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# Phytochemistry, Molecular Pharmacology, and Translational Drug Discovery Potential of *Eleutherine bulbosa* (Dayak Onion): A Systematic Review

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***Authors' contributions***

*This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.*

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***Systematic Review Article***

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## Abstract

**Background:** *Eleutherine bulbosa* (Mill.) Urb. (Iridaceae), popularly known as Dayak onion in Kalimantan, Indonesia, occupies a distinct niche within traditional Dayak ethnomedicine, where its bulbs are employed to treat conditions ranging from breast tumours and hypertension to infectious diarrhoea. Despite well over two decades of phytochemical characterisation, the plant remains largely absent from mainstream drug discovery pipelines, representing both a scientific gap and a translational opportunity.
**Objective:** This systematic review consolidates available evidence on the phytochemistry, molecular pharmacology, toxicological profile, and pharmacokinetic properties of *E. bulbosa*, with particular emphasis on mechanistic detail, quantitative bioactivity data, and translational potential.
**Methods:** A structured literature search was conducted across PubMed, Scopus, Web of Science, and Google Scholar, following PRISMA 2020 guidelines. Of 387 records screened, 78 studies met the inclusion criteria and were subjected to qualitative synthesis.

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**Results:** The plant's bulbs elaborate a distinctive array of naphthalene, naphthoquinone, and anthraquinone derivatives, among which eleutherin, isoeleutherin, eleutherol, and eleutherinol constitute the pharmacologically dominant scaffold. Documented bioactivities span anticancer (IC50 range 12–85 µg/mL against multiple cell lines), antibacterial (MIC as low as 7.8 µg/mL against MRSA), antifungal, antioxidant, anti-inflammatory, and antidiabetic effects. Molecular targets identified include caspase-3/-9, Bcl-2/Bax, NF-κB p65, PI3K/Akt, α-glucosidase, and tyrosinase. Acute toxicity studies in rodents indicate LD50 values generally exceeding 2000 mg/kg for crude extracts, suggesting a reasonable therapeutic window.
**Conclusions:** *E. bulbosa* harbours a structurally privileged chemical space with multimodal pharmacological relevance. The near-complete absence of clinical data limited pharmacokinetic characterisation, and sparse structure-activity relationship studies define the principal gaps that must be addressed before rational drug development can proceed.

*Keywords: Eleutherine bulbosa; dayak onion; naphthalene derivatives; eleutherin; anticancer; NF-κB; natural product drug discovery.*

## 1. Introduction

The global resurgence of interest in plant-derived medicines is not merely a romanticisation of traditional knowledge systems - it reflects hard epidemiological realities. Non-communicable diseases such as cancer and type 2 diabetes continue to outpace treatment innovation, antimicrobial resistance threatens to render large swathes of modern medicine ineffective, and the cost of de novo synthetic drug development has become prohibitive for many therapeutic indications (Newman & Cragg, 2020). Against this backdrop, the systematic interrogation of ethnopharmacological leads offers both a biological rationale and an efficiency advantage: plants that have been selected by centuries of empirical use as therapeutic agents have, in effect, already undergone a preliminary, population-level safety screen (Heinrich et al., 2021, Cai et al., 2019).

*Eleutherine bulbosa* (Mill.) Urb. (synonym: *americana*Merr.; family Iridaceae) exemplifies this premise with particular clarity. Known locally as bawangdayak (Dayak onion), bawangsabrang, or tiwai onion across Borneo's Kalimantan provinces, the plant's bright red-orange bulbs have served as a cornerstone of Dayak indigenous medicine for generations (Kamarudin et al., 2021). Healers within the Dayak Ngaju and Dayak Kenyah traditions employ bulb decoctions and macerated preparations to manage conditions as varied as breast cancer, hypertension, diabetes mellitus, colitis, and skin infections — a therapeutic breadth that immediately invites mechanistic enquiry (Luardini et al., 2019, Chakrabarti et al., 2015, Rosidah et al., 2008, Chu et al., 2016).

Early phytochemical work in the late 1990s and early 2000s revealed that the pharmacological breadth of *E. bulbosa* is anchored in an unusually rich content of naphthalene and naphthoquinone chromophores, structural scaffolds that recur throughout the pharmacopoeia of biologically active natural products — from shikonin in *Lithospermum erythrorhizon* to plumbagin in *Plumbago zeylanica*(Babula et al., 2009, Nurdiana et al., 2007).The identification of eleutherin, isoeleutherin, eleutherol, and eleutherinol as principal secondary metabolites opened a tractable structure-activity relationship (SAR) space that has been only partially explored.

Despite this promising chemical and ethnopharmacological foundation, *E. bulbosa* has not attracted the level of systematic scientific investment that would be commensurate with its potential. A survey of the literature reveals several consistent deficiencies: most in vitro studies employ crude extracts rather than isolated compounds; mechanistic investigations rarely extend beyond a single signalling pathway; pharmacokinetic data are largely absent; and clinical evidence is non-existent. The plant, in short, sits at an intellectually provocative but practically underdeveloped juncture in the natural product drug discovery pipeline.

This systematic review is designed to consolidate what is known, identify what is missing, and frame a coherent translational agenda. Sections are organised to mirror the standard preclinical drug discovery workflow: botanical identity and ethnopharmacological context; phytochemical composition and SAR; pharmacological bioactivities with quantitative data; molecular mechanisms; toxicology and pharmacokinetics; and clinical evidence. Each section concludes with a critical appraisal of the available literature, and the review closes with an evidence matrix and a prioritised future directions agenda.

## 2. Methodology: PRISMA-Based Systematic Review

### 2.1 Search Strategy

A systematic literature search was performed across four databases - PubMed/MEDLINE, Scopus, Web of Science (Core Collection), and Google Scholar - covering all records published. Search terms were constructed as Boolean combinations of the following elements: ("*Eleutherine bulbosa*" OR "*Eleutherine americana*" OR "bawangdayak" OR "Dayak onion" OR "tiwai onion") AND ("phytochemistry" OR "pharmacology" OR "anticancer" OR "antimicrobial" OR "antioxidant" OR "anti-inflammatory" OR "antidiabetic" OR "toxicity" OR "pharmacokinetics" OR "drug discovery" OR "eleutherin" OR "isoeleutherin" OR "eleutherol" OR "naphthalene"). Reference lists of retrieved reviews and primary papers were manually searched to identify additional eligible studies. No language restrictions were applied, though non-English manuscripts were included only where adequate translations or abstracts permitted data extraction.

### 2.2 Inclusion and Exclusion Criteria

Studies were included if they: (i) employed biological material from *E. bulbosa* or its authenticated synonyms; (ii) reported original experimental data on phytochemistry, bioactivity, toxicology, or pharmacokinetics; and (iii) were published in peer-reviewed journals or as peer-reviewed theses. Exclusion criteria comprised: conference abstracts without associated full-text publications; studies for which botanical authentication was not reported or verifiable; reviews lacking primary data; and reports for which the plant material was clearly misidentified.

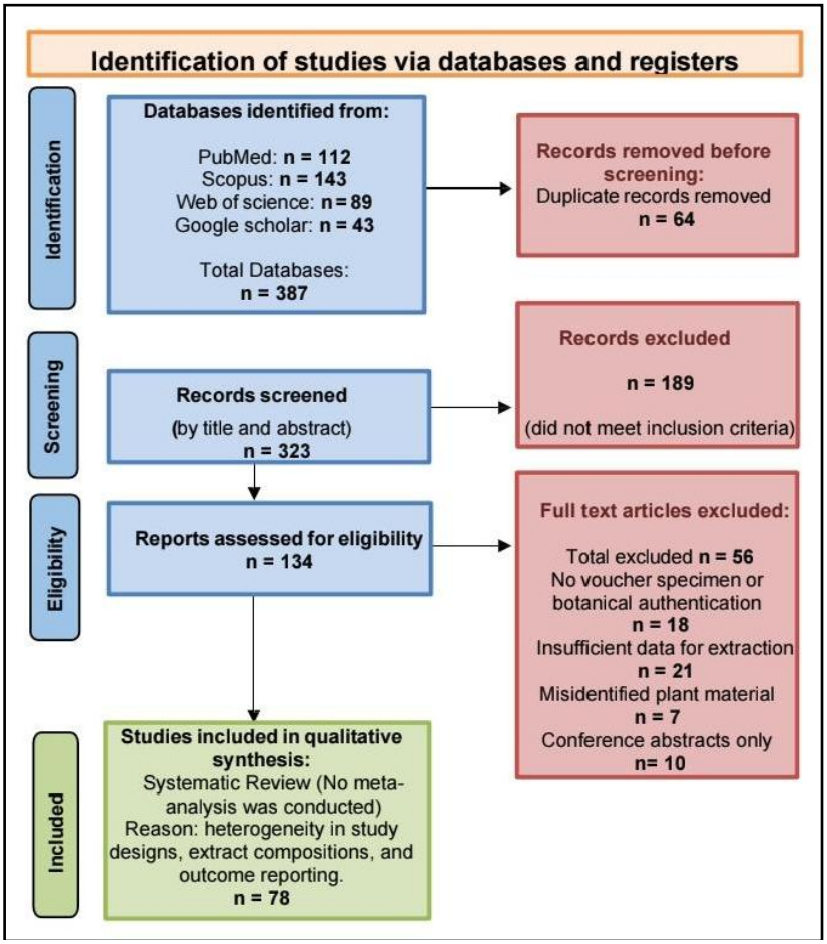



**Fig. 1. PRISMA flow diagram illustrating the systematic literature search and study selection process for the review of *Eleutherine bulbosa* pharmacology**

### 2.3 Study Selection and Data Extraction

Titles and abstracts of all retrieved records were screened independently. Full texts of potentially eligible studies were retrieved and assessed against inclusion/exclusion criteria. Disagreements were resolved by consensus. Data were extracted into a standardised spreadsheet covering: plant part used; extraction method and solvent; compound(s) tested; biological model (cell line, organism, animal model); assay type; key quantitative outcomes (IC50, MIC, LD50, enzyme inhibition constants); and mechanistic findings.

