



# resveratrol re-imagined



**Update on Clinical Studies**

**April, 2020**

**Marcia da Silva Pinto  
(Technical Manager)**

# Update on the Ongoing Clinical Studies

Healthy Living Series | Clinical Studies Review | March 2020



## Revitalizing Resveratrol for Healthy Living

A Closer Look at Veri-te™ Sponsored Clinical Studies

Prepared by Johannes Haerle, PhD

### Resveratrol, an Ingredient Supporting Healthy Living

As our body combats daily stress and ages, maintaining healthy circulation is important for all bodily functions. Supplementation of a healthy diet with vasoactive ingredients can be a key strategy for healthy living. 'Vasoactive ingredient' is a term that describes specific bioactive compounds that can boost blood flow in all tissues, including the brain, by enhancing endothelial function.

One of the most potent vasoactive ingredients found in nature is resveratrol, a polyphenol produced in low levels in plants such as grapes and berries to protect themselves from environmental stress and pathogens. Resveratrol is one of the best characterized polyphenols today with over 170 published and 30 ongoing clinical studies. Research indicates that resveratrol supplementation holds great potential for maintaining healthy bodily functions such as brain health by supporting healthy vascular function as the body reacts to stress or changes brought on by age.

Evolve is deeply committed to the expansion of resveratrol research and provides nutraceutical manufacturers with a range of innovative resveratrol solutions under its Veri-te resveratrol brand. This clinical review of Veri-te sponsored studies highlights the multi-functional benefits of resveratrol for healthy living with a specific focus on cutting edge research around resveratrol supplementation and cognitive performance, gut microbiota, oral health and postmenopausal bone and muscle loss.

New research using Veri-te resveratrol at the University of Newcastle in Australia is conducting the largest and longest running resveratrol study, titled "Resveratrol Supporting Healthy Aging in Women" (RESHAW). Of particular interest are the positive results for counteracting the age and menopause-related accelerated cognitive decline in the aging population. Other interim results coming from RESHAW are further outlined in this report.

This review also outlines research coming from the polyphenol research group within the Brain Performance and Nutrition Research Centre at Northumbria University in the United Kingdom. This group is investigating the effects of Veri-te resveratrol supplementation on gut microbiota, systemic inflammation and brain function.

This research highlights that resveratrol follows a multifaceted approach and its beneficial effects are based on its molecular structure, cellular and systemic functions. Ultimately, resveratrol can potentially help rejuvenate the mitochondria and counteract the negative effects of stress and aging.

It is clear that supplementation with Veri-te resveratrol can be a key strategy for the design and delivery of supplements that can support healthy living. Please note that the administered levels cited in the clinical studies were determined by independent researchers conducting the studies. Please refer to local regulations when establishing daily doses to be delivered by dietary supplements.

Evolve's Veri-te resveratrol produced via fermentation has a neutral taste and is odorless and colorless, making it easily formulated into many applications from capsules to instant powder beverages. Evolve continues its commitment to supporting customers with research-backed science and concept development for new product development with Veri-te resveratrol.

Evolve  
www.evolve.com  
evolve www.veriteresveratrol.com

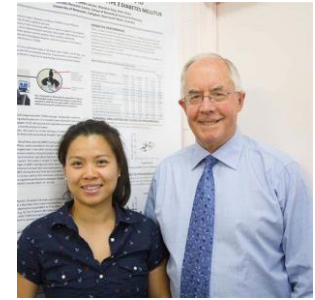


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- RESHAW study
- Gut-Brain Axis studies
- PK study: Veri-Sperse™
- What is next? Future studies

# RESHAW Study

*The largest and longest clinical trial on resveratrol supplementation*



**Title:** Resveratrol for Healthy Ageing in Women “RESHAW” (Reg. Nr. 370696)

**Principal Investigators:** Prof Peter Howe & Dr. Rachel Wong (Clinical Nutrition Research Centre, University of Newcastle, Australia)

