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Review Article

Neuroprotective Effects of *Salvia rosmarinus* in Cognitive Stress

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ABSTRACT

Cognitive impairment under conditions of sustained physiological stress, such as chronic workload or extreme environments like spaceflight, presents a critical challenge to human performance and operational safety. This review aimed to synthesize the multimodal neuroprotective profile of *Salvia rosmarinus* (*R. officinalis*) and its main bioactive compounds (carnosic acid, rosmarinic acid, and 1,8-cineole) against oxidative, inflammatory, and cholinergic dysregulation. A comprehensive narrative review of mechanistic, preclinical, and human clinical trials was conducted to map the evidence. The synthesis demonstrated that the herb's constituents exert a convergent protective synergy: carnosic acid activates the NRF2 pathway and suppresses NF-κB (anti-inflammatory/antioxidant); rosmarinic acid directly scavenges ROS and protects mitochondrial potential; and 1,8-cineole acts as a competitive AChE inhibitor (cholinergic support). Critically, human studies confirmed that improvements in attention, processing speed, and working memory correlated directly with the plasma concentration of 1,8-cineole, validating its central bioavailability and functional relevance. This review concludes that *S. rosmarinus* offers a highly relevant, multifaceted phytotherapeutic strategy for enhancing cognitive resilience and neural integrity against the complex stressors encountered in demanding operational settings. Future research should focus on dose–response characterization in space-analogue stress models.

Keywords: 1,8-cineole, Carnosic acid, Cognitive function, Neuroprotection, Rosmarinic acid, *Salvia Rosmarinus*.

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INTRODUCTION

Salvia rosmarinus (syn. *Rosmarinus officinalis*) is a Mediterranean aromatic shrub traditionally used for cognitive and neurological purposes. Although historical references associate rosemary with memory enhancement, contemporary research has identified specific phytochemical constituents with neuroactive properties. Among these, 1,8-cineole, rosmarinic acid, and carnosic acid are the principal compounds demonstrating Central Nervous System (CNS) bioavailability and relevance to cognitive regulation (Abuhamdah *et al*., 2015; Al-Otaibi *et al*., 2016; Begum *et al*., 2013).

Oxidative stress and neuroinflammation are key convergent mechanisms in cognitive impairment. Excessive production of Reactive Oxygen Species (ROS) leads to mitochondrial dysfunction, synaptic instability, and impairment of long-term potentiation, a foundational process for learning and memory (Duke, 2002). Concurrently, chronic activation of microglia contributes to the release of pro-inflammatory cytokines (e.g., IL-1β, TNF-α), amplifying neuronal damage and reducing neuronal plasticity (El Omri *et al*., 2019). These processes are also accompanied by dysregulation of the cholinergic system, particularly through increased Acetylcholinesterase (AchE) activity, which decreases acetylcholine availability and compromises attention, working memory, and executive control (González-Trujano *et al*., 2007).

Experimental evidence demonstrates that rosmarinic acid exhibits potent antioxidant activity, reducing lipid peroxidation and preserving mitochondrial membrane potential (Habtemariam, 2016). Carnosic acid, a lipophilic diterpenoid, confers neuroprotective and anti-inflammatory effects by modulating NRF2 and suppressing NF-κB signaling, thereby reducing microglial activation (Leahy *et al*., 2019). Meanwhile, 1,8-cineole crosses the blood-brain barrier and directly inhibits AchE and butyrylcholinesterase inhibition, supporting cholinergic neurotransmission (Abuhamdah *et al*., 2015). These mechanisms collectively position *Salvia rosmarinus* as a multimodal herbal agent capable of influencing oxidative balance, inflammatory tone, and synaptic efficiency.

Human studies further support these mechanistic findings. Controlled clinical and behavioral trials show that rosemary essential oil and standardized extracts are associated with

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improvements in attention, processing speed, and working memory, with effects correlating to circulating levels of 1,8-cineole (Moss *et al*., 2003; Moss & Oliver, 2012). Although the magnitude of effect varies across study designs, the mechanistic plausibility, dose-dependence, and reproducibility support translational relevance.

