The Enigma of Dementia: Should Medicinal Plants Play a Role?

Kerry Bone

DISCLOSURE OF CONFLICT OF INTEREST

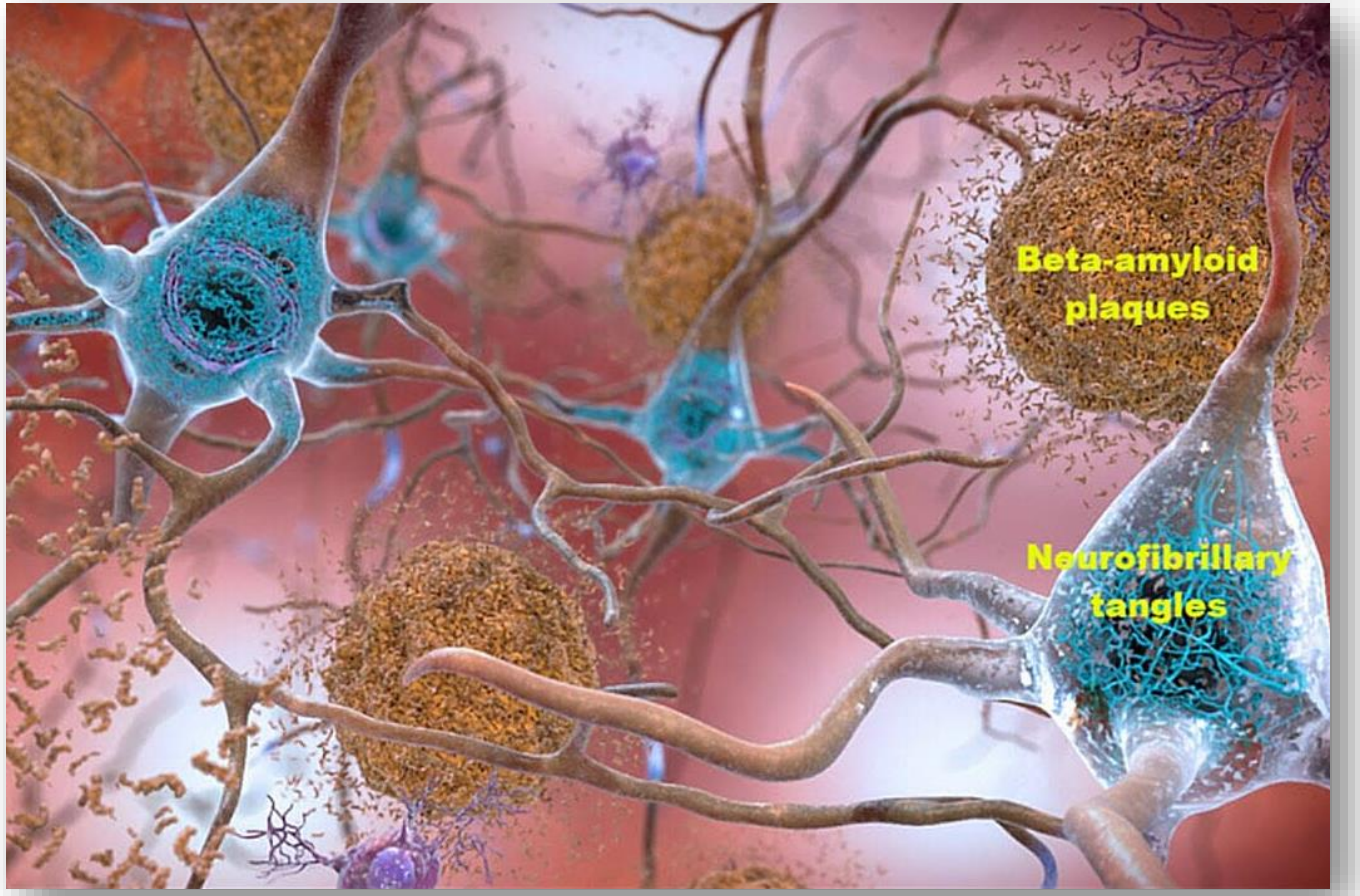
I work as a consultant for Integria Healthcare/MediHerb. However, this presentation is prepared and delivered in my free time as a herbal clinician. I have received no payment from any person or organisation for this lecture

I work as a naturopathic/herbal practitioner and hence am biased towards promoting the vastly underestimated role of natural remedies in modern healthcare

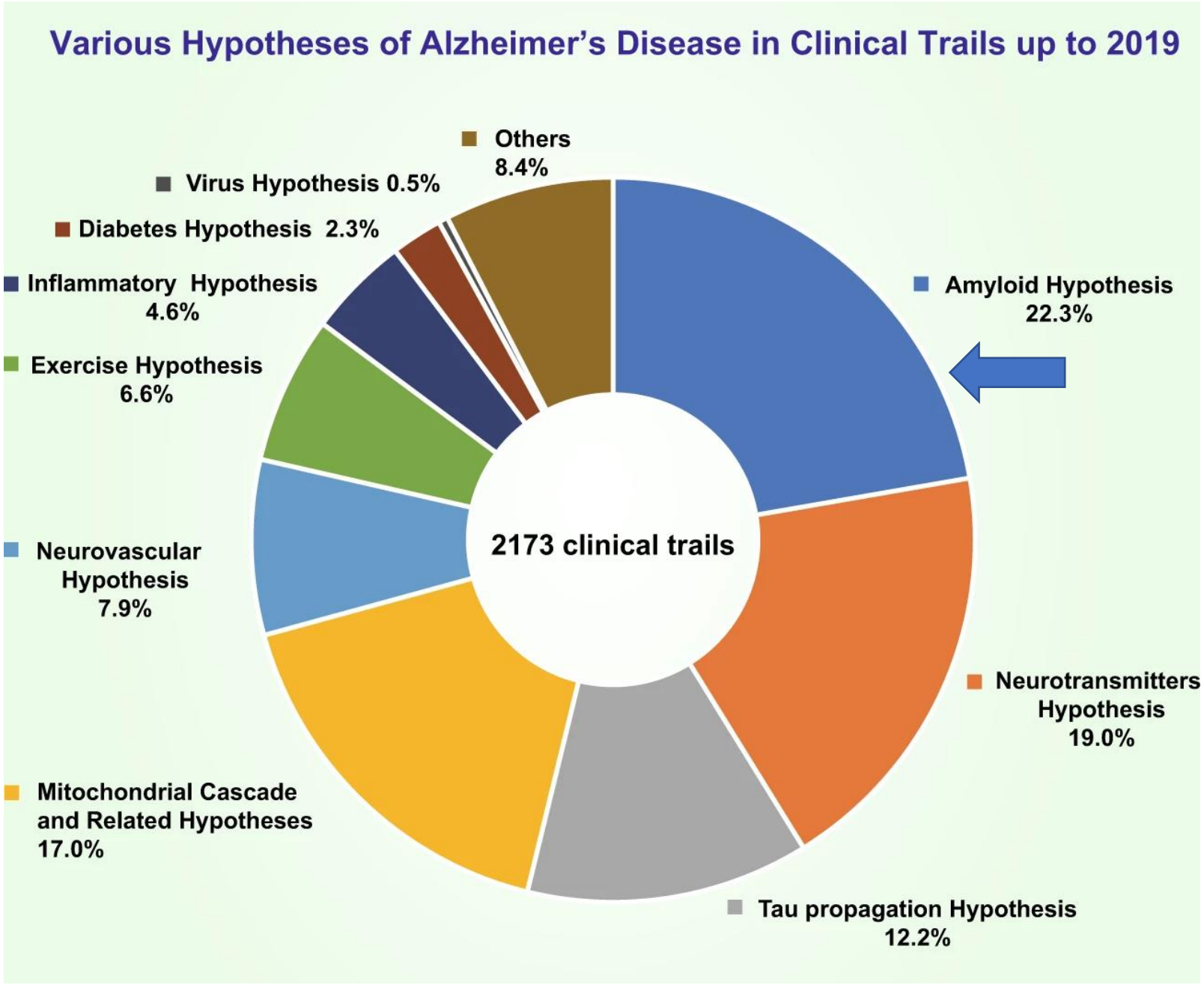
I have written a new book about Functional Herbal Therapy, which is a theme underlying this presentation, **and I would really like you to buy it**

