Circulatory benefits of resveratrol
a key to healthy brain ageing

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Healthy Aging Summit
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Preventive Health for an Aging Population

addressing the increasing gap between life expectancy and health-adjusted life expectancy


Preventive Health for an Aging Population

**Functional capacity (physical & mental fitness)**

- early life
- adult life
- older age

- Disability threshold
- range of function in individuals

**Age**

**WHY ARE PEOPLE LIVING LONGER?**

- genes
- diet
- lifestyle

**The shape of things to come?**

The Economist, 2003

**Metabolic Syndrome**

- obesity
- high blood pressure
- high blood fats
- high blood glucose, insulin

**Inflammation**

- predisposes to heart disease, diabetes
- chronic inflammatory conditions
- cognitive decline and dementia

**Singapore Longitudinal Ageing Study Cohort**
(Tze Pin Ng et al JAMA Neurol 2016)

**Increased risk of incident MCI**
MetS 1.5; obesity 1.4; T2DM 2.8; dyslipidemia 1.5; ≥3 CVR risk factors 1.6

**Increased risk of MCI → dementia**
MetS 4.3; T2DM 2.5; ≥3 CVR risk factors 4.9
Cerebral blood flow is reduced in mild cognitive impairment.


- No damage
- Neuronal dysfunction
- Cell death

Cerebral blood flow

- Mild hypoperfusion
  - Impaired learning & memory

- Moderate-severe hypoperfusion
  - ↓ neuron action potential
  - pH, H2O & electrolyte shifts
  - White matter damage
  - ↑ accumulation of toxins (Aβ, tau, heavy metals)

Impact of diet/lifestyle on the circulation

Flow mediated dilatation (FMD)

(assess endothelial function non-invasively)

Metabolic Syndrome
- Abdominal obesity
- High blood pressure
- High blood sugar
- High blood fat
- High salt intake
- Physical inactivity
- Smoking

endothelial dysfunction

- regulates vasomotor tone
- inhibits cell adhesion, platelet aggregation
- controls capillary exchange (selective permeability)
- controls vascular integrity (counteracts hypertrophy)

Impaired vascular function

Aging

Hypertension
- Coronary disease
- Stroke
- Kidney disease
- Cognitive impairment
- Alzheimer's disease
- Metabolic disorders; falls; exercise intolerance

Impaired vascular function and its pathological consequences can be prevented or attenuated by regular aerobic exercise and supplementation with selected bioactive (vasoactive) nutrients, e.g. omega-3, plant polyphenols.
Bioactive nutrients from plants

**Phytochemicals >10,000**

- Alkaloids
- Sterols
- Carotenoids (lutein)
- Phenolics
- Terpenes
- Fiber
- Organo S & Se Compounds

**Flavonoids >6,000**

- Phenolic Acids
  - Hydroxybenzoic acid
  - Hydroxycinnamic acid
- Flavonoids
  - Flavanols (e.g., catechins)
  - Flavones (e.g., naringenin)
- Tannins
  - Derived tannins (e.g., theaflavins)
  - Hydrolyzable tannins (e.g., gallic/ellagic acid esters)
- Coumarins
- Stilbenes
  - Resveratrol

**Generic antioxidants?**

or mediators of specific physiological functions, e.g. anti-inflammatory, endothelial dilatation?

**Phytochemicals**

- Flavonoids
  - Proanthocyanidins (berries, nuts)
  - Flavanones
  - Anthocyanidins
  - Isoflavones (soy)

Cocoa flavanol supplementation for 12 weeks improves FMD (Davison K et al. Int J Obesity 2008)

- independent of antioxidant activity
- mediated by epicatechin → NO↑

“Cocoa flavanols help maintain endothelium-dependent vasodilation, which contributes to normal blood flow”

They can also lower BP, improve insulin sensitivity, increase cerebral blood flow, enhance cognitive function

Multi-faceted benefits of resveratrol

Cardiovascular protection
Counteracts neuro-degeneration
Reduces chronic inflammation
Improves fat regulation & metabolism
Implements oxidative stress (anti-aging)
Cancer protection
Protects against bone loss
Improves insulin sensitivity

