

# Endothelial Dysfunction

Tying together cardiometabolic risk factors

**IAN BREAKSPEAR**

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Ian Breakspear is a herbal and naturopathic clinician, educator and researcher with 30 years of experience in the profession. In addition to his undergraduate clinical qualifications, Ian holds a Masters Degree in Herbal Medicines from the Faculty of Pharmacy, University of Sydney.

Ian divides his time between clinical practice (with a speciality in supporting patients with cardiovascular disease), his role as a Senior Learning Facilitator at Torrens University, and various research and consultancy roles. He is a committed leader within the profession and served for 8 years on the Board of Directors of the NHAA, and in 2006 was awarded Fellowship of the NHAA for “meritorious work in the profession of herbalism”. Currently Ian is Chair of the NHAA’s Board Member Advisory Committee, an advisor to the global not-for-profit Natural Health Science Foundation, an Expert Contributor for the Olive Wellness Institute, and a member of the Boundary Bend Olives Expert Scientific Steering Committee.

Ian’s research work focuses on herbal quality, safety and efficacy, and he is currently engaged in a clinical trial assessing the value and safety of olive leaf extract in Type 2 diabetics. He is the author of numerous journal papers, conference presentations, and a chapter on cardiovascular therapeutics in a popular naturopathic textbook. In 2021 Ian was the recipient of the Bioceuticals Integrative Medicine Award for Contribution to Research & Education.

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# What is the vascular endothelium?

(Krüger-Genge et al., 2019; Rajendran et al., 2013)

- Single cell layer lining which covers the luminal surface of blood vessels
- It is the cellular interface between blood and the underlying tissue of the blood vessels
- Has an estimated surface area of 3000-6000m<sup>2</sup> – equivalent to half to a full soccer field

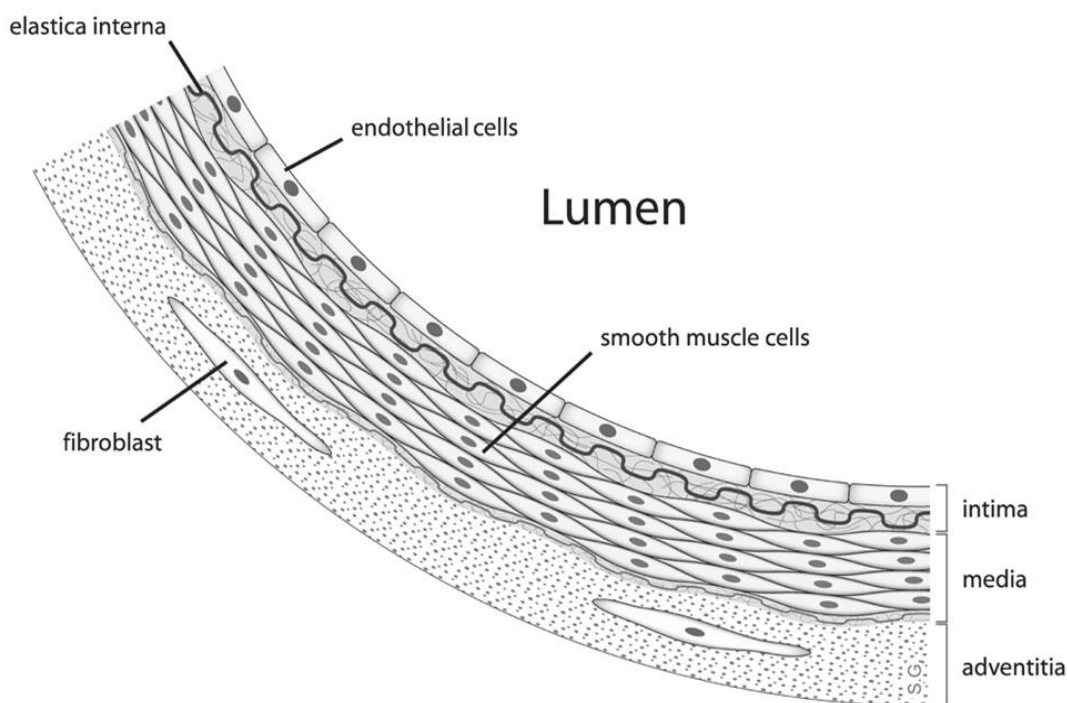


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# A delicate balance

(Esper et al., 2006; Rajendran et al., 2013)