Our Topics

- How safe and effective are current drugs?
- Key herbs overview
- Ginkgo
- Saffron
- Bacopa
- Curcumin



How Effective are Current Drugs?



Liu PP et al. History and progress of hypotheses and clinical trials for Alzheimer's disease. Signal Transduct Target Ther. 2019 Aug 23; 4: 29. doi: 10.1038/s41392-019-0063-8

New Alzheimer Antibody Drugs

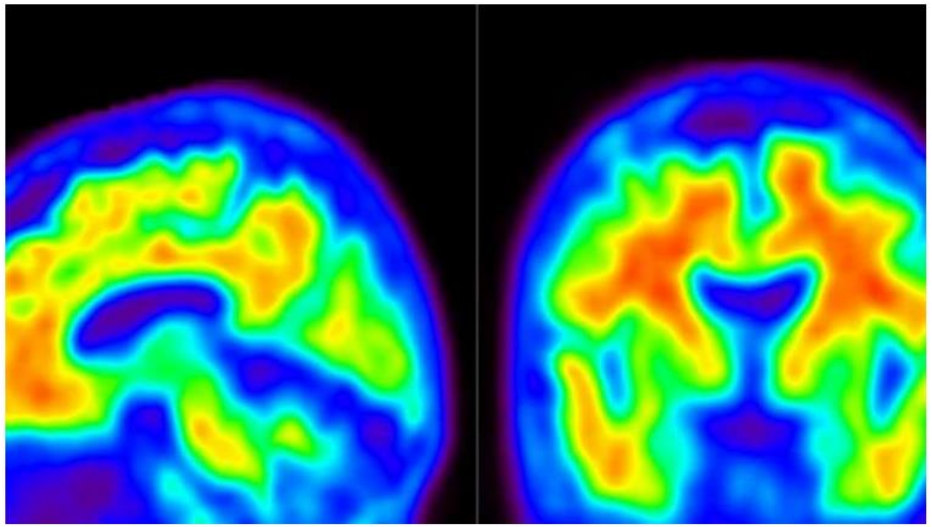
- Aimed at dissolving beta-amyloid plaque (Aβ)
- Aducanumab (now discontinued)
- Lecanemab
- Donanemab Maybe

ABC NEWS

New class of Alzheimer's drugs showing promise in patients in early stage of disease

By the Specialist Reporting Team's Alison Branley

Posted Tue 18 Jul 2023 at 3:37am, updated Tue 18 Jul 2023 at 5:26am



Sixteen Australians took part in the donanemab trial. *(Supplied: Eli Lilly)*

For decades scientists and families have been frustrated by the intractable nature of Alzheimer's disease.

As the population ages and more people develop the devastating condition, there have been no new treatments coming onto the market and for many, no hope in sight.

That was until two years ago.

In a short time, decades of research has started to come to fruition, with at least three new drugs demonstrating the first glimmers of promise.

Key points:

- A study showed donanemab could slow Alzheimer's disease progression by 35pc in patients in the earliest stages of the disease
- Geriatrician Michael Woodward says the medical community is excited by the results

slow Alzheimer's disease progression by 35pc…

…medical community is excited…

https://www.abc.net.au/news/2023-07-18/alzheimers-disease-new-drugs-showing-promise/102612162

"We now have three drugs that have been shown that can critically slow down the decline."

How does the new drug work?

Donanemab is a monoclonal antibody designed to clear the brain of amyloid plaque, which experts believe plays a role in Alzheimer's disease.

