MODERN AND CONTEMPORARY RESEARCH IN HEALTH SCIENCES

All Sciences Academy

MODERN AND CONTEMPORARY RESEARCH IN HEALTH SCIENCES

Editor
Prof. Dr. Fatih HATİPOĞLU

Modern and Contemporary Research in Health Sciences
Editor: Prof. Dr. Fatih HATİPOĞLU

Design: All Sciences Academy Design
Published Date: August 2026
Publisher's Certification Number: 72273
ISBN: 978-625-8839-76-0

www.allsciencesacademy.com
allsciencesacademy@gmail.com

CONTENT

AI-Enhanced Virtual Reality for Human Anatomy Education Learning Efficiency, Cognitive Load, and Future Research Directions

Nasir MUSTAFA[1]

Assistant Professor; Gelisim University, Faculty of Health and Sciences, Department of Nursing. nmustafa@gelisim.edu.tr ORCID No: 0000-0002-5821-9297

ABSTRACT

Background and Objective Traditional medical anatomy instruction often delivers limited spatial interactivity, creating gaps in long-term retention and diagnostic reasoning. While immersive technologies offer a solution, evidence evaluating the synergistic combination of artificial intelligence (AI) and virtual reality (VR) remains fragmented. This narrative review aims to synthesize the current evidence regarding VR-based anatomy learning outcomes and examine the technical feasibility, early cognitive-load impact, and instructional efficacy of emerging integrated AI-VR platforms.

Methods A narrative review was conducted of peer-reviewed literature (2019–2026) retrieved from PubMed/PMC, Scopus-indexed journals, ResearchGate, arXiv, and publisher databases (Springer, Wiley, Sage, JMIR). The search was executed using combinations of the terms: artificial intelligence, virtual reality, anatomy education, learning outcomes, and cognitive load. Because few studies isolate an AI-VR combination specifically within anatomy curricula, closely related systematic reviews, meta-analyses, and randomized controlled trials (RCTs) of VR-only and AI-only anatomy or procedural training were also included to contextualize findings.

Results Across the reviewed systematic reviews and trials, VR-based anatomy instruction is associated with improved short-term knowledge acquisition, higher learner satisfaction, and favorable usability ratings relative to traditional teaching, although retention effects and behavior-level outcomes are less consistently reported. Emerging AI-VR systems—such as generative-AI conversational tutors embedded in VR and AI-driven automated segmentation feeding VR visualization—demonstrate technical feasibility and early promise for adaptive, personalized instruction. However, controlled comparative trials isolating the AI-VR combination (as opposed to VR alone) remain scarce. Cognitive-load data from related immersive-technology RCTs suggest lower NASA Task Load Index scores in technology-assisted arms compared with traditional training.

Conclusions Available evidence supports VR as an effective adjunct to anatomy education, and preliminary work suggests AI integration may add adaptivity and efficiency. However, rigorously designed RCTs that isolate the incremental contribution of AI within VR anatomy instruction—using pre-test/post-test/retention-test designs and validated workload measures—are critically needed before strong efficiency claims can be made.

Keywords: artificial intelligence; virtual reality; anatomy education; medical education; cognitive load; NASA-TLX; immersive learning

INTRODUCTION

Human anatomy education is a cornerstone of medical, dental, nursing, and allied-health curricula, providing the structural and spatial knowledge that underlies clinical reasoning and procedural competence. For over a century, cadaveric dissection has been regarded as the gold-standard method for teaching gross anatomy, complemented by plastic models, prosected specimens, and two-dimensional atlases. However, dissection-based teaching faces well-documented constraints: high cost, specimen scarcity, biosafety and ethical considerations, limited repeatability, and difficulty representing dynamic or physiological processes.Virtual reality (VR) has emerged over the past decade as a scalable alternative or complement to traditional methods, offering interactive, repeatable, three-dimensional visualization of anatomical structures without the resource constraints of a dissection laboratory. A substantial body of systematic reviews and meta-analyses now supports the general effectiveness of VR in anatomy education, reporting improvements in short-term knowledge acquisition, learner engagement, and satisfaction relative to conventional teaching (Adnan et al., 2025; Minouei et al., 2024; Odogwu et al., 2025; Salimi et al., 2024).More recently, artificial intelligence (AI)—including generative conversational agents, automated image segmentation, and adaptive assessment algorithms—has begun to be layered onto VR anatomy platforms (Pandurangam et al., 2024). In principle, AI can make a VR anatomy environment adaptive: answering learner questions in natural language, adjusting content difficulty to individual performance, and automatically generating three-dimensional models from imaging data rather than requiring manual modeling (Chheang et al., 2023; Giri et al., 2026). Whether this AI-VR combination measurably improves the efficiency of anatomy learning—defined here as achieving equivalent or superior knowledge and retention in less time, with lower cognitive burden, than traditional methods—is a comparatively new empirical question, and the evidence base specific to this combination remains limited (Chance, 2025).Furthermore, data from related clinical simulation spheres evaluating advanced visualization tools reveal critical baselines regarding procedural performance and mental stress (Liao et al., 2024; Kim et al., 2025; Yang & Ma, 2026).

This review addresses three questions:

(1) What does the existing literature show about the effect of VR, with and without AI integration, on anatomy learning outcomes relative to traditional teaching?

(2) What is currently known about the cognitive load and usability of AI-VR anatomy tools?

(3) What methodological features—including RCT design, pre-/post-/retention-testing, and validated workload instruments such as the NASA Task Load Index (NASA-TLX)—are needed in future studies to more definitively establish the efficiency gains of AI-enhanced VR in anatomy education?

MATERIALS AND METHODS

Literature Search and Information Sources

This narrative review examined the integration of artificial intelligence (AI), virtual reality (VR), augmented reality (AR), and mixed reality (MR) in anatomy education, with particular emphasis on educational effectiveness, learner performance, cognitive load, engagement, usability, and technological feasibility. The literature search covered publications from January 2019 to February 2026, reflecting the period in which AI-enhanced immersive technologies have undergone substantial development and increasing application within medical and anatomy education.

Literature was identified from multiple biomedical, multidisciplinary, academic, and publisher-based sources. The search included PubMed/PMC, Scopus-indexed literature, ResearchGate/arXiv, and publisher databases including Wiley and Springer. The initial records were distributed as follows:

- PubMed/PMC: n = 45
- Scopus: n = 35
- ResearchGate/arXiv: n = 15

The use of multiple information sources was intended to capture both peer-reviewed biomedical literature and emerging research involving rapidly evolving AI, VR, AR, and MR technologies, including feasibility studies and educational technology applications that may not yet be extensively represented in traditional medical databases.

Study Identification and Screening

An initial 125 records were identified from the selected sources. Following the removal of duplicate records and preliminary exclusions, 68 records proceeded to title and abstract screening. Screening was performed according to the predefined relevance of each publication to anatomy education, medical education, immersive learning technologies, and AI-supported educational applications.

At the title and abstract stage, 41 records were excluded. The principal reasons for exclusion were:

- Irrelevance to anatomy or medical education/training (n = 18);
- Purely technical or engineering-focused publications without educational assessment (n = 15); and
- Non-English or abstract-only publications (n = 8).

Following title and abstract screening, 27 full-text articles were assessed for eligibility. Full-text assessment examined whether the studies provided meaningful evidence relating to educational outcomes, learner performance, cognitive workload, usability, feasibility, or other outcomes relevant to the objectives of the review.

A further 16 full-text articles were excluded. Ten studies (n = 10) did not report measurable learning outcomes or cognitive-load outcomes, while six (n = 6) were excluded because they fell outside the predefined timeline or scope, including dissertation-only work.

Ultimately, 11 studies satisfied the eligibility criteria and were included in the narrative synthesis. The overall selection process is presented in Figure 1.

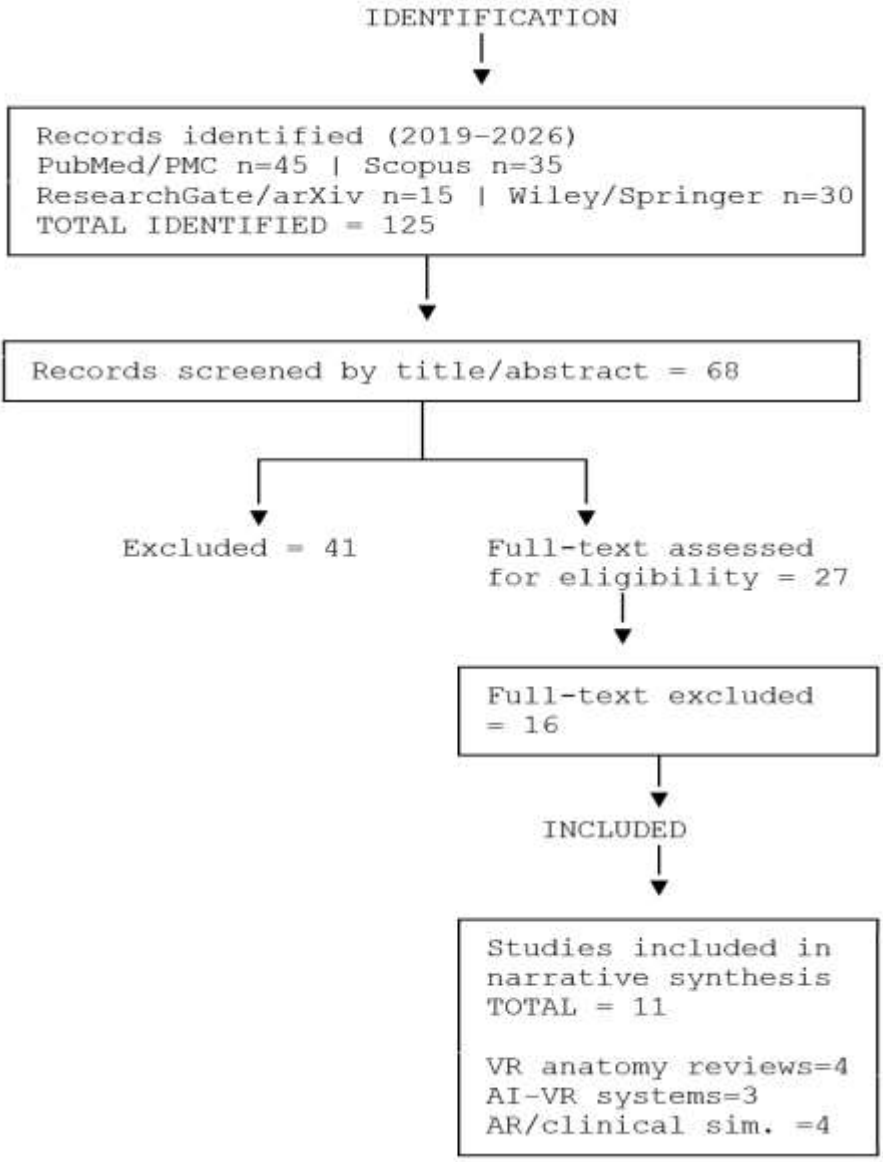

Figure 1. Flow diagram of study identification, screening, eligibility assessment, and inclusion (2019–2026).

