Evaluation Of Natural Flavonoid Compounds In Amyloid-β (Aβ) Inhibition For Alzheimer Treatment

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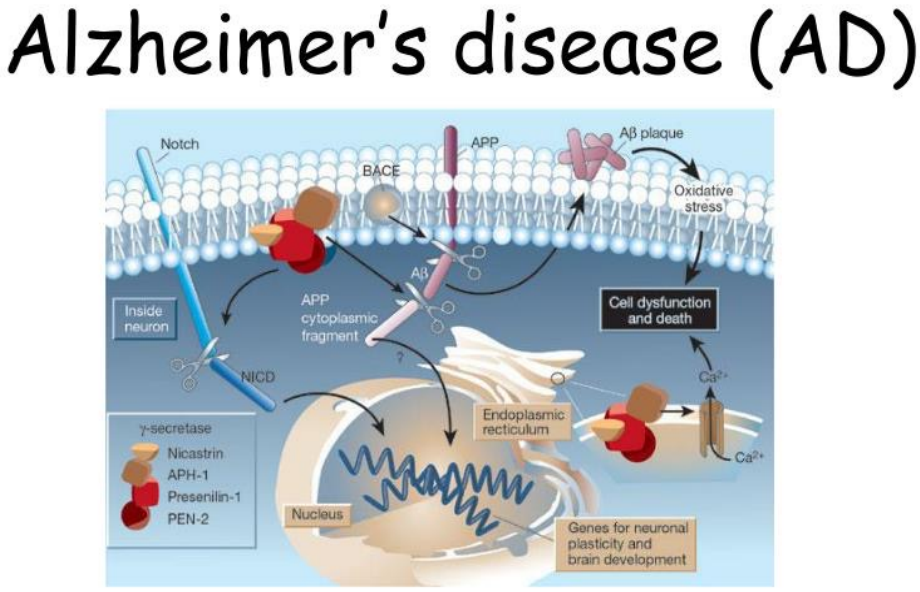
Introduction to Alzheimer's Disease

Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline.

The accumulation of amyloid-β (Aβ) plaques in the brain is a hallmark of AD pathology.

Effective treatments targeting Aβ aggregation are critical for managing Alzheimer's Disease.



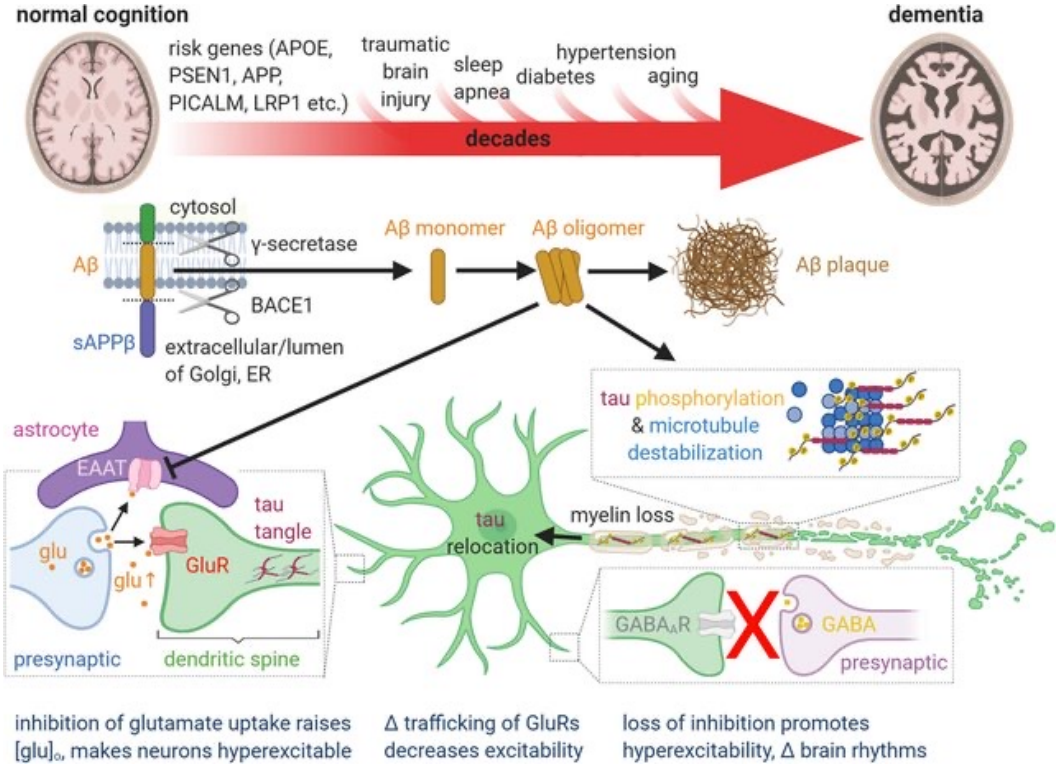
The γ-secretase protein quartet, and its roles in brain development and Alzheimer's disease. **Presenilin-1, nicastrin, APH-1** and **PEN-2** form a functional **γ-secretase complex**, located in the plasma membrane and endoplasmic reticulum (ER) of neurons. The complex cleaves **Notch** (left) to generate a fragment (**NICD**) that moves to the nucleus and regulates the expression of genes involved in brain development and adult neuronal plasticity. The complex also helps in generating the **amyloid β-peptide** (Aβ; centre). This involves an initial cleavage of the amyloid precursor protein (**APP**) by an enzyme called **BACE** (or β-secretase). The γ-secretase then liberates Aβ, as well as an APP cytoplasmic fragment, which may move to the nucleus and regulate gene expression. Mutations in presenilin-1 that cause early-onset Alzheimer's disease enhance γ-secretase activity and Aβ production, and also perturb the ER calcium balance. Consequent neuronal degeneration may result from membrane-associated oxidative stress, induced by aggregating forms of Aβ (which create Aβ plaques), and by the perturbed calcium balance. **Mattson, M. 2003 Nature**

Understanding Amyloid-β (Aβ)

Amyloid-β is a peptide that aggregates to form plaques, disrupting neuronal function.

