*Status Paper*

# Green tea polyphenols against renal disorders

**Theertham P. Rao[1], Lekh Raj Juneja[1],Tsutomu Okubo[1], Djong-Chi Chu[1], and Takako Yokozawa[2]**

**ABSTRACT**

Green tea, exclusively rich in powerful antioxidant and active free radical scavenger polyphenols, is known for various therapeutic and prophylactic uses. The pharmacological functions of green tea polyphenols against chronic renal failure and related complications were examined in rat models and humans. The polyphenols were found effective in easing the pains concerned with renal failure. The application of polyphenols were improved the renal function by inhibiting the mesangial cells proliferation. The polyphenols have relieved the high oxidation stress condition and renal hypertension by inhibiting the production of oxidative uremic toxins and improving the renal blood circulating state, respectively. The antioxidant activities of green tea polyphenols against free radicals that are involved in the above complications have established the activity of green tea in regulating renal function.

**Keywords :** antioxidant, glomerular function, glomerular sclerosis, green tea polyphenols renal hypertension, uremia

## Introduction

The kidneys are indispensable organs for the excretion of waste metabolites such as urea and toxins from the body. Functional disorders of the organ may lead to the accumulation of these toxins leading to a state of renal failure. Once the renal failure becomes chronic, the process is irreversible and progressive, eventually leading to the cessation of renal function.

Glomerulonephritis and diabetic nephropathy are recognized as the main functional disorders underlying in the development of renal failure. Histological studies have characterized these disorders with deteriorated glomerular filtration by excessive proliferation of mesangial cells. The succession of renal failure is then associated with the accumulation of highly oxidative uremic toxins. Hence, the symptoms of uremia, high oxidative stress conditions are a common phenomenon in the renal failure patients (Fillet et al 1981; Flament et al. 1986; Giardini et al. 1984; Kuroda et al. 1985).

1. Nutritional Foods Division, Taiyo Kagaku Co., Ltd. Yokkaichi, Mie 510 0844 Japan,
2. Institute of Natural Medicine, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-0194, Japan.

The uremic toxins are mainly produced by the involvement of hydroxyl radicals (Ienaga et al. 1991; Nakamura et al. 1991; Yokozawa et al. 1991a,b, 1992, 1997a, b). It is, therefore, suggested that the treatment with scavengers of hydroxyl radical, superoxide anion and hydrogen peroxide may ease the oxidative stress conditions in renal failure patients (Diamond et al. 1986; Rehan et al. 1984; Shah and Walker 1988; Yokozawa et al. 1993b).

Lately, green tea polyphenols are emerging as a powerful antioxidant and active scavenger of free radicals (Chen and Ho 1995; Chu and Juneja 1998; Koketsu 1997; Hara 2001; Nakagawa et al 2002; Serafini et al 1996; Xie et al 1993), have been effective in the prevention of various diseases like cancer, cardiovascular diseases and arthritis, the diseases which are involved with free radical component (Ames 1983). Our laboratory in collaboration with Dr. Yokozawa group (Toyama Medical and Pharmaceutical University, Toyama, Japan) has exclusively examined the physiological functions of green tea polyphenols on renal failure using animal models and human**s**. A refined form of green tea polyphenols 'Sunphenon®' (Taiyo Kagaku Co., Ltd, Japan) was used in all our studies. In this paper, we have summarized all

our studies in the form of a review on its effects improving various complications related to the renal failure, such as glomerulonephritis, uremia oxidative stress, renal hypertension, glomerular hypertrophy and glomerular sclerosis.

**Inhibitory effect on proliferation of mesangial cells**

Nearly 70 to 80% of chronic renal failure patients have the background of either glomerulonephritis or diabetic nephropathy disorders. These disorders, which are associated with deteriorated glomerular filtration, are characterized histologically by excessive proliferation of mesangial cells. Grond et al (1985) suggested that mesangial cells affect the hemodynamics of glomerular capillaries via vascular contraction and relaxation thereby regulates the glomerular filteration. Apparently it suggests that the proliferation of mesangial cells may interfere with the function of glomerular filtration (Kashgarian and Sterzel 1992).

