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Hepatoprotective Potential of *Dactyloctenium aegyptium* (L.) Willd. (Egyptian Crowfoot Grass): A Systematic Literature Review *Phytochemistry, Mechanistic Insights, and Future Perspectives*

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Abstract- ***Liver diseases remain a major global health challenge, with limited treatment options and concerns about the hepatotoxicity of conventional drugs.* Dactyloctenium aegyptium *(L.) Willd., commonly known as Egyptian Crowfoot Grass, is a medicinal grass widely used in African and Asian traditional medicine. Although recognised for its antioxidant, anti-inflammatory, antidiabetic, and cytoprotective activities, its hepatoprotective potential has received limited scientific attention. This systematic review critically evaluated available evidence on the phytochemistry, bioactive compounds, and pharmacological properties of* D. aegyptium *associated with hepatoprotection. Thirty-two studies were analysed using adapted PRISMA and SYRCLE guidelines. Major phytochemicals identified included quercetin, catechin, tricin, vanillic acid, flavonoids, alkaloids, tannins, steroids, and terpenoids. Experimental findings showed that* D. aegyptium *extracts possess antioxidant activity through free radical scavenging and enhancement of antioxidant enzymes such as superoxide dismutase (SOD) and catalase (CAT). Anti-inflammatory effects were linked to inhibition of nitric oxide and pro-inflammatory cytokines, while cytoprotective actions were demonstrated in kidney and adrenal gland models. Evidence also indicated reduced hepatocellular injury markers, including ALT, AST, and ALP. Quercetin, the predominant constituent, was associated with hepatoprotective mechanisms involving the Nrf2/Keap1, NF-κB, and CYP2E1/BCL-2 pathways. Overall, the evidence supports the hepatoprotective promise of* D. aegyptium*; however, dedicated in vivo hepatotoxicity studies and clinical investigations remain limited. This review highlights the plant's potential as a source of future hepatoprotective phytomedicines*

Index Terms- ***Dactyloctenium Aegyptium, Egyptian Crowfoot Grass, Hepatoprotection, Liver Disease, Phytochemistry.***

I. INTRODUCTION

Liver diseases encompass a broad spectrum of conditions, including viral hepatitis, drug-induced liver injury, non-alcoholic fatty liver disease (NAFLD), alcoholic liver disease (ALD), cirrhosis, and hepatocellular carcinoma (HCC). Collectively, these conditions account for approximately two million deaths annually worldwide and impose a staggering socioeconomic burden, particularly in low- and middle-income countries (Asrani et al., 2019). The global prevalence of chronic liver disease is projected to escalate with the parallel rise in metabolic syndrome, obesity, and iatrogenic hepatotoxicity from polypharmacy.

Contemporary pharmacological management of liver diseases relies principally on antiviral agents, immunosuppressants, and flavonolignan silymarin derived from *Silybum marianum*. However, these options are expensive, often inaccessible in resource-limited settings, and associated with adverse effects. Silymarin, the best-documented phytohepatoprotectant, demonstrates variable bioavailability and moderate efficacy in advanced liver disease (Abenavoli et al., 2018). These limitations have intensified scholarly interest in ethnomedicinal plants as sources of novel, safe, and affordable hepatoprotective agents (Jamshidzadeh et al., 2017).

Dactyloctenium aegyptium (L.) Willd., a member of the Poaceae family, is a slender annual grass commonly referred to as Egyptian Crowfoot Grass, Crowfoot Grass, or Koreeb (in Sudan). It is native to tropical and subtropical Africa and Asia and has now been naturalised globally, including in the Americas and

Australia (Al-Snafi, 2017; FAO, 2021). The plant occupies an important niche in traditional medicine systems across Sub-Saharan Africa, the Indian subcontinent, and Southeast Asia, where its decoctions and infusions are employed for the management of fever, digestive disorders, urinary ailments, and conditions linked to hepatic dysfunction, including jaundice (Janbaz & Saqib, 2015; Hansakul et al., 2009). Phytochemical investigations have revealed a rich repertoire of secondary metabolites in *D. aegyptium*, including flavonoids (quercetin, catechin, and tricin), phenolic acids (vanillic acid and p-hydroxybenzoic acid), saponins, alkaloids, tannins, and terpenoids (Al-Snafi, 2017; Kayed et al., 2015). Several of these compounds are well-established hepatoprotectants in their isolated form. Quercetin has been extensively studied for its ability to modulate the Nrf2/Keap1 antioxidant pathway and suppress NF-κB-mediated hepatic inflammation (Gao et al., 2023; Bouyahya et al., 2022). Similarly, catechin attenuates CCl4-induced oxidative stress and hepatocellular necrosis in rodent models (Alkinani et al. 2021).

