Extended Abstract

Fisetin nanosuspension: Potential inhibitor of monoamine oxidase in Aβ(25-35) induced mice

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ABSTRACT

The key pathological hallmarks of Alzheimer's disease (AD) include extracellular β-amyloid (Aβ) plaques and intracellular neurofibrillary tangles. Fisetin, a neuroprotective antioxidant, is widely consumed through fruits and vegetables but has low bioavailability, poor solubility and high metabolism, limiting its therapeutic potential. This study aimed to develop a fisetin nanosuspension to improve its bioavailability and neuroprotective effects in Aβ(25-35) induced dementia mice. The nanosuspension was prepared by nanoprecipitation method and characterised. For *in vivo* study, mice were treated with 10 and 20 mg/kg of fisetin or 10 mg/kg fisetin nanosuspension daily for 21 days, followed by intracerebroventricular Aβ(25–35) injection (ICV) on day 15. Memory and learning tests were conducted on day 20, and biochemical analyses were performed on brain tissues. The nanosuspension had an average particle size of 225.4 ± 2.95 nm, polydispersity index (PDI) of 0.19 and zeta potential of -19.13 ± 1.17 mV. *In vivo* results showed significant memory and learning improvement ($P < 0.01$) and reduced monoamine oxidase-A (MAO-A) levels ($P < 0.01$), suggesting neuroprotection against Aβ peptide-induced amnesia. The fisetin nanosuspension effectively enhanced oral bioavailability and inhibited MAO-A activity, presenting a promising approach for future AD drug development.

Keywords: Alzheimer's disease, fisetin, nanosuspension, monoamine oxidase

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1.0 Introduction

The aggregation of Aβ protein and hyperphosphorylated tau protein are the neuropathological hallmarks of Alzheimer's disease (AD). These pathological changes escalate the production of monoamine oxidase (MAO) enzymes, among many others, with imbalanced neurotransmitters (dopamine, serotonin) in the brain. Fisetin (3, 7, 3',4'-tetrahydroxyflavone) is a plant flavanol commonly found in various fruits and vegetables, has demonstrated antioxidant and neuroprotective properties (1). However, its therapeutic potential is limited by characteristics such as low oral bioavailability, poor aqueous solubility, and extensive intestinal and hepatic metabolisms (2). To address these limitations, nano-formulation has been introduced as an alternative delivery method to enhance fisetin's solubility and stability

2.0 Innovation

Fisetin nanosuspension was formulated via the nanoprecipitation method. The organic phase consisted of a 1:2 ratio of fisetin to PDLG 5002A, dissolved in a 1:4 mixture of DMSO and acetone. The organic phase was then injected into 10 mL of aqueous phase containing a chosen stabilizer (PVA) during ultrasonication. After evaporation, the mixture was centrifuged to obtain the supernatant. The fisetin nanosuspension was assessed for its optimized properties, such as particle size, zeta potential and PDI. As a result, the optimized nanosuspension significantly reduced the level of MAO-A in an *in vivo* setting.

3.0 Uniqueness

PDLG [poly(d,l-lactic-co-glycolic acid)] 5002A, a specific type of PLGA [poly(lactic-co-glycolic acid)], was used in the preparation of fisetin nanosuspension. It is biodegradable, biocompatible and exhibits low toxicity level (3).

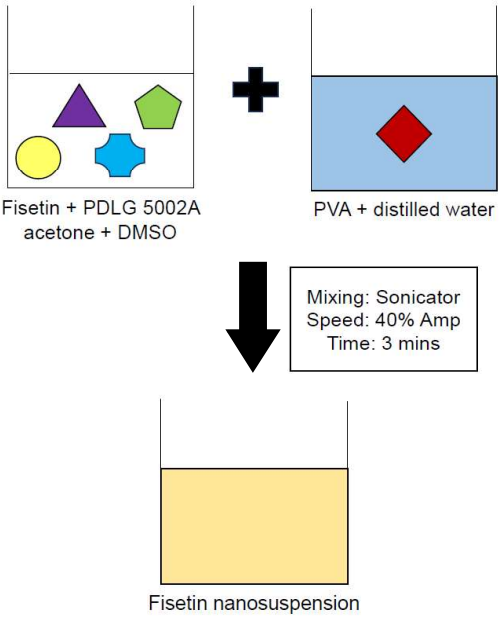

Figure 1: Preparation of fisetin nanosuspension using the nanoprecipitation method.

4.0 Commercialisation Potential

Compared to commercially available drugs, fisetin, as a natural bioactive compound, has the potential to minimize adverse effects. Furthermore, the prepared fisetin nanosuspension enhanced its solubility and stability. This is supported by evidence showing that the nanosuspension significantly reduced ($P < 0.01$) the concentration of monoamine oxidase-A (MAO-A) enzymes and increased ($P < 0.01$) memory and learning performances in Aβ peptide-induced mice.

5.0 Impact on Quintuple Helix

Fisetin is derived from natural products that align with environmental sustainability goals. Its use in medicine can encourage the development of eco-friendly drug formulation and production practices. Fisetin's integration into the Quintuple Helix model can enhance interdisciplinary

collaboration, promote health and sustainability, and drive innovation in various sectors.

6.0 Conclusion

Fisetin nanosuspension enhanced bioavailability with its optimized properties and exhibited effective neuroprotection through the inhibition of MAO enzymes.

Authorship contribution statement

SZIZ: Writing – original draft, Writing - review & editing, Conceptualization, Methodology, Formal analysis. **HSJC:** Writing – review & editing, Supervision, Data curation. **MHH:** Supervision. **SAJ:** Supervision. **AKJ:** Methodology, Supervision.

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Conflict of Interest

All authors declared that there is no conflict of interest.

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