Evidence for circulatory benefits of resveratrol in humans

Resveratrol

- eNOS production
- NO inactivation
- NO bioavailability

Endothelial vasodilator function
Cerebral perfusion
Cognitive performance

adapted from Chachay et al, Br J Clin Pharm 2011

adapted from Xia N et al, Molecules 2014
adapted from Li & Forstermann, Cardiovasc Drugs Ther 2009
Clinical evaluation of circulatory and health benefits of resveratrol

Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure

R.H.X. Wong*, P.R.C. Howe*, J.D. Buckley*, A.M. Coates*, I. Kunz*, N.M. Berry*

Red wine polyphenol extract (600mg)
Cocoa flavanols (902mg)
Tea (450ml)
EGCG (300mg)

Acute dose-response study

FMD response (%)
Resveratrol dose (mg)
0 30 90 270
+2.5% +2.4% +3.7%
+1.9% +2.4% +3.4%
+1.5%

Chronic supplementation trial
Resveratrol 75mg/d for 6 weeks

FMD (%)
P=0.021
* -1.4% = 20% ↓ in CVD risk

Placebo Resveratrol

Resveratrol improved word reading (speed and accuracy) in Stroop CWT
Can resveratrol improve cognition by enhancing cerebral blood flow?
We use bilateral TCD probes to assess:

- steady state mean blood flow velocity and pulsatility index (arterial stiffness) in the middle cerebral artery
- cerebrovascular responsiveness (CVR) to hypercapnic or cognitive stimuli (dynamic measures similar to FMD)

**Global vasodilatation breathing CO2 (CVR to hypercapnia)**

**Regional vasodilatation during performance of a cognitive task**

\[
CVR (%) = \frac{\text{Peak velocity} - \text{Basal velocity}}{\text{Basal velocity}} \times 100
\]
Effects of resveratrol on cerebrovascular responsiveness (CVR) in T2DM

**Why diabetes?**
- Cognitive decline is accelerated in T2DM
- CVR is reduced in T2DM
- Cognitive deficits are associated with ↓CVR (Nealon R et al, J Diabetes Complications 2017)

Double-blind crossover trial
36 older adults with stable T2DM took single doses at weekly intervals

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**Original Article**

**Chronic resveratrol consumption improves brachial flow-mediated dilatation in healthy obese adults**

Rachel H.X. Wong¹, Narelle M. Berry⁴, Alison M. Coates⁵, Jonathan D. Buckley⁴, Janet Bryan⁶, Iris Kung⁴ and Peter R.C. Howe⁴,*

**Article**

**Acute Resveratrol Consumption Improves Neurovascular Coupling Capacity in Adults with Type 2 Diabetes Mellitus**

Rachel H.X. Wong¹, Daniel Raederstorff² and Peter R.C. Howe¹,*

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**CVR (%) to performing a demanding cognitive test**

*P=0.019

↑35%
Why postmenopausal women?

- Both systemic and cerebral vasodilator function declines more rapidly after menopause than in age-matched men.
- Risks of dementia and osteoporosis are far greater in elderly women than men.
- These changes are partly attributable to loss of protective effects of estrogen.
- Resveratrol activates both ERα and ERβ.

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Cerebrovascular and cognitive benefits of resveratrol in postmenopausal women

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Prevalence of dementia in Australia

AIHW 2012

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Clinical Evaluation of Effects of Chronic Resveratrol Supplementation on Cerebrovascular Function, Cognition, Mood, Physical Function and General Well-Being in Postmenopausal Women—Rationale and Design

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Effects of Resveratrol on Cognitive Performance, Mood and Cerebrovascular Function in Post-Menopausal Women; A 14-Week Randomised Placebo-Controlled Intervention Trial

Hamish M. Evans, Peter R.C. Howe and Rachel H.X. Wong.

