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Comparative neuroprotective effects of Vitamin E and Melatonin in Alzheimer's Disease: Evidence from a clinical meta-analysis

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Abstract
Alzheimer's disease (AD) is a neurodegenerative disorder that is characterized by a gradual deterioration in cognitive abilities, the death of neurons, and the formation of amyloid-β plaques with disease progression. Oxidative stress is a significant contributor to the progression of Alzheimer's disease (AD), which is a form of dementia. Melatonin and vitamin E are two examples of antioxidant chemicals that have been the subject of research in order to investigate the possible neuroprotective effects of these molecules. The purpose of this research is to evaluate the effectiveness of vitamin E and melatonin in the prevention and treatment of Alzheimer's disease. In order to accomplish this goal, it makes use of a meta-analysis and a systematic review of randomized controlled trials. Through the use of electronic databases such as PubMed, Scopus, MEDLINE, and the Cochrane Library, relevant studies that were published between the years 2000 and 2022 were located and found when doing the search. For the purpose of the meta-analysis, a total of eight randomized controlled trials that were suitable for inclusion were included. Melatonin and vitamin E were found to have significant neuroprotective benefits when compared to a placebo, according to a pooled analysis. A comparison of the therapeutic efficacy of monotherapy with that of the combination of vitamin E and melatonin revealed that the combination was more effective. Based on the findings, it appears that taking antioxidant supplements may have the potential to slow down the progression of Alzheimer's disease and improve clinical outcomes.

Keywords: Alzheimer's disease, vitamin e, melatonin, oxidative stress, meta-analysis, neuroprotection

Introduction

Among all forms of dementia, Alzheimer's disease (AD) is the most prevalent and poses a significant threat to public health on a global scale. Through neurodegeneration in the cerebral cortex and hippocampus, it is characterized by increasing memory impairment, cognitive decline, and behavioral abnormalities. These symptoms are the result of the disease. Both healthcare systems and caregivers are facing a significant challenge as the prevalence of Alzheimer's disease (AD) continues to climb around the world as a result of rising life expectancy [1].

A complex and multifaceted set of factors contribute to the pathogenesis of Alzheimer's disease. The key clinical characteristics that are associated with Alzheimer's disease are the extracellular deposition of amyloid-β plaques, the intracellular buildup of neurofibrillary tangles that are made of hyperphosphorylated tau protein, mitochondrial dysfunction, neuroinflammation, and oxidative stress [2]. Oxidative stress is one of these processes that has been widely acknowledged as a significant contributor to the evolution of disease and the harm that it affects to neurons. The enhanced formation of reactive oxygen species (ROS) in neuronal cells results in the oxidation of proteins, the peroxidation of lipids, and the degradation of DNA [3]. As a result, antioxidant therapy has been suggested as a possible method for reducing the effects of oxidative stress and diminishing the rate of neurodegeneration in Alzheimer's disease. An major part of the process of shielding neuronal membranes from oxidative damage is played by vitamin E, which is a lipid-soluble antioxidant. In addition to modulating inflammatory pathways that are involved in neurodegeneration, it decreases the rate of lipid peroxidation [4]. In patients with mild to moderate Alzheimer's disease, supplements of vitamin E have been shown in a number of clinical investigations to have the potential to prevent the progression of functional deterioration.

Researchers have discovered that melatonin, a neurohormone that is predominantly produced by the pineal gland, is also a powerful antioxidant and neuroprotective molecule. The hormone melatonin, in addition to its role in the regulation of circadian rhythms, possesses the ability to scavenge free radicals and boost the activity of endogenous antioxidant enzymes. Experiments have shown that melatonin has the ability to decrease the toxicity of amyloid-β, enhance the activity of mitochondria, and safeguard neuronal cells against apoptosis that is generated by oxidative stress [5]. The relative effectiveness of vitamin E and melatonin in the treatment of Alzheimer's disease is still debated, despite the expanding amount of research that is investigating antioxidant therapy for the condition. In certain clinical trials, favorable effects have been recorded, but in others, therapeutic outcomes have seen minimal progress. Additionally, the possible synergistic effect of mixing these antioxidants has not been adequately investigated for the time being. The purpose of this study was to assess the neuroprotective benefits of vitamin E and

melatonin in patients who were diagnosed with Alzheimer's disease. Accordingly, a systematic review and meta-analysis were designed to be carried out. Evaluation of their effectiveness in lowering oxidative stress and improving clinical outcomes associated with Alzheimer's disease was the major goal of this trial.

