Tailoring antioxidant activity of phenolic acids by lipophilization: cut-off effect and mitochondria targeting

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Nowadays, it is admitted that cancers are associated with oxidative stress caused by an imbalance between ROS and antioxidants. Since mitochondria are the major site of ROS production, they represent a prime subcellular target to deliver antioxidants. To target mitochondria and consequently to improve the antioxidant properties, we developed here a new strategy consisting in fine-tuning the hydrophobicity of phenolic compounds by the grafting of various aliphatic chains. This lipophilization has been achieved on rosmarinic acid to obtain rosmarinate esters (from methyl to octadecyl). The incubation of these lipophilized antioxidants on cancerous ROS-overexpressing fibroblasts showed a cut-off effect of the alkyl chain length on the antioxidant activity with an optimal activity for the decyl rosmarinate. Indeed, increasing the chain length leads to an increase of the antioxidant activity until a threshold is reached and beyond which any lengthening of the alkyl chain resulted in a significant decrease of antioxidant activity. Interestingly, we evidenced by confocal microscopy that esters have different locations in the subcellular compartments and that these locations are directly correlated to the type of alkyl chain grafted on the phenolic structure: mitochondria for medium chain esters and cytosolic location for long chain rosmarinate esters. Furthermore, dynamic light scattering demonstrated that rosmarinate esters with medium and long alkyl chains, depending on their concentrations can self-assemble in nano-objects. The longer the chain length, the bigger the aggregate. Taken together, these results suggest that the penetration of antioxidant in mitochondria is size-dependant and that only a medium chain confers to the corresponding ester the adequate size and lipophilicity to enter the mitochondria.