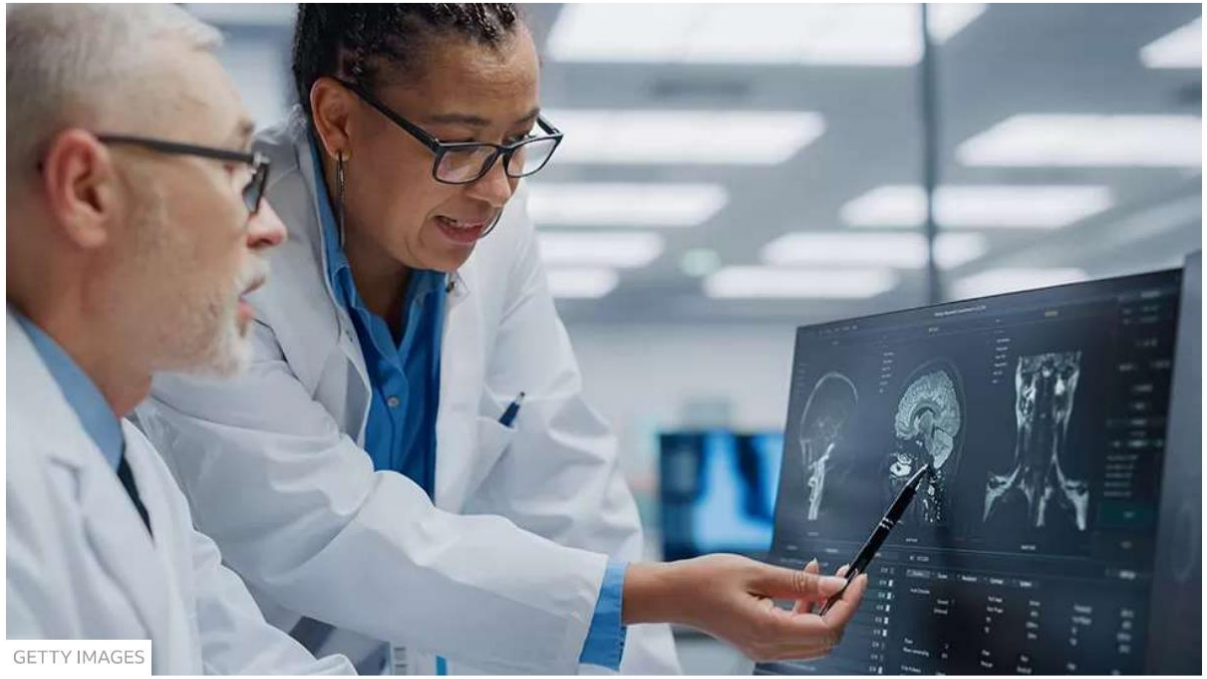
Researchers have long been trying to work out whether a protein called beta-amyloid plaque (BAP) or another protein called tau is responsible for Alzheimer's, or a combination of the two.

Those in the study were all in the early stages of Alzheimer's and aged between 60 and 85.

At the 12-month mark, the researchers said 47 per cent had no evidence of amyloid plaques, compared with 29 per cent in the placebo group.

Drug donanemab seen as turning point in dementia fight

17 July



GETTY IMAGES

By Fergus Walsh and Michelle Roberts
BBC News

A new drug, donanemab, is being hailed as a turning point in the fight against Alzheimer's, after a global trial confirms it slows cognitive decline.

The antibody medicine helps in the early stages of the disease by clearing a protein that builds up in the brains of people with this type of dementia.

Although not a cure, charities say the results in the journal **JAMA** mark a new era where Alzheimer's can be treated.

Health

Everything we know about breakthrough Alzheimer's drug Donanemab

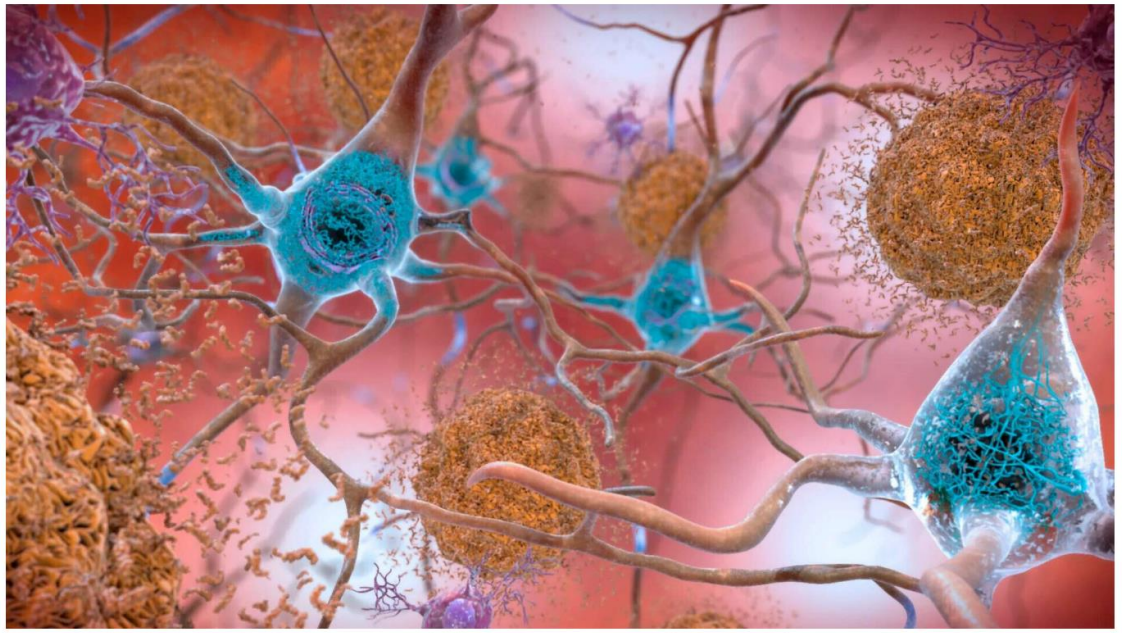
Alzheimer's disease is the most common cause of dementia in the UK

Maryam Zakir-Hussain • Monday 17 July 2023 16:22 • Comments

The Harvard Gazette

HEALTH & MEDICINE

Start of new era for Alzheimer's treatment



NIH via AP

Expert discusses recent lecanemab trial, why it appears to offer hope for those with deadly disease

Alvin Powell
Harvard Staff Writer
June 5, 2023

EDITORIAL

APOE Genotype in the Era of Disease-Modifying Treatment With Monoclonal Antibodies Against Amyloid-β

Rik Ossenkoppele, PhD; Wiesje M. van der Flier, PhD

The era of disease-modifying treatment?