Endothelial cells (EC's) sense various physical and chemical stimuli within the blood vessels

In response they alter morphology & function of blood vessels

This is achieved through a homeostatic interaction between agonistic and antagonistic mediators produced by EC's ...

- vasodilators and vasoconstrictors
- procoagulants and anticoagulants
- inflammatory and anti-inflammatory substances
- oxidising and reducing agents
- fibrinolytic and antifibrinolytic agents
- growth factors and antiproliferative factors

Thus the vascular endothelium can be considered to be ...

- autocrine (i.e. producing substances which act on the cells which produce them)
- paracrine (i.e. producing substances which act on other cells nearby)
- endocrine (i.e. producing substances which act remotely on other tissues via blood distribution)

It is when this balance is disrupted, that pathological processes commence

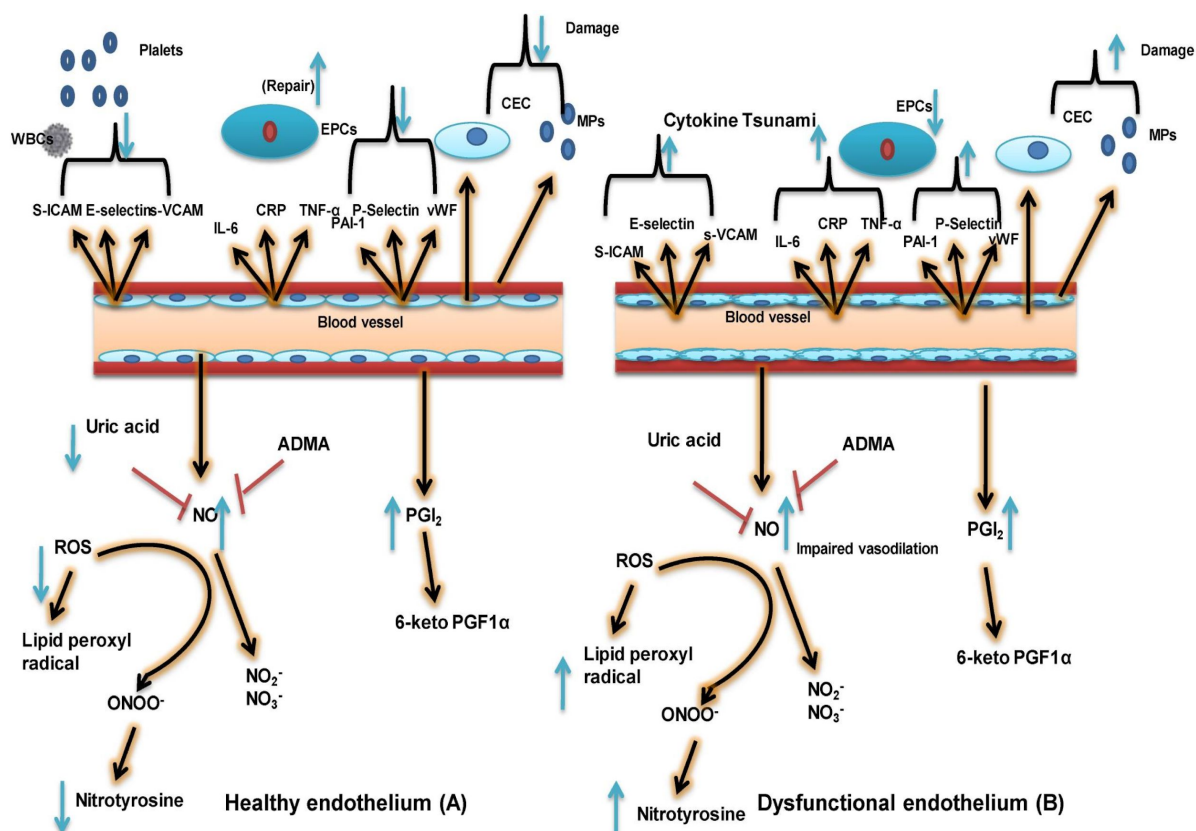
This is what is known as **“endothelial dysfunction” (ED)**

