Part I

MRN-100 and Alzheimer's disease

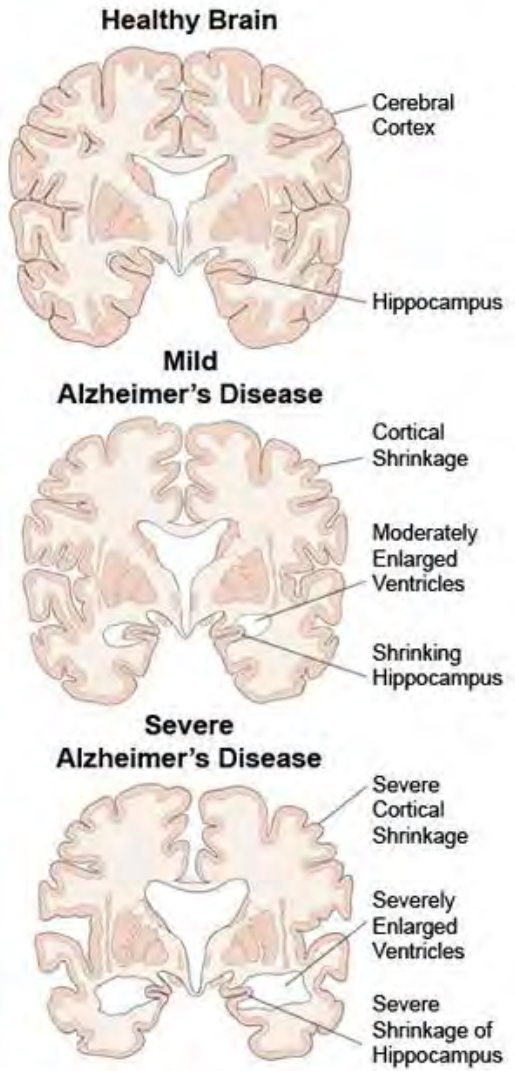
Alzheimer's Disease

Alzheimer's disease

- **Alzheimer's disease (AD)** is a neurodegenerative disorder characterized by a progressive decline of memory and cognition

Definition

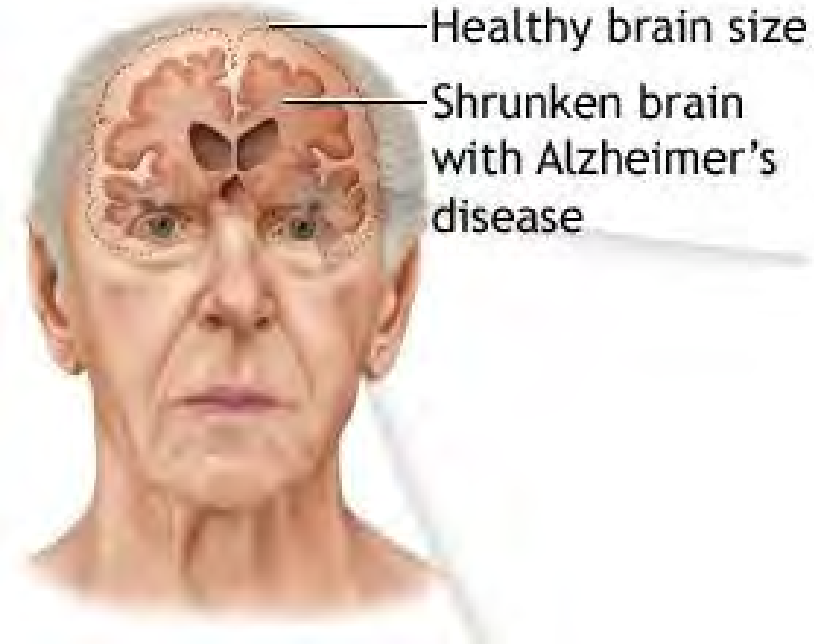
- Alzheimer's disease is a degenerative brain disease and the most common cause of dementia.
- Causes decline in memory, language, problem-solving, cognitive skills
- Areas of the brain for bodily functions also become affected
- Ultimately fatal

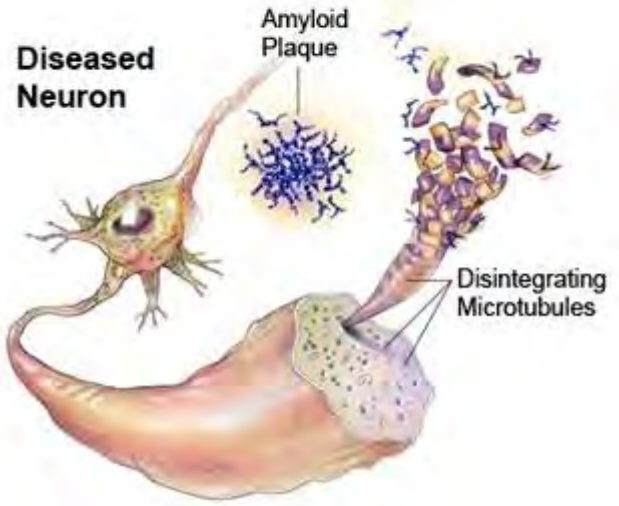


BrightFocus® Foundation
Cure in Mind. Cure in Sight.

Alzheimer's Mechanism

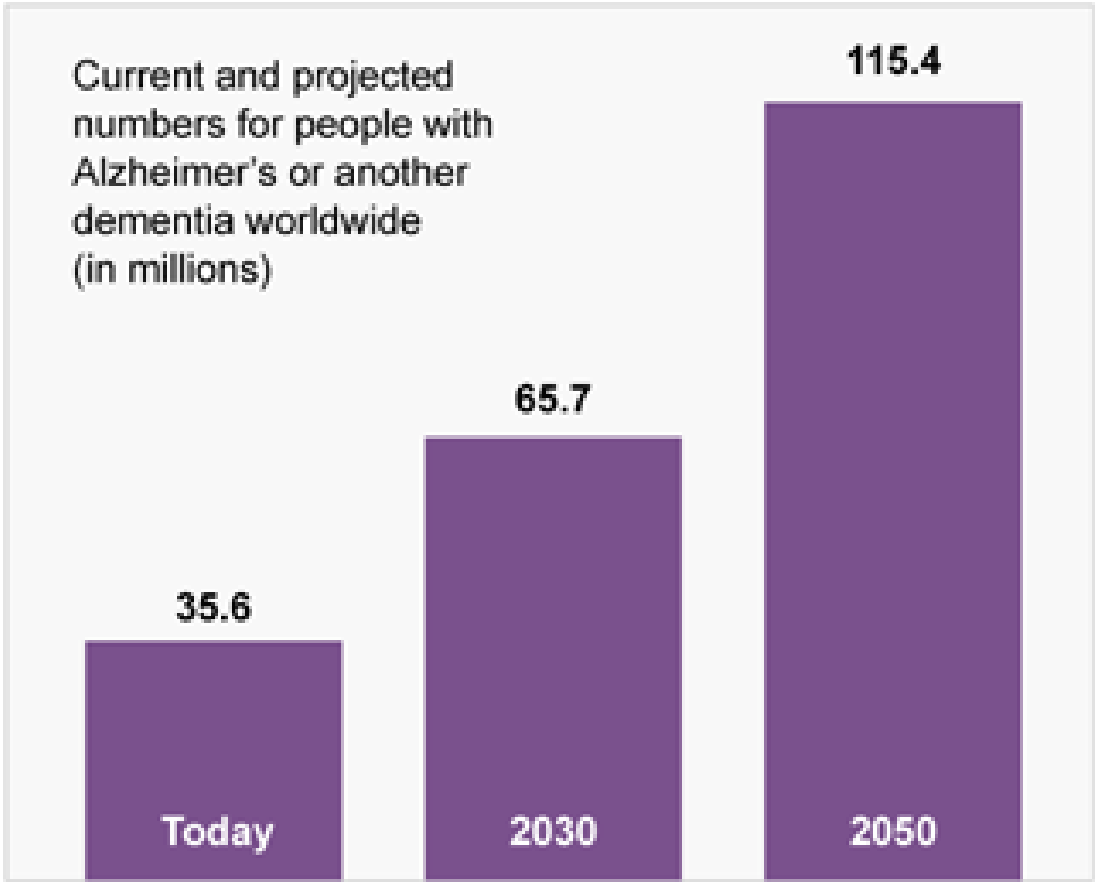
- Nerve cells (neurons) in parts of the brain involved in cognitive function become damaged or destroyed, and the damage spreads rapidly.





