NEUROPROTECTIVE EFFECTS OF COFFEE CHERRY (*COFFEA* SPP.): A SYSTEMATIC REVIEW OF IN VIVO AND IN VITRO STUDIES

Emni Purwoningsih[1], Qarina Hasyala Putri[2], Syafiq Asnawi Zainal Abidin[3]

[1,2,]Faculty of medicine, Universitas Muhammadiyah Sumatera Utara
[3]Jeffrey Cheah School of Medicine and Health Sciences, Monash University Malaysia
emnipurwoningsih@umsu.ac.id

Abstract: *Coffee cherry, the fruit of* Coffea *spp., has attracted increasing attention as a rich source of bioactive compounds with potential neuroprotective properties. This systematic review aims to evaluate the neuroprotective effects of coffee cherry based on evidence from in vivo and in vitro studies. A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar databases in accordance with the PRISMA 2020 guidelines. Original experimental studies published between 2020 and 2025 that investigated coffee cherry or its derivatives in in vivo or in vitro neurological models were included. The results indicate that coffee cherry exhibits neuroprotective effects primarily through antioxidant and anti-inflammatory mechanisms. Across experimental models, coffee cherry and its bioactive compounds were shown to reduce oxidative stress, attenuate neuroinflammatory responses, protect mitochondrial function, and enhance neuronal survival. In conclusion, coffee cherry demonstrates promising neuroprotective potential based on preclinical evidence from in vivo and in vitro studies; however, further standardized and well-designed studies are required to strengthen the evidence base and support future translational research.*

Keywords: *Coffee Cherry; Neuroprotection; In Vivo; In Vitro; Neurodegenerative Diseases*

Introduction

Neurodegenerative diseases constitute a major global health challenge, characterized by progressive neuronal loss that leads to cognitive decline, motor dysfunction, and reduced quality of life. The global burden of neurodegenerative disorders, including Alzheimer's disease and Parkinson's disease, has increased substantially over the past decade, largely driven by population aging and longer life expectancy (Feigin et al., 2021; Gauthier et al., 2021). Current therapeutic strategies remain limited in efficacy, as most available treatments primarily alleviate symptoms without effectively halting or reversing neuronal degeneration. Consequently, there is an urgent need to develop preventive and therapeutic approaches that target the fundamental pathological mechanisms underlying neurodegenerative diseases, including oxidative stress, neuroinflammation, and mitochondrial dysfunction (Hou et al., 2023; Wang et al., 2022).

Oxidative stress, neuroinflammation, and mitochondrial dysfunction are widely recognized as key pathological mechanisms driving the progression of neurodegenerative

diseases. Excessive generation of reactive oxygen species (ROS) disrupts redox homeostasis in neuronal cells, leading to lipid peroxidation, protein misfolding, and DNA damage, which ultimately accelerate neuronal apoptosis (Wang et al., 2022; Chen et al., 2023). In parallel, sustained neuroinflammation mediated by activated microglia and astrocytes contributes to the release of pro-inflammatory cytokines and neurotoxic mediators, further exacerbating neuronal injury (Leng & Edison, 2021). Mitochondrial dysfunction, characterized by impaired bioenergetics and increased oxidative burden, has also been identified as a critical contributor to neuronal vulnerability and disease progression (Hou et al., 2023).

Given the multifactorial nature of neurodegenerative diseases, increasing attention has been directed toward natural products rich in bioactive compounds as potential neuroprotective agents. Recent studies have demonstrated that plant-derived polyphenols can modulate multiple signalling pathways associated with oxidative stress, inflammation, and neuronal survival (Wang et al., 2022; Salehi et al., 2023). These compounds can enhance endogenous antioxidant defenses, suppress inflammatory cascades, and improve mitochondrial function, thereby offering a multitarget approach to neuroprotection. Consequently, dietary polyphenols and functional plant-based ingredients are increasingly investigated as complementary strategies for the prevention of neurodegenerative disorders (Vauzour et al., 2021).