The aggregation of Aβ leads to neuroinflammation and oxidative stress in the brain.

Targeting Aβ aggregation is a promising therapeutic approach for Alzheimer's Disease.



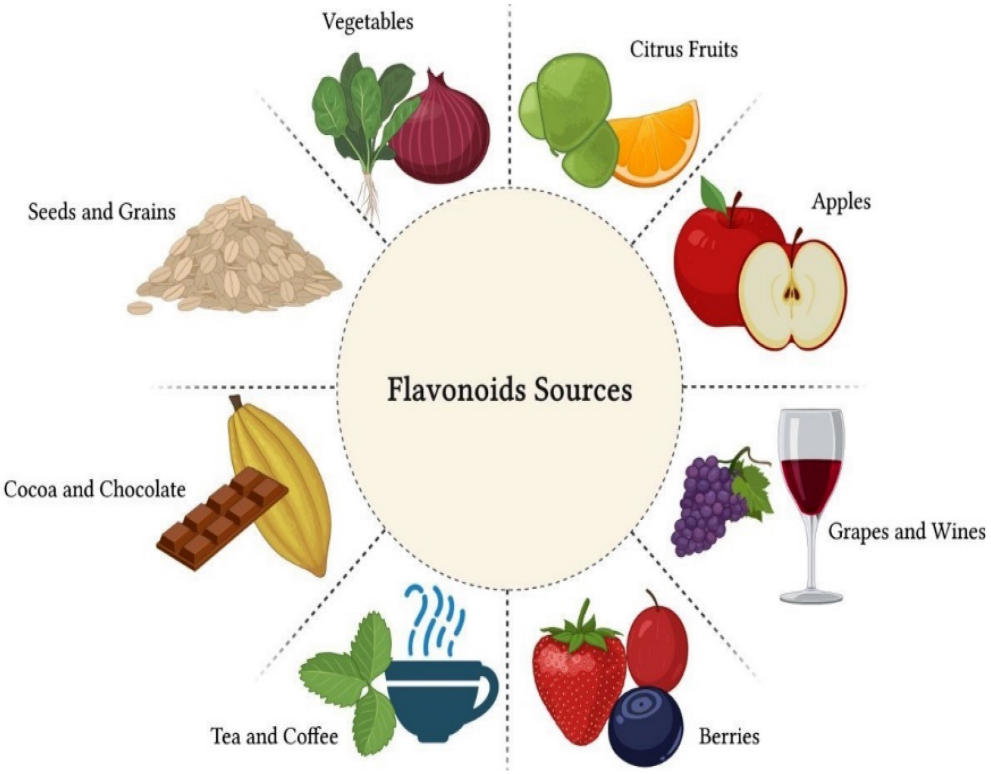
https://www.researchgate.net/publication/344003757_Cerebral_blood_flow_decrease_as_an_early_pathological_mechanism_in_Alzheimer%27s_disease/figures?lo=1

Natural Flavonoids Overview

Flavonoids are a diverse group of phytonutrients found in fruits, vegetables, and beverages.

They possess antioxidant, anti-inflammatory, and neuroprotective properties.

Natural flavonoids are being explored for their potential in inhibiting Aβ aggregation.

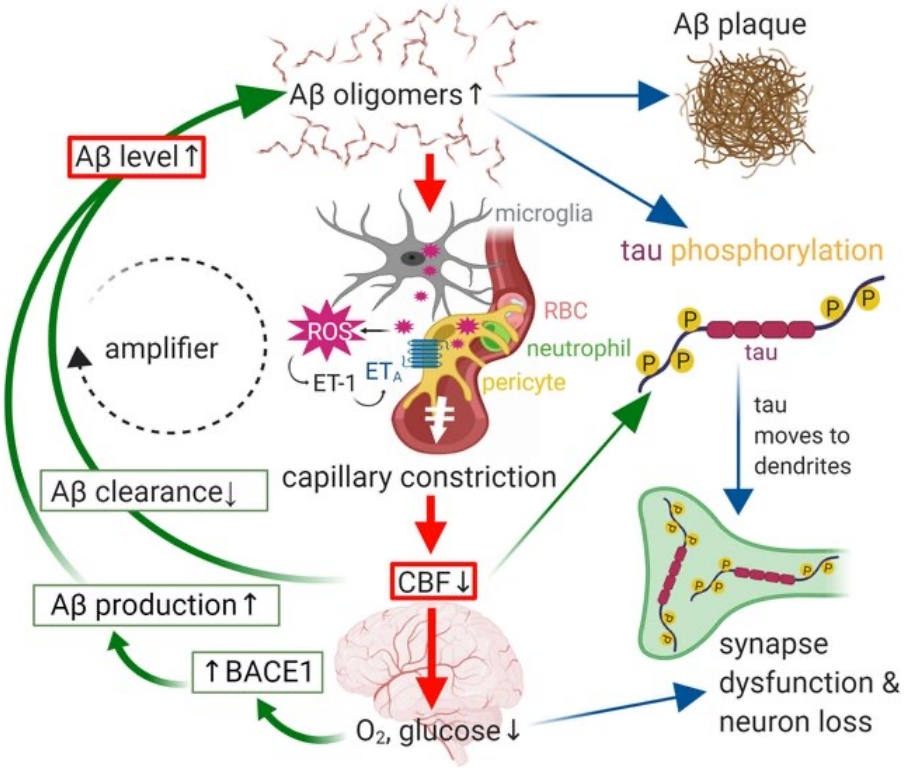


Mechanism of Flavonoids in Aβ Inhibition

Flavonoids can interact with Aβ peptides, preventing their aggregation into toxic forms.