Alzheimer's Statistics

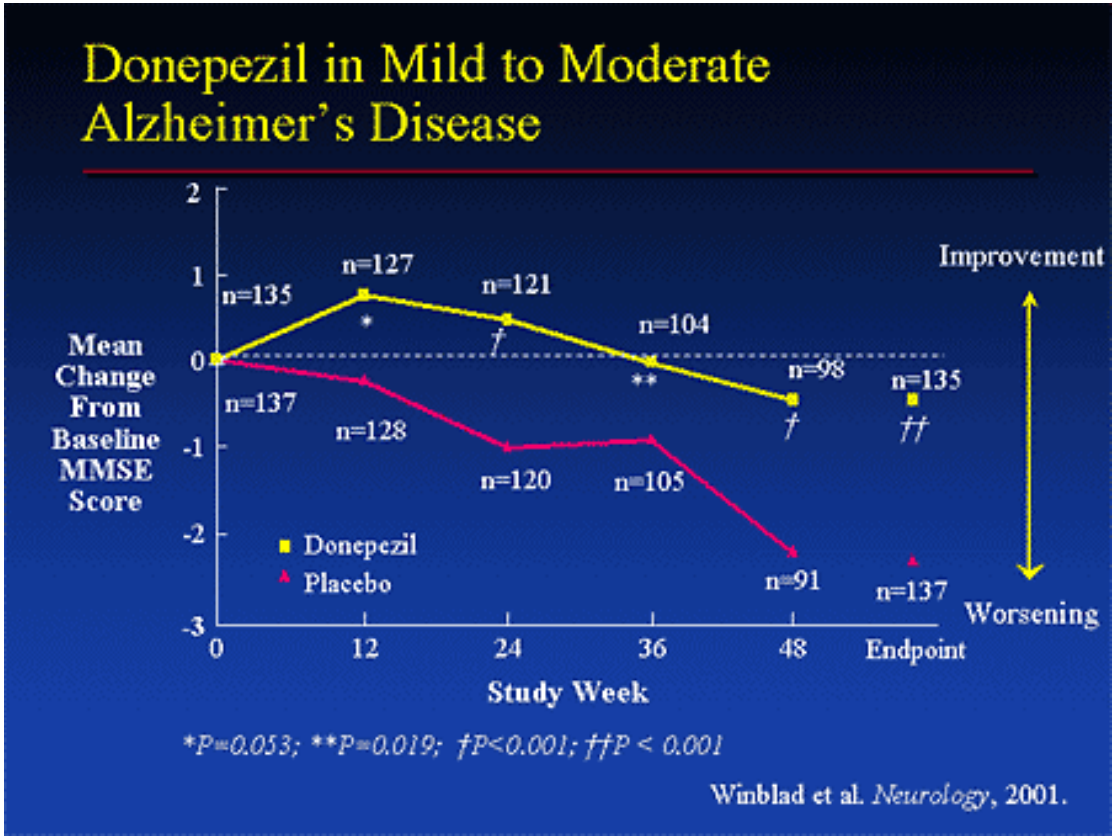
- Alzheimer's will impact more people as human longevity increases



Source: ***2009 World Alzheimer Report***, from Alzheimer's Disease International (ADI), a London-based nonprofit, international federation of 71 national Alzheimer organizations including the Alzheimer's Association.

Current treatments are inadequate

- Current treatments (donezepil, known as “Aricept”) slow the progression of nerve damage, but degeneration still continues.
- Side effects of the best treatments are numerous and undesirable



- Drowsiness, malaise, loss of appetite, cramps, insomnia, tremor, nausea, diarrhea, vomiting, possible seizures, possible chest pains.

Antioxidants as new treatments for AD

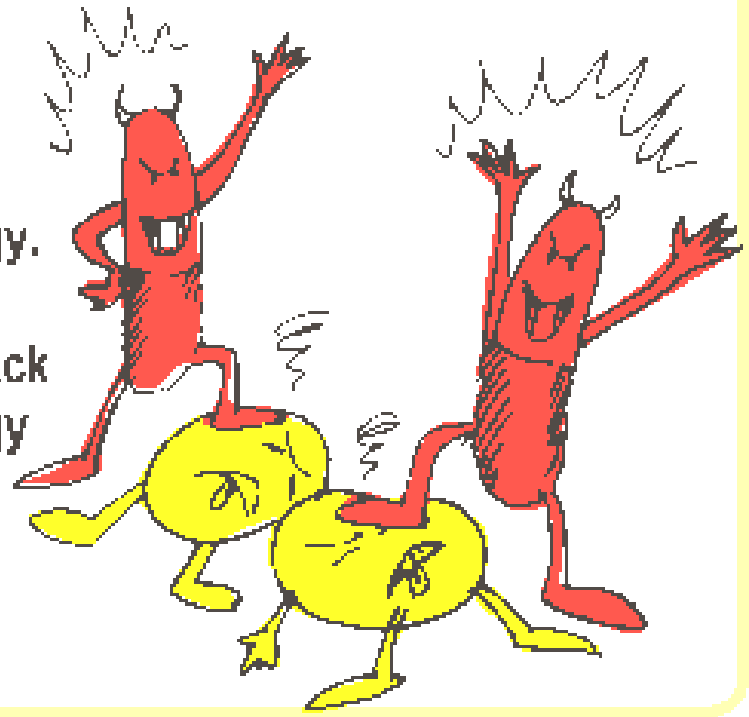
- Antioxidants are believed to play a role in preventing the development of such chronic diseases as Alzheimer's disease (AD)
  - For example, antioxidants emerged as potential AD preventive agents based upon epidemiological evidence and animal studies.*
- The imbalance between free radicals and antioxidants in neurons plays a key role in the development of AD.
  - This is called oxidative stress.
  - Oxidative stress occurs when the production of harmful molecules called **free radicals** is beyond the protective capability of the antioxidant defenses.
- Free radicals containing oxygen, known as **reactive oxygen species** (ROS), are the most biologically significant free radicals.

* Zhou et al. Am J Transl Res. 2016;8:246-69.

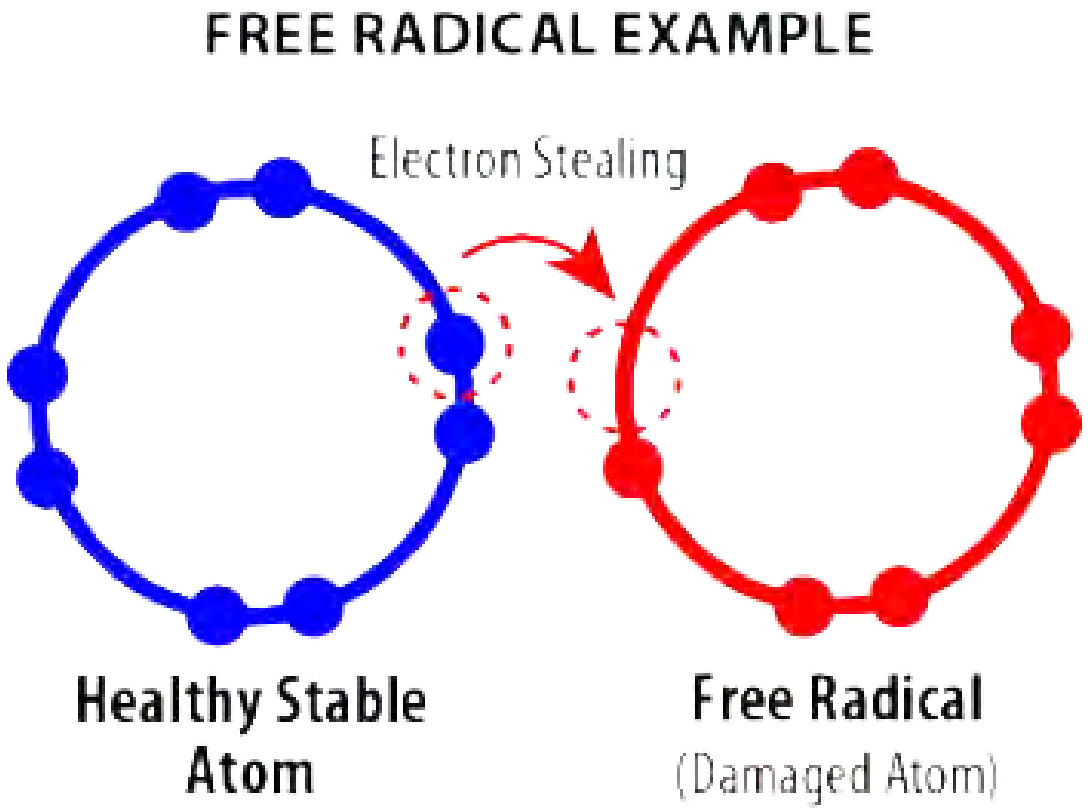
Free Radicals

What are Free radicals ?