The apolipoprotein E (*APOE*) ε4 allele has long been recognized as the strongest genetic risk factor for sporadic Alzheimer disease (AD). Compared with *APOE* ε3/ε3 (the most common genotype), ε4 heterozygosity (ie, 1 ε4 allele) and ε4 homozygosity (ie, ε4/ε4) incur a 3- to 4-fold and 10- to 15-fold increased risk of developing AD, respectively.[1]

Related articles pages 1295 and 1284

However, these risk estimates fluctuate considerably across studies, which may partly be attributable to differences in key demographic variables (eg, age, sex, race, and ethnicity).[2] Furthermore, although 66% of individuals with biologically defined AD carry at least 1 *APOE*-ε4 allele,[3] the mechanisms through which *APOE* genotype contributes to the AD hallmark pathologies amyloid-β and tau are insufficiently understood. Belloy et al[4] took an epidemiological perspective and provided to date the largest overview of *APOE* specific associations with AD risk. Steward et al[5] used neuroimaging techniques to get a better mechanistic understanding of how *APOE*-ε4 carriership impacts the accumulation of amyloid-β and tau (and the interaction between these pathological processes) in the brain. These 2 studies are timely in the context of recently published phase 3 results testing monoclonal antibodies against amyloid-β, 1 of which (lecanemab) recently received traditional approval by the US Food and Drug Administration.[6-8] Aducanumab, lecanemab, and donanemab all reduced amyloid-β plaques in the brains of individuals with early symptomatic AD, which translated into a modest slowing of cognitive deterioration relative to the placebo groups. Importantly, both treatment efficacy and risk profiles for adverse events of these antibodies seem to be affected by individuals' *APOE* genotype. Consequently, while assessment of *APOE* status has never been an ancillary diagnostic test in the clinical workup of AD, this is likely to change in the dawning era of disease-modifying treatment. Below we outline 3 scenarios in which knowing *APOE* status could impact patient treatment and highlight how findings reported by Belloy et al[4] and Steward et al[5] may guide future medical decision-making.

In the first scenario, *APOE* status impacts the decision whether or not to initiate treatment as the risk/benefit ratio of anti-amyloid-β immunotherapies differs as a function of *APOE*-ε4 carriership. The phase 3 studies demonstrated a potential *APOE*-dependent treatment response, as lecanemab[7] and donanemab[8] showed a significant slowing on their primary cognitive end points in *APOE*-ε4 noncarriers and *APOE*-ε4 heterozygotes but not in ε4/ε4 carriers. In contrast, the treatment response with aducanumab favored *APOE*-ε4 carriers over *APOE*-ε4 noncarriers.[6] In additi
APOE-ε4 effect on the risk of symptom
amyloid-related imaging abnormalitie
mentioned trials. ARIA can relate to v
gray and white matter or effusion in the sulcal space (ie, ARIA-E) or to hemosiderin deposits, including microhemorrhages and superficial siderosis (ie, ARIA-H). ARIA-E rates were 5.4% (lecanemab), 15.7% (donanemab), and 18% to 23% (aducanumab) for *APOE*-ε4 noncarriers; 10.9% (lecanemab) and 22.8% (donanemab) for *APOE*-ε4 heterozygotes; and 32.6% (lecanemab) and 35.0% (donanemab) for *APOE*-ε4/ε4 carriers. For aducanumab, ARIA-E rates were approximately 43% for all *APOE*-ε4 carriers (gene-dose data were not presented). Hence, a positive *APOE* ε4 status yielded a less favorable risk/benefit ratio for treatment with monoclonal antibodies against amyloid-β and, particularly for *APOE*-ε4 homozygotes, potential refrainment from this drug class could be recommended.

The complexity further increases when contemplating the interactions between *APOE* genotype and other known disease modifiers, such as age, sex, gender, and socioeconomic status. Exploratory subgroup analyses of the phase 3 trials have already generated some thought-provoking results, such as a potentially less favorable treatment response in female patients (for aducanemab and lecanemab) compared with male patients and a tendency across trials toward a smaller clinical benefit in younger (<65 years) vs older (>65 years) individuals. Both could be related to the underlying tau load, which has been shown to be higher for female individuals and relatively younger individuals at similar clinical stages of AD,[9] as the donanemab phase 3 results clearly indicate that individuals with higher tau load are less likely to experience clinical benefit.[8] Furthermore, due to the considerable underrepresentation of Hispanic, non-Hispanic Black, and East Asian individuals in the clinical trials, no meaningful subgroup analyses regarding race and ethnicity could be performed. A strength of the study by Belloy et al[4] was that their more representative sample enabled them to show that the association between *APOE*-ε4 and risk of developing AD was less pronounced among Hispanic and non-Hispanic Black individuals. When current disease-modifying treatments are introduced in real-world clinical practice and (hopefully) reach more historically underserved populations and the strict exclusion criteria for the trials no longer apply, close monitoring of both efficacy and risks are warranted, with the ultimate goal that these treatments be prescribed to those who are most likely to benefit and least likely to experience adverse effects.[10]

In the second scenario, *APOE* status may influence start and stop criteria of anti-amyloid-β immunotherapies. The main

The key paper

JAMA | Original Investigation

Donanemab in Early Symptomatic Alzheimer Disease
The TRAILBLAZER-ALZ 2 Randomized Clinical Trial

John R. Sims, MD; Jennifer A. Zimmer, MD; Cynthia D. Evans, PhD; Ming Lu, MD, MS, MPH; Paul Ardayfio, PhD; JonDavid Sparks, PhD; Alette M. Wessels, PhD; Sergey Shcherbinin, PhD; Hong Wang, PhD; Emel Serap Monkul Nery, MD; Emily C. Collins, PhD; Paul Solomon, PhD; Stephen Salloway, MD; Liana G. Apostolova, MD; Oskar Hansson, MD, PhD; Craig Ritchie, MD, PhD; Dawn A. Brooks, PhD; Mark Mintun, MD; Daniel M. Skovronsky, MD, PhD; for the TRAILBLAZER-ALZ 2 Investigators

IMPORTANCE There are limited efficacious treatments for Alzheimer disease.

OBJECTIVE To assess efficacy and adverse events of donanemab, an antibody designed to clear brain amyloid plaque.

DESIGN, SETTING, AND PARTICIPANTS Multicenter (277 medical research centers/hospitals in 8 countries), randomized, double-blind, placebo-controlled, 18-month phase 3 trial that enrolled 1736 participants with early symptomatic Alzheimer disease (mild cognitive impairment/mild dementia) with amyloid and low/medium or high tau pathology based on positron emission tomography imaging from June 2020 to November 2021 (last patient visit for primary outcome in April 2023).

INTERVENTIONS Participants were randomized in a 1:1 ratio to receive donanemab (n = 860) or placebo (n = 876) intravenously every 4 weeks for 72 weeks. Participants in the donanemab group were switched to receive placebo in a blinded manner if dose completion criteria were met.

MAIN OUTCOMES AND MEASURES The primary outcome was change in integrated Alzheimer Disease Rating Scale (iADRS) score from baseline to 76 weeks (range, 0-144; lower scores indicate greater impairment). There were 24 gated outcomes (primary, secondary, and exploratory), including the secondary outcome of change in the sum of boxes of the Clinical Dementia Rating Scale (CDR-SB) score (range, 0-18; higher scores indicate greater impairment). Statistical testing allocated α of .04 to testing low/medium tau population outcomes, with the remainder (.01) for combined population outcomes.