Environmental and occupational contexts characterized by prolonged cognitive effort, sleep restriction, or physiological stress-such as shift work, neuropsychological burnout, and microgravity exposure during spaceflight-may intensify oxidative and cholinergic imbalance (Strangman *et al*., 2014; Hupfeld *et al*., 2020). In these settings, lightweight, low-risk neuroprotective adjuncts are of practical interest. While rosemary has not yet been evaluated in operational aerospace environments, its established multimodal mechanisms align precisely with targets relevant to cognitive resilience under sustained physiological stress.

Therefore, this review examines the neuroprotective and cognitive effects of *Salvia rosmarinus*, focusing on its roles in oxidative stress modulation, neuroinflammatory control, and cholinergic regulation. The primary objective is to synthesize mechanistic, preclinical, and clinical evidence to rigorously assess the plant's potential utility as a phytotherapeutic strategy for maintaining cognitive performance and resilience in conditions of extreme physiological or psychological strain.

METHODOLOGY

This study follows an integrative review framework, aiming to synthesize mechanistic, preclinical, and clinical evidence regarding the neurocognitive effects of *Salvia rosmarinus*. Searches were conducted in PubMed, Scopus, Web of Science, and Embase between January 2005 and January 2025.

The search terms used in combination with Boolean operators were

1. "*Salvia rosmarinus*" OR "*Rosmarinus officinalis*".

2. "1,8-cineole" OR "rosmarinic acid" OR "carnosic acid".

3. "Oxidative stress" OR "microglia" OR "neuroinflammation".

4. "Acetylcholinesterase" OR "cholinergic".

5. "Cognitive performance" OR "working memory".

Inclusion criteria

1. Articles in English or Portuguese.

2. Experimental *in vitro* or *in vivo* studies.

3. Human clinical or behavioral trials.

4. And mechanistic or pharmacological analyses relevant to cognitive outcomes.

Exclusion criteria

1. Non-peer-reviewed sources.

2. Studies without neurocognitive parameters.

3. Or formulations containing mixed herbal compounds without rosemary isolation.

Data extraction was performed independently by two reviewers, and disagreements were resolved by consensus. Findings were categorized by mechanistic domain

1. Oxidative stress and mitochondrial function.

2. Neuroinflammation and microglial activity.

3. Cholinergic neurotransmission.

4. Behavioral and cognitive outcomes.

This structure guided the organization of the Results and Discussion section, as illustrated in the schematic overview (Figure 1).

Ethical Statement

Ethical approval was not required for this comprehensive narrative review, as it is based exclusively on the synthesis of published, peer-reviewed literature. The analysis does not involve new studies utilizing human participants or animal subjects.

Statistical Analysis

Statistical analysis was not performed, as this study utilized an integrative review framework focused on qualitative synthesis and mechanistic mapping of preclinical and clinical evidence.

RESULTS

Oxidative Stress and Mitochondrial Protection

Oxidative stress is a central mechanism in cognitive impairment, arising from an imbalance between Reactive Oxygen Species (ROS) production and antioxidant defense systems. Excessive ROS accumulation leads to lipid peroxidation, protein oxidation, mitochondrial membrane depolarization, and disruption of neuronal energy metabolism, ultimately impairing synaptic plasticity and long-term potentiation (Duke, 2002). In hippocampal and cortical circuits, these processes correlate with deficits in attention, working memory, and executive function.

Rosmarinic acid is a predominant phenolic compound in *Salvia rosmarinus* and exhibits high radical-scavenging capacity through direct hydrogen-donation and metal-chelation activity (Habtemariam, 2016). Experimental models demonstrate its ability to reduce Malondialdehyde (MDA) levels, restore mitochondrial membrane potential, and prevent cytochrome c leakage into the cytosol, indicating preservation of mitochondrial integrity (Leahy *et al*., 2019). These effects are accompanied by upregulation of endogenous antioxidant pathways, including

increased activity of Superoxide Dismutase (SOD) and Glutathione Peroxidase (GPx) (Habtemariam, 2016).