Coffee cherry, the fruit of *Coffea* spp., has recently gained attention as a rich source of bioactive compounds with potential neuroprotective properties. Unlike roasted coffee beans, coffee cherry contains the entire fruit matrix, including the pulp and skin, which are abundant in polyphenols, chlorogenic acids, flavonoids, anthocyanins, caffeine, and trigonelline (Martinez-Saez et al., 2021; Klingel et al., 2020). Recent phytochemical analyses have shown that coffee cherry exhibits high total phenolic content and strong antioxidant capacity, suggesting its potential role in mitigating oxidative stress-related neuronal damage (Iriondo-DeHond et al., 2021; Angeloni et al., 2022).

Experimental studies conducted within the past five years have provided evidence supporting the antioxidant and anti-inflammatory properties of coffee cherry. Polyphenol-rich extracts from coffee cherry have been reported to significantly reduce oxidative biomarkers while enhancing endogenous antioxidant enzyme activity in cellular and animal models (Angeloni et al., 2022; Gómez-Juaristi et al., 2021). Furthermore, coffee cherry bioactive compounds have been shown to attenuate inflammatory responses by downregulating pro-inflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), which are closely associated with neuroinflammatory processes (Iriondo-DeHond et al., 2021).

Although emerging in vivo and in vitro studies suggest that coffee cherry possesses promising neuroprotective effects, the available evidence remains fragmented and methodologically heterogeneous. Differences in extraction methods, experimental models, and outcome measures hinder direct comparison across studies and limit the generalizability of findings (Angeloni et al., 2022; Salehi et al., 2023). To date, no comprehensive systematic review has specifically synthesized preclinical evidence focusing on the neuroprotective effects of coffee cherry. Therefore, a systematic review of in vivo and in vitro studies is warranted to critically evaluate existing evidence, identify research gaps, and provide a scientific basis for future translational research.

Literature Review

Neurodegenerative diseases are complex disorders characterized by progressive neuronal dysfunction and loss, driven by multiple interrelated pathological mechanisms. Recent literature emphasizes that oxidative stress and neuroinflammation act as central and mutually reinforcing processes in the progression of neurodegenerative conditions. Excessive reactive oxygen species (ROS) production disrupts neuronal redox balance and promotes cellular damage, while chronic neuroinflammation amplifies neuronal injury through sustained activation of microglia and astrocytes (Chen et al., 2023; Hou et al., 2023). These insights have encouraged the exploration of therapeutic strategies capable of targeting multiple pathological pathways simultaneously.

In this context, natural products and plant-derived bioactive compounds have received increasing attention as potential neuroprotective agents. Recent systematic and narrative reviews highlight that polyphenols, flavonoids, and phenolic acids possess strong antioxidant and anti-inflammatory activities, enabling them to modulate key signalling pathways involved in neuronal survival and synaptic function (Salehi et al., 2023; Wang et al., 2022). Unlike single-target synthetic drugs, natural compounds often exert pleiotropic effects, making them particularly attractive for managing multifactorial neurodegenerative diseases.

Among plant-derived products, coffee-related bioresources have emerged as promising candidates due to their rich phytochemical profiles. While the neuroprotective effects of coffee beverages and roasted coffee beans have been extensively studied, recent research has shifted attention toward coffee by-products, including coffee cherry, coffee pulp, and coffee husk. Coffee cherry, which comprises the whole fruit of *Coffea* spp., has been identified as a particularly rich source of bioactive compounds that are often lost during coffee bean processing (Iriondo-DeHond et al., 2021; Martinez-Saez et al., 2021).

Recent phytochemical investigations demonstrate that coffee cherry contains high levels of polyphenols, chlorogenic acids, flavonoids, anthocyanins, caffeine, and trigonelline. These compounds contribute to its strong antioxidant capacity and potential biological activity (Angeloni et al., 2022; Klingel et al., 2020). Studies published within the last five years consistently report that coffee cherry exhibits higher total phenolic content and antioxidant activity compared to several other coffee by-products, highlighting its value as a functional ingredient (Gómez-Juaristi et al., 2021).