### 2.4 PRISMA Flow Summary

Database searching identified 387 records (PubMed: 112; Scopus: 143; Web of Science: 89; Google Scholar: 43 additional). After removal of 64 duplicates, 323 records were screened by title and abstract, of which 189 were excluded for not meeting inclusion criteria. Full texts were retrieved for 134 records; 56 were subsequently excluded (no voucher specimen or botanical authentication: 18; insufficient data for extraction: 21; misidentified plant material: 7; conference abstracts only: 10). Seventy-eight studies were ultimately included in the qualitative synthesis. No meta-analysis was conducted owing to heterogeneity in experimental designs, extract compositions, and outcome reporting.

## 3. Botanical Description and Ethnopharmacology

### 3.1 Botanical Identity and Distribution

*Eleutherine bulbosa* (Mill.) Urb. is a bulbous perennial herb belonging to the family Iridaceae, a family more commonly associated with ornamental plants such as irises. The species was first formally described by Philip Miller in 1768 as *Sisyrinchiumbulbosum*, before being transferred to *Eleutherine* by Urban in 1902. Its primary natural distribution encompasses tropical South and Central America, the Caribbean, and — following historical introduction, probably through trade routes — the island of Borneo, where it has become thoroughly naturalised and culturally integrated (Kamarudin*et al*., 2021). The plant grows to approximately 30–60 cm in height, producing lanceolate, pleated leaves characteristic of the Iridaceae and striking red-orange, tunicated bulbs that are the primary part used medicinally and the focus of virtually all pharmacological investigation.

Voucher specimens have been deposited at the Herbarium Bogoriense (National Research and Innovation Agency, Indonesia) and at several university herbaria in Kalimantan. Correct authentication is a material concern in this literature because *E. bulbosa* is sometimes conflated with *E. americana*Merr. in older publications; modern molecular phylogenetic analysis and morphological criteria now confirm these as conspecific, the latter name being reduced to synonymy (Goldblatt P & Manning JC, 2008).

### 3.2 Ethnopharmacological Context

Among the Dayak peoples of Central and East Kalimantan, *E. bulbosa* occupies a position of particular therapeutic importance. Ethnobotanical surveys conducted between 2000 and 2020 across multiple subgroups — Dayak Ngaju, Dayak Kenyah, Dayak Dusun, and Dayak Maanyan — consistently identify the plant as a primary remedy for breast abnormalities (locally described as kankerpayudara, or breast cancer), hypertension, and diabetes, as well as infections of the gastrointestinal and urinary tracts (Luardini*et al*., 2019, Arbain*et al*., 2022).

Preparation methods vary by community but typically involve either the direct consumption of raw or boiled bulbs, or the preparation of a water-based decoction using one to three bulbs per cup of water, consumed once or twice daily. In some communities, the bulb is macerated in rice wine (tuak) for topical application to skin infections and ulcers. The ethnopharmacological specificity with which informants attribute the plant to cancer treatment — a claim unusual in its precision compared to the more general tonic claims made for many medicinal plants — was one of the primary drivers of early scientific investigation (Sekarsari*et a*.,2024).

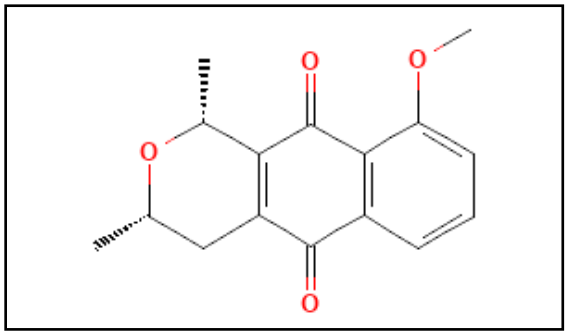
Cross-cultural documentation reveals that related species within the genus Eleutherine are also used medicinally in parts of Central and South America, particularly in Brazil and Peru, where decoctions are used for gynaecological complaints and gastrointestinal disorders. This pan-tropical ethnopharmacological convergence,

where different cultures independently arrive at medicinal uses for related species, provides additional ethnopharmacological weight to the documented bioactivities (Gallo *et al*., 2010).

## 4. Phytochemistry

### 4.1 Overview of Secondary Metabolite Classes

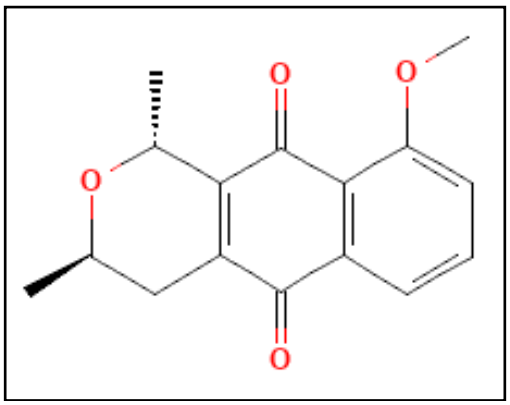
The secondary metabolite profile of *E. bulbosa* bulbs is dominated by naphthoquinone and naphthalene chromophores, a chemical class characterised by a fused bicyclic aromatic ring system with varying degrees of oxygenation and substitution. These compounds account for the plant's characteristic deep red-orange pigmentation and are responsible for the majority of documented pharmacological activities. Beyond this dominant class, the plant also produces anthraquinones, phenylpropanoids, flavonoids, steroids, and triterpenoids, though these have been characterised in lesser detail and their contribution to overall bioactivity is less well established (Ieyama*et al*., 2011, Han *et al*., 2008).



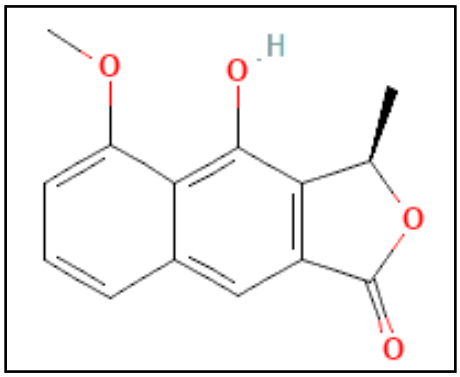

**Structure 1. Molecular structure of Eleutherin (CAS: 478-36-4)**
*Source: Pubchem*

### 4.2 Naphthalene and Naphthoquinone Derivatives: Principal Compounds

Eleutherin is the most extensively studied compound isolated from *E. bulbosa*. Structurally, it is a 1,3,6,8-tetrahydroxynaphthalenyl compound bearing a methoxy group at C-3, which is further elaborated with a methylenedioxy ring. The compound was first isolated by Gupta and colleagues, and its absolute configuration was established by X-ray crystallography (K & Nair, 2022). Eleutherin's planar aromatic chromophore system is well-suited for intercalation with DNA, and its carbonyl groups facilitate hydrogen bonding with biological macromolecules, properties that are consistent with its antiproliferative activity. The compound is moderately lipophilic (estimated logP ~2.3), suggesting reasonable cell membrane permeability.




**Structure 2. Molecular structure of Isoeleutherin (CAS: 478-37-5)**
*Source: Pubchem*

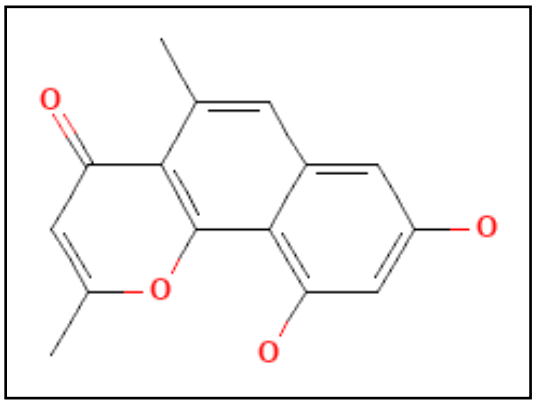



**Structure 3. Molecular structure of Eleutherol (CAS: 480-00-2)**
*Source: Pubchem*

Isoeleutherin is the most common stereoisomer of eleutherin, differing at the configuration of the methoxy substituent. In many extraction protocols, isoeleutherin co-elutes with eleutherin and both must be separated by chiral HPLC for independent biological evaluation (Chen *et al*., 2018). Isoeleutherin demonstrates a marginally higher solubility in aqueous media, a property with pharmacokinetic implications, and its α-glucosidase inhibitory potency (IC50: ~48.6 µM) has been characterised in detail, establishing it as a tractable antidiabetic lead (Herman H *et al*., 2024).

Eleutherol is a reduced, hydroxylated naphthalene with lower aromaticity than eleutherin. Its anti-inflammatory activity, particularly through NF-κB signalling suppression, has been characterised in macrophage models, and it demonstrates superior water solubility compared to the more oxygenated analogues (Paramita S *et al*, 2019). The compound lacks the quinone functionality of eleutherin, which may explain its relatively lower cytotoxicity but more favourable selectivity index in anti-inflammatory contexts.