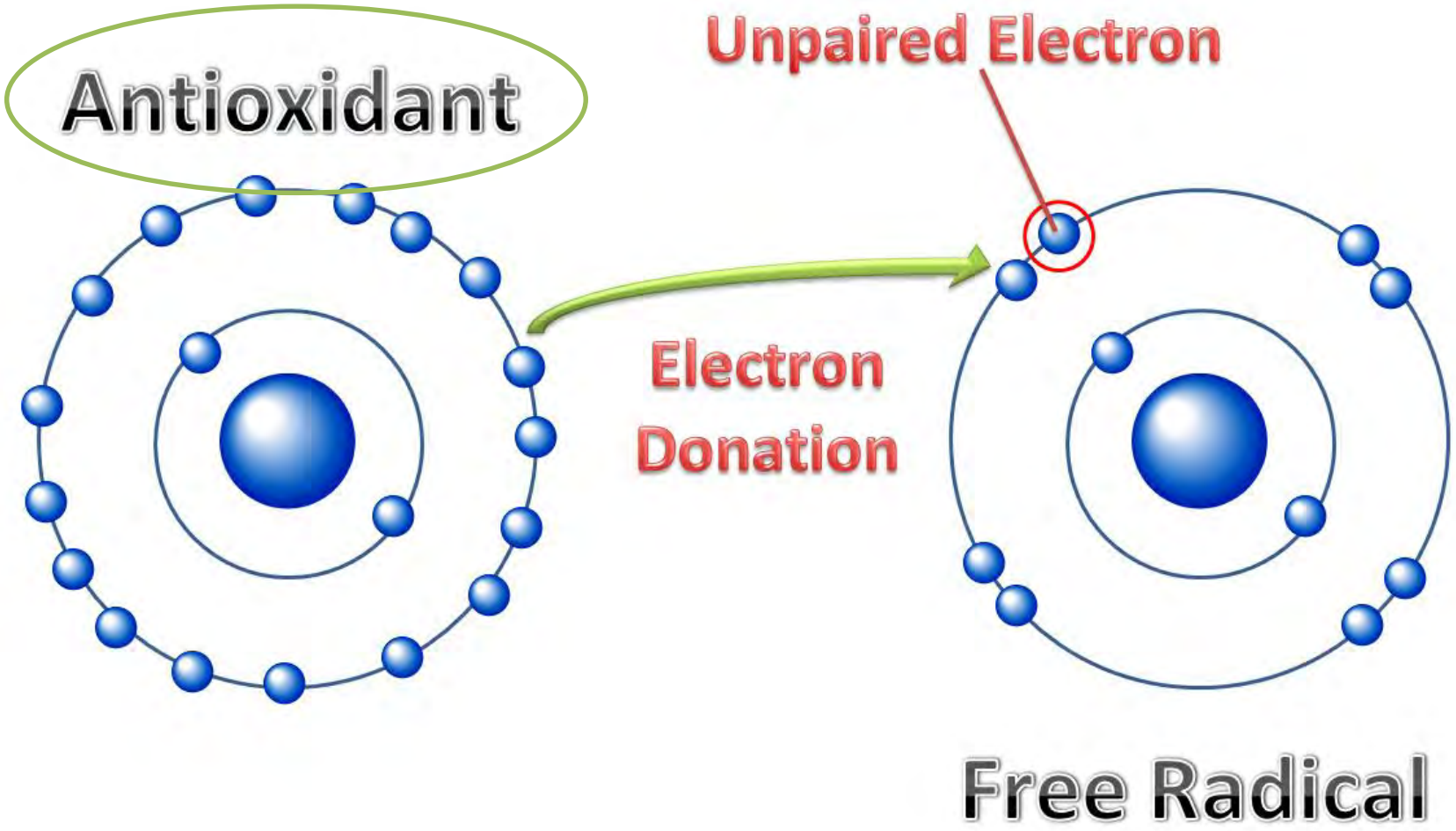
- Free radicals are like robbers which are deficient in energy.
- Free radicals attack and snatch energy from the other cells to satisfy themselves.