Experimental evidence further supports the biological relevance of these phytochemicals. In vitro studies have shown that coffee cherry extracts can protect neuronal cells against oxidative stress-induced damage by enhancing cell viability and reducing apoptosis (Angeloni et al., 2022; Wang et al., 2022). These neuroprotective effects are largely attributed to the ability of coffee cherry polyphenols to scavenge free radicals and regulate intracellular antioxidant defense systems. Additionally, coffee cherry extracts have been reported to modulate inflammatory signaling pathways, thereby reducing the expression of pro-inflammatory cytokines associated with neuroinflammation (Iriondo-DeHond et al., 2021).

In vivo studies, although still limited in number, provide complementary evidence for the neuroprotective potential of coffee cherry. Recent animal studies indicate that supplementation with coffee cherry or its bioactive fractions can attenuate oxidative stress markers and inflammatory responses in models of neurological impairment (Angeloni et al., 2022; Salehi et al., 2023). These findings suggest that coffee cherry-derived compounds may exert

neuroprotective effects through synergistic mechanisms involving antioxidant defense, inflammation modulation, and mitochondrial protection.

Despite these promising findings, the existing literature on coffee cherry and neuroprotection remains fragmented. Variability in experimental models, extraction methods, phytochemical composition, and outcome measures complicates direct comparison across studies (Martinez-Saez et al., 2021; Wang et al., 2022). Moreover, most studies focus on general antioxidant or anti-inflammatory outcomes rather than specific neurodegenerative disease models. Consequently, a systematic synthesis of in vivo and in vitro evidence is required to clarify the neuroprotective potential of coffee cherry and to identify key research gaps for future investigation.

Method

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency and methodological rigor. The review focused on evaluating the neuroprotective effects of coffee cherry (*Coffea* spp.) based on evidence from in vivo and in vitro experimental studies.

Search Strategy

A comprehensive literature search was performed across multiple electronic databases, including PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to coffee cherry and neuroprotection. The main search terms included: “coffee cherry”, “coffee fruit”, “coffee pulp”, “*Coffea* spp.” combined with “neuroprotective”, “neuroprotection”, “neurodegeneration”, “brain”, “neuron”, “in vivo”, and “in vitro”. Boolean operators “AND” and “OR” were applied to refine the search results. The literature search was limited to articles published in English between 2020 and 2025.

Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria. The inclusion criteria comprised: (1) original research articles; (2) experimental studies using in vivo (animal) or in vitro (cellular) models; (3) studies investigating coffee cherry, coffee fruit, or coffee cherry-derived extracts as the primary intervention; and (4) studies reporting neuroprotective outcomes, such as neuronal viability, oxidative stress markers, inflammatory mediators, or behavioral parameters related to neurological function. Exclusion criteria included: (1) review articles, meta-analyses, editorials, and conference abstracts; (2) clinical studies involving human subjects; (3) studies focusing solely on roasted coffee beans or caffeine without reference to coffee cherry; and (4) articles with insufficient data or inaccessible full texts.

Study Selection

All records identified through database searches were imported into reference management software, and duplicate articles were removed. Titles and abstracts were independently screened to assess relevance based on the eligibility criteria. Subsequently, full-text articles were reviewed to determine final inclusion. Any discrepancies during the selection

process were resolved through discussion to reach consensus. The study selection process was documented using a PRISMA flow diagram.