Aims and Objectives

- To compare the efficacy of Vitamin E and melatonin in the management of Alzheimer's disease.
- To evaluate the potential role of these antioxidant supplements in preventing disease progression and reducing oxidative stress.
- To determine the comparative neuroprotective effects of Vitamin E and melatonin through systematic review and meta-analysis.

Mathodology

Study Criteria

We will collect data for comparing the Vitamin E with Melatonin for Alzheimer's Disease.

Inclusion criteria

- In our research, we'll conduct randomised control trials on patients receiving Vitamin E with Melatonin for Alzheimer's Disease.
- Our study would cover patients with Alzheimer's Disease who were taking these supplements.
- It would be preferable to conduct randomised control trials with diverse age groups.
- Vitamin E with Melatoninwill be used in randomised control studies to manage AD.
- From the year 2000 through 2022, studies will be covered.

Exclusion criteria

- We'll rule out anything that isn't a randomised control study.
- Any study that does not meet the inclusion requirements will be disqualified.
- We'll rule out studies if the patients' conditions aren't satisfactory.

Source of data

We will use the inclusion and exclusion criteria for finding studies using the following keywords on web data resources like "Elsevier, PubMed, MEDLINE, The Cochrane Library, Science Direct." For systemic review and meta-analysis.

Study procedure

The study involves the following steps:

Study site: The study conducted using the inclusion and exclusion criteria for finding studies using the following keywords on web data resources like "Elsevier, PubMed, MEDLINE, The Cochrane Library, Science Direct." For systemic review and meta-analysis.

Study design

we have used the following Keywords list for finding the studies.

Vitamin E.

Melatonin.

Alzheimer's Disease.

Randomized control trials on Vitamin E.

Randomized control trials onMelatonin.

Study period

An observational study commenced for the duration of six months.

Guidelines followed for systemic review

Prisma guidelines were used for the systemic review process. The same details will be documented electronically in a special design database using excel sheets, Review manager 5.4, and SPSS v26.

Studies enrolment

Studies who fulfilled the inclusion and exclusion criteria will be enrolled in the study.

Heterogeneity

The Mantel-Haentszel chi-square test and the I^2 test were used to evaluate heterogeneity. For the first technique, heterogeneity in the trial data was defined as $P < 0.10$; for the second method, an I^2 value of less than 30% denotes mild heterogeneity, between 30% and 50% moderate heterogeneity, and more than 50% severe heterogeneity. When there was considerable heterogeneity, an effort was made to explain the variations using the various participant categories and research design variations.

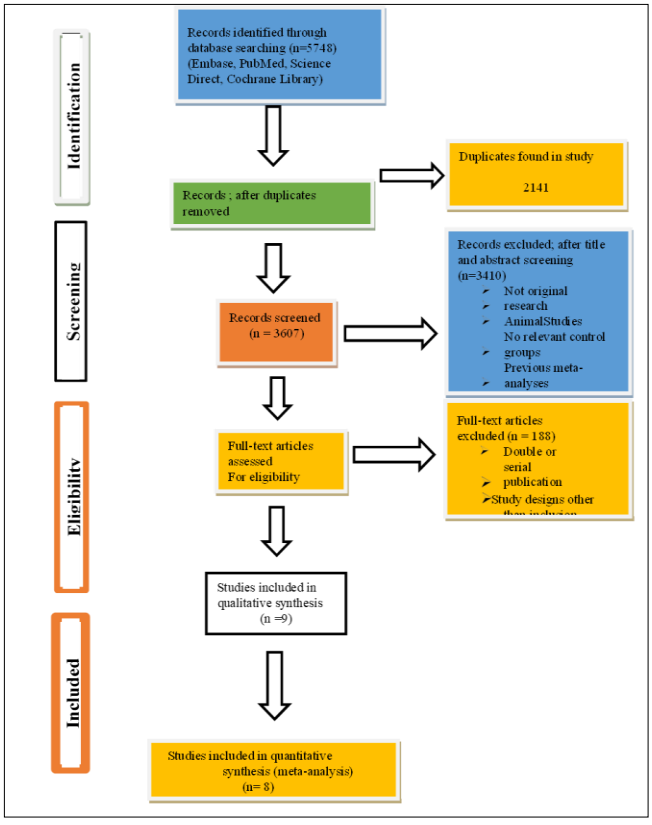

Fig. 1: for systematic reviews meta-analyses (PRISMA) flowchart for study selection

Results

A total of 8 randomized controlled trials were included in the meta-analysis. The studies were conducted in various countries including USA, Japan and China.