They may also enhance the clearance of Aβ from the brain through various pathways.

Understanding these mechanisms is crucial for developing effective AD treatments.



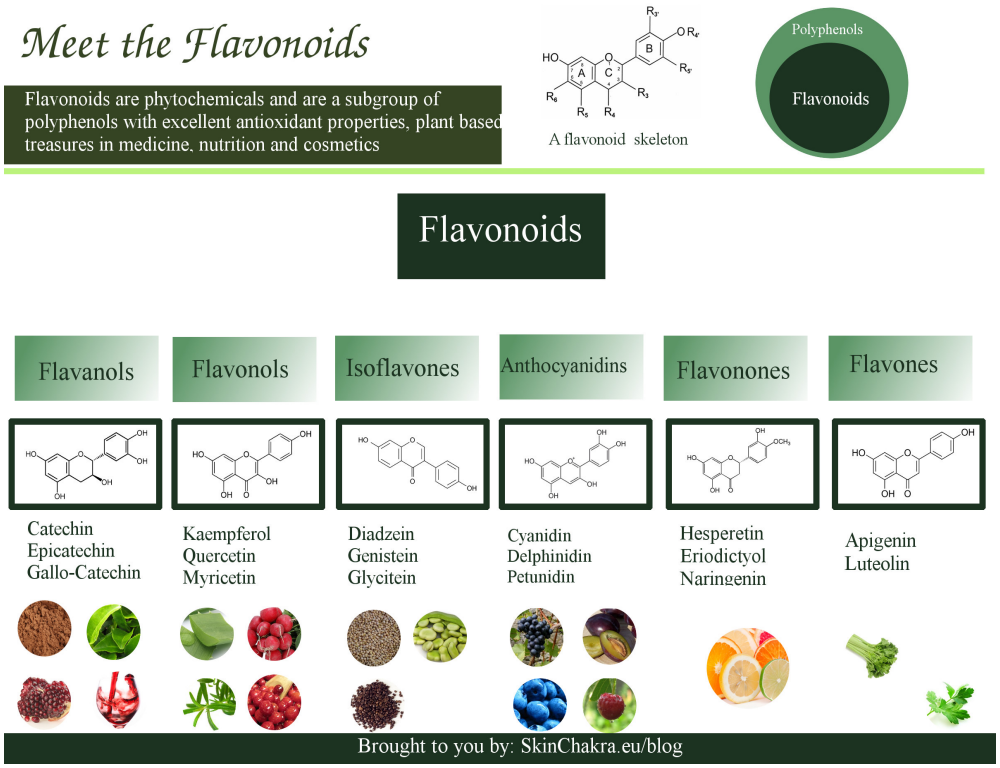
https://www.researchgate.net/publication/344003757_Cerebral_blood_flow_decrease_as_an_early_pathological_mechanism_in_Alzheimer%27s_disease/figures?lo=1

Common Natural Flavonoids

Some well-studied flavonoids include quercetin, catechins, and flavonols.

These compounds are abundant in foods like berries, tea, and citrus fruits.

Their dietary availability makes them attractive candidates for therapeutic development.



https://skinchakra.eu/blog/archives/322-Meet-the-flavonoids.html

Catechins and Their Effects

Catechins, including epicatechin, particularly found in **green tea**, have shown promise in Aβ inhibition.

They can disrupt the formation of Aβ fibrils and promote their disaggregation.

Research indicates that catechins may enhance cognitive function in aging populations.

Side Effects Of Green Tea

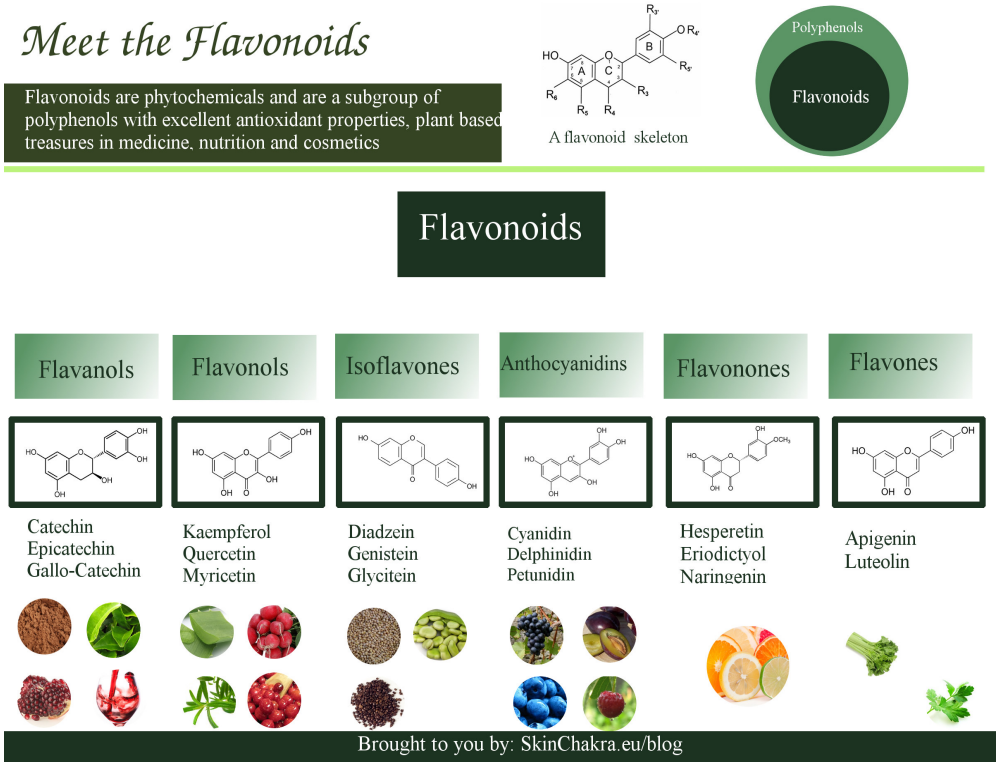
Green tea contains caffeine, catechins and tannic acids. All three substances have been linked to pregnancy risks. In addition, drinking a large amount may cause neural tube birth defect in babies.