**Student investigator:** Jay Jay Thaug Zaw (Clinical Nutrition Research Centre, University of Newcastle, Australia)

125 women (60+)  
24 months  
2x 75 mg/day

**RCT**  
**Placebo vs. Treatment**  
*Data analysis:*

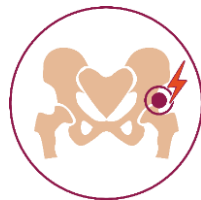
- Parallel (12 months)
- Crossover (24 months)



Vasoactivity



Cognition performance



Bone formation



Quality of life

**Veri-te™**  
RESVERATROL

“Our clinical trials with resveratrol indicate that this bioactive polyphenol can be considered one of the most potent vasoactive nutrients that we have ever studied. The RESHAW study results point to multiple positive impacts of resveratrol for counteracting the development and progression of chronic diseases afflicting our aging Western population.”

-Professor Peter Howe

Dr. Rachel Wong and Emeritus Professor Peter Howe from the University of Newcastle, Australia are the principal investigators of RESHAW.

## Women’s Health

### Resveratrol Supporting Healthy Aging in Women (RESHAW)

As a result of reduced estrogen production, menopause heightens a woman’s risk of osteoporosis, cognitive decline as well as mental and physical discomfort.<sup>1</sup> Postmenopausal women can benefit from resveratrol supplementation, which has been shown to have phytoestrogen activity and combats the cellular aging processes. Since resveratrol can be easily incorporated into a daily diet, it is a well known strategy to support healthy living.<sup>2</sup>



### A brief introduction to RESHAW

RESHAW is a two-year clinical trial of resveratrol in 125 post-menopausal women conducted by Professor Howe, Dr. Wong and PhD student Jay Jay Thaug Zaw at the University of Newcastle, Australia. A National Health and Medical Research Council funded initiative, RESHAW is the largest and longest running study of its kind and was designed to investigate the impact of Veri-te™ resveratrol supplementation on cognitive performance, along with a wide range of secondary outcomes including body composition and perception of wellbeing, physical function and pain. With over 170 human clinical studies, resveratrol has continued to gain attention as one of the most active natural activators of SIRT1, a protein which directs the cell cycle and longevity.<sup>3</sup> This vast amount of research proves that Veri-te resveratrol can be a key strategy for the design and delivery of effective supplements that support healthy aging.<sup>4</sup>

Interim RESHAW results indicate that Veri-te resveratrol supports healthy living in postmenopausal women



#### Peak brain health supported by:

- Enhancing cognitive performance in individual cognition tests
- Improving the arterial function, particularly in the brain by increasing cerebral circulation
- Increasing healthy blood flow and reducing arterial stiffness



#### Quality of life significantly impacted by:

- Improving mental performance, especially mood and pain perception
- Reducing menopausal symptoms and sleep disturbance, while improving general wellbeing



#### Bone health increased by:

- Improving the bone mineral density measured in the lumbar spine and neck of femur
- Reducing the risk of bone fracture



#### Overall health improved by:

- Increasing hand grip strength while reducing loss of muscle strength
- Supporting healthy blood glucose levels and insulin sensitivity

125 post-menopausal women, 24 months, 75 mg Veri-te resveratrol twice daily, cardio-metabolic, brain and bone health parameters as well as cognitive task performance

**Status:** Completed

**Veri-te™**  
RESVERATROL

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RESVERATROL

resveratrol  
re-imagined

# RESHAW Study: Results & Deliverables



Article

## Sustained Cerebrovascular and Cognitive Benefits of Resveratrol in Postmenopausal Women

Jay Jay Thaug Zaw<sup>1</sup>, Peter R.C. Howe<sup>1,2,3</sup> and Rachel H.X. Wong<sup>1,2,\*</sup>

<sup>1</sup> School of Biomedical Sciences and Pharmacy, University of Newcastle, Callaghan, New South Wales 2308, Australia

