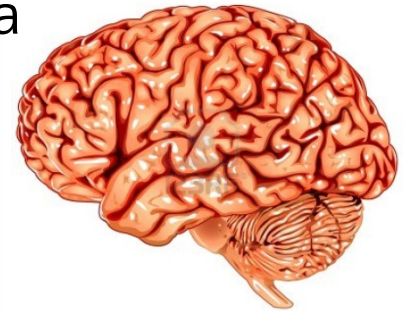


Polyphenols in the Prevention of Alzheimer's Disease:

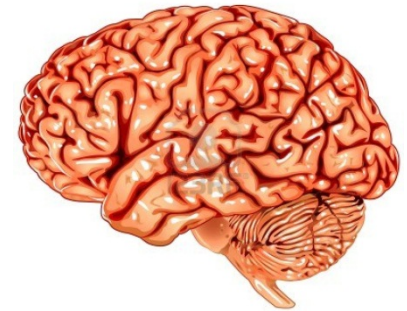
some food for thought?

By: Georgette-Marie Camilleri
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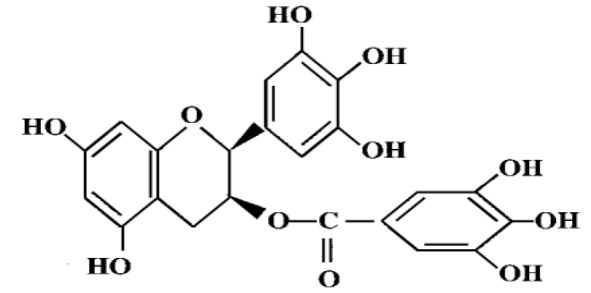


Contents

- What are polyphenols?
- Pathogenesis of Alzheimer's disease
- Epidemiological studies illustrating the role of polyphenols in the prevention of Alzheimer's disease
- Mechanisms by which polyphenols exert their neuroprotective role
- Challenges for Research on Polyphenols in Alzheimer's Disease
- Conclusion



What are polyphenols?



(-)-epigallocatechin-3-gallate (EGCG)

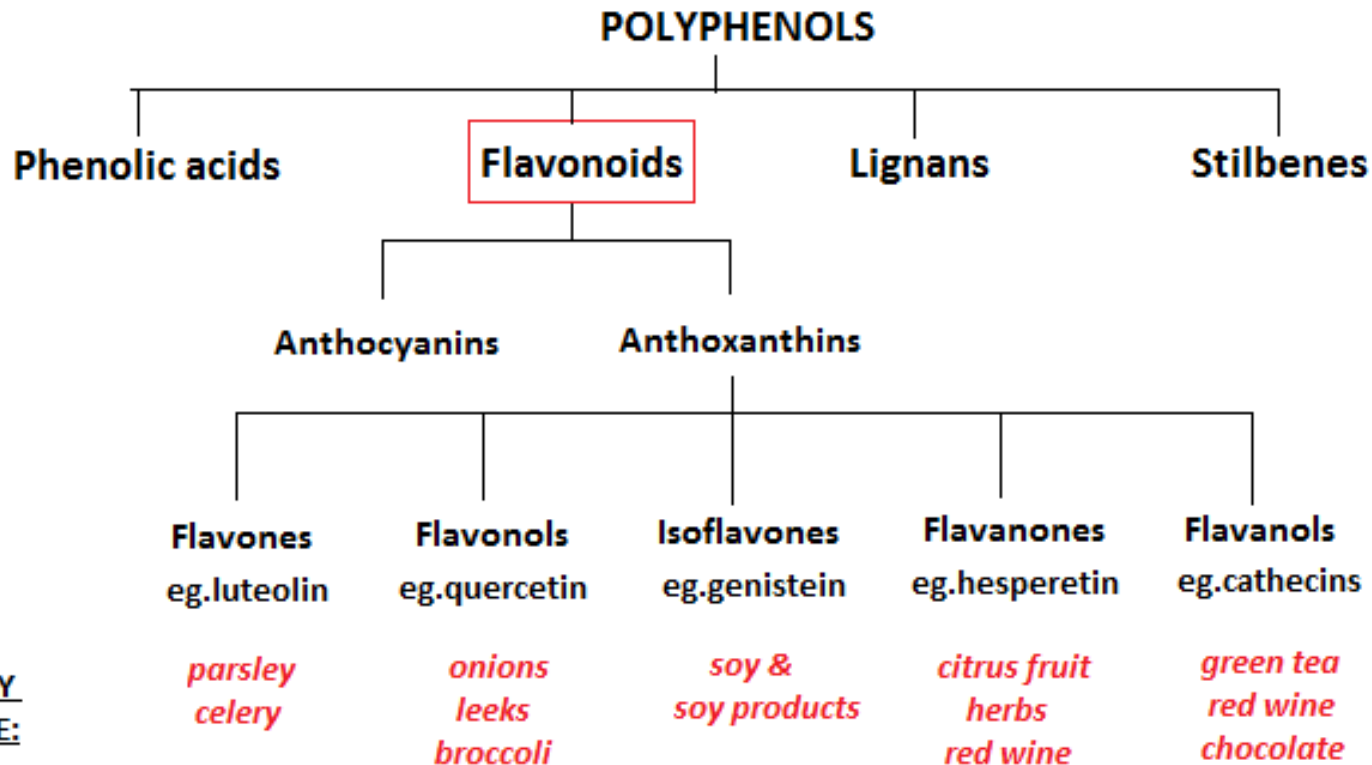
- A class of organic compounds
- Characterised by the presence of more than one phenol structural unit
- Phytochemicals – have a protective role in plants
- They are thus present in our diet in plant-based food