In parallel, carnosic acid, a lipophilic diterpenoid, exerts a complementary protective mechanism by activating the Nuclear factor erythroid 2-related factor 2 (NRF2) pathway (Leahy *et al*., 2019). NRF2 translocation to the nucleus promotes the transcription of Antioxidant Response Elements (AREs), enhancing cellular resistance to oxidative injury. Carnosic acid has also been shown to suppress NF-κB activation, thereby reducing ROS-associated inflammatory amplification loops (Hupfeld *et al*., 2020). This dual action by rosmarinic and carnosic acids helps maintain redox homeostasis, stabilize synaptic membranes, and reduces neuronal vulnerability to oxidative insult under sustained cognitive demand.

Preclinical studies in neuronal and glial cell lines consistently support these effects, demonstrating reduced ROS generation and improved cell viability after exposure to standardized rosemary extracts or isolated carnosic/rosmarinic acid (Habtemariam, 2016; Villareal *et al*., 2012; González-Trujano *et al*., 2007). These mechanistic findings provide a strong pharmacological basis for the neuroprotective claims associated with *Salvia rosmarinus* and justify its investigation in contexts characterized by systemic oxidative overload and mitochondrial vulnerability.

Microglial Modulation and Neuroinflammation

Microglial activation represents a key mediator of neuroinflammatory processes associated with cognitive dysfunction. Under physiological conditions, microglia maintain synaptic pruning, extracellular matrix stability, and surveillance of neuronal microenvironments. However, chronic exposure to stressors-such as oxidative imbalance, mitochondrial dysfunction, or glucocorticoid elevation-induces a phenotypic shift toward a pro-inflammatory state, characterized by upregulated expression of IL-1β, IL-6, and TNF-α, increased Nitric Oxide (NO) synthesis, and release of cytotoxic mediators (Mahmoudian *et al*., 2024; Kosmopoulou *et al*., 2024). This inflammatory cascade contributes to synaptic degradation, reduced long-term potentiation, and impaired neuroplasticity, particularly in hippocampal circuits involved in memory and learning (Howes *et al*., 2003).

Phenolic constituents of *Salvia rosmarinus*, particularly rosmarinic acid, demonstrate potent direct microglial inhibitory activity, reducing cytokine release and attenuating NF-κB pathway activation (El Omri *et al*., 2019). *In vitro* models of Lipopolysaccharide (LPS)-stimulated microglia show significant reductions in IL-1β and TNF-α production following exposure to standardized rosemary extracts (Leahy *et al*., 2019). In parallel, carnosic acid exhibits a dual regulatory action by activating NRF2 and suppressing MAPK signaling, thereby decreasing oxidative-inflammatory coupling at the mitochondrial interface (Leahy *et al*., 2019).

These anti-inflammatory effects are functionally relevant for synaptic preservation. Studies in rodent models demonstrate that administration of rosmarinic or carnosic acid prevents hippocampal dendritic spine loss, maintains glutamatergic receptor density, and supports long-term potentiation maintenance under inflammatory challenge (Leahy *et al*., 2019; El Omri *et al*., 2019). The ability of *S. rosmarinus* to modulate microglial phenotypes and suppress key inflammatory signaling pathways (NF-κB and MAPK) is critical for preserving neuronal function in states of chronic neurochemical stress.

Cholinergic Neurotransmission and Acetylcholinesterase Inhibition

Cognitive processes such as attention, working memory, and executive control depend on adequate cholinergic neurotransmission, particularly in hippocampal and prefrontal circuits. Acetylcholine (ACh) levels in the synaptic cleft are tightly regulated by Acetylcholinesterase (AChE) and Butyrylcholinesterase (BChE), which hydrolyze ACh and terminate cholinergic signaling (González-Trujano *et al*., 2007). Increased cholinesterase activity is associated with cognitive decline in aging, neurodegenerative conditions, metabolic stress, and sustained cognitive load states (Johns Hopkins APL, 2022).

Bioactive constituents of *Salvia rosmarinus*, especially 1,8-cineole, exhibit competitive and reversible inhibition of AChE and BChE, resulting in an increased synaptic availability of Ach (Perry *et al*., 2000). *In vitro* enzymatic assays demonstrate dose-dependent cholinesterase inhibition comparable to low-potency pharmacological inhibitors, while preserving a favorable safety margin (Kosmopoulou *et al*., 2024). These findings are supported by molecular docking studies, showing binding interactions between 1,8-cineole and the peripheral anionic site of AChE, which modulates substrate access to the catalytic gorge (Perry *et al*., 2000).