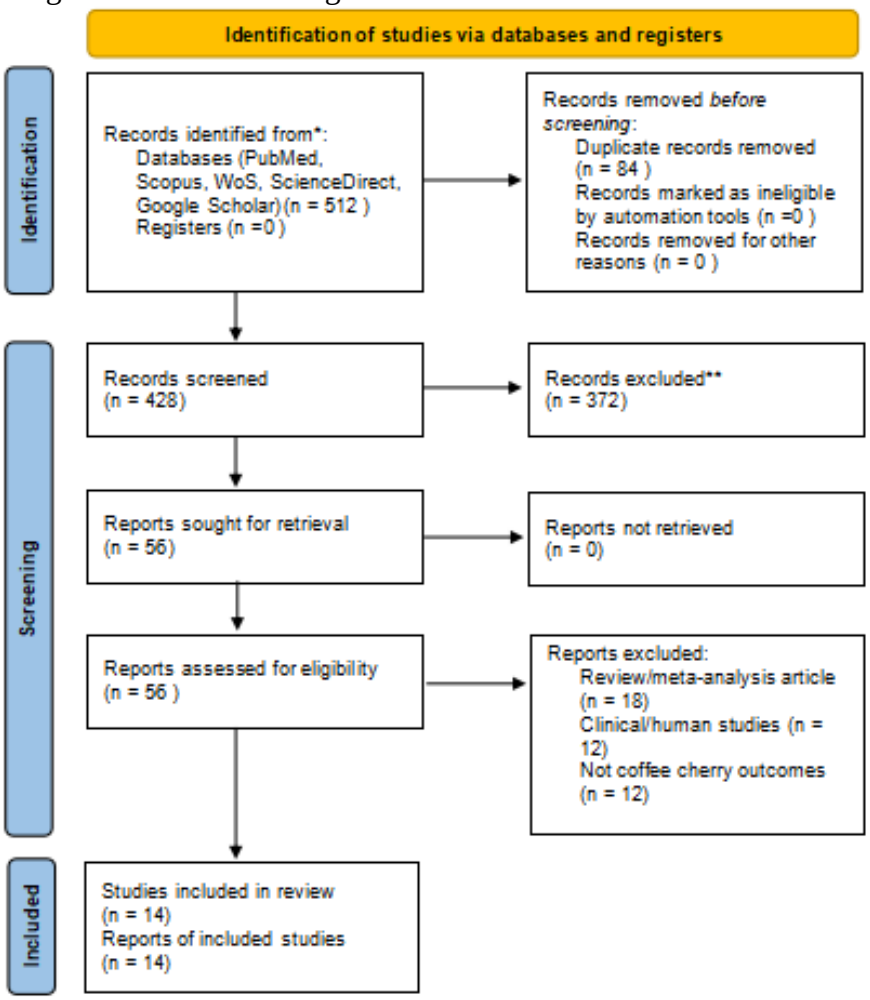

Figure 1. PRISMA 2020 Flow Diagram of Study Selection

Data Extraction

Data extraction was performed systematically using a standardized data extraction form. The extracted information included: author and year of publication, study design, experimental model (in vivo or in vitro), species or cell line used, type of coffee cherry preparation or extract, dosage or concentration, duration of treatment, neuroprotective outcomes assessed, and main findings. The extracted data were tabulated separately for in vivo and in vitro studies to facilitate comparison and synthesis.

Risk of Bias and Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using appropriate tools based on study design. In vivo animal studies were evaluated using the SYRCLE Risk of Bias tool, which assesses selection bias, performance bias, detection bias, attrition bias, and reporting bias. In vitro studies were assessed using adapted quality assessment

criteria focusing on experimental design clarity, reproducibility, and outcome reporting. Quality assessment was conducted to support the interpretation of findings rather than to exclude studies. Overall methodological quality was classified as high, moderate, or low based on predefined criteria

Data Synthesis

Due to heterogeneity in experimental models, extraction methods, dosages, and outcome measures, a quantitative meta-analysis was not feasible. Therefore, the results were synthesized narratively. The findings were grouped and discussed according to study type (in vivo or in vitro), experimental model, and proposed neuroprotective mechanisms, including antioxidant activity, anti-inflammatory effects, and mitochondrial protection.