# Healthy & dysfunctional endothelium

## KEY:

- 6-keto PGF $1\alpha$ : 6-keto prostaglandin F $1$ -alpha
- ADMA: asymmetric dimethyl arginine
- CEC: circulating endothelial cell
- CRP: C-reactive protein
- EPC's: endothelial progenitor cells
- IL-6: interleukin-6
- MP's: endothelial microparticles
- NO: nitric oxide
- NO $_2^-$ : nitrite
- NO $_3^-$ : nitrate
- ONOO $^-$ : peroxynitrite
- PAI-1: plasminogen activator inhibitor 1
- PGI $_2$ : prostaglandin I $_2$  (prostacyclin)
- ROS: reactive oxygen species
- sICAM: soluble intercellular adhesion molecule
- sVACM: soluble vascular adhesion molecule
- TNF- $\alpha$ : tumour necrosis factor alpha
- VSMC: vascular smooth muscle
- vWF: von Willebrand factor
- WBC's: white blood cells

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# Predisposing, Excitatory & Sustaining Factors for Endothelial Dysfunction (ED)

Blood vessel morphology which encourages low flow or oscillatory flow patterns (Krüger-Genge et al., 2019)

Smoking (Rajendran et al., 2013)

Physical inactivity (Rajendran et al., 2013)

Insulin resistance/dysglycaemia, metabolic syndrome, diabetes (Rajendran et al., 2013)

Systemic inflammatory diseases, including some infectious diseases (Botts et al., 2021; Rajendran et al., 2013)

Imbalance between oxidative load and antioxidant capability (Rajendran et al., 2013)

Prolonged elevation of circulating glucocorticoids and mineralocorticoids (Ullian, 1999)