Data Categorization and Synthesis

The included studies were organized into three principal thematic categories according to the primary technology and educational application investigated:

1. VR Anatomy Systematic Reviews — n = 4:

Studies evaluating the educational role, effectiveness, usability, and learning applications of standalone VR-based anatomy education.

2. AI–VR Integration and Feasibility Studies — n = 3:

Studies examining the incorporation of AI into VR-based learning environments, including intelligent interaction, adaptive or personalized learning, automated educational support, and the feasibility of AI-enhanced immersive anatomy systems.

3. AR/MR and Clinical Simulation Studies — n = 4:

Studies investigating augmented or mixed-reality applications and immersive clinical simulation environments relevant to anatomy education and the transition from anatomical knowledge to clinical learning.

Data were qualitatively extracted and synthesized according to several key domains: educational application, learner performance, knowledge acquisition, spatial understanding, engagement, usability, technological feasibility, cognitive workload, and reported educational outcomes. Where quantitative outcome measures were available, particular attention was given to standardized instruments used to evaluate cognitive workload and user experience.

Educational and Cognitive Outcomes

The review placed particular emphasis on whether immersive and AI-enhanced technologies produced measurable educational benefits rather than simply demonstrating technological functionality. Relevant outcomes included improvements in anatomical knowledge, spatial understanding, learner performance, retention, engagement, confidence, usability, and perceived educational value.

Cognitive workload was also considered an important outcome because increasingly sophisticated immersive learning environments may provide greater interactivity while simultaneously increasing the cognitive demands placed on learners. Where reported, studies using standardized instruments such as the NASA Task Load Index (NASA-TLX) or comparable cognitive-load measures were examined to determine the perceived mental, physical, and temporal demands associated with technology-enhanced learning.

Scope of the Review

The review therefore considered both the educational and technological dimensions of AI-augmented immersive anatomy education. Rather than focusing exclusively on the technical development of VR, AR, MR, or AI systems, the synthesis evaluated how these technologies may influence the learning process and whether their implementation demonstrates practical educational value.

Particular attention was given to their potential contribution to three-dimensional anatomical visualization, spatial reasoning, learner engagement, interactive learning, personalized or adaptive instruction, clinical simulation, and educational performance. The review also considered technological feasibility and usability as important factors influencing the potential integration of these systems into undergraduate medical education and anatomy curricula.

Overall, the narrative synthesis aimed to identify the current evidence base, clarify the educational applications of AI-enhanced immersive technologies, and highlight areas where further empirical research is required, particularly regarding objective learning outcomes, cognitive load, long-term retention, comparative effectiveness, scalability, and integration into formal medical education curricula.

THEORITICAL FRAMEWORK

Figure 1 summarizes a conceptual framework, synthesized from the reviewed literature, of how AI and VR components are proposed to jointly influence anatomy learning efficiency: AI contributes adaptive tutoring, natural-language interaction, and automated model generation, while VR contributes immersive three-dimensional visualization and interactive manipulation; together these are hypothesized to support the learning mechanisms (spatial visualization, adaptive feedback, self-paced repetition, reduced extraneous cognitive load) that in turn drive measurable educational outcomes.

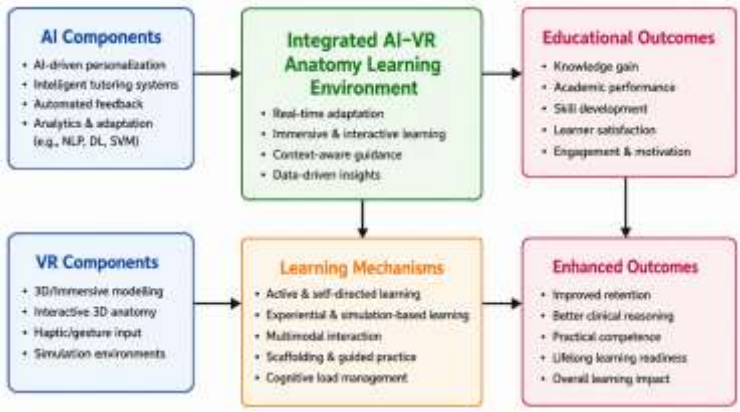

Figure 2. Conceptual framework linking AI and VR components, learning mechanisms, and measured educational outcomes in anatomy education.

RESULTS / SYNTHESIS OF THE LITRATURE

Overview of reviewed studies

Table 1 summarizes representative systematic reviews, a meta-analysis, an RCT, and AI-VR feasibility studies identified through the search.

Study (Year)	Design / Sample	Technology	Focus	Key reported findings
Odogwu et al. (2025), Cureus	Systematic review	VR simulation	Anatomy learning outcomes vs. conventional teaching	VR consistently associated with improved knowledge and engagement across included trials
Adnan et al. (2025), Anat. Sci. Educ.	Systematic review (15 studies)	VR	Adoption of VR in anatomy education, health sciences/allied health	~50% of studies reported statistically significant gains in knowledge acquisition/retention; consistent gains in confidence

Study (Year)	Design / Sample	Technology	Focus	Key reported findings
Minouei et al. (2024), BMC Med. Educ.	Systematic review (24 studies)	VR	VR effectiveness on anatomy achievement	High learner satisfaction and improved outcomes; inconsistent effects at higher (behavioral) evaluation levels
Salimi et al. (2024), Anat. Sci. Educ.	Systematic review + meta-analysis	VR and AR	Efficacy of VR/AR in anatomy education	Pooled analysis supports superiority of immersive tools over traditional methods on knowledge tests
Schwind et al. (2023), arXiv preprint	Pilot experimental study (n = 16)	Generative-AI virtual assistant embedded in VR	AI-driven verbal Q&A support during VR anatomy learning	No significant difference between avatar vs. screen-based assistant; feasibility demonstrated
Chance (2025), BMC Med. Educ.	Narrative review	AI + VR	Combined AI-VR impact on interdisciplinary healthcare learning and patient safety	AI-VR combination linked to improved adaptability and realism relative to static simulation
VISTA-MED (2026), Discov. journal	Technical feasibility study	AI segmentation + VR visualization	Real-time MRI visualization and brain-tumor segmentation for teaching	Demonstrated technical feasibility; effectiveness/usability studies flagged as future work
Frontiers in Medicine (2026) RCT	RCT (n = 60)	Mixed reality (HoloLens 2)	Interactive 3D anatomy training for scrub nurses	MR group scored higher on theoretical knowledge (92.47 vs. 86.33) and reported lower NASA-TLX cognitive load

Knowledge acquisition and retention

Multiple systematic reviews report that VR-based anatomy instruction produces knowledge-test gains comparable to or exceeding traditional teaching. Adnan and colleagues found that half of the studies assessing knowledge acquisition and retention reported statistically significant improvements following VR adoption, alongside consistently enhanced conceptual understanding and learning confidence. A separate systematic review and meta-analysis by Salimi and colleagues similarly concluded that pooled evidence supports an advantage for immersive VR/AR tools over conventional methods on anatomy test performance. Retention — measured via delayed post-tests — was reported less consistently across the literature, representing a persistent gap the field has not yet closed.

Cognitive load and usability

Cognitive load, most commonly measured with the NASA-TLX, was reported favorably for immersive-technology-assisted training arms in several RCTs identified in adjacent procedural-training domains. In a 2026 randomized trial of mixed-reality (HoloLens 2) training for spine-surgery scrub nurses, the MR group achieved higher theoretical-knowledge scores (92.47 vs. 86.33) and reported a lower overall NASA-TLX cognitive-load score than the traditionally trained group. In a prospective randomized pilot of a 5G tele-supervised ultrasound education platform, trainees receiving tele-supervision reported significantly lower NASA-TLX mental-demand, effort, and frustration scores than those under direct supervision, alongside higher System Usability Scale ratings. Figure 2 illustrates the direction of these reported differences.

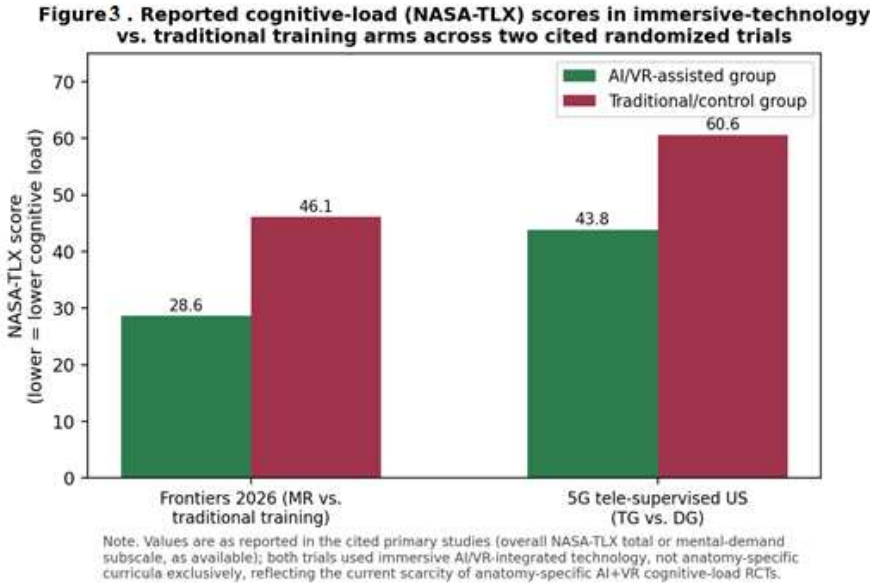

Figure 3. NASA-TLX cognitive-load scores reported for immersive/technology-assisted versus traditional training arms in two cited randomized trials (lower score indicates lower cognitive load).

Table 2 summarizes the outcome domains and instruments most commonly used across the reviewed literature, together with the general direction of reported effects.

