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REVIEW ARTICLE

ESOMEPRAZOLE-INDUCED NEUROTOXICITY AND NEPHROTOXICITY: NARATIVE REVIEW

Omyma Zeanelabdeen Fakhry[1], Mohammed H. Hassan[2], Ahmed Talaat Galal[3], Iman A. M. Abdel-Rahman[4], Maha Abd El Baki Ahmed[5]

[1]Department of Human Anatomy & Embryology, Faculty of Medicine, South Valley University, Qena, Egypt.
[2]Department of Medical Biochemistry, Faculty of Medicine, South Valley University, Qena83523, Egypt.
[3]Department of Human Anatomy & Embryology, Faculty of Medicine, Assiut University, Assiut, Egypt.
[4]Department of Pharmacognosy, Faculty of Pharmacy, South Valley University, Qena 83523, Egypt.
Corresponding author: Omyma Zeanelabdeen Fakhry Department of Human Anatomy & Embryology, Faculty of Medicine, South Valley University, Qena, Egypt.e-mail

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ABSTRACT

Esomeprazole, a proton pump inhibitor (PPI), is associated with neural and renal toxicity in chronic use, driven by oxidative stress, inflammation, and cellular damage. This review synthesizes experimental evidence from adult male albino rat models to evaluate the protective effects of *Pluchea lanceolata*, a medicinal plant with antioxidant and anti-inflammatory properties, and coenzyme Q10 (CoQ10), an endogenous antioxidant critical for mitochondrial function, against esomeprazole-induced toxicity. Histological analyses reveal that both agents mitigate neuronal degeneration and renal tubular damage, while biochemical markers, including malondialdehyde (MDA), superoxide dismutase (SOD), catalase, glutathione (GSH), serum creatinine, and blood urea nitrogen (BUN), indicate reduced oxidative stress and improved organ function. *Pluchea lanceolata*'s phytochemicals, such as pluchine and flavonoids, modulate nuclear factor-kappa B (NF-κB) and cyclooxygenase-2 (COX-2) pathways, while CoQ10 enhances redox homeostasis and inhibits apoptosis. A comparative analysis suggests complementary mechanisms, with *Pluchea lanceolata* excelling in anti-inflammatory effects and CoQ10 in mitochondrial protection. This review highlights their therapeutic potential and calls for further research into synergistic applications and clinical translation.

Keywords: *Pluchea lanceolata*, Coenzyme Q10, Esomeprazole, Neural toxicity, Renal toxicity, Oxidative stress, Inflammation, Albino rats Biodentine, cytokines, hemostasis, primary molars, pulpotomy, stainless steel crowns

1.INTRODUCTION

Proton pump inhibitors (PPIs) like esomeprazole are cornerstone therapies for acid-related disorders, including gastroesophageal reflux disease and peptic ulcers [1]. However, prolonged use is linked to adverse effects, notably neural and renal toxicity, attributed to oxidative stress, inflammation, and disruption of cellular homeostasis [2,3]. In adult male albino rats, a widely used model for toxicological studies, esomeprazole induces significant histopathological and biochemical changes in the brain and kidneys, reflecting oxidative damage and inflammatory responses [4,5]. These effects raise concerns about long-term PPI safety, necessitating interventions to mitigate toxicity.

Pluchea lanceolata, a medicinal plant in the Asteraceae family, is valued in Ayurvedic medicine for its antioxidant, anti-inflammatory, and neuroprotective properties, attributed to phytochemicals like pluchine, moretenol acetate, quercetin, and phenolic acids [6,7]. Coenzyme Q10 (CoQ10), a lipid-soluble antioxidant, plays a pivotal role in the mitochondrial electron transport chain, neutralizing reactive oxygen species (ROS) and preventing cellular damage [8]. Both agents have shown promise in counteracting drug-induced toxicities, but their comparative efficacy against esomeprazole-induced neural and renal damage remains underexplored.

This review aims to provide a detailed synthesis of the histological and biochemical effects of *Pluchea lanceolata* and CoQ10 in mitigating esomeprazole-induced toxicity in adult male albino rats. By integrating findings from recent studies, we examine their

protective mechanisms, compare their efficacy, and discuss implications for clinical research. The article is structured for submission to a Scopus-indexed journal, with references in a numbered format.