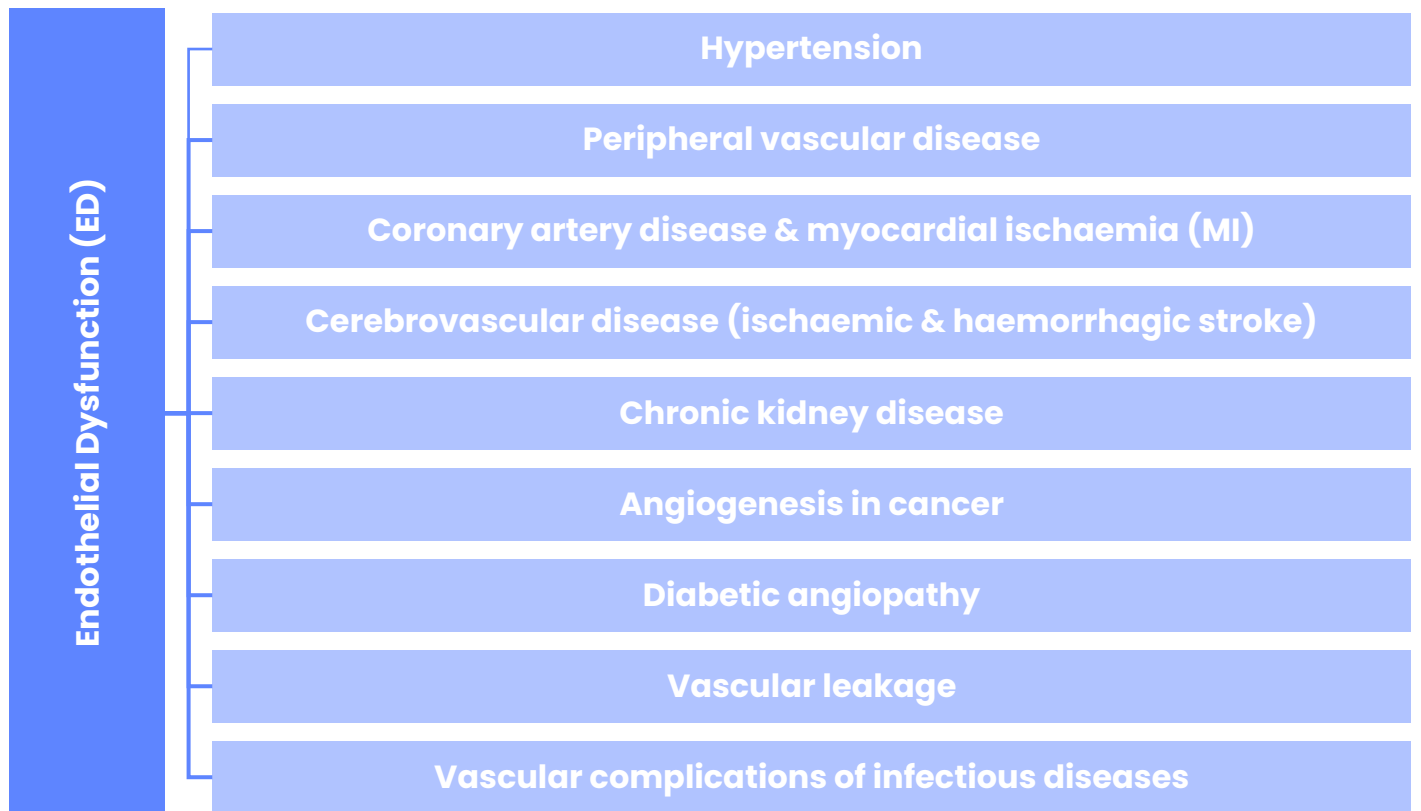
# Tying it all together

- Vascular endothelial dysfunction ties together many of the pathological processes considered to important in the development of vascular disease
- Many traditional & novel risk factors have an adverse effect on endothelial function, e.g. ...
  - diet low in fruit & vegetables, EFA's
  - smoking
  - endothelial function and integrity is impaired by hypertension, but also contributes to hypertension



(Deanfield et al., 2007; Rajendran et al., 2013)