Outcome domain	**Instruments / metrics reported in the literature**	**General direction of effect reported**
Knowledge acquisition	Pre-/post-test multiple-choice or short-answer anatomy examinations	Favors AI/VR-assisted groups in the majority of cited studies
Knowledge retention	Delayed post-test administered days-to-weeks after the intervention	Mixed but generally favorable; fewer studies report this outcome
Time-to-mastery / efficiency	Task-completion time, number of attempts to reach a criterion	Favors immersive/AI-assisted

Outcome domain	Instruments / metrics reported in the literature	General direction of effect reported
		conditions in procedural-skill studies
Cognitive load	NASA Task Load Index (NASA-TLX) — total score and subscales	Lower (more favorable) cognitive load reported in AI/VR- and MR-assisted arms
Usability / user experience	System Usability Scale (SUS), custom Likert satisfaction surveys	Consistently rated above-average usability for VR/AI-VR platforms
Learner perception	Engagement, confidence, spatial-reasoning self-report	Consistently positive across qualitative and mixed-methods studies

The specific contribution of AI within VR anatomy platforms

A smaller set of studies addresses AI integration within VR anatomy environments directly. Schwind and colleagues introduced a VR environment featuring a generative-AI embodied virtual assistant capable of answering anatomy questions of varying cognitive complexity through verbal interaction; a pilot study (n = 16) found the approach feasible, with no significant difference between avatar-based and screen-based assistant configurations in task-completion time. The VISTA-MED platform combines AI-driven automated MRI segmentation with real-time VR visualization, and its authors describe the work as establishing technical feasibility for future educational modules while explicitly identifying usability and educational-impact evaluation as necessary future work rather than completed findings. A broader narrative review of combined AI-VR applications across healthcare education concluded that the pairing offers greater adaptability and realism

than static VR or AI applied alone, but the primary evidence base supporting this claim remains largely descriptive rather than experimental.

DISCUSSION

The reviewed literature supports a reasonably mature evidence base for VR as an effective adjunct to human anatomy education, with consistent gains in short-term knowledge acquisition, engagement, and usability relative to traditional teaching. Evidence for the specific incremental value of layering AI onto VR anatomy platforms is considerably earlier-stage: existing AI-VR anatomy studies are largely feasibility or pilot work rather than adequately powered comparative trials, and cognitive-load data supporting the efficiency argument are drawn substantially from adjacent procedural-training RCTs rather than anatomy-specific AI-VR trials.

This pattern suggests two things for the field. First, the theoretical case for AI-enhanced VR — that adaptive, conversational, and automatically generated content could reduce extraneous cognitive load and personalize pacing — is plausible and consistent with cognitive load theory, but remains to be demonstrated empirically within anatomy curricula specifically. Second, the RCT design outlined in the introduction (pre-test/post-test/retention-test, time-to-mastery tracking, and NASA-TLX-based usability assessment, focused on discrete anatomical regions such as the cardiac, neuroanatomical, or musculoskeletal systems) represents exactly the kind of study that is currently missing and would meaningfully advance the field.

LIMITATIONS

This review has several limitations. It is narrative rather than a registered PRISMA systematic review, and does not report exhaustive database search counts or independent dual-reviewer screening; conclusions should therefore be read as a synthesis of currently available secondary and primary literature rather than as a formal quantitative meta-analysis. Because directly comparable AI-VR anatomy RCTs are scarce, several cognitive-load comparisons are drawn from adjacent immersive-technology training contexts (e.g., surgical and ultrasound skills training) rather than anatomy instruction proper, which limits direct generalizability. Finally, the field is moving quickly; studies published after the search window may alter the balance of evidence.

CONCLUSIONS

Virtual reality is well supported as an effective tool for enhancing human anatomy education relative to traditional methods, particularly for short-term knowledge acquisition, engagement, and usability. Artificial intelligence integration within VR anatomy platforms is technically feasible and theoretically promising for adaptivity and personalization, but the evidence base specifically isolating AI's incremental contribution to learning efficiency and cognitive load in anatomy education remains preliminary. We recommend that future work adopt randomized controlled designs with pre-test/post-test/retention-test batteries, objective time-to-mastery measures, and validated workload instruments such as the NASA-TLX, applied to clearly defined anatomical regions, to rigorously establish whether and how much AI adds to VR-based anatomy instruction.

REFERENCES

1. Odogwu, T. S., Mohamed, E. A. H., Mishu, L., & Umahi, I. (2025). Effect of virtual reality simulation on anatomy learning outcomes: A systematic review. *Cureus*, *17*(4), Article e81893. doi.org
2. Adnan, S., McCumiskey, M., & Taylor, M. (2025). How virtual reality is being adopted in anatomy education in health sciences and allied health: A systematic review. *Anatomical Sciences Education*, *18*(5), 496–525. doi.org
3. Minouei, M. A., Omid, A., Mirzaie, A., & Mahdavifard, H. (2024). Effectiveness of virtual reality on medical students' academic achievement in anatomy: Systematic review. *BMC Medical Education*, *24*(1), Article 1407. doi.org
4. Salimi, S., Asgari, Zahra., Mohammadnejad, A., & Teimazi, A. (2024). Efficacy of virtual reality and augmented reality in anatomy education: A systematic review and meta-analysis. *Anatomical Sciences Education*. Advance online publication. doi.org
5. Chheang, V., Sharmin, S., Márquez-Hernández, R., Patel, M., Rajasekaran, D., & Schwind, V. (2023). *Towards anatomy education with generative AI-based virtual assistants in immersive virtual reality environments* (arXiv:2306.17278). arXiv. doi.org *(Note: Formatted as a preprint; published subsequently in IEEE AIxVR).*
6. Chance, E. A. (2025). The combined impact of AI and VR on interdisciplinary learning and patient safety in healthcare education: A narrative review. *BMC Medical Education*, *25*(1), Article 7589. doi.org
7. Giri, P., Witzenburg, M., & Schwind, V. (2026). VISTA-MED: Integrating AI-based MRI segmentation with virtual reality for medical education. *Discover Education*, *5*(1), Article 1229. doi.org
8. Yang, W., & Ma, T. (2026). Randomized controlled trial evaluating mixed reality technology for training scrub nurses in anterior cervical spine surgery. *Frontiers in Medicine*, *13*, Article 1818354. doi.org
9. Kim, M., Son, M. H., Moon, S., Cha, W. C., Jo, I. J., & Yoon, H. (2025). A mixed reality–based telesupervised ultrasound education platform on 5G network compared to direct supervision: Prospective randomized pilot trial. *JMIR Serious Games*, *13*(1), Article e63448. doi.org

10. Liao, S. C., Shao, S. C., Gao, S. Y., & Lai, E. C. C. (2024). Augmented reality visualization for ultrasound-guided interventions: A pilot randomized crossover trial to assess trainee performance and cognitive load. *BMC Medical Education*, *24*(1), Article 1058. doi.org
11. Pandurangam, G., Gurajala, S., & Nagajyothi, D. (2024). Artificial intelligence in anatomy teaching and learning: A literature review. *National Journal of Clinical Anatomy*, *13*(3), 158–163. doi.org

Plant-Based Diets: The Role of Healthcare Professionals in Clinical Counseling and Preventive Intervention

Rebeka Borsos [1]
István Kiss [2]
Zsuzsanna Lelovics [3*]

[1]Medical School, University of Pécs, Pécs, Hungary

[2]Department of Public Health Medicine, Medical School, University of Pécs, Pécs, Hungary

[3]Department of Public Health Medicine, Medical School, University of Pécs, Pécs, Hungary
[*](lelovics@yahoo.com)

ABSTRACT

Plant-based diets, particularly whole-food plant-based diets (WFPBD), have gained increasing attention due to their potential health benefits and sustainability. This study aimed to evaluate the experiences, perceptions, and dietary supplement use of individuals following plant-based diets, with emphasis on the role of healthcare professionals in prevention and patient counseling. A cross-sectional anonymous questionnaire survey was conducted between January 2024 and December 2024 among 100 adult participants. Most respondents were female (81%) and aged 18–35 years. The most common dietary patterns were vegan (25%) and semi-vegetarian (21%), with 41% following their diet for more than five years. Results showed that 56% of participants adopted plant-based diets for disease prevention, and the same proportion reported improvement or resolution of certain conditions, including obesity, hormonal disorders, hypercholesterolemia, insulin resistance, and hypertension. Participants also reported increased energy, improved digestion, and better overall well-being. However, adverse symptoms such as fatigue (21%), anemia (12%), and gastrointestinal complaints were observed. Although 60% reported no deficiencies, the risk of inadequate micronutrient intake remains relevant. The most commonly used supplements were vitamin D, vitamin C, and vitamin B12, with more than half of participants purchasing them in pharmacies. While 73% expressed a need for professional consultation, only 39% had sought expert advice, highlighting the importance of healthcare professionals in providing evidence-based guidance and preventing deficiencies. The findings emphasize that carefully planned plant-based diets, supported by professional counseling, can optimize health outcomes, support disease prevention, and align with sustainable and conscious dietary practices. Further research is warranted to monitor nutrient adequacy and enhance patient education for long-term adherence and safety.

Keywords – Plant-based nutrition, Whole-food plant-based diets (WFPBD), Health promotion, Nutrient deficiency, Professional guidance

I. INTRODUCTION

A whole-food, plant-based diet (WFPBD) consists exclusively of foods of plant origin, emphasizing minimally processed foods, and excludes processed products. This dietary approach promotes the consumption of whole, unprocessed or minimally processed foods, which differentiates it from a standard vegan diet. While a vegan diet primarily excludes animal-derived foods, usually for ethical reasons, the WFPBD focuses on health promotion. Consequently, processed plant-based products, such as convenience foods, are not recommended. The WFPBD emphasizes whole,

plant-derived, minimally processed foods. Vegetables, fruits, whole grains, legumes, and seeds form the foundation of this diet.

The WFPBD excludes both animal-based and processed foods. Processed foods include products containing added sugar, refined flour, and refined oils. Instead, the consumption of whole nuts and seeds is encouraged to provide essential plant-based fatty acids naturally. The diet also emphasizes food quality and, whenever possible, promotes the consumption of locally sourced, minimally treated, or chemical-free produce [1, 2].

In recent years, the WFPBD has gained increasing recognition alongside other plant-based diets, though general awareness remains limited. Numerous studies indicate that this diet has multiple beneficial effects on human health. It contributes to achieving and maintaining optimal body weight and supports the prevention of cardiovascular disease, cancer, age-related cognitive decline, and type 2 diabetes mellitus. It also benefits gut microbiome health and may alleviate symptoms of existing inflammatory conditions [3, 4].

Many individuals discover the WFPBD after trying several dietary approaches, finding it particularly beneficial for managing various health issues. In addition to its positive health effects, following this diet has a smaller ecological footprint than diets including animal products.

Adherence to this diet can pose challenges, as it differs significantly from a "typical Central European" diet and may require careful planning. Moreover, WFPBD or vegan options are often limited in Hungarian restaurants. Attention to adequate micronutrient intake is critical to prevent deficiencies. Supplementation with vitamin B12 is mandatory, and vitamin D supplementation is recommended for individuals following plant-based diets. Research also indicates that iron, zinc, iodine, and calcium levels are generally lower in plant-based dieters compared to those on omnivorous diets.

II. MATERIALS AND METHOD

The study aimed to investigate the impact of plant-based diets on the body, their benefits, and the challenges faced by individuals following such diets long-term (up to several years). The goal was to assess the experiences, opinions, and dietary supplement use of individuals adhering to a whole-food, plant-based diet. With an increasing proportion of the population adopting plant-based diets, healthcare professionals need to be informed to provide proper guidance during patient interactions. Within pharmaceutical care, preventing, identifying, and managing potential deficiencies can effectively support patients.

