martinez-Martinez S, Calvo V, Armesilia AL, Redondo J: JNK is a target for antioxidants in T lymphocytes. *J BiolChem* 271;26335–40, 1996.
58. De La Fuente M, Ferrandez MD, Del Rio M, Sol Burgos M, Miguel J: Enhancement of leukocyte functions in aged mice supplemented with the antioxidant thioproline. *Mech Age Development* 104:213–25,1998.
59. Blackwell TS, Blackwell TR, Holden EP, Christman BW, Christman JW: In vivo antioxidant treatment suppresses NF-kB activation and neutrophilic lung inflammation. *J Immunol* 157:1630–1637, 1996.
60. Springer TA: Traffic signals on endothelium for lymphocyte recirculation and leukocyte emigration. *Ann Rev Physiol* 57:827–72,1995.
61. Ferran C, Millan MT, Csizmadia V, Cooper JT, Brostjan C, Bach FH, Winkler H: Inhibition of NF-kB by pyrrolidine dithiocarbamate blocks endothelial cell activation. *Biochem Biophys Res Comm* 214:212–223,1995.
62. Khachigian LM, Collins T, Fries JWU: N-acetylcysteine blocks mesangial VCAM-1 and NF-kB expression. *Am J Path* 151:1225–1230, 1997.
63. Gerritsen ME, Carley WW, Ranges GE, Shen CP, Phan SA, Ligand GF, Perry CA: Flavanoids inhibit cytokine induced endothelial cell adhesion protein gene expression. *Amer J Pathol* 147:278–292, 1995.
64. Seljeflot I, Arensen H, Brude IR, Nenseter MS, Drevan CA, Hjermann I: Effect of ω-3 fatty acids and/or antioxidants on endothelial cell markers. *Eur J Clin Invest* 28:629–635, 1998.
65. Cominocini L, Garbin U, Pasini AF, Davioli A: Antioxidants inhibit the expression of ICAM-1 and VCAM-1 induced by oxidised LDL on human umbilical vein cells. *Free Rad Biol Med* 22:117–127, 1997.
66. Holt S, Goodier D, Marley R, Patel D, Burroughs A, Fernando E, Harry D, Moore K: Improvement in renal function in hepato-renal syndrome with N-acetylcysteine. *Lancet* 353:294–5, 1999.
67. Miller DD, Edwards A: Food antioxidants vol 4, pp 43-54 in Encyclopaedia of Human Biology Ed R Dulbecco. Academic Press 1997.
68. Zeng L-H, Fung K-P, Wu T-W: Morin hydrate protects cultured rat glomerular mesangial cells against oxyradical damage. *Life Science* 55:351–357, 1994.
69. Veroart L, Ronden JE, Thijssen H: The potent antioxidant activity of the vitamin K cycle in microsomal lipid peroxidation. *Biochem Pharmacol* 54:871–876, 1997.
70. Potter SM: Soy protein and cardiovascular disease. *Nutrition Reviews* 56:231–235, 1998.
71. Wardle EN: Soyprotein diet therapy in renal disease. Nephron 78:328–331, 1998.
72. Wei H, Bowden R, Cai O, Barnes S, Wang Y:.Antioxidant and antipromotional effects of the soybean isoflavone genistein. *Proc Soc Exp Biol Med* 208:124–130, 1995.
73. Mitchell SH,Gardner PT, McPhail DE, Morrice PC, Collins AR, Duthie GG: Antioxidant efficacy of phytoestrogens in chemical and biological model systems. *Arch Biochem Biophys* 360:142–148, 1998.

74. Tham DM, Gardner CD, Haskell WL: Potential health benefits of dietary phytoestrogens. *J Clin End Metab* 83:2223–2234, 1998.
75. Wiseman H, Plitzanopoulos P, O'Reilly J: Antioxidant properties of ethanolic and aqueous extracts of green tea compared to black tea. *Biochem Soc Trans* 24:390S, 1996.
76. Sanbongi C, Suzuki N, Sakana T: Polyphenols in chocolate,which has antioxidant activity, modulate immune function in human in vitro. *Cell Immunology* 177:129– 136, 1997.
77. Petroni A: Inhibition of platelet aggregation and eicosanoid production by phenolic components of olive oil. *Thrombos Res* 78:151–160, 1995.
78. de la Puerta R, Gutierrez VR, Hoults SHS: Inhibition of leukocyte 5-lipoxygenase by phenolics from virgin olive oil. *Biochem Pharmacol* 57:445–449, 1999.