# Contribution to disease



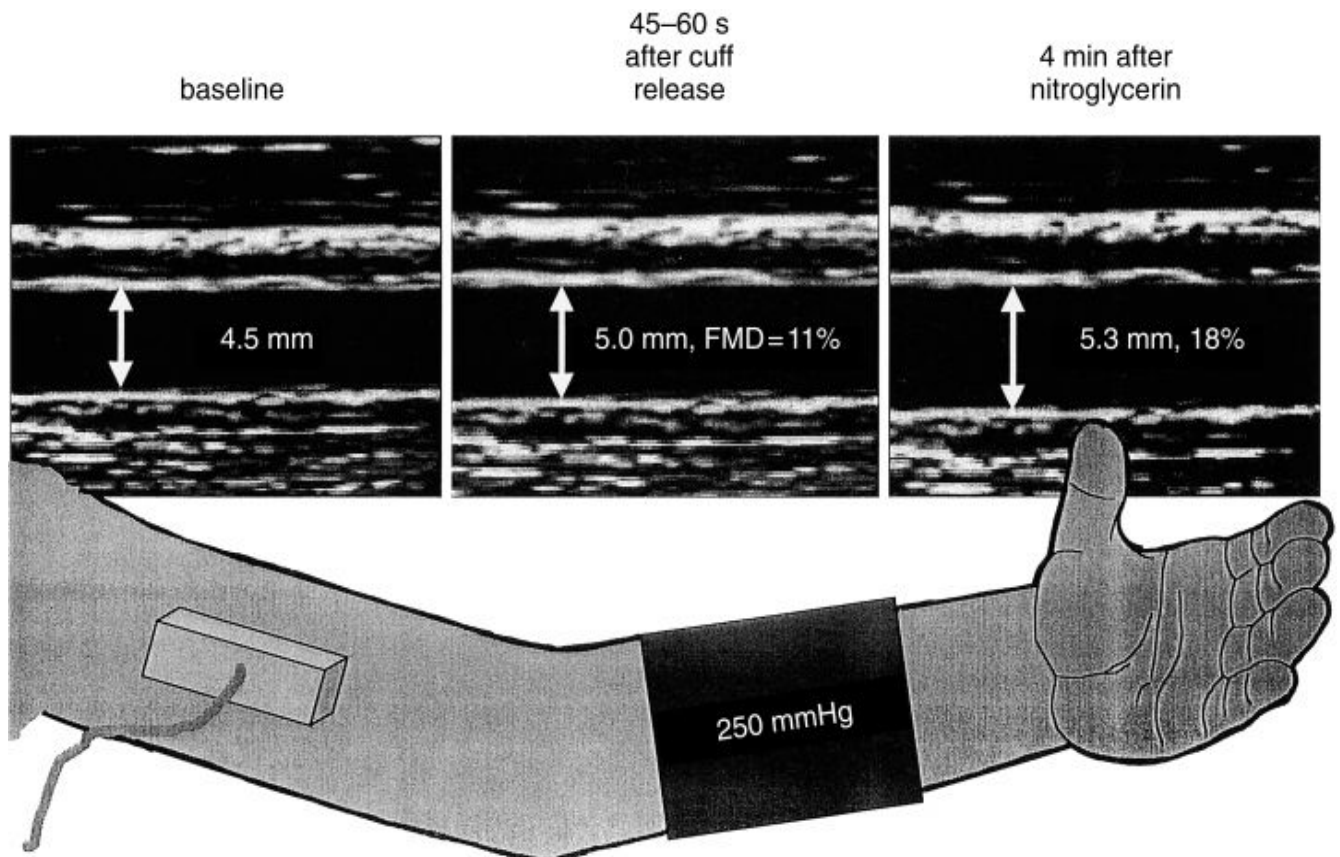
(Deanfield et al., 2007; Rajendran et al., 2013)



# Testing for endothelial dysfunction

(Raitakari & Celermajer, 2000; Thijssen et al., 2019)

- Flow-mediated dilatation (FMD) is the only current test considered to be reliable
- Not available for testing in most clinical settings – still mostly used in research



## Lifestyle Interventions for Suspected/Confirmed Endothelial Dysfunction

● Ceasing any and all forms of tobacco use, including e-cigarettes, vaping and waterpipe products (Ambrose & Barua, 2004; Klag, 2012; Münzel et al., 2020)

● Regular exercise – benefits are similar across aerobic, resistance and combined training. However Type 2 diabetic patients show lower levels of improvement in FMD from exercise compared to non-diabetics (Gao et al., 2022; Pedralli et al., 2020; Qiu et al., 2018)