In vivo investigations further reinforce the translational relevance of these mechanisms. Rodent models treated with rosemary essential oil or standardized extracts show improved performance in Morris water maze, novel object recognition, and radial arm maze tasks, correlating with reduced AChE expression in hippocampal tissue (Tildesley *et al*., 2003). Human trials report improvements in processing speed, working memory, and task accuracy, with effect magnitude proportional to measured plasma concentrations of 1,8-cineole, confirming central nervous system penetration and functional bioavailability (Moss *et al*., 2003; Moss & Oliver, 2012).

The cholinergic enhancement observed in these studies is mechanistically complementary to the antioxidant and anti-inflammatory actions described in Sections 3.1 and 3.2. By simultaneously supporting synaptic signaling, mitochondrial stability, and cytokine regulation, *Salvia rosmarinus* demonstrates a multimodal neuroprotective profile that aligns

with contemporary strategies in cognitive resilience and neuroprotection.

The main bioactive compounds and their mechanisms are summarized in Table 1.

Cognitive and Behavioral Performance Evidence

Evidence from human behavioral and neuropsychological studies supports the mechanistic findings described in Sections 3.1-3.3. Controlled trials involving healthy adults demonstrate that exposure to rosemary essential oil and standardized extracts is associated with improvements in working memory, processing speed, and sustained attention, with measurable correlations to circulating levels of 1,8-cineole. These outcomes align with the hypothesis that cholinergic enhancement and redox stabilization contribute directly to cognitive performance efficiency (Moss *et al*., 2003; Moss & Oliver, 2012).

In a randomized, placebo-controlled study, participants exposed to rosemary aroma exhibited higher accuracy and faster response times in computerized attention tasks, with cognitive performance positively correlated with plasma 1,8-cineole concentration. These data indicate that central nervous system penetration of monoterpenes is not only pharmacokinetically demonstrable but also functionally relevant (Moss & Oliver, 2012). Comparable findings were reported in tasks assessing memory recall and cognitive vigilance, further reinforcing the cholinergic facilitation model (Perry *et al*., 2000).

Dietary intake of rosemary extracts has also demonstrated cognitive effects. Supplementation with standardized polyphenolic fractions resulted in improvements in working memory span and recall precision, consistent with enhanced synaptic efficiency in hippocampal networks (Leahy *et al*., 2019). Notably, these behavioral outcomes occurred alongside reductions in self-reported mental fatigue, suggesting a positive interaction between neurochemical modulation and subjective cognitive effort. These effects are consistent with the adaptogenic and stress-regulatory properties described for rosemary constituents in preclinical models (Section 3.2).

DISCUSSION

Collectively, these findings support the interpretation that *Salvia rosmarinus* exerts multimodal cognitive benefits through the integration of:

1. Cholinergic support (AChE/BChE inhibition → ↑ acetylcholine).

2. Mitochondrial and synaptic protection under oxidative load.

3. Microglial and inflammatory tone regulation, preserving network stability.

This mechanistic convergence is highly consistent with contemporary frameworks of cognitive resilience under sustained cognitive demand, reinforcing the translational potential of *Salvia rosmarinus* as a compelling neuroprotective phytotherapeutic agent for extreme environments, converging toward cognitive resilience as shown in the integrative diagram (Figure 2).

Future Directions and Research Gaps

Despite the consistent mechanistic and clinical evidence supporting the neuroprotective potential of *Salvia rosmarinus*, several critical research gaps remain. Future studies should prioritize the standardization of extract compositions, particularly regarding the relative concentrations of 1,8-cineole, rosmarinic acid, and carnosic acid, to improve reproducibility

across trials. Dose-response studies are needed to establish minimal effective doses, safety thresholds, and optimal delivery routes for cognitive outcomes.