<sup>2</sup> Institute for Resilient Regions, Springfield Central, University of Southern Queensland, Queensland 4300, Australia

<sup>3</sup> School of Health Sciences, University of South Australia, Adelaide, South Australia 5000, Australia

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Received: 14 February 2020; Accepted: 17 March 2020; Published: 20 March 2020

**Abstract:** Deficits in the cerebral microcirculation contribute to age-related cognitive decline. In a pilot study of postmenopausal women, we found that supplementation with a low dose of resveratrol, a phytoestrogen, for 14 weeks improved cerebrovascular and cognitive functions. We have since undertaken a larger, longer term study to confirm these benefits. Postmenopausal women aged 45–85 years ( $n = 129$ ) were randomized to take placebo or 75 mg trans-resveratrol twice daily for 12 months. Effects on cognition, cerebral blood flow, cerebrovascular responsiveness (CVR) and cardiometabolic markers (blood pressure, diabetes markers and fasting lipids) were assessed. Compared to placebo, resveratrol improved overall cognitive performance ( $P < 0.001$ ) and attenuated the decline in CVR to cognitive stimuli ( $P = 0.038$ ). The latter effect was associated with reduction of fasting blood glucose ( $r = -0.339$ ,  $P = 0.023$ ). This long-term study confirms that regular consumption of resveratrol can enhance cognitive and cerebrovascular functions in postmenopausal women, with the potential to slow cognitive decline due to ageing and menopause.

**Keywords:** resveratrol; ageing; menopause; cognitive decline; cerebrovascular function; neurovascular coupling; phytoestrogen; nutraceutical

### 1. Background

Since 1990, the number of people globally living with dementia has more than doubled. This is mainly due to increased population growth and ageing [1]. Importantly, independent of life expectancy, dementia mortality rates in women in 2016 were almost twice that of men. This may be partly attributable to the abrupt decline of estrogen at menopause and the associated loss of its protective effects on cardiovascular [2] and neural functions [3].

Estrogen activates estrogen  $\alpha$  and  $\beta$  receptors (ER) on endothelial cells to facilitate vasodilatation by increasing endothelial nitric oxide (NO). Thus, estrogen deprivation can accelerate age-related arterial stiffening and impair tissue perfusion by reducing endothelium-dependent vasodilatation. This not only increases the risk of cardiovascular disease postmenopausally [4] but also reduces cerebrovascular responsiveness (CVR) in postmenopausal women compared to pre-menopausal women and men [5,6]. Reduced cerebral blood flow (CBF) and CVR are associated with cognitive impairment [7]. We have also reported that reduced CVR during mental task activation (neurovascular coupling) is predictive of poor cognitive performance in postmenopausal women [8]. A meta-analysis has shown that postmenopausal women perform worse on verbal memory and executive function tests compared to peri-menopausal women [9]. Therefore, maintaining the health of the cerebral vasculature may slow cognitive decline in postmenopausal women.

