effect of CMN on circulating lipids in plasma and lipid peroxidation products in alcohol and polyunsaturated fatty acid-induced toxicity. In-vitro findings support the hypothesis that CMN inhibits free radical induced apoptosis in cell lines [47]. Sreejayan et al claimed that the CMN inhibit iron-catalyzed lipid peroxidation in rat brain tissue homogenates by chelation of iron[48].

More and more studies now established the ability of CMN to mainly eliminate the hydroxyl radical [49], superoxide radical [50], singlet oxygen[51], nitrogen dioxide[52] and NO[53]. It has also been demonstrated that CMN inhibits the generation of the superoxide radical[54]. In our study, CsA administration caused marked deterioration of endogenous antioxidant profile as evidenced by decrease in SOD and CAT activities, an effect which was effectively reversed by CMN treatment. Vajragupta et al., [23] have reported that CMN manganese complex and acetylcurcumin manganese complex, low molecular weight synthetic compounds, showed much greater SOD activity and an inhibitory effect on lipid peroxidation. Priyadarsini et al. [55] have shown, by DPPH scavenging in vitro, that origin of the antioxidant activity of CMN is mainly from the phenolic OH group, although a small fraction may be due to the $>CH_2$ site.

Further GSH, a major nonprotein thiol in living organisms plays a crucial role in coordinating the body's antioxidant defense processes. Results in the present study indicate that CsA administration drastically lowered the levels of GSH in the kidney. Improvement of renal GSH levels in CMN treated rats in comparison to CsA administered rats further demonstrates the anti-antioxidative effect of CMN. CMN has been shown to increase the levels of glutathione reductase in ischemic brains of rats as well as alveolar and human leukemia cell [20,56,57]. Chronic treatment of CMN also improved the levels of two key antioxidant enzymes SOD and catalase in CsA administered rats.

Peroxynitrite anions have been generated by the reaction of nitric oxide with superoxide anion. These peroxynitrite anions oxidize biomolecules, which finally leads to lipid peroxidation and tubular cell damage [58]. Large amounts of nitric oxide can lead to the depletion of cellular ATP which can inactivate enzymes that contain iron-sulfur clusters, such enzymes involved in mitochondrial electron transport [59]. Nitrosylation of sulfhydryl groups or tyrosine residues in proteins may impair the functional properties of these proteins. Nitric oxide damages DNA, and this in turn, stimulates the DNA repair enzyme poly-ADP-ribose synthetase [60]. Studies done by Amore and colleagues demonstrate that CsA induces apoptosis in various renal cell lines, and this effect is mediated by the induction of iNOS [61]. In line with studies where CMN is reported to inhibit iNOS gene expression in isolated BALB/c mouse peritoneal macrophages and also in the livers of lipopolysaccharide injected mice [62], our study shows that CsA-induced nitrosative stress was significantly and dose dependently attenuated by CMN. Very recently, Sumanont [24] have studied the effect of CMN and its analogues on peroxynitrite anions scavenging activity in vitro using sodium nitroprusside (SNP) generating nitric oxide system. All compounds effectively reduced the generation of NO radicals in a dose dependent manner. They exhibited strong NO radical scavenging activity with low IC(50) values. It is also known that ROS mediates peroxidation of lipid structures of the tissue, resulting in subcellular damage, as observed in histopathological examination. In our study, the kidney of CsA treated rats has shown characteristic morphological findings such as interstial fibrosis and arteriolar hyalinosis. The vasoconstriction induced by CsA produces an ischemic local environment, which leads to a number of cellular changes such as deterioration in membrane integrity the marked histological changes are prominent in the outer cortex and medullary region of the kidney. Because limited oxygen availabity these structures are particularly vulnerable to ischemia. These changes were not observed in the group treated CMN (15 mg/kg) suggesting the protective effect of CMN in attenuating CsA-induced morphological changes.

Conclusion

In conclusion this study demonstrates that CMN through its marked antioxidant activity coupled with favorable haemodynamic effects salvages CsA nephrotoxicity.

Methods

Animals

Wistar albino rats of either sex (150–200 g) were housed in 3 per cage, with food and water ad libitum for several days before the beginning of the experiment. The animals were kept on straw bedding in animal quarters with a natural light: dark cycle. The animals had free access to standard rodent food pellets and water. Animals were acclimatized to the laboratory conditions one day before the start of experiment and daily at least for one hour before the experiment. All the experiments were conducted between 09.00 and 17.00 hrs. The experimental protocols were approved by the Panjab University Animal Ethical Committee.

Drugs

Curcumin (Sigma Chemicals USA) was suspended in 0.5% Carboxy methyl cellulose (CMC) and administered orally. CsA was a gift from Panacea Biotech India.