Visual Abstract
Editorial
Supplemental content

Sims JR et al. Donanemab in Early Symptomatic Alzheimer Disease: The TRAILBLAZER-ALZ 2 Randomized Clinical Trial. JAMA. 2023 Aug 8; 330(6): 512-527. doi: 10.1001/jama.2023.13239. PMID: 37459141

Let’s have a reality check…

HEALTHCARE & PHARMA

JANUARY 8, 2018 / 5:59 AM / UPDATED 6 YEARS AGO

Pfizer ends research for new Alzheimer's, Parkinson's drugs

By Reuters Staff

NEW YORK (Reuters) - Pfizer Inc PFE.N is abandoning research to find new drugs aimed at treating Alzheimer's and Parkinson's disease, the U.S. pharmaceutical company announced on Saturday.

Pfizer has invested heavily in research for Parkinson's and Alzheimer's, and is one of several drugmakers, along with GlaxoSmithKline GSK.L and Eli Lilly LLY.N, that is part of the Dementia Discovery Fund, a venture capital fund launched in 2015 by industry and government groups that seeks to develop treatments for Alzheimer's.

However, some of Pfizer's investments have resulted in disappointment. In 2012, Pfizer and partner Johnson & Johnson JNJ.N called off additional work on the drug bapineuzumab after it failed to help patients with mild to moderate Alzheimer's in its second round of clinical trials.

Viewpoint

July 31, 2023

Are New Alzheimer Drugs Better Than Older Drugs?

Susan Molchan, MD[1]; Adriane Fugh-Berman, MD[2]

» Author Affiliations | Article Information

JAMA Intern Med. 2023;183(9):902-903. doi:10.1001/jamainternmed.2023.3061

In July 2023, the US Food and Drug Administration (FDA) provided full approval for an amyloid-β–directed antibody, lecanemab (Leqembi), for treating Alzheimer disease. The prescribing information states that treatment, which is administered as an intravenous infusion, should be initiated in patients with mild cognitive impairment or the mild dementia stage of the disease, which is the population in which the treatment was studied in clinical trials. Lecanemab is the second monoclonal antibody targeting β-amyloid protein to be approved; the first was aducanumab (Aduhelm) in 2021. The FDA approved lecanemab via its accelerated approval program in January 2023 based solely on the decline in β-amyloid as estimated on positron emission tomography scans in the brains of patients taking the drug compared with placebo. The agency granted full approval of lecanemab based on clinical efficacy data from a clinical trial with 1795 participants.[1] Advocacy groups were pressuring the US Centers for Medicare & Medicaid Services to pay for the drug.

In the lecanemab trial reported by van Dyck et al,[1] the primary outcome measure was the change from baseline on the Clinical Dementia Rating–Sum of Boxes (CDR-SB) scale, a commonly used scale of cognition and daily function (range, 0-18). The mean decline from baseline over 18 months was 1.21 points with lecanemab and 1.66 points with placebo, an absolute difference of 0.45 points (95% CI, −0.67 to −0.23), which was reported as a 27% slower decline with lecanemab than with placebo.[1]

This review provides convincing arguments in support of the conclusion that newer Alzheimer disease drugs are not meaningfully better than older Alzheimer disease drugs, and reasonably convincing arguments that neither class of drugs provides clinically meaningful benefits

Molchan S, Fugh-Berman A. Are New Alzheimer Drugs Better Than Older Drugs? JAMA Intern Med. 2023 Jul 31. doi: 10.1001/jamainternmed.2023.3061. Epub ahead of print. PMID: 37523164

Are New Alzheimer Drugs Better Than Older Drugs?

- In July 2023, the US FDA approved lecanemab, an amyloid-β-targeting antibody, for treating Alzheimer disease (AD)
- The lecanemab trial showed a “27% slower cognitive decline” compared to placebo on the CDR-SB scale over 18 months, but this reported improvement was **not clinically significant**
- Cholinesterase inhibitors, the first drugs for AD, had similar effect sizes in earlier trials
- Stated another way, neither the lecanemab trial nor the donepezil trials found clinically significant beneficial effects
- Lecanemab and aducanumab, the first approved β-amyloid-targeting antibody, have been associated with brain oedema and brain haemorrhages
- A review suggests these drugs may accelerate brain atrophy and ventricular enlargement

What About Donanemab?

- Donanemab was very effective at eliminating its target, cerebral amyloid; at 76 weeks amyloid plaques were cleared in 80% of the treatment group
- But the clinical effect was comparatively weak: overall, cognition and daily function continued to decline in **all participants**, but treatment with donanemab delayed progression on the primary outcome (the integrated AD Rating Scale) by about 4 months
- Similar to trials of lecanemab and aducanumab, this donanemab trial did not provide sufficient evidence of safety or efficacy among people racialised as American Indian or Alaska Native, Asian, Black or Hispanic

Manly JJ, Deters KD. Donanemab for Alzheimer Disease-Who Benefits and Who Is Harmed? JAMA. 2023 Aug 8;330(6):510-511. doi: 10.1001/jama.2023.11704. PMID: 37459138

What About Donanemab?

- Treatment with donanemab was associated with significant safety risks, including three deaths determined to be drug related
- In the treatment group, amyloid-related imaging abnormalities were seen in about 37% vs 15% in the placebo group
- Microhaemorrhage occurred in 26.8% in the donanemab group vs 12.5% in the placebo group
- “Clinicians and the public will need to weigh the potential benefit of treatment (delay of progression of about 4 months on average) with the financial and quality-of-life costs of infusions, MRI monitoring, and risk of amyloid-related imaging abnormalities”

Manly JJ, Deters KD. Donanemab for Alzheimer Disease-Who Benefits and Who Is Harmed? JAMA. 2023 Aug 8;330(6):510-511. doi: 10.1001/jama.2023.11704. PMID: 37459138

Key Herbs for Cognition and Dementia

Key Herbs for Boosting Cognition

- Evidence from dementia trials: Bacopa, Ginkgo, Saffron, curcumin, Korean Ginseng, resveratrol, Sage
- Evidence from trials in older people with MCI: Ginkgo, cocoa, Saffron, Withania, Korean Ginseng
- Evidence from trials in healthy older people: curcumin, Bacopa, Gotu Kola, resveratrol, cocoa, Ginkgo, Rosemary, Sage, blueberries, curcumin