Free Radicals
-Damaging healthy, stable cells

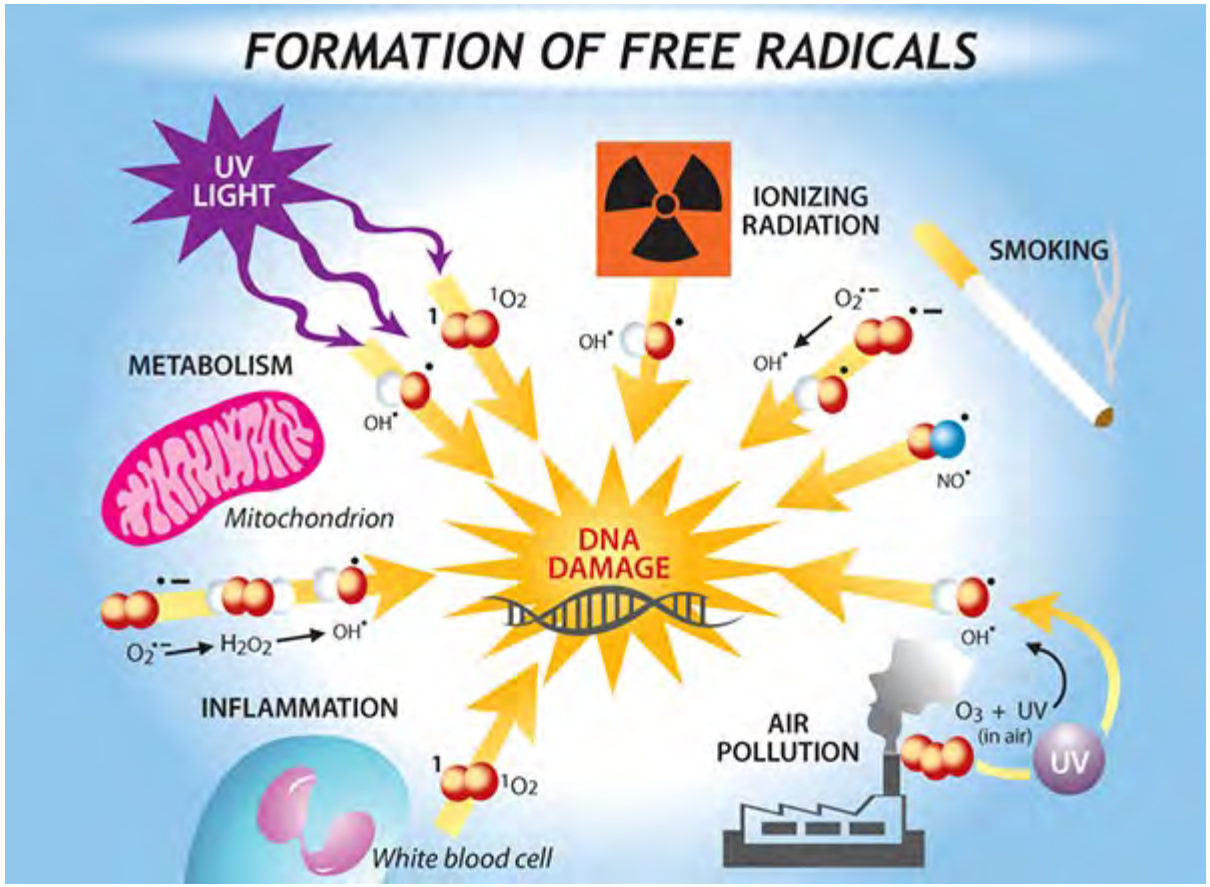


Free Radicals



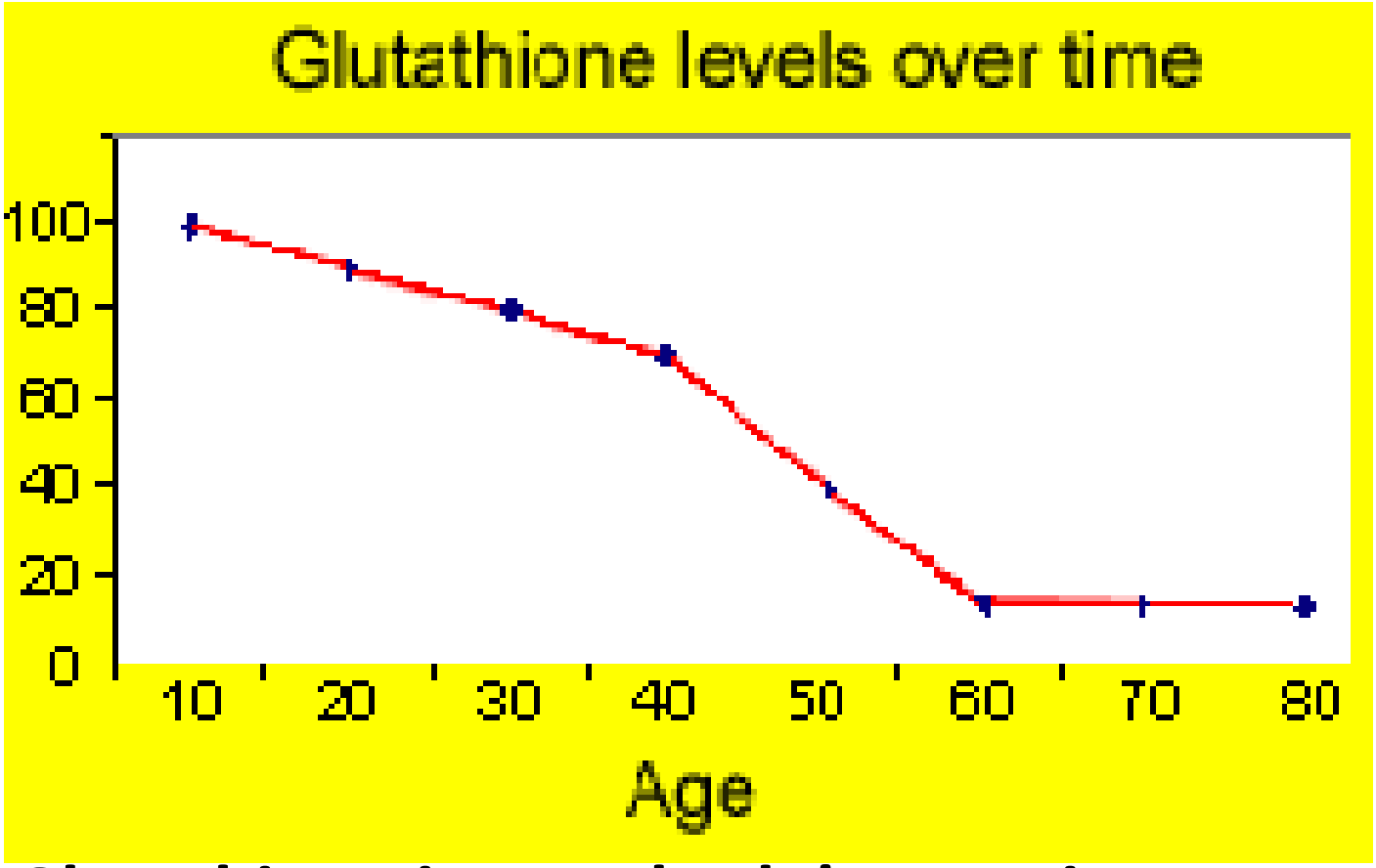
Free Radical: Environmental Factors

Free radicals can form from environmental factors such as pollution, sunlight, exhausting exercise, X-rays, smoking and alcohol.



Free Radical and Aging

Our antioxidant systems are not perfect, so as we age, cell parts damaged by oxidation accumulate.



Glutathione is your body's most important detoxifying agent.

Source - Cellular Health Foundation

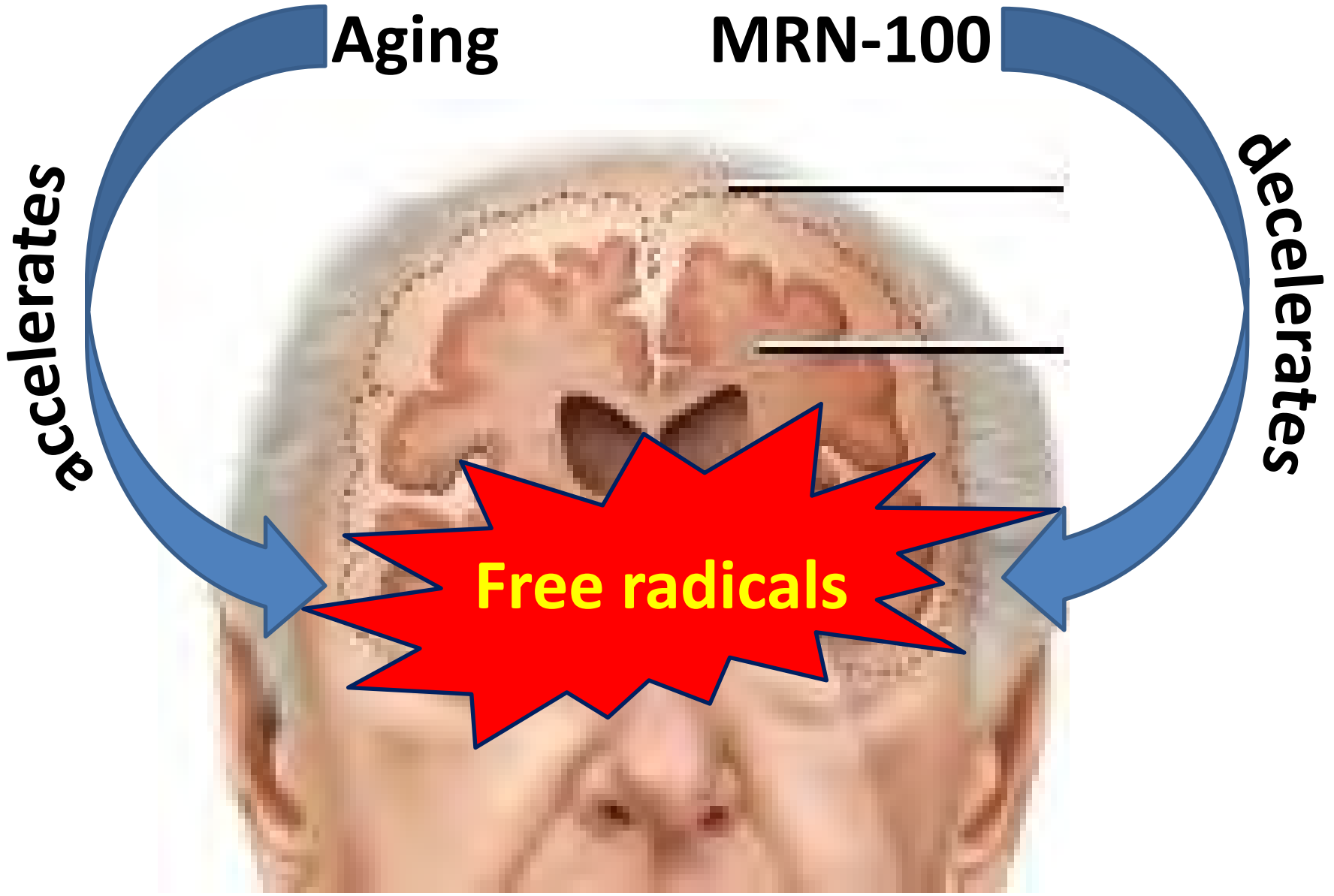
MRN-100 is a potent Antioxidant agent

MRN-100 demonstrated its effectiveness as an antioxidant by:

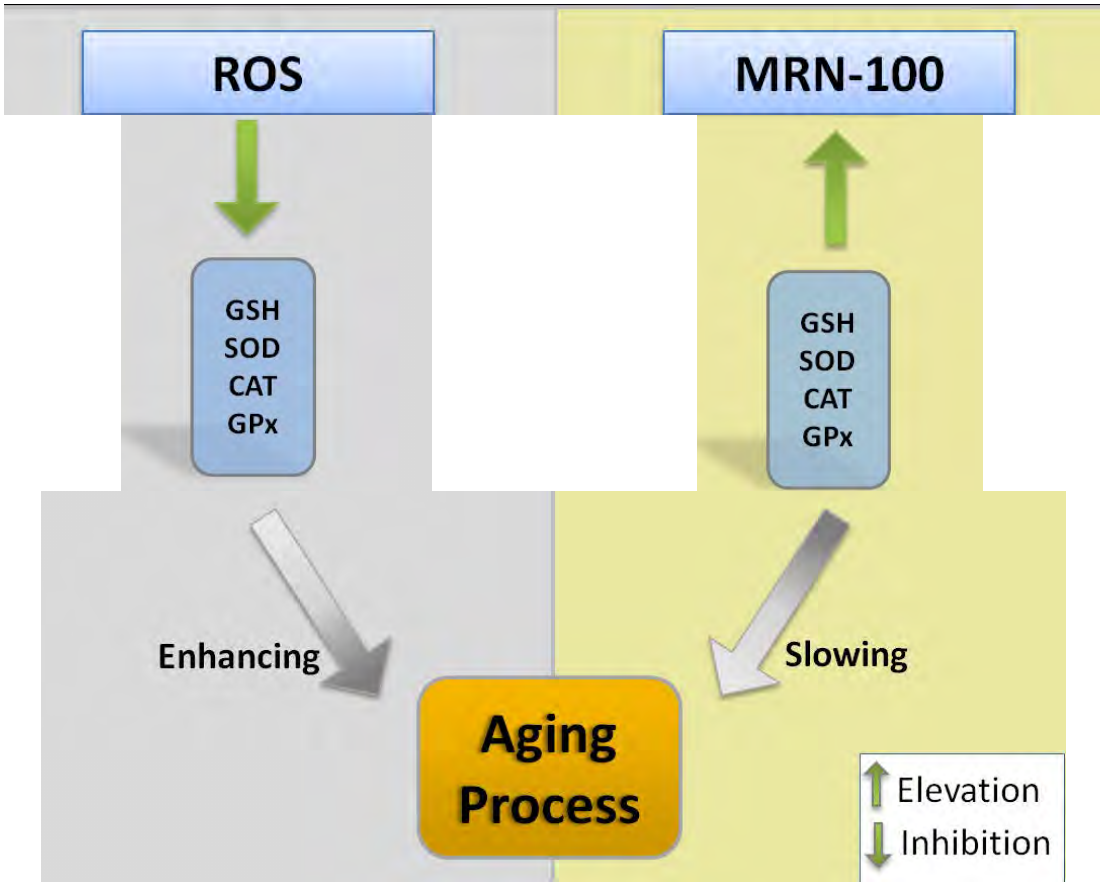
1. Increasing the levels of Glutathione (GSH; free radical scavenger)