Yokozawa et al (1993a) have examined the effect of green tea polyphenols using Sunphenon® on the proliferation of mesangial cells. They determined the proliferation in terms of [$^3$H]thymidine uptake in cultured mouse mesangial cells. Mesangial cells were isolated from mouse renal glomeruli and cultured in D-valine (D-Val MEM) containing 20% fetel calf serum (FCS) for ten days. For the measurement of [$^3$H]thymidine uptake the cultured mesangial cells were seeded in a 96-well microtiter plate at a density of $10^4$ cells/well in 0.2 ml D-Val MEM containing 20% FCS and incubated for 48 hours with or without Sunphenon® (6.25 to 200 mg ml$^{-1}$). Twelve hours prior to the end of incubation period, the cultures were pulsed with 1 m Ci of [$^3$H]thymidine. At the end of incubation period, the cells were harvested and the radioactivity was measured. Simultaneously the effect of individual catechins; EGCg and ECg on mesangial cell proliferation was also examined in similar method.

A concentration depended decrease in the uptake of [$^3$H] thymidine was observed with polyphenols in mesangial cells (Fig. 1). A dose of 25 mg ml$^{-1}$ of polyphenols, either as Sunphenon® or EGCg or ECg, has completely inhibited the uptake. The EGCg exerted inhibitory effects even at relatively low concentrations. Since EGCg is the strongest antioxidant of all the green tea polyphenols, the inhibitory effects could be attributed to this major component present in Sunphenon®. These results suggest that green tea polyphenols inhibit the proliferation of mesangial cells and could improve the function of glomerular filtration. This was noticed when an oral administration of ECg induced an increase in the glomerular filtration in rats (Oura and Yokozawa 1990).

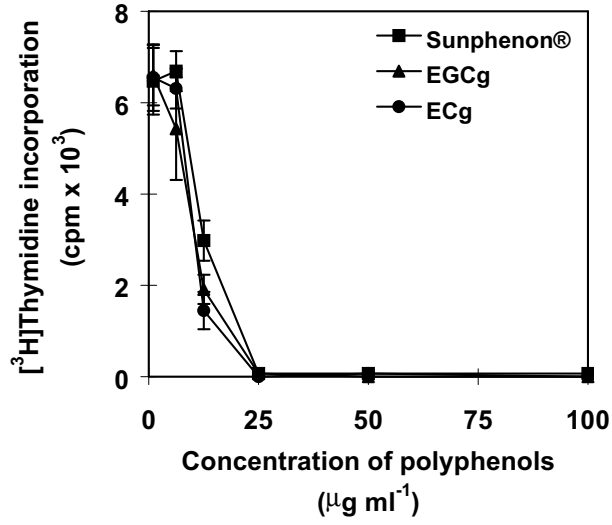


**Fig. 1.** Effect of green tea polyphenols and individual polyphenol on the proliferation of mesangial cells (Yokozawa et al. 1993a).

**Inhibition of uremia**

At the onset of chronic renal failure the concentration of uremic toxins increases leading to the state of uremia, a high oxidation stress condition (Sakanaka and Kim 1997; Giovannetti et al. 1973). The toxins currently known include methylguanidine, guanidinosuccinic acid, dimethylamine, myoinositol and $\beta_2$-microglobulin. Amongst all these toxins, methylguanidine has been pertinent toxin to induce the uremia condition (Giovannetti et al. 1968). Examination of urine specimens from the chronic renal failure patients revealed that methylguanidine is produced from

creatinine via creatol (5-hydroxycreatinine) by the hydroxyl radical (Ienaga et al. 1991; Nakamura et al. 1991; Yokozawa et al. 1991a,b). Green tea polyphenols known for its active free radical scavenging activity have inhibited the production of methylguanidine and thus alleviated the renal failure both in animals (Sakanaka and Kim 1997; Yokozawa et al. 1992, 1994, 1996a, 1997a,b) and in humans (Sakanaka and Kim 1997; Yokozawa et al. 1996b).

In rats, Yokozawa et al (1992, 1993b) examined the effect of green tea polyphenols on adenine-induced renal failure. They examined the urinary methylguanidine excretion as an index of scavenging reaction. The rats were administered with different doses of green tea polyphenols (as Sunphenon®) or only the EGCg orally for 14 days after the adenine administration for 20 days. A dose depended decrease in methylguanidine excretion was observed (Fig. 2), where a dose of 0.5 mg $day^{-1}$ of green tea polyphenol or the EGCg did not show any appreciable inhibition in the production of methylguanidine. However, a slight increase in the dose to 1.0 or 2.0 mg $day^{-1}$ strongly inhibited the production of methylguanidine. The methylguanidine production was about 40% lower