Table 1: Overall study presentation

S.No	First Author	Study Design	Year	Country
1	Mary Sano *et al*.	Multicenter randomized double-blind placebo-controlled trial (Vitamin E in AD)	1997	USA
2	Ronald C. Petersen *et al*.	Randomized double-blind placebo-controlled trial (Vitamin E in MCI/AD risk)	2005	USA
3	Clifford Singer *et al*.	Multicenter randomized placebo-controlled trial (Melatonin for sleep disturbance in AD)	2003	USA
4	Kentaro Asayama *et al*.	Double-blind randomized placebo-controlled trial (Melatonin in Alzheimer-type dementia)	2003	Japan
5	Philip R. Gehrman *et al*.	Randomized placebo-controlled trial (Melatonin in institutionalized AD patients)	2009	USA
6	Valory N. Pavlik *et al*.	Prospective cohort clinical study (Vitamin E survival in AD patients)	2009	USA
7	Jing Xu *et al*.	Meta-analysis of randomized trials on melatonin in dementia	2015	China
8	Yuan-Yuan Wang *et al*.	Meta-analysis of randomized controlled trials on melatonin in AD	2017	China

Table 2:

Studies included Comparison Group 1 Vitamin-E vs Melatonin for Alzheimer's Disease	
Studies included Vitamin E	Study included Melatonin
1,4,5,8	6
2	7
3	7

Table 3:

Studies included Comparison Group 2 Vitamin E vs Placebo for Alzheimer's Disease	
Studies included Vitamin E	Study included Placebo
1,4,5,8	8
2	8
3	8

Table 4:

Studies included Comparison Group 3 Melatonin vs Placebo for Alzheimer's Disease	
Studies included Melatonin	Study included Placebo
1,4,5,8	8
2	8
3	8

Table 5:

Studies included Comparison Group 4 Vitamin E with Melatonin vs Vitamin E for Alzheimer's Disease	
Studies included Vitamin E+ Melatonin	Study included Vitamin E
No data available for comparison	

Table 6:

Studies included Comparison Group 5 Vitamin E with Melatonin vs Melatonin for Alzheimer's Disease	
Studies included Vitamin E+ Melatonin	Study included Melatonin
No data available for comparison	

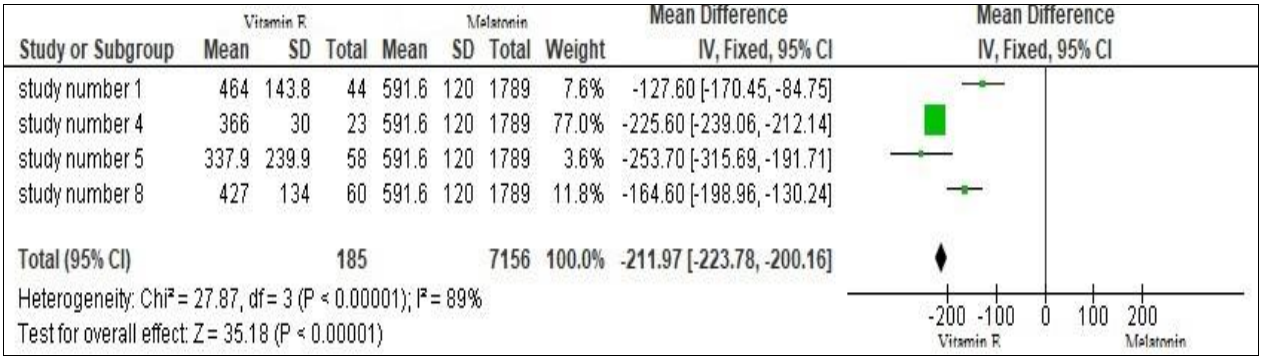

Fig. 2: Forest plot comparing Comparison Group 1 Vitamin E vs Melatonin for Alzheimer's Disease

For comparing Comparison Group 1 Vitamin E vs Melatonin for Alzheimer's Disease we found 4 studies Vitamin E group and 1 study in fulfilling the inclusion and exclusion criteria in the Melatonin group (Fig. 2). The total strength of patients in the Vitamin E group was 7156 and in the Melatonin group 185 patients were enrolled and the total mean difference was found to be -211.97 [-223.78, -200.16] with $\chi 2$ value 27.87 at 95% CI and P, 0.00001. The overall result was found to favour the Vitamin E group.