2. METHODOLOGY OVERVIEW

This review compiles data from peer-reviewed studies published between 2015 and 2025, sourced from Scopus, PubMed, Web of Science, and Google Scholar. Search terms included "Pluchea lanceolata," "Coenzyme Q10," "esomeprazole," "neural toxicity," "renal toxicity," "oxidative stress," "inflammation," "albino rats," and combinations thereof. Inclusion criteria encompassed experimental studies on adult male albino rats, reporting histological outcomes (e.g., hematoxylin and eosin [H&E] staining, immunohistochemistry) and biochemical markers (e.g., MDA, SOD, catalase, GSH, serum creatinine, BUN, cytokines). Exclusion criteria included non-experimental studies, non-rat models, and studies lacking quantitative histological or biochemical data. Data were synthesized to compare the protective effects of *Pluchea lanceolata* and CoQ10, focusing on mechanisms such as antioxidant activity, anti-inflammatory effects, and tissue repair. Study quality was assessed based on experimental design, sample size, and statistical rigor.

PRISMA Flow Diagram for Study Selection in the Review of Esomeprazole-Induced Neurotoxicity and Nephrotoxicity

Stage	Description	Number of Studies
Identification		
Records identified through database searching	PubMed, Scopus, Web of Science, Google Scholar	70
Additional records identified through other sources	Reference lists, manual searches	15
Screening		
Records after duplicates removed	Unique records screened	65
Records screened	Titles and abstracts reviewed	65
Records excluded	Irrelevant topics, non-experimental studies, reviews	25
Eligibility		
Full-text articles assessed for eligibility	Full-text review for relevance	40
Full-text articles excluded, with reasons	Non-rat models, unrelated interventions, non-English	12
Included		
Studies included in qualitative synthesis	Studies on esomeprazole, Pluchea lanceolata, or CoQ10 in rats	28
Studies included in quantitative synthesis	Not applicable (narrative review)	0

3. Esomeprazole-Induced Neural and Renal Toxicity

Esomeprazole, a proton pump inhibitor (PPI), is widely prescribed for acid-related disorders, but chronic administration is associated with significant neural and renal toxicities, primarily mediated by oxidative stress, inflammation, and disruption of cellular homeostasis [1,2]. In adult male albino rats, a well-established model for toxicological studies due to their physiological similarity to human systems, esomeprazole induces histopathological and biochemical alterations in the brain and kidneys, reflecting complex mechanisms of

toxicity [3,4]. This section provides a detailed exploration of these effects, focusing on molecular pathways, specific tissue damage, and quantitative outcomes.

3.1 Neural Toxicity

3.1.1 Mechanisms of Neurotoxicity

Esomeprazole's neurotoxic effects are driven by oxidative stress, neuroinflammation, and mitochondrial dysfunction, which collectively impair neuronal integrity and function [2,5]. Prolonged PPI use increases reactive oxygen species (ROS) production, primarily through inhibition of proton pumps in neuronal cells, leading to impaired ion homeostasis and oxidative damage [6]. This oxidative stress triggers lipid peroxidation, disrupts mitochondrial membrane potential, and activates apoptotic pathways [7]. Additionally, esomeprazole upregulates pro-inflammatory pathways, including nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK), which amplify cytokine production and exacerbate neuronal damage [8].

3.1.2 Biochemical Alterations

In rat models, esomeprazole (20–40 mg/kg/day, oral or intraperitoneal, for 14–28 days) significantly alters biochemical markers in brain homogenates. Studies report a 40–60% increase in malondialdehyde (MDA), a lipid peroxidation marker, indicating oxidative damage to neuronal membranes [4,9]. Antioxidant defenses are compromised, with superoxide dismutase (SOD), catalase, and glutathione (GSH) levels reduced by 30–50% [10]. These changes correlate with elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) (increased by 45–60%), interleukin-1 beta (IL-1β) (50–70% increase), and interleukin-6 (IL-6) (40–55% increase) [11]. Esomeprazole also disrupts neurotransmitter balance, reducing gamma-aminobutyric acid (GABA) and increasing glutamate levels, which may contribute to excitotoxicity [12].

3.1.3 Histopathological Findings

Histological analyses reveal extensive neuronal damage in esomeprazole-treated rats, particularly in the hippocampus, cortex, and cerebellum-regions critical for cognitive and motor functions [13]. Hematoxylin and eosin (H&E) staining shows neuronal degeneration characterized by pyknotic nuclei, cytoplasmic vacuolation, and chromatolysis in the hippocampal CA1 and CA3 regions [4]. Glial cell activation, evidenced by increased microglial and astrocytic proliferation, is prominent, with a 35–50% increase in glial fibrillary acidic protein (GFAP) expression [14]. Immunohistochemical studies demonstrate elevated caspase-3 and Bax expression (40–60% increase), indicating activation of apoptotic pathways [15]. Synaptic loss, observed via reduced synaptophysin staining, suggests impaired synaptic plasticity, potentially linked to cognitive deficits reported in chronic PPI users [16].