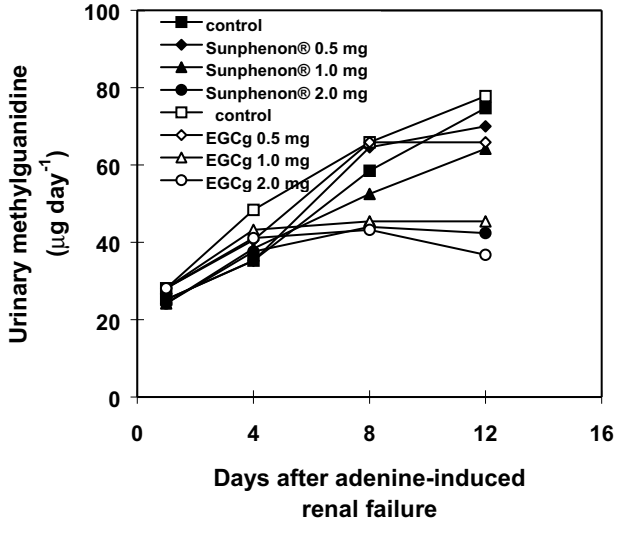


**Fig. 2.** Effect of different doses of green tea polyphenols (Sunphenon®) (closed symbols) or EGCg (open symbols) on the urinary methylguanidine excretion in adenine-induced renal failure rats (Yokozawa et al. 1992).

compared to control with the administration of 2 mg green tea extract at 12 days (32nd day) after adenine-induced renal failure. While a similar decrease (40%) or much further inhibition (about 50%) was noticed with the administration of exclusively EGCg at the rate of 1.0 and 2.0 mg $day^{-1}$, respectively. These results suggested that EGCg, the powerful antioxidant component of green tea polyphenols, has strong inhibitory effect on methylguanidine production and thereby may induce the recovery from oxidative stress.

The clinical efficacy of green tea polyphenols in suppression of creatinine and methygluanidine production was observed in 50 dialysis patients (Yokozawa et al. 1996b). The patients were administered twice a day 200 mg green tea polyphenols in the form of either jelly or capsules consecutively for six months. The blood samples were collected just before dialysis of each month and analysed for the contents of creatinine and methylguanidine. The creatinine level was significantly lowered after three months of administration, showing almost 8% decrease in 5-6 months (Table 1). A decrease in methylguanidine preceded the decrease of creatinine, reaching a significantly low level within a month. In 5 months the level of methylguanidine was 20% lower than the initial level. These results suggested that green tea polyphenols influenced the radicals involved in the production of methylguanidine from creatinine, which was clearly evident in the ratio of methylguanidine/ creatinine. Concurrently a significant decrease in $\beta_2$-microglobulin was also observed within 1 month of green tea administration in the patients with high oxidative stress (Table 1). Aggressive removal of $\beta_2$-microglobulin is desirable to prevent the complications of prolonged dialysis including the amyloidosis. It was noteworthy that the administration of green tea polyphenols has relieved 35 to 100% of the pain in shoulder, knee, hips, cubitus, coxa and fingers of dialysis patients (Table 2). These results suggest that the green tea polyphenols are very effective in the suppression of the oxidative stress and the post dialysis arthralgia in dialysis patients.

**Table 1. Changes in creatinine (Cr), methylguanidine (MG), MG/Cr ratio and $\beta_2$-microglobulin in serum during the application of green tea polyphenol (Sunphenon®) in dialysis patients (Yokozawa et al. 1996b)**

| Duration of treatment month | Creatinine (Cr) mg $dl^{-1}$ | Methylguanidine (MG) mg $dl^{-1}$ | MG/Cr (x $10^{-3}$) | $\beta_2$-Microglobulin mg $L^{-1}$ |
|---|---|---|---|---|
| 0 | 13.51 | 56.43 | 4.12 | 39.0 |
| 1 | 13.33 | 53.65* | 3.99 | 35.0*** |
| 2 | 13.28 | 51.92** | 3.86* | 37.5 |
| 3 | 12.81*** | 48.66*** | 3.78** | 36.4** |
| 4 | 12.65*** | 49.42*** | 3.87* | 36.1*** |
| 5 | 12.37*** | 45.06*** | 3.62** | 35.7** |
| 6 | 12.43*** | 48.41*** | 3.85* | 35.4** |

Significantly different from the pre-treatment value: $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$.