Additionally, given the increasing interest in cognitive resilience in extreme environments, controlled studies in space-analog conditions-such as bed rest, hypoxia, isolation, and circadian

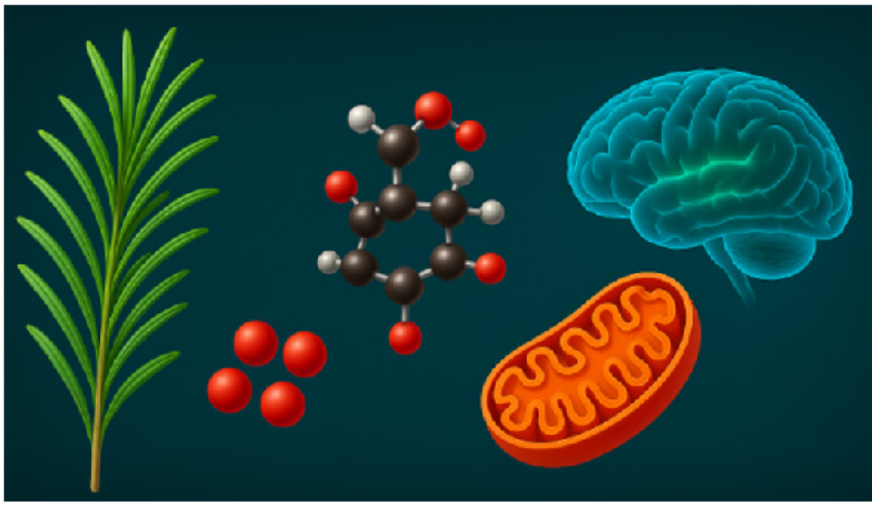

Figure 1: Schematic representation of rosemary-derived carnosic acid modulating mitochondrial Reactive Oxygen Species (ROS) and supporting neuroprotection in neural tissues relevant to microgravity-induced cognitive stress.

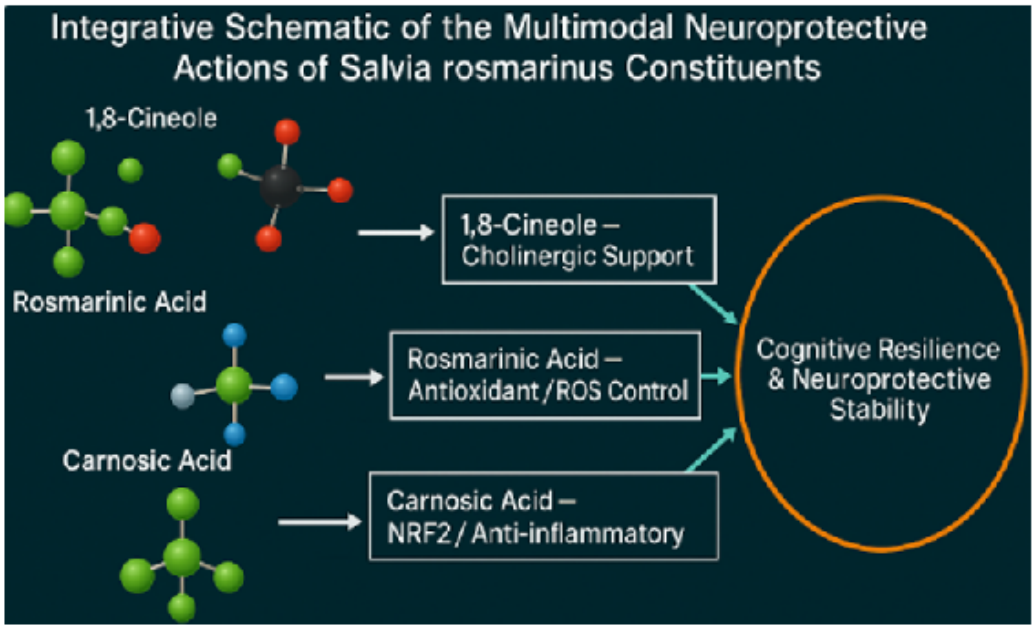

Figure 2: Integrative schematic illustrating the multimodal neuroprotective actions of Salvia rosmarinus constituents, showing cholinergic support by 1,8-cineole, NRF2-mediated antioxidant.

Table 1: Principal bioactive compounds of *Salvia rosmarinus* and neurocognitive relevance.

