


Using Animal Models to Evaluate the Impact of Botanicals on Aging, Lifespan, and Healthspan


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Objectives



- To understand the importance of animal models in pre-clinical aging research.
- To discuss an experimental algorithm to study anti-aging natural products
- To understand the importance of the quality of botanical extracts in research

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Aging, Lifespan and Healthspan



- Aging research has focused mostly on increasing lifespan
- Healthspan pharmacology: Interventions to improve healthspan
 From Pre-Clinical (Animal Models) to Clinical (Humans) Studies

UCI Center for Healthspan Sciences

Lifespan/Healthspan Graph: Tim Peterson, Institute for Public Health

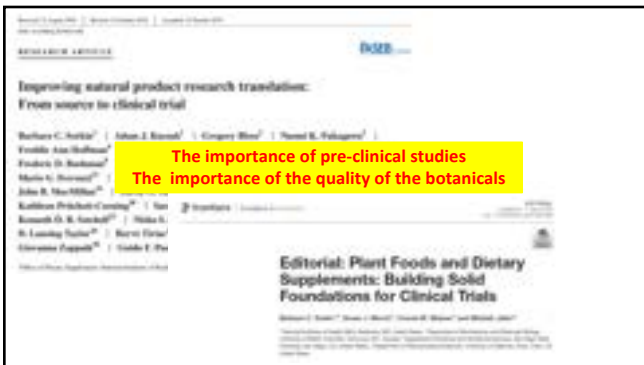
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Why Using Animal Models in Pre-clinical Aging Research?



- We can learn a lot from animal studies during the pre-clinical phase!
- Cost-effective/Practical/Shorter Lifespans
- Understanding Fundamental Mechanisms
- Genetic Manipulation
- Modeling Age-Related Diseases
- Testing Interventions
Pharmaceuticals and Natural Products
- Diversity of Animal Models
Mice: many physiological similarities to humans
Fruit flies and worms: high-throughput lifespan and healthspan studies.

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Commonly Used Animal Models in Aging, Lifespan and Healthspan Research



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Common Animal Models in Aging Research

Animal	Pros	Cons
Worms (<i>C. elegans</i>)	1. Insect, Short lifespan 2. Genetically defined & Mutants 3. Low maintenance costs and easy to handle in laboratory settings.	1. Significant physiological differences from humans 2. Limited complexity can oversimplify some aging processes.
Fruit Flies (<i>Drosophila melanogaster</i>)	1. Insect, Short lifespan 2. Genetically defined & Mutants 3. More complex than worms, allowing for studies of more sophisticated biological and physiological processes. 4. Conservation of many aging-related genes and 75% of disease genes with humans.	1. Still significantly different from humans in physiology. 2. Limited in modeling some human-specific aging aspects such as cognitive decline.
Mice (<i>Mus musculus</i>)	1. Mammal, Physiologically and genetically closer to humans. 2. Genetically defined & Mutants. 3. Complex organ systems and diseases related to aging. 4. Suitable for pharmacological and intervention studies.	1. Longer lifespan requires more time and resources for aging studies. 2. Higher maintenance costs and ethical considerations compared to invertebrate models. 3. Still some genetic and physiological differences from humans.

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Fruit Fly *Drosophila melanogaster*



Short lifespan and easy to maintain

Powerful genetics

~77% human disease genes

~40% protein sequences with mammalian homologs

Conserved nutrient sensing pathways

TOR, Insulin-IGF, sirtuins

Easy to evaluate healthspan



Pandey UB, Nichols CD. 2011. *Pharmacol Rev* 63:411-36. Jafari M. 2012. *FLY*.

Fontana et al. 2010. *Science*. Vol. 328 (5976): 321-326.

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Do you know what male flies do when they get rejected by female flies?