**Table 2. Effect of green tea polyphenols (Sunphenon®) on arthralgia in dialysis patients. Values in parenthesis indicate the percentage to the total patients (Yokozawa et al. 1996b)**

| | Number of patients with althralgia | | | |
|---|---|---|---|---|
| | **Disappearance** | **Relief** | **No change** | **Total** |
| Shoulder | 5 (31) | 1(6) | 10 (63) | 16 |
| Knee | 4 (31) | 1(8) | 8 (62) | 13 |
| Finger | 3 (23) | 4 (31) | 6 (46) | 13 |
| Coxa | 5 (50) | 1(10) | 4 (40) | 10 |
| Hip | 5 (83) | 1(17) | 0 (0) | 6 |
| Cubitus | 1(100) | 0 (0) | 0 (0) | 1 |

## Inhibition of renal hypertension

Besides relieving the oxidative stress and improving the glomerular filtration during the renal failure, the green tea polyphenols also found to be effective in controlling the renal hypertension by manipulating the blood pressure in kidneys. The kinin-kallikrein system seems to be involved in the mechanism of blood pressure regulation by its mutual action with other vasoactive systems such as the renin-angiotensin-aldosterone, sympathetic nerve vasopression, and prostaglandin systems and by its direct action on cardiovascular system and the mechanism for water and sodium (Abe 1981; Abe et al. 1978; Levinsky 1979). Decreased production by the kinin-kallikrein system in patients with essential hypertension has been reported, suggesting its involvement in the etiology of this condition (Margolius et al. 1974; Zineer et al. 1976). On the other hand, prostaglandin $E_2$ ($PGE_2$) is thought to be involved not only with maintaining the blood flow but also with sodium metabolism, and it has been suggested to act as a modulator of the hemodynamic changes associated with hypertension (Coleman et al.1975).

Yokozawa et al (1994) examined the changes in blood pressure, kallikrein and $PGE_2$ with the administration of green tea polyphenols in adenine induced renal failure rats. After the induction of renal failure, the rats were administered green tea polyphenols (as Sunphenon®) at the rate of 2 or 4 mg $kg^{-1}$ BW for 24 consecutive days. The polyphenols were dissolved in water and given to the rats as drinking water. A 24 hour urine samples were collected and analysed for kallikrein and $PGE_2$. Simultaneously, systolic, mean and diastolic

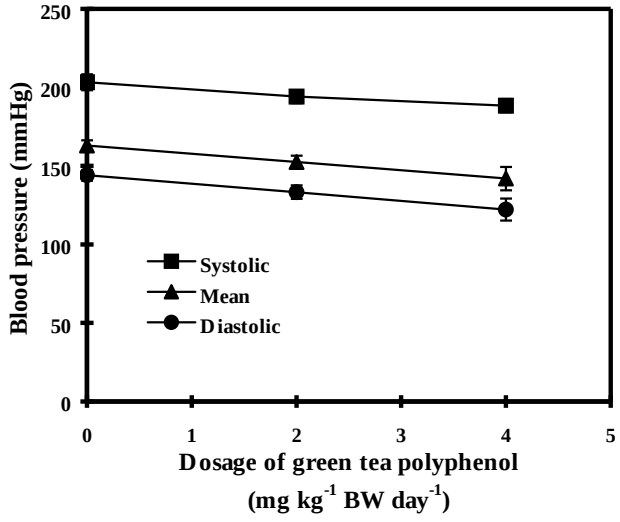


**Fig. 3.** Effect of green tea polyphenol (Sunphenon®) on systolic, mean and diastolic blood pressure in adenine-induced renal failure rats. Significantly different from the control (0 mg $kg^{-1}$ BW $day^{-1}$) value: *p<0.05.

blood pressures were determined by a tail-pulse pickup method. The administration of green tea polyphenols has significantly reduced the systolic, mean and diastolic blood pressure (Fig. 3). On the other hand, the green tea administration significantly increased the urinary kallikrein level, the excretion of $PGE_2$ and sodium (Table 3). These data suggest that green tea polyphenols may ameliorate the development of hypertension by improving the renal circulating state. Stokes and Kokko (1977) have found in a study on isolated perfused tubules that $PGE_2$ caused direct tubular inhibition of sodium reabsorption. Ruilope et al. (1982) have demonstrated the protective role of renal $PGE_2$ in the maintenance of hypertension. Thus, it appears that the antihypertensive effect of green tea polyphenols resulted from its direct action in the kidney.

**Table 3. Effect of green tea polyphenols (GTP; Sunphenon®) on the urinary excretion of $PGE_2$, kallikrein and sodium (Yokozawa et al. 1994).**

| | Dose of green tea polyphenol (mg $kg^{-1}$ BW $day^{-1}$) | | |
|---|---|---|---|
| | 0 | 2 | 4 |
| $PGE_2$ (ng $day^{-1}$) | 8.00 | 14.87*** | 20.07*** |
| Kallikrein (mU $day^{-1}$) | 14.87 | 21.44** | 31.81*** |
| Na (mM $day^{-1}$) | 1.50 | 1.72 | 1.96* |

Significantly different form control value, *$p$<0.05, **$p$<0.01 and ***$p$<0.001.