79. Simopoulos AP, Norman HA, Gillaspy SE: Purslane in human nutrition and its potential for world agriculture. Plants in Human Nutrition. (Ed) AP Simopoulos *World Rev Nutr Diet* 77:47-74, 1995 Karger.
80. Chen SD, Wu Y-Z, Tao ZL, Chen ZM, Liu XP: Hawthorn drink and its lowering effect on blood lipid levels in humans and rats (Ed) AP Sinopoulos *World Rev Nutr Diet* 77:147–154, 1995 Karger.
81. Roback J, Gryglewski RJ: Bioactivity of Flavanoids. *Polish J Pharmacol* 48:555–564, 1996.
82. Chen ZY: Antioxidant activity of natural flavanoids is goverened by number and location of their aromatic hydroxy-groups. *Chem Phys Lipids* 79:157–163, 1996.
83. Greenspan HC, Aruoma OI: Oxidative stress and apoptosis in HIV infection. *Immunology Today* 15:209–13, 1994.
84. Vinson SA: Flavanoids in foods as in vitro and in vivo antioxidants. *Adv Exp Med Biol* 439:151–164, 1998.
85. Velussi M, Cernigoi AM, DeMonte A, Dapas F, Caffau C, Zilli M: Long term treatment with antioxidant drug silymarin in cirrhotic diabetic patients J Hepatology 26:871–879, 1997.
86. Chaurasia S: Antioxidant and antiinflammatory action of Sandhika: a compound herbal drug. *Indian J Exp Biol* 33:428–436, 1995.
87. Sundaram V, Hanna AN, Lubow CP, Koneru L, Falko JM, Sharma HM: Inhibition of LDL oxidation by oral herbal mixtures in hyperlipidemic patients. *Amer J Med Sci* 314:303–10, 1997.
88. Agarwal S, Rao AV: Tomato lycopene and LDL oxidation: a human dietary intervention study. *Lipids* 33:981–984, 1998.
89. Rao AV, Agarwal S: Bioavailability and in vivo antioxidant properties of lycopene from tomato products and their possible role in the prevention of cancer. *Nutrition & Cancer* 31:199–203, 1998.
90. Cao G, Russell RM, Lischner N, Prior RL: Serum antioxidant capacity is increased by consumption of strawberries, spinach, red wine or vitamin C in elderly women. *J Nutrition* 128:2383–2390, 1998.
91. Xu YX, Pindolia KR, Janakiraman N, Noth CJ, Chapman RA, Gautam SC: Curcumin,a compound with antiinflammatory and antioxidant properties downregulates chemokine expression in bone marrow stromal cells. *Exp Haematol* 25:413–422, 1997.
92. Beukleman CJ, van den Berg AJ, Kroes BH, Labadie RP, Mattson EE, van Dijk H: Plant derived metabolites with synergistic antioxidant activity. *Immunology Today* 16:108, 1995.
93. Trachtman H, Del Pizzo R, Futterweit S, Levine D, Rao PS, Valderrama E, Sturm JA: Taurine attenuates renal disease in chronic puromycin aminonucleoside nephropathy. *Am J Physiol* 262:117–123, 1992.
94. Denis M: Antioxidant therapy partially blocks immune induced lung fibrosis. *Inflammation* 19:207–219, 1995.
95. Schlotte V, Sevanian A, Hochstein P, Weithmann KV: Effect of uric acid and chemical analogues on oxidation of human LDL *in vitro*. *Free Rad Biol Med* 25:839–847, 1998.
96. Sanaka T, Nakano Y, Nishimura H, Shinobe M, Higuchi C, Omata M, Nihei H, Sugino H: Therapeutic effect of a newly developed antioxidative agent OPC-15161 on experimental immune complex nephritis. *Nephron* 76:315–322, 1997.
97. Toffer M, Mohsen M, Samuni AA: Superoxide dismutase mimicry underlies the role of nitroxides in protecting papain from oxidative inactivation. *Free Rad Biol Med* 25:832–838, 1998.
98. van der Zee J, Eling TE, Mason RP: Formation of free radical metabolites in the reaction between soybean lipoxygenase and its inhibitors. *Biochemistry* 28:8363–8367, 1989.
99. Garvin PJ, Niehoff ML, Robinson SM, Mistry P: Renoprotective effects of the 21 aminosteroid U74389G in ischemia-reperfusion injury and cold storage preservation. *Transplant* 63:194–201, 1997.
100. Remmers D, Dwenger A, Grotz M, Seekamp A, Pap HC, Gruner A, Hafemann R, Regel G: Attenuation of multiple organ dysfunction in a chronic sheep model by 21 aminosteroid U74389 G. *J Surg Res* 62:278–283, 1996.