(Vauzour, 2012; Manach *et al.*, 2004)



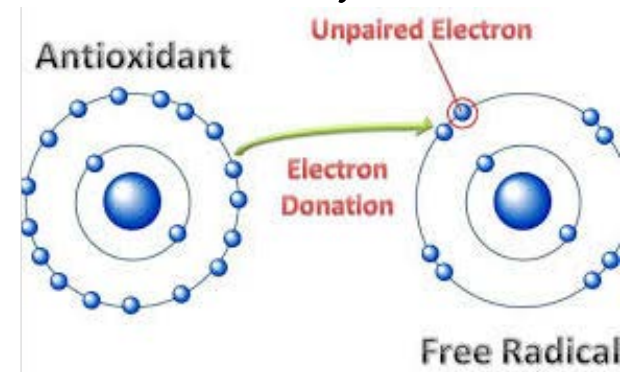
What are polyphenols? (cont..)

- More than 8000 naturally occurring polyphenols are known to exist and can be grouped in 4 categories: (Vauzour, 2012; Manach *et al.*, 2004)



What are polyphenols? (cont...)

- An important chemical property of polyphenols is their **ANTIOXIDANT ACTIVITY**
 - Their ability to inhibit oxidative damage within cells by “mopping up” reactive oxygen species

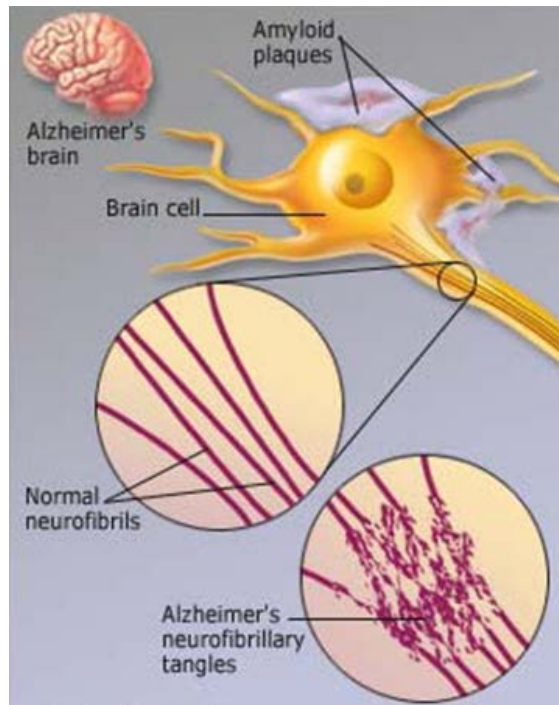


- Current evidence strongly supports a contribution of polyphenols to the prevention of:
 - Cardiovascular disease
 - Cancer
 - Neurodegenerative disease: **ALZHEIMER’S DISEASE**