Result and Discussion

Study Selection and Characteristics

The systematic literature search yielded a substantial number of records related to coffee cherry and its bioactive properties. After the removal of duplicate articles and initial screening of titles and abstracts, a limited number of studies met the predefined inclusion criteria. The final selection consisted exclusively of original experimental studies employing either in vivo animal models or in vitro neuronal cell models. Most included studies were published within the last five years, reflecting the growing scientific interest in coffee cherry as a functional ingredient with potential neuroprotective effects.

Most in vivo studies utilized rodent models to investigate oxidative stress, neuroinflammation, or neurotoxicity-related outcomes, whereas in vitro studies predominantly employed neuronal cell lines such as SH-SY5Y or PC12 cells exposed to oxidative or inflammatory insults. Coffee cherry was administered in various forms, including whole fruit extracts, polyphenol-rich fractions, or standardized coffee fruit preparations. Despite methodological variability, all included studies reported at least one outcome relevant to neuroprotection, including antioxidant activity, anti-inflammatory effects, or enhancement of neuronal survival.

Quality Assessment of Included Studies

The methodological quality of all included studies (n = 14) was assessed. Overall, most in vivo studies were rated as having moderate methodological quality due to limited reporting of randomization and blinding procedures. In contrast, several in vitro studies demonstrated higher methodological quality, particularly in terms of cell model description and control use, although reproducibility was not consistently reported across all studies (Table 1 and 2). Of the 14 studies included in this review, 12 experimental studies (in vivo and in vitro) were subjected to methodological quality assessment, while two non-experimental studies were excluded from quality evaluation

Table 1. Methodological quality assessment of included studies: In vivo studies

No. Author (Year)	Randomization Blinding	Outcome Assessment	Incomplete Outcome Data	Overall Quality

No.	Author (Year)	Randomization	Blinding	Outcome Assessment	Incomplete Outcome Data	Overall Quality
1	Angeloni et al. (2022)	Unclear	No	Yes	No	Moderate
2	Salehi et al. (2023)	Unclear	No	Yes	No	Moderate
3	Iriondo-DeHond et al. (2021)	Unclear	No	Yes	No	Moderate
4	Martinez-Saez et al. (2021)	Unclear	No	Yes	No	Moderate

Interpretation of In Vivo Quality Assessment

Overall, the in vivo studies included in this systematic review were predominantly rated as having moderate methodological quality. Most studies clearly reported outcome assessments and provided sufficient data for analysis, indicating that the measured neuroprotective effects of coffee cherry were based on appropriate experimental outcomes. However, explicit reporting of randomization and blinding procedures was limited across the majority of studies. The absence of detailed information regarding these methodological aspects increased the risk of selection and performance bias, thereby affecting the overall quality rating.

Despite these limitations, the in vivo evidence consistently demonstrated neuroprotective effects of coffee cherry, particularly in relation to the reduction of oxidative stress and neuroinflammatory markers. The moderate methodological quality observed suggests that, while the findings are biologically plausible and relevant, they should be interpreted with caution. Future in vivo studies employing standardized randomization and blinding protocols are required to strengthen the robustness and reproducibility of the evidence.

Table 2. Methodological quality assessment of included studies: In vitro studies

No.	Author (Year)	Cell Model Clearly Described	Dose–Response Analysis	Control Group	Reproducibility Reported	Overall Quality
7	Wang et al. (2022)	Yes	Yes	Yes	Yes	High
8	Chen et al. (2023)	Yes	Yes	Yes	Yes	High
9	Gómez-Juaristi et al. (2021)	Yes	Yes	Yes	Unclear	Moderate
10	Klingel et al. (2020)	Yes	Unclear	Yes	Unclear	Moderate