Data were collected via an anonymous questionnaire between January 2024 and December 2024 among voluntary participants aged 18 and above who follow a plant-based diet (n = 100). Of the respondents, 81.0% were female and 19.0% male. Regarding age distribution, half of the respondents

(50.0%) were between 18–25 years, and 26.0% were between 26–35 years. The largest group of respondents (43.0%) had a secondary school education, and 36.0% had a university degree.

III. RESULTS

A. Diet Types and Duration

The majority of respondents followed vegan (25.0%) and semi-vegetarian (21.0%) diets. Two participants followed an Adventist diet, one a paleo diet, and one a "Krishna believer" diet (lacto-vegetarian, excluding onion and egg).

Regarding the duration of adherence, 41.0% had followed their diet for more than five years, 33.0% for 1–5 years, 6.0% for 6–12 months, and 20.0% had adopted a plant-based diet in the past six months. Nearly two-thirds (62.0%) of respondents consulted websites and blogs, 41.0% participated in online groups, and only 39.0% sought professional advice regarding their dietary approach. Dietary deviations may limit nutrient intake, making professional guidance important. Online sources are not always reliable or evidence-based, which may increase the risk of inadequate nutrient intake and overlooked deficiencies.

Regarding children under 12, 44.0% of respondents believed animal-derived nutrients were unnecessary for proper growth, while 56.0% disagreed, highlighting the need for professional guidance on critical nutrient intake and supplementation.

B. Health Effects of Diet

Responses to the questions "Have you had any illnesses that improved or disappeared due to the diet?" and "Are you following the diet for disease prevention?" aligned closely. A total of 56.0% adopted the diet for disease prevention, and the same proportion reported improvements or resolution of an illness, suggesting that plant-based diets may be effective for primary, secondary, and tertiary prevention according to subjective reports.

Specifically, 57.0% reported improvement or resolution of one or more health conditions due to the diet. Notable benefits were observed for obesity (18.0%), hormonal problems (12.0%), high cholesterol (10.0%), insulin resistance (8.0%), hypertension (7.0%), and fungal infections (6.0%). Improvements in specific conditions included abdominal pain (3.0%), bronchial asthma (2.0%), reflux (3.0%), skin conditions such as acne and psoriasis (7.0%), and food allergies/sensitivities (5.0%). These results suggest plant-based diets may help prevent certain diseases and alleviate symptoms.

Table 1. Nutrient Deficiencies and Adverse Symptoms.

Observed Symptom	Occurrence [%]
Fatigue	21.0%
Anemia	12.0%
Weight gain	11.0%
Reduced cold tolerance	10.0%
Constipation	10.0%
Dry skin and/or itchy rash	6.0%
Numbness in hands or feet	4.0%
Loss of appetite	3.0%
Unintentional weight loss	1.0%

Table 1 summarizes adverse effects reported by respondents.

60.0% of respondents reported no deficiency symptoms, while 14.0% believed deficiencies could not develop on a WFPBD.

Dietary Supplement Use and Pharmaceutical Counseling Needs

Most respondents (55.0%) purchased dietary supplements from pharmacies, while others obtained them from drugstores, herbal/organic shops, or online (Table 2).

Table 2. Dietary Supplement Use and Pharmaceutical Counseling Needs.

Purchase Location	Occurrence [%]
Pharmacy	55.0%
Drugstore	39.0%
Herbal/organic store	25.0%
Internet	21.0%
Grocery store	6.0%
Abroad	2.0%
MLM network	2.0%
Mail-order service	2.0%

Most respondents (55.0%) purchased dietary supplements from pharmacies, while others obtained them from drugstores, herbal/organic shops, or online (Table 2).

These data suggest that individuals following plant-based diets frequently interact with pharmacists.

Participants' views on the availability of plant-based supplements in pharmacies were mixed: 22.0% considered them well-stocked, 20.0% moderately stocked, and 21.0% poorly stocked. Regarding plant-based medications, 22.0% rated pharmacies as well-stocked, 12.0% moderately, and 20.0% poorly stocked.

90.0% of respondents had not sought advice in the pharmacy on healthier lifestyles, yet 73.0% expressed interest in pharmacist consultations to prevent potential deficiencies while following a WFPBD.

Most commonly used supplements included vitamin D (59%), vitamin C (51%), vitamin B12 (48%), vitamin B6 (44%), and magnesium (41%) (Table 3).

Table 3. Frequency of dietary supplements used by active ingredient (n = 100)

Supplement Active Ingredient	Occurrence [%]
Vitamin D	59.0%
Vitamin C	51.0%
Vitamin B12	48.0%
Vitamin B6	44.0%
Magnesium	41.0%
Multivitamin	26.0%
Iron	23.0%
Omega-3 fatty acids	22.0%
Zinc	22.0%
Selenium	15.0%
Calcium	12.0%
Iodine	5.0%

B12 supplementation was associated with reduced symptoms such as numbness, dry skin, itching, reduced cold tolerance, and loss of appetite.

A. Positive changes experienced by participants after adopting the diet

Among the respondents, 24.0% reported increased energy levels, while 17.0% indicated an improvement in overall well-being. Improved digestion was reported by 13.0% of participants, and 7.0% experienced a resolution of abdominal complaints. Additionally, 7.0% noted reduced overeating tendencies, and overall, 17.0% achieved intentional weight loss following the dietary change (objective measurements were not required).

Furthermore, 9.0% of participants reported the resolution of skin problems or lesions, while 6.0% experienced improvements in their blood test results.

IV. DISCUSSION

The findings of this study suggest that plant-based diets may contribute to improved health outcomes, particularly in the prevention and management of metabolic and cardiovascular conditions. The reported benefits, such as improvements in obesity, cholesterol levels, and digestion, are consistent with existing literature on the positive effects of plant-based nutrition.

At the same time, the presence of adverse symptoms, including fatigue and anemia, indicates that inadequately planned diets may lead to nutritional

deficiencies. These results highlight the importance of ensuring sufficient intake of key micronutrients, particularly vitamin B12, iron, and vitamin D.

A notable finding of this study is the discrepancy between the demand for professional support and its actual utilization. While a majority of participants expressed interest in consultation, only a minority sought advice from healthcare professionals. This emphasizes the critical role of healthcare providers in patient education, prevention of deficiencies, and promotion of safe dietary practices.

The study has several limitations. The relatively small sample size and reliance on self-reported data may introduce bias. Furthermore, the absence of objective clinical measurements limits the generalizability of the findings.

Overall, the results demonstrate that plant-based diets offer significant health benefits; however, proper planning and professional guidance are essential to ensure their long-term safety and effectiveness.

V. CONCLUSION

Plant-based diets may play an important role in the prevention and management of chronic diseases, including obesity, diabetes mellitus, and cardiovascular conditions. When appropriately planned, such diets can contribute to improved health outcomes and reduced need for pharmacological interventions.

However, inadequate nutrient intake may lead to deficiencies and associated health risks. Therefore, the involvement of healthcare professionals is essential in providing evidence-based guidance, supporting dietary adherence, and ensuring safe implementation.

Physicians, pharmacists, and other healthcare professionals play a key role in identifying potential deficiencies, recommending appropriate dietary supplementation, and educating patients. Strengthening collaboration among these professionals in preventive care may significantly improve patient health outcomes.

REFERENCES

[1] J. Clem, and B. Barthel. A look at plant-based diets, *Mo Med*., vol. 118, pp. 233–238, 2021.

[2] M. McMacken, and S. Shah. A plant-based diet for the prevention and treatment of type 2 diabetes, *J Geriatr Cardiol.*vol. 14, pp. 342–354, 2017.

[3] S. Ivanova. C. Delattre, D. Karcheva-Bahchevanska, N. Benbasat, V. Nalbantova, and K. Ivanov K. Plant-based diet as a strategy for weight control. *Foods,* vol. 10, pp. 3052, 2021.

[4] S. R. Ahmad. Plant-based diet for obesity treatment, *Front Nutr.,* vol. 9, pp. 952553, 2022.

Alzheimer's Disease: A Systemic Review of Recent Substantial Amyloid Beta Disaggregation Therapeutics

Ritik Manyania[1,a)]
Manpreet Kaur Aulakh[1,b)]

Department of Chemistry, Chandigarh University, Gharuan-140413, Mohali, Punjab, India E-mail: [a)]ritikmanyania01@gmail.com

ABSTRACT

Alzheimer's disease (AD) is a progressive neurodegenerative disease associated with impaired cortical as well as cognitive functions. The aggregation of β-amyloid (Aβ) plaques outside and around the nerve cell is one of the reasons which causes AD. The accumulation of Aβ peptides inside the neurons involves in cognitive impairment, synaptic dysfunction and constitution of amyloid plaques. Still no effective treatment has been made which can slow down the progression of these Aβ plaques. Based on various researches, different anti-Aβ drugs have been made to decrease the production of Aβ plaques by inhibiting the β and γ secretase enzymes and also to stimulate the breakdown of preexisting Aβ plaques in the brain. Globally, many drug companies have performed clinical trials on AD patients, based upon amyloid hypothesis, to synthesize anti-amyloid drugs. Many researchers have dismissed the Aβ hypothesis of AD due to the failure of several amyloid-targeted therapies in various clinical trials performed on mild to moderate AD patients, as discussed in this article. Researchers are still developing and testing various therapies for an ideal drug of AD, in ongoing clinical trials. In this article, such anti-amyloid drugs are discussed which can prevent the formation of Aβ oligomer and suppress their toxicity.

Keywords: Alzheimer's disease; β-amyloid; Amyloid cascade hypothesis; APOE4 genotype; Anti-amyloid antibodies; β-secretase inhibitors

1. INTRODUCTION

Alzheimer's disease (AD) is the most prevalent type of dementia, a terminology refers to memory loss and other cognitive dysfunction that are severe enough to cause difficulty in daily activities, causing patients and their families enormous suffering. About 50 million people are currently suffering from AD worldwide [1]. After cardiovascular and cerebrovascular disorders and malignant tumors, AD has risen to become the third most frequent cause of disability and mortality among older adults [1]. AD is a neurodegenerative illness results in memory loss and cognitive impairment [2]. Dementia is a disorder marked by progressive decrease in more than two cognitive domains, like memory, language, visuospatial function, behavior, and personality as a result of which the ability to execute essential everyday activities are lost [3]. AD is designated globally as a public health concern by the World Health Organization (WHO). As of yet, no specific treatment has been discovered for this sickness [4].

About a century ago, Alois Alzheimer hospitalized a 51-year-old patient named Auguste D., for growing cognitive impairment. After some years of

her death, Alzheimer's histological tests of her brain lead him to the conclusion that he was witnessing a distinct clinical-chronic process, which was later termed AD [5]. AD is a multifaceted illness that is influenced by a number of factors. The exact pathophysiology of AD is still unknown because of the human brain complexity. Many hypotheses have been proposed for AD, such as the Aβ cascade hypothesis, cholinergic, tau, presenilin, oxidative stress, calcium inflammation hypothesis, and so on. As a result, a lot of work has gone into developing anti-AD medications depending on these hypotheses [6].