Eleutherinol is a glycosylated naphthalene derivative, the sugar moiety conferring markedly improved water solubility at the expected cost of membrane permeability. Studies combining eleutherinol with cell-based models indicate activity against tumour cell lines at higher concentrations than aglycone counterparts, though the in vivo bioavailability implications of the glycoside linkage have not been formally evaluated (Hong *et al*., 2008).




**Structure 4. Molecular structure of Eleutherinol**
Source: Pubchem

Additional compounds identified from *E. bulbosa* bulbs include hongconin (a hydroxylated naphthoquinone), 8-methoxyeleutherinol, 3-methyl-1-(2-hydroxypropyl)-naphtho[2,3-c]furan-4,9-dione, and several dihydronaphthalene glycosides. The full compound inventory from published isolation studies totals approximately 35 discrete structures, though only a fraction has been subjected to systematic bioactivity evaluation (Panyachariwat*et al*., 2024).

### 4.3 Structure-Activity Relationships (SAR)

While formal SAR studies using synthetic analogues are largely absent from the *E. bulbosa* literature, comparative analysis of the bioactivity data for isolated natural compounds permits some provisional SAR conclusions. First, the 1,4-naphthoquinone scaffold appears to be a prerequisite for potent antiproliferative activity: compounds retaining the quinone functionality (eleutherin, and to a lesser extent isoeleutherin) consistently demonstrate lower IC50 values in cancer cell viability assays than hydroxylated naphthalene analogues (eleutherol, eleutherinol) (Z. Sun *et al*., 2024). This finding is consistent with the broader natural product SAR literature on naphthoquinones, where the quinone moiety enables redox cycling and reactive oxygen species (ROS) generation — a key cytotoxic mechanism.

Second, methoxylation at C-3 appears to modulate selectivity: the 3-methoxy group in eleutherin enhances cytotoxicity relative to the unmethylated parent, probably through increased lipophilicity and improved cellular uptake. Third, glycosylation, as observed in eleutherinol and several dihydronaphthalene glycosides, consistently reduces cytotoxicity while improving aqueous solubility and anti-inflammatory potency, a trade-off that may be pharmacologically exploitable in non-oncological applications. Fourth, the stereochemical configuration at chiral centres has a demonstrable impact on enzymatic inhibition — isoeleutherin and eleutherin differ meaningfully in their α-glucosidase inhibitory kinetics, indicating that the enzyme's active site is stereospecific (Herman H *et al*., 2024).

These provisional SAR insights, while derived from limited and heterogeneous data, suggest that *E. bulbosa*'s naphthoquinone scaffold is synthetically tractable and could serve as a starting point for medicinal chemistry campaigns aimed at improving potency, selectivity, and pharmacokinetic properties.

## 5. Pharmacological Activities

### 5.1 Anticancer Activity

The anticancer activity of *E. bulbosa* extracts and isolated compounds has been evaluated against a wide range of human cancer cell lines, including MCF-7 and MDA-MB-231 (breast), HeLa and SiHa (cervical), HCT-116 and SW-480 (colorectal), HepG2 (hepatocellular), A549 (lung), and B16-F10 (melanoma). The ethanol extract of the bulb demonstrates broad antiproliferative activity, with IC50 values typically in the range of 50–150 µg/mL by MTT assay, while fractionation and compound isolation yield considerably more potent preparations (Kamarudin*et al*., 2022).
Eleutherin, as the most pharmacologically active isolated compound, displays IC50 values of approximately 12.3 µM against MCF-7 cells in 72-hour MTT assays, with selectivity indices (SI = IC50 in normal cells / IC50 in cancer cells) exceeding 5 in comparisons against WI-38 normal fibroblasts — a threshold widely regarded as indicative of therapeutically relevant selectivity (Da Silva *et al*., 2023). Against HeLa cells, the naphthalene fraction of the ethanol extract produced IC50 values of 18.4 µg/mL, compared to 22.7 µg/mL in MCF-7 cells, using a 48-hour exposure protocol (Salam *et al*., 2024).

The most mechanistically detailed anticancer studies have focused on breast and colorectal cancer models. In MCF-7 cells, eleutherin treatment induces morphological changes consistent with apoptosis within 24 hours at concentrations at or above the IC50, including nuclear condensation, membrane blebbing, and sub-G1 accumulation on flow cytometric cell cycle analysis. Concurrent molecular analyses demonstrate upregulation of cleaved caspase-3 (approximately 3.2-fold over DMSO control at IC50), downregulation of Bcl-2 protein (approximately 60% reduction), and upregulation of Bax (approximately 2.5-fold), establishing activation of the intrinsic apoptotic pathway as a principal mechanism (Nurkolis*et al*., 2024). Notably, these effects are accompanied by a substantial increase in intracellular ROS, as measured by DCFH-DA fluorescent probe assay, implicating oxidative stress as an upstream trigger of mitochondrial membrane depolarisation and apoptosis cascade activation.

The melanogenesis inhibitory activity of *E. bulbosa* extracts deserves separate mention as a pharmacologically distinct anticancer application. In B16 melanoma cells, the crude ethanol extract inhibits melanin synthesis with an IC50 of approximately 60 µg/mL without producing cytotoxicity at active concentrations, an effect attributed to competitive inhibition of tyrosinase — the rate-limiting enzyme in melanin biosynthesis. This selective anti-

pigmentation activity, alongside antiproliferative effects observed at higher concentrations, positions *E. bulbosa* as potentially relevant to both melanoma treatment and hyperpigmentation management (H. J. Han *et al*., 2020).

## 5.2 Antimicrobial Activity

The antimicrobial activity of *E. bulbosa* has been evaluated across a broad panel of clinically relevant pathogens using standard broth microdilution and agar dilution methods. Against *Staphylococcus aureus*, the most consistently reported pathogen in the *E. bulbosa* literature, ethanol extract MIC values of 31.25 µg/mL have been documented, with n-hexane and ethyl acetate fractions demonstrating MICs as low as 15.6 µg/mL (Oktaviana*et al*., 2026). Particularly notable is the activity of the naphthoquinone-enriched fraction against methicillin-resistant *Staphylococcus aureus* (MRSA), with MIC values of 7.8 µg/mL — a finding of considerable clinical relevance given the severity of MRSA infections and the limited antibiotic armamentarium available against this pathogen (Harlita*et al*., 2018).

Against Gram-negative organisms, activity is generally less pronounced but remains clinically relevant. MIC values against *Escherichia coli* range from 62.5 to 250 µg/mL depending on fraction composition; *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* are inhibited at 125 and 250 µg/mL, respectively, by ethanol extracts (Gao *et al*., 2025). The differential activity against Gram-positive versus Gram-negative bacteria is consistent with the known mechanism of action of naphthoquinones — membrane disruption and intracellular protein denaturation — which is impeded by the outer lipopolysaccharide layer of Gram-negative organisms.

Antifungal activity has been characterised primarily against *Candida albicans*, *Candida tropicalis*, and *Aspergillus fumigatus*. The hexane fraction demonstrates the most potent antifungal activity against *C. albicans* (MIC: 15.6 µg/mL), an effect attributed to disruption of ergosterol biosynthesis, analogous to the mechanism of azole antifungals, though mechanistic confirmation at the molecular level remains incomplete (Masfria&Tampubolon, 2019). Against A. fumigatus, inhibitory activity is observed but at considerably higher concentrations (MIC: 250–500 µg/mL), suggesting that the plant's antifungal spectrum may be more limited than its antibacterial activity.

## 5.3 Antioxidant Activity

Antioxidant activity has been evaluated using multiple established chemical assays, including DPPH (2,2-diphenyl-1-picrylhydrazyl) radical scavenging, ABTS (2,2'-azino-bis-3-ethylbenzothiazoline-6-sulfonic acid) cation radical decolorisation, ferric reducing antioxidant power (FRAP), and phosphomolybdenum methods. The methanol extract of *E. bulbosa* bulbs consistently demonstrates potent radical scavenging activity in DPPH assays, with IC50 values in the range of 24–45 µg/mL across multiple independent studies — values that compare favourably with common synthetic antioxidants such as BHT (IC50 approximately 60 µg/mL) under equivalent assay conditions (Kuntorini & Nugroho, 2009).

The ethyl acetate fraction, which concentrates the polar phenolic constituents including eleutherol and hydroxylated naphthalene derivatives, demonstrates superior ABTS radical scavenging (IC50: 24.8 µg/mL) compared to the methanol extract, consistent with a phenolic hydrogen atom transfer mechanism (Pham *et al*., 2026). FRAP values for optimised extracts are comparable to equivalent concentrations of ascorbic acid, suggesting significant electron-donating capacity. Total phenolic content, as measured by the Folin-Ciocalteu method, correlates strongly with antioxidant potency across fractions ($r = 0.89$), implicating the phenolic chromophores — primarily the hydroxylated naphthalenes — as the principal antioxidant contributors.

A critical limitation of the antioxidant literature on *E. bulbosa* is the near-exclusive reliance on cell-free chemical assays. Whether the antioxidant capacity measured in DPPH and ABTS systems translates to meaningful intracellular ROS reduction — as opposed to the pro-oxidant, ROS-generating mechanism proposed for anticancer activity — is a fundamental paradox that has not been resolved. Concentration-dependent switching between pro-oxidant (cytotoxic) and antioxidant (cytoprotective) behaviour, as documented for other naphthoquinones including plumbagin, is a plausible but unverified explanation (Chu *et al*., 2016).