Nutrients 2020, 12, 826; doi:10.3390/nu12030826

www.mdpi.com/journal/nutrients

Change in z-scores for cognitive domains

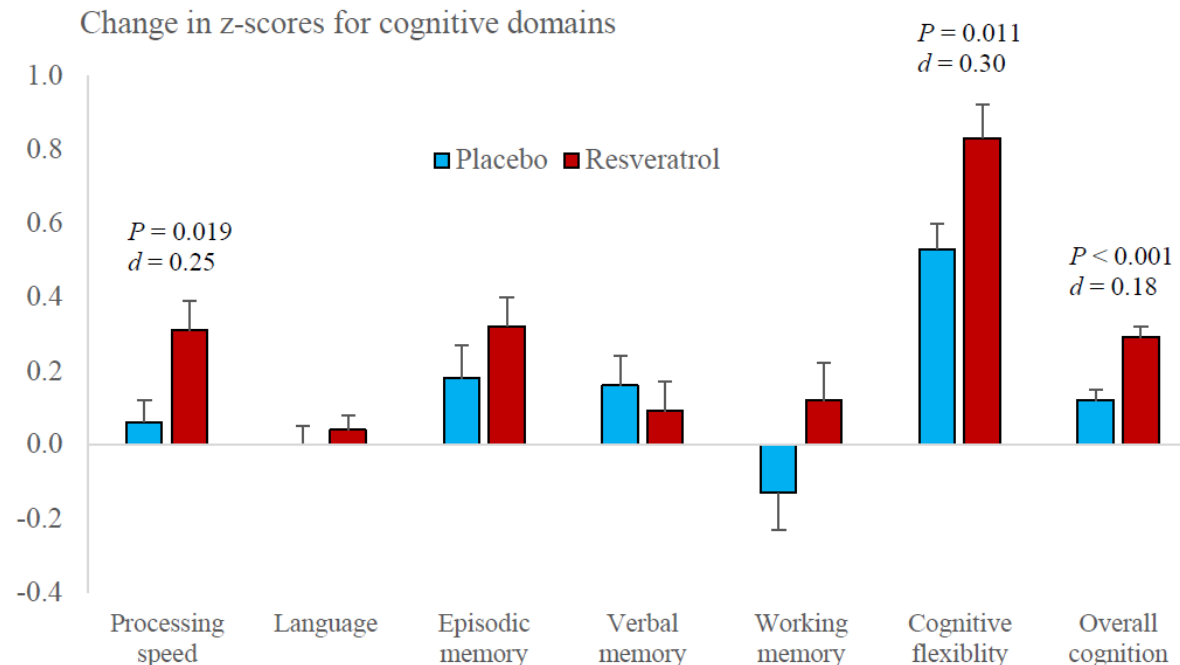


Figure 2. Performance changes in cognitive domains following placebo and resveratrol treatments.

*“Our findings support the adoption of resveratrol as a low-cost, effective intervention to help counteract the age and menopause-related accelerated cognitive decline in our ageing population.*

*Subsequent publications from this study will report effects of resveratrol on bone health, physical function and quality of life measures which, collectively, will establish resveratrol as a viable intervention to promote healthy ageing in women.”*

# RESHAW Study: Results & Deliverables

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**Abstract accepted for oral presentation (August 22<sup>nd</sup>, 2020) – Dr. Rachel Wong**  
*“Resveratrol benefits bone health in postmenopausal women – outcomes of the two-year RESHAW trial”*

**Q2, 2020: 3 more scientific publications in *peer reviewed* journals**

# Gut-Brain Axis with Veri-te™: Cognition, Inflammation and Gut Microbiota Composition



**Researchers:** Dr. Emma Wightman (Principal Investigator) & Ellen Smith (Doctorate Student), The Brain Performance and Nutrition Research Centre, Northumbria University, UK

**Title:** The Acute and Chronic Effects of Resveratrol Supplementation on Cognitive Function, Gastrointestinal Microbiota and Cerebral Blood Flow (*Identifier: NCT03448094*)

Veri-te™  
RESVERATROL



Study 1

- 100 participants, BMI > 25, 2 x 250 mg/day, 3 months
- Veri-te™ benefits on promoting: healthy gut, brain health (memory, attention and mood), normal blood pressure and reduction of inflammation



Study 2

- 100 participants, BMI 18.5 - 40, 2 x 250 mg/day, 1 month
- Effect of diet and Veri-te™ on brain health (memory, attention and mood) and response to inflammation



# Gut-Brain Axis with Veri-te™: Cognition, Inflammation and Gut Microbiota Composition



**Study 3?**

Status: Completed

Most of the data has been collected with some further analysis being performed at the moment (microbiota profile/composition)