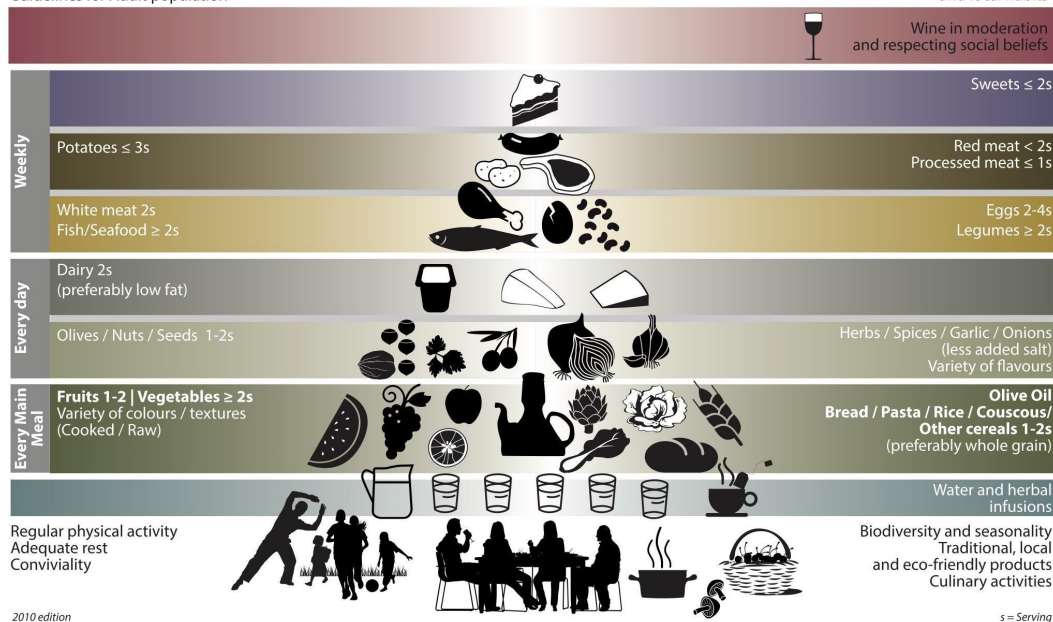
# Dietary Interventions for Suspected/Confirmed Endothelial Dysfunction

- Avoidance of ultra-processed foods – strong association with overall cardiovascular disease and other adverse health outcomes (Du et al., 2021; Elizabeth et al., 2020; Srour et al., 2019)
- Adopt a Mediterranean Diet, which has been shown to improve FMD regardless of health status, body mass index, or age (Shannon et al, 2020)
- Extra-virgin olive oil (EVOO) is now considered to be an independent contributor to health, reducing the risk of obesity, dyslipidaemia, overall cardiovascular disease, inflammation, dysglycaemia, and other adverse health outcomes (Guasch-Ferré, et al, 2020; Kargin et al., 2019; Mazzocchi et al., 2019; Soriguer et al., 2009; Violi et al., 2015)
  - Recommended daily intake of EVOO is 25–50mL (Njike et al., 2021; Violante et al., 2009)
  - Take care to ensure that it is truly EVOO – considerable adulteration occurs across the world (Mailer & Gafner, 2020)

## Mediterranean Diet Pyramid: a lifestyle for today

Guidelines for Adult population

Serving size based on frugality and local habits



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The use and promotion of this pyramid is recommended without any restriction



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Predimed  
Prevención con Dieta Mediterránea



Ciiscam



(CIHEAM – Mediterranean Agronomic Institute of Chania, n.d.; Fundación Dieta Mediterránea, 2010)

# Key Role of Plant Biophenols

(Obied, 2013)

- The term “biophenols” was first introduced in 1996, and is a more accurate term than the more commonly used term “polyphenols”
- Whilst some biophenols are polyphenolic in structure, others are not
- The key source is a plant-food rich diet, especially low-starch vegetables, and berries