2. Increasing antioxidant scavenger enzymes SOD, CAT and GPx

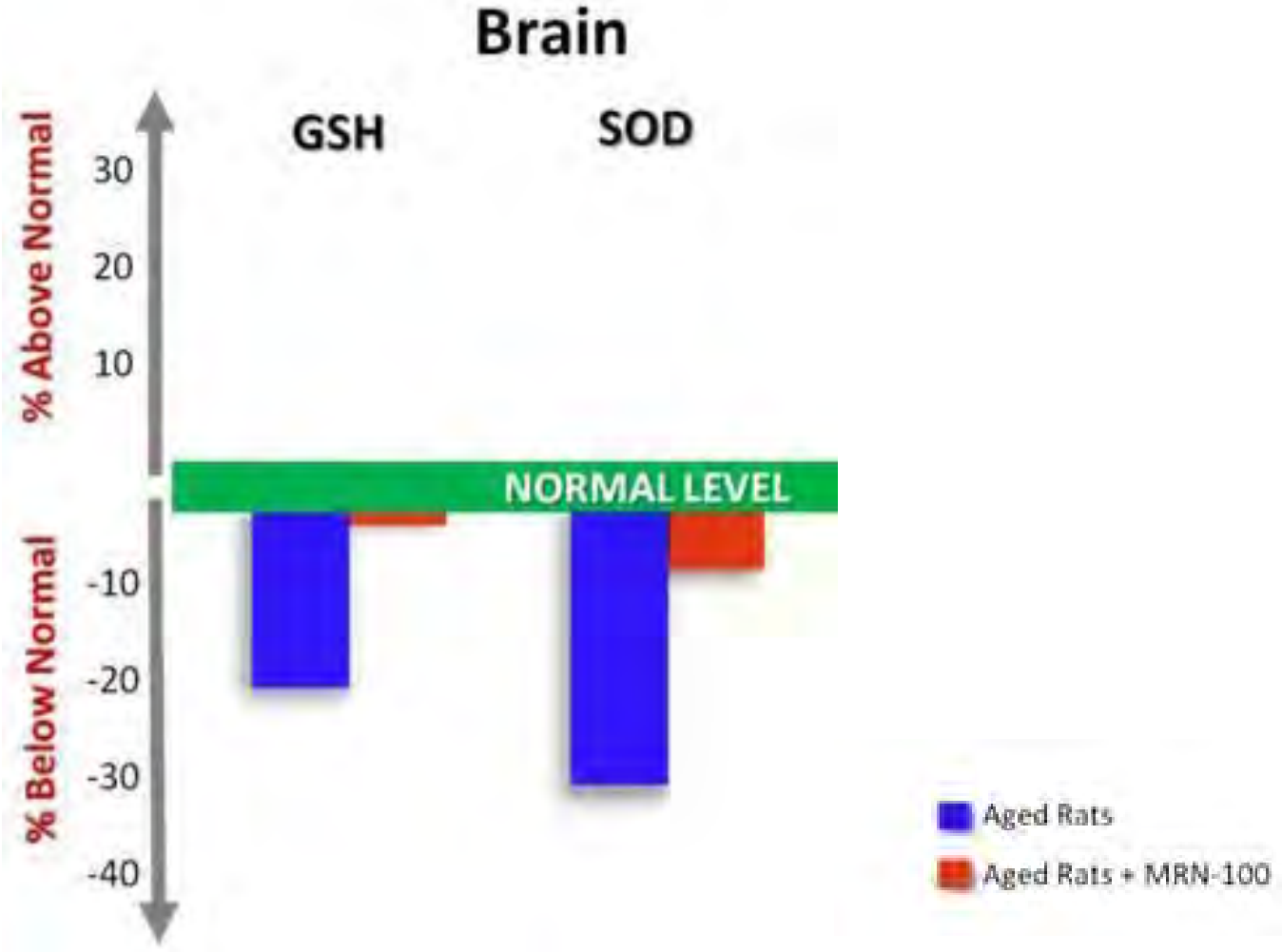
3. Prevention of Free Radicals


Aging
MRN-100
accelerates
decelerates
Free radicals

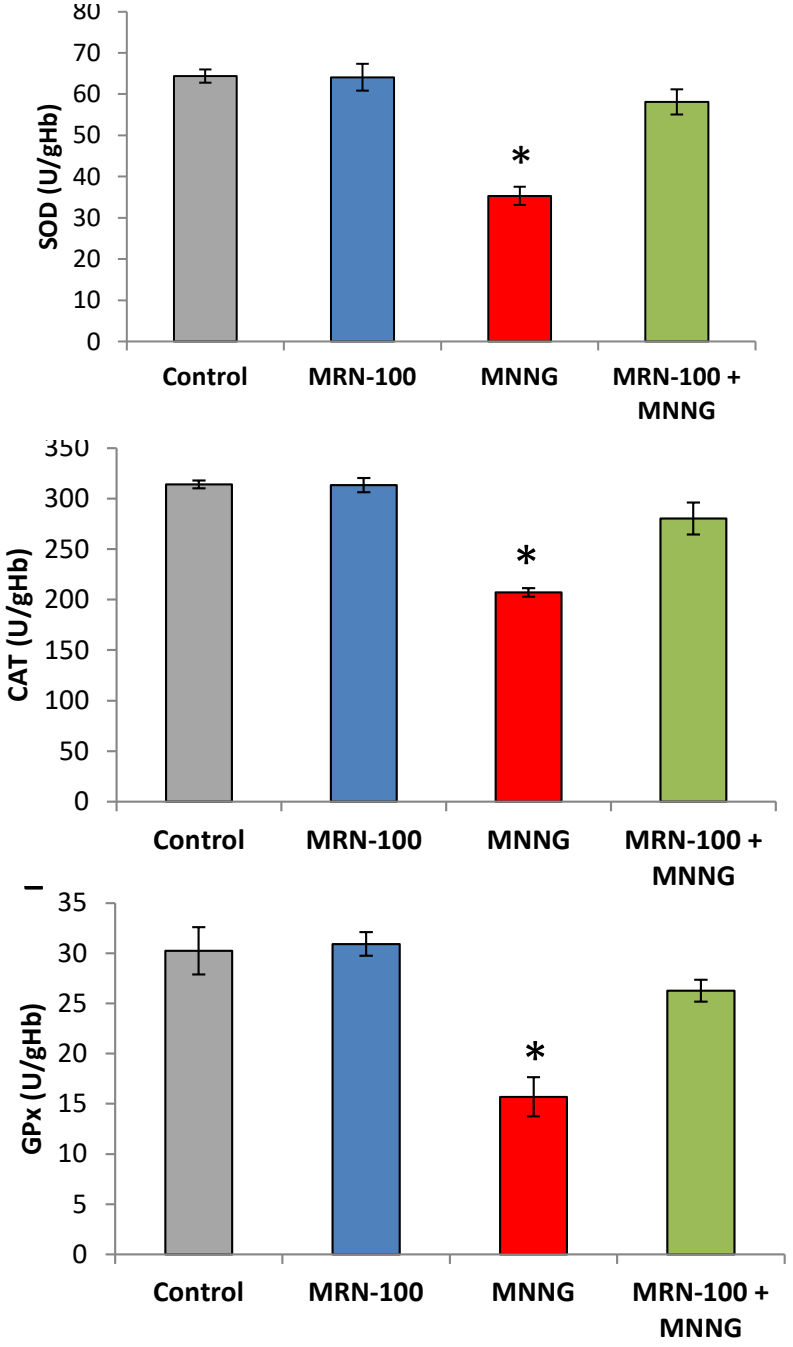
ROS enhances the aging process while MRN-100 counteracts this effect of ROS