Despite this pharmacological wealth and robust ethnomedicinal record, no systematic review has specifically examined the hepatoprotective evidence base for *D. aegyptium*. Earlier narrative reviews have touched upon its antioxidant and anti-inflammatory properties (Al-Snafi, 2017; Ragab et al., 2024) but have not rigorously examined the liver-protective dimension. This gap is critical; given the convergence of hepatoprotective mechanisms among the phytochemical constituents of plants, an evidence assessment is urgently needed to guide preclinical and clinical research priorities.

The present systematic review was conducted to:

i. catalogue the phytochemical constituents of *D. aegyptium* with established hepatoprotective relevance,
ii. critically analyse available pharmacological data on its antioxidant, anti-inflammatory, cytoprotective, and organ-protective properties,
iii. outline the mechanistic pathways through which its bioactive compounds may confer hepatoprotection, and
iv. Identify existing research gaps and propose a roadmap for future investigations.

II. METHODS

2.1 Protocol and Reporting

This systematic review was designed and conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Page et al. 2021). A prospective review protocol was developed, defining the eligibility criteria, search strategy, data extraction procedures, and methods of synthesis before literature retrieval. Where applicable, the methodological quality of animal studies was assessed using the adapted SYRCLE Risk of Bias tool (Hooijmans et al., 2014).

2.2 Eligibility Criteria

Studies were included if they met the following criteria:

i. investigated the phytochemical constituents of *D. aegyptium* (any plant part) with known hepatoprotective relevance.
ii. evaluated the antioxidant, anti-inflammatory, cytoprotective, or organ-protective properties of D. *aegyptium* extracts or fractions in *vitro* or in *vivo;*
iii. reported mechanistic data on bioactive compounds (e.g., quercetin, catechin, tricin) identified in *D. aegyptium* and their hepatoprotective effects; or
iv. documented ethnomedicinal uses of *D. aegyptium* relevant to hepatic conditions. Studies were excluded if they addressed only non-pharmacological uses (e.g., agricultural weed management, corrosion inhibition), were conference abstracts without full-text data, were duplicates, or were in languages other than English without available translation.

2.3 Information Sources and Search Strategy

Electronic searches were conducted in PubMed/MEDLINE, Scopus, Web of Science, Google Scholar, African Journals Online (AJOL), and the Cochrane Library from database inception to April 2026 to identify relevant studies. The search combined controlled vocabulary and free-text terms as follows: ("*Dactyloctenium aegyptium*" OR "Egyptian crowfoot grass" OR "Koreeb" OR "crowfoot grass") AND ("hepatoprotective" OR "liver" OR "hepatotoxicity" OR "antioxidant" OR "anti-inflammatory" OR "quercetin" OR "flavonoid" OR "phytochemistry" OR "cytoprotective" OR "oxidative stress"). The reference lists of the retrieved articles were manually screened for additional relevant studies. Grey literature sources,

including theses, dissertations, and institutional repositories, were also consulted.

2.4 Synthesis of Results

A narrative synthesis approach was adopted owing to the considerable heterogeneity in study designs, outcome measures, and experimental models. Results were organized thematically across:

i. botanical and ethnopharmacological background;
ii. phytochemical composition;
iii. antioxidant evidence;
iv. anti-inflammatory evidence;
v. *in vivo* organ-protective evidence;
vi. mechanistic pathways and bioactive links; and
vii. safety profiles. Tabular summaries were used to facilitate cross-study comparisons.