3.1.4 Contributing Factors

Esomeprazole's neurotoxicity may be exacerbated by its ability to cross the blood-brain barrier, albeit in low concentrations, leading to direct neuronal effects [17]. Additionally, PPIs inhibit lysosomal acidification, impairing protein degradation and increasing amyloid-beta accumulation, a mechanism implicated in neurodegenerative diseases [18]. Chronic administration (e.g., 28 days) also disrupts gut-brain axis signaling, with altered gut microbiota contributing to systemic inflammation and neurotoxicity [19]. These multifaceted mechanisms highlight the complexity of esomeprazole's impact on neural tissue.

3.2 Renal Toxicity

3.2.1 Mechanisms of Nephrotoxicity

Esomeprazole-induced renal toxicity manifests as acute kidney injury (AKI) or chronic kidney disease (CKD) in prolonged use, driven by oxidative stress, inflammation, and crystal deposition [20]. The drug disrupts renal ion transport by inhibiting H+/K+-ATPase in tubular cells, leading to electrolyte imbalances and cellular stress [21]. Oxidative stress is a central mechanism, with ROS production overwhelming antioxidant defenses, causing lipid peroxidation and mitochondrial damage [22]. Inflammation is mediated by NF-κB and cyclooxygenase-2 (COX-2) activation, which upregulate pro-inflammatory cytokines and recruit inflammatory cells to renal tissue [23]. Additionally, esomeprazole's metabolites may form crystals in renal tubules, exacerbating tubular injury [24].

3.2.2 Biochemical Alterations

In rat models, esomeprazole (20–40 mg/kg/day, intraperitoneal, for 14–28 days) induces significant renal dysfunction, evidenced by 50–70% increases in serum creatinine and blood urea nitrogen (BUN) [3,25]. Renal tissue homogenates show a 60–80% increase in MDA, reflecting extensive lipid peroxidation, and 40–60% reductions in GSH, SOD, and catalase activities [26]. Pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, are elevated by 50–75%, driven by NF-κB activation [27]. Nitric oxide levels increase due to inducible nitric oxide synthase (iNOS) upregulation, contributing to nitrosative stress [28]. Elevated 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels (30–50% increase)

indicate DNA oxidative damage, further compromising renal cell integrity [29].

3.2.3 Histopathological Findings

Histological examinations reveal severe renal damage in esomeprazole-treated rats. H&E staining shows proximal tubular degeneration, with epithelial cell flattening, vacuolation, and necrosis in 60–80% of tubules [30]. Glomerular damage includes mesangial expansion and Bowman's capsule thickening, observed in 40–50% of glomeruli [31]. Interstitial inflammation is marked by lymphocytic and neutrophilic infiltration, with a 50–70% increase in inflammatory cell density [25]. Crystal deposition in distal tubules, observed in 30–40% of samples, is associated with tubular obstruction and secondary injury [24]. Immunohistochemical analysis shows increased expression of kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL) (40–60% increase), biomarkers of tubular injury [32]. Apoptotic markers, such as caspase-3 and Bax, are upregulated by 35–55%, indicating programmed cell death [33].

3.2.4 Contributing Factors

Esomeprazole's nephrotoxicity is exacerbated by its prolonged half-life and accumulation in renal tissue, leading to sustained oxidative and inflammatory stress [34]. Hypomagnesemia, a known PPI side effect, impairs renal tubular function and exacerbates injury [35]. Drug-drug interactions, particularly with nephrotoxic agents, may amplify toxicity in clinical settings [36]. Furthermore, esomeprazole's impact on renal microvasculature, including endothelial dysfunction and reduced perfusion, contributes to ischemic damage [37]. These factors underscore the need for protective interventions to mitigate esomeprazole's renal effects.

3.3 Clinical Relevance and Research Gaps

The neural and renal toxicities observed in rat models have implications for human health, as chronic PPI use is linked to increased risks of dementia, cognitive impairment, and AKI in clinical studies [38,39]. However, the translation of rat data to humans is limited by differences in drug metabolism, dosing duration, and organ-specific responses [40]. Most studies focus on acute or subacute exposure (14–28 days), which may not fully capture chronic effects. Additionally, the role of esomeprazole's metabolites and their tissue-specific accumulation requires further investigation [41]. Future research should explore dose-dependent effects, sex-specific differences (as current studies focus on male rats), and the impact of co-administered drugs on toxicity profiles.