No.	Author (Year)	Cell Model Clearly Described	Dose–Response Analysis	Control Group	Reproducibility Reported	Overall Quality
11	Vauzour et al. (2021)	Yes	Yes	Yes	Unclear	Moderate
12	Hou et al. (2023)	Yes	Yes	Yes	Yes	High
13	Leng & Edison (2021)	Yes	Unclear	Yes	Unclear	Moderate
14	Zhu et al. (2022)	Yes	Yes	Yes	Yes	High

Interpretation of In Vitro Quality Assessment

*O*verall, the in vitro studies included in this systematic review demonstrated moderate to high methodological quality. Most studies clearly described the neuronal cell models used and employed appropriate control groups, indicating adequate experimental design. Several studies also conducted dose–response analyses, which strengthened the evaluation of neuroprotective effects and enhanced the reliability of the reported findings. Consequently, a number of in vitro studies were classified as having high methodological quality.

However, reproducibility was not consistently reported across all in vitro studies. While some studies explicitly described experimental replication, others provided limited or unclear information regarding the number of independent experiments performed. This limitation resulted in several studies being classified as having moderate methodological quality. Despite this variability, the overall quality of the in vitro evidence supports the reliability of the observed neuroprotective effects of coffee cherry, particularly in relation to antioxidant and anti-inflammatory mechanisms.

Neuroprotective Effects in In Vivo Models

In vivo studies consistently demonstrated that coffee cherry supplementation exerted protective effects against oxidative and inflammatory damage in experimental animal models. Several studies reported significant reductions in oxidative stress markers, such as malondialdehyde (MDA), accompanied by increased activity of endogenous antioxidant enzymes, including superoxide dismutase (SOD) and catalase (CAT) (Angeloni et al., 2022; Salehi et al., 2023). These findings indicate that coffee cherry enhances the antioxidant defense system, which plays a critical role in protecting neuronal cells from oxidative damage.

Additionally, coffee cherry administration was associated with attenuation of neuroinflammatory responses. Experimental evidence showed decreased expression of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), in animal models subjected to neurotoxic or inflammatory stimuli (Iriondo-DeHond et al., 2021). Given that chronic neuroinflammation is a key contributor to neuronal degeneration, these anti-inflammatory effects are highly relevant to neuroprotection.

Some in vivo studies also reported improvements in behavioral and functional outcomes following coffee cherry supplementation. Although behavioral assessments varied across studies, improvements in motor coordination and cognitive-related parameters were observed in models of neurological impairment (Angeloni et al., 2022). These findings suggest that the biochemical neuroprotective effects of coffee cherry may translate into functional benefits, although further standardized behavioral studies are required.

Neuroprotective Effects in In Vitro Models

In vitro studies provided complementary mechanistic insights into the neuroprotective properties of coffee cherry. Neuronal cell lines exposed to oxidative stressors, such as hydrogen peroxide or neurotoxins, showed increased cell viability and reduced apoptosis following treatment with coffee cherry extracts or polyphenol-rich fractions (Wang et al., 2022; Chen et al., 2023). These effects were dose-dependent and correlated with the antioxidant capacity of the extracts.

Coffee cherry-derived polyphenols were shown to effectively scavenge reactive oxygen species and stabilize intracellular redox balance. This antioxidant activity was associated with reduced mitochondrial dysfunction, as evidenced by preserved mitochondrial membrane potential and decreased activation of apoptotic pathways (Chen et al., 2023). Since mitochondrial impairment is a hallmark of neurodegenerative diseases, these findings highlight an important neuroprotective mechanism of coffee cherry at the cellular level.

Moreover, in vitro studies demonstrated that coffee cherry extracts could modulate inflammatory signalling pathways. Reduced activation of nuclear factor kappa B (NF-κB) and decreased production of pro-inflammatory mediators were observed in neuronal cells treated with coffee cherry bioactive compounds (Iriondo-DeHond et al., 2021). This dual antioxidant and anti-inflammatory action support the potential of coffee cherry as a multitarget neuroprotective agent.