Flavonols as Therapeutics

Flavonols, such as kaempferol and myricetin, have been investigated for their Aβ inhibitory effects.

These compounds can modulate signaling pathways involved in Aβ metabolism.

Their neuroprotective properties make them potential candidates for AD treatment.

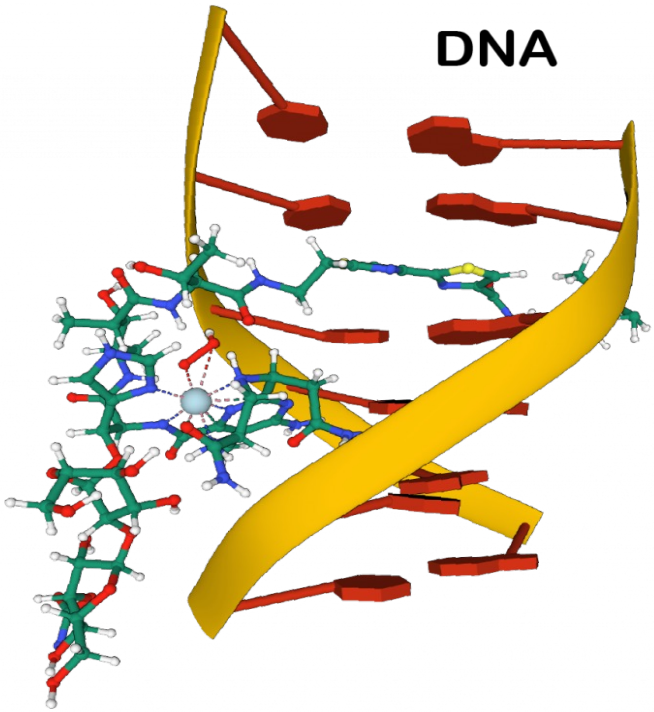


Ligand-Binding Analysis

Ligand-binding analysis studies the interaction between a drug (ligand) and its target molecule.

It provides information about binding affinity, kinetics, and structural details.

Various techniques like molecular docking, crystallography, and NMR spectroscopy are used for ligand-binding analysis.



Drug: Bleomycin a2

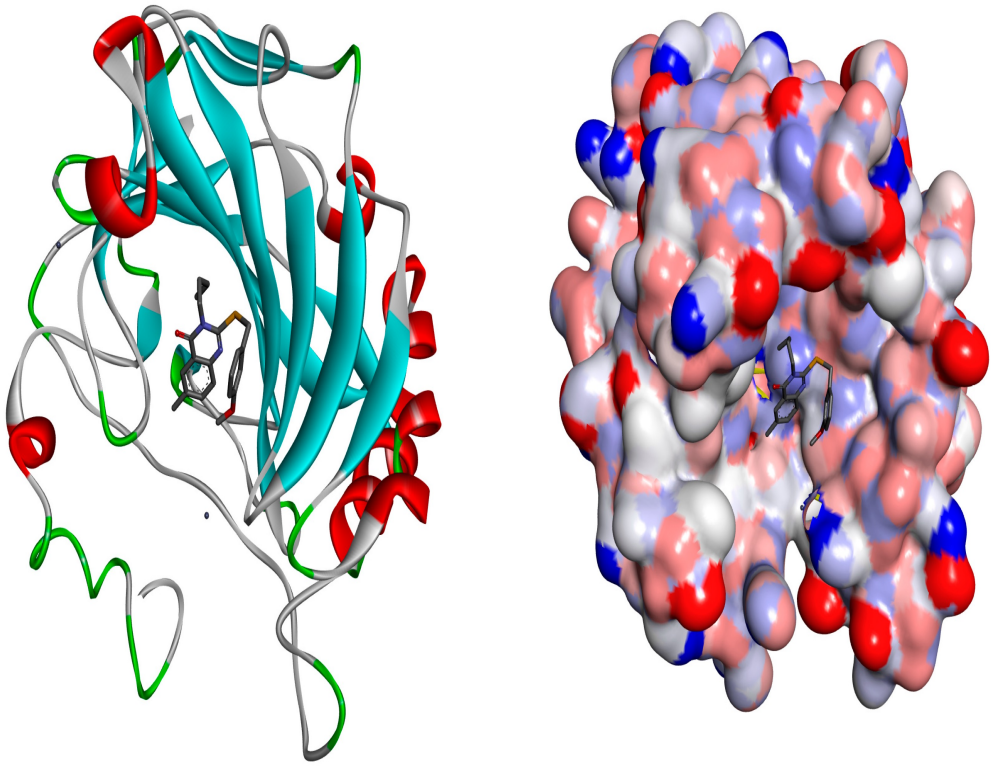
https://www.ebi.ac.uk/training/online/courses/biomacromolecular-structures/ligand-small-molecule-2/

Molecular Docking

Molecular docking predicts the binding pose and affinity of a drug to its target.

It involves the generation of multiple conformations and orientations of the ligand within the target's binding site.

Scoring functions evaluate the binding free energy to rank the ligand poses.