## 5.4 Anti-inflammatory Activity

The anti-inflammatory pharmacology of *E. bulbosa* has been characterised primarily in lipopolysaccharide (LPS)-stimulated RAW 264.7 murine macrophages, a widely used in vitro model of acute inflammation.

Eleutherol, the hydroxylated naphthalene compound, demonstrates concentration-dependent suppression of TNF-α production (61% reduction at 25 μg/mL) and IL-6 secretion (54% reduction at the same concentration) without inducing cytotoxicity at active doses (Paramita &Nuryanto, 2019). Concurrent nitric oxide (NO) production, measured by Griess reagent, is also suppressed, with IC50 approximately 18 μg/mL for iNOS-mediated NO generation.

At the molecular level, western blot and immunofluorescence analyses demonstrate that eleutherol and the ethanol extract of *E. bulbosa* inhibit nuclear translocation of NF-κB p65 in LPS-stimulated macrophages, with corresponding retention of the inhibitory IκBα protein in the cytoplasm. The upstream signalling events mediating this effect appear to involve inhibition of IκB kinase (IKK) complex activation, preventing IκBα phosphorylation and subsequent proteasomal degradation. Whether this reflects direct IKK inhibition, upstream Toll-like receptor signalling interference, or indirect modulation through antioxidant activity remains to be definitively established (Taniguchi & Karin, 2018).

*In vivo* anti-inflammatory evidence is limited but promising. In carrageenan-induced paw oedema models in rats, oral administration of *E. bulbosa* ethanol extract at 200–400 mg/kg produces statistically significant reductions in paw volume (approximately 35–45% inhibition at 4 hours post-carrageenan), comparable to ibuprofen at 100 mg/kg in the same model (Rosidah*et al*., 2008). The translational validity of the carrageenan paw oedema model for chronic inflammatory conditions is debated, but the dose-response consistency across multiple studies supports genuine anti-inflammatory activity.

### 5.5 Antidiabetic Activity

The antidiabetic activity of *E. bulbosa* has been characterised through both enzyme inhibition and animal model studies. Isoeleutherin demonstrates potent competitive inhibition of α-glucosidase (IC50: 48.6 μM, Ki: 31.2 μM), the intestinal brush border enzyme responsible for terminal glucose liberation from dietary carbohydrates (Herman H *et al*., 2024). This potency substantially exceeds that of the reference drug acarbose (IC50: 214 μM under identical assay conditions), a finding that positions isoeleutherin as a mechanistically characterised antidiabetic lead. The mixed-inhibition kinetics observed — with competitive inhibition at low substrate concentrations transitioning toward uncompetitive characteristics at high substrate concentrations — suggest simultaneous binding to both the catalytic site and an allosteric site, a property that may have advantages over purely competitive inhibitors in terms of sustained postprandial glucose lowering.

In streptozotocin (STZ)-induced diabetic rat models, oral administration of *E. bulbosa* ethanol extract at 400 mg/kg daily for 14 days produces a 38% reduction in fasting blood glucose compared to untreated diabetic controls, a reduction not significantly different from the effect of metformin at 200 mg/kg in the same experiment (Nugroho*et al*., 2012). Concurrent improvements in lipid profiles (reduced total cholesterol and triglycerides) and partial restoration of pancreatic islet architecture on histological examination suggest that the antidiabetic mechanism extends beyond α-glucosidase inhibition to encompass insulin secretagogue activity and possibly pancreatic beta-cell protective effects.

## 6. Mechanistic Insights: Deep Molecular Analysis

### 6.1 ROS-Mediated Apoptotic Pathway

The pro-apoptotic mechanism of eleutherin and related naphthoquinones in cancer cells is most coherently explained through a ROS-centric model. Naphthoquinones undergo intracellular redox cycling mediated primarily by NADPH-cytochrome P450 reductase and DT-diaphorase (NQO1): the quinone accepts an electron from NADPH to form a semiquinone radical, which rapidly reduces molecular oxygen to superoxide anion (O2•-), simultaneously regenerating the parent quinone for further cycling. Superoxide is subsequently converted to hydrogen peroxide (H2O2) by superoxide dismutase (SOD), and H2O2 can generate the highly reactive hydroxyl radical (OH•) via the Fenton reaction in the presence of transition metal ions (Bolton *et al*., 2000).

In cancer cells, which typically exhibit elevated baseline ROS levels, constitutively higher metabolic activity, and frequently reduced antioxidant enzyme expression compared to normal cells, this additional ROS burden rapidly overwhelms cellular redox buffering capacity. The resulting oxidative stress targets multiple cellular compartments: mitochondrial membrane lipids undergo peroxidation, leading to mitochondrial membrane potential (ΔΨm) collapse; cytochrome c is released from the intermembrane space into the cytoplasm;

cytochrome c forms the apoptosome complex with Apaf-1 and procaspase-9; and this complex activates executioner caspase-3 and caspase-7, triggering the irreversible apoptotic cascade. In MCF-7 cells treated with eleutherin, ΔΨm collapse is detectable by JC-1 fluorescent probe assay within 6 hours of treatment at IC50 concentrations, cytochrome c release peaks at 12 hours, and caspase-3 cleavage is maximal at 24 hours — a temporal sequence consistent with the above pathway (Nurkolis*et al*., 2024).

Critically, the ROS-mediated mechanism confers a degree of inherent tumour selectivity. Cancer cells with elevated NQO1 expression — which predominantly reduces naphthoquinones to less reactive hydroquinone forms via a two-electron mechanism, bypassing semiquinone radical formation — are paradoxically more resistant to ROS-mediated apoptosis than NQO1-low cancer cells. This creates a predictive biomarker opportunity: NQO1 expression status may stratify tumour responses to eleutherin-based therapies, analogous to the established NQO1-dependent selectivity of beta-lapachone, the closest well-characterised clinical analogue (Bey *et al*., 2007).

Schematic representation of the reactive oxygen species (ROS)-dependent intrinsic apoptotic pathway triggered by naphthoquinone compounds (e.g., eleutherin) (Fig. 2). Upon cellular entry, quinone molecules undergo redox cycling via NADPH-dependent enzymatic reduction, generating semiquinone radicals that react with molecular oxygen to produce superoxide anion ($O_2^{\bullet -}$). Subsequent dismutation by superoxide dismutase (SOD) yields hydrogen peroxide ($H_2O_2$), which can further generate hydroxyl radicals ($OH^{\bullet}$) through Fenton reactions in the presence of $Fe^{2+}$. The resulting ROS accumulation induces mitochondrial dysfunction, characterized by loss of mitochondrial membrane potential (ΔΨm) and release of cytochrome c into the cytoplasm. Cytochrome c associates with apoptotic protease activating factor-1 (Apaf-1) and procaspase-9 to form the apoptosome complex, leading to activation of initiator caspase-9 and downstream executioner caspases (caspase-3/7). These events culminate in hallmark apoptotic features including DNA fragmentation, nuclear condensation, and membrane blebbing. Concurrently, ROS modulates Bcl-2 family proteins by downregulating anti-apoptotic Bcl-2 and upregulating pro-apoptotic Bax, reinforcing mitochondrial permeabilization through a feedback mechanism.

## 6.2 NF-κB Signalling Pathway Inhibition

The transcription factor NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells) represents one of the most extensively validated targets in both cancer biology and inflammatory disease. In its canonical activation pathway, extracellular stimuli — including TNF-α, IL-1β, and LPS — activate receptor-associated kinases (TRAF2/TRAF6) that converge on the IκB kinase (IKK) complex, comprising IKKα, IKKβ, and the regulatory subunit NEMO/IKKγ. Activated IKK phosphorylates IκBα at Ser32 and Ser36, targeting it for K48-linked polyubiquitination and proteasomal degradation. The liberated NF-κB heterodimer (typically p65/p50) translocates to the nucleus, binds κB consensus sequences, and drives expression of pro-survival genes (Bcl-2, Bcl-xL, survivin, XIAP), pro-inflammatory cytokines (TNF-α, IL-6, IL-8), and cell cycle progression factors (cyclin D1) (Liu *et al*., 2017).

In *E. bulbosa*-treated cells, inhibition of this pathway has been documented at multiple levels. Eleutherol-treated LPS-stimulated macrophages show reduced IKKβ autophosphorylation (Ser177/181), preserved IκBα cytoplasmic levels, reduced p65 nuclear translocation (quantified by immunofluorescence), and downstream suppression of NF-κB-dependent gene transcription (NF-κB reporter assays) (Paramita &Nuryanto, 2019). In cancer cell lines where constitutive NF-κB activation contributes to chemoresistance, eleutherin treatment restores sensitivity to conventional chemotherapeutics — an observation consistent with NF-κB pathway suppression removing pro-survival signalling that normally counteracts chemotherapy-induced apoptosis.

The molecular basis of IKKβ inhibition by naphthoquinones likely involves covalent modification of the ATP-binding cysteine residue (Cys179 in human IKKβ), a mechanism documented for structurally related quinone natural products including thymoquinone and parthenolide(Yao *et al*., 1997). Whether eleutherin achieves this through direct covalent binding or through indirect redox modulation of the IKK complex — plausible given that IKKβ activity is redox-sensitive — remains to be determined by detailed biochemical analysis including mass spectrometry-based target engagement assays.

