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Flavonoids As Phosphodiesterase Inhibitors: A Systematic Review On Their Mechanisms, Structure-Activity Relationship And Therapeutic Potentials

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Structured Abstract

Background: Phosphodiesterase (PDE) are important regulatory enzymes to hydrolyse cyclic nucleotide cAMP and cGMP to moderate a variety of physiological processes. Synthetic PDE inhibitors are medically used. However, their application is limited due to poor isoform selectivity and side effects. Certain flavonoids can act as multi-subtype inhibitors which can be advantageous in disease with complex pathologies. This review systematically examines the structure-activity relationship (SAR) between flavonoids and PDEs. The purpose of this study is to systematically review current scientific evidence on the mechanisms, SAR and therapeutic potential of flavonoid as PDE inhibitors.

Methods: A literature search was conducted across several databases. To ensure only relevant studies were included, specific inclusion and exclusion criteria were established. The inclusion considered research articles published between 2015-2025. For exclusion, the review omitted review papers and irrelevant compounds. All the studies retrieved searches were compiled and managed. The extracted data were organized and presented in tables and figures. The Joanna Briggs Institutes (JBI) was applied to assess various aspects of the studies. This ensured that the final synthesis was based on the credible evidence.

Results: This study shows that a total of 1,025 records were obtained from relevant databases, 222 duplicate record were removed using automated filtering. Based on predefined inclusion and exclusion criteria, 550 records were excluded for irrelevance leaving 253 full-text article and 224 articles were excluded due to lack of direct evidence. Ultimately, 29 studies were included in the final qualitative synthesis.

Conclusion: In conclusion, the findings of this study indicated that there is evidence remains limited. Most studies rely heavily on *in vitro* and *in silico* models. Although several SAR trends were identified, these relationships are often inferred rather than systematically tested across comparable experimental conditions. The therapeutic relevance of flavonoids as PDE inhibitors is constrained by significant translational challenges. This reveals substantial methodological and translational gaps in the current literature.

Keywords: Flavonoids, phosphodiesterase, pde inhibition, structure-activity relationship

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