At microscopic level, it is studied that the characteristic nodules in AD were also extracellular senile plaques, formed by Aβ peptide reserves, and intraneuronal fibrillary clumps formed by abnormally hyperphosphorylated tau protein in the medial temporal lobe structures as well as cortex brain regions. The mechanism responsible for causing AD is still not entirely known, but hereditary, pathological, and metabolic evidence suggests that gradual manufacturing and subsequent growth of Aβ, a proteolytic subunit of the membrane-associated amyloid precursor protein (APP), plays a very important role. Aβ peptide, the principal factor of neuritic plaque, is generated in excessive proportions by an abnormal breakdown of APP, a membrane-bound glycoprotein whose principal objective is unknown till now, however, it has been linked to neuronal plasticity and neuron synapse formation [7]. The primary physiological pathway of APP digestion in neurons is followed out by α-secretase and γ-secretase to form P3 protein. However, in AD, an amyloid precursor protein pathway is promoted by the breakdown of APP by β-secretase, accompanied by γ-secretase, to form Aβ peptides comprising 39 to 42 amino acid residues. According to biochemical investigations on cell lysates as well as brains, the most prevalent are Aβ 1-40 (90%) and Aβ 1- 42 (10%). Cells in the brain secrete this protein in a dissolved form, which is normally eliminated. However, when aberrant conditions make more APP susceptible to β-secretase cleavage, the Aβ elimination mechanism in the process becomes overwhelmed. This ultimately results in the accumulation of Aβ, which forms oligomeric, multimeric, and fibrillar clumps, causing neurodegeneration. The aggregation as well as deposition of Aβ results in the production of extracellular plaques, which are one of the physiological markers of the illness [8].

2. AMYLOID PRECURSOR PROTEIN (APP) AND β-AMYLOID PRODUCTION

Initially, amyloid protein was isolated and distinguished from the AD patient's cerebral vasculature of brain and thereafter the cloning of APP was done [9]. The cleavage of APP is done with the help of secretases enzyme, as it is a type-I transmembrane protein. The APP gene can be found on chromosome 21 and three major isoforms (or homologs) can be prepared from its mRNA by the process of alternative splicing. Amino acid homologue i.e. 695 mainly found in neurons, preferentially 751 and 770 homologue amino acids systematically expressed. The Aβ region in the APP is found partly inside the ectodomain and transmembrane region of APP as the peptides of 40-43 amino acid residues. Aβ42 is the disease-associated isoform of Aβ, accounting for 5-10% total amount of Aβ generated [10]. The amyloid plaques which are deposited initially seen in the brains, suffering from AD, are generated due to Aβ42. APP is processed by proteolysis by enzymes α, β, and γ-secretases. At amino acid 17, α-secretase enzyme cleaves the majority of APP in the Aβ domain, which results in the non-generation of Aβ, and it generates soluble αAPP which subsequently released in non-amyloidogenic pathway. APP, on the other hand, is also cleaved by β-secretases and γ-secretases in the Aβ domain at the N-terminus and C-terminus respectively, which results in the generation of Aβ in amyloidogenic mechanism [11]. A larger amount of APP is present in patients suffering with Down syndrome due to the trisomy of chromosome 21. The AD is generally known to grow too soon in people suffering with Down syndrome [12]. In addition, automatic transmission dominant mutations of APP and presenilin associated with contagious forms of premature AD have been demonstrated to increase Aβ output and to generate more Aβ aggregation. So Aβ peptide has become central focus to AD research on the basis of these genetic markers. Aβ was originally created at the plasma membrane and supposed to be released in the extracellular form of Aβ. It is postulated that in AD patients, released Aβ progressively accumulates in extracellular environment till it begins the formation of clumps of β-pleated amyloid fibrils which are insoluble in nature and are made up of 7-9 nm broad antiparallel-pleated sheets of fibres. Several theories suggests that these extracellular Aβ fibrils have a detrimental impact on the neighboring nerve cells and their functions [13]. Recently, it has been proposed that intermediary products of Aβ fibril synthesis, such as Aβ oligomers having lower molecular weight and protofibrils, are extremely harmful to neurons and alter neuroplasticity than Aβ fibrils [14].

Furthermore, soluble Aβ interacts more with brain functions in the AD brain than insoluble Aβ . Protofibrils is a soluble form of Aβ and these soluble Aβ groups are generally assumed to have significant pathogenic impacts [15].

3. Aβ CASCADE HYPOTHESIS

The transmembrane protein APP, which is a component of many cell types, including neurons and glial cells, is broken down into peptide Aβ during the proteolysis process. There are several versions of the molecule produced by substitution concatenation in humans, with APP695 being the most prevalent [16][17][18]. The enzyme protein complex -α, -β, and -γ secretase, which is made up of presenilin and nicastrin molecules, cleaves APP into smaller peptide pieces, one of which is Aβ. When APP is catabolized by α-secretase, two fragments are produced: a soluble sAPPα fragment that stays in the extracellular space and an 83 carboxyterminal amino acid fragment (C83) that is attached to the plasma membrane [19][20][21]. In addition to improving synaptic plasticity, learning, and memory, sAPPα also helps to reduce metabolic stress and regulate neural excitability. APP is selectively cleaved by β-secretase 1 (BACE) in neuropathic conditions, resulting in the fragmentation of APP into sAPPβ and a fraction of 99 amino acids (C99). The peptides Aβ(1-40) and Aβ(1-42), which are produced after further processing of C99 cleavage by γ-secretase, are believed to be responsible for the development of neuritic plaques [22]. According to the amyloid cascade hypothesis, the pathophysiology of AD, which results in neurotoxicity and neuronal degeneration, is heavily influenced by the production, aggregation, and deposition of Aβ peptides, particularly Aβ(1-42) [23]. The development of fibrillar plexuses and enhanced Tau phosphorylation are two additional effects of excessive extracellular Aβ. The amyloid cascade hypothesis, however, falls short in describing the fundamental reasons of rare AD, where formation of Aβ is unlikely to have a clear hereditary basis [24][25].

3.1. Antiamyloidogenic Pathways as Potential Therapeutic Targets for Modifying the Progression of AD

The pharmaceutical industry has mostly concentrated on amyloid-centric approaches during the past 20 years, investing significant resources to create effective AD medicines. Experts have questioned the strategy's practicality, nevertheless, in light of the numerous clinical trial failures of drug candidates [21][22][25]. Lack of biomarkers that can reliably identify AD in its early stages is one likely cause of failure. The people who are currently being enrolled in phase III studies appear to be suffering from advanced stages of AD, rendering any suggested treatment ineffective. New diagnostic

tools which are able to do early detection are therefore critically needed. Meanwhile, numerous new medications that target the mechanism of amyloid production are continually being developed. The inhibition of γ- and β-secretase can lower the Aβ production from APP, and increasing α-secretase activity must be taken into account [26].

3.1.1. β-Secretase Inhibitors and its Modulators

The amyloidogenic APP-processing pathway's early stages involve the β-secretase enzyme complex. Because this complex also includes multiple additional substrates in addition to the APP, it is challenging to make β-secretase inhibitors. For instance, β-secretase's ultimate target is neuregulin-1, which is crucial for CNS axon myelination and synaptic plasticity [18]. Even if the enzyme is specifically inhibited, a wide range of substrates might cause considerable adverse effects. Nonetheless, MK8931 (clinical trial ID# NCT01739348), E2609 (NCT01600859), and LY2886721 (NCT01807026 and NCT01561430) have all showed effectiveness in reducing Aβ production in the cerebrospinal fluid (CSF) by up to 80–90% in people. So yet, no β-secretase inhibitors have reached the market [27][28][29][30].

3.1.2. Inhibitors of γ-Secretase and its Modulator

The production of Aβ(1-40) and Aβ(1-42) is the result of the final step of amyloidogenesis, which is carried out by the γ-secretase complex. Inhibiting -secretase was once thought to be a potential method for treating diseases. On the other hand, β-secretase inhibitors have similar problems with substrate promiscuity. Notch protein controls cell multiplication, differentiation, growth and cell transmission, is primary targets of γ-secretase [31]. Similar to β-secretase inhibitors, side effects like off-target are a big worry [32].

γ-secretase inhibitor like semagacestat (LY450139) decreases the levels of Aβ in human blood and CSF [33]. Results of clinical trials (NCT00762411, NCT01035138 and NCT00762411) recruited more than 3000 patients an example of the worst possible consequences. It has been reported that treatment with semagacestat was associated with exacerbations of the ability to carry out daily life activities of AD patients (ADAS-cog scale). Moreover, side effects include weight loss, more risk of skin cancer and infection. Avagacestat is one more example of γ-secretase inhibitor discontinued due to lack of efficacy [34][35][36].

The selective γ-secretase modulator (SGSM), which is linked to significant enzyme inhibition, is theoretically created to prevent undesirable outcomes.

Therefore, the goal of these treatments is to prevent the processing of the APP from occurring without the use of other signalling pathways, including Notch [37]. The discovery that several non-steroidal anti-inflammatory medicines (NSAIDs) reduced Aβ peptide (1-42) levels in vitro and in vivo was the catalyst for the development of SGSM. Ibuprofen, sulindac and flurbiprofen are a few examples of this category of medication [38]. The commonly accepted mechanism of action (MOA) for NSAIDs is the suppression of the cyclooxygenase (COX) enzyme. R-flurbiprofen (Tarenflurbil), unlike ibuprofen, does not block the COX enzyme, hence its ability to lower levels of Aβ cannot be attributed to this. Sadly, in their respective clinical studies, tarenflurbil and ibuprofen failed to demonstrate efficacy for the treatment of AD [38][39]. CHF5074 is an NSAID without COX inhibitory action, just like R-flurbiprofen. By impeding the γ-secretase complex, CHF5074 prevented the formation of Aβ(1- 42) in vitro [40][41][42]. This substance has been labelled as a microglial modulator in recent studies due to its ability to decrease amyloid burden and microglial activation. The results of a phase II trial in people with moderate cognitive impairment (MCI) show that CHF5074 therapy enhances a number of cognitive tests and lowers inflammatory marker levels in the CSF. Interest in NSAIDs as a medicine relatively effective for decreasing Aβ(1- 42) levels was inspired by the prospect that long-term NSAID usage would provide some protection against AD. However, negative outcomes from NSAID-related clinical research demonstrate that this idea has to be improved further [43].

