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SYSTEMATIC REVIEW: THERAPEUTIC POTENTIAL OF VITAMIN E AND COENZYME Q10 IN TRAUMATIC BRAIN INJURY (TBI)

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ABSTRACT

Traumatic brain injury (TBI) is one of the major neurological problems with high incidence and disability rates globally. To date, there is no fully effective standard therapy available to treat nerve damage caused by TBI, necessitating new approaches targeting the primary pathophysiological mechanisms, particularly oxidative stress and inflammation. This narrative review aims to explore the therapeutic potential of vitamin E and coenzyme Q10 as neuroprotective agents in TBI. The study was conducted by reviewing literature from various scientific databases, focusing on publications from 2020–2025 that discuss the effects of these two compounds on TBI. Vitamin E, particularly α-tocopherol, acts as a lipophilic antioxidant that protects neuronal cell membranes from lipid peroxidation, suppresses inflammatory responses, and supports neuroplasticity. Coenzyme Q10 functions as a cofactor in the mitochondrial electron transport chain, maintaining ATP production, and possesses strong antioxidant and anti-inflammatory effects. Preclinical studies indicate that supplementation with vitamin E and coenzyme Q10 can reduce oxidative stress biomarkers, improve neurological function, and reduce brain lesion volume and neuronal cell death in animal models of TBI. Clinical data is still limited, but there are indications of benefits as supportive therapy. The combination of these two antioxidants also shows synergistic effects in protecting brain tissue. In conclusion, vitamin E and coenzyme Q10 have significant potential as adjunctive therapies in TBI management, although further clinical trials are needed to confirm their efficacy and safety.

Keywords: antioxidant; coenzyme q10; traumatic brain injury (TBI); vitamin E

INTRODUCTION

Traumatic brain injury (TBI) involves brain damage induced by external mechanical forces, such as impact, blows, strong shocks to the head or body, and penetration by foreign objects into the skull. Traumatic brain injury can cause temporary or permanent impairments in brain function, affecting cognitive, motor, emotional, and behavioral aspects of an individual.(Morley & Gandy, 2023) Based on its severity, TBI is categorized into three primary levels and assessed using the Glasgow Coma Scale (GCS): mild (GCS 13–15), moderate (GCS 9–12), and severe (GCS 3–8).(Morley & Gandy, 2023),(Maas et al., 2022)

Currently, TBI is one of the most common neurological disorders globally and significantly contributes to the burden of disease and long-term disability. This condition not only affects the individual but also has widespread social and economic consequences for families, communities, and healthcare systems. Globally, in 2021, traumatic brain injury accounted for approximately 20.84 million incident cases and 37.93 million prevalent cases, resulting in an estimated 5.48 million Years Lived with Disability (YLDs). The data also indicate that TBI incidence rises with age and is more common in males than in females. In 2021, falls were the leading global cause of TBI, followed by road traffic accidents, interpersonal violence, and exposure to mechanical forces.(Zhong et al., 2025)

To date, there is no gold-standard therapy that is fully effective in addressing the impact of TBI. Available therapeutic approaches generally focus on stabilizing acute conditions,

preventing secondary damage, and physical and cognitive rehabilitation.(Mantle et al., 2025) The limitations of conventional therapies in addressing oxidative damage and inflammation in TBI have driven the search for more effective neuroprotective agents. In this context, antioxidant compounds such as Vitamin E and Coenzyme Q10 have begun to gain attention as potential candidates.(Nwafor et al., 2022),(Vachirarojpisan et al., 2024) Vitamin E, especially α-tocopherol, is recognized as a fat-soluble antioxidant that defends cell membranes against lipid peroxidation and free radical-induced damage, and exhibits neuroprotective properties in neurological disorders.(Nwafor et al., 2022) Coenzyme Q10 (CoQ10) is essential for mitochondrial function and also serves as an antioxidant and anti-inflammatory compound. Studies indicate that CoQ10 can enhance mitochondrial biogenesis, improve antioxidant mechanisms, and protect neural tissue from oxidative and inflammatory damage.(Vachirarojpisan et al., 2024) This narrative review aims to explore the therapeutic potential of Vitamin E and Coenzyme Q10 in the management of TBI based on current evidence.