## Olive Leaf Extract (OLE)

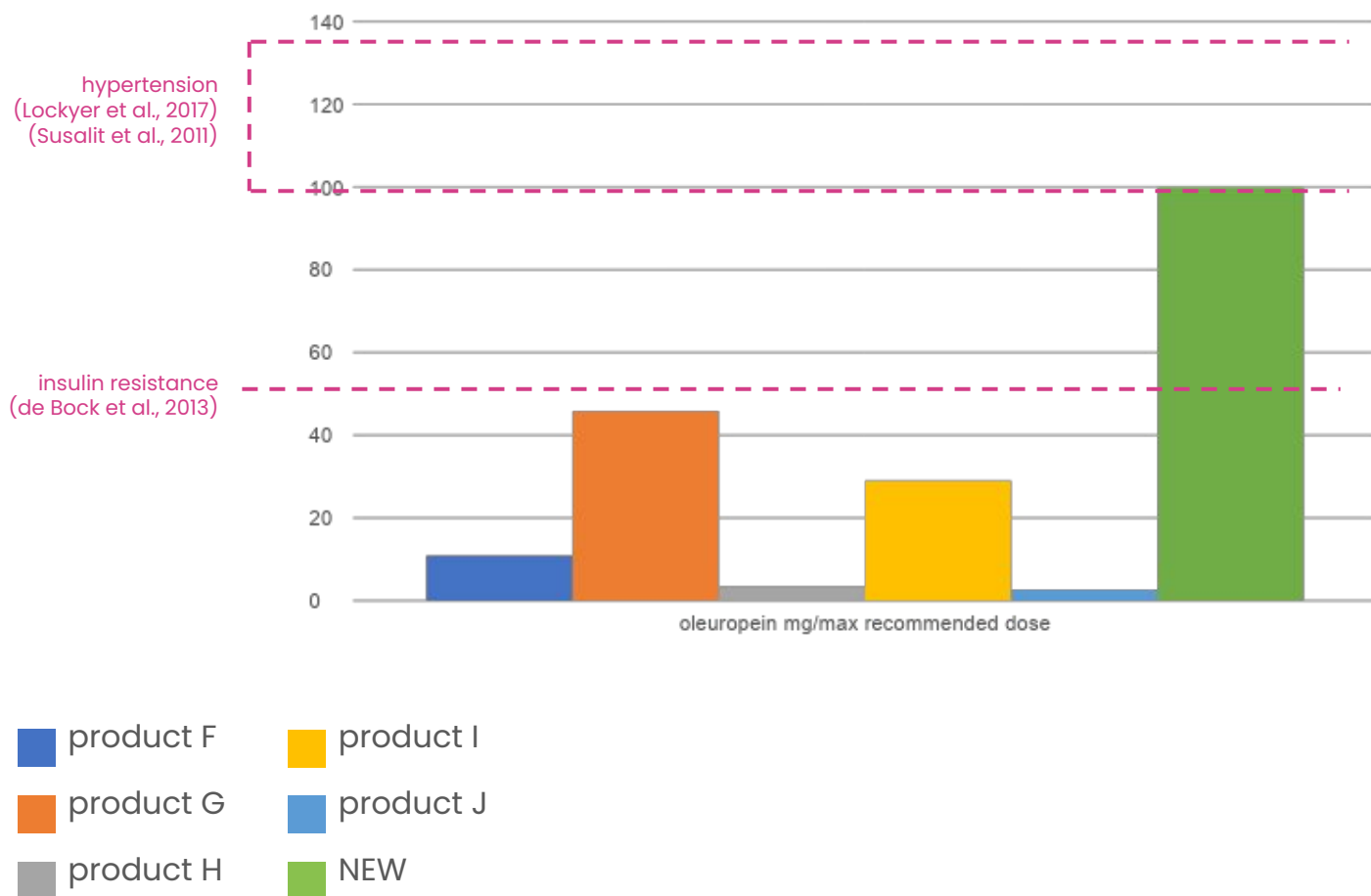
- Rich in a range of biophenols, especially oleuropein and hydroxytyrosol
- Reduces expression of inflammatory markers such as IL-6, IL-8, TNF- $\alpha$  (Javadi et al., 2019; Lockyer et al., 2015)
- Improves insulin sensitivity in overweight men 35-55 years, to a level that is greater than expected with metformin prescription (de Bock et al., 2013)
- Contributes to a modest but clinically relevant lowering in blood pressure in pre- and early stage hypertensive patients (Perrinjaquet-Moccetti et al., 2008; Susalit et al., 2011)

