SUMMARY

A number of environmental contaminants and pharmaceutical agents including heavy metals and antibiotics dramatically alter the structure and function of various tissues and produce multiple adverse effects in the liver, kidney, intestine and heart. These environmental variables are also known to influence the incidence and expression of various diseases. The heavy metals such as mercury, lead, chromium, platinum and uranium have been shown to cause severe damage to kidney leading to acute renal failure (ARF) [Cronin and Thompson, 1991; Domingo, 1994; Stochs et al., 2000; Sanchez et al., 2001; Fatima et al., 2004; Barbier et al., 2005].

Aminoglycoside antibiotics including gentamicin (GM) are important drugs used in the treatment of life threatening bacterial infections. However, GM induced nephrotoxicity and ototoxicity limits its long term clinical use [Humes, 1988; Tulkens, 1989]. The specificity of GM for renal toxicity is apparently related to its accumulation in the renal proximal convoluted tubule causing a number of morphological and biochemical alterations in humans and experimental animals [Kacew and Bergeron, 1990; Ali, 1995; Mingeot-Leclercq and Tulkens, 1999a]. GM has been shown to cause marked histological damage in particular to renal proximal convoluted tubules (S₁ and S₂ subsegments) [Humes and Connor, 1988; Abdel-Gayoum et al., 1994] resulting in swelling, vacuolization and necrosis of epithelial cells and accumulation of myelin-like bodies [Ali and Bashir, 1994; Pedraza-Chaverri et al., 2000]. The adverse interaction of the drug with critical intracellular processes leads to renal cortical phospholipidosis disrupting functions of membranes and organelles including BBM, BLM, mitochondria, lysosomes and microsomes [Cronin and Henrich, 1996; Mingeot-Leclercq and Tulkens, 1999a].

Uranium, the heaviest of the naturally occurring elements is widely present in the environment and invariably carries an exposure risk for industrial workers as well as general population. The extensive use of depleted uranium in both civilian and military applications has increased the number of human beings exposed to this compound. It is believed that the major health effect of uranium is chemical kidney toxicity rather than a radiation hazard [Miller et al., 1998; 2002]. Uranyl nitrate (UN) induced nephropathy has been extensively studied in animal models [Haley et al., 1982; Anthony et al., 1994; Gilman et al., 1998; Sanchez et al., 2001].
Histopathological examinations showed severe damage to kidney and liver by UN exposure [Haley et al., 1982]. It was further demonstrated that UN caused specific damage to pars recta (S2 and S3 subsegments) of renal proximal tubules [Haley, 1982; Haley et al., 1982; Gilman et al., 1998]. Some of the known effects include increased lysosomal and vacuolar mass; variations in mitochondrial mass; epithelial cell degeneration with a focal loss of brush borders, thickening and splitting of basolateral membrane (BLM) and occasionally cell necrosis [McDonald-Taylor et al., 1997; Gilman et al., 1998]. UN is presumed to cause renal damage because of interactions with enzyme protein sulphydryl (thiol) groups in the acidic luminal membrane [Weiner and Jacobs, 1983] causing phospholipid derangement and alteration in membrane permeability.

Although both GM and UN cause alterations in the structure and functions in of kidney and other major tissues, these appear to be two dissimilar models of ARF. GM appears to primarily affect the structure and function of membrane phospholipids whereas UN causes renal damage due to interactions with enzyme protein thiol groups in the membrane [Cronin et al., 1986]. GM produces marked histological damage in particular to S1 and S2 subsegments whereas UN primarily affects the S3 segment of renal proximal tubules [Haley et al., 1982; Abdel-Gayoum et al., 1994; Banday et al., 2008a; 2008b]. Recently, reactive oxygen species (ROS) are considered important mediators in chemical/drug induced toxic insult and related cell/tissue injury [Walker et al., 1995; Taulan et al., 2004]. A potential therapeutic approach to reverse ARF caused by both GM and UN would be of immense importance in increasing the safety of the drug and for protection against uranium exposure.