Data is still blinded

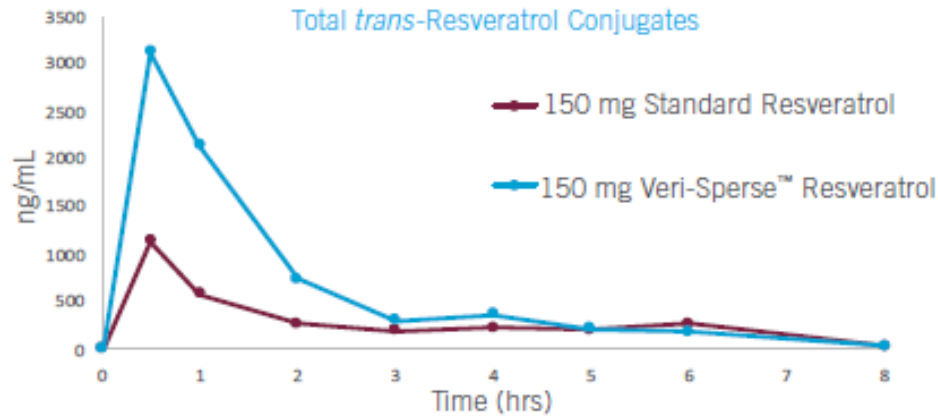
**Q2/Q3, 2020:** at least 2 scientific publications in *peer reviewed* journals

# PK Clinical Study

Principal Investigators: **Dr. David Briskey** (School of Human Movement and Nutrition Sciences, University of Queensland, Australia) & **Amanda Rao** (RDC Clinical, Australia)

37 subjects (> 18 yo)  
8 hours  
75 mg or 150 mg

Single dose  
Veri-te™ with or without  
the applied LipiSperse®  
dispersion technology



Veri-Sperse™ vs. Standard Resveratrol

**Bioavailability: approx. 2 times ↑**

**Maximum concentration (C<sub>max</sub>): 3-fold ↑**

**Status: Completed**

Veri-Sperse™ RESVERATROL | Cold Water Dispersible (CWD)

With consumers seeking products that offer proven efficacy and maximized absorption, the bioavailability of an ingredient can be an important consideration when developing a new product with resveratrol.

**Veri-Sperse™ resveratrol advantage:**

- Enhanced bioavailability supported by a clinical pharmacokinetics study
- High active loading capacity
- Improved dispersibility
- Powder form for ease of storage and formulation
- Neutral tasting

**Veri-Sperse™ resveratrol is perfect for:**

- Instant powder beverages
- Oral dispersible tablets
- Effervescent tablets
- Nutraceuticals

**Veri-Sperse™ resveratrol with enhanced bioavailability**

Evolva has partnered with Pharmako Biotechnologies to create Veri-Sperse™ resveratrol, using LipiSperse® Dispersion Technology, which is proven to enhance bioavailability. Veri-Sperse™ is an innovative delivery solution. With a 90% *trans*-resveratrol content, this unique ingredient system is designed to deliver resveratrol into aqueous environments in a simple and effective way.

Veri-Sperse™ resveratrol has been recently demonstrated to have improved bioavailability as evidenced by a pharmacokinetic (PK) clinical study where participants were supplemented with Veri-Sperse™ resveratrol.

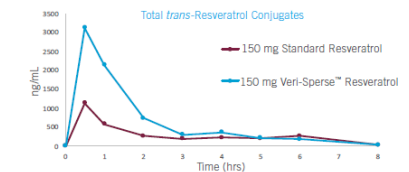
**How does it work?**

Unlike other technologies, LipiSperse® coats every particle ensuring they do not agglomerate in aqueous environments. Proper dispersion also accounts for the increased bioavailability.

- This technology offers two key benefits:
- Better absorption in the body due to the increased effective surface area
  - High active load of 90%

**LipiSperse® increases the absorption and improves the bioavailability of resveratrol**

Resveratrol absorption was measured from blood samples taken prior to the start and in the course of 24 hours post supplementation. Plasma *trans*-resveratrol and conjugates were measured as a change from the baseline for each participant at each time-point. At 24 hours, no metabolites were detected (data not shown).



