Nephrolithiasis encompasses a family of disorders that culminate in a common pathology, the deposition of stones within the kidney. A number of risk factors favor the development and progression of stone disease, among which cellular injury is a predisposing factor. However, there is no recognized molecular mechanism which could explain oxalate-induced cellular injury. The present study analyzed the contribution of mitochondrial dysfunction and inflammation towards renal injury. The role of fucoidan, a naturally occurring GAG to prevent renal aberrations was also analyzed. The salient findings of the present study are highlighted as follows

✓ Increase in supersaturation plays an important role in providing a milieu for stone formation. Increase in stone forming constituents and decrease in urinary inhibitors in hyperoxaluria was effectively prevented by fucoidan. Urinary crystal analysis and polarized microscopic studies support the anti-adherence property of fucoidan. Decrease in pH and the diuresis on administration of fucoidan adds credit to its anti-urolithic potential.

✓ Oxalate-induced membrane damage is essential for crystal adherence. Membrane damage inflicted by oxalate was evidenced through increased urinary enzymes, altered redox status and decreased ATPases. Fucoidan administration successfully ameliorated the aberrant changes.

✓ Oxalate induced macromolecular damage triggers the initiation of abnormal lithogenic events. Increased protein carbonyl and decreased thiol are an evidence of oxalate-induced macromolecular damage. Protein carbonyl formation and thiol depletion in hyperoxaluria was culminated by fucoidan administration in an appreciable manner.
Increased nitrosative stress during hyperoxaluria was effectively circumvented with fucoidan administration as fucoidan was able to decrease the expression of iNOS.

Mitochondrial dysfunction is the primary event in lithogenesis. Decreased TCA cycle enzymes, loss in transmembrane potential, swelling and decrease in Bcl-2 mRNA emphasize the mitochondrial breaching in hyperoxaluria. Fucoidan was able to maintain the integrity of mitochondrial membrane and hence prevent the mitochondrial malfunction in hyperoxaluria.

Inflammation contributes to stone formation by inducing renal damage through ROS production. Activation of NF-κB and increase in inflammatory cytokines like IL-1β, IL-6 and TNF-α during hyperoxaluria accentuate the inflammatory stress during hyperoxaluria. Fucoidan was able to prevent the increase in cytokines due to its antioxidant potential.

Inflammation apart from inducing ROS production also increases tissue remodeling. An increased collagen and decreased MMP-2 level along with an increased TGF-β1 and osteopontin expression demonstrates the tissue fibrosis that occurs during hyperoxaluria. Fucoidan was able to decrease renal fibrosis, prevent the exposure of crystal binding molecules and thereby decrease crystal retention.

Activation of renin-angiotensin system plays a critical role in renal fibrosis and oxidative stress during hyperoxaluria. Fucoidan was able to restore the normal levels of Ang II.
Cell line studies were initiated to characterize oxalate mediated apoptosis. In MDCK cells oxalate exposure increased ROS production, decreased mitochondrial function. Fucoidan prevented ROS production and maintained the mitochondrial integrity in oxalate exposed MDCK cells.

As mitochondria is the central point in intrinsic pathway of apoptosis, mitochondrial damage led to the release of cytochrome c and caspase activation in oxalate exposed MDCK cells. Maintenance of mitochondrial membrane integrity by fucoidan prevented the release of cytochrome c, caspase activation and eventually apoptosis.

Light microscopic and transmission electron microscopic studies showed the ultra structural alterations in renal tissue during hyperoxaluria. The restoration of near normal architecture of renal tissue on administering fucoidan, is the standing evidence of fucoidan’s protective effect against oxalate - induced renal damage.