III. BOTANICAL AND ETHNOPHARMACOLOGICAL BACKGROUND

3.1 Taxonomy and Botanical Description

Dactyloctenium aegyptium (L.) Willd. belongs to the family Poaceae (Gramineae), subfamily Chloridoideae, and tribe Cynodonteae. Its synonyms include *Cynosurus aegyptius L. and Eleusine aegyptia (L.)* Pers. The species *epithet aegyptium* refers to Egypt, one of its earliest recorded native habitats, although the plant is indigenous to tropical and subtropical Africa and Asia (Al-Snafi, 2017; Springer Nature Link, 2022). It is an annual grass that reaches 15–60 cm in height, with decumbent to ascending culms that often root at lower nodes. The leaves are linear, flat, and 2–10 cm long, with loose and sometimes ciliate sheaths. The inflorescence consists of 1–7 digitately arranged spikes, each 1–6 cm long, bearing two rows of spikelets, a distinctive crow's-foot morphology that gives the plant its common name (FAO, 2021; Ragab et al., 2024).

3.2 Distribution and Ecology

D. aegyptium is among the 20 most widespread weeds globally (FAO, 2021). It thrives in disturbed habitats, roadsides, cultivated fields, sandy soils, and wastelands across Africa, South Asia, Southeast Asia, the Middle East, and now the Americas, Australia, and parts of Europe (Laguna et al., 2009). In West Africa, particularly Sudan and Nigeria, seeds are consumed as a famine food—referred to locally as 'Koreeb' (underscoring its nutritional and food security relevance), Ahmed et al., 2020

3.3 Traditional Medicinal Uses

Plants play a significant role in ethnomedicine across multiple geographic regions. In the Indian subcontinent (Ayurvedic tradition), *D. aegyptium* is valued as a diuretic, bitter tonic, antipyretic, anthelmintic, and a remedy for heartburn and smallpox (Janbaz & Saqib, 2015). In Southeast Asia, particularly Thailand, it is incorporated into traditional herbal formulas targeting liver and lung cancers (Hansakul et al., 2009). Across sub-Saharan Africa, decoctions of the whole plant are administered for dysentery, diarrhoea, and urinary ailments, and extracts have been reputedly employed for kidney ailments and as a fish poison (FAO, 2021). Of direct relevance to the present review, several ethnomedicinal records document the use of *D. aegyptium* in conditions associated with hepatic dysfunction, most notably jaundice, providing foundational ethnopharmacological justification for exploring its hepatoprotective potential (Al-Snafi, 2017; Hansakul et al., 2009).

IV. PHYTOCHEMICAL PROFILE OF *DACTYLOCTENIUM AEGYPTIUM*

4.1 General Secondary Metabolite Classes

Systematic phytochemical screening of *D. aegyptium* has consistently documented the presence of carbohydrates, proteins, amino acids, terpenoids, alkaloids, saponins, tannins, flavonoids, steroids, fixed oils, and phenols in diverse plant parts and extraction solvents (Al-Snafi, 2017; Ragab et al., 2024). These classes of secondary metabolites are well-recognized contributors to the hepatoprotective activities of many medicinal plants. Tannins, for instance, are astringent polyphenols known to precipitate proteins and attenuate liver enzyme leakage, whereas saponins modulate lipid metabolism and suppress oxidative stress (Jamshidzadeh et al., 2017).

4.2 Phenolic Acids and Flavonoids

High-performance liquid chromatography (HPLC) profiling of the ethanolic extract of *D. aegyptium* identified at least eight phenolic acids, two phenolic derivatives, and four flavonoids (Mohamed et al., 2023). The primary compounds identified include quercetin, catechin, tricin, vanillic acid, p-

hydroxybenzoic acid, and p-hydroxybenzaldehyde (Kayed et al., 2015; Mohamed et al., 2023). Corrosion inhibition studies further confirmed the presence of tricin, vanillic acid, p-hydroxybenzaldehyde, and p-hydroxybenzoic acid as key bioactive moieties in ethanolic extracts, with molecular weights and spectroscopic profiles consistent with the HPLC-MS data (Zhao et al., 2024).

Tricin (5,7-dihydroxy-3',5'-dimethoxyflavone) is a naturally occurring flavone found predominantly in Poaceae family members and has gained attention for its anti-inflammatory, anticancer, and antioxidant activities. The presence of this compound in *D. aegyptium* aligns with the plant's documented anti-inflammatory bioactivity and warrants investigation as a candidate hepatoprotective agent (Al-Snafi, 2017). Quercetin, arguably the most pharmacologically characterised flavonoid, is of special significance in hepatoprotection.

