FUJI CHEMICAL INDUSTRY CO., LTD.

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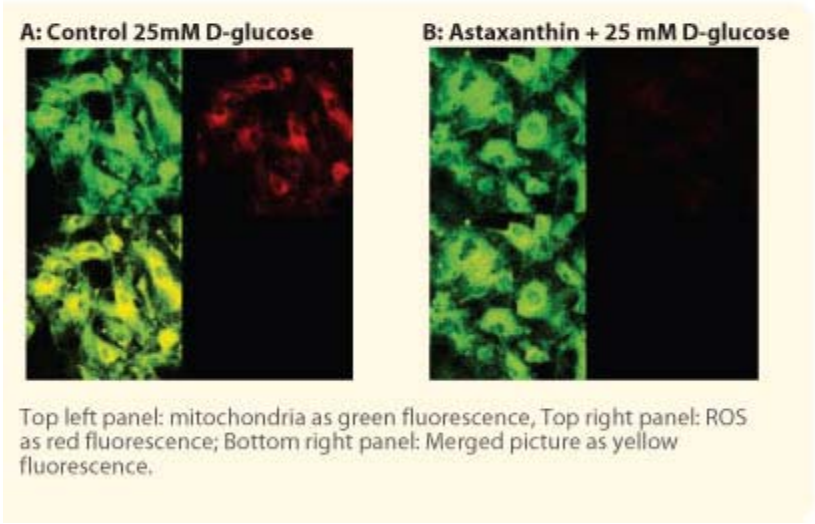
Astaxanthin Research Update

Astaxanthin May Protect Against the Onset and Progression of Kidney Damage Associated with Diabetes Mellitus Type 2

Scientists from the Kyoto Prefectural University of Medicine, Japan (sponsored by Fuji Chemical Industry) confirmed that astaxanthin significantly suppressed ROS production, biomarkers of oxidative damage and proinflammatory responses in mitochondria of Normal Human Mesangial Cells (NHMC) exposed to high-levels of glucose.

Manabe *et al*., (2007) exposed NHMC to 25 mM D-glucose (equivalent to 400 mg/dl in humans) to investigate the oxidative damage reported in diabetic nephropathy or kidney damage (Figure 1). Chronic high-blood-glucose levels increase Reactive Oxygen Stress (ROS) production in mitochondria. ROS affects not only on the development of diabetes but also on its complications such as mesangial cell damage which leads to loss of kidney function. Since the progress of kidney damage is mostly irreversible and has an extremely poor prognosis, it is important to prevent the onset and progression of the nephropathy in the early stage of Diabetes Mellitus (DM) Type 2. The scientists from Kyoto suggested using astaxanthin, a powerful antioxidant, to scavenge ROS in the prevention of diabetic nephropathy.

Figure 1. Astaxanthin (10^{-6} M) reduced high-glucose-induced mitochondria-dependant ROS production in NHMCs. Detection by fluorescence technique. Astaxanthin reduced ROS production (indicated by no red fluorescence and no yellow fluorescence).



Top left panel: mitochondria as green fluorescence, Top right panel: ROS as red fluorescence; Bottom right panel: Merged picture as yellow fluorescence.

Furthermore, an oxidative lipid peroxidation marker, 4-hydroxy-2,3-nonenal (4HNE), was significantly reduced ($P<0.05$) by 50% with astaxanthin (Figure 2). For the first time, astaxanthin was also confirmed to localize in the cell mitochondrial membrane of NHMC by quantitative analysis.

Figure 2. Astaxanthin inhibited high-glucose induced production of 4-HNE oxidative stress-modified proteins in the mitochondria of NHMCs. *P<0.01 vs. Normal Glucose #P<0.05 vs. High Glucose