Several approaches, utilizing different mechanisms, have been attempted to reduce nephrotoxicity of GM and related aminoglycoside antibiotics. These mechanisms include decreasing or preventing drug accumulation by the kidneys or decreasing binding to BBM [Mingeot-Leclercq and Tulkens 1999b]. Many different agents and strategies have been reported to ameliorate GM nephrotoxicity in experimental animals [Ali, 2003; Nagai and Takano, 2004]. Among them, protection against GM nephrotoxicity was mainly focused on the use of various antioxidant agents including the extracts from medicinal plants with antioxidant properties [Ali, 2003]. Similarly, certain complexing and chelating agents and other compounds having antioxidant properties were used to reduce UN-induced nephrotoxicity [Durakoviae, 1999].
However, none of these approaches have been found safe/suitable for clinical practice due to known and unexplored side effects.

In past few years, much interest has been centered on the role of naturally occurring dietary substances for the control and management of various chronic diseases such as cancer and cardiovascular disorders [Connor, 2000; Hardman, 2002; Larsson et al., 2004; Williams et al., 2007; Kakar et al., 2008; Leaf, 2008]. From ancient times the physicians and scholars in Asia have understood that food have both preventive and therapeutic value and are integral part of health. Omega-3 polyunsaturated fatty acids (ω-3 PUFA) enriched fish oil provide one such dietary source of biologically active components that has been shown to be co-preventative and co-therapeutic in a wide variety of ailments [Doughman et al., 2007].

A number of investigations have already demonstrated that diet supplemented with fish oil (FO) enriched in ω-3 PUFA has profound beneficial health effects against various pathologies including cancers, cardiovascular disorders, diabetes, depression, arthritis, asthma and inflammatory and immune disorders of the kidney and intestine [De Caterina et al., 1994; Tsujikawa et al., 2000; Barbosa et al., 2003; Bhattacharya et al., 2006]. Recently, ω-3 PUFA from some plants/seeds e.g. flaxseed oil (FXO) showed many similar health benefits as demonstrated by ω-3 PUFA from FO [Freese and Mutanen 1997; Ide et al., 2000; Kim and Choi 2001; Nannicini et al., 2006; Paschos et al., 2007]. ALA (α-linolenic acid) from vegetable sources including grains and oils, offer an alternative source for those who are unable to regularly consume fish for religious or other reasons [Harper and Jacobson, 2001]. Although ω-6 PUFA, usually consumed in excess in the western world from sources such as margarine, safflower oil and corn oil (MO) also showed certain health benefits e.g. in growth and development and in the protection of various cardiovascular diseases [Galli and Marangoni, 1997], they are known to produce pro-inflammatory factors promoting inflammation, tumor growth and most degenerative disorders [Simopoulos, 2001; Berquin et al., 2008]. In view of numerous beneficial health effects of ω-3 PUFA "we hypothesized that: dietary FO and FXO enriched in ω-3 PUFA but not MO (rich in ω-6 PUFA) would be able to prevent/reduce GM/UN induced nephrotoxic and other adverse effects in the rat kidney and intestine."

To address this hypothesis the present work was undertaken to study the detailed biochemical events/cellular response/mechanism of GM and UN induced nephrotoxic
and other adverse effects in rat kidney and intestine. The effects of dietary ω-3 and ω-6 PUFA were also determined to observe any protection provided by them against GM/UN nephrotoxicity. *The following parameters were determined:*

(a) Certain biochemical parameters in serum/urine.

(b) The activities of certain enzymes of carbohydrate metabolism involved in glycolysis, TCA cycle, gluconeogenesis and HMP-shunt pathway in renal cortex and medulla and small intestine.

(c) The activities of BBM and lysosomal marker enzymes in renal cortical and mucosal homogenates and BBM marker enzymes in isolated BBM preparations from renal cortex and intestinal mucosa.

(d) The transport of $^{32}$Pi in renal cortical BBM.

(e) The enzymatic and non-enzymatic parameters of antioxidant defense system in renal cortex and medulla and small intestine.

# THE RESULTS OBTAINED ARE SUMMARIZED AS FOLLOWS:

## PART-I: EFFECT OF DIETARY FISH OIL (FO), FLAXSEED OIL (FXO) AND CORN OIL (MO)

(a) *Serum/Urine Parameters:*

Serum creatinine was not affected by FO and FXO-diet but increased by MO-diet. However, BUN conspicuously decreased by FO/FXO/MO-diet. Serum glucose, Pi and phospholipids significantly but differentially increased by these diets. Serum cholesterol significantly lowered by FO/FXO-diet but increased by MO-diet. Urine flow rate and creatinine clearance significantly increased by FO/FXO but decreased by MO. Excretion of protein and phosphate decreased by FO/FXO but glucose excretion was not altered.