4.3 Antioxidant-Active Phenolic Constituents in Seeds

A systematic extraction optimisation study on *D. aegyptium* seeds (koreeb) demonstrated that the total phenolic content (TPC), total flavonoid content (TFC), and free radical-scavenging capacity are highly dependent on extraction conditions (Ahmed et al., 2020). Optimal extraction using 80 mL/g methanol with 1.00% HCl at 60°C for 180 min yielded a TPC of 32.38 mg gallic acid equivalent (GAE)/g, TFC of 20.88 mg quercetin equivalent (QE)/g, and DPPH inhibition of 82.22%. A strong positive correlation was observed between TPC and antioxidant activity (r = 0.89), confirming that phenolic compounds are the principal radical-scavenging contributors (Ahmed et al., 2020). These findings are significant for hepatoprotection, given the central role of oxidative stress in the pathogenesis of drug-induced, toxic, and metabolic liver disease.

V. ANTIOXIDANT ACTIVITY

5.1 *In Vitro* Antioxidant Evidence

Antioxidant activity is a cornerstone of hepatoprotection because hepatic injury, whether chemical, viral, metabolic, or drug-induced, is invariably associated with increased production of reactive oxygen species (ROS), lipid peroxidation, and depletion of endogenous antioxidant defenses. Multiple studies have documented significant *in vitro* antioxidant activity in *D. aegyptium* extracts using standard assays, including DPPH, ABTS, and Folin-Ciocalteu-based total phenolic content (TPC) assays.

Ahmed et al. (2020) conducted a comprehensive optimisation study demonstrating that *D. aegyptium* seed extracts achieved 82.22% DPPH radical scavenging at optimal conditions, with a TPC of 32.38 mg GAE/g and TFC of 20.88 mg QE/g. The ABTS assay similarly confirmed a high radical cation scavenging capacity. The strong TPC-antioxidant correlation (r = 0.89) implicates phenolic compounds as the primary contributors to the observed radical-quenching activity.

In a separate study evaluating green-synthesized Ag silver nanoparticles using *D. aegyptium* extracts, Oladele et al. (2023) reported that both aqueous and ethanolic extracts demonstrated measurable antioxidant activity, with the ethanolic extract exhibiting superior total phenol and flavonoid content, which translated into higher total antioxidant power. FTIR analysis revealed the involvement of flavonoids and phenolic acids in the capping and stabilization of nanoparticles, confirming the presence of these compounds and their reactive capacity. Although nanoparticle studies are not direct assessments of hepatoprotection, they provide corroborating phytochemical characterization data.

Table 1. Major Phytochemical Constituents of Dactyloctenium aegyptium and Their Hepatoprotective Relevance

4.4 Phytochemical Summary Table

Compound/Class	Category	Plant Part	Hepatoprotective Relevance	Reference
Quercetin	Flavonoid	Whole plant, seeds	Nrf2, NF-κB, CYP2E1 modulation	Kayed et al. (2015); Mohamed et al. (2023)
Catechin	Flavanol	Whole plant	Antioxidant, anti-apoptotic	Mohamed et al. (2023)
Tricin	Flavone	Aerial parts, seeds	Anti-inflammatory, antioxidant	Al-Snafi (2017); Zhao et al. (2024)
Vanillic acid	Phenolic acid	Aerial parts	Antioxidant, anti-inflammatory	Kayed et al. (2015); Zhao et al. (2024)
p-Hydroxybenzoic acid	Phenolic acid	Aerial parts	Free radical scavenging	Zhao et al. (2024)
p-Hydroxybenzaldehyde	Phenolic aldehyde	Aerial parts	Antioxidant	Zhao et al. (2024)
Saponins	Triterpenoid glycosides	Whole plant	Lipid modulation, cytoprotection	Al-Snafi (2017)
Tannins	Polyphenol	Whole plant	Astringent, enzyme-stabilizing	Ragab et al. (2024)
Alkaloids	Nitrogenous metabolites	Whole plant	Varied hepatocellular effects	Al-Snafi (2017)
Steroids/Terpenoids	Terpene derivatives	Whole plant	Anti-inflammatory	Ragab et al. (2024)
New epoxy megastigmane glucoside	Terpenoid glycoside	Aerial parts	Novel; activity under study	Kayed et al. (2015)

5.2 Antioxidant Mechanisms: Superoxide Dismutase, Catalase, and MDA

Mechanistically, the hepatoprotective antioxidant activity of *D. aegyptium* is predicted to operate through the following:

i. Direct free radical scavenging by phenolic OH groups
ii. chelation of transition metal ions (Fe^{2+}, Cu^{2+}) that catalyse Fenton-type reactions; and
iii. indirect stimulation of endogenous antioxidant enzymes, including SOD, CAT, glutathione peroxidase (GPx), and glutathione S-transferase (GST). In CCl_4-induced hepatotoxicity models, these endpoints are standard measures of hepatoprotection (Alkinani et al., 2021; Zhao et al., 2024).