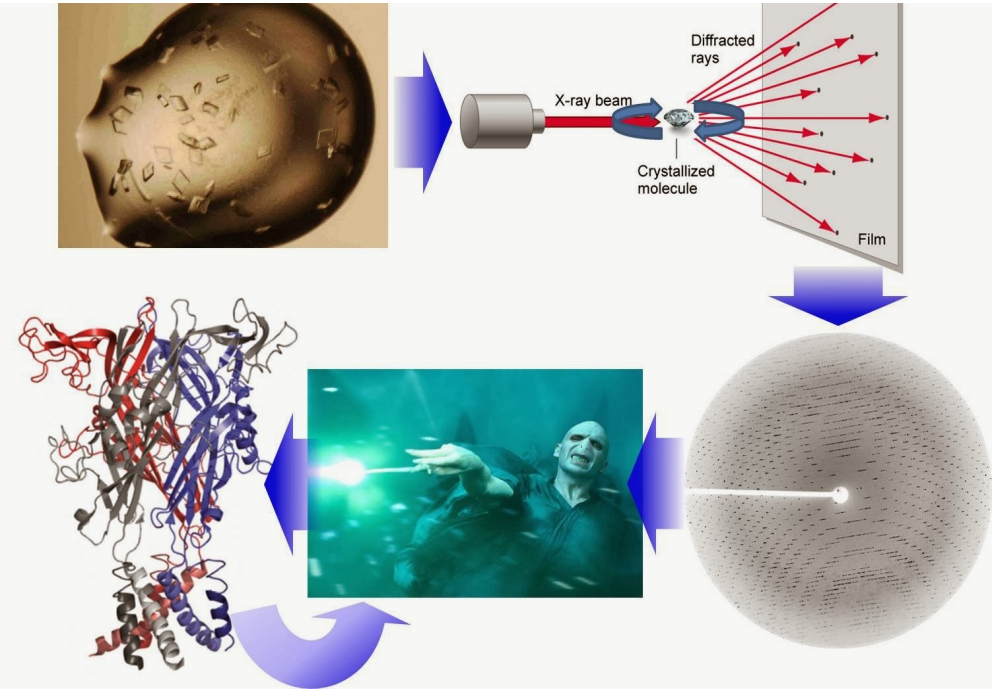


https://ganeshwaghule.blogspot.com/p/molecular-docking.html

Research Objective

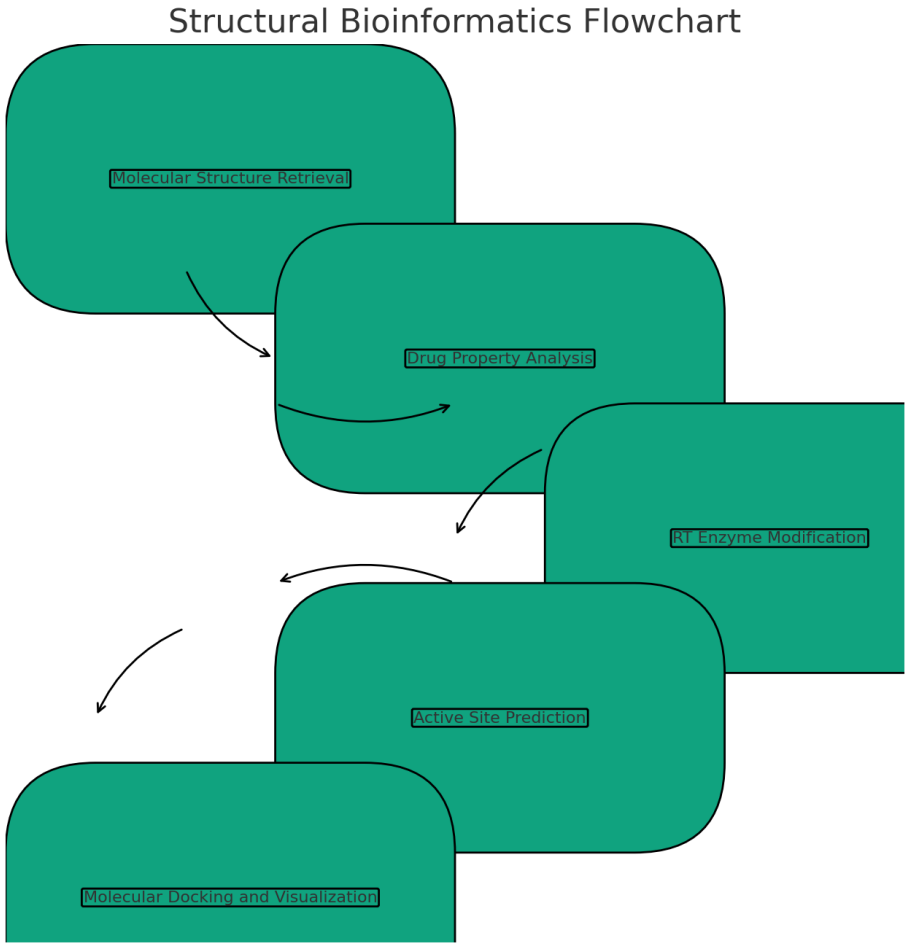
- in silico analyses will be done to examine the pharmacological properties of natural flavonoids, as well as their binding affinity with amyloid.