(b) *Enzymes of carbohydrate metabolism:*

The activities of HK, LDH, MDH, G6Pase and FBPase significantly increased by FO/FXO-diet in renal cortex and medulla. All but MDH were also increased in the
intestine. The activity of G6PDH (HMP-shunt pathway) was decreased in the cortex but significantly increased by FO/FXO in the medulla and intestine. On the other hand, the activity of malic enzyme (ME) slightly lowered in the kidney but significantly decreased in the intestine. In contrast to FO/FXO-diet, MO caused differential effects on the enzymes of carbohydrate metabolism. The activity of HK increased in the renal cortex and medulla but decreased in the intestine. The activity of LDH increased in the intestine and renal medulla, whereas decreased in the cortex. MDH activity, however, significantly decreased in all tissues. The activity of G6Pase and FBPase significantly increased in the intestine but was not affected in renal tissues by MO-diet. Like FO/FXO, MO significantly lowered G6PDH activity in the cortex but increased in the medulla and intestine. However, MO caused significant decrease in the activity of ME in the kidney and intestine alike.

(c) Marker enzymes of BBM and lysosomes:

The activities of AlkPase and GGTase significantly increased and that of LAP decreased in the homogenates of renal cortex, medulla and small intestine by FO/FXO diet. The activities of AlkPase, GGTase were moderately increased in the homogenate of cortex, medulla and intestine by MO-diet. However, the increase in enzyme activities by MO was relatively small compared to the effect of FO/FXO. The activity of LAP, however, significantly declined by MO-diet in renal cortex and medulla but not affected in the intestine. Sucrase activity significantly decreased in the intestine only by FXO-diet.

The activity of acid phosphatase (ACPase, lysosomes) was not affected significantly by FO/FXO/MO in the cortex. However, the activity decreased by FO and increased by FXO in the medullary homogenate. The activity of ACPase was also not affected by FO/MO but increased by FXO in the intestine.

The effect of FO/FXO/MO on BBM marker enzymes was more apparent in isolated BBM preparations from renal cortex and intestinal mucosa than observed in the respective homogenates. The activities of AlkPase and GGTase markedly increased, whereas LAP decreased by FO/FXO in the BBMV both from cortex and intestine. Sucrase activity was also significantly declined by FO/FXO-diet. The effect of MO on these enzymes in general was relatively mild compared to FO/FXO-diet.
(d) Na\textsuperscript{+}-dependent transport of \textsuperscript{32}Pi in the BBMV isolated from renal cortex:

The rate of concentrative uphill uptake of \textsuperscript{32}Pi in the presence of a Na-gradient \{Na\textsubscript{outside} (Na\textsubscript{o})>Na\textsubscript{inside} (Na\textsubscript{i})\} measured at 10 s and 30 s was markedly enhanced by both FO and FXO-diets alike. The uptake of \textsuperscript{32}Pi measured in the absence of Na-gradient and at 120 min (the equilibrium phase) remained unchanged, indicating specificity of the effect only in the presence of Na-gradient.

(e) Enzymatic and non-enzymatic parameters of antioxidant defense mechanism:

The activities of antioxidant enzymes, Cu, Zn superoxide dismutase (SOD) and catalase significantly increased in the cortex, medulla and intestine by FO or FXO diet. The activity of glutathione peroxidase (GSH-Px) increased significantly by FO/FXO in the cortex and intestine but decreased in the medulla. In contrast, MO had no significant effect on the activities of these enzymes in the kidney and intestine except SOD activity which was significantly increased in the intestine. Total-SH levels were significantly increased by FO/FXO in the cortex and medulla without any effect on lipid peroxidation.

\textbf{Interpretation:} In general, FO/FXO-diet significantly enhanced the activities of enzymes of carbohydrate metabolism involved in glycolysis, TCA cycle and gluconeogenesis, BBM and oxidative stress in the kidney and intestine. Except for some isolated effects, MO-diet was relatively less effective.