NIC5-15 is another probable instance of SGSM. It is a chemical that is found in nature and is also referred to as pinitol. NIC5-15 is a natural cyclic sugar alcohol [40]. It is reported that this compound can probably regulate γ-secretase and also reduce the production of Aβ without affecting the Notch in substrate cutting. Because there is no any reviewed data, therefore, for this chemical, any stated outcomes should be regarded as a statement of future prospects that need hard scientific evidences. However, the compound is asserted to have enhanced memory and cognitive performance in a model of preclinical AD neurological pathology. These results suggest that NIC5-15 might serve as a promising therapeutic agent to use in the treatment of AD for two distinct reasons: (a) helps to retain Notch activation, and (b) it has the potential to be an insulin sensitizer, assuming the data are accurate. It should also be the subject of research to serve as an anti-inflammatory inhibitor because it can stop microglia from activating. Yet additional researchers have not yet confirmed these results [26].

3.2. Inhibition of β-Amyloid Peptides Aggregation

Aggregation of Aβ peptides results in the formation of amyloid plaques. To inhibit the production of senile plaques, the following chemicals were produced.

3-amino-1-propaneosulfonic acid (3-APS, Alzhemed, tramiprosate) is the only Aβ aggregation inhibitor that has progressed to phase III studies. This medication was developed to interfere with or inhibit the interaction of soluble Aβ with endogenous glycosaminoglycans. It has been discovered that glycosaminoglycans promote the synthesis and deposition of Aβ amyloid fibrils. However, this chemical has been banned in Europe as a result of the phase III clinical trial unsatisfactory results in 2007 [44].

A proline-rich polypeptide complex i.e. colostrinin present in human colostrum, ovine, and bovine, lowers Aβ-aggregation and neurotoxicity in cell experiments and improves memory retention in numerous mice models. After 15 months of therapy, participants in a phase II trial who had moderate AD showed modest improvements on the mini mental state examination, but these positive effects were not maintained after another 15 months of ongoing therapy [45].

Scyllo-inositol (ELND005) is another example of amyloid anti-aggregation drug that may be taken orally that reduces Aβ toxicity in the hippocampus of mouse. Patients with mild to moderate stages of AD participated in a phase II clinical trial which lasted for 18-months using ELND005. The major clinical efficiency objectives of this trial weren't accomplished [46].

The metal-chelating 8-hydroxiquinolines (8-HQ) molecules clioquinol and PBT2 were also used in clinical trials for the treatment of AD [47]. Although the precise mode of action is uncertain, it is thought that these kinds of molecules prevent base metals from attaching to the A peptides of brain. It has been suggested that copper ions sticking to A, which results in the metal-mediated production of reactive oxygen species (ROS), may contribute to the higher levels of oxidative stress found in the brains of AD patients [48]. Additionally, it was suggested that 8-HQs could balance out the amounts of copper and zinc in cells while preventing Aβ aggregation. Unfortunately, due to lack of efficiency, these compounds failed in clinical development phase II and III [26].

3.3. Aβ Aggregates Removal Compounds

Another possible amyloidogenic pathway-based therapy strategy is promoting the eradication of already existing aggregates as well as plaques. Three distinct tactics have been tested in order to accomplish this.

3.3.1. Transmission Modulation of Aβ Between the Peripheral Circulation and the Brain

The transmission of Aβ between the peripheral circulation and the CNS is done by low density lipoprotein receptor-related protein (LRP-1), apolipoproteins (APOE) and receptor for advanced glycation end products (RAGE). The main function of LRP-1 is to increase the Aβ discharge from the brain to blood whereas RAGE enhances Aβ transmission throughout the blood-brain barrier [49][50][51]. Any therapy based on this strategy aims to minimize cerebral amyloid burden by aiming to limit Aβ to the peripheral circulation. A variety of techniques, including the peripheral delivery of LRP-1, have been proposed to achieve this goal. Yet, RAGE inhibitors and modulators are the sole therapeutic candidates which have progressed to the clinical stage. They consist of TTP4000, which successfully completed its phase I trial, and PF-0449470052, which did not succeed in phase II trials. The findings of this experiment have not been made public [51].

3.3.2. Degradation of Amyloid Plaques by Enzyme Activation

The degradation of aggregates and amyloid plaques is aided by a number of proteases, particularly plasmin, IDE, neprilysin, angiotensin converting enzyme, endothelin transforming enzyme and metalloproteinases. In AD, there is a reduction in the protein levels associated with these enzymes, which causes Aβ to be produced and deposited. Absolutely no drugs with this MOA progressed to advanced therapeutic uses, despite being a convincing method for creating disease-modifying medications due to a lack of specificity [24][52].

3.3.3. Anti-Amyloid Immunotherapy

Active immunotherapy is the immunotherapy technique intended to improve Aβ elimination in AD in order to lessen the amyloid burden. In transgenic AD mouse models, the active immunization is effectively tested with Aβ(1-42) or alternative synthetic components. Assays are often predicated on activating microglia's phagocytic capability in order to stimulate immunological responses, T cells and B cells. Human testing was originally encouraging, however, treatment with the very first vaccination (AN1792) resulted in substantial side effects, forcing the phase II study to be halted. AN1792 was made up of a synthetic Aβ(1-42) peptide and an adjuvant known as QS-21. 6% of patients experienced cerebral inflammation brought on by a T cell-mediated autoimmune reaction, which result in aseptic meningoencephalitis [26].

Second-generation vaccinations were developed employing a condensed Aβ(1-6) peptide sequence to prevent the nonspecific immune response observed with the full-length immunization. The second-generation vaccine to enter the clinical stages of development was CAD 106, created by Novartis, for the first time [53]. A phase II clinical trial found that 75% of the participants treated had an Aβ-specific antibody response without triggering any unfavorable inflammatory reactions. Janssen developed a drug ACC-001 which have finished two phase II studies (NCT00479557 and NCT01284387), while a third phase II trial (NCT01227564) remain in progress. The pharmaceutical industry nevertheless has given up on further developing this vaccine. There are several other vaccines in various phases of preclinical advancement, particularly tetra-palmitoylated Aβ(1-15) which is remanufactured in a liposome (ACI-24), AF205 and MER5101 [54][55][56][57].

Passive immunotherapy constitutes the delivery of monoclonal or polyclonal antibodies targeting Aβ. Anti-Aβ antibodies are administered intravenously to the patient as part of this treatment. The absence of proinflammatory T cell-mediated immune responses is a benefit of this method over active vaccination. Passive vaccination decreases cerebral amyloid burden and enhances cognition in transgenic rats, despite the fact that the number of amyloid plaques is not greatly decreased. The reason for this might be explained by soluble amyloid oligomers elimination, that are now known to be vital components along the pathophysiologic chain of AD [26].
Monoclonal antibodies which have successfully reached relatively advanced phases in their clinical trials are bapineuzumab and solanezumab [58]. Two phase III clinical investigations, though, were unsuccessful in 2012 because they were ineffective for AD patients. Targeting Aβ(1-6) and Aβ(12-28), bapineuzumab and solanezumab are humanizing monoclonal antibodies respectively. Bapineuzumab did not significantly improve cognitive function throughout clinical trials, despite being reported to significantly reduce brain amyloid deposits and phosphorylated Tau in CSF fluid. AD patients who participated in a research trial were given 400 mg of solanezumab or a placebo once each month for 80 weeks. Statistical significance was not achieved in this study, despite the fact that the results revealed that solanezumab may enhance cognitive function in those with moderate Alzheimer's disease. The effectiveness of solanezumab in treating AD in patients as well as older people with normal cognitive function who may be at risk of getting AD as they age is now being investigated in phase III clinical trials [59][60].

Researchers are currently studying gantenerumab, another monoclonal antibody, in individuals who have genetic abnormalities that put them at risk of developing presenile AD. In one clinical trial (NCT01760005), the gantenerumab and solanezumab efficacy was assessed in the early stages of the illness. Additionally, two further phase III trials are being conducted to evaluate the effectiveness of gantenerumab in people with mild to moderate AD. A completely human-derived IgG1 antibody called gantenerumab has been created to attach to Aβ fibres' structural epitope with great affinity. The recruitment of microglia and subsequent phagocytosis will probably result in amyloid plaque destruction. This idea is supported by experimental research in transgenic mice [26][61].

There have been several monoclonal antibodies created to target Aβ, such as PF-04360365 (ponezumab), MABT5102A and GSK933776A. PF-04360365 is a drug that targets amino acids 33–40 at the free carboxy terminal of the Aβ peptide. Meanwhile, MABT5102A has a strong binding affinity for Aβ monomers, fibrils and oligomers. On the other hand, GSK933776A attaches to the N-terminal Aβ(1–5) and shares similarities with bapineuzumab. These medications have diverse methods of action and target various parts of the Aβ peptide, which may have an impact on their efficacy and safety profiles. Additionally, numerous additional passive immunotherapies, including NI-101, SAR-228810, and BAN-2401, are in phase I clinical studies [56][57][61]. Monoclonal antibody crenezumab, often referred to as MABT5102A, has an IgG4 backbone. In April 2014, a phase II clinical trial examining the security and effectiveness of crenezumab in people with AD was finished. A recently completed phase II trial, which started in November 2013, is testing crenezumab's effectiveness as well as safety in E280A carriers having no symptoms of the autosomal-dominant PSEN1 mutation [62].

The large-scale clinical research with aducanumab, known as the EMERGE study, demonstrated the efficacy of amyloid targeting in individuals with AD. In the treatment of early-stage AD, the anti-amyloid antibody BAN2401, which targets soluble Aβ protofibrils, has also produced encouraging results. Phase 2 of BAN2401's trial is complete, and phase 3 testing is already taking place. ALZ-801, an oral medication, has also been demonstrated to entirely halt the onset of AD. The effectiveness of ALZ-801 has shown promising results in subgroup analysis of prespecified groups of patients, specifically those with Aβ oligomers but without plaque binding. Patients with an elevated load of A oligomers who are APOE4 carriers seem to respond better to BAN2401 and ALZ-801 than non-carriers [62].