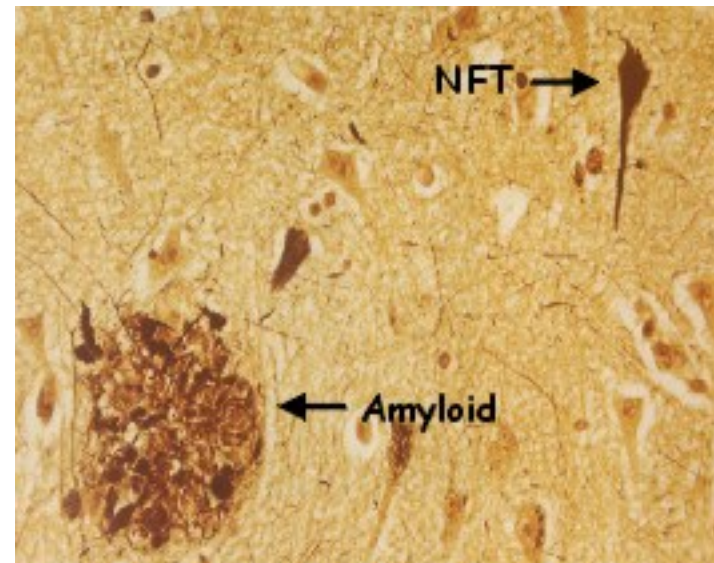
(Manach *et al.*, 2004)

Pathogenesis of Alzheimer's disease

- When an AD brain is examined under the microscope, 2 defining neuropathological features of AD are observed:
 - Extracellular β -amyloid plaques
 - Intracellular neurofibrillary tangles



(Swerdlow, 2007; Ortega *et al.*, 2013)



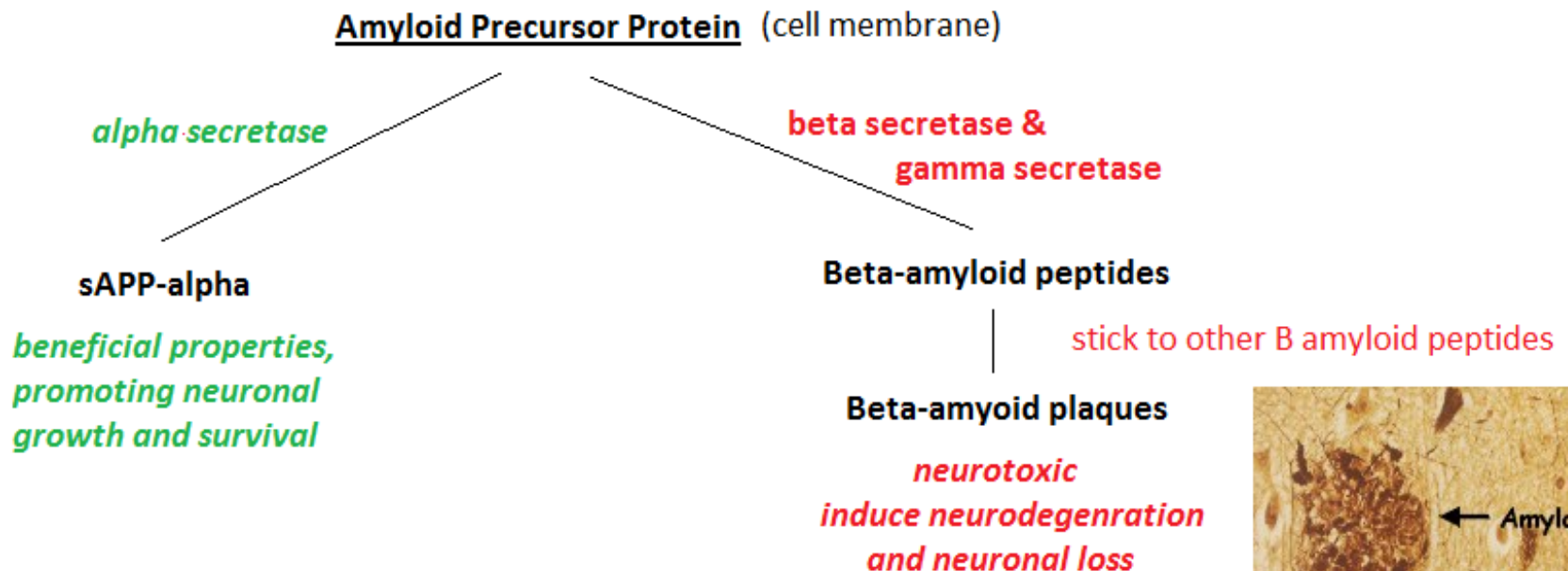
<https://gbiomed.kuleuven.be/english/research/50000622/50525540/alzheimers-disease>