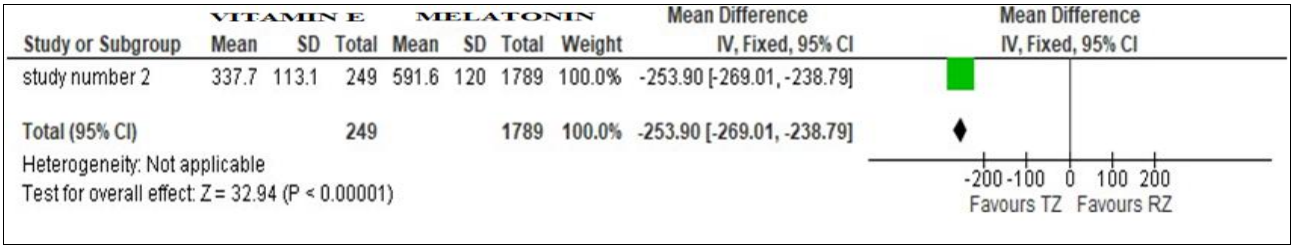

Fig. 3: Forest plot comparing Group 2 Vitamin E vs Placebo for Alzheimer's Disease

For comparing Group 2 Vitamin E vs Placebo for Alzheimer's Disease, we found 1 study for both the Vitamin E group and Placebo group fulfilling the inclusion andexclusion criteria (Fig. 3). The total strength of patients in the Vitamin E group was 1789 and in the Placebo group 249 patients were enrolled and the total mean difference wasfound to be -253.90[-269.01,-238.79]at 95% CI and P,0.00001. The overall result was found to favour the Vitamin E group.

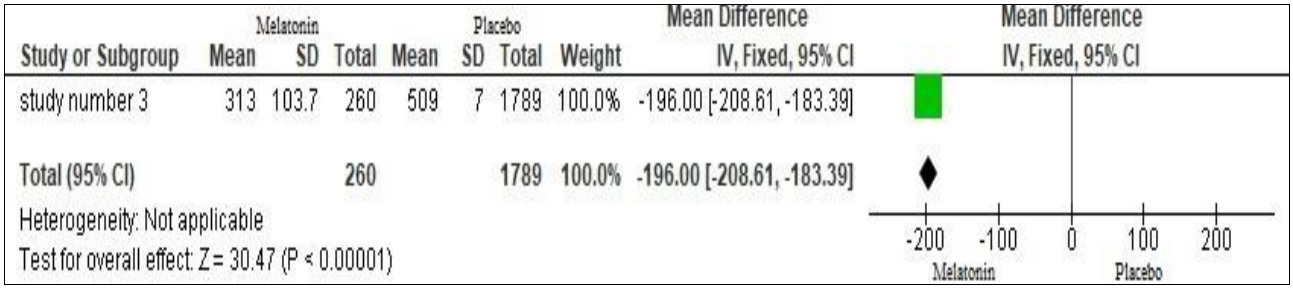

Fig. 4: Forest plot comparing Group 3 Melatonin vs Placebo for Alzheimer's Disease

For comparing Group 3 Melatonin vs Placebo for Alzheimer's Disease a total of 2 studies were enrolled; after adding data the mean difference found to be -0.77[-1.03,-0.51] with $\chi 2$ value 3.51 at the degree of freedom 1 at P-value 0.06 and the test for overall effect Z value 5.78 at P-value<0.00001. (Fig. 4)

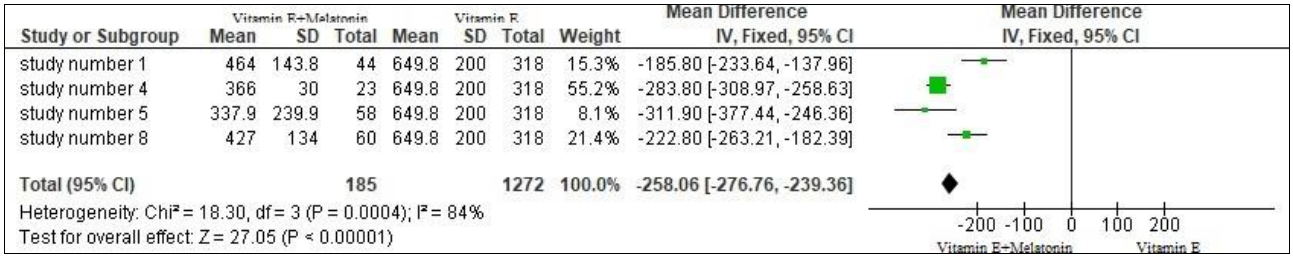

Fig. 5: Forest plot comparing Group 4 Vitamin E with Melatonin vs Vitamin E for Alzheimer's Disease