Table 1: Anti-amyloid drugs undergoing clinical trials [63]:

Drug	Study Phases	Sponsor	Start Date	Expected Completion Date	Status (CT.gov ID)
LY3372993	1	Eli Lilly	Jul 2020	Feb 2022	Recruiting (NCT04451408)
Abvac40	2	Araclon Biotech	Feb 2018	Feb 2022	Recruiting (NCT03461276)
ALZ-801	2	Alzheon	Sept 2020	May 2023	Recruiting (NCT04693520)
APH-1105	2	Aphios	Jun 2021	Dec 2022	Not yet recruiting (NCT03806478)
Crenezumab	2	Genentech, NIA Banner Alzheimer's Institute	Dec 2013	Feb 2022	Active, not recruiting (NCT01998841)
Donanemab (LY3002813)	2	Eli Lilly	Dec 2017	Nov 2021	Active, not recruiting (NCT03367403)
Gantenerumab	2	Roche	Dec 2020	Feb 2024	Recruiting (NCT04592341)
IVIG (NewGam 10%)	2	Sutter Health	Jan 2011	Dec 2019	Active, not recruiting (NCT01300728)
Lecanemab (BAN2401)	2	Eisai	Dec 2012	Feb 2025	Active, not recruiting (NCT01767311)
PQ912	2	Vivoryon Therapeutics AG, ADCS, NIA	Jun 2021	Jan 2023	Not yet recruiting (NCT03919162)
RO7126209	2	Roche	Mar 202	Oct 2024	Recruiting (NCT0463905

			1		0)
Thiethylperazine (TEP)	2	Immungenetics AG	Nov 2017	Jul 2021	Active, not recruiting (NCT03417986)
Aducanumab	3	Biogen	Mar 2020	Oct 2023	Enrolling by invitation (NCT04241068)
Azeliragon	3	vTv Therapeutics	Jun 2019	Jul 2023	Active, not recruiting (NCT03980730)
Gantenerumab	3	Roche	Mar 2014	Apr 2021	Active, not recruiting (NCT02051608)
		Roche	Jun 2018	Nov 2023	Recruiting (NCT03444870)
		Roche	Aug 2018	Nov 2023	Active, not recruiting (NCT03443973)
		Roche	May 2020	Feb 2023	Recruiting, extension study (NCT04339413)
		Roche	Feb 2021	Dec 2024	Not yet recruiting, extension study (NCT04374253)
Gantanerumab & solanezumab	3	Washington University, Eli Lilly, Roche, NIA, Alzheimer's Association	Dec 2012	July 2022	Recruiting (NCT01760005)

Lecanemab (BAN2401)	3	Eisai, Biogen	Mar 2019	Aug 2024	Recruiting (NCT03887455)
		Eisai, Biogen, ACTC, NIA	Jul 2020	Oct 2027	Recruiting (NCT04468659)
Solanezumab	3	Eli Lilly, ATRI	Feb 2014	Jan 2023	Active, not recruiting (NCT02008357)

4. CONCLUSION

In conclusion, data reveals that AD neuropathology is complex and includes several biological processes. Since the amyloid cascade hypothesis has greatly influenced the field for more than two decades, a lot of work has been done on preventing and getting rid of Aβ and senile plaques. Nevertheless, despite this amyloid-centric strategy, AD medicines haven't shown that they significantly improve patients' cognitive function. When creating novel experimental treatments, it is important to keep in mind that dendritic spine defects are a contributing component to the cognitive impairment found in this condition. To better comprehend the aetiology of AD, we need take into account activities occurring at the synapse as well as the amyloid cascade theory. It is critical to investigate alternative therapeutic approaches in light of the amyloid immunotherapies and BACE1 program repeated failures. As Aβ oligomers are frequently cited as major factors in AD pathology, inhibitors of these oligomers may prove to be successful AD treatments. Clinical trials may be more successful if they target APOE4 carriers in the early stages of disease and use drug concentrations that decrease Aβ oligomers in verified CSF testing.

REFERENCES

[1] X. Du, X. Wang, and M. Geng, “Alzheimer’s disease hypothesis and related therapies,” *Transl. Neurodegener.*, vol. 7, no. 1, pp. 1–7, 2018, doi: 10.1186/s40035-018-0107-y.

[2] E. Nam, G. Nam, and M. H. Lim, “Synaptic Copper, Amyloid-β, and Neurotransmitters in Alzheimer’s Disease,” *Biochemistry*, vol. 59, no. 1, pp. 15–17, 2020, doi: 10.1021/acs.biochem.9b00775.

[3] J. Weller and A. Budson, “Current understanding of Alzheimer’s disease diagnosis and treatment,” *F1000Research*, vol. 7, no. 0, pp. 1–9, 2018, doi: 10.12688/f1000research.14506.1.

[4] G. Palareti *et al.*, “Comparison between different D-Dimer cutoff values to

assess the individual risk of recurrent venous thromboembolism: Analysis of results obtained in the DULCIS study," *Int. J. Lab. Hematol.*, vol. 38, no. 1, pp. 42–49, 2016, doi: 10.1111/ijlh.12426.

[5] G. K. Gouras, C. G. Almeida, and R. H. Takahashi, "Intraneuronal Aβ accumulation and origin of plaques in Alzheimer's disease," *Neurobiol. Aging*, vol. 26, no. 9, pp. 1235–1244, 2005, doi: 10.1016/j.neurobiolaging.2005.05.022.

[6] J. Cummings *et al.*, "Drug development in Alzheimer's disease: The path to 2025," *Alzheimer's Res. Ther.*, vol. 8, no. 1, pp. 1–12, 2016, doi: 10.1186/s13195-016-0207-9.

[7] F. Re *et al.*, "Beta Amyloid Aggregation Inhibitors: Small Molecules as Candidate Drugs for Therapy of Alzheimers Disease," *Curr. Med. Chem.*, vol. 17, no. 27, pp. 2990–3006, 2010, doi: 10.2174/092986710791959729.

[8] S. S. Sisodia and P. H. St George-Hyslop, "γ-Secretase, notch, Aβ and alzheimer's disease: Where do the presenilins fit in?," *Nat. Rev. Neurosci.*, vol. 3, no. 4, pp. 281–290, 2002, doi: 10.1038/nrn785.

[9] R. H. Takahashi, T. Nagao, and G. K. Gouras, "Plaque formation and the intraneuronal accumulation of β-amyloid in Alzheimer's disease," *Pathol. Int.*, vol. 67, no. 4, pp. 185–193, 2017, doi: 10.1111/pin.12520.

[10] G. K. Gouras *et al.*, "Intraneuronal Aβ42 accumulation in human brain," *Am. J. Pathol.*, vol. 156, no. 1, pp. 15–20, 2000, doi: 10.1016/S0002-9440(10)64700-1.

[11] Q. Wang *et al.*, "Tanshinones Inhibit Amyloid Aggregation by Amyloid-ß Peptide , Disaggregate Amyloid Fibrils , and Protect Cultured Cells Tanshinones Inhibit Amyloid Aggregation by Amyloid-β Peptide , Disaggregate Department of Chemical and Biomolecular Engineering Depart," 2013.

[12] A. M. Goate *et al.*, "Predisposing Locus for Alzheimer'S Disease on Chromosome 21," *Lancet*, vol. 333, no. 8634, pp. 352–355, 1989, doi: 10.1016/S0140-6736(89)91725-X.

[13] C. J. Pike, D. Burdick, A. J. Walencewicz, C. G. Glabe, and C. W. Cotman, "Neurodegeneration induced by β-amyloid peptides in vitro: The role of peptide assembly state," *J. Neurosci.*, vol. 13, no. 4, pp. 1676–1687, 1993, doi: 10.1523/jneurosci.13-04-01676.1993.

[14] D. M. Walsh and D. J. Selkoe, "Deciphering the molecular basis of memory failure in Alzheimer's disease," *Neuron*, vol. 44, no. 1, pp. 181–193, 2004, doi: 10.1016/j.neuron.2004.09.010.

[15] M. Sakono and T. Zako, "Amyloid oligomers: Formation and toxicity of Aβ oligomers," *FEBS J.*, vol. 277, no. 6, pp. 1348–1358, 2010, doi: 10.1111/j.1742-4658.2010.07568.x.

[16] P. T. Francis, A. Nordberg, and S. E. Arnold, "A preclinical view of cholinesterase inhibitors in neuroprotection: Do they provide more than symptomatic benefits in Alzheimer's disease?," *Trends Pharmacol. Sci.*, vol. 26, no. 2, pp. 104–111, 2005, doi: 10.1016/j.tips.2004.12.010.

[17] W. Thies and L. Bleiler, "2012 Alzheimer's disease facts and figures," *Alzheimer's Dement.*, vol. 8, no. 2, pp. 131–168, 2012, doi: 10.1016/j.jalz.2012.02.001.

[18] K. Chiang and E. H. Koo, "Emerging therapeutics for alzheimer's disease," *Annu. Rev. Pharmacol. Toxicol.*, vol. 54, pp. 381–405, 2014, doi:

10.1146/annurev-pharmtox-011613-135932.
[19] L. Muckle and D. Sekloe, “Neurotoxicity of Amyloid β -Protein : Synaptic and Network,” *Cold Spring Harb. Perspect. Med.*, pp. 1–17, 2014.
[20] C. Haass, C. Kaether, G. Thinakaran, and S. Sisodia, “Trafficking and proteolytic processing of APP,” *Cold Spring Harb. Perspect. Med.*, vol. 2, no. 5, pp. 1–26, 2012, doi: 10.1101/cshperspect.a006270.
[21] M. A. Castello and S. Soriano, “Rational heterodoxy: Cholesterol reformation of the amyloid doctrine,” *Ageing Res. Rev.*, vol. 12, no. 1, pp. 282–288, 2013, doi: 10.1016/j.arr.2012.06.007.
[22] D. A. Drachman, “The amyloid hypothesis, time to move on: Amyloid is the downstream result, not cause, of Alzheimer’s disease,” *Alzheimer’s Dement.*, vol. 10, no. 3, pp. 372–380, 2014, doi: 10.1016/j.jalz.2013.11.003.
[23] J. Hardy and D. J. Selkoe, “The amyloid hypothesis of Alzheimer’s disease: Progress and problems on the road to therapeutics,” *Science (80-.).*, vol. 297, no. 5580, pp. 353–356, 2002, doi: 10.1126/science.1072994.
[24] N. Nalivaeva, L. Fisk, N. Belyaev, and A. Turner, “Amyloid-Degrading Enzymes as Therapeutic Targets in Alzheimers Disease,” *Curr. Alzheimer Res.*, vol. 5, no. 2, pp. 212–224, 2008, doi: 10.2174/156720508783954785.
[25] M. A. Castello and S. Soriano, “On the origin of Alzheimer’s disease. Trials and tribulations of the amyloid hypothesis,” *Ageing Res. Rev.*, vol. 13, no. 1, pp. 10–12, 2014, doi: 10.1016/j.arr.2013.10.001.
[26] J. Folch *et al.*, “Current Research Therapeutic Strategies for Alzheimer’s Disease Treatment,” *Neural Plast.*, vol. 2016, 2016, doi: 10.1155/2016/8501693.
[27] D. Rossi, “Astrocyte physiopathology: At the crossroads of intercellular networking, inflammation and cell death,” *Prog. Neurobiol.*, vol. 130, pp. 86–120, 2015, doi: 10.1016/j.pneurobio.2015.04.003.
[28] R. Yan and R. Vassar, “Targeting the β secretase BACE1 for Alzheimer’s disease therapy,” *Lancet Neurol.*, vol. 13, no. 3, pp. 319–329, 2014, doi: 10.1016/S1474-4422(13)70276-X.
[29] P. C. May *et al.*, “The potent BACE1 inhibitor LY2886721 elicits robust central Aβ pharmacodynamic responses in mice, dogs, and humans,” *J. Neurosci.*, vol. 35, no. 3, pp. 1199–1210, 2015, doi: 10.1523/JNEUROSCI.4129-14.2015.
[30] K. W. Menting and J. A. H. R. Claassen, “β-secretase inhibitor; a promising novel therapeutic drug in Alzheimer’s Disease,” *Front. Aging Neurosci.*, vol. 6, no. JUN, pp. 1–20, 2014, doi: 10.3389/fnagi.2014.00165.
[31] D. Kumar, A. Ganeshpurkar, D. Kumar, G. Modi, S. K. Gupta, and S. K. Singh, “Secretase inhibitors for the treatment of Alzheimer’s disease: Long road ahead,” *Eur. J. Med. Chem.*, vol. 148, pp. 436–452, 2018, doi: 10.1016/j.ejmech.2018.02.035.
[32] R. S. Doody *et al.*, “A Phase 3 Trial of Semagacestat for Treatment of Alzheimer’s Disease,” *N. Engl. J. Med.*, vol. 369, no. 4, pp. 341–350, 2013, doi: 10.1056/nejmoa1210951.
[33] V. Coric *et al.*, “Safety and tolerability of the γ-secretase inhibitor avagacestat in a phase 2 study of mild to moderate Alzheimer disease,” *Arch. Neurol.*, vol. 69, no. 11, pp. 1430–1440, 2012, doi: 10.1001/archneurol.2012.2194.
[34] G. Tong *et al.*, “Effects of single doses of avagacestat (BMS-708163) on

cerebrospinal fluid Aβ levels in healthy young men," *Clin. Drug Investig.*, vol. 32, no. 11, pp. 761–769, 2012, doi: 10.1007/s40261-012-0006-4.