101. Batna A, Fuchs C, Spiteller C: Lipid peroxides in presence of ebselen. *Chem Phys Lipids* 87:149–158, 1997.
102. Lubec B, Aufricht C, Amman G, Kitzmuller E, Hoger H: Arginine reduces kidney collagen accumulation,

crosslinking lipid peroxidation, glycoxidation, kidney weight and albuminuria in the diabetic kk mouse. *Nephron* 75:213–218, 1997.
103. Novelli GP, Casali R, Bonizzoli M, Giorgi L, Lemma M, Piscitelli P: Antioxidative action of gabexate mesilate in an experimental model of endotoxin shock. *Minerva Anaesthesiol* 61:509–513, 1995.
104. Reibnegger G, Oettl K, Dlikalov S, Freisleben HJ, Mickusch W: Spin trapping study of antioxidant properties of neopterin 7,8 dihydroneopterin. Biochim *Biophys Res Comm* 234:774–778, 1997.
105. Thresiamma KC, Kuttan R: Inhibition of liver fibrosis by ellagic acid. *Indian J Physiol Pharmacol* 40:363–366. 1996.
106. Magil A: Inhibition of progression of chronic puromycin aminonucleoside nephrosis by probucol. *JAS Nephrol* 7:2340–2347,1996.
107. Keaney JF, Xu A, Cunningham D, Jackson T, Frei B, Vita JA: Dietary Probucol preserves endothelial cell function in cholesterol fed rabbits limiting vascular oxidative stress and superoxide generation. *J Clin Invest* 95:2520–2529, 1995.
108. Naito H, Hirano T: Probucol suppresses development of chronic renal failure in Dahl salt sensitive rat: an animal model of spontaneous focal and segmental glomerulosclerosis. *Nephron* 67:125–126, 1994.
109. Hanna AN, Feller DR, Witiak DT, Newman H: Inhibition of LDL oxidation by thyronines and probucol. *Bioch.Pharmacol* 45:753–762, 1993.
110. Igawa K ,Maruyama R, Katayama IM, Nishioka K: Antioxidation therapy with oral dapsone improved annular elastolytic giant cell granuloma. *J Dermatol* 24:328–331, 1997.
111. Hoffbrand BI: Dapsone treatment for Henoch-Schönlein purpura. *Postgrad Med J (UK)* 67:961–962, 1991.
112. Campbell RK: Clinical update on pentoxifylline therapy for diabetes induced peripheral vascular disease. *Ann Pharmacol* 27:1099–1105, 1993.
113. Mandy Y, Farkas G, Ocsovszky I, Nagy Z: Inhibition of TNFa production and ICAM-1 expression by pentoxifylline: beneficial effects in sepsis syndrome. *Res Exptl Med* 195:297–307, 1995.
114. Wardle EN: Can pentoxifylline prevent renal disease? *Renal Failure* 20:437–440, 1998.
115. Iuliano L, Colavita AR, Camastra C, Bello V: Protection of lDL oxidation at chemical and cellular level by the antioxidant drug dipyridamole. *Brit J Pharmacol* 119:1438–1446, 1996.
116. Wardle EN: Dipyridamole in the nephritides. *Am J Therap* 5:107–109, 1998.
117. Grant D, Long WF, Mackintosh G, Williamson FB: The antioxidant activity of heparins. *Biochem Soc Trans* 24:194S, 1996.
118. Wardle E N Heparins for proliferative nephritides Nephron 73, 515–19, 1996.
119. Aruoma 0I, Smith C, Cecchini R, Evans PJ, Halliwell B: Free radical scavenging and inhibition of lipid peroxidation by beta-blockers and by agents that interfere with calcium metabolism. *Biochem Pharmacol* 42:735–743, 1991.
120. Dupont AG: Carvedilol and the kidney. *Clinical Investigation* 70:S127–S131, 1992.
121. Yue T-L, Cheng H-Y, Lysko PG, McKenna PJ, Feuerstein R, Gu J-L, Lysko K: Carvedilol, a new vasodilator and adrenoreceptor antagonist is an antioxidant and free radical scavneger. *J Pharm Exp Therap* 263:92–98, 1992.
122. Kramsch DM, Sharma RC: The benefits amlodipine as an anti-atherosclerotic agent. *J Human Hypertension* 9(suppl 1):S3–S9, 1995.
123. Sugawara H, Tobise K, Kikuchi K: Antioxidant effects of calcium antagonists on rat myocardial membrane lipid peroxidation. *Hypertension Res* 19:223–228, 1996.