See subsequent slides and relevant monographs in Bone KM, Mills SY. *Principles and Practice of Phytotherapy: Modern Herbal Medicine* 2nd edition, Elsevier, UK, 2013

Key Herbs for Boosting Cognition

- Evidence from trials in **healthy young people**:
  - Bacopa, resveratrol, Rosemary, Sage, Korean Ginseng, Ginkgo, cocoa, Schisandra, Eleuthero (Siberian Ginseng), blueberries
- Weak preliminary human data: Lion's Mane

See relevant monographs in Bone KM, Mills SY. *Principles and Practice of Phytotherapy: Modern Herbal Medicine* 2nd edition, Elsevier, UK, 2013

Ginkgo is Key for Brain Health

Ginkgo ticks every functional medicine box:

- Neuroprotective and increases BDNF
- Nrf2 boosting and anti-inflammatory
- Supports microcirculation
- Boosts mitochondrial function
- Neuroregenerative (used in stroke recovery in China)

nutrients

MDPI

Article

Effects of Six-Week *Ginkgo biloba* Supplementation on Aerobic Performance, Blood Pro/Antioxidant Balance, and Serum Brain-Derived Neurotrophic Factor in Physically Active Men

Ewa Sadowska-Krępa [1,*], Barbara Kłapcińska [1], Ilona Pokora [1], Przemysław Domaszewski [2], Katarzyna Kempa [1] and Tomasz Podgórski [3]

[1] Department of Physiological and Medical Sciences, The Jerzy Kukuczka Academy of Physical Education, 40-065 Katowice, Poland; b.klapcinska@awf.katowice.pl (B.K.); i.pokora@awf.katowice.pl (I.P.); k.kempa@awf.katowice.pl (K.K.)

[2] Department of Tourism and Health Promotion, University of Technology, Faculty of Physical Education and Physiotherapy, 45-758 Opole, Poland; domaszewskiprzemek@wp.pl

[3] Department of Biochemistry, Poznan University of Physical Education, 61-871 Poznań, Poland; podgorski@awf.poznan.pl

* Correspondence: e.sadowska-krepa@awf.katowice.pl; Tel.: +48-32-207-54-71

Received: 11 May 2017; Accepted: 24 July 2017; Published: 26 July 2017

Abstract: Extracts of *Ginkgo biloba* leaves, a natural source of flavonoids and polyphenolic compounds, are commonly used as therapeutic agents for the improvement of both cognitive and physiological performance. The present study was aimed to test the effects of a six-week supplementation with 160 mg/day of a standardized extract of *Ginkgo biloba* or a matching placebo on aerobic performance, blood antioxidant capacity, and brain-derived neurotrophic factor (BDNF) level in healthy, physically active young men, randomly allocated to two groups (n = 9 each). At baseline, as well as on

"Our results show that six weeks' supplementation with *Ginkgo biloba* extract in physically active young men may provide some marginal improvements in their endurance performance expressed as VO_2max and blood antioxidant capacity, as evidenced by specific biomarkers, and elicit somewhat better neuroprotection through **increased exercise-induced production of BDNF**."

Dose was 160 mg per day of extract, equivalent to about 8 g of leaf

Ginkgo: Dementia Meta-analyses

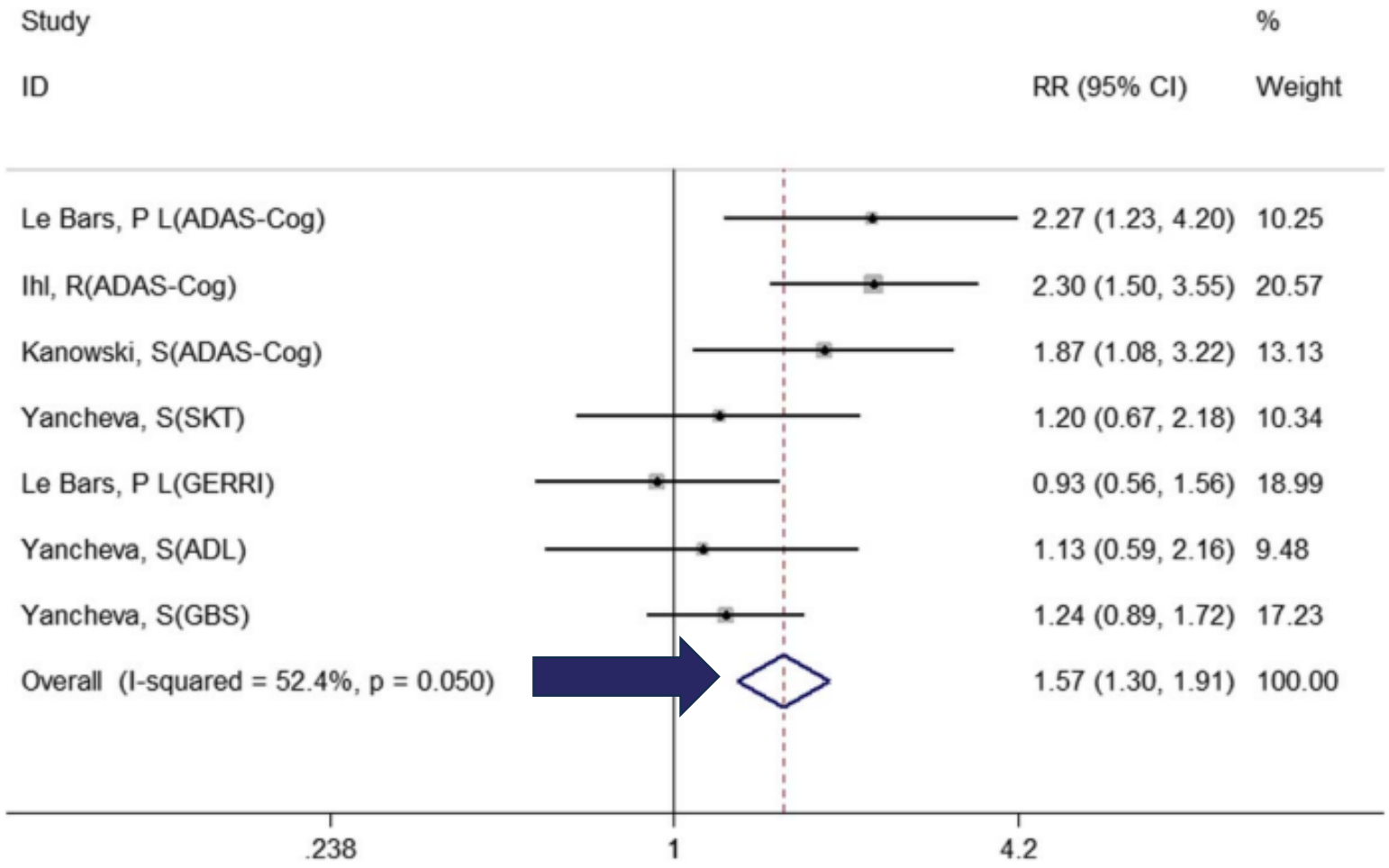
- Four RCTs involving 1,628 outpatients with mild to moderate dementia: differences for change from baseline in cognition, daily living, clinical global impression and quality of life favoured Ginkgo[1]
- Seven RCTs involving 2,625 patients with dementia: superiority of Ginkgo over placebo was confirmed by responder analyses, as well as for patients suffering from dementia with neuropsychiatric symptoms[2]
- Four RCTs involving 1,628 outpatients with mild to moderate dementia: Ginkgo improved behavioural and psychological symptoms (except psychotic-like features) and caregiver distress[3]