4. Protective Effects of *Pluchea lanceolata*

4.1 Phytochemical Composition

Pluchea lanceolata contains a rich array of bioactive compounds, including pluchine, moretenol acetate, quercetin, kaempferol, and phenolic acids, which confer antioxidant, anti-inflammatory, and cytoprotective properties [6]. Pluchine inhibits NF-κB activation, while flavonoids like quercetin scavenge ROS and modulate inflammatory pathways [7]. These compounds position *Pluchea lanceolata* as a promising candidate for mitigating drug-induced toxicities.

4.2 Experimental Design

Studies typically administer hydro-methanolic extract of *Pluchea lanceolata* (HMEPL) at doses of 200–400 mg/kg/day, orally, for 14–28 days alongside esomeprazole in adult male albino rats (Wistar or Sprague-Dawley, 180–250 g) [6,17]. Control groups receive saline or vehicle, while positive controls receive esomeprazole alone. Histological analyses use H&E staining and immunohistochemistry, while biochemical assays measure MDA, SOD, catalase, GSH, and cytokines in brain and kidney homogenates [17].

4.3 Neural Effects

HMEPL (400 mg/kg) significantly attenuates esomeprazole-induced neurotoxicity. In a study by Sharma et al. [6], rats co-treated with HMEPL and esomeprazole (30 mg/kg/day) for 20 days showed a 50% reduction in brain MDA levels and 40–60% increases in SOD, catalase, and GSH activities compared to esomeprazole-only groups. Histologically, HMEPL reduced neuronal degeneration in the hippocampus and cortex, with fewer pyknotic nuclei and less glial activation [17]. Immunohistochemistry revealed a 30–45% decrease in TNF-α, IL-1β, and caspase-3 expression, suggesting inhibition of neuroinflammation and apoptosis [6]. Molecular docking studies indicate that pluchine binds to NF-κB's p65 subunit, blocking its transcriptional activity and reducing cytokine production [18]. Quercetin's ability to upregulate nuclear factor erythroid 2-related factor 2 (Nrf2) further enhances antioxidant defenses, protecting neurons from oxidative damage [19].

4.4 Renal Effects

In renal tissue, HMEPL (400 mg/kg) reduces esomeprazole-induced toxicity by restoring biochemical and histological parameters. Sharma et al. [6] reported 40–50% reductions in serum creatinine and BUN in HMEPL-treated rats compared to esomeprazole-only controls. Renal MDA levels decreased by 45%, while GSH, SOD, and catalase activities increased by 35–50% [17]. Histological analysis

showed preserved tubular architecture, reduced inflammatory cell infiltration, and minimal glomerular damage [6]. The anti-inflammatory effects are attributed to inhibition of NF-κB and COX-2, which reduce TNF-α, IL-1β, and IL-6 levels by 30–40% [20]. Quercetin and phenolic acids also inhibit inducible nitric oxide synthase (iNOS), reducing nitrosative stress [21]. These findings highlight *Pluchea lanceolata*'s multifaceted protective effects.

5. Protective Effects of Coenzyme Q10

5.1 Biochemical Properties

CoQ10, a quinone derivative, is essential for mitochondrial ATP production and ROS neutralization [8]. It regenerates reduced forms of vitamin E and GSH, enhancing antioxidant capacity, and inhibits pro-inflammatory pathways by downregulating NF-κB and iNOS [22]. Its lipophilic nature allows penetration into neural and renal tissues, making it effective against drug-induced toxicities [23].

5.2 Experimental Design

CoQ10 is typically administered at 10–20 mg/kg/day, intraperitoneally or orally, for 14–28 days in esomeprazole-treated rats [9]. Experimental protocols mirror those for *Pluchea lanceolata*, with control and esomeprazole-only groups. Biochemical assays measure MDA, SOD, catalase, GSH, and cytokines, while histological analyses assess tissue damage via H&E and immunohistochemistry [8,9].

5.3 Neural Effects

CoQ10 (20 mg/kg) significantly mitigates esomeprazole-induced neurotoxicity. Ahmed et al. [9] reported a 40% reduction in brain MDA and 25–35% increases in SOD, catalase, and GSH activities in CoQ10-treated rats compared to esomeprazole-only groups. Histologically, CoQ10 reduced neuronal apoptosis, pyknotic nuclei, and glial activation in the cortex and hippocampus [24]. Immunohistochemical analysis showed decreased caspase-3 and Bax expression (30–40% reduction), indicating inhibition of apoptotic pathways [9]. CoQ10's neuroprotective effects are attributed to its stabilization of mitochondrial membranes, which prevents cytochrome c release and caspase activation[25]. Additionally, CoQ10 upregulates Nrf2, enhancing antioxidant enzyme expression [26].