- Furthermore, the absorption, distribution, metabolism, excretion, and toxicity of both drugs were also examined



Methodology

- **Molecular Structure Retrieval**: The first step where you obtain the 3D structure of the molecule, usually from databases like the Protein Data Bank (PDB). **Only natural substances of flavonoids that directly prevent or modify amyloid aggregation were chosen**. They are based on an earlier research conducted by Velander et al. (2017),
- **Drug Property Analysis**: This step involves analyzing the physicochemical properties of the drug molecule, such as hydrophobicity and charge distribution. (preADMET 2.0)
- **RT Enzyme Modification**: This phase focuses on altering the structure of the reverse transcriptase enzyme, possibly to enhance its functionality or specificity. (Pymol 2.5.2)
- **Active Site Prediction**: Here, the active sites on the enzyme where the drug molecule can potentially bind are identified. (CASTp)
- **Molecular Docking and Visualization**: The final step involves simulating the interaction between the drug and the enzyme to predict binding affinity and visualizing the binding pose. (Pyrx)



Result: Drug-likeness Evaluation Screening

Compound	Lipinski violations	Ghose violations	Veber violations	Egan violations	Muegge violations
Apigenin	0	0	0	0	0
Baicalin	2	0	1	1	3
Baicalein	0	0	0	0	0
Datiscetin	0	0	0	0	0
Epicatechin	0	0	0	0	0
Epigallocatechin gallate (EGCG)	2	0	1	1	3
Genistein	0	0	0	0	0
Glabridin	0	0	0	0	0
Icariin	3	3	1	1	4
Kaempferol	0	0	0	0	0
Morin	0	0	0	0	0
Myricetin	1	0	1	1	2
Proanthocyanidin	3	3	1	1	3
Quercetin	0	0	0	0	0
Rutin	3	4	1	1	4
Taxifolin	0	0	0	0	0

- Red highlight implies ineligible compounds (PreADMET)

Result: Toxicity Prediction

Compound	Toxicity Class
Apigenin	class 5
Baicalein	class 5
Datiscetin	class 5
Epicatechin	class 6
Genistein	class 5
Glabridin	class 4
Kaempferol	class 5
Morin	class 5
Quercetin	class 3
Taxifolin	class 4

- Red highlight implies ineligible compounds (PreADMET)

Result: Compound Biological Activity Prediction

Compound	Amyloid beta aggregation inhibitor		Beta amyloid protein antagonist	
	Pa	Pi	Pa	Pi
Apigenin	0,232	0,012	0,122	0,033
Baicalein	-	-	-	-
Datiscetin	0,151	0,028	0,116	0,038
Epicatechin	0,428	0,006	0,300	0,005
Genistein	0,118	0,048	0,202	0,010
Glabridin	-	-	-	-
Kaempferol	0,182	0,019	0,102	0,057
Morin	0,152	0,028	0,119	0,036
Quercetin	0,213	0,014	0,104	0,053

- Two main activities were observed, and there are some leads to bioacitivity. (PASS Server)

Result: Molecular Docking (1)

Molecular docking analysis

Compound	Binding Energy	Contact residues
Apigenin	-5.2	ALA2 GLU3 HIS6 ASP7 TYR10
Baicalein	-5.3	GLU3 HIS6 GLY9 TYR10
Datiscetin	-5.5	ALA2 GLU3 HIS6 ASP7 GLY9 TYR10
Epicatechin	-5.1	GLU3 PHE4 ARG5 HIS6 ASP7 TYR10 GLU11
Genistein	-5.0	ALA2 GLU3 HIS6 ASP7 TYR10
Kaempferol	-5.2	ALA2 GLU3 HIS6 GLY9 TYR10
Morin	-5.3	ALA2 GLU3 HIS6 ASP7 GLY9 TYR10

- Epicathecin has most contact residues, suggesting a broader and potentially more stable interaction between the ligand and the protein (Pyrx)

Result: Molecular Docking (2)

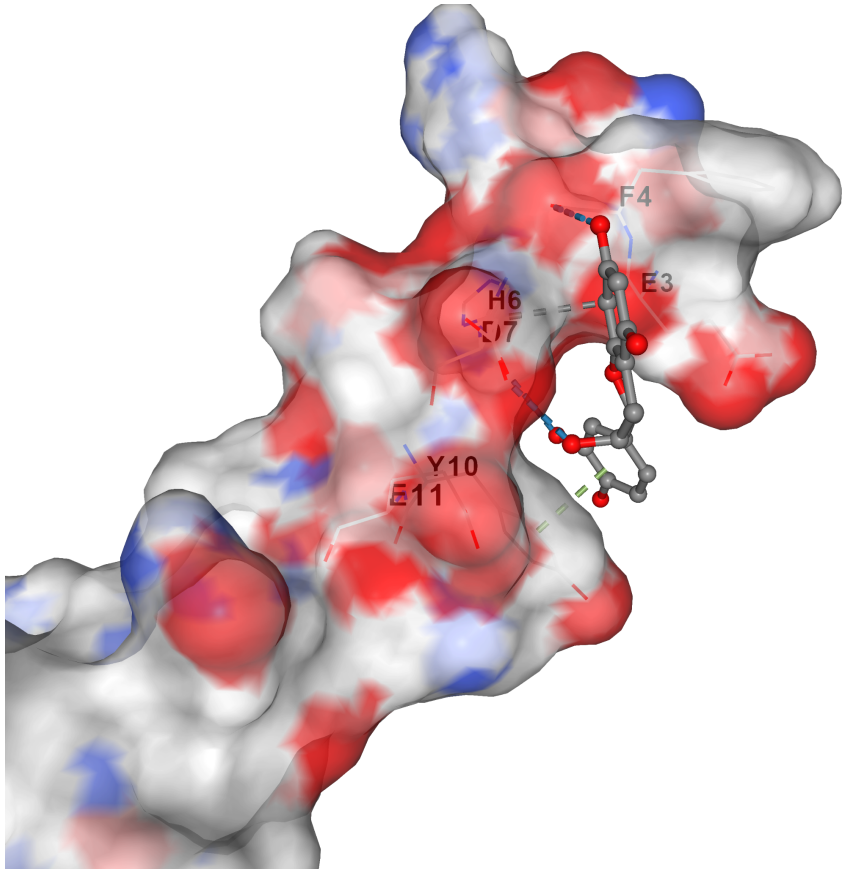


Figure 2. *Pose 1 of bound epicatechin. VINA binding score: -5.1. Cavity volume: 21 Å^3.*