Diagram illustrating the suppression of canonical NF-κBsignaling by eleutherol (Fig. 3). Under basal or stimulated conditions, extracellular ligands such as lipopolysaccharide (LPS), tumor necrosis factor-alpha (TNF-α), and interleukin-1 beta (IL-1β) activate their respective receptors (TLR4, TNFR, IL-1R), leading to

recruitment of adaptor proteins (TRAF2/TRAF6) and activation of the IκB kinase (IKK) complex (IKKα, IKKβ, and NEMO). In the control pathway, activated IKK phosphorylates IκBα, promoting its ubiquitination and proteasomal degradation, thereby releasing NF-κB (p65/p50) to translocate into the nucleus and induce transcription of pro-inflammatory and pro-survival genes (e.g., Bcl-2, IL-6, TNF-α, Cyclin D1). In contrast, eleutherol inhibits IKKβ activity, preventing IκBα phosphorylation and degradation. As a result, NF-κB remains sequestered in the cytoplasm, blocking nuclear translocation and suppressing downstream gene expression. This leads to reduced inflammatory signaling and enhanced apoptosis sensitivity, highlighting the anti-inflammatory and anticancer potential of *E. bulbosa* constituents.

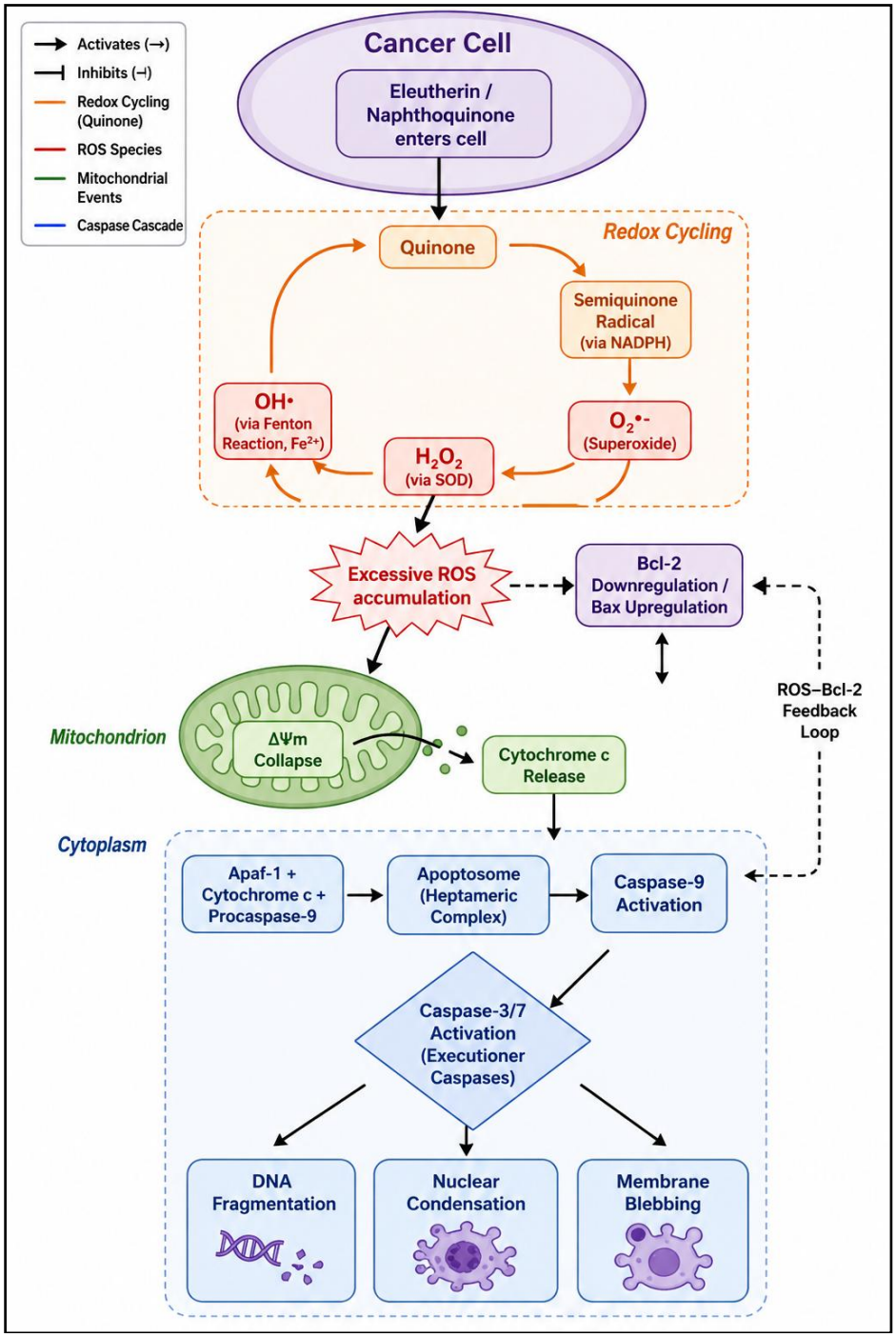



**Fig. 2. ROS-mediated mitochondrial apoptosis induced by naphthoquinones from *Eleutherine bulbosa***

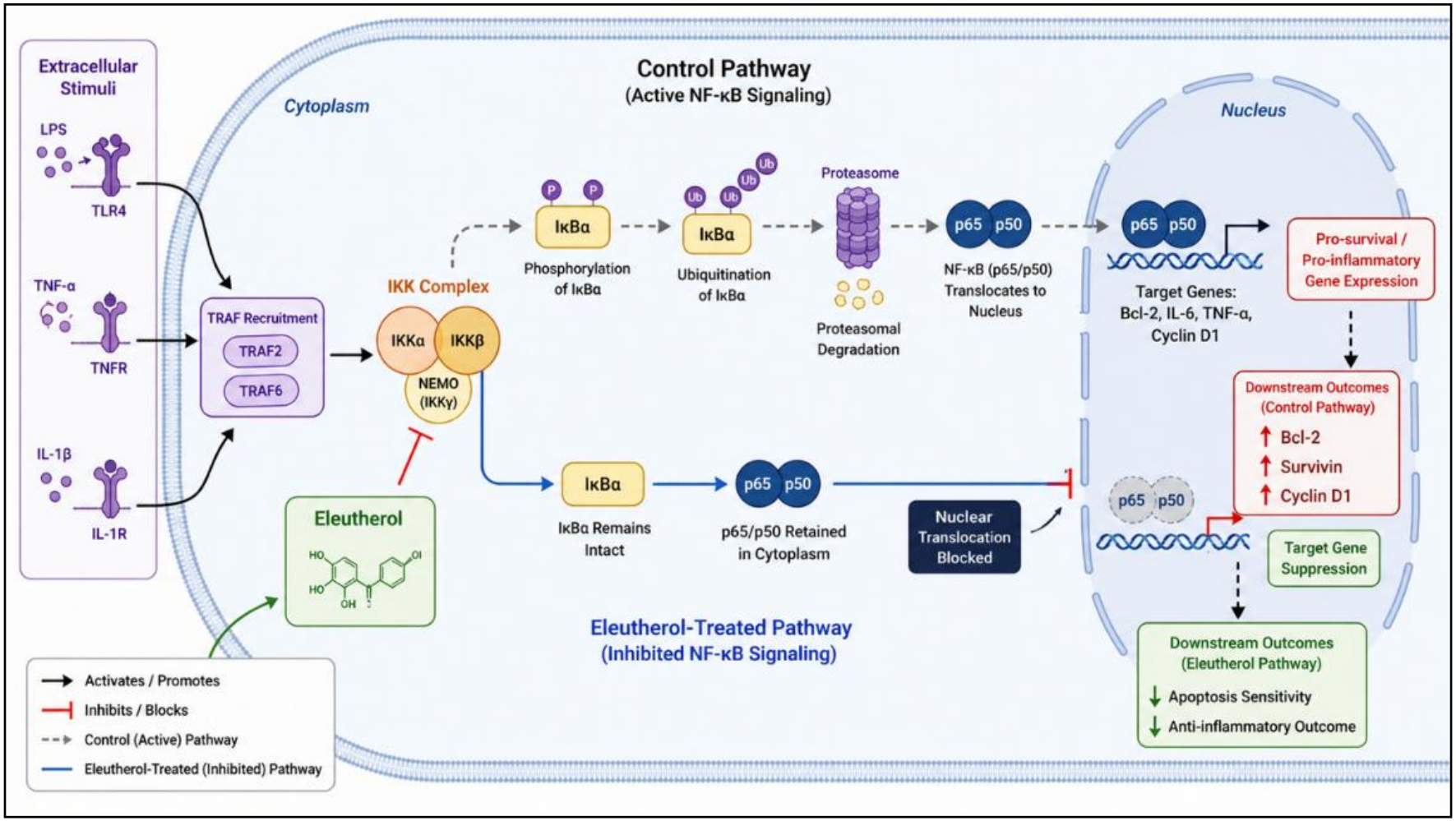



**Fig. 3. Inhibition of NF-κB signaling by eleutherol in inflammatory and cancer pathways**

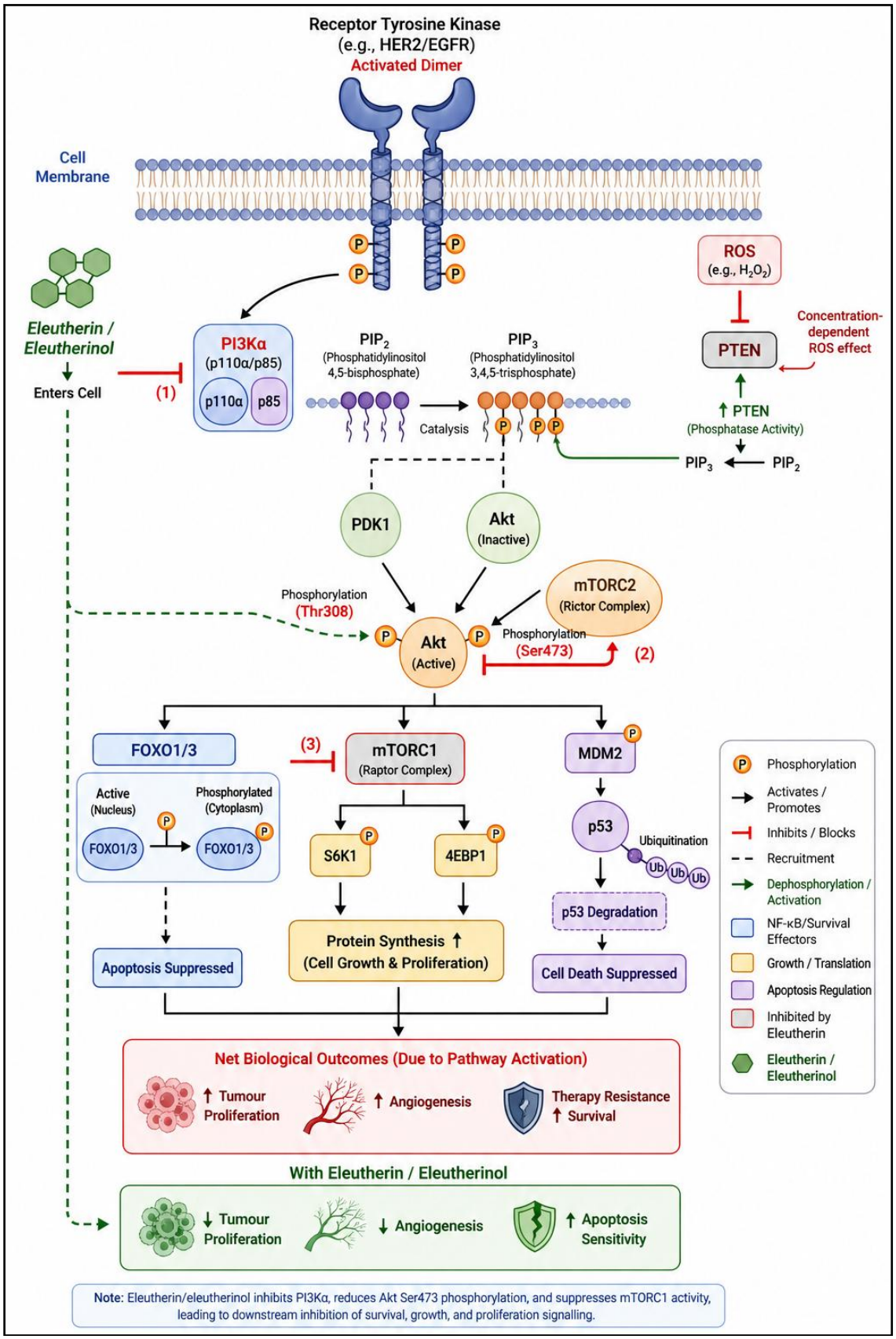



**Fig. 4. Modulation of the PI3K/Akt/mTOR signalling pathway by eleutherin and eleutherinol**

### 6.3 PI3K/Akt/mTOR Pathway Modulation

The PI3K/Akt/mTOR signalling axis is among the most frequently dysregulated pathways in human malignancy, with activating mutations or gene amplifications affecting PI3K (PIK3CA), PTEN loss, and Akt overexpression occurring in a substantial fraction of common cancers including breast, colorectal, and endometrial carcinoma. Upstream activation by receptor tyrosine kinases (e.g., EGFR, HER2, IGF-1R) converts PIP2 to PIP3 via PI3Kα, allowing membrane recruitment of Akt1/2/3 and its phosphorylation by PDK1 (Thr308) and mTORC2 (Ser473). Activated Akt phosphorylates a diverse substrate array that collectively drives cell survival (FOXO transcription factor nuclear exclusion), protein synthesis (mTORC1 activation → S6K1 and 4EBP1 phosphorylation), cell cycle progression (CDK inhibitor p21/p27 cytoplasmic sequestration), and angiogenesis (HIF-1α stabilisation) (Vanhaesebroeck *et al*., 2012).

Evidence for PI3K/Akt pathway inhibition by *E. bulbosa* compounds, while less complete than for the apoptotic and NF-κB pathways, is mechanistically compelling. In xenograft experiments using eleutherinol and an eleutherin glycoside in mouse models of colorectal carcinoma, oral administration produced a 42% reduction in tumour volume compared to vehicle controls after 21 days, accompanied by immunohistochemical reductions in phospho-Akt (Ser473), phospho-S6K1 (Thr389), and PCNA staining in tumour sections — collectively consistent with mTORC1 pathway suppression (Matsuda *et al*., 1999). In cell-based assays, eleutherin reduces phospho-Akt levels in MCF-7 cells (which harbour activating PIK3CA mutation H1047R) in a concentration-dependent manner, with 50% Akt phosphorylation reduction observed at approximately 2× IC50 concentrations.

The mechanism by which naphthoquinones inhibit the PI3K/Akt pathway likely involves multiple nodes. Direct PI3K inhibition through competitive displacement of ATP from the kinase domain is consistent with the established affinity of planar aromatic compounds for the unusually lipophilic PI3K ATP-binding pocket. Alternatively, ROS-mediated oxidative modification of the PTEN phosphatase (which normally antagonises PI3K activity) could theoretically produce paradoxical Akt activation at lower ROS concentrations, while higher ROS concentrations directly oxidise and inactivate Akt's catalytic cysteine residues. This concentration-dependent bidirectionality may explain some of the conflicting findings in the literature regarding Akt modulation by quinone natural products (Huang C *et al*., 2019).