## Inhibition of renal tissue lesions

To analyse the effect of green tea polyphenol on renal tissue lesions, Yokozawa et al (1996a) examined the mesangial proliferation and glomerular sclerosis index in nephrectomized rats. An experimental model to induce non-inflammatory renal failure was established by the excision of a part of kidney. It was earlier pointed out that, following the subtotal nephrectomy, growth factors may simultaneously induce glomerular hypertrophy and mesangial proliferation, the former leading to a disorder in the glomerular basement membrane or epithelial cells resulting in protein leakage, and the latter leading to glomerular sclerosis. In the study, the urinary creatinine clearance and protein excretion and kidney cells oxidative activities were measured with the administration of 10 or 20 mg $kg^{-1}$ body weight green tea polyphenol (as Sunphenon®) for 80 consecutive days.

Nephrectomized rats receiving oral green tea polyphenol exhibited milder lesions. The decrease in creatinine clearance was also significantly reversed after administration of green tea polyphenol (Fig. 4). These results suggested that

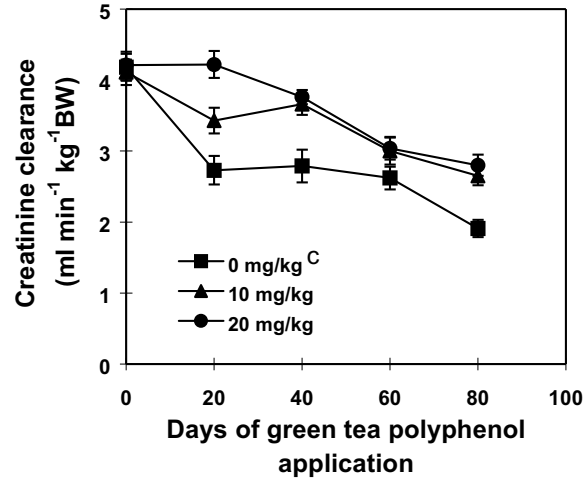


**Fig. 4.** Effect of different dosage (mg $kg^{-1}$ BW $day^{-1}$) of green tea polyphenols (Sunphenon®) on creatinine clearance in nephrectomized rats (Yokozawa et al. 1996a).

green tea polyphenols have inhibited the mesangial cell proliferation to retain the function of the glomeruli and thereby inhibiting the progression of glomerular sclerosis. The study also showed that green tea polyphenol suppressed the leakage of urinary protein (Fig. 5), suggesting that the green tea polyphenols are also delayed the progression of glomerular hypertrophy.

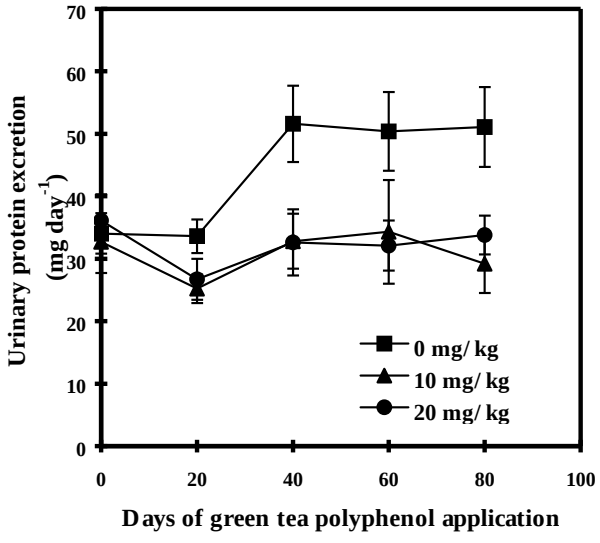


**Fig. 5.** Effect of green tea polyphenols (Sunphenon®) on urinary protein excretion in nephrectomized rats (Yokozawa et al. 1996a).