A. Formation of β -amyloid plaques

- B-amyloid plaques (Extracellular)
 - Composed of β -amyloid peptides
 - Formed by abnormal processing of its parent protein – AMYLOID PRECURSOR PROTEIN (APP)
 - The 2 pathways of APP processing: (Swerdlow, 2007; Ortega *et al.*, 2013)

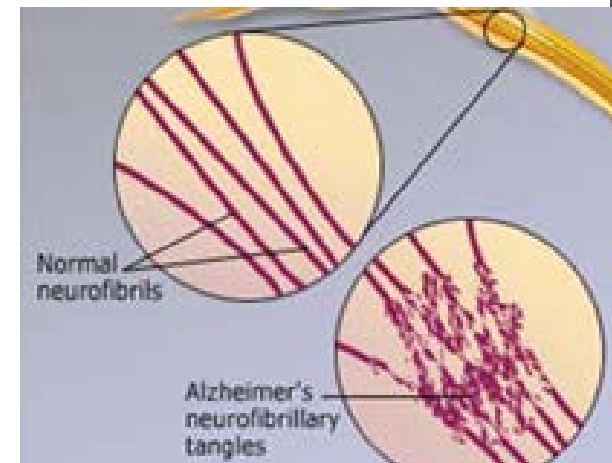
BENIGN PATHWAY

HARMFUL PATHWAY



B. Formation of Neurofibrillary tangles

- Neurofibrillary tangles (Intracellular)
 - Chief component: tau protein
 - Function of tau in healthy neurons: to bind to microtubules, stabilising them
 - (In healthy neurons, microtubules function in transport of nutrients and cellular components along axon)
 - In AD:
 - HYPERPHOSPHORYLATION of tau proteins
 - Tau proteins detach from microtubules
 - They aggregate forming neurofibrillary tangles
 - Microtubules disintegrate in the process collapsing the neuron's internal transport network
- (Serrano-Pozo *et al.*, 2011)



Pathogenesis of Alzheimer's disease (cont...)

- What triggers the formation of β -amyloid plaques & neurofibrillary tangles?

***Increased oxidative stress
(Reactive oxygen species)***

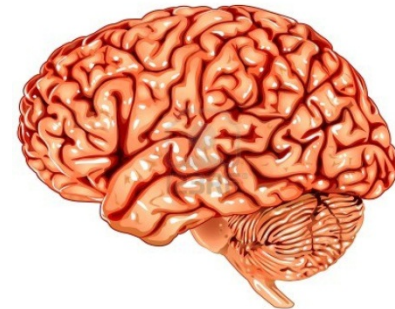
***Depletion of endogenous
antioxidants***

***Glutamatergic
excitotoxicity***

Neuroinflammation

***Increased concentration
of metal ions***

(Vazour *et al.* 2010; Vauzour, 2012)



The role of Polyphenols in the Prevention of Alzheimer's Disease

- Several epidemiological studies suggest that diets rich in polyphenols beneficially affect human brain function
 - Improving memory and cognition in normal aging
 - Delaying the onset of neurodegenerative diseases, including Alzheimer's disease
 - Halting the progression of Alzheimer's disease

(Commenges *et al.*, 2000; Spencer, 2008; Nurk *et al.*, 2009; Beking & Vieira, 2010)



Epidemiological studies illustrating the role of Polyphenols in the Prevention of Alzheimer's disease

- When a cross-sectional study was carried out to investigate the relation between intake of 3 common foods which are high in flavonoids (chocolate, red wine and tea) and cognitive performance,
 - Those who consumed all 3 food items had the highest cognitive test scores
 - Association was dose dependent, with maximum effect at intakes of
 - 10g chocolate/ day
 - 75-100mL wine/ day
 - The relationship was approximately linear for tea

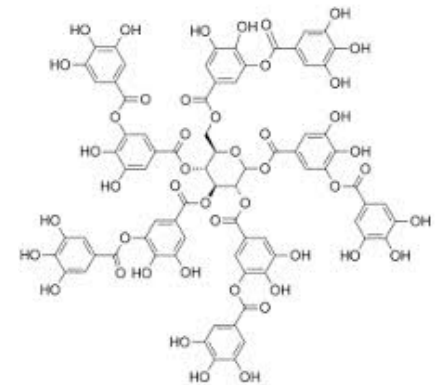
(Nurk *et al.*,2009)

- This relationship was observed even after adjusting for confounding factors!
- This relationship was still strong after adjusting for the high levels of antioxidant vitamins present in a typical plant based diet!