Compound	Primary Mechanism	Cognitive Relevance
1,8-Cineole	AChE/BChE inhibition; crosses the BBB	Increases synaptic acetylcholine; improves attention and memory
Rosmarinic acid	Antioxidant; cytokine modulation	Synaptic protection under oxidative stress
Carnosic acid	NRF2 activation; NF-κB suppression	Neuronal preservation and plasticity
Borneol / Camphor	Mild neurotransmission modulation	General cognitive support

Note: AChE = acetylcholinesterase; BChE = butyrylcholinesterase; BBB = blood-brain barrier.

misalignment-are warranted. These models closely replicate the oxidative, inflammatory, and cholinergic stressors observed in aerospace operations. Rigorous human trials evaluating rosemary-derived compounds on attention, memory performance, fatigue resistance, and psychophysiological indicators would significantly strengthen translational applicability.

Large-scale randomized trials and longitudinal assessments are essential to determine long-term safety, sustained efficacy, and possible interactions with pharmacological cholinesterase inhibitors or adaptogenic supplements. Integrating neuroimaging, biomarker analysis, and pharmacokinetic modeling could further clarify central nervous system penetration and mechanistic pathways.

Together, these research directions will refine the clinical relevance of *S. rosmarinus* and support evidence-based recommendations for its use in cognitive performance programs.

CONCLUSION

Salvia rosmarinus demonstrates a multimodal neuroprotective profile, supported by converging mechanistic, preclinical, and clinical evidence. Its principal bioactive constituents-1,8-cineole, rosmarinic acid, and carnosic acid-exert complementary actions involving acetylcholinesterase inhibition, oxidative stress attenuation, and microglial inflammatory modulation. Together, these mechanisms contribute to the preservation of synaptic function, neuronal resilience, and cognitive performance under conditions of sustained physiological or cognitive demand.

Human behavioral studies corroborate these findings, indicating improvements in working memory, processing speed, and attention, with outcomes consistent with measurable central bioavailability of rosemary-derived monoterpenes. These results robustly support the translational relevance of *Salvia rosmarinus* as a phytotherapeutic strategy for maintaining cognitive efficiency and neural integrity in high-stress, cognitively demanding occupations.

Future research should prioritize dose-response characterization, standardization of extract composition, and controlled trials in operational environments associated with chronic cognitive load, specifically including space-analog conditions and high-tempo operational stressors. Such investigations are essential to establish evidence-based guidelines for the clinical and functional use of *Salvia rosmarinus* in cognitive support and resilience programs.

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ABBREVIATIONS

Ach: Acetylcholine; **AchE:** Acetylcholinesterase; **AREs:** Antioxidant Response Elements; **BBB:** Blood-Brain Barrier; **BchE:** Butyrylcholinesterase; **CNS:** Central Nervous System; **GPx:** Glutathione Peroxidase; **HPA axis:** Hypothalamic-Pituitary-Adrenal axis; **IL-1β:** Interleukin 1 beta; **IL-6:** Interleukin 6; **LPS:** Lipopolysaccharide; **MAPK:** Mitogen-Activated Protein Kinase; **MDA:** Malondialdehyde; **NF-κB:** Nuclear Factor kappa B; **NO:** Nitric Oxide; **NRF2:** Nuclear Factor Erythroid 2-Related Factor 2; **ROS:** Reactive Oxygen Species; **SOD:** Superoxide Dismutase; **TNF-α:** Tumor Necrosis Factor alpha.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

FUNDING

This research received no external funding.

SUMMARY

This review summarizes current mechanistic, preclinical, and clinical evidence supporting the multimodal neuroprotective effects of *Salvia rosmarinus* under conditions of sustained cognitive and physiological stress. The findings highlight convergent actions involving antioxidant defense, cholinergic modulation, mitochondrial protection, and neuroinflammatory regulation. Together, these mechanisms support the translational potential of *Salvia rosmarinus* as a phytotherapeutic strategy for enhancing cognitive resilience and performance in demanding operational and high-stress environments.

- Rosemary acts as a multimodal neuroprotective agent in cognitive stress.
- 1,8-cineole crosses the blood-brain barrier and increases acetylcholine.
- Rosmarinic and carnosic acids reduce oxidative and neuroinflammatory damage.
- Rosemary essential oil modulates the HPA axis and supports stress resilience.
- Potential application for cognitive maintenance during long-duration spaceflight.

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