Schrier et al (1988) and Harris et al (1988) have suggested that free radicals are involved in various ways in the occurrence and progression of renal failure. The renal failure model produced by partial resection of the renal parenchyma, as used in this study, results in swelling of the remaining kidney tissue, which might cause increased oxygen consumption and enhanced ATP synthesis, where active free radicals could involve. In such scenario, the measurements of the antioxidative enzymes such as superoxide dismutase (SOD), catalase and glutathione peroxide (GSH-Px) activities, may suggest the level of free radical-scavenging activity in the system. In the current study the activities of SOD and catalase were significantly higher in the rats given green tea polyphenol after nephrectomy (Table 4). Since these rats showed

**Table 4. Effect of green tea polyphenols (GTP; Sunphenon®) on the activities of oxygen reactive species-scavenging enzymes in rats after excision of 3/4 of their kidney volume (Yokozawa et al. 1996a).**

| Active oxygen scavenging enzymes Dosage of GTP (mg kg$^{-1}$ BW day$^{-1}$) | Enzyme activity (U mg$^{-1}$ protein) | | |
|---|---|---|---|
| | 0 | 10 | 20 |
| SOD | 8.75 | 10.68$^{**}$ | 11.66$^{***}$ |
| Catalase | 142.7 | 213.2$^{***}$ | 224.4$^{***}$ |
| GSH-Px | 69.63 | 71.91 | 76.97$^{*}$ |

SOD, superoxide dimutase; GSH-Px, Glutathione eroxidase. $^{*}p<0.05$; $^{**}p<0.01$; $^{***}p<0.001$; *i.e.*, significantly different from the control value.

low activity of GSH-Px (an enzyme which presents in mitochondrial matrix and eliminates $H_2O_2$, like the enzyme catalase), it was speculated that the site of action of green tea polyphenol is the peroxisome. These results suggest that green tea polyphenols maintain the enzyme activities, which are related to free radical scavenger action, thereby inhibit the renal tissue lesions.

## Conclusions

Green tea, a simple refreshing beverage, was believed to have therapeutic uses for many centuries. Recently enormous research findings have confirmed the therapeutic functions of green tea extract in preventing wide range of diseases, in particular the diseases concerned with modern life (Weisburger and Chung 2002) like cancer (Katiyar and Mukthar 1996; Yang and Wang 1993), cardiovascular diseases (Ross 1993) and allergy (Matsuo et al. 2000). Nevertheless, the green tea extract has been noted for number of physiological functions such as antibacterial (Juneja et al. 2000), antiviral (Ebina 1991), anticariogenic (Ahn et al. 1991), antimutagenic (Nakagawa et al. 2002), antiatherogenic (Luo et al. 1997), anticarcinogenic (Katiyar and Mukthar 1996; Yang and Wang 1993; Weisburger 1997) and so on. Therefore, if listed, the functions of green tea in various disease preventions will be endless. Scientists recognized that these wide ranges of physiological functions in green tea are due to the low molecular weight

polyphenols, which are abundant especially in green tea. They also recognized that the efficacy of green tea polyphenols over others was related to its powerful antioxidant and free radical scavenging activities.

Our studies were particularly examined the effect of green tea polyphenols on renal failure; yet another functional disorder encountered by many people in modern world. We examined the effect of refined green tea polyphenols (Sunphenon®, Taiyo Kagaku Co. Ltd, Japan) on renal failure and related complications both in animal models and human. The studies showed that the application of green tea polyphenol has significant impact in the alleviation of many complications related to renal failure. Green tea polyphenols were found effective in 1) the inhibition of mesangial cells proliferation improving the glomerular function, 2) the inhibition of methylguandine production, a prominent uremic toxin causes uremia, relieving the oxidative stress in dialysis patients, 3) the regulation of blood pressure suppressing the hypertension, and 4) scavenging the free radicals preventing the renal tissue lesions and relieving the pain from renal failure complications. These studies suggested not only the therapeutic use of green tea polyphenols in renal failure but also extended its physiological functions as 'antinephropathic' activity.

## References


Abe K 1981. The kinins and prostaglandins in hypertension. Clin. Endocrinol. Metab. 10: 577-605.

Abe K, Irokawa N, Yasujima M, Seino M, Chiba S, Sakurai Y, Yoshinaga K and Saito T 1978. The kallikrein-kinin system and prostaglanduar in the kidney: this relation to forosenide-induced dieresis and to the renin-angiotensin-aldosterone. Circ. Res. 43: 254-260.

Ahn AJ, Kawamura T, Kim M, Yamamoto T and Mitsuoka T 1991. The catechins: Selective growth inhibitors of *clostridium spp.* Agric. Biol. Chem. 55: 1425-1427.

Ames BN 1983. Dietary carcinogens and anticarcinogens: oxygen radical and regeneration diseases. Science 221: 1256-1264.

Chen CW and Ho CT 1995. Antioxidant properties of polyphenols extracted from green and black teas. J. Food Lipids 2: 35-37.

Chu DC and Juneja LR 1998. Chemical and physiological functions of green tea polyphenols. Innov. Food Tech.

Coleman TG, Manning RD, Norman RA and DeClue 1975. The role of the kidneys in spontaneous hypertension. Am. Heart J. 89: 94-98.