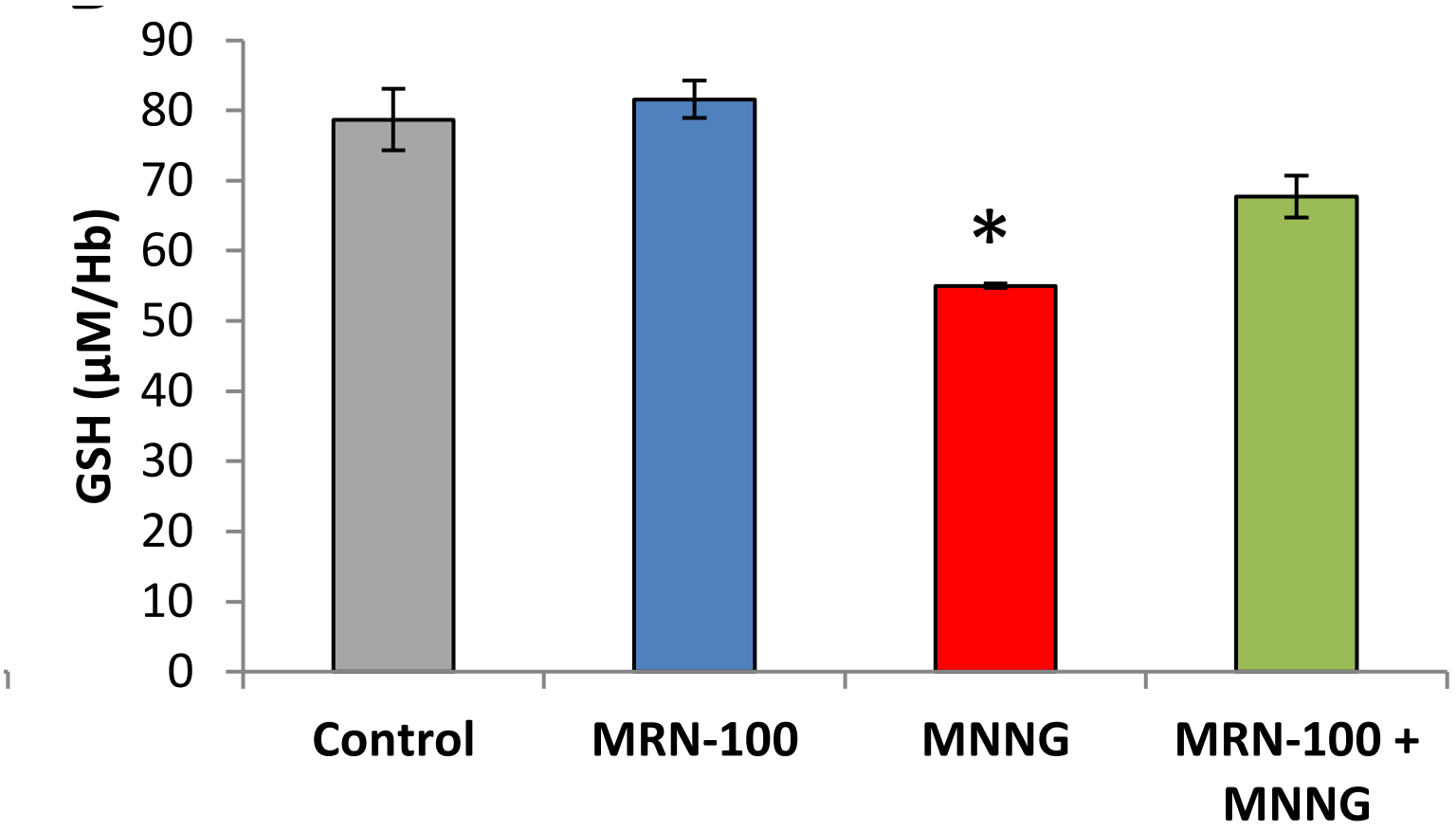
In aged rats, MRN-100 restores the levels of GSH and SOD to normal levels in the brain



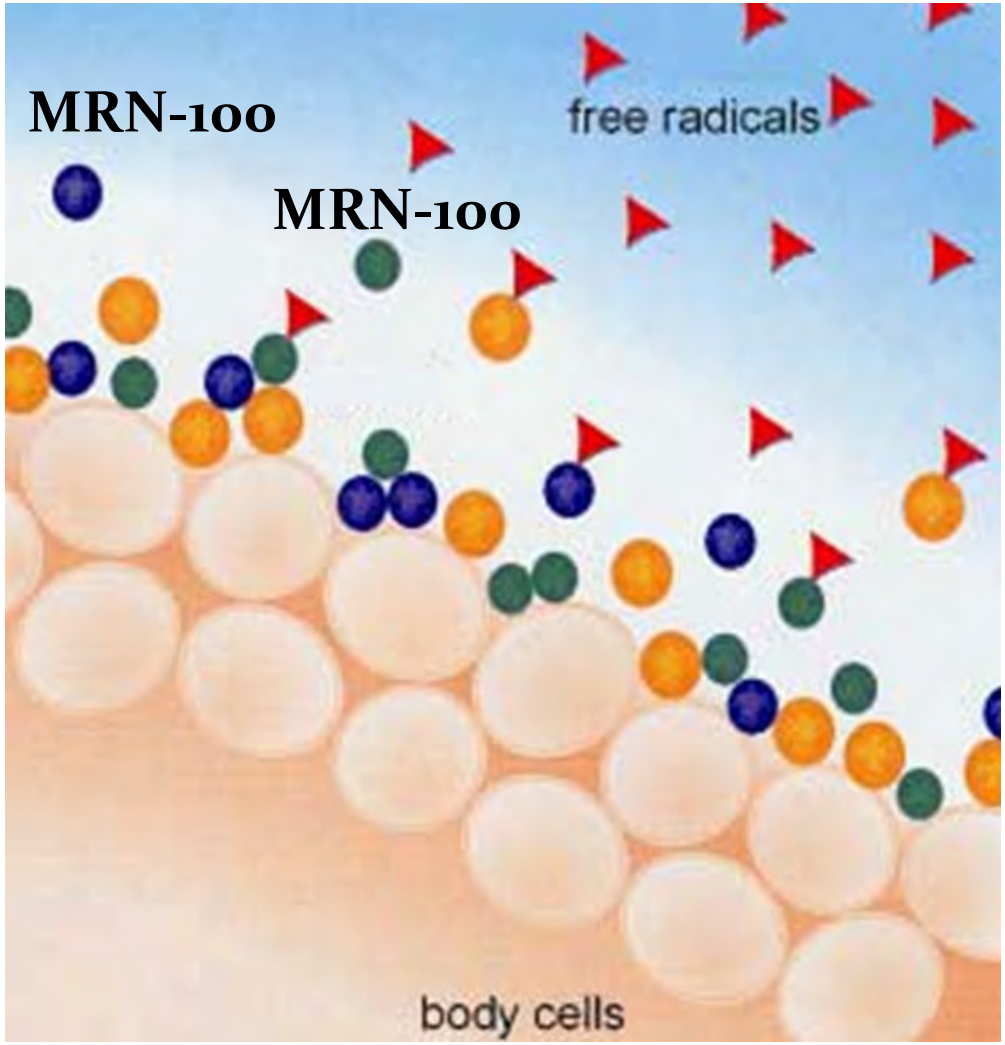
MRN-100 increases the levels of antioxidant enzymes SOD, CAT and GPx



MRN-100 increase the level of glutathione (GSH), (ROS quencher/ Free radical scavenger)