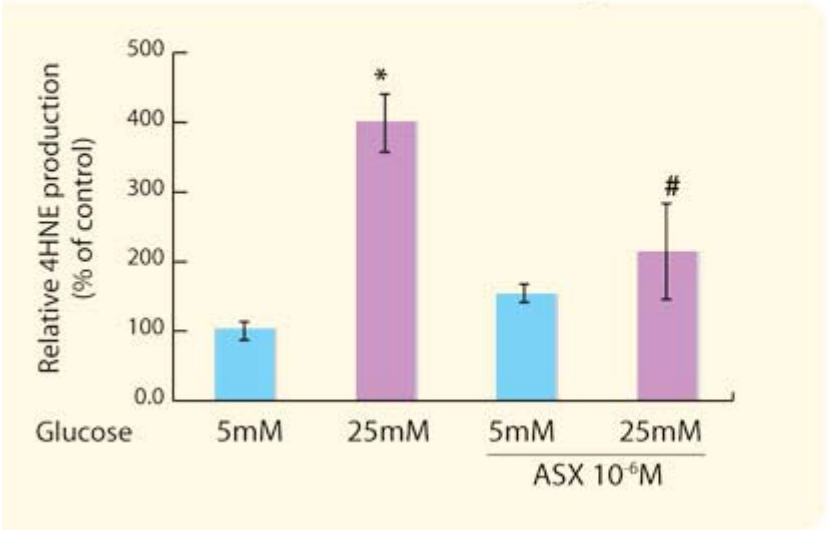
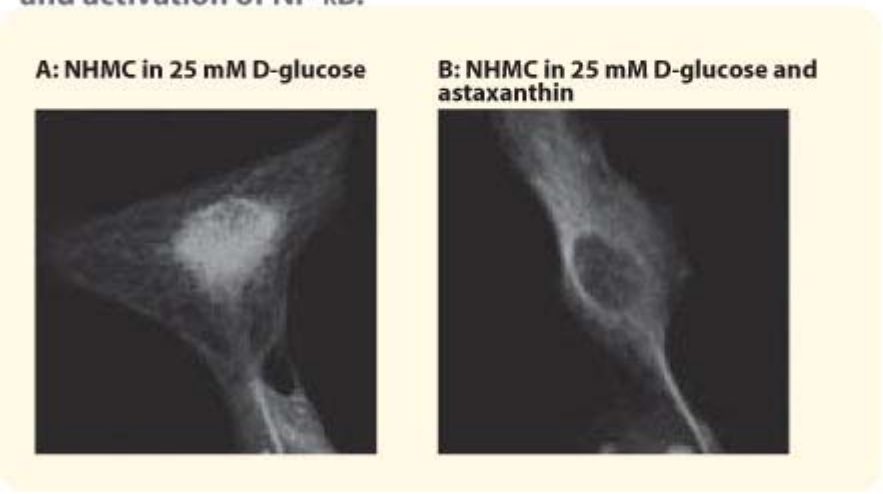


Figure 3. Astaxanthin suppressed high-glucose induced nuclear translocation and activation of NF-κB.



NHMCs pre-incubated with astaxanthin reduced the inflammatory response. For example, NF-kB activation and subsequent movement to the cell nucleus for inflammatory gene activation was inhibited (Figure 3). Astaxanthin also reduced AP-1 activation and expression/production of COX-2, MCP-1, and TGFB1. If not suppressed, these factors will promote the pathogenesis and mesangial cell injury.

Although the mechanism by which astaxanthin suppresses ROS has to be further investigated, the researchers postulated that astaxanthin may affect part of the electron transport chain and protect mitochondria from the detrimental effects of glucose toxicity.

In summary, astaxanthin may scavenge excess ROS, reduce ROS-protein damage, and inhibit inflammatory process. Therefore, the onset of nephropathy may expect to be prevented or delayed.

Globally, Diabetes Mellitus and its complications is the third largest killer (WHO 1995). At the current rate, the diabetic population of 171 million will increase to 366 million by 2030. One of the most common complications associated with DM is nephropathy or kidney damage.

In a separate study, randomized glycemic control reduced or normalized mitochondrial ROS production and delayed the onset and progression of early stage diabetic complications. Furthermore, previous studies sponsored by Fuji Chemical Industry showed that astaxanthin reduced kidney damage in diabetic mouse models and many other biomarkers (reduced DNA damage, improved glucose-tolerance test, lowered NF-kB). Even though the previous studies demonstrated that astaxanthin could suppress ROS and reduce nephropathy, the mechanism remained unclear to how astaxanthin could reduce renal damage until now.

Reference: *Manabe et al., 2007. Astaxanthin protects mesangial cells from hyperglycemia-induced oxidative signaling. Journal of Cellular Biochemistry Online Publication 22 Oct 2007.*

Further Reading :
Naito Y., et al., (2006). Microarray profiling of gene expression patterns in glomerular cells of astaxanthin-treated

diabetic mice: a nutrigenomic approach. Int. J. Mol. Med. 18:685-695.

Naito Y., et al., (2004). Prevention of diabetic nephropathy by treatment with astaxanthin in diabetic db/db mice. BioFactors 20:49-59.

Uchiyama K., et al., (2002). Astaxanthin Protects –cells against glucosetoxicity in diabetic db/db mice. Redox Report 7:290-292.

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