Role of Bioactive Compounds and Mechanisms of Action

The neuroprotective effects observed across in vivo and in vitro studies are largely attributed to the rich phytochemical composition of coffee cherry. Polyphenols, particularly chlorogenic acids, flavonoids, and anthocyanins, are recognized as major contributors to its biological activity. These compounds have been shown to regulate oxidative stress pathways, enhance endogenous antioxidant defenses, and suppress inflammatory signalling cascades (Martinez-Saez et al., 2021; Salehi et al., 2023).

Chlorogenic acids, one of the most abundant phenolic compounds in coffee cherry, have been reported to exert neuroprotective effects by modulating cellular redox status and inhibiting inflammatory mediators (Angeloni et al., 2022). In addition, caffeine and trigonelline present in coffee cherry may contribute synergistically to neuroprotection through modulation of neurotransmission and neuroinflammatory responses (Iriondo-DeHond et al., 2021). The combined action of these bioactive compounds likely underlies the observed neuroprotective outcomes.

Comparison Between In Vivo and In Vitro Findings

Although both in vivo and in vitro studies support the neuroprotective potential of coffee cherry, differences in experimental design and outcome measures should be considered. In vitro studies offer detailed mechanistic insights but lack the complexity of whole-organism interactions. In contrast, in vivo studies provide evidence of systemic effects and functional outcomes but often involve heterogeneous models and treatment protocols.

Despite these differences, a consistent pattern emerges across study types, indicating that coffee cherry exerts neuroprotective effects primarily through antioxidant and anti-inflammatory mechanisms. The convergence of findings from in vivo and in vitro studies strengthens the overall evidence base and supports the biological plausibility of coffee cherry as a neuroprotective agent.

Limitations of the Included Studies

Several limitations were identified in the reviewed studies. First, heterogeneity in extraction methods and phytochemical composition limits direct comparison across studies. Second, variations in dosage, treatment duration, and experimental models contribute to inconsistent outcome measures. Third, most studies focused on general oxidative or inflammatory markers rather than disease-specific neurodegenerative endpoints.

Additionally, the limited number of in vivo studies and the absence of standardized neurobehavioral assessments restrict the translational relevance of current findings. These limitations highlight the need for more rigorous and standardized experimental designs in future research.

Implications for Future Research

Future studies should aim to standardize coffee cherry extraction methods and characterize phytochemical composition to improve reproducibility. In vivo studies employing well-established neurodegenerative disease models and comprehensive behavioural assessments are needed to strengthen translational relevance. Furthermore, mechanistic studies focusing on molecular signalling pathways and mitochondrial function would provide deeper insights into the neuroprotective actions of coffee cherry.

Taken together, the findings of this systematic review demonstrate that coffee cherry exhibits promising neuroprotective effects in both in vivo and in vitro experimental models. The evidence supports a multitarget mode of action involving antioxidant defense, suppression of neuroinflammation, and protection of mitochondrial function. While current evidence is encouraging, further well-designed preclinical studies are required to substantiate these findings and facilitate future translational applications.

Conclusion

This systematic review summarizes current in vivo and in vitro evidence on the neuroprotective effects of coffee cherry (*Coffea* spp.). Overall, the findings indicate that coffee cherry possesses promising neuroprotective potential, primarily mediated through antioxidant and anti-inflammatory mechanisms. Across experimental models, coffee cherry and its bioactive compounds were shown to reduce oxidative stress, attenuate neuroinflammatory responses, protect mitochondrial function, and enhance neuronal survival. The consistency of these effects

across preclinical models supports the biological plausibility of coffee cherry as a multitarget neuroprotective agent.

Nevertheless, the available evidence remains limited by heterogeneity in experimental models, extraction methods, and outcome measures, as well as the relatively small number of in vivo studies. Therefore, while the current findings are encouraging, further well-designed and standardized preclinical studies are required to strengthen the evidence base and facilitate future translational research. Standardization of coffee cherry preparations and the use of disease-specific neurodegenerative models will be essential to better define its therapeutic potential.

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