



GLOBAL SKIN HEALTH

A SALICYLIC ACID DERIVATIVE EXTENDS THE LIFESPAN OF CAENORHABDITIS ELEGANS BY ACTIVATING AUTOPHAGY AND THE MITOCHONDRIAL UNFOLDED PROTEIN RESPONSE

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Plant extracts containing salicylates are probably the most ancient remedies to reduce fever and ease aches of all kind. Recently, it has been shown that salicylates activate adenosine monophosphate activated kinase (AMPk), which is now considered as a promising target to slow down aging and prevent age-related diseases in humans. Beneficial effects of AMPk activation on lifespan have been discovered in the model organism *Caenorhabditis elegans*, a roundworm. Indeed, salicylic acid and acetyl salicylic acid extend lifespan in worms by AMPk and the forkhead transcription factor DAF-16/FOXO. Here, we investigated whether another salicylic acid derivative 5-octanoyl salicylic acid (C8-SA), developed as a controlled skin exfoliating ingredient, had similar properties using *C. elegans* as a model. We show that C8-SA increases lifespan of *C. elegans* and that a variety of pathways and genes are required for C8-SA mediated lifespan extension. C8-SA activates AMPK and inhibits TOR both in nematodes and in primary human keratinocytes. We also show that C8-SA can induce both autophagy and the mitochondrial unfolded protein response (UPRmit) in nematodes. This induction of both processes is fully required for lifespan extension in the worm. In addition, we found that the activation of autophagy by C8-SA fails to occur in worms with compromised UPRmit, suggesting a mechanistic link between these two processes. Mutants that are defective in the mitochondrial unfolded protein response exhibit constitutive high autophagy levels. Taken together, these data therefore suggest that C8-SA positively impacts longevity in worms through induction of autophagy and the UPRmit. It has been described before that autophagy plays an important role in the keratinization process during epidermal differentiation. Therefore, these new findings indicate that, beyond previously demonstrated exfoliating properties, salicylic derivatives might also show interesting anti-aging benefits for the skin.