\textbf{PART-II: INFLUENCE OF DIETARY FISH OIL (FO), FLAXSEED OIL (FXO) AND CORN OIL (MO) ON GM-INDUCED NephROTOXIC AND OTHER ADVERSE EFFECTS}

(a) Serum/Urine Parameters:

GM administration caused severe nephrotoxicity as characterized by significant increase in serum creatinine, cholesterol, phospholipids and BUN accompanied by massive polyuria, proteinuria, glucosuria and decreased creatinine clearance. GM significantly decreased serum Pi and glucose. FO or FXO-diet given to GM rats markedly prevented many of the GM induced alterations in various serum and urine parameters. Both FO and FXO prevented GM induced increase of serum creatinine,
cholesterol, BUN and decrease of serum Pi and glucose. GM induced proteinuria, phosphaturia and glucosuria were also retarded by FO/FXO-diets. In contrast to FO/FXO, MO-diet caused partial reversal in some of the GM induced effects. Increased serum cholesterol, Pi, phospholipids and proteinuria persisted after MO-diet to GM rats.

(b) *Enzymes of carbohydrate metabolism:*

(i) GM treatment caused significant decrease in the activities of MDH, G6Pase, FBPase and ME but the activity of LDH increased in renal cortex and medulla. The activity of G6PDH increased in the cortex and in the medulla whereas ME activity profoundly decreased both in the cortex and medulla by GM treatment. As shown in “Part I”, many of these metabolic enzyme activities were enhanced by FO/FXO alone. Feeding of FO/FXO similarly prevented/retarded GM induced decrease of MDH, G6Pase, FBPase and ME activities in the cortex and medulla. In contrast, MO-diet failed to prevent GM elicited decrease of MDH, G6Pase and FBPase in the cortex/medulla. The activity of ACPase (lysosomal enzyme) significantly declined in the cortex and medulla by GM treatment. FO/FXO to some extent but not MO retarded/lessened the GM induced alterations.

(ii) GM caused differential effect on various metabolic enzymes in the intestine. GM significantly increased the activities of LDH, G6Pase, FBPase and G6PDH but decreased MDH and ME activity. FO/FXO prevented/retarded GM induced decrease of MDH and ME activity. The activities of other enzymes further enhanced or remained higher by dietary FO/FXO supplementation to GM rats. In contrast, MO could not prevent GM elicited decrease in MDH and ME activities. GM induced decrease in ACPase activity was also prevented by FO/FXO-diets but not by MO-diet.

(c) *Marker enzymes of BBM:*

(i) GM caused significant decrease in the activities of AlkPase, GGTase and LAP whereas FO/FXO significantly increased the activities of AlkPase and GGTase in renal cortical homogenates. However, LAP activity decreased by FO/FXO. FO/FXO-diet given to GM rats not only prevented GM-induced decrease in the
BBM enzymes but the activity of AlkPase and GGTase remained significantly higher compared to control/GM rats. MO significantly decreased LAP activity but like FO/FOXO did not increase AlkPase and GGTase activity, failing to prevent GM elicited decrease in activities of BBM enzymes. The effects of GM and FO/FOXO/MO were much more apparent in isolated BBMVs preparations than observed in the respective homogenates. The magnitude of enzyme activities increased (5-8 folds) in the membrane preparations compared with respective values for the homogenates in control and treated groups for renal cortex indicating that the quality of the membrane prepared by the procedure was uniform for the various experimental groups.

(ii) In contrast to the kidney, GM caused significant increase in AlkPase, LAP and sucrase activities both in mucosal homogenates and to much greater extent in intestinal BBMVs. However, GGTase activity decreased by GM. FO/FOXO significantly increased the activity of AlkPase and GGTase, whereas decreased LAP and to some extent sucrase activity both in the homogenate and BBMVs. The activities of AlkPase, GGTase remained significantly higher after FO/FOXO feeding to GM rats, particularly in BBM preparations. MO also increased AlkPase, GGTase and LAP activities and to some extent they remained higher after GM treatment but sucrase activity was decreased.

(d) \( \text{Na}^+ \)-dependent transport of \( ^{32}\text{Pi} \) in the BBMV isolated from renal cortex:

The rate of concentrative uphill uptake of \( ^{32}\text{Pi} \) in the presence of a Na-gradient \( \{\text{Na}_{\text{outside}}(\text{Na}_o) > \text{Na}_{\text{inside}}(\text{Na}_i)\} \) measured at 10 s and 30 s was markedly decreased by GM whereas profoundly increased by both FO and FXO-diets alike. GM-induced decrease in \( ^{32}\text{Pi} \) uptake was not only prevented by FO/FOXO-diet but remained significantly much higher in FOGM/FXOGM rats compared to control/GM rats. The uptake of \( ^{32}\text{Pi} \) measured in the absence of Na-gradient and at 120 min (the equilibrium phase) remained unaltered.

