

19th International Conference on

Medicinal Chemistry & Multi Targeted Drug Delivery

International Conference on **Catalysis and Pyrolysis**

November 05-06, 2018 | San Francisco, USA

Lyso-DGTS lipid isolated from microalgae enhances PON1 activities *in vitro* and *in vivo*, increases paraoxonase1 penetration into macrophages and decreases cellular lipid accumulation

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High-density lipoprotein (HDL) plays an important role in preventing atherosclerosis. The antioxidant effect of HDL is mostly associated with paraoxonase1 (PON1) activity. Increasing PON1 activity using nutrients might improve HDL function and quality and thus, decrease atherosclerotic risk. We previously isolated and identified a novel active compound, lyso-DGTS (C20:5,0) from *Nannochloropsis* sp. ethanol extract. In the present study, its effect on PON1 activities was examined and the mechanism by which the compound affects PON1 activity was explored. Lyso-DGTS elevated recombinant PON1 (rePON1) lactonase and esterase activities in a dose- and time-responsive manner and further stabilized and preserved rePON1 lactonase activity. Incubation of lyso-DGTS with human serum for 4h at 37°C also increased PON1 lactonase activity in a dose-responsive manner. Using tryptophan-fluorescence-quenching assay, lyso-DGTS was found to interact with rePON1 spontaneously with negative free energy ($\Delta G = -22.87$ KJ/mol at 25°C). Thermodynamic parameters and molecular modeling calculations showed that the main interaction of lyso-DGTS with the enzyme is through a hydrogen bond with supporting van der Waals interactions. Furthermore, lyso-DGTS significantly increased rePON1 influx into macrophages and prevented lipid accumulation in macrophages stimulated with oxidized low-density lipid dose-dependently. *In vivo* supplementation of lyso-DGTS to the circulation of mice fed a high-fat diet via osmotic mini-pumps implanted subcutaneously significantly increased serum PON1 lactonase activity and decreased serum glucose concentrations to the level of mice fed a normal diet. Our findings suggest a beneficial effect of lyso-DGTS on increasing PON1 activity and thus, improving HDL quality and atherosclerotic risk factors.

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