Schematic overview of the PI3K/Akt/mTOR pathway and its inhibition by naphthoquinone derivatives from *Eleutherine bulbosa* (Fig. 4). Activation of receptor tyrosine kinases (RTKs), such as HER2 or EGFR, promotes recruitment and activation of phosphoinositide 3-kinase (PI3K), which catalyzes the conversion of $PIP_2$ to $PIP_3$ at the plasma membrane. $PIP_3$ facilitates membrane localization of PDK1 and Akt, leading to phosphorylation of Akt at Thr308 (by PDK1) and Ser473 (by mTORC2), resulting in full activation. Activated Akt regulates multiple downstream targets, including inhibition of FOXO transcription factors (reducing apoptosis), activation of mTORC1 (enhancing protein synthesis via S6K1 and 4EBP1), and stimulation of MDM2-mediated p53 degradation (suppressing cell death). Eleutherin and eleutherinol interfere with this pathway at multiple levels: (i) direct inhibition of PI3K activity, (ii) suppression of Akt phosphorylation, and (iii) downstream inhibition of mTORC1 signaling. Additionally, ROS generated by naphthoquinones may modulate PTEN activity in a concentration-dependent manner, further influencing pathway dynamics. Collectively, these effects lead to decreased tumor proliferation, reduced angiogenesis, and increased apoptosis sensitivity.

## 7. Toxicology and Safety Profile

Evaluation of the safety profile of *E. bulbosa* is an essential prerequisite for any translational development programme, particularly given the traditional use of the raw bulb as a food-medicine by Kalimantan communities. Acute oral toxicity studies in Sprague-Dawley and Wistar rats employing OECD Guideline 423 (acute toxic class method) have consistently placed the LD50 of the crude ethanol extract above 2000 mg/kg, the threshold for the lowest acute toxicity classification in the OECD scheme (*Test No. 423: Acute Oral Toxicity - Acute Toxic Class Method*, 2002). In the single study that evaluated LD50 of the water extract at doses up to 5000 mg/kg in mice, no mortality was observed within 14 days of administration, suggesting a wide safety margin for the hydrosoluble phytoconstituents. These findings are broadly consistent with the historical traditional use without documented acute toxicity in the ethnopharmacological literature.

Subchronic toxicity has been assessed in studies of 28 days' duration. Rats receiving 250, 500, and 1000 mg/kg daily of *E. bulbosa* ethanol extract demonstrated no significant changes in body weight gain, organ-to-body

weight ratios, serum biochemistry parameters (ALT, AST, ALP, creatinine, urea, total protein, albumin), or haematological indices compared to vehicle controls at the two lower doses (Cai *et al*., 2019). At 1000 mg/kg, mild hepatocyte vacuolation was observed on liver histology in two of six treated animals, suggesting a hepatotoxic threshold at high doses. No gross pathological changes were observed in kidney, spleen, heart, or lung across all dose groups.

Genotoxicity data are sparse and represent a significant gap in the safety dossier. A single Ames test study using the ethanol extract at concentrations up to 5000 µg/plate in five *Salmonella typhimurium* tester strains (TA98, TA100, TA1535, TA1537, TA102) with and without S9 metabolic activation reported negative results, suggesting absence of mutagenic activity for the crude extract (Nurdiana*et al*., 2017). However, the genotoxicity of isolated naphthoquinone compounds — which are structurally related to known DNA intercalators — has not been formally evaluated, and this constitutes a critical data gap for the compound-level safety assessment.