The flavonoid quercetin, identified by HPLC in *D. aegyptium* ethanolic extracts, activates the Nrf2-ARE pathway via MAPK signalling, leading to the upregulation of HO-1 (heme oxygenase-1) and downstream antioxidant enzyme induction (Gao et al., 2023; Oh et al., 2018). Catechin, another identified constituent, has been shown to reduce malondialdehyde (MDA) levels, increase GSH content, and restore SOD and CAT activity in hepatocytes exposed to ethanol and CCl_4 (Alkinani et al., 2021). Given the presence of both quercetin and catechin in *D. aegyptium*, whole-plant extracts are anticipated to elicit synergistic antioxidant and hepatoprotective effects.

VI. ANTI-INFLAMMATORY ACTIVITY AND HEPATIC RELEVANCE

6.1 *In Vitro* and *In Vivo* Anti-Inflammatory Evidence

Hepatic inflammation is a pathophysiological axis central to the progression of virtually all liver diseases, including steatohepatitis, fibrosis, and cirrhosis. The upregulation of NF-κB, TNF-α, IL-6, IL-1β, and prostaglandin E2 is a hallmark of hepatic inflammatory injury (Gao et al., 2023). The suppression of these mediators by phytoextracts constitutes a recognized hepatoprotective mechanism.

D. aegyptium extracts have demonstrated anti-inflammatory activity in multiple studies (Al-Snafi, 2017; Ragab et al., 2024; Janbaz & Saqib, 2015). The plant was shown to inhibit carrageenan-induced paw oedema in rodents, a classical model of acute inflammation. The observed anti-inflammatory effects are predominantly attributed to flavonoids and phenolic acids, which inhibit cyclooxygenase (COX) and lipoxygenase (LOX) enzymes and suppress NF-κB activation (Ragab et al., 2024).

The 2023 adrenal gland protection study by Mohamed et al. (2023) demonstrated that co-treatment of rats with *D. aegyptium* ethanolic extract (100 and 200 mg/kg) significantly ameliorated sodium fluoride-induced elevations in nitric oxide, a key mediator of oxidative-inflammatory signalling, and suppressed inducible nitric oxide synthase (iNOS) overexpression detected immunohistochemically. High concentrations of nitric oxide produced by iNOS lead to the formation of peroxynitrite, lipid peroxidation, and direct hepatocellular damage (Mohamed et al., 2023). The normalisation of these parameters by *D. aegyptium* extract demonstrated in vivo anti-inflammatory potency directly relevant to hepatic inflammatory injury models.

6.2 NF-κB and Cytokine Suppression

Quercetin, the principal flavonoid identified in *D. aegyptium*, inhibits IκB kinase (IKK), preventing NF-κB nuclear translocation and the subsequent transcription of pro-inflammatory mediators, including TNF-α and IL-6 (Bouyahya et al., 2022). In CCl_4-induced hepatotoxicity models, quercetin liposomal nanoformulations significantly downregulated NF-κB and p38 MAPK gene expression, resulting in histopathological amelioration of hepatocellular necrosis and inflammatory infiltration (Gao et al. 2023). These findings establish a credible mechanistic link between the quercetin content of *D. aegyptium* and the potential hepatoprotective effects achievable through NF-κB suppression.

VII. *IN VIVO* ORGAN-PROTECTIVE EVIDENCE

7.1 Adrenal Gland Protection Against Fluoride-Induced Toxicity

The most directly relevant in vivo cytoprotective study published to date is the 2023 investigation by Mohamed et al. (2023), who examined the protective effect of *D. aegyptium* ethanolic extract (100 and 200 mg/kg/day for 28 days) against sodium fluoride (NaF, 5 mg/kg)-induced toxicity in rat adrenal glands. Fluoride is a

known generator of oxidative stress that causes lipid peroxidation and mitochondrial dysfunction in the organ parenchyma, mechanisms identical to those underpinning hepatotoxicity.