METHOD

In writing this literature review article, a literature search was conducted through various scientific databases such as Google Scholar, PubMed, ScienceDirect, and Scopus to obtain credible and comprehensive reference sources. This review aimed to investigate the therapeutic roles of Vitamin E and Coenzyme Q10 in treating traumatic brain injury (TBI). Various keywords and synonyms were used to expand the scope of the results, including: "Vitamin E or alpha-tocopherol or tocopherol or antioxidant vitamin E, Coenzyme Q10 or CoQ10 or ubiquinone or ubiquinol or mitochondrial coenzyme Q" as well as TBI-related terms such as "traumatic brain injury or TBI or traumatic brain injury" and therapeutic terms such as "antioxidant therapy or oxidative stress or neuroinflammation."

Inclusion criteria include articles in English or Indonesian published between 2020 and 2025, available in full text, and explicitly discussing the effects of Vitamin E and/or Coenzyme Q10 on TBI conditions. Articles excluded from the review were those that were irrelevant, lacked full-text access, or were not categorized as research or review papers. All qualifying articles were subsequently reviewed narratively to provide a thorough understanding of the mechanisms, therapeutic benefits, and clinical potential of both compounds in relation to traumatic brain injury.

RESULT

Several preclinical and limited clinical studies have investigated the role of Vitamin E (α-tocopherol) and Coenzyme Q10 (ubiquinone) in mitigating secondary injury mechanisms following Traumatic Brain Injury (TBI). Experimental and clinical literature consistently report that TBI induces two main phases of damage: primary injury, which occurs immediately during trauma and is irreversible, and secondary injury, which develops over hours to days and involves excitotoxicity, oxidative stress, inflammation, mitochondrial dysfunction, and cerebral hemodynamic disturbances (Hajivalili et al., 2025; Giordano & Lifshitz, 2021).

In animal studies, administration of Vitamin E after TBI significantly reduced malondialdehyde (MDA) levels, increased antioxidant enzyme activity such as superoxide dismutase (SOD) and catalase, decreased cerebral edema, and improved neurological scores compared to control groups (Rizwana et al., 2022). In addition, Vitamin E supplementation reduced microglial and astrocyte activation, indicating an anti-inflammatory effect in brain tissue (Rizwana et al., 2022). Observational clinical studies also reported that combined administration of vitamin C and vitamin E in severe TBI patients was associated with lower mortality and better Glasgow Outcome Scale scores after 30 days (Khalili et al., 2022).

Similarly, animal model studies of Coenzyme Q10 (CoQ10) demonstrated increased ATP levels, reduced oxidative stress biomarkers such as MDA and nitrotyrosine, smaller lesion volumes, and improved motor and cognitive scores compared to untreated groups (Fesharaki-Zadeh, 2022). CoQ10 also modulated apoptosis-related genes by decreasing pro-apoptotic Bax expression and increasing anti-apoptotic Bcl-2 levels, while simultaneously suppressing inflammatory cytokines such as TNF-α and IL-6 and promoting hippocampal neuroplasticity (Peng et al., 2024; Tripathi et al., 2024).

Furthermore, combined administration of Vitamin E and CoQ10 in both in vivo and in vitro studies resulted in greater reductions in oxidative stress markers, restoration of mitochondrial function, suppression of microglial activation, and decreased neuronal apoptosis compared to either agent alone (Bhargavi et al., 2025; Msheik et al., 2024). These findings suggest that a multimodal antioxidant approach may offer superior neuroprotection in TBI compared to monotherapy.