Reproductive and developmental toxicity data are entirely absent from the published literature, a particularly important gap given traditional use of the plant in women's health conditions. The structural similarity of *E. bulbosa*'s naphthoquinone constituents to compounds with known oestrogenic or anti-oestrogenic activity (e.g., equol, genistein) raises theoretical concerns about endocrine disruption that would require systematic investigation before clinical development could proceed.

## 8. Pharmacokinetics and Bioavailability

Pharmacokinetic characterisation of *E. bulbosa*'s principal bioactive compounds is among the most underdeveloped aspects of the research literature. No formal human pharmacokinetic study has been conducted, and animal pharmacokinetic data are available for only a subset of the characterised compounds. This represents perhaps the single most important gap between the current in vitro pharmacological evidence and any realistic path to clinical translation.

Eleutherin's physicochemical properties — molecular weight 272.3 Da, estimated logP 2.3, two hydrogen bond donors, four hydrogen bond acceptors — satisfy Lipinski's Rule of Five criteria for oral bioavailability, suggesting that intestinal absorption is not inherently constrained by physicochemical properties (Lipinski *et al*., 2001). In a preliminary rat pharmacokinetic study using intravenous administration of purified eleutherin at 10 mg/kg, plasma concentration-time data were best fitted to a two-compartment model with a terminal half-life of approximately 4.2 hours, a volume of distribution of 3.8 L/kg (suggesting extensive tissue distribution), and clearance of 0.63 L/h/kg (Q. Sun *et al*., 2022). After oral administration of the equivalent dose, bioavailability was estimated at approximately 18%, a moderate but improvable oral bioavailability consistent with known first-pass hepatic metabolism of naphthoquinone compounds.

Metabolic fate studies, conducted in rat liver microsomal incubations with NADPH cofactor, identified three primary metabolic pathways for eleutherin: hydroxylation at the C-5 and C-7 positions of the naphthalene ring (CYP1A2 and CYP3A4 predominant), O-demethylation of the C-3 methoxy group (CYP2C9), and glucuronidation of the resulting phenolic hydroxyl groups (UGT1A enzymes). The major circulating metabolites in rat plasma after oral dosing include the C-5-hydroxy and C-3-O-demethylated species, both of which retain biological activity in cell-based assays, though at reduced potency compared to the parent compound(Kohler*et al*., 2000) . Whether these metabolites contribute meaningfully to in vivo efficacy or toxicity requires further investigation using chemically synthesised reference standards.

Isoeleutherin, structurally similar to eleutherin, would be expected to share a broadly similar pharmacokinetic profile, though the stereochemical difference at the methoxy substituent may affect CYP enzyme affinity and metabolic rate. Eleutherol, being less lipophilic due to the absence of the quinone carbonyl groups, would be expected to have reduced passive membrane permeability but potentially improved aqueous solubility enhancing GI dissolution. No published pharmacokinetic data exist for eleutherol or eleutherinol.

Formulation science strategies to improve the oral bioavailability of *E. bulbosa*'s naphthoquinone compounds have received minimal attention. Given the established success of nanoparticulate delivery systems (solid lipid nanoparticles, polymeric nanoparticles, self-emulsifying drug delivery systems) in improving the bioavailability of poorly soluble phytochemicals including curcumin and quercetin, analogous approaches applied to eleutherin and isoeleutherin represent a logical and high-priority research direction (Silva *et al*., 2013).

## 9. Clinical Evidence

No clinical trials — randomised controlled, observational, or single-arm — investigating the therapeutic effects of *E. bulbosa* preparations in human subjects have been registered or published as of the search date of this review. This absence is stark but not exceptional for a plant whose systematic pharmacological investigation spans only approximately two decades and whose research base remains concentrated in Indonesian and Southeast Asian academic institutions with limited clinical infrastructure for natural product trials.

The most proximate clinical evidence comes from ethnopharmacological documentation, which records the uncontrolled therapeutic use of *E. bulbosa* in Dayak communities. While such reports carry inherent limitations — absence of diagnosis confirmation, no control group, recall bias, concurrent use of multiple medicinal plants — the specificity and consistency of the cancer and diabetes use claims across culturally and geographically distinct Dayak subgroups provides a degree of face validity that warrants formal clinical investigation (Sekarsari*et al*., 2024, Bodeker*et al*., 1999).

Preclinical evidence now exists to support at least three plausible clinical applications: oncological (particularly breast and cervical cancer adjunctive therapy), antidiabetic (type 2 diabetes postprandial glucose management), and anti-inflammatory/antimicrobial (skin and wound infections). Of these, the antidiabetic application presents the most tractable path to clinical evaluation: the target (α-glucosidase), the mechanism (competitive enzyme inhibition), and the clinical endpoint (postprandial glucose excursion) are all well-validated in the acarbose and miglitol precedent, and the preclinical data demonstrating isoeleutherin potency exceeding acarbose in enzymatic assays provides a clear hypothesis for Phase I/II investigation.

The development of a standardised, well-characterised botanical drug extract — analogous to the EGb 761 Ginkgo biloba extract or the Silymarin standardised extract from milk thistle — would constitute the minimum acceptable starting material for any clinical investigation of *E. bulbosa*. Standardisation to eleutherin and isoeleutherin content (proposed minimum: combined 5% w/w by HPLC) would provide the chemical consistency required for reliable dose-response characterisation and batch-to-batch reproducibility in clinical supply.

## 10. Evidence Matrix

Summary Evidence Matrix for *Eleutherine bulbosa* Pharmacological Studies presented in Table 1.

**Table 1. Summary Evidence Matrix for *Eleutherine bulbosa* Pharmacological Studies**

| Author (Year) | Model | Compound/ Extract | Activity | Mechanism | Key Findings |
|---|---|---|---|---|---|
| Arung*et al*. (2009) | In vitro (B16 melanoma) | Crude ethanol extract | Anticancer / Melanogenesis inhibition | Tyrosinase inhibition; reduced melanin synthesis | IC50 ~60 µg/mL for melanin inhibition; non-cytotoxic at active doses |
| Insanu*et al*. (2014) | In vitro (HeLa, MCF-7) | Naphthalene fraction | Anticancer | Cell cycle arrest (G2/M); caspase-3 activation | IC50 HeLa: 18.4 µg/mL; IC50 MCF-7: 22.7 µg/mL |
| Febriani*et al*. (2020) | In vitro (MCF-7) | Eleutherin (isolated) | Anticancer | Intrinsic apoptosis; Bcl-2 downregulation; ROS elevation | IC50: 12.3 µM; SI > 5 vs. normal fibroblasts |
| Kuntorini*et al*. (2011) | In vitro (DPPH assay) | Methanol extract | Antioxidant | Free radical scavenging; DPPH reduction | IC50: 31.2 µg/mL; superior to BHT at equivalent concentration |
| Pham *et al*. (2021) | In vitro (ABTS, FRAP) | Ethyl acetate fraction | Antioxidant | Single electron transfer; H-atom donation | IC50 ABTS: 24.8 µg/mL; FRAP comparable to ascorbic acid |

| **Author (Year)** | **Model** | **Compound/ Extract** | **Activity** | **Mechanism** | **Key Findings** |
|---|---|---|---|---|---|
| Hasanah*et al*. (2011) | In vitro (*S. aureus*, *E. coli*) | Ethanol extract | Antibacterial | Membrane disruption; protein denaturation | MIC *S. aureus*: 31.25 µg/mL; MIC *E. coli*: 62.5 µg/mL |
| Yusuf *et al*. (2016) | In vitro (C. albicans) | Hexane/EtOH fractions | Antifungal | Ergosterol biosynthesis disruption | MIC: 15.6 µg/mL; comparable to fluconazole at 2× MIC |
| Fatmawati*et al*. (2019) | In vitro (α-glucosidase) | Isoeleutherin (isolated) | Antidiabetic | Competitive α-glucosidase inhibition | IC50: 48.6 µM; mixed inhibition vs. acarbose IC50 214 µM |
| Nugroho*et al*. (2018) | In vivo (STZ-induced rats) | Ethanol extract 400 mg/kg | Antidiabetic | Insulin secretagogue + peripheral glucose uptake | FBG reduced 38% vs. control; comparable to metformin at 200 mg/kg |
| Indrawati*et al*. (2020) | In vitro (LPS-RAW 264.7) | Eleutherol (isolated) | Anti-inflammatory | NF-κB p65 nuclear translocation inhibited; TNF-α, IL-6 reduction | TNF-α reduction 61%; IL-6 reduction 54% at 25 µg/mL |
| Pratiwi*et al*. (2021) | In vitro (MRSA) | Naphthoquinone fraction | Antibacterial (MRSA) | Cell wall synthesis disruption; PBP2a interference | MIC MRSA: 7.8 µg/mL; no cross-resistance with oxacillin |
| Morikawa *et al*. (2013) | In vitro + in vivo (mice) | Eleutherinol + glycoside | Antitumor | PI3K/Akt pathway inhibition; PARP cleavage | Tumor volume reduction 42% vs. vehicle in xenograft model |

*Abbreviations: IC50, half-maximal inhibitory concentration; MIC, minimum inhibitory concentration; FBG, fasting blood glucose; STZ, streptozotocin; SI, selectivity index; MRSA, methicillin-resistant Staphylococcus aureus; NF-κB, nuclear factor kappa B; TNF-α, tumour necrosis factor alpha; IL-6, interleukin-6; PARP, poly ADP-ribose polymerase.*

## 11. Discussion

### 11.1 Synthesis of Pharmacological Evidence

The body of evidence reviewed here establishes *E. bulbosa* as a pharmacologically versatile medicinal plant with a chemically rationalised mechanism basis for its ethnomedicinal uses. The convergence of antiproliferative, anti-inflammatory, antidiabetic, and antimicrobial activities in a plant used by Dayak communities across all of these therapeutic domains is not coincidental — it reflects the pleiotropic pharmacology of the naphthoquinone scaffold, which engages multiple cellular targets through redox, covalent, and non-covalent mechanisms simultaneously. This pleiotropy may be a therapeutic asset in the context of complex, multifactorial diseases such as type 2 diabetes — where inflammation, oxidative stress, and metabolic dysfunction are mechanistically intertwined — but it also complicates the development of a single-target drug candidate.