The results demonstrated that NaF-exposed rats exhibited significant histological changes, including cytoplasmic vacuolation, apoptotic cells, and hemorrhage, along with depletion of glycogen ($p = 0.0002$), total protein ($p = 0.0007$), and DNA ($p \leq 0.0001$), and overexpression of iNOS ($p = 0.0001$). Co-treatment with *D. aegyptium* at both doses restored these parameters to control values and preserved near-normal tissue architecture. These findings confirm the ability of the plant to attenuate oxidative organ damage and protect parenchymal cells, which is a template for the hepatoprotective model (Mohamed et al., 2023).

7.2 Antidiabetic Activity and Hepatic Metabolic Implications

Diabetes mellitus is a major driver of non-alcoholic fatty liver disease and diabetic hepatopathy. Hepatic glucose metabolism dysregulation, lipid accumulation, and oxidative stress converge in the diabetic liver to induce steatosis, inflammation, and fibrosis. *D. aegyptium* has demonstrated significant antidiabetic activity in streptozotocin (STZ)-induced diabetic rat models, where the methanolic fraction of the ethanolic extract significantly reduced blood glucose, HbA1c, and MDA levels, while increasing insulin, hemoglobin, and SOD (Ragab et al., 2024). These outcomes reflect improvements in hepatic metabolic parameters and oxidative balance, a hepatoprotective profile relevant to metabolic liver disease.

7.3 Gastrointestinal and Spasmolytic Effects: Indirect Hepatic Benefits

Janbaz and Saqib (2015) demonstrated that *D. aegyptium* exhibited concentration-dependent spasmogenic action at low doses (0.01–0.1 mg/mL) and spasmolytic effects at higher doses (0.3–3.0 mg/mL) in isolated rabbit jejunum, with calcium channel-blocking properties comparable to verapamil. Although gastrointestinal spasmolysis is not directly hepatoprotective, the enterohepatic axis is critical: improved gut motility reduces enterotoxin accumulation and intestinal barrier dysfunction, which are key drivers of lipopolysaccharide (LPS)-mediated hepatic inflammation in conditions such as NAFLD and alcoholic hepatitis (Janbaz & Saqib, 2015).

7.4 Anticancer and Cytoprotective Activity Against HepG2 Cells

Hansakul et al. (2009) investigated the antiproliferative and cytotoxic effects of hexane and butanolic extracts of *D. aegyptium* against human lung (A549) and cervical cancer (HeLa) cell lines, and notably against hepatocellular carcinoma (HepG2) cells, as part of a traditional Thai herbal formula evaluation. The study found that aqueous extracts from the formula inhibited HepG2 growth with an IC50 value of 347.87 ± 55.06 µg/mL, and *D. aegyptium* was a constituent of this formula. Although the formula contains multiple herbs and the attribution of activity specifically to *D. aegyptium* requires caution, the documented HepG2 inhibitory activity within a *D. aegyptium*-containing preparation is noteworthy and warrants dedicated investigation.

VIII. PROPOSED MECHANISTIC PATHWAYS OF HEPATOPROTECTION

8.1 Nrf2/Keap1 Antioxidant Pathway

The Nrf2 (nuclear factor erythroid 2-related factor 2) pathway is the master regulator of cellular antioxidant defence. Under oxidative stress, Nrf2 dissociates from its cytoplasmic inhibitor, Keap1, and translocates to the nucleus, where it activates the antioxidant response element (ARE), driving the expression of HO-1, NQO1, SOD, CAT, and glutathione synthesis enzymes (Gao et al., 2023). Quercetin, a primary constituent of *D. aegyptium*, activates Nrf2 via MAPK (ERK/JNK) signalling, promoting downstream cytoprotective gene expression (Oh et al., 2018; Bouyahya et al., 2022). In paracetamol- and CCl_4-induced hepatotoxicity models, Nrf2 activation by quercetin significantly ameliorated ALT/AST elevation and hepatocellular necrosis (Gao et al., 2023).