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Low dose resveratrol improves cardiovascular health

R.H.X. Wong, R.S. Nealon, A. Scholey, P.
RESFEM study
Resveratrol improves cerebrovascular responsiveness and cognition

Change in CVR (%) to hypercapnia

Improvements in overall cognitive scores correlate with improvements in overall CVR to cognitive tasks (r= 0.363, P = 0.01)
**RESFEM study**
Resveratrol improves mood and reduces pain perception

- **Change in mood score**
  - Tension
  - Depression
  - Anger
  - Fatigue
  - Confusion
  - Total mood disturbances
  - Vigour

- **Change in pain score**

**Short form McGill Pain Questionnaire**
includes scores for overall pain (15 descriptors), present pain intensity and Visual Analogue rating

- Reduction in overall pain correlated with improvements in CVR to both hypercapnic ($r=-0.404$) and cognitive ($r=-0.459$) stimuli

- **Pain scores**
  - VAS (cm)
  - Pain intensity

- **P-values**:
  - Placebo vs Resveratrol:
    - Tension: $P<0.033$
    - Depression: $P=0.032$
    - Anger: $P=0.004$
    - Fatigue: $P=0.010$
    - Confusion: $P=0.004$
    - Total mood disturbances: $P<0.033$
    - Vigour: $P=0.010$
Clinical evaluation of circulatory and health benefits of resveratrol

Resveratrol (2x75mg/day) for 14 weeks improved:
- cerebrovascular function
- cognitive performance
- pain symptoms
- overall well-being

in postmenopausal women
Aim

Conduct a larger, longer term trial to evaluate effects of resveratrol in post-menopausal women on

- Cognition (Primary outcome)
- Cardiovascular function
- Body composition
- Cardiometabolic biomarkers
- Mood and well being

Cognitive domains

- Attention
- Processing speed
- Semantic memory
- Episodic memory
- Working memory

Rey’s Auditory Verbal Learning Test
Forward Spatial Span Test
Trail Making Task
Addenbrooke’s Cognitive Exam-III

Overall cognitive performance = sum of Z-scores for each test

Systemic circulation

- Blood pressure, heart rate
- Large artery elasticity
- Small artery elasticity
- Systemic vascular resistance

Cerebral circulation

- Blood flow velocity
- Cerebral artery stiffness
- CVR to hypercapnia
- CVR to cognitive stimuli

Plasma lipids
Glucose, insulin
CRP
FSH
Alk-P
Osteocalcin

Cerebral circulation

- Blood flow velocity
- Cerebral artery stiffness
- CVR to hypercapnia
- CVR to cognitive stimuli

Measures

<table>
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<tr>
<th>Measures</th>
<th>Questionnaires</th>
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<tr>
<td>Mood states</td>
<td>Profile of Mood States (POMS)</td>
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<tr>
<td>Depressive symptoms</td>
<td>Center for Epidemiological Studies Depression Scale (CES-D)</td>
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<td>Pain</td>
<td>Short-form McGill Pain questionnaire</td>
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<td>Menopausal symptoms</td>
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<td>Sleep quality</td>
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<td>Quality of Life</td>
<td>Short Form-36 (SF-36)</td>
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<td>Subjective memory complaints</td>
<td>20 questions on everyday memory difficulties</td>
</tr>
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</table>

Reshaw trial
(Resveratrol Supporting Healthy Ageing in Women)

Study design

2 × 12 month Crossover RCT (powered on 86, enrolled 146: 65 yrs, 15 yrs postmenopausal)

Randomisation (146)

Baseline visit

12 month visit (129)

Placebo
2 × 75 mg resveratrol

24 month visit (125)

Placebo
2 × 75 mg resveratrol
**RESSAW trial: summary of interim findings**

**Overall Conclusions**

*Supplementing postmenopausal women for 12 months with low-dose resveratrol:*-

- improved cerebrovascular function
- improved overall cognitive performance
- reduced symptoms of pain
- improved overall well-being

confirming observations from our preliminary 14 week (RESFEM) study.

*Additionally, resveratrol supplementation in the RESHAW trial:*-

- slowed bone loss in the lumbar spine and proximal femur, reducing risk of fractures
- lowered blood insulin and increased insulin sensitivity

We anticipate further positive outcomes from the 24-month crossover analysis.

We attribute these benefits of resveratrol (at least partially) to circulatory improvements.

By helping to maintain a healthy circulation, supplementation with vasoactive nutrients such as resveratrol can help to counteract heightened risks of cardiovascular disease, diabetes, osteoporosis and dementia in our ageing population.

Long term trials of resveratrol and other vasoactives, alone or in combination, should be undertaken in other target populations (e.g. older men, men and women with T2DM or hypertension) to determine efficacy and optimal dose requirements for each indication.

**Acknowledgements**

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