MRN-100 neutralizes free radicals and protects the cells from their damage



第38巻第2号平成24年2月25日発行（毎月1回25日発行）　昭和54年8月27日第3種郵便物認可
ISSN 1347-4340

Medical Science Digest

MSD

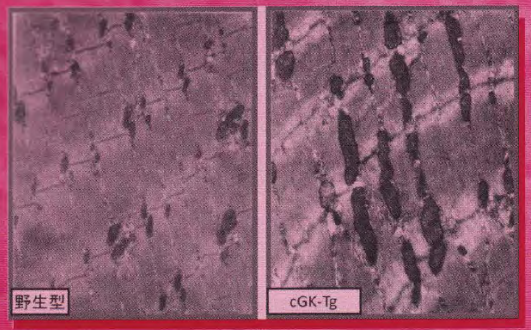
Vol.38
No.2
2012
通巻491号
2

メディカル・サイエンス・ダイジェスト

特集

生活習慣病とミトコンドリア異常

特集編輯　伊藤　裕
（慶應義塾大学腎臓内分泌代謝内科）



Digestシリーズ

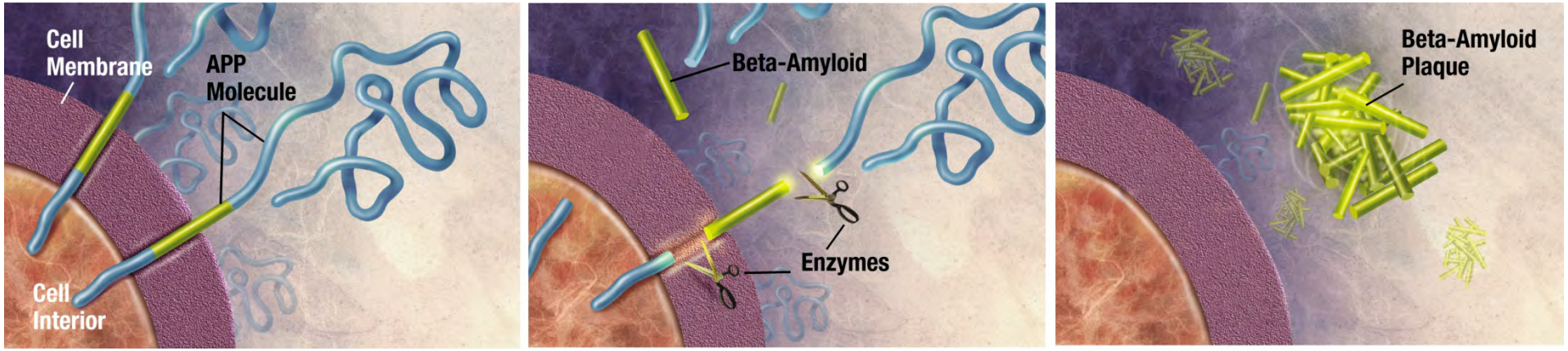
ニューサイエンス社

Antia:

a new product containing several edible mushrooms and plants treated with LC-13 which may have anti-Alzheimer's properties

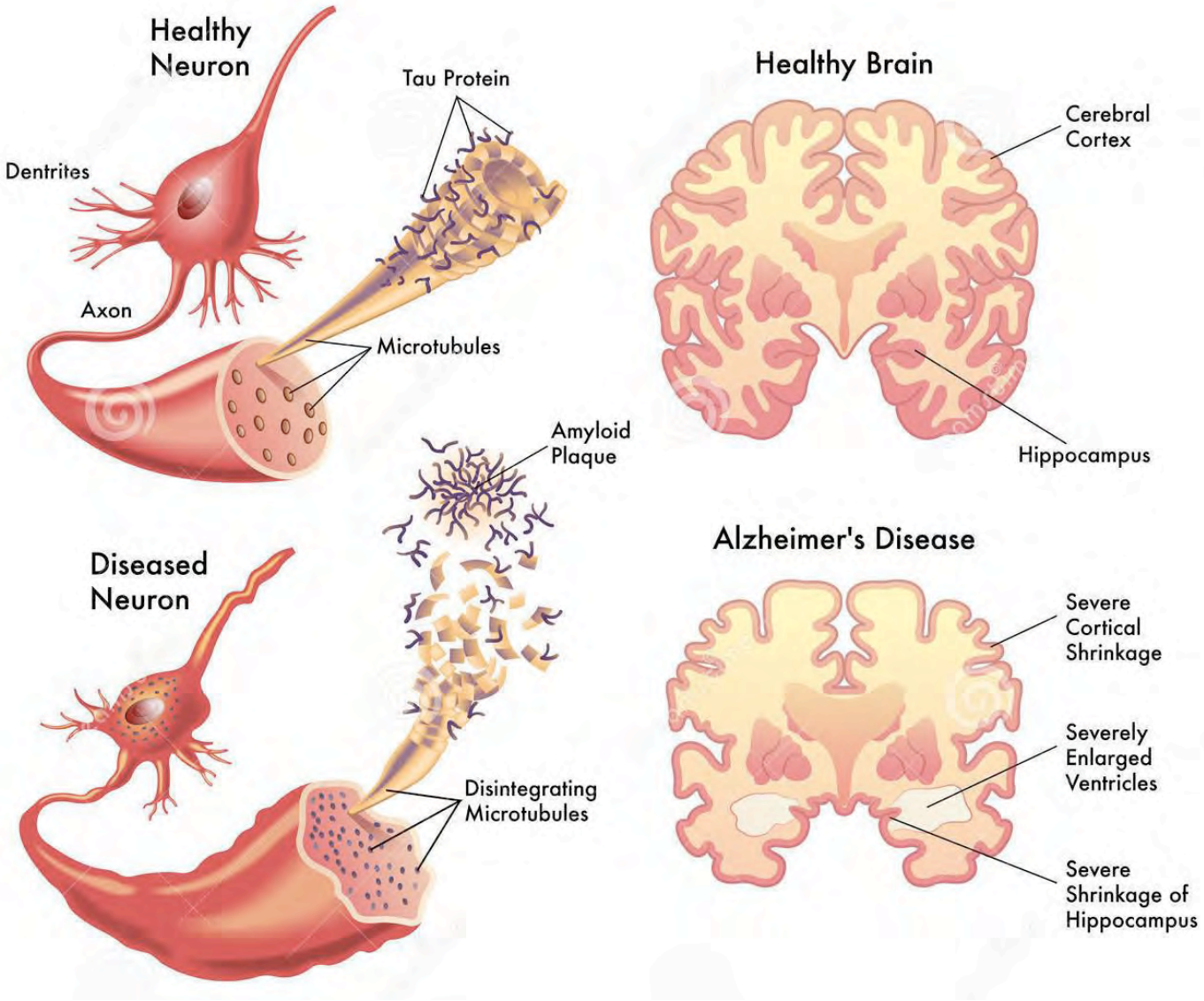
- Recently, ACM company produced a new product called Antia.
- Antia contains extracts from several edible plants and mushrooms including:
  - gotsukora
  - Yamabushitake
  - Japanese yam (also known as climbing yam)
- **treated with LC13, a modified form of MRN-100.**

Formation of Beta-Amyloid Plaque in the Brain



Amyloid Precusor Proteins (APP) are broken apart by enzymes in the brain. Once separated, pieces of APP become beta-amyloid and bind together to make plaque, a characteristic of Alzheimer's Disease.

Healthy Neuron vs Diseased Neuron



Yamabushitake (Hericium erinaceus)

- An edible mushroom
- Habitat: humid forests of North America, Europe, Asia
- Used for centuries for its neuroregenerative properties

Yamabushitake (Hericium erinaceus)

• Recent study by Bing-Ji Ma *et* al. at Henan Agricultural University (China) found that **yamabushitake mushrooms synthesize a nerve growth factor** *Mycology*, volume 1, pages 92-98 (2010).

• Bing-Ji Ma's article suggests the value of H. erinaceus for the **treatment and prevention of dementia.**

• Erinacines have potential as **medicines for degenerative neuronal disorders** such as Alzheimer's disease.

Gotsukora (Centella asiatica)

•An herb with edible leaves, used in India for centuries as a holistic medicine (ayurvedic) for stimulation and regeneration of the nervous system.

•Gotsukg India, Thailand, Vietnam, and Indonesia.

•Dhanasekaran et al. (College of Medicine, Texas A&M University) found that gotsukora extracts reduced the beta-amyloid levels in the Alzheimer's-stricken brains of laboratory animals. Phytotherapy Research, volume 23, pages 14-19 (2009)

Centella Asiatica extract (CaE) treatment reduces Reactive Oxygen Species (ROS) in Alzheimer's Mice