Diamond JR, Bonventre JV and Karnovsky MJ 1986. A role for oxygen free radicals in aminonucleoside nephrosis. Kidney Int. 29: 478-483.

Ebina T 1991. Infantile gastroenteritis: prevention and treatment of rotavirus diarrhea. J. Anibact. Antifung. Agents. 19: 349-351.

Fillit H, Elion E, Sullivan J, Sherman R and Zabriskie JB 1981. Thiobarbituric acid reactive material in uremic blood. Nephron 29: 40-43.

Flament J, Goldman M, Waterlot Y, Dupont E, Wybran J and Vanherwegem JL 1986. Impairment of phagocyte oxidative metabolism in hemodialyzed patients with iron overload. Clin. Nephrol. 25: 227-230.

Giardini O, Gallucci MT, Lubrano R, Tenore GR, Bandino D, Silvi I, Ruberto U and Casciani CI 1984. Evidence of red blood cell membrane lipid peroxidation in haemodialysis patients. Nephron 36: 235-237.

Giovannetti B, Cioni L, Balestri PL and Biagini M 1968. Evidence that guanidines and some related compounds cause haemolysis in chronic uremia. Clin. Sci. 34: 141-148.

Giovannetti S, Balestri PL and Barsotti 1973. Methylguanidine in uremia. Arch. Intern. Med. 131: 709-713.

Grond J, Koudstaal J and Elema JD 1985. Mesangial function and glomerular sclerosis in rats with aminonucleoside nephrosis. Kidney Int. 27: 405-410.

Hara Y 2001. Antioxidative action of tea polyphenols. *In* Green tea: health benefits and applications, O.R. Fennema, M. Karel, G.W. Sanderson, P. Walstra and J.R. Whitaker (Eds), Marcel Dekker Inc. New York, pp: 26-47.

Harris DCH, Chan L and Schrier RW 1988. Remnant kidney hyper metabolism and progression of chronic renal failure. Am. J. Physiol. 254: F267-F276.

Ienaga K, Nakamura K, Yamakawa M, Toyomaki Y, Matuura H, Yokozawa T, Oura H and Nakano K 1991. The use of $^{13}$C-labelling to prove that creatinine is oxidized by mammal into creatol and 5-hydroxyl-1-methylhydantoin. J. Chem. Soc. Chem. Commun. 509-510.

Juneja LR, Okubo T and Hung P 2000. Catechins. *In* Natural Food Antimicrobial Systems, A.S. Naidu (Ed.), CRC Press, New York. pp. 381-398.

Kashgarian M and Sterzel RB 1992. The pathobiology of the mesangium, Kidney Int. 41: 524-529.

Katiyar S and Mukthar H 1996. Tea in chemoprevention of cancer: epidemiological and experimental studies (review). Int J Onc 8:221-238.

Koketsu M 1997. Antioxidant activity of tea polyphenols. *In* Chemistry and applications of green tea. Yamamoto T, Juneja LR, Chu DC and Kim (Eds.). CRS Press, New York. pp. 37-50.

Kuroda M, Asaka B, Tofuku Y and Takeda R 1985. Serum antioxidant activity in uremic patients. Nephron 41: 293-298.

Levinsky NG 1979. The renal kallikrein-kinin system. Circ. Res. 44: 441-451.

Luo M, Kannan K, Wahlqvist ML and O'Brein RC 1997. Inhibition of LDL oxidation by green tea extract. Lancet 349: 360-361.

Margolius HS, Horwitz D, Pisano JJ, and Keiser HR 1974. Urinary kallikrein excretion in normal men. Relationships to sodium intake and sodium-retaining steroids. Cir. Res. 35: 820-825.

Matsuo N, Yamada K, Mori M, Shoji K, Ueyama T, Yunoki S, Yamashita K, Ozeki M and Sugano M 2000. Inhibition by dietary tea polyphenols of chemical mediator release from rat peritoneal exudates cells. Biosci. Biotech. Biochem. 64: 1437-1443.

Nakagawa T, Yokozawa T, Terasawa K, Shu S and Juneja LR 2002. Protective activity of green tea against free radical- and glucose-mediated protein damage. J. Agric. Food Chem. 50: 2418-2422.

Nakamura K, Ienaga K, Yokozawa T, Fujitsuka N and Oura H 1991. Production of methylguanidine from creatinine via creatol by active oxygen species: analyses of the catabolism in vitro. Nephron 58: 42-46.

Oura H and Yokozawa T 1990. Pharmacological action of tannins. J. Trad. Sino-Jpn. Med. 11: 67-74.