(e) Enzymatic and non-enzymatic parameters of antioxidant defense mechanism:

GM caused significant decrease in the activities of SOD, catalase and GSH-Px in the cortex and medulla which was associated with marked increase in LPO and decrease in total-SH levels. GM caused decrease in the activities of SOD and
catalase but increase in the activity of GSH-Px in the intestine. By the virtue of their antioxidant defense strengthening/enhancing ability (as described in part-I), both FO/FXO-diet protected well against GM induced perturbation of oxidants/antioxidants. GM induced decrease of SOD/catalase/GSH-Px in the kidney and that of SOD/catalase in the intestine and increase in LPO were ameliorated by FO and/or FXO-diet. However, MO-diet could not prevent GM elicited decrease in SOD/catalase/GSH-Px and increase in LPO in the cortex and medulla. In the intestine, MO was able to prevent GM induced decrease in SOD but not in catalase activity.

Interpretation: In general, GM caused severe adverse effects on various serum/urine parameters and on the enzymes of carbohydrate metabolism, BBM and antioxidant defense system in rat kidney and intestine. FO and/or FXO but not MO-diet similarly protected against GM-induced nephrotoxic and other adverse effects most likely due to their intrinsic biochemical and antioxidant properties.

PART-III: INFLUENCE OF DIETARY FISH OIL (FO), FLAXSEED OIL (FXO) AND CORN OIL (MO) ON UN-INDUCED NEPHROTOXIC AND OTHER ADVERSE EFFECTS

(a) Serum/Urine Parameters:

UN administration caused severe nephrotoxicity as manifested by elevated serum creatinine, glucose, cholesterol, phospholipids and BUN but decreased serum Pi, accompanied by massive polyuria, proteinuria, phosphaturia, glucosuria and decreased creatinine clearance. FO or FXO-diet given to UN treated rats markedly prevented/retarded UN-induced increase of serum creatinine, glucose, cholesterol, and BUN. UN-induced proteinuria, phosphaturia and glucosuria were prevented and serum Pi was significantly elevated by FO/FXO-diets. In contrast, MO-diet to some extent lowered UN elicited increase of serum creatinine, Pi and BUN; however, UN-induced increase in serum cholesterol, glucose and phospholipids remained significantly increased and proteinuria persisted after MO-diet to UN treated rats.
(b) **Enzymes of carbohydrate metabolism:**

(i) UN treatment caused decrease in the activities of MDH, G6Pase, FBPase and G6PDH whereas activities of LDH and ME increased significantly in renal cortex and medulla. As shown in “Part I”, many of these metabolic enzyme activities were enhanced by FO/FXO alone. Feeding of FO/FXO similarly prevented/retarded UN-induced decrease of MDH, G6Pase, FBPase and G6PDH activities in the cortex and medulla. In contrast, MO-diet could not prevent UN elicited decrease of these enzymes in the cortex/medulla. UN caused significant increase in the activity of ACPase (lysosomal enzyme) both in the cortex and medulla. FO/FXO-diet to UN rats but not MO-diet lessened the UN-induced alterations.

(ii) UN caused similar increase in LDH activity but decrease in MDH, G6Pase, FBPase, G6PDH and ME activities in the intestine. FO/FXO-diet similarly prevented/retarded UN-induced alterations in the enzymes of carbohydrate metabolism. MO-diet prevented UN elicited increase in LDH activity and decrease in G6Pase, FBPase and G6PDH activities. However, the activity of MDH and ME further declined by MO-diet in UN treated rats. UN caused significant increase in ACPase activity. The enhanced ACPase activity was brought back to near control values by FO/FXO but not by MO-diet.

(c) **Marker enzymes of BBM:**

(i) UN caused significant decrease in the activities of AlkPase, GGTase and LAP in cortical homogenates. In contrast, FO/FXO-diet alone increased the activities of AlkPase and GGTase but decreased LAP. Both FO and FXO-diet given to UN treated rats significantly prevented/retarded UN-induced decrease in AlkPase, GGTase and LAP activity. In contrast, MO-diet failed to ameliorate the UN-induced decline in the activities of these enzymes. The effects of UN and FO/FXO/MO were much more apparent in isolated BBMV preparations than observed in the homogenates. The magnitude of enzyme activities increased (5-8 folds) in the membrane preparations compared with respective values in cortical homogenates in control and treated groups. Similar to the pattern in cortical homogenates, prevention of decrease in BBM enzyme activities was observed in
FO/FXO fed UN treated rats (FOUN/FXOUN) but not in MO fed UN treated rats (MOUN).