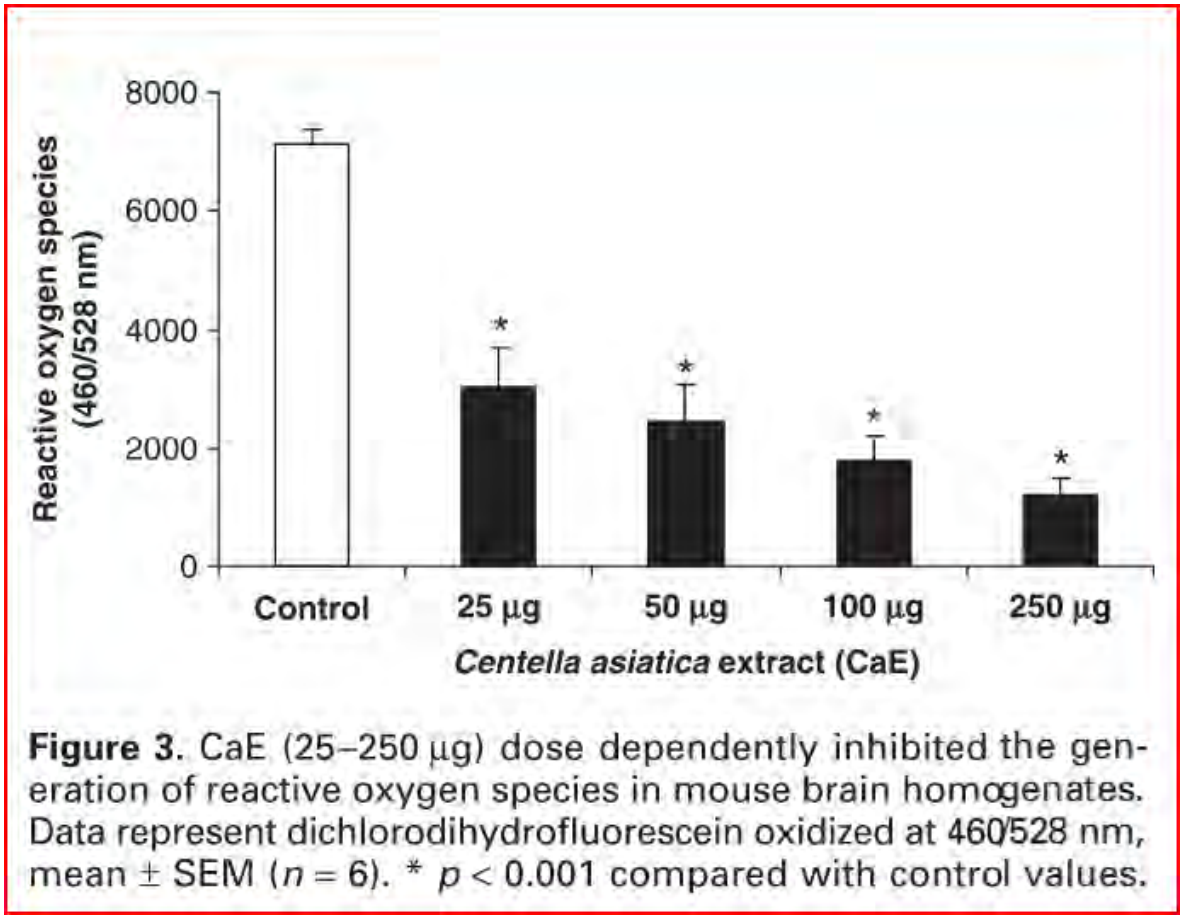


Figure 3. CaE (25–250 µg) dose dependently inhibited the generation of reactive oxygen species in mouse brain homogenates. Data represent dichlorodihydrofluorescein oxidized at 460/528 nm, mean ± SEM ($n = 6$). * $p < 0.001$ compared with control values.

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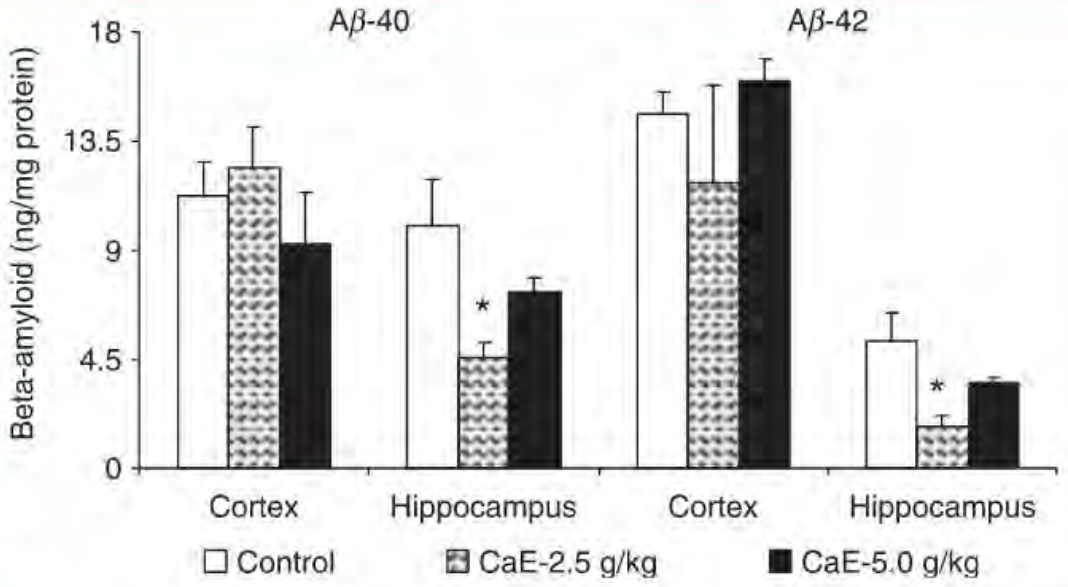

Figure 1. CaE treatment (2.5 g/kg) for 8 months, significantly reduced beta amyloid 1–40 and 1–42 in the hippocampus of PSAPP mice, in comparison with the mice treated with a control diet (* $p < 0.05$). The data represent beta-amyloid ng/mg protein. Beta amyloid 1–40 and 1–42 levels were measured by ELISA in brain homogenates from the cortex and hippocampus.

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Diosgenin

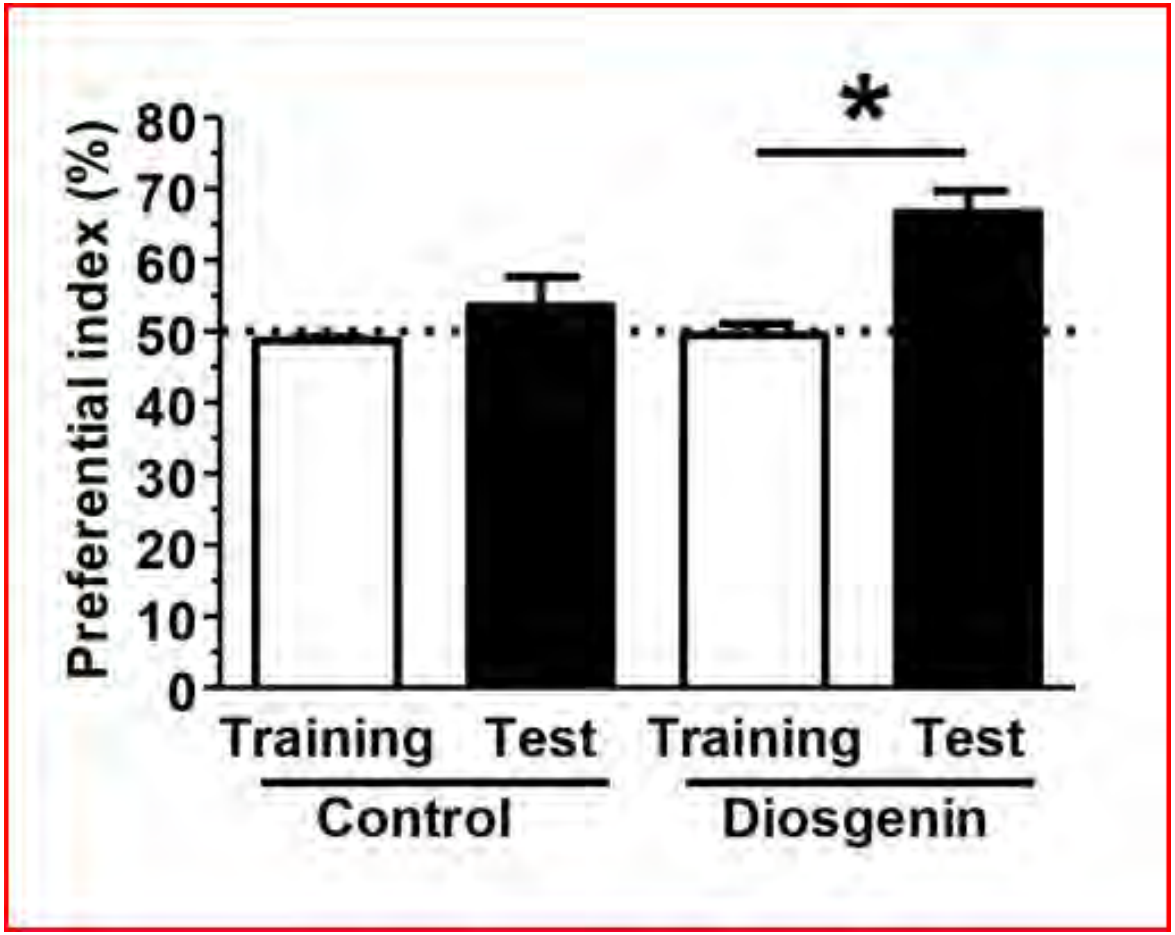
•An herb with edible roots, used in China for centuries to treat heart disease

•Native to temperate forests, especially in China, Japan.

•Diosgenin, a neuroregenerative hormone precursor, is found in the roots

•Tohda *et al.* (Institute of Natural Medicine, Japan) recently published a study showing how diosgenin enhances the cognitive performance of mice. *Scientific Reports*, volume 3, article 3395 (2013).

Diosgenin treatment significantly enhanced object recognition memory in normal mice.



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Conclusion

MRN-100 may be a useful for fighting against Alzheimer's disease via its potent antioxidant effect