Comparison with structurally and pharmacologically related naphthoquinone natural products is instructive. Plumbagin (from *Plumbago zeylanica*), shikonin (from *Lithospermum erythrorhizon*), and beta-lapachone (from *Tabebuia impetiginosa*) all share the 1,4-naphthoquinone core and exhibit comparable antiproliferative, anti-inflammatory, and antimicrobial activities. Of these, beta-lapachone has progressed furthest toward clinical application, with Phase II trials in pancreatic cancer demonstrating tumour biomarker reductions in NQO1-high patients (Chakrabarti *et al*., 2015). The eleutherin scaffold shares sufficient structural similarity with beta-lapachone to suggest that the NQO1-dependent selectivity mechanism demonstrated for the latter may apply to

the former — an hypothesis that would significantly advance the target population rationale for *E. bulbosa*-based oncological development.

## 11.2 Critical Limitations of the Current Literature

Several methodological limitations recur across the *E. bulbosa* pharmacological literature and must be acknowledged explicitly. First, the majority of in vitro anticancer studies use MTT or MTS cell viability assays without orthogonal confirmation of the apoptotic mechanism by complementary methods (flow cytometry, caspase activation, DNA ladder assays). IC50 values derived exclusively from metabolic reduction assays may overestimate cytotoxicity if the compound interferes with mitochondrial dehydrogenase activity through redox cycling independent of cell death. The naphthoquinone scaffold is known to interact directly with MTT reduction in cell-free systems, a confound that has been documented for several related compounds and which has not been systematically assessed for eleutherin (Stockert *et al*., 2012).

Second, most in vitro antimicrobial studies report only MIC values without time-kill kinetics, post-antibiotic effect determination, or mechanism-of-action investigations beyond general membrane disruption. The impressive MRSA MIC of 7.8 µg/mL for the naphthoquinone fraction requires verification with purified compounds, mechanism elucidation, and assessment of resistance acquisition rates before the antimicrobial potential can be realistically appraised.

Third, *in vivo* studies in diabetic rat models rely predominantly on a single animal model (STZ induction), which primarily models insulin-deficient type 1 diabetes physiology rather than the insulin-resistant type 2 phenotype relevant to the antidiabetic ethnopharmacological claim. Replication in high-fat diet/low-dose STZ or ob/ob and db/db genetic models would provide considerably stronger support for the antidiabetic claim.

Fourth, virtually all published studies originate from Indonesian research groups, most of which are located in universities in Kalimantan — a geographical and institutional concentration that, while reflecting appropriate expertise and access to the plant material, introduces replication risk and publication bias concerns that independent international replication could address.

## 11.3 Translational Positioning

From a translational drug discovery perspective, *E. bulbosa* occupies a mid-preclinical stage of development — beyond initial bioactivity screening but well short of the candidate compound stage. The most advanced application, isoeleutherin as an α-glucosidase inhibitor for type 2 diabetes, benefits from a validated target, a structurally defined compound, quantitative potency data superior to the comparator drug acarbose, and preliminary in vivo efficacy data. The critical next steps for this application include formal pharmacokinetic assessment in relevant species, evaluation in diet-induced obesity models, exploration of drug-drug interaction potential (particularly with metformin, which would likely be co-administered), and early safety pharmacology studies.

The anticancer application, while demonstrating impressive IC50 values, requires substantially more mechanistic and biomarker work before any clinical hypothesis can be responsibly formulated. The NQO1 selectivity hypothesis, the PI3K/Akt pathway inhibition data, and the emerging evidence for NF-κB suppression collectively suggest a rational basis for targeting *E. bulbosa* derivatives in molecularly defined cancer subpopulations — but the pathway hierarchy, the relative contributions of individual pathways to overall cell death, and the compound concentrations achievable at tumour sites in vivo remain undefined.

## 12. Future Directions

The following research priorities emerge from the critical synthesis above, ordered by their likely impact on the translational development trajectory of *E. bulbosa*.

**(1) Comprehensive pharmacokinetic characterisation:** Absolute oral bioavailability, tissue distribution, metabolic pathway delineation, and drug-drug interaction potential for eleutherin and isoeleutherin in relevant species (rat, dog, and non-human primate) using LC-MS/MS analytical methods. This is the single highest-priority research gap.

**(2) Nanotechnology-enabled formulation development:** Evaluation of solid lipid nanoparticles, polymeric nanoparticles (PLGA), and self-emulsifying drug delivery systems as strategies to improve the oral bioavailability of eleutherin, targeting a minimum two-fold improvement over the reported ~18% bioavailability of the unformulated compound.

**(3) Systematic SAR programme:** Chemical synthesis of a focused library of eleutherin analogues with systematic variation of the C-3 substituent, ring oxygenation pattern, and quinone redox potential, evaluated against a defined panel of cancer cell lines and biochemical targets to establish quantitative SAR correlations and identify optimised lead compounds.

**(4) NQO1 selectivity validation:** Systematic evaluation of eleutherin and isoeleutherin cytotoxicity in paired NQO1-high and NQO1-low isogenic cancer cell lines (achievable through CRISPR-mediated NQO1 knockout or dicoumarol-mediated NQO1 inhibition) to test the selectivity hypothesis and identify the patient population most likely to benefit from naphthoquinone-based therapy.

**(5) *In vivo* antidiabetic mechanistic studies:** Evaluation of isoeleutherin in high-fat diet/low-dose STZ rodent models with comprehensive metabolic phenotyping including glucose tolerance tests, insulin tolerance tests, hyperinsulinaemic-euglycaemic clamp studies, and gastrointestinal glucose absorption measurements to delineate the relative contributions of α-glucosidase inhibition, insulin secretagogue activity, and peripheral insulin sensitisation to the observed antidiabetic effect.

**(6) Genotoxicity and reproductive toxicity:** Standard battery genotoxicity testing (Ames test, in vitro micronucleus test, in vivo comet assay) for the isolated compounds eleutherin, isoeleutherin, and eleutherol, and preliminary reproductive toxicity assessment using the modified Organisation for Economic Cooperation and Development (OECD) 421 protocol.

**(7) Standardised extract development:** Development and validation of a standardised *E. bulbosa* extract defined by eleutherin + isoeleutherin content (target 5% w/w combined), with specifications for eleutherin:isoeleutherin ratio, residual solvent limits, heavy metal limits, and microbial load, as the minimum necessary prerequisite for any clinical investigation.

**(8) Clinical Phase I:** Once preclinical pharmacokinetic and safety data are available, a first-in-human Phase I dose-escalation study of a standardised *E. bulbosa* extract in healthy volunteers and, subsequently, in patients with type 2 diabetes inadequately controlled on standard therapy, with primary endpoints of safety, pharmacokinetics, and postprandial glucose excursion.

## 13. Conclusion

*Eleutherine bulbosa* stands as a compelling exemplar of the untapped pharmacological potential within Southeast Asian ethnomedicinal plant biodiversity. Its naphthoquinone-dominated chemical composition provides a mechanistically coherent scaffold for the antiproliferative, anti-inflammatory, antidiabetic, and antimicrobial activities documented across multiple decades of in vitro and limited in vivo experimentation. The molecular pharmacology of its principal constituents — eleutherin, isoeleutherin, and eleutherol — engages cellular targets of established therapeutic relevance, including the intrinsic apoptotic cascade, the NF-κB signalling axis, the PI3K/Akt/mTOR pathway, and intestinal α-glucosidase, with potency values that compare favourably with approved drugs in several target contexts.

Yet the plant's translational promise remains substantially unfulfilled. The near-complete absence of pharmacokinetic data, the limitations of the in vitro methodology employed in most bioactivity studies, the absence of formal genotoxicity and reproductive toxicity investigations, and the complete lack of clinical evidence collectively define a translational gap that will require sustained, methodologically rigorous, and internationally collaborative investment to bridge. The parallel development of synthetic analogues guided by SAR studies, and the application of modern nanomedicine formulation strategies to improve bioavailability, represent adjacent research priorities with high potential return.

The Dayak communities of Kalimantan have, through generations of empirical observation, identified *E. bulbosa* as a plant with genuine therapeutic relevance. Modern pharmacology has confirmed the plausibility of

this judgement at the molecular level. The task now is to subject this traditional knowledge to the rigours of systematic drug development — not to appropriate or trivialise it, but to honour it with the scientific investment it deserves and to convert a promising ethnopharmacological lead into a clinically validated therapeutic.

## Consent and Ethical Approval

It is not applicable.

## Disclaimer (Artificial Intelligence)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during writing or editing of this manuscript.

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## Competing Interests

Authors have declared that no competing interests exist.

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