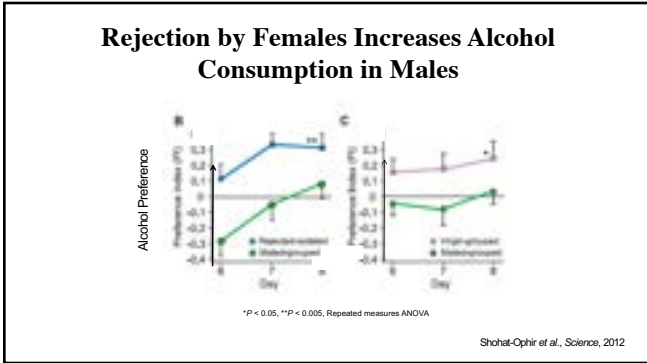


<https://www.mpg.de/12136139/fly-courtship-neuron> MPI of Neurobiology/ Kuhl

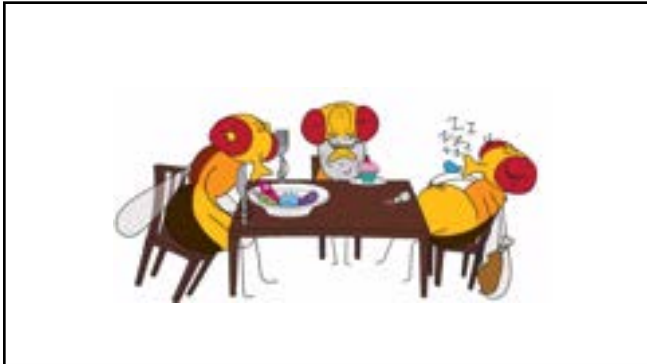
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Healthspan Pharmacology:
Interventions to add healthy years to human life.

Animal models present a great screening and pre-clinical system. We need to keep in mind:

The quality of the botanical extracts should be evaluated before the study and during the study (presence of the same biomarker compounds)

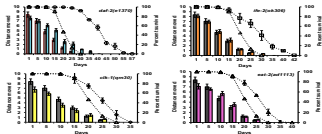
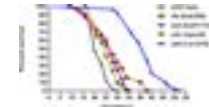
The results should be replicated in other model systems (yeast, worms, flies and mice)

The impact of the natural product on conserved pathways of aging (mechanism of action, impact on transcriptomics and not just phenotypes) should be evaluated

Animal models are great, but they are not humans....

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Uncoupling Lifespan and Healthspan in *C. elegans* Longevity Mutants

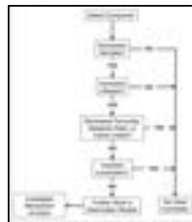


**Increasing lifespan
Not improving healthspan**

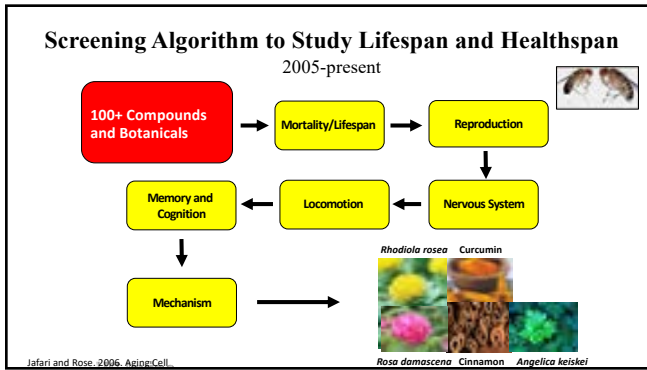
Bansal et al, PNAS 2015

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Drosophila melanogaster as a model system for the evaluation of anti-aging compounds



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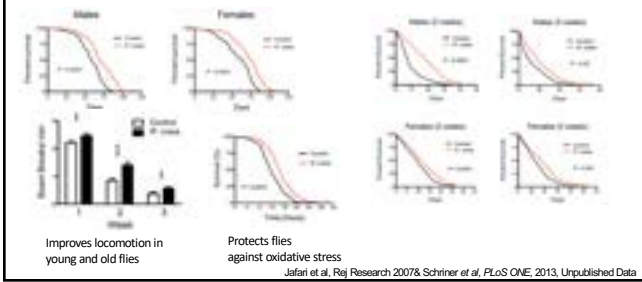
Rhodiola rosea (Golden Root)

Biomarker Molecules

- Used in traditional medical practices as an adaptogenic plant
- Arctic and dry regions: Siberia, part of China, and now Alaska
- High quality *Rhodiola rosea*:
 About 3% rosavins and 1% salidroside
- The importance of high quality pre-clinical studies

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Rhodiola rosea Extends Lifespan and Improves Healthspan



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Rhodiola rosea Mechanism of Action

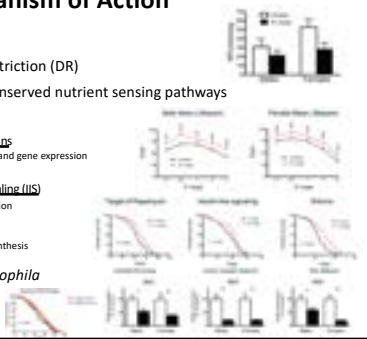
- Decreases ROS in mitochondria
- Acts independently from dietary restriction (DR)
- Acts independently from 3 major conserved nutrient sensing pathways (longevity-related genes)

Silent information regulator 2 (Sir2) proteins
Senses NAD⁺ levels to regulate protein activity and gene expression
Activation extends lifespan

Insulin and insulin-like growth factor signaling (IIS)
Senses nutrient levels to regulate gene expression
Inhibition extends lifespan