124. Mak IT, Boehme P, Weglicki WB: Protective effects of calcium channel blockers against free radical impaired endothelial cell proliferation. *Biochem Pharmacol* 50:1531–1534, 1995.
125. Karmansky I, Gruener NA: Mechanisms of antioxidant activity of calcium antagonist verapamil against LDL oxidation. *Clin Chem Acta* 259:177–182, 1997.
126. Chaffman M: Indapamide. *Drugs* 28:189–235 1984.
127. Aruoma OI: Characterization of drugs as antioxidant prophylactics. *Free Rad Biol Med* 20: 675–705. 1996.
128. Barnes S, Sfakianos J, Coward L, Kirk M: Soy isoflavanoids and cancer prevention: underlying biochemical and pharmacological issues. *Adv Exp Med Biol* 401:87–100, 1996.
129. Anderson JW, Diwadkar VA, Bridges SR: Selective effects of different antioxidants on oxidation of lipoproteins from rats. *Proc Soc Exp Biol Med* 218:376–381, 1998.
130. Sanbongi C, Suzuki N, Sakane T: Polyphenols in chocolate, which have antioxidant activity, modulate immune functions in humans in vitro. *Cellular Immunol* 177:129–136, 1997.
131. Kumar A, Dhawan S, Hardegan NJ, Aggarwal BB: Curcumin inhibition of TNF mediated adhesion of monocytes to endothelial cells by suppression of cell surface expression of adhesion molecules and NF-kB activation. *Biochem Pharmacol* 55:775–783, 1998.

132. Morrissey JJ, Klahr S: Enalapril decreases nuclear factor kappa-B activation in the kidney with ureteral obstruction. *Kidney Int* 52:926–933, 1997
133. Mak IT, Arroya CM, Weglicki WB: Inhibition of sarcolemmal carbon centred free radical formation by propanalol. *Circ Res* 65:1151–1156, 1989.
134. Cabell KS, La L, Johnson P: Effects of antihypertensive drugs on rat tissue antioxidant enzyme activities and lipid peroxidation levels. *Biochem Pharmacol* 54:133–141, 1997.
135. Tarif N, Bakris G L: Preservation of renal function: the spectrum of effects by calcium channel blockers. *Nephrol Dial Transplant* 12:2244–2250, 1997.
136. Feuerstein GZ, Ruffolo RR. Carvedilol, a novel multiple action antihypertensive agent with antioxidant activity and the potential for myocardial and vascular protection. *Eur Hrt J*.16, sup F, 38–42, 1995.
137. Frishman W: Carvedilol. *New Engl J Med* 339:1759–1765, 1998.
138. van den Branden C, Gabriels M, Vamecq J, Vanden Houte J, Verbeelen D: Carvedilol protects against glomerulosclerosis in rat remnant kidney without changes in antioxidant status. *Nephron* 77:319–324, 1997.
139. Molyneux I.M, Willey K.A, Yue DK: Indapamide is as effective as captopril in the control of microalbuminuria in diabetes . *J Cardiovasc Pharmacol* 27:424–427, 1996
140. Uehara Y, Kawabata Y, Shirahase H, Wada K, Hashizume Y, Morishita S, Numabe A, Iwai J: Oxygen radical scavengers and renal protection by indapamide diuretic in salt induced hypertension of Dahl strain rats. *J Cardiovasc Pharmacol* 22, suppl 6: S42–S46, 1993.
141. Numberg W, Grabbe J, Czarnetski E: Synergistic effects of pentoxifylline and dapsone in leucocytoclastic vasculitis. *Lancet* 343,:491, 1994.
142. Castellot JJ, Karnovsky MJ, Wright TC: Effect of heparin on cellular proliferation Semin Thromb.Haemostas 13:489–502, 1987.
143. Roccatello D, Mengozzi G, Ferro M, Cesano G: Isosorbide 5 mononitrate increases nitric oxide blood levels and reduces proteinuria in IgA glomerulonephritis patients with abnormal urine endothelin e GMP ratio. *Clin Nephrology* 44:103–108, 1995.
144. Trachtman H, Futterweit S, Singjal PC: Nitric oxide modulates synthesis of extracellular matrix proteins in cultured rat mesangial cells. *Biochem Biophys Res Commun* 207:120–125, 1995.
145. Prior RL, Cao G: Antioxidant capacity and polyphenolic components of teas: implications for altering in vivo antioxidant status. *Proc Soc Exp Biol Med* 220:255–261, 1999