DISCUSSION

Traumatic Brain Injury

Traumatic brain injury (TBI) is a disorder of the structure and/or function of the brain caused by external mechanical forces that exceed the tolerance threshold of nerve tissue. Clinically, TBI is classified based on severity (mild, moderate, severe) and can be focal (e.g., hematoma, contusion) or diffuse (e.g., diffuse axonal injury/DAI).(Hajivalili et al., 2025)·(Orr et al., 2024)·(Freire et al., 2023) However, regardless of classification, the biological mechanisms of brain injury can generally be examined through two phases: primary injury and secondary injury.(Giordano & Lifshitz, 2021)

1. Primary injury

Primary injury occurs instantly during the trauma and involves direct mechanical damage to brain tissue. The force of impact or rapid acceleration-deceleration can cause vascular rupture, cortical contusion, subdural/subarachnoid hemorrhage, and disruption of axonal fibers (DAI). This injury is irreversible because it causes direct tissue death due to compression, laceration, or stretching of brain structures.(Giordano & Lifshitz, 2021)

2. Secondary injury

Secondary injury develops progressively over a period of hours to days post-trauma, unlike the immediate primary injury. This phase is more critical because it is potentially reversible and is the primary target of therapy. Secondary injury involves complex interactions between excitotoxicity, oxidative stress, neurogenic inflammation, energy metabolism disorders, and blood-brain barrier (BBB) dysfunction.(Giordano & Lifshitz, 2021)

Glutamate excitotoxicity is a key initial event in secondary injury. Following trauma, excessive glutamate release occurs at synapses, activating ionotropic receptors such as NMDA and AMPA. This leads to massive influx of calcium ions (Ca^{2+}) into neurons. Intracellular Ca^{2+} accumulation triggers the activation of proteolytic enzymes (calpain), lipolytic enzymes (phospholipase A2), and endonucleases, which collectively damage cytoskeletal proteins, cell membranes, and genetic material.(Thapa et al., 2021)·(Marklund & Tenovuo, 2020)

Calcium influx also directly impacts mitochondrial dysfunction, leading to increased production of free radicals and reduced energy output (ATP). The intrinsic apoptosis pathway is activated by cytochrome c release following mitochondrial damage, involving caspase-9 and caspase-3.(Thapa et al., 2021) Oxidative stress worsens this condition, occurring when the generation of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS) surpasses the ability of endogenous antioxidant defenses like superoxide dismutase (SOD), glutathione, and catalase. Reactive Oxygen Species (ROS) trigger lipid peroxidation in cell

membranes and myelin, altering membrane integrity and increasing ion permeability, which further exacerbates excitotoxicity and cellular edema.(Marklund & Tenovuo, 2020)

Brain trauma concurrently stimulates inflammatory processes through microglial and astrocyte activation. These glial cells produce pro-inflammatory cytokines including TNF-α, IL-1β, and IL-6, which mobilize peripheral immune cells and amplify the inflammatory response locally. This inflammation contributes to increased blood-brain barrier permeability, allowing leukocyte and plasma protein infiltration into the brain parenchyma, triggering vasogenic edema and increasing intracranial pressure.(Freire et al., 2023)·(Marklund & Tenovuo, 2020). Cerebral hemodynamic disturbances are also an important component of secondary injury. Local ischemia due to reduced cerebral perfusion exacerbates the metabolic condition of neurons and astrocytes.(Thapa et al., 2021) Vasospasm, microvascular obstruction by platelet or leukocyte aggregates, and vascular autoregulatory dysfunction worsen brain tissue hypoxia, causing the damage zone to spread beyond the primary injury area.(Marklund & Tenovuo, 2020).

The end result of all these pathways is cell death, either through necrosis due to acute cellular disruption or apoptosis as a result of internal molecular signaling. Both types of cell death not only affect neurons but also astrocytes, oligodendrocytes, and endothelial cells, thereby expanding the spectrum of post-traumatic neurological dysfunction. By deeply understanding the complexity of TBI pathophysiology, it can be concluded that the processes involved are not linear but rather interconnected and mutually reinforcing. Therefore, ideal therapeutic interventions must be multifactorial, targeting more than one molecular pathway. This is where the important role of agents such as Vitamin E and Coenzyme Q10 as antioxidants and mitochondrial modulators becomes intriguing for further investigation in the context of neuroprotective strategies.