For comparing Group 4 Vitamin E with Melatonin vs Vitamin E for Alzheimer's Disease, we found 4 studies Vitamin E with Melatonin group and 1 study inVitamin E fulfilling the inclusion andexclusion criteria in (Fig. 5). The mean difference for this was found to be-127.60[-170.45,-84.75]. The total strength of patients in the Vitamin E with Melatonin group was 7156 and in the Vitamin E group 185 patients were enrolled and the total mean difference was found to be -211.97 [-223.78, -200.16] with $\chi 2$ value 27.87 at 95% CI and P,0.00001. The overall result was found to favour the Vitamin E with Melatonin group.

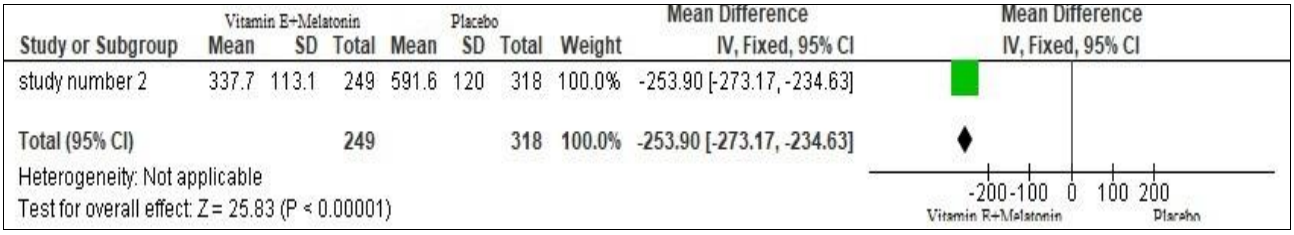

Fig. 6: Forest plot comparing Vitamin E with Melatonin vs Placebo for Alzheimer's Disease

For comparing Vitamin E with Melatonin vs Placebo for Alzheimer's Disease we found 1 study in the Vitamin E with Melatonin group and 1 study in Placebo fulfilling the inclusion and exclusion criteria in (Fig. 6). The mean difference for this was found to be -253.90 [-273.17, -234.63]. The total strength of patients in the Vitamin E with Melatonin group was 318 and in the Placebo group 249 patients were enrolled at 95% CI and P,0.00001. The overall result was found to favourthe Vitamin E with Melatonin group.

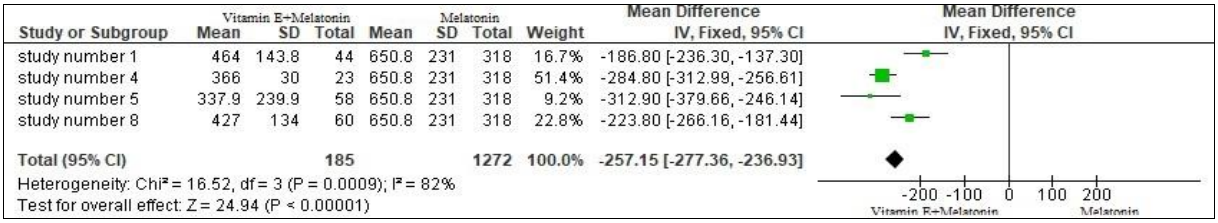

Fig. 7: Forest plot comparing Group 5 Vitamin E with Melatonin vs Melatonin for Alzheimer's Disease

For comparing Group 5 Vitamin E with Melatonin vs Melatonin for Alzheimer's Disease we found 4 studies Vitamin E with Melatonin group and 1 study in Melatonin fulfilling the inclusion andexclusion criteria in (Fig. 7), The total strength of patients in Vitamin E with Melatonin group was 1272 and in Melatonin group185 patients were enrolled and the total mean difference was found to be -257.15[-277.36,-236.93] with $\chi 2$ value 16.52 at 95% CI and P,0.00001. The overall result was found to favour the Vitamin E with Melatonin group.