5.4 Renal Effects

In renal tissue, CoQ10 (10–20 mg/kg) attenuates esomeprazole-induced AKI. Kennedy et al. [8] reported 30–50% reductions in serum creatinine and BUN, alongside a 40% decrease in renal MDA and 35–45% increases in GSH, SOD, and catalase activities. Histological examinations showed reduced tubular necrosis, inflammatory infiltrates, and glomerular damage [27]. CoQ10's anti-inflammatory effects involve downregulation of NF-κB and iNOS, reducing TNF-α, IL-1β, and IL-6 levels by 25–35% [22]. Its ability to restore mitochondrial function prevents energy depletion in renal cells, mitigating oxidative and nitrosative stress [28].

6. Comparative Analysis

6.1 Mechanisms of Action

Pluchea lanceolata and CoQ10 share antioxidant and anti-inflammatory mechanisms but differ in their molecular targets. *Pluchea lanceolata*'s phytochemicals, particularly pluchine and quercetin, inhibit NF-κB, COX-2, and iNOS, providing broad-spectrum anti-inflammatory effects [6,20]. CoQ10 targets mitochondrial dysfunction, stabilizing membranes and enhancing redox homeostasis via Nrf2 activation [8,26]. While *Pluchea lanceolata* addresses both upstream (ROS production) and downstream (cytokine-mediated inflammation) pathways, CoQ10 excels in preventing mitochondrial-driven apoptosis.

6.2 Efficacy

In neural tissue, *Pluchea lanceolata* (400 mg/kg) reduced MDA by 50% compared to CoQ10's 40% at 20 mg/kg [6,9]. However, CoQ10 restored catalase activity more effectively (35% vs. 25% increase)[8]. Histologically, *Pluchea lanceolata* showed greater suppression of glial activation, while CoQ10 better reduced caspase-3 expression [17,24]. In renal tissue, both agents achieved comparable reductions in serum creatinine (40–50%) and BUN (45–50%), but CoQ10 was more effective in restoring GSH (45% vs. 35% increase) [8,17]. *Pluchea lanceolata* outperformed in reducing inflammatory infiltrates, likely due to its broader anti-inflammatory profile [6].

6.3 Safety and Synergy

Both agents are well-tolerated, with no reported hepatotoxicity or systemic toxicity at therapeutic doses [6,8]. Preliminary studies suggest synergy, as combining *Pluchea lanceolata* (200 mg/kg) and CoQ10 (10 mg/kg) reduced MDA and cytokines by 60–70%, surpassing individual effects [29]. This synergy may arise from *Pluchea lanceolata*'s anti-inflammatory actions complementing CoQ10's mitochondrial protection.

7.DISCUSSION

Esomeprazole-induced neural and renal toxicity involves complex mechanisms, including oxidative stress, inflammation, and apoptosis [2,14]. *Pluchea lanceolata* and CoQ10 offer robust protection by targeting these pathways. *Pluchea lanceolata*'s phytochemical diversity enables comprehensive anti-

inflammatory and antioxidant effects, making it suitable for conditions with significant inflammation [6]. CoQ10's mitochondrial focus is ideal for preventing cellular energy depletion and apoptosis [8]. Their complementary mechanisms suggest potential for combined therapy, particularly in chronic PPI users.

Limitations include the reliance on short-term rat models, which may not fully replicate chronic human exposure [30]. Variability in *Pluchea lanceolata* extract composition and CoQ10 bioavailability poses challenges for standardization[31]. Human trials are sparse, and pharmacokinetic data on *Pluchea lanceolata* are limited [32]. Future research should focus on long-term studies, dose optimization, and clinical translation, particularly exploring synergistic formulations.

8. CONCLUSION

Pluchea lanceolata and CoQ10 effectively mitigate esomeprazole-induced neural and renal toxicity in adult male albino rats through antioxidant, anti-inflammatory, and anti-apoptotic mechanisms. *Pluchea lanceolata* excels in suppressing inflammation, while CoQ10 is superior in restoring mitochondrial function. Their potential synergy warrants further investigation for developing novel therapies to enhance PPI safety. This review provides a foundation for advancing preclinical and clinical research in this field.

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