Rehan A, Johnson KJ, Wiggins RC, Kunkei RG and Ward PA 1984. Evidence for the role of oxygen radicals in acute nephrotoxic nephritis. Lab. Invest. 51: 396-403.

Ross R 1993. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 362: 801-809.

Ruilope L, Robles RG, Bernis C, BarrientosA, Alcazar J, Tresguerres JAF, Sancho J and Rodicio JL 1982. Role of renal prostaglandin $E_2$ in chronic renal disease hypertension. Nephron 32: 202-206.

Sakanaka S and Kim M 1997. Supressive effect of uremic toxin formation by tea polyphenols. *In* Chemistry and applications of green tea. Yamamoto T, Juneja LR, Chu DC and Kim (Eds.). CRS Press, New York. pp. 75-86.

Schrier RW, Harris DCH, Chan J, Shapiro JI and Caramelpo C 1988.Tubular hyper metabolism as a factor in the progression of chronic renal failure. Am. J. Kidney Disease 12: 243-249.

Serafini M, Ghiselli A and Ferro-Luzzi A 1996. In vivo antioxidant effect of green and black tea in man. Euro. J. Clin. Nutri. 50: 28-32.

Shah SV and Walker PD 1988. Evidence suggesting a role for hydroxyl radical in glycerol-induced acute renal failure. Am. J. Physiol. 255: F438-F443.

Stokes JB and Kokko JP 1977. Inhibition of sodium transport by prostaglandin $E_2$ across the isolated perfused rabbit collecting tubule. J. Clin. Invest. 59: 1099-1104.

Weisburger JH 1997. Tea and health: a historical perspective. Cancer lett. 114: 315-317.

Weisburger JH and Chung FL 2002. Mechanisms of chronic disease causation by nutritional factors and tobacco products and prevention by tea polyphenols. Food Chem Toxicol 40: 1145-1154.

Xie B, Shi H, Chen Q and Ho CT 1993. Antioxidant properties of fractions and polyphenol constituents from green, oolong and black teas. Proc. Nat. Sci. Council 17: 77-84.

Yang CS and Wang ZY 1993. Tea and cancer (review). J Nat Cancer Inst 85: 1038-1049.

Yokozawa T, Chung HY, He LQ and Oura H 1996a. Effectiveness of green tea tannin on rats with chronic renal failure. Biosci. Biotech. Biochem. 60: 1000-1005.

Yokozawa T, Dong E and Oura H 1997a. Proof that green tea tannin suppresses the increase in the blood methylguanidine level associated with renal failure. Exp. Toxicol. Pathol. 49: 117-122.

Yokozawa T, Fujitsuka N and Oura H 1991a. Contribution of hydroxyl radical to the production of methyguanidine from creatinine. Nephron 59: 662-663.

Yokozawa T, Fujituka N, Oura H, Ienaga K and Nakamura K 1991b. Comparison of methylguanidine production from creatinine and creatol *in vivo*. Nephron 58: 125-126.

Yokozawa T, Oura H, Hattori M, Iwano M, Dohi K, Sakanaka S and Kim M 1993a. Inhibitory effect of tannin in green tea on the proliferation of mesangial cells. Nephron 65: 596-600.

Yokozawa T, Oura H, Ienaga K and Nakamura K 1993b. Comparison of renal effects of creatinine, creatol and methylguanidine in rats with adenine-induced chronic renal failure. Nephron 64: 424-428.

Yokozawa T, Oura H, Sakanaka S and Kim M 1992. Effect of tannins in green tea on the urinary methylguanidine excretion in rats indicating a possible radical scavenging action. Biosci. Biotech. Biochem. 56: 896-899.

Yokozawa T, Oura H, Sakanaka S, Ishigaki S and Kim M 1994. Depressor effect of tannin in green tea on rats with renal hypertension. Biosci. Biotech. Biochem. 58: 855-858.

Yokozawa T, Oura H, Shibata T, Ishida K, Kaneko M, Hasegawa M, Sakanaka S and Kim M 1996b. Effects of green tea tannin in dialysis patients. J. Trad. Med. 13: 124-131.

Yokozawa T, Fujitsuka N, Oura H, Ienaga K and Nakamura K 1997b. *In vivo* effect of hydroxyl radical scavenger on methylguanidine production from creatinine. Nephron 75: 103-105.

Zinner SH, Margolius HS, Rosner B, Keiser HR and Kass EH 1976. Familial aggregation of urinary kallikrein concentration in childhood: relation to blood pressure, race and urinary electrolytes. Am. J. Epidemiol. 104: 124-132.