Vitamin E (*α-tocopherol*)

Vitamin E (α-tocopherol) is an essential lipophilic vitamin that acts as a major antioxidant in lipid-rich biological environments, such as neuronal cell membranes. Its main mechanism in the central nervous system is to neutralize free radicals and stop the chain reaction of lipid peroxidation.(Jacquens et al., 2022) Brain injury leads to a substantial increase in the generation of Reactive Oxygen Species (ROS), including superoxide, hydrogen peroxide, and hydroxyl radicals, which damage polyunsaturated fatty acids in neuronal membranes, compromise cell structure integrity, and initiate cell death.(Jacquens et al., 2022)·(Denniss & Barker, 2023)

Vitamin E acts by donating hydrogen atoms to Reactive Oxygen Species (ROS), producing tocopheroxyl radicals that are relatively stable and can be readily reduced by antioxidants like vitamin C and glutathione.(Di Pietro et al., 2020) Beyond its antioxidant activity, vitamin E has been reported to exert anti-inflammatory effects by decreasing the expression of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) and proinflammatory cytokines like TNF-α and IL-1β. This is especially significant in TBI, where secondary inflammation critically worsens brain tissue damage following the initial injury.(Di Pietro et al., 2020) Furthermore, vitamin E has the ability to upregulate Brain-Derived Neurotrophic Factor (BDNF), which is important for neuroplasticity and the regeneration of nerve tissue.(Di Pietro et al., 2020)·(Khalili et al., 2022)

A number of preclinical studies have provided strong evidence of the benefits of vitamin E in reducing brain tissue damage and improving neurological function. Rats subjected to traumatic brain injury and administered vitamin E intraperitoneally showed a significant reduction in malondialdehyde (MDA) levels, a major marker of lipid peroxidation, as well as

increased activity of superoxide dismutase (SOD) and catalase enzymes.(Rizwana et al., 2022) Similar results were also found in other animal models, where vitamin E supplementation was able to reduce the level of cerebral edema and significantly improve neurological scores compared to the control group. Vitamin E has also shown potential in reducing the activation of microglia and astrocytes, two types of glial cells that play an important role in mediating inflammatory responses in the brain.(Rizwana et al., 2022)

In the clinical field, data related to the use of vitamin E in TBI patients are still limited and mostly observational studies with small sample sizes, but there are reports that the administration of vitamins C and E as adjunctive therapy in patients with severe TBI can reduce mortality rates and improve Glasgow Outcome Scale scores after 30 days.(Khalili et al., 2022) Although the exact mechanism in the human population still needs further research, these results show the great potential of vitamin E as a supportive therapy. In addition, in systematic reviews, vitamin E has consistently shown protective effects against oxidative stress and neuronal apoptosis in various animal models of TBI, as well as showing a positive trend in clinical studies.(Fesharaki-Zadeh, 2022) Currently, there is still a large variation in dosage, dosage form (oral/intravenous/intramuscular) and time of administration which may affect the final outcome.(Khalili et al., 2022),(Fesharaki-Zadeh, 2022),(Park et al., 2022)

Coenzyme Q10 (*Ubiquinone*)

Coenzyme Q10 (CoQ10) or ubiquinone is a lipophilic compound involved in the mitochondrial electron transport chain as an electron carrier between complexes I/II and complex III.(Yang et al., 2025) Its main function is the production of ATP, the primary energy molecule in cells, including neurons. In addition, the reduced form of CoQ10 (ubiquinol) has strong antioxidant activity capable of neutralizing various ROS such as superoxide, peroxyl, and hydroxyl radicals.(Yang et al., 2025),(Peng et al., 2024),(Tripathi et al., 2024)

In cases of TBI, perfusion disorders and mitochondrial damage lead to decreased ATP production, accumulation of ROS, as well as the formation of mitochondrial permeability transition pores (mPTP) that worsen necrosis and apoptosis. Coenzyme Q10 (CoQ10) acts as a structural and functional protector of mitochondria by stabilizing the mitochondrial membrane, preventing the release of cytochrome C, and suppressing the activation of the caspase pathway.(Bagheri et al., 2023). Apart from its role as a mitochondrial cofactor, CoQ10 also exhibits anti-inflammatory activity through mechanisms that suppress the expression of proinflammatory cytokines (such as TNF-α and IL-6) and reduce microglial activation.(Yang et al., 2025) Several studies have shown that CoQ10 supplementation after TBI can decrease the expression of pro-apoptotic genes such as Bax and increase the expression of the anti-apoptotic protein Bcl-2.(Peng et al., 2024),(Tripathi et al., 2024) Coenzyme Q10 (CoQ10) also affects neurotrophin expression and supports brain tissue regeneration by increasing neuroplasticity, especially in the hippocampal area, which is highly susceptible to injury. This is particularly important given that TBI often leads to long-term memory and cognitive dysfunction.(Yang et al., 2025),(Peng et al., 2024),(Tripathi et al., 2024).

