Summary
Most people enthusiastically welcome knowledge of new ways to slow or reverse aging because aging affects us all. While much attention has been focused on cosmetic remedies, the underlying mechanisms that lead to aging are still not well understood and will have to be better defined before any meaningful ways of making us age more gracefully can be achieved. Despite our meager understanding, it is becoming increasingly clear that oxidants ("reactive oxygen species") and the accumulation of oxidative damage are important factors in the overall decline during aging. Our study focused on mitochondria because this organelle is the chief producer of both energy and oxidants inside the cell. Oxidants released from the mitochondria can damage important biomolecules, such as DNA, lipids, and protein. ROS can also have profound effect on ionic homeostasis and can mediate apoptotic cell death. Moreover, mitochondria may themselves be important targets for aging because of their vital importance to overall cellular metabolism. Given importance to the crucial factors, the present study was undertaken to explore the beneficial role of mitochondrial metabolites, carnitine and lipoic acid in alleviating mitochondrial function in skeletal muscle of aged rats. The possible combined effect of L-carnitine (300 mg/kg body weight/day) and DL-α-Lipoic acid (100 mg/kg body weight/day) for 30 days on age associated biochemical and molecular alterations in skeletal muscle mitochondria have been observed and summarized as follows:

- A significant decrease in carnitine and lipoic acid content was observed in skeletal muscle of aged rats than young rats. Carnitine and lipoic acid content were found to be increased in
aged rats with exogenous supplementation of carnitine and lipoic acid.

- An Increase in ROS generation and H₂O₂ release by mitochondria were found to be increased in skeletal muscle of aged rats. Carnitine and lipoic acid effectively scavenged the free radical generation in aged rats.

- A significant increase in lipid peroxidation, protein oxidation and DNA damage was observed in skeletal muscle mitochondria of aged rats than young rats. Carnitine and lipoic acid effectively prevented the increase in lipid peroxidation, protein oxidation and DNA damage in aged rats.

- A significant decrease in the activities of TCA cycle enzymes such as isocitrate dehydrogenase; α-ketoglutarate dehydrogenase, succinate dehydrogenase, and malate dehydrogenase and electron transport chain complexes was observed in skeletal muscle mitochondria of aged rats. The combined supplementation of carnitine and lipoic acid improved the activities of these enzymes in aged rats.

- Mitochondrial respiration state 3, respiratory control ratio, ADP:O, were found to be decreased in aged rats whereas increase in state 4 respiration and mitochondrial swelling was observed. Supplementation of carnitine and lipoic acid to aged rats reversed these changes to near normalcy.
• An increase in the 4.8 kb mitochondrial DNA deletion was observed in aged rats than young rats. The combined supplementation of carnitine and lipoic acid decrease the mitochondrial DNA deletion in aged rats.

• The extent of apoptosis was found to be high in skeletal muscle of aged rats as evidenced by observed increase in intracellular calcium, release of cytochrome c, activation of caspase-3, DNA fragmentation and decreased level of Bcl-2. Administration of carnitine and lipoic acid to aged rats reduced the incidence of apoptosis indicating the cytoprotective role of carnitine and lipoic acid in aged rats.

These results provide compelling evidence that mitochondrial dysfunction occur during aging and also suggest that this process can be slowed or even reversed by dietary supplementation of carnitine and lipoic acid.