Target of rapamycin (TOR)
Senses amino acid levels to regulate protein synthesis
Inhibition extends lifespan

- Decreases RNA expression of 3 *Drosophila* Insulin-like peptides
- Acts independently of autophagy



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Labenstein et al. *Cell Hosts Microbes* 2016, 19(1):1-12
Microbiology and Pathogen-Host Interactions

Gut Pathogens

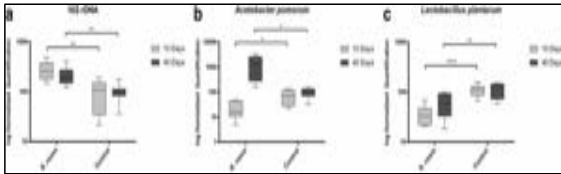
RESEARCH Open Access

The impact of *Rhodiola rosea* on the gut microbial community of *Drosophila melanogaster*

Manuela E. Labenstein, Doro Blank, Eugenio N. Santolucito, Sebastian C. Scherke and Matthias Müller

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***Rhodiola rosea* Modulates the Microbiome:
Increases *Acetobacter* and Decreases *Lactobacillales***



Labachyan K. et al. Gut Pathogens 2018;10:1-10

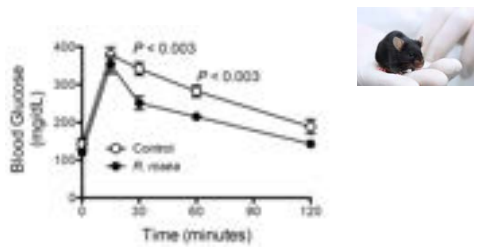
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Testing *Rhodiola rosea* in Mice



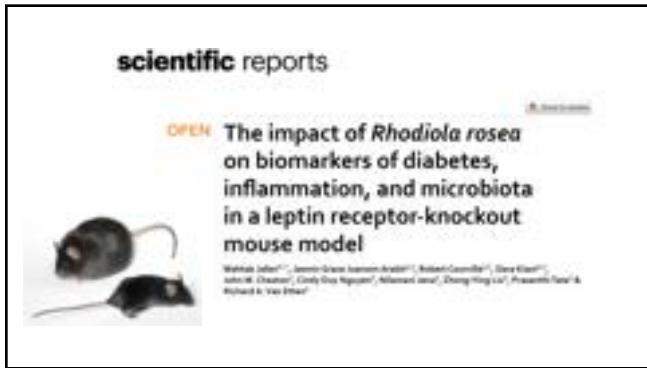
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***Rhodiola rosea* Improved Glucose Tolerance in Mice**

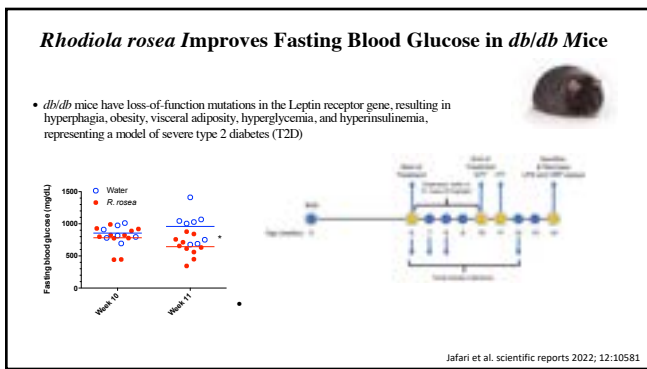


NIH. Jafari and De Cabo. 2008. Unpublished data

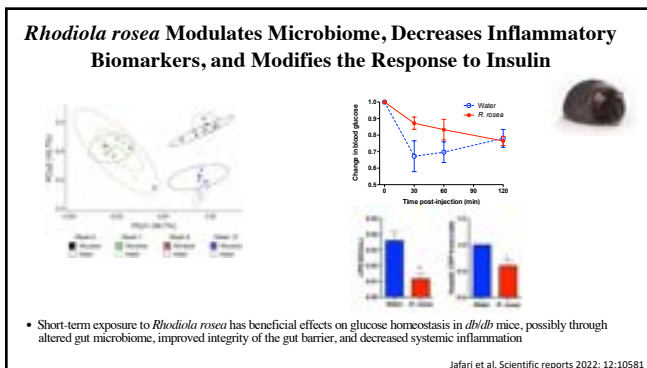
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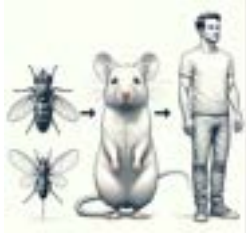
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Animal models are great, but they are not human!

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Aging Research....

*“The secret of staying young is to live honestly,
eat slowly, and lie about your age.” Lucille Ball*

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Acknowledgments

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