The calculated area under the curve (AUC<sub>0-24h</sub>) values were 6297 ng·h/mL for Veri-Sperse™ versus 3145 ng·h/mL for standard resveratrol. As shown by the strong increase in AUC<sub>0-24h</sub> value:

- The bioavailability of Veri-Sperse™ in humans is nearly twice as high compared to standard resveratrol at an equal dose
- Maximum concentration (C<sub>max</sub>) of Veri-Sperse™ resveratrol is increased three-fold

Please note that these are the summary results from unpublished data. The complete data will be published in the coming months.

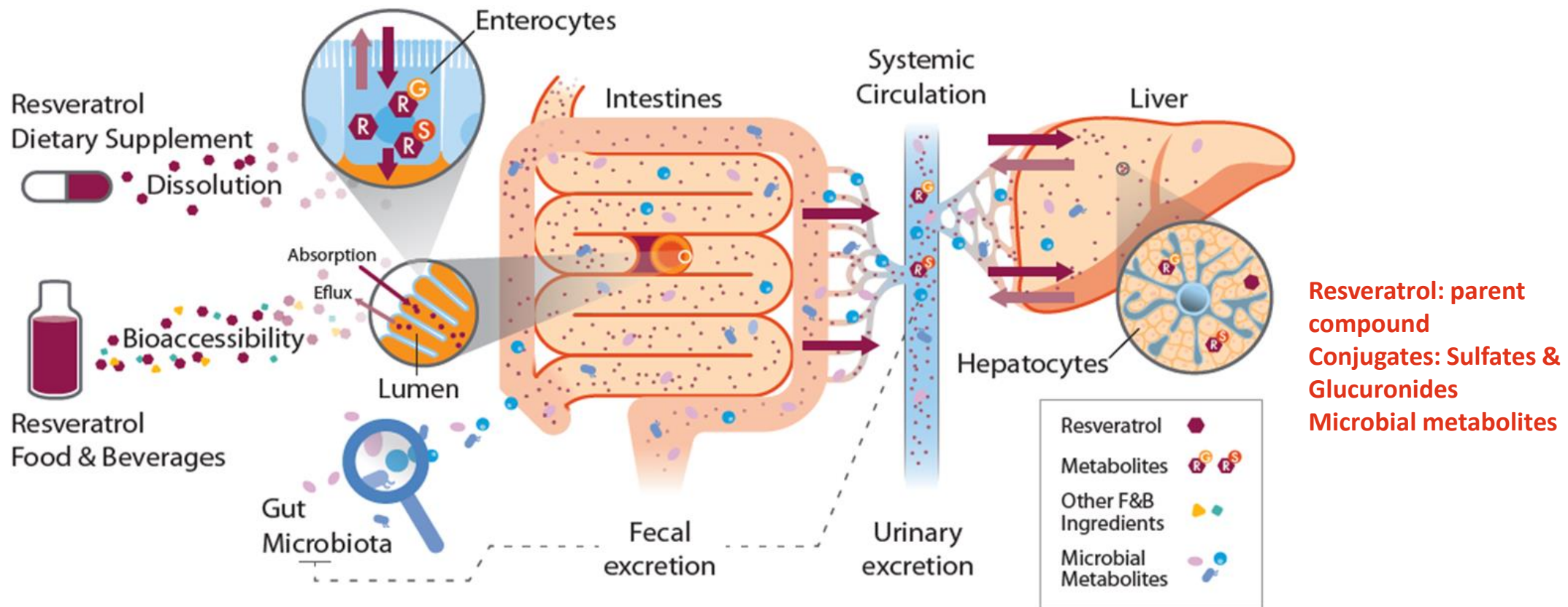
Design: Randomized Controlled Trial (RCT), 39 healthy men and women (18+ yrs.), 150 mg standard resveratrol vs. 150 mg Veri-te™ resveratrol with LipiSperse® dispersion technology, single intake. 10 plasma blood samples were taken.