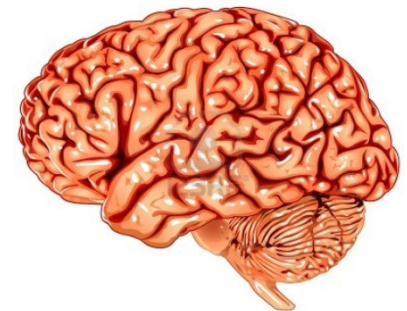
Epidemiological studies illustrating the role of Polyphenols in the Prevention of Alzheimer's disease

- Several epidemiological studies have also been carried out on the effect of the Mediterranean diet on risk of AD:
 - Higher adherence to the Mediterranean diet: associated with lower risk of AD
(Vallas-Peret *et al.*, 2012)
- One limitation of most studies: dietary assessment is often performed at ages close to the onset of dementia (mostly >65), when oxidative stress levels are already high and most neurons degenerated



Mechanisms by which Polyphenols exert their Neuroprotective effect

1. Protection via ANTIOXIDANT capabilities
(radical scavenging activity)
2. METAL CHELATION
3. Modulation of ENZYME ACTIVITY
4. Effect on NEURONAL SIGNALLING PATHWAYS



1. Protection via Antioxidant Capabilities

- The brain is particularly susceptible to oxidative stress because of:

***High content
of
long chain fatty acids***

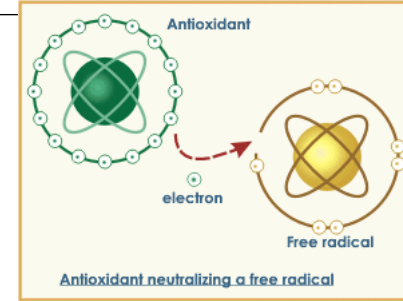
***High level of
in situ production of
free radicals***

- ***brain consumes more than 20% of all oxygen in the body***
- ***reactions specific to the brain, which produce free radicals***
- ***neurotransmitters auto-oxidise and produce free radicals***

- Oxidative stress plays a major role in the pathogenesis of AD

(Massaad, 2011)

1. Protection via Antioxidant Capabilities (Cont...)



- When green tea polyphenol EGCG (a catechin) was investigated, it was shown to be capable of reducing the death of cultured hippocampal neuronal cells exposed to β -amyloid

On exposure to β -amyloid:

an INCREASE in caspase & malondialdehyde activity was noted

increased neuronal death

On treatment with EGCG:

a DECREASE in caspase & malondialdehyde activity was noted,

improved neuronal survival

- **Malondialdehyde = biomarker of oxidative stress**
 - **Caspase = role in cell death**

(Choi *et al.*, 2001)

