

Subject: Second Round of Revisions

Thank you for the modifications made to the manuscript. The revised version meets the conditions requested in the initial review. However, it is necessary to modify a paragraph in the Abstract to ensure consistency with the Introduction. Specifically, the paragraph in the Abstract (Lines 23-27) should be revised to align with the content in the Introduction (Lines 50-55; Cummings et al., 2016) and Line 66, where it is stated that “AD has a multifactorial etiopathogenesis that includes epigenetic factors, involvement of vascular and other systems (Kisler et al., 2017; Solis et al., 2020; Jara-Medina et al., 2024). The ‘two-hit hypothesis’ provides a framework for”

Abstract, Line 23-27.

“However, concerns are arising regarding the younger population, **where acute and chronic abuse of alcohol and neurotoxic substances is increasing, resulting in permanent nervous system damage and the onset of dementia.** Alzheimer’s disease (AD) accounts for 60% of dementia cases and most therapies used so far have been unsuccessful”

This phrasing suggests that alcohol and drug use in young individuals are the primary causes of dementia and AD, which is not entirely accurate. While substance abuse is a contributing factor, AD is a multifactorial disease influenced by several other elements, including vascular alterations, sedentary lifestyle, diet, and epigenetic changes, as discussed in the Introduction. The current sentence could be misinterpreted as prioritizing two factors over others, rather than acknowledging the complexity of AD's pathogenesis.

To ensure a more accurate and balanced presentation of risk factors, we kindly request a revision of this section in the Abstract to reflect the multifactorial nature of AD, as supported by the literature (*Breijyeh Z, Karaman R. Comprehensive Review on Alzheimer's Disease: Causes and Treatment. Molecules. 2020 Dec 8;25(24):5789. doi: 10.3390/molecules25245789. PMID: 33302541; PMCID: PMC7764106*)

Thank you for your time and consideration. Please let us know if further clarifications are needed.

Best regards,