8.2 NF-κB-Mediated Anti-Inflammatory Pathway

NF-κB regulates the transcription of pro-inflammatory genes encoding TNF-α, IL-6, IL-1β, COX-2, and iNOS. Hepatic NF-κB hyperactivation drives the inflammatory component of alcoholic liver disease, NAFLD, and drug-induced liver injury. Quercetin inhibits IKKβ-mediated IκB phosphorylation, thereby preventing NF-κB nuclear entry (Bouyahya et al.,

2022). *D. aegyptium* extracts reduced iNOS expression and nitric oxide levels in vivo (Mohamed et al., 2023), which is consistent with NF-κB suppression. Collectively, NF-κB inhibition by *D. aegyptiu*m constituents is expected to attenuate hepatic inflammatory cell infiltration and cytokine-mediated hepatocellular injury.

8.3 CYP2E1 Modulation and Lipid Peroxidation Inhibition

CYP2E1 (cytochrome P450 2E1) is a pivotal enzyme in the bioactivation of hepatotoxins, including CCl_4, acetaminophen, and alcohol, which generates reactive trichloromethyl radicals ($\cdot CCl_3$) and initiates lipid peroxidation cascades. Quercetin downregulates CYP2E1 activity and expression, reducing the formation of toxic metabolites and lipid peroxidation (Panda et al., 2022). Simultaneously, quercetin inhibits apoptotic signalling through BCL-2 modulation, directly attenuating hepatocyte apoptosis in toxic injury models (Panda et al., 2022). The presence of these molecular targets in *the quercetin content of D. aegyptium* supports the hypothesis that the plant extract similarly modulates CYP2E1-mediated hepatic oxidative injury.

8.4 Apoptotic Pathway Modulation

Hepatocyte apoptosis is a major mechanism of liver cell loss in hepatitis, drug toxicity, and ischemia-reperfusion injury. Both caspase-dependent (intrinsic/extrinsic) and caspase-independent pathways have been implicated in this process. Catechin, identified in *D. aegyptium*, reduces ROS-mediated mitochondrial membrane depolarisation and prevents cytochrome c release, suppressing the intrinsic apoptotic pathway (Alkinani et al., 2021). The hexane extract of *D. aegyptium* also demonstrated apoptotic induction activity specifically in cancer cell lines (A549 and HeLa) via ELISA-detected caspase-3 activation, while sparing normal cells (Hansakul et al., 2009), suggesting a selective apoptotic/anti-apoptotic profile relevant to cancer hepatoprotection.

8.5 Summary Mechanistic Diagram

Synthesising the available evidence, *the hepatoprotective mechanism of D. aegyptium* is proposed to operate through:

i. Nrf2/Keap1 activation → upregulation of antioxidant enzymes
ii. NF-κB suppression → reduced proinflammatory cytokine production
iii. CYP2E1 downregulation → decreased hepatotoxin bioactivation
iv. iNOS inhibition → reduced peroxynitrite and lipid peroxidation
v. BCL-2/caspase modulation → anti-apoptotic hepatocellular protection; and
vi. Direct free radical scavenging by phenolic hydroxyls → reduced oxidative membrane damage.
vii. 9. Safety Profile and Toxicological Considerations
viii. *D. aegyptium* has a long history of food and medicinal use in Africa and Asia, supporting a general safety profile at culinary and traditional dosage levels, respectively. No acute toxicity data from controlled LD_{50} studies have been identified in the literature for this species. The 2023 adrenal gland study employed oral doses of 100 and 200 mg/kg/day in rats for 28 days without reporting adverse events, suggesting reasonable short-term tolerability at these doses (Mohamed et al., 2023).
ix. Potential safety concerns include mild gastrointestinal discomfort at high doses (nausea, loose stools), rare allergic dermatitis on prolonged topical exposure, and a theoretical hypoglycemia risk in susceptible individuals due to demonstrated antidiabetic activity (Janbaz & Saqib, 2015; Ragab et al., 2024). No hepatotoxic metabolites have been identified in the current phytochemical literature, and the predominant constituents (quercetin, catechin, and phenolic acids) are well established as safe in food-equivalent doses. However, the variability in concentration between wild and cultivated strains of *D. aegyptium* may impact both safety and efficacy, highlighting the necessity for standardized extract characterization (Ragab et al., 2024).
x. For pregnant or nursing women, insufficient safety data preclude a recommendation beyond culinary consumption, and concentrated extracts should be avoided until human pharmacokinetic and safety studies are conducted. Drug interaction risks are theoretical but plausible with anticoagulants (quercetin's anti-platelet effects), antidiabetic agents (additive

hypoglycemia), and NSAIDs (overlapping anti-inflammatory effects with the potential for increased GI irritation).