[35] R. Dockens *et al.*, "A placebo-controlled, multiple ascending dose study to evaluate the safety, pharmacokinetics and pharmacodynamics of avagacestat (BMS-708163) in healthy young and elderly subjects," *Clin. Pharmacokinet.*, vol. 51, no. 10, pp. 681–693, 2012, doi: 10.1007/s40262-012-0005-x.

[36] D. Jaturapatporn, I. Mgekn, J. Mccleery, and N. Tabet, "Aspirin , steroidal and non-steroidal anti-inflammatory drugs for the treatment of Alzheimer ' s disease (Review)," no. 2, 2012.

[37] J. L. Eriksen *et al.*, "NSAIDs and enantiomers of flurbiprofen target γ-secretase and lower Aβ42 in vivo," *J. Clin. Invest.*, vol. 112, no. 3, pp. 440–449, 2003, doi: 10.1172/jci200318162.

[38] M. Miguel-Álvarez *et al.*, "Non-steroidal anti-inflammatory drugs as a treatment for Alzheimer's disease: a systematic review and meta-analysis of treatment effect," *Drugs Aging*, vol. 32, no. 2, pp. 139–147, 2015, doi: 10.1007/s40266-015-0239-z.

[39] T. E. Golde, E. H. Koo, K. M. Felsenstein, B. A. Osborne, and L. Miele, "γ-Secretase inhibitors and modulators," *Biochim. Biophys. Acta - Biomembr.*, vol. 1828, no. 12, pp. 2898–2907, 2013, doi: 10.1016/j.bbamem.2013.06.005.

[40] J. Pitt, M. Thorner, D. Brautigan, J. Larner, and W. L. Klein, "Protection against the synaptic targeting and toxicity of Alzheimer's-associated Aβ oligomers by insulin mimetic chiro-inositols," *FASEB J.*, vol. 27, no. 1, pp. 199–207, 2013, doi: 10.1096/fj.12-211896.

[41] N. Ronsisvalle, G. Benedetto, C. Parenti, S. Amoroso, R. Bernardini, and G. Cantarella, "CHF5074 Protects SH-SY5Y Human Neuronal-like Cells from Amyloidbeta 25-35 and Tumor Necrosis Factor Related Apoptosis Inducing Ligand Toxicity In Vitro," *Curr. Alzheimer Res.*, vol. 11, no. 7, pp. 714–724, 2014, doi: 10.2174/1567205011666140618104430.

[42] B. P. Imbimbo *et al.*, "Pharmacokinetics and pharmacodynamics of CHF5074 after short-term administration in healthy subjects," *Alzheimer Dis. Assoc. Disord.*, vol. 27, no. 3, pp. 278–286, 2013, doi: 10.1097/WAD.0b013e3182622ace.

[43] O. Zanetti *et al.*, "A randomized controlled study on effects of ibuprofen on cognitive progression of Alzheimer's disease* Aging Clinical and Experimental Research," *Aging Clin Exp Res*, vol. 21, no. 2, pp. 102–110, 2009.

[44] R. Gupta-Bansal, R. C. A. Frederickson, and K. R. Brunden, "Proteoglycan-mediated inhibition of Aβ proteolysis. A potential cause of senile plaque accumulation," *Journal of Biological Chemistry*, vol. 270, no. 31. pp. 18666–18671, 1995. doi: 10.1074/jbc.270.31.18666.

[45] A. Bilikiewicz and W. Gaus, "Colostrinin1 (a naturally occuring, proline-rich, polypeptide mixture) in the treatment of Alzheimer's disease," *J. Alzheimer's Dis.*, vol. 6, no. 1, pp. 17–26, 2004, doi: 10.3233/JAD-2004-6103.

[46] S. Salloway *et al.*, "A phase 2 randomized trial of ELND005, scyllo-inositol, in mild to moderate Alzheimer disease," *Neurology*, vol. 77, no. 13, pp. 1253–1262, 2011, doi: 10.1212/WNL.0b013e3182309fa5.

[47] K. E. S. Matlack *et al.*, “Clioquinol promotes the degradation of metal-dependent amyloid-ß (Aß) oligomers to restore endocytosis and ameliorate Aß toxicity,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 111, no. 11, pp. 4013–4018, 2014, doi: 10.1073/pnas.1402228111.

[48] A. Robert, Y. Liu, M. Nguyen, and B. Meunier, “Regulation of copper and Iron homeostasis by metal chelators: A possible chemotherapy for alzheimers disease,” *Acc. Chem. Res.*, vol. 48, no. 5, pp. 1332–1339, 2015, doi: 10.1021/acs.accounts.5b00119.

[49] R. Deane, A. Sagare, and B. Zlokovic, “The Role of the Cell Surface LRP and Soluble LRP in Blood-Brain Barrier Aβ Clearance in Alzheimers Disease,” *Curr. Pharm. Des.*, vol. 14, no. 16, pp. 1601–1605, 2008, doi: 10.2174/138161208784705487.

[50] R. J. Deane, “Is RAGE still a therapeutic target for Alzheimers disease?,” *Future Med. Chem.*, vol. 4, no. 7, pp. 915–925, 2012, doi: 10.4155/fmc.12.51.

[51] D. Galasko *et al.*, “Clinical trial of an inhibitor of RAGE-Ab interactions in Alzheimer disease,” *Neurology*, vol. 82, no. 17, pp. 1536–1542, 2014, doi: 10.1212/WNL.0000000000000364.

[52] M. Higuchi, N. Iwata, and T. C. Saido, “Understanding molecular mechanisms of proteolysis in Alzheimer’s disease: Progress toward therapeutic interventions,” *Biochim. Biophys. Acta - Proteins Proteomics*, vol. 1751, no. 1, pp. 60–67, 2005, doi: 10.1016/j.bbapap.2005.02.013.

[53] C. Wiessner *et al.*, “The second-generation active Aβ immunotherapy CAD106 reduces amyloid accumulation in APP transgenic mice while minimizing potential side effects,” *J. Neurosci.*, vol. 31, no. 25, pp. 9323–9331, 2011, doi: 10.1523/JNEUROSCI.0293-11.2011.

[54] A. Muhs *et al.*, “Liposomal vaccines with conformation-specific amyloid peptide antigens define immune response and efficacy in APP transgenic mice,” *Proc. Natl. Acad. Sci. U. S. A.*, vol. 104, no. 23, pp. 9810–9815, 2007, doi: 10.1073/pnas.0703137104.

[55] B. Liu *et al.*, “MER5101, a novel Aβ1-15:DT conjugate vaccine, generates a robust anti-Aβ antibody response and attenuates Aβ pathology and cognitive deficits in APPswe/PS1δE9 transgenic mice,” *J. Neurosci.*, vol. 33, no. 16, pp. 7027–7037, 2013, doi: 10.1523/JNEUROSCI.5924-12.2013.

[56] F. Panza, V. Solfrizzi, B. P. Imbimbo, R. Tortelli, A. Santamato, and G. Logroscino, “Amyloid-based immunotherapy for Alzheimer’s disease in the time of prevention trials: The way forward,” *Expert Rev. Clin. Immunol.*, vol. 10, no. 3, pp. 405–419, 2014, doi: 10.1586/1744666X.2014.883921.

[57] F. Panza, V. Solfrizzi, B. P. Imbimbo, and G. Logroscino, “Amyloid-directed monoclonal antibodies for the treatment of Alzheimer’s disease: The point of no return?,” *Expert Opin. Biol. Ther.*, vol. 14, no. 10, pp. 1465–1476, 2014, doi: 10.1517/14712598.2014.935332.

[58] S. Salloway *et al.*, “Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer’s Disease,” *N. Engl. J. Med.*, vol. 370, no. 4, pp. 322–333, 2014, doi: 10.1056/nejmoa1304839.

[59] R. S. Doody *et al.*, “Phase 3 Trials of Solanezumab for Mild-to-Moderate Alzheimer’s Disease,” *N. Engl. J. Med.*, vol. 370, no. 4, pp. 311–321, 2014, doi: 10.1056/nejmoa1312889.

[60] H. O. Tayeb, E. D. Murray, B. H. Price, and F. I. Tarazi, “Bapineuzumab

and solanezumab for Alzheimer's disease: Is the 'amyloid cascade hypothesis' still alive?," *Expert Opin. Biol. Ther.*, vol. 13, no. 7, pp. 1075–1084, 2013, doi: 10.1517/14712598.2013.789856.

[61] B. Bohrmann *et al.*, "Gantenerumab: A novel human anti-Aβ antibody demonstrates sustained cerebral amyloid-β binding and elicits cell-mediated removal of human amyloid-β," *J. Alzheimer's Dis.*, vol. 28, no. 1, pp. 49–69, 2012, doi: 10.3233/JAD-2011-110977.

[62] M. Tolar, S. Abushakra, and M. Sabbagh, "The path forward in Alzheimer's disease therapeutics: Reevaluating the amyloid cascade hypothesis," *Alzheimer's Dement.*, vol. 16, no. 11, pp. 1553–1560, 2020, doi: 10.1016/j.jalz.2019.09.075.

[63] J. Cummings, G. Lee, K. Zhong, J. Fonseca, and K. Taghva, "Alzheimer ' s disease drug development pipeline : 2021," no. April, pp. 1–24, 2021, doi: 10.1002/trc2.12179.