2. Metal chelation

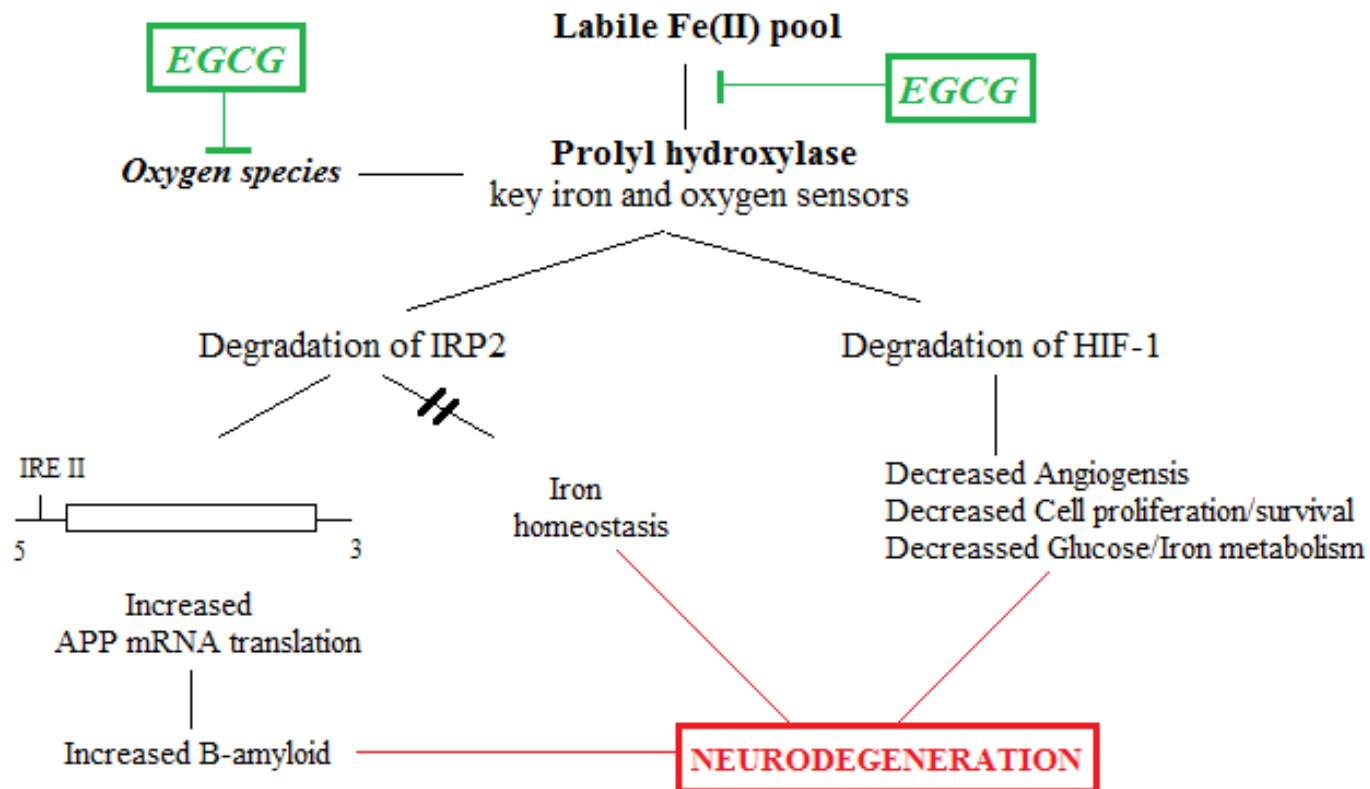
- When curcumin (polyphenol found in turmeric) was tested on animal models of AD, it was found to decrease the levels of β -amyloid plaques and prevent cognitive deficits
 - This was attributed to its ability to bind metal ions in the brain, such as Fe(II) and Cu(II) ions.
 - These ions form part of the structure of β -amyloid plaques
 - Metal chelation
 - Reduces the amount of ROS generated by the Fenton and Haber Weiss reactions, reducing oxidative stress
 - Reduces the availability of metal ions for the formation of β -amyloid plaques
 - Reduces the availability of Fe(II), for the upregulation of translation of APP

(Baum *et al.*, 2004)

2. Metal chelation

- Metal chelation slows down the process of Fe-induced neurodegeneration

(Mandel *et al.*, 2006)