Various studies in animal models have shown that administration of CoQ10 can increase ATP levels in brain tissue, decrease oxidative stress biomarkers such as MDA and nitrotyrosine, reduce brain lesion volume in TBI-induced rat models, and improve motor and cognitive scores compared to control groups.(Fesharaki-Zadeh, 2022). Interestingly, CoQ10 also shows protective effects when combined with other agents such as vitamin E or omega-3, indicating that multimodal interventions may be more effective in dealing with the complexity of brain injury.(Mantle et al., 2025) Clinical data on the use of CoQ10 in TBI patients is still very

limited. Most studies have been conducted in other populations such as neurodegenerative patients (Parkinson's, Alzheimer's) and heart failure patients, where the protective effects on nerve and mitochondrial tissue have been proven, but the same pharmacological principles are expected to be relevant in the context of TBI.(Mantle et al., 2025),(Modi et al., 2024),(Hasanloei et al., 2021)

Interaction between Vitamin *E* and Coenzim Q10

Vitamin E and Coenzyme Q10 are two main lipophilic antioxidants that play an important role in maintaining the integrity of nerve cells, especially under severe oxidative stress conditions such as traumatic brain injury (TBI).(Mantle et al., 2025) Their interaction is synergistic, where each works on complementary molecular pathways to provide more optimal neuroprotective effects than when used alone.(Bhargavi et al., 2025),(Msheik et al., 2024). Vitamin E, especially α-tocopherol, acts as a chain breaker of free radicals in the cell lipid membrane. It stops lipid peroxidation, protects the structure of nerve cell phospholipids, and prevents mitochondrial membrane damage. After neutralizing radicals, Vitamin E itself turns into a radical form (α-tocopherol-radical) that must be reduced again to remain active.(Bhargavi et al., 2025)

This is where the important role of Coenzyme Q10 emerges. Coenzyme Q10 has the ability to reduce the oxidized form of Vitamin E, thus allowing the antioxidant cycle to continue. In addition, Coenzyme Q10 directly stabilizes the mitochondrial membrane, improves electron transport chain function, and reduces ROS (Reactive Oxygen Species) production. Thus, the presence of Coenzyme Q10 supports the antioxidant efficiency of Vitamin E and strengthens cell defenses against oxidative damage. (Msheik et al., 2024),(Persico et al., 2023). Studies conducted both in vivo and in vitro reveal that the combination of Vitamin E and Coenzyme Q10 decreases oxidative stress markers such as malondialdehyde (MDA), increases the activity of antioxidant enzymes including superoxide dismutase (SOD) and glutathione peroxidase (GPx), and restores mitochondrial function in injured brain tissue. This synergy is also associated with reduced neuronal apoptosis, suppressed microglial inflammatory response, and improved neurological outcomes.(Bhargavi et al., 2025),(Msheik et al., 2024). Overall, the synergistic interaction between Vitamin E and Coenzyme Q10 offers the potential for a promising combination therapy approach to support neuroregenerative processes and reduce secondary damage from TBI, but more clinical trials in humans are needed to confirm these benefits and determine the optimal dose and effective duration of administration.

CONCLUSION

Vitamin E and Coenzyme Q10 have potential as adjunctive therapies in traumatic brain injury (TBI) due to their antioxidant and anti-inflammatory effects. Both can reduce secondary damage through protection against oxidative stress and mitochondrial dysfunction, but further research is needed to determine their effectiveness, administration methods, and optimal doses in humans.

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