# Let's talk about Bioavailability

*Bioavailability is the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action" (US FDA & EMA)*

*"Resveratrol is highly absorbed orally (~70%), yet has poor systemic bioavailability (~0.5%)"*



# Bioavailability & Bioefficacy

- ❖ More than 170 clinical studies showing efficacy of resveratrol supplementation
- ❖ Systematic reviews and meta-analyses showing positive results
- ❖ How about the studies not showing effect?
  - *Daily dose administered: 5 mg to 5000 mg*
  - *Duration of treatment: acute (1 day) to months*
  - *Target populations: healthy and diseased*
  - *Gender: men and women*
  - *Clinical endpoints*

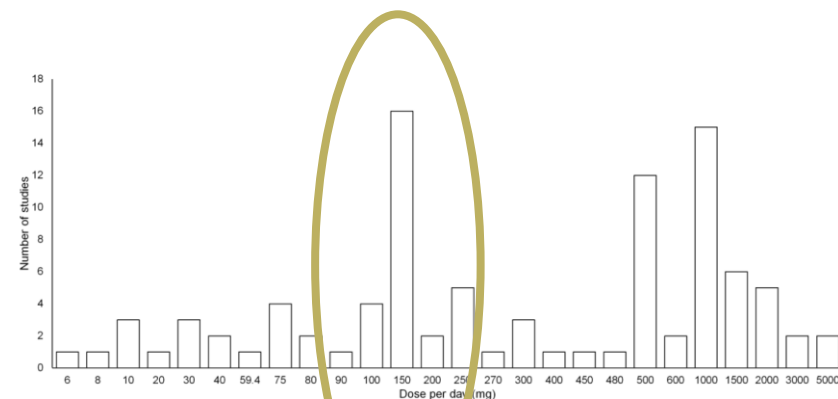


Fig. 3. Frequency distribution of daily resveratrol dosage administered in human trials. The publications were searched using PubMed (accessed August-28-2018; search term: resveratrol; limit: clinical trials). In total, 79 trials were reported.

Pezzuto (2019)

## Urgent Need:

Well-designed studies with robust hypothesis that provide scientific-based evidence

# Bioavailability 101



## Bioavailability

### What is the "resveratrol paradox"?

Although it is thought that resveratrol has low bioavailability, the evidence of bio-activity with more than 170 published clinical studies seems unquestionable. Additionally, numerous systematic reviews and meta-analysis have reported positive associations. Therefore, it is clear that the low levels of resveratrol found in blood plasma are not telling us the whole story, and resveratrol is considered to have high bio-efficacy.<sup>2,3</sup>

### Rethink bioavailability for resveratrol

Bioavailability is classically defined as "the rate and extent to which the active substance or active moiety is absorbed from a pharmaceutical form and becomes available at the site of action."<sup>1</sup>

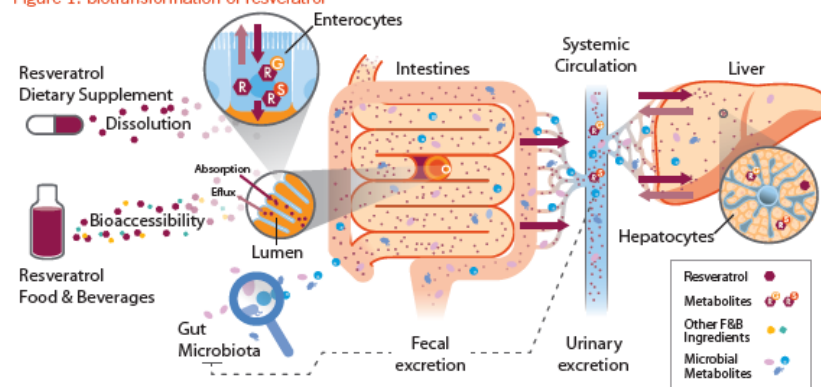
Although monitoring the circulating levels of a compound in the blood may be informative, it is important to consider that many compounds undergo *in situ* activation. Due to this activity, many compounds can be transformed into one or more active metabolites and potentially contribute to the observed clinical response. Another critical point to consider is the definition of "site of action." The site of action or target can be an organ, tissue, or impact humans and animals on a cellular level; this is a critical factor when considering bio-efficacy.<sup>1</sup> This broadened understanding is key, particularly with dietary supplements containing bio-active compounds such as resveratrol, since resveratrol metabolites should be considered as part of the answer to bio-efficacy.

