Summary and Conclusion
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ADR is an anthracyclin drug applied in chemotherapy against leukemias, lymphomas, myeloma and a variety of solid tumors. However, immense therapeutic potential of ADR, is hampered by associated side effects paramount among these is nephrotoxicity which may derive from the fact that ADR generates $O_2^-$ and $^\bullet$OH in two ways: redox - cycling and a Haber-Weiss type reaction due to Fe-ADR (formation of perferyl complex). The use of antioxidants in combination with cytostatics to alleviate the toxicity of ADR strongly encourage a new therapeutic approach in cancer chemotherapy.

Biochemical approaches are often fundamental in illuminating the causes of diseases and in designing appropriate therapeutical interventions. Hence the judicious use of various biochemical laboratory tests has formed an integral component of diagnosis and monitoring the toxicity imposed by ADR.

In the present study, single/multiple injections of ADR produced a model of acute and chronic renal dysfunctions. The therapeutic potency of LA in assuaging the nephrotoxic effect of the anticancer drug ADR has been the hallmark of this study. The salient findings are briefly highlighted hereunder. Administration of ADR, both acute and chronic adversely affected the cellular biochemistry of the treated rats as enumerated below.

⇒ Renal tubular damage was evident in both acute and chronic administrations of ADR from brush border membraneuria, lysosomal enzymeuria and proteinurias as reflected in enhanced activity of Alkaline phosphatase, Acid phosphatase, Lactate dehydrogenase, N-acetyl glucosaminidase, $\gamma$-glutamyl transferase, $\beta$-glucuronidase, $\beta$-galactosaminidase and Leucine amino peptidase.
Biomolecular loss of renal tissue marker enzymes such as Alkaline phosphatase, Acid phosphatase, Lactate dehydrogenase, Aspartate transaminase, Alanine transaminase, N-acetyl glucosaminidase, γ-glutamyl transferase, β-glucuronidase, β-galactosaminidase, Leucine amino peptidase and 5'-nucleotidase suggest ADR to be a potent nephrotoxin.

Carbohydrate metabolism was adversely affected by the inhibition of key glycolytic enzymes - Hexokinase, phosphoglucoisomerase, and aldolase, gluconeogenic enzymes - fructose, 1,6-diphosphatase and glucose-6-phosphatase and TCA cycle enzymes - isocitrate dehydrogenase, succinate dehydrogenase and malate dehydrogenase.

Alterations in tissue lipids - an increase in Total cholesterol, Triglyceride and decrease in phospholipids and Free fatty acids, increase in plasma lipids - total cholesterol, triglyceride, phospholipids, free fatty acids and increase in lipoproteins - LDL, VLDL, HDL were also observed in ADR administrated rats.

Increase in malondialdehyde levels suggests the involvement of reactive oxygen species during ADR administration. This was accompanied by an onslaught in the antioxidant defense armoury consisting of glutathione, catalase, superoxide dismutase, glutathione peroxidase, glutathione-S-transferase, glutathione reductase, vitamin A, vitamin C and vitamin E which were maintained on pretreatment with LA.
A significant decline in the activities of phosphohydrolases: Na⁺,K⁺-ATPase, Mg²⁺-ATPase and Ca²⁺-ATPase was observed in rats administered with ADR, which was brought to near normal with LA pretreatment suggesting the membrane protective action of LA.

The involvement of oxygen derived free radicals in rats administered with ADR was conspicuous from a rise in hemolysis of red blood cells and membrane lipid peroxidation, along with a steep fall in the antioxidants - catalase, superoxide dismutase, glutathione, glutathione peroxidase, vitamin A, vitamin C and vitamin E. LA pretreatment enhanced the antioxidant status of the red blood cells with a concomitant decline in membrane lipid peroxidation.

Hematological indices (Hb and Ht) also faced a fierce attack owing to the redox cycling of ADR resulting in appreciate decrease in the contents of both Hb and Ht leading to anemia. LA pretreatment maintained the Hb and Ht content to nearly normal.

Enhanced levels of SGOT and SGPT were observed in rats administered with ADR which were reverted to near normal levels upon pretreatment with LA. The influence of ADR toxicity on other organs was evident from the elevated levels of serum transaminases.

Decrease in the activities of alkaline phosphatase, acid phosphatase, γ-glutamyl transferase, β-glucuronidase and Na⁺,K⁺-ATPase activities in isolated renal brush border membranes after ADR administration reflected increased renal cellular damage.
Induction of apoptosis as investigated in Vero cell lines was clearly evident from

- Increased apoptotic score of 42 ± 9 in ADR treated cells compared to 7 ± 2 in controls (12 hours).
- Decreased in the activities of lactate dehydrogenase, N-acetyl glucosaminidase and γ-glutamyl transferase in the spent medium containing ADR, which were significant from that of the controls.

The damaging effect of ADR on DNA was revealed from an increased tail length which was assessed by alkaline single cell gel electrophoresis (Comet assay).

Histopathological studies revealed tubular dilation in the collecting tubules and mild tubular epithelial damage in renal sections subjected to acute ADR administrations. Rats subjected to chronic exposure to ADR showed an increase in glomerular cellular proliferation, crescent formation and focal hyalinisation leading to glomerulonephritis, which were seen maintained upon LA pretreatment.

The observed alterations on biochemical and cellular indices undoubtedly reflected renal damage due to ADR administration. The degree of protection afforded by LA in minimizing the lethal side effects of ADR was also investigated.