## Olive Leaf Extract – Dosage & Quality

- In Perrinjaquet-Moccetti et al., (2008) positive outcomes in SBP and LDL-C only seen in 208mg oleuropein per day
- However Susalit et al., (2011) showed positive outcomes for SBP and DBP and LDL-C at 99.5mg oleuropein per day
- Lockyer et al., (2017) showed positive results on SBP, DBP, total cholesterol, LDL-C, and triglycerides at 136mg oleuropein per day
- Very recent 8 week RCT (Stevens et al., 2021) assessed effects of OLE vs placebo on blood pressure, lipids, oxidised LDL, glucose, insulin levels in overweight and mildly hyperlipidaemic 18-70 year olds, and showed no effect
  - 500mg OLE per day, 16.7% oleuropein = 83.5mg oleuropein per day
- Recent phytochemical profiling has shown that at maximum recommended dosages, none of the tested Australian practitioner OLE liquid products (available in 2018) provided oleuropein to match the levels used in clinical trials. In fact, none of them reached a daily dosage of 50mg oleuropein, and one provided as low as 2.7mg oleuropein/day at its maximum dosage (Breakspear & Guillaume, 2020).

# Dosing for efficacy

(Breakspear & Guillaume, 2020)



## Garlic

(Kunimura et al., 2021; Lau, 2001; Li et al., 2022; Pérez-Rubio et al., 2022)

Hypotensive

Hypolipidaemic

Some research indicates a midrange dosage of aged-garlic extract (480mg/day) to be more efficacious over a 12 week period for blood pressure regulation (Ried et al., 2012)

## Blueberries

(Rodriguez-Mateos et al., 2019)

In acute dosing both the blueberry drink and an anthocyanin drink (matched to approximately the same anthocyanin concentration) resulted in similar improvements in FMD from baseline at 2 and 6hrs, compared to control drinks

There was a clear dose-dependant increase in FMD from baseline to 2hrs and 6hrs after consumption of pure anthocyanins

Daily high dose blueberry drink consumption (11g freeze dried extract in 500mL water, twice daily, equiv 200g fresh blueberries/day, 300mg anthocyanin/day) resulted in significant improvements in FMD up to 2 weeks after commencing, then plateaued

Daily high dose blueberry drink consumption for 28 days increased FMD from baseline after overnight fasting (compared to controls) by 2.3% - with no additional improvement when it was consumed acutely on day 28 (indicating a saturation of effect from chronic usage)

Important to note that this was high dose – equivalent to 200g of fresh blueberries per day, every day

## Grape seed extract (GSE)

Chronic administration improves blood pressure response in both healthy and in overweight individuals, and in pre-hypertensive individuals (Dillon et al., 2022; Odai et al., 2019; Schön et al., 2021)

Improves insulin resistance in adolescents with metabolic syndrome (Mohammad et al., 2021)

Combined with a reduced calorie diet over 12 weeks in overweight or obese individuals, it lowered LDL-C and triglycerides, raised HDL-C, and lowered visceral adiposity index, compared to placebo plus diet (Yousefi et al., 2021)

Demonstrates positive effects on a range of inflammatory markers, oxidative stress, diabetic retinopathy and nephropathy, and has probable neuroprotective effects (Sochorova et al., 2020)

Extract equivalent to 24,000–36,000mg of dried seed per day is a broad guideline based on various studies (Breakspear & Hechtman, 2019)

But be careful – research indicates that a number of commercial available extracts are either entirely substituted with, or adulterated with, peanut skin – intentional adulteration (Villani, et al, 2015)



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