References For the Previous Slide

1. von Gunten A et al. Efficacy of Ginkgo biloba extract EGb 761(®) in dementia with behavioural and psychological symptoms: A systematic review. *World J Biol Psychiatry.* 2016 Dec; 17(8): 622-633

2. Gauthier S et al. Efficacy and tolerability of Ginkgo biloba extract EGb 761® in dementia: a systematic review and meta-analysis of randomized placebo-controlled trials. *Clin Interv Aging*. 2014 Nov 28; 9: 2065-2077. doi: 10.2147/CIA.S72728

3. Savaskan E et al. Treatment effects of Ginkgo biloba extract EGb 761® on the spectrum of behavioral and psychological symptoms of dementia: meta-analysis of randomized controlled trials. *Int Psychogeriatr.* 2018 Mar; 30(3): 285-293. doi: 10.1017/S1041610217001892



Ginkgo has reliable efficacy of cognitive function and global clinical assessment and safety in the treatment of AD

For the measures of cognitive function and activities of daily living

Liao Z et al. Meta-analysis of Ginkgo biloba Preparation for the Treatment of Alzheimer's Disease. Clin Neuropharmacol. 2020 Jul/Aug; 43(4): 93-99. doi: 10.1097/WNF.0000000000000394

TABLE 2 | Consensus statements of EGb from the Asian Clinical Expert Group on Neurocognitive Disorders.

No	Consensus statement	Concrete content
1	Efficacy of EGb 761® in AD, VaD, and BPSD	Best practice for the pharmacological treatment as follows: AD: AChEI, memantine, EGb VaD: AChEI, memantine, EGb, antiplatelet therapy BPSD: ChEI, nonpharmacological treatment, antipsychotics (off-label), memantine, SSRIs, sedatives, and EGb
2	Management of MCI	EGb may be considered for use in patients with MCI
3	How to use EGb	EGb can be used as a single agent, and allow sufficient time to take effect
4	The dosage	EGb at daily dose of 240 mg
5	Lack of efficacy or intolerance of standard drugs may warrant use of EGb	EGb was recommended to treat AD, VaD, and mixed dementia, when the patients unable to tolerate the side effects of standard treatments
6	Adjunctive therapies	EGb was one of the key management options adjunctive to standard pharmacological therapy for AD, VaD, and BPSD
7	Management of comorbidities	EGb played an important role in the management of co-morbidities, such as hypertension, in patients with AD, VaD, and BPSD
8	Does not appear to prevent dementia	EGb was not recommended for prevention of dementia
9	Well tolerated	EGb had a good tolerability profile in the treatment of MCI, AD, VaD, and BPSD
10	No overall increased bleeding risk	EGb appeared to be no overall added risk of bleeding
11	No significant interaction with anticoagulants or antiplatelet agents	EGb had been demonstrated no significant interaction with anticoagulants and antiplatelet agents

AD, Alzheimer's disease; VaD, vascular dementia; BPSD, behavioral and psychological symptoms of dementia; MCI, mild cognitive impairment; AChEI, acetylcholinesterase inhibitors; SSRIs, Selective Serotonin Reuptake Inhibitors.

From the Asian Clinical Expert Group

In the guideline, several compelling evidences supported the inclusion of Ginkgo extract as part of the treatment armamentarium for AD or VaD

Liu H et ak. An Updated Review of Randomized Clinical Trials Testing the Improvement of Cognitive Function of *Ginkgo biloba* Extract in Healthy People and Alzheimer's Patients. Front Pharmacol. 2020 Feb 21; 10: 1688. doi: 10.3389/fphar.2019.01688

Journal of Alzheimer's Disease 86 (2022) 703–709
DOI 10.3233/JAD-215348
IOS Press

Association Between *Ginkgo Biloba* Extract Prescriptions and Dementia Incidence in Outpatients with Mild Cognitive Impairment in Germany: A Retrospective Cohort Study

Jens Bohlken[a], Oliver Peters[b,c] and Karel Kostev[d,*]
[a]*Institute for Social Medicine, Occupational Medicine, and Public Health (ISAP) of the Medical Faculty at the University of Leipzig, Leipzig, Germany*
[b]*Department of Psychiatry, Charité-Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany*
[c]*German Center for Neurodegenerative Diseases (DZNE), Berlin, Germany*
[d]*Epidemiology, IQVIA, Frankfurt am Main, Germany*

Accepted 27 December 2021
Pre-press 3 February 2022

Abstract.
Background: Clinical trials have demonstrated a significant effectiveness of *Ginkgo biloba* therapy versus placebo in patients with dementia.
Objective: The present study aims to analyze the impact of *Ginkgo biloba* drug prescriptions on dementia incidence in patients with mild cognitive impairment (MCI) in a real-world setting.
Methods: This retrospective study was based on the IQVIA Disease Analyzer database and included patients aged 65 or older with a first diagnosis of MCI from January 2000 to December 2019. Each patient was followed for up to 20 years after MCI diagnosis until February 2021. Date of the first diagnosis of dementia or loss to follow-up, whichever occurred first, was noted. To estimate the association between *Ginkgo biloba* prescriptions during the follow-up and dementia incidence, a multivariable Cox regression analysis was performed, adjusted for age, sex, health insurance, documented co-diagnoses, and prescription of cholinesterase inhibitors.
Results: Overall, 24,483 MCI patients (mean age: 77.0 years, 56.3% women) were included. It was found that > 2 prescriptions of *Ginkgo biloba* were significantly associated with a reduced dementia incidence (HR: 0.71 (95% CI: 0.55–0.91), $p = 0.007$), as compared with no *Ginkgo biloba* prescription. The effect of receiving > 3 *Ginkgo biloba* prescriptions was even stronger, with an HR of 0.64 (95% CI: 0.48–0.86), $p = 0.003$), while for > 4 prescriptions the HR was 0.58 (95% CI: 0.41–0.82) ($p = 0.002$).
Conclusion: All-cause dementia incidence decreased with higher numbers of *Ginkgo biloba* prescriptions in MCI patients.

Keywords: Dementia, *Ginkgo biloba* extract, mild cognitive impairment, outpatients

- Overall, 24,483 mild cognitive impairment patients (mean age: 77.0 years, 56.3% women) were included
- > 2 prescriptions of Ginkgo were significantly associated with a reduced dementia incidence (hazard ratio, HR: 0.71 (95% CI: 0.55-0.91), p = 0.007), as compared with no Ginkgo prescription
- > 3 Ginkgo prescriptions was an even stronger association, with an HR of 0.64 (95% CI: 0.48-0.86), p = 0.003)
- For > 4 prescriptions the HR was 0.58 (95% CI: 0.41-0.82) (p = 0.002)

Bohlken J et al. Association Between Ginkgo Biloba Extract Prescriptions and Dementia Incidence in Outpatients with Mild Cognitive Impairment in Germany: A Retrospective Cohort Study. J Alzheimers Dis. 2022; 86(2): 703-709. doi: 10.3233/JAD-215348

Saffron and AD and MCI

- Saffron (30 mg/day stigma extract) versus donepezil (10 mg/day) in 54 patients with moderate AD ⇒ equal efficacy after 22 weeks[1]
- Saffron more effective than placebo (same dose) in 46 AD patients over 16 weeks[2]
- Saffron (same dose) versus memantine (20 mg/day) in 68 patients with moderate to severe AD ⇒ equal efficacy after 12 months[3]
- Small single blind trial showed that MCI patients on Saffron had improved Mini-Mental State Examination scores ($p = 0.015$), while the control group deteriorated; also MRI and EEG showed improvement in specific domains[4]

References For the Previous Slide

1: Akhondzadeh S et al. A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. Psychopharmacology (Berl). 2010 Jan; 207(4): 637-643. doi: 10.1007/s00213-009-1706-1.

2: Akhondzadeh S et al. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. J Clin Pharm Ther. 2010 Oct; 35(5): 581-588. doi: 10.1111/j.1365-2710.2009.01133.x.

3: Farokhnia M et al. Comparing the efficacy and safety of Crocus sativus L. with memantine in patients with moderate to severe Alzheimer's disease: a double-blind randomized clinical trial. Hum Psychopharmacol. 2014 Jul; 29(4): 351-359. doi: 10.1002/hup.2412

4: Tsolaki M et al. Efficacy and Safety of Crocus sativus L. in Patients with Mild Cognitive Impairment: One Year Single-Blind Randomized, with Parallel Groups, Clinical Trial. J Alzheimers Dis. 2016 Jul 27; 54(1): 129-33. doi: 10.3233/JAD-160304

Bacopa Systematic Reviews

- Five trials reviewed for AD: three used Bacopa in combination with other herbs, two used Bacopa extracts only
- Two studies compared Bacopa with donepezil, while the others used a placebo
- All studies reported statistically significant difference between Bacopa and comparator in at least one AD-related outcome, but trial quality was low[1]
- Meta-analysis (9 trials, n = 518) suggested that Bacopa has the potential to improve cognition, particularly speed of attention, trials were deemed small[2]

1. Basheer A et al. Bacopa monnieri in the treatment of dementia due to Alzheimer's disease: A systematic review of randomised controlled trials. Interact J Med Res. 2022 May 25. doi: 10.2196/38542
2. Kongkeaw C et al. Meta-analysis of randomized controlled trials on cognitive effects of Bacopa monnieri extract. J Ethnopharmacol. 2014; 151(1): 528-535. doi: 10.1016/j.jep.2013.11.008

Curcumin is Key for Brain Health

- Double blind placebo-controlled three-arm comparative study, involving 48 people (n = 16/group) with moderate dementia due to the onset of AD
- Supplemented with 400 mg × 2/day of either placebo, an unformulated standard curcumin complex with 95% purity (USC), or CGM (curcumin galactomannosides, delivering a daily dose of around 400 mg of curcumin) for six months
- CGM produced significant ($p < 0.05$) improvements in the Mini-Mental State Examination (MMSE) and the Geriatric Locomotive Function Scale (GLFS) scores in both intra- and inter-group comparison
- Analysis of the serum levels of specific biomarkers (BDNF, Aβ42, tau protein, IL-6, and TNF-α) also revealed a significant ($p < 0.05$) improvement among CGM subjects, as compared to placebo and the USC group. Aβ42 is a component of amyloid plaque

Das S S et al. Influence of CurQfen®-curcumin on cognitive impairment: a randomized, double-blinded, placebo-controlled, 3-arm, 3-sequence comparative study. Front. Dement; 13 September 2023; doi.org/10.3389/frdem.2023.1222708

Curcumin is Key for Brain Health

- MMSE scores showed a significant ($p < 0.001$) deterioration in placebo from 16.09 ± 1.86 to 13.81 ± 1.72
- However, CGM supplementation significantly enhanced MMSE from 16.07 ± 1.81 to 19.27 ± 1.67 (19.83%; $p < 0.001$); the increase in the USC group was not significant
- Pairwise comparison of Aβ42 revealed 13.16% ($p = 0.019$) and 2.68% ($p = 0.064$) reductions in the CGM and USC groups, respectively, whereas the placebo group showed 11.16% ($p = 0.001$) increase compared to baseline
- Pairwise comparison showed a massive 54.12% decrease in serum IL-6 for CGM ($p < 0.001$) and a 15.11% reduction for USC ($p > 0.05$), placebo showed 30.16% increase compared to baseline
- Reductions in TNFα were 54.83% ($p < 0.003$) and 16.33% ($p < 0.073$) for the CGM and USC groups, with a 20.58% increase ($p < 0.001$) for placebo

Das S S et al. Influence of CurQfen®-curcumin on cognitive impairment: a randomized, double-blinded, placebo-controlled, 3-arm, 3-sequence comparative study. Front. Dement; 13 September 2023; doi.org/10.3389/frdem.2023.1222708

Thank you!