### How bioavailable is resveratrol?

Resveratrol has been reported as being highly absorbed orally (~70%) in humans, yet has low systemic bioavailability (~0.5%), meaning that only low levels are found in the blood plasma.<sup>4</sup> Figure 1 summarizes the metabolic fate and bio-transformation of resveratrol in the human gastrointestinal tract and metabolism in different organs.

The reason for the referred low systemic bioavailability is that resveratrol undergoes a rapid metabolism into resveratrol sulfate and glucuronide conjugates. In addition, resveratrol can be further metabolized by the gut microbiota. All these metabolites coming from the conjugation with sulfates and glucuronides and from microbial metabolism can be further absorbed into the systemic circulation and therefore reach different organs and have an effect.

Figure 1. biotransformation of resveratrol



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# What is next? 2020 Clinical Studies



**Continue bringing science-based evidence on resveratrol supplementation by collaborating with Key Opinion Leaders and Experts**

**Menstrual  
migraine**

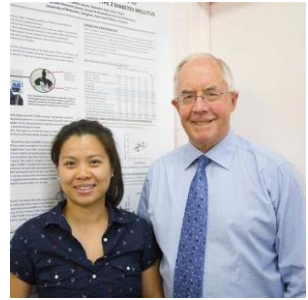
**Skin Health**

**Sports  
Nutrition**

# RESFORMM Study

## Can resveratrol supplementation mitigate menstrual migraine?

(Reg. ACTRN12620000180910)



Principal Investigators: **Prof Peter Howe & Dr. Rachel Wong** (Clinical Nutrition Research Centre, University of Newcastle, Australia)

Student investigator: **Jemima Dzator** (Clinical Nutrition Research Centre, University of Newcastle, Australia)

**Hypothesis:** Resveratrol can counteract menstrual migraine by improving the circulation of blood in the brain

RCT  
Placebo vs. Treatment  
Crossover  
*Duration: 3 months*



### Outcomes:

- ✓ Menstrual migraine burden
- ✓ Cerebral blood flow
- ✓ Quality of life
- ✓ Gene expression

**Status:** Currently enrolling participants

# Skin Health: Beauty from Inside & Out



Study lead by Evolva: **Marcia da Silva Pinto, Jerome De La Baume & Clare Panchoo**

CRO in France specialized in skin health studies

RCT

Placebo vs. Treatment  
Parallel

*Duration: 2 months*

Oral (capsules)

Topical (cream)

Oral + Topical



## Outcomes:

- ✓ Skin appearance: wrinkles, firmness, radiance (color + age spots, texture)

**Status:** Protocol discussion

**Expected outcome:** Q4/2020

# Sports Nutrition: Endurance and Recovery



Principal Investigator: **Dr. Stephen Bailey** (School of Sport, Exercise and Health Sciences, Loughborough University, UK)

RCT  
Placebo vs. Treatment  
Crossover



## Expected outcomes:

- ✓ Effect of resveratrol supplementation on endurance and post-exercise recovery

**Status:** Protocol discussion

**Expected start:** Q3/2020



### Disclaimer

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Thank You

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