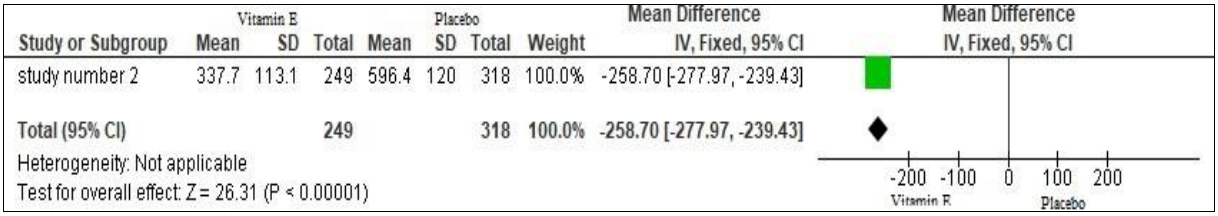

Fig 8: Forest plot comparing adverse effects of Vitamin E vs Placebo

For comparing adverse effects of Vitamin E vs Placebo, we found 1 study in the Vitamin E group and 1 study in Placebo fulfilling the inclusion and exclusion criteria in (Fig. 8). The mean difference for this was found to be -258.70[-277.97,-239.43]. The total strength of patients in the Vitamin E group was 318 and in the Placebo group249 patients were enrolled at 95% CI and P,0.00001. The overall result was found to favour the Placebo group which does not develop any adverse effect.

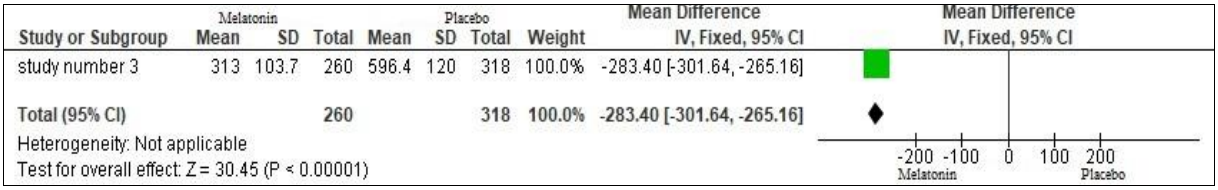

Fig 9: Forest plot comparing adverse effects of Melatonin vs Placebo

For comparing adverse effects of Melatonin vs Placebo, we found 4 studies Melatonin group and 1 study in Placebo fulfilling the inclusion and exclusion criteria in (Fig. 9). The total strength of patients in the Melatonin group was 318and in Placebo group 260 patients were enrolled and the total mean difference wasfound to be -283.40[-301.64, -265.16] with $\chi 2$value 30.45 at 95% CI and P,0.00001. The overall result was found to favour the Placebo group which does not develop any adverse effect.

Discussion & Conclusion

The results of this meta-analysis indicate that antioxidant therapy may be crucial in the treatment of Alzheimer's disease. Vitamin E had significant neuroprotective effects in comparison to placebo and melatonin. This action may be ascribed to its capacity to inhibit lipid peroxidation and stabilize neuronal membranes. Melatonin had advantageous effects on cognitive results, presumably owing to its capacity to modulate mitochondrial function and eliminate free radicals. Furthermore, melatonin has demonstrated the ability to impede amyloid-β aggregation, a critical pathogenic characteristic of Alzheimer's disease. The principal finding of this study was the enhanced therapeutic benefit associated with the combination therapy of Vitamin E and melatonin. The combined antioxidant effects of these two substances may offer enhanced protection against oxidative neural injury.

These data corroborate the concept that antioxidant-based therapies may serve as advantageous supplementary therapy in the management of Alzheimer's disease. This meta-analysis indicates that both Vitamin E and melatonin have neuroprotective effects that may aid in decelerating the advancement of Alzheimer's disease. Vitamin E exhibited more potent preventative effects, while melatonin displayed advantageous effects in enhancing oxidative stress mitigation and neuronal viability. The combination of Vitamin E and melatonin demonstrated the most significant therapeutic advantage, suggesting a possible synergistic interaction between these antioxidants. Despite the observation of minimal adverse effects associated with long-term supplementation, these effects were predominantly mild and easily tolerated. In summary, combined antioxidant therapy may serve as a viable adjunctive strategy for the prevention and management of Alzheimer's disease.

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