(ii) In contrast to the kidney, UN caused significant increase in AlkPase, GGTase, LAP and sucrase activities both in mucosal homogenates and to much greater extent in intestinal BBMV. FO/FXO alone significantly increased the activity of AlkPase and GGTase whereas decreased LAP and to some extent sucrase activity in the homogenate and BBMV. Activity of AlkPase profoundly increased but the activities of rest of the enzymes were brought to near control values by FO/FXO when given to UN rats. MO-diet which had little effect on intestinal BBM enzymes, appeared not to influence UN-induced alterations of marker BBM enzymes.

(d) **Na^+**- dependent transport of $^{32}$Pi in the BBMV isolated from renal cortex:

The rate of concentrative uphill uptake of $^{32}$Pi in the presence of a Na-gradient \{Na$_\text{outside}$ (Nao)$>$Na$_\text{inside}$ (Na$_i$)\} measured at 10 s and 30 s was markedly decreased by UN, whereas profoundly increased by both FO and FXO-diets alike. UN-induced decrease in $^{32}$Pi uptake was not only prevented by FO/FXO-diet but remained significantly enhanced by FO/FXO-diets when given in combination with UN treatment. The uptake of $^{32}$Pi measured in the absence of Na-gradient and at 120 min (the equilibrium phase) were not altered by any experimental conditions.

(e) **Enzymatic and non-enzymatic parameters of antioxidant defense mechanism:**

UN treatment significantly increased the activities of SOD and GSH-Px but decreased that of catalase, associated with marked elevation of LPO and decrease in total-SH levels in the cortex and medulla. As shown earlier, FO/FXO alone significantly increased SOD, catalase and GSH-Px activities in these tissues. FO/FXO-diet when given to UN treated rats significantly ameliorated the UN-induced imbalance in the antioxidant defense system. LPO was decreased, whereas total-SH increased and the activities of the antioxidant enzymes remained significantly higher in FO/FXO fed-UN treated rats compared to control/UN rats. However, MO-diet which had little effect on antioxidant enzymes did not influence the UN-induced alterations of oxidant/antioxidant parameters. Similar
protection by FO/FXO-diets against UN elicited peroxidative effects was observed in the intestine.

**Interpretation:** UN treatment caused severe damage to the kidney and intestine as reflected by increase in serum creatinine and BUN and decrease in biomarker BBM enzymes. There appeared to be a shift from aerobic to anaerobic metabolism most likely due to UN induced mitochondrial damage. UN also increased oxidative stress as indicated by increased LPO and decreased total-SH levels associated with imbalances in the activities of antioxidant enzymes. FO/FXO but not MO-diet prevented/retarded UN-induced alterations in various biochemical parameters and enzyme activities most likely due to their incorporation in cellular membranes and antioxidant properties.

**Conclusion:**

In conclusion, GM/UN elicited deleterious nephrotoxic effects by causing major damage to mitochondria, lysosomes and in particular to BBM of renal proximal tubule and intestinal mucosa as reflected by significant decrease in the activities of their specific biomarker enzymes, confirming the morphologic and toxicogenomic observations that showed these organelles as prime GM/UN targets. Both GM and UN seem to enhance glycolytic enzyme LDH in order to increase energy dependence on glycolysis due to mitochondrial damage and depressed TCA cycle enzymes. These nephrotoxic and other adverse effects appeared to be mediated in part due to GM/UN elicited oxidative damage. Dietary ω-3 PUFA enriched fish oil and flaxseed oil to a larger extent prevented GM/UN-induced nephrotoxicity parameters by enhancing nutrition/energy metabolism and $^{32}$Pi transport capacity, by strengthening antioxidant defense mechanism and by altering membrane organization/fluidity/permeability. However, corn oil enriched in ω-6 PUFA failed to reverse many GM/UN-induced nephrotoxicity parameters and oxidative damage. Based on our present observations and already known numerous health benefits, we propose that ω-3 PUFA enriched FO/FXO may provide a cushion for a prolonged therapeutic option against drug/chemical induced nephropathy without harmful side effects. Similar protective effects of FO and FXO provide a much needed relief for millions of vegetarians who do not eat fish/fish oil for religious or other reasons.