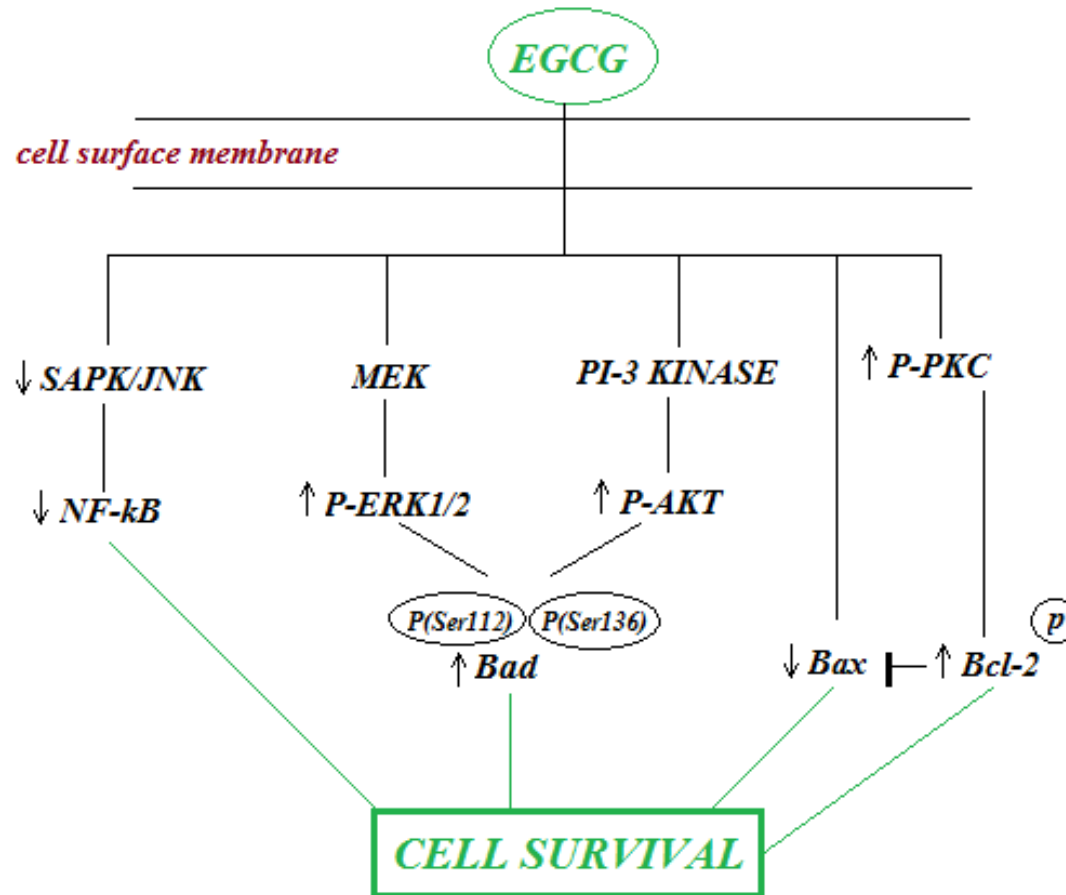
3. Modulation of enzyme activity

- Green tea polyphenol EGCG has been shown to be able to promote non-amyloidogenic processing of APP by
 - upregulating alpha-secretase
 - Suppressing beta- and gamma-secretase
- This shifts the pathway
 - away from β -amyloid plaque formation
 - towards formation of sAPP-alpha, which promotes neuronal growth and survival

(Smith *et al.*,2010; Zhang *et al.*,2011)

4. Effect on Neuronal Signalling Pathways

- Polyphenols also act by altering expression of anti-apoptotic and pro-apoptotic genes (Weinreb *et al.*, 2004)



Challenges for Research on Polyphenols in Alzheimer's disease

- Most polyphenols and their neuroprotective effect have been studied in vitro and in animal studies - only few have progressed successfully into active clinical trials
- More research is also required to investigate the bioavailability and pharmacokinetics of polyphenols
 - To determine the dosage and frequency required for a significant neuroprotective effect

(Singh *et al.*, 2008)

Bioavailability of Polyphenols: Absorption... Metabolism...crossing the BBB

- Bioavailability varies widely from one polyphenolic compound to another
 - It depends on chemical structure:
 - molecular weight
 - solubility in water
 - Type of sugar moiety present
 - Examples of plasma concentrations reached after polyphenol consumption:
 - 0.3 – 0.75 $\mu\text{mol/L}$ after consumption of 80-100mg quercetin
 - 1.3 – 2.2 $\mu\text{mol/L}$ after consumption of 130-220mg hesperetin (Manach *et al.* 2004)
 - Generally, polyphenols are rapidly metabolised and excreted from plasma, showing that daily consumption is required to maintain high concentrations in the blood stream
 - Although EGCG has been reported to cross the BBB, more studies are required to determine which polyphenols can permeate the BBB, and localise within brain tissue

(Singh *et al.*, 2008)

Conclusion



- As the elderly population is rapidly increasing, age-associated neurodegenerative disorders, such as Alzheimer's disease, represent a growing Public Health concern, with major socioeconomic burden
- The lack of curative treatment for cognitive decline and dementia argues for improvement of preventative strategies
 - To include prevention through dietary measures, such as consuming a diet rich in polyphenolic compounds

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Thank you for your attention!