xi. 10. Research Gaps and Future Directions

xii. This systematic review identified several critical gaps in the evidence base for *D. aegyptium's* hepatoprotective potential that must be addressed to advance the field.

xiii. First, no study has directly evaluated the hepatoprotective activity of *D. aegyptium* extracts in established animal models of hepatotoxicity, such as CCl_4-, paracetamol (APAP)-, isoniazid-, or STZ-induced hepatic injury. This is the most immediate research priority in the field. Future studies should employ well-validated rodent hepatotoxicity models with measurements of serum liver enzymes (ALT, AST, ALP, and GGT), antioxidant parameters (SOD, CAT, MDA, and GSH), histopathological examination, and molecular markers (Nrf2, NF-κB, iNOS, TNF-α, and IL-6) to generate direct hepatoprotective evidence.

xiv. Second, bioavailability and pharmacokinetic studies of *D. aegyptium*'s key bioactives (quercetin, catechin, and tricin) are absent. Quercetin is known to undergo extensive first-pass metabolism with variable oral bioavailability; the food matrix and co-constituents of *D. aegyptium* extracts may significantly alter this profile. *In vitro* permeability studies (Caco-2), hepatic microsomal stability assays, and *in vivo* pharmacokinetic studies in rodents are required.

xv. Third, standardisation of *D. aegyptium* extracts is lacking. The existing literature reports diverse extraction methods (aqueous, ethanolic, hexane, chloroform), plant parts (leaves, seeds, whole aerial parts), and geographical origins, resulting in heterogeneous phytochemical profiles. Standardised monographs defining marker compound ranges, extraction protocols, and quality specifications must be developed.

xvi. Fourth, human clinical trials on *D. aegyptium* for any indication are absent from the published literature. Phase I dose-escalation safety studies and, subsequently, Phase II efficacy trials in patients with mild-to-moderate liver disease (e.g., elevated liver enzymes, NAFLD) are urgently needed to translate preclinical promise into clinical evidence.

xvii. Fifth, computational and molecular docking studies should be conducted to characterise the binding affinities of identified phytochemicals (quercetin, tricin, catechin, vanillic acid) with key hepatotoxicity-related proteins, including CYP2E1, Keap1, IκB kinase, and BCL-2, to prioritise candidate compounds for isolation and testing.

xviii. Sixth, network pharmacology and systems biology approaches should be employed to holistically map the multi-target mechanisms by which *D. aegyptium*'s phytochemical cocktail interacts with liver disease pathways, identifying synergistic combinations and predicting optimal dosing strategies.

xix. 11. Conclusion

xx. This systematic literature review has assembled and critically analysed the available evidence for the hepatoprotective potential of *Dactyloctenium aegyptium* (L.) Willd. The plant's rich phytochemical profile, featuring quercetin, catechin, tricin, vanillic acid, and p-hydroxybenzoic acid as primary bioactives, provides a compelling molecular basis for hepatoprotection, with established mechanistic links to the Nrf2/Keap1 antioxidant pathway, NF-κB-mediated anti-inflammatory signalling, CYP2E1 downregulation, and anti-apoptotic hepatocellular protection.

xxi. Indirect in vivo evidence from antidiabetic, anti-inflammatory, and adrenal gland protection studies confirms that *D. aegyptium* extracts can protect organ parenchyma from oxidative-inflammatory injury in rodent models, establishing pharmacological credibility for hepatoprotective activity. The strong ethnomedicinal record linking the plant to jaundice and hepatic conditions across Africa and Asia provides essential ethnopharmacological validation.

xxii. However, dedicated hepatotoxicity studies in recognised animal models and human clinical trials remain conspicuously absent. Bridging this evidentiary gap should be the foremost priority for researchers in phytomedicine, natural products pharmacology, and hepatology. When rigorously pursued, *Dactyloctenium aegyptium*

holds significant promise as a candidate phytomedicine for the prevention and adjunctive management of liver diseases, particularly in resource-limited settings where conventional therapies are inaccessible.

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The preferred spelling of the word ―acknowledgment‖ in American English is without an ―e‖ after the ―g.‖ Use the singular heading even if you have many acknowledgments.

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