Result: Molecular Docking (3)

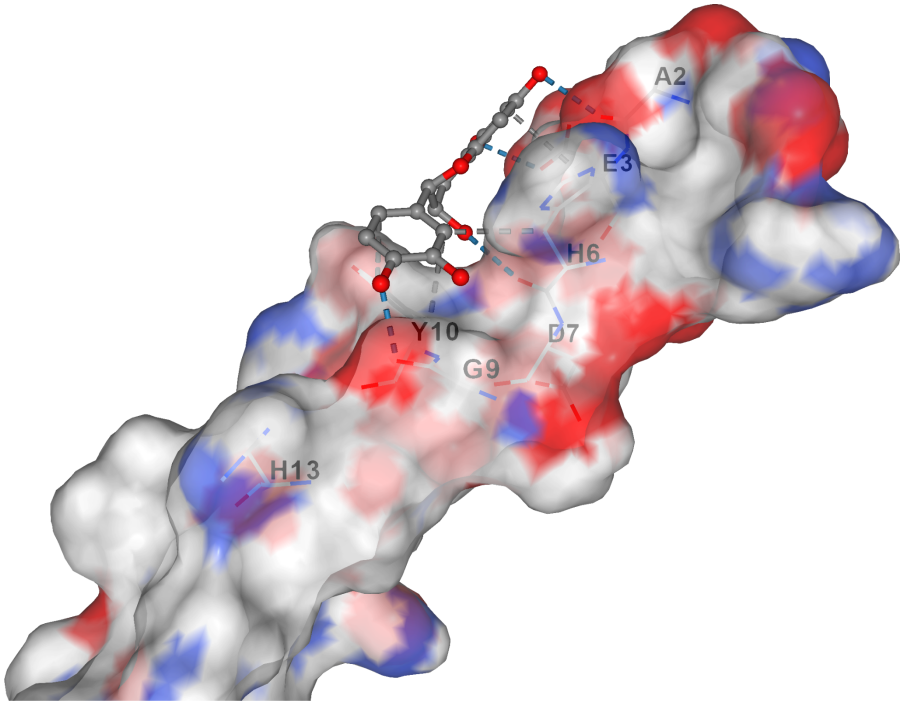


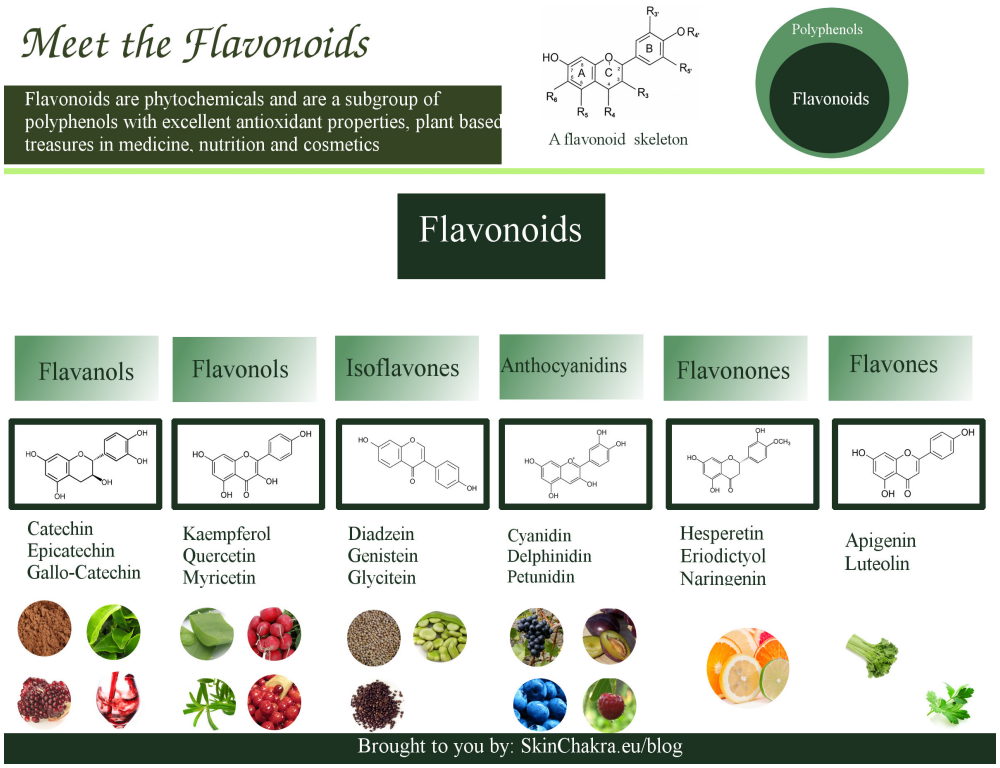
Figure 3. *Pose 2 of bound epicatechin. VINA binding score: -5.1. Cavity volume: 9 Å^3*

Challenges in Flavonoid Research

Challenges include variability in flavonoid content in dietary sources and formulations.

Standardization of flavonoid extracts is necessary for consistent results.

Understanding the pharmacokinetics of flavonoids in humans remains a significant hurdle.



Future Directions in Flavonoid Research

Future research should focus on optimizing flavonoid formulations for better bioavailability.

Investigating the effects of flavonoids in diverse populations can provide valuable insights.

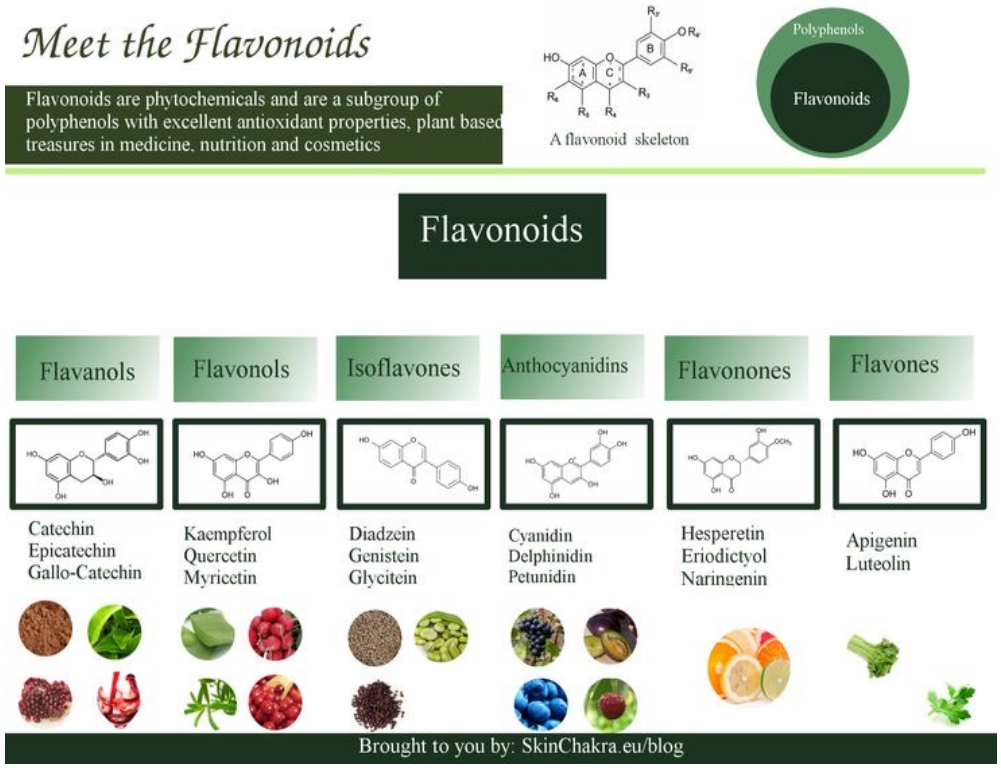
Exploring novel delivery methods, like nanoparticles, may enhance therapeutic efficacy.

Conclusion on Flavonoid Compounds

Natural flavonoids present a promising avenue for Aβ inhibition in Alzheimer's treatment, especially **epicatechin**.

Their multifaceted mechanisms and dietary availability make them attractive candidates.

Continued research is essential to fully elucidate their potential in AD management.



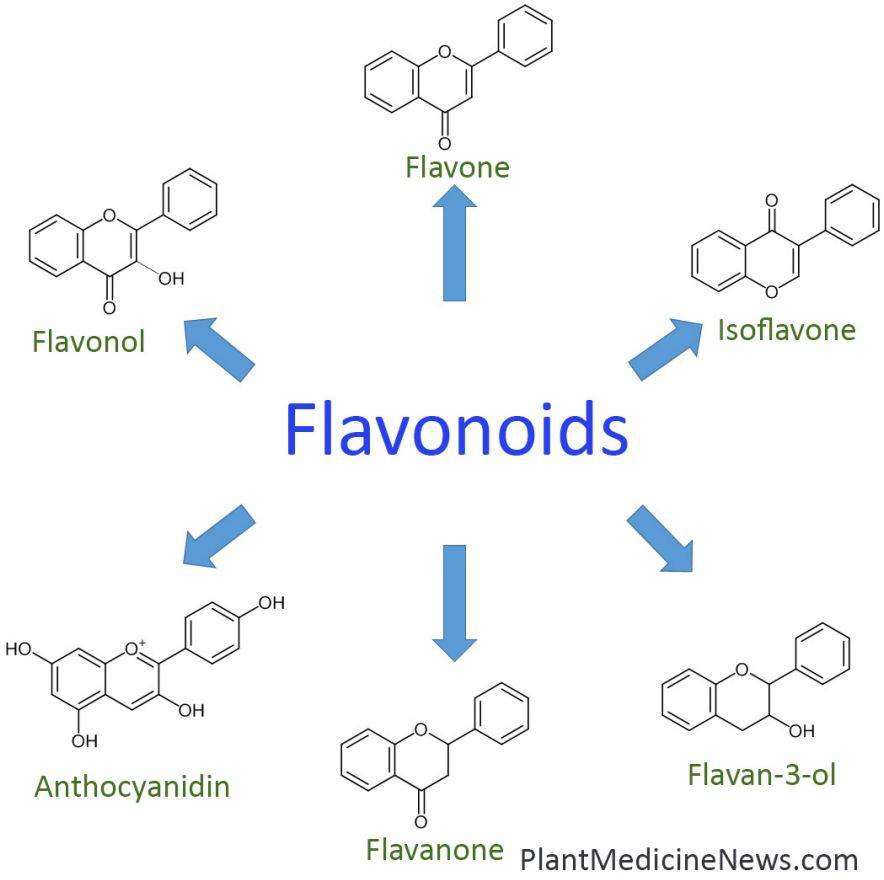
Key Takeaways

Flavonoids show potential in inhibiting Aβ aggregation and improving cognitive function.

Ongoing research and clinical trials are necessary to validate their therapeutic effects.

A multi-faceted approach involving dietary and supplemental flavonoid